2024

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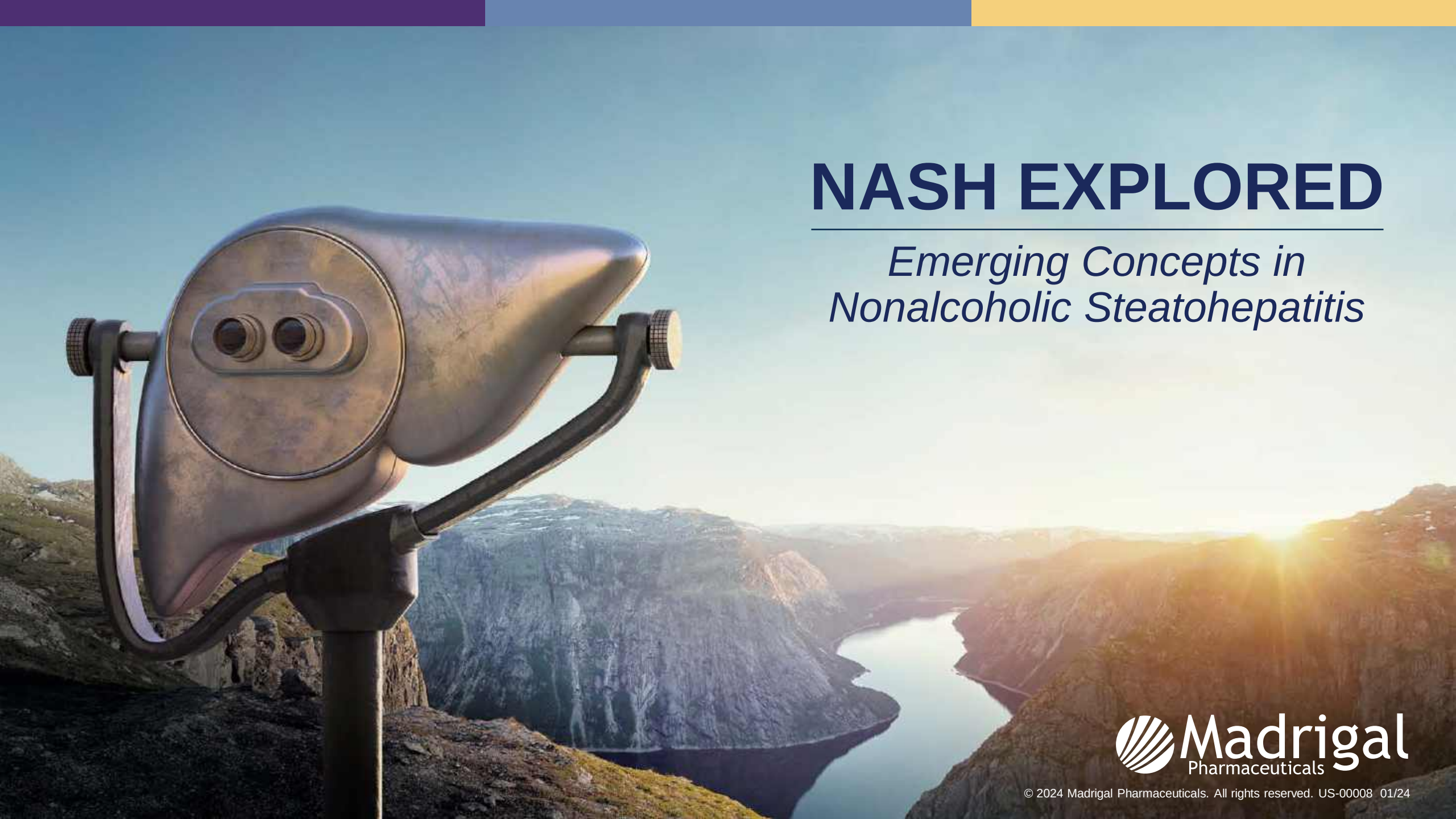

NASH EXPLORED

Emerging Concepts in Nonalcoholic Steatohepatitis

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NASH Presentation Overview

- Definitions, Epidemiology, & Comorbidities
- Pathophysiology
- Morbidity & Mortality
- Patient Identification & Perspective
- NASH Management

Definitions, Epidemiology, & Comorbidities

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Nonalcoholic Fatty Liver Disease Ranges From Simple Steatosis To Nonalcoholic Steatohepatitis, A Chronic And Progressive Liver Disease[1-5]

NAFLD: Nonalcoholic Fatty Liver Disease

- Entire spectrum of fatty liver disease in individuals without significant alcohol consumption

NAFL: Nonalcoholic Fatty Liver

- Isolated steatosis (fat in ≥5% of hepatocytes)

NASH: Nonalcoholic Steatohepatitis

- Steatosis
- Ballooning
- Inflammation

NASH with Fibrosis

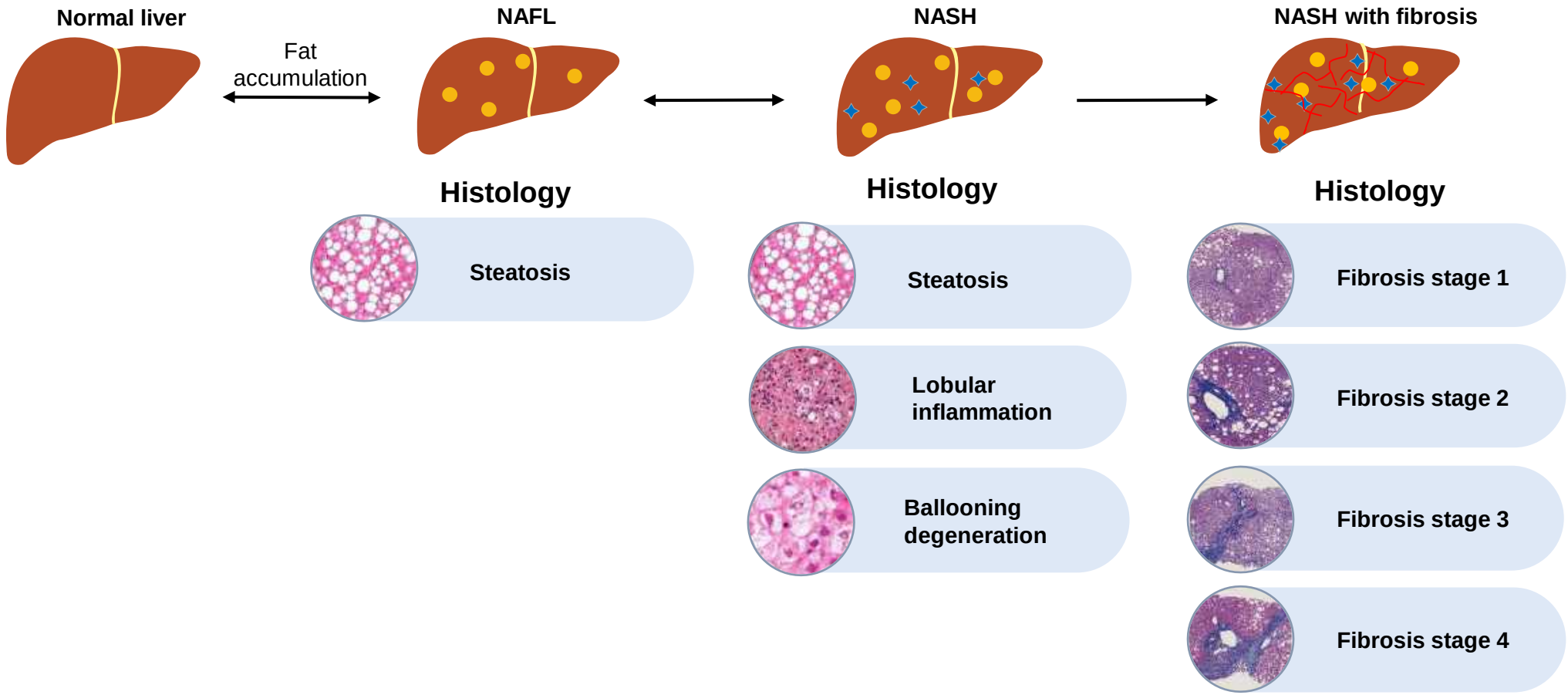
- **NASH** (steatosis, ballooning, inflammation)
- **Mild**: fibrosis stage 1 (F1)
- **Significant**: fibrosis stages 2 and 3 (F2/F3)
- **Cirrhosis**: fibrosis stage 4 (F4)

F, fibrosis stage; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Sheka AC, et al. *JAMA*. 2020;323(12):1175-83. 2. Alkhouri N, McCullough AJ. *Gastroenterol Hepatol (N Y)*. 2012;8(10):661-8. 3. EASL–EASD–EASO. *J Hepatol*. 2016;64:1388-402.
4. Diehl AM, Day C. *N Engl J Med*. 2017;377:3063-72. 5. Honda et al. *Int J Mol Sci*. 2020;21:4039.

Nonalcoholic Fatty Liver Disease Ranges From Simple Steatosis To Nonalcoholic Steatohepatitis, A Chronic And Progressive Liver Disease

NASH is the inflammatory subtype of NAFLD, which can progress to cirrhosis, liver cancer, or result in death[1-5]



NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Sheka AC, et al. *JAMA*. 2020;323(12):1175-83. 2. Alkhouri N, McCullough AJ. *Gastroenterol Hepatol* (N Y). 2012;8(10):661-8. 3. EASL–EASD–EASO. *J Hepatol*. 2016;64:1388-402.
4. Diehl AM, Day C. *NEJM*. 2017;377:3063-72. 5. Honda et al. Int J Mol Sci. 2020;21:4039.

Comorbidities Associated With Nonalcoholic Fatty Liver Disease

Common conditions associated with NAFLD	Other conditions associated with NAFLD
▪ Obesity ▪ T2D ▪ Dyslipidemia ▪ Polycystic ovary syndrome ▪ Metabolic syndrome*	▪ Hypothyroidism ▪ Obstructive sleep apnea ▪ Hypopituitarism ▪ Hypogonadism ▪ Psoriasis

*** Metabolic syndrome is defined by the presence of ≥3 of the following features or established conditions:**

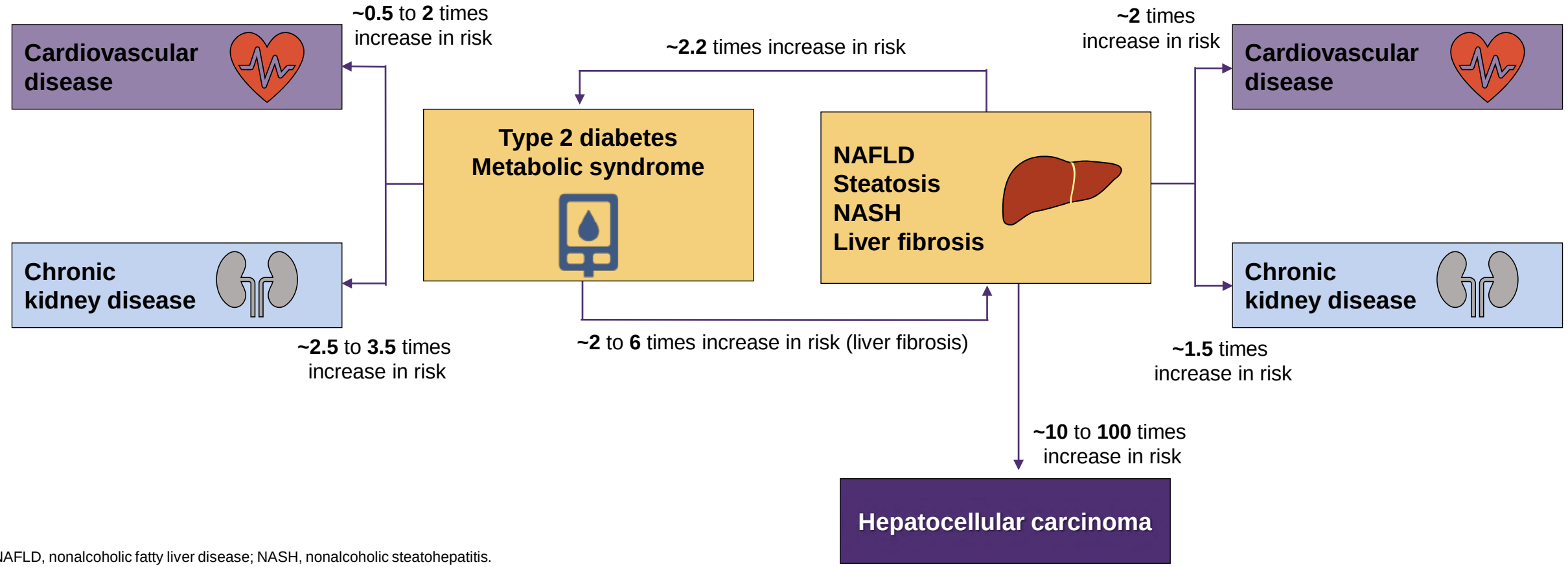
- Obesity or waist circumference >102 cm in men or >88 cm in women
- Triglyceride level ≥150 mg/dL or more
- HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
- Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or on treatment for hypertension
- Fasting plasma glucose level 110 mg/dL or greater

HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes.

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

Bidirectional Relationships Between Nonalcoholic Fatty Liver Disease, Type 2 Diabetes And Metabolic Syndrome

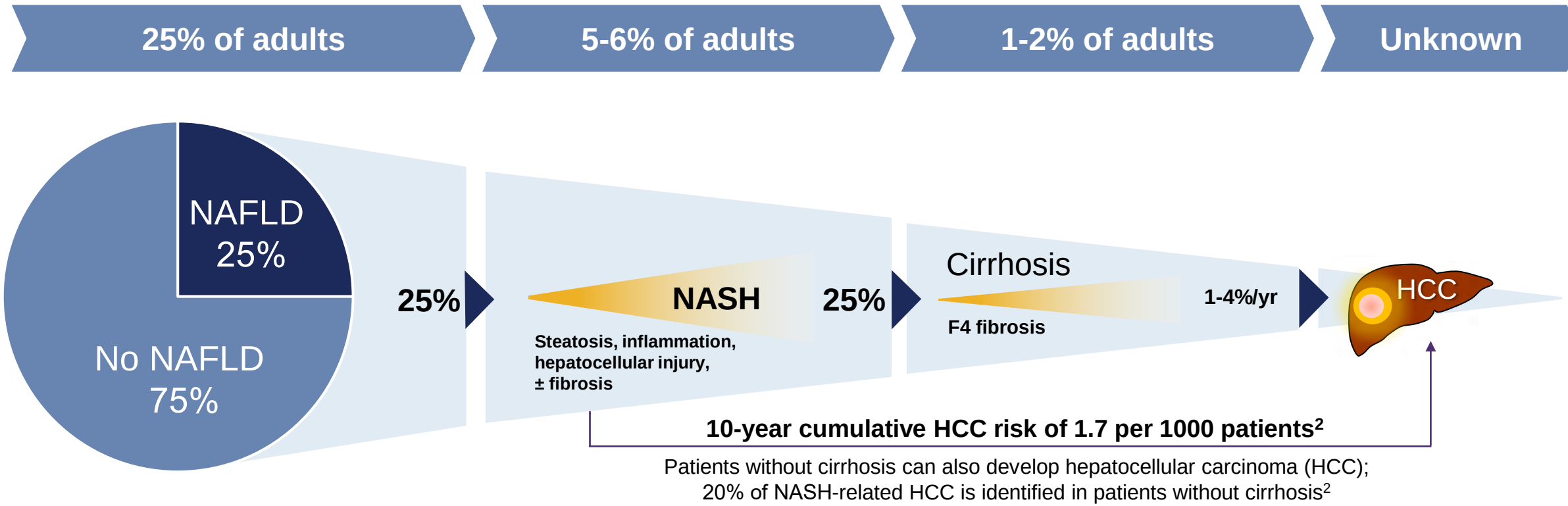
- There is an association between NAFLD/NASH and the risk of developing multiple extrahepatic complications
- The magnitude of risk is linked to the severity of disease, particularly the stage of liver fibrosis



NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Adapted from Targher G, et al. *Lancet Gastroenterol Hepatol*. 2021;6:578-88.

Progression Of Nonalcoholic Steatohepatitis Can Lead To Cirrhosis And Hepatocellular Carcinoma

Prevalence in the US (2016)[1]



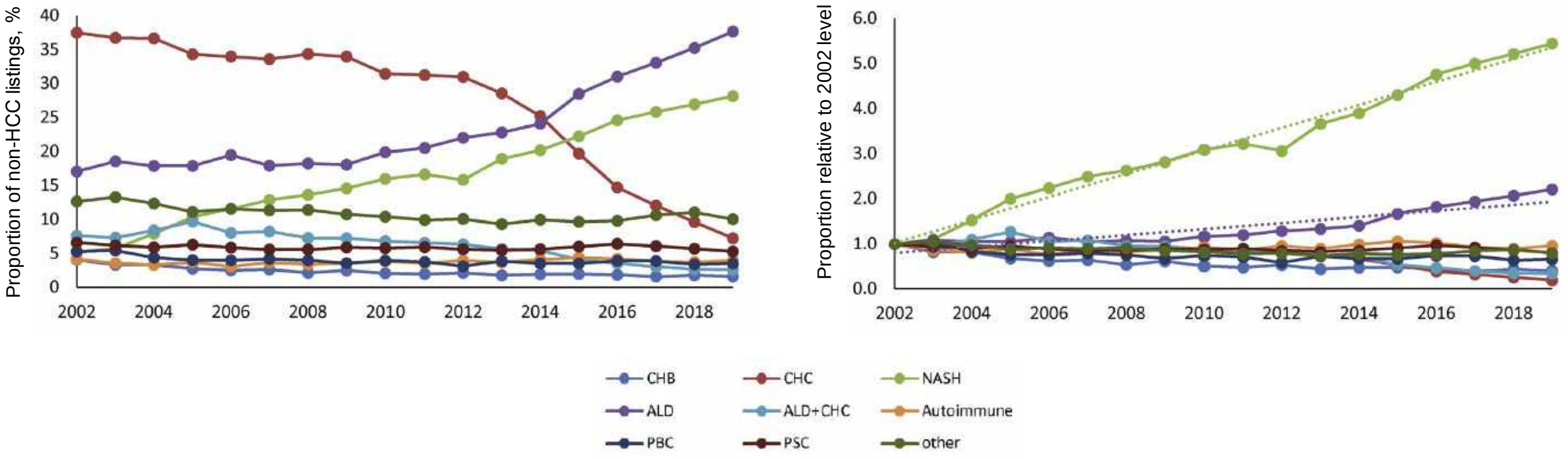
Patients without cirrhosis can also develop hepatocellular carcinoma (HCC);
20% of NASH-related HCC is identified in patients without cirrhosis[2]

F, fibrosis stage; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Diehl AM, Day C. *NEJM*. 2017;377:3063-72. 2. Kanwal F, et al. *Gastroenterology*. 2018;155(6):1828-1837

Nonalcoholic Steatohepatitis Is An Increasing Indication For Liver Transplantation In The US

Prevalence of the most common chronic liver disease (CLD) etiologies in waitlisted liver transplant candidates without HCC.[1]



NASH is currently the leading cause for liver transplant (LT) waitlist registration/liver transplantation in females and the second leading cause overall [1,2]

ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CLD, chronic liver disease; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

1. Younossi et al. *Clin Gastroenterol Hepatol.* 2021;19:580-589. 2.Noureddin et al. *Amer. J. Gastroenterol*. 2018;113:1649-1659.

Pathophysiology

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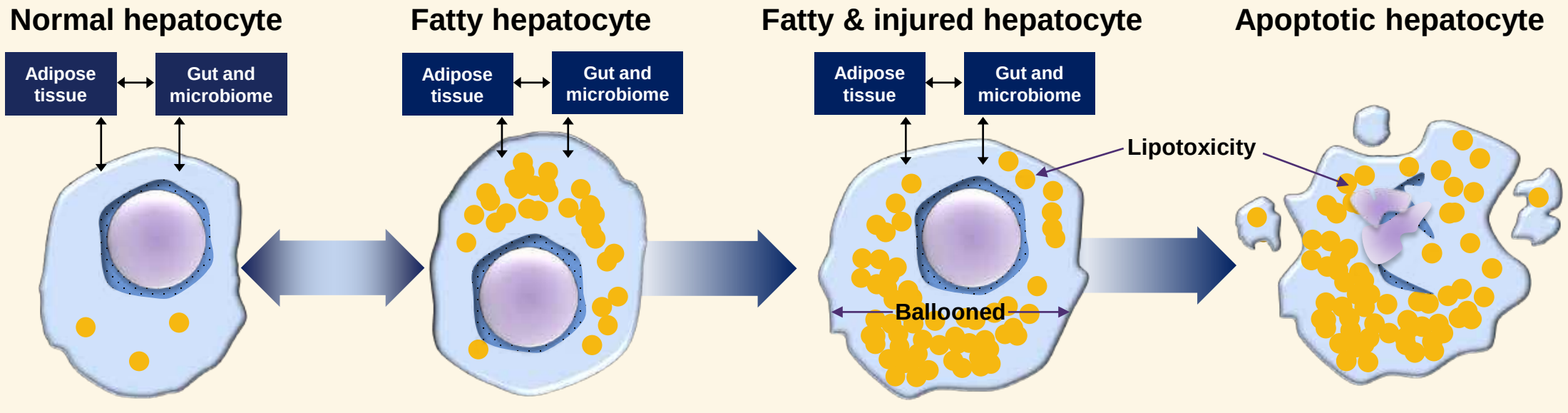
Hepatic Lipotoxicity Is A Key Driver Of Nonalcoholic Steatohepatitis And Fibrosis In The Liver



- Various factors can induce chronic liver steatosis leading to metabolic, oxidative and endoplasmic reticulum stress (ie., lipotoxicity)
- **Lipotoxicity** further leads to hepatocyte injury & apoptosis
- Repair-related cells accumulate and initiate wound-healing responses including collagen deposition

NASH is the sum of injury and repair responses triggered by lipotoxicity

Cell signals

Repair-related cells

Immune cells | Activated sinusoidal endothelium | Myofibroblastic stellate cell | Reactive ductal cells

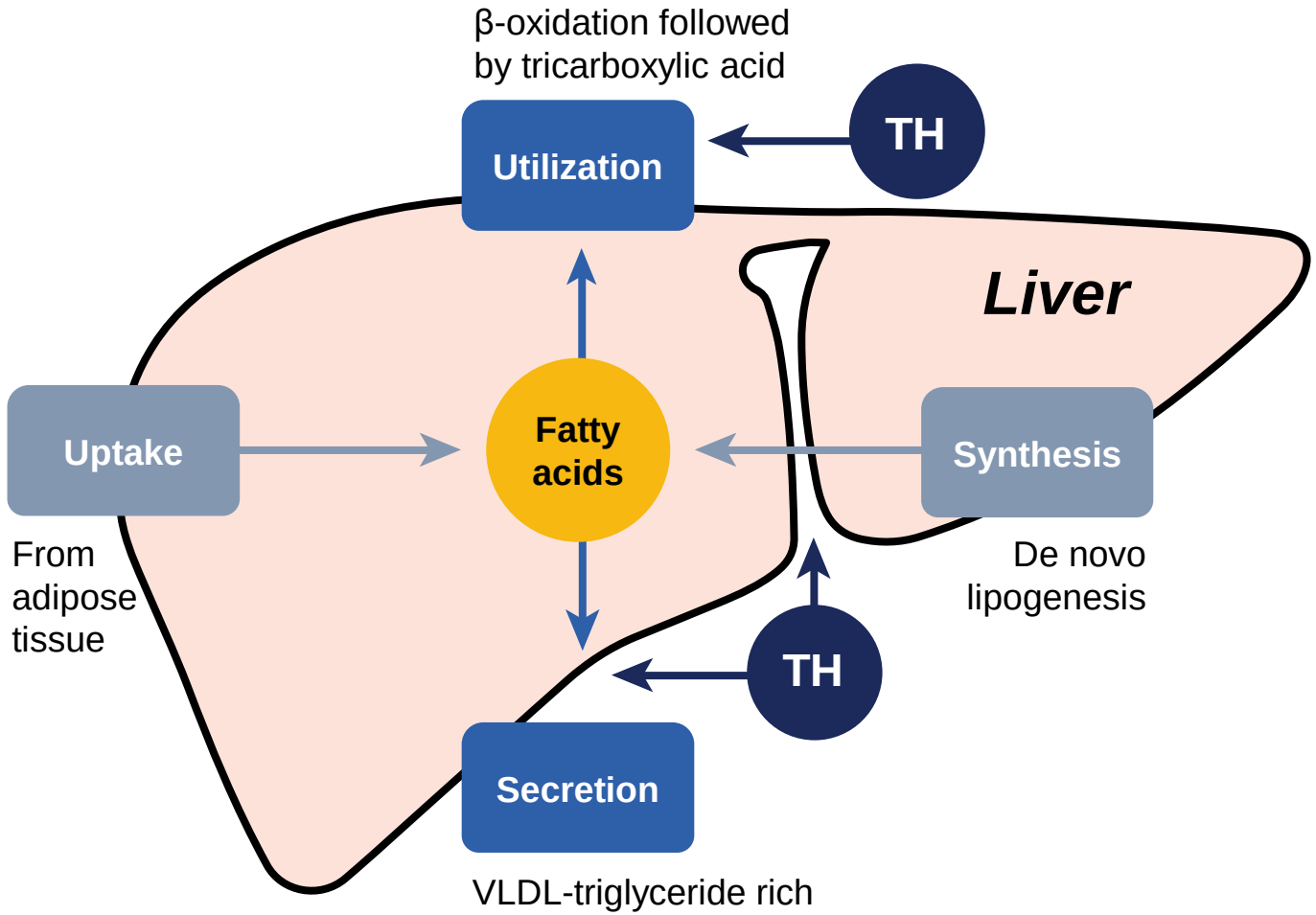
Wound-healing responses

Inflammation, vascular remodeling, fibrogenesis, and accumulation of immature liver epithelial cells

Adapted from Diehl AM and Day C. *NEJM.* 2017;377:3063-72.

Intrahepatic Thyroid Hormone Signaling Plays A Critical Role In Lipid Metabolism In The Liver

- In a healthy liver, **intrahepatic thyroid hormone signaling activates lipid metabolism** and contributes to normal liver function[1-5]
- In an injured (or unhealthy) liver, there can be **impairment of intrahepatic thyroid hormone signaling**[4]
- Impaired hepatic thyroid hormone signaling can **lead to hepatic steatosis and the accumulation of lipotoxic fat species**[3-5]



TH, thyroid hormone.

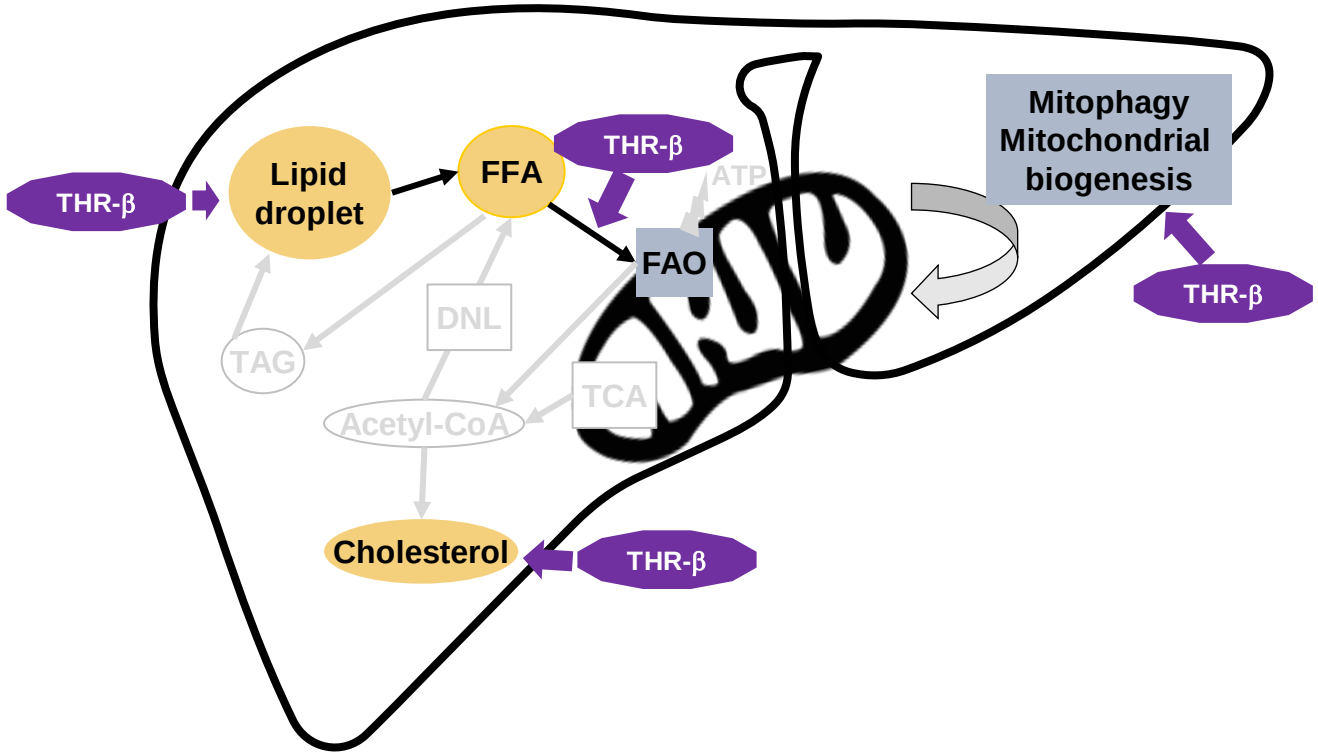
1. Ritter, et al. *Hepatology*. 2020;72(2):742-752. 2. Sinha, et al, *Nat Rev Endocrinol*. 2018;14(5):259–269. 3. Moran, et al. *J Clin Endocrinol Metab*. 2021;106(5):e2005-e2014. 4. Bohinc et al. *Endocrinology*. 2014;155(11):4591–4601. 5. Bano et al. *J Clin Endocrinol Metab*. 2016;101(8):3204-3211. 6. Mantovani et al. *Thyroid*. 2018;28(10):1270-1284.

The Thyroid Hormone Receptor-β Pathway Plays A Key Role In Hepatic Lipid Metabolism

- Thyroid hormones (TH) act on multiple pathways to maintain homeostasis in the liver by controlling[1-4]:
  - Fatty acid oxidation
  - Mitophagy and mitochondrial biogenesis
  - Cholesterol metabolism
  - Carbohydrates metabolism

- THR-β is responsible for TH effects on metabolism in the liver as determined in preclinical models[2]

- In clinical trials, THR-β agonism has demonstrated beneficial effects on lipid metabolism[5,6]



ATP, adenosine triphosphate; DNL, de novo lipogenesis; FAO, fatty acid beta oxidation; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAG, triacylglycerol; TCA, tricarboxylic acid; THR-β, thyroid hormone receptor β; VLDL, very low-density lipoprotein.

1. Ritter et al. *Hepatology*. 2020; 72(2):742-752. 2. Saponaro et al. *Front Med*. 2020; 7:331. 3. Sinha et al. *Nat Rev Endocrinol.* 2018;14(5):259-26. 4. Taub R, et al. *Atherosclerosis*. 2013;230(2013):373-380. 5. Taub et al. NASH-TAG 2018 Poster. 6. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024.

Morbidity & Mortality

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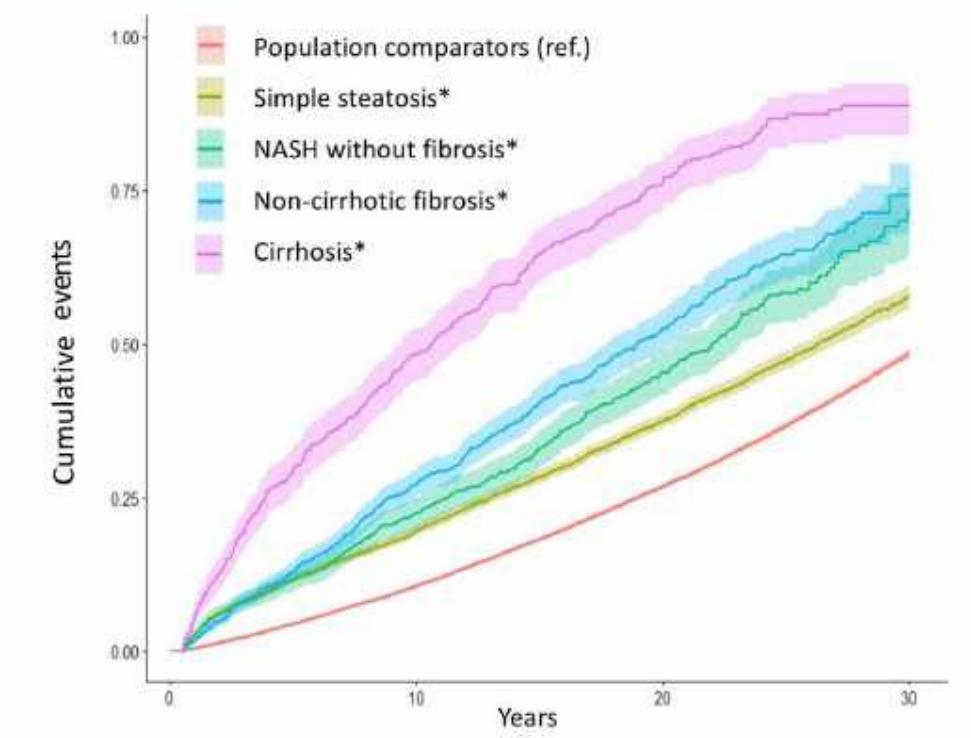
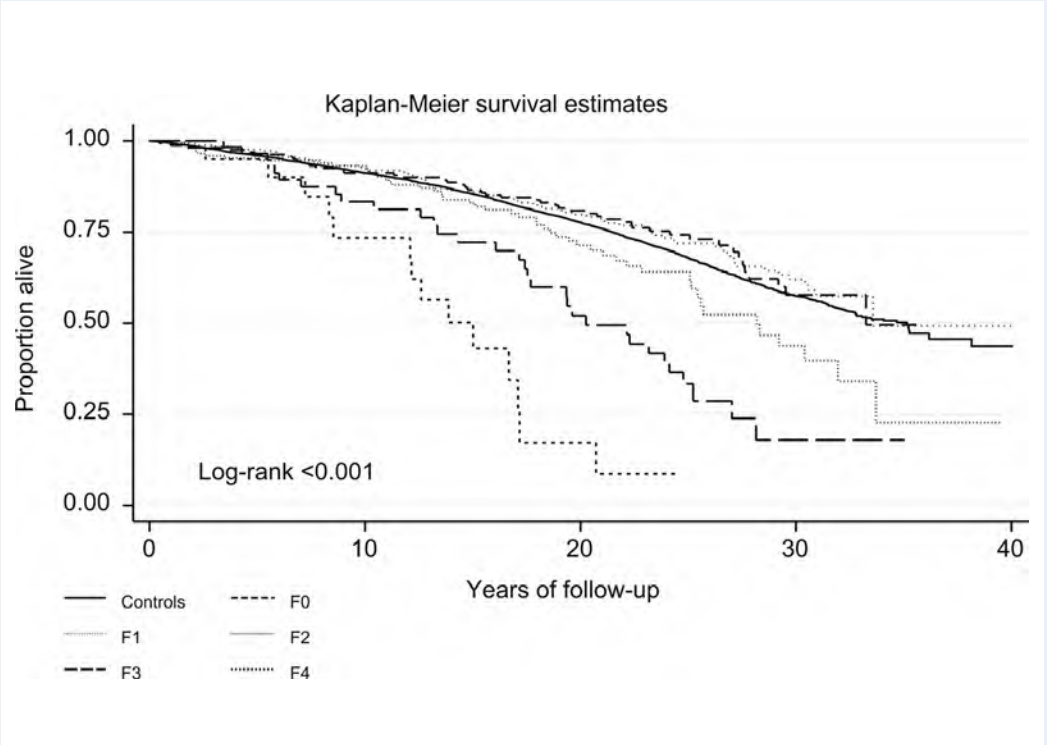
NASH With Fibrosis Is Associated With An Increased Rate Of Mortality

All NAFLD histological stages were associated with significantly increased overall mortality, and this risk increased progressively with worsening histology



Cumulative incidence of all-cause mortality according to the presence and histological severity of NAFLD[1]

All NAFLD fibrosis stages were associated with significantly increased overall mortality, and this risk increased progressively with worsening fibrosis stage



Cumulative incidence of all-cause mortality according to the histological fibrosis stage in NAFLD[2]

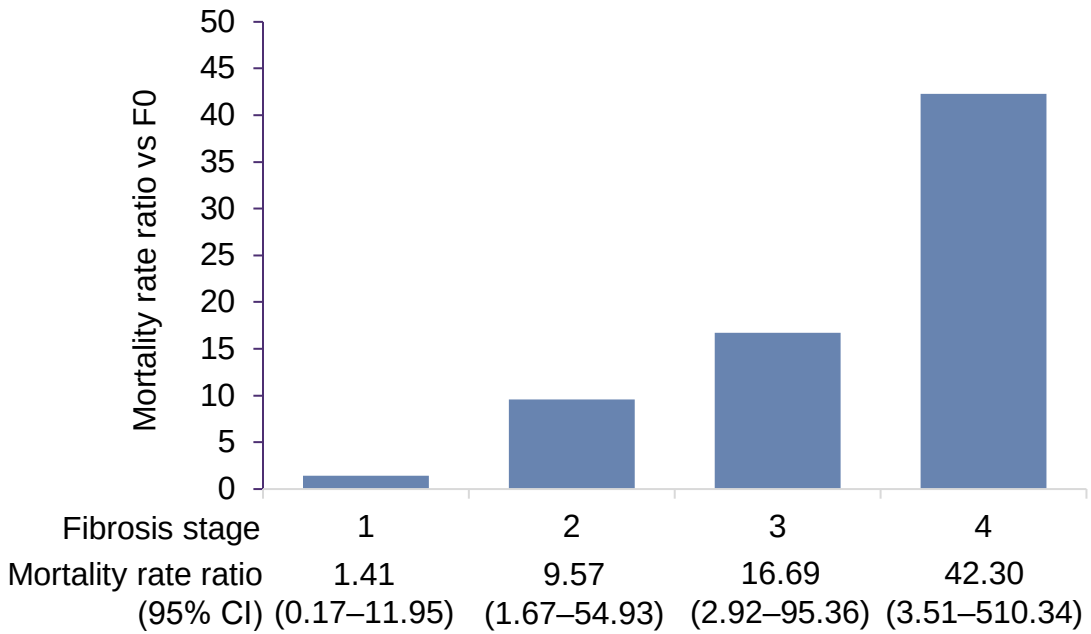
HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
1. Simon et al. *Gut.* 2021;70:1375-1382. 2. Hagström et al. *J Hepatol.* 2017;67:1265-1273.

*Histological severity of NAFLD was defined in 4 categories, as simple steatosis, NASH without fibrosis, non-cirrhotic fibrosis, and cirrhosis.

Fibrosis Severity Is Increasingly Associated With Morbidity And Mortality

The risk of liver-related death is statistically higher only after progression to F2 or higher[1]

Fibrosis stage-specific liver-related mortality rate ratios[1]



Among patients with NASH, those with cirrhosis are at greater risk for decompensation, HCC or death compared with less advanced fibrosis[2]

Clinical Outcomes	F3 (n=159)	F4 CTP A5 (n=222)	F4 CTP A6 (n=77)
Overall mortality or liver transplantation	3%	11%	58%
First occurrence of a major clinical event	16%	28%	66%
Hepatic decompensation	19%	59%	85%
HCC	8%	19%	15%
Non-hepatic malignant neoplasm	38%	16%	0
Major vascular event	35%	6%	0

CI, confidence interval; CTP, Child–Turcotte–Pugh; F, fibrosis stage; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis.
Adapted from: 1. Dulai et al. *Hepatology.* 2017;65:1557-156. 2. Vilar-Gomez, et al. *Gastroenterology.* 2018;155:443–457.

Major Causes Of Death In Patients With Nonalcoholic Fatty Liver Disease

Liver Events and Causes of Death

Outcome, n (%)	Number (n=193)
Death or OLT	
Cardiovascular disease	74 (38.3%)
Non-liver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
Hepatocellular carcinoma	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8%)
Other	35 (18.1%)
Unknown	15 (7.8%)

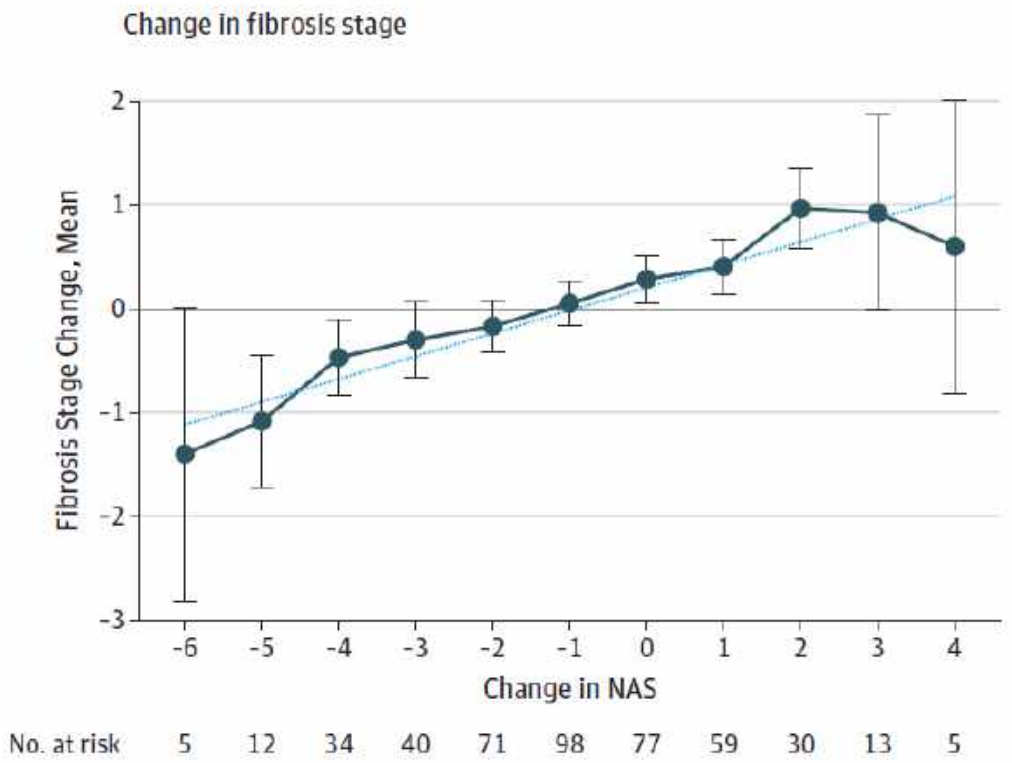
CVD, cardiovascular diseases; NAFLD, nonalcoholic fatty liver disease; OLT, orthotopic liver transplant.

1. Angulo P, et al. *Gastroenterology.* 2015;149:389-397.

Changes In Disease Activity (NAS) Are Associated With Changes In Fibrosis[1]

- High NAS at baseline has been associated with progression to fibrosis stage F3-F4.
  - NAS (NAFLD activity score) is the sum of scores for steatosis, lobular inflammation, and ballooning; scores range, 0 to 8, with 8 indicating more severe disease
- An improvement (ie., reduction) in NAS is associated with a decrease in fibrosis stage.
  - Specifically, a 2-point or greater reduction in NAS is associated with fibrosis regression.
- Development and progression of fibrosis in patients with NAFL alone was associated with development of steatohepatitis.

The trajectory of fibrosis change is directly associated with changes in disease activity (NAS) and is independent of changes in body weight



NAFL, nonalocholic fatty liver; NAS, NAFLD activity score

1. Kleiner et al. *JAMA Network Open*. 2019 2(10).

Patient Identification

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Imaging And Biomarkers Modalities To Identify And Monitor Patients With Nonalcoholic Steatohepatitis

1. Simple Evaluation Scores

- Easily calculated using information from standard liver tests and patient data[1]
- **FIB-4, NFS,** and **APRI** are recognized in guidelines as clinically useful in identifying patients with a higher probability of F3/F4 fibrosis[1,2]

2. Imaging Techniques

- **Conventional ultrasound:** historically used to identify steatosis despite known limitations[1]
- **MRI/MRI-PDFF:** accurate for detecting and quantifying steatosis[1]
- **FibroScan® (VCTE):** can assess both steatosis (CAP) and fibrosis (LSM); point-of-care[1]
- **MRE:** accurate for detecting and quantifying fibrosis[1]

3. Proprietary Serum Tests

- Tests for biomarkers to determine the presence of advanced fibrosis (F3/F4) or active NASH[1,3]
- **ELF:** FDA recently granted marketing authorization via the De Novo review pathway, and ELF is also widely used outside the US to determine the presence of F3/F4[4]
- Other investigational serum tests include: **PRO-C3** or **NIS-4**[3,5]

APRI, aspartate aminotransferase to platelet ratio index; CAP, controlled attenuation parameter; CK-18, cytokeratin 18; ELF, enhanced liver fibrosis; FDA, Food and Drug Administration; F, fibrosis stage; FIB-4, fibrosis-4 index for liver fibrosis; LSM, liver stiffness measurement; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NFS, NAFLD fibrosis score; PRO-C3, N-terminal type 3 collagen propeptide; VCTE, vibration-controlled transient elastography.

1. European Association for Study of Liver. *J Hepatol*. 2021;75(3):659-89. 2. A Chalasani N, et al. *Hepatology*. 2018;67(1):328-57. 3. Loomba R, Adams LA. *Gut.* 2020;69:1343–1352. 4. https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test (accessed January 2022). 5. https://nis4.com/ (accessed January 2022).

Various Noninvasive Tests Predict Outcomes

Fibroscan® and FibroMeter™, MRE, and ELF are examples of noninvasive tests correlated to outcomes[1-3]

Figure 1 - Fibroscan® and FibroMeter™

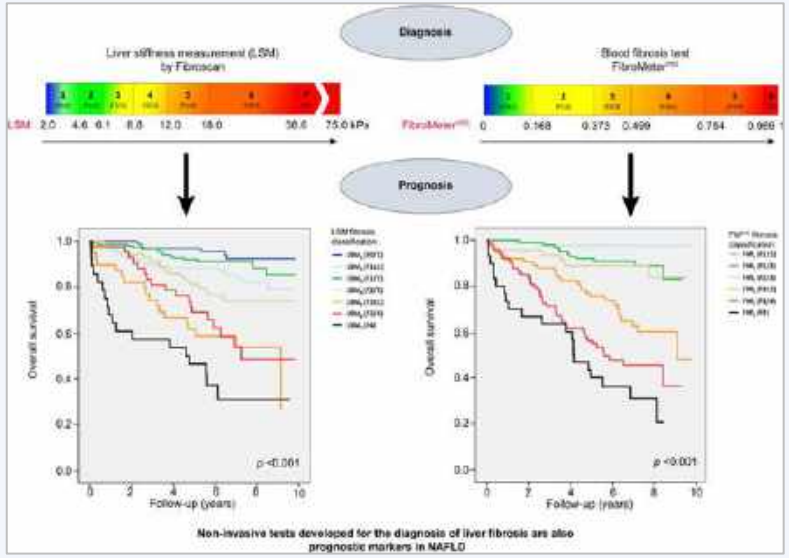


Figure 2 - MRE

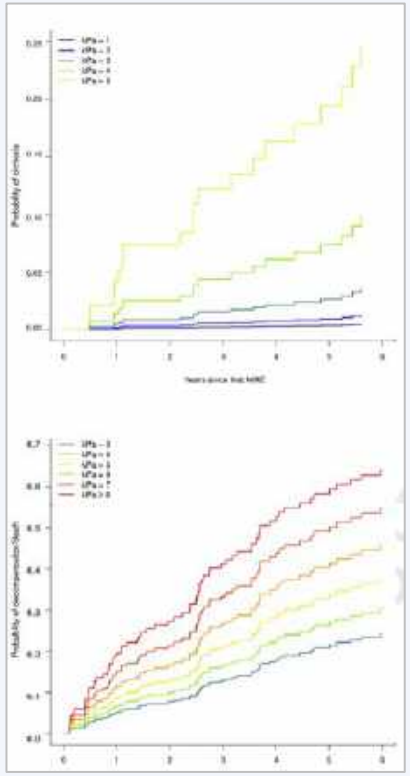
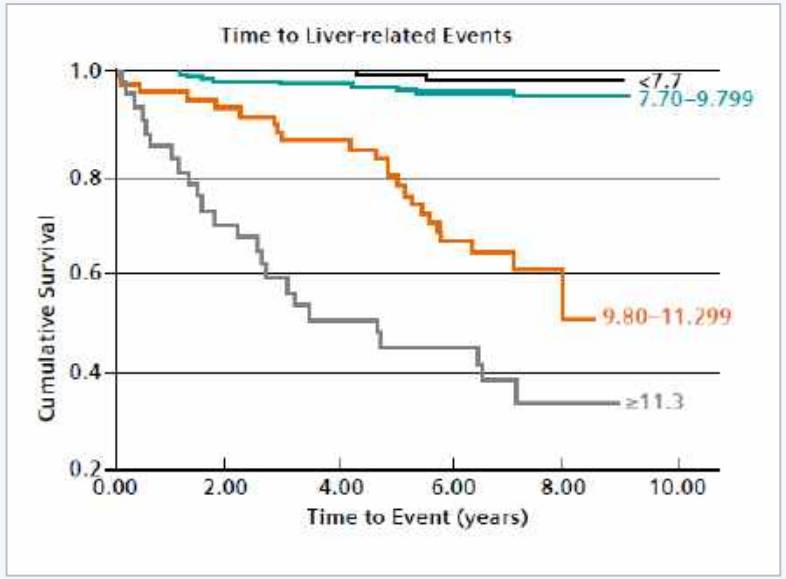


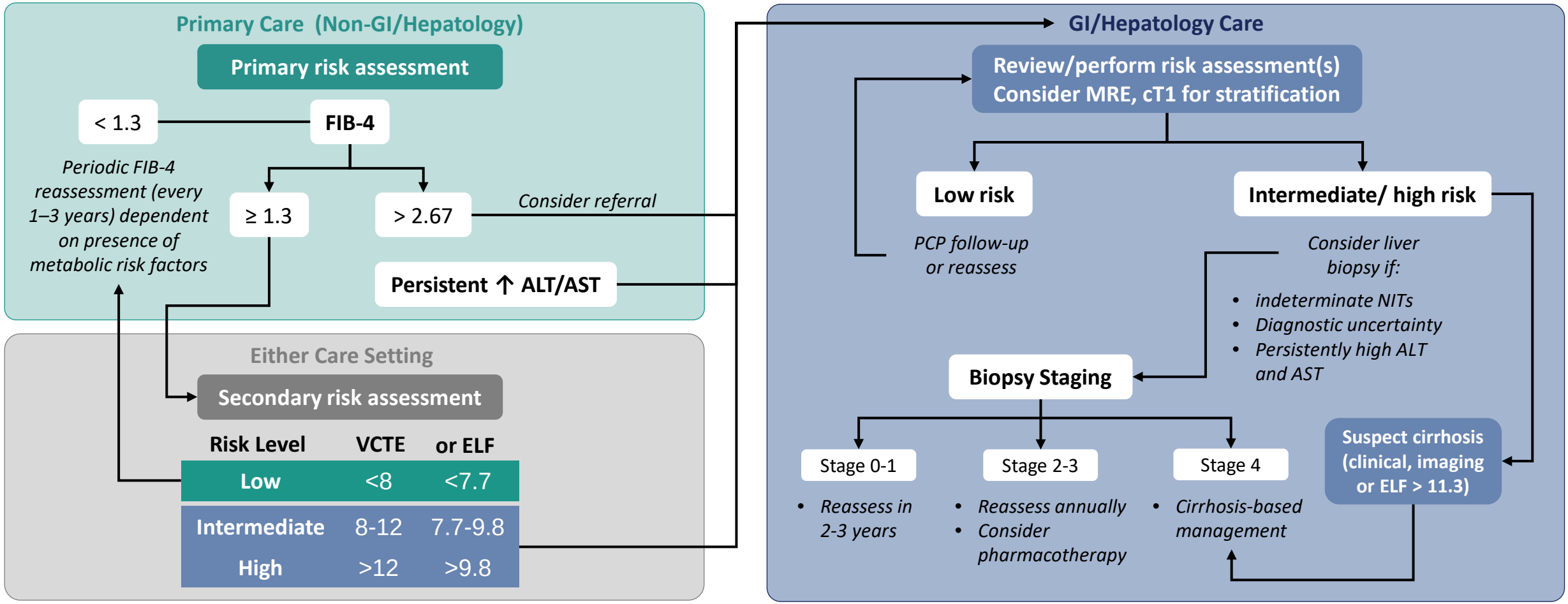
Figure 3 - ELF



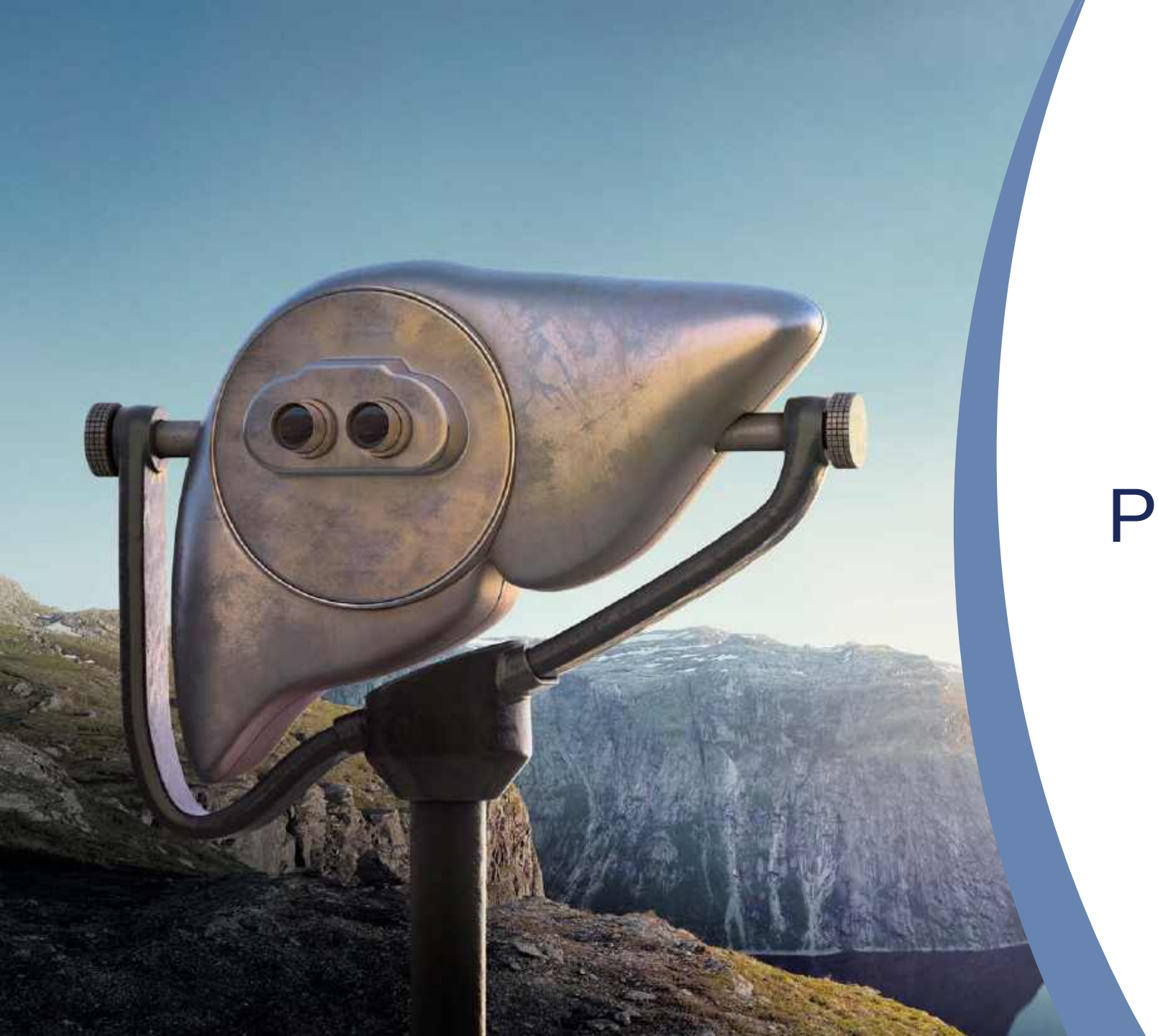
ELF, enhanced liver fibrosis; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease

1. Boursier J, et al. *J Hepatol.* 2016;65(3):570-578 2. Gidener T, et al. *Clin Gastroenterol Hepatol.* 2021;19(9):1915-1924. 3. Younossi. *Gastroenterology*, 2020.

AASLD Screening Algorithm Related To Nonalcoholic Fatty Liver Disease



AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cT1, corrected T1; ELF, elevated liver fibrosis; FIB-4, fibrosis-4 index; GI, gastroenterology; MRE, magnetic resonance elastography; NIT, non-invasive tests; PCP, primary care physician; VCTE, vibration-controlled transient elastography.
Adapted from Rinella M et al. *Hepatology*. 2023;77(5):1797-1835.



Patient Perspective

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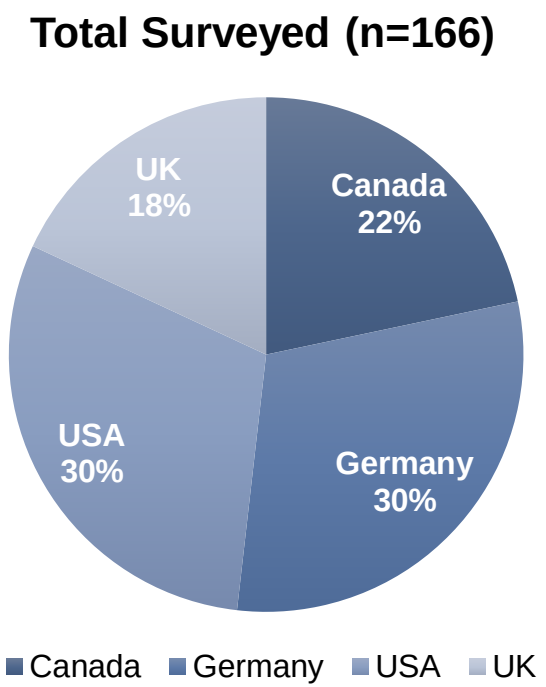
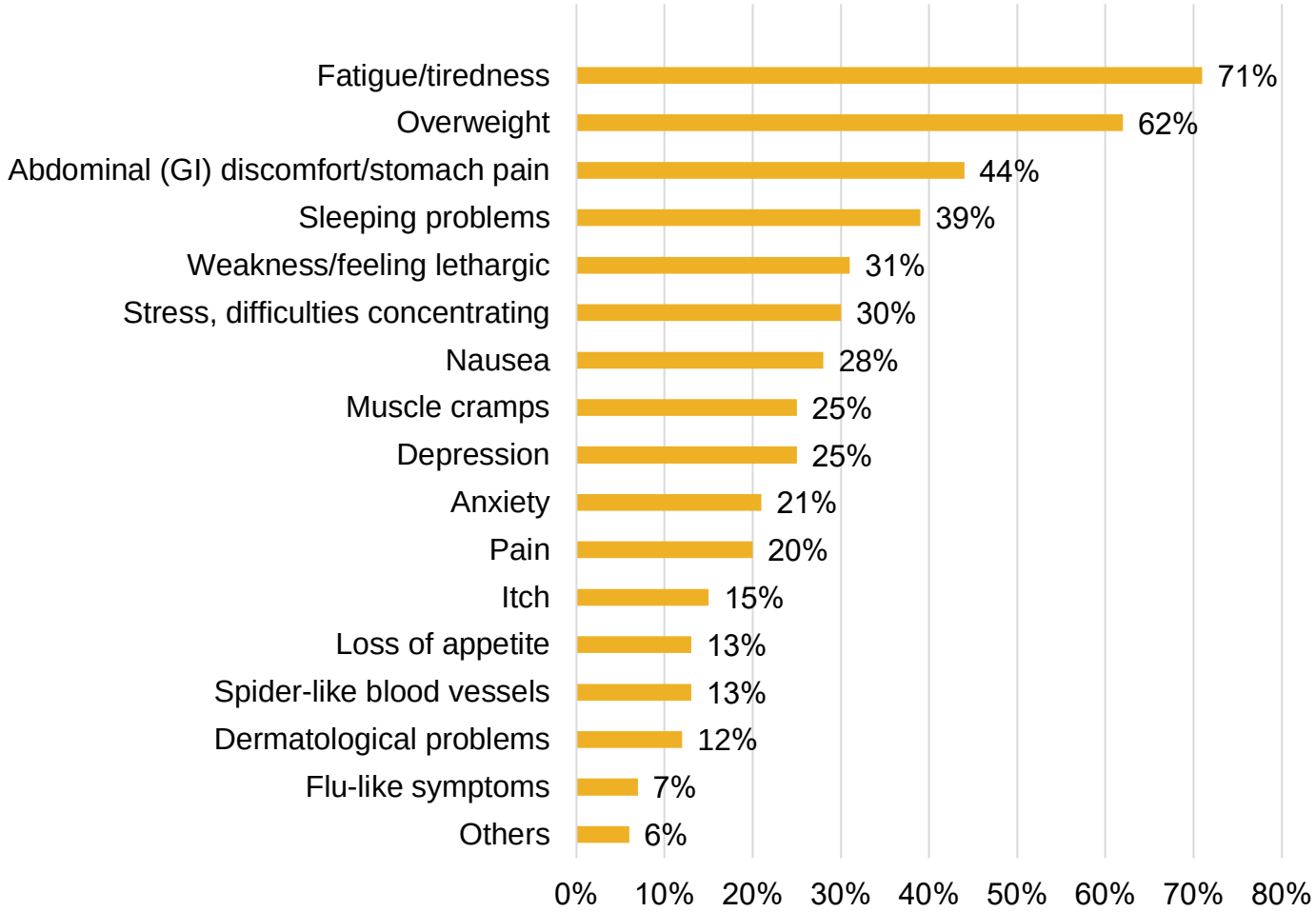
Patient Reported Symptoms Of Nonalcoholic Steatohepatitis

There are often no specific symptoms associated with NASH, the most common are fatigue, overweight and abdominal pain





NASH, nonalcoholic steatohepatitis.
Adapted from Cook, et al. *Front Med.* 2019;6:1-14.

NASH Management

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Components Of Lifestyle Approach To Manage Nonalcoholic Fatty Liver Disease

Energy restriction
- Calorie restriction (500-1,000/day)
- 7-10% weight loss target
- Long-term maintenance approach

Coffee consumption
- No liver-related limitations

Macronutrient composition
- Low-to-moderate fat intake
- Low-carbohydrate ketogenic or high protein diets
- Mediterranean diet rich in monounsaturated fatty acids, with high intakes of olive oil, nuts, vegetables, fruits, legumes, whole grains, and fish

Comprehensive lifestyle approach

Reduce fructose intake
- Avoid fructose-containing food and drink

Control daily alcohol intake
- Strictly below 30 g for men and 20 g for women

Increase physical activity
- 150-200 min/week moderate intensity in 3-5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

Adapted from EASL–EASD–EASO CPG NAFLD. *J Hepatol* 2016;64:1388–1402. Hallsworth and Adams, JHEP Reports 2019;1:468–479.

There Are Currently No FDA-Approved Therapies For NASH

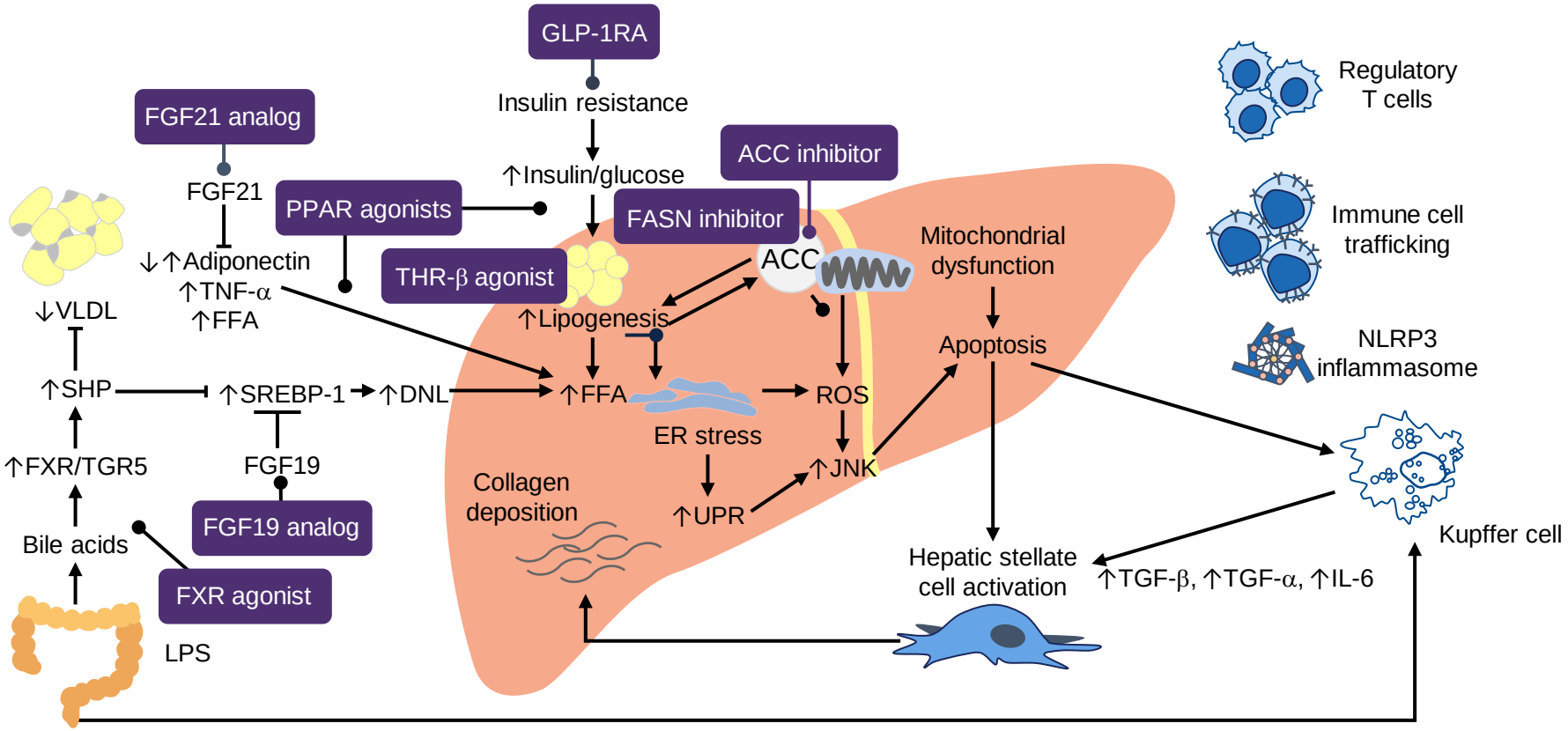
- Lifestyle management is the cornerstone of therapy in patients with NASH, but success is difficult to achieve and maintain over time[1]
  - Weight loss has been associated with improvements in measures of NAFLD
    - Including pharmacological derived weight loss
  - Weight loss has been associated with fibrosis reduction
    - Bariatric surgery[2]
  - Not all drugs associated with driving improvements in insulin sensitivity lower the NAS[3,4]
- There is strong scientific rationale for mechanisms that restore metabolic processes in the liver[5]

NAFLD, nonalcoholic fatty liver disease; NAS, NASH activity score; NASH, nonalcoholic steatohepatitis

1. Tapper and Lai. *Hepatology*. 2016;63:1184–1189. 2. Laissailly et al. *Gastroenterology*. 2020;159:1290-1301 3. Shields et al *Ther. Adv. Gastroenterol*. 2009, 2:157-163
4. Cui et al *J. Hepatol*. 2016, 65:3969-376 5. Vuppalanchi et al. *Nature Reviews*. 2021;18(6):373-392.

Several Treatments Are In Development Targeting Different Molecular Pathways Involved In NASH, Including Metabolic Processes

NASH is a multifactorial disease, and multiple pathways contribute to its pathophysiology



ACC, acetyl-CoA carboxylase; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FASN, fatty acid synthase inhibitor; FFA, free fatty acid; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family pyrin domain containing 3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SHP, small heterodimer partner; SREBP-1, sterol regulatory element binding protein-1; TGR5, Takeda G protein-coupled receptor 5; TGF-β, transforming growth factor beta; THR_{β}, thyroid hormone receptor β; TNF-α, tumor necrosis factor alpha; UPR, unfolded protein response; VLDL, very-low-density lipoprotein.

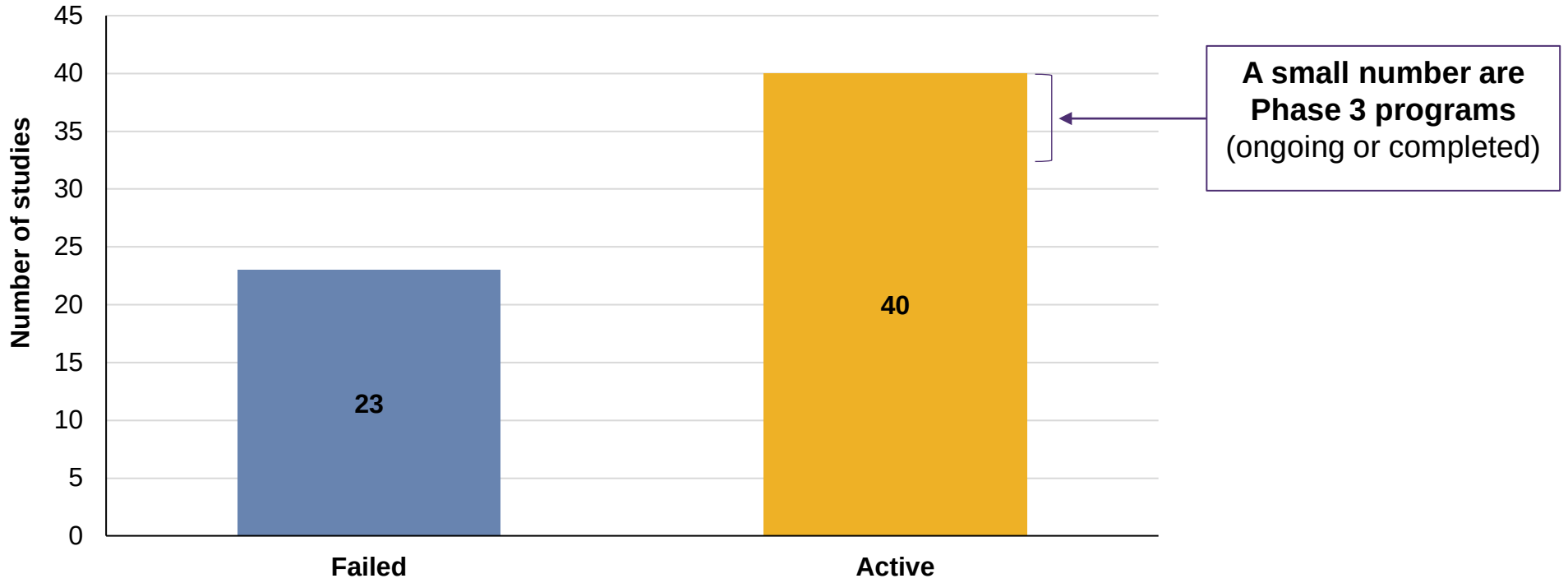
Figure adapted from Konerman MA, et al. *J Hepatol*. 2017;68:362-75.

Clinical Development Landscape For NASH

There are several investigational drugs for NASH in Phase 3 studies; however, failure rate has been high[1]

NASH treatment is complex, and many investigational drugs thus far have failed to show efficacy and safety:

Number of active and failed Phase 2/3 studies in NASH[1]



1. Pharmaceutical Online. 2020. Available at: https://www.pharmaceuticalonline.com/doc/analysis-of-the-non-alcoholic-steatohepatitis-nash-drug-pipeline-market-sizing-up-the-first-wave-0001 [accessed March 2022]. For a current list of active Phase 3 programs, please visit: https://clinicaltrials.gov/

Key Disease Considerations

- Chronic and excessive steatosis induces lipotoxicity, inflammation and hepatocellular injury followed by fibrogenesis
- NASH with significant fibrosis can progress to cirrhosis and other outcomes with approximately 20% progressing rapidly
- When identifying NASH patients with significant fibrosis, it is critical to screen for metabolic comorbidities, rule out other causes of liver disease, and evaluate degree of fibrosis (which can be done using noninvasive approaches)
- There are no FDA-approved therapies for NASH; weight loss (via lifestyle modifications) is a key management strategy, but success is challenging to achieve and sustain over time for the majority of patients

NASH, nonalcoholic steatohepatitis.

2024

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Drug-Induced Liver Injury (DILI) – A Clinical Update

Desert Conference - March 2024

Raj Vuppalanchi, MD

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Indiana University School of Medicine

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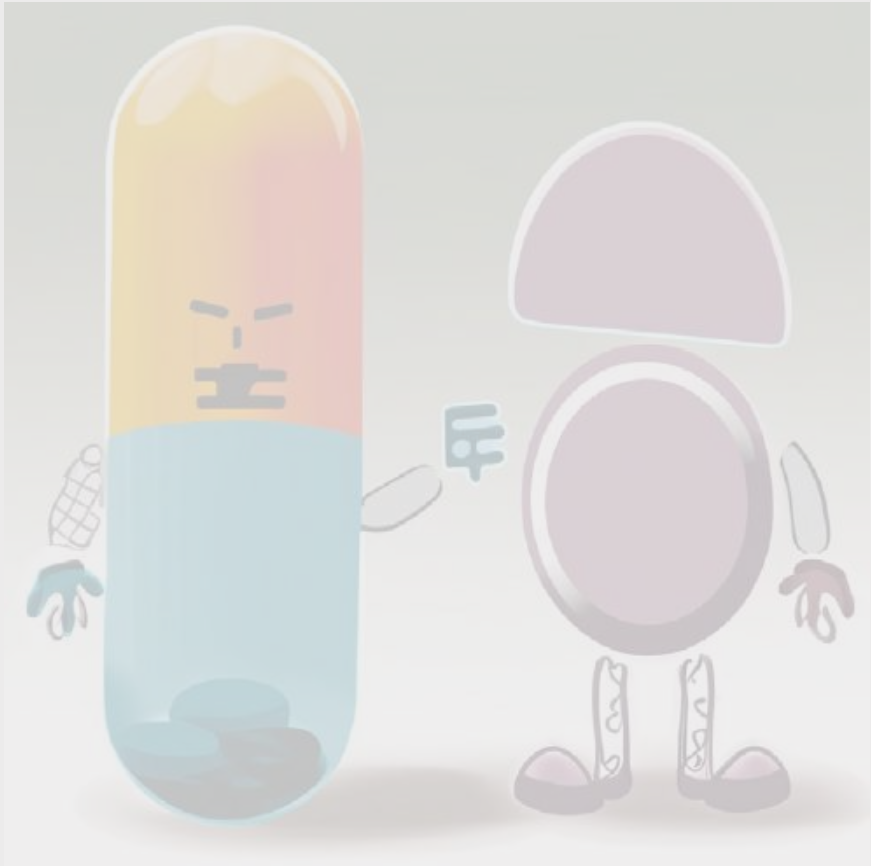
Basics & Epidemiology

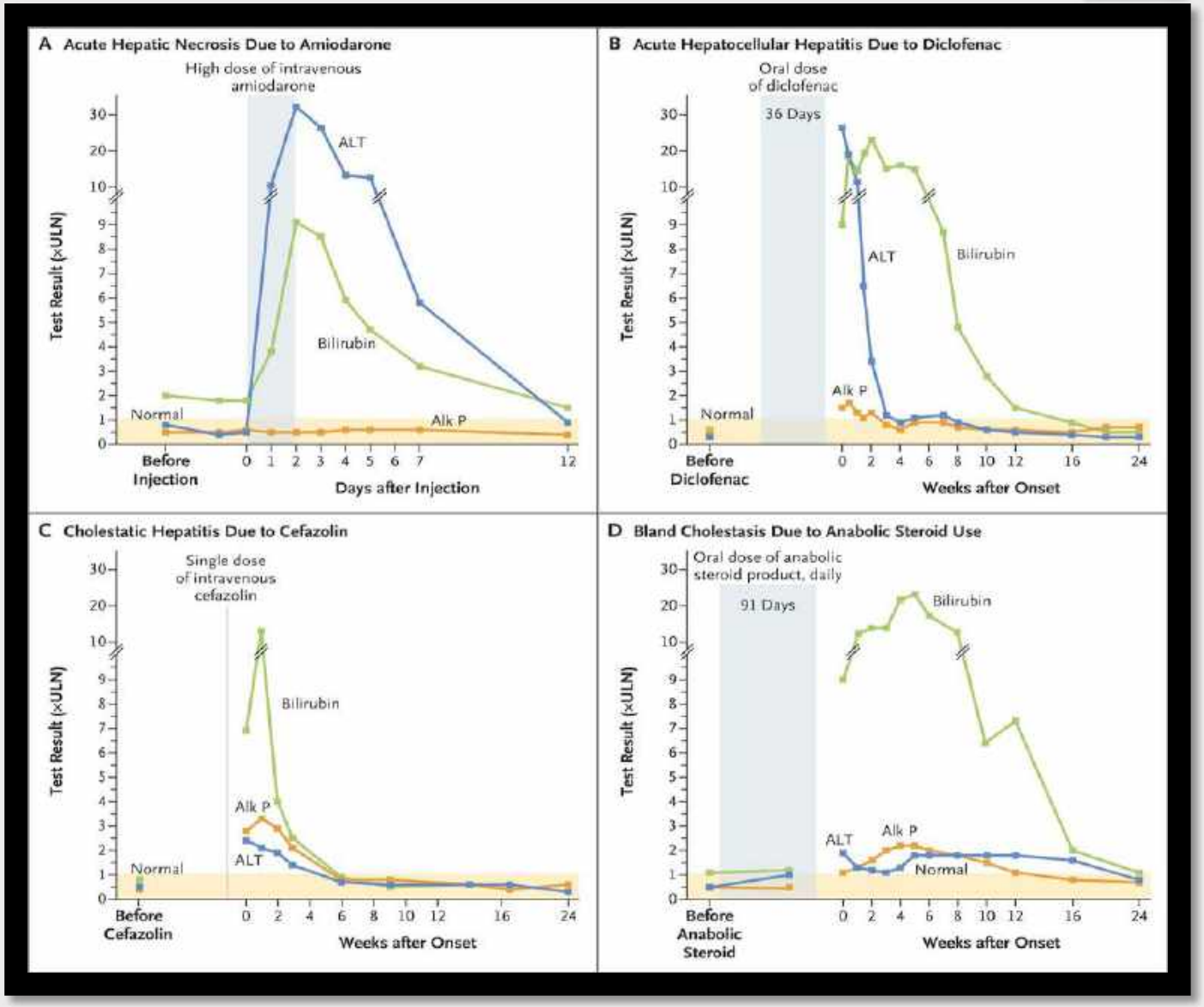
Evaluation and Management

Events of Special Interest and Recent Updates



Terminology

- Jaundice |Icterus | Hyperbilirubinemia
- Hepatotoxicity
  - clinical report of jaundice or icterus
  - total serum bilirubin >2 x ULN (FDA)
  - >2.5 x ULN (DILIN)
- Liver enzymes - AST/ALT
- Biliary enzymes - ALP/GGT
- Hepatocellular injury →histologic changes
- Hepatocellular pattern
  - R ratio ≥5 (ALT/ULN ÷ ALP/ ULN) – DILIN
  - ALT or AST (≥3x) and ALP (≤3x) – FDA



Hoofnagle et al. N Engl J Med 2019;381:264-73.

Sources of DILI Literature

Investigator initiated	Clinical Trials	Pharmacovigilance Database	DILI Registries
Case reports	Safety Data	VigiBase TM (WHO)	Spanish DILI (1994)
Case series (single center)	Adjudication committees	FAERS (FDA)	US DILIN (2004)
		National databases	LATINDILI (2011)
		Institutional databases	IN-DILI (2013)

DILI Network (DILIN)- 2003 to present

Registry

- Retrospective
- Prospective (injury w
- Causality assessme

https://dilin.org/

Types and Phenotypes of DILI

Table 1. Drug-In

Variable
Frequency
Dose-related
Predictable
Reproducible in models
Latency (time to
Phenotypes
Most commonly cated agents
Cause

* IV denotes intra

Table 2. Phenotypes of Drug-Induced Liv

Phenotype	Type of Liver Injury
Acute hepatic necrosis	Direct
Enzyme elevations	Direct
Acute hepatitis	Idiosyncratic, indirect
Cholestatic hepatitis	Idiosyncratic
Mixed hepatitis	Idiosyncratic
Chronic hepatitis	Idiosyncratic, indirect
Bland cholestasis	Unknown, possibly idiosyncratic
Acute fatty liver, lactic acidosis, and hepatic failure	Direct
Nonalcoholic fatty liver	Indirect, direct
Sinusoidal obstruction syndrome	Direct
Nodular regenerative hyperplasia	Direct

* The phenotypes are listed very generally
P denotes alkaline phosphatase, ALT ala

Table 3. Most Frequent Causes of Idiosyncratic Prescription Drug–Induced Liver Injury.*

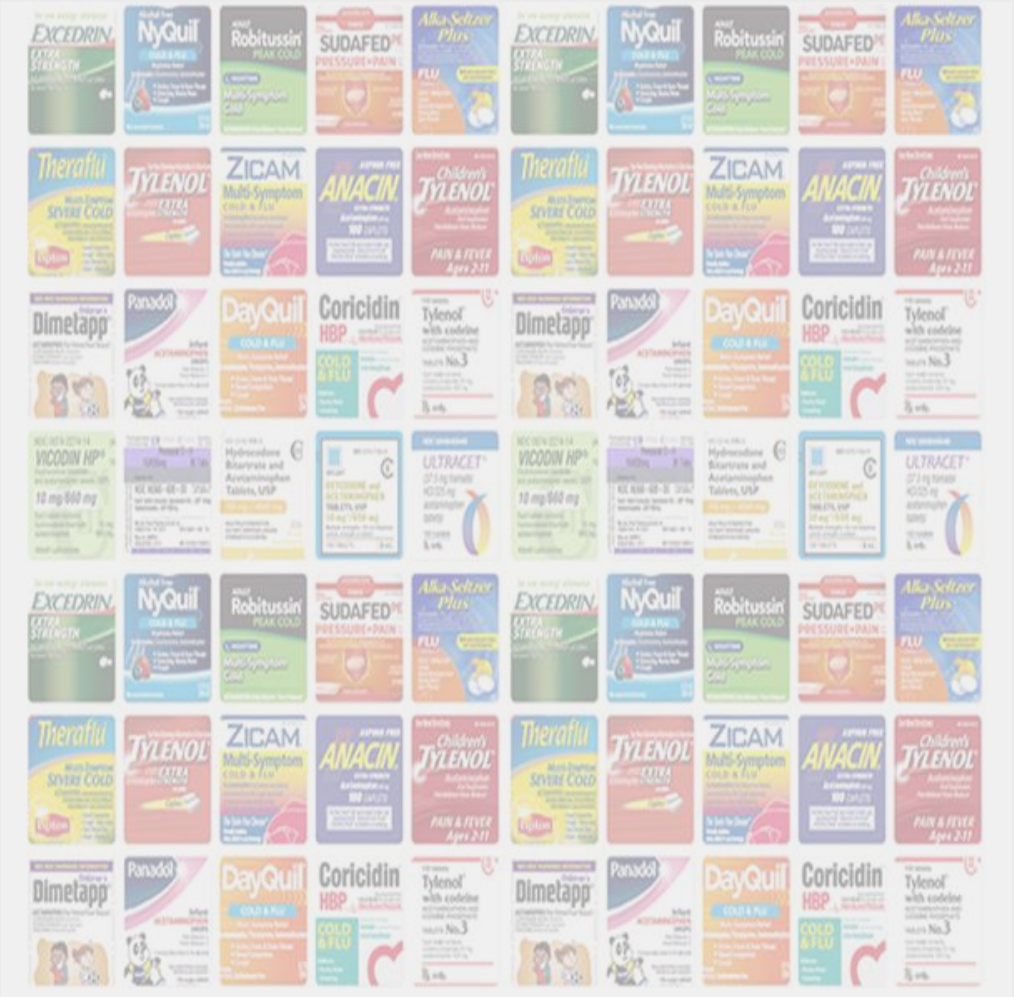
Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin–clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

* Data are from Chalasani et al.[13] The listed agents are those most frequently implicated in a total of 1257 cases of drug-induced liver injury reported between 2004 and 2013; agents were classified as definite, highly likely, or probable causes (in 899 cases). Agents that ranked from 14th to 25th in frequency were hydralazine, lamotrigine, and mercaptopurine (9 cases each); atorvastatin and moxifloxacin (8 cases each); and allopurinol, amoxicillin, duloxetine, rosuvastatin, telithromycin, terbinafine, and valproic acid (7 cases each). FDA denotes Food and Drug Administration.
† The percentages have been calculated on the basis of a total of 899 cases of drug-induced liver injury.

Hoofnagle et al. N Engl J Med 2019;381:264-73.

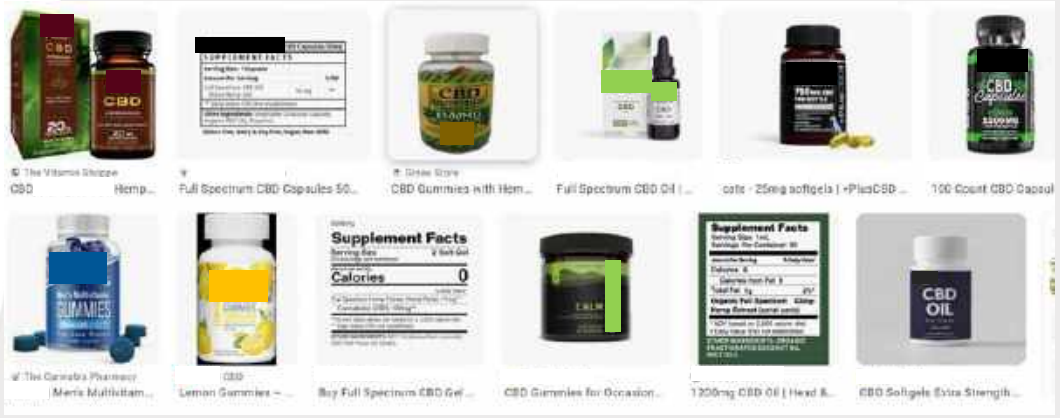
Intrinsic DILI (Direct Hepatotoxicity)

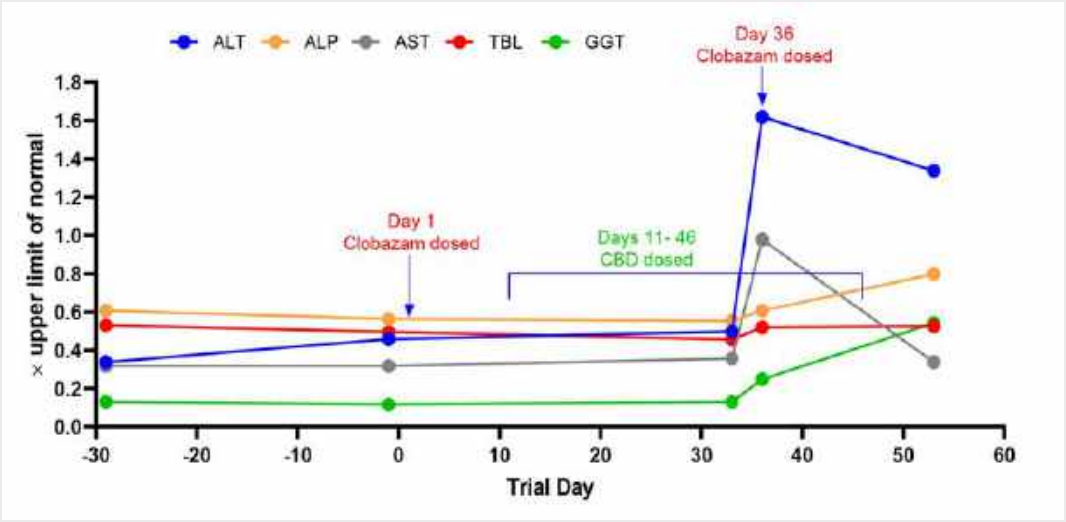
- dose-dependent at sublethal doses
- reproducible in animals
- predictable latency period
- distinct liver histology
- inflammatory milieu increases the risk of liver injury
- identified in preclinical or clinical trials



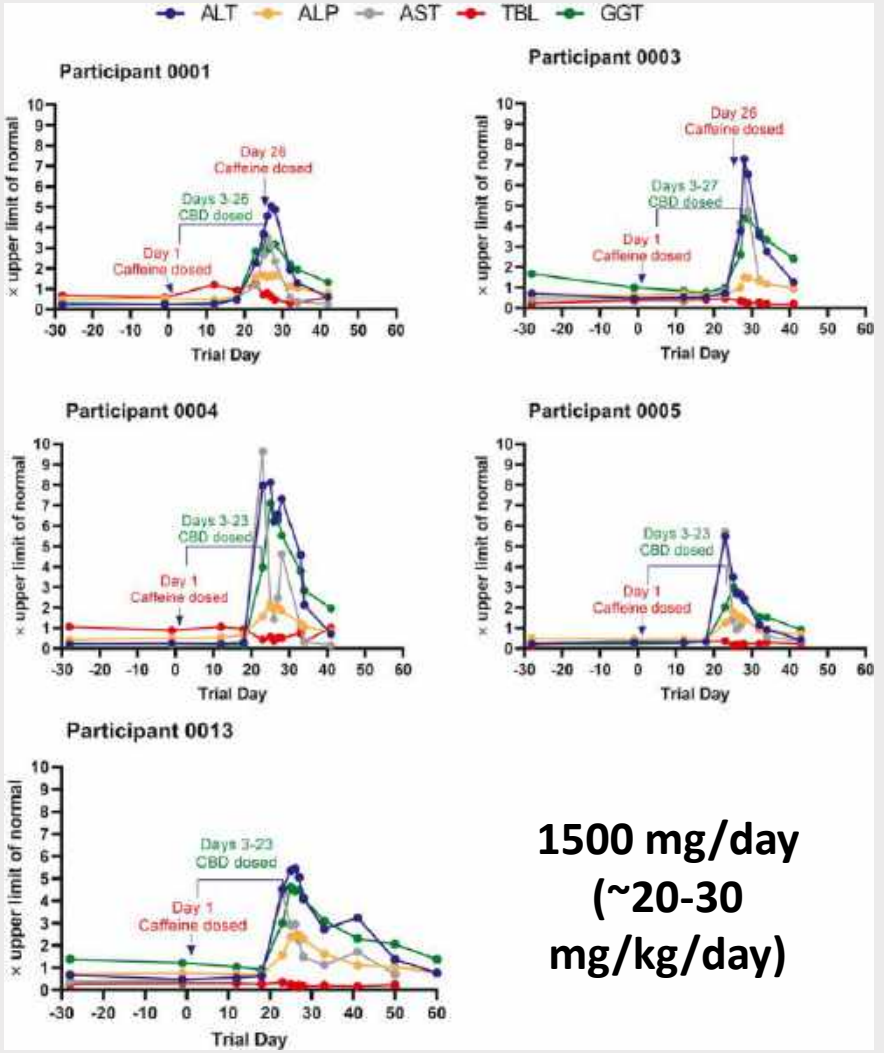
- Overdose settings
- Hepatic impairment

CBD- ALT elevations within 2–4 weeks





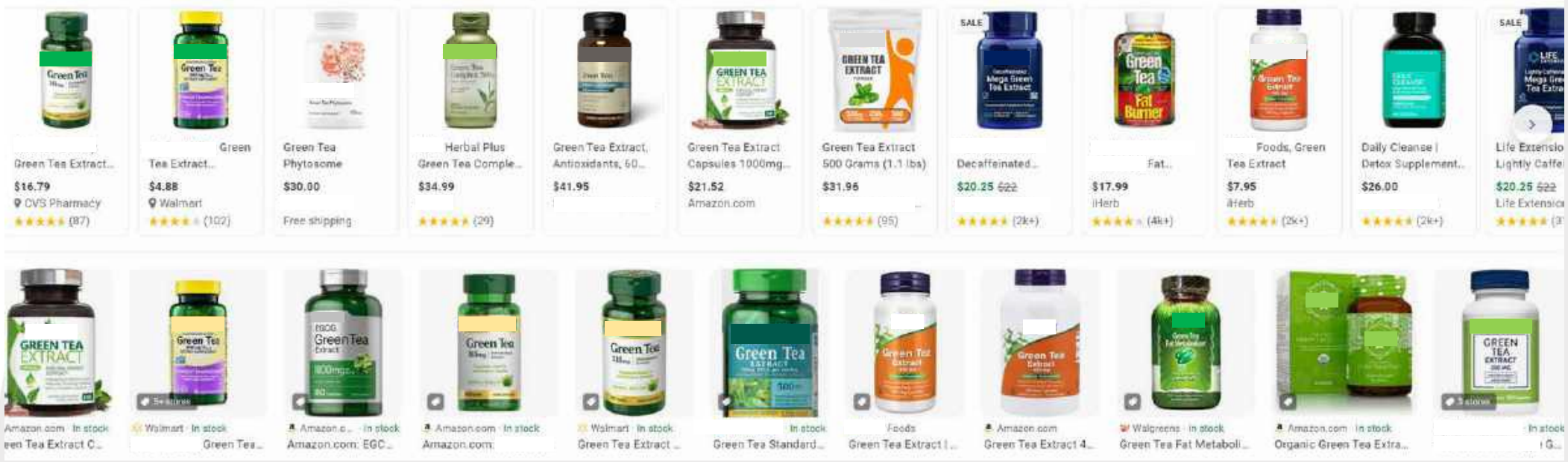
Lower dose ~ 5 mg/kg/day



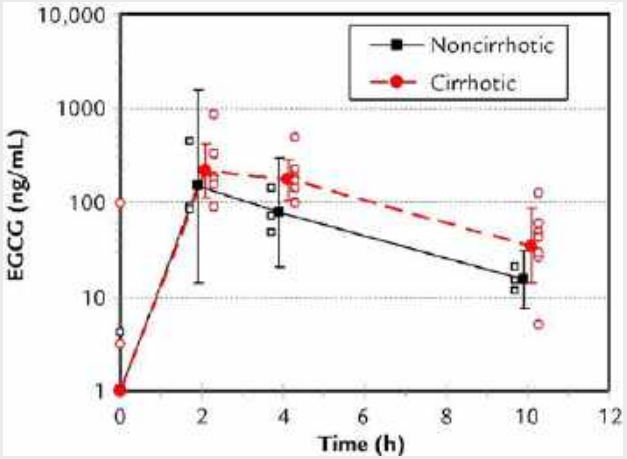
1500 mg/day (~20-30 mg/kg/day)

Watkins PB et al. Clin Pharmacol Ther. 2021 May;109(5):1224-1231

Green Tea Extract (GTE)



- Epigallocatechin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE, comprising typically ~40% of the total polyphenol content.
- open-label, single-dose|single oral dose of 400 mg
- 94% pure EGCG



Halegoua-De Marizio et al. Clinical Therapeutics Volume 34, Issue 12, December 2012

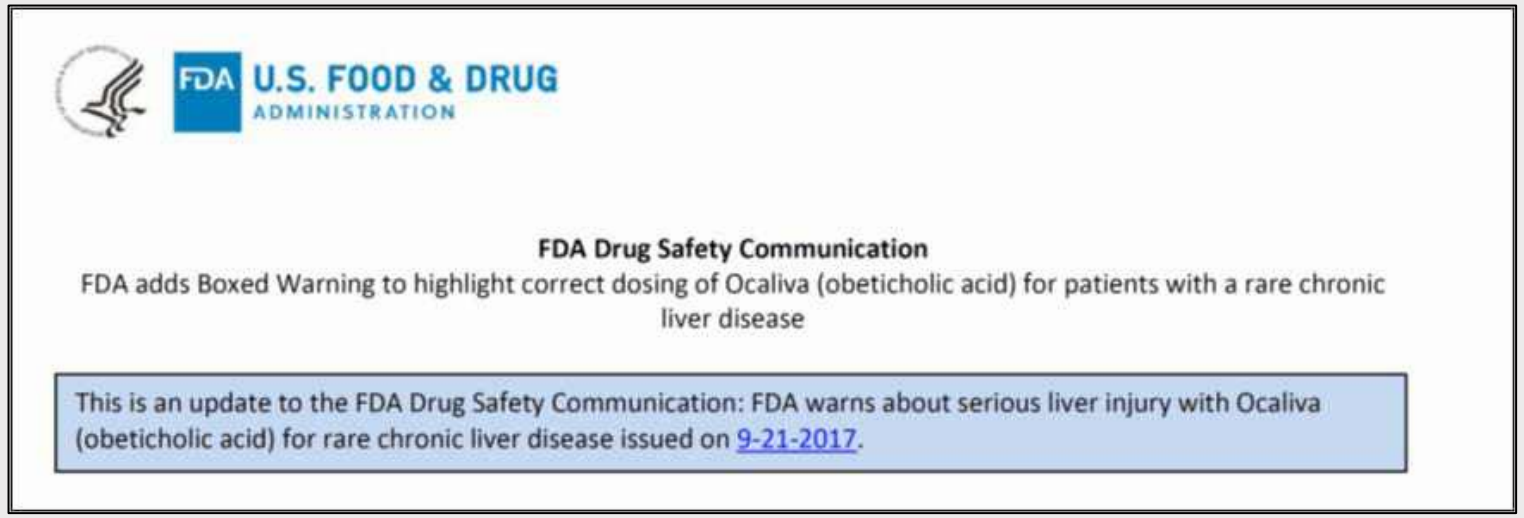
Obeticholic acid in Cirrhosis

	Baseline total bilirubin <2X ULN (n=4)		Baseline total bilirubin >2X ULN (n=4)	
Number of patients with PBC/PSC	2/2		4/0	
Age, years	52 ± 21		52 ± 9	
Female	2		4	
Caucasian	3		4	
BMI, kg/m2	31 ± 2		22 ± 1	
Cirrhosis or portal hypertension at baseline	3 of 4		4 of 4	
OCA start dose	5 mg once daily		5 mg once weekly	
OCA dosages at the time of jaundice	5 mg daily, 10 mg daily, 10 mg three times weekly		Not applicable	
OCA dose at the time of decompensation			5 mg once weekly (n=1), 5 mg daily (n=1), 10 mg daily (n=2)	
Duration of OCA use, days	193 ± 114		200 ± 89	
Liver biochemistries	**Onset**	**Peak**	**Onset**	**Peak**
• ALT, U/L	88 ± 53	156 ± 68	147 ± 92	216 ± 86
• AST, U/L	100 ± 52	156 ± 64	164 ± 60	205 ± 37
• Alkaline Phosphatase, U/L	464 ± 121	476 ± 121	699 ± 364	981 ± 508
• Total bilirubin, mg/dL	7.6 ± 5.1	13.6 ± 5.0	7.9 ± 3.4	14.7 ± 6.3
• R value	1.0 ± 0.6		0.9 ± 0.3	
• INR	1.2 ± 0.1		1.4 ± 0.5	
RUCAM score	6 ± 1		2 ± 0	
DILIN severity score	4 (n=3), 5 (n=1)		4 (n=1), 5 (n=3)	
Decompensating event	Ascites (2)		Ascites (2), Variceal hemorrhage (1)	
Liver transplantation	1 of 4		3 of 4	

John E Eaton [1], Raj Vuppalanchi [2], et al. Liver Injury in Patients With Cholestatic Liver Disease Treated With Obeticholic Acid Hepatology. 2020 Apr;71(4):1511-1514

Obeticholic acid Box Warning

Dose



Disease state

https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-highlight-correct-dosing-ocaliva-obeticholic-acid-patients-rare-chronic-liver

Indirect Hepatotoxicity

- Indirect action of the drug/agent on the liver or immune system
  - Antineoplastic agents/steroids/rituximab in patients with past exposure to hepatitis B (core positive)
  - **Immune checkpoint inhibitors**
  - **SARS-CoV-2 vaccine-induced autoimmune like hepatitis.**


Letter to the Editor

JOURNAL OF HEPATOLOGY

Unexplained liver test elevations after SARS-CoV-2 vaccination

Guardiola J et al. J Hepatol. 2022 Mar 5:S0168-8278(22)00121-0.

Idiosyncratic

- may be dose-related
- drug-specific factors (metabolism/solubility/permeability)
- patient-specific factors (HLA and non-HLA genes)
- not recognized in preclinical studies
- may not be recognized in clinical trials
- most commonly identified post-marketing

Hepatic Etiology (N = 406, 55%)		Extra-Hepatic Etiology (N = 326, 45%)	
Decompensation of pre-existing chronic liver disease	20.5%	Sepsis/abnormal hemodynamics	22%
Gilbert's syndrome	5.6%	Gall stone disease	14%
Alcoholic hepatitis	16%	Hemolysis	2.5%
Acute viral liver disease		Malignancy	
HBV	5%	Pancreato-biliary	2.7%
HCV	2%	Metastatic	3.5%
HAV	1%		
EBV	0.5%		
HIV	0.3%		
DILI			
Acetaminophen	3.3%		
HAART	0.4%		
Valproate	0.1%		
Metabolife	0.1%		
Acute autoimmune hepatitis	0.3%		

Vuppalanchi et al. The American Journal of Gastroenterology volume 102, pages 558–562 (2007)

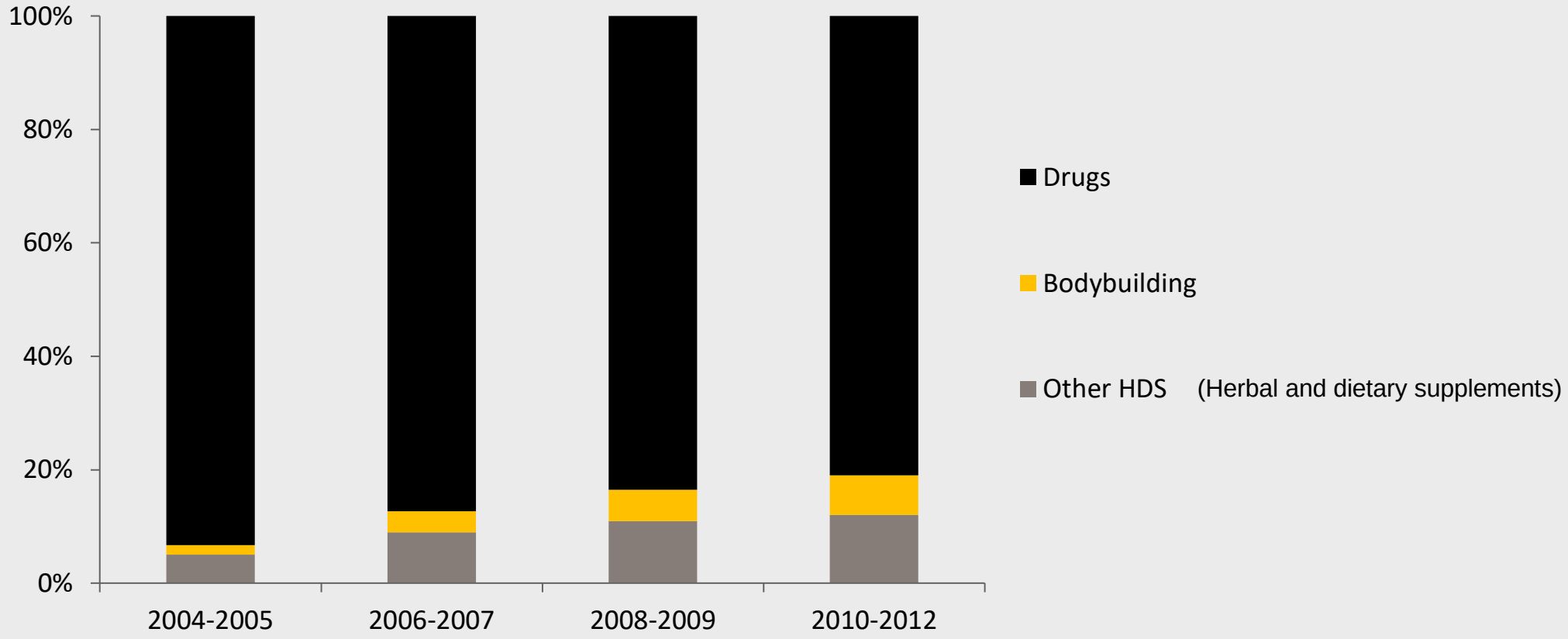
Top 10 Drugs and Mortality

Chalasani N et al. (2015) N = 899 (USA)		Andrade et al. (2005) N = 461 (Spain)		Bessone et al. (2017) N = 206 (Latin America)		Bessone et al. (2017) N = 867 (Spain)	
AMX/CLA	91 (10.1%)	AMX/CLA	59 (12.8%)	AMX/CLA	20 (9.7%)	AMX/CLA	186 (21.5%)
Isoniazid	48(5.3%)	INH +R + Pyr	22 (4.8%)	Diclofenac	12 (5.8%)	Diclofenac	16 (1.8%)
Nitrofurantoin	42(4.7%)	Ebrotidin	22 (4.8%)	Nimesulide	11 (5.3%)	Nimesulide	9 (1.0%)
Cotrimoxazole	31 (3.4%)	Ibuprofen	18 (3.9%)	Nitrofurantoin	11 (5.3%)	Nitrofurantoin	-
Minocycline	28 (3.1%)	Flutamide	17 (3.7%)	Cyproterone	9 (4.4%)	Cyproterone	3 (0.3%)
Cefazolin	20 (2.2%)	Ticlopidine	13 (2.8%)	Ibuprofen	7 (3.4%)	Ibuprofen	22 (2.5%)
Azithromycin	18 (2.0%)	Diclofenac	12 (2.6%)	INH + R + Pyr	7(3.4%)	INH + R + Pyr	29 (3.3%)
Ciprofloxacin	16 (1.8%)	Isoniazid	9 (2.0%)	Carbamazepine	5 (2.4%)	Carbamazepine	8 (0.9%)
Levofloxacin	13 (1.4%)	Medical Herbs	9 (2.0%)	Phenytoin	4(1.9%)	Phenytoin	3 (0.3%)
Diclofenac	12 (1.3%)	Nimesulide	9 (2.0%)	Thiamazole	4 (1.9%)	Thiamazole	7 (0.8%)
Mortality	**10%***				**4.6%**		**4%**

- * 16% mortality in patients with pre-existing liver disease.
- * 5.2% in those without pre-existing liver disease.
- * Four of nine patients with Stevens-Johnson Syndrome (SJS) died.

Chalasani N et al. Gastroenterology. 2015 Jun;148(7):1340-52.e7

Temporal Trends in DILIN

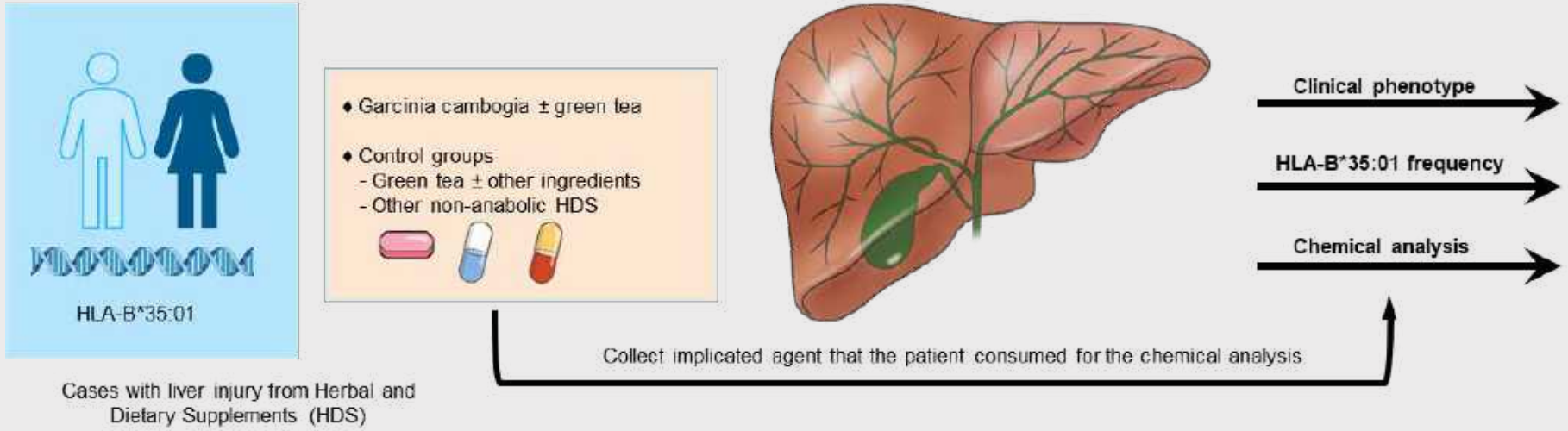


Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, Seeff LB, Serrano J, Sherker AH, Stolz A, Talwalkar J, Vega M, Vuppalanchi R. Hepatology. 2014 Oct;60(4):1399-408.*

Revolving Cast of HDS Agents

- Black cohosh (2008)
- Hydroxycut (2009)
- Herbalife (2010)
- Oxy-Elite Pro (2015) (PMID: 24113901)
- Anabolic steroids (2019) (PMID: 30934130)
- Green tea extract (2019) (PMID: 32892374)
- Ashwagandha (2020) (PMID: 31991029)
- Garcinia Cambogia (2021) (PMID: 34400337)
- Kratom (2021) (PMID: 33257199)
- Turmeric (PMID: 36252717)

Liver injury from G. *cambogia* ± *GTE*



Age: 17 to 54 years,

Onset: 3 to 223 days (median = 51) after the start

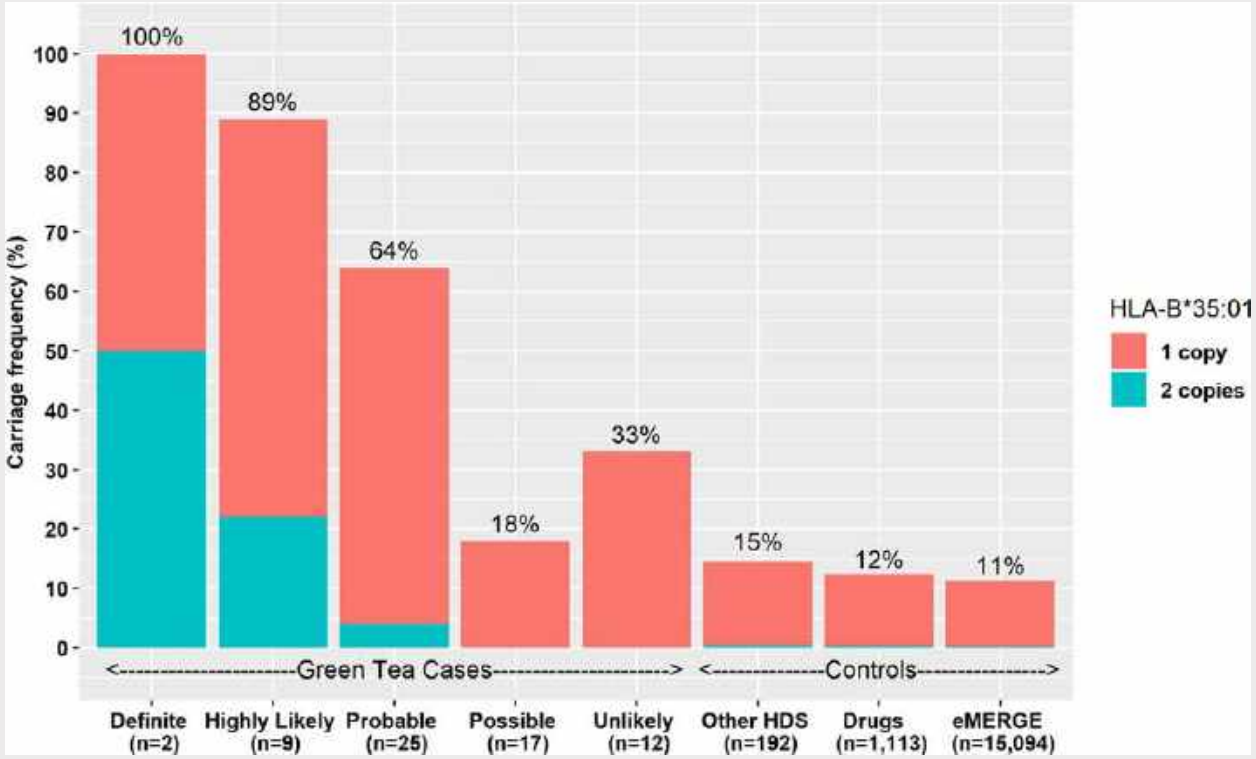
Phenotype: The liver injury was hepatocellular with jaundice (peak values of aminotransferase were significantly higher (2001 ± 1386 U/L). HLA-B*35:01 allele was significantly higher in the *G. cambogia* containing HDS (55%) compared to patients due to other HDS (19%) ($p = 0.002$) and those with acute liver injury from conventional drugs (12%) ($p = 2.55 \times 10^{-6}$).

Outcomes: One patient died, one required liver transplantation, and 91% were hospitalized.

Vuppalanchi et al. Clin Gastroenterol Hepatol. 2022 Jun;20(6):e1416-e1425.

HLA-B*35:01 and Green Tea-Induced Liver Injury

- Symptoms 15-448 days
  (median = 72 days) after start
- The liver injury was typically hepatocellular (95%).
- Most patients were jaundiced (83%)
- The course was judged as severe in 14 patients (35%), necessitating liver transplantation in 3 (8%)
- Rarely resulting in chronic injury (3%)
- HLA-B*35:01, found in 72% of green tea cases



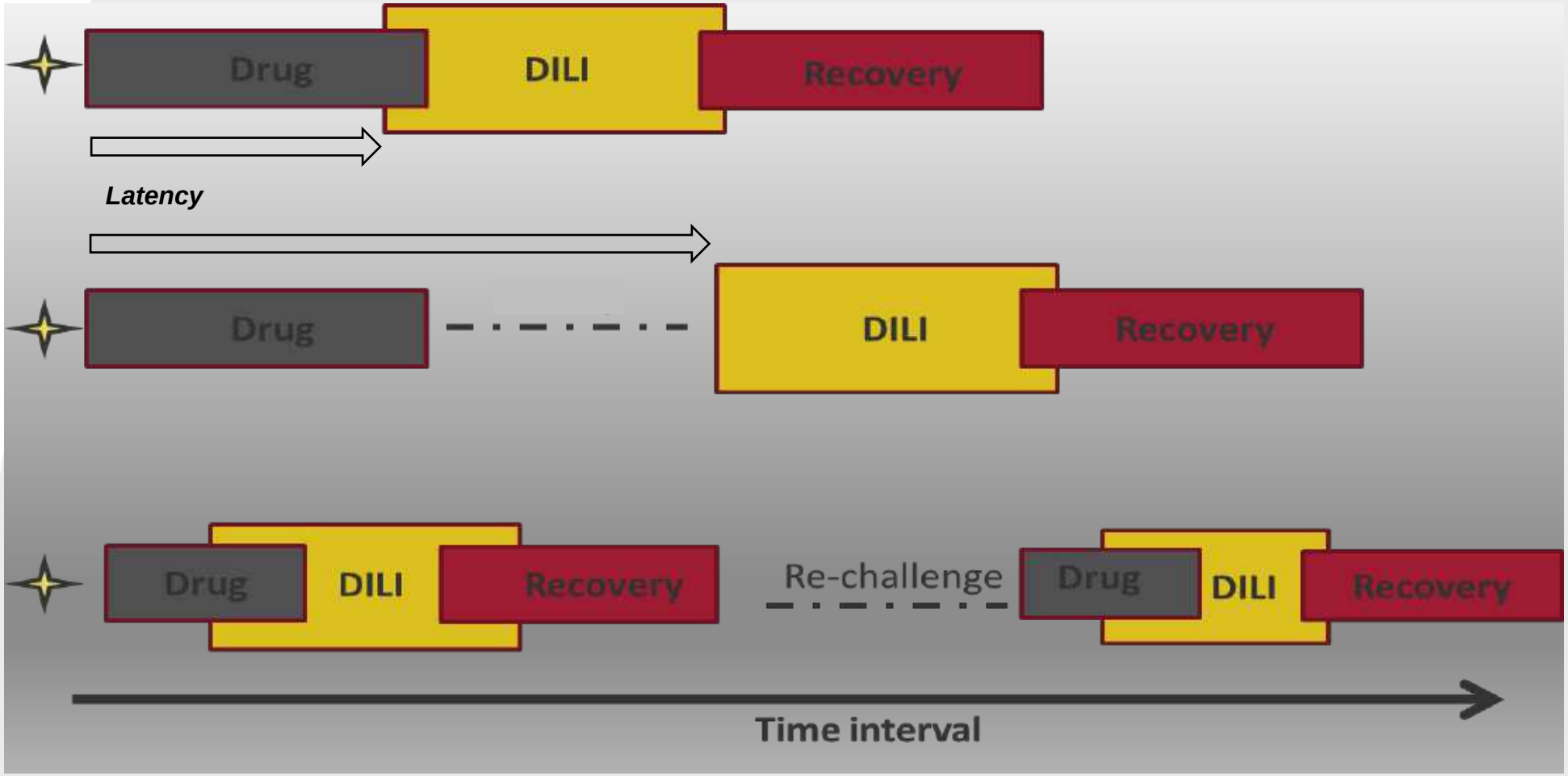
Hoofnagle JH et al. Hepatology 2021 Jun;73(6):2484-2493

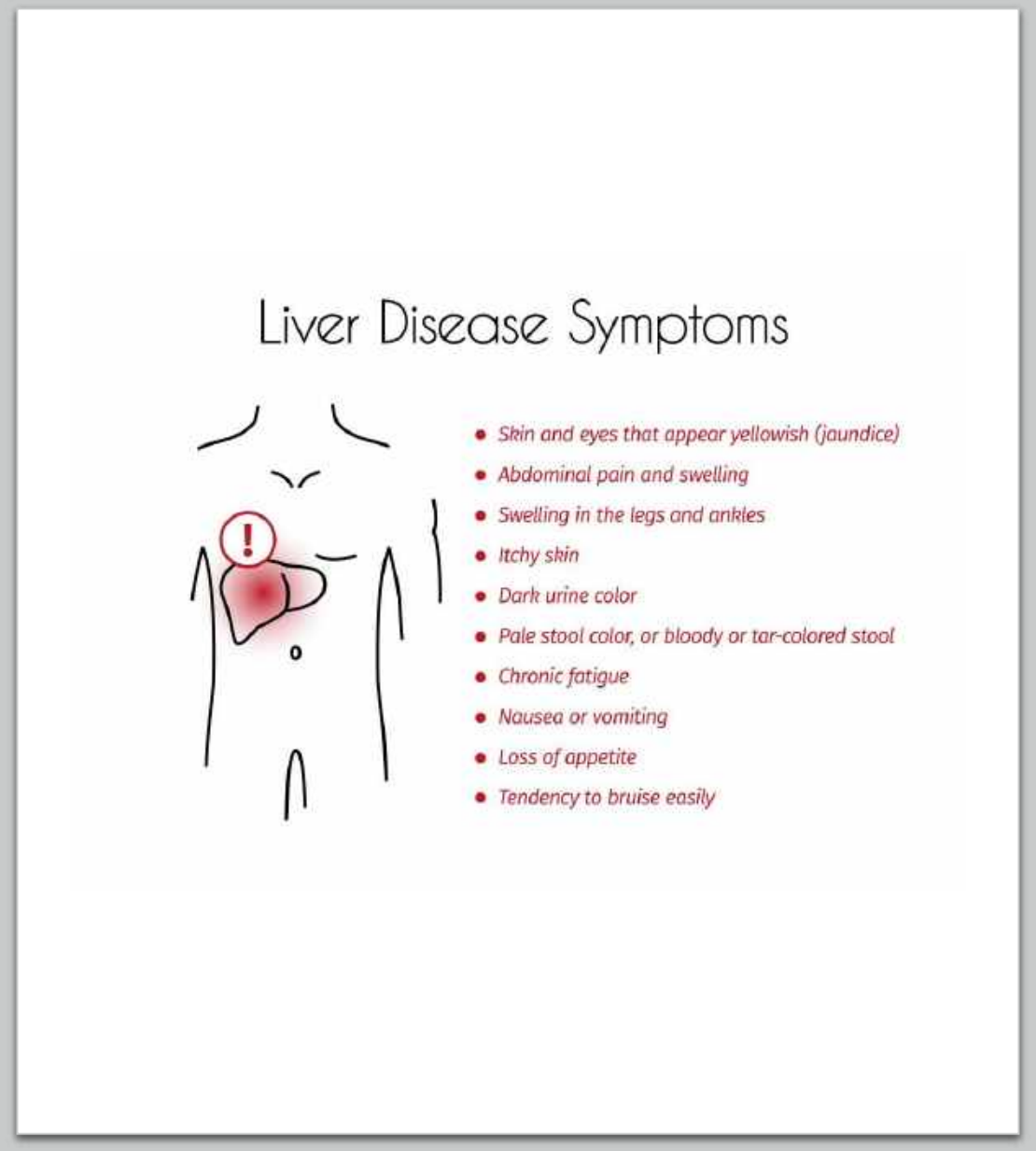
Chemical Analysis of Implicated Agents

Patient		*Garcinia cambogia* /HCA		GT Extract/EGCG	Total Catechins	EGCG
		Label Claim	**Chemical profiling**	**Label Claim**	**Chemical profiling**	
1.	Mega-T Green Tea Extract	NO	Not detected	*YES*	*Detected*	*Detected*
2.	Hydroxycut	*YES*	*Detected*	*YES*	*Detected*	*Detected*
3.	Quick Loss Diet Spray with Hoodia	*YES*	*Detected*	**YES**	**Not detected**	**Not detected**
4.	Visalus Sciences Vi-Slim Metab-Awake	NO	Not detected	*YES*	*Detected*	*Detected*
	OmegaKrill Pure Concentrated Krill Oil	NO	Not detected	NO	Not detected	Not detected
	Visalus Sciences Neuro	NO	Not detected	*YES*	*Detected*	*Detected*
	Visalus Sciences Vi-Trim	*YES*	*Detected*	NO	Not detected	Not detected
5.	Hydroxycut	NO	Not detected	*YES*	*Detected*	*Detected*
6.	Fat Burner	*YES*	*Detected*	*YES*	*Detected*	*Detected*
	Great Start-Energy Formula	NO	Not detected	*YES*	*Detected*	*Detected*
7.	Garcinia Cambogia X Treme	*YES*	*Detected*	NO	Not detected	Not detected
8.	Super Plus Weight Loss Enhancer	**Yes**	**Not detected**	*Yes*	*Detected*	*Detected*

Vuppalanchi et al. Clin Gastroenterol Hepatol. 2022 Jun;20(6):e1416-e1425.

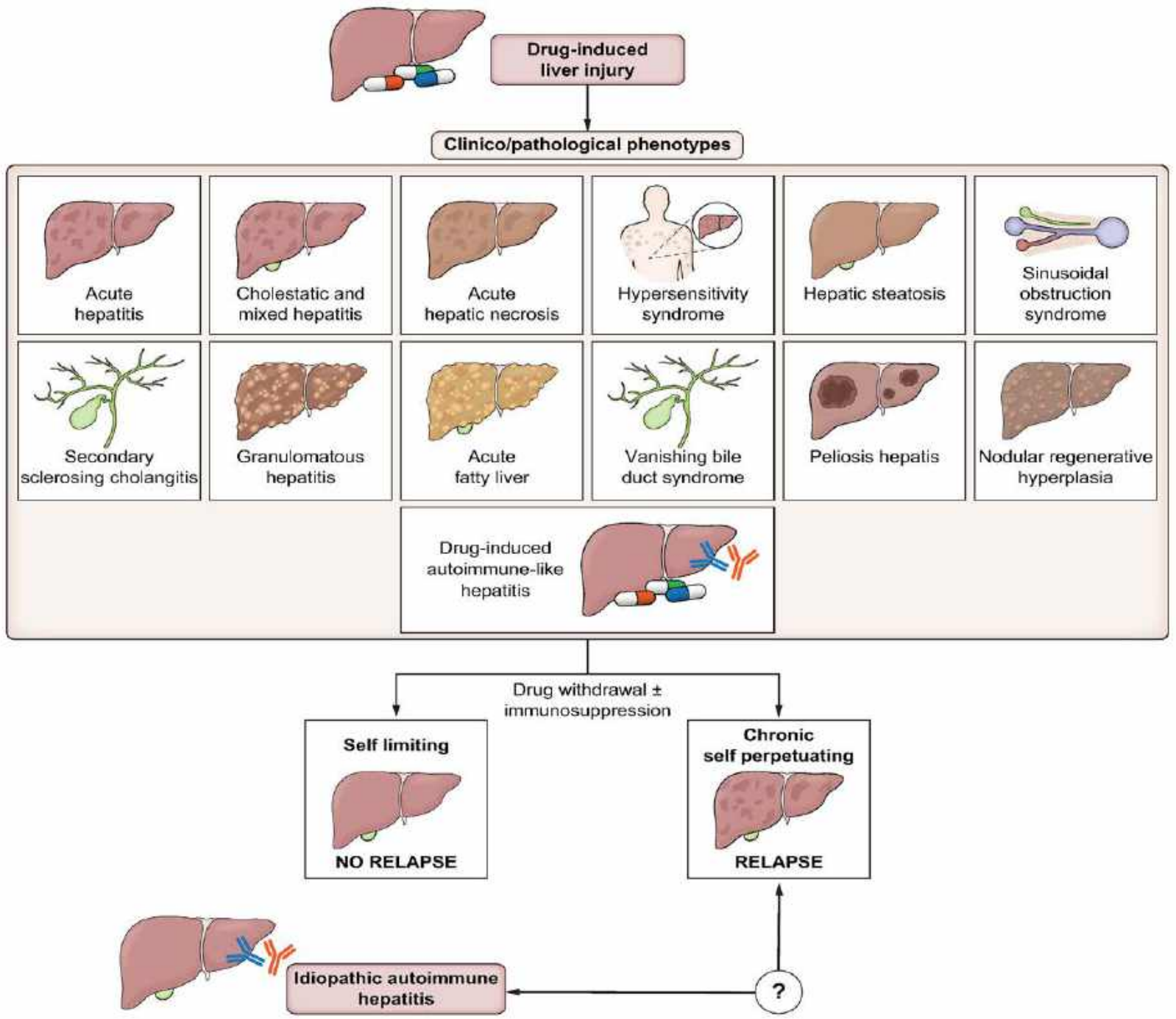
DILI Clinical Scenarios





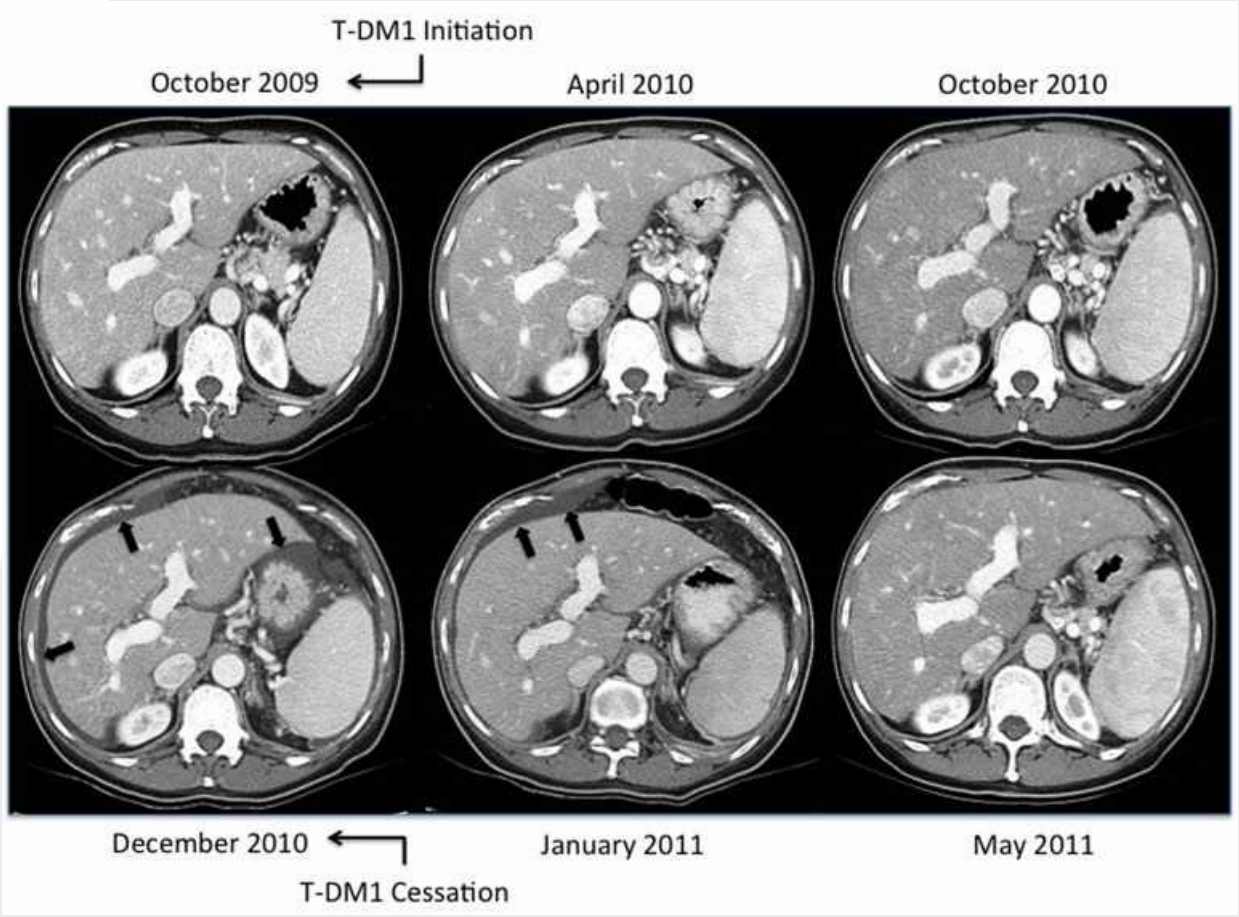
Clinical Presentations of DILI

- **Asymptomatic (liver enzyme abnormalities)**
  - **Any one of the following**
    - ≥ 5 ULN of ALT
    - ≥ 2 ULN of Alk P (of liver origin)
    - ≥ 3 ULN of ALT **&** ≥ 2 ULN of total bilirubin
  - **In the absence of a competing etiology**
- **Symptomatic**
  - Systemic symptoms
    - General (fatigue, itching, pain etc.)
    - Immuno-allergic (fever, rash, eosinophilia)
  - Jaundice/coagulopathy/ascites
  - Fulminant hepatic failure



RJ Andrade et al. Journal of Hepatology 2023 79853-866DOI: (10.1016/j.jhep.2023.04.033)

Nodular Regenerative Hyperplasia



- 66-year old woman with new-onset ascites while participating in a phase Ib/II clinical trial (NCT00875979) to receive T-DM1 3mg/kg intravenously every 3 weeks plus pertuzumab 840mg intravenous loading dose once, followed by 420 mg intravenously every 3 weeks

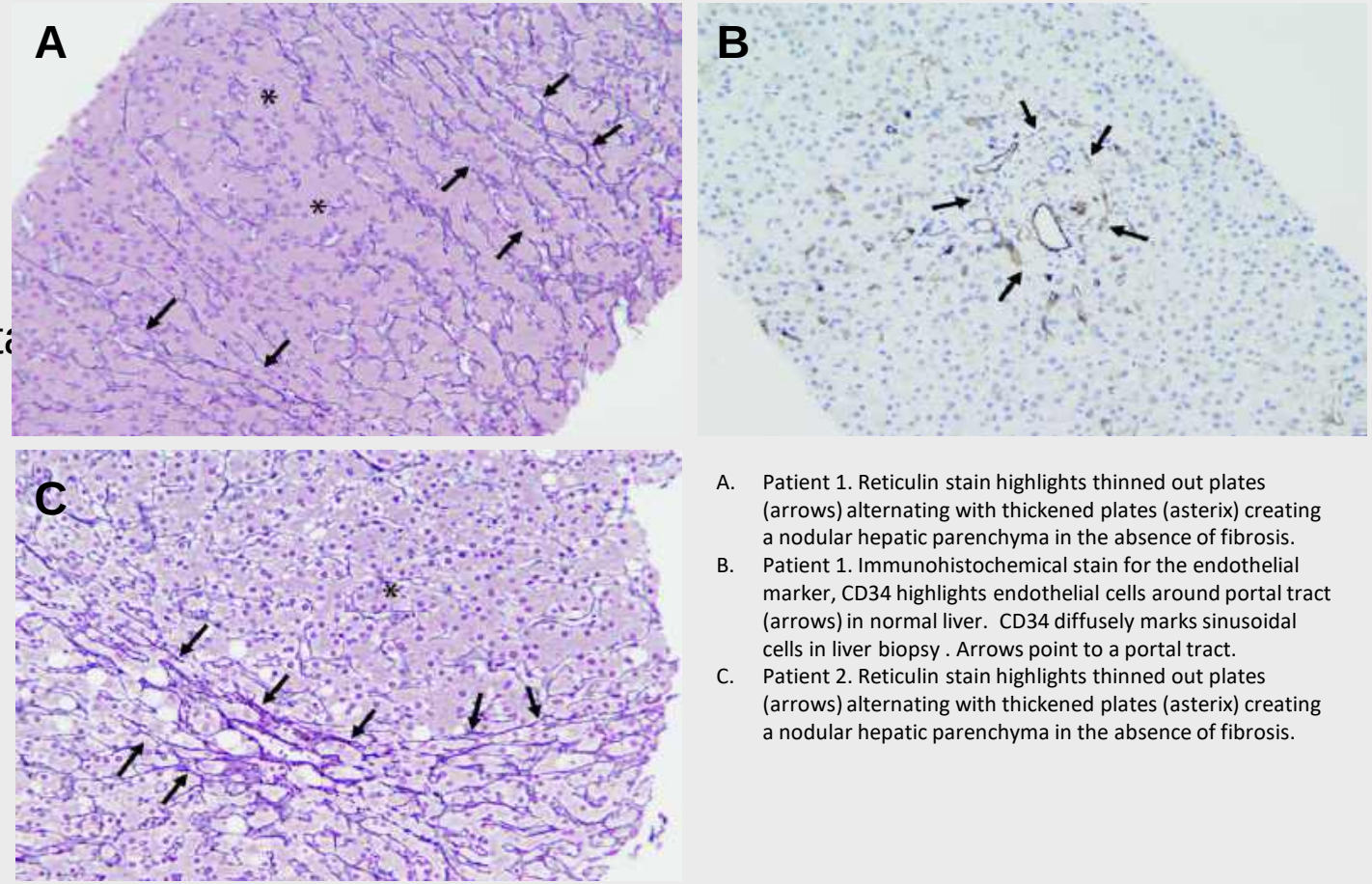
Nodular Regenerative Hyperplasia After Treatment With Trastuzumab Emtansine. Force J, Saxena R, Schneider BP, Storniolo AM, Sledge GW Jr, Chalasani N, **Vuppalanchi** R. J Clin Oncol. 2016 Jan 20;34(3):e9-12.

Non-cirrhotic Portal Hypertension

- Ascitic fluid analysis

  SAAG: >1.1

- Transjugular liver biopsy and porta
  pressure measurements
  - WHVP: 28 mm Hg
  - FHVP: 15 mm Hg
  - HVPG: 13 mm Hg

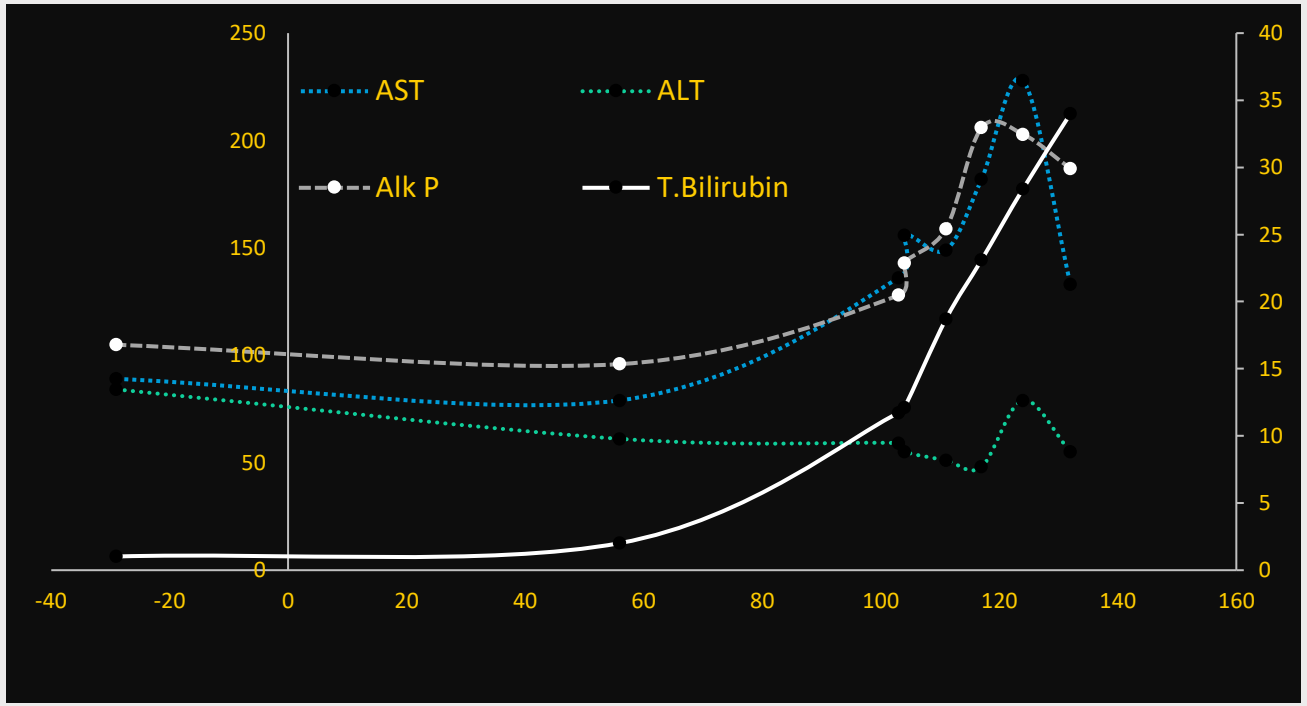


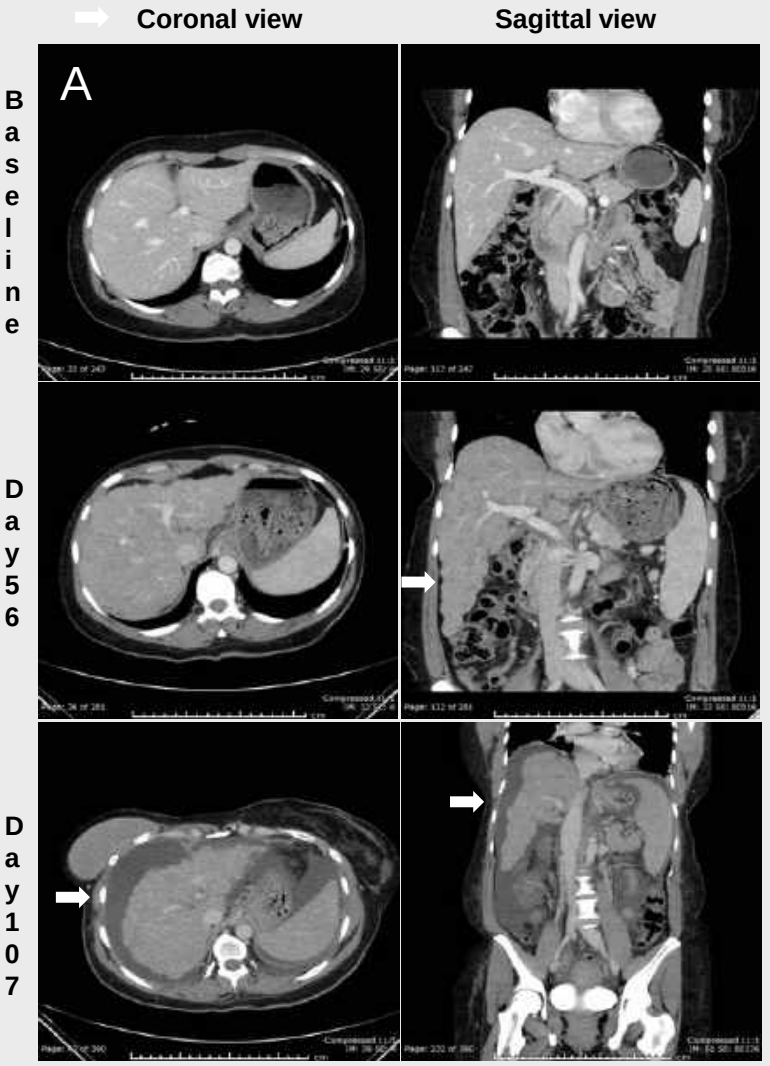
A. Patient 1. Reticulin stain highlights thinned out plates (arrows) alternating with thickened plates (asterix) creating a nodular hepatic parenchyma in the absence of fibrosis.
B. Patient 1. Immunohistochemical stain for the endothelial marker, CD34 highlights endothelial cells around portal tract (arrows) in normal liver. CD34 diffusely marks sinusoidal cells in liver biopsy . Arrows point to a portal tract.
C. Patient 2. Reticulin stain highlights thinned out plates (arrows) alternating with thickened plates (asterix) creating a nodular hepatic parenchyma in the absence of fibrosis.

Nodular Regenerative Hyperplasia After Treatment With Trastuzumab Emtansine. Force J, Saxena R, Schneider BP, Storniolo AM, Sledge GW Jr, Chalasani N, **Vuppalanchi** R. J Clin Oncol. 2016 Jan 20;34(3):e9-12.

Pseudocirrhosis and Liver Failure

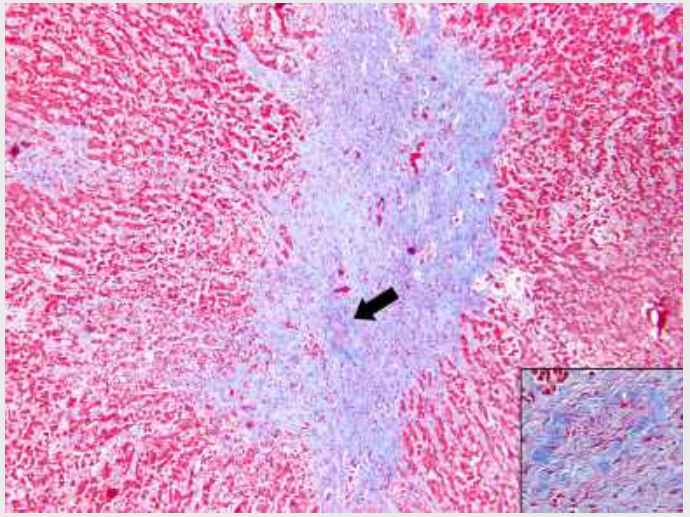
47-year-old woman with new-onset jaundice and ascites while on therapy with Palbociclib and letrozole for recurrent breast Ca





Vuppalanchi et al. Hepatology 2017 May;65(5):1762-1764.

Sinusoidal Obstruction Syndrome



Vuppalanchi et al. Hepatology 2017 May;65(5):1762-1764.

Manifestations of DILI

Typical		Atypical
Common	**Uncommon**	**Uncommon**
Acute liver injury - hepatocellular - mixed - cholestatic	Auto-immune hepatitis (minocycline, nitrofurantoin)	Drug-induced steatosis + steatohepatitis (amiodarone, valproic acid, tamoxifen, lomitapide, mipomersen, peg-aspargase)
	Bland cholestasis (anabolic steroids)	Hepatic neoplasms (oral contraceptive pills, vinyl chloride, thorostat, danazol)
	Granulomatous hepatitis (allopurinol, TMP-SMX, hydralazine, diltiazem)	Hepatocellular deposits (amiodarone, hypervitaminosis A, phenobarbital)
	Vanishing bile duct syndrome (amoxicillin-clavulanate, carbamazepine, chlorpromazine)	Hepatoportal sclerosis (hypervitaminosis, vinyl chloride, arsenicals)
	Chronic liver injury or cirrhosis (nitrofurantoin, amiodarone, tamoxifen, methotrexate)	Peliosis hepatis (danazol, oxaliplatin, vinyl chloride)
	Isolated alkaline phosphatase elevations (anti-seizure medications)	Nodular regenerative hyperplasia (Azathioprine, mercaptopurine, Trastuzumab emtansine, oxaliplatin, didanosine)
		Sinusoidal obstruction syndrome (busulfan, alkaloids, gemtuzumab, palbociclib)

Vuppalanchi et al. September 2018 Current Hepatology Reports 17(Suppl 1)

Diagnosis of DILI

- Temporal relationship
- Dechallenge
- Signature pattern
- Exclusion of competing etiology
- Known hepatotoxin
- Rechallenge

Temporal Relationship

- **Latency: variable and drug-specific**
  - **Short:** 24 to 72 hours after starting
    - Sulfonamides, macrolide antibiotics
  - **Long latency:** 3 to 12 months after starting
    - isoniazid, flutamide
  - **Very long latency:** several years after starting
    - Minocycline, nitrofurantoin, amiodarone

Time to Recovery

- **Improves within a few days to a week**
  - Rapid (acetaminophen and niacin)
  - Complete resolution (several weeks)
- **Chronic (>6 months)**
  - Complete resolution
  - Persistent


1450 ORIGINAL CONTRIBUTIONS

LIVER

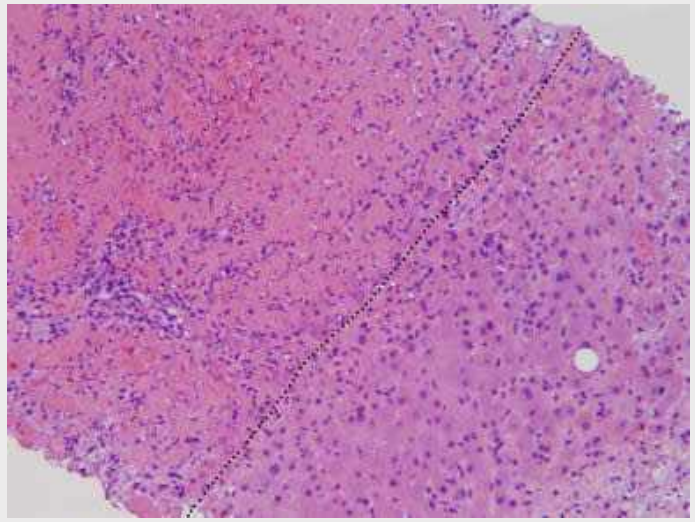
Persistent Liver Biochemistry Abnormalities Are More Common in Older Patients and those With Cholestatic Drug Induced Liver Injury

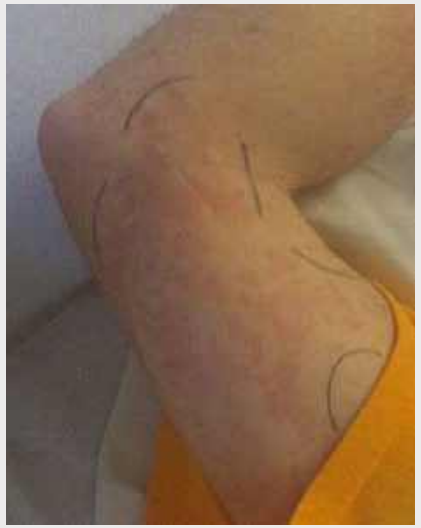
Robert J. Fontana, MD[1], Paul H. Hayashi, MD[2], Huiman Barnhart, PhD[3], David E. Kleiner, MD, PhD[4], K. Rajender Reddy, MD[5], Naga Chalasani, MD[6], William M. Lee, MD[7], Andrew Stolz, MD[8], Thomas Phillips, MS[3], Jose Serrano, MD, PhD[9] and Paul B. Watkins, MD[7] for the DILIN Investigators

Fontana et al. Am J Gastroenterol 2015; 110:1450–1459

Clinical Signature

- **Injury pattern (R: ALT/ULN ÷ ALP/ULN)**
  - R<2: Cholestatic (e.g. anabolic steroids)
  - 2-5: Mixed (e.g. Augmentin)
  - R>5: Hepatocellular (e.g. INH)
- **Immuno-allergic hepatitis** (rash, fever, facial edema, myalgia, arthralgia, eosinophilia and atypical lymphocytosis)
  - Short latency (e.g. allopurinol)
  - DRESS syndrome (e.g. telaprevir)





Severe drug-induced skin and liver injury from rivaroxaban. Barrett P[1], Vuppalanchi R, et al. Dig Dis Sci. 2015

Work Up – R/O Competing Etiology

- Very high index of suspicion
- A careful history
  - Risk factors for viral hepatitis, alcohol use, weight gain, history of autoimmune disease, history of cardiac failure, shock, or septicemia, history of all drug intake, including time of starting and stopping prescription and nonprescription (over-the-counter) drugs and herbals within the previous 3 month
- Laboratory and Imaging

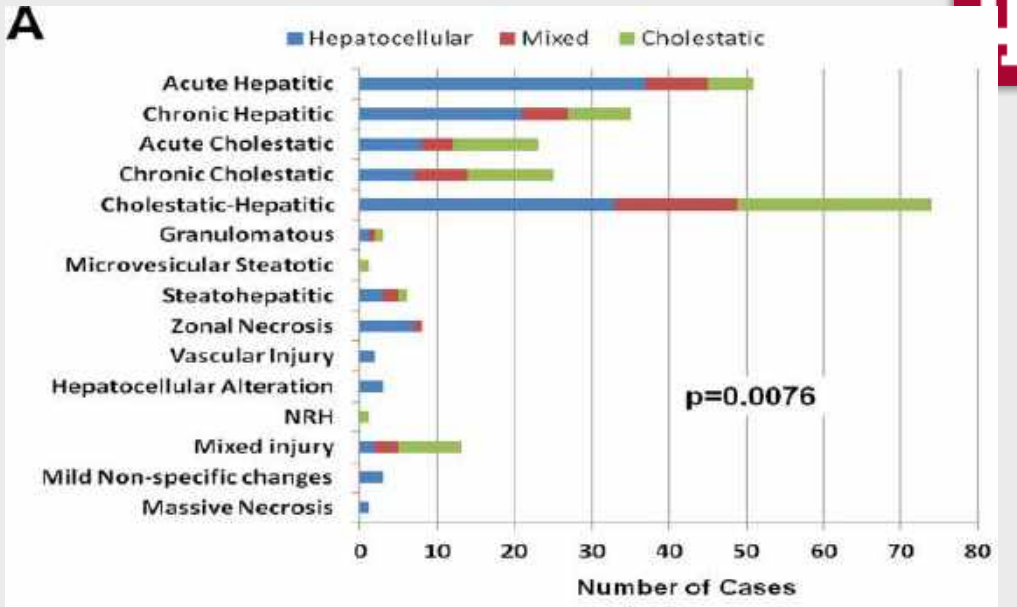
Lab	Imaging
Viral hepatitis*	US/CT/MRI-MRCP
Autoimmune hepatitis	EUS/ERCP

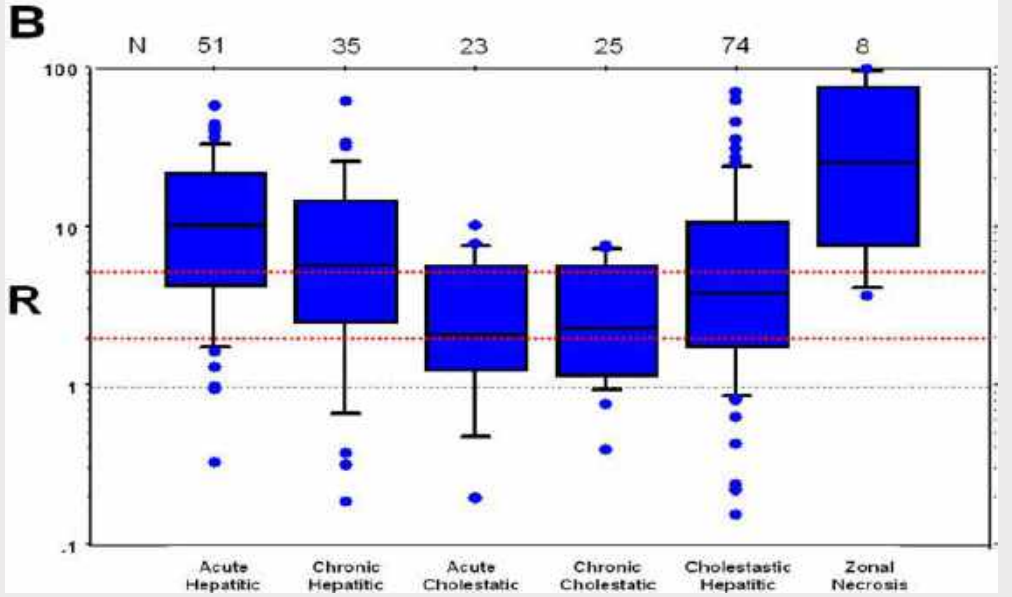
*Epstein-Barr virus, hepatitis E, Cytomegalovirus, Herpes simplex virus

Hepatic Histology

- Can be helpful but not mandatory for diagnosis
- May serve as a prognostic tool

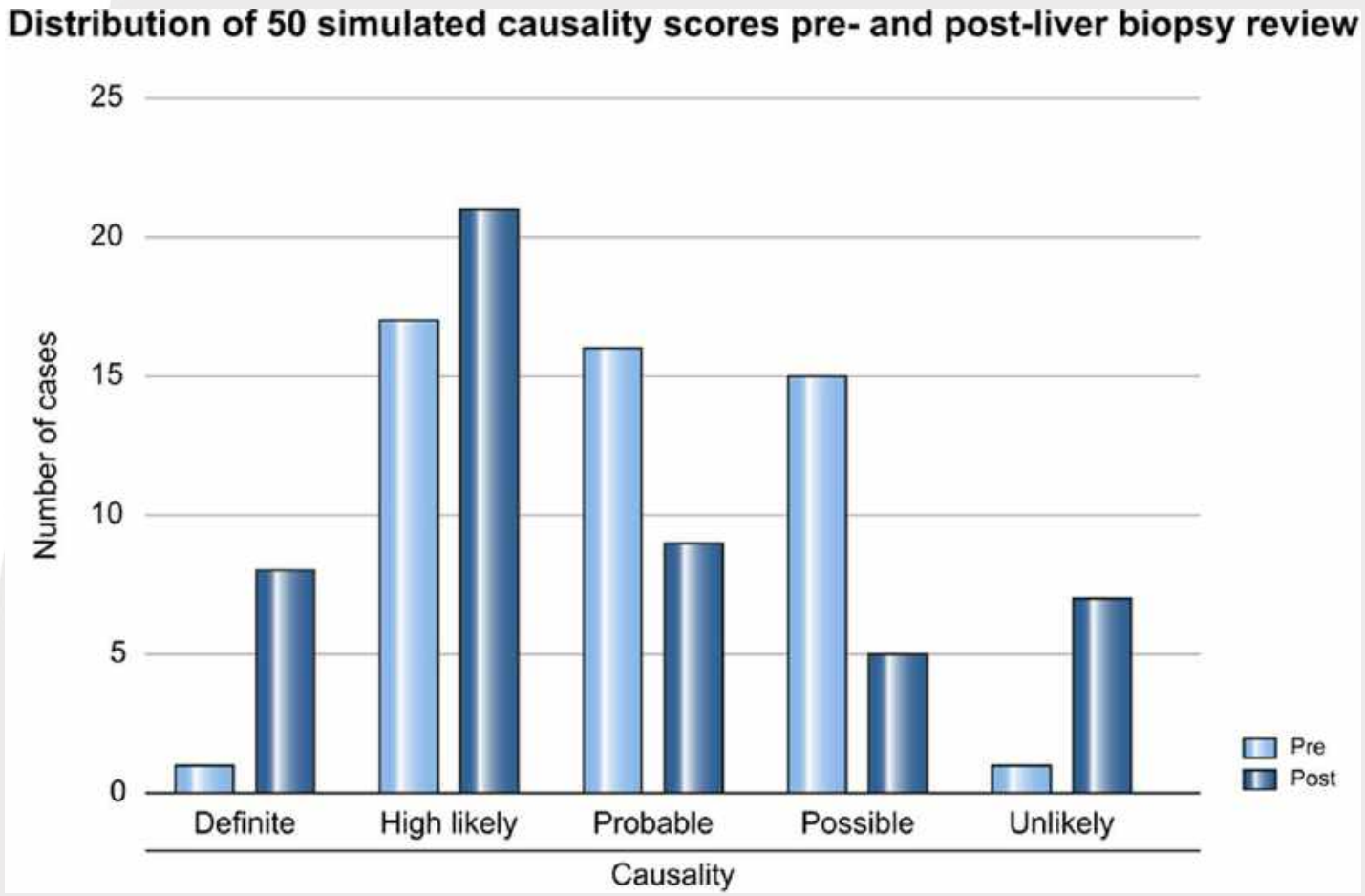
Relationship between pathological injury patterns and biochemical presentation.





Kleiner DE, et al for Drug-Induced Liver Injury Network (DILIN). Hepatology. Volume: 59, Issue: 2, Pages: 661-670 2014

Value of Liver Biopsy



- Liver histology review changed the causality score in 68% of patients
- Clarified the diagnosis of DILI in cholestatic or equivocal cases

Ahmad J et al. DILIN. J Hepatol. 2022 May;76(5):1070-1078.

RUCAM Score

• Temporal relationship	(0 to 2)
• Course	(-2 to 3)
• Risk factors	(0 to 2)
• Concomitant drug	(0 to -3)
• Non-drug causes	(-3 to 2)
• Prior reports/ information	(0 to 2)
• Rechallenge	(-2 to 3)

Score (-8 to 14)

Highly probable	**>8**
Possible	**3-5**
Probable	**6-8**
Unlikely	**1-2**
Excluded	**≤0**

Downloadable link with instructions: http://www.livertox.nih.gov/livertoxrucamv5.pdf

Management of DILI

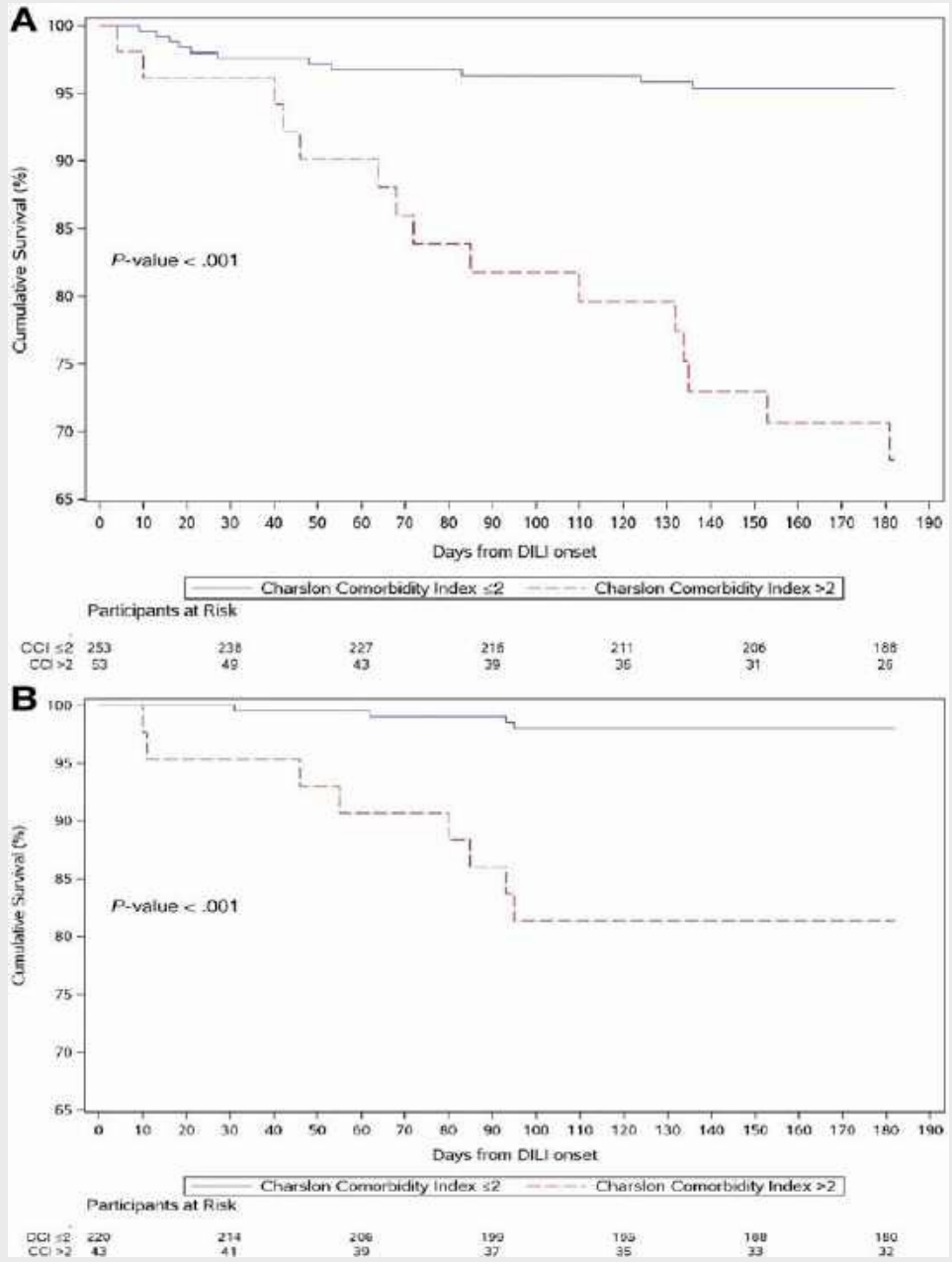
- Stop all non-essential drugs
- Symptomatic

  Jaundice: low-fat diet/antipruritic agents (doxepin, hydroxyzine)
- DILI specific
  - N-acetylcysteine (Mucomyst PO or IV) for acetaminophen or ALF
  - L-carnitine (IV) for valproate
  - Cholestyramine for Leflunomide
  - Cholestyramine and ursodiol for cholestatic
  - Steroid only for drug-induced autoimmune hepatitis

Prognosis

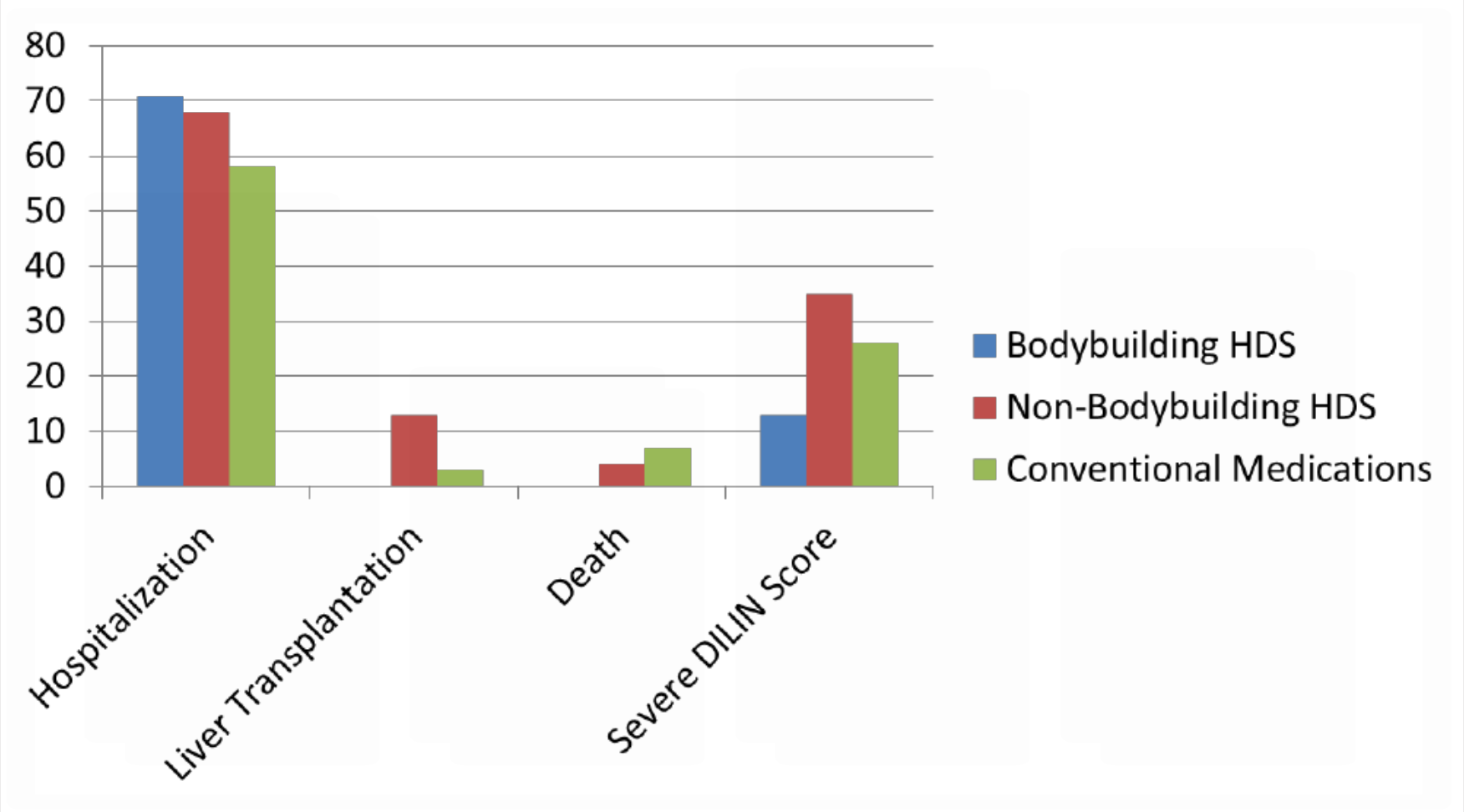
- MELD score
- Development and Validation of a Model Consisting of Comorbidity Burden to Calculate Risk of Death Within 6 Months for Patients With Suspected Drug-Induced Liver Injury

http://gihep.com/calculators/hepatology/dili-cam/



Ghabril M et al. Gastroenterology. 2019 Nov;157(5):1245-1252.

Outcomes



Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, Seeff LB, Serrano J, Sherker AH, Stolz A, Talwalkar J, Vega M, Vuppalanchi R. Hepatology. 2014 Oct;60(4):1399-408.

Mortality from DILI

	Hepatocellular (%)	Cholestatic (%)	Mixed (%)
Andrade et al. 2005	7	5	2
Bjornsson and Olsson. 2008	12.7	7.8	2.4
Chalasani et al (2015) - Death/transplant - Liver transplant Proportion of deaths due to liver failure	 11.6¶ 6.2 58%	 11.9¶ 2.9 56%	 5.4¶ 0 18%

Chalasani N, et al. Gastroenterology 2008
Chalasani N, et al. Gastroenterology 2015
Andrade R, et al. Gastroenterology 2005
Bjornsson E, et al. Hepatology 2005

Chronic DILI – How Common is it?

Study	Rate of Chronicity	Study Cohort	Definition of chronicity	Follow-up or time set for chronic determination	Population based
Aithal & Day	30% (13/44)	Hospitalized DILI cases at single center identified in histology database	Abnormal liver biochemistries and/or liver imaging at invited clinic follow-up	5 years (range 1–19)	No
SADRAC	1.5% (11/712)	Hospitalized DILI cases identified in a national hospital database	Abnormal liver biochemistries and/or cirrhosis unexplained on subsequent admission(s)	13 years (range 6–19)	No
Spanish Registry	5.7% (28/493)	DILI cases referred from across Spain	Abnormal liver biochemistries	3–6 months	No
DILIN	12% (74/598)	DILI cases enrolled at 10 participating centers	Abnormal liver biochemistries, liver imaging, or histology	12 months	No
Iceland Study	7% (7/96)	DILI cases from total population of Iceland	Abnormal liver biochemistries	6 months	Yes

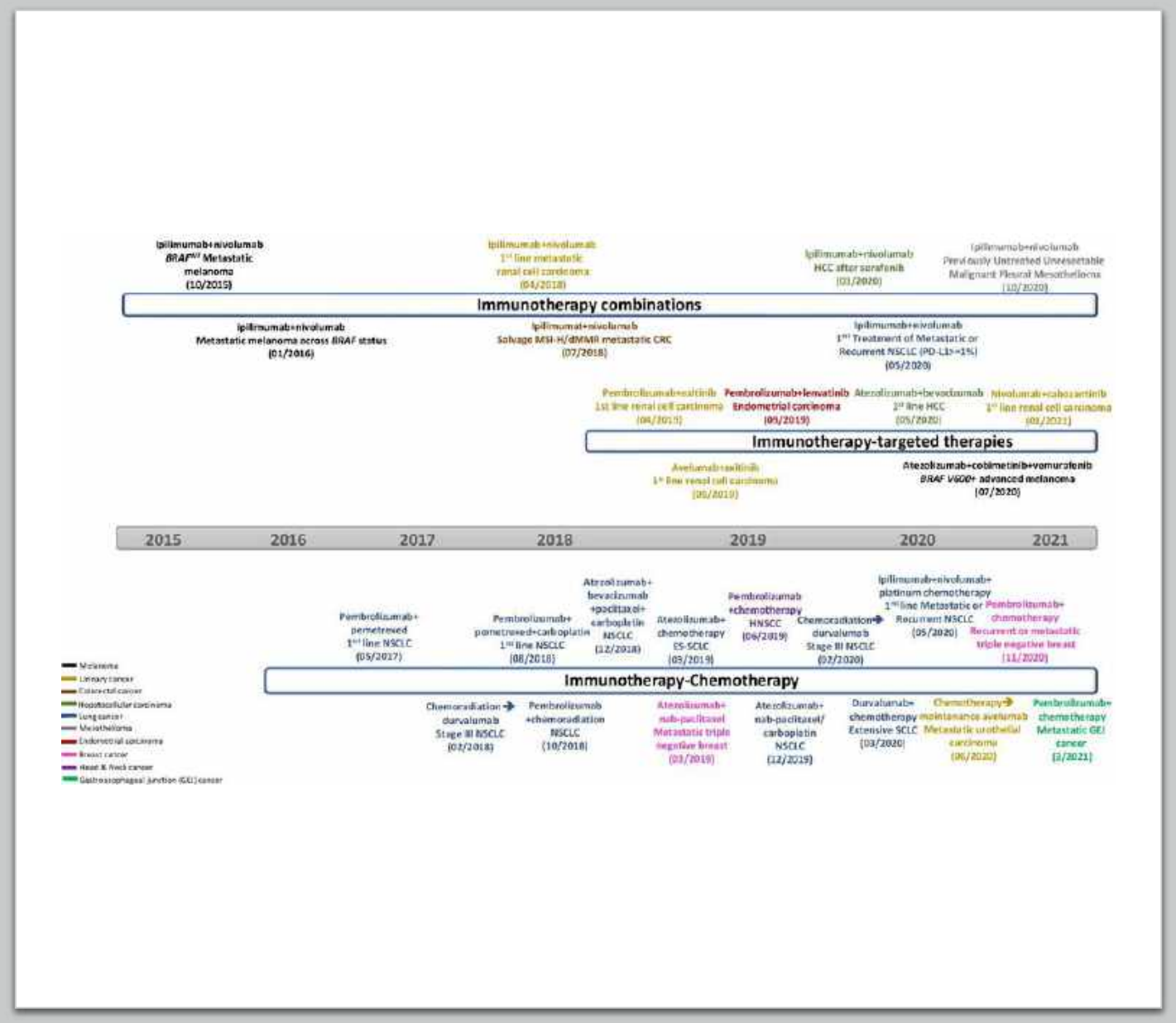
Hayashi et al. Curr Hepatology Rep (2018) 17:292–299

Drug-induced autoimmune-like hepatitis (DI-ALH)

Definite drug association	Probable drug association	Possible drug association	Possible HDS
Nitrofurantoin	Atorvastatin	Adalimumab	Black cohosh
Minocycline	Diclofenac	Cephalexin	Germander
Methyldopa	Propylthiouracil	Meloxicam	Hydroxycut
Hydralazine	Infliximab	Indomethacin	Ma huang
Imatinib/Masitinib	INH	Rosuvastatin	Dai-saiko-to
Alemtuzumab (monoclonal anti-CD52 antibody)		Terbinafine	

Test: antibodies	% positive in AIH cases	% positive in 'normal' population
ANA 1:60	68%-75%	15% (<40 ♀) - 24% (>40 ♀)
ASMA	52%-59%	Up to 43%
IgG >1,600 mg/dl	86%	5%
Anti-LKM	4%-20%	1%

RJ Andrade et al. Journal of Hepatology 2023 79853-866DOI: (10.1016/j.jhep.2023.04.033)

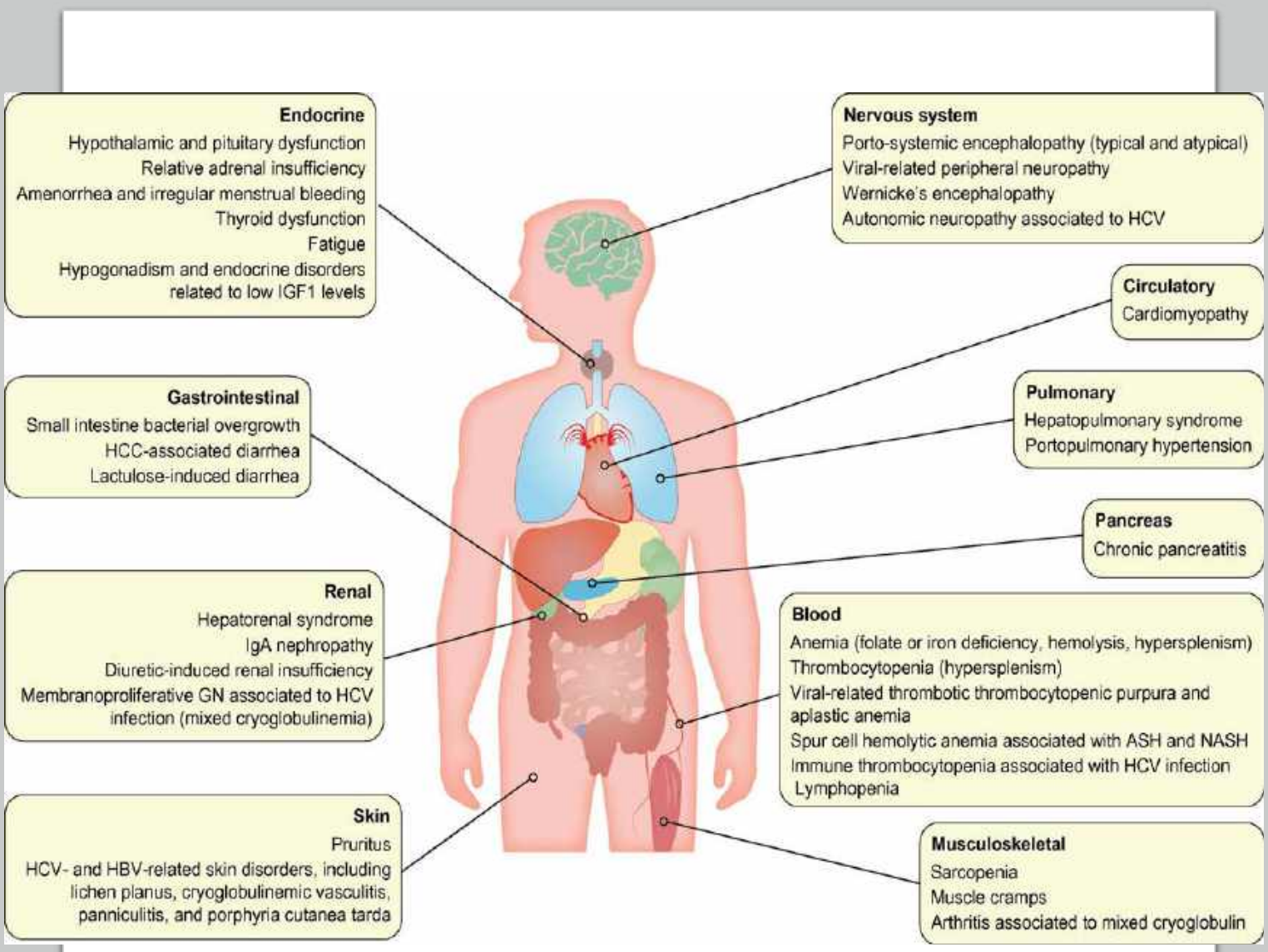


Immune Checkpoint Inhibitors

- 3 types
  - CTLA-4 (cytotoxic T lymphocyte-associated protein 4)
  - PD-1 (programmed cell death protein 1)
  - PD-L1 (programmed cell death ligand 1)

Toxicities of ICI

Blockade of inhibitory checkpoint molecules results in a broad range of immune-related adverse events (irAEs), resulting from impaired self-tolerance which may involve almost every organ.



Sangro et al. Journal of Hepatology Volume 72 Issue 2 Pages 320-341 2020 72320-341

Liver Injury from ICI

Class	Agent	Ref.	Indication	Incidence of hepatoxicity (all grades) % (no. of patients)	Incidence of ≥ grade 3 hepatoxicity % (no. of patients)
CTLA-4	Ipilimumab (standard dose) 3 mg/kg	Hodi et al[71], 2018	Melanoma	0.3 (1/311)	**0 (0/311)**
		Weber et al[72], 2009	Melanoma	15.5 (9/58)	10.3 (6/58)
		Hodi et al[2], 2010	Melanoma	3.8 (5/131)	0 (0/131)
			Melanoma	2.1 (8/380) Ipilimumab with gp100	1.1 (4/380) ipilimumab with gp100
		Wolchok et al[73], 2010	Melanoma	26.4% (19/72)	0 (0/72)
		Robert et al[74], 2011	Melanoma	29.1 (72/247)	**20.6 (51/247)**
	Ipilimumab (high dose) 10 mg/kg	Wolchok et al[73], 2010	Melanoma	70.4 (50/71)	15.5 (11/71)
	Tremelimumab	Ribas et al[75], 2013	Melanoma	0.6 (2/325)	0.6 (2/325)
Anti-PD-1	Nivolumab	Hodi et al[71], 2018	Melanoma	0.3 (1/313)	0.3 (1/313)
		Weber et al[76], 2017	Melanoma	1.9 (11/576)	0.7 (4/576)
		Brahmer et al[77], 2015	Squamous cell NSCLC	1.5 (2/131)	0 (0/131)
		Borghaei et al[78], 2015	Non-squamous NSCLC	3.1 (9/287)	0 (0/287)
		Robert et al[79], 2014	Melanoma	1.1 (1/89)	1.1 (1/89)
	Pembrolizumab	Robert et al[79], 2014	Melanoma	0 (0/84)	0 (0/84)
		Eggermont et al[80], 2018	Melanoma	1.8 (9/509)	1.4 (7/509)
	Cemiplimab	Migden et al[81], 2018	Cutaneous Squamous-Cell Carcinoma	8.5 (5/59)	0 (0/59)
Anti-PD-L1	Atezolizumab	Jotte et al[82], 2020	Squamous NSCLC	17.4 (58/334)	5.4 (18/334)
	Atezolizumab + Bevacizumab	Finn et al[3], 2020	HCC	33.4 (110/329)	10.6 (35/329)
	Avelumab	D'Angelo et al[83], 2020	Metastatic Merkel cell carcinoma	1.1 (1/88)	1.1 (1/88)
	Durvalumab	Garassino et al[84], 2018	Advanced NSCLC	0.2 (1/444)	0.2 (1/444)
Combination Therapy	Ipilimumab + Nivolumab	Hodi et al[71], 2018	Melanoma	3.2 (10/313)	2.6 (8/313)
		Postow et al[85], 2015	Melanoma	22.3 (21/94)	10.6 (10/94)
		Larkin et al[86], 2015	Melanoma	17.6 (55/313)	8.3 (26/313)
		Wolchok et al[73], 2010	Melanoma	20.8 (11/53)	11.3 (6/53)

CPIs-induced liver injury was found to improve spontaneously in 33–50% without corticosteroids, and the rate of patients who were treated responded to steroids in 33–100% (mean 72%).

Remash D, Prince DS, McKenzie C, Strasser SI, Kao S, Liu K. Immune checkpoint inhibitor-related hepatotoxicity: A review. *World J Gastroenterol* 2021; 27(32): 5376-5391

Management of ICI Hepatitis

Grade 1 (AST or ALT >ULN to 3× ULN and/or total bilirubin >ULN to 1.5× ULN)**:** Continue with close monitoring (except for some neurologic, hematologic, and cardiac toxicities)

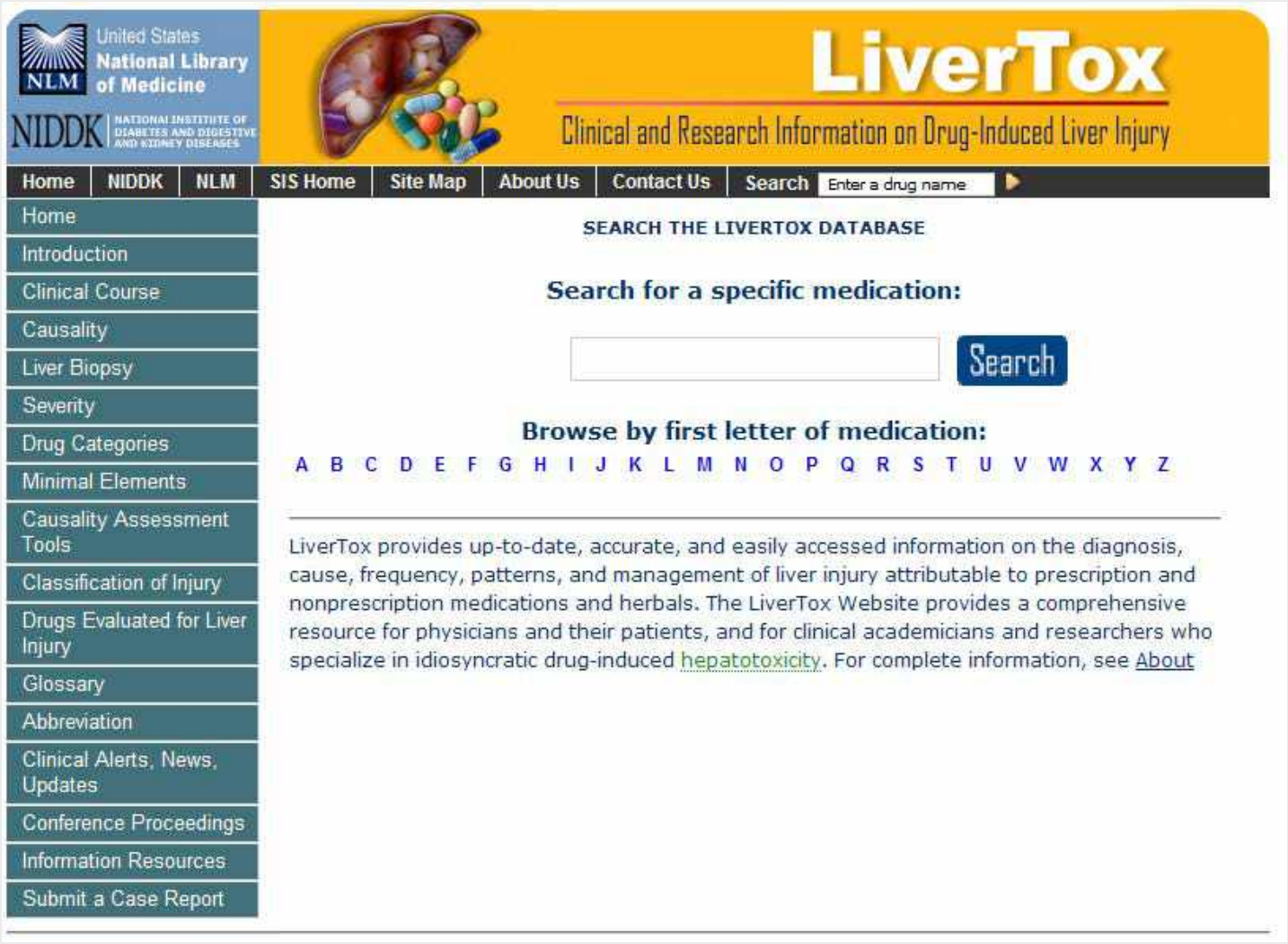
Grade 2 (AST or ALT >3 to <5× ULN and/or total bilirubin >1.5 to <3× ULN)**:** Hold and consider resume when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) and tapered over at least a month.

Grade 3 (symptomatic dysfunction, fibrosis found on a liver biopsy, compensated cirrhosis, reactivation of chronic hepatitis, AST or ALT 5-20× ULN, and/or total bilirubin 3-10× ULN)**:** Hold and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, mycophenolate mofetil may be offered.

Grade 4 (decompensated liver function, AST OR ALT >20× ULN, and/or total bilirubin >10× ULN)**:** Permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement.

American Society of Clinical Oncology Clinical Practice Guideline J Clin Oncol. 2018 Jun 10; 36(17): 1714–1768.

LiverTox (http://livertox.nih.gov/)



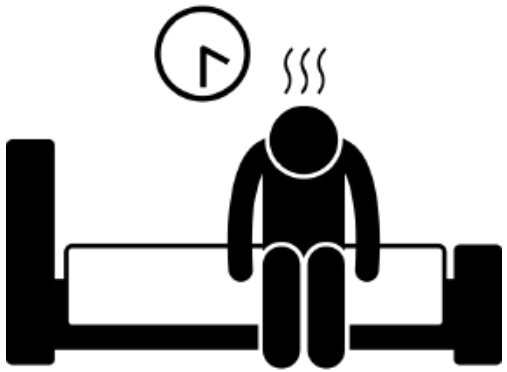
Symptoms of Cirrhosis

Elliot B. Tapper MD
Director, University of Michigan Cirrhosis Program
@ebtapper

Symptom control is high quality care

Quality of life is often poor

Hepatology 2019;69:1676-1685

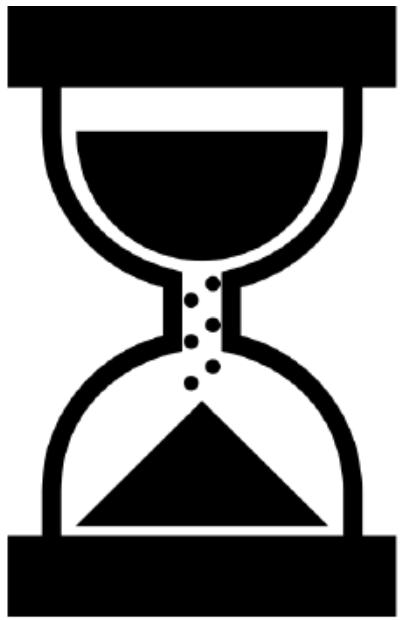


Patients expect us to address their symptoms

TABLE 3. Patient Ratings of Patient-Reported Outcomes

Patient-Reported Item	Not Important (%)	Somewhat Important (%)	Very/Extremely Important (%)
Fluid in the legs (edema)	8.9	14.1	76.9
Fluid in the belly (ascites)	3.8	5.1	91.1
Confusion (encephalopathy)	1.3	10.1	88.6
Concentration/memory	6.4	16.7	76.9
Itching (pruritus)	5.2	12.9	81.8
Muscle cramps	12.9	36.4	50.7
Falls	12.8	17.9	69.2
Medication side effects	8.9	17.9	73.1
Depression	7.6	21.7	70.5
Stigma of having liver disease	5.1	14.1	80.8
Ability to drive	10.1	22.8	67.1
Burden on family	35.1	5.2	59.8
Ability to avoid alcohol	17.1	18.4	64.4

Hepatology. 2019;69(4):1787-1797



During the past month, how would you rate your sleep quality overall?

(a 5-point Likert from Very Good to Very Bad)

Advanced

Basics:
Quiet
No TV
Reading
Caffeine

Medications (hydroxyzine, melatonin) Am J Gastroenterol. 2007 Apr;102(4):744-53.

Meditation

Clinical and Translational Gastroenterology (2017) 8, e108;

Lactulose

Metab Brain Dis (2017) 32:595–605

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Histamine H1 Blocker Hydroxyzine Improves Sleep in Patients With Cirrhosis and Minimal Hepatic Encephalopathy: A Randomized Controlled Pilot Trial

Laurent Spahr, M.D.,[1] Alessandra Coeytaux, M.D.,[2] Emiliano Giostra, M.D.,[1] Antoine Hadengue, M.D.,[1] and Jean-Marie Annoni, M.D.[2]

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Hydroxyzine

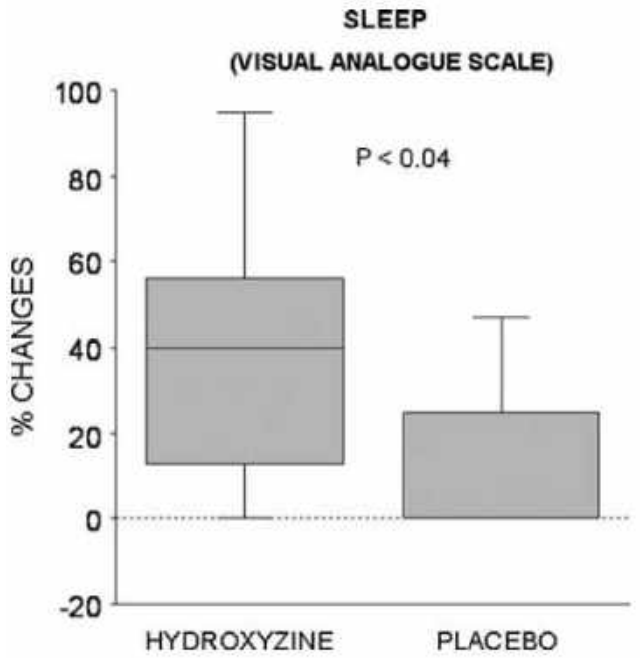


Figure 3. Evolution of sleep (percent changes) as assessed subjectively using a visual analog scale, in hydroxyzine- and placebo-treated patients. Values are expressed as median and interquartile range (25–75th percentiles).

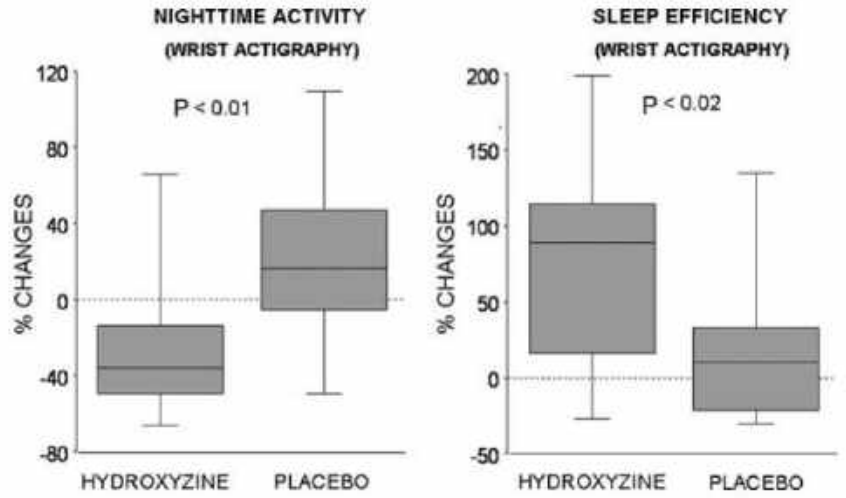


Figure 4. Evolution of sleep behavior (percent changes) as measured using wrist actigraphy during 4 days and overnight periods prior to and during the last 4 days of treatment, in hydroxyzine- and placebo-treated patients. Values are expressed as median and interquartile range (25–75th percentiles). Nighttime activity recorded by the Actiwatch relates to fragmented sleep and frequent awakenings. Sleep efficiency is the total time spent in bed for sleeping purposes divided by the nighttime activity, multiplied by 100.

Melatonin or... Placebo?!

JGH Open An open access journal of gastroenterology and hepatology Open Access JGHF

doi:10.1002/jgh3.12356

ORIGINAL ARTICLE

Low-dose melatonin for sleep disturbances in early-stage cirrhosis: A randomized, placebo-controlled, cross-over trial

Arjuna P De Silva,* Madunil A Niriella,* Dileepa S Ediriweera,* Jerome P De Alwis,† Isurujith K Liyanage,† Ushanthani Ettickan,* Kasun V Liyanapathirana,* Chandimani Undugodage,‡ H. Asita de Silva* and H. Janaka de Silva*

*Faculty of Medicine, University of Kelaniya, †University Medical Unit, Colombo North Teaching Hospital, Ragama and ‡Faculty of Medical Sciences, University of Sri Jayawardenapura, Nugegoda, Sri Lanka

Table 3 Preadministration and postadministration scores of Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS) and Short Form Health Survey (SF 36) among melatonin and placebo groups

	Melatonin mean (SD)			Placebo mean (SD)		
Indicator	Preadministration score	Postadministration score	*P* value	Preadministration score	Postadministration score	*P* value
PSQI score	12.6 (3.1)	9.6 (3.1)	<0.01	11.4 (2.9)	7 (3.4)	<0.01
ESS score	11.8 (4.7)	9.4 (4.9)	<0.01	11.7 (4.5)	8.7 (4.0)	0.01
SF1	59.1 (24.3)	57.2 (26)	0.45	65.7 (20.6)	68.8 (20.0)	<0.01
SF2	14.9 (24.6)	17.6 (31.1)	0.50	19.1 (32.6)	28.3 (37)	0.08
SF3	27.9 (41.2)	32.4 (42.7)	0.28	43.1 (41.5)	53.3 (41.6)	0.16
SF4	49.3 (20.0)	53 (17.1)	0.11	61.8 (14.3)	63.7 (14.9)	0.08
SF5	57.6 (14.9)	59.8 (13.9)	0.21	65.3 (13.9)	67.9 (14.3)	0.14
SF6	60.1 (22)	61.4 (21.7)	0.47	65.4 (18.0)	67.9 (16.3)	0.12
SF7	50.6 (28.5)	52.6 (24.4)	0.36	57.5 (22.2)	59.6 (21.7)	0.54
SF8	32.2 (16.9)	35.5 (14.7)	0.05	42.5 (14.0)	43.5 (13.8)	0.89
SF9	49.3 (29.7)	48 (26.6)	0.42	57.1 (26.3)	57.5 (27.2)	0.92

Maybe caring to ask is enough?

PLoS One 2010;5:e15591

BMJ open. 2017 Jun 1;7(6):e015516

Meditation

Table 1 Change in Patient Questionnaires

Patients	Pre-group	Post-group	*P*-value
MELD score	12.9 ± 5.7	12.5 ± 5.5	0.48
Beck Depression Inventory	19.0 ± 10.6	15.6 ± 8.2	0.012
% with depression	20 (100%)	9 (45%)	0.0001
Beck Anxiety Inventory	11.9 ± 10.1	12.3 ± 10.4	0.51
Total SIP	25.0 ± 13.2	17.7 ± 14.0	0.005
Psychosocial SIP	25.1 ± 15.9	17.3 ± 13.2	0.01
Physical SIP	18.5 ± 17.4	13.1 ± 12.5	0.001
Pittsburgh Sleep Quality Index	7.2 ± 3.7	5.5 ± 3.7	< 0.001
Epworth Sleepiness Scale	7.1 ± 3.5	5.7 ± 4.4	0.13
PHES score median (IQR)	−7 (−10 to −4)	−6 (−8 to −3)	0.42
Covert HE by PHES (%)	55%	50%	0.75

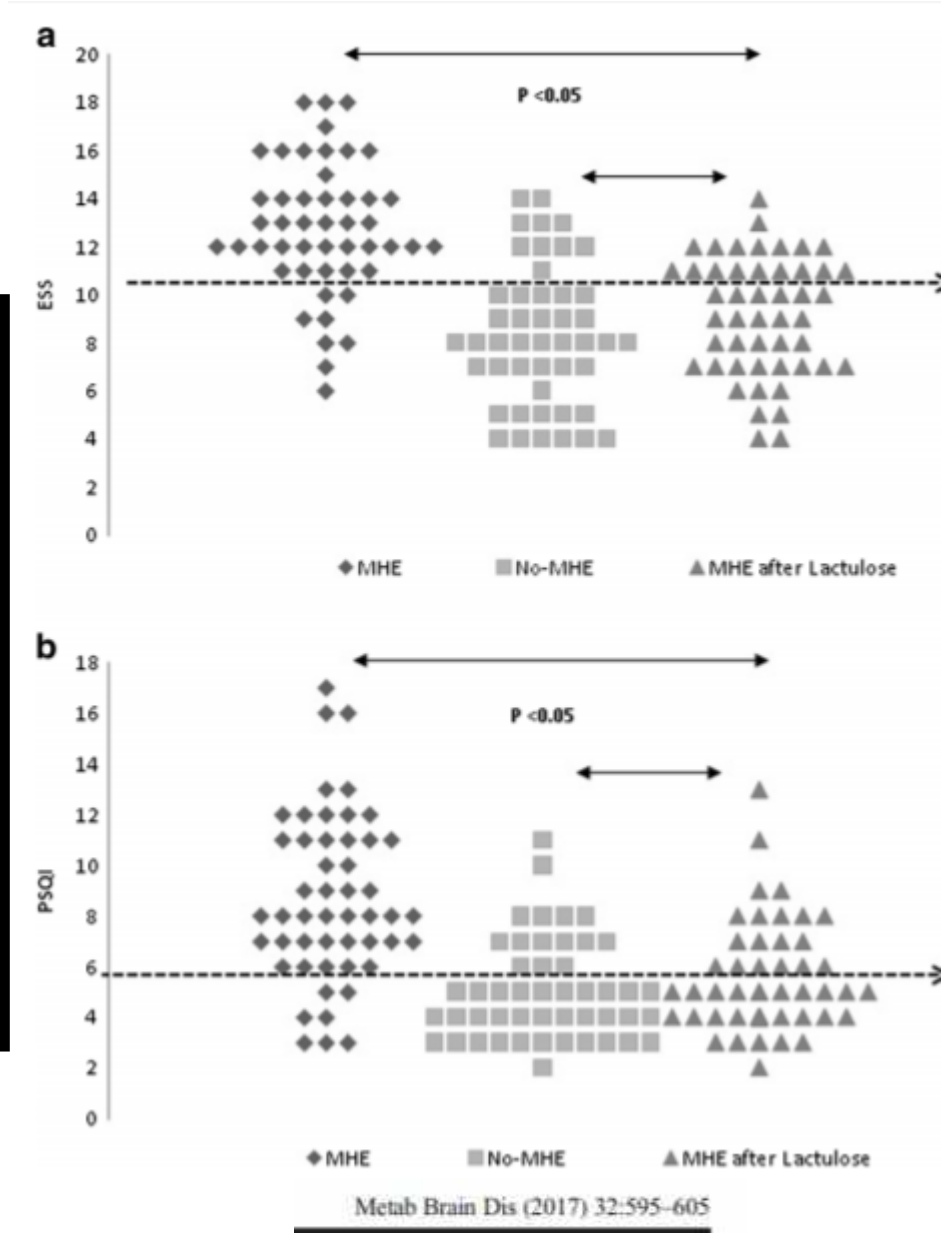
Table 2 Change in Caregiver Questionnaires

Caregivers	Pre-group	Post-group	*P*-value
Zarit Burden Interview-SF	13.0 ± 9.0	9.8 ± 6.9	0.04
Perceived Caregiver Burden	72.1 ± 29.9	63.0 ± 14.5	0.05
Beck Depression Inventory	9.1 ± 7.8	5.9 ± 6.0	0.03
Beck Anxiety Inventory	5.5 ± 5.2	5.2 ± 7.1	0.80
Total SIP	6.5 ± 9.7	6.1 ± 9.1	0.52
Psychosocial SIP	6.4 ± 9.6	8.0 ± 12.6	0.51
Physical SIP	4.9 ± 9.8	4.7 ± 9.4	0.82
Pittsburgh Sleep Quality Index	7.2 ± 3.7	5.5 ± 3.7	< 0.001
Epworth Sleepiness Scale	7.2 ± 3.4	5.7 ± 4.4	0.11

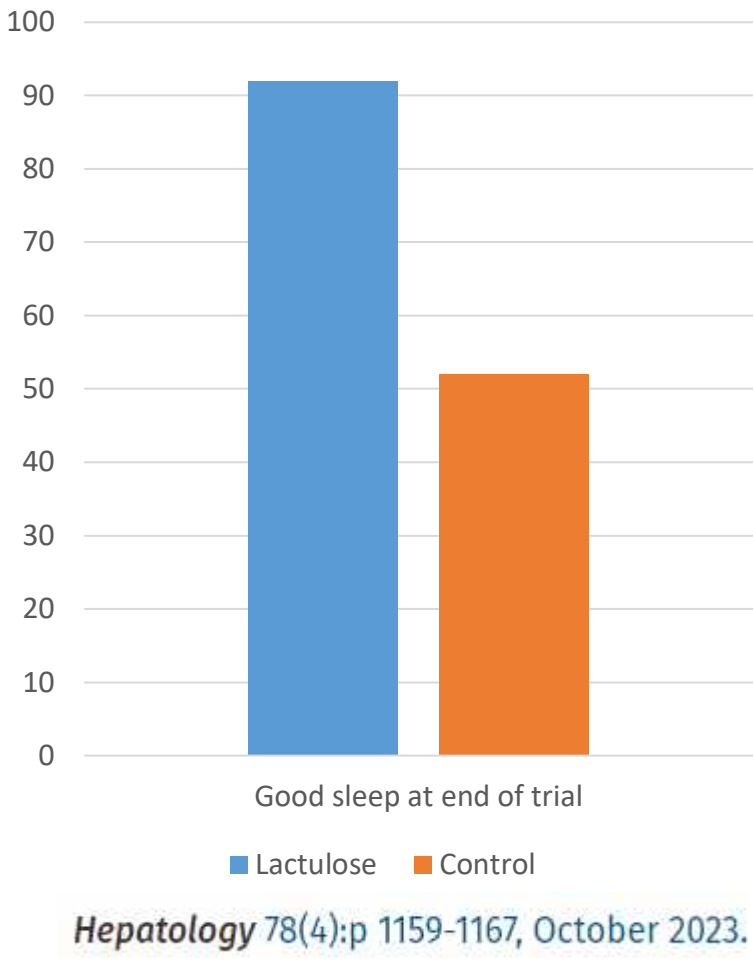
SIP, Sickness Impact Profile.
Data is presented as mean ± s.d. unless stated otherwise. A high score on all these values indicates worse functioning.

Clinical and Translational Gastroenterology (2017) 8, e108;

Lactulose improves sleep quality



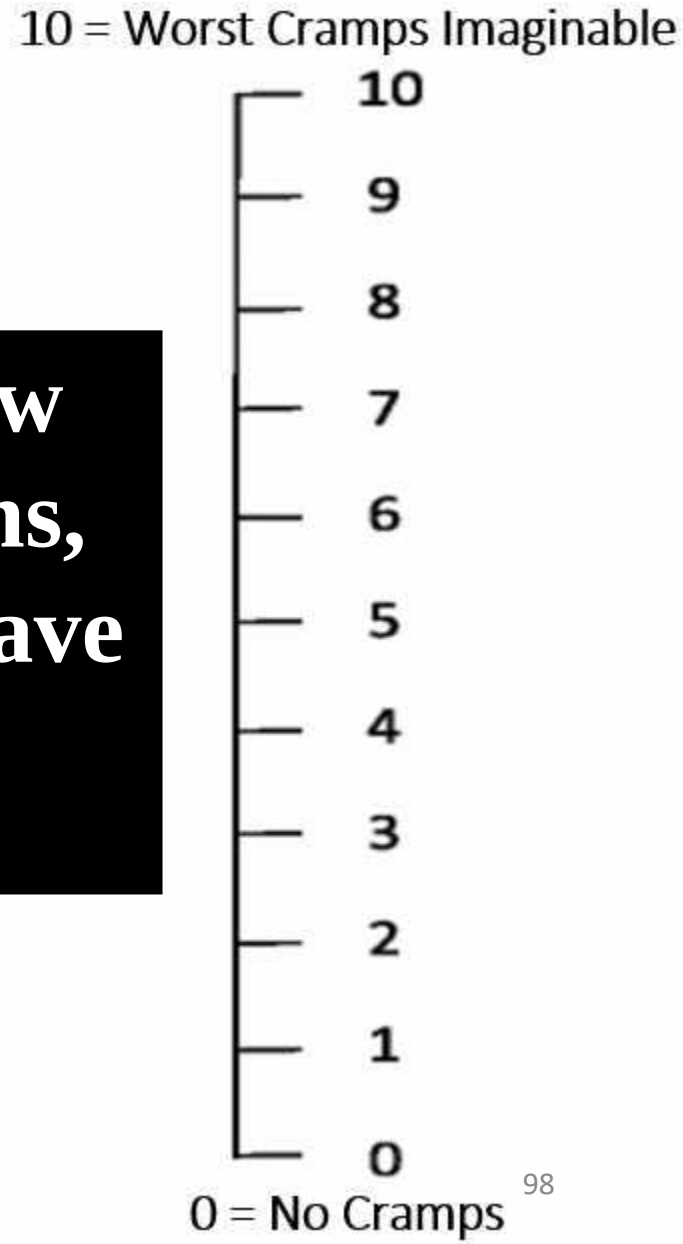
Metab Brain Dis (2017) 32:595–605



Hepatology 78(4):p 1159-1167, October 2023.

During the past month, how many painful muscle spasms, cramps, or charley horses have you had?

Do they bother you?



Advanced

Basics: Normalize electrolytes, hydration

Frequency as main problem:
Taurine 3g daily,
Baclofen 5-10mg

Severity/duration as main problem:
Pickle Juice – 1 sip/tbsp at cramp onset

PICCLES trial

80 patients

Pickle juice vs tap water

Reduced cramp severity

No effect on frequency, sleep, or QOL

The American Journal of Gastroenterology: June 2022 - Volume 117 - Issue 6 - p 895-901

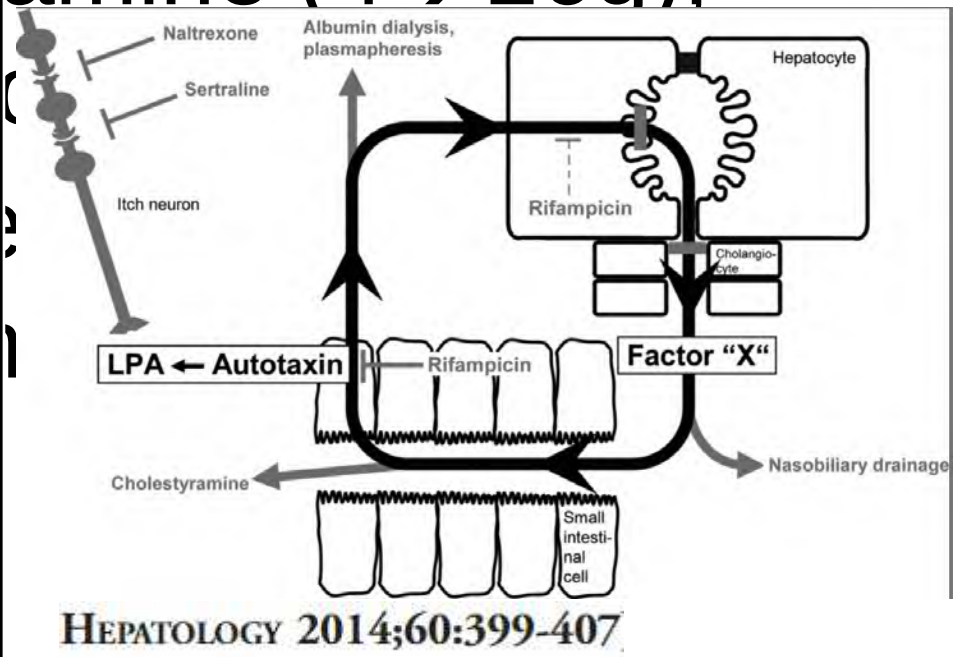
How much of the time have you been troubled by itching during the last two weeks?

Advanced

Basics:
Showers
Moisture
Hydroxyzine

I am not sure how effective these are for people with non-biliary cirrhosis

amine (4→16g),



Fenofibrate (100-145mg)

Have you had any sexual activity in the past few weeks? How satisfied were you with your sexual function during the past few weeks?

“Advanced”

‘Basics’
Alcohol
Depression
Smoking

I respect that this may be uncomfortable

Hepatology 2019;69:2683-2695

Table 3. Alterations in Vaginal Flora and pH in the Two Groups.*

VARIABLE	ESTRIOL GROUP (N = 36)	PLACEBO GROUP (N = 24)
Positive vaginal cultures — no. (%)		
Pretreatment		
Lactobacilli	0	0
Enterobacteriaceae	24 (67)	16 (67)
After 1 mo of treatment		
Lactobacilli	22 (61)	0†
Enterobacteriaceae	11 (31)	15 (63)‡
After 8 mo of treatment		
Lactobacilli	21 (58)	0†
Enterobacteriaceae	10 (28)	17 (71)‡
Vaginal pH		
Pretreatment	5.5±0.7	5.8±1.2
After 1 mo of treatment	3.8±0.8	6.2±1.2†
After 8 mo of treatment	3.6±1.0	6.1±2.0†

*Only women who had cultures at the one- and eight-month visits were included in the analysis. Plus–minus values are means ±SE.

†P<0.001 for the comparison between groups.

‡P<0.005 for the comparison between groups.

(N Engl J Med 1993;329:753-6.)

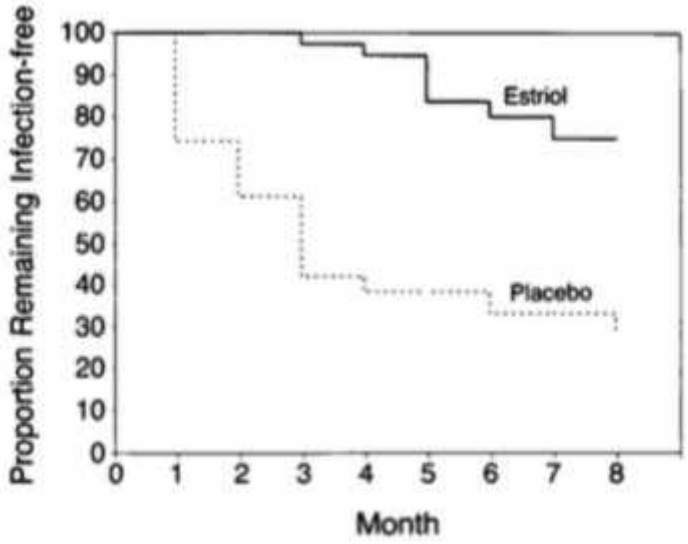


Figure 1. Kaplan–Meier Analysis Showing the Cumulative Proportions of Women Remaining Free of Urinary Tract Infections in the Estriol and Placebo Groups (P<0.001 by the Log-Rank Test).

Vaginal estrogen and UTIs

Low T
Sarcopenia
Anemia
Sex life

Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial

Marie Sinclair[1,2,*], Mathis Grossmann[1,3], Rudolf Hoermann[1], Peter W. Angus[1,2,†], Paul J. Gow[1,2,†]

ble 3. Median changes of parameters from baseline to end-of-trial in study completers (n = 47), which represents per protocol analysis.

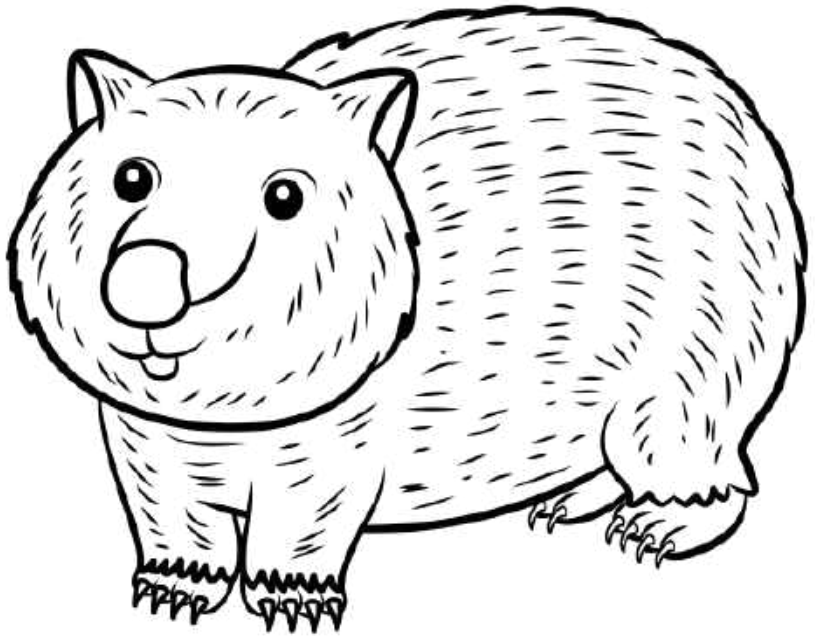
	All	Testosterone	Placebo	*p* value
APLM (kg), n = 45	0.59 [-0.65;2.13]	+1.69 [0.81;2.49]	-0.05 [-0.89;0.61]	0.014
Lean mass (kg), n = 45	0.54 [-1.83;4.06]	+3.43 [0.54;5.34]	-0.77 [-2.07;0.89]	0.017
Fat mass (kg), n = 45	1.05 [-3.04;4.06]	-2.42 [-5.27;1.56]	1.62 [0.97;6.26]	0.008
Bone mass (kg), n = 45	0.02 [-0.10;0.11]	+0.03 [-0.05;0.13]	-0.01 [-0.14;0.06]	0.092
Lumbar T score, n = 45	0.00 [-0.20;0.30]	0.10 [-0.10;0.40]	-0.10 [-0.30;0.22]	0.105
NOF T score, n = 45	-0.10 [-0.30;0.20]	0.10 [-0.10;0.30]	-0.20 [-0.41;0.10]	0.006
Hb (g/L), n = 47	2.00 [-3.00;16.0]	5.00 [1.00;17.0]	0.00 [-5.25;11.2]	0.055
HbA1c (%), n = 42	0.00 [-0.40;0.20]	-0.25 [-0.68;0.10]	0.00 [-0.30;0.30]	0.130

esults displayed as median [95% confidence interval]. APLM, appendicular lean mass; NOF, neck of femur; Hb, haemoglobin; HbA1c, percentage glycosylated haemoglobin.

Considerations: No HCC, No prostate Ca, counsel re: risk of CVA/MI

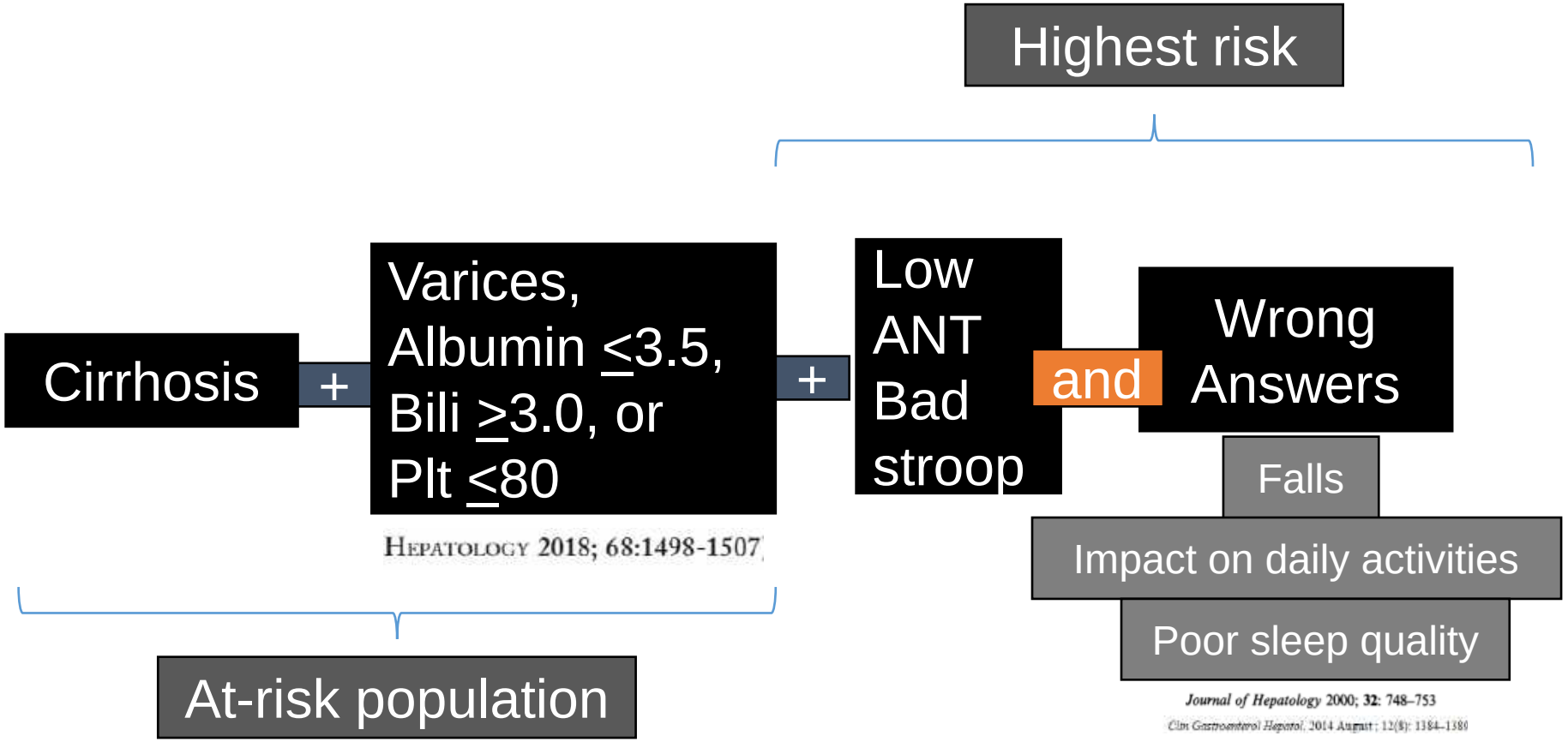
Journal of Hepatology **2016** vol. 65 | 906–913

Subclinical, covert HE is associated with: poor QOL, poor sleep, falls, frailty

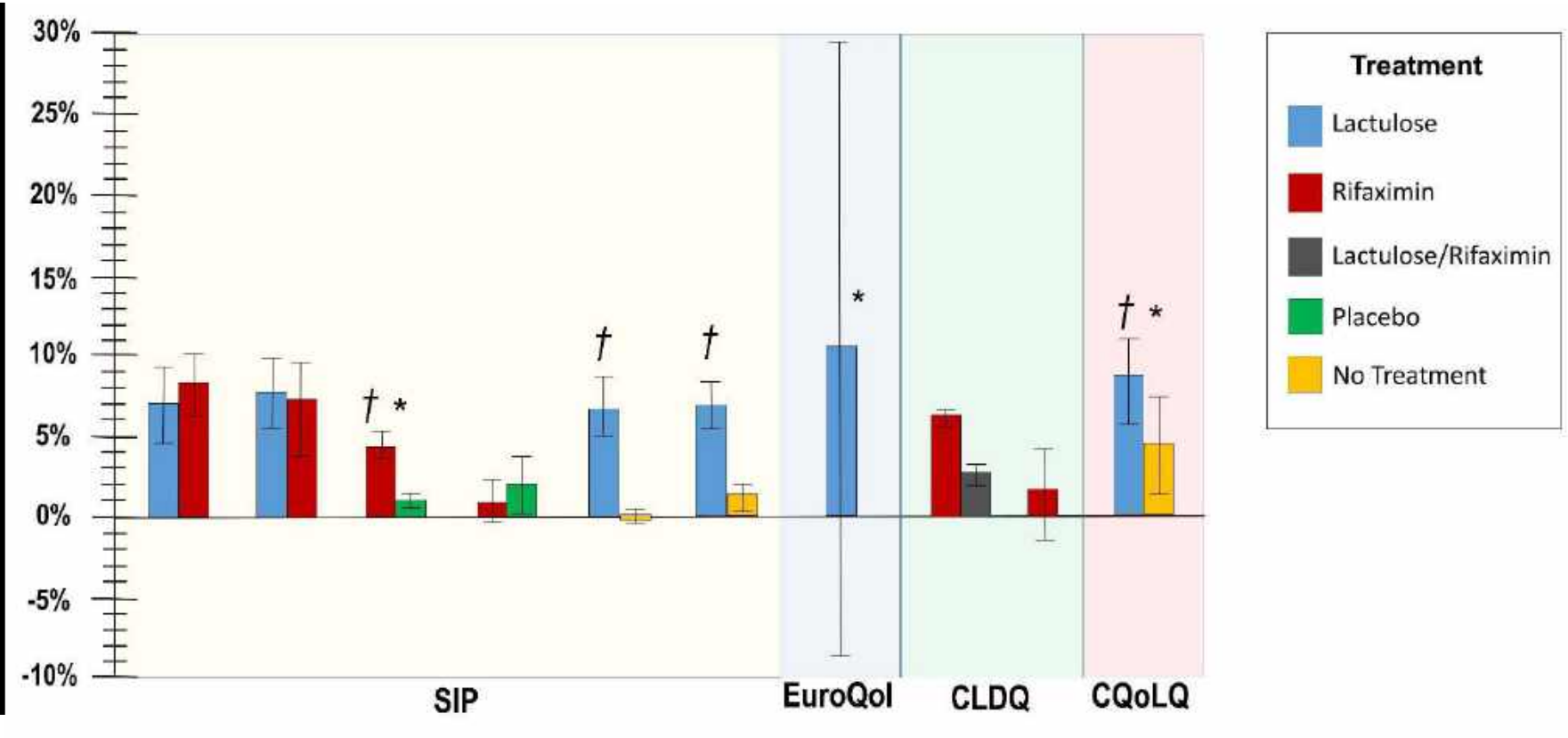



Stroop Test
New Test
Test Results
Quick Play

Make patient-centered decisions



Identifying and treating HE improves QOL



Moon….Tapper. AJG 2023

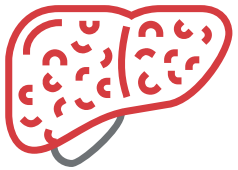
How Should You Take Lactulose?

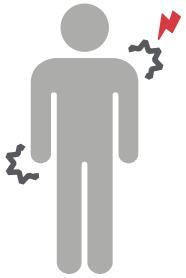
- Straight from the spoon
- In water with or without ice
- Mix in hot or cold drink of your choosing
  - It may settle at the bottom, mix thoroughly

	Each day, fill in how many bowel movements (BMs) you had the day before	*Use BMs column to guide your lactulose dose for the day*			*Check off each completed dose*	
Day	**How Many BMs Yesterday?**	**BMs**	**Morning Dose**	**Midday Dose**	**Dose Completed**	
					Morning	Midday
1		Any	1 tbsp	0		
2		Any	1 tbsp	1 tbsp		
3		Any	1 tbsp	1 tbsp		
4		If 0-1	2 tbsps	1 tbsp		
		If 2-5	1 tbsp	1 tbsp		
		If 6+	0	0		

Pain control for patients with cirrhosis

e Burden and Impact of Pain and Pain Mismanagement in Cirrhosis





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Advanced

Basics:
Acetaminophen

PT

Classify the pain type

Suggest non-pharmacologic interventions

scites

Bleeding

Pain Guide
Self-care

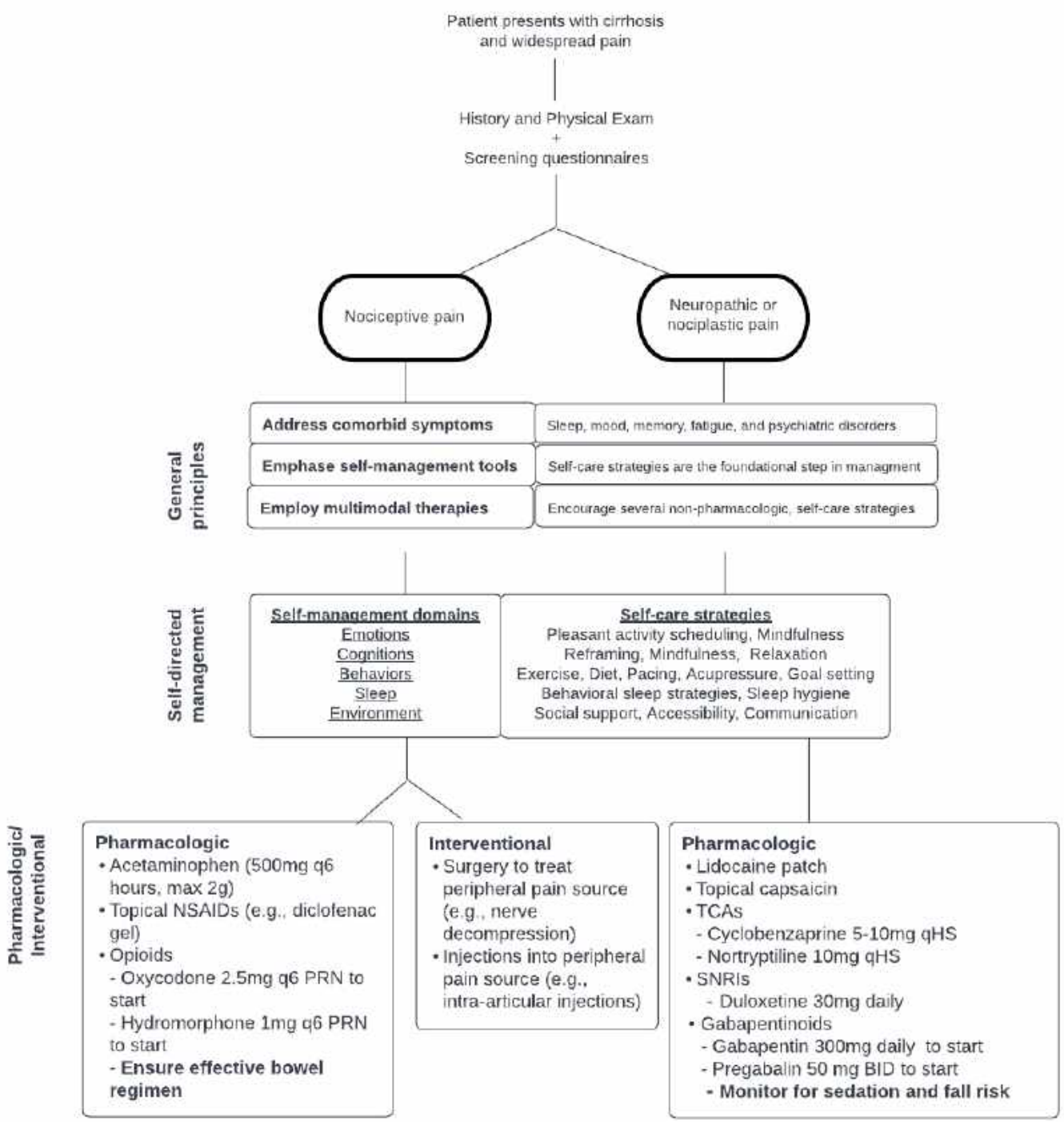
Relaxation

Activation

Ideas for safer pharmacology

Topical NSAIDs

Neuropathy: Lidocaine, Capsaicin TCA / Duloxetine



Hepatology. 2023 Jan 1;77(1):290-304.

Thank you!

Ask your patients!

Track symptoms!

Do something about it!

The End

@ebtapper

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Liver Transplant (101): The Non-Specialist

MOISES ILAN NEVAH, MD

Banner University Medical Center – Phoenix Transplant Institute

Associate Professor of Medicine – University of Arizona College of Medicine

Disclosures

No Financial Disclosures

Outline

1. Cirrhosis and Portal hypertension

2. MELD score: application

3. Liver Transplant evaluation

Cirrhosis and Portal Hypertension Trivia

True or False

1. Do all patients with portal hypertension have cirrhosis?

Cirrhosis and Portal Hypertension Trivia

True or False

1. Do all patients with portal hypertension have cirrhosis?

FALSE

Cirrhosis and Portal Hypertension Trivia

True or False

1. Do all patients with portal hypertension have cirrhosis?

FALSE

2. Do all patient with cirrhosis have portal hypertension?

Cirrhosis and Portal Hypertension Trivia

True or False

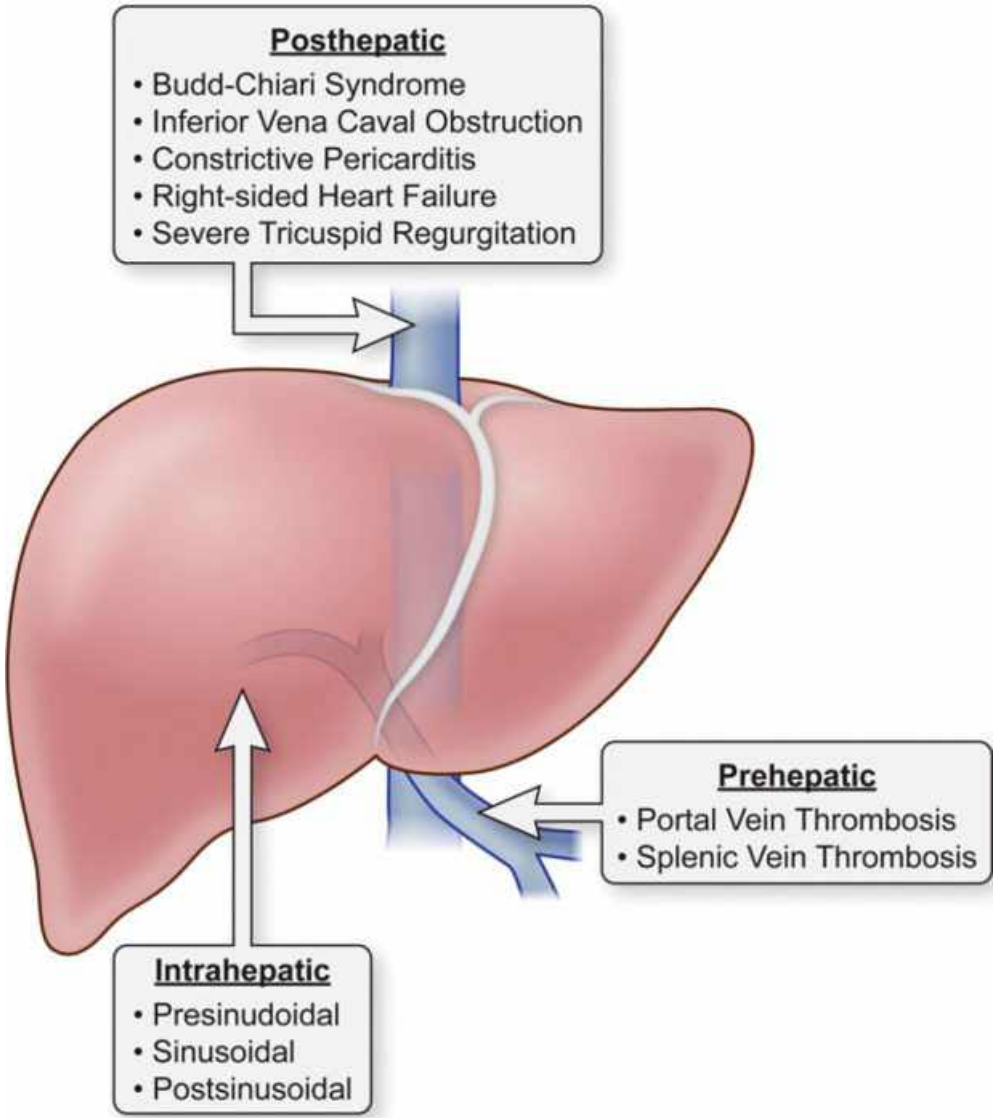
1. Do all patients with portal hypertension have cirrhosis?

FALSE

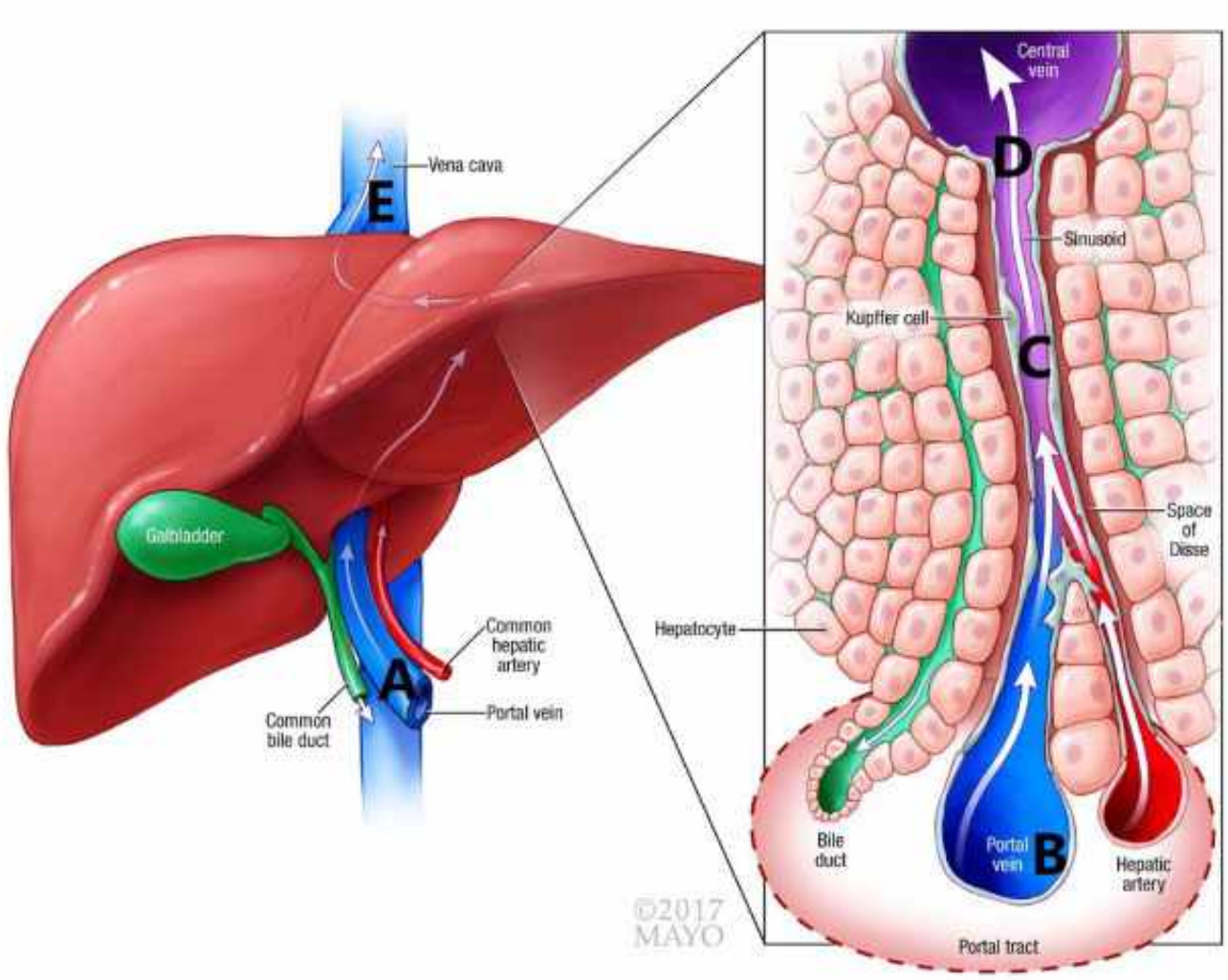
2. Do all patient with cirrhosis have portal hypertension?

FALSE

Portal Hypertension



Portal Hypertension: Intrahepatic

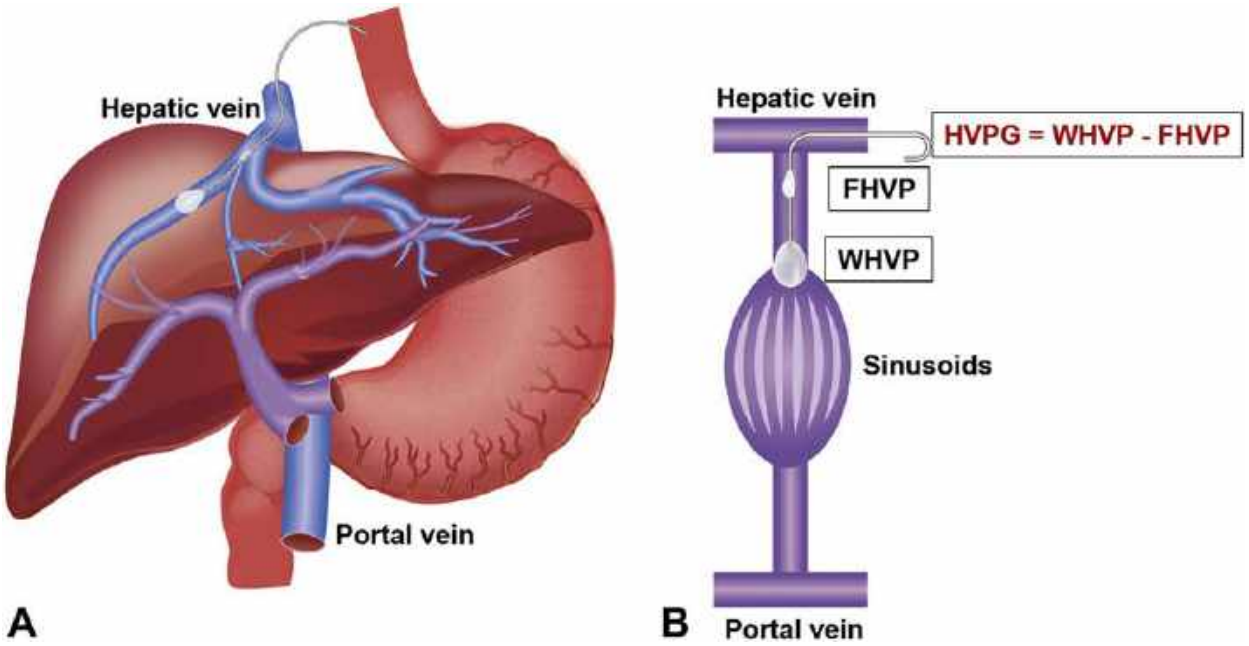


Post Sinusoidal:
Sinusoidal obstruction syndrome (VOD)

Sinusoidal:
Chronic Viral Hepatitis
MASLD/ALD
Wilson/HH/A1AT

Pre Sinusoidal
Portal Vein – NRH & Schistosoma
Bile Duct – PBC

Portal Hypertension: Portosystemic Gradient



- Difference between the pressure in the portal system and systemic system
- Portosystemic Gradient = Hepatic Venous Pressure Gradient
- HVPG = WHVP - FHVP
- Portal HTN = HVPG ≥ 6mmHg

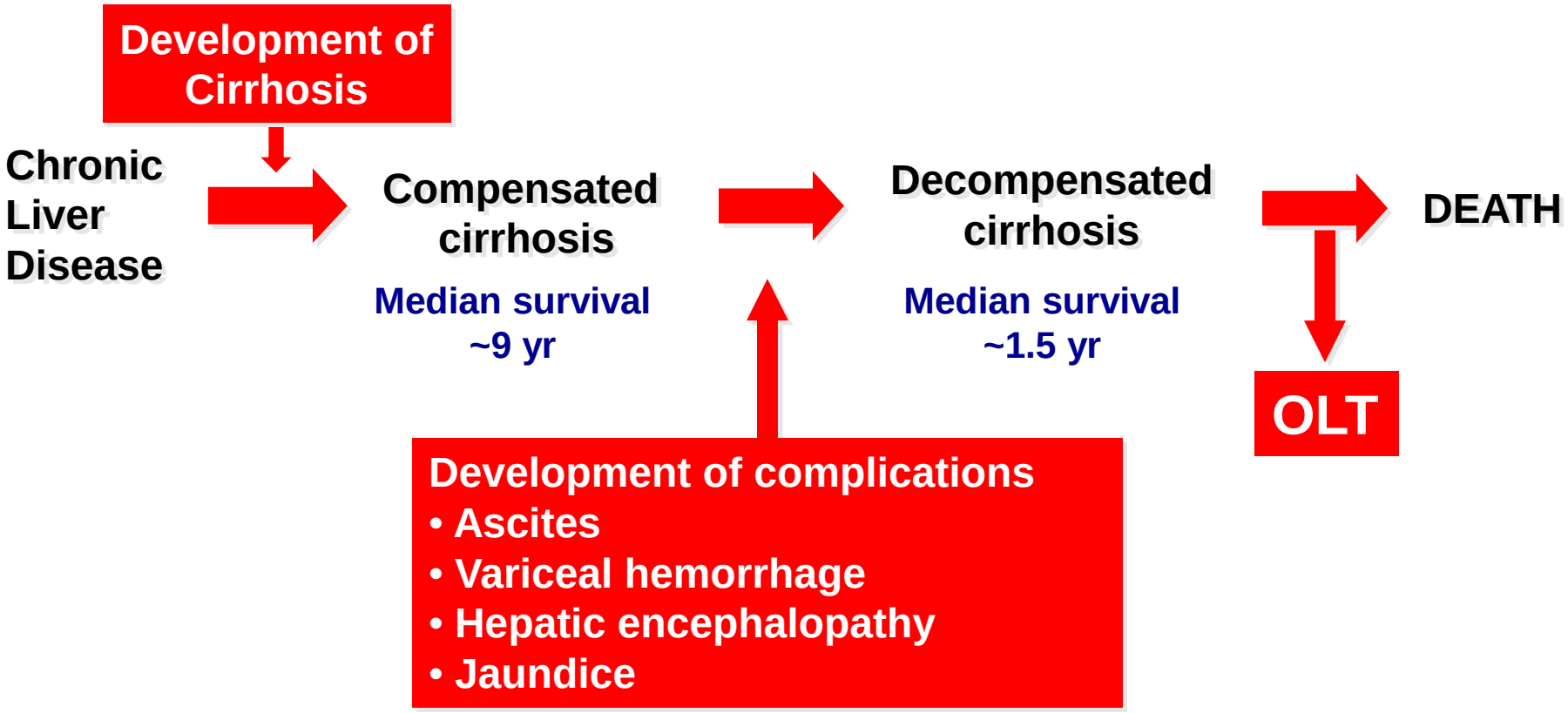
Cirrhosis: Definitions

- End stage of any chronic liver disease

- Characterized histologically by regenerative nodules surrounded by fibrous tissue

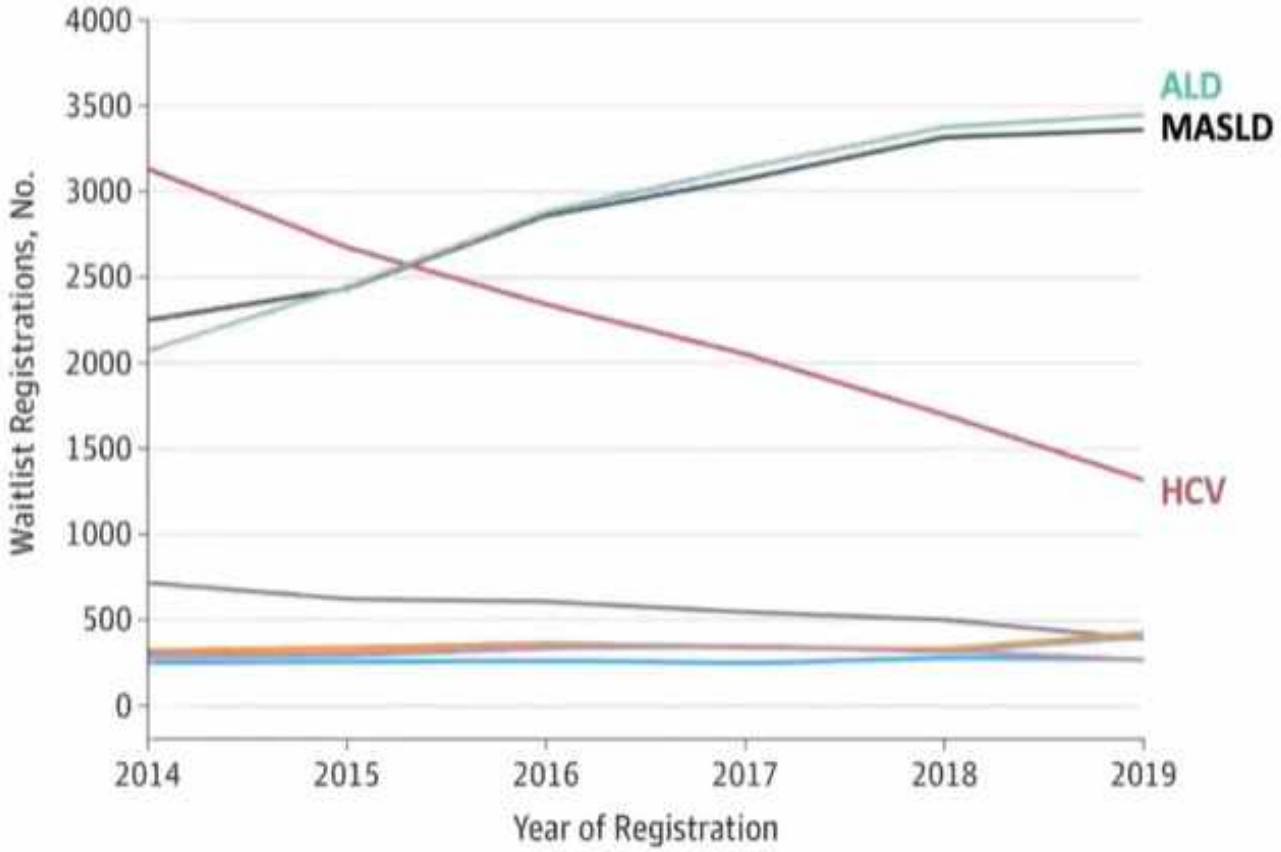
- Clinically there are two types of cirrhosis:
  - Compensated
  - Decompensated

Natural History of Chronic Liver Disease



Liver Disease Burden in the United States

- ~18 % increase in Liver transplants in the past 5 years
- 10,660 Liver transplants 2023
  - Increase in 11% vs 2022
  - Increase utilization living donors
  - Higher risk donors
    - DCD
    - New Perfusion technologies
    - Donors > 50
- Landscape of Liver Disease



Indications for Lier Transplantation

- End Stage Liver disease
- Hepatic Neoplasms
- Acute Liver Failure
- Metabolic disorders

Decompensated Liver disease

- **Synthetic dysfunction**
- **Ascites / Hydrothorax**
- **Variceal hemorrhage**
- **Hepatic encephalopathy**

PVCLD

Hepatorenal syndrome

ACLF

Indications for Lier Transplantation

- End Stage Liver disease
- Hepatic Neoplasms
- Acute Liver Failure
- Metabolic disorders

Hepatocellular Carcinoma

Cholangiocarcinoma

Polycystic Liver Disease

Metastatic Malignancies

- **NET**
- **Colorectal Cancer**

Indications for Lier Transplantation

- End Stage Liver disease
- Hepatic Neoplasms
- Acute Liver Failure
- Metabolic disorders

- **Wilson Disease**
- **DILI**
- **AIH**
- **Idiopathic**
- **Acute Alcohol Associated Hepatitis**

Indications for Lier Transplantation

- End Stage Liver disease
- Hepatic Neoplasms
- Acute Liver Failure
- Metabolic disorders

Acute Alcohol Associated Hepatitis

- **6 Month Sobriety rule**
- **Program dependent**
- **Young**
- **Female**
- **Post Pandemic**
- **Specific Criteria**

Acute Alcohol Associated Hepatitis

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., et al.

SPECIAL ARTICLE

Meeting Report: The Dallas Consensus Conference on Liver Transplantation for Alcohol Associated Hepatitis

Asrani, Sumeet K.[*,1,†]; Trotter, James[1,†]; Lake, Jack[2]; Ahmed, Aijaz[3]; Bonagura, Anthony[4]; Cameron, Andrew[5]; DiMartini, Andrea[6]; Gonzalez, Stevan[7]; Im, Gene[8]; Martin, Paul[9]; Mathurin, Philippe[10]; Mellinger, Jessica[11]; Rice, John P.[12]; Shah, Vijay H.[13]; Terrault, Norah[14]; Wall, Anji[1]; Winder, Scott[11]; Klintmalm, Goran[1]

Author Information

Liver Transplantation 26(1):p 127-140, January 2020. | **DOI:** 10.1002/lt.25681

TABLE 4. Listing Criteria and Program Components for LT for AH

	Primary criteria	Secondary considerations
AH assessment	First presentation with decompensated AH	No prior liver-related hospitalization
	Absence of severe medical comorbidities	• Assessment of frailty debility, and multiorgan failure • No other contraindications to LT
	Nonresponse to medical therapy	• Contraindications: disease severity, multiorgan failure, infection, renal failure, and low likelihood for response • Consider nonresponders using Lille score ≥0.45 or worsening of liver function by days 4 or 7 • Monitor for signs of recovery after listing
AUD assessment	Establish acceptable risk of relapse as assessed by a multidisciplinary psychosocial team composed of a social worker and at least 1 addiction specialist	• Not intubated • Consider independent team of specialists in addiction, social workers, and mental health providers • Ideally first member of LT team to evaluate • Consider independent mechanisms for regional or local review
	Direct assessment of patient possible by an addiction specialist	• Not intubated or floridly encephalopathic
	A maximum of 1 prior failed attempt at rehabilitation	
	Lack of other active substance use/dependency or active untreated psychiatric disorder	
	Acceptance of diagnosis/insight	
	Commitment of patient/family to sobriety and formalized agreement to adhere to lifelong total alcohol abstinence	Establish contract and participation in addiction rehabilitation following transplant
	Presence of close, supportive family members or caregivers	
Committee decision making	Consensus of paramedical and medical staff	Consider blinded voting in committee deliberations Consider absolute consensus
Program components	Transparency in selection process	• Creation of internal policies/procedures consistently followed by the transplant program • Willingness to share, publish, or have policies/procedures reviewed by outside agents • Documentation of transplant program experiences with AH in CONSORT flow diagram, including those assessed for eligibility, those excluded and reasons for the exclusion, treatment responders, transplant outcomes, and elements of selection criteria • Enhanced reproducibility by use of standard definitions and common data elements • Consistent and timely structured data reporting
	Independent psychosocial assessment	• Mental health professional with addiction background/training • Mental health professional familiar with transplant process
	Structured post-LT follow-up mechanism in place	• Documentation of AUD management plan before and after LT • Dedicated addiction specialist/mental health professional for longitudinal management • Commitment for regular monitoring for alcohol use, PEth, and urinary ethyl glucuronide • Structured monitoring program for posttransplant alcohol relapse and, in the event of alcohol relapse, provide resources to assist the patient in recovery
	Mental health team	• Consider formal addiction education for transplant staff

Acute Alcohol Associated Hepatitis

Favorable Factors

1. Insight into addiction
2. Strong social support
3. Substitute activities
4. Perception of negative consequences of alcohol

Unfavorable Factors

1. Prior failed EtOH rehabilitation
2. Use despite negative consequences
3. Family history of alcoholism
4. History of alcohol dependence
5. Active psychiatric disease

Indications for Lier Transplantation

- End Stage Liver disease
- Hepatic Neoplasms
- Acute Liver Failure
- Metabolic disorders

Urea Cycle Disorder

Porphyria

Familial Amyloid polyneuropathy

Primary Hyperoxaluria

Phenylketonuria

Glycogen Storage Disease

How Do We Determine Severity of Disease?

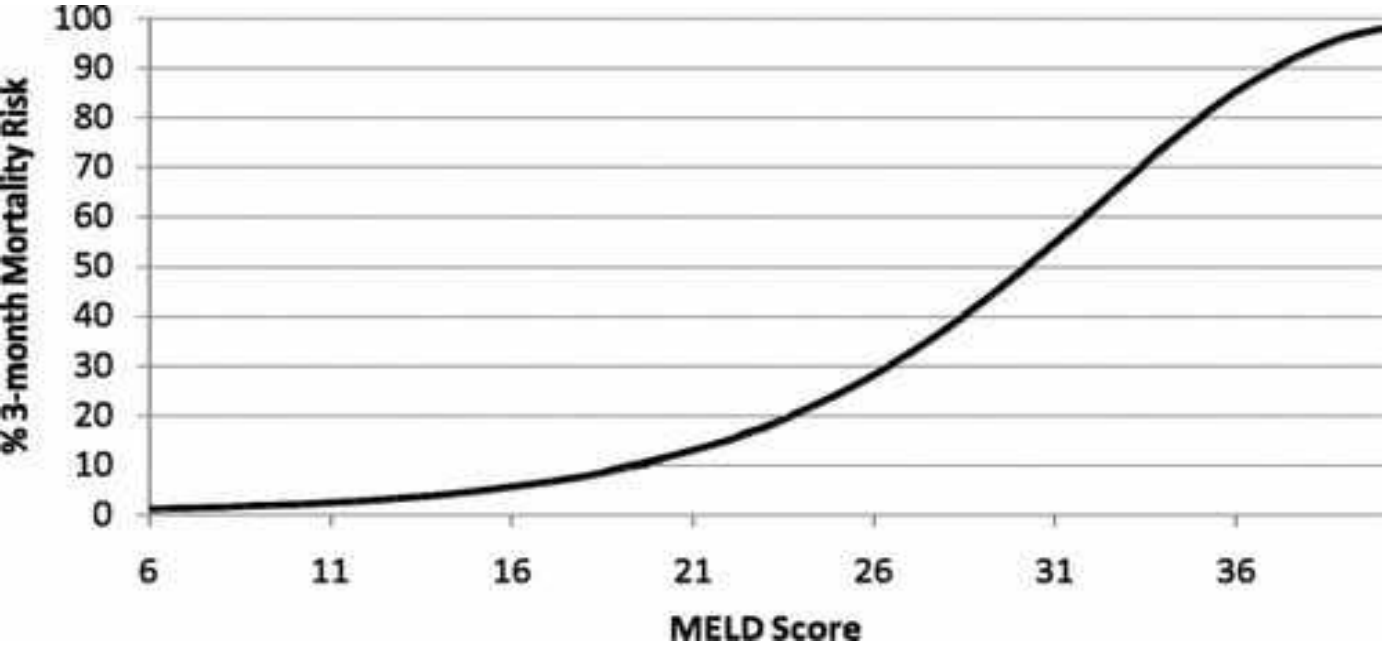
- Clinically
- Biochemically

  CPT Score

  MELD

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

MELD: Model for End-Stage Liver Disease

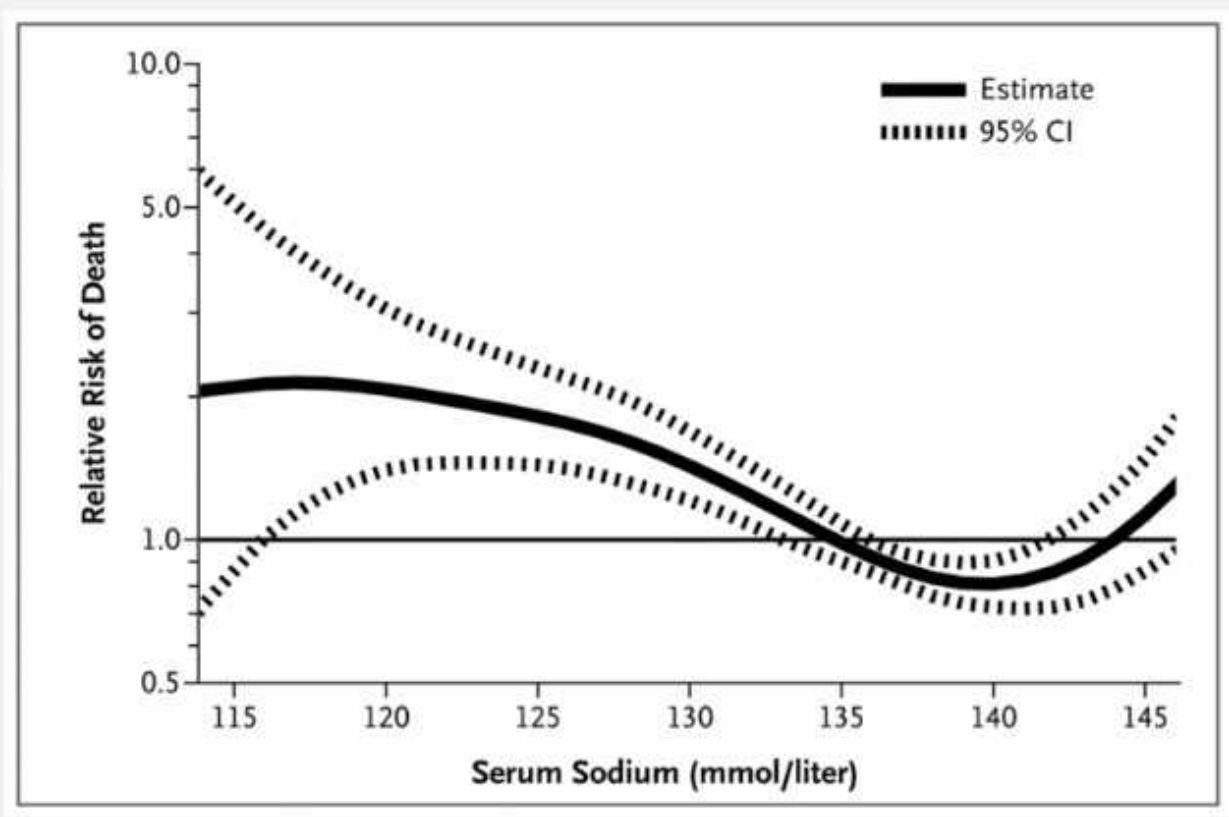


MELD = 3.8*loge(serum bilirubin [mg/dL]) + 11.2*loge(INR) + 9.6*loge(serum creatinine [mg/dL]) + 6.4

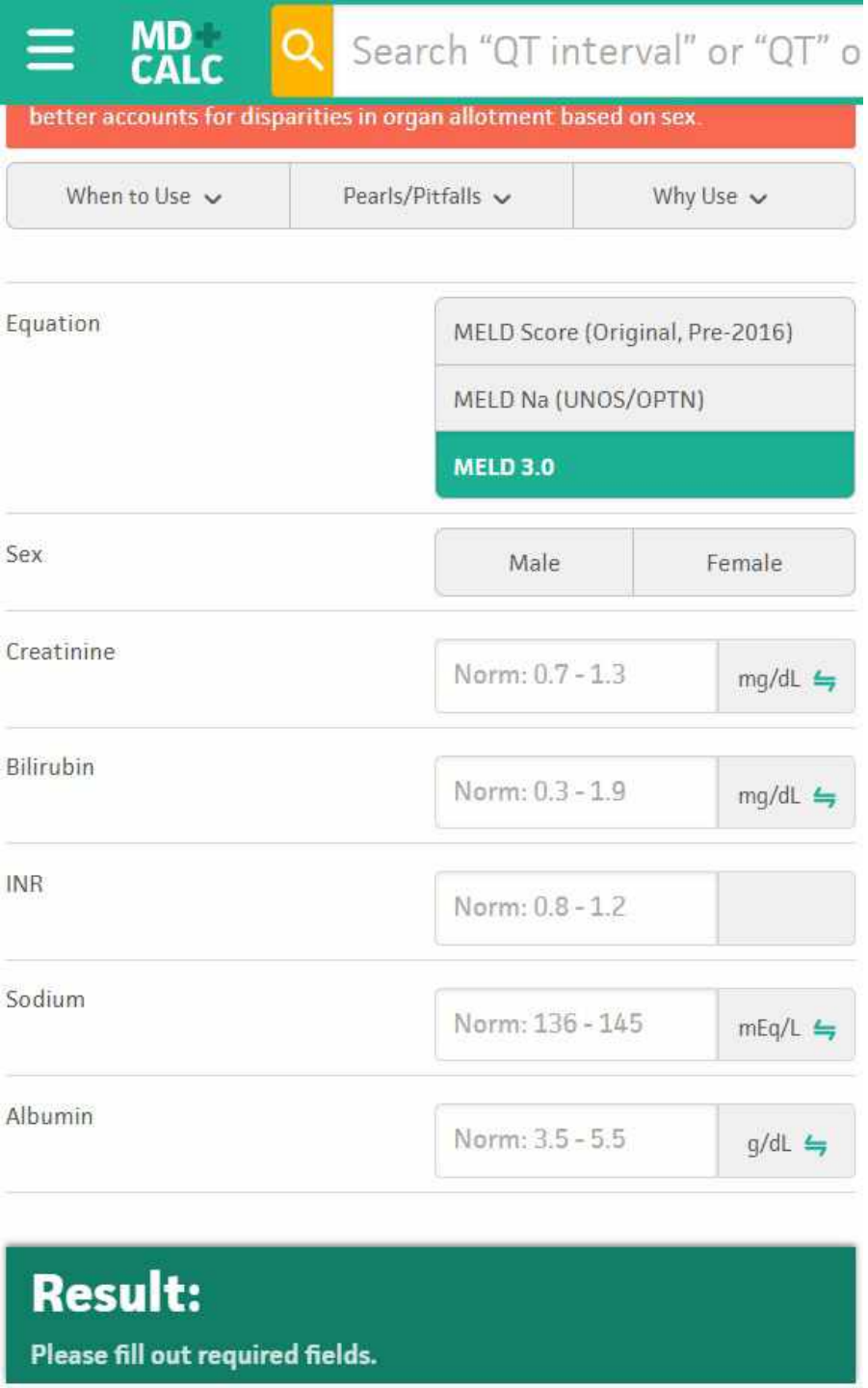
Max creatinine level = 4mg/dL (also assigned to HD)

- Initial use: Predict 3-month mortality after TIPS placement
- MELD uses laboratory values:
  1. Serum bilirubin
  2. INR
  3. Serum creatinine
- Range: 6 – 40
- MELD predicted survival of waitlisted patients
  - 2002 UNOS adopted as main allocation tool (priority on WL)

MELD-Na



- Na better predictive power for mortality than the MELD score alone.
  - Increased by 5% / mmol decrease (125 – 140 mmol/L)
- 2016 → UNOS updated allocation system to include sodium
- Limitations
  - Diuretics
  - IVF

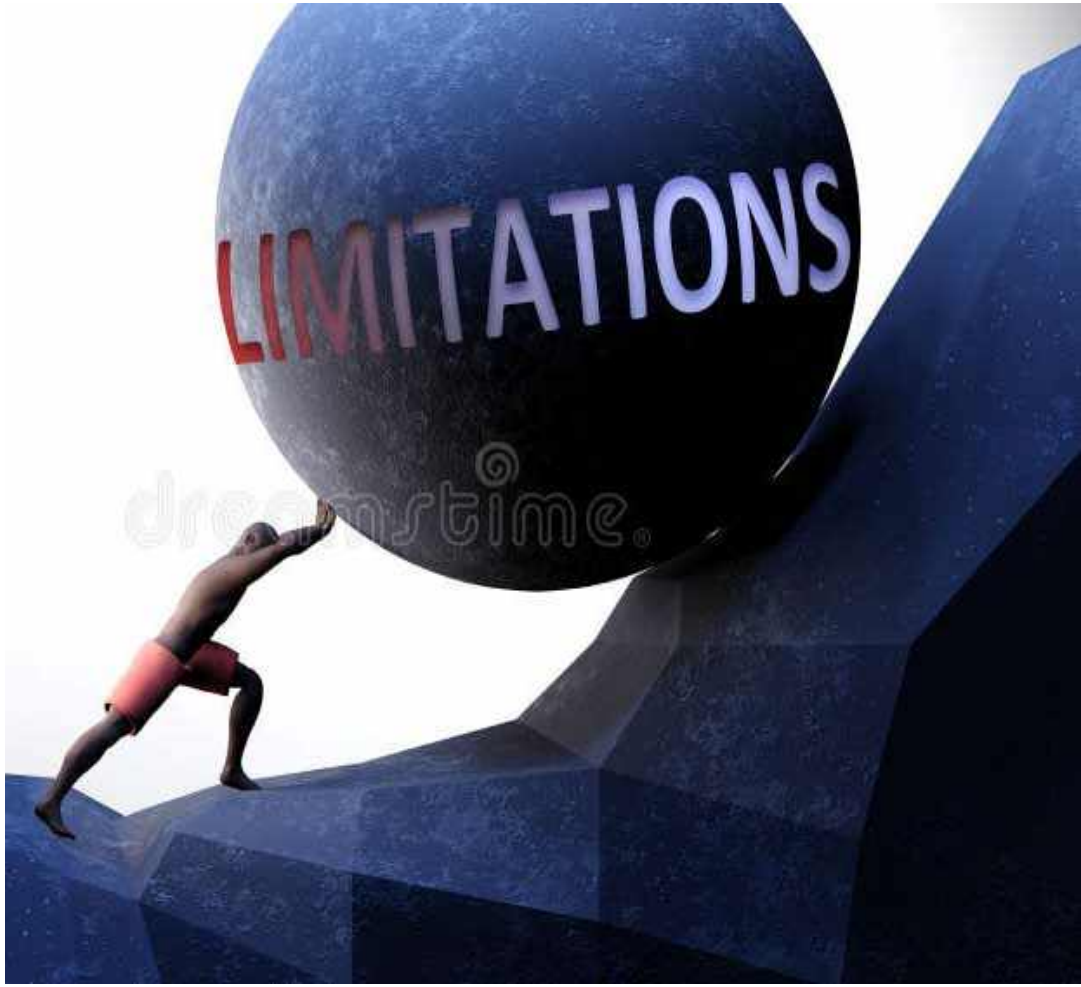


MELD 3.0

- Females compared to males
  - Decreased odds of LT within 3 years of listing
  - WL - Increased mortality and increased removal
- New Variable
  - Albumin
  - Gender
- Update on the coefficient of the variable
- Introduces interaction
  - Bilirubin and sodium
  - Albumin and creatinine
- Creatinine capped at 3.0 mg/dL

MELD Limitations

- Sodium
  - Diuretics and volume status
- Creatinine
  - Racial and gender disparities
  - Not true reflection of GFR
- INR
  - Varies according to thromboplastin reagent
  - Int'l sensitivity Index (ISI)
  - Vitamin K antagonist – Warfarin
- Bilirubin
  - Hepatitis C vs MASH



The Challenge of Liver Transplantation

- Organ shortage = Demand and Supply
  - Minimize waitlist mortality
  - Excellent post transplant survival
- Refinement of **allocation** policies
  - Allocation → Recipient
- Refinement of **distribution** policies
  - Distribution → Donors

Goals of Liver Transplantation

- Provide maximum benefit to patients with liver failure without no additional medical/surgical alternative for survival
- Likely prolongs life at least 5 years
- Restores patient to normal or near normal functional status

Liver Transplant Evaluation: Time to Refer

- EARLY REFERRAL IS BEST
  - Before life-threatening complication
- Cirrhosis
  - At first sign of decompensation
  - MELD > 10
  - MELD ≥ 15 – recommend listing
  - MELD > 35 – Increased mortality
- Hepatocellular carcinoma
- Hospitalized patient
  - Acute Liver Failure (fulminant)
    Encephalopathy
    Coagulopathy
    No prior history of liver disease
  - Acute on Chronic Liver failure
    Hepatorenal Syndrome
    Hepatopulmonary Syndrome
    Portopulmonary Hypertension

Patient Selection Criteria for Liver Transplant

- All LT candidates require evaluation for comorbidities
  - CV, respiratory, renal
  - Infections (fungal and parasitic)
  - Nutrition / Frailty
  - Anatomy
  - Neoplastic lesions
  - Social assessment
  - Psychiatric and addiction

- There is no formal age limit
  - Patients >65 years of age need a multidisciplinary evaluation

- LT has been performed successfully in patients >70 years
  - Increased risk of CV complications

Questions for Successful Liver Transplantation

- Can patient survive surgery/postoperative period?
- Can patient comply/adhere to complex medical regimen after transplantation?
- Comorbid conditions that can compromise patient/graft survival and make transplantation futile?

Absolute Contraindications for Liver Transplant

- Irreversible brain damage or neurological deficit
- Advanced/Incurable cardiopulmonary or other systemic disease
- Multi-system failure not correctable by liver transplantation
- Active extrahepatic malignancy (not skin cancer)
- Active infections
- Active substance abuse and non-adherence
- Psychosocial concerns / Lack of adequate social support
- Anatomic abnormalities
- Frailty / Malnutrition

Relative Contraindications to Liver Transplant

- Age
- Prior Treated Extrahepatic Malignancies
- BMI
- Recent infection with Multidrug Resistant Organism

Liver Transplant Selection Committee

- Review of history and physical
- Review of psychosocial interview
- Review of laboratory studies

- Determination of medical need & psychosocial clearance
- May be accepted, declined, or deferred

Liver Transplant Selection Outcomes

Not Candidate

Defer

Candidate

Delisting Criteria

- Patient transplanted
- Recovery of Native Liver Function
- Patient would not derive survival benefit
    - Transplant risks outweigh benefits
- Substance abuse
- Loss of social support

Liver Allocation

- All candidates sorted in the following order
  - Status/MELD
  - Blood type
    - Identical → Compatible → Incompatible
  - Distance from the Donor Hospital
  - Time
    - Wait time at current MELD
    - Time since submission on initial approved MELD exception
    - Total waiting time

Liver Transplant Evaluation: What Can My Patient Do?

- Social Support
- Get involved in chemical dependency treatment program if indicated and DOCUMENT attendance
- Lose weight (BMI<35 recommended) – Control of comorbid conditions
- Quit smoking NOW
- Avoid narcotic use if possible
- Methadone should NOT be a barrier to transplantation
- Improved nutrition

Summary

1. Cirrhosis and portal hypertension are different
2. MELD score is the most objective tool for severity of liver disease
3. Not all MELD score are the same
4. Refer patients with cirrhosis early
5. Liver transplantation is a process

Panel Discussion

Moderator: Stephen Harrison, MD, FACP, FAASLD

Raj Vuppalanchi, MD

Elliot Tapper, MD

Moises Nevah Rubin, MD

Break & Exhibits

10:05 AM – 10:20 AM

Steatotic Liver Disease (SLD)
New Nomenclature: Implications and Implementation

Meena B. Bansal, MD
Professor of Medicine
System Chief, Division of Liver Diseases
Director, MASLD/MASH Center of Excellence

Desert Liver Conference
March 2, 2024

Disclosures

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- Consultant/Advisory Board: Madrigal, Theratechnologies, NOVO Nordisk, Intercept, The Kinetix Group, Fibronostics, Merck, GSK

Agenda

- Rationale for change
- Reaching Consensus
- Implications
- Implementation

The evolution of NAFLD nomenclature

1980

Term "NASH" coined by Ludwig et al.

2002

First AASLD STC on NAFLD: Alternatives to name discussed

2020

Metabolic dysfunction associated fatty liver disease (MAFLD) proposed

- Calling 'what it is v. what its not'
- Stigma from alcohol in name
- Positive diagnosis
- Recognize close relationship with metabolic disorders

Gastroenterology 2020;158:1999–2014

MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease



Mohammed Eslam[1] *Arun J. Sanyal*[2] *Jacob George*[1], *on behalf of the International Consensus Panel*

Acknowledgments
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The evolution of NAFLD nomenclature

2020

Metabolic dysfunction associated fatty liver disease (MAFLD) proposed

- Calling 'what it is v. what its not'
- Stigma from alcohol in name
- Positive diagnosis
- Recognize close relationship with metabolic disorders

2020

MAFLD defined and promoted as the new nomenclature

- **Elimination of 'steatohepatitis'**
- **Allowance of more liberal alcohol use**

Concern raised over validity of process and impact of MAFLD name and definition change

HEPATOLOGY

AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 73, NO. 3, 2021

From NAFLD to MAFLD: Implications of a Premature Change in Terminology

- Concern over validity of process
- Impact on disease awareness and stigma
- Drug/biomarker development
- Impact of alcohol
- Lack of clarity on metabolic dysfunction
- Adaptability to emergence of disease phenotypes

JOURNAL OF HEPATOLOGY

A new definition for metabolic dysfunction-associated f… disease: An international expert consensus statement

…LD as well)

Vlad Ratziu[1], Mary Rinella[2,*], Ulrich Beuers[3], Rohit Loomba[4], Quentin M. Anstee[5], Stephen Harrison[6], Sven Francque[7], Arun Sanyal[8], Philip N. Newsome[9,*], Zobair Younossi[10]

[1]Sorbonne Université, Hôpital Pitié-Salpêtrière, Institute for Cardiometabolism and Nutrition (ICAN) and INSERM UMRS 1138 CRC, Paris, France; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, the Netherlands; [4]NAFLD Research Center, University of California at San Diego, La Jolla, CA, USA; [5]Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; [6]Pinnacle Clinical Research, San Antonio, TX, USA; [7]Department of Gastroenterology and Hepatology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; [8]Division of Gastroenterology, Virginia Commonwealth University, Richmond, VA, USA; [9]National Institute for Health Research Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, UK; [10]Inova Medicine, Inova Health System, Falls Church, VA

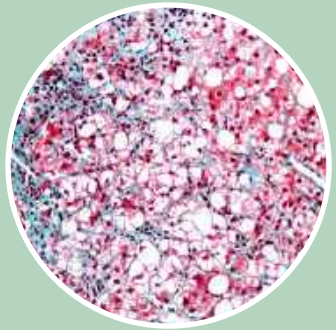
Eslam et al. Gastroenterology 2020; Eslam et al. J Hepatol 2020; Younossi et al. Hepatology 2021; Ratziu et al. J Hepatology 2021

Global NAFLD Nomenclature involvement

- 264 nominees from EASL, AASLD, ALEH, APASL, AMAGE, proportionate to association member size
- 56 countries represented

Renaming NAFLD: Key Questions to Address

What are issues with current nomenclature and can they be addressed?



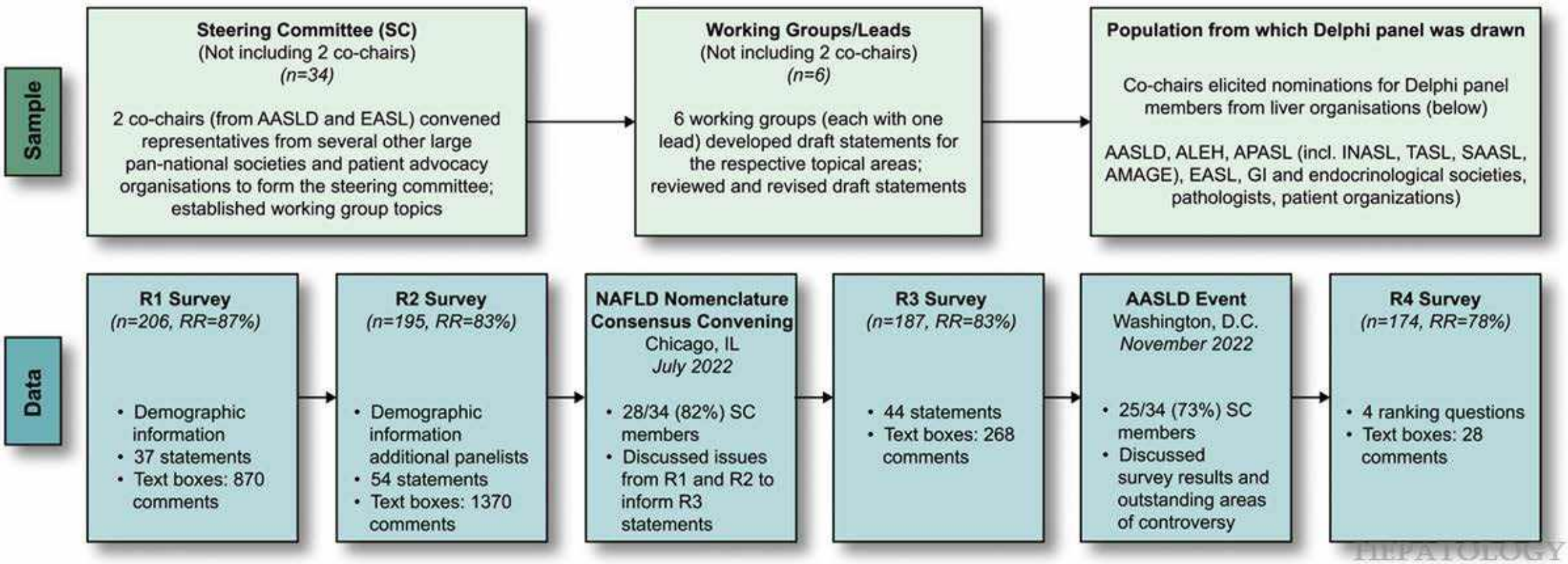
What is the importance of steatohepatitis in disease definition and endpoints?

How should the role of alcohol be accounted for (or not)?

How might name change impact disease awareness, clinical trials and regulatory approval pathways?

Can an alternate name reduce heterogeneity and allow for future advances ?

Summary of the DELPHI Process



Rinella, Mary E; Lazarus, Jeffrey V; Ratziu, Vlad; Francque, Sven M; Sanyal, Arun J; Kanwal, Fasiha; Romero, Diana; et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology ():10.1097/HEP.0000000000000520, June 24, 2023. | DOI: 10.1097/HEP.0000000000000520

Areas of strong consensus (>80%)

Role of Steatohepatitis

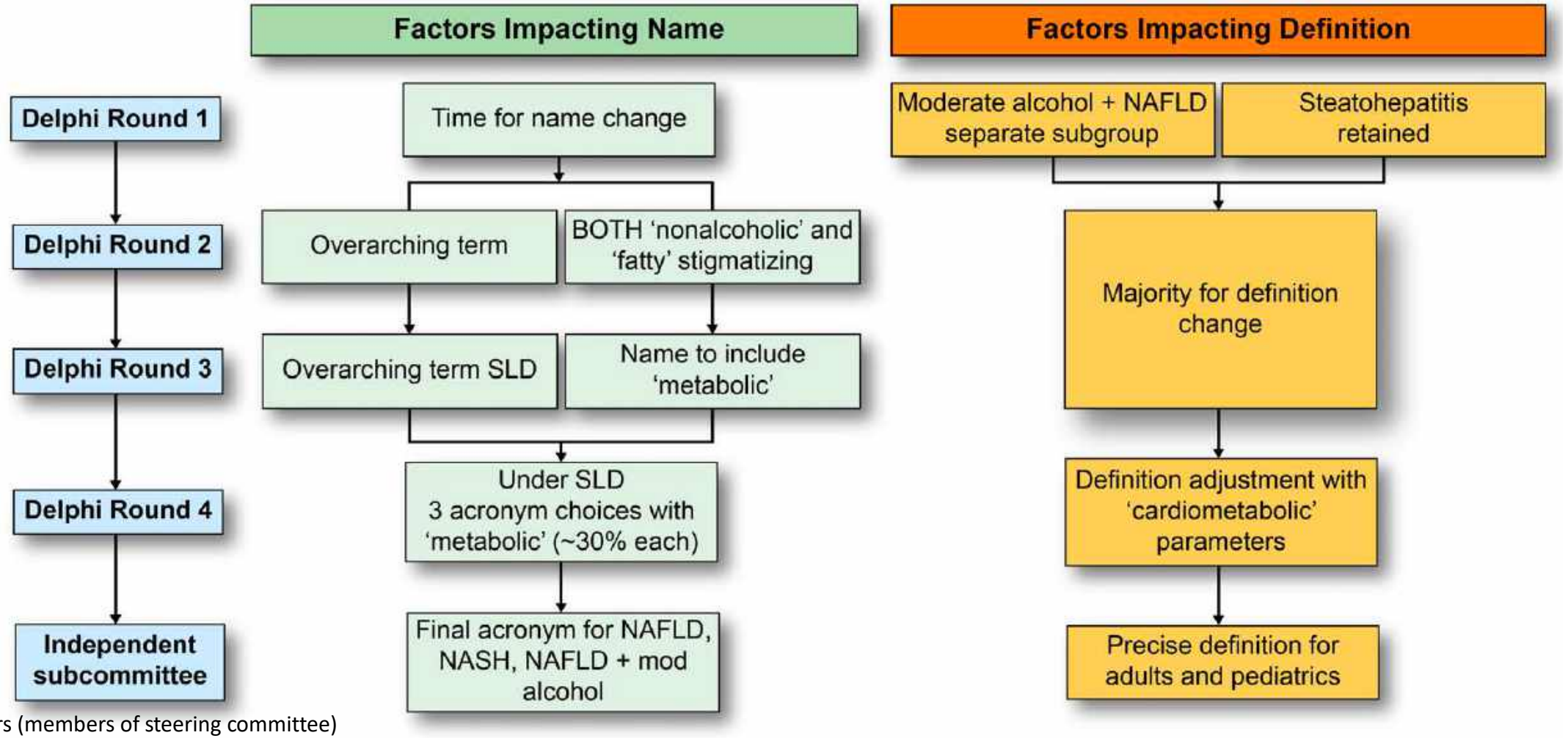
- The distinction between steatosis and **steatohepatitis has prognostic implications**
- NASH resolution should remain an important classifier of disease activity **(93%)**

Disease classification

- Those with steatosis without Met RF should be characterized separately (81%)
- The term ‘metabolic dysfunction’ highlights a central aspect of disease pathophysiology **(86%)**

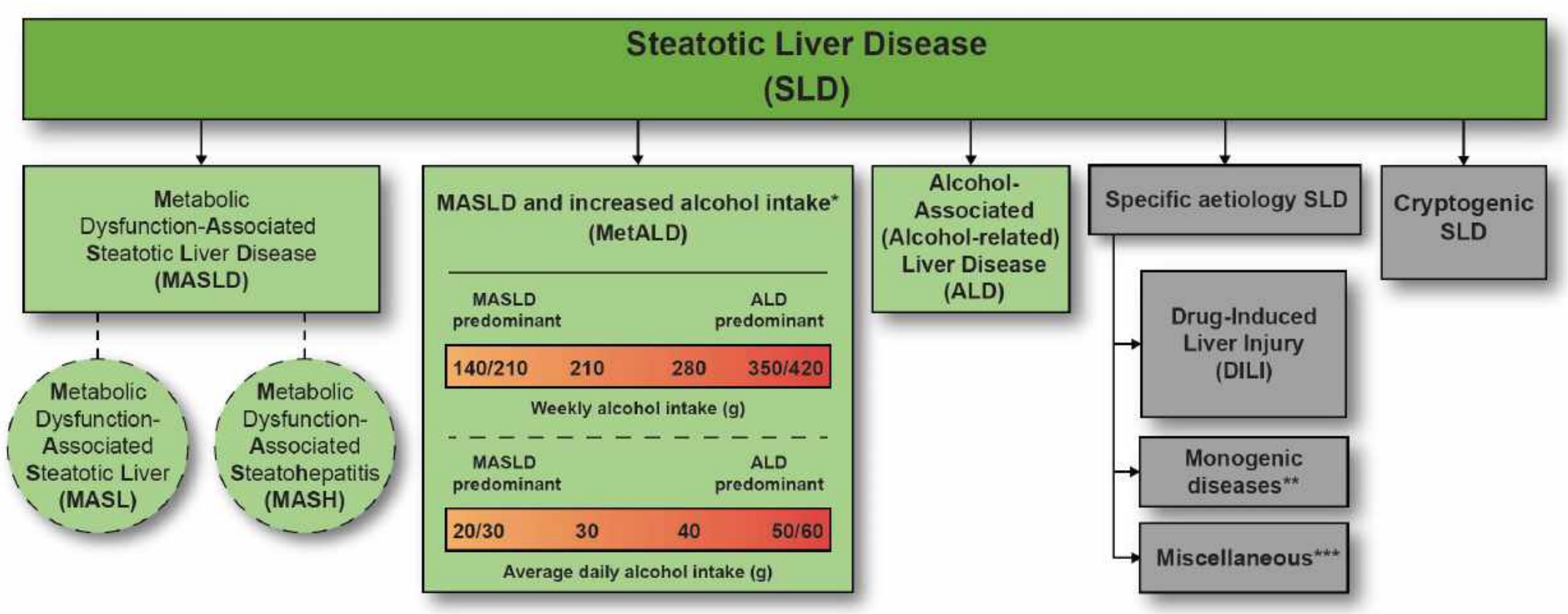
Role of alcohol

- 30-60 g/day of EtOH alters natural history of disease **(95%)**, may alter response to therapeutics **(90%)**
- 30-60 g/day in combo with Met RF should be an independent category **(83%)**
- >60g/d + Met RF = ALD with Met dysfunction **(86%)**
- >60g/day (irrespective of Met RF) = ALD **(82%)**



2 chairs (members of steering committee)
13 new members who were content experts from hepatology, endocrinology, pediatrics and patient advocacy representatives

Consensus Nomenclature



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

Kanwal, Tetri, Loomba, Rinella. Metabolic dysfunction-associated steatotic liver disease (MASLD) in context: Implications for the AASLD clinical practice guidance on nonalcoholic fatty liver disease. Hepatology 2023*, in press;*

Adapted from Rinella, Lazarus, Ratziu…Newsome, on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature *Hepatology* 2023; Rinella et al. *Journal of Hepatology* 2023; Rinella et al. *Annals of Hepatology* 2023

Definition

- Affirmative set of diagnostic criteria for MASLD.
- Near universal agreement to err on side of being inclusive
- Minimize patient heterogeneity and be adaptable to future insights
- Simple, readily available and easily measurable parameters
- The diagnostic criteria were also selected to align with cardiometabolic risk factors already well established and validated in other metabolic health disorders
- The set of criteria for adults was then submitted to a subcommittee of five pediatric hepatologists who adapted them for the pediatric population

Power in Numbers

Overlap between NAFLD and MASLD

- Impact interpretation of previously published data?
- Impact on clinical trials?
- Impact on qualification of biomarkers?

Near complete overlap in biomarker population

Metabolic risk factor (MRF)	Entire database (N=2187)		Subcohort with all five MRF available (N=1369)
	Missing data* %, (n)	Criteria fulfilled#, % (n)	Criteria fulfilled#, % (n)
BMI ≥25 kg/m^2 OR waist circumference >94 cm (M) 80 cm (F)	2.2 (49)	96.7 (2 067)	98.4 (1347)
Fasting serum glucose ≥5.6 mmol/l OR HbA1c ≥5.7% OR type 2 diabetes OR treatment for type 2 diabetes	18.9 (413)	87.0 (1 544)	84.8 (1161)
Blood pressure ≥130/85 mm Hg OR specific antihypertensive drug treatment	24.5 (536)	84.7 (1 399)	82.5 (1130)
Plasma triglycerides ≥1.70 mmol/l OR lipid lowering treatment	15.3 (335)	74.8 (1 386)	77.8 (1065)
Plasma HDL-cholesterol ≤1.0 mmol/ (M) and ≤1.3 mmol/l (F) OR lipid lowering treatment	15.5 (340)	81.0 (1 496)	84.8 (1161)
No MRF present		1.6 (35§)	0.1 (1)
At least one MRF present		98.4 (2 152)	99.9 (1 368)
At least two MRFs present		89.8 (1 963)	97.7 (1 338)
At least three MRFs present		77.3 (1 690)	92.1 (1 261)
At least four MRFs present		58.3 (1 275)	79.3 (1 085)
All five MRFs present		37.1 (812)	59.3 (812)

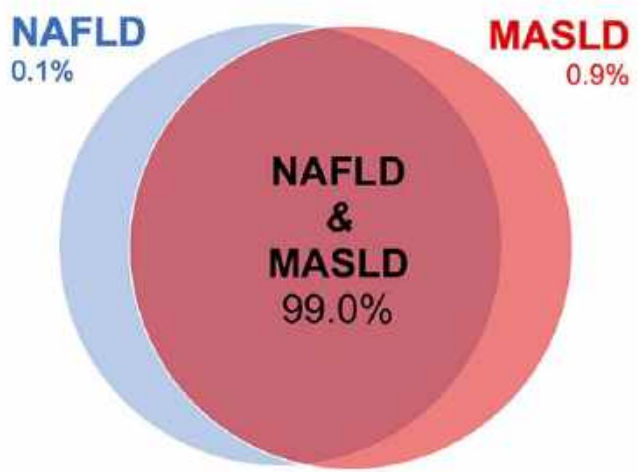
Pre-proof

- Data acquired for NAFLD are valid for MASLD
- Nomenclature change will not impact biomarker development

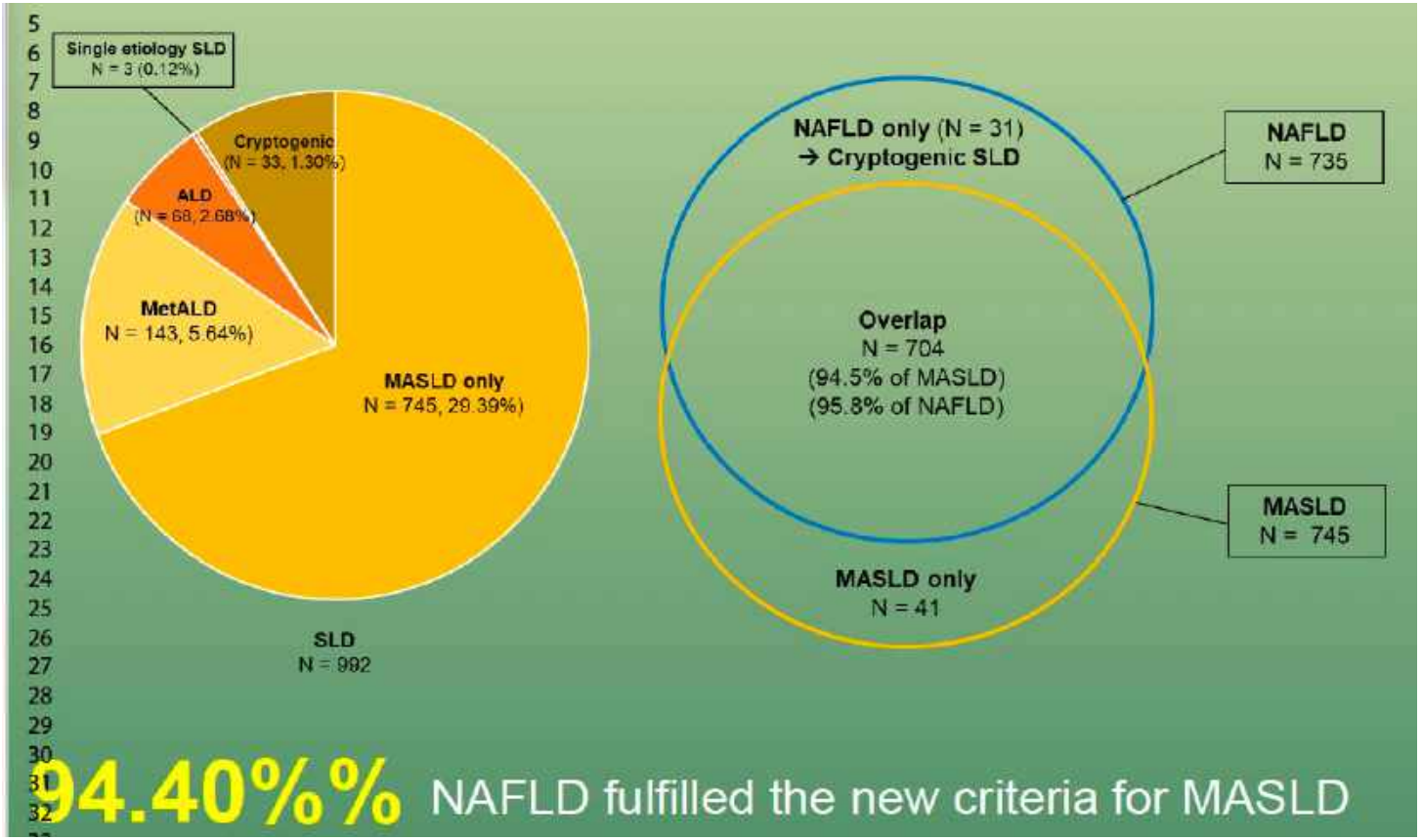
Ratziu et al. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. J Hep 2023

Excellent Overlap between NAFLD and MASLD

NHANES



Korean Primary Care Population



Lee C. et al. Prevalence, Distribution and Hepatic Fibrosis Burden of the Different Subtypes of Steatotic Liver Disease in Primary Care Settings Hepatology 2023; Lee, Dodge and Terrault, National prevalence estimates for steatotic liver disease and subclassifications using consensus nomenclature. Hepatology 2023

NIMBLE stage 1 circulating workstream study cohort derived from NASH CRN

		Stage 0 N= 222	Stage 1 N=114	Stage 2 N= 262	Stage 3 N= 277	Stage 4 N=198
Age (yrs)	Mean (SD)	47.8 (12.2)	48.1 (13.8)	51.7 (11.5)	54.4 (11.2)	56.2 (9.8)
Males	n (%)	99 (44.6%)	52 (45.6%)	102 (38.9%)	91 (32.9%)	60 (30.3%)
Caucasian	n (%)	158 (71.2%)	68 (59.6%)	199 (76.2%)	217 (78.9%)	169 (86.2%)
T2DM	n (%)	45 (20.3%)	41 (36.0%)	113 (43.1%)	162 (58.5%)	129 (65.2%)
BMI (kg/m2)	Mean (SD)	32.8 (6.6)	33.3 (6.1)	34.5 (6.3)	36.1 (6.6)	36.4 (7.3)
HbA1C (%)	Mean (SD)	5.8 (1.1)	6.0 (1.2)	6.4 (1.1)	6.7 (1.2)	6.7 (1.4)
AST (IU/l) ALT (IU/l) Alk phos (IU/l)	Mean (SD) Mean (SD) Mean (SD)	27.8 (13.3) 38.5 (25.4) 86.6 (30.5)	31.9 (17.7) 45.0 (34.6) 80.6 (28.2)	50.3 (29.3) 65.5 (43.1) 87.0 (28.0)	58.3 (39.8) 68.1 (47.8) 93.0 (33.2)	51.9 (28.9) 49.1 (34.5) 114.5 (53.2)
Bilirubin (mg/dl)	Mean (SD)	0.5 (0.3)	0.6 (0.5)	0.5 (0.3)	0.5 (0.4)	0.8 (0.8)
INR	Mean (SD)	1.0 (0.1)	1.0 (0.2)	1.0 (0.1)	1.1 (0.1)	2.8 (4.3)
LDL-Cholesterol (mg/dl)	Mean (SD)	117.5 (36.5)	105.9 (36.6)	112.0 (39.2)	106.1 (38.1)	100.7 (35.3)
NASH	n (%)	27 (12.2%)	91 (79.8%)	262 (100%)	277 (100%)	178 (89.9%)
NAS	Mean (SD)	2.5 (0.6)	2.5 (0.6)	4.8 (1.5)	5.2 (1.6)	4.2 (1.6)

7/1073 (< 1%) were reclassified as cryptogenic steatotic liver disease

Sanyal et al, Nature Medicine 2023; 29:2656–2664

NAFLD & MASLD Comparable

Swedish Cohort

*LITMUS

Table 1. Baseline characteristics and outcomes of patients with NAFLD and MASLD, respectively.

Parameter	NAFLD (n = 1,333)	MASLD (n = 1,329)
Age (years)	52 (40-61)	52 (40-61)
Sex (male)	780 (58.5)	777 (58.5)
Body mass index (kg/m^2)	29.3 (26.8-32.3)	29.3 (36.8-32.3)
FIB-4 score	1.04 (0.72-1.62)	1.04 (0.72-1.62)
Fibrosis stage[1]		
F0	223 (16.7)	223 (16.7)
F1	373 (27.9)	370 (27.8)
F2	211 (15.8)	211 (15.9)
F3	100 (7.5)	99 (7.5)
F4	55 (4.1)	55 (4.1)
NASH[1]	545 (40.9)	544 (40.9)
Cardiometabolic criteria		
Body mass index ≥25 kg/m^2	1,179 (88.5)	1,179 (88.7)
Insulin resistance*	809 (60.7)	809 (60.8)
Hypertension**	1,114 (83.6)	1,114 (83.8)
High triglycerides***	969 (72.7)	969 (72.1)
Dyslipidemia****	783 (58.7)	783 (58.7)
Outcomes		
Liver-related outcome	143 (10.7)	142 (10.7)
Overall mortality	402 (30.2)	401 (30.2)

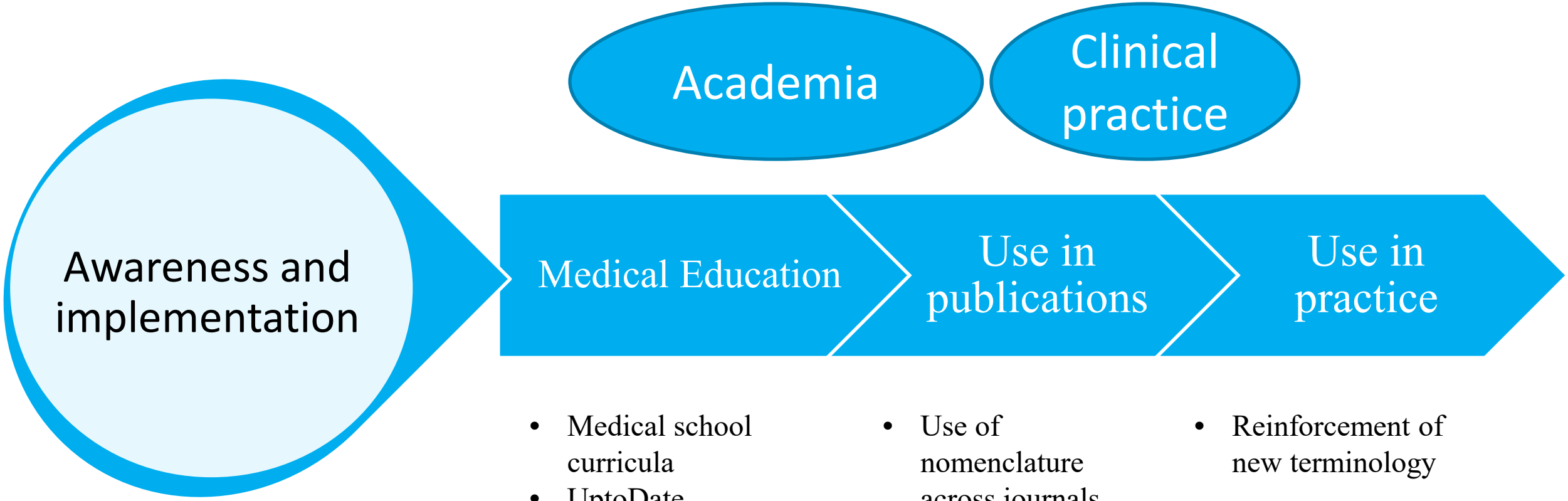
<2% of the Registry cohort would be ‘lost’ based on absence of any metabolic syndrome criteria as defined in the current document

[1] Hagstrom et al. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. J Hepatol 2023.

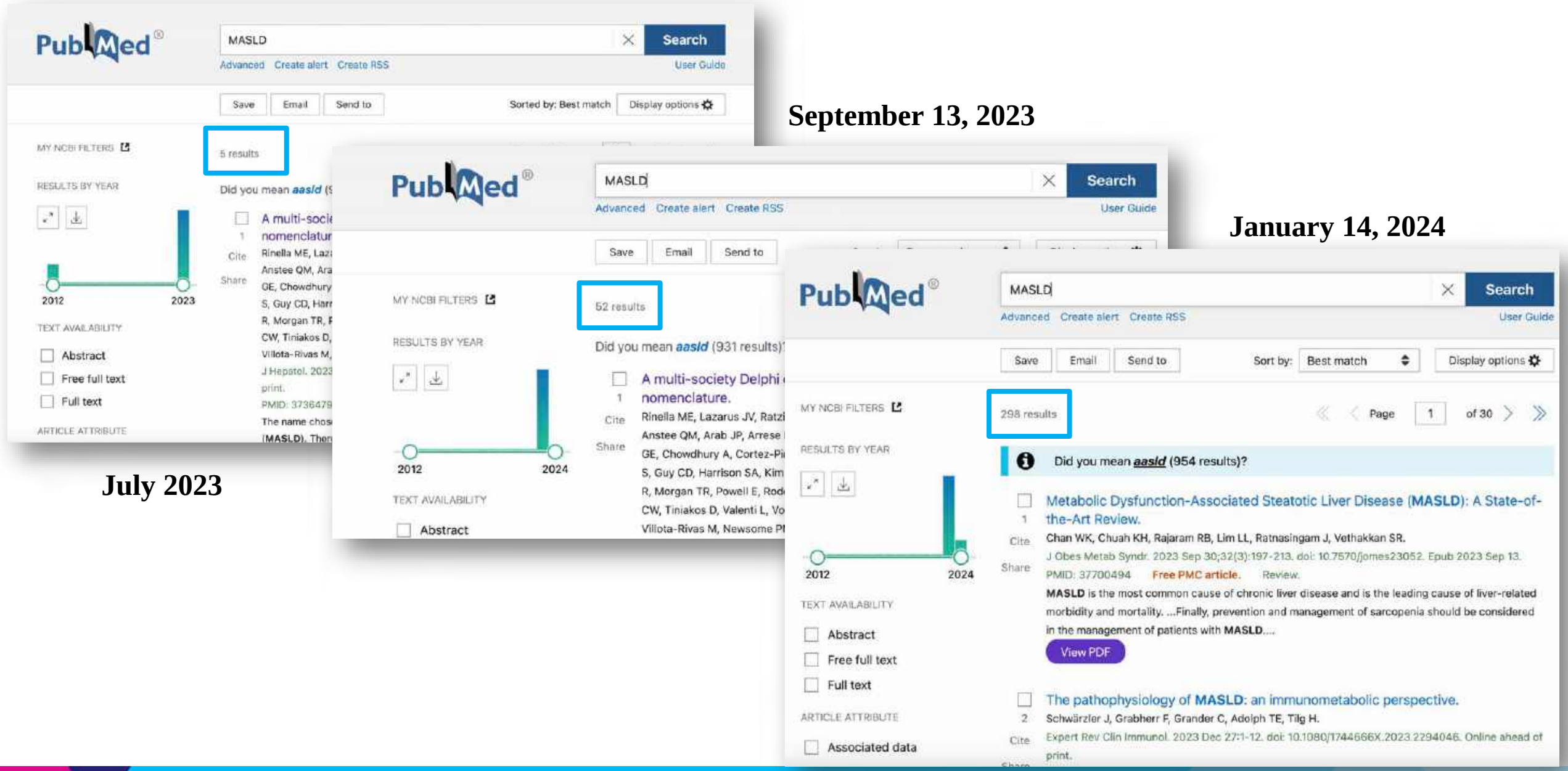
*Data courtesy of Quentin Anstee

MetALD

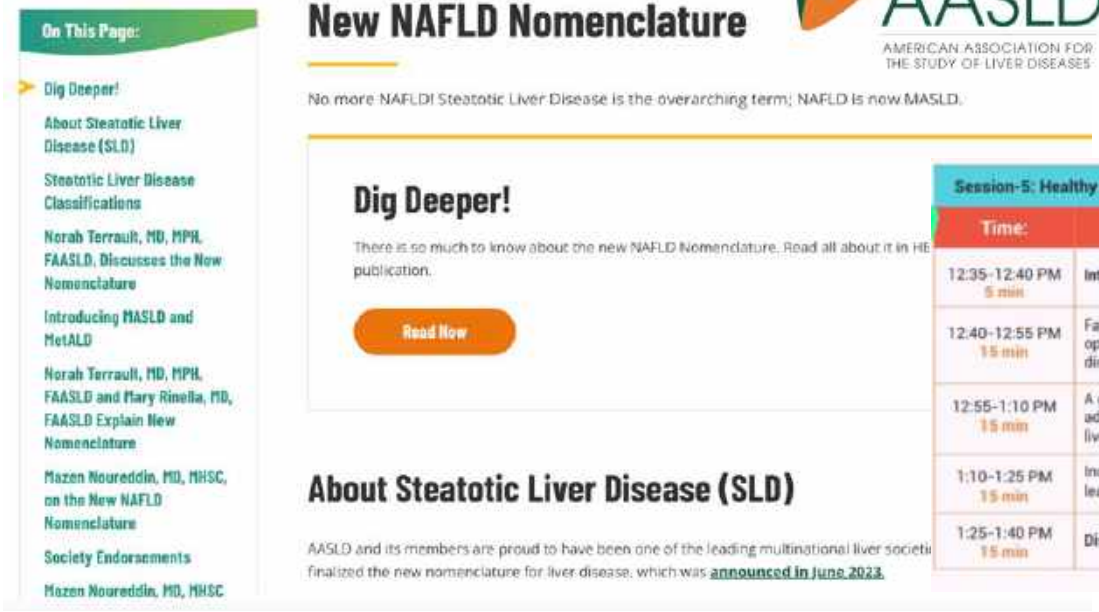
- Addresses the role of stigma
- ‘Elevates’ mutual importance of BOTH harmful alcohol use AND cardiometabolic risk as drivers of liver disease
- Opportunities for research
  - Inclusion into clinical trials
  - Personalized understanding of drivers of fibrosis progression rates
- Refine definition working with ALD partners


Academia
Clinical practice
Awareness and implementation
Medical Education
Use in publications
Use in practice
• Medical school curricula
• UptoDate
• Use of nomenclature across journals
• Editorials highlighting change
• Reinforcement of new terminology

Increasing use in scientific publications



Global adoption



- Webpage translated into Spanish, French, and Portuguese


AASLD
2023 MASLD Decision Tree
Explanations At A Glance
START HERE
Does the patient have elevated liver enzymes?
ALT> 33 males
ALT> 25 females
No
Yes
Does the patient have hepatic steatosis?
As identified by ...
Imaging
Biopsy
No
Yes
Have you ruled out Hepatitis B, C or other causes of chronic liver disease?
Yes
No
The patient has steatotic liver disease.
Does the patient have features suggestive of cirrhosis?
Does the adult patient meet any one of the cardiometabolic criteria?
No. it is likely not Metabolic Dysfunction Associated Steatotic Liver Disease.
No
Yes
Does the patient have hepatitis steatosis?
Check Hepatitis C Ab with Reflex to PCR
Hepatitis BsAg, sAb, cAb
Ceruloplasmin
Immunoglobulins
ANA, ASMA, AMA
Iron Studies
Celiac Antibodies
Alpha-1-AT levels
OR
Rule out other underlying etiologies of liver diseases
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
Does the adult patient meet any one of the cardiometabolic criteria?
No
You should investigate for other underlying liver etiologies
Yes
Your patient may have Metabolic Dysfunction Associated Steatotic Liver Disease cirrhosis.
*We also encourage you check for other discernable causes.
Yes
No
Are there any other causes of steatosis, such as ALD, Drug-Induced Liver Injury (DILI), Monogenic diseases or Miscellaneous (see SLD Classifications)?
Yes
No
Your patient may have cryptogenic SLD or possible MASLD.
See Practice Guideline
Does your patient regularly drink >50 g/day for females or >60 g/day for males?
Your patient has primarily ALD.
Does your patient regularly drink alcohol (140–350 g/week (20–50 g/day) for females or 210–420 g/week (30–60 g/day) for males)?
Yes
No
Your patient has Met-ALD.
*Multiple etiologies may coexist in a patient, thus exclude other causes of liver disease as appropriate.
Your patient has MASLD.
*Multiple etiologies may coexist in a patient, thus exclude other causes of liver disease as appropriate.

Govt

Public

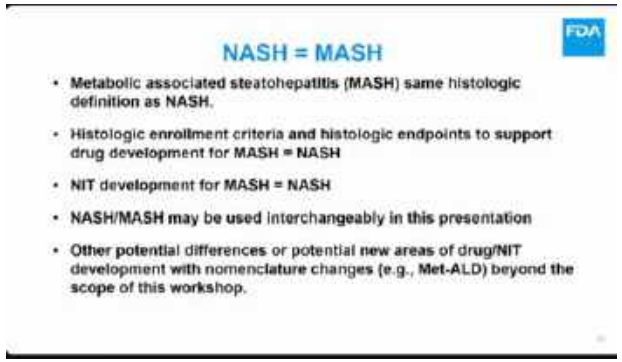
Global

High level adoption

Regulators

Industry

Billing/coding



- Ongoing trials
- Awareness campaigns
- New FDA filings

- Request submitted to ICD-10 classification team at CDC
- AASLD, EASL and ALEH working group to submit request to WHO

Implementation Plan Actions

Technical Implementation

- Understand what needs to be changed for EMR, EPIC, etc. and begin outreach to make those changes.
- Engage CMS to adjust coding and adopt quality metrics focused on screening high-risk populations for significant fibrosis in MASLD/MASH

Community Adoption

- Identify and develop clinical resources needed to help clinicians use and explain the new nomenclature to patients.
- Develop materials for institutions to help educate administrators.
- Draft papers for publication/articles for media explaining the nomenclature change and identifying what remains the same despite the nomenclature change.

Met-ALD Term Refinement

- Convene working group of MASLD and ALD experts to examine Met-ALD definition and make revisions/recommendations based on expert opinion.

DE&I Elevation

- Partner with minority health groups to develop patient and practice materials.
- Conduct seminars/speak at DE&I/minority conferences to engage community on MASLD.
- Establish presence (i.e., Booth participation) in adjacent specialty conferences and develop materials for dissemination.

Impact of New Nomenclature in a nutshell

Understanding disease and stigma

- If stigmatizing language can be avoided, it should
- Affirmative diagnosis reflecting disease underpinnings

Why SLD is helpful?

- Doesn't change the nature of the disease, clinical studies, or progress on NITs
- More inclusive construct that is expandable
- Sets the stage for more research and subclassifications

Progress on NITs and treatment

- No impact on natural history as NAFLD and MASLD fully overlap – 99%
- NASH=MASH
- Full overlap with biomarker and clinical trial populations

Introducing MetALD

- Previously ignored, MetALD patients will benefit from enhanced research and care pathways, ensuring no patient is left behind
- Opportunities for therapies targeting both diseases (e.g. cravings, genetic approaches)

Thank you!!

Meena.bansal@mssm.edu

All You Need to Know on Diagnosing MASLD: From Risk Stratification to Treatment Monitoring

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Professor of Medicine
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Houston Methodist Research Institute
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Director Houston Research Institute
CSO Summit Clinical Research
Houston, Texas

Disclosures

- Principal Investigator for a Drug Study: Allergan, Akero, BMS, Gilead, Galectin, Genfit, GSK, Conatus, Corcept, Enanta, Madrigal, Novartis, Novo Nordisk, Shire, Takeda, Terns, Viking and Zydus
- Advisory Board: : Altimmune, BI, Cytodyn, Corcept, 89BIO, GSK, Madrigal, Merck, Novo Nordisk, Northsea therapeutics, Terns and Takeda
- Stockholder: Rivus Pharma, Cytodyn, and ChronWell
- Associate Editor: Clinical Gastroenterology and Hepatology
- Federal funding: NIH/NIDDK (CO-I, Site PI)

Vino
49-year-old American who is of Italian and Mexican Descent

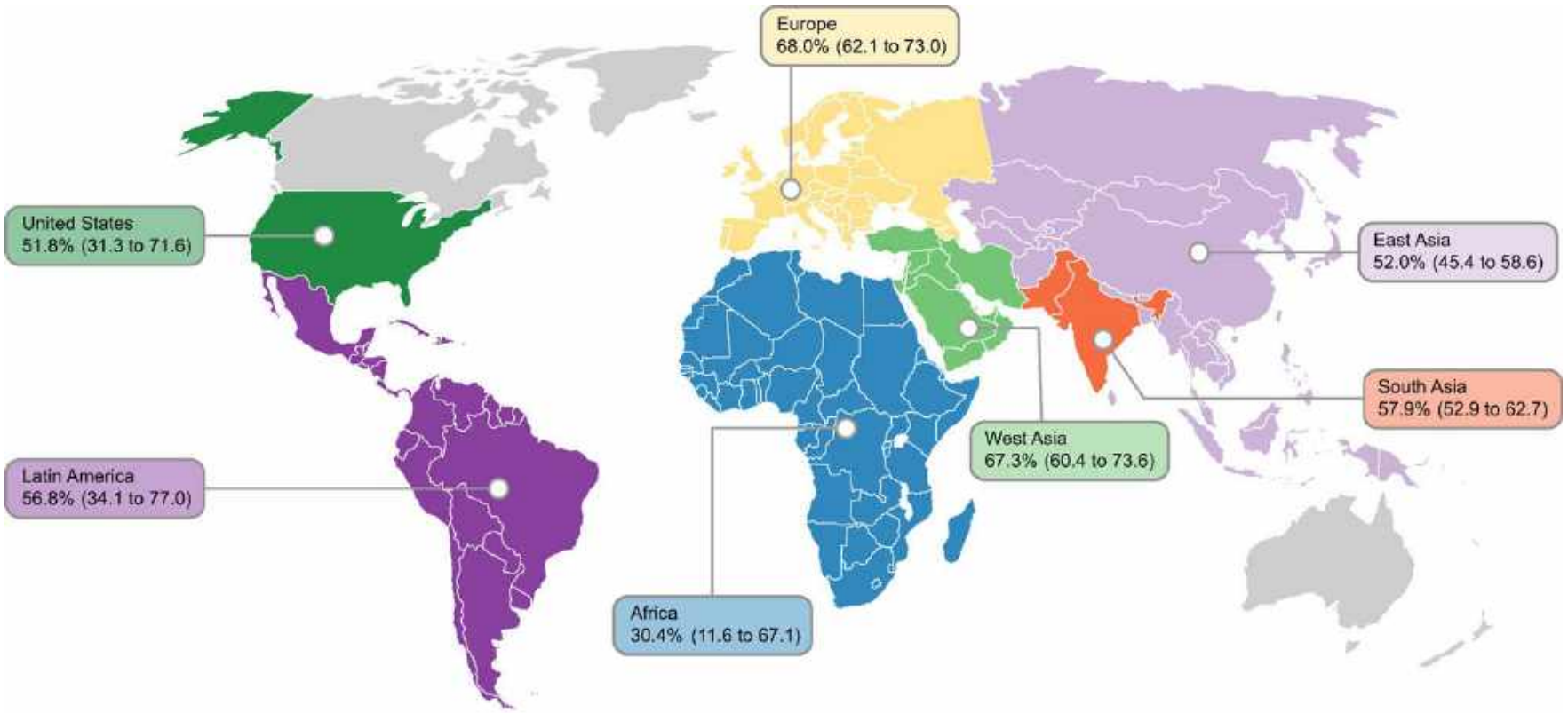
Vino presents to GI clinic referred by his PCP for assessment of his liver

- **Medical history:** T2DM x 15 yrs, dyslipidemia x 2 yrs
- **Family history:** Mother had diabetes and father had HTN
- **Social History:**
  - He doesn't exercise, but walks the dog daily
  - Works as a malpractice attorney
  - **Drinks 1 beer a day when he goes home**
- **Prior Exam** was normal except for central obesity (BMI of 33 kg/m2)
- **Symptoms:** Has some right upper quadrant discomfort
- **Medications:** Metformin 500 mg po twice a day and fish oil

Vino's Labs

Todays' Laboratory Values	
ALT	69 U/L
AST	77 U/L
Total Bilirubin	0.8 mg/dL
Albumin	4.0 g/dL
Platelets	175,000/µL
LDL	130 mg/dL
HDL	39 mg/dL
Triglyceride	240 mg/dL
Hgb A1C	6.9

Prevalence of NAFLD in Patients with Diabetes

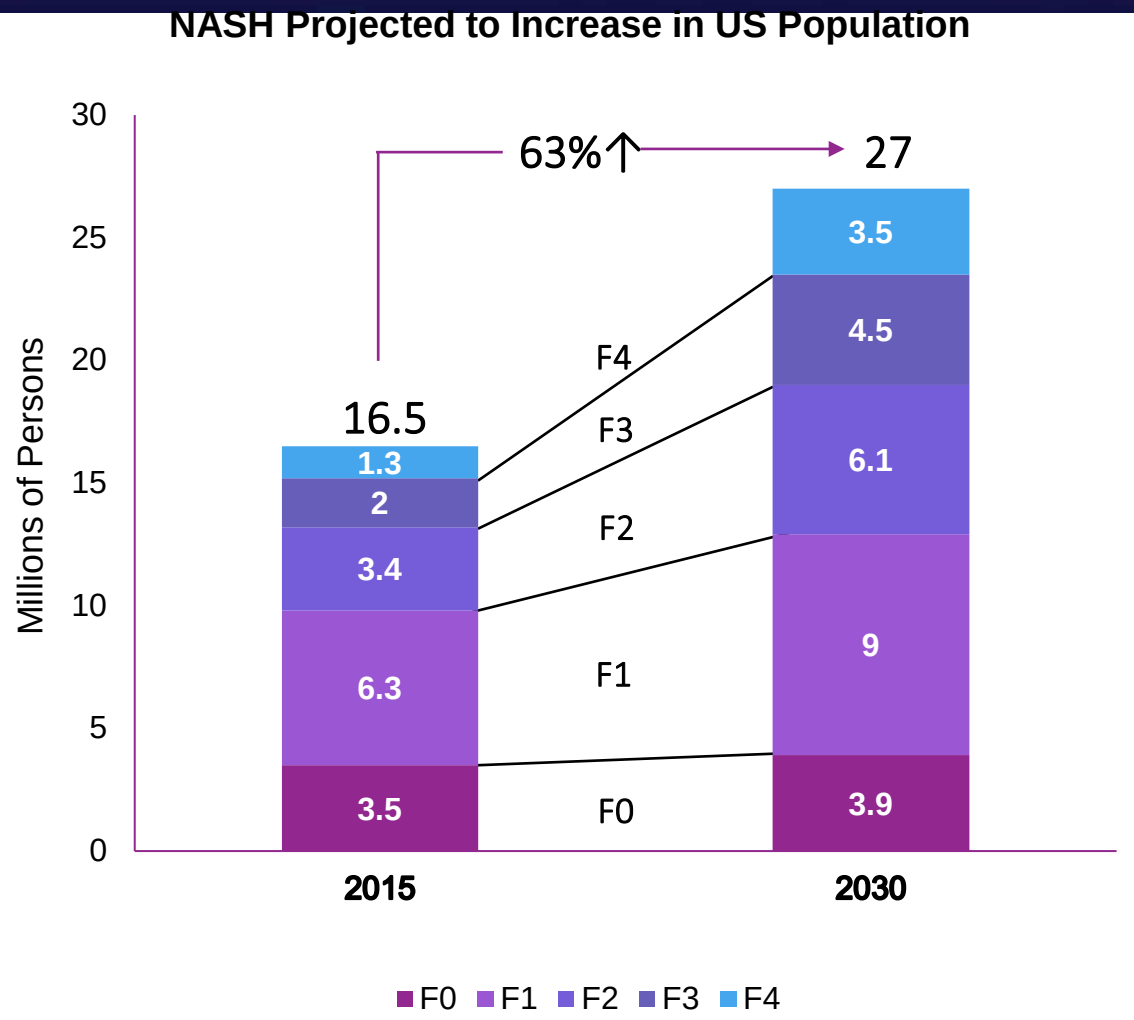


Global prevalence of NAFLD among T2DM patients 55.5%
(95% confidence interval: 47.3-63.7)

- Overall global prevalence of NASH among T2DM patients is 37.3%
- 17% of biopsied diabetics have advanced fibrosis (fibrosis ≥ F3)

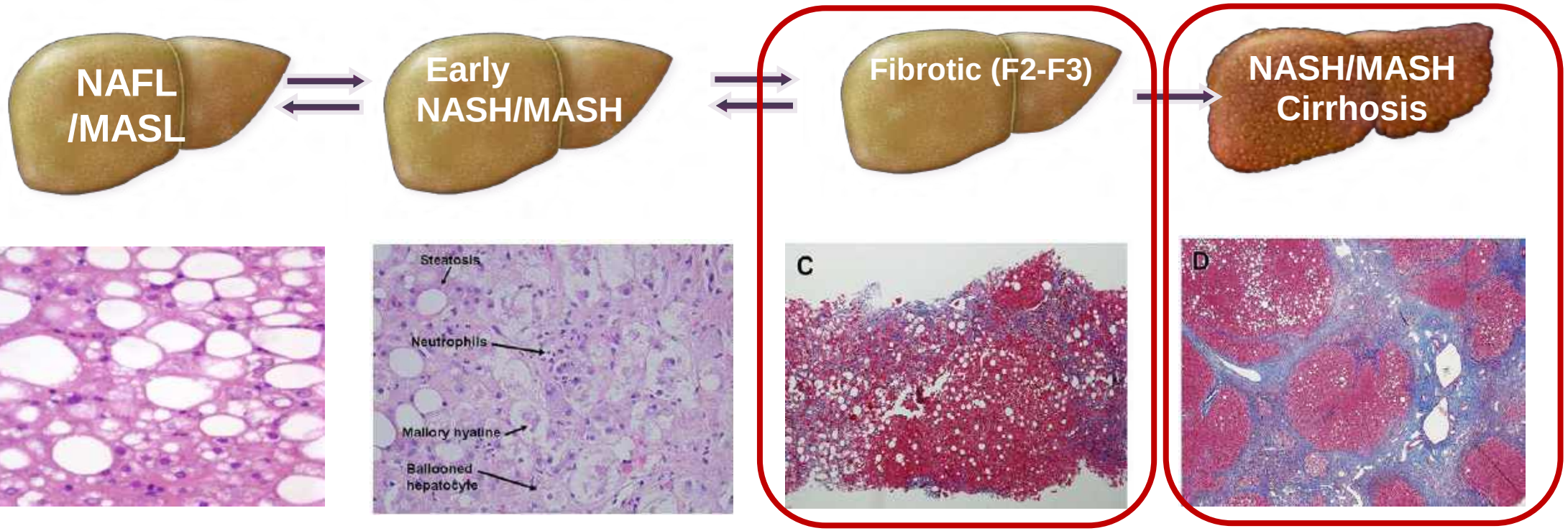
Younossi ZM, et al. J Hepatol. 2019;71(4):793-801.

Modeling The Epidemic Of Nonalcoholic Steatohepatitis Demonstrates An Exponential Increase In Burden Of Disease



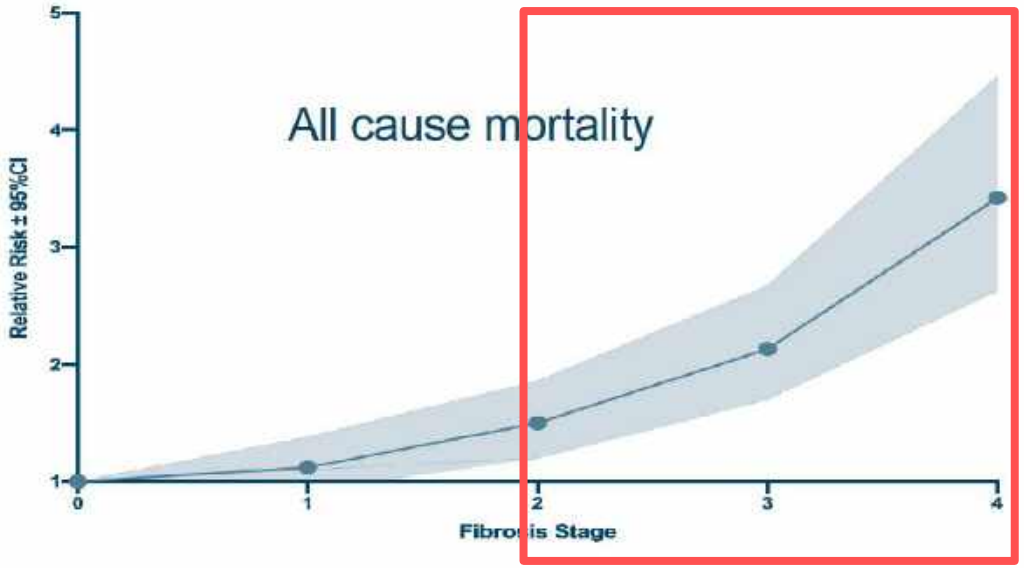
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Adapted from Estes C, et al. *Hepatology*. 2018;67:123-133.

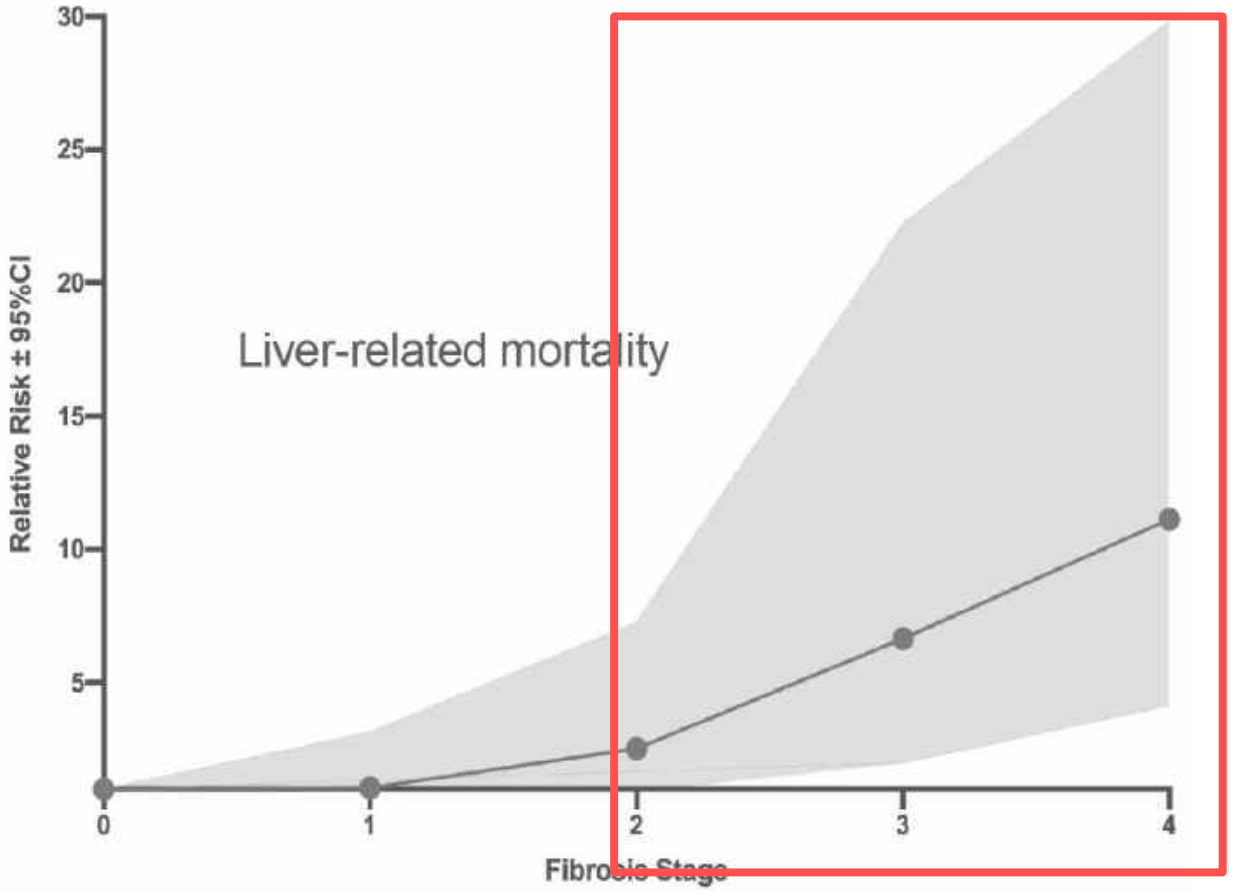
NAFLD/MASLD Rules: Natural History



NASH/MASH Rules: Baseline Fibrosis Stage Predicted Mortality and Time To Development of Severe Liver Disease

- Systematic review and meta-analysis of 13 studies 4,428 NAFLD patients (2,875 with histological NASH).





Taylor RS, et al. *Gastroenterol*. 2020;158:1611-25.

The NASH CRN Prospective Data

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

1773
Adults with nonalcoholic fatty liver disease
(median follow-up, 4 yr)

	Fibrosis Stage		
	F0 to F2 No, mild, or moderate fibrosis N=1237	**F3** Bridging fibrosis N=369	**F4** Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Increasing fibrosis stage is associated with increased risks of liver-related complications and death.

A.J. Sanyal et al. 10.1056/NEJMoa2029349

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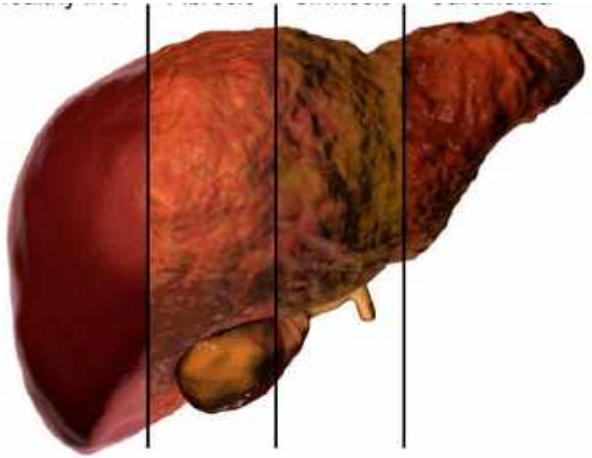
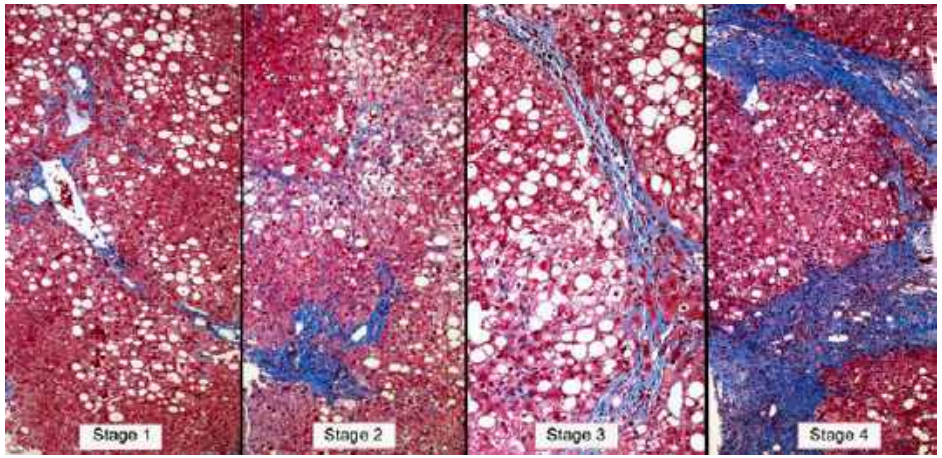
Non-Invasive Tests (NITs): Context of Use

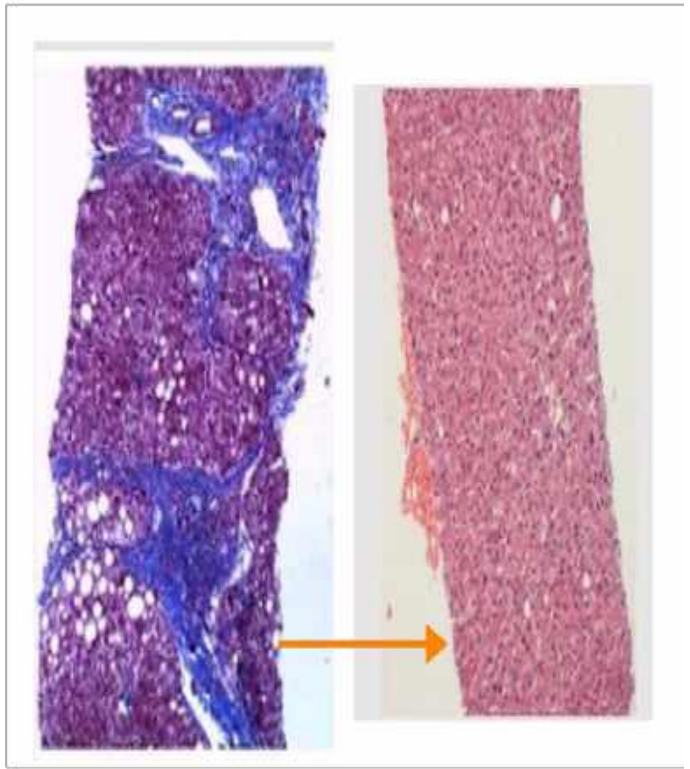
Fibrosis



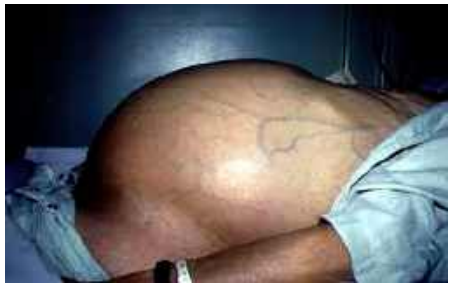
NASH/MASH with NAS ≥ 4 + ≥ F2

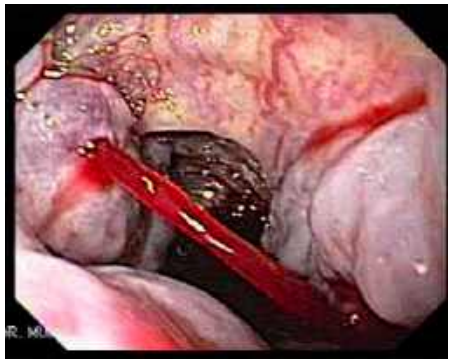


Monitoring Response to Therapy



Major Clinical Liver Events (MALO)





AGA 2021

Primary care, endocrinologists, gastroenterologists and obesity specialists should screen for NAFLD with advanced fibrosis

Step 1: Identify patients at risk

- 2 or more metabolic risk factors[1]
- Type 2 diabetes
- Steatosis on any imaging modality or elevated aminotransferases

Step 2: History & lab tests: Excessive alcohol intake, CBC, liver function tests

Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, ASLT, ALT & platelet count)

- FIB-4 <1.3
- FIB-4 ≥1.3 to 2.67
- FIB-4 >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

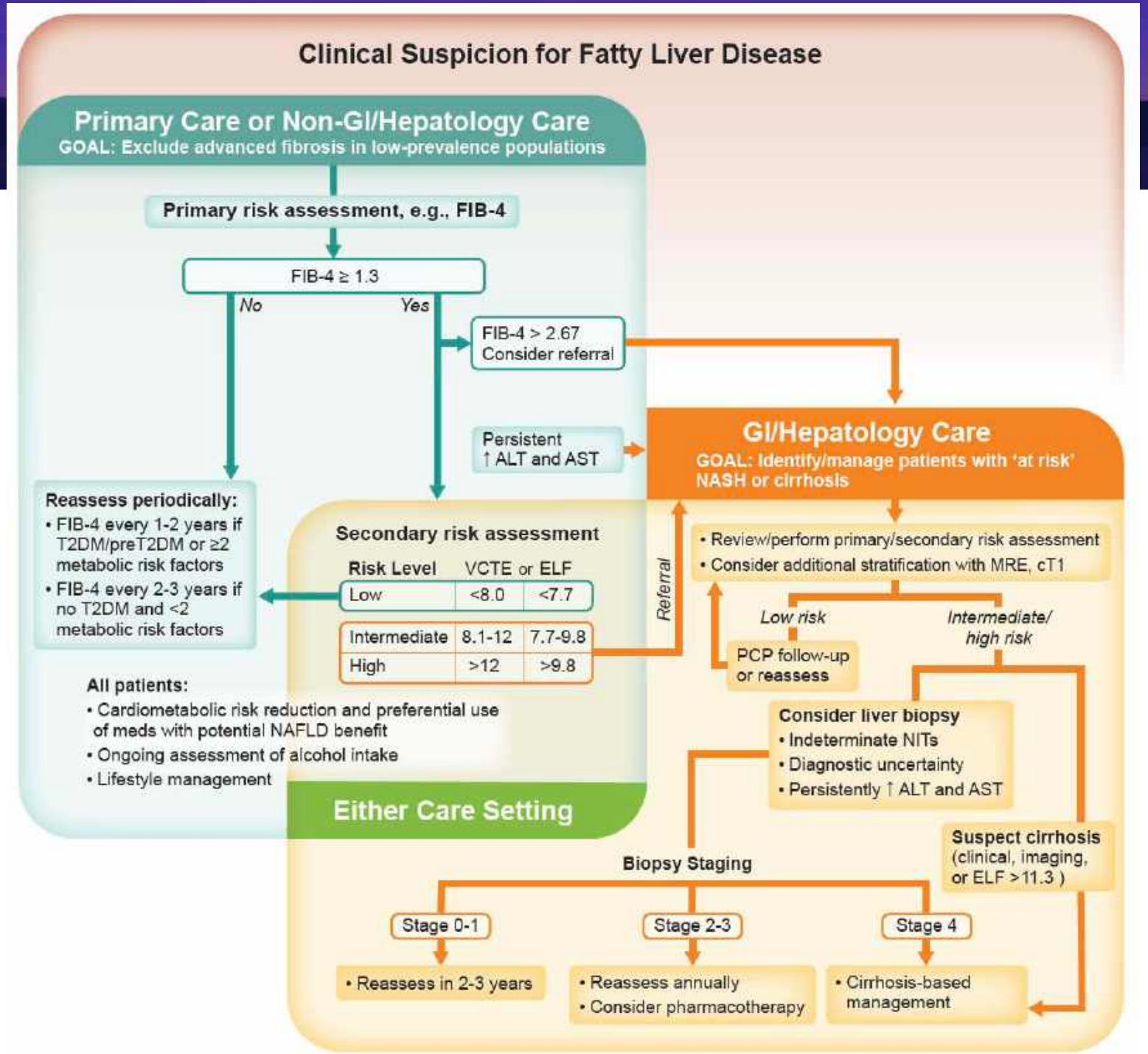
Indeterminate Risk
Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2–3 years

High Risk
Refer to hepatologist

1. Metabolic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes, or insulin resistance. 2. For patients age >65, use FIB-4 <2.0 as the lower cutoff. Higher cutoff does not change. 3. Other NITs derived from routine laboratories can be used instead of FIB-4. 4. Many online FIB-4 calculators are available such as https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. 5. Ultrasound acceptable if vibration-controlled transient elastography (VCTE, FibroScan®) is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasound who are indeterminate or high risk based on FIB-4. 6. LSM values are for VCTE (FibroScan®). Other techniques such as bidimensional shear wave elastography or point shear wave elastography can also be use used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI, or where LSM unavailable. 7. Eddowes et al. uses 8.2 and 12.1 kPa as cutoffs for LSM using VCTE. Valdiation of simple (rounded) cutoffs reported by Papatheodoridi et al.
Adapted from:

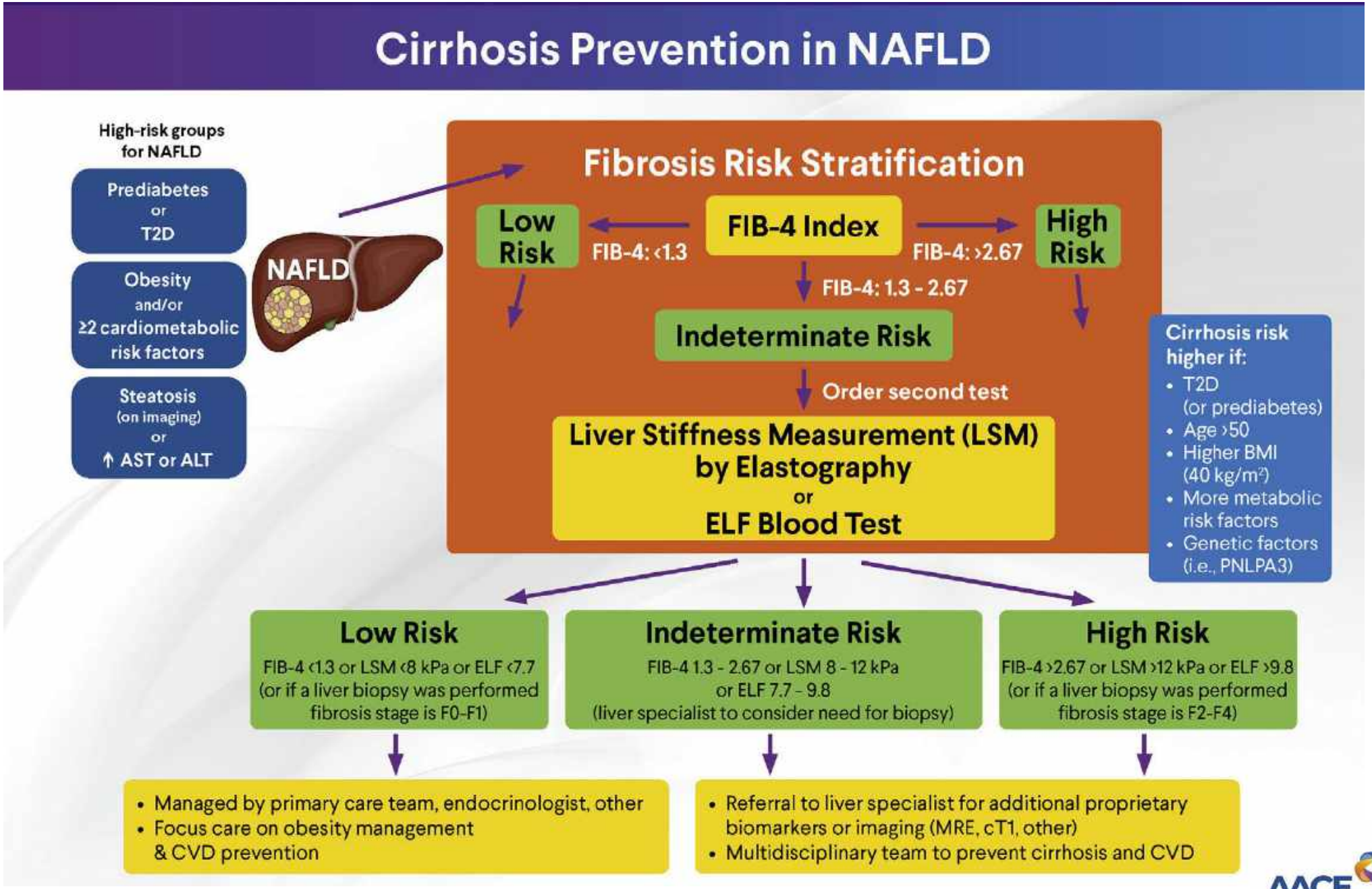
Kanwal F et al. Gastroenterol. 2021

AASLD 2023 Guidance



Rinella et al; Hepatology 2023

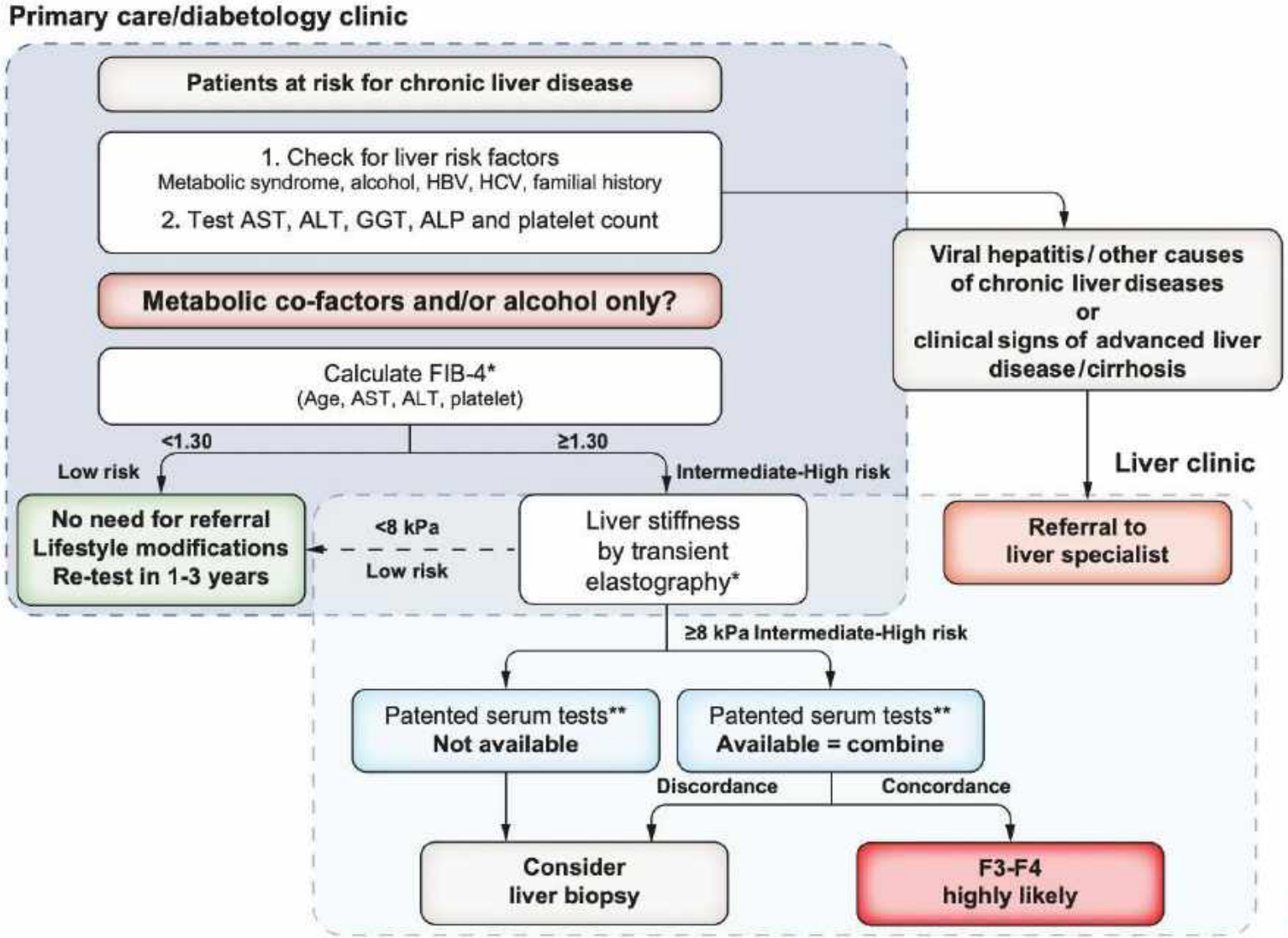
Cirrhosis Prevention in NAFLD



Cusi et al; Endo Practice 2022

EASL 2021

- Primary care providers are essential in identifying patients with NAFLD and referring them to specialists
- Studies have shown that PCPs screen asymptomatic individuals less often than specialists do



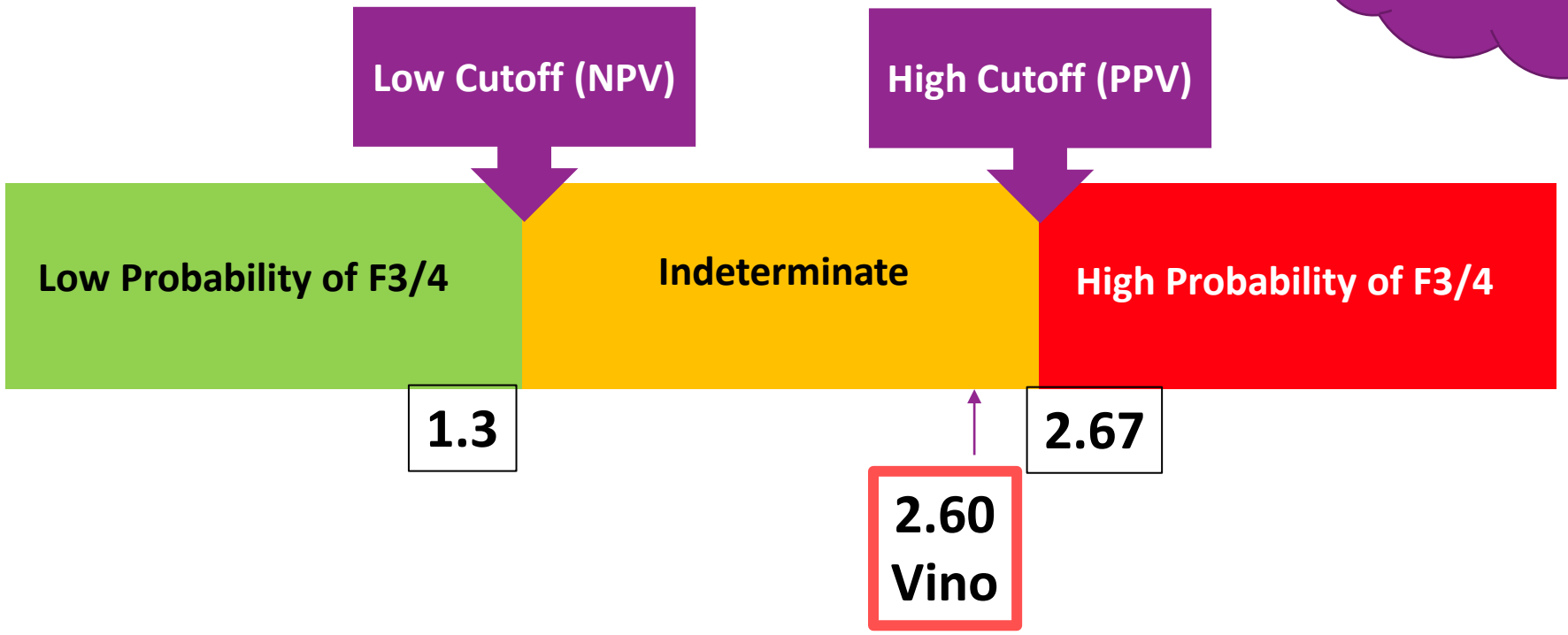
EASL. J Hepatol, 2021

FIB-4 for Predicting Presence of Advanced (F3/4) Fibrosis

FIB-4 Score

- = (**Age** * **AST**) / (**Platelets** * Sqrt (**ALT**))
- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)

Age >65
T2DM



Angulo et al. Hepatology. 2007; Sterling et al. Hepatology. 2006; McPherson et al. Gut. 2010

Vino’s FIB4 score: 2.60

The referral was appropriate

What is Next?


In the GI/Hepatology Office

	CAP (dB/m)	E (kPa)	
SD	MEAN	MEDIAN	IQR/Med
7			12%
	316	9.8	

218.0 lb

Unknown

AGA 2021

Primary care, endocrinologists, gastroenterologists and obesity specialists should screen for NAFLD with advanced fibrosis

Step 1: Identify patients at risk

- 2 or more metabolic risk factors[1]
- Type 2 diabetes
- Steatosis on any imaging modality or elevated aminotransferases

Step 2: History & lab tests: Excessive alcohol intake, CBC, liver function tests

Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, ASLT, ALT & platelet count)

- FIB-4 <1.3 → **Low Risk**
  Repeat NIT in 2–3 years unless clinical circumstances change
- FIB-4 ≥1.3 to 2.67 → **Indeterminate Risk**

Step 4: Liver stiffness measurement (LSM)[,5,6,7]

- LSM <8 kPa → **Low Risk**
  Repeat NIT in 2–3 years unless clinical circumstances change
- LSM 8 to 12 kPa → **Indeterminate Risk**
  Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2–3 years
- LSM >12 kPa → **High Risk**
  Refer to hepatologist

- FIB-4 >2.67 → **High Risk**
  Refer to hepatologist

1. Metabolic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes, or insulin resistance. 2. For patients age >65, use FIB-4 <2.0 as the lower cutoff. Higher cutoff does not change. 3. Other NITs derived from routine laboratories can be used instead of FIB-4. 4. Many online FIB-4 calculators are available such as https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. 5. Ultrasound acceptable if vibration-controlled transient elastography (VCTE, FibroScan®) is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasound who are indeterminate or high risk based on FIB-4. 6. LSM values are for VCTE (FibroScan®). Other techniques such as bidimensional shear wave elastography or point shear wave elastography can also be use used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI, or where LSM unavailable. 7. Eddowes et al. uses 8.2 and 12.1 kPa as cutoffs for LSM using VCTE. Valdiation of simple (rounded) cutoffs reported by Papatheodoridi et al.
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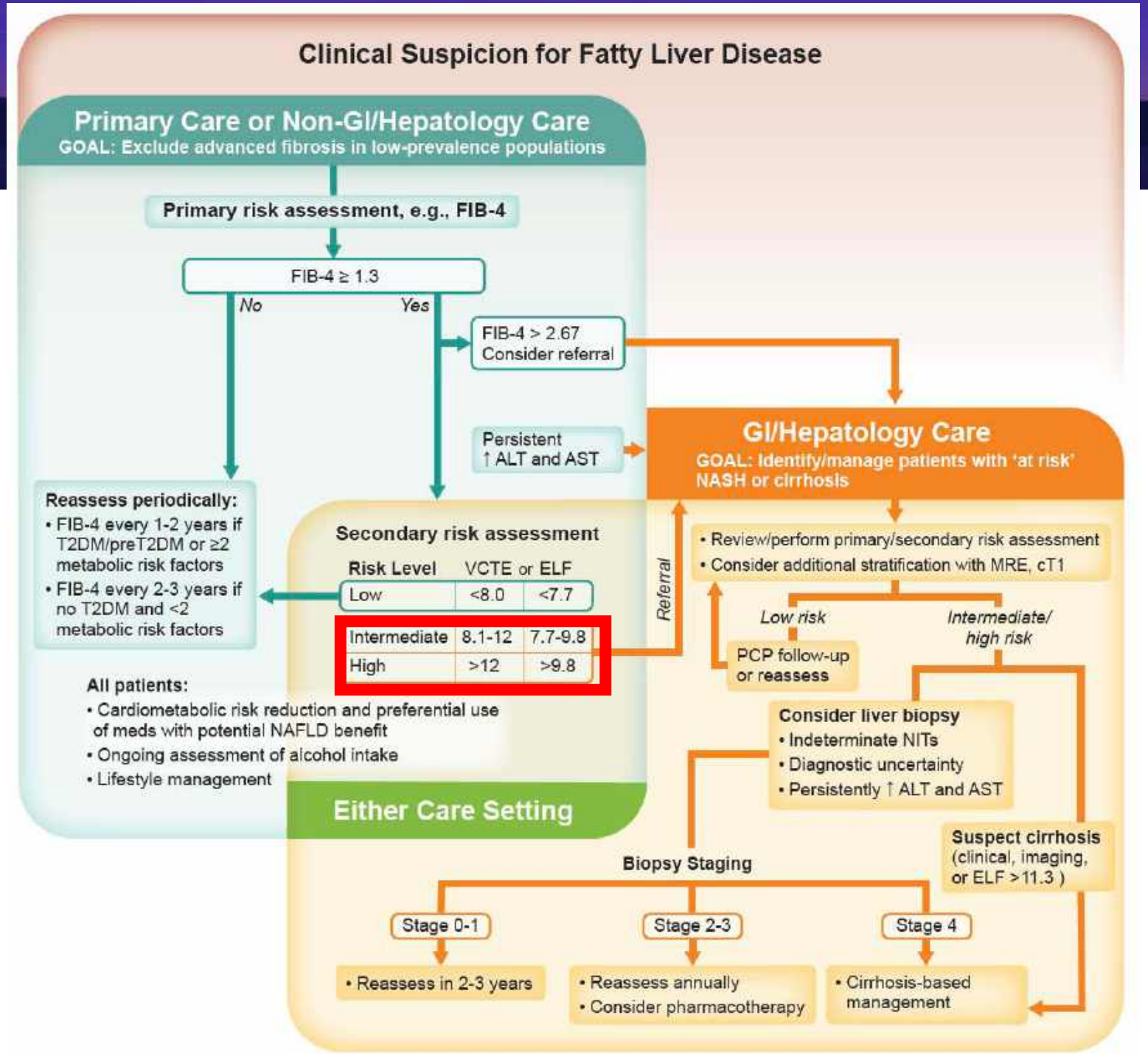
AASLD 2023



Rinella et al; Hepatology 2023

Imaging Techniques - VCTE

Vibration-controlled transient elastography (**VCTE**)

Fibrosis	Steatosis
Liver stiffness	**CAP**
• Obtained through a VCTE measurement • Correlated to extent of fibrosis	• Quantification of ultrasound attenuation obtained in VCTE measurement • Correlated to liver steatosis

Siddiqui MS et al. Clin Gastroenterol Hepatol. 2019 Jan;17(1):156-163.e2

VCTE: CAP Assessment for Steatosis

Sensitivity Priority Based Steatosis Assessment

383 NAFLD Subjects With CAP & Paired Biopsy

Steatosis Stage	Sensitivity Threshold (dB/m)	Sensitivity	Specificity	PPV	NPV
≥ S1	274	0.90	0.60	0.99	0.47
≥ S2	290	0.90	0.44	0.74	0.71
S3	302	0.90	0.38	0.45	0.87

Vino
316 dB/m →

The above threshold values are from the cited peer review publication. Clinical usage of threshold values are determined by the provider based on their preferred threshold value reference.

Eddowes et al; Gastroenterology (2019) https://www.gastrojournal.org/article/S0016-5085(19)30105-2/pdf

VCTE: Youden's Index Based Fibrosis Assessment

384 NAFLD Subjects With VCTE & Paired Biopsy

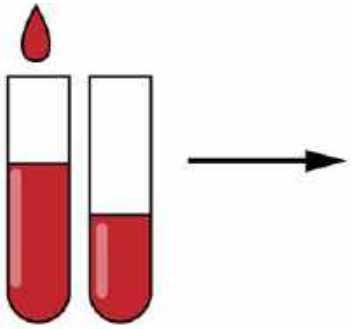
Fibrosis Stage	Youden's Threshold (kPa)	AUROC	Sensitivity	Specificity	PPV	NPV
F0-F1 vs ≥ F2	8.2	0.77	0.71	0.70	0.78	0.61
F0-F2 vs ≥ F3	9.7	0.80	0.71	0.75	0.63	0.81
F0-F3 vs F4	13.6	0.89	0.85	0.79	0.29	0.98

Vino 9.8 kPa

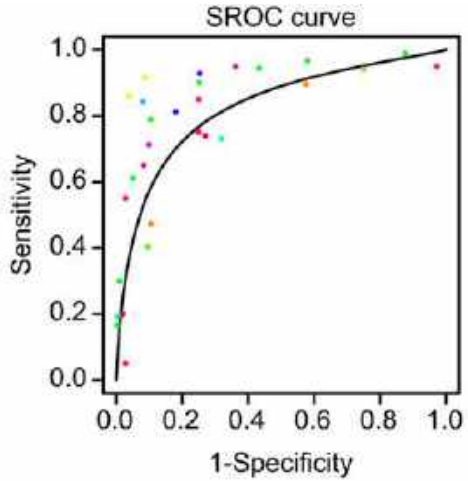
The above threshold values are from the cited peer review publication. Clinical usage of threshold values are determined by the provider based on their preferred threshold value reference.

Eddowes et al; Gastroenterology (2019) https://www.gastrojournal.org/article/S0016-5085(19)30105-2/pdf

Serum Tests – ELF



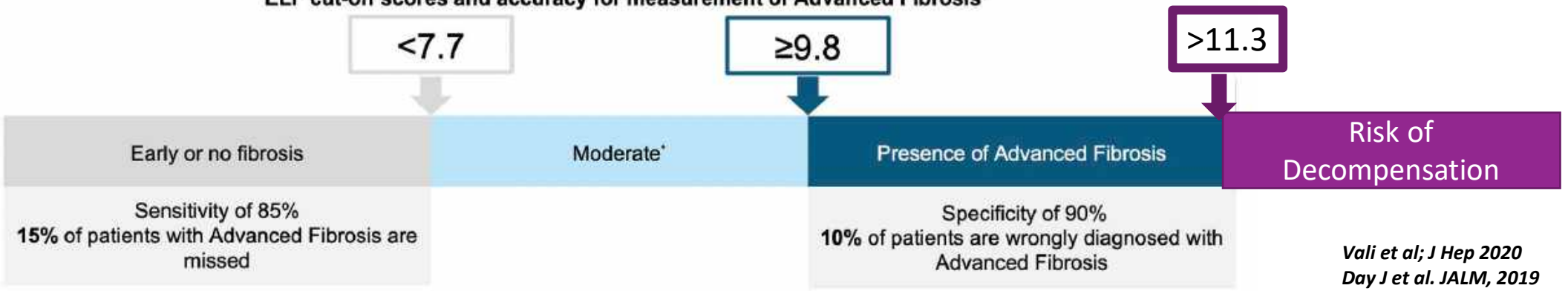
Enhanced Liver Fibrosis test;
A blood based biomarker for
diagnosis advanced fibrosis



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[4]



Vali et al; J Hep 2020
Day J et al. JALM, 2019

	CAP (dB/m)	E (kPa)	
SD	MEAN	MEDIAN	IQR/Med
7			12%
	316	9.8	

218.0 lb

Unknown

AGA 2021

Primary care, endocrinologists, gastroenterologists and obesity specialists should screen for NAFLD with advanced fibrosis

Step 1: Identify patients at risk

- 2 or more metabolic risk factors[1]
- Type 2 diabetes
- Steatosis on any imaging modality or elevated aminotransferases

Step 2: History & lab tests: Excessive alcohol intake, CBC, liver function tests

Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, ASLT, ALT & platelet count)

- FIB-4 <1.3 → **Low Risk**
  Repeat NIT in 2–3 years unless clinical circumstances change
- FIB-4 ≥1.3 to 2.67 → **Indeterminate Risk**

Step 4: Liver stiffness measurement (LSM)[5,6,7]

- LSM <8 kPa → **Low Risk**
  Repeat NIT in 2–3 years unless clinical circumstances change
- LSM 8 to 12 kPa → **Indeterminate Risk**
  Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2–3 years
- LSM >12 kPa → **High Risk**
  Refer to hepatologist

- FIB-4 >2.67 → **High Risk**
  Refer to hepatologist

1. Metabolic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes, or insulin resistance. 2. For patients age >65, use FIB-4 <2.0 as the lower cutoff. Higher cutoff does not change. 3. Other NITs derived from routine laboratories can be used instead of FIB-4. 4. Many online FIB-4 calculators are available such as https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. 5. Ultrasound acceptable if vibration-controlled transient elastography (VCTE, FibroScan®) is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasound who are indeterminate or high risk based on FIB-4. 6. LSM values are for VCTE (FibroScan®). Other techniques such as bidimensional shear wave elastography or point shear wave elastography can also be use used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI, or where LSM unavailable. 7. Eddowes et al. uses 8.2 and 12.1 kPa as cutoffs for LSM using VCTE. Valdiation of simple (rounded) cutoffs reported by Papatheodoridi et al.
Adapted from:

Kanwal F et al. Gastroenterol. 2021

Advanced Steps


Liver Biopsy is still an option
BUT!!!!!!!

AASLD: Noninvasive parameters for advanced fibrosis and cirrhosis

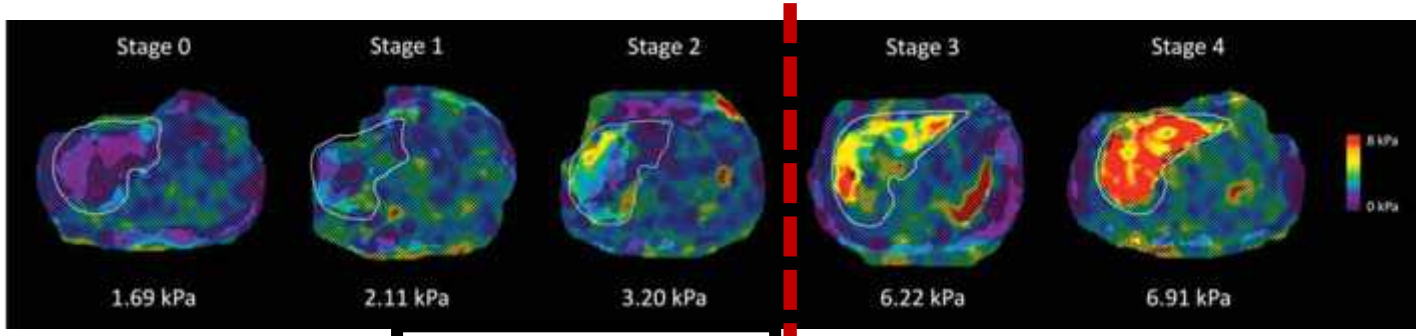
• Detection of advanced fibrosis				
Serum	FIB-4	≥ 2.67	<1.3	• No added cost[1-3] • Not accurate in age < 35 years and lower rule-out threshold among high-risk individuals who have high pre-test probability
Serum	ELF	≥ 9.8	<7.7	• Blood test sent to a reference laboratory[4] • Cost
Imaging	VCTE	≥12 kPa	< 8 kPa	• Point of care[5]
Imaging	MRE	≥3.63 kPa	<2.55 kPa	• MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[6]

• Diagnosis of cirrhosis (rule-in or rule out)				
		Rule-in	Rule-out	
CPR	FIB-4	≥3.48	< 1.67	• 90% specificity cut-point for ruling-in and 90% sensitivity for ruling-out cirrhosis, respectively[6, 7]
Serum	ELF	≥11.3	<7.7	• ELF ≥ 11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[4]
Imaging	VCTE	≥ 20 kPa	< 8 kPa	• LSM by VCTE ≥ 20 kPa is associated with cirrhosis but for ruling out cirrhosis optimal cut-point is < 8 kPa[5]
Imaging	MRE	≥ 5 kPa	< 3 kPa	• LSM by MRE ≥ 5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[8, 9]

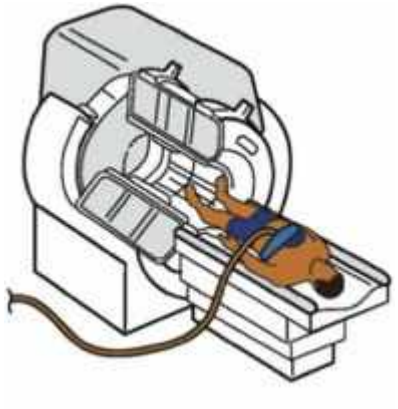
Rinella et al; Hepatology 2023

Imaging Techniques - MRE

Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)



Vino: 3.3 kPa

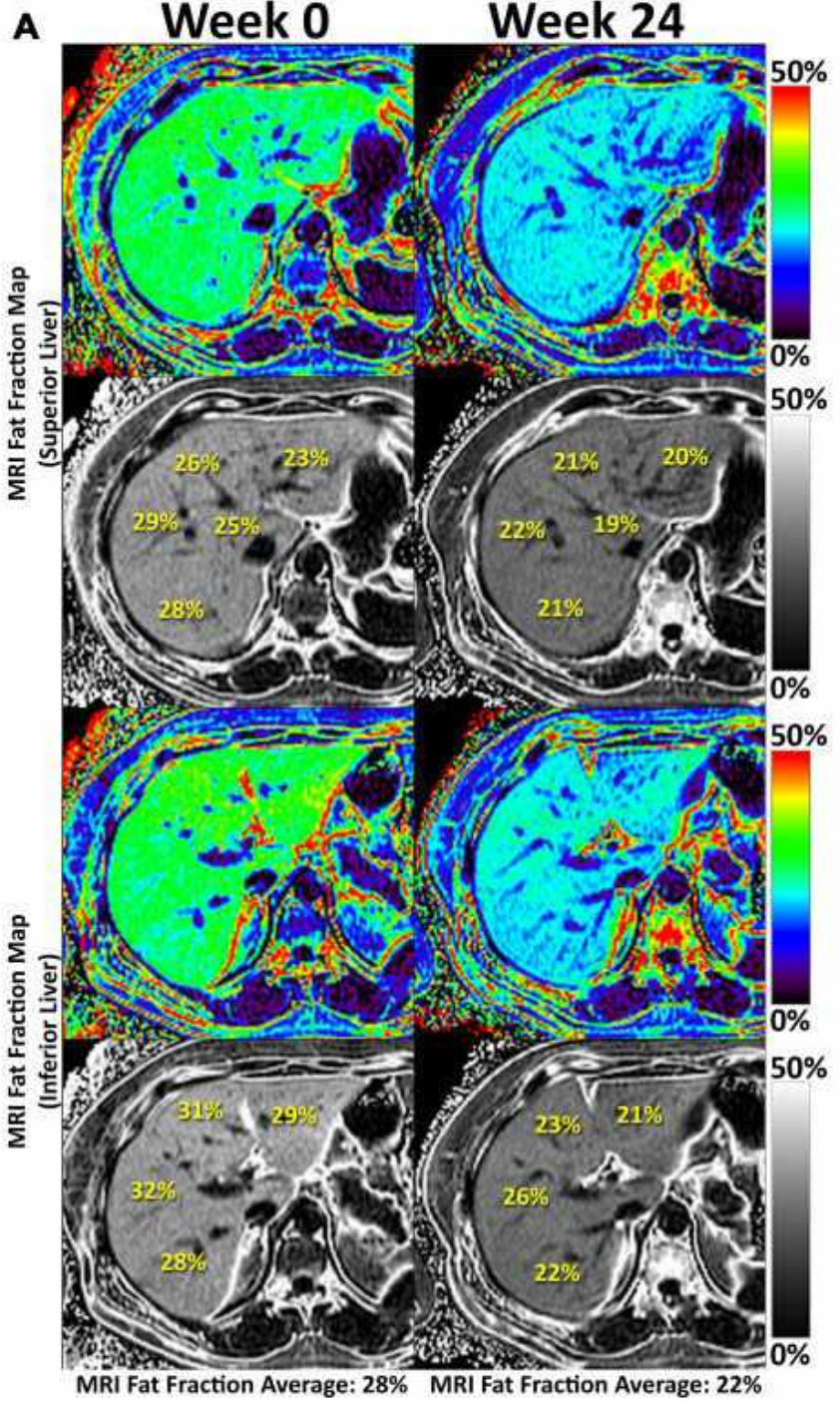


Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥ 3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

Loomba et al. Hepatology. 2014;
Patel et al. Ther Adv Gastroenterol.. 2016
Han, Noureddin. Liver Int 2020

MRI-PDF

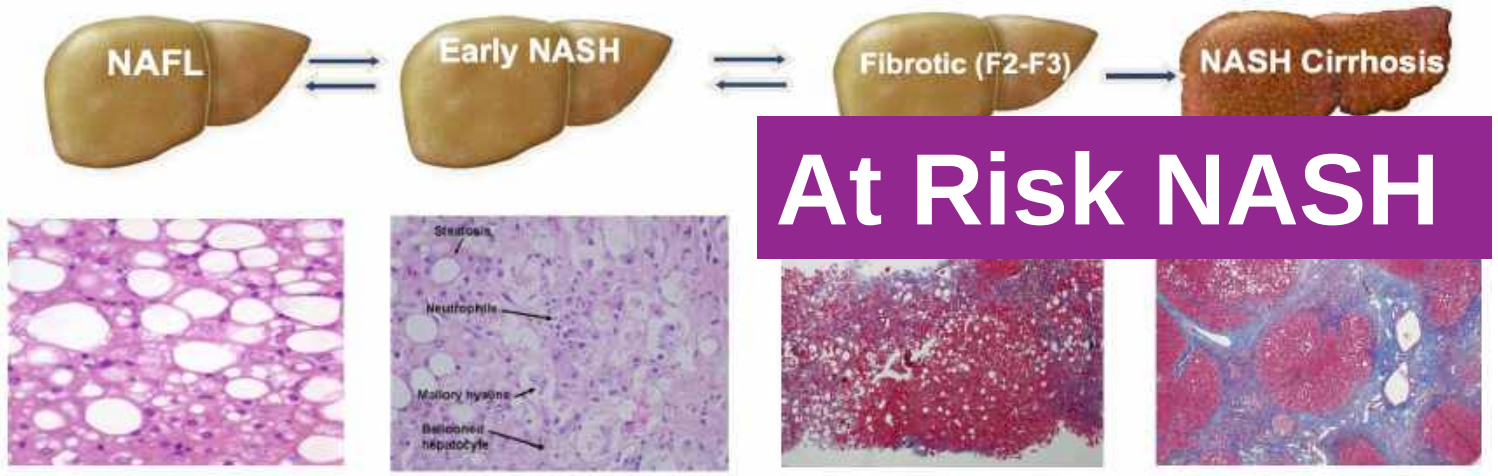
Vino's MRI-PDFF: 28



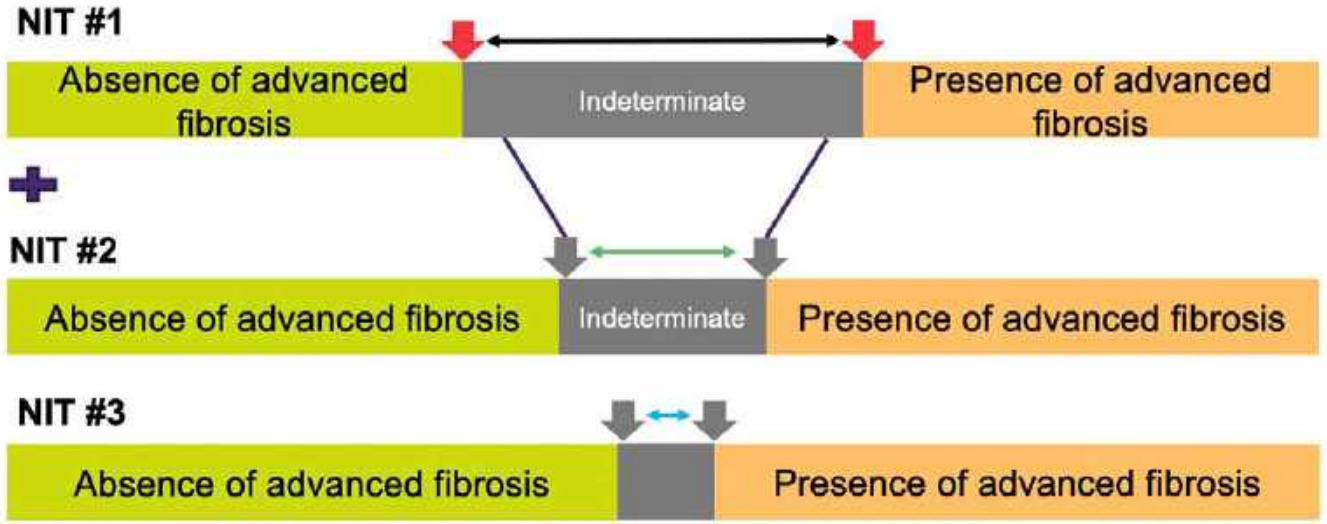
Noureddin, Hepatology 2013
Loomba Hepatology 2015

Sequential Testing is Key!!!!

- Liver biopsy is historically required to diagnose liver fibrosis and NASH
- Can be useful when non-invasive tests give indeterminate or conflicting results



- However, sequential utilization of NITs can lead to better detection of advanced fibrosis and cirrhosis, especially when patients fall into the indeterminate zone



Anstee et al; Hepatology 2019

AASLD: Noninvasive parameters for ‘at risk’ NASH/MASH

Identification of ‘at risk’ NASH				
Combined	FAST	≥0.67	<0.35	• ≤0.35 (sensitivity 90%) • ≥ 0.67 (specificity 90%) • In validation cohorts, the PPV of FAST ranged between 0.33 and 0.81.(1-2)
Combined	MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 < 1.6 plus MRE < 3.3 kPa	• Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV.(3)
	MAST	≥0.242	≤0.165	0.242 (specificity 90%), 0.165 (sensitivity 90%)(4)
	cT1	≥ 875 msec	< 825 msec	• Requires further validation as data is derived from one study(4)

Newsome et al. Lancet Gastro Hep 2020 [1]; Woreta et al PLoSONE 2022 [2]; Jung et al. Gut 2021 [3]; Noureddin M et al. J Hepatol 2022 [4] Andersson et al. CGH 2022 [5]

Rinella et al; Hepatology 2023

FAST: For NASH/MASH with NAS ≥ 4 and ≥ F2

	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)			Grey zone (FAST 0·35–0·67)		Rule-in zone (FAST ≥0·67)			
										Specificity	Sensitivity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)								0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)								0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28								0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36								0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9							92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)						4%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)			(34/36)		59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

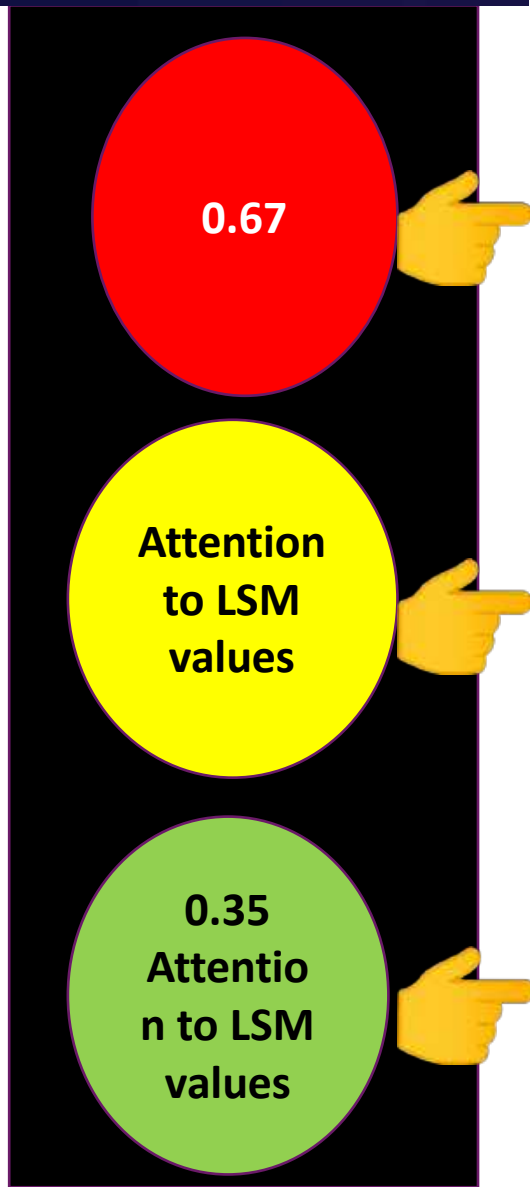
Online or App Calculator

FAST: CAP+LSM+AST

0.35 | **0.67** | **Vino 0.69**

Low Probability of At Risk NASH	Indeterminate	HIghProbability of At Risk NASH

Newsome et al; Lancet Gastro Hep 2020
Noureddin N et al; Hepatology 2020



MAST score: MRI-Based Score to Identify Patients with NASH/MASH and Significant Fibrosis

Methods

2016-2020: NAFLD patients who underwent liver biopsy, MRI, Fibroscan, and lab testing

Derivation cohort (n = 103)

Goal: Identify [illegible] NASH + NAFLD activity + significant fibrosis (≥F2)

Findings

	Sensitivity	Specificity	PPV	NPV
	1.4%	72.9%	42.5%	98.4%
	%	73.1%	30.1%	98.1%
	%	64.1%	25.0%	98.6%
		52.9%	30.5%	100.0%
	%	66.6%	18.7%	92.5%
	88.9%	74.7%	42.1%	97.0%
	20.7%	95.5%	37.5%	90.2%

CoulditbeNASH.org

0.165 | **0.242** | **Vino's 0.481**

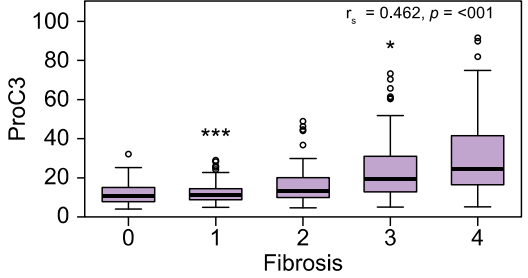
Low Probability of At Risk NASH	Low Probability of At Risk NASH	High Probability of At Risk NASH

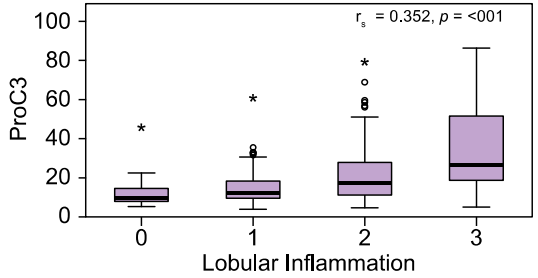
Conclusions

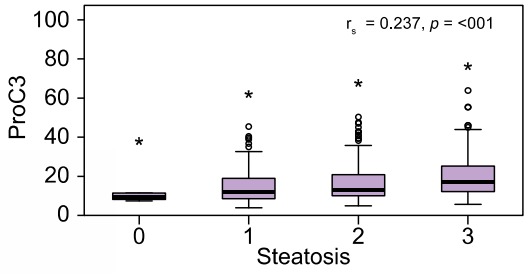
The MAST score is an accurate, MRI-serum-based score that outperforms the NAFLD fibrosis (NFS), Fib-4, and FAST scores in non-invasively identifying patients at higher risk of Fibro-NASH.

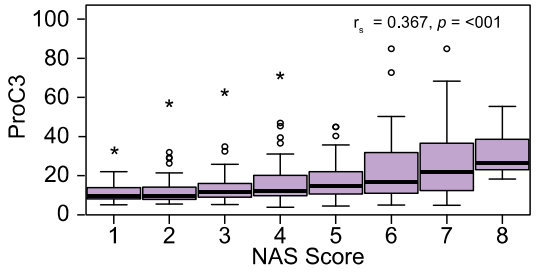

ON THE
HORIZON

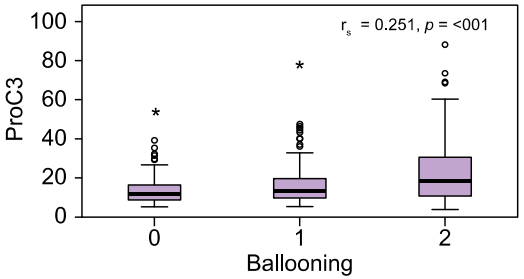
PRO-C3



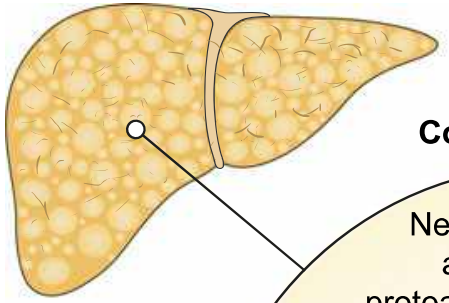




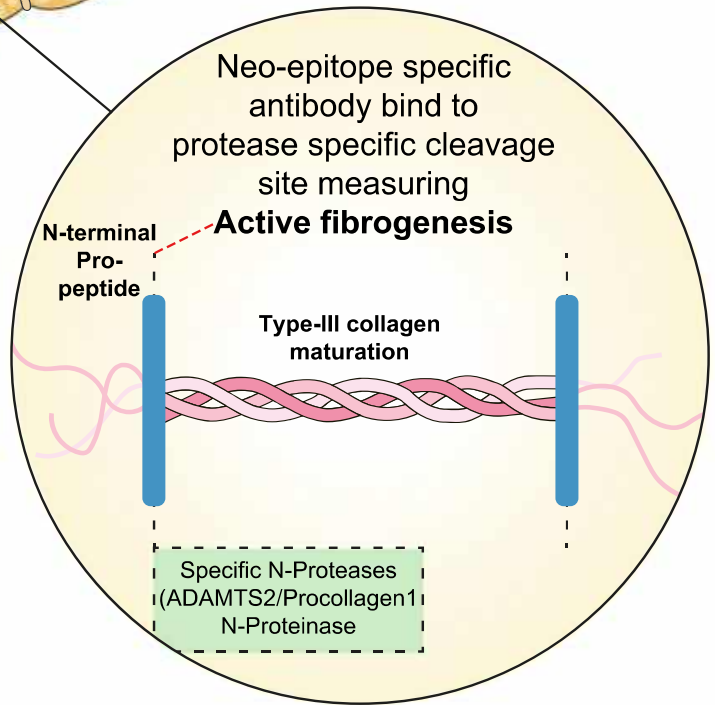




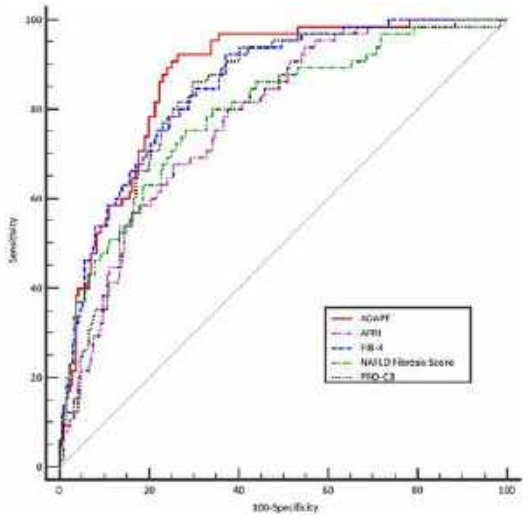
NAFLD fibrosis



Collagen PRO-C3



ADAPT.



ABC3D/FIBC3

PRO-C3 platelets

+ Age BMI T2DM

ABC3D
(Age >50 = 1, BMI >30 = 1, Platelet count <200, Pro-C3 >15.5 = 1, T2DM = 2
Score >3

FIBC3
FIBC3 score >-0.4

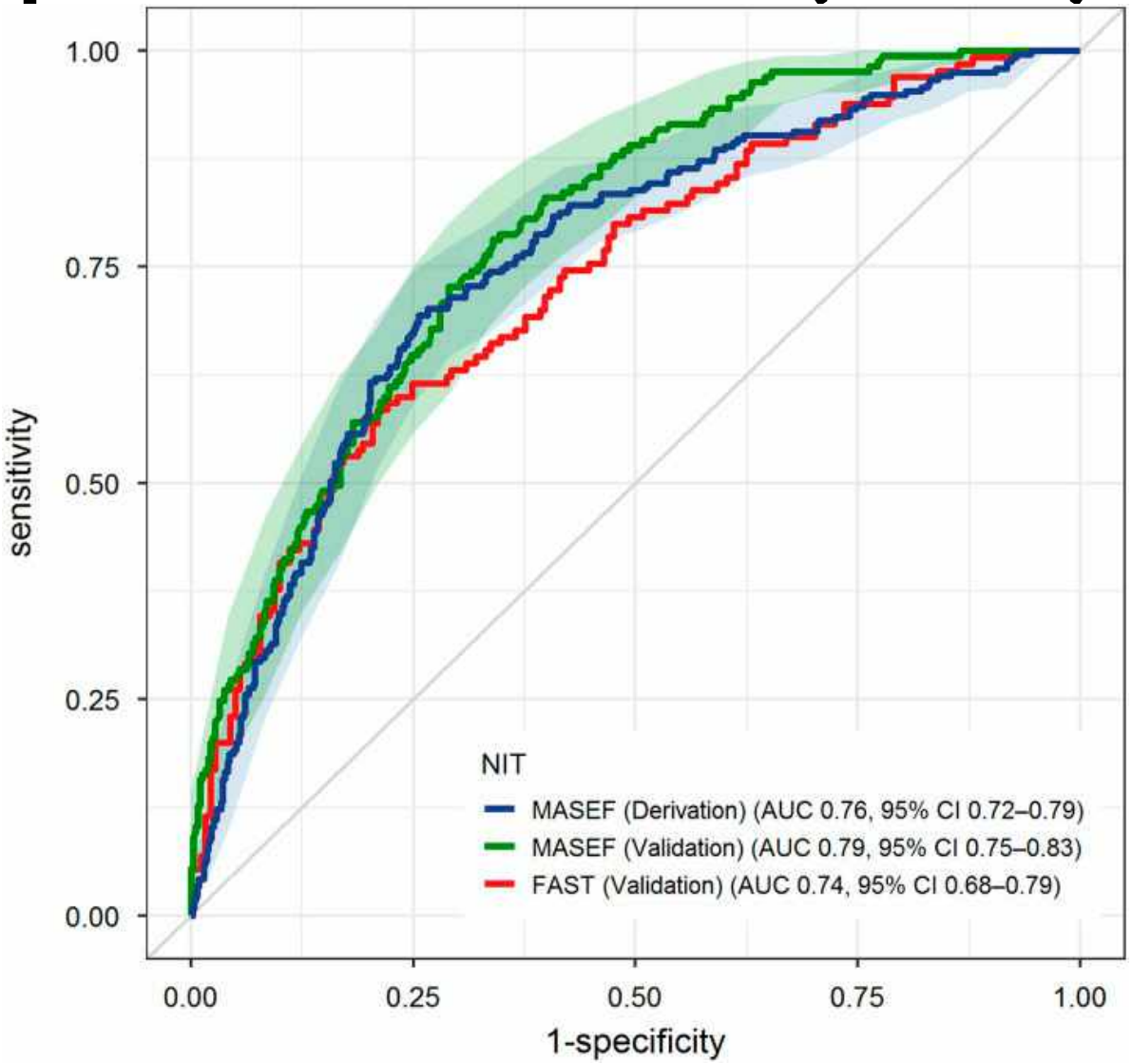
	FIBC3	FIB4	ABC3D
AUROC	0.83	0.76	0.81
Sensitivity	75.00	21.00	66.00
Specificity	75.00	94.00	75.00

Boyle et al; J Hep Reports 2019
Daniel SJ; Hepatology 2019

The serum identification of At-Risk MASH: The Metabolomics-Advanced steatohepatitis fibrosis score (MASEF)

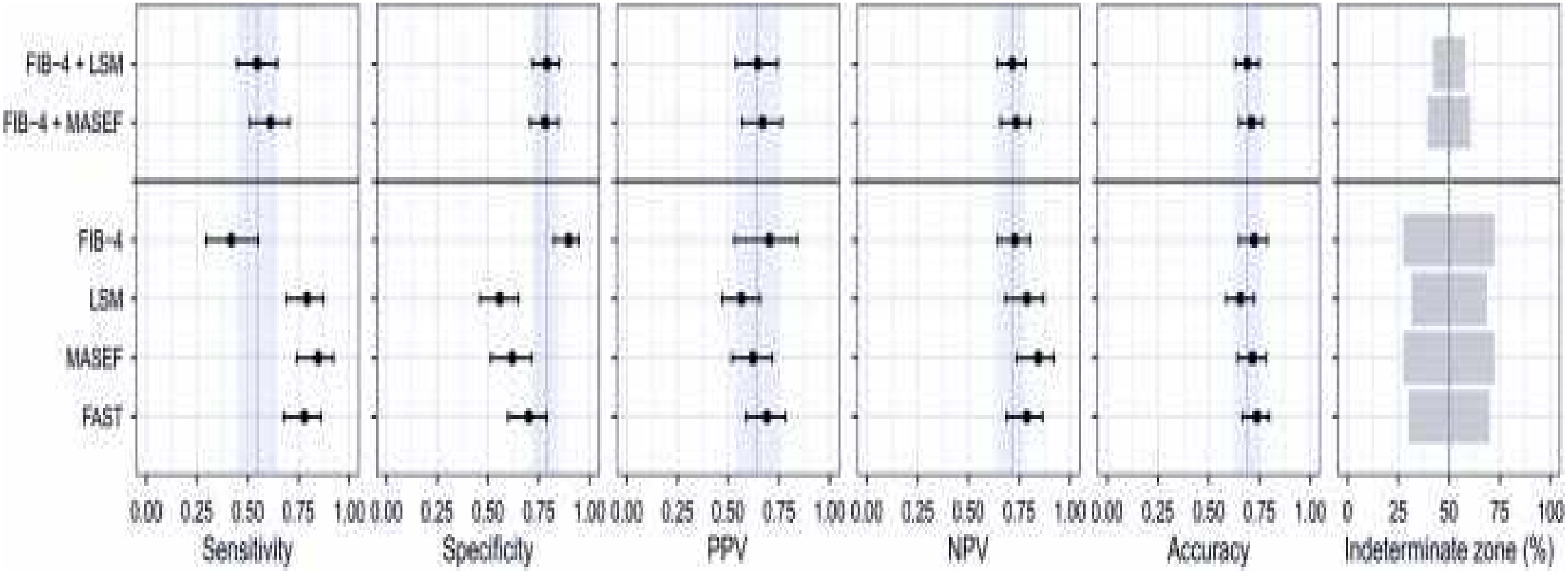
- Metabolomics serum-based test:
  12 lipids, BMI, AST and ALT

- Derivation: 790
  Validation:565



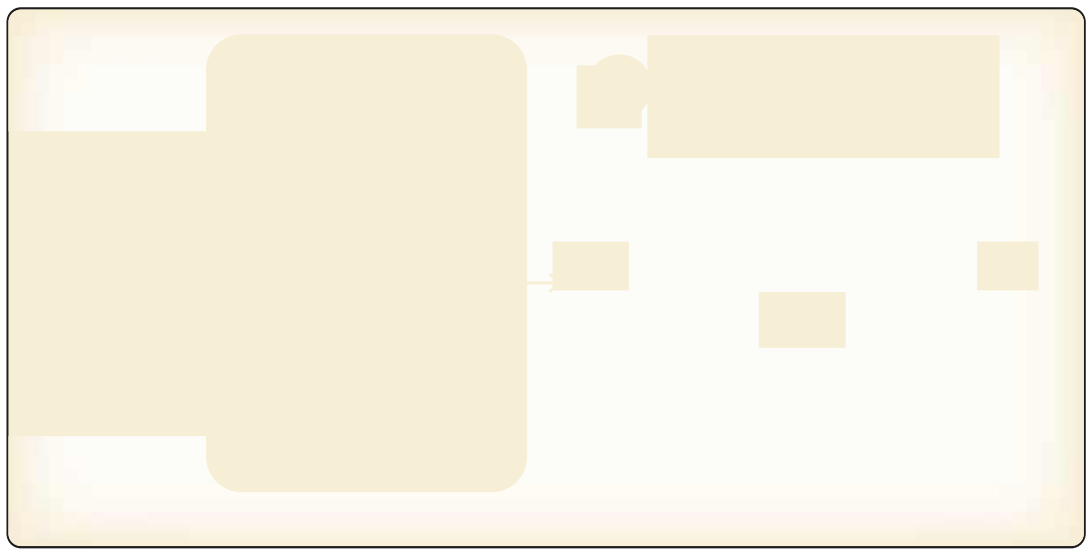
Noureddin et al Hepatology 2023

The serum identification of At-Risk MASH: The Metabolomics-Advanced steatohepatitis fibrosis score (MASEF)



Noureddin et al Hepatology 2023

NIS-2 score

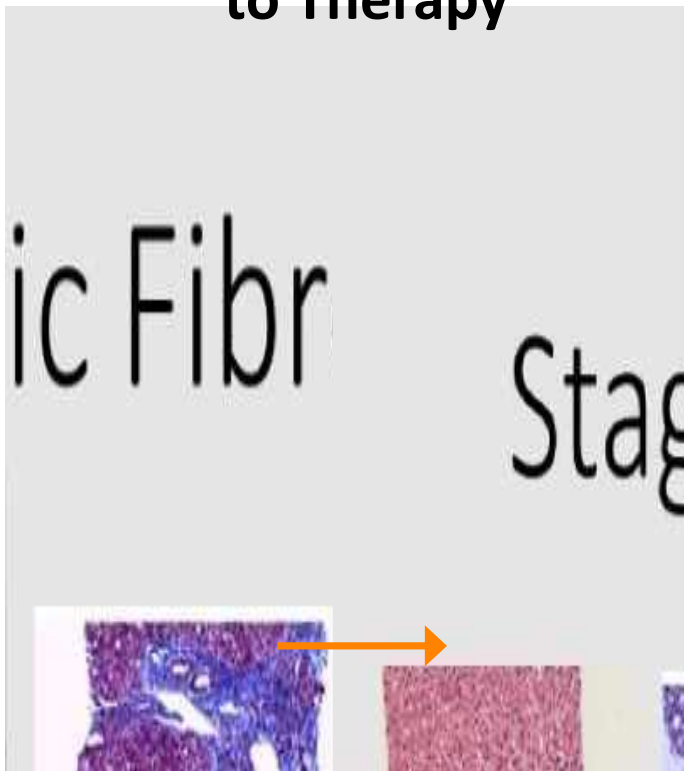


Harrison et al; J Hep 2023

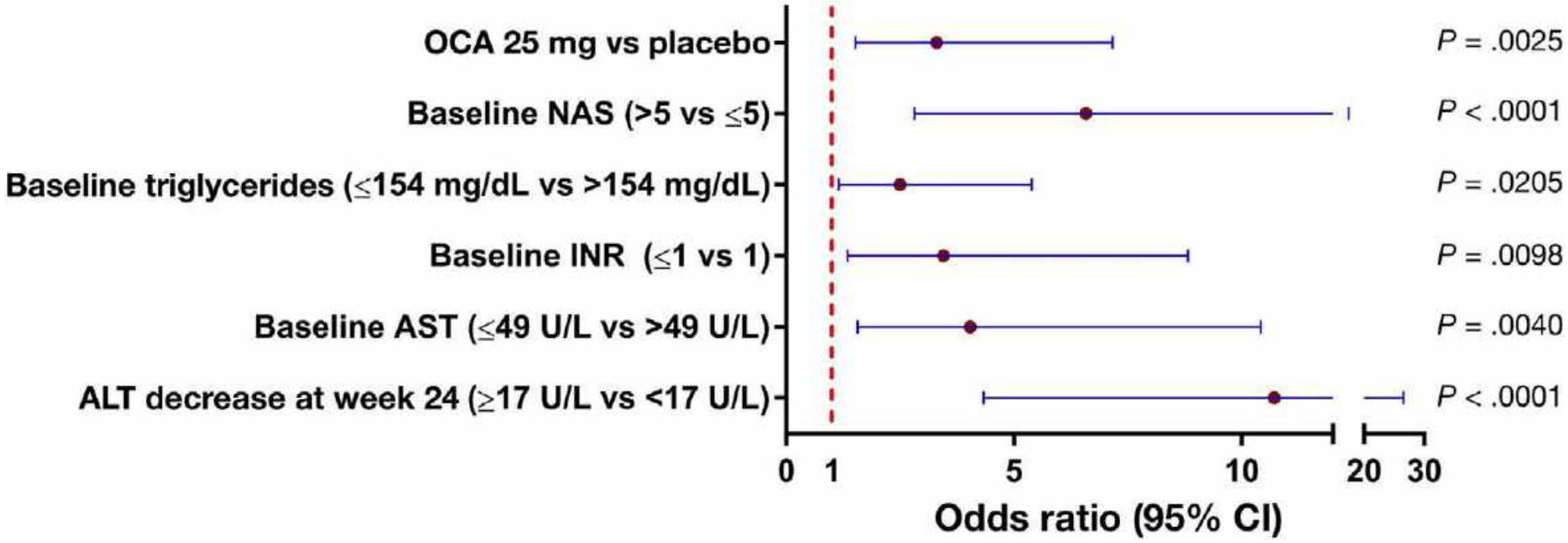

PUT IT ALL
TOGETHER!

How do I monitor response?

Monitoring Response to Therapy



ALT



Factors Associated With Histologic Response in Adult Patients With Nonalcoholic Steatohepatitis in the FLINT trial

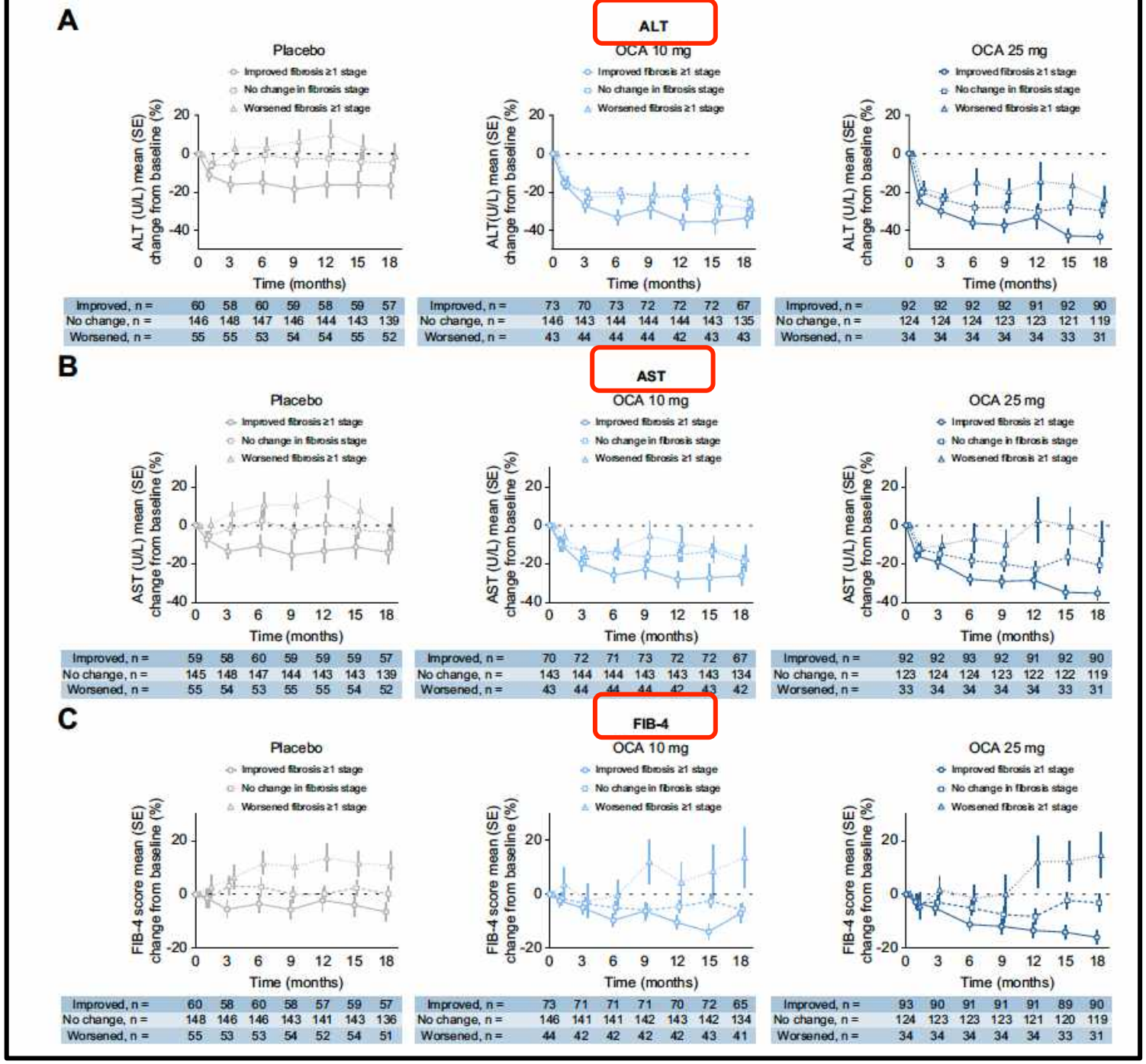
Loomba et al; Gastroenterology 2019

Longitudinal Assessment of NITs from the REGENERATE study

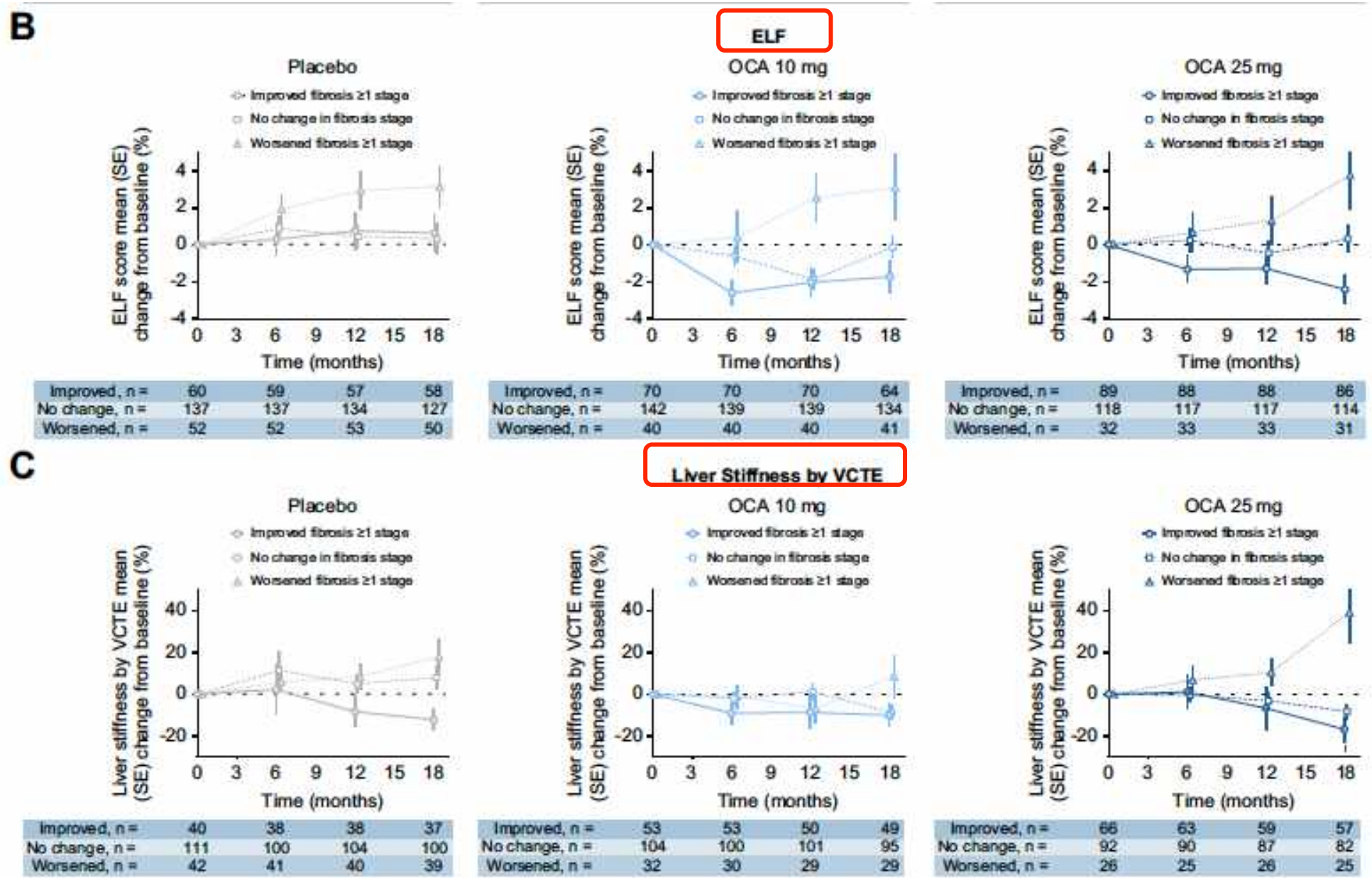
Patients with ≥-stage fibrosis improvement had the greatest improvement in NITs, while patients with ≥1-stage fibrosis worsening typically showed no NIT improvement.

AUROC values for each of these were suggestive of only weak association

NIT improvements observed in REGENERATE are associated with fibrosis improvement at Month 18, individual NIT changes are not likely to be effective univariate clinical predictors of fibrosis improvement by Month 18.



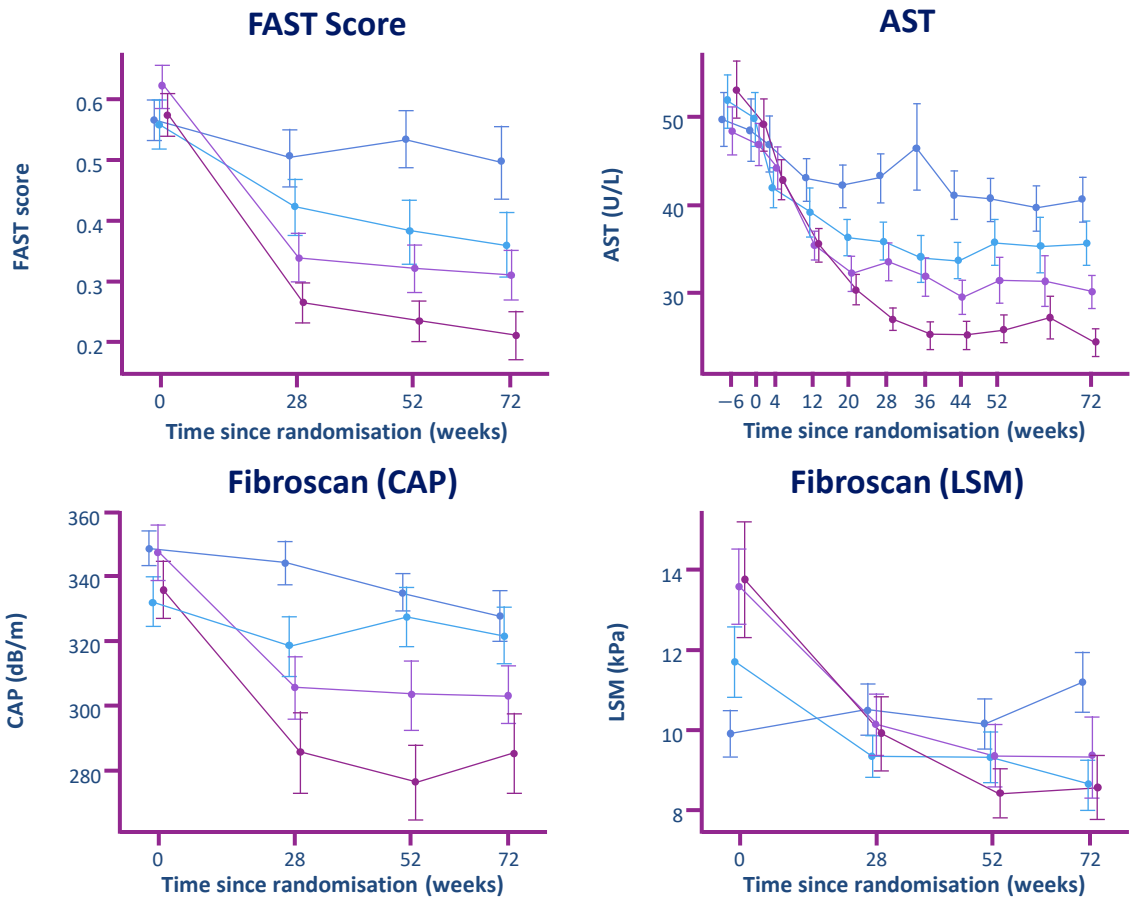
Rinella et al; J Hep 2022

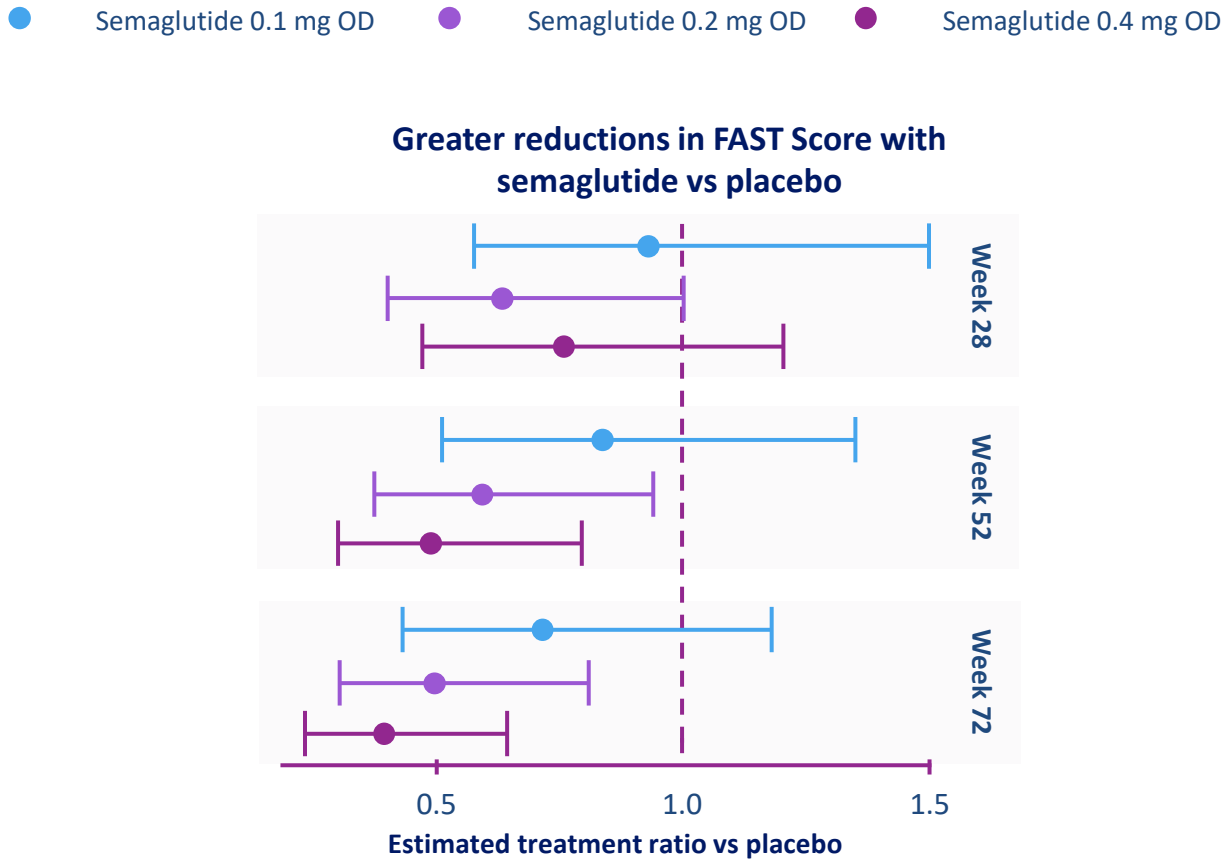


Rinella et al; J Hep 2022

Changes in FAST score during semaglutide treatment

BASELINE TO WEEK 72 – SUBSET ANALYSIS (N=161)





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Faculty of Medicine
The Chinese University of Hong Kong

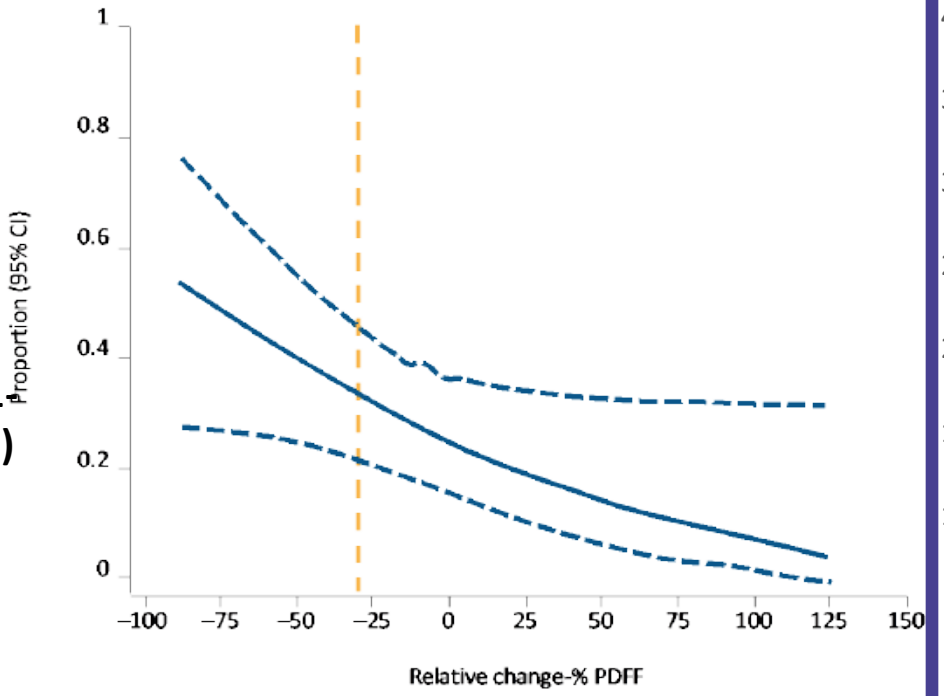
AST, FibroScan CAP and FibroScan LSM are the individual components of the FAST score. Data are for patients with FAST scores at baseline during the on-treatment period. Line plots are observed mean (±SEM). AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FAST, FibroScan aspartate aminotransferase; LSM, liver stiffness measurement; OD, once-daily; SEM, standard error of the mean.

Wong VW et al. EASL 2021 (OS-1556)

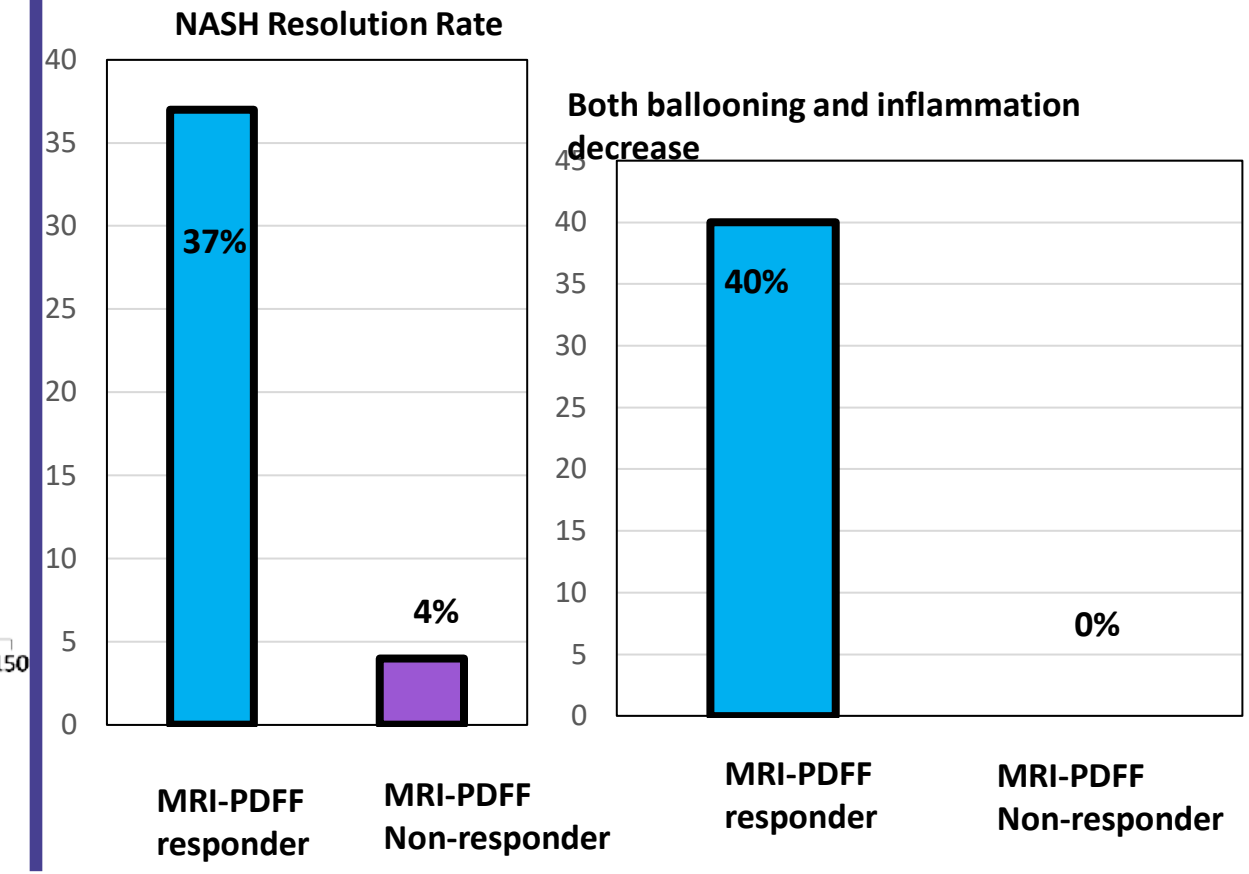
PDFF-Changes in Recent Trials

MRI-PDFF responders had significantly higher odds of histologic response , ballooning with OR 2.9 (95% CI, 1-8.2, p-value 0.05)

Flint Trial



Resmetirom Trial



Patel et al. Advances in Gastro 2016
Loomba EASL 2020
Loomba et al. Hepatology 2020
Harrison et al. Lancet 2019

NITs with Data Linked to Histology/Treatment Response

Monitoring Response to Therapeutic Interventions

Blood	Imaging	Combination
• ALT • Pro-C3 • FIB-4 • ELF	• cT1 • VCTE • MRI-PDFF • MRE	• FAST • MAST (Non-histology but through MASTRO-NAFLD)

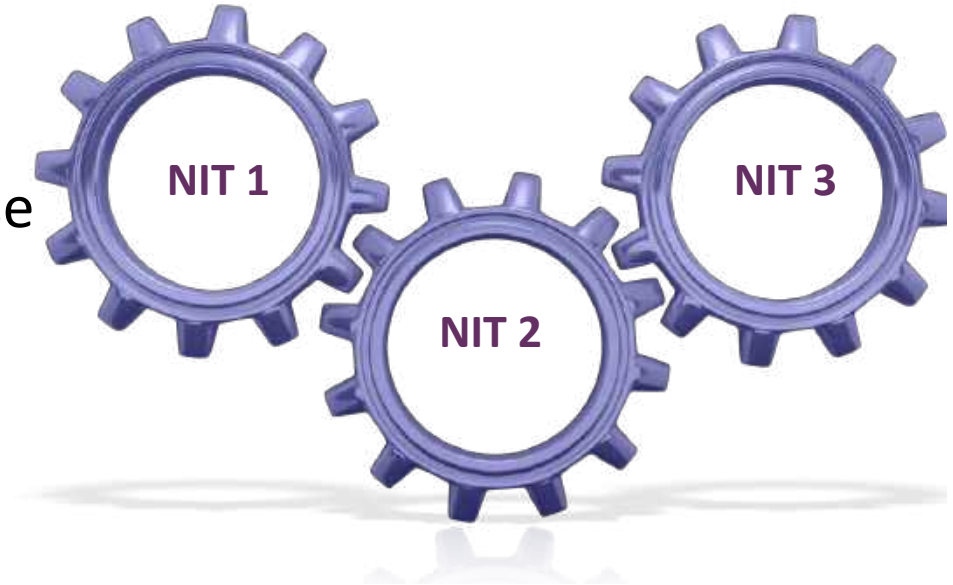
uthor and AASLD. Permission is required from both AASLD and the author for reuse.

Is a change in 1 NIT enough to monitor therapeutic response ?

The use of combined NITs increases the diagnostic accuracy of at risk NASH

Is that true for therapeutic response monitoring?

If yes, how many and which ones are needed?



Courtesy of S. Harrison

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Putting it Together!

FiB-4

T2DM or Obesity and 2 metabolic risk factors

Or ELF

If >8 If >7.7

GI/Hep

6-12 months

NITs

Treatment for At Risk NASH/MASH (THB-R, PPAR, GLP1)

ALT

Ideal Combo is 2 that includes steatohepatitis & Fibrosis and one is Related to outcomes

NITs: Repeat the Same

Response

6-12 months

Treatment for At Risk NASH/MASH

No Response

6-12 months

Partial: ?Add

None: ?Switch

Summary

- We have new algorithms to guide referral from PCP to Hepatology/Gastro (Amazing progress)
- These algorithms might change over time
- Combination of serum biomarkers and imaging appear to be the way to go
- NITs predict outcomes

Thank you

"Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning." -- *Albert Einstein*

@noureddinmd

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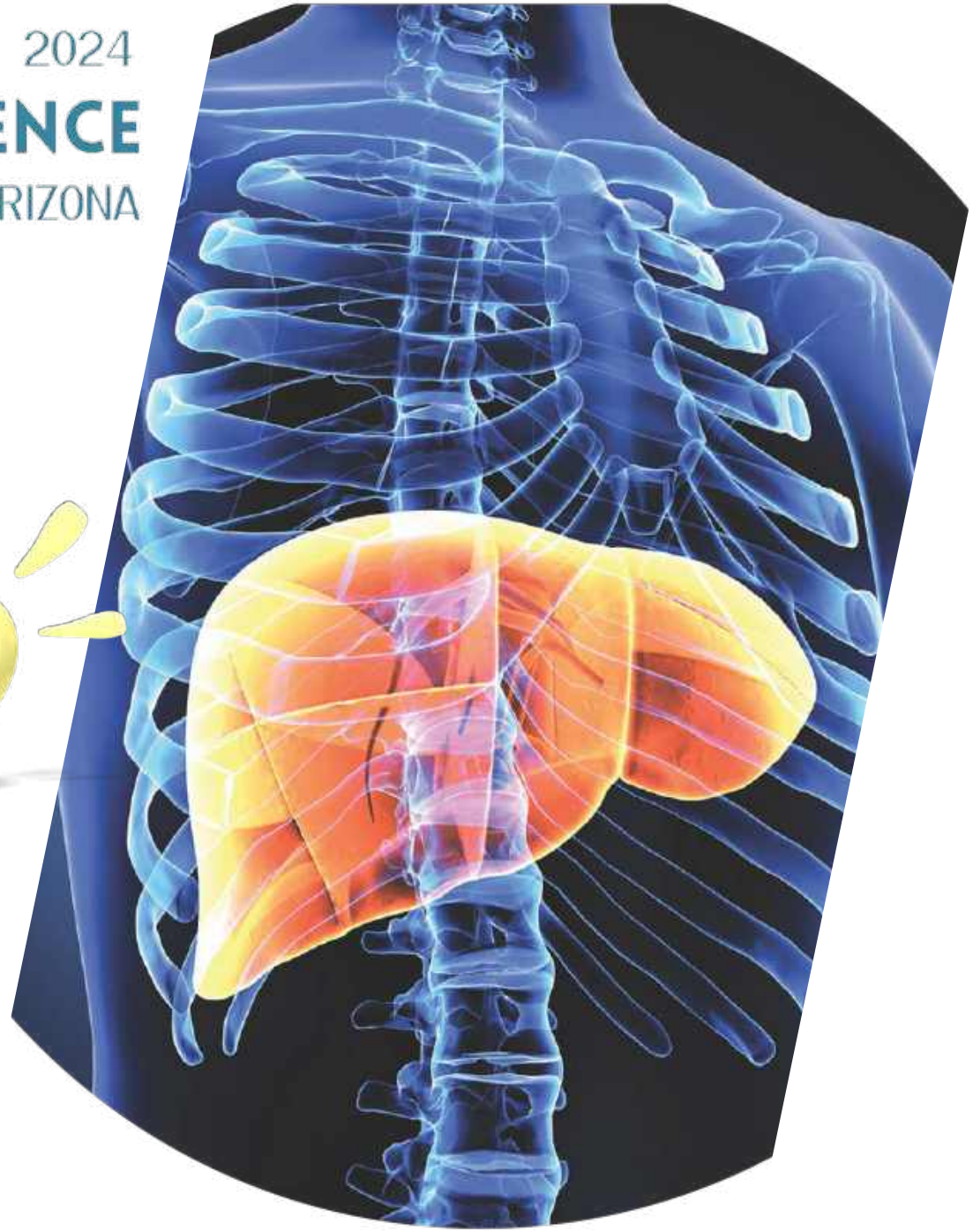
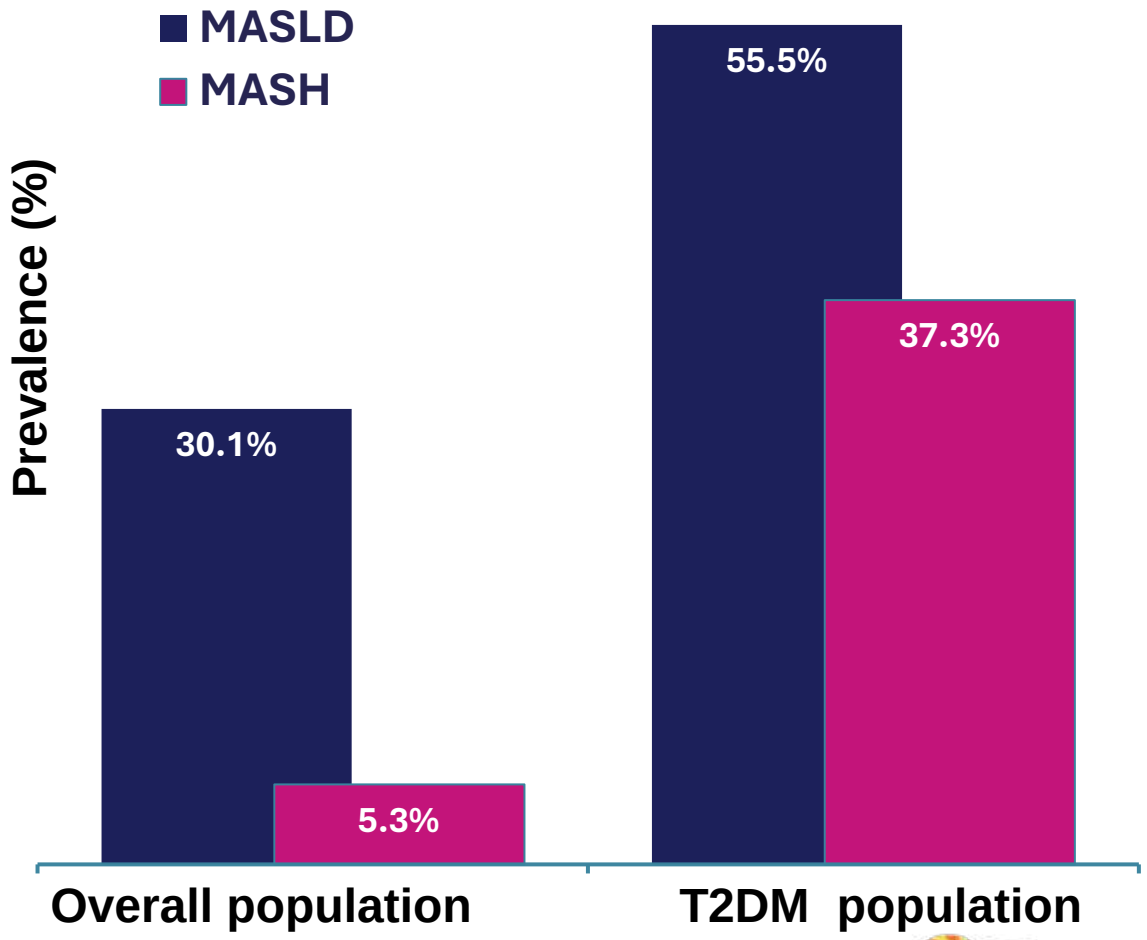
Management of MASH with New Drugs: The Future is Bright



Stephen A. Harrison, MD, COL (Ret.), FAASLD
Visiting Professor of Hepatology
Radcliffe Department of Medicine, University of Oxford
Chairman and Founder, Pinnacle Clinical Research
Chairman and Co-Founder, Summit Clinical Research

Global Epidemiology of MASH & Type 2 Diabetes

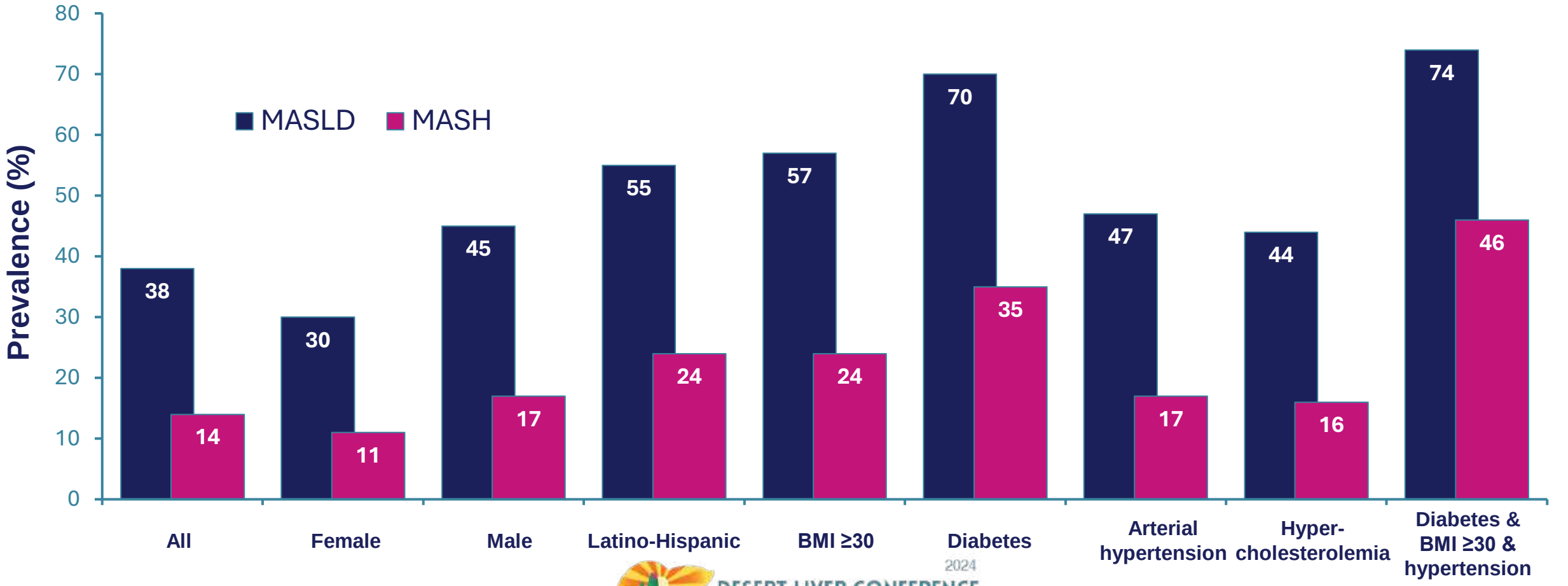


- **No approved treatments currently available**
- 16.5 million cases projected to grow to 27 million cases by 2030
- Expected to become the leading cause of liver transplant

Younossi ZM et al. Hepatology. 2023 Apr 1;77(4):1335-1347
Younossi et al. J Hepatol. 2019 Oct;71(4):793-801

MASLD and MASH Prevalence in Different Groups

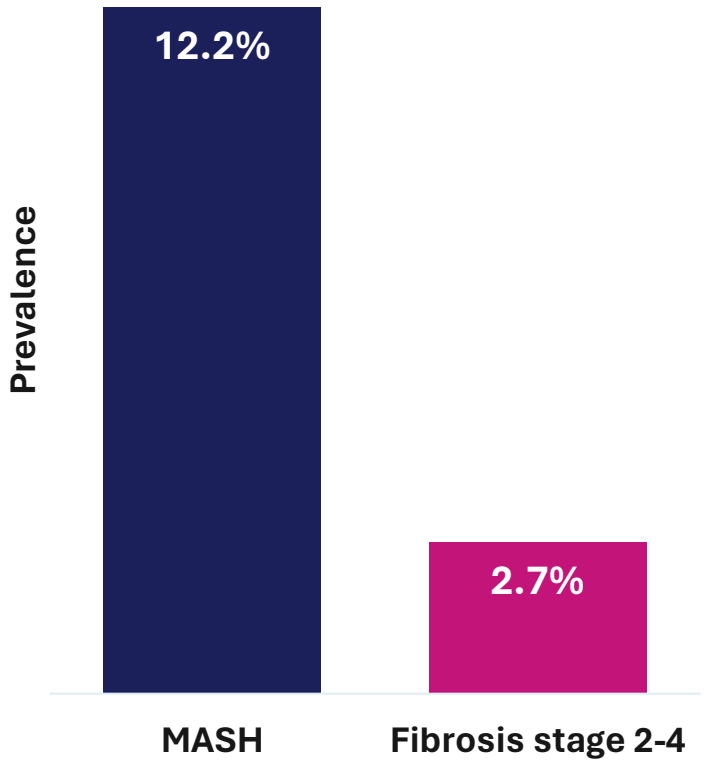
US Middle-Aged Cohort - N=664



Harrison SA et al. J Hepatol. 2021;S0168-8278:00176-8.

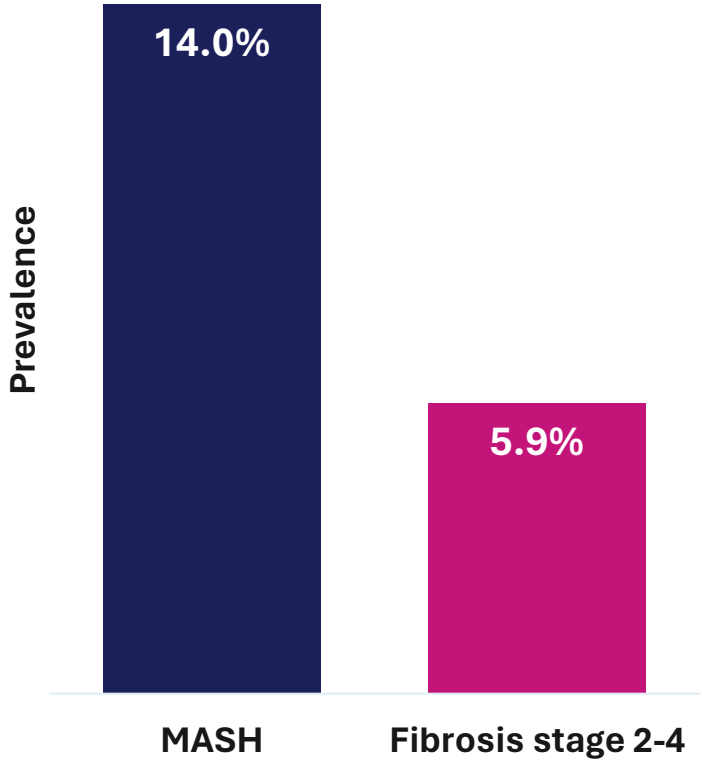
Prevalence of MASH Among US Middle-Aged Cohorts

JAN 2007 – MAR 2010
N=328



2 prospective MASH prevalence studies

AUG 2015 – JUL 2018
N=664

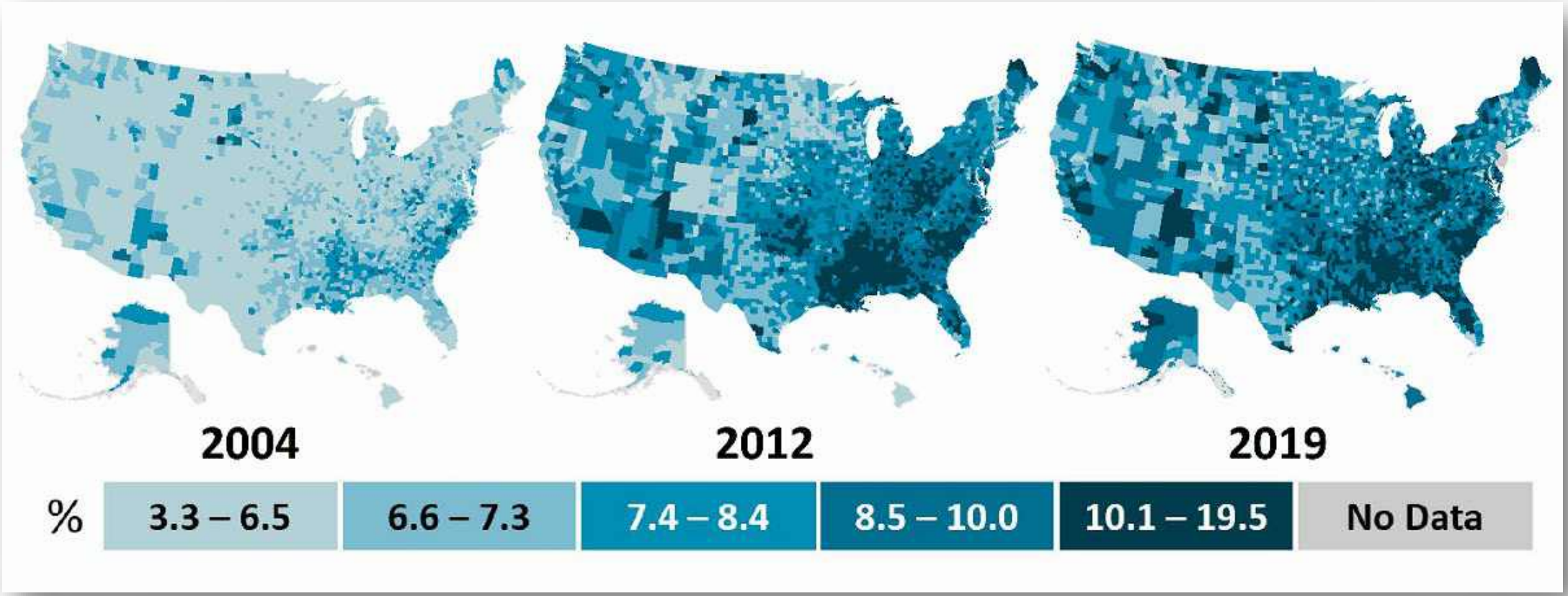


Williams CD, et al. Gastroenterology. 2011;140:124–31; 2
Harrison SA, et al. J Hepatol. 2021;S0168-8278:00176-8.

Disease Burden of MASH – Diabetes Epidemics

MASH prevalence could grow along with the rapid increase in diabetes and obesity

Age-adjusted, county-level prevalence of diagnosed diabetes among adults aged 20 years or older, United States, 2004, 2012, and 2019



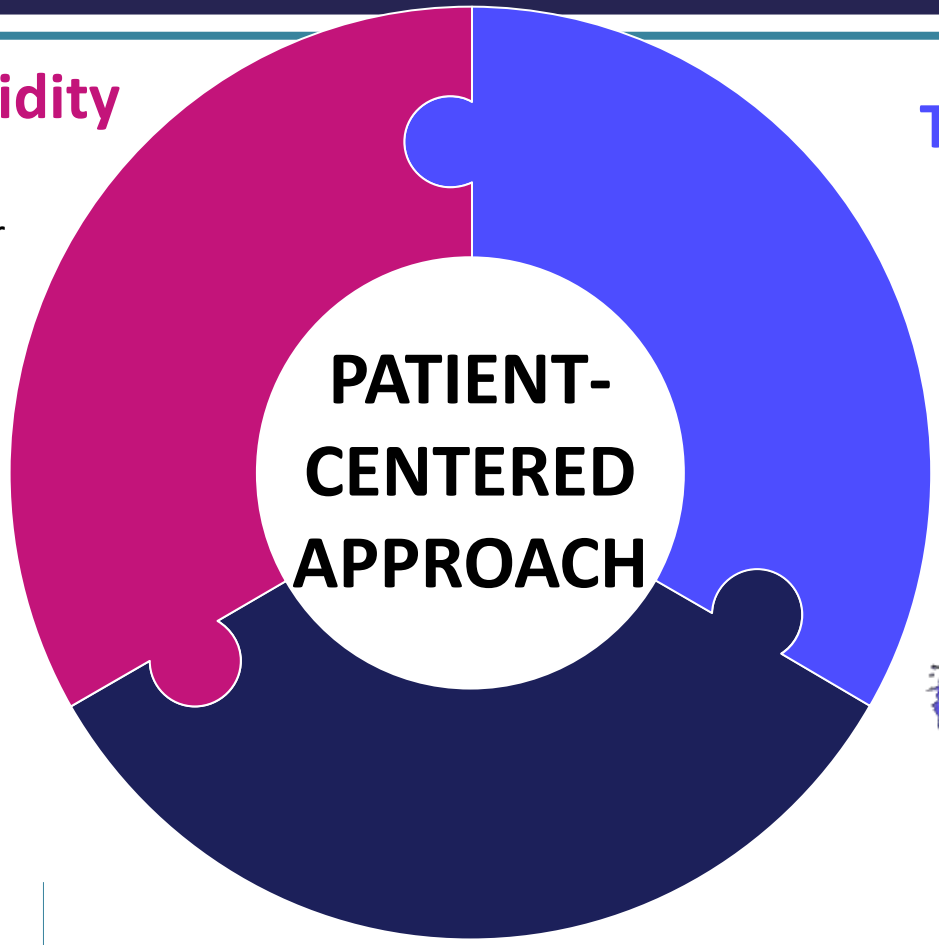
Centers for Disease Control and Prevention. National Diabetes Statistics Report website


Incidence of MASH cirrhosis in the US
1990: 178,430 cases
2017: 367,780 cases (106% increase)

In Absence of FDA-Approved Therapies

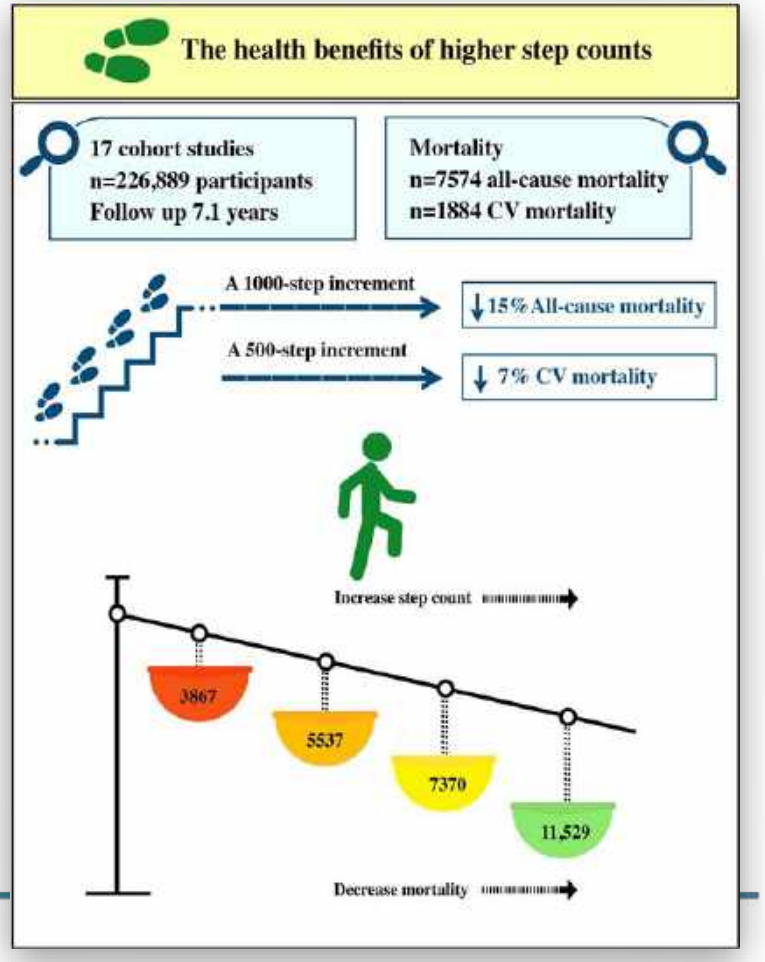
Treat Each Comorbidity

Obesity – GLP1-RA
Diabetes – Pioglitazone and/or GLP1-RA
Dyslipidemia
Hypertension
Sleep Apnea



Tackle Overweight / Obese status

Weight Loss
Exercise
Diet



Cofactors Dietary Modifiers

Alcohol, smoking, fructose, coffee

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AACE 2022 - Cusi. Endocr Pract. 2022;28:528
Banach M et al. Eur J Prev Cardiol. 2023 Aug 9

Lifestyle Recommendations for Treating MASH

Caloric intake reduction
≥30% or
~750-1,000 kcal/day
improved insulin resistance and hepatic steatosis

Limit consumption of fructose-enriched beverages

Weight loss
of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve MASH/fibrosis

Exercise
alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption
Insufficient data to guide recommendations regarding nonheavy alcohol consumption

Drink ≥ 2 cups of caffeinated coffee daily

Chalasani N et al. Hepatology. 2018;67(1):328-357
Diehl AM, Day C. New Engl J Med. 2017; 377:2063-72.

Evidence from PIVENS Trial: Vitamin E & Pioglitazone

Endpoint Mean change in score	Placebo N=72	Vitamin E N=80	Pioglitazone N=70
Steatosis	-0.1	**-0.7***	**-0.8***
Inflammation	-0.2	**-0.6***	**-0.7***
Ballooning	-0.2	**-0.5***	**-0.4***
NAS	-0.5	**-1.9***	**-1.9***
Fibrosis	-0.1	-0.3	-0.4
Resolution of NASH, % of responders	21%	**36%***	**46%***

* statistically significant versus placebo

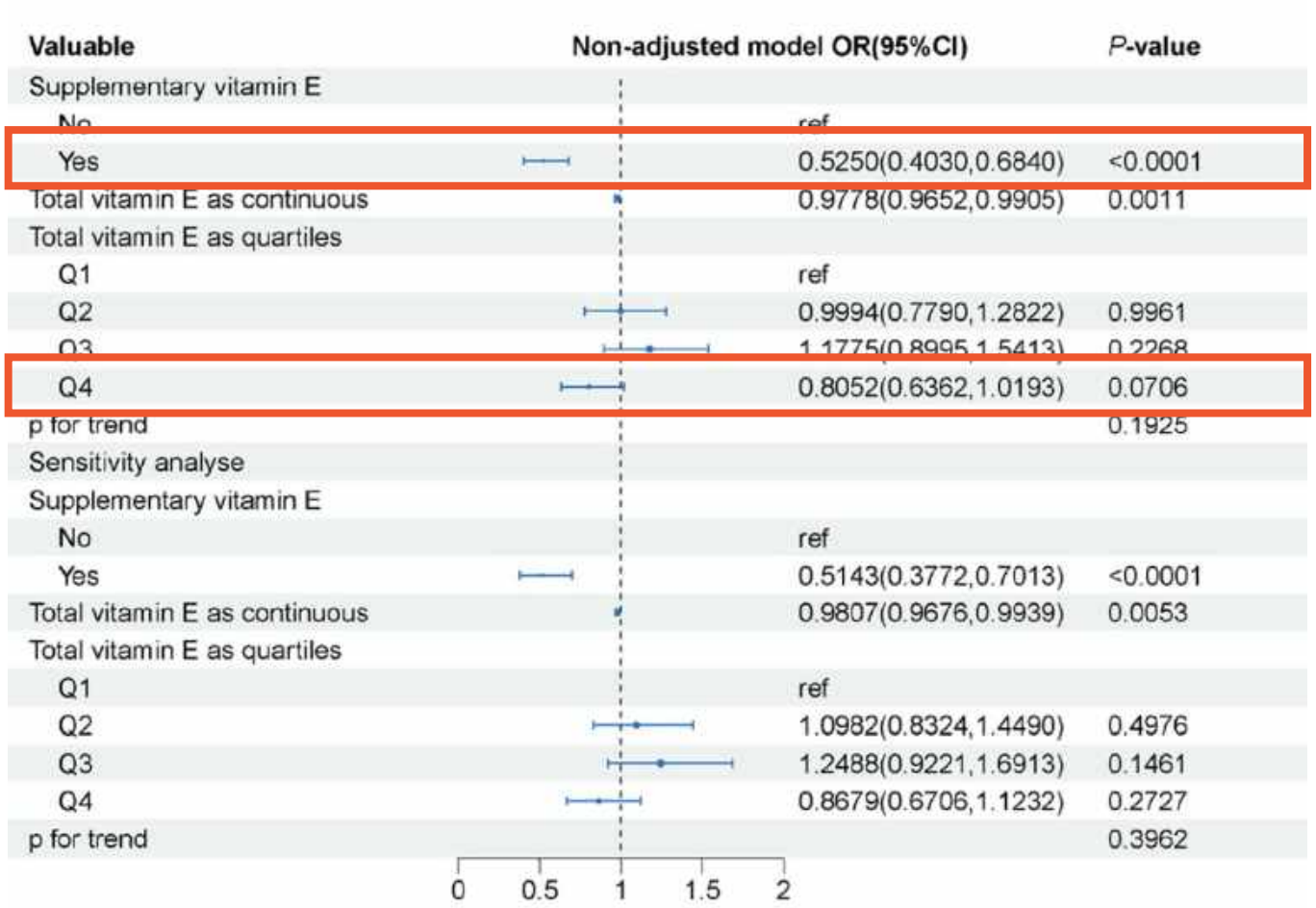
Sanyal 2010 - NEJM 362, 1675-1685

Vitamin E

Cross-sectional study from the National Health and Nutrition Examination Survey (2017 – 2020)

Diagnosis bases on CAP

6,112 participants



Valuable	Non-adjusted model OR(95%CI)	*P*-value
Supplementary vitamin E		
No	ref	
Yes	0.5250(0.4030,0.6840)	<0.0001
Total vitamin E as continuous	0.9778(0.9652,0.9905)	0.0011
Total vitamin E as quartiles		
Q1	ref	
Q2	0.9994(0.7790,1.2822)	0.9961
Q3	1.1775(0.8995,1.5413)	0.2268
Q4	0.8052(0.6362,1.0193)	0.0706
p for trend		0.1925
Sensitivity analyse		
Supplementary vitamin E		
No	ref	
Yes	0.5143(0.3772,0.7013)	<0.0001
Total vitamin E as continuous	0.9807(0.9676,0.9939)	0.0053
Total vitamin E as quartiles		
Q1	ref	
Q2	1.0982(0.8324,1.4490)	0.4976
Q3	1.2488(0.9221,1.6913)	0.1461
Q4	0.8679(0.6706,1.1232)	0.2727
p for trend		0.3962

Qi et al. Sci Rep. 2024 Jan 31;14(1):2592.

Regulatory Framework for Drug Approval

Full Approval

Based on major adverse liver outcomes

Conditional Approval

Based on surrogate endpoint reasonably likely to predict clinical benefits

FDA

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

VERSUS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MASH resolution with no worsening of fibrosis
AND
At least 1 stage fibrosis improvement with no worsening of MASH

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FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

EMA. Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious diseases (PBC, PSC, NASH). 2018

MASH Development

A Climb to the Goal

Drugs in Phase 3

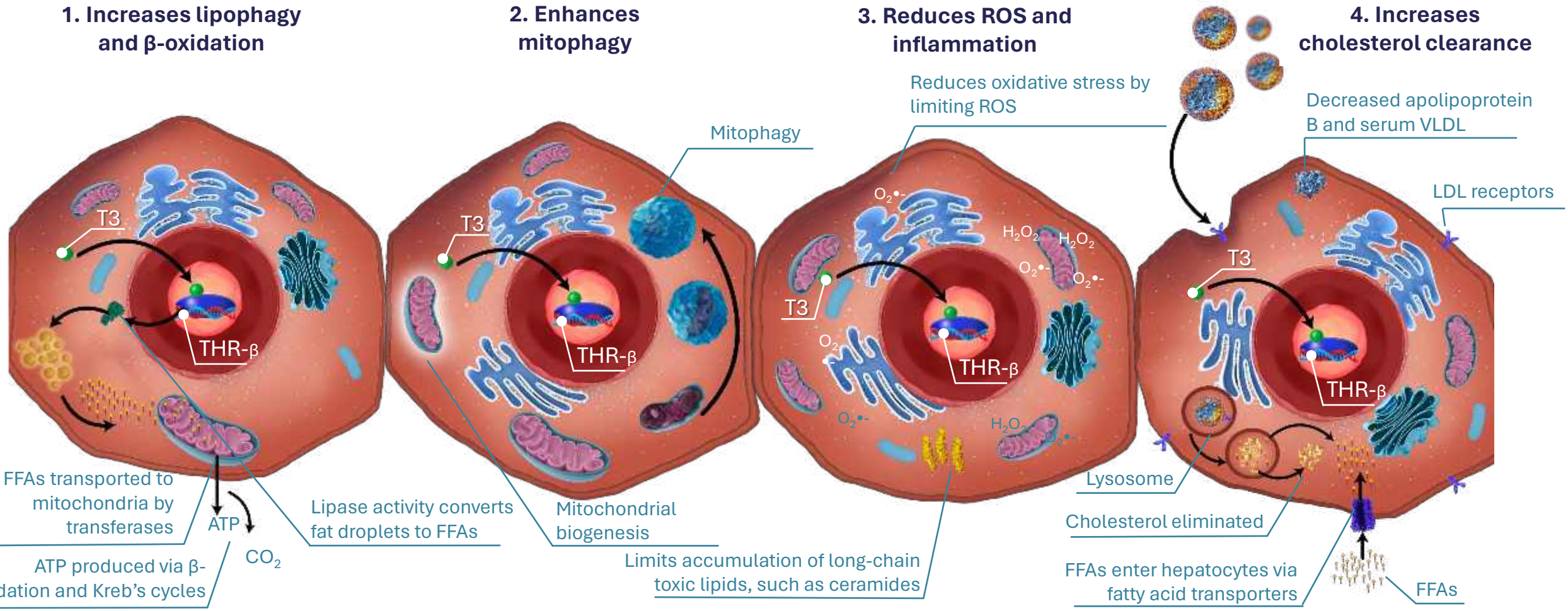
Oral agents

- Resmetirom
- Lanifibranor

Injectable/infusion

- Semaglutide
- Efruxifermin
- Pegozafermin

Role of THR-β in Hepatic Lipid Metabolism



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.

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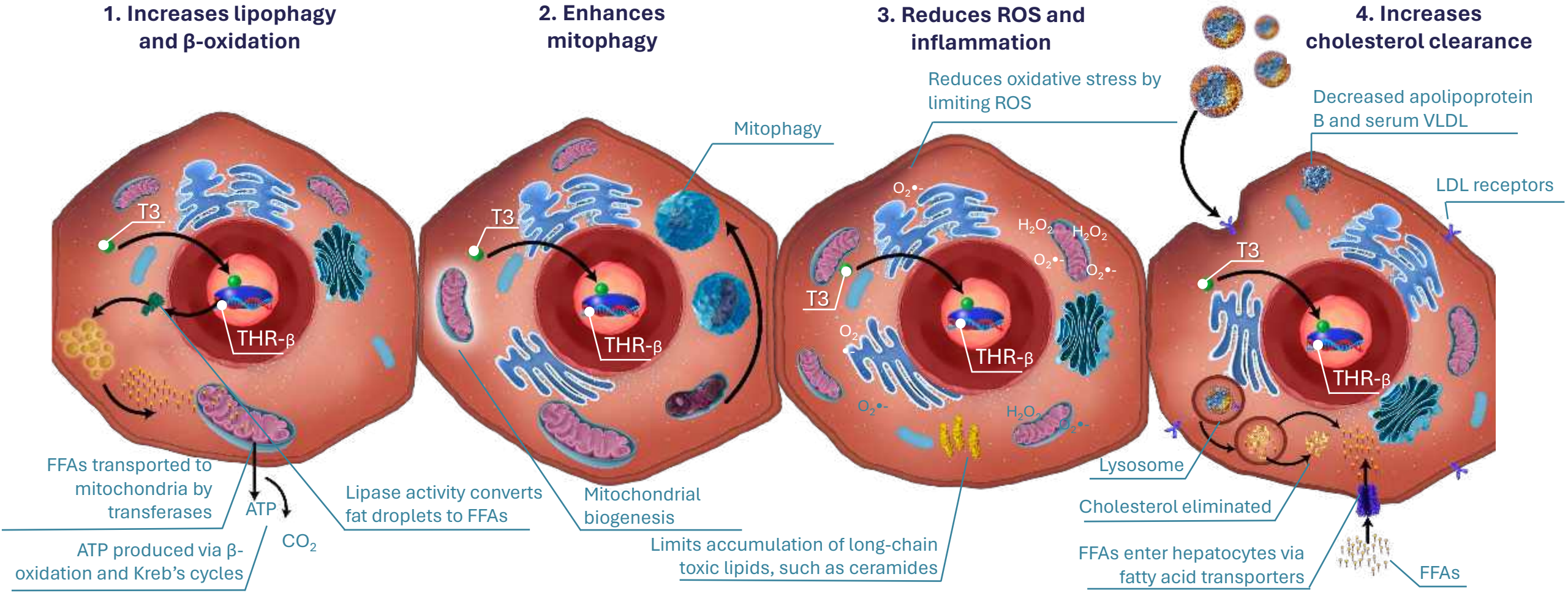
Taub R, et al. Atherosclerosis. 2013;230:373-380.
Taub R, et al. (NASH-TAG Conference; 04-06 Jan 2018; Park City, UT.
Harrison SA, et al. Lancet. 2019;394:2012-2024.

Role of THR-β in Hepatic Lipid Metabolism



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Saponaro F, et al. Front Med (Lausanne). 2020;7:331.
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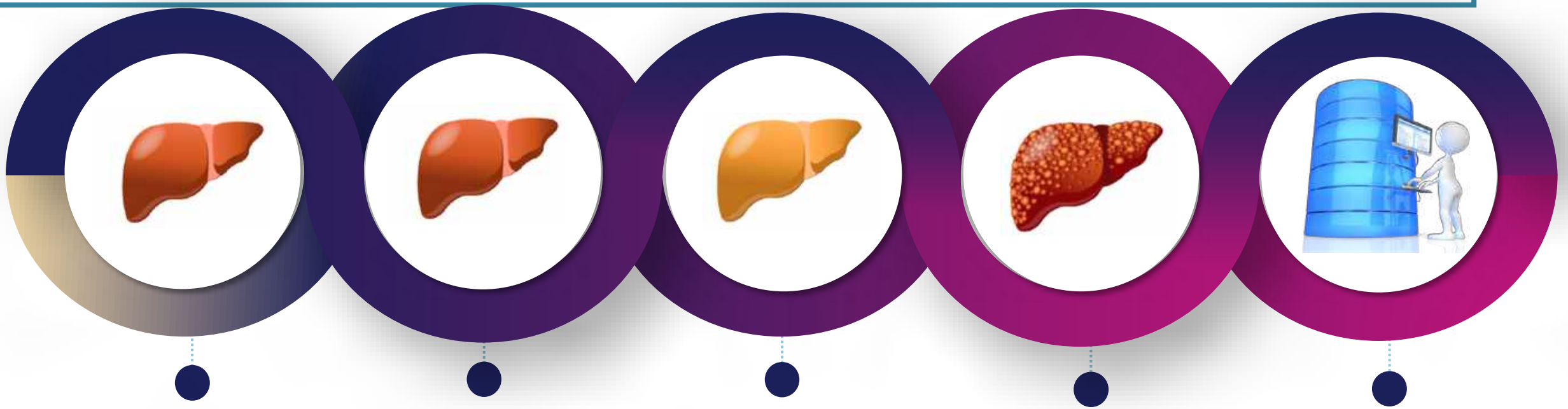
Harrison SA, et al. Lancet. 2019;394:2012-2024.

Resmetirom – Phase 3 Program



MAESTRO NAFLD-1

Safety and tolerability as measured by incidence of AEs over 52 weeks in >1200 patients

MAESTRO NAFLD-OLE

52-week extension to MAESTRO-NAFLD-1 in >700 patients: Safety & tolerability by incidence of AEs over 52 weeks

MAESTRO NASH

Subpart H:
NASH resolution or fibrosis improvement on serial liver biopsy at Week 52
Outcomes
(54 months – ongoing)

MAESTRO NASH OUTCOMES

Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis

A total of > 1500 patients at the top dose of 100 mg and > 2000 patients on at least 80 mg to support accelerated approval

.

Resmetirom – Phase 3 Program

KEY ELIGIBILITY CRITERIA

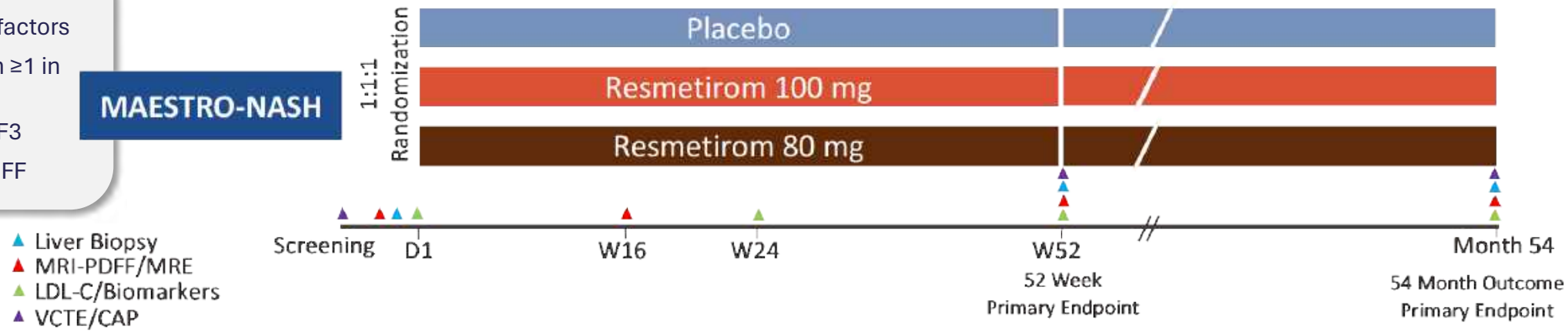
Presence of ≥3 metabolic risk factors

NASH on biopsy: NAS ≥4 (with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH



DUAL PRIMARY ENDPOINT AT WEEK 52

MASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis

≥1-stage improvement in fibrosis with no worsening of NAS

Harrison S, et al. N Engl J Med. 2024 Feb 8;390(6):497-509

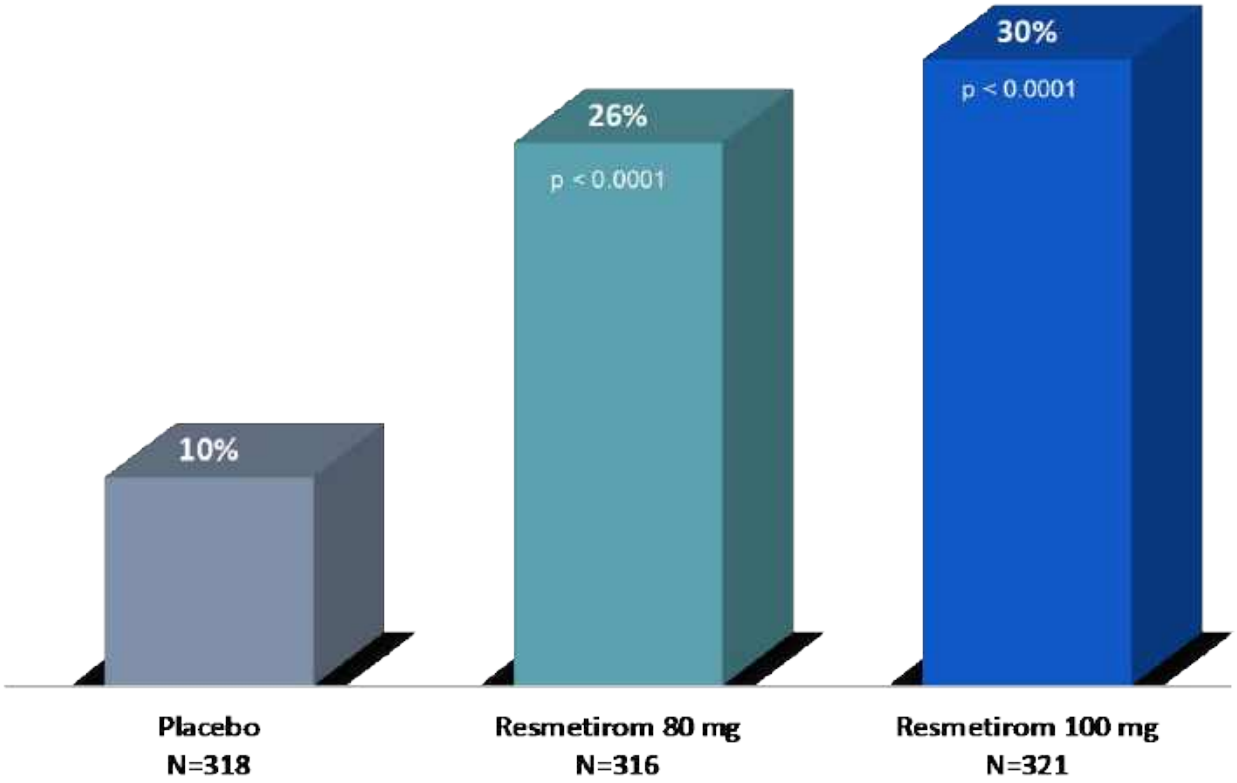
Resmetirom – Phase 3 Program

RESMETIROM

Oral, once-daily

Phase 3
52 weeks

MASH Resolution
with no worsening of fibrosis



Harrison S, et al. N Engl J Med. 2024 Feb 8;390(6):497-509

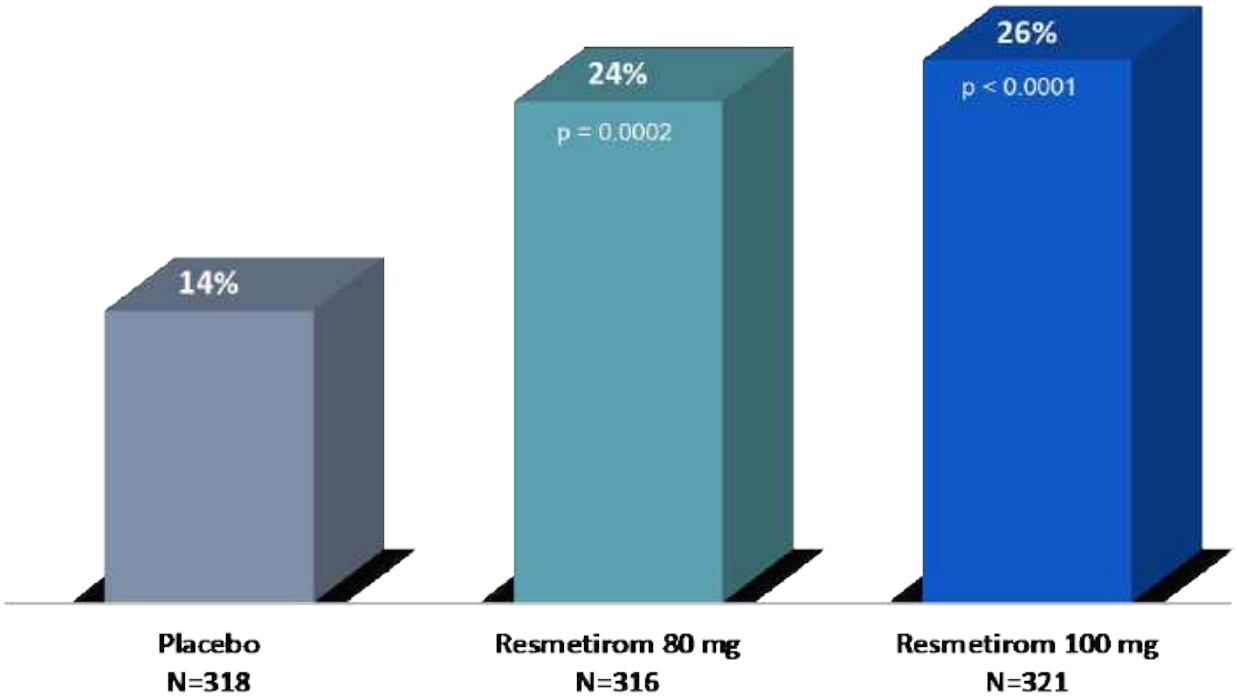
Resmetirom – Phase 3 Program

RESMETIROM

Oral, once-daily

Phase 3
52 weeks

Fibrosis Improvement (≥ 1 stage)
with no worsening of MASH



Harrison S, et al. N Engl J Med. 2024 Feb 8;390(6):497-509

Resmetirom – Phase 3 Program

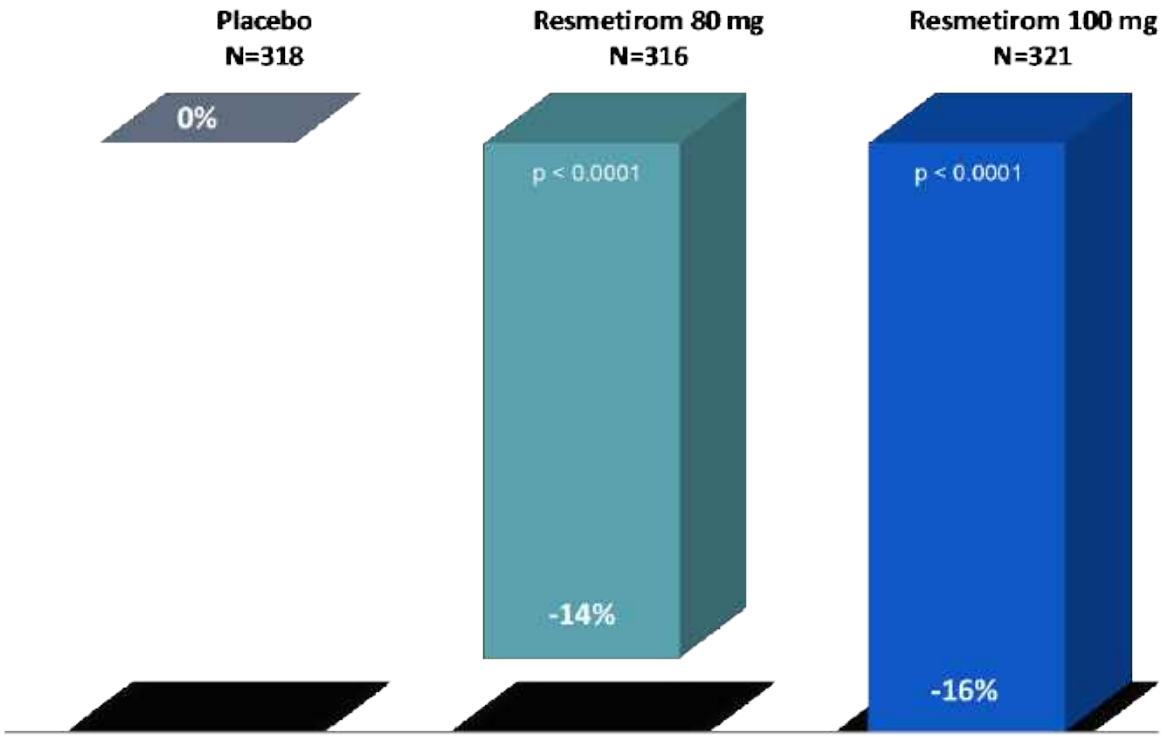
RESMETIROM

Oral, once-daily

Phase 3
52 weeks

Additional Benefits

Key secondary endpoint: LDL-cholesterol



Harrison S, et al. N Engl J Med. 2024 Feb 8;390(6):497-509

Resmetirom – Phase 3 Program

RESMETIROM

Oral, once-daily

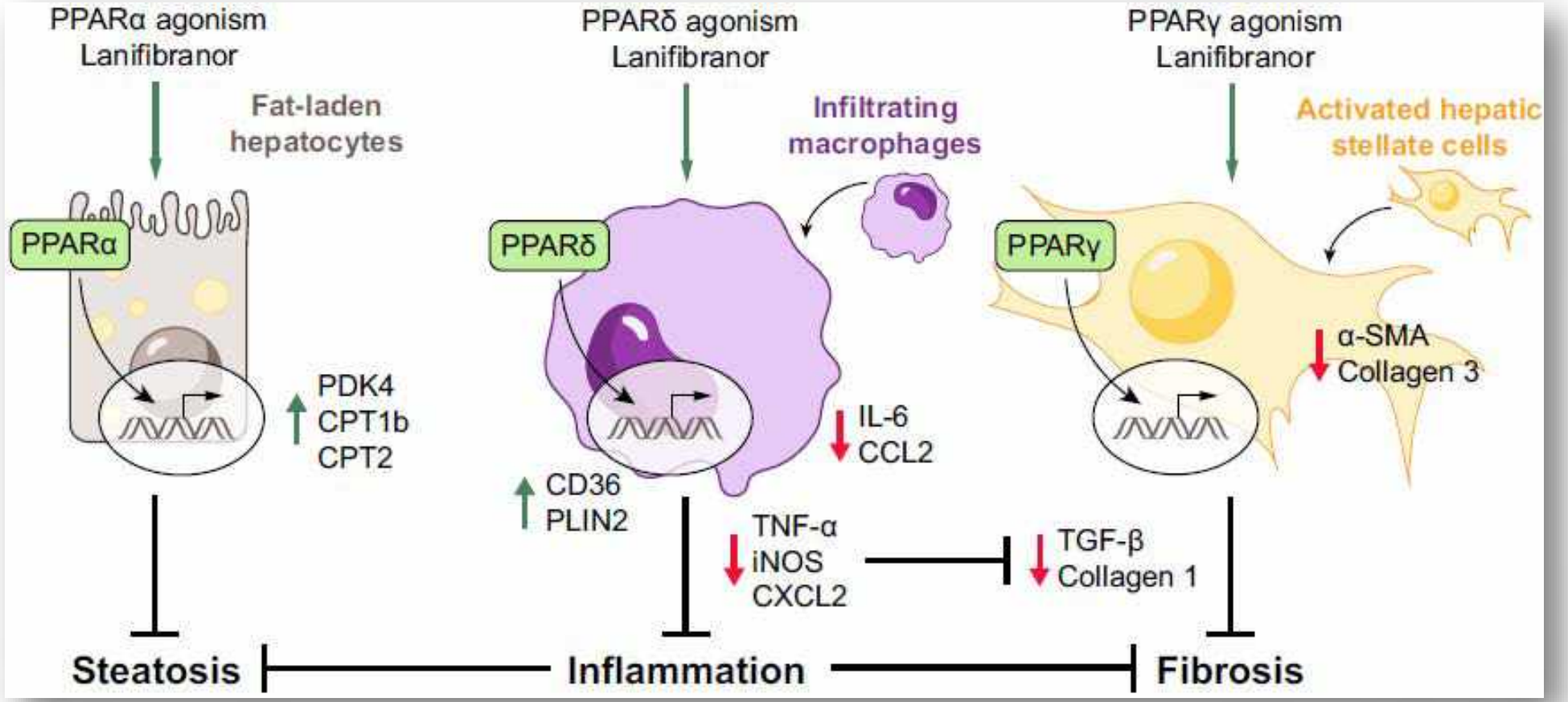
Phase 3
52 weeks

Safety Overview

- Overall, well tolerated
- Gastrointestinal disorders
  - Nausea
  - Diarrhea
- Minimal reduction in prohormone free T4
  No effect on active hormone free T3 or TSH

Harrison S, et al. N Engl J Med. 2024 Feb 8;390(6):497-509

Lanifibranor – Mechanism of Action



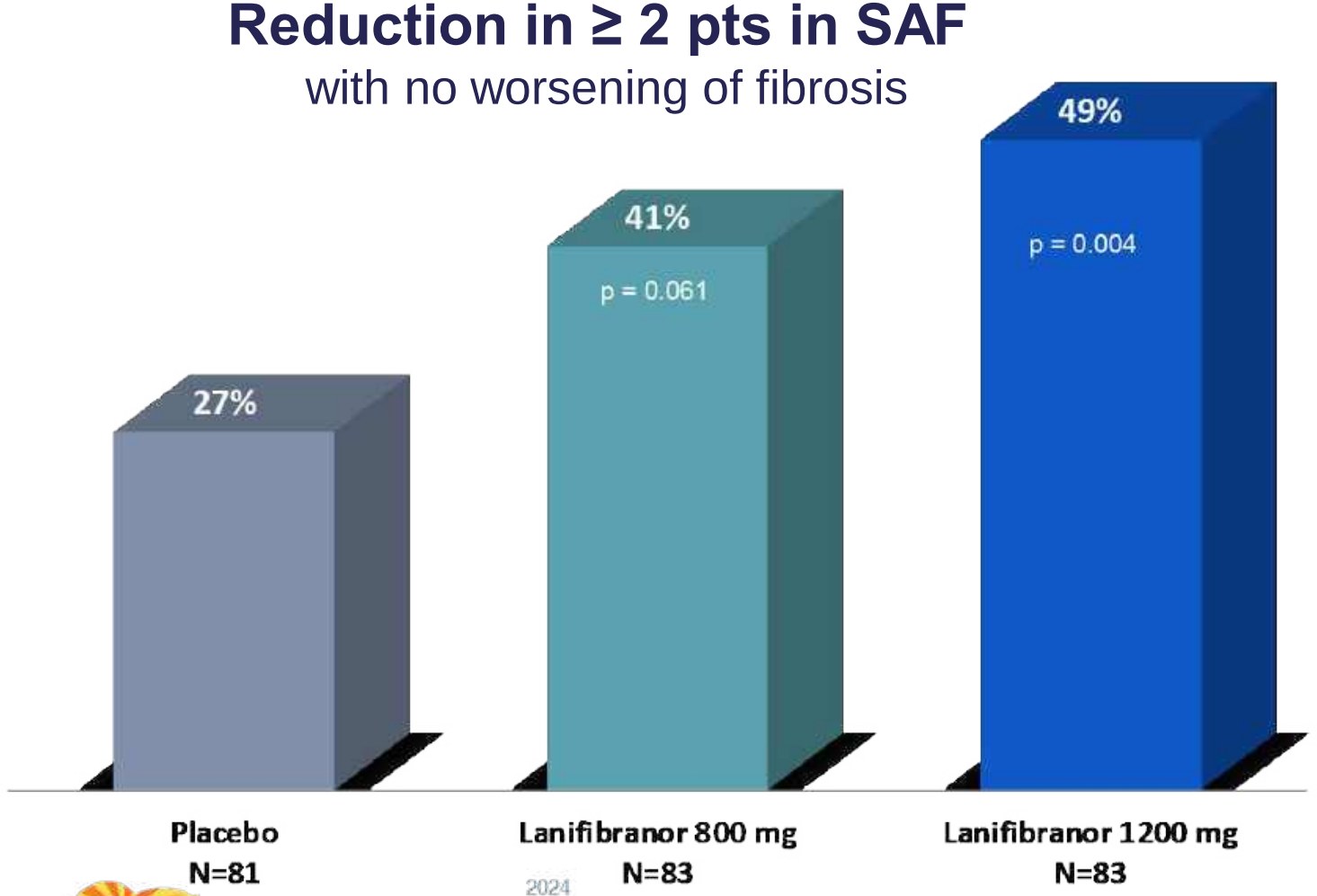
Newsome PN et al. N Engl J Med 2021;384:1113-1124

Lanifibranor – Phase 2b

LANIFIBRANOR

Oral, once-daily

Phase 2 b
24 weeks



Newsome PN et al. N Engl J Med 2021;384:1113-1124

Lanifibranor – Phase 2b

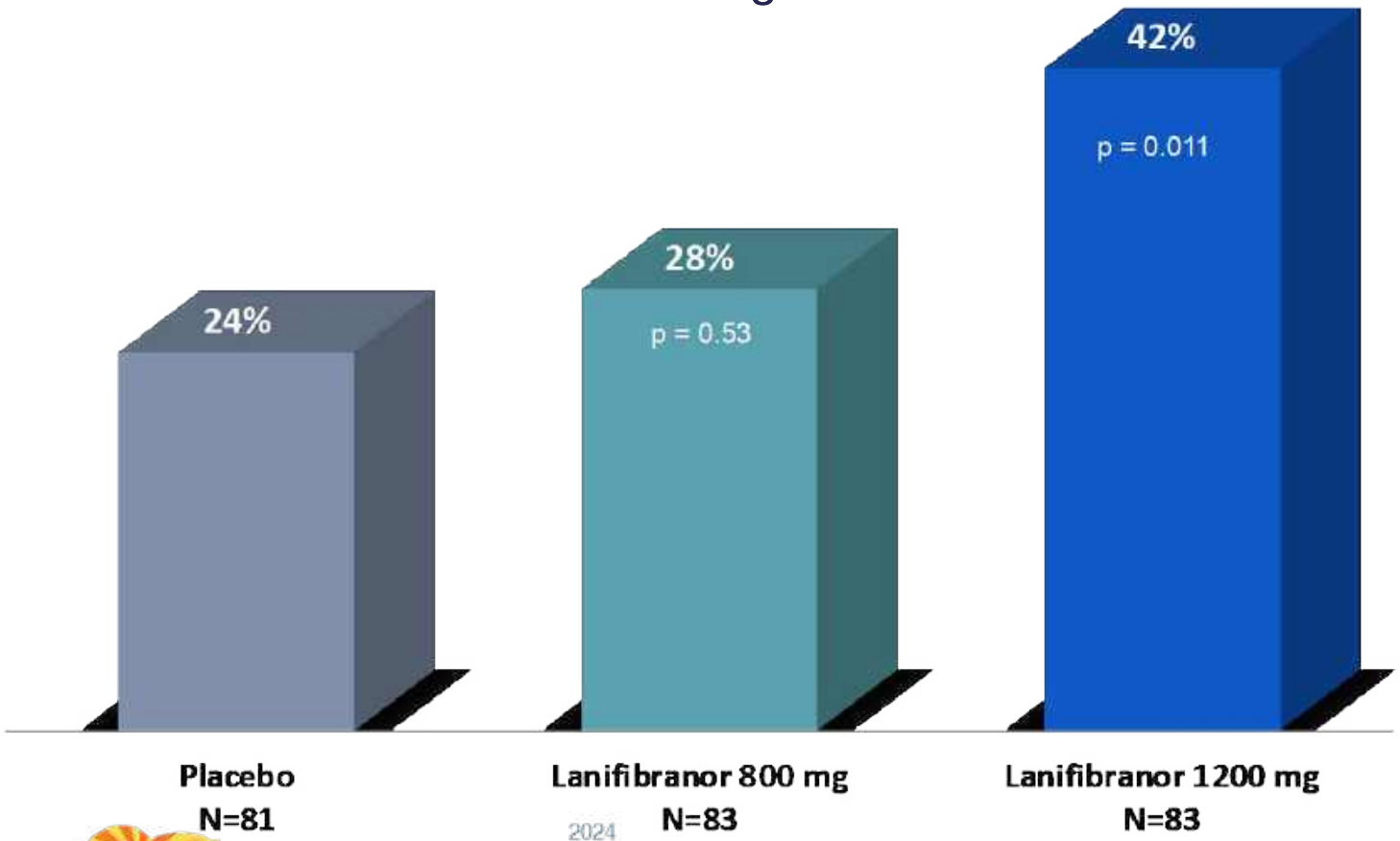
LANIFIBRANOR

Oral, once-daily

Phase 2 b
24 weeks

Fibrosis Improvement (≥ 1 stage)

with no worsening of MASH



Newsome PN et al. N Engl J Med 2021;384:1113-1124

Lanifibranor – Phase 2b

LANIFIBRANOR

Oral, once-daily

Phase 2 b
24 weeks

Additional Benefits

Lipid and glycemic control

Absolute Change from Baseline

	Placebo N=74	Lani 800 mg N=77	Lani 1200 mg N=77
TG, mmol/L	**0.06** (-0.12 to 0.23)	**-0.49** (-0.66 to -0.31)	**-0.44** (-0.61 to -0.27)
HOMA-IR	**-1.47** (-2.59 to -0.35)	**-5.79** (-6.92 to -4.65)	**-5.46** (-6.60 to -4.32)
HbA1c	**0.07** (-0.02 to 0.17)	**-0.38** (-0.47 to -0.28)	**-0.41** (-0.51 to -0.32)

Newsome PN et al. N Engl J Med 2021;384:1113-1124

Lanifibranor – Phase 2b

LANIFIBRANOR

Oral, once-daily

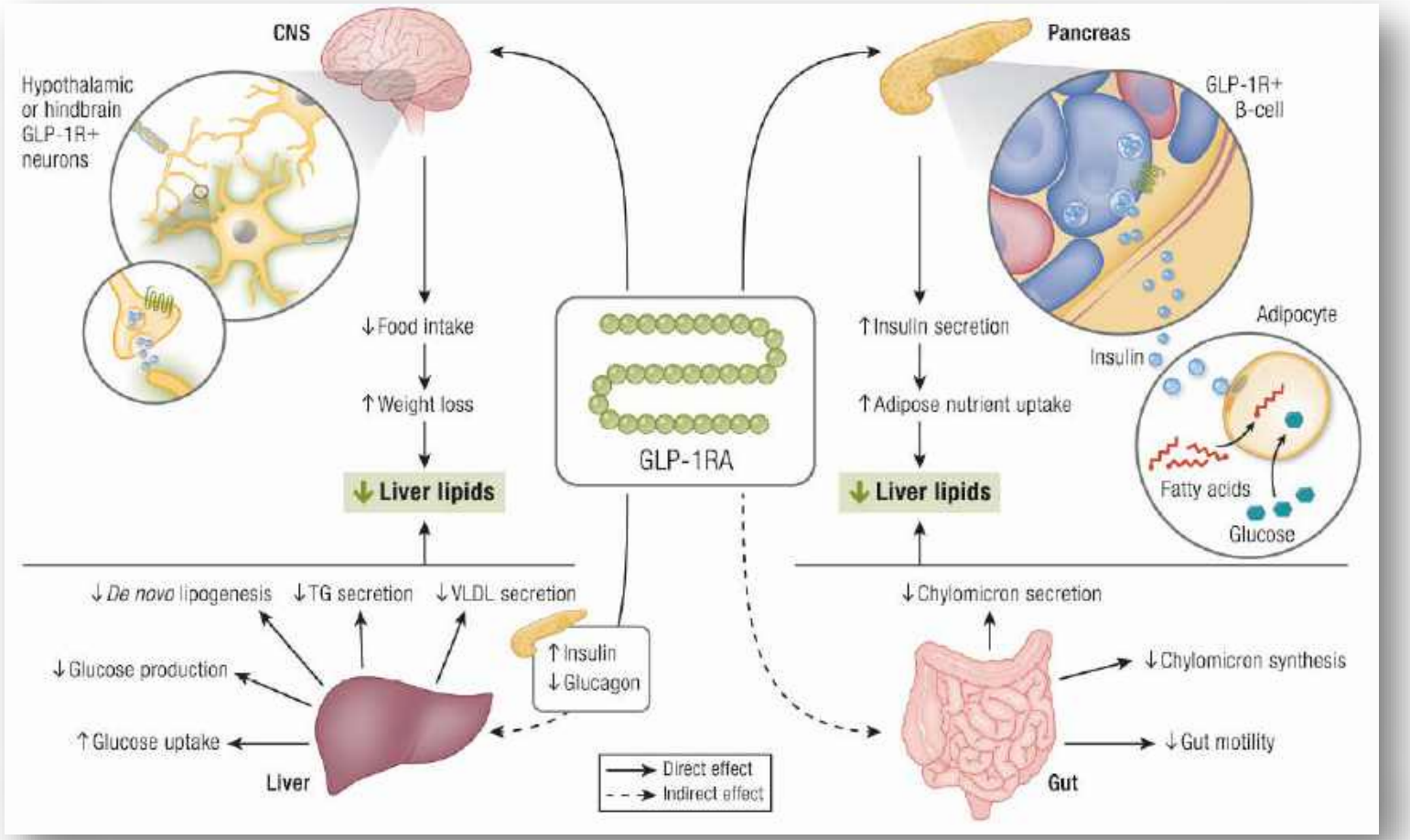
Phase 2 b
24 weeks

Safety Overview

- Overall, well tolerated
- Gastrointestinal disorders
  - Nausea
  - Diarrhea
- PPAR related side effects
  - Pitting edema
  - Gain weight
  - Anemia

Newsome PN et al. N Engl J Med 2021;384:1113-1124

GLP1-RA – Mechanism of Action



Yabut JM. Endocr Rev 2022

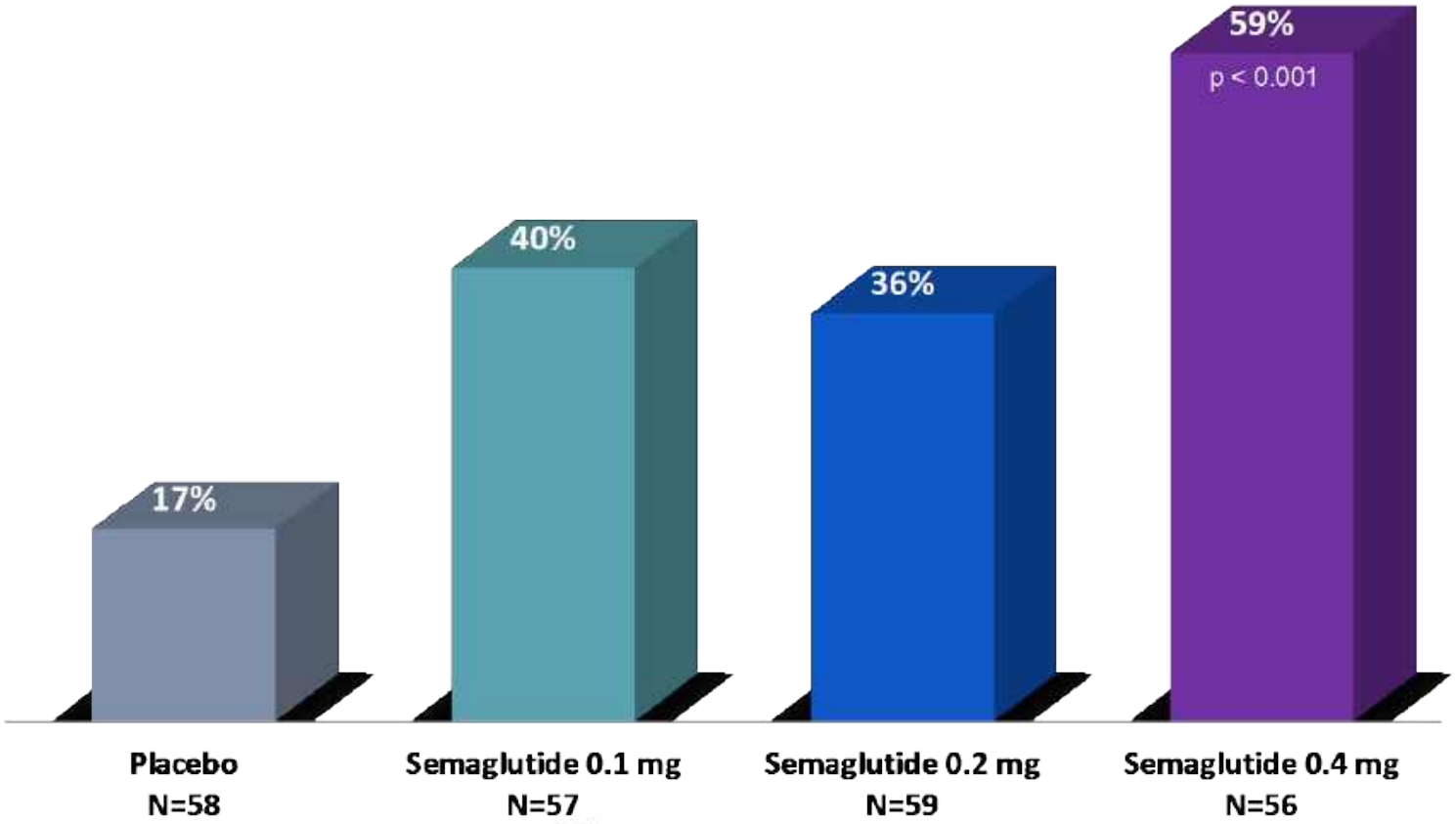
Semaglutide – Phase 2b

SEMAGLUTIDE

Subcutaneous, QW

Phase 2 b
72 weeks

MASH Resolution
with no worsening of fibrosis



Newsome PN et al. N Engl J Med 2021;384:1113-1124.

Semaglutide – Phase 2b

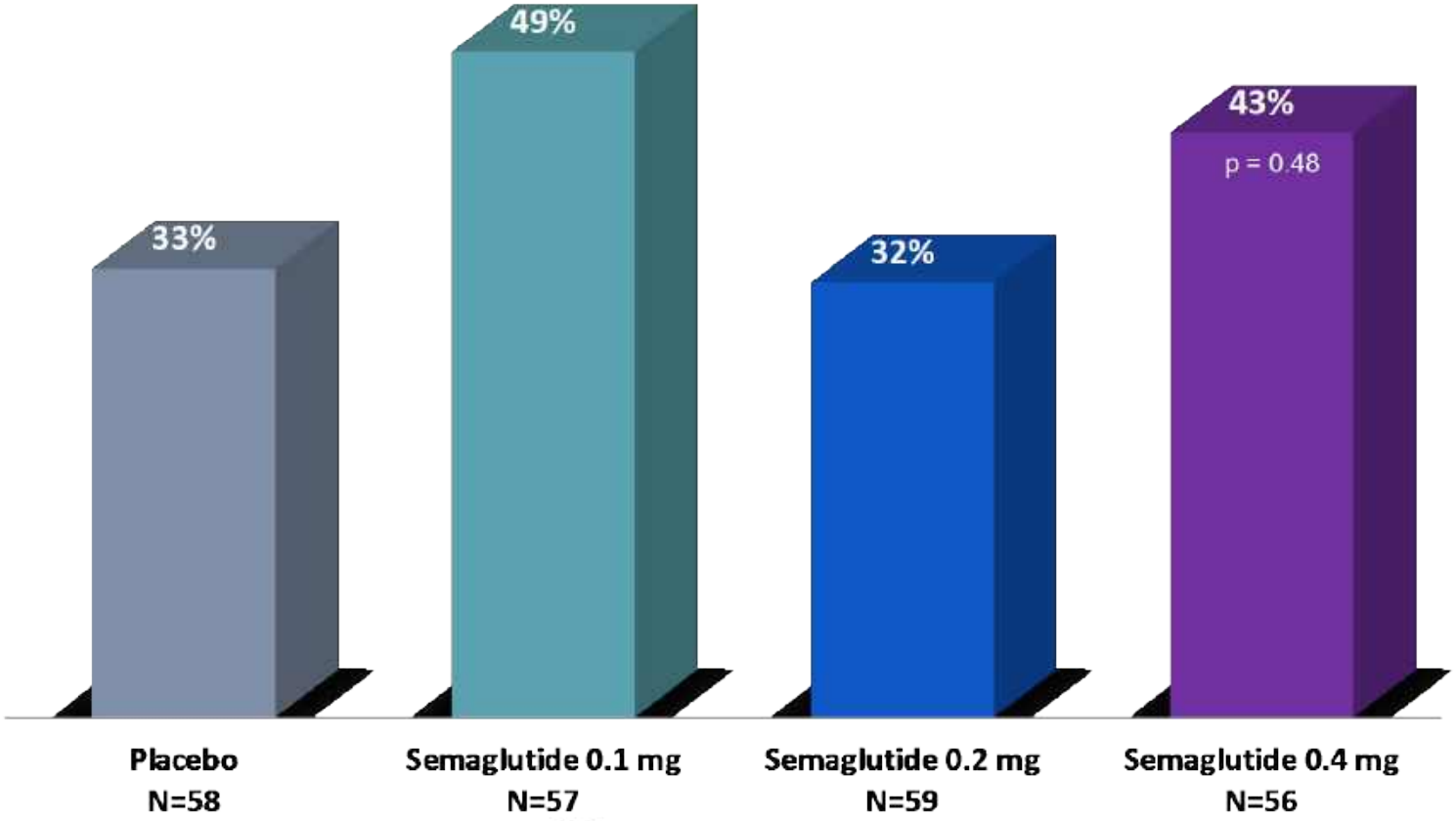
SEMAGLUTIDE

Subcutaneous, QW

Phase 2 b
72 weeks

Fibrosis Improvement (≥ 1 stage)

with no worsening of MASH



Newsome PN et al. N Engl J Med 2021;384:1113-1124.

Semaglutide – Phase 2b

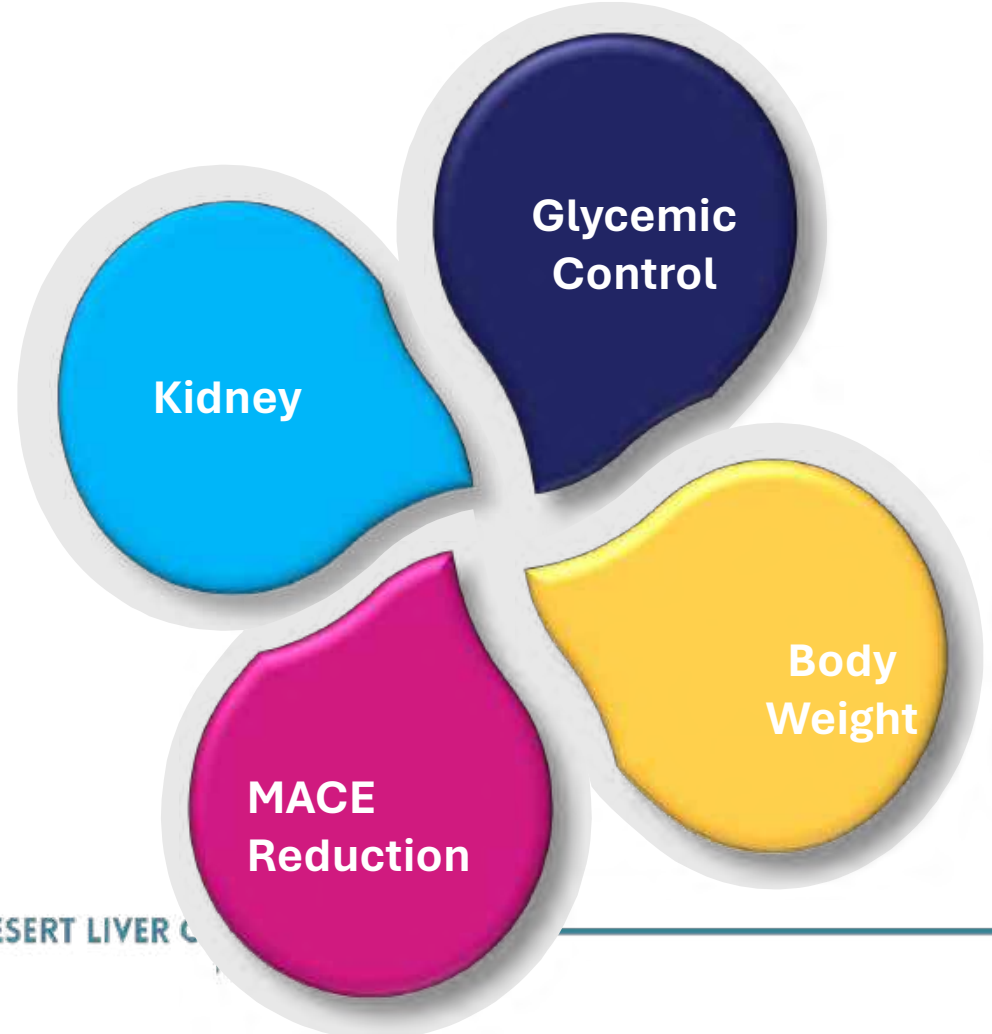
SEMAGLUTIDE

Subcutaneous, QW

Phase 2 b
72 weeks

Additional Benefits

Evidence from T2DM & Obesity Clinical Development



DESERT LIVER

Michos ED et al. Am J Prev Cardiol. 2023 May 24;14:100502

Semaglutide – Phase 2b

SEMAGLUTIDE

Subcutaneous, QW

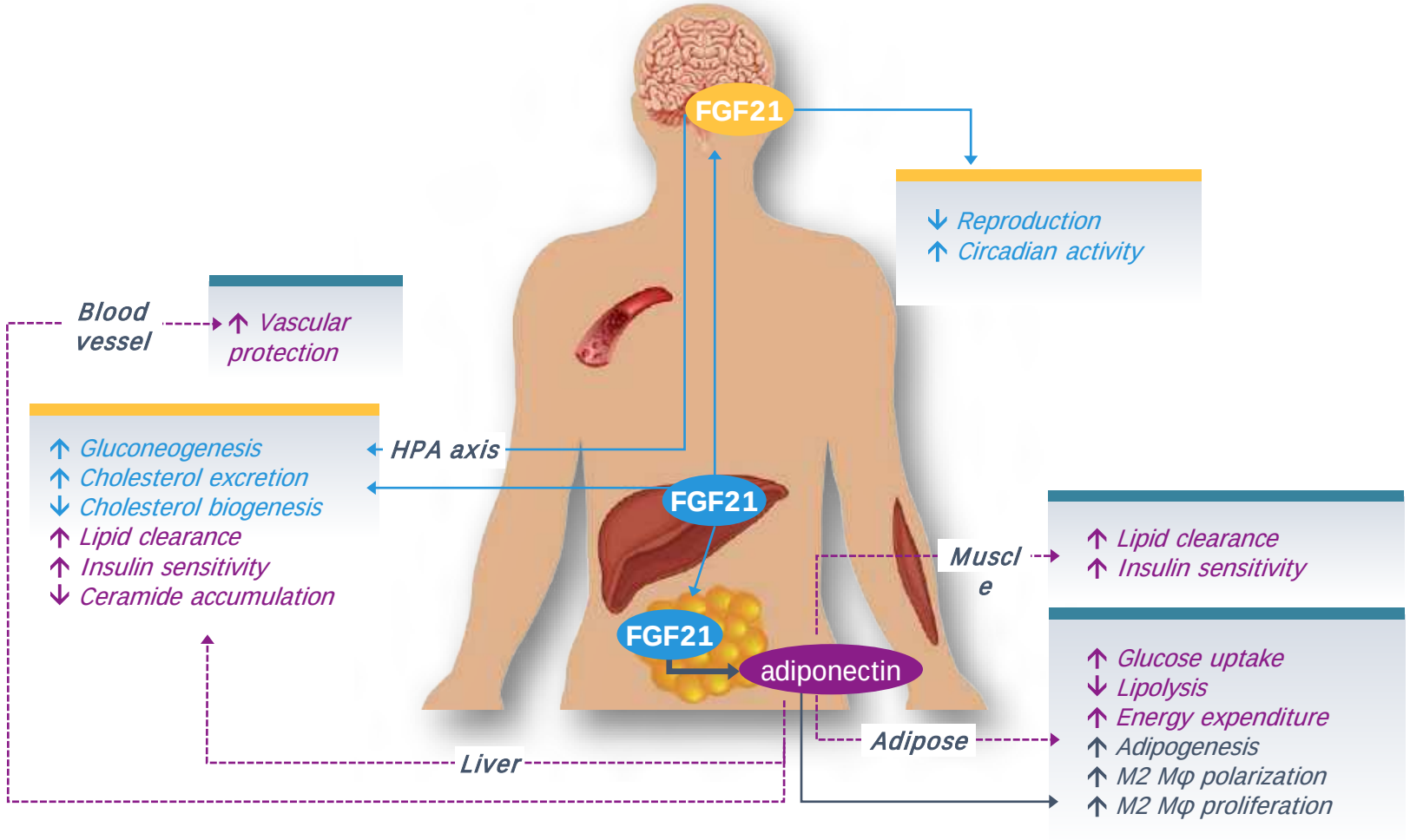
Phase 2 b
72 weeks

Safety Overview

- Overall, well tolerated
- Gastrointestinal disorders
  - Nausea
  - Diarrhea
- Sarcopenia

Newsome PN et al. N Engl J Med 2021;384:1113-1124.

FGF-21 Has Potential to Be Mainstay of Therapy



Endogenous metabolic hormone that regulates energy expenditure and glucose and lipid metabolism

Reduces liver fat by action within liver and from periphery

Impacts liver fibrosis via metabolic pathway and upregulation of adiponectin

Native FGF21 has a **short half-life** of < 2 hours

Geng L, et al. Nat Rev Endocrinol. 2020 Nov;16:654-667.

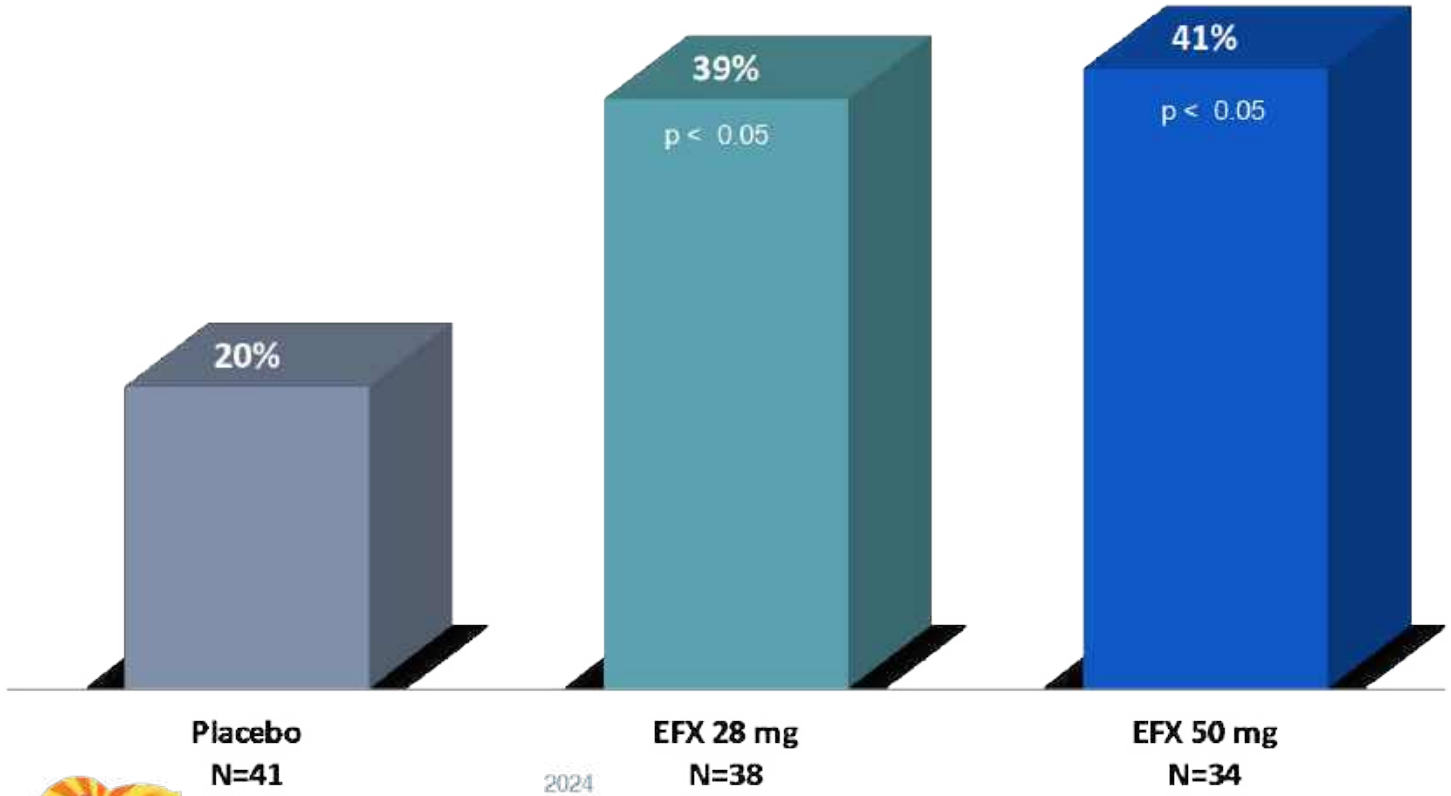
Efruxifermin – Phase 2b

EFRUXIFERMIN

Subcutaneous, QW

Phase 2 b
24 weeks

Fibrosis Improvement (≥ 1 stage)
with no worsening of MASH



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Harrison SA et al. Lancet Gastroenterol Hepatol. 2023 Dec;8(12):1080-1093

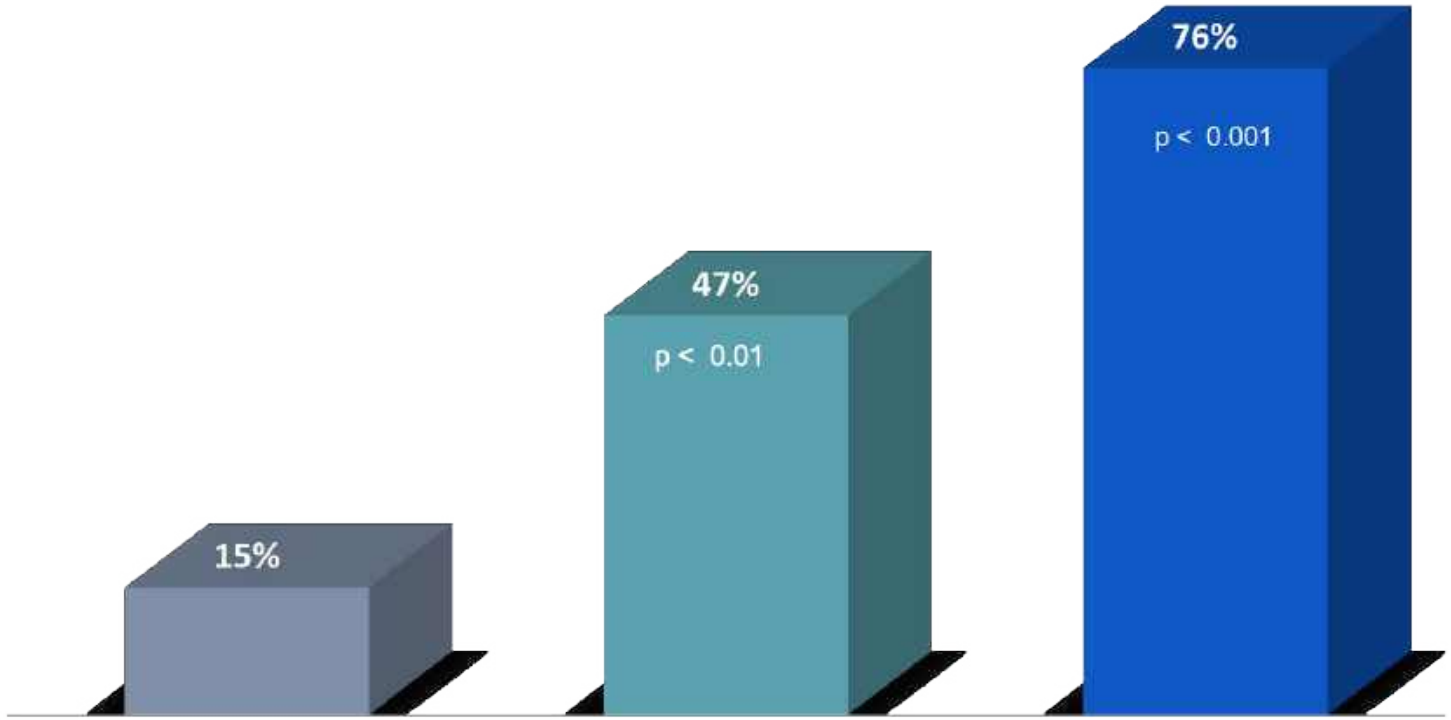
Efruxifermin – Phase 2b

EFRUXIFERMIN

Subcutaneous, QW

Phase 2 b
24 weeks

MASH Resolution
with no worsening of fibrosis



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Harrison SA et al. Lancet Gastroenterol Hepatol. 2023 Dec;8(12):1080-1093

Efruxifermin – Phase 2b

EFRUXIFERMIN

Subcutaneous, QW

Phase 2 b
24 weeks

Additional Benefits

Lipid & glycemic control, and body weight reduction

Absolute Change from Baseline

	Placebo	EFX 28 mg	EFX 50 mg
Body weight	-0.6	-0.2	-2.9
HbA1c	0	-0.3	-0.4

Percent Change from Baseline

	Placebo	EFX 28 mg	EFX 50 mg
TG	+9	-25	-29
LDL-c	+9	-8	-8

Harrison SA et al. Lancet Gastroenterol Hepatol. 2023 Dec;8(12):1080-1093

Efruxifermin – Phase 2b

EFRUXIFERMIN

Subcutaneous, QW

Phase 2 b
24 weeks

Safety Overview

- Overall, well tolerated
- Gastrointestinal disorders
  - Nausea
  - Diarrhea

Harrison SA et al. Lancet Gastroenterol Hepatol. 2023 Dec;8(12):1080-1093

Pegozafermin – Phase 2b

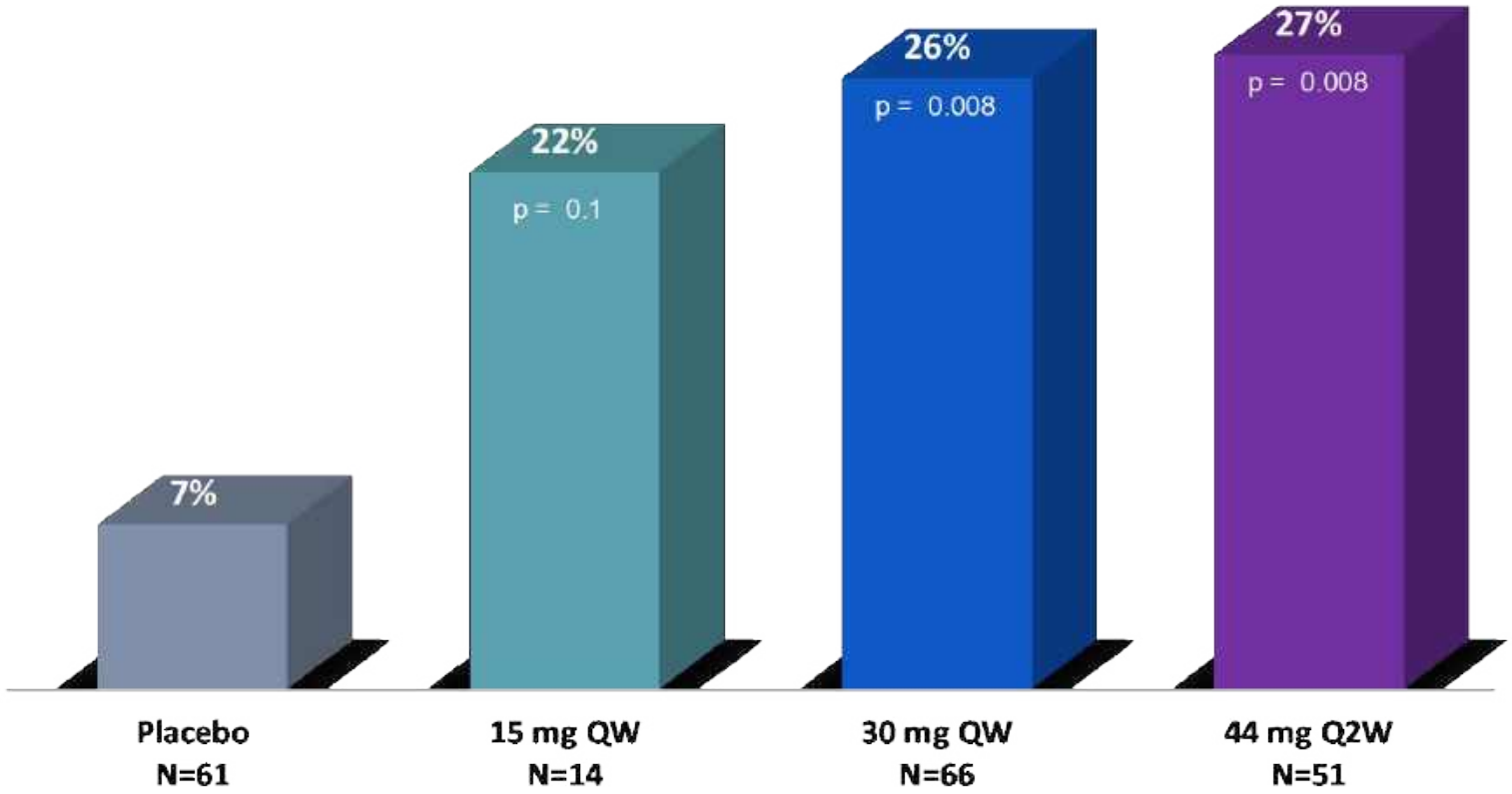
PEGOZAFERMIN

Subcutaneous
QW or Q2W

Phase 2 b
24 weeks

Fibrosis Improvement (≥ 1 stage)

with no worsening of MASH



Loomba et al. N Engl J Med. 2023 Sep 14;389(11):998-1008

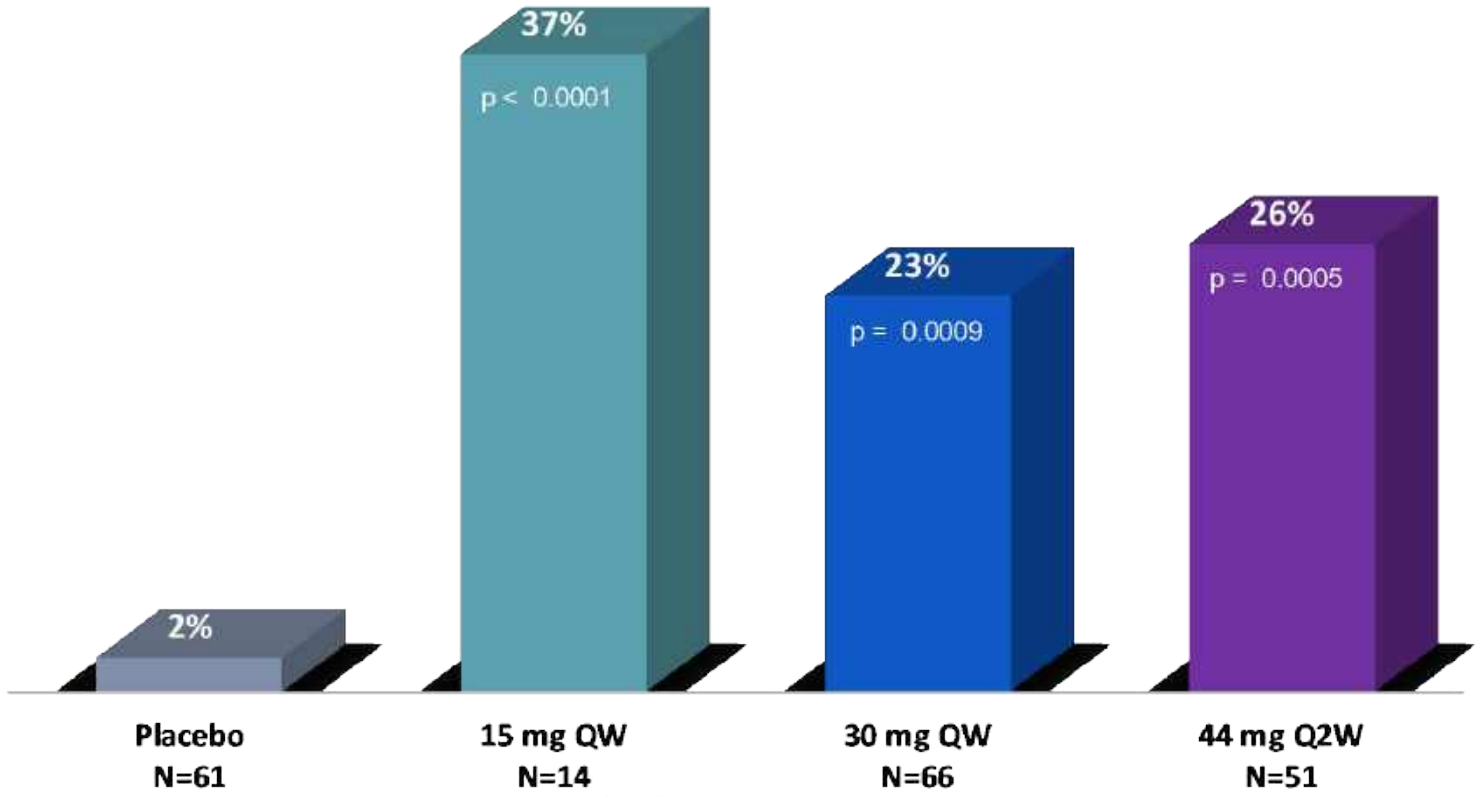
Efruxifermin – Phase 2b

PEGOZAFERMIN

Subcutaneous
QW or Q2W

Phase 2 b
24 weeks

MASH Resolution
with no worsening of fibrosis



Loomba et al. N Engl J Med. 2023 Sep 14;389(11):998-1008

Efruxifermin – Phase 2b

PEGOZAFERMIN

Subcutaneous
QW or Q2W

Phase 2 b
24 weeks

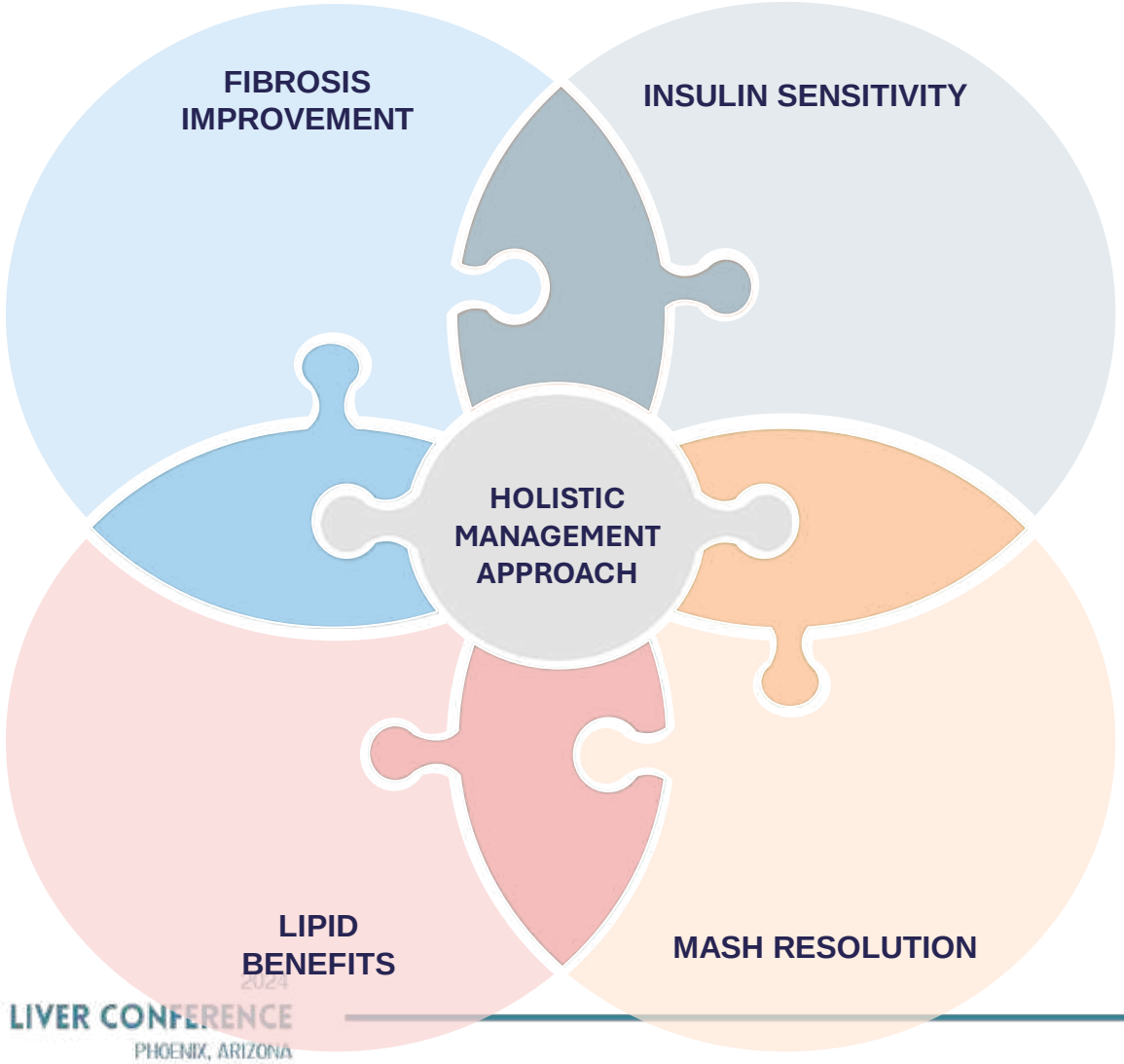
Safety Overview

- Overall, well tolerated
- Gastrointestinal disorders
  - Nausea
  - Diarrhea

Loomba et al. N Engl J Med. 2023 Sep 14;389(11):998-1008

My Perspective on Non-Cirrhotic NASH

What looks like the IDEAL TREATMENT



My Perspective on Non-Cirrhotic NASH

Drugs in Phase 3	Administration	NASH Resolution	Fibrosis Improvement	Insulin Sensitivity	Lipid Benefits	Safety Tolerability
Resmetirom		✓	✓		✓	✓
Lanifibranor		✓	✓	✓	✓	✗
Semaglutide		✓		✓		✗
Efruxifermin		✓	✓	✓	✓	✗
Pegozafermin		✓	✓	✓	✓	✗

My Perspective on Non-Cirrhotic NASH

Completed Phase 2	Administration	NASH Resolution	Fibrosis Improvement	Insulin Sensitivity	Lipid Benefits	Safety Tolerability
PXL065				✓		✓
Icosabutate				✓	✓	✓
Denifanstat		✓	✓			✓
Tirzepatide		✓		✓		✓
Survodutide		✓	✓	✓		✓

My Perspective on Patient Management with New Drugs

Obese (with or without T2DM)
Patients with Mild Disease F0-F2

First line = > GLP1-Ra

Second line = > Resmetirom

My Perspective on Patient Management with New Drugs

Non-T2DM Obese Patients with Advanced Disease F3

First line = > Resmetirom

Second line = > FGF-21

My Perspective on Patient Management with New Drugs

T2DM Obese Patients with Advanced Disease F3

First line = > FGF-21

Second line = > Resmetirom

THANK YOU

2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

Practical SLD Cases and Panel Discussion

- **Naim Alkhouri, MD**
- Chief Medical Officer
- Director of the Steatotic Liver Program
- Arizona Liver Health (ALH)
- Chandler, AZ

ARIZONA LIVER HEALTH™

Objectives

- Discuss the implementation of screening and risk stratification pathways in primary care and endocrinology clinic.

- Describe the management of MASLD/ MASH in specialty care (hepatology and GI).

- @AlkhouriNaim

Real-World Case 1: Primary Care

Jack

Weakness

- 41 y.o. M with BMI of 41 kg/m2 but no T2D or MetS.
- Presents with incidental finding of fatty liver on US done to assess for RUQ pain.
- ALT 56 U/L (10-30 U/L)
- AST 36 U/L (10-30 U/L)
- Albumin 4.4 g/dL (3.5-4.5 g/dL)
- Platelet count 279 k/uL (150-400 k/uL)

FIB4= 0.71 (Low) → Keep in Primary Care → Lifestyle intervention → Repeat FIB4 in 2-3 years

Real World Case 2: Primary Care

Tina

Weakness

- 59 y.o. F with BMI of 42 kg/m2 and MetS presents with elevated LFTs.
- ALT 66 U/L (10-30 U/L)
- AST 61 U/L (10-30 U/L)
- Albumin 4.1 g/dL (3.5-4.5 g/dL)
- Platelet count 191 k/uL (150-400 k/uL)

FIB4= 2.32 (Intermediate) → 2nd NIT

ELF = 9.2 (> 7.7) → Refer to a specialist

Real-World Case 2: Primary Care

Tony

Weakness

- 60 y.o. M with T2D, BMI of 39 kg/m2 and MetS.
- Presents with persistently elevated liver enzymes and fatty liver on US.
- ALT 66 U/L (10-30 U/L)
- AST 76 U/L (10-30 U/L)
- Albumin 3.5 g/dL (3.5-4.5 g/dL)
- Platelet count 147 k/uL (150-400 k/uL)

FIB4= 3.79 (High) → Refer to a specialist

Introducing Mrs T

- Age: 55 years
- BMI: 42 kg/m^2
- LDL-C: 98 mg/dL
- BP: 128/78 mm Hg
- A1C: 6.2%

Medically complicated obesity

Current medications

Atorvastatin: 80 mg daily
Losartan: 50 mg daily

AASLD Practice Guidance: Screening for Advanced Fibrosis in High-Risk Populations

Prevalence of advanced fibrosis in background population: 0.9% to 2.0%

Groups recommended for screening	Prevalence of advanced fibrosis
Medically complicated obesity	4% to 33%
T2D	6% to 19%
MASLD in people with moderate alcohol use	17%
First-degree relatives of people with MASLD cirrhosis	18%

Rationale for screening

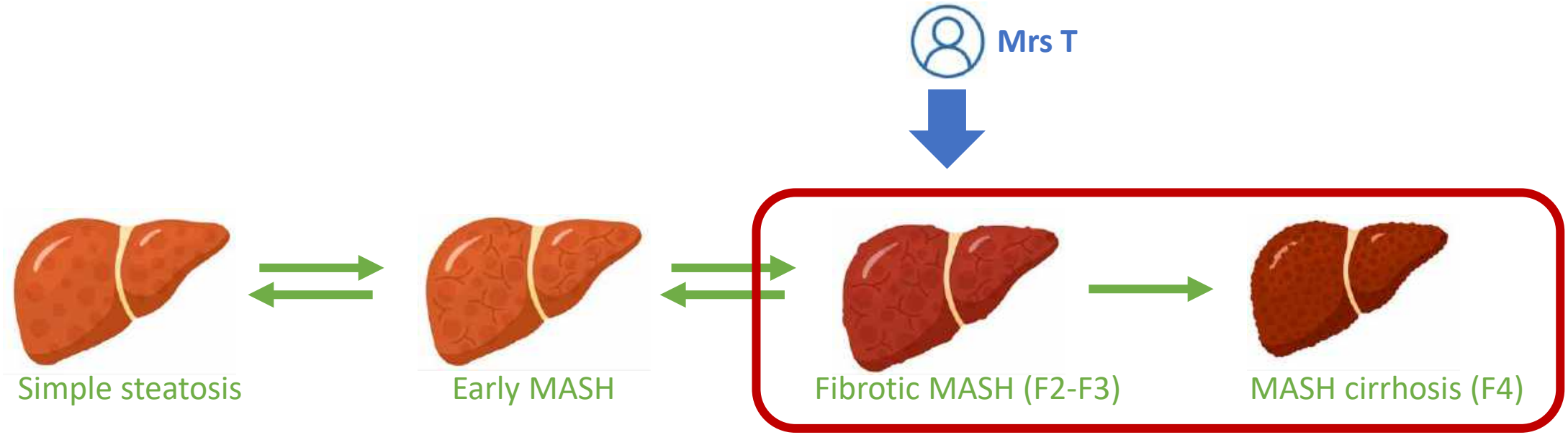
- Certain populations have an elevated risk for advanced fibrosis
- Delayed diagnosis linked to increased morbidity, mortality, and cost
- Off-label use of available medications with mortality benefit (nonhepatic) and probable benefit on MASLD based on trial data

Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835.

Mrs T's Test Results From Primary Care

- ALT: 90 U/L
- AST: 76 U/L
- Albumin: 4.0 g/dL
- Platelet count: 202 k/µL
- Initial FIB-4 in primary care = **2.18** → Sequential testing → Second NIT
- LSM = 9.9 kPa, triggering specialist referral

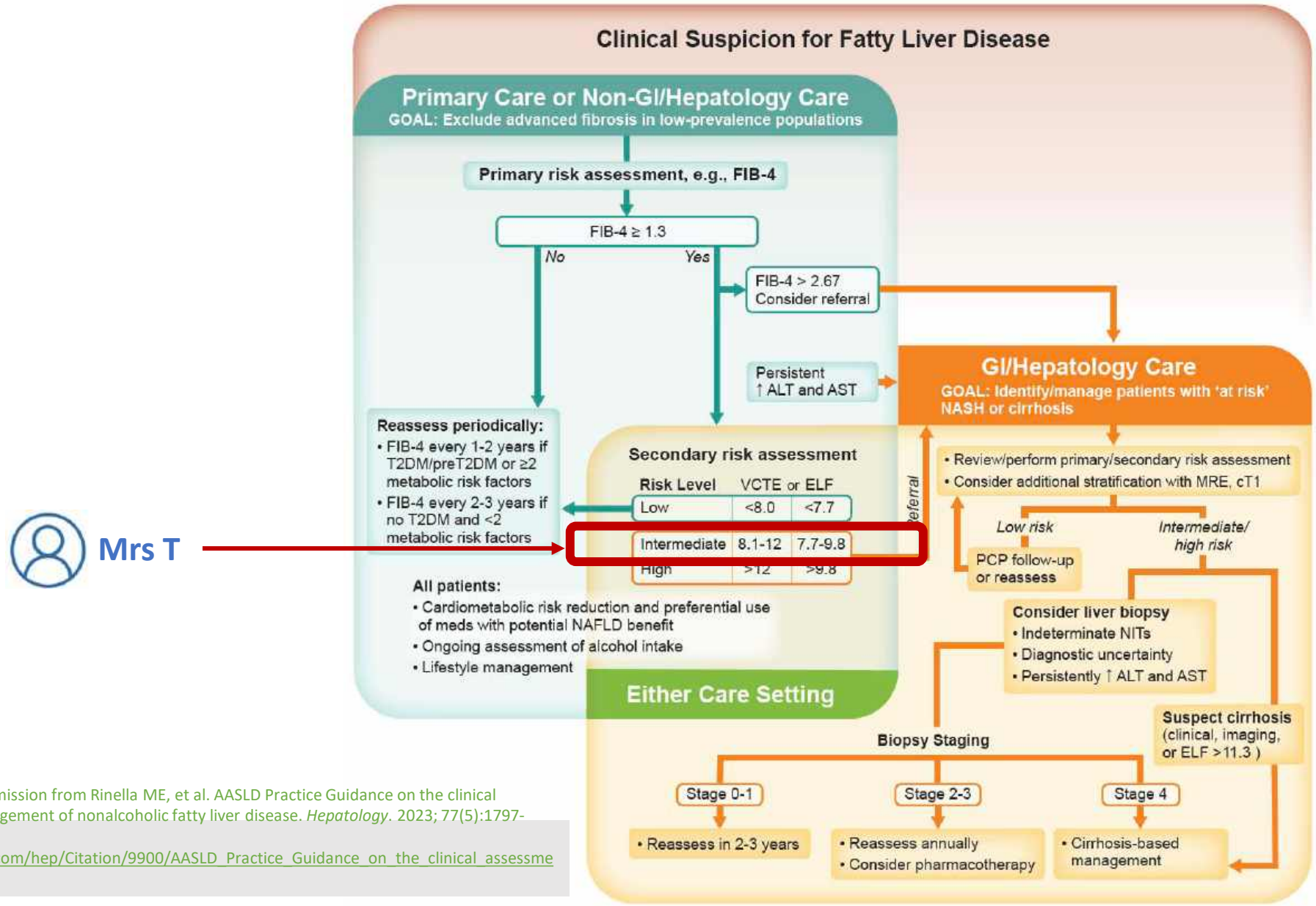
Target Population for Hepatology Care



At-risk MASH = MASH + F2 or higher

Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835.

AASLD Practice Guidance: Primary Care or Specialist Care?



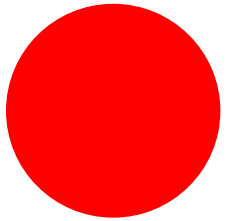
Reproduced with permission from Rinella ME, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023; 77(5):1797-1835; https://journals.lww.com/hep/Citation/9900/AASLD_Practice_Guidance_on_the_clinical_assessment.293.aspx

New Scores for Identifying At-Risk MASH in Specialty Care: FAST

FAST (FibroScan-AST): Composite score calculated from LSM, CAP, and AST

Diagnostic performance across derivation and validation cohorts[1]	
AUROC	0.80-0.95
Rule-out (FAST ≤0.35)	
Sensitivity	0.64-1.00
Specificity	0.35-0.86
NPV	0.73-1.00
Rule-in (FAST ≥0.67)	
Specificity	0.82-0.99
Sensitivity	0.25-0.75
PPV	0.33-0.83

FAST for MASH[2]



≥0.67: high probability of at-risk MASH → enroll in MASH clinical trials

People in the "gray zone" (≈30%) → sequential testing with another test

≤0.35: low probability of at-risk MASH → sequential testing for people with high LSM values

FAST score calculator: https://www.echosens.com/products/fast/

1. Newsome PN, et al. *Lancet Gastroenterol Hepatol*. 2020;5(4):362-373; 2. Noureddin N, et al. *Hepatology*. 2020; 72(6):2228-2230.

Mrs T's Test Results in Hepatology Care

- Mrs T had a risk factor for at-risk MASH (medically complicated obesity) so underwent additional assessment
- VCTE: CAP 343 dB/m, LSM 9.9 kPa → suggestive of moderate-to-advanced fibrosis (F2/F3)
- FAST score: 0.74 → **Mrs T has at-risk MASH with significant fibrosis**

Audience Question

Which of the following interventions would you consider? You may choose more than one.

1. Lifestyle interventions
2. Cardiovascular risk reduction
3. Weight management
4. Pharmacotherapy with proven benefit in MASH such as resmetirom[a]

[a] No pharmacological agent is FDA approved for the treatment of MASH.

Treatment

- Mrs T is already on a statin and antihypertensive agent to manage her lipids and BP; blood glucose is at recommended levels

- Weight management is essential due to high BMI (42 kg/m^2), pre-diabetes, and at-risk MASH with significant fibrosis:
  - Structured lifestyle interventions tailored to the individual
  - Consideration of additional interventions to achieve greater weight loss/manage risk

Audience Question

Would you consider any of the following interventions for Mrs T? You may choose more than one.

1. Bariatric surgery
2. GLP-1 RA (at doses approved for obesity treatment)
3. Pioglitazone
4. SGLT2 inhibitor
5. Vitamin E

Treatment

- You start Mrs T on semaglutide with titration up to 2.4 mg weekly for weight management.
- At her 1-year follow up visit, she has lost 21 lbs and her BMI now is down from 42 to 37 kg/m2:
- ALT: 90 → 65 U/L
- AST: 76 → 61 U/L
- Platelet count: 202 → 211 k/µL
- LSM = 9.9 → 10.4 kPa and CAP 343 → 322.
- If resmetirom is FDA-approved, would you consider starting it for this patient?
  - Heck yeah!
  - Absolutely not!

Introducing Mr F

- Age: 60 years
- BMI: 34 kg/m^2
- LDL-C: 95 mg/dL
- BP: 152/86 mm Hg
- A1C: 6.9% (T2D diagnosed at age 54)

- ALT: 66 U/L
- AST: 76 U/L
- Albumin: 3.5 g/dL
- Platelet count: 147 k/µL
- FIB-4 in primary care = **3.82 (high)**, triggering specialist referral for additional tests

Current medications

Metformin: 1000 mg BID
Sitagliptin: 100 mg daily

Further Assessments in Hepatology Clinic

- VCTE: CAP 302 dB/m; LSM 21.1 kPa → suggestive of cirrhosis (F4)
- Abdominal ultrasound showed nodular liver and splenomegaly of 14.5 cm

Audience Question

What evidence supports the presence of cirrhosis in this individual?

1. VCTE LSM > 20 kPa
2. FIB-4 score > 3.5
3. Nodular liver on ultrasound
4. Splenomegaly
5. All of the above

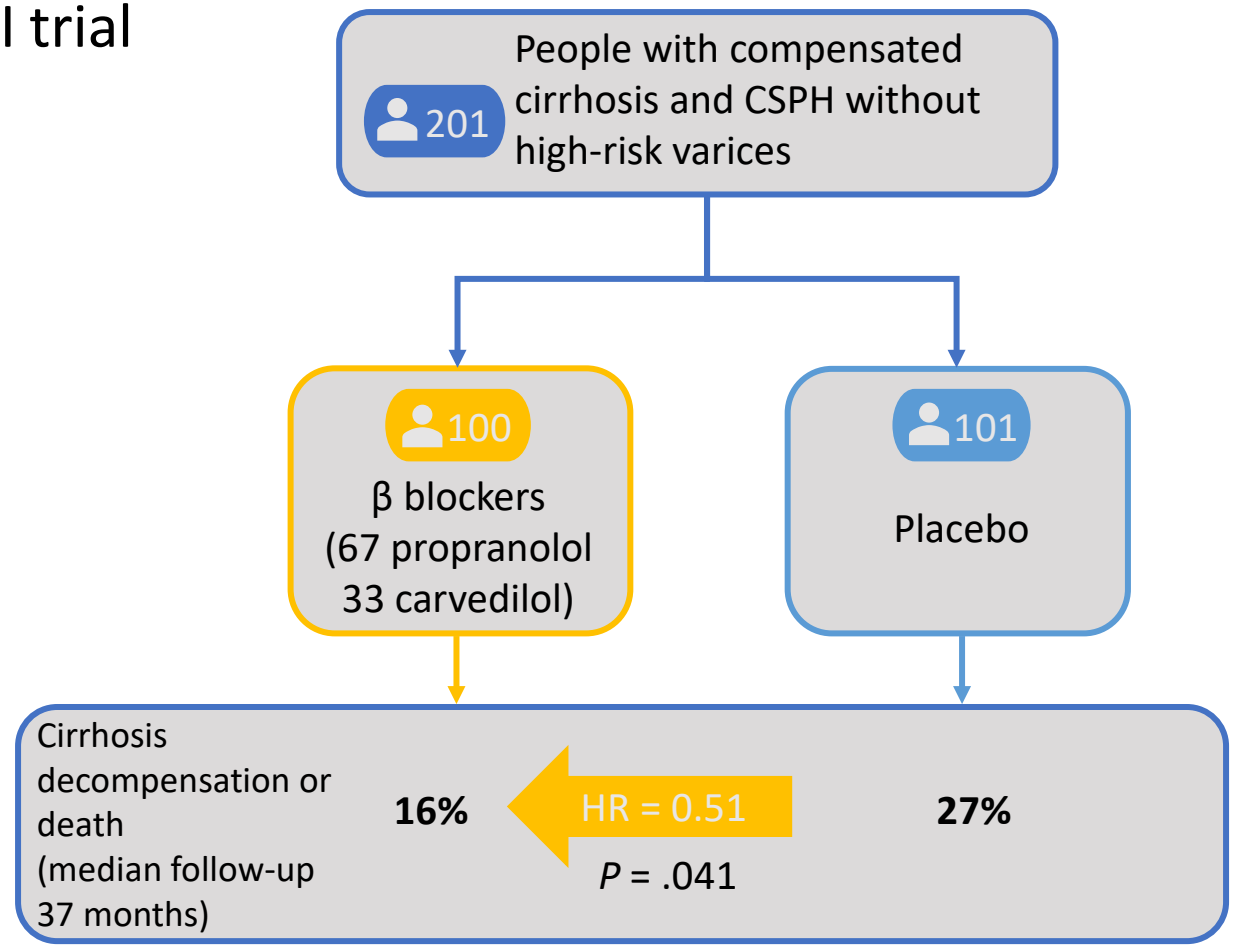
Audience Question

Which of the following interventions would you consider? You may choose more than one.

1. Lifestyle interventions
2. Cardiovascular risk reduction
3. Weight management
4. Initiation of carvedilol for clinically significant portal hypertension
5. Hepatocellular carcinoma surveillance and EGD to screen for varices

β Blockers to Prevent Decompensation of Cirrhosis in Clinically Significant Portal Hypertension

The PREDESCI trial



Villanueva C, et al. *Lancet.* 2019;393(10181):1597-1608.

New Paradigm in the Management of Compensated Cirrhosis

Goal: Prevent clinical decompensation (ascites, variceal hemorrhage, encephalopathy)

LSM and PLT count	Action
LS >25 kPa	CSPH → start carvedilol
LS >20-25 kPa + PLT <150K	CSPH → start carvedilol
LS <20 kPa or PLT >150K	Annual LS and PLT measurement

Garcia-Tsao G, Abraldes JG. *Gastroenterology*. 2021;161(3):770-773.

Treatment

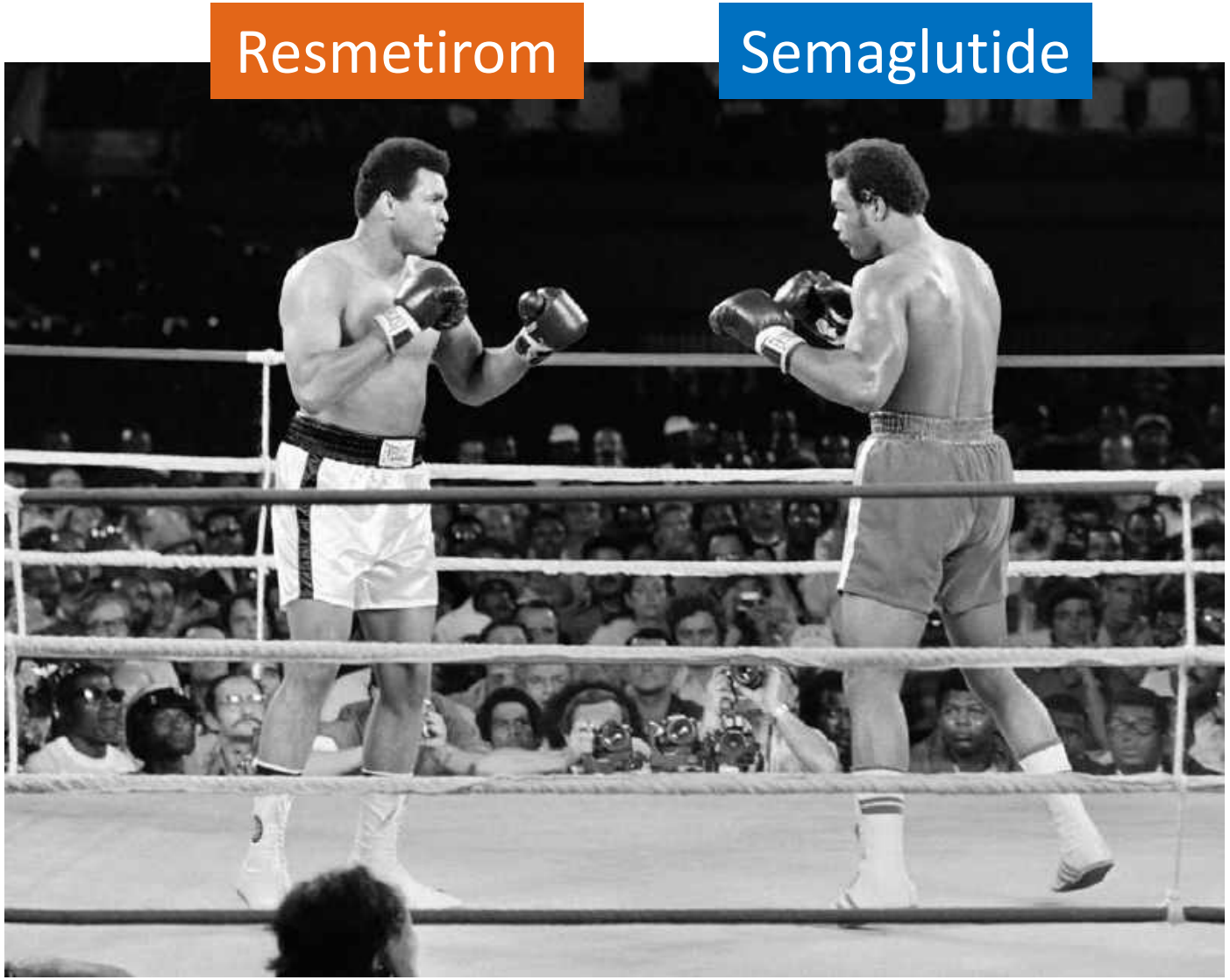
- Weight management is essential due to high BMI (34 kg/m^2):
  - Structured lifestyle interventions tailored to the individual
  - Strong need for additional interventions to achieve greater weight loss/manage risk
- Mr F also has T2D, which is managed with medication

Audience Question

Considering the whole clinical picture, would you suggest any changes to Mr F's T2D medication?

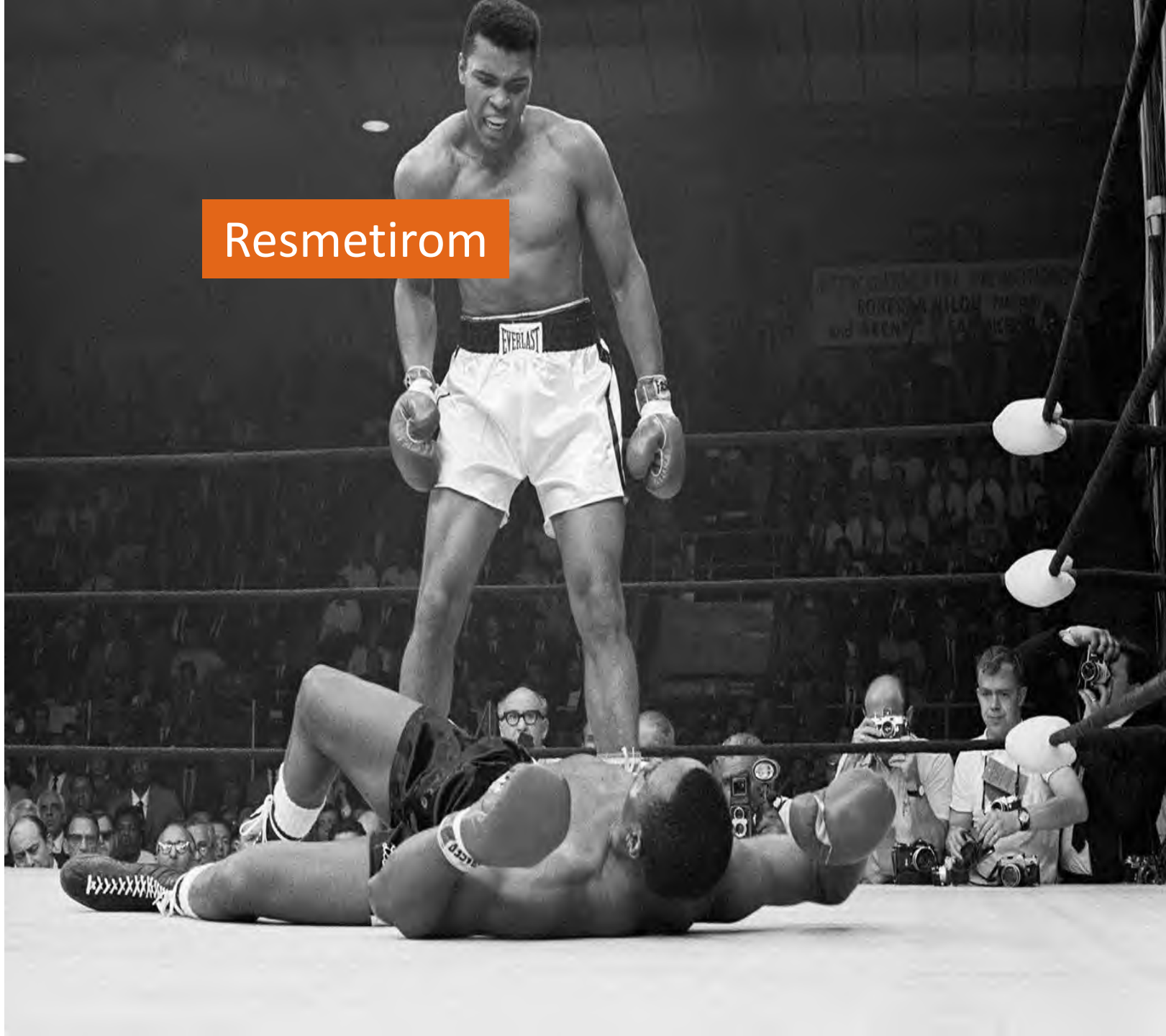
1. No, leave it unaltered
2. Yes, replace the DPP-4 inhibitor with a GLP-1 RA
3. Yes, replace the DPP-4 inhibitor with pioglitazone
4. Yes, replace the DPP-4 inhibitor with an SGLT2 inhibitor
5. Yes, replace the DPP-4 inhibitor with insulin

The Big Fight/ The Rumble in the Jungle



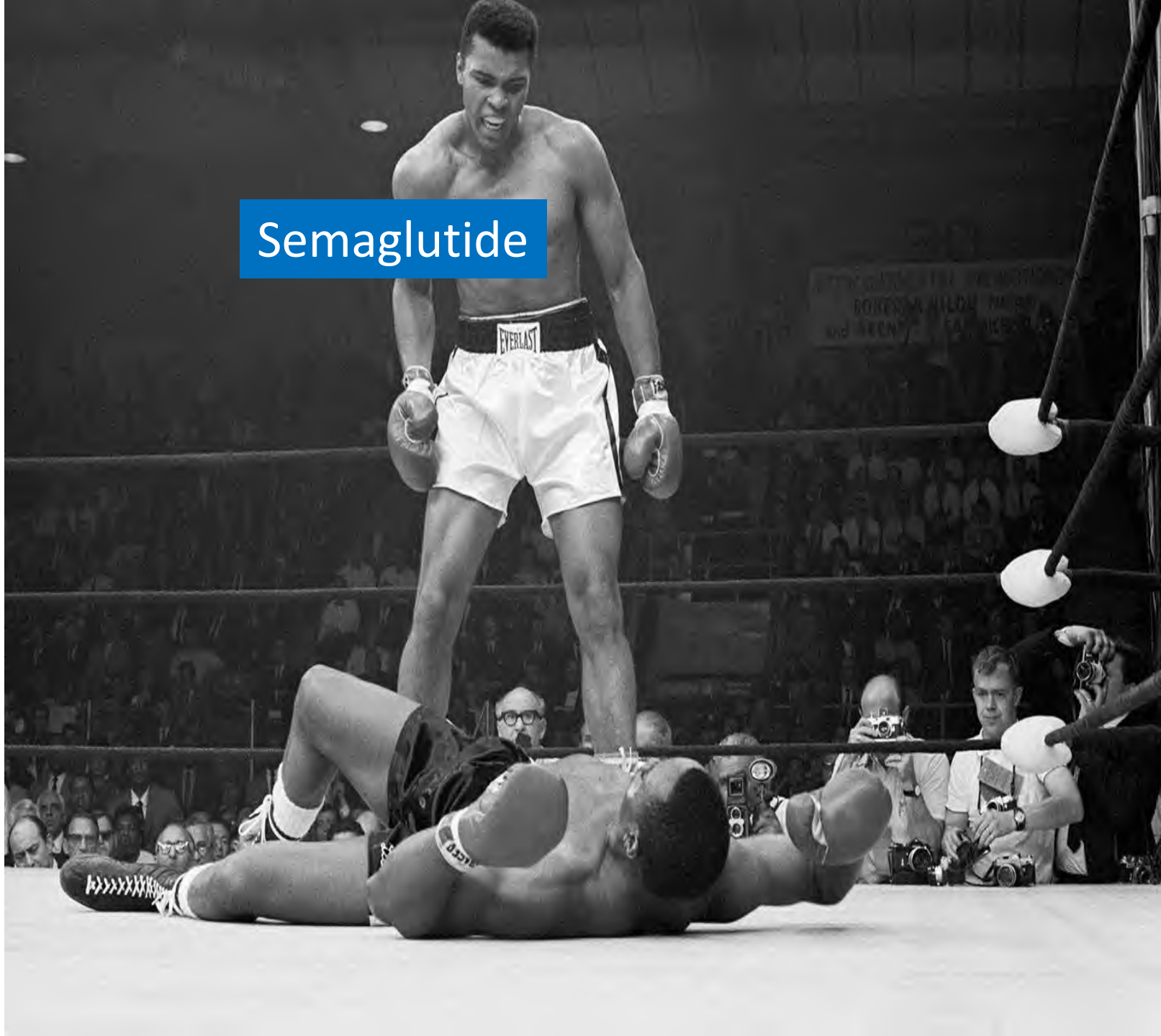
Fight 1

- 56 y.o. with PMHx of T2DM for 12 years who has been on Dulaglutide (Trulicity) for the past 5 years.
- BMI is 29.1 and HbA1C is at 6.4%.
- Fibroscan: LSM 11.3 kPa c/w F3 fibrosis and CAP of 362 dB/M c/w S3 steatosis.



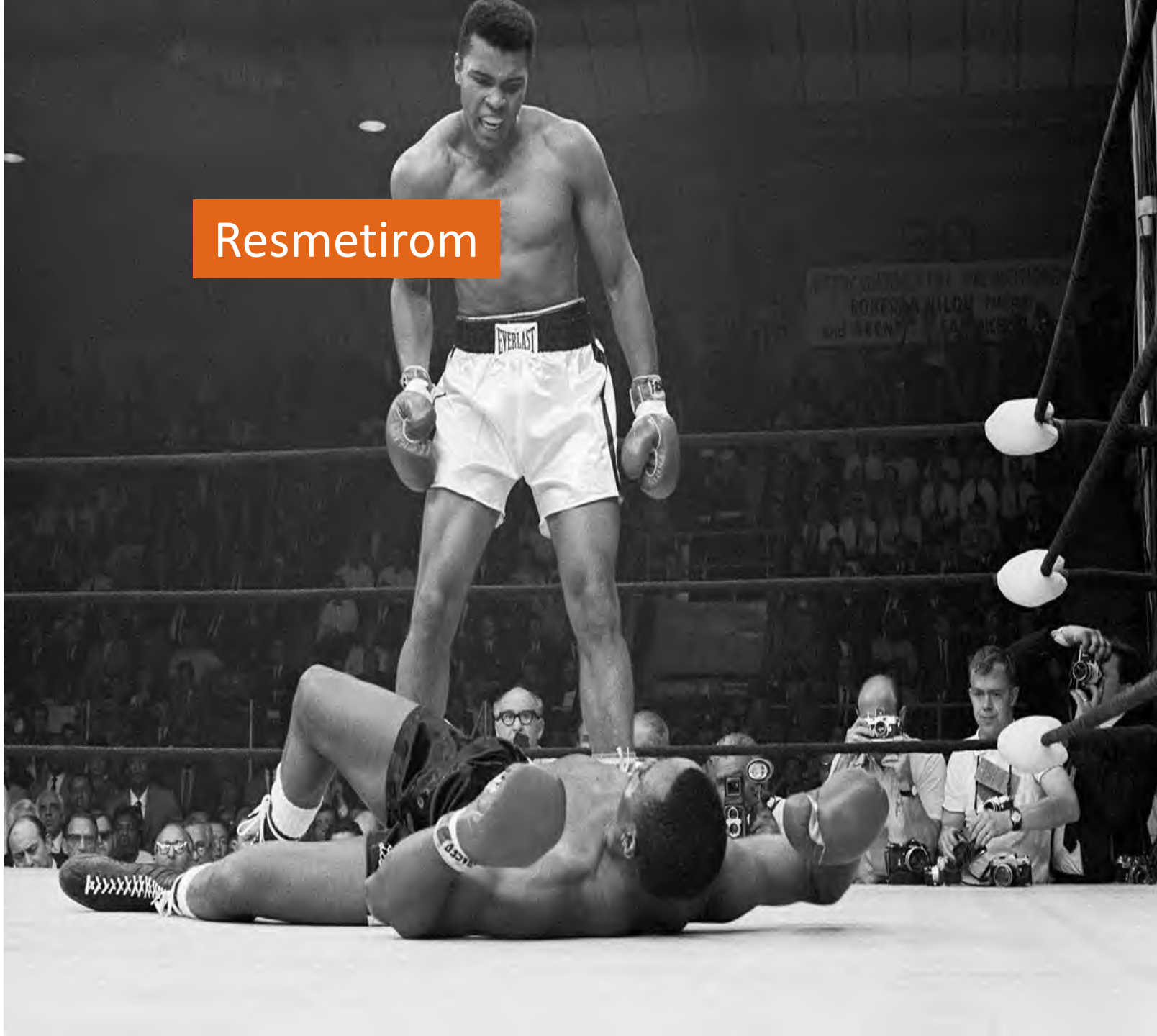
Fight 2

- 53 y.o. male with PMHx of HTN, OSA and obesity (BMI 37.2) presents with incidental finding of hepatosplenomegaly on US.
- Fibroscan: LSM 8.6 kPa c/w F2 fibrosis and CAP of 371 dB/M c/w S3 steatosis.



Fight 2

- 61 y.o. Asian-American female with history of dyslipidemia and BMI of 22 kg/m2 presents with mild elevation in AST and ALT.
- Fibroscan: LSM 9.4 kPa c/w F2 fibrosis and CAP of 302 dB/M c/w S2 steatosis.



Take Home Messages

- Patients with at-risk MASH will be the target for new pharmacological treatments once approved.
- Patients may get started on a medication for weight loss initially, but liver-directed therapies will be needed in those with no significant improvement.
- Patients with advanced fibrosis need medications with proven anti-fibrotic efficacy.
- Identifying MASH cirrhosis is critical:
  - Start HCC surveillance
  - Start carvedilol/nonselective beta-adrenergic blocker in those with CSPH

Panel Discussion

Moderator: Naim Alkhouri, MD, FAASLD, ABOM

Meena Bansal, MD

Mazen Noureddin, MD, MHSc

Stephen Harrison, MD, FACP, FAASLD

CME/MOC Form

CME University

- Login or Create a New Account
- Type in **18380** at the top of the page – follow instructions
- Form is in your Folder
- Virtual Attendance – link will be sent to you via email

Lunch Break

12:15 – 12:45 PM Break & Exhibits
12:45 – 1:15 PM Product Theater / Lunch Available
1:15 – 1:45 PM Break & Exhibits

Identifying and managing risk of disease progression in patients with PBC

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- Faculty are speaking on behalf of Ipsen and being compensated for their time
- This presentation is not a continuing medical education (CME) program

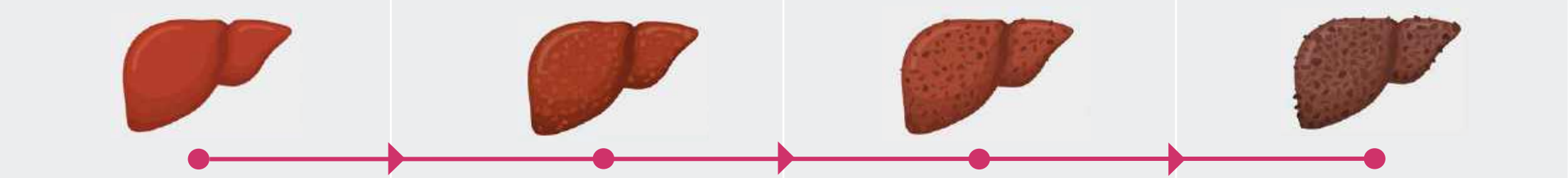
Objectives

The aim of this session is to:

- Examine the progression of PBC and its major stages
- Review risk factors for disease progression and the need for ongoing monitoring
- Examine the demographics, incidence, and prevalence of PBC
- Review the AASLD diagnostic criteria for PBC
- Differentiate and respond to the distinct experiences and symptoms of each patient with PBC
- Identify prognostic risk factors and distinguish between those identified at diagnosis and those that require ongoing monitoring throughout the disease course
- Discuss strategies for frequent and early reassessment with a focus on personalized care
- Discuss patient case studies depicting common scenarios encountered by physicians managing patients with PBC

PBC progression is highly variable, but may ultimately lead to end-stage liver disease and death[1,2]

- PBC typically advances through distinct stages, and, if left untreated, can lead to **cirrhosis** and **end-stage liver disease**[2]



Inflammation	Cholestasis	Fibrosis	Cirrhosis
Resulting from damage to small bile ducts[2]	Synthesis and transport of bile is impaired[2]	Chronic cholestasis leads to fibrosis[2]	Eventual development of cirrhosis may warrant liver transplantation[2]

Nearly half (46%) of patients with biochemically early-stage PBC progress to a **moderately advanced stage within 5 years**[3,a]

PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid. [a] Based on Rotterdam treatment response criteria, defined normal bilirubin and albumin concentrations after treatment with UDCA when one or both parameters were abnormal before treatment, or as normal bilirubin or albumin concentrations after treatment when both were abnormal at entry.[4] 1415 patients (87.6%) in this cohort were treated with UDCA.[3]

1. Lindor KD et al. *Hepatology*. 2019;69(1):394-419. 2. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 3. Gatselis NK et al; Global Primary Biliary Cholangitis Study Group. *Clin Gastroenterol Hepatol.* 2020;18(3):684-692; 4. Kuiper EMM et al; Dutch PBC Study Group. *Gastroenterology*. 2009;136(4):1281-1287.

Advancements in PBC care improve prognosis and reduce transplants, despite persistent cirrhosis risks[1-3]

- More effective treatments for PBC mean **disease progression is slower** and higher clinical remission rates can be expected if patients are treated early[1]

PBC prognosis is improving, likely due to earlier identification and availability of noninvasive treatments[1]	**Cirrhosis-related complications** are strongly associated with a **poor prognosis** and a **reduced life expectancy**[3]
The proportion of **liver transplantations** for PBC decreased from **20.3% in 1986** to **3.7% in 2015**[2,a]	Patients with **cirrhosis-related complications** may eventually require a liver transplant, which is associated with potential complications, including **recurrence of PBC**[3]

PBC, primary biliary cholangitis. [a] Data collected from 6029 patients with PBC transplanted in European Liver Transplantation Registry-associated centers from 1986 to 2015.[2]

1. Al-Harthy N et al. *Hepat Med*. 2012;4:61–71; 2. Harms MH et al. *Ailment Pharmacol Ther.* 2019;49:285–295; 3. Younossi ZM et al. *Am J Gastroenterol.* 2019;114:48–63.

PBC is a chronic inflammatory autoimmune cholestatic liver disease that disproportionally affects women[1,2]

Demographics	Incidence	Prevalence
 Females account for **approximately 92% of reported cases of PBC (10:1)[2]**	**0.9 to 5.8** cases per 100,000 individuals on an annual basis[2,a]	**1.9 to 40.2** cases per 100,000 individuals and has been rising over time[2]

PBC, primary biliary cholangitis. [a] Data collected from studies conducted in Europe, North America, Asia, and Australia.[2]

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. Sarcognato et al. *Pathologica*. 2021;113(3):170–84.

PBC symptomatology may influence both patient experience and therapeutic outcomes[1,2]

Fatigue or **pruritus** affect **>50% of patients** with PBC[1]	**Symptom severity may fluctuate over time** – not always correlated with the severity of underlying liver disease[1]
Worsening symptoms, particularly pruritus and fatigue, affect patients' **quality of life**[1]	Some patients initially present as **asymptomatic**, but may develop new or additional symptoms over time[2]

- Symptoms associated with PBC include **cholestatic pruritus, sicca complex, abdominal discomfort, restless legs, sleeplessness, depression** and **cognitive dysfunction**[1]
- The presence of symptoms, particularly **severe pruritus** in a ductopenic variant of PBC, has been shown to be **predictive of a poorer response to UDCA therapy**[1,2]
- **EHAIDs** are common in PBC patients, affecting initial symptoms but not the disease outcome[3]

EHAIDS: extrahepatic autoimmune diseases; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. Lindor KD et al. *Hepatology*. 2019;69(1):p394-419. 3. Efe C et al. *J Gastroenterol Hepatol*. 2021; 36(4):936-942.

AASLD provides criteria for the diagnosis of PBC[1]

- A diagnosis of PBC can be made when **≥2 AASLD diagnostic criteria** are met[1]:

AASLD diagnostic criteria[1]	
1	**Biochemical evidence** of cholestasis based on **ALP elevation**
2	**Presence of AMA** or other PBC-specific autoantibodies, including **sp100** or **gp210**
3	**Histologic evidence** of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
Liver biopsy is not generally required for the diagnosis of PBC, though inconclusive laboratory results may warrant a liver biopsy	

- **Differential diagnoses:** cholestatic drug reaction, biliary obstruction, sarcoidosis, AIH, and PSC[1]

AASLD, American Association for the Study of Liver Disease; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AMA, antimitochondrial autoantibody; gp210, 210 kDA glycoprotein; PBC, primary biliary cholangitis; sp100, speckled 100 kDA protein.

1. Lindor KD et al. *Hepatology.* 2019;69:394-419.

Multiple studies have reported an association between demographic risk factors and disease outcomes with PBC[1-6]

- **Age, sex**, and **ethnicity** or **race** are predictors of response to UDCA therapy at diagnosis, including symptom control, as well long-term outcomes with PBC[1-6]

Age & Sex[1,2]

- **Patients diagnosed with PBC before 45 years** are frequently symptomatic and less likely to respond favorably to first-line treatment with UDCA
- **Males with PBC** tend to experience a more severe disease and a poorer prognosis compared with women.

Ethnicity/Race[3-6]

- **People of color living with PBC** tend to have more severe disease at diagnosis and experience worse long-term outcomes compared with Caucasian patients
- Compared with Caucasian patients, African American and Hispanic patients with PBC at presentation have a:
  - 2.8x greater prevalence of **ascites**
  - 4.3x greater prevalence of **hepatic encephalopathy**
  - 2.9x greater history of **variceal bleeding**

PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. John BV et al. *Hepatology*. 2021;74:879–891. 3. Peters MG et al. *Hepatology*. 2007;46(3):769–75.
4. Cholankeril G et al. *Clin Gastroenterol Hepatol*. 2018;16(6):965-973.e2. 5. Galoosian A et al. *Dig Dis Sci*. 2020;65(2):406–15. 6. Sayiner M et al. *Hepatology*. 2019;69(1):237–44.

LSM, FIB4 index, and APRI score can be used as indicators of fibrosis at diagnosis and to monitor disease progression[1-4]

Serum measures of fibrosis – FIB4 & APRI score*

- The **FIB4 index** can be used to screen individuals at a high risk of liver disease – calculated from age, ALT, AST, and platelet count[1]
- An **elevated APRI score** (>0.54) at diagnosis is associated with a higher risk of complications[2]

- **LSM utilizing VCTE** is recognized as a highly reliable surrogate marker for the identification of cirrhosis or severe fibrosis[3,4]
- **Liver stiffness of ≥10 kPa** indicates a higher stage of fibrosis, suggesting a potential risk for disease progression and adverse outcomes, including liver decompensation, transplantation, or death[3,4]
- Changes in LSM may indicate PBC progression[3]

FIB4 index, APRI score, and LSM with VCTE can serve as crucial markers for identifying advanced fibrosis and predicting the risk of disease progression and adverse outcomes in PBC[1-4]

*FIB4 index and APRI score are not fully validated measures for stratifying risk of disease progression in cholestatic liver disease.

APRI, AST to Platelet Ratio Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; kPa, kilopascals; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; VCTE, vibration-controlled transient elastography.

1. Blanco-Grau A et al. *Diagnostics*. 2021;11(12):2236. 2. Trivedi PJ et al. *J Hepatol*. 2014;60(6):1249–58. 3. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 4. Kowdley KV et al. *Am J Gastroenterol*. 2023;118(2):232-242.

Case study: New diagnosis with prognostic risk factors

Patient: 44-year-old male, White/Caucasian

- **Presenting symptoms:** Fatigue, pruritus
- **Medical history:** Hypertension, obesity, hyperlipidemia
- **Current medications:** Antihypertensive medications
- **Allergies:** No reported allergies
- **Social history:** Nonsmoker, occasional alcohol intake

Actor portrayal

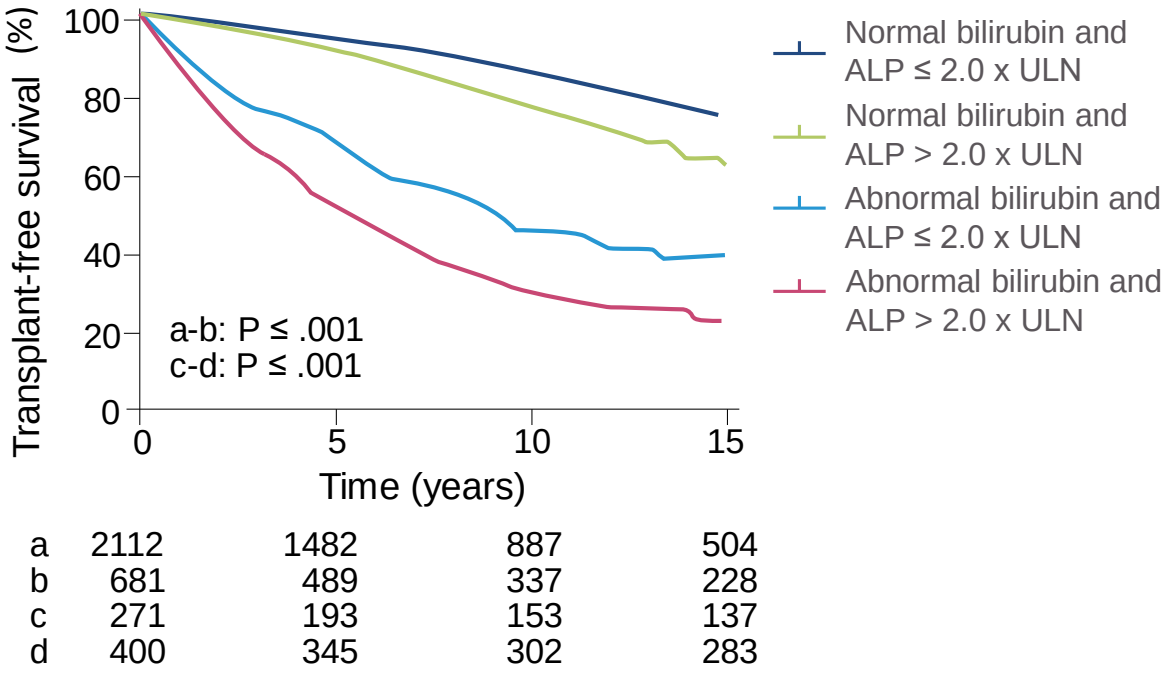
Laboratory results:

- **Elevated ALP:** 264 U/L; 1.8 X ULN
- **PBC-specific ANA positive**
- **Bilirubin:** 0.4 mg/dL
- **LSM:** 9.5 kPa (VCTE), **CAP score:** 290 dB/m
- **Liver biopsy:** Not performed

ANA, anti-nuclear antibody; ALP, alkaline phosphatase; kPa, kilopascals; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography.

Early-stage biochemical responses to UDCA therapy are crucial for better disease outcomes[1]

- Albumin and bilirubin levels are strong predictors of risk for progression, liver transplant, and death in patients with PBC[2]



a	2112	1482	887	504
b	681	489	337	228
c	271	193	153	137
d	400	345	302	283

Adapted from Lammers WJ et al, 2014[1]

ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Lammers WJ et al. *Gastroenterol*. 2014;147:1338–1349. 2. Lindor KD et al. *Hepatology*. 2019;69:394–419. 3. Corpechot C et al. *Clin Res Hepatol Gastroenterol*. 2022;46(1):101770. 4. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 5. Hirschfield GM et al. *Gut*. 2018;67:1568–1594. 6. Younossi ZM et al. *Am J Gastroenterol*. 2019;114(1):48–63.

ALP[1-5]

- High ALP levels are a persistent and early indicator of disease progression
- Very high ALP levels at diagnosis (**>5 X ULN**) are usually indicative of **severe/symptomatic disease** with a lower likelihood of response to treatment
- UDCA-treated patients with ALP levels **>1.67 X ULN** should be considered for second-line therapy

Total bilirubin[1,6]

- High bilirubin levels predict poor survival
- Elevations may occur as PBC progresses – significant **hyperbilirubinemia** indicates advanced disease

Case study: Inadequate biochemical response to first-line therapy with UDCA

Patient: 58-year-old female, Black/African-American

- **PBC history:** Diagnosed 6 months ago, on UDCA
- **Current symptoms:** Persistent pruritus, steatorrhea
- **Medical history:** Diabetes mellitus
- **Current medications:** UDCA, metformin
- **Allergies:** Penicillin

Actor portrayal

Laboratory results:

- **Liver enzymes:** ALP remains elevated despite UDCA therapy (2.1 X ULN)
- **Bilirubin:** 0.8 mg/dL decreased to 0.6 mg/dL on therapy
- **LSM:** 7.4 kPa (VCTE); 7.0 kPa at last check-up 15 months ago
- **Liver biopsy:** Not performed
- **Symptomatology:** No significant relief from pruritus

ANA, anti-nuclear antibody; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; kPa, kilopascals; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography.

Inadequate treatment response may also present as continued symptom presentation and signs of progression[1-4]

- While many patients respond biochemically to treatment, some may **experience worsening symptoms**, as ALP and bilirubin levels do not always correlate to symptom severity[1-3]
- **Symptom presence** itself may predict poorer response to UDCA and worse prognosis[4]
- Patients may experience an initial response to treatment, followed by **rising markers of liver function, including liver enzyme levels,** years later, indicating disease progression[5]

UDCA, ursodeoxycholic acid.

1. Hirschfield GM et al. *Gut*. 2018;67:1568–1594. 2. Carbone M et al. *Gastroenterology*. 2013;144(3):560–569. 3. Mells GF et al. *Hepatology*. 2013;58(1):273-283. 4. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 5. Gatselis NK et al. Global Primary Biliary Cholangitis Study Group. *Clin Gastroenterol Hepatol*. 2020;18(3):684-692.

Case study: Symptomatic despite biochemical response to UDCA

Patient: 61-year-old female, White/Caucasian

- **PBC history:** Diagnosed 12 months ago, on UDCA
- **Current symptoms:** Fatigue, abdominal discomfort
- **Medical history:** No significant past illness
- **Current medications:** UDCA
- **Allergies:** No reported allergies

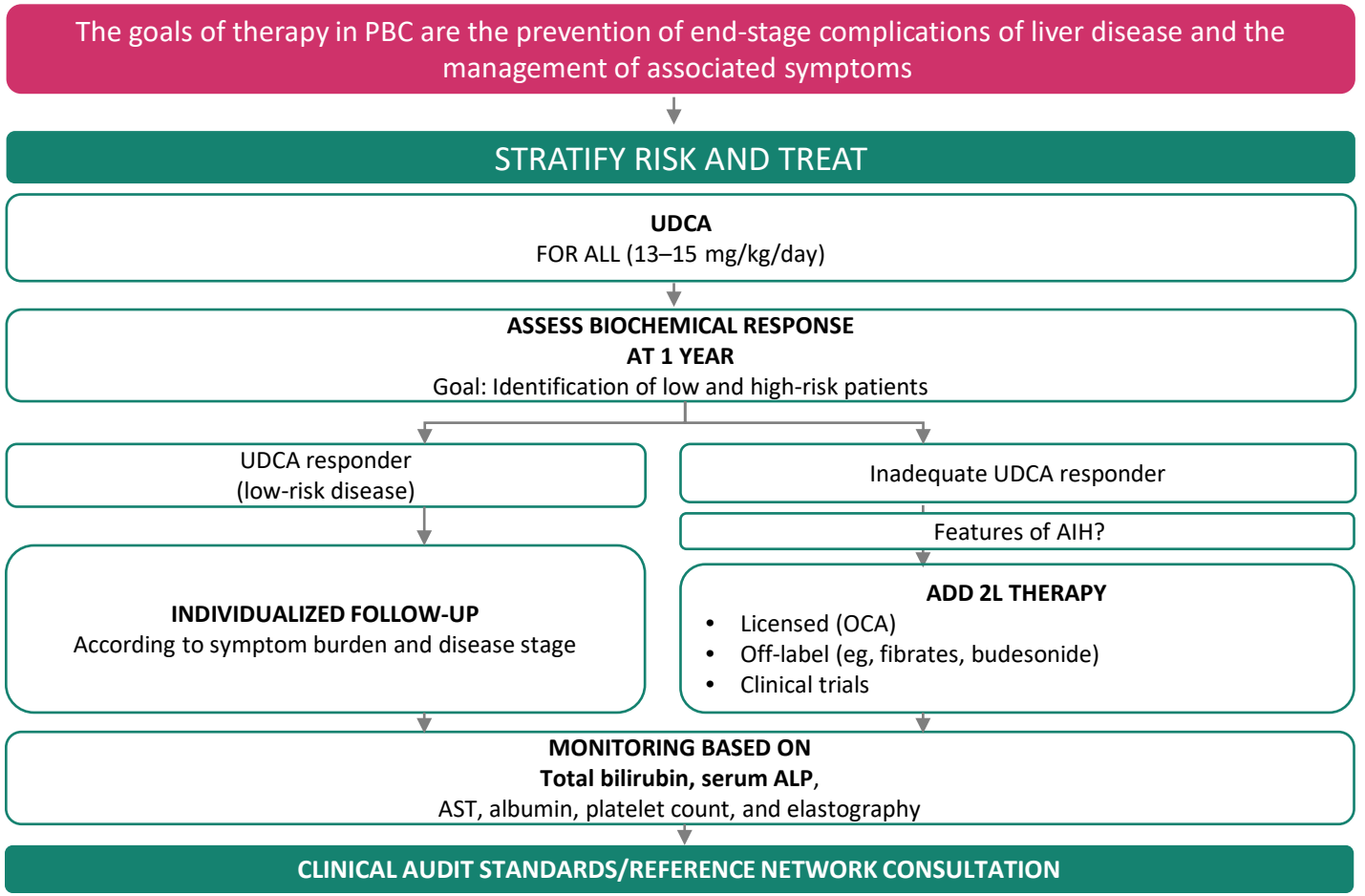
Actor portrayal

Laboratory results:

- **Liver enzymes:** Normalization of ALP, AST, ALT with UDCA
- **LSM:** 7.0 kPa (VCTE); 7.3 kPa at last check-up 9 months ago
- **Liver biopsy:** Not performed
- **Symptomatology:** Symptoms persist despite biochemical response to UDCA

ANA, anti-nuclear antibody; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; kPa, kilopascals; LSM, liver stiffness measurement; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; VCTE, vibration-controlled transient elastography.

AASLD risk stratification guidelines consider UDCA therapy response and treatment-emergent factors[1]

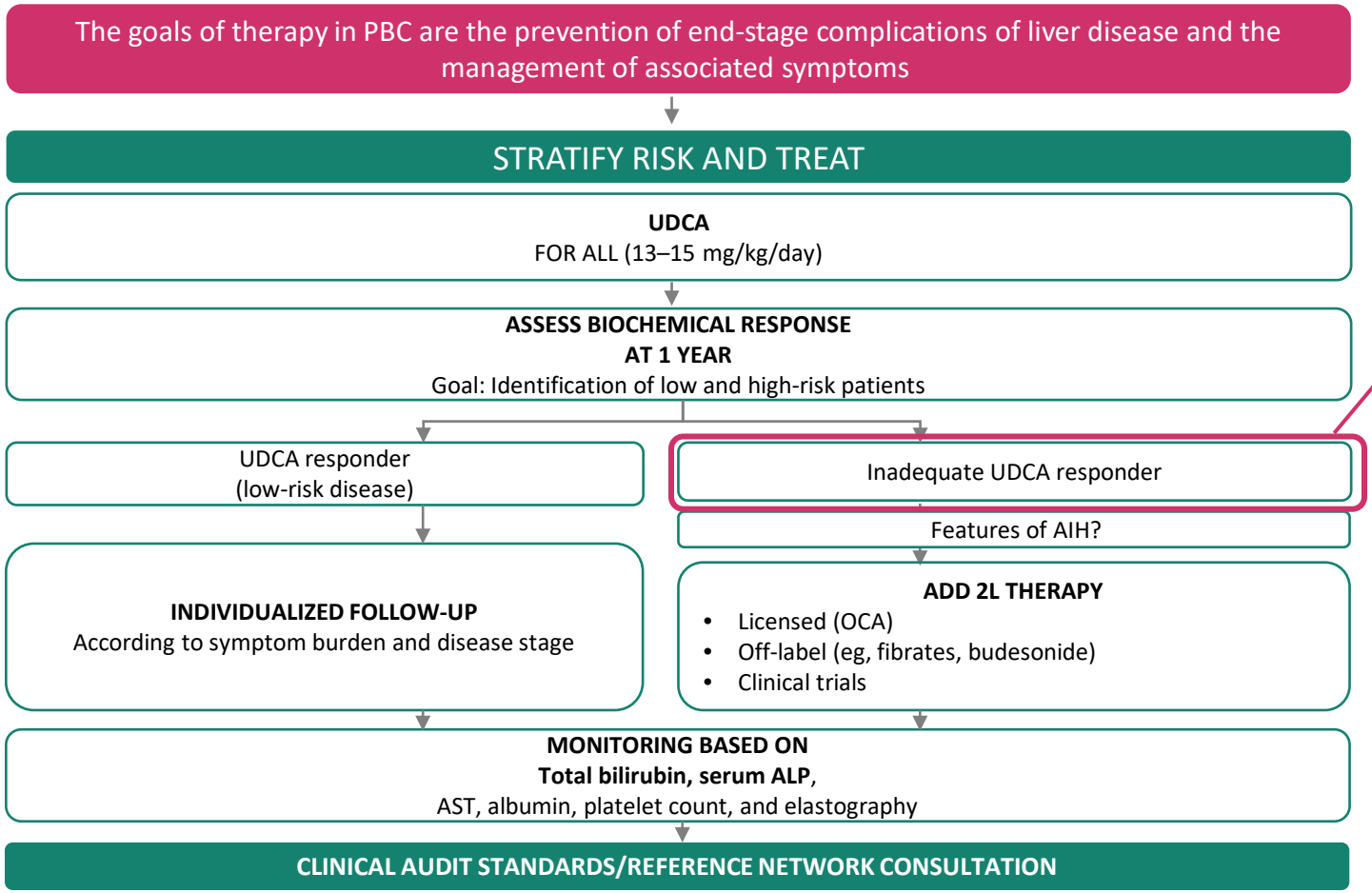


Adapted from AASLD 2018 guidelines[1]

2L, second-line; AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; AST, aspartate aminotransferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Lindor KD et al. *Hepatology.* 2019;69:394–419.
2. Yoshida EM. *Can Liver J.* 2022;5(3):372-387.

AASLD risk stratification guidelines consider UDCA therapy response and treatment-emergent factors[1]



Adapted from AASLD 2018 guidelines[1]

Up to 50% of patients with PBC will have an inadequate biochemical response to first-line UDCA therapy[2]

2L, second-line; AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; AST, aspartate aminotransferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Lindor KD et al. *Hepatology.* 2019;69:394–419.
2. Yoshida EM. *Can Liver J.* 2022;5(3):372-387.

Prognostic factors should be used to stratify risk of progression at diagnosis and monitored during management[1]

Risk factors at diagnosis[1-4]	Treatment-emergent risk factors[1,4-8]

• Younger age
• Male
• Non-Caucasian patients (eg, African American, Hispanic patients)
• Presence of symptoms
• Very high ALP levels (>5 x ULN)
• Elevated total bilirubin levels
• Low albumin
• Presence and degree of cirrhosis
	• Inadequate response to UDCA at 6 or 12 months
	  • Unchanged or worsening symptoms
	  • Inadequate biochemical response
	• Rising total bilirubin levels
	• Decreasing albumin levels
	• LSM ≥10 kPa
	• Portal hypertension

ALP, alkaline phosphatase; kPa, kilopascals; LSM, liver stiffness measurement; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 2. Peters MG et al. *Hepatology*. 2007;46(3):769–75; 3. Corpechot C et al. *Clin Res Hepatol Gastroenterol*. 2022;46(1):101770; 4. Lammers WJ et al. *Gastroenterol*. 2014;147:1338–1349; 5. Trivedi PJ et al. *J Hepatol*. 2014;60:1249–58; 6. Kowdley KV et al. *Am J Gastroenterol*. 2023;118(2):232-242; 7. Lindor KD et al. *Hepatology*. 2019;69(1):p394-419; 8. Murillo Perez CF et al. *Liver Int*. 2023;43:1497-1506.

Implementing a structured, 6- or 12-monthly reassessment schedule to evaluate treatment response and disease status

- **Biochemical response to UDCA**, usually assessed after 12 months of initiating therapy, is a validated method to identify patients who may benefit from second-line therapies[1]
- A **6-month assessment period** has emerged as an equally discerning assessment period, providing earlier insight into patient responsiveness to UDCA[1]
  - Recent research has suggested that second-line therapy can be considered at **6 months**[2,3]
  - **90%** of improvements in liver tests typically occur in the **first 6–9 months of treatment with UDCA**[4]
- As PBC progresses, it is recommended that the frequency of liver biochemistry assessments be increased to **every 3–6 months** to closely monitor potential complications[4]
- Due to the increased risk of HCC in patients with cirrhosis, **ultrasound surveillance every 6 months** is recommended[4]
- Regular follow-up intervals should be determined by the **severity of symptoms** and the **patient's risk profile**[5]

Evaluating UDCA response at 6 months may offer early insights, while more frequent biochemistry checks are vital as PBC progresses[1-4]

ALP, alkaline phosphatase; HCC, hepatocellular carcinoma; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 2. Murillo Perez CF et al. *Liver Int*. 2023;43:1497-1506; 3. Kowdley KV et al. *Am J Gastroenterol*. 2023;118(2):232-242; 4. Lindor KD et al. *Hepatology*. 2019;69(1):p394-419; 5. Hirschfield GM et al. *Expert Rev. Gastroenterol. Hepatol.* 2021;15(8):929-939.

Implementing personalized management strategies for ongoing PBC care

- Regularly utilize biochemical, histological, and clinical evaluations to assess the progression of PBC and coordinate treatment plans[1-3]
- Evaluate symptoms and perform liver function tests to monitor the patient's response to first-line therapy[3]
- Proactively address and manage **fatigue** and **pruritus** symptoms using both pharmaceutical and nonpharmacological interventions[1,2]
- Identify high-risk patients, including those with **multiple, severe**, or **intractable symptoms** – referral for specialized care may be necessary[3]
- Continuously assess patients for **signs of advanced disease**, such as portal hypertension, ascites, and bleeding varices, which may warrant treatment adjustments[3]

Collaborative care, inclusive of patients, helps ensure individualized, informed, and shared decision-making, leading to better health outcomes and enhanced quality of life[4]

PBC, primary biliary cholangitis.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. Lindor KD et al. *Hepatology*. 2019;69(1):p394-419; 3. Hirschfield GM et al. *Gut*. 2018;67:1568–1594; 4. Vahdat S et al. *Iran Red Crescent Med J.* 2014;16(1):e12454.

Enhanced, regular risk assessment and collaborative care can help ensure an adaptive and personalized approach[1-3]

Ensure continuous assessment of prognostic risk factors and treatment response

- Consider establishing **6-monthly disease and risk factor evaluations** to ensure early detection of progression and disease complications[1,2]
- Adopt procedures for tracking the progression of PBC and conducting systematic disease assessments[3]

Develop adaptive disease management plans

- Focus disease management on **initiating UDCA** and **assessing response** for all patients[3]
- **Risk stratification** based on baseline and on-treatment factors, including response to treatment[3]

Involve patients in care decisions

- Commit to **collaborative decision-making with patients** and furthering their knowledge of the disease state and available treatment options[3]

Questions?

PBC, primary biliary cholangitis.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. Murillo-Perez CF et al. *Liver Int*. 2023;43:1497-1506; 3. Hirschfield GM et al. *Gut*. 2018;67:1568–1594.

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HEPATITIS B and DELTA: BAD BEDFELLOWS

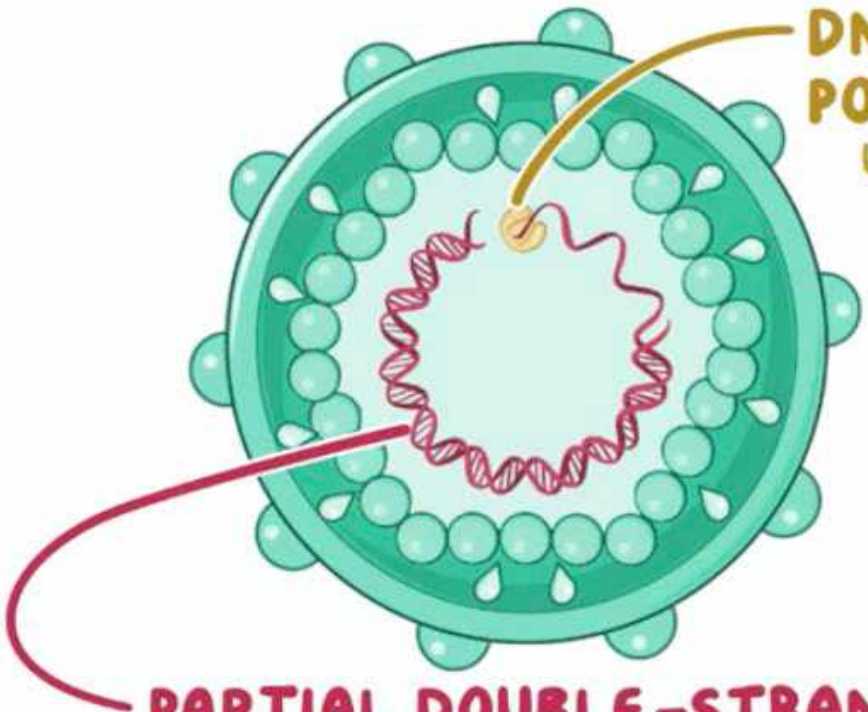
Julio Gutierrez, MD
Associate Professor
Scripps Center for Organ Transplant
La Jolla, CA

VIROLOGY, EPIDEMIOLOGY AND SCREENING

Scripps

HEP B VIRUS

└ DNA VIRUS



DNA POLYMERASE

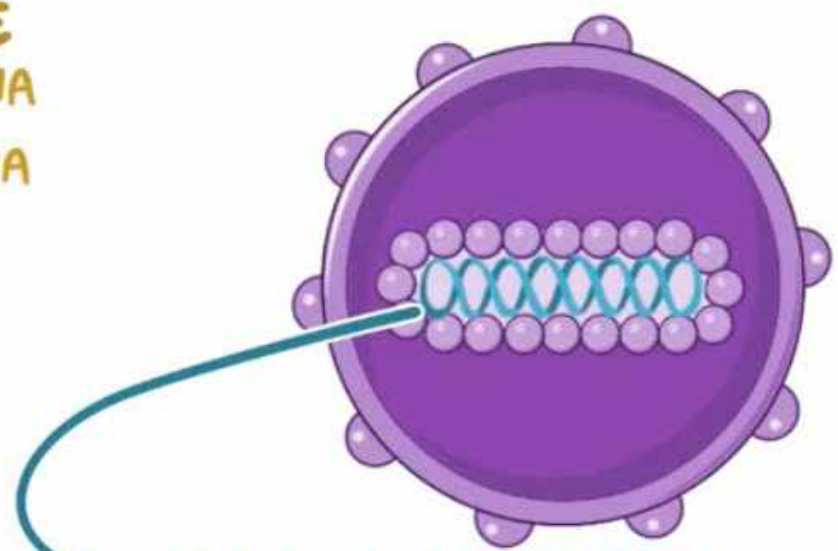
└ DNA → RNA & RNA → DNA

PARTIAL DOUBLE-STRANDED CIRCULAR DNA

└ LONG & SHORT STRAND

HEP D VIRUS

└ RNA VIRUS



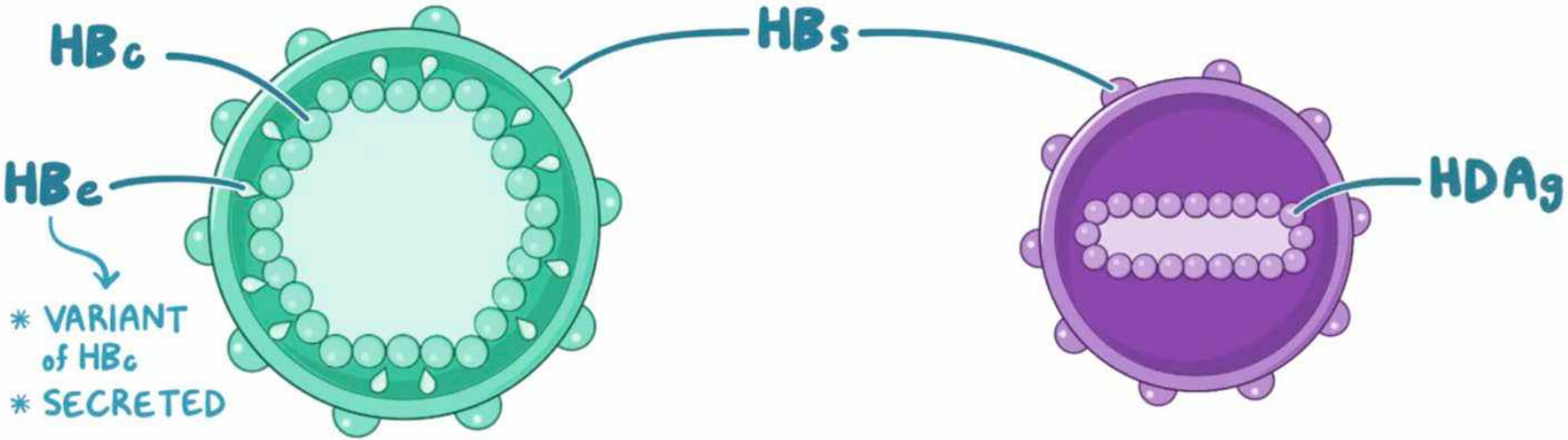
SINGLE-STRANDED CIRCULAR RNA

└ ROD-LIKE FOLDED STRUCTURE

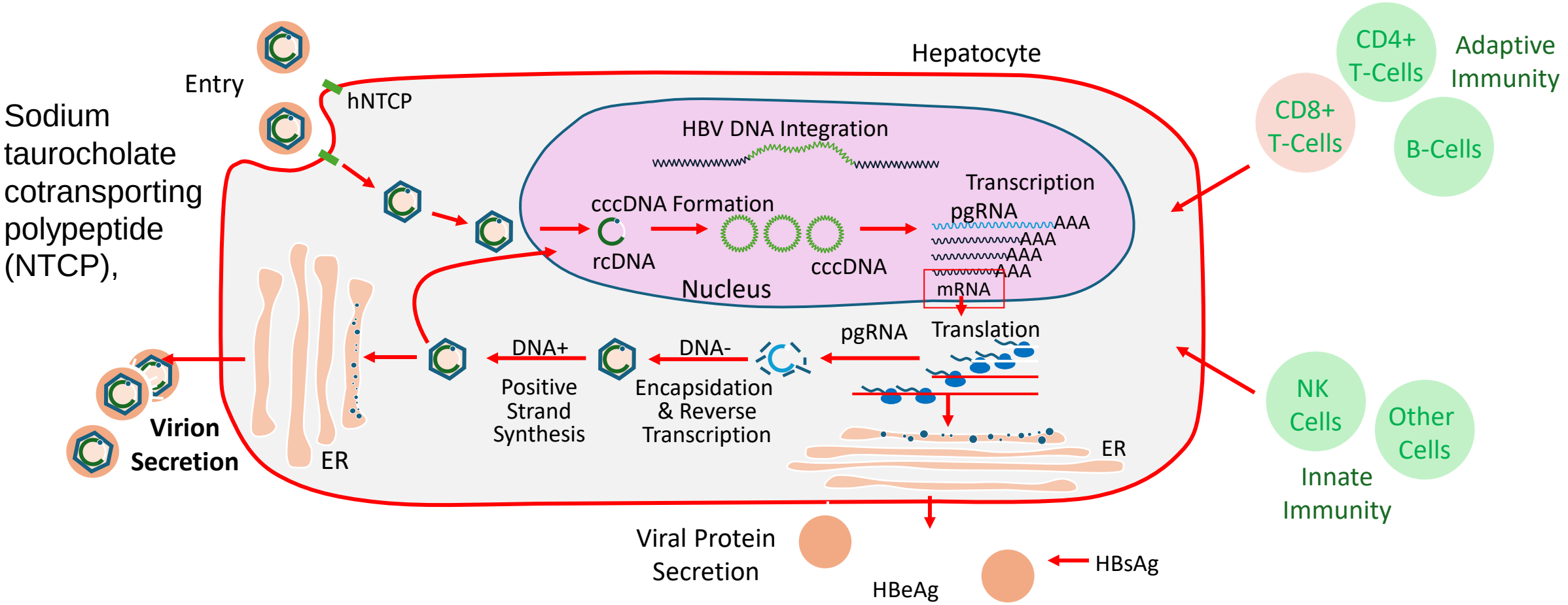
Osmosis.com

HEP B VIRUS

HEP D VIRUS

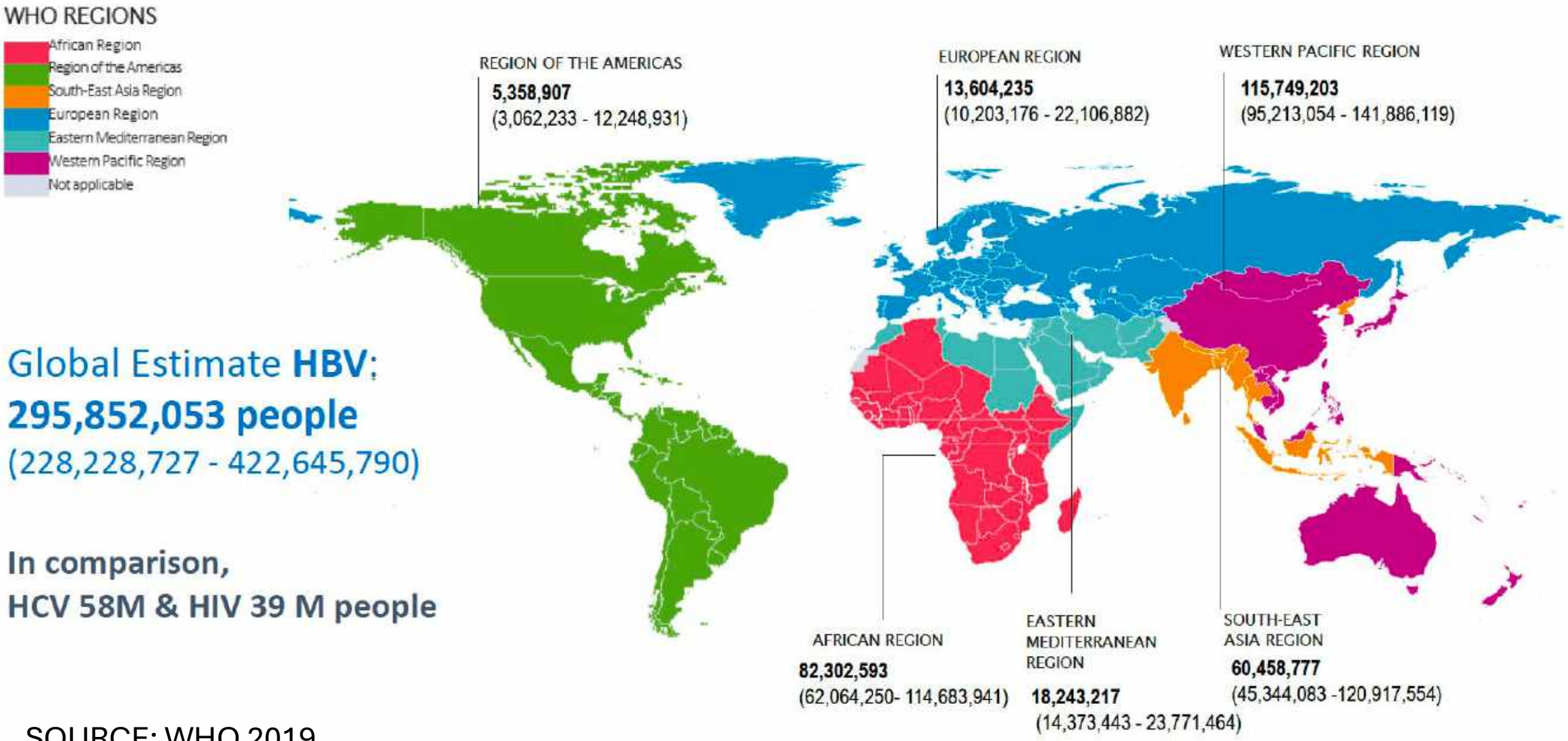


HBV Persistence: Viral Integrants and cccDNA



Zoulim. Cold Spring Harb Perspect Med. 2015;5:a021501.

GLOBAL BURDEN OF HEPATITIS B



Global Estimate **HBV**:

295,852,053 people

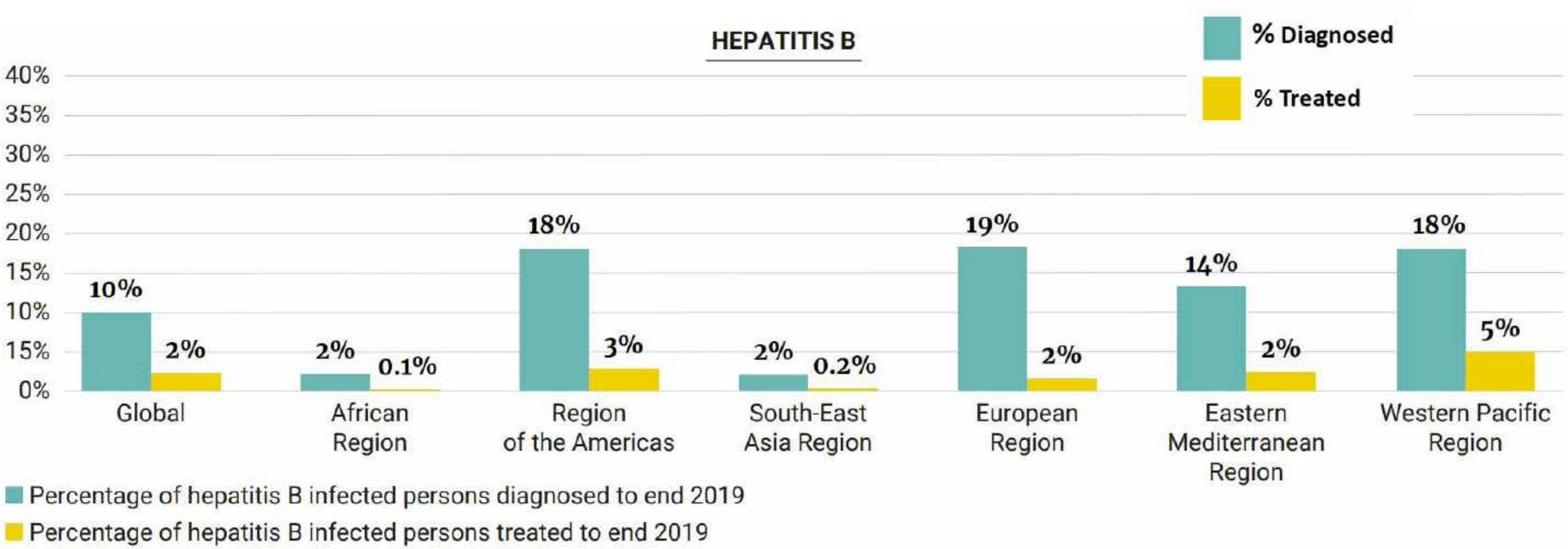
(228,228,727 - 422,645,790)

In comparison,

HCV 58M & HIV 39 M people

SOURCE: WHO 2019

GLOBAL HBV: DIAGNOSIS AND TREATMENT



WHO, 2021

CALL TO ACTION: CDC 2023 REC

Universal hepatitis B virus (HBV) screening

- HBV screening at least once during a lifetime for adults aged ≥18 years (new recommendation)
- During screening, test for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and total antibody to HBcAg (total anti-HBc) (new recommendation)

Screening pregnant persons

- HBV screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing*
- Pregnant persons with a history of appropriately timed triple panel screening and without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening) only need HBsAg screening

Risk-based testing

- Testing for all persons with a history of increased risk for HBV infection, regardless of age, if they might have been susceptible during the period of increased risk†
- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposures, while risk for exposures persists†

Universal Screening with Expanded Testing is Here!
All adults, whole panel - HBsAg, anti-HBs, and anti-Hbc total
EXPANDED RISK BASED TESTING!

GUTIERREZ JA 2024

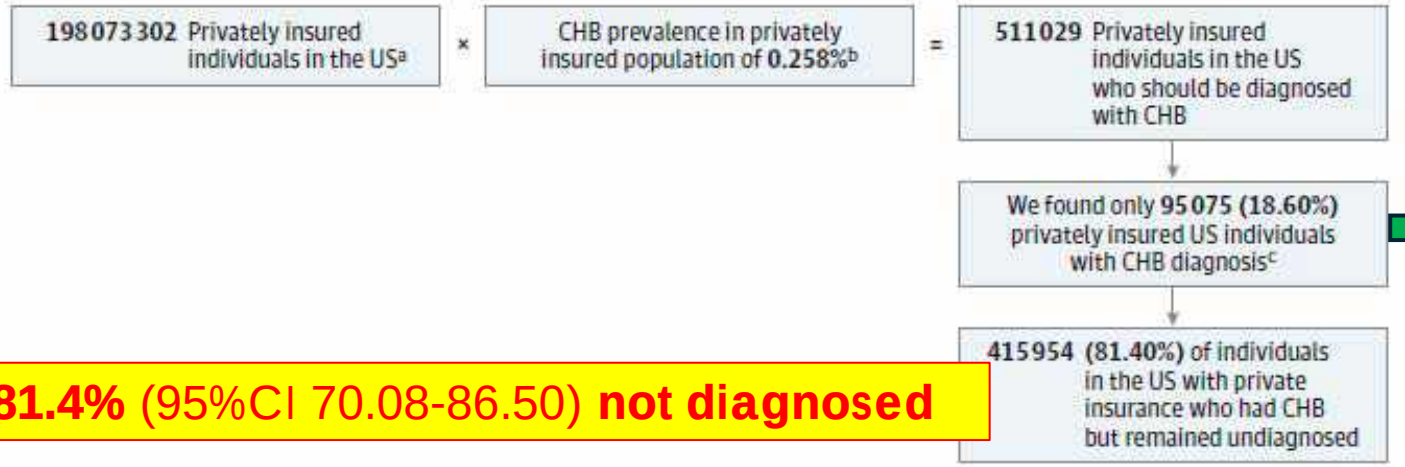
Scripps

Original Investigation | Gastroenterology and Hepatology

Diagnosis Rates of Chronic Hepatitis B in Privately Insured Patients in the United States

Eiichi Ogawa, MD, PhD; Yee Hui Yeo, MD, MSc; Nolan Dang, BS; Michael H. Le, MS; Donghak Jeong, MS; Sally Tran, BS; Linda Henry, PhD; Ramsey Cheung, MD; Mindie H. Nguyen, MD, MAS

Figure. Graphical Study Overview and Summary

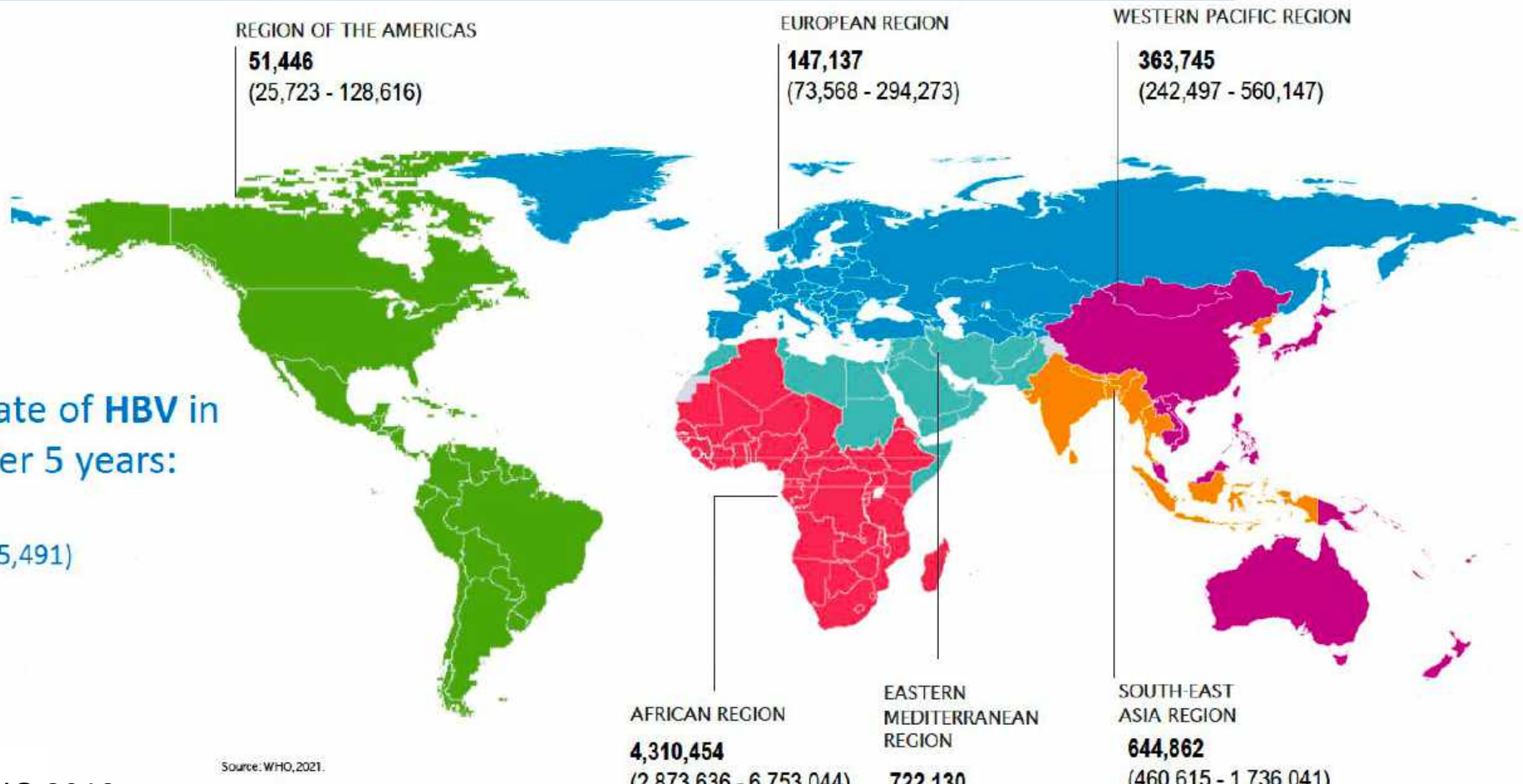


81.4% (95%CI 70.08-86.50) **not diagnosed**

IN CARE
Cirrhosis: 34.79% treated,
95%CI 33.31-36.27
HCC: 48.64% treated,
95%CI 45.59-51.89

Le MH/Nguyen MH, Hepatology 2020, PMID: 31228279; Nguyen V/Nguyen MH, Clin Gastroenterol Hepatol 2018; PMID:30326298.

PREVALENCE OF HBV IN CHILDREN <5



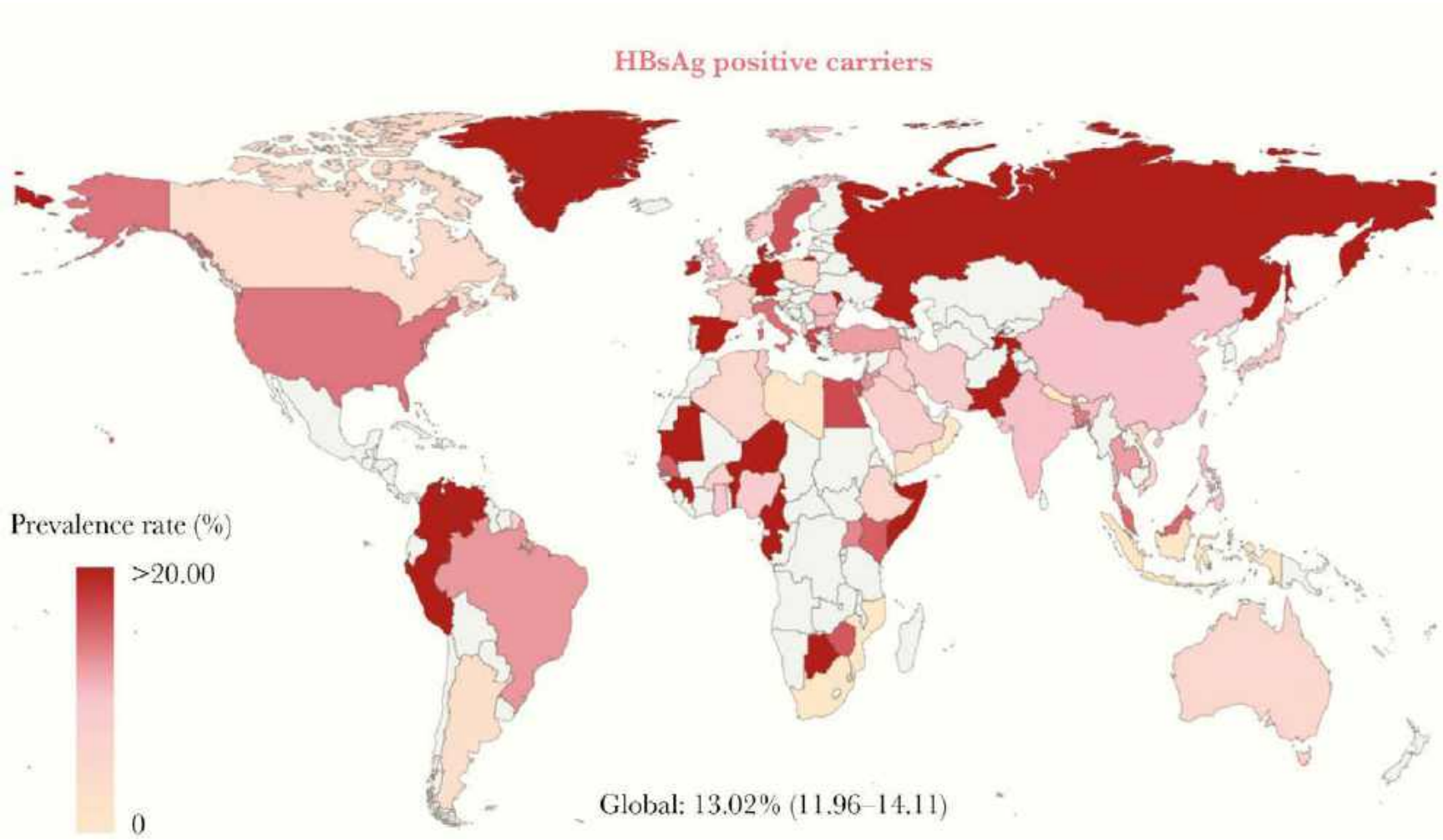
Global estimate of **HBV** in Children under 5 years:

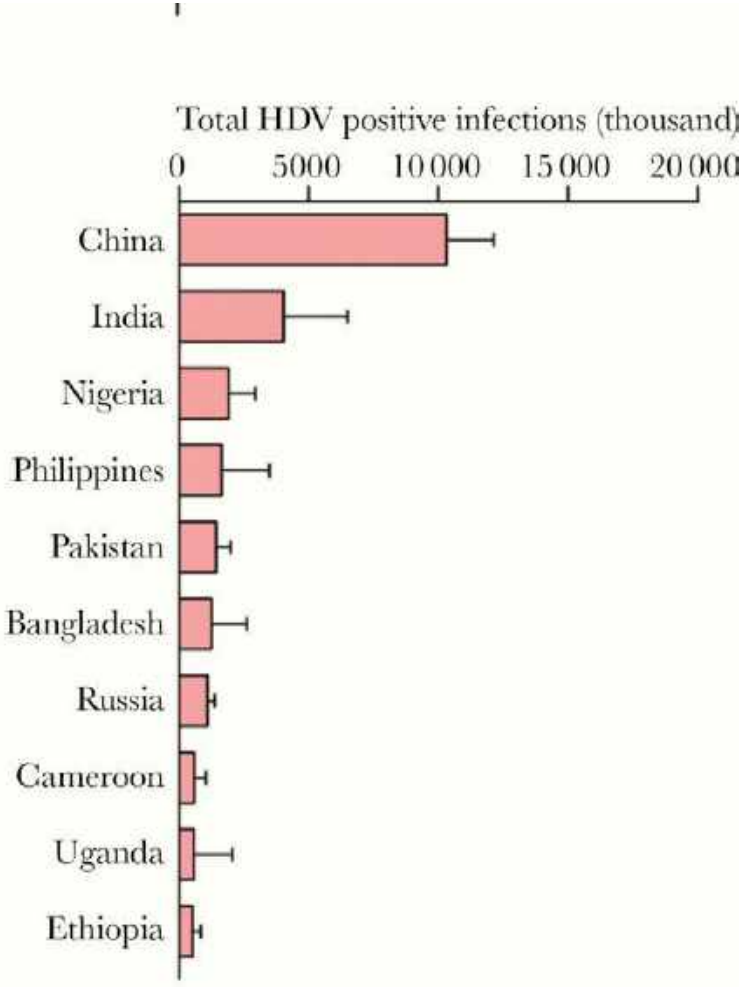
6,367,336

(4,408,156 - 10,775,491)

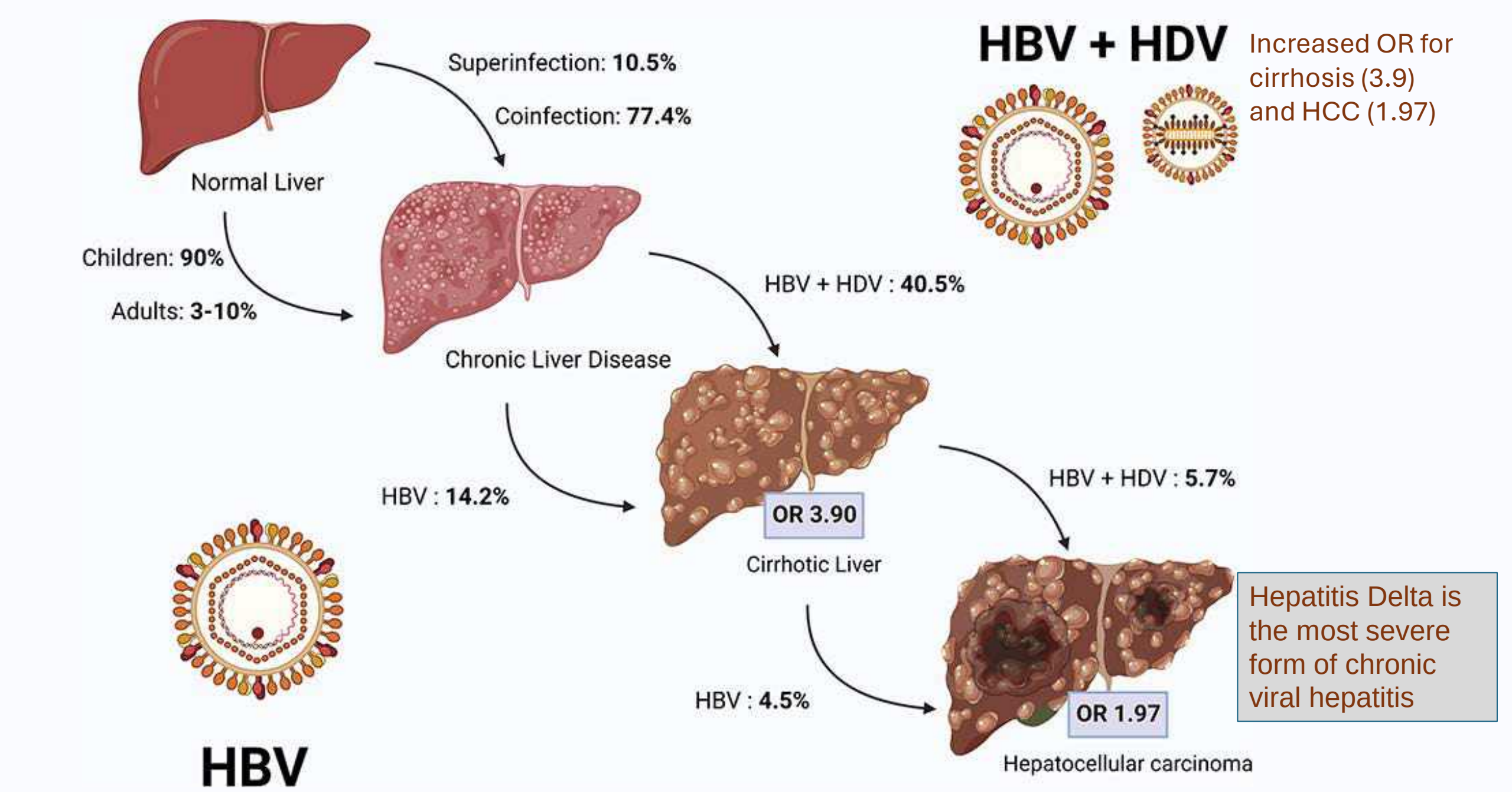
SOURCE: WHO 2019

HEPATITIS DELTA GLOBAL EPIDEMIOLGY

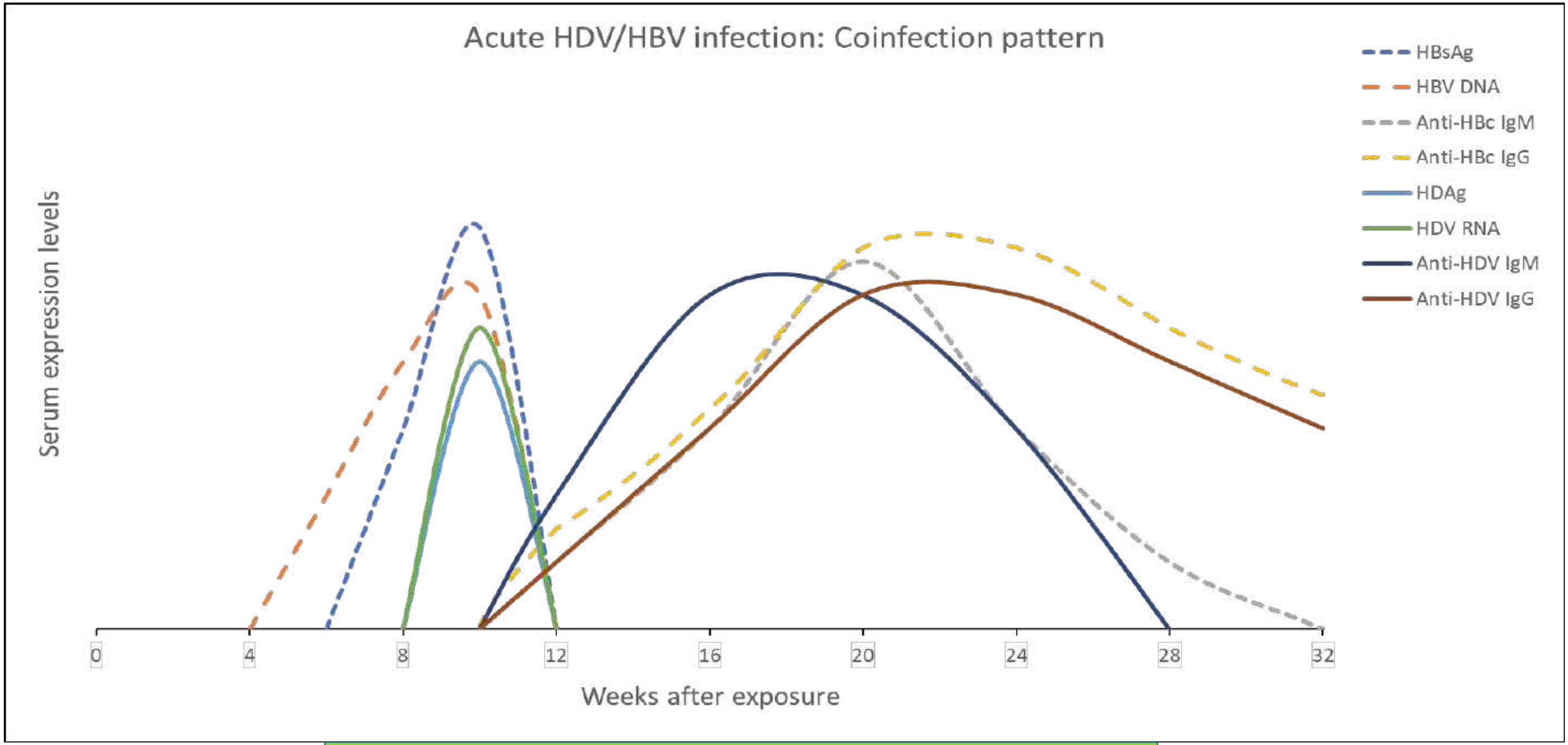




The Journal of Infectious Diseases, Volume 221, Issue 10, 15 May 2020, Pages 1677–1687,

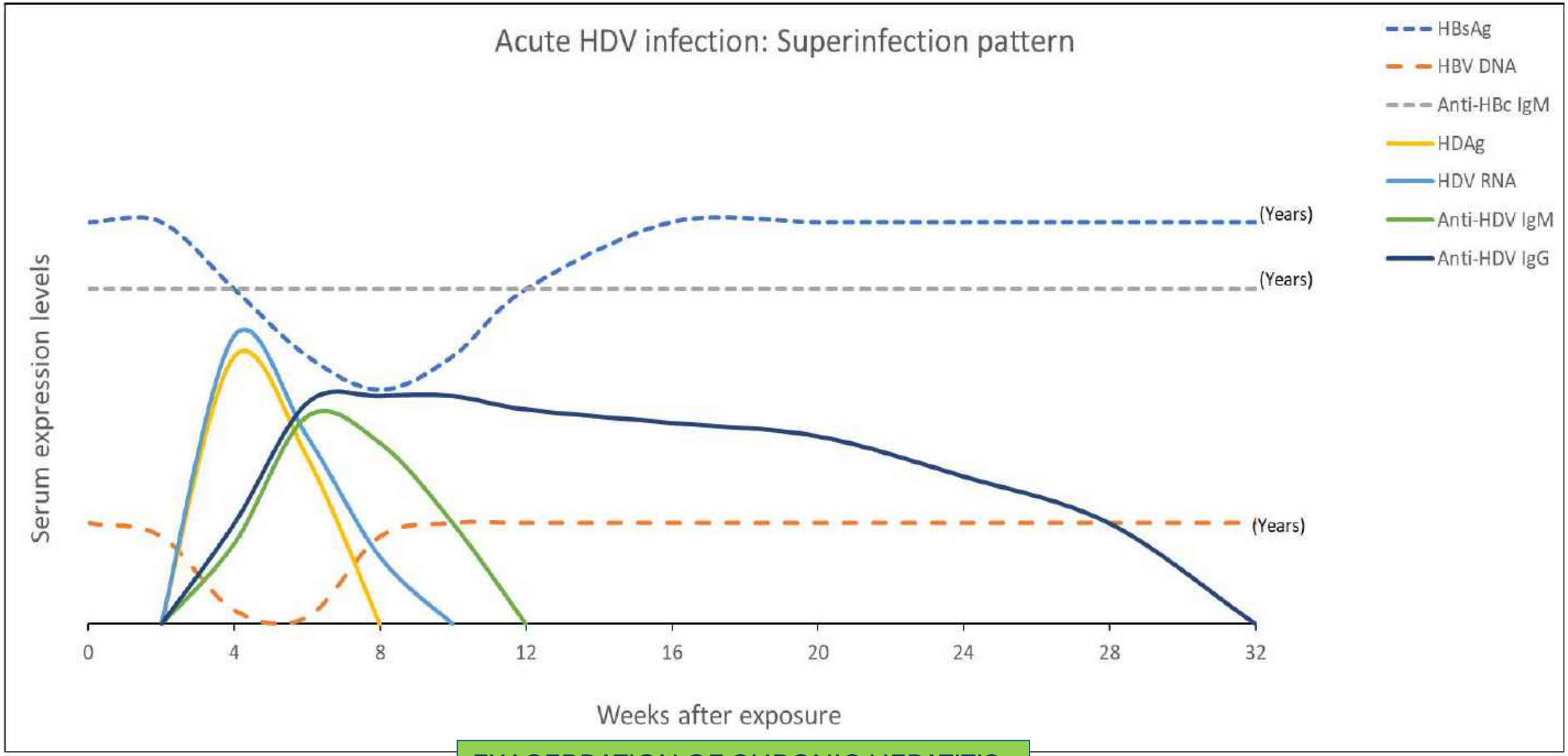


Costante F. *J Hepatocell Carcinoma*. 2023;10:713-724



ACUTE CONCURRENTION INFECTION:
INDISTINGUISHABLE FROM ACUTE HBV MONO-INFECTION

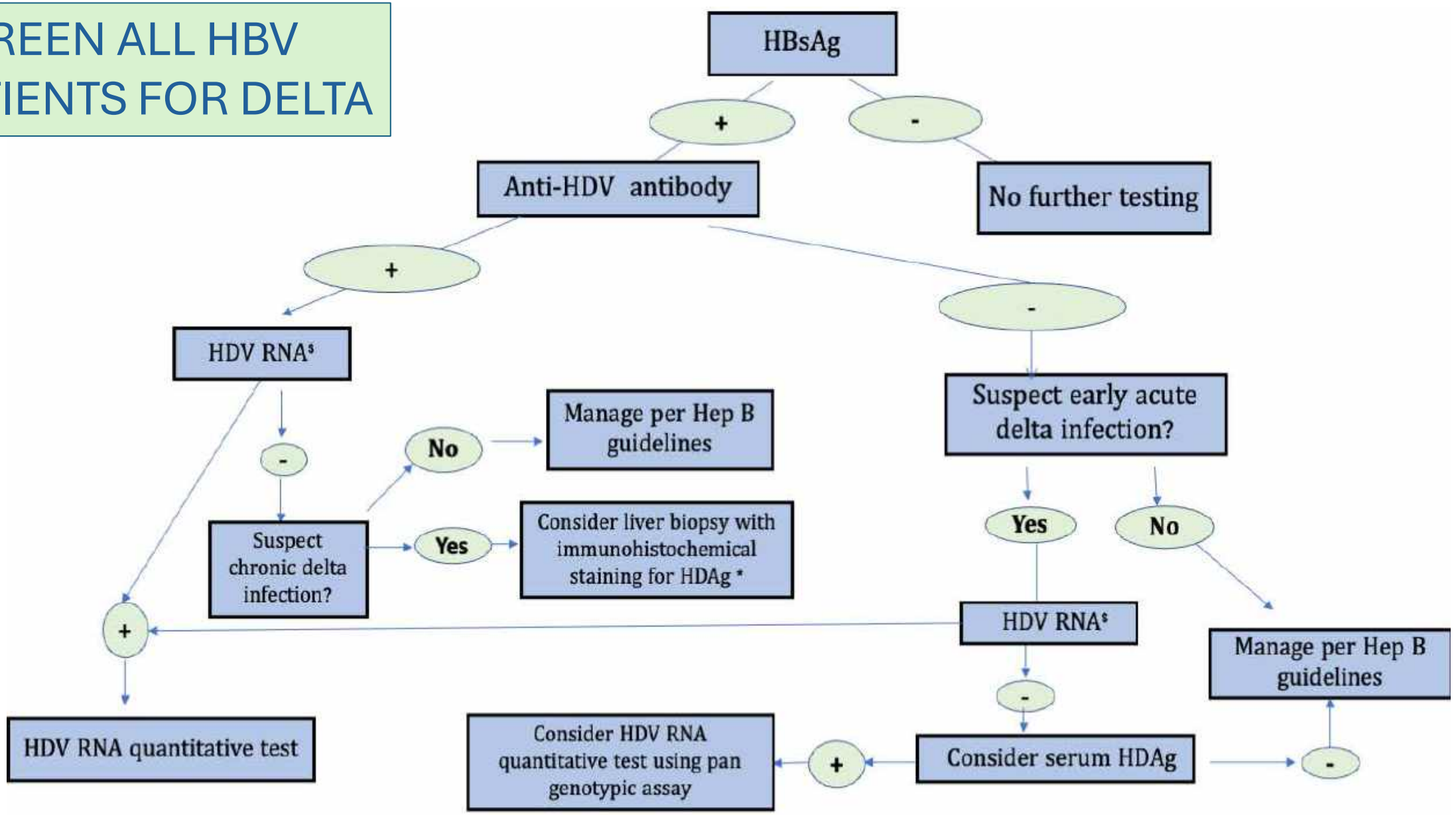
Gutierrez JA. Clin Liver Dis. 2023 Nov;27(4):937-954.



EXACERBATION OF CHRONIC HEPATITIS:
CLINICAL CLUE IN HBV DNA

Gutierrez JA. Clin Liver Dis. 2023 Nov;27(4):937-954.

SCREEN ALL HBV PATIENTS FOR DELTA



Gutierrez JA. Clin Liver Dis. 2023 Nov;27(4):937-954.

WHICH HBV PATIENT NEEDS TREATMENT

GUTIERREZ JA 2024

Scripps

AASLD CURRENT TREATMENT GUIDELINES

- **Requires consideration of 3 labs results HBeAg, HBV DNA, ALT and fibrosis stage**

HBeAg	HBV DNA IU/mL	ALT U/L
Positive	>20,000	≥2XULN
Negative	>2000	≥2XULN

- Active CHB = elevated ALT and HBV DNA
- Advanced fibrosis/cirrhosis
- Positive history of liver cancer

Special populations:

- HIV
- Immuno-modulatory therapy
- Pregnancy
- Transplant recipients

- **Supported by strong evidence base for treatment benefit**

Norah Terrault, How to Simplify Treatment Criteria Under the Current HBV Guidelines. AASLD 2023.

PHASES OF HBV, NOMECLATURE & BIOMARKERS

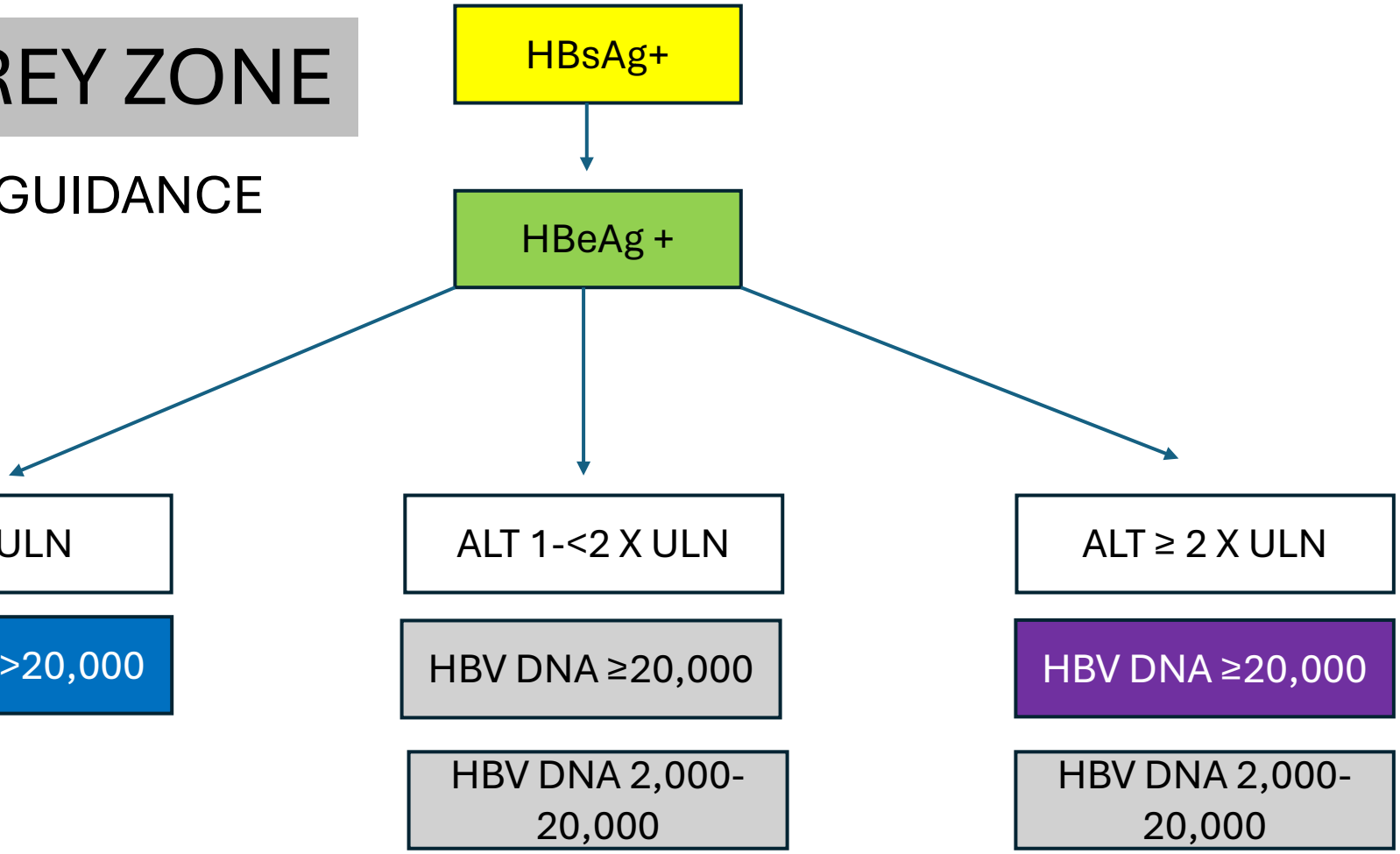
	HBeAg POS, Chronic	HBeAg POS Chronic	HBeAg NEG Chronic	HBeAg NEG Chronic	”Gray Zone”	Occult
Other Name	Immune Tolerant	Immune (re)active	Inactive Carrier	HBeAg Neg Disease	Indeterminate	None
HBsAg	+	+	+	+	+	-
HBeAg	+	+	-	-	-	-
HBV DNA	$>10^7$	$>10^5$-10^7	$<10^3$	$>10^3$- $<10^5$	2k-20k	detectable
ALT	<ULN	>ULN	<ULN	>ULN	Fluctuates	<ULN
Histology	Minimal findings	Necroinflammation with varying fibrosis	Minimal findings	Necroinflammation with varying fibrosis	Minimal or low necroinflmmation	Minimal findings but fibrosis can be present

WHY IT IS SO HARD

IN THE GREY ZONE

ALT BASED GUIDANCE

eAg POS



DO NOT TREAT: Monitor ALT and HBV DNA q 3-6 months

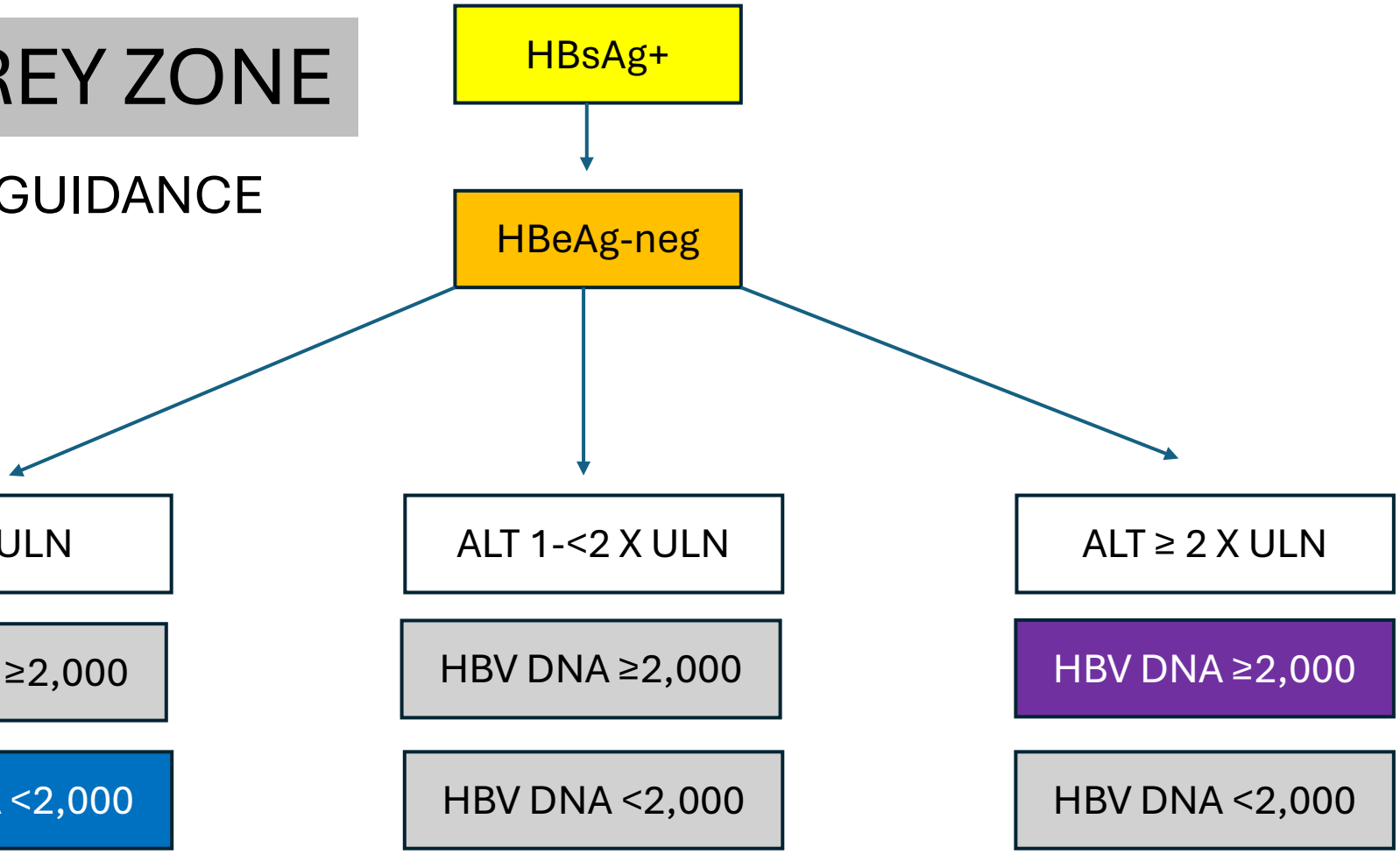
TREAT	If ALT ≤ULN, monitor ALT and HBV DNA q 6 m If >ULN evaluate, if advanced liver disease or >40 y treat

Hepatology67(4):1560-1599, April 2018.

IN THE GREY ZONE

ALT BASED GUIDANCE

eAg NEG



DO NOT TREAT: Monitor ALT and HBV DNA q 3-6 months

TREAT

If ALT ≤ULN, monitor ALT and HBV DNA q 6 m
If >ULN evaluate, if advanced liver disease treat

Hepatology67(4):1560-1599, April 2018.

ALTERNATE CAUSES OF ALT ELEVATIONS IN HBV

- Always consider alternative causes of ALT elevations
  - Other drivers may increase HCC and cirrhosis risk
  - ALT ULN 35 (men) and 25 U/L (women)
- Half of HBV patients with ALT elevations may be due to other causes
  - Alcohol and MASLD are the most common
  - Carefully evaluate in those with T2D

ALTERNATE CAUSES OF ALT ELEVATIONS IN HBV

IN AGE AND VIRAL LOAD WE TRUST

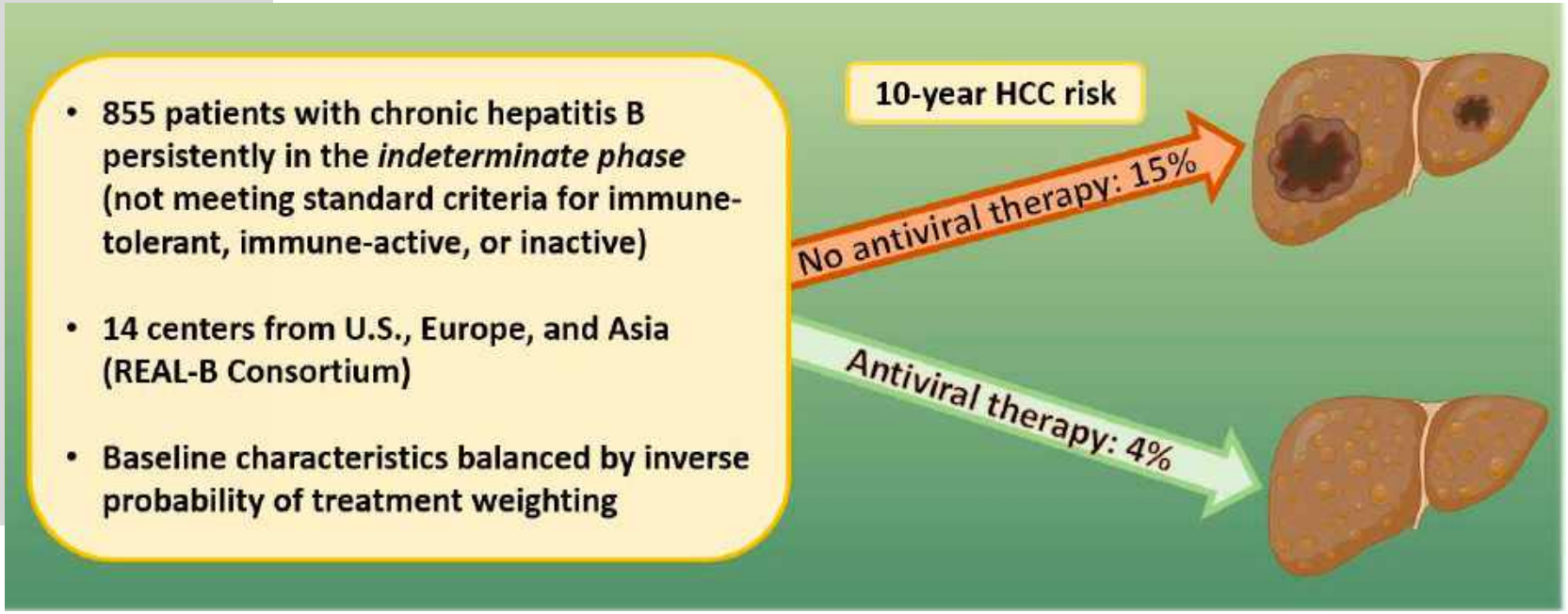
- Half of HBV patients with ALT elevations may be due to other causes
  - Alcohol and MASLD are the most common
  - Carefully evaluate in those with T2D

WHY THE INDETERMINATE PATIENTS IS IMPORTANT

MOST COMMON GRAY ZONE PATIENT

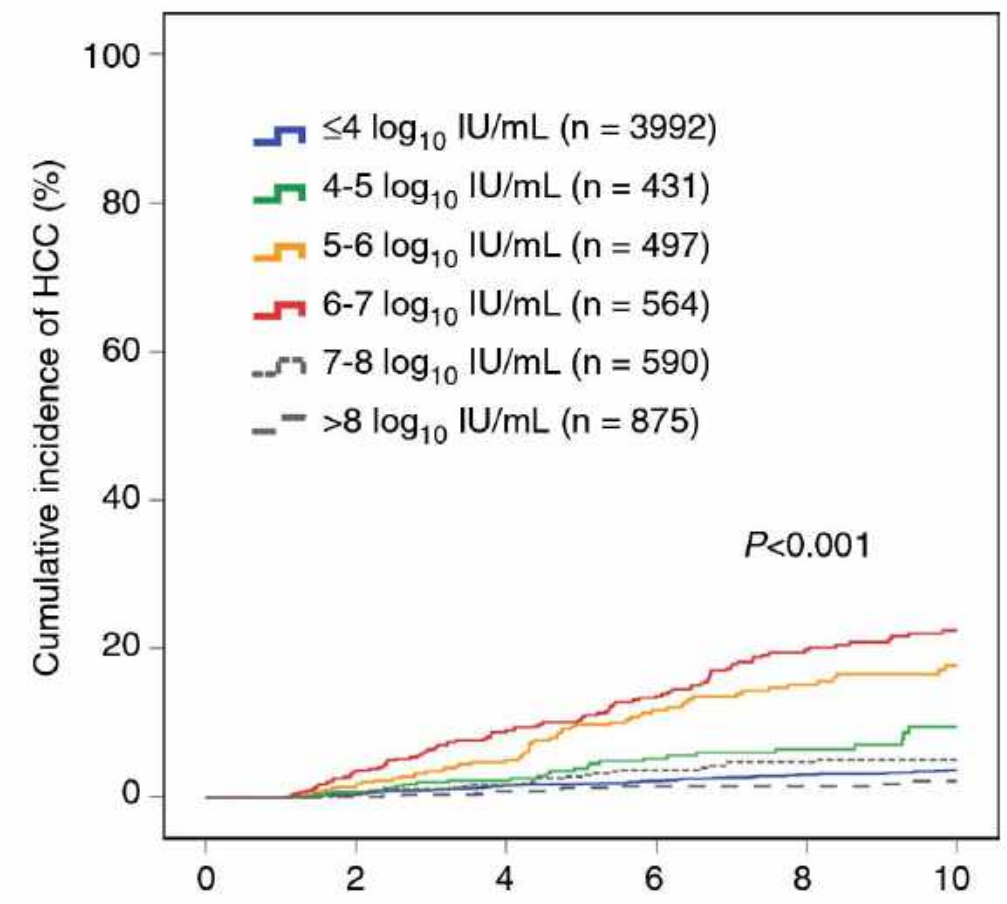
- Represent up to 38% of patients
- Most common scenario
  - HBeAg negative
  - HBV DNA <2000 IU/mL
  - Elevated ALT

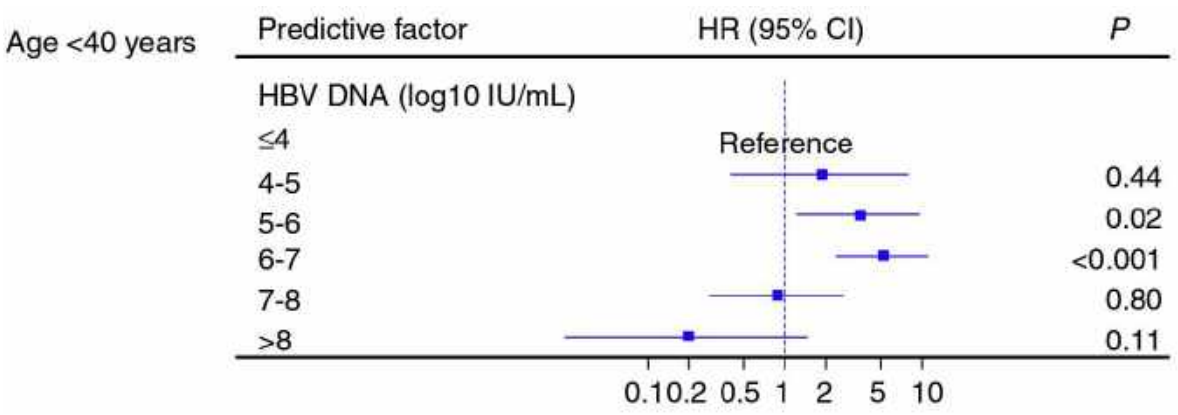
- Simplification of Guidance would improve care, reduce errors and decrease burden of hepatocellular carcinoma.



Yao K, JVH 2021;28:1025-1033. Huang D, Clin Gastroenterol Hepatol 2021:S1542-3565. Huang D/Nguyen MD et al, Hepatol 2023; 78(5):1558-1568

AGE AND VIRAL LOAD DEFINE IMMUNE TOLERANT PHASE



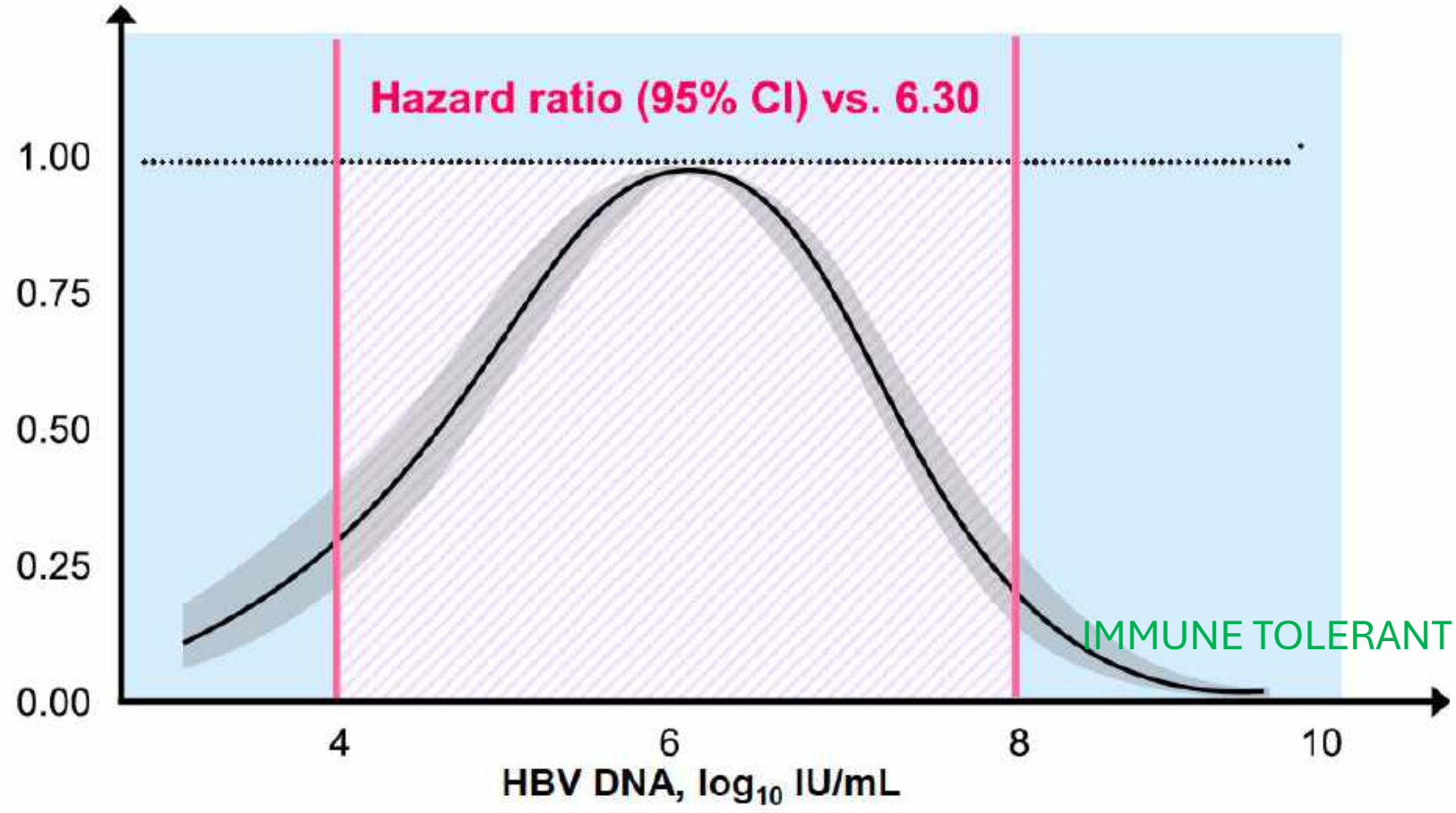


- HBV DNA levels ≥7 log associated with no significant increased risk of HCC
- HBV DNA levels 6-7 log-IU/mL associated with highest risk of HCC
- HBV DNA levels 6 log-IU/mL= 1,000,000

IMMUNE TOLERANT= IT

Kim G-A, APT 2020 Jun;51(11):1169-1179

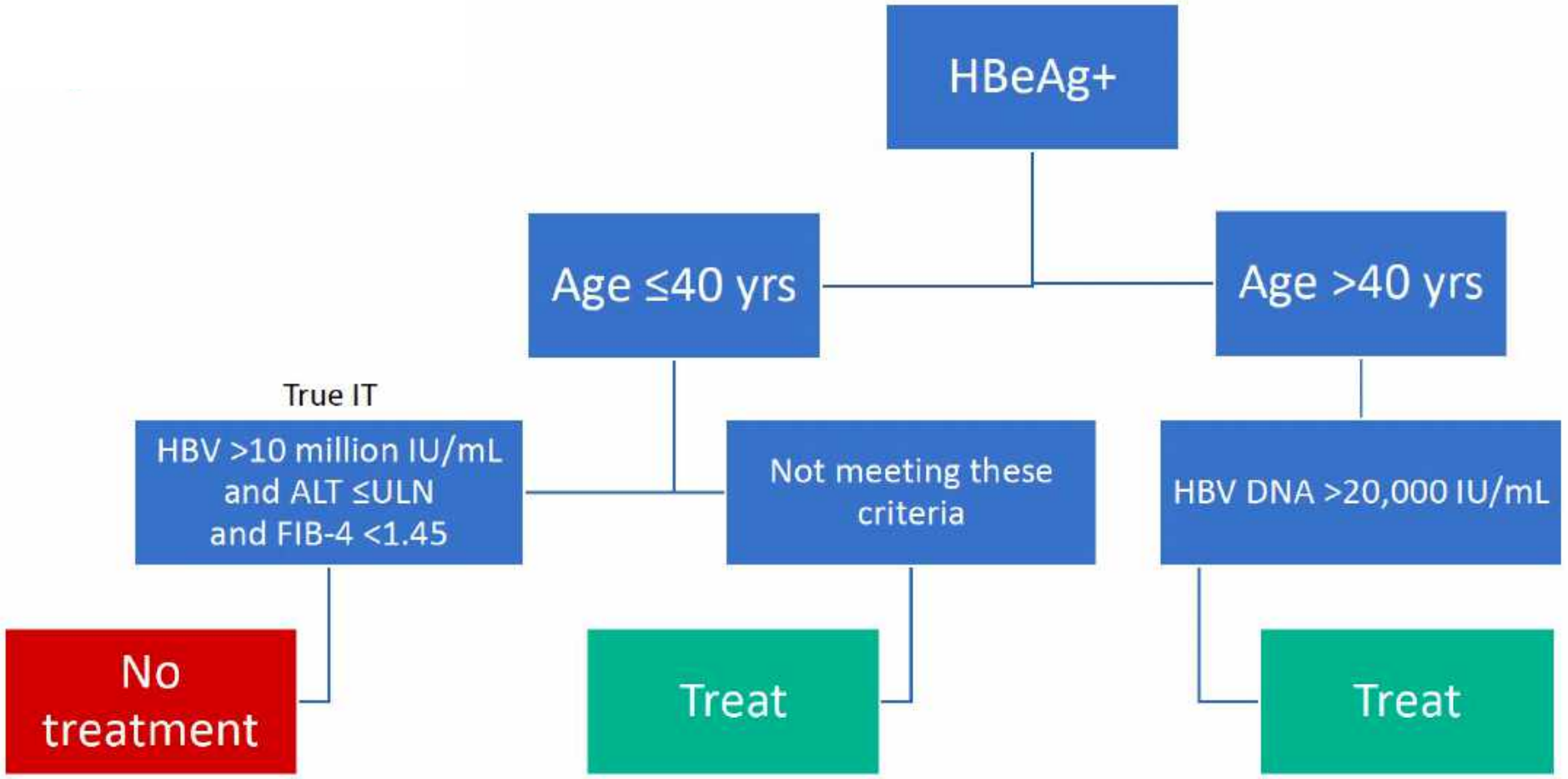
HCC RISK BY HBV DNA: NON-LINEAR PARABOLIC



HCC risk was 4 times higher with moderate HBV DNA around 6 log_{10} IU/mL compared with 8 log_{10} IU/mL in CHB patients without significant ALT elevation.

Kim GA, Lim YS, et al. Aliment Pharmacol Ther. 2020;51:1169–79.

SIMPLIFIED HBV GUIDANCE: HBeAg-POS



Norah Terrault, How to Simplify Treatment Criteria Under the Current HBV Guidelines. AASLD 2023.

SIMPLIFIED HBV GUIDANCE: HBeAg-NEG

HBeAg Negative

HBV DNA <2000

Don't treat
Evaluate carefully for other causes of CLD if ALT elevated

HBV DNA 2000-10,000

Treat if age>50 or significant fibrosis (FIB-4 >2.67 or VCTE>9kPa)

All others – don't treat

HBV DNA ≥10,000

Treat

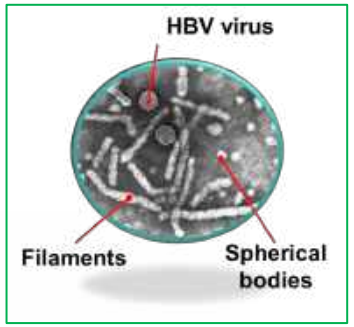
Norah Terrault, How to Simplify Treatment Criteria Under the Current HBV Guidelines. AASLD 2023.

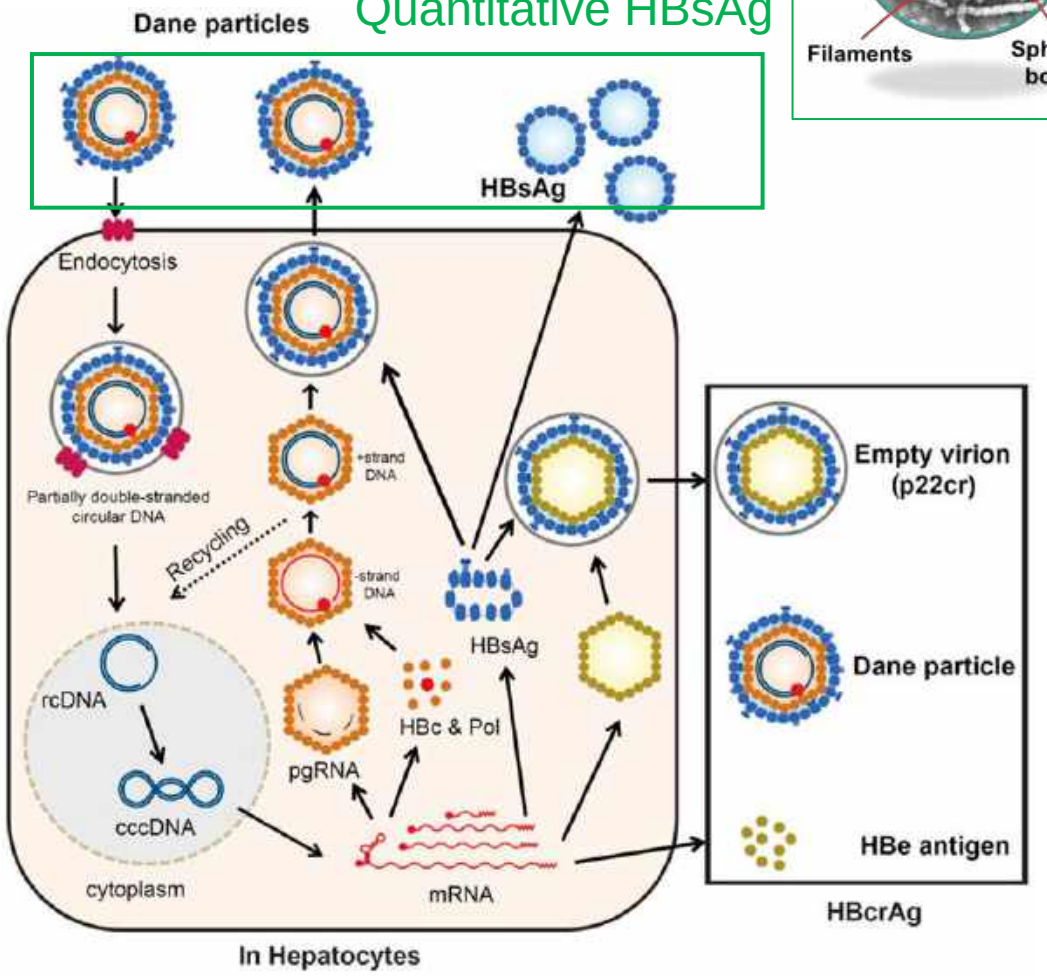
PLEASE TELL ME YOU ARE DONE: qHBsAg

NOVEL HBV BIOMARKERS: qHBsAg

Quantitative HBsAg

- HBsAg clearance = functional cure
- Surrogate for Immune Control
- Low level - predict HBsAg clearance1,2
- <10-100 predictor of relapse after stopping NA
- Response to new therapies

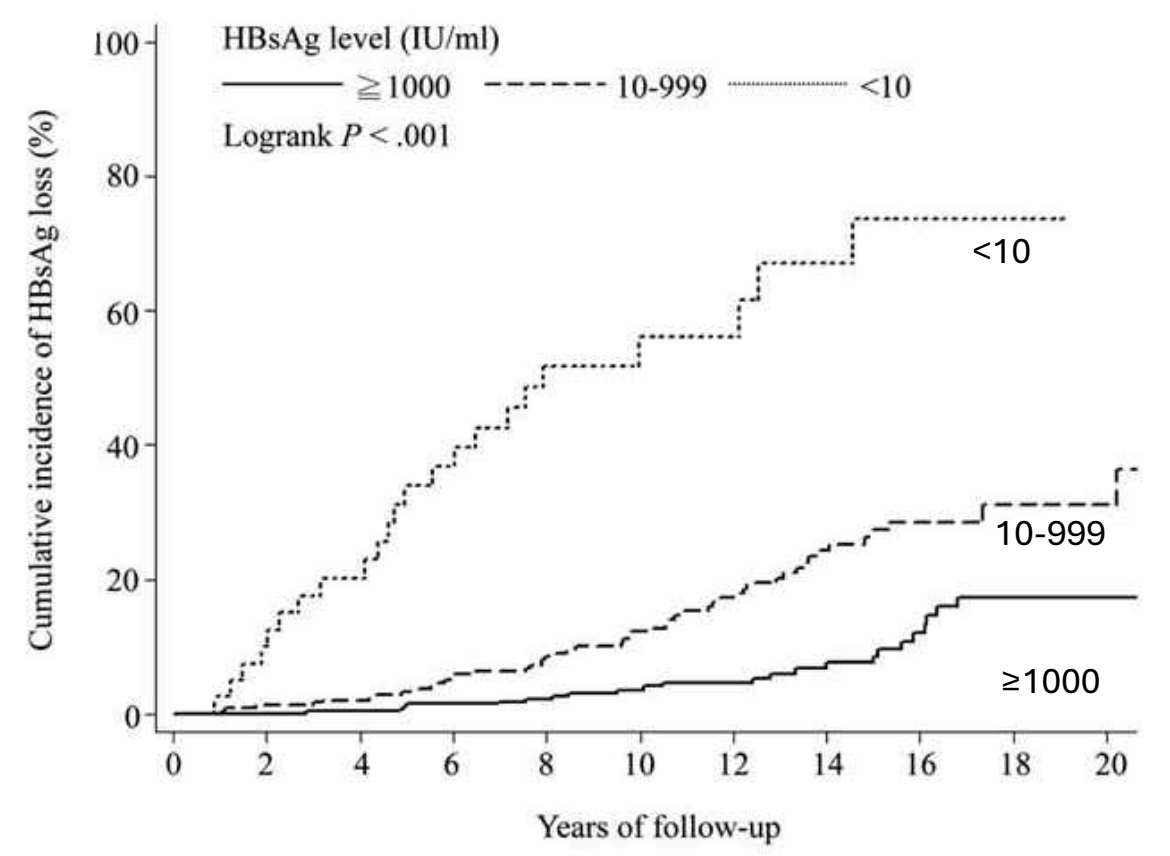




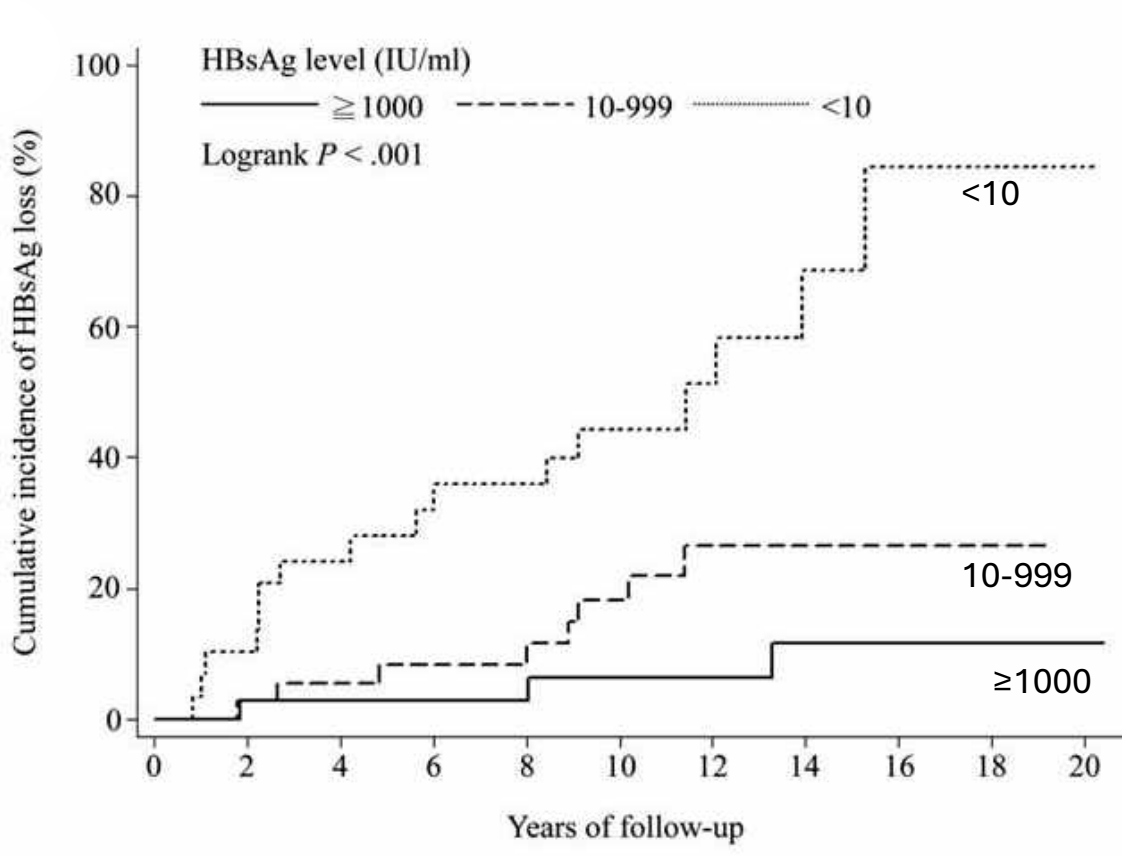
Hepatology, V64, p 381; 2012; Terrault et al., Hepatology 2021; Jeng W et al., Hepatology 2018; Cornberg M et al., Hepatology V 71. (3) 2020

INCIDENCE OF HBsAg LOSS IN CHRONIC CARRIERS

HBV DNA 15-999 IU/mL

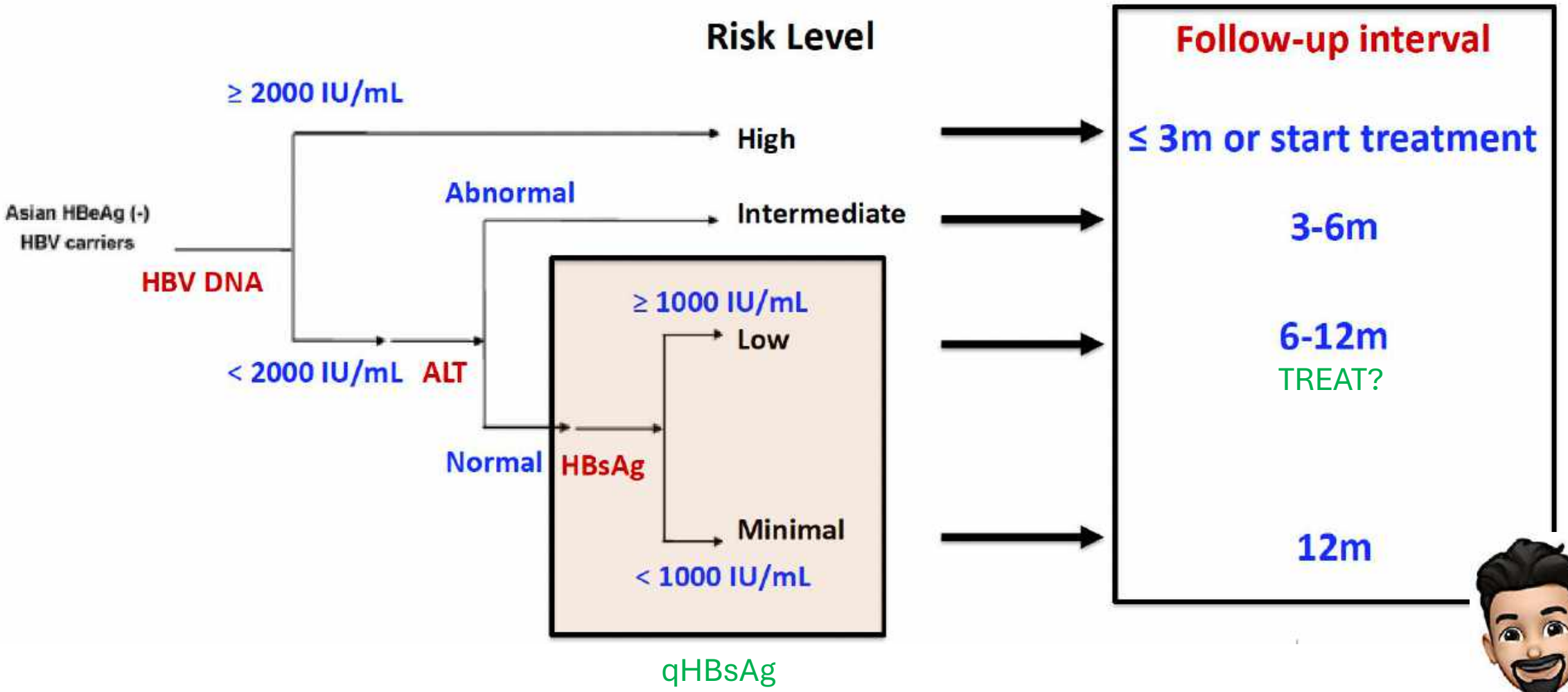


HBV DNA <15 IU/mL



Tseng et al. Hepatology. 2012 Jan;55(1):68-76.

qHBsAg COULD BE USEFUL IN EVALUATION



JORDAN FELD, AASLD 2023. TSENG HEPATOLOGY 2013

HOW TO CURE HBV

STATE OF THE ART: THERAPY FOR HBV

- **NUCs: tenofovir, entecavir**
  - Delay progression of cirrhosis
  - Reduce (but not eliminate) the risk of HCC,
  - Reduce the need for liver transplantation
- **Interferon**
  - 7-10% additional HBsAg loss on top of NA
  - Toxic side effects impact tolerability and limit use

- But.....
  - NUCs do not target cccDNA or integrated HBV DNA
  - A cure is seldom achieved on NUC therapy (<5%).
  - Most HBsAg pos patients do not meet NA treatment starting criteria
  - Life-long treatment gives cumulative costs and toxicity (TDF)
  - Patients remain to have an HBV stigma and psychosocial problems

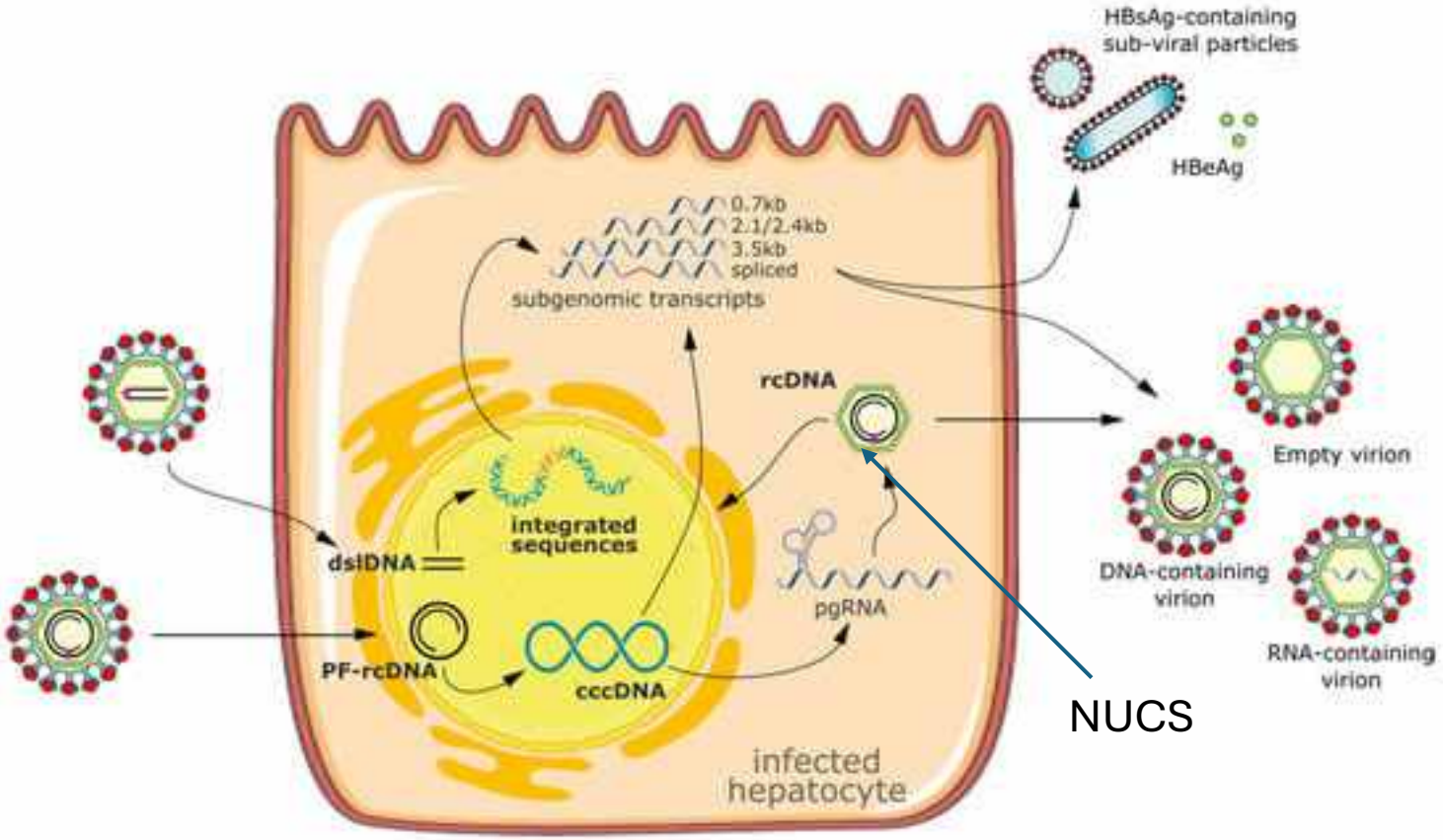
HBV: Approaching Functional Cure

	Sterilizing Cure	Idealistic Functional Cure	Realistic Functional Cure	Attainable Partial Functional Cure
	Never infected	Recovery after acute HBV	Chronic HBV with HBsAg loss	Inactive carrier off treatment
HBsAg	NEG	NEG	NEG	**POS**
Anti-HBs	NEG/POS	POS	POS/NEG	NEG
HBeAg	NEG	NEG	NEG	NEG
HBV DNA	Not Detected	Not Detected	Not Detected	Low Level
Hepatic DNA cccDNA	Not Detected	Detected	Detected	Detected
Integrated HBV DNA	Not Detected	Detected?	Detected	Detected
Liver Disease	None	None	Inactive, fibrosis	Inactive
Risk of HCC	Not increased	Not increased	Declines	Risk lower vs active hepatitis
	2034		2024	

Cornberg Hepatology, March 2020

BARRIERS TO FUNCTIONAL CURE

- Persistence of cccDNA
  - Long half-life
  - Continuous replenishment
- HBsAg produced from integrated HBV DNA



Guadalupe. Viruses **2022**, *14*(12), 2654;

BACK TO THE FUTURE: COMBO THERAPY

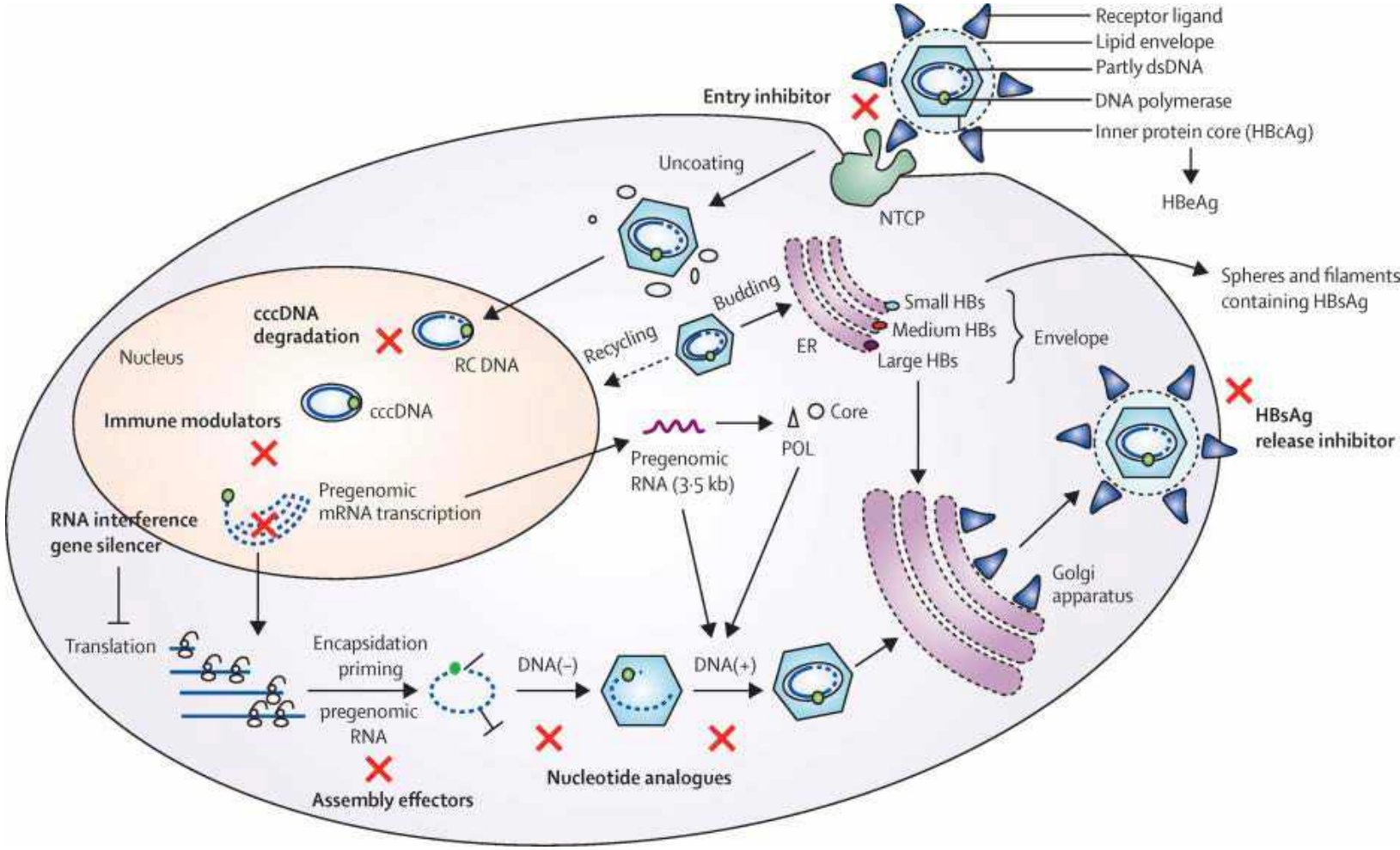
Entry inhibitors
NUCs
Capsid Assembly Inhib

siRNA
Antisense oligonucleotides
Nucleic Acid Polymers
RNA destabilizers
FXR agonists

Interferons
TLR7 and TLR8
Anti-PD1 and PDL1
Therapeutic Vaccines
Car-T cell
Anti HBs Mab

EMERGING TARGETS

- Initial HBV Cure regimens will combine multiple agents that inhibit replication, reduce antigen burden and restore host immune control needed to maintain sAg loss post-treatment



HepB Foundation Drug Watch Site. Brahmania M, Feld J, Arif A, Janssen HL.Lancet Infect Dis. 2016 Feb;16(2):e10-21.

HOW TO CURE HEPATITIS DELTA

Scripps

HDV TARGETS

Chronic on-therapy endpoints:

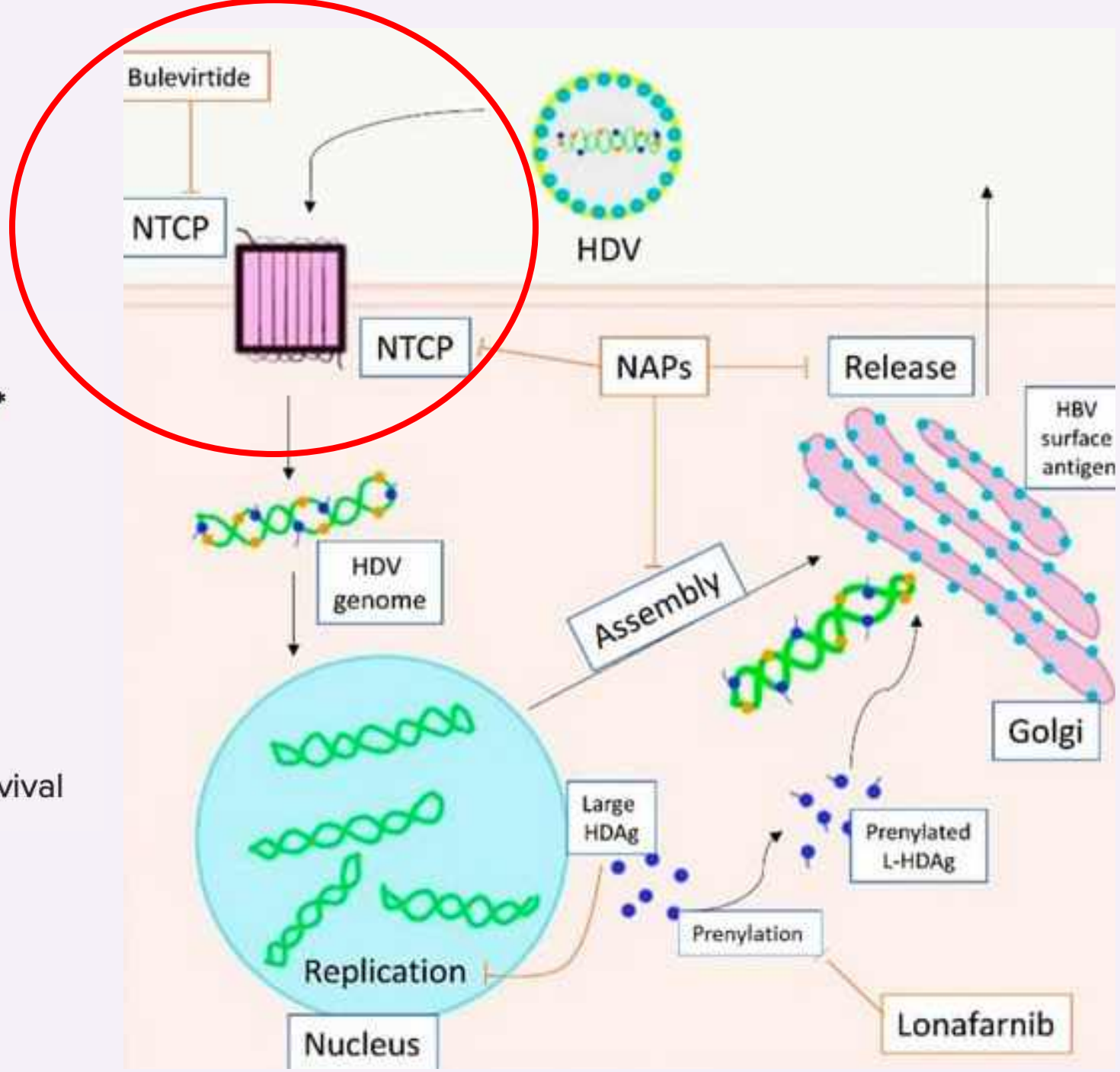
HDV viral load ≥2-log$_{10}$ decline*

and

ALT normalisation

Goals of therapy:

- Control disease progression
- Prevent HCC development
- Improve quality of life and survival

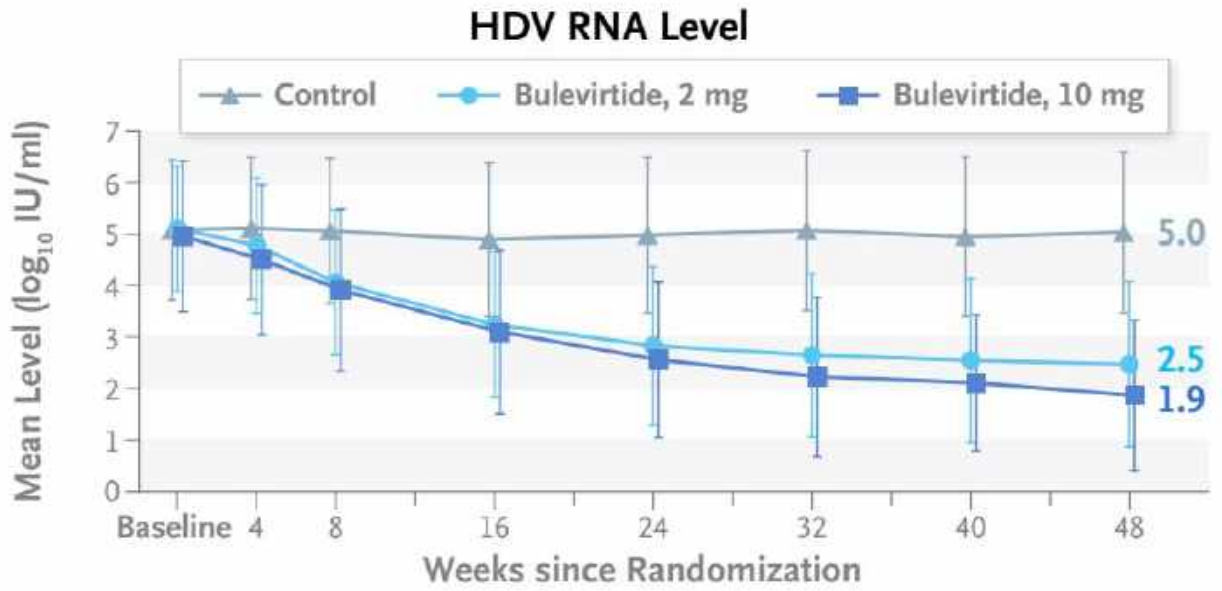


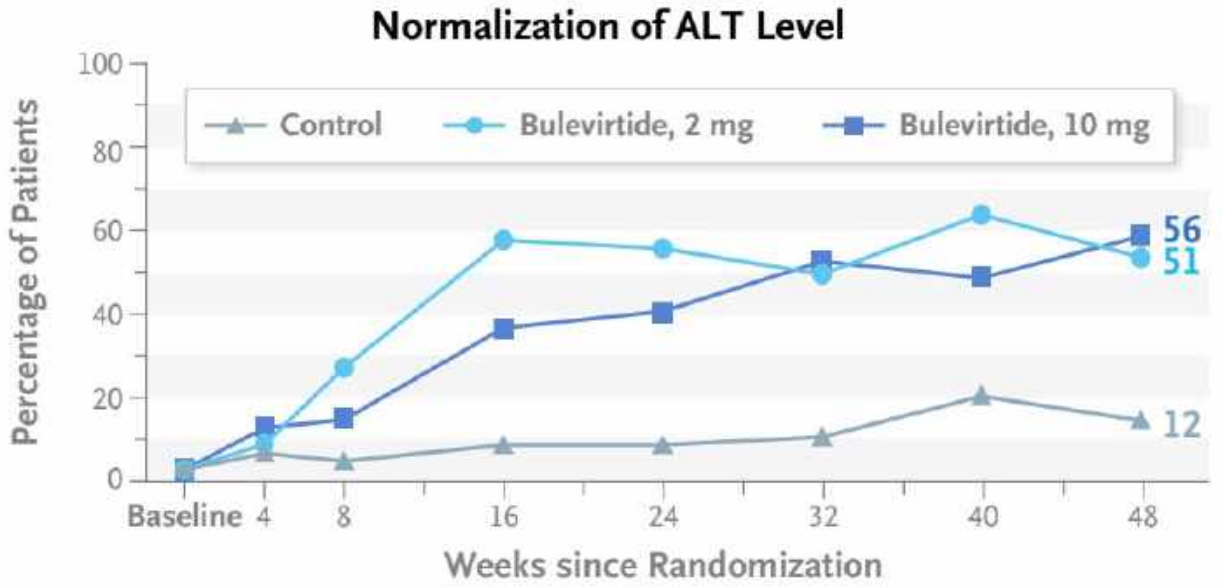
Life **2021**, *11*(2), 169

BULEVIRTIDE

The NEW ENGLAND JOURNAL of MEDICINE

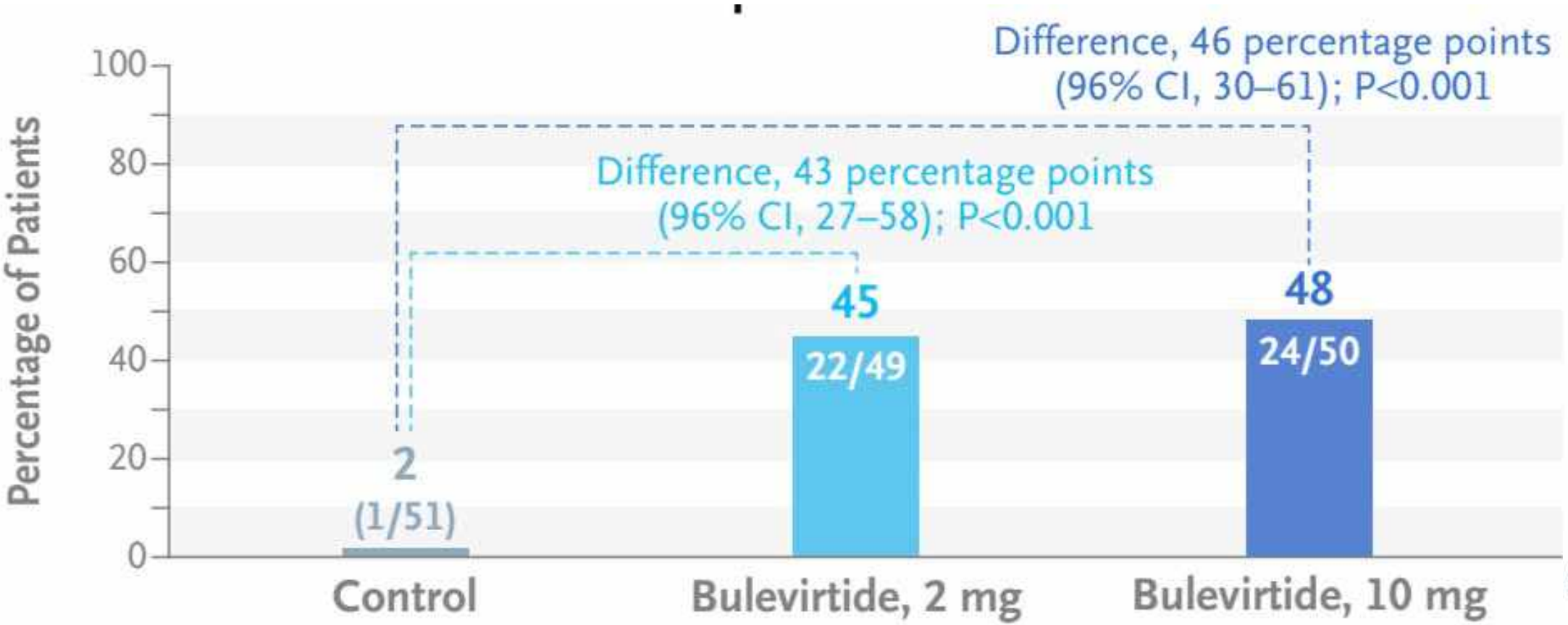
- Ongoing phase 3 trial, which includes 144 weeks of treatment and 96 weeks of post-treatment follow-up.
- Combined Primary outcome at w48 of undetectable HDV RNA, or level decreased by at least 2 $\log_{10}$ IU/mL from baseline, and normalization of ALT.





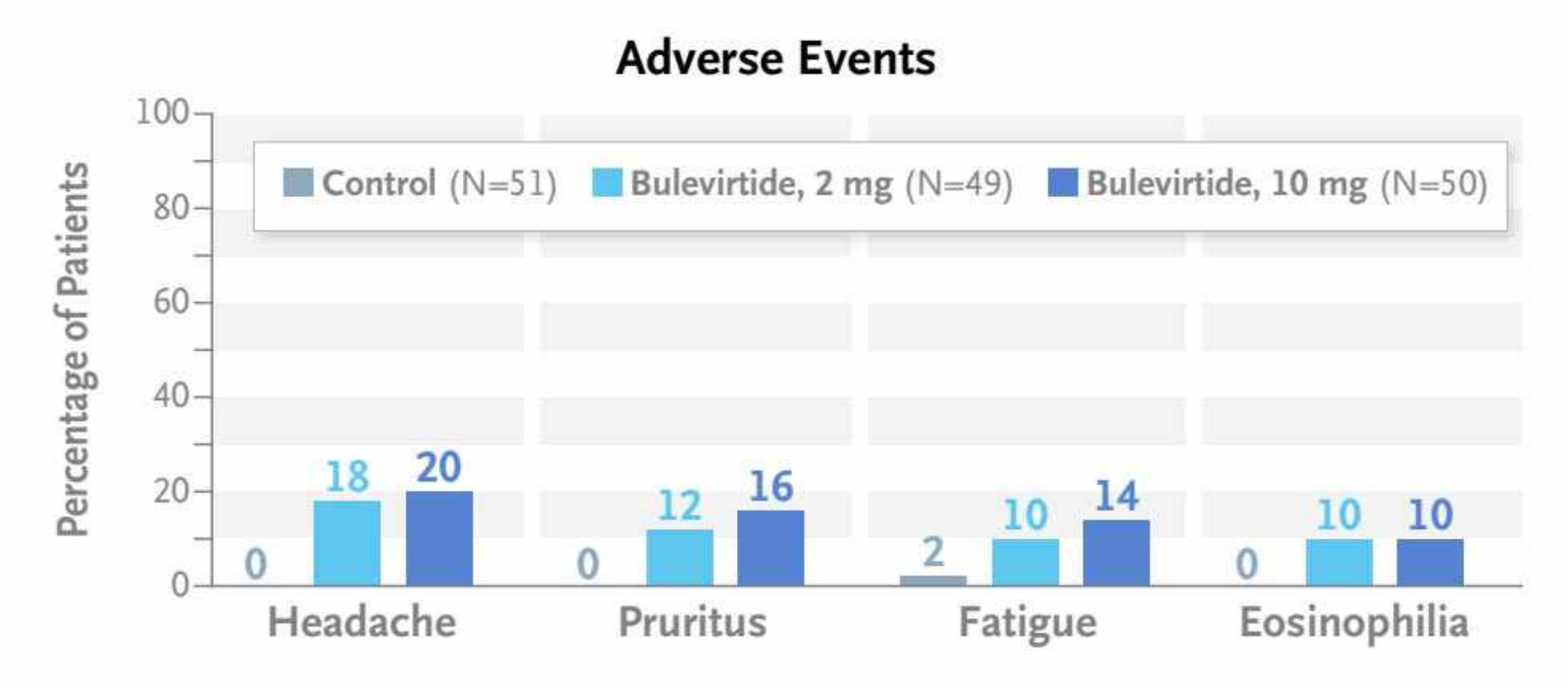
Wedemeyer. N Engl J Med 2023; 389:22-32

BULEVIRTIDE: COMBINED RESPONSE AT W48



Wedemeyer. N Engl J Med 2023; 389:22-32

BULEVIRTIDE: WELL TOLERATED



Wedemeyer. N Engl J Med 2023; 389:22-32

iStock

SCIENCE NEWS

FDA Declines Approval of First Hepatitis D Treatment

SUMMARY FOR BAD BEDFELLOWS: B AN D

- Screen all your patients for hepatitis B
- Screen HBV patients for Delta: HDV AB w/reflex HDV RNA
- Treating HBV in the “Grey Zone” can reduce HCC
- Simplify care of HBV eAg POS:
  - eAg POS: <40 Y+ risk= Treat; >40 Y + HBV DNA >20k(or risk) = Treat
    - Don’t’ treat Immune Tolerant
  - eAg NEG: HBV DNA 2-10K + risk= Treat or >10k= Treat
- qHBsAg can help stratify low HBV DNA patients
- Functional Cure may be achieved with future combo therapies
- Bulevirtide is safe and effective but not approved by the FDA.

GUTIERREZ JA 2024

Scripps

2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

HCV Elimination: Where are we now?

Anita Kohli, MD, MS

Infectious Disease

CEO Arizona Liver Health & Research Medical Director

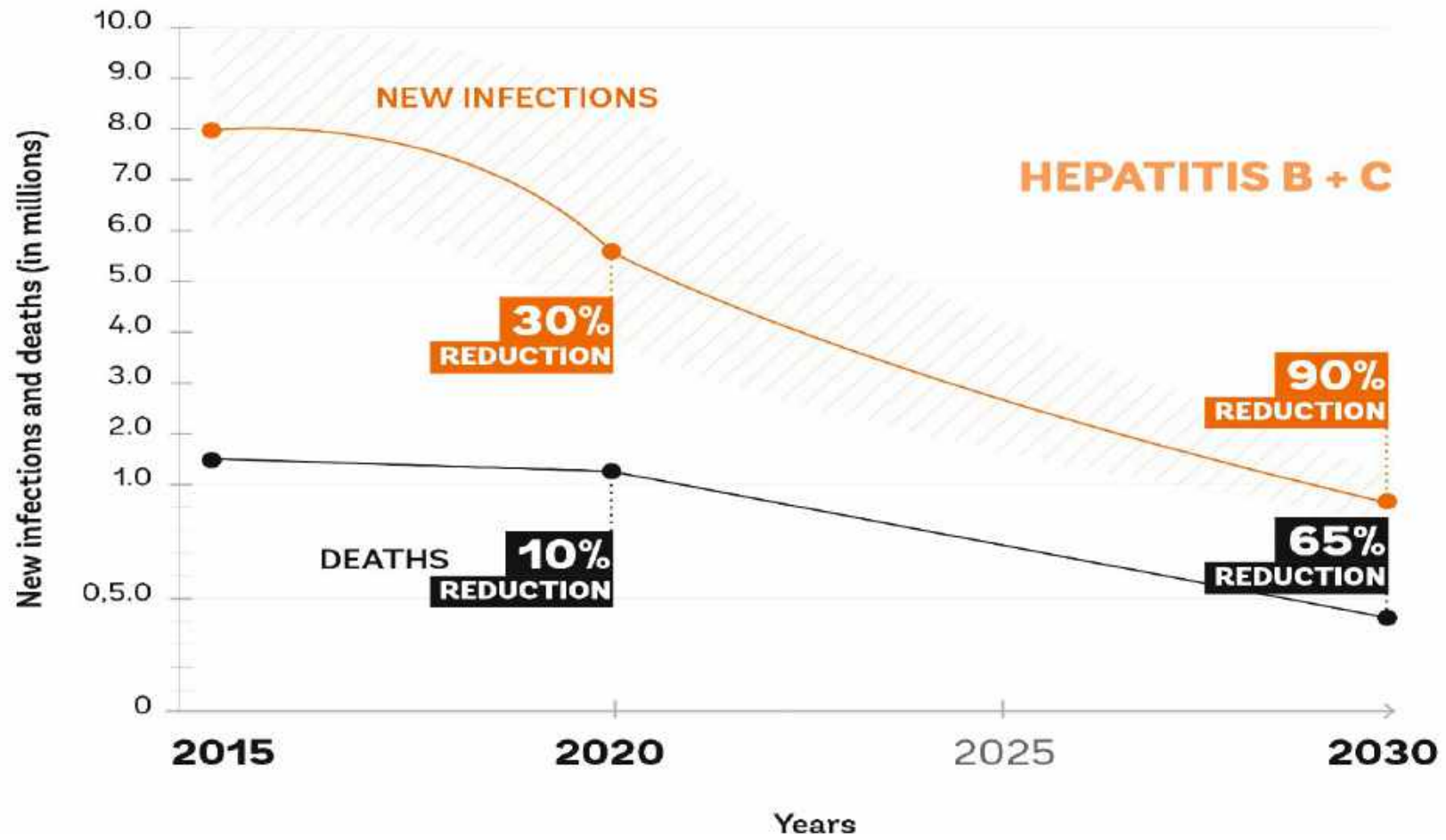
HCV: State of Affairs

- **Chronic illness results in cirrhosis, liver cancer and premature deaths**
- **No vaccine available**

Simple, well tolerated treatment of 8-12 weeks cures 95-98% of people!

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

HCV State of Affairs: WHO's goal is to eliminate viral hepatitis as a major public health problem by 2030



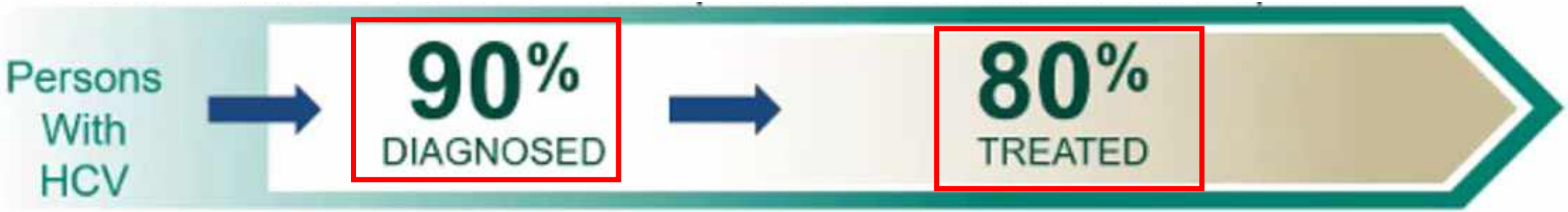
6-10 million infections (in 2015) to 900,000 infections (by 2030)

1.34 million deaths (in 2015) to under 500,000 deaths (by 2030)

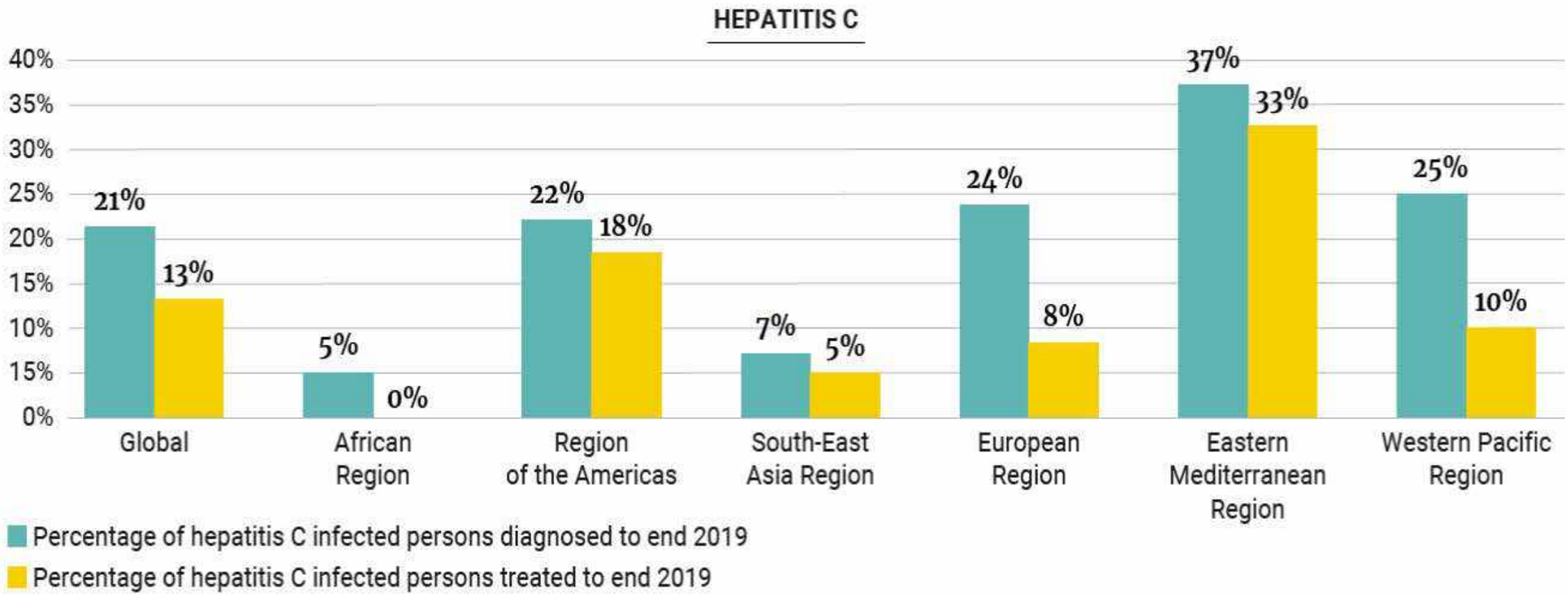
Source: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021

WHO Global Elimination of HCV Targets

The elimination of HCV as a public health threat requires:

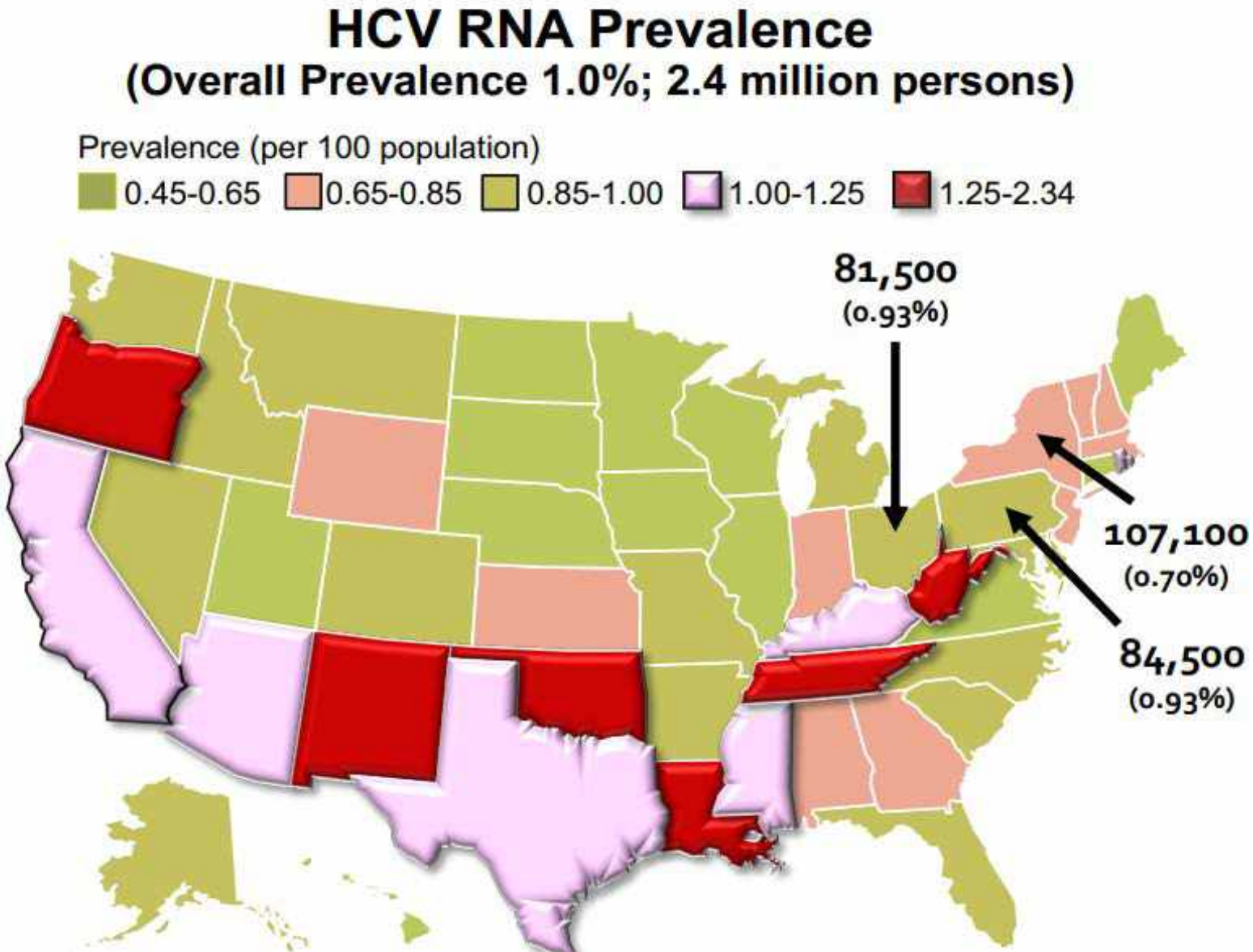


WHO Global Elimination of HCV Targets: Only 21% of ~ 58 million people with chronic HCV infection diagnosed



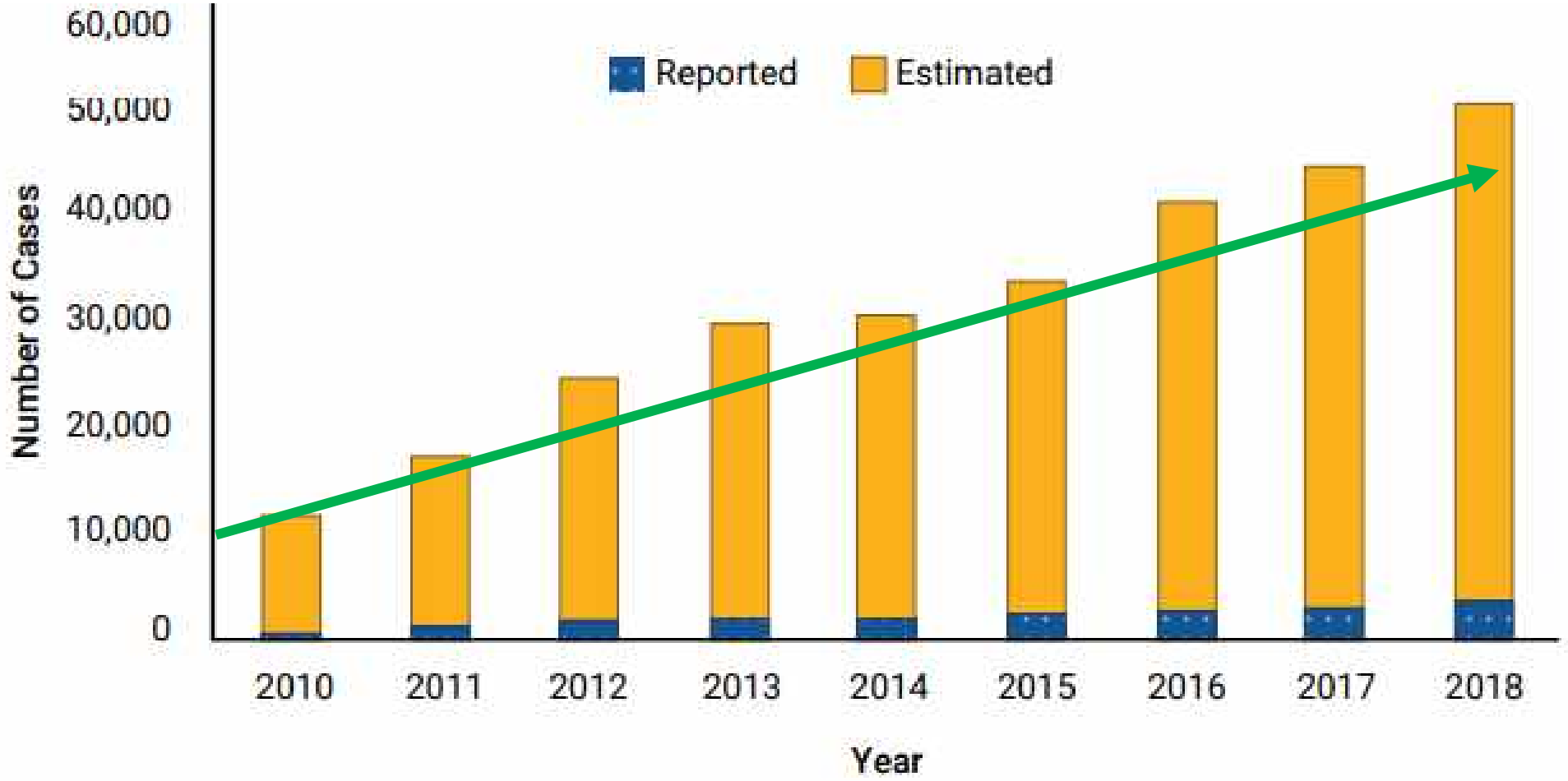
Source: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021

Hepatitis C- State of Affairs in the USA



Rosenberg ES et al. Jama Netw Open. 2018; 1e186371
National Academies of Sciences, Engineering and Medicine. A national strategy for the elimination of hepatitis B and C: Phase 2 report

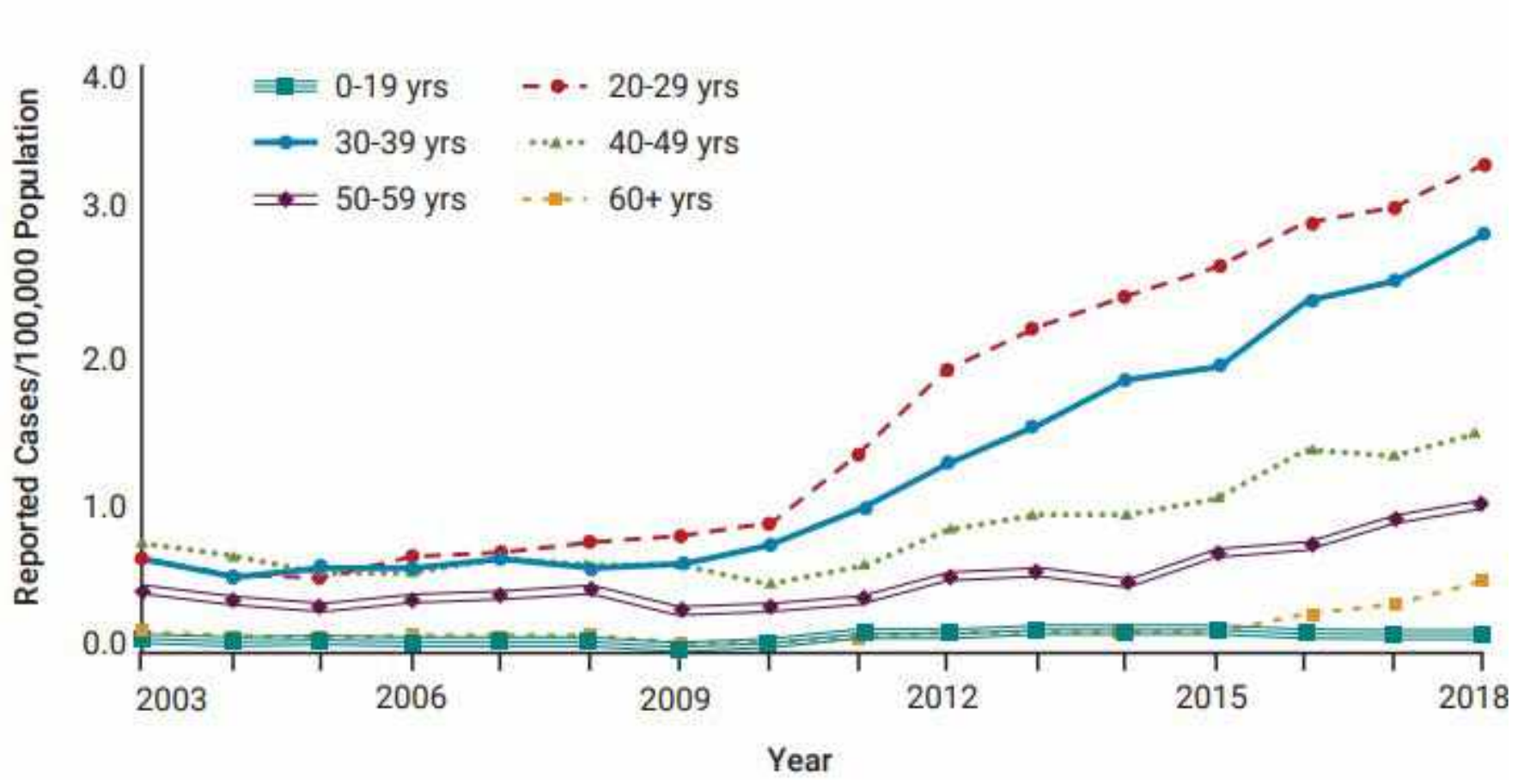
New Cases of HCV are Actually Rising



Reported and estimated number of acute HCV cases- USA 2010-2018

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

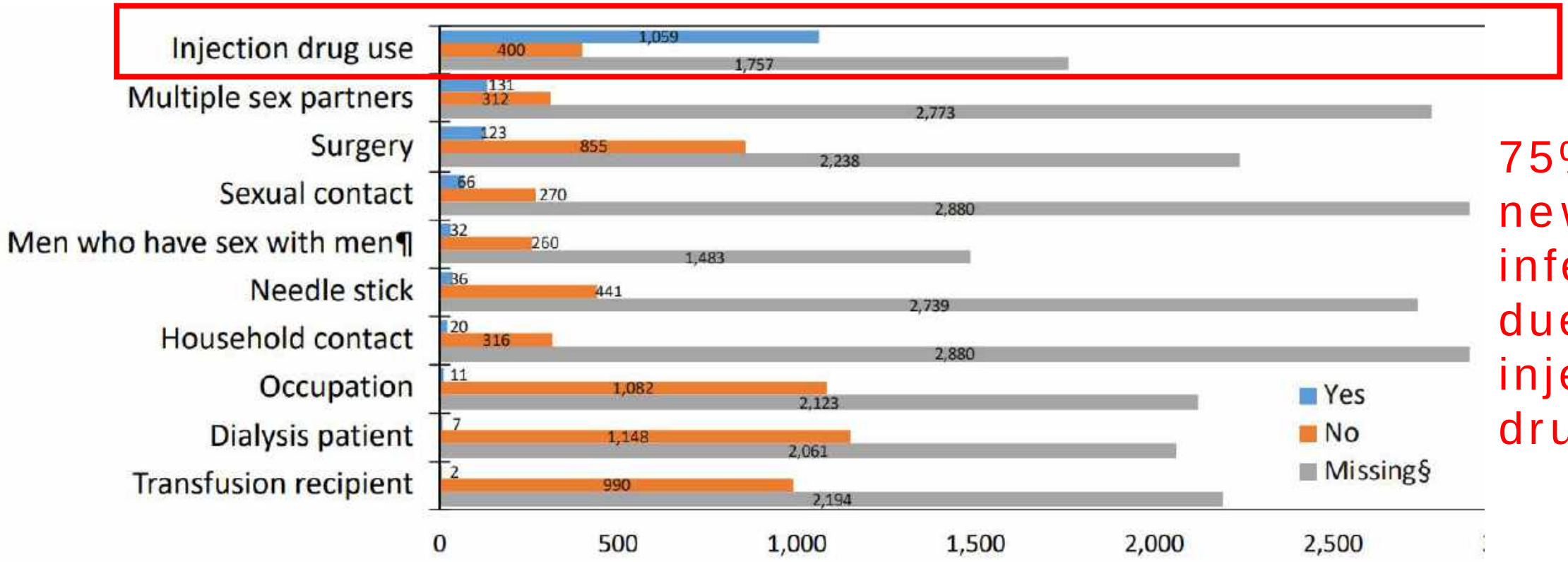
Young People Disproportionate New Infections



Rate of reported acute hepatitis C, by age group- USA 2003-2018

1. CDC.gov. Updated May 14, 2021. Accessed October 26, 2023. https://www.cdc.gov/hepatitis/statistics/2019surveillance/HepC.htm

Risk Factors in Acute HCV Cases, 2017 USA

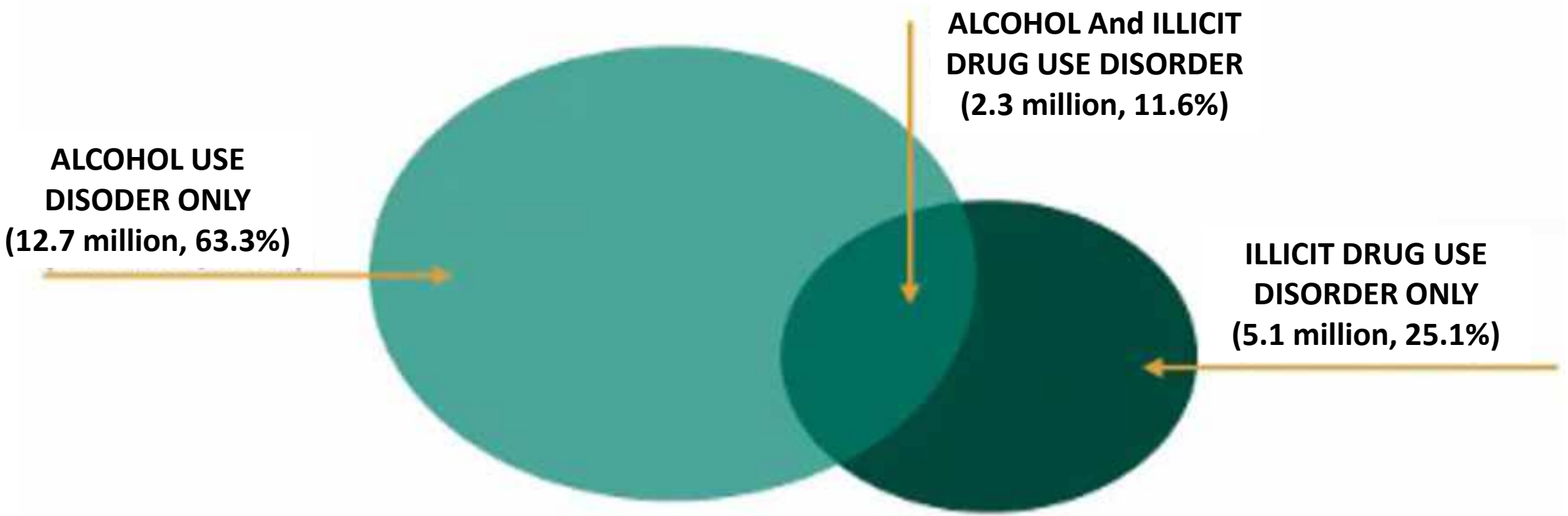


Source: CDC, National Notifiable Diseases Surveillance System.

75% of new infections due injection drug use

Substance Use Disorder in the United States

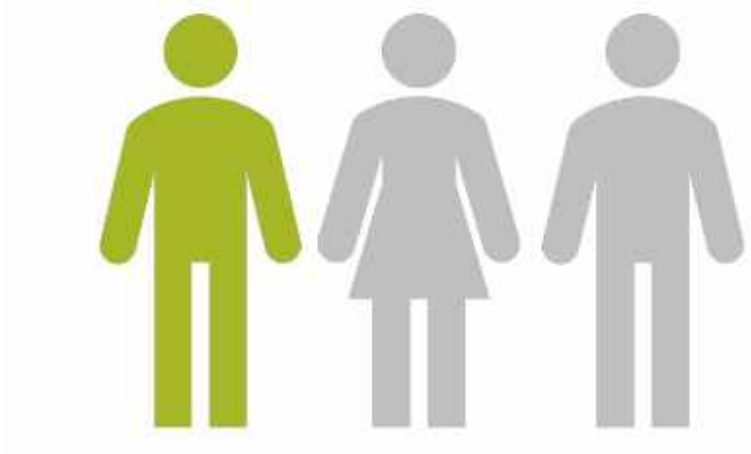
- **In 2016, more then 20 million Americans over 12 years old had a Substance Use Disorder in the Past Year**



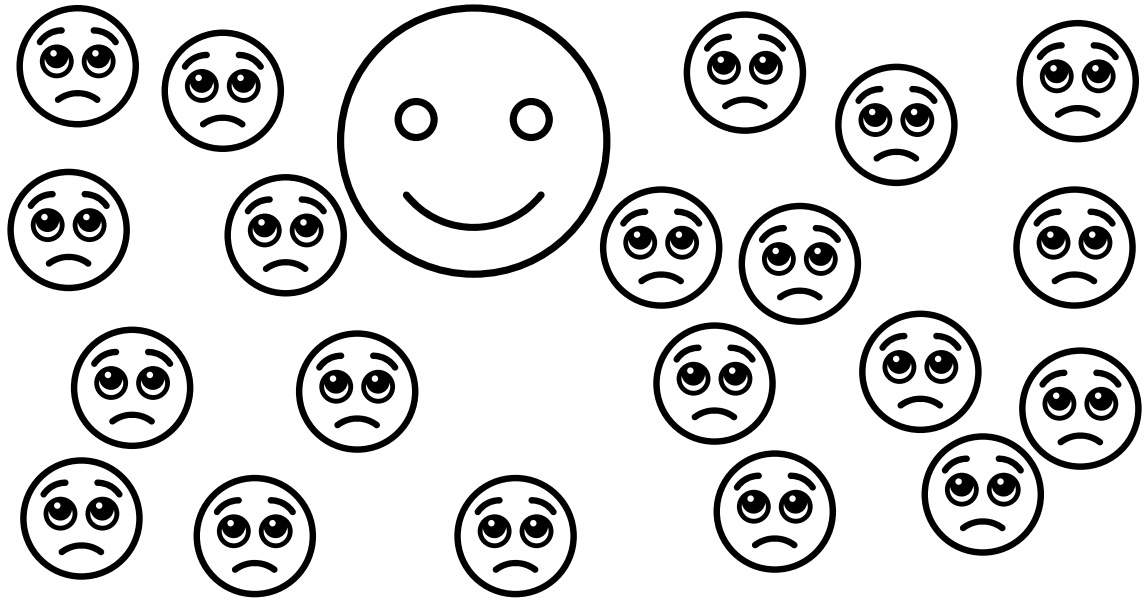
Department of Health and Human Services, Substance Abuse and Mental Health Services Administration

Two Intertwined Epidemics: HCV is a Consequence of Injection Drug Use

- **HCV Antibody prevalence among people who inject drugs (PWIDS) is 70-77%**



1 of 3 PWIDs acquires HCV in their first year of injecting



Each PWID with HCV infects ~20 other people within their first 3 years of infection

Hagan H, et al, Am J Eidemiol. 2008; 168 (10): 1099-1109
2021 NIH National Institute on Drug Abuse Heroin Research Report

HCV Infection Rate Increases with Injection Frequency and Number of Partners

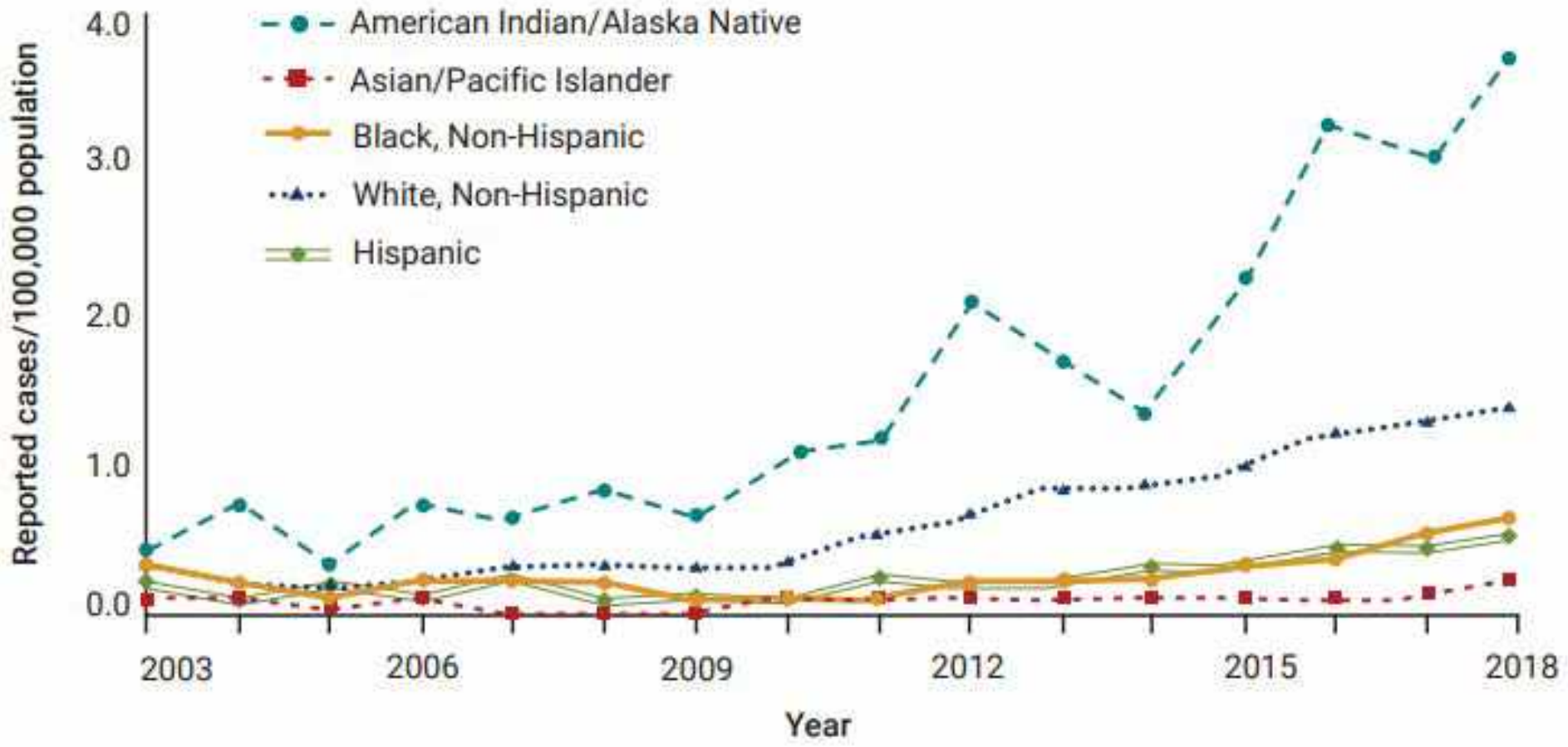
Each additional network partner increases incidence rate by 5.8-6.9 HCV infections per 100 PY

Increasing the frequency of infection from less than daily to daily or more increased the rate of HCV infection 67% (15.6-23.1 per 100 PY)

Delaying treatment in PWIDS prolongs the time during which they are infectious

Hellard M et al, Int J Drug Policy 2015: 26(10): 958-962; Rolls DA et al J Theor Biol 2012: 297: 73-87

High rates of New Cases in AI/NA



Rate of reported acute HCV, by race/ethnicity- United States, 2003-2018

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

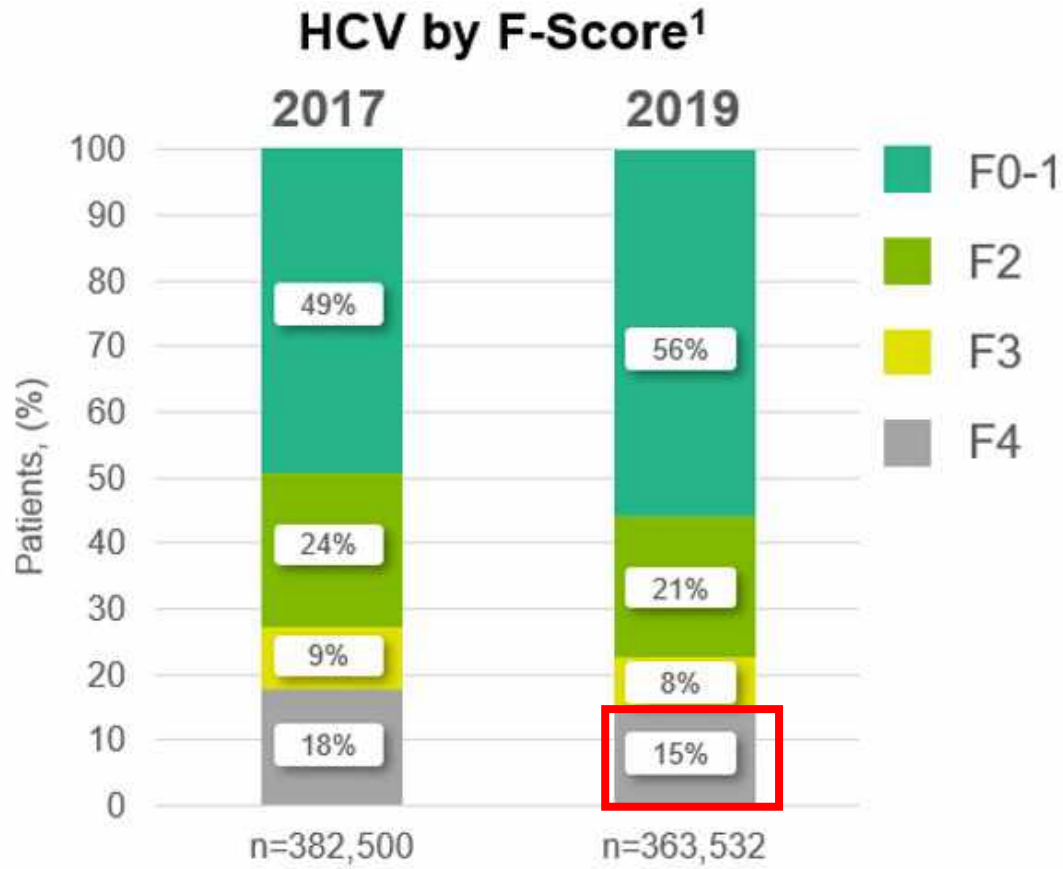
15% of HCV Patients Have Compensated Cirrhosis

- **Individuals screened from 2017-2019 by two large US lab companies**
- **Modified FIB-4 used to determine fibrosis stage**

Results

- **98.4% GT1-3,**
- **65% of GT3 were in PWID**
- **15% of HCV patients cirrhotic**
- **GT3 in patients with cirrhosis historically most difficult to cure**

- **Limitations: High risk patients such as prison not included, IVDU likely to be underrepresented**

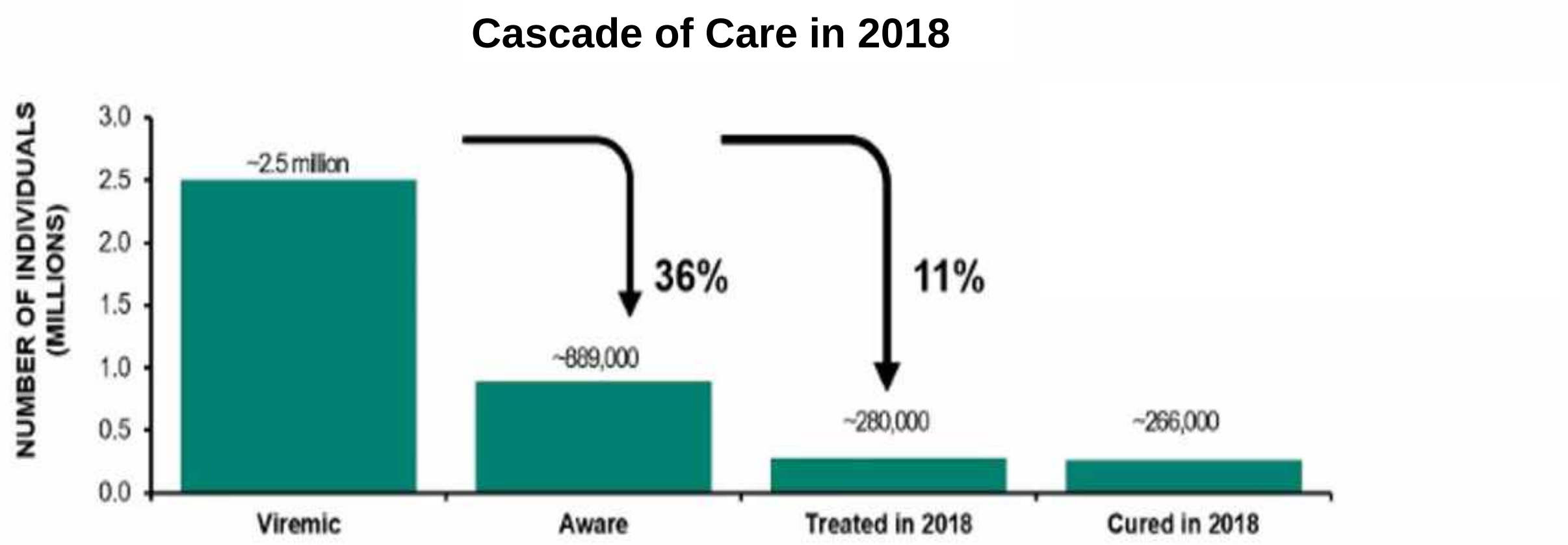


These patients will need lifetime HCC screening- challenging in PWID

Cure=sustained virologic response (SVR12), defined as HCV RNA less than the lower limit of quantification (LLOQ) at 12 weeks after the end of treatment. FIB-4=fibrosis-4. GT=genotype.

1. Reau N, et al. *Adv Ther*. 2021;38(12):5777-5790. 2. Messina JP, et al. *Hepatology*. 2015;61:77-87. 3. Flamm S, et al. *J Viral Hepat*. 2019;26:337-349.

HCV Remains Underdiagnosed and Undertreated



The number of persons alive or had or ever had HCV is estimated to be ~4 million in 2018
Chhatwal J et al. Presented at AASLD 2018, The Liver Meeting, Nov 9-13, San Francisco, CA
Zibbell JE, et al Am J Public Health 2018; 108(2):175-181

Viral Hepatitis National Strategic Plan: 2021–2025 A Roadmap to Elimination

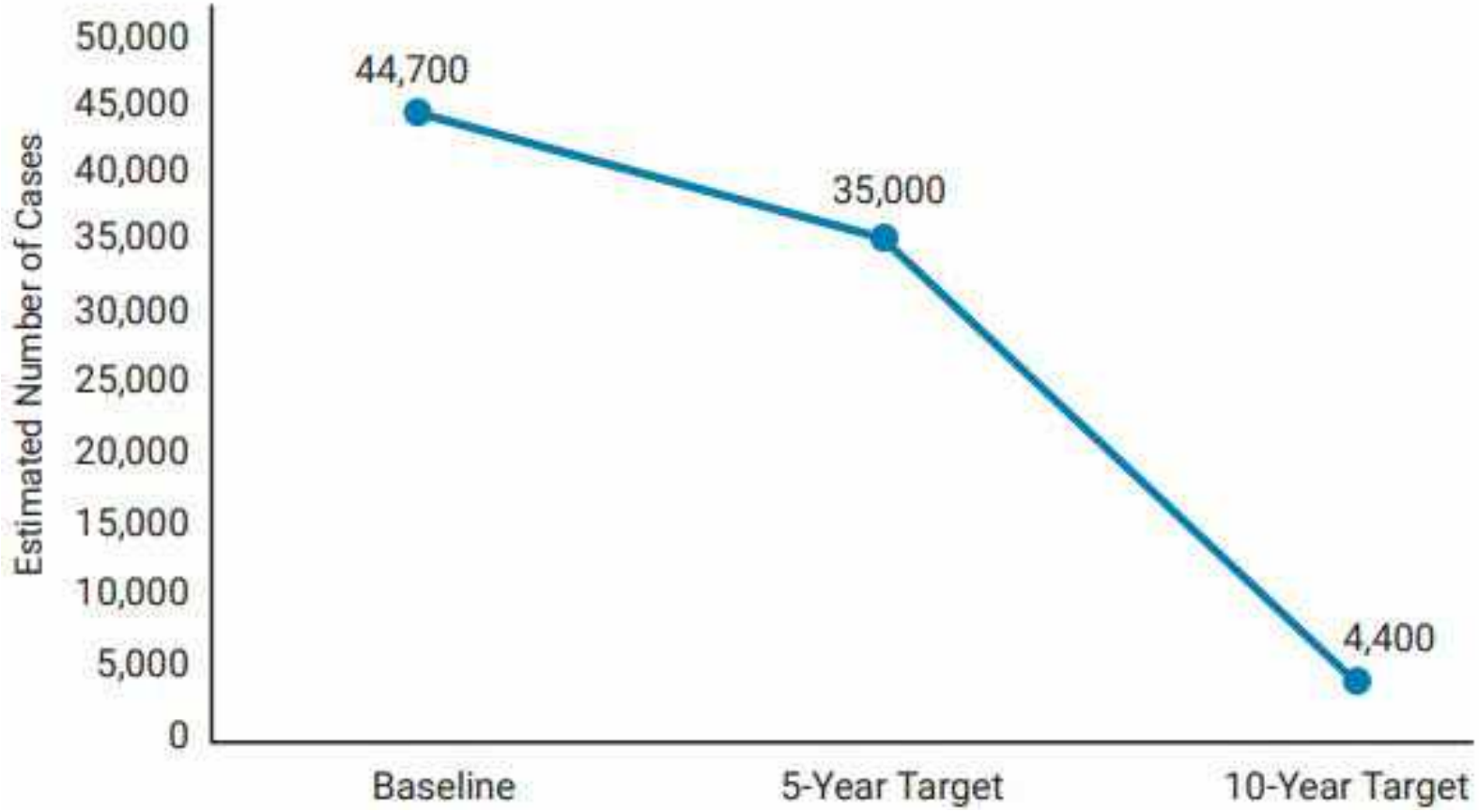
- **The Office of the Assistant Secretary for Health (OASH) and its Office of Infectious Disease and HIV/AIDS Policy (OIDP) of the U.S. Department of Health and Human Services (HHS)**

- **5 Goals**
- **8 Core Indicators of Success**
  - **3 specifically related to HCV**

Viral Hepatitis National Strategic Plan: 2021–2025 A Roadmap to Elimination

- Prevent new viral hepatitis infections
- Improve viral hepatitis- related health outcomes of people with viral hepatitis
- Reduce viral hepatitis- related disparities and health inequities
- Improve viral hepatitis surveillance and data usage
- Achieve integrated, coordinated efforts that address the viral hepatitis epidemics among all partners and stakeholders

HCV Core Plan Indicators: Reduce HCV Infections



Reduce acute HCV infections for 20% by 2025 and 90% at 2030

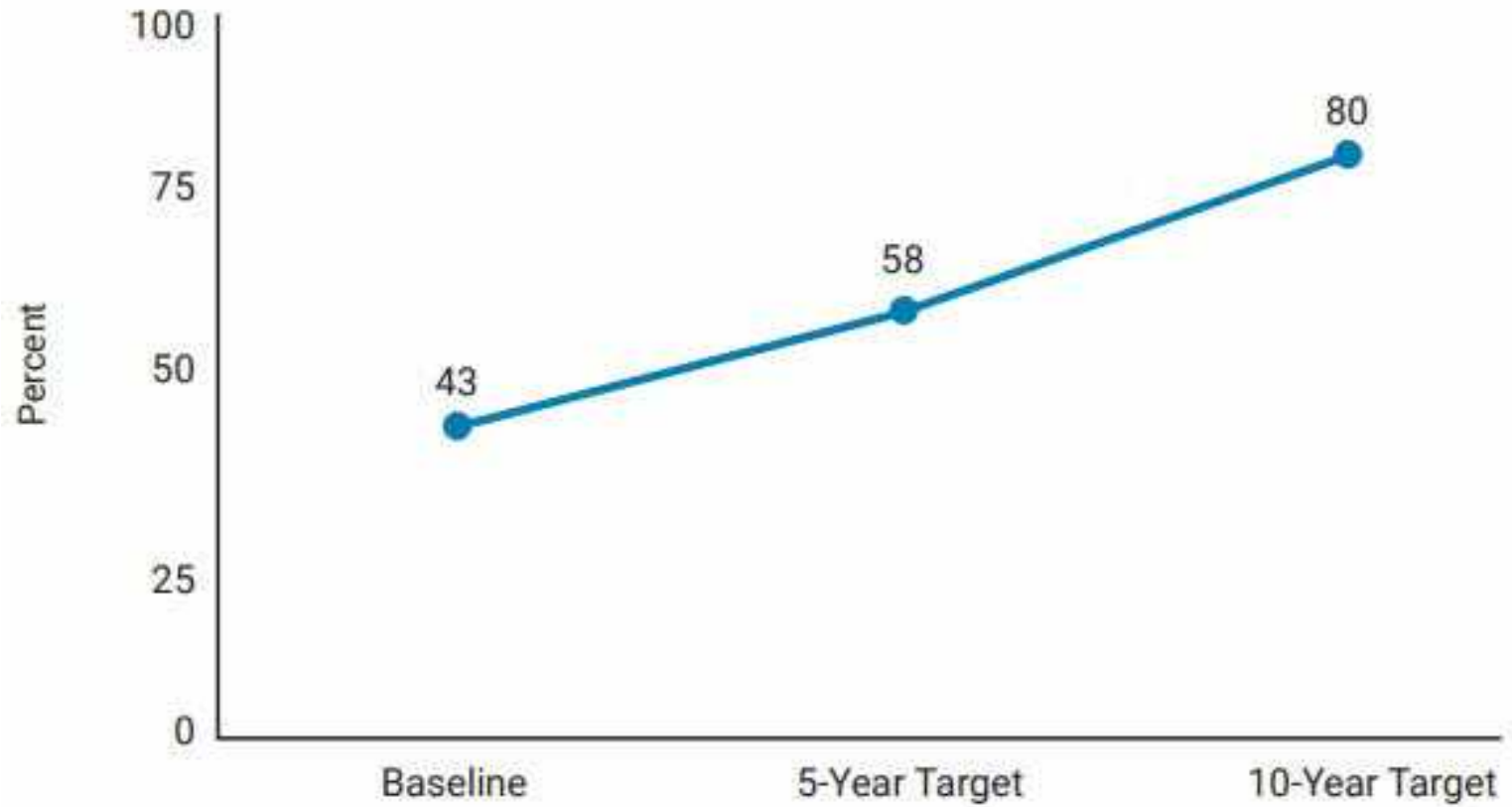
https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

HCV Core Plan Indicators: Reduce HCV Infections

Estimated new HCV infections and annual targets by year

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

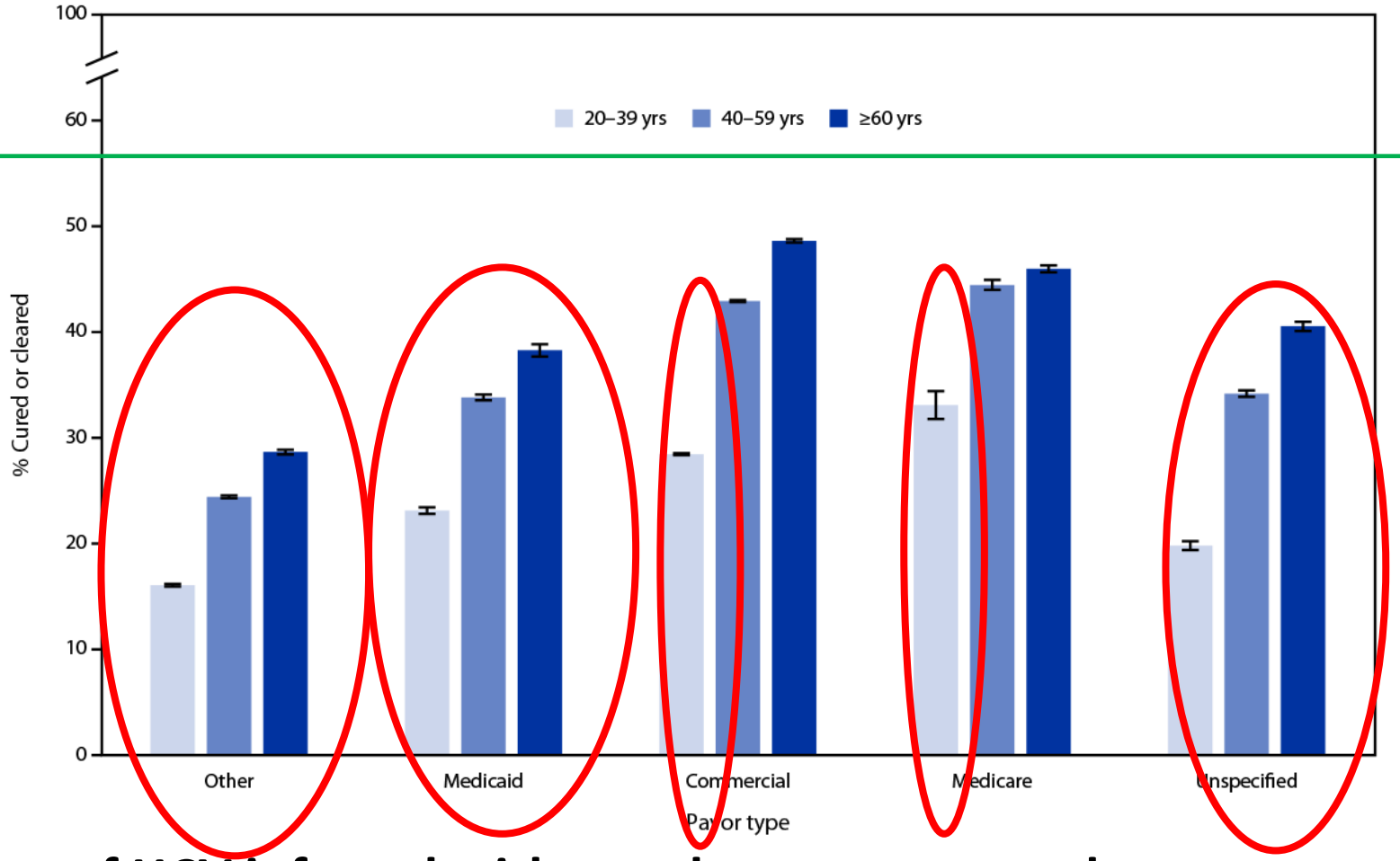
HCV Core Plan Indicators: Increase Clearance/Cure



Increase proportion of people who are cured of HCV to 58% by 2025 and 80% by 2030

https://www.cdc.gov/hepatitis/policy/npr/2023/NationalProgressReport-HepC-ReduceDeaths.htm

HCV Core Plan Indicators: Increase Clearance/Cure

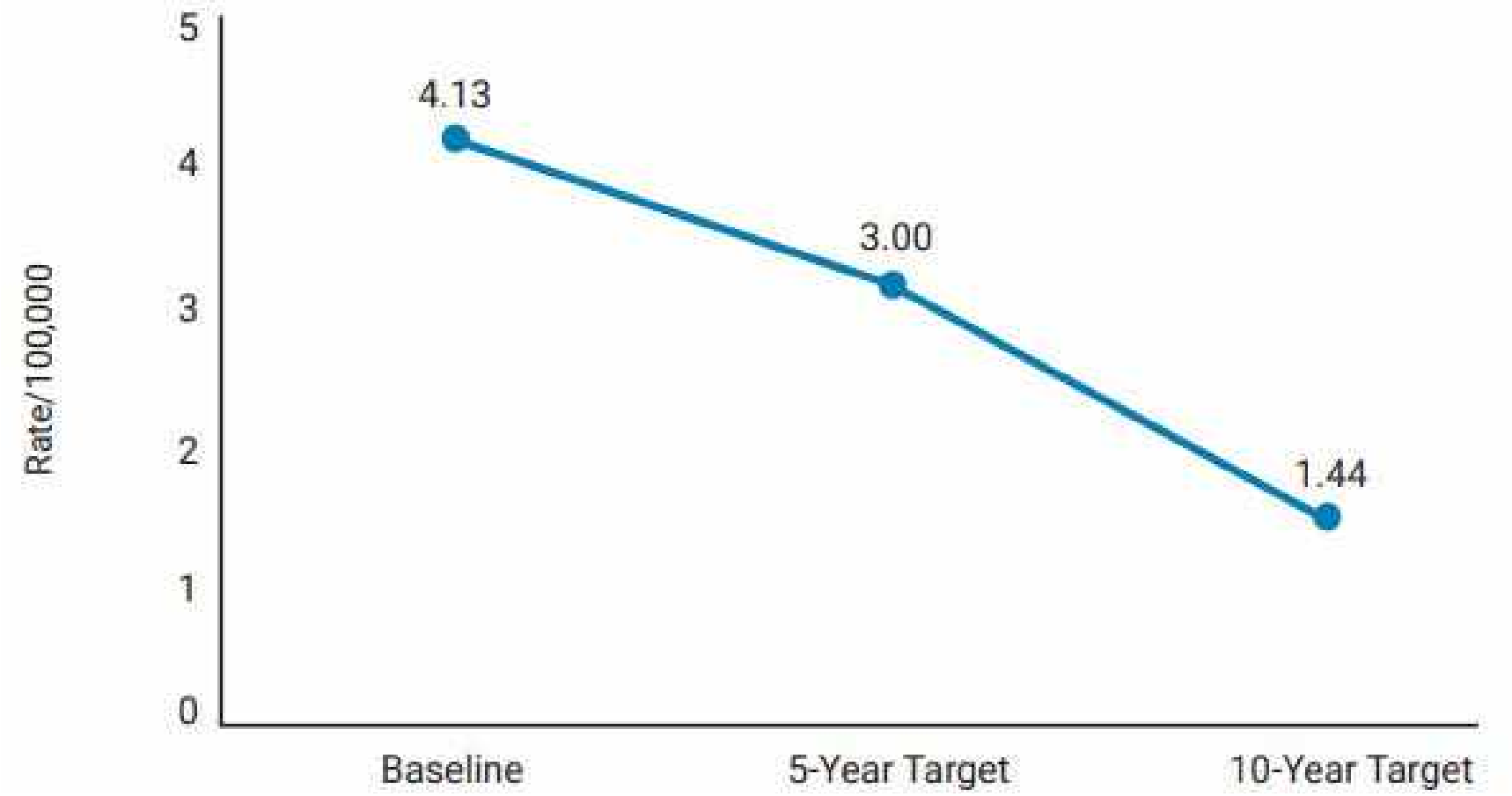


58% HCV Cure goal 2025

Proportion of HCV infected with cure by age group and payor type, USA 2013-2022

https://www.cdc.gov/mmwr/volumes/72/wr/mm7226a3.htm#F1_down

HCV Core Plan Indicators: Reduce HCV Deaths



Reduce rate of HCV related deaths by 25% by 2025 and 65% by 2023

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

Hepatitis Core Plan Indicators: Reduce HCV Deaths

Age Adjusted Rate of HCV Related deaths and annual targets for USA by year

https://www.cdc.gov/hepatitis/policy/npr/2023/NationalProgressReport-HepC-ReduceDeaths.htm

WHAT NOW? Eliminating Barriers and Challenges

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

STATES REMOVING HCV TREATMENT RESTRICTIONS

STATES ARE REMOVING HCV TREATMENT RESTRICTIONS[1]

Majority of Patients Can Be Treated Regardless of Fibrosis Score

	States with restrictions at any level	Description
Prior authorization criteria*	51 / 27	Between June 2022 and August 2023, prior authorizations were removed in Arizona, Colorado, Delaware, the District of Columbia, Florida, Hawaii, Illinois, Oklahoma, Oregon, Pennsylvania, and Texas
Prescribers†	29 / 4	States that absolutely prohibited nonspecialists from prescribing decreased by 86% **Arkansas, Iowa, Illinois, Nevada**
Sobriety†	37 / 10	Only 3 states still require abstinence **Arkansas, Nebraska, North Dakota**
F-scores	34 / 1	Arkansas is the only state with an F-score restriction remaining in 2023

Data are based on publicly available Medicaid coverage criteria for all 50 states, the District of Columbia, and Puerto Rico.
*Additional prior authorization requirements may apply for treatment-experienced patients, treatment failure or reinfection. See state program information for more details. †This does not include all State Medicaid restrictions. Additional restrictions may include sobriety screening and counseling, varying abstinence time frames, and provider restrictions requiring prescribing by or in consultation with a specialist.

1. Hepatitis C State of Medicaid Access. Updated August 2023. Accessed October 26, 2023. https://stateofhepc.org/ 2. Hepatitis C State of Medicaid Access. Accessed October 26, 2023. https://stateofhepc.org/wp-content/uploads/2021/07/State-of-HepC_2017_FINAL.pdf

VEN: AN ALH INITIATIVE

VEN

POWERED BY ARIZONA LIVER HEALTH

VISION

ELIMINATE VIRAL HEPATITIS

MISSION

EQUAL ACCESS TO VIRAL HEPATITIS & STI CARE

VALUES

COMPASSION
Care And Treatment With Dignity And Respect

EQUITY
Care And Treatment With Dignity And Respect

COLLABORATION
Partnership With Communities And Organizations

ADVOCACY
Innovation in Public Policy Change and Initiatives

EXCELLENCE
Leaders In Clinical Care, Public Health, And Research

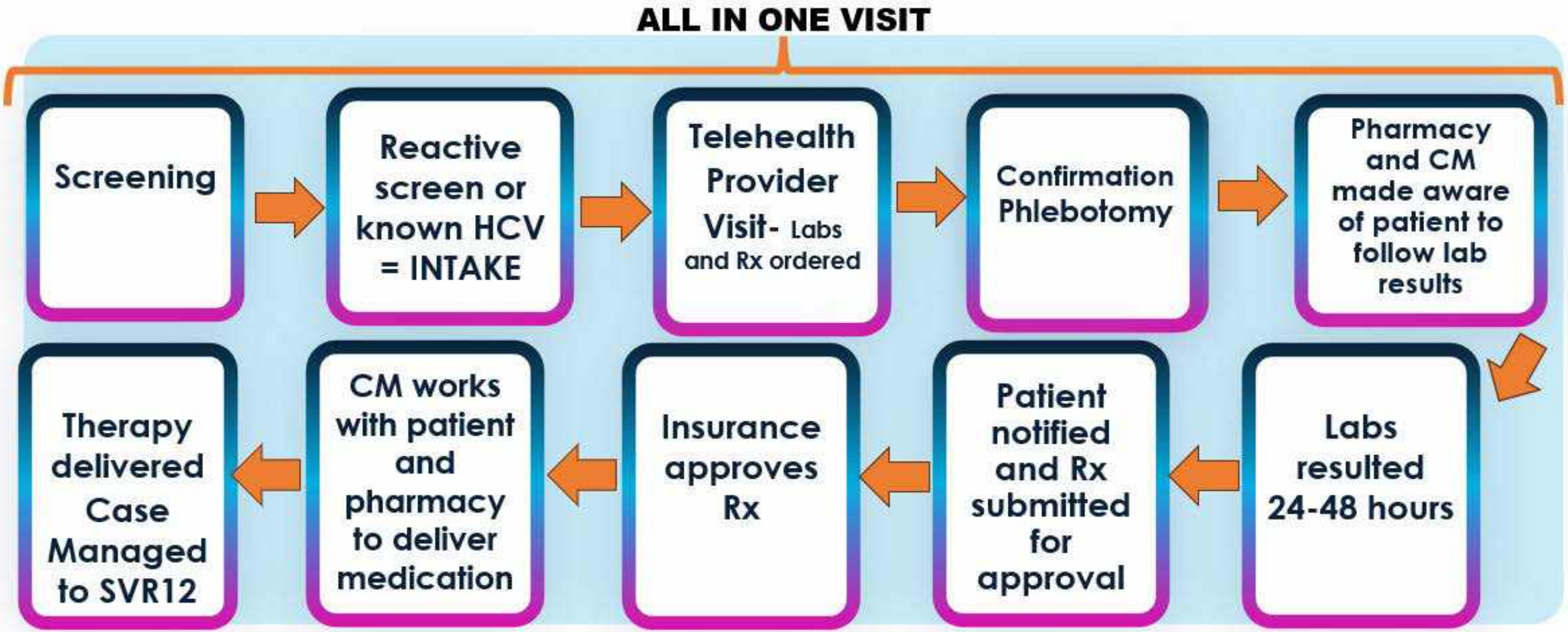
Meet patients where they are

10 Outreach team testing and linkage to care daily

- **Needle exchange**
- **Rehab centers**
- **Prison rentry facilities**
- **Homeless camps**
- **Parks**

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

VEN: AN ALH INITIATIVE

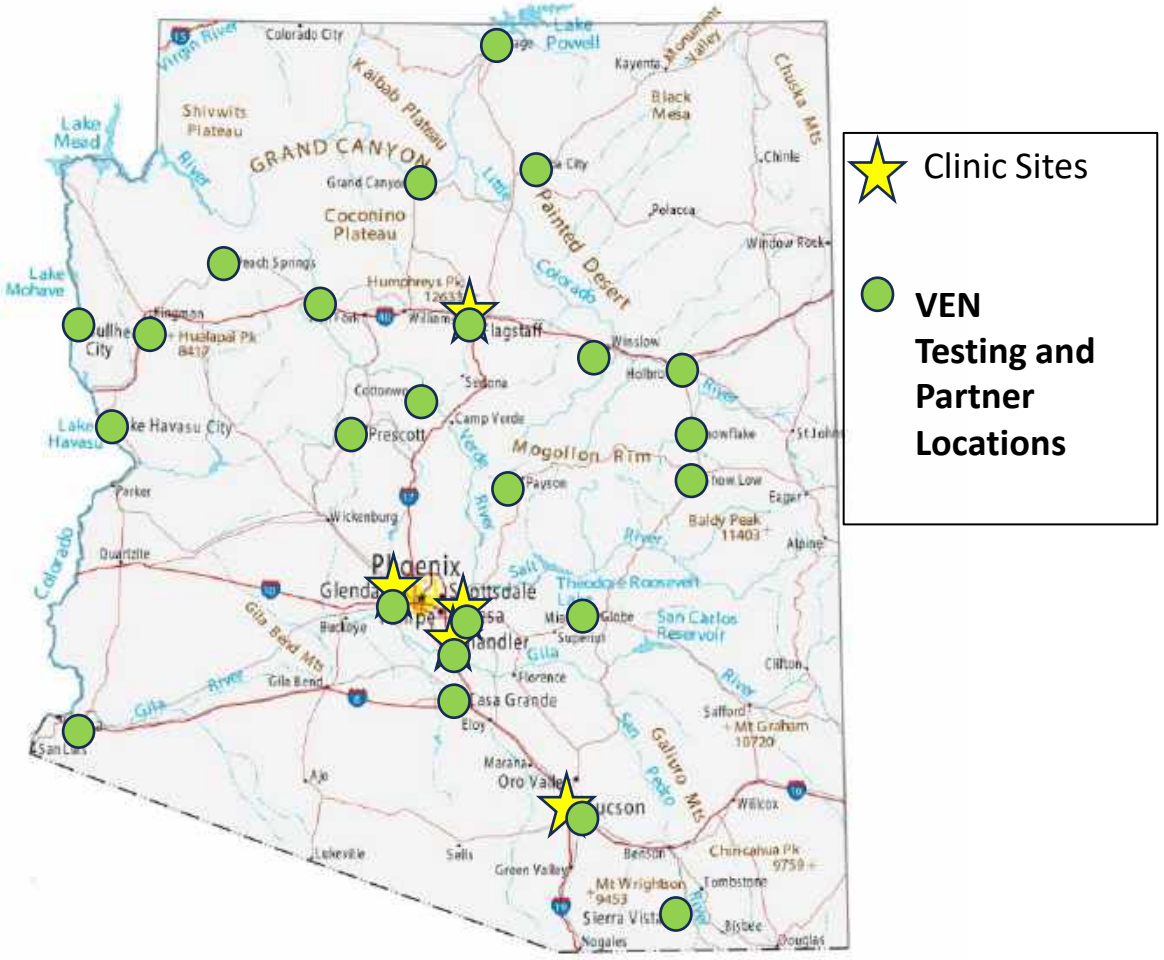


https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

VEN CENTERS

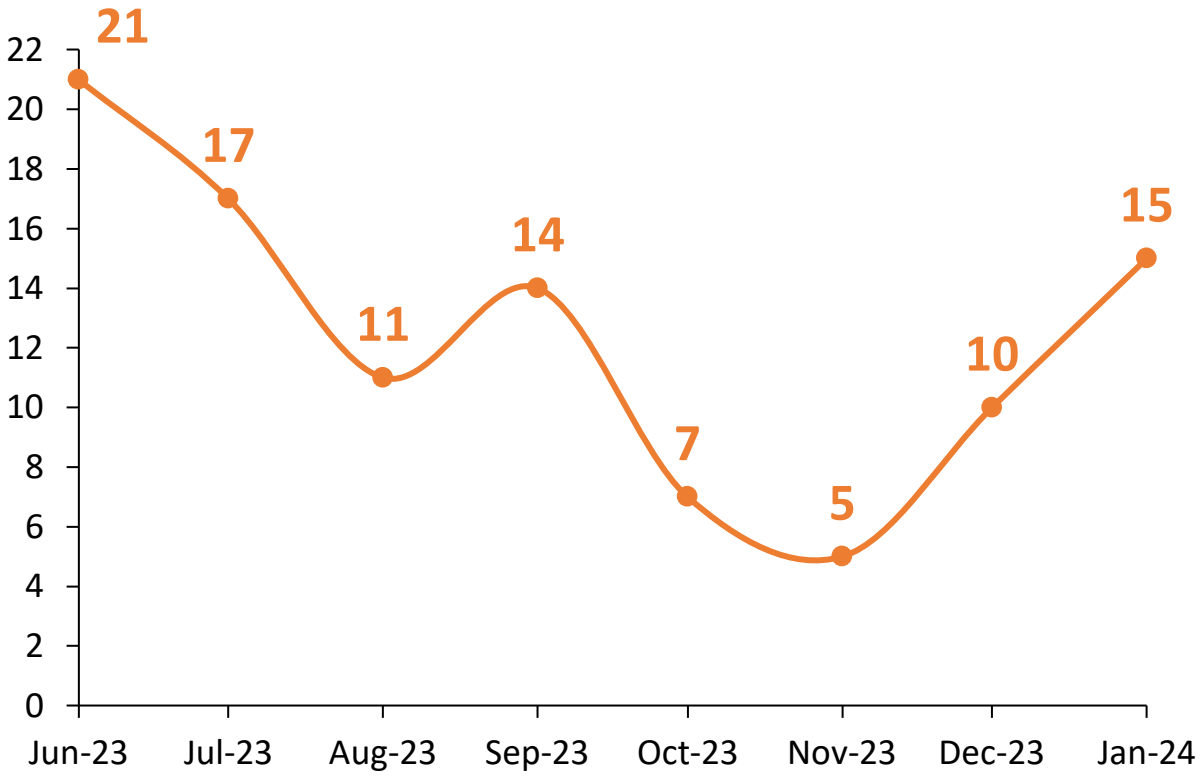
VEN: Outreach Across Arizona

- **Northern Arizona**
  - ☆ **Flagstaff**
- **Central Arizona**
  - ☆ **Peoria**
  - ☆ **Chandler**
  - ☆ **Mesa**
- **Southern Arizona**
  - ☆ **Tucson**

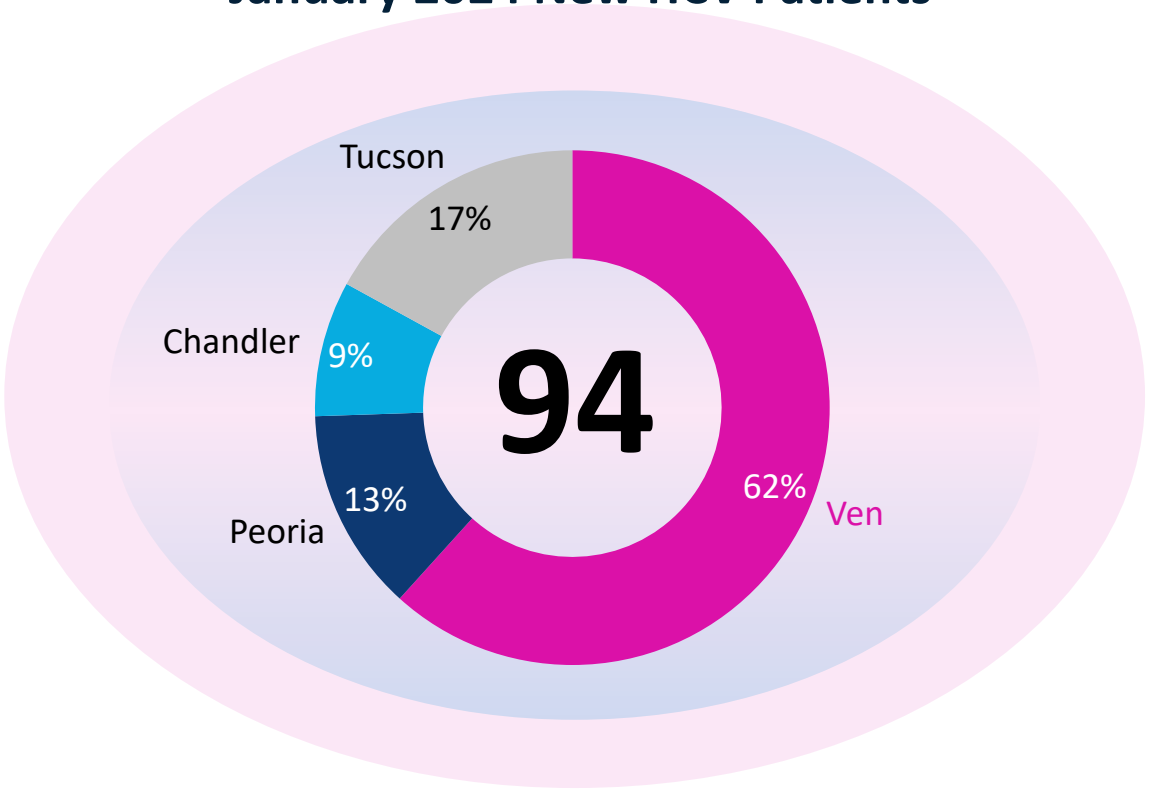


VEN Testing: 15-20% Ab Positive

HCV Ab Screen Positivity Rate

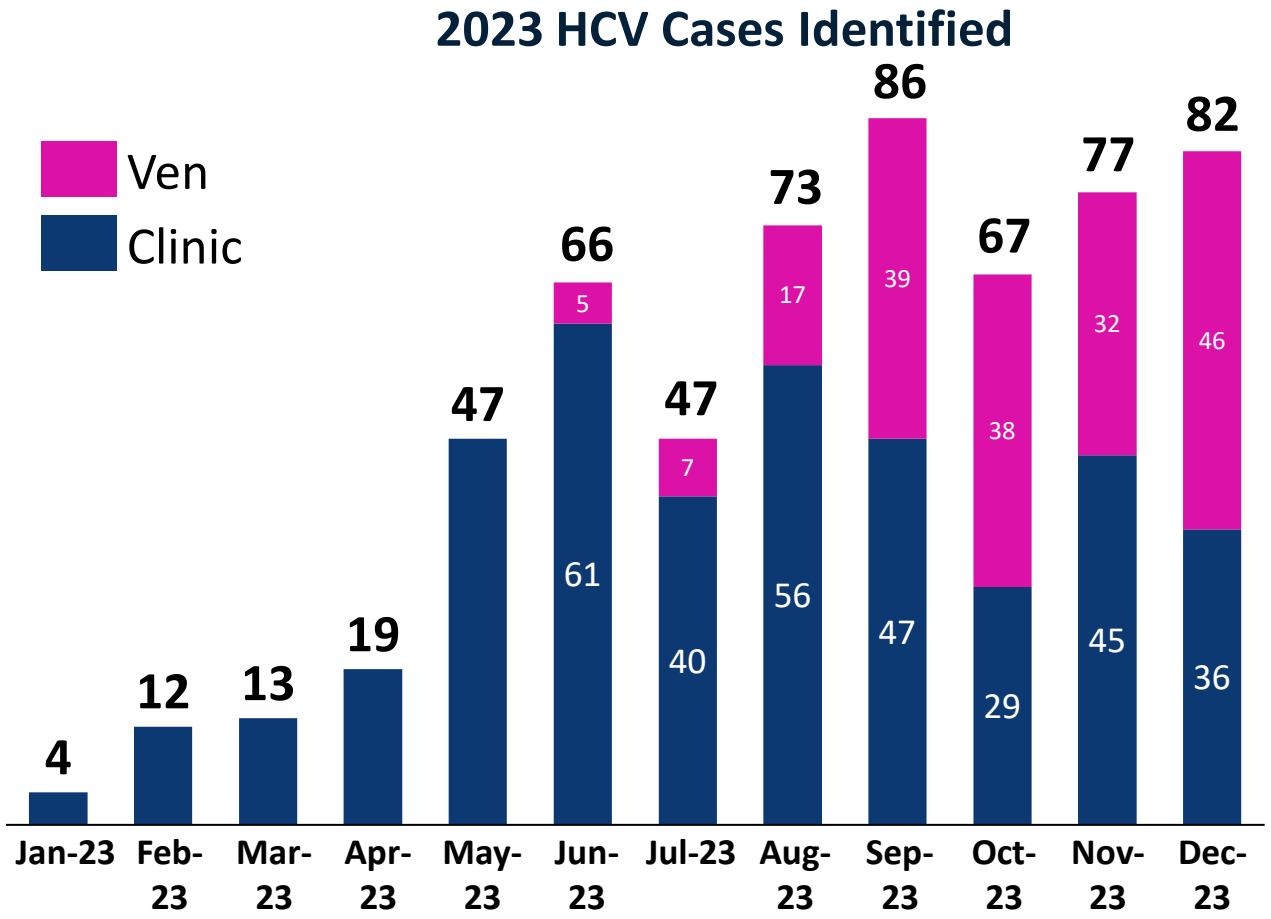


January 2024 New HCV Patients



VEN CENTERS

VEN: Doubled Identification and Linkage to Care within 6 months of Inception

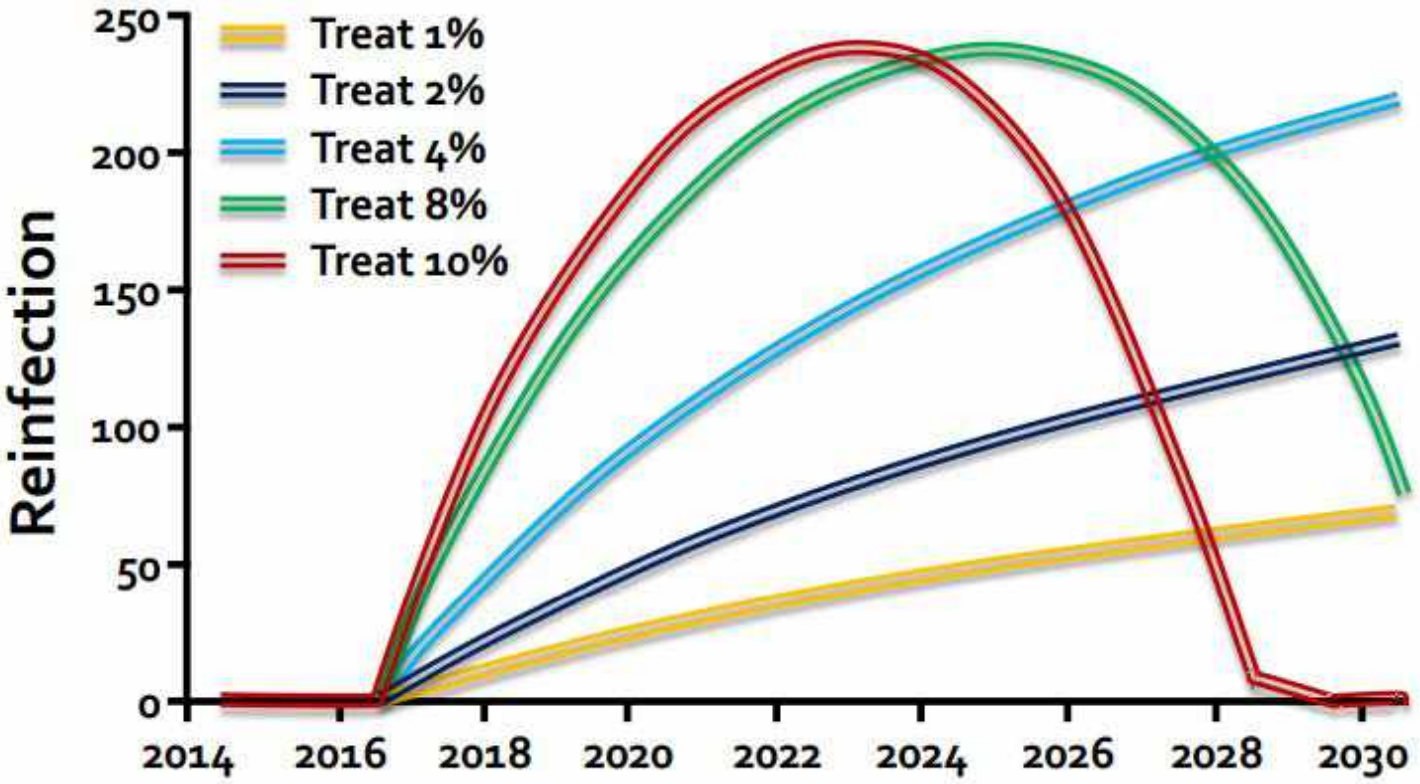


- 92% of patients with HCV RNA start treatment
- 98% of patients' treatment who start finish
- SVR12 data pending

*This includes individuals screened with + HCV Ab but no HCV RNA

HCV Treatment as Prevention: Harm Reduction is Essential Component

The more PWIDs Treated, the Faster we Get to HCV Elimination



To do this, we must concomitantly scale up harm reduction measures

- **Medication assisted treatment**
- **Syringe services**
- **Increased intensity of HCV management- eg Directly observed therapy**
- **Patient education and counseling**
- **Increased HCV treater workforce**

HCV Elimination: Where are We

The New York Times

OPINION

GUEST ESSAY

We Are Squandering One of the Most Important Medical Advances of the 21st Century

Nov. 28, 2023

Todd Heisler/The New York Times

Thank you!

PBC Therapeutics Update

New Drugs Coming Your Way Soon

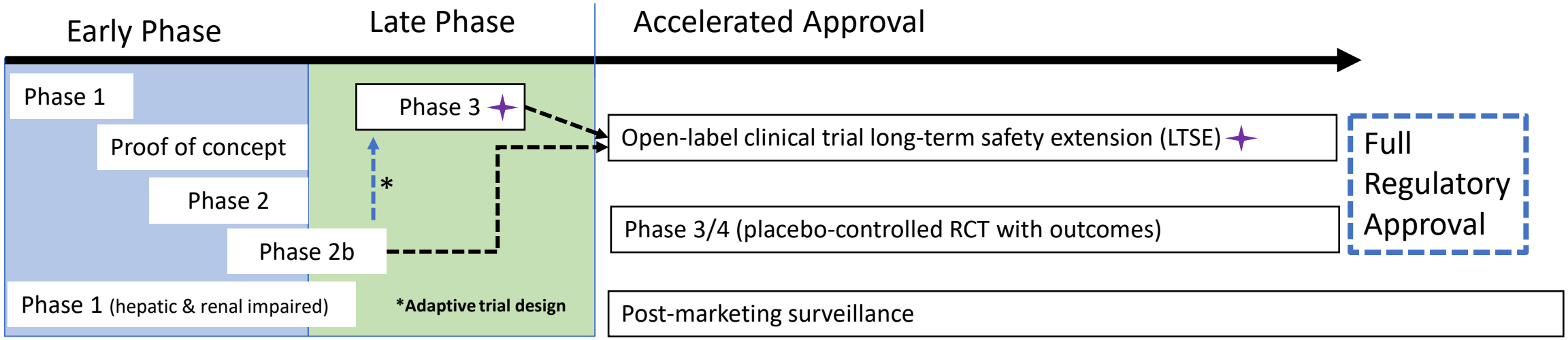
Raj Vuppalanchi, MD

Professor of Medicine | Director of Hepatology

Division of Gastroenterology and Hepatology

rvuppala@iu.edu |@rajvuppalanchi

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

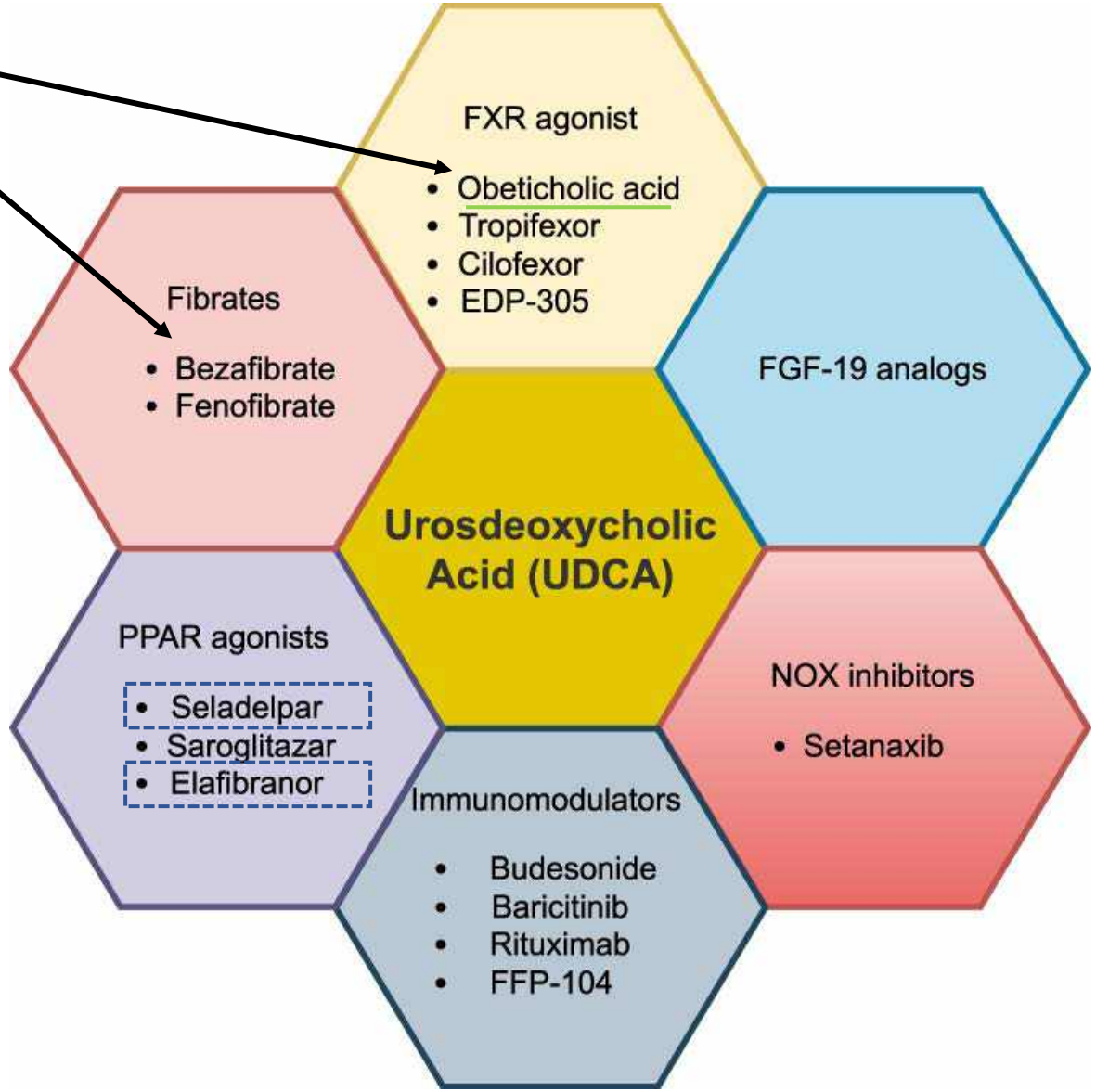


Open-label clinical trial LTSE		Phase 3|4 Placebo-controlled RCT	
Pros	Cons	Pros	Cons
Extended safety data	No control arm	Placebo-arm	Hard to recruit
Incremental efficacy data	Open-label	Confirms clinical benefit	
Offer IP to subjects previously randomized to the placebo arm		Clinical outcomes trial	
		Supports full regulatory approval	

Vuppalanchi R and Kowdley KV. The Evolving Paradigms and Treatments for Primary Biliary Cholangitis Aliment Pharmacol Ther. 2024 Jan;59(2):280-281.

Landscape

OCA 5-10 + B200 | B400



Phase 3

Sohal A et al. Hepat Med. 2023 Jun 8;15:63-77

FDA Designations of Phase 3 PPARs in PBC

	Orphan Drug Designation	Accelerated approval	Fast Track	Priority review	Breakthrough therapy
Elafibranor	X	X			X
Seladelpar	X	X			X *
Saroglitazar	X	X	X		

* Revised Breakthrough Therapy designation for pruritus with adults with or without cirrhosis

Safety Concerns with PPARs in PBC

- Renal
- Muscle
  - → myalgias
  - → rhabdomyolysis
- Liver
  - → dose dependent toxicity
  - → overlap syndrome with AIH

BEZURSO trial with Bezafibrate 400 mg once daily for 2 years

- Creatinine level ↑5% (↓3% in the placebo group)
- Myalgia rate 20% (10% in the placebo group)
  - Rhabdomylosis with concomitant statin therapy (1 out of 50)
- ALT >5×ULN in 3 (1 in placebo group)
  - 2 developed overlap syndrome requiring steroids
  - 1 spontaneous resolution with drug discontinuation

N Engl J Med. 2018 Jun 7;378(23):2171-2181

Other safety concerns with fibrates

→Cholelithiasis

→Drug-drug interactions

→Gastrointestinal

→Allergic reactions

Warning Label

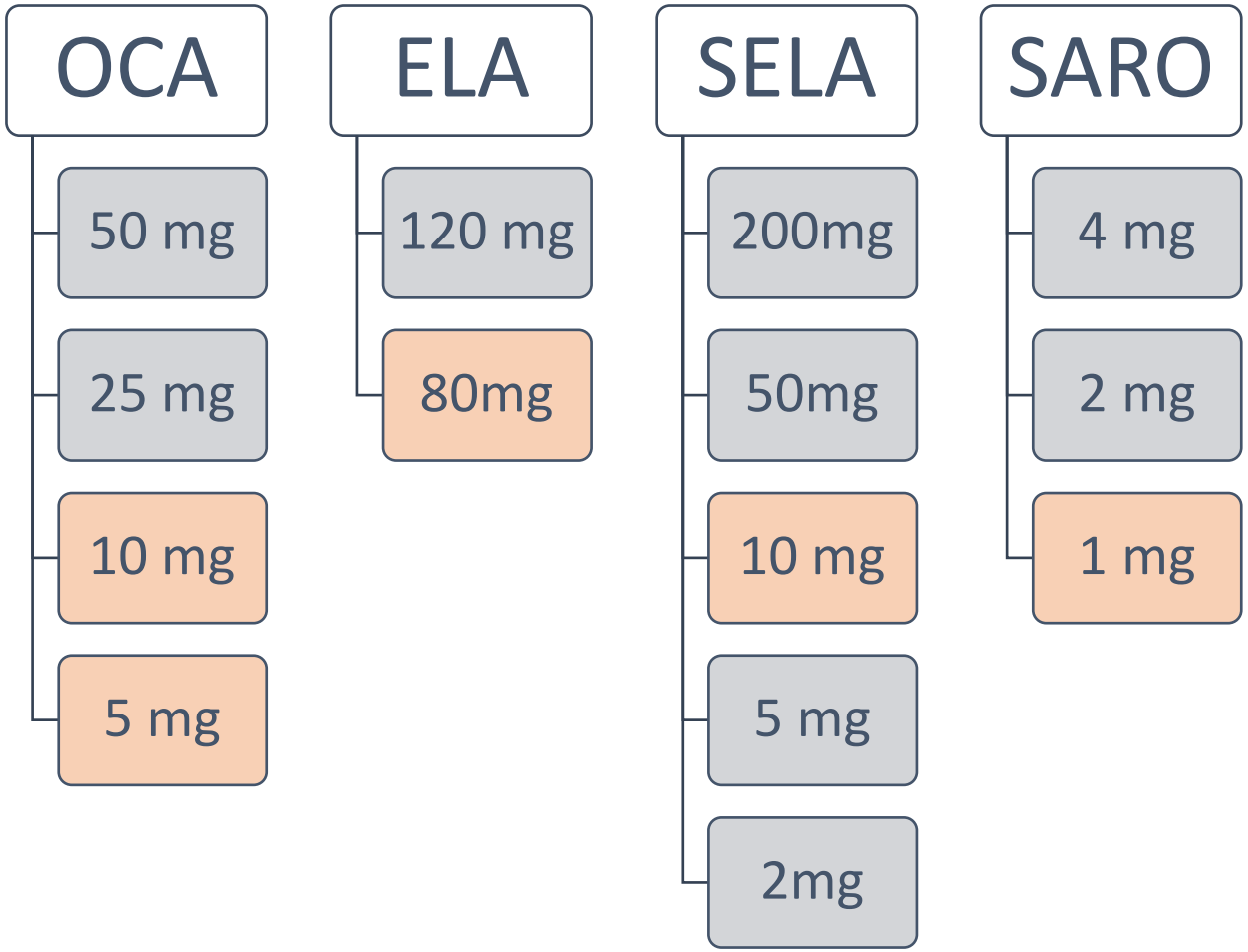
→PBC

→Gall stones

→Concurrent use of MAO

→Pregnancy

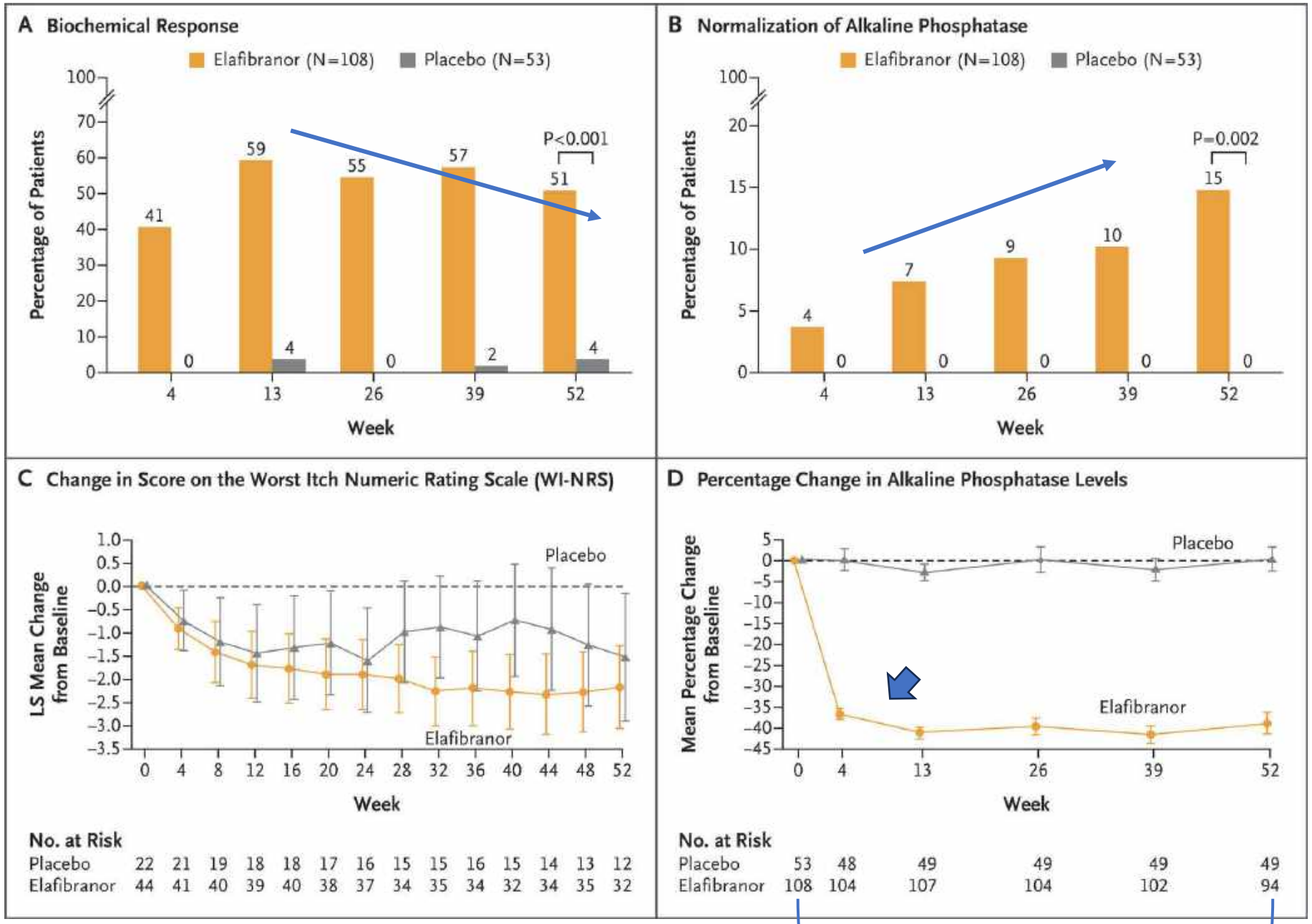
PPARs for PBC: Search for Optimal Dose



PPARs for PBC - Efficacy

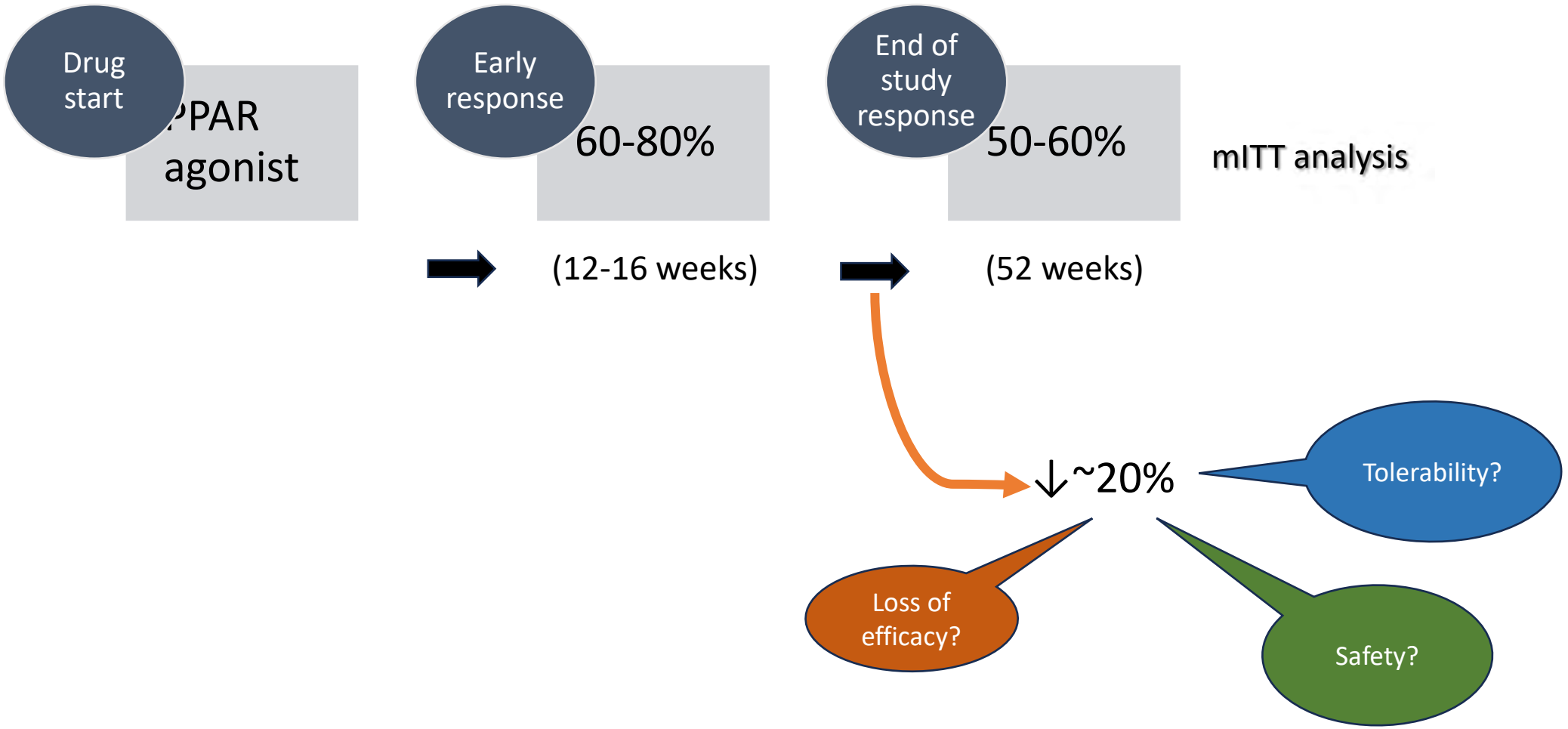
POISE criteria	Phase 2		Sample size	Phase 3	
	n	EOS		Early	EOS (52 weeks)
Elafibranor 80 mg (N=45)	15	67% (12 weeks)	161 (ELA =108) ELATIVE	59% (13 weeks)	51%
Seladelpar 10 mg (N=121)	55	67% (12 weeks)	193 (SEL: 128) RESPONSE	Unknown	62%
			265 (SEL: 89) ENHANCE*	78% (12 weeks)	Terminated
Saroglitazar 2 mg (N=37)	14	71% (12 weeks)	140 (SARO: 90) EPICS-III	Ongoing	
Bezafibrate 400 mg (N=100)			100 (BEZA: 50)		31% (24 months)

*Patients were randomized 1:1:1 to oral seladelpar 5 mg (n=89), 10 mg (n=89), placebo (n=87) daily



Kowdley KV et al. N Engl J Med. 2023 Nov 13

Lower Efficacy Rates in Phase 3 compared to 2



Differentiators

- Efficacy and Safety Profile
- Mechanism of Action
- Study Population
- Convenience and Administration
- Post-Market Surveillance
- Labeling and Indication Expansion
- Clinical Trial Data
- Cost and Access
- Brand and Marketing Campaigns
- Patient Support Programs

1 – Complete Normalization of ALP

ALP normalization	Phase 2		Sample size	Phase 3	
	n	EOS		Early	EOS (52 Wks)
Elafibrinor 80 mg (N=45)	15	13% (12 weeks)	161 (ELA =108) ELATIVE	7% (13 weeks)	15%
Seladelpar 10 mg (N=121)	55	31% (12 weeks) 33% (52 weeks)	193 (SEL: 128) RESPONSE	Not reported	25%
			265 (SEL: 89) ENHANCE	27% (12 weeks)	N/A
Saroglitazar 2mg (N=37)	14	50% (12/16 weeks)	140 (SARO: 90) EPICS-III	Ongoing	
Bezafibrate 400 mg (N=100)			100 (BEZA: 50)		67% (24 months)

→ **Rate of complete normalization of ALP could be a major differentiator**

2 - Confirmatory Phase 3|4

Drug	Design	Sample size	Duration	Inclusion criteria	Efficacy
Elafibranor (Elfidence)	RCT DB	450	7 years	• UDCA for at least 12 months • Compensated cirrhosis included	Event free survival
Seladelpar (AFFIRM)*	RCT DB	192	3 years	• Only compensated cirrhosis • CTP class A or B	Event free survival
Seladelpar (IDEAL)	RCT DB	75	1 year	• UDCA for 12 months • ALP x ULN and <1.67 x ULN	ALP normalization
Saroglitazar	RCT DB	400	7 years	• UDCA for 6 months • No cirrhosis: ALP ≥1.67 x ULN • Cirrhosis: ALP >ULN	Event free survival

* Prior exposure to seladelpar is an exclusion criteria

3 – Cirrhosis

Drug	Sample size	Phase	Duration	Inclusion criteria	Outcome
OCA 5 mg once wkly to twice weekly (up titrate)	22	4	48 weeks	CP-A, CP-B or CP-C	PK and safety
Elafibranor	30	1	1 dose	Cirrhosis with mild, moderate and severe HI of any etiology	PK and safety
Seladelpar 10 mg	24	1	28 days	CP-A, CP-A+PHT, CP-B or CP-C	PK and safety
Saroglitazar 1 and 2 mg	24	1	28 days	CP-A, CP-B or CP-C	PK and safety

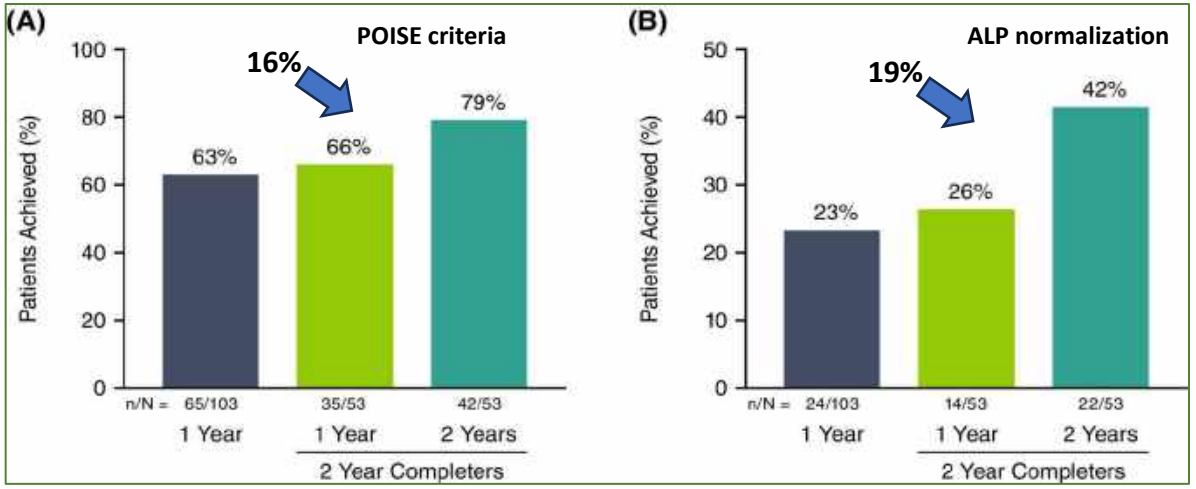
CP-A and CP-B completed

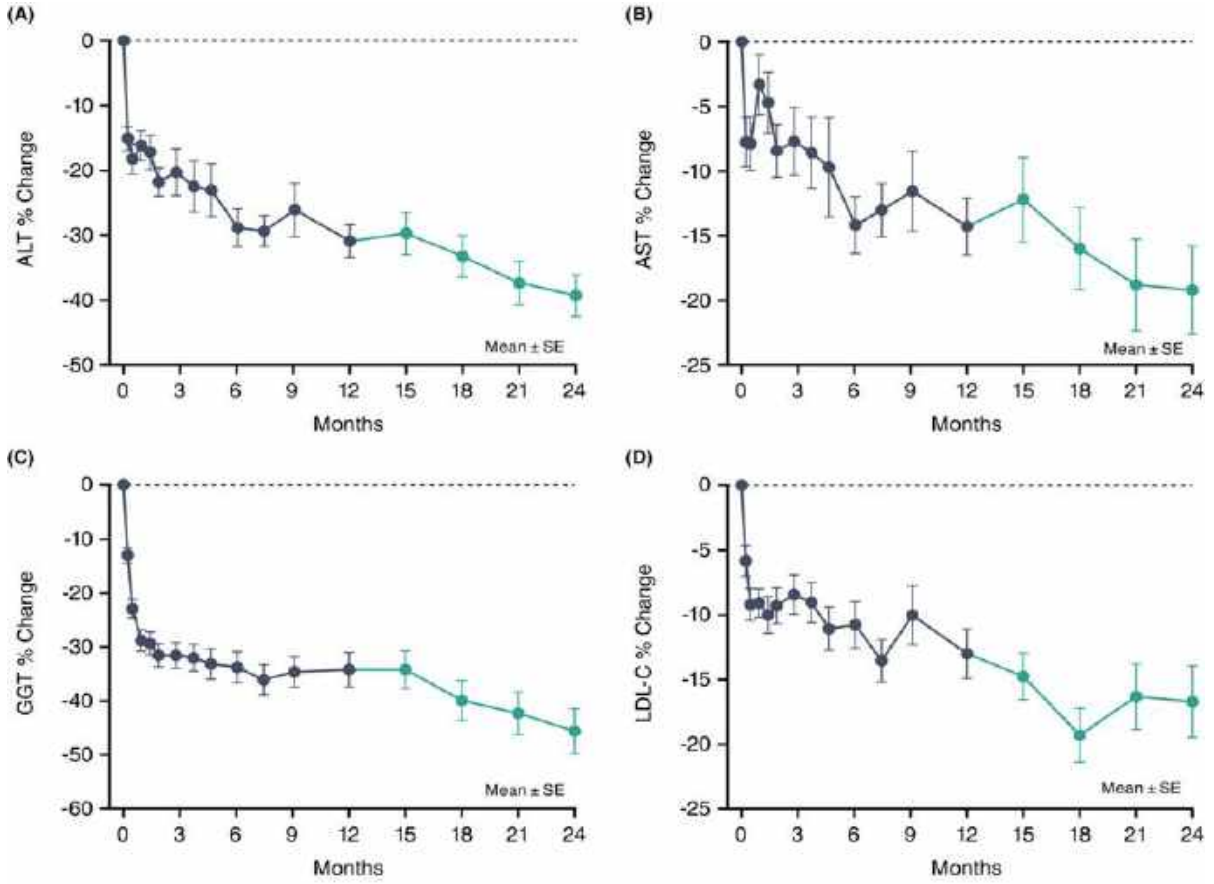
4 – Open Label Clinical Trial LTSE

Drug	Sample size	Duration	Inclusion criteria	Comment
Seladelpar 5 mg and 10 mg (ASSURE)	106	5 years	• Prior participation in SELA study • MELD <12	2-year data published
Elafibranor 80 mg	~ 161	5 years	• All subjects from ELATIVE (phase 3) will be rolled over	
Saroglitazar 1mg	~ 180	5 years	• Prior participation in SARO study • MELD <12	Interim analysis at 3 years

4 – Open Label Clinical Trial LTSE

Open-label, clinical trial extension: Two-year safety and efficacy results of seladelpar in patients with primary biliary cholangitis





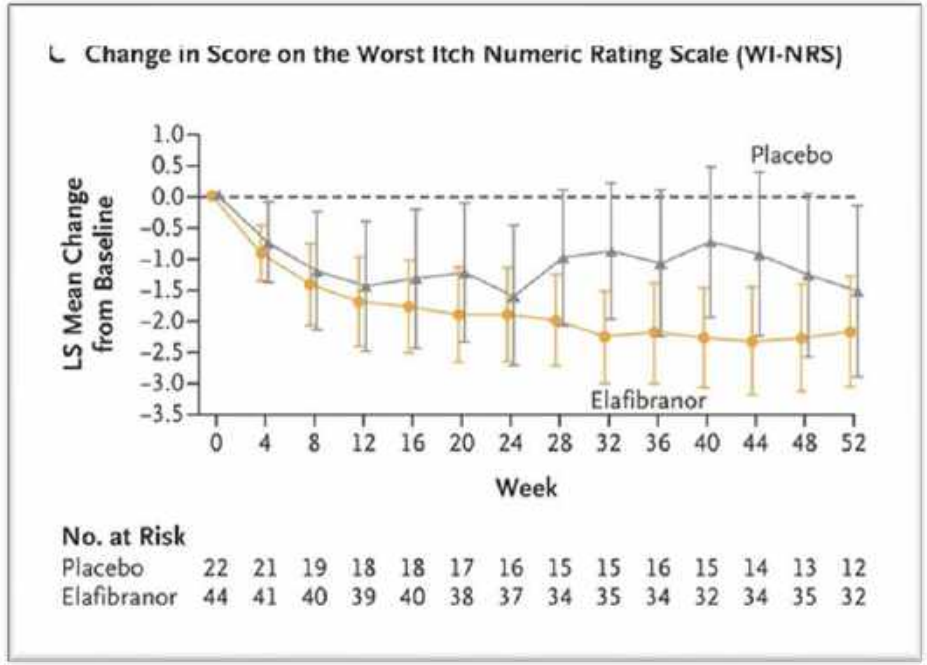
All Patients	M0	M3	M6	M9	M12	M15	M18	M21	M24
N	104	102	103	103	103	100	80†	65	53

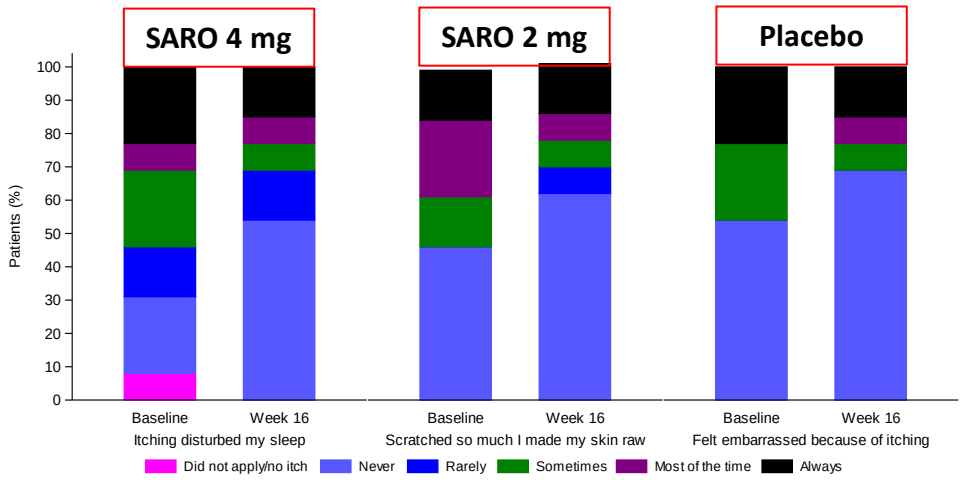
Mayo M et al. Aliment Pharmacol Ther. 2024;59:186-200

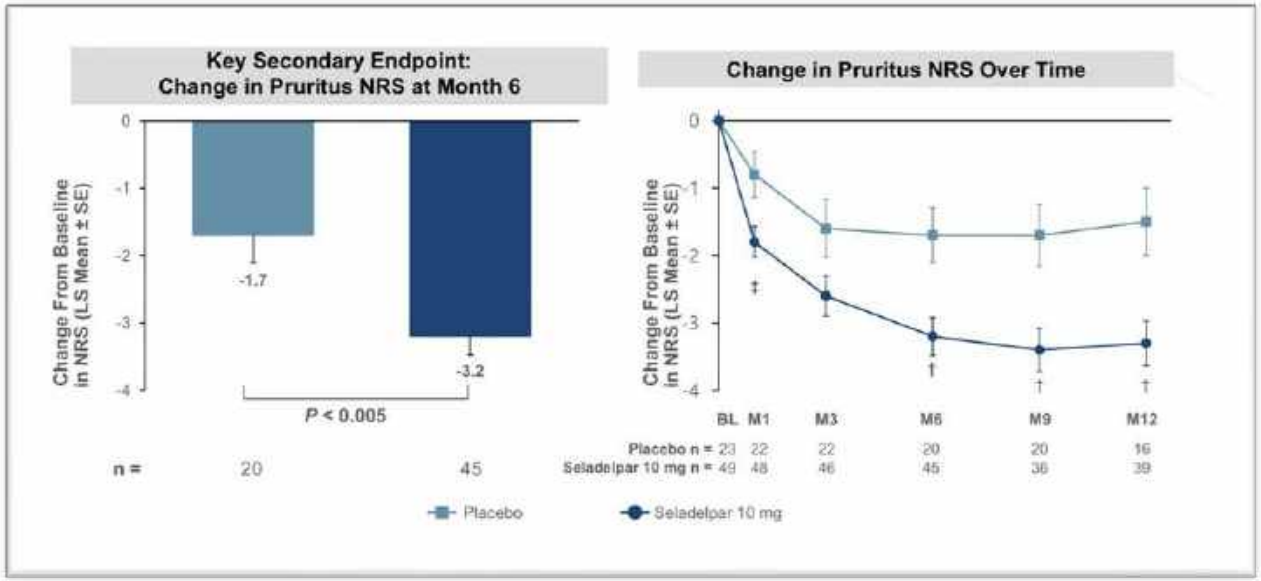
5 - Pruritus

Drug	Effect on Pruritus	Instrument
Elafibrinor 80 mg	−1.93 vs. −1.15; Δ= −0.78; 95% CI, −1.99 to 0.42; P = 0.20	WI-NRS
Seladelpar 10 mg	-3.2 vs. -1.7; difference, -1.5; P <0.005 (baseline NRS ≥ 4)	NRS
Saroglitazar 1mg	Unknown (baseline 5D itch score ≥12)	5D itch PBC-40

NRS: Numerical Rating Scale







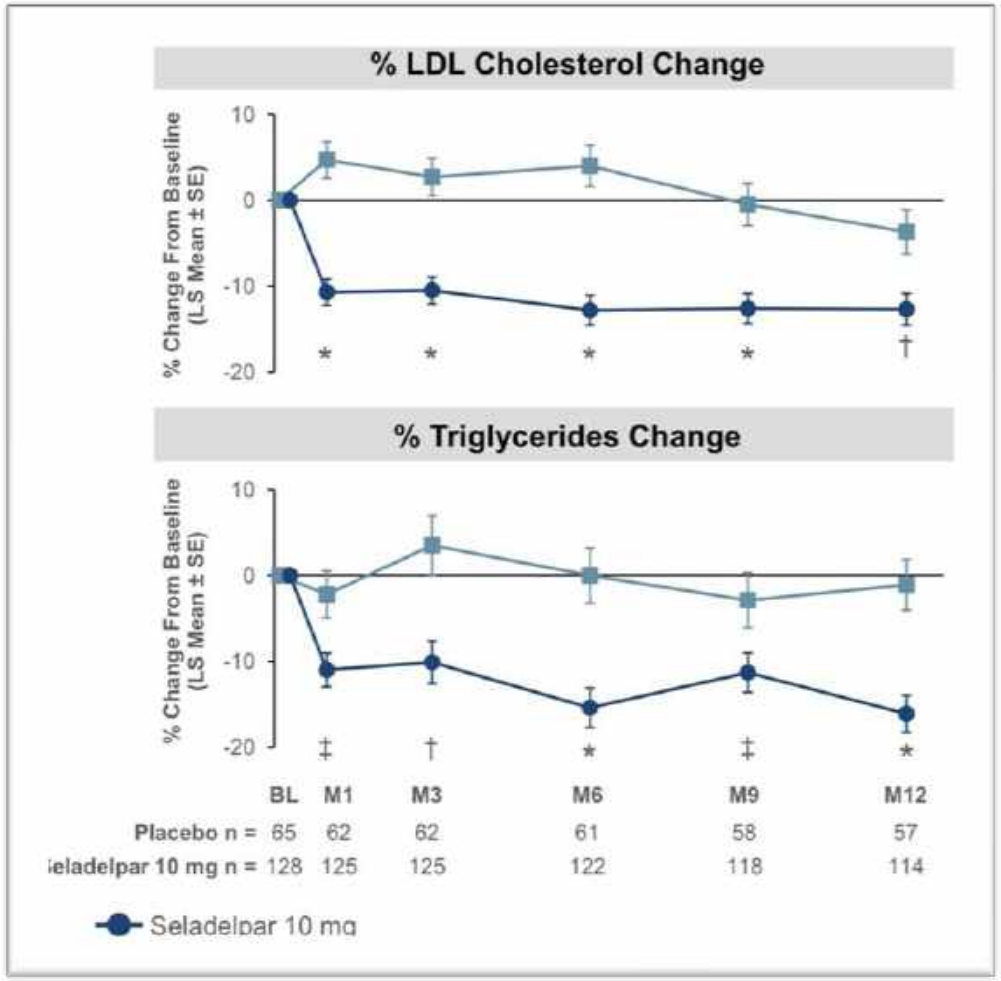
5. Clinical Trials for Cholestatic Itch

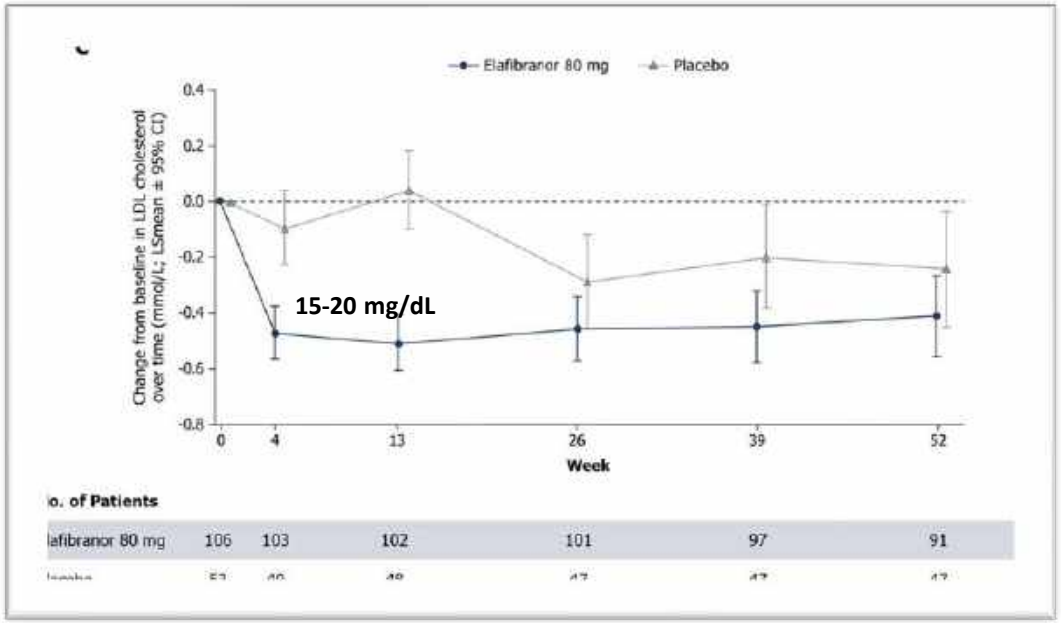
Interventions	Clinicaltrials.gov	Mechanism of action	Conditions	Age criteria	Sample size	Duration	Instrument used for Pruritus Assessment
Phase 2							
EP547	NCT04510090	MrgprX4 antagonist	Cholestasis	18 to 80 years	58	6 weeks	WI-NRS
	NCT05525520		PBC | PSC		58	6 weeks	WI-NRS
Terminated → Difelikefalin	NCT03995212	kappa opioid receptor agonist	Cholestatic Pruritus		60	16 weeks	WI-NRS
Colesevelam	NCT00756171	Bile acid resin	Chronic liver disease	>18 years	38	3 weeks	Visual analogue scale
Volixibat	NCT04663308	IBAT inhibitor	PSC	>18 years	200	28 weeks	Adult ItchRO
Volixibat	NCT05050136	IBAT inhibitor	PBC	>18 years	260	28 weeks	Adult ItchRO
Negative → *Linerixibat*	*NCT02966834*	*IBAT inhibitor*	*PBC (GLIMMER)*	*18 to 80* years	*147*	*16 weeks*	*MWDI on Numerical Rating Scale (NRS)*
Maralixibat	NCT02057692	IBAT inhibitor	Alagille Syndrome	1 to 18 years	37	13 weeks	ItchRO [Obs]
Maralixibat	NCT02160782	IBAT inhibitor	Alagille Syndrome		31	48 weeks	ItchRO (Obs)
Phase 3							
Odevixibat	NCT03566238	IBAT inhibitor	PFIC 1 and 2	0.5 to 18 years	62	24 weeks	Albiero Observer-reported outcome (ObsRO)
Odevixibat	NCT04674761	IBAT inhibitor	Alagille Syndrome	>0.5 years	63	24 weeks	Albireo ObsRO
Maralixibat	NCT03905330	IBAT inhibitor	PFIC	1 to 17 years	93	26 weeks	ItchRO (Obs)
Recruiting → Linerixibat	NCT04950127	IBAT inhibitor	PBC (GLISTEN)	18 to 80 years	230	24 weeks	*NRS*
Bezafibrate	NCT02701166	PPAR agonist	PBC | PSC | SSC	>18 years	84	3 weeks	Itch intensity on a scale of 0-10 cms

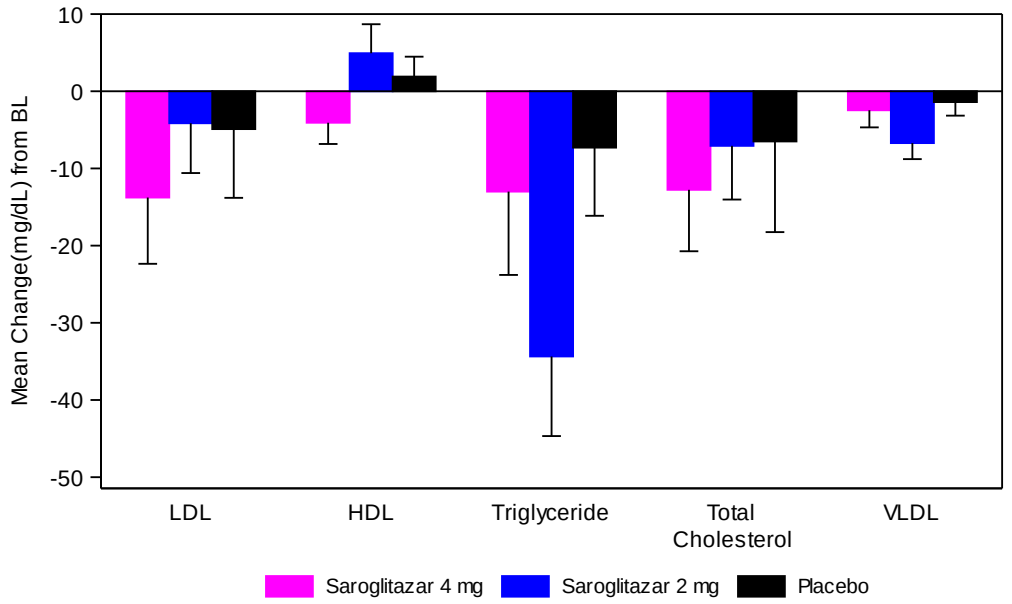
PSC: Primary Sclerosing Cholangitis, **PBC:** Primary Biliary Cholangitis, **SSC:** Secondary Sclerosing Cholangitis, **PFIC:** Progressive Familial Intrahepatic Cholestasis, **WI-NRS:** Worst Itch Numeric Rating Scale, **PPAR**: peroxisome proliferator-activated receptors, **IBAT** inhibitor: Ileal Bile Acid Transporter inhibitor, **MWDI:** mean worst daily itch score

Vuppalanchi R et al. Clin Gastroenterol Hepatol. 2023 Jul;21(7):1706-1707

6. Lipids


% LDL Cholesterol Change
% Change From Baseline (LS Mean ± SE)
10
0
-10
-20
* * * * †
% Triglycerides Change
% Change From Baseline (LS Mean ± SE)
10
0
-10
-20
‡ † * ‡ *
BL M1 M3 M6 M9 M12
Placebo n = 65 62 62 61 58 57
eladelpar 10 mg n = 128 125 125 122 118 114
Seladelpar 10 mg


Elafibranor 80 mg
Placebo
Change from baseline in LDL cholesterol over time (mmol/L; LSmean ± 95% CI)
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
15-20 mg/dL
0 4 13 26 39 52
Week
o. of Patients
lafibranor 80 mg 106 103 102 101 97 91


Mean Change(mg/dL) from BL
10
0
-10
-20
-30
-40
-50
LDL
HDL
Triglyceride
Total Cholesterol
VLDL
Saroglitazar 4 mg
Saroglitazar 2 mg
Placebo

7.Safety

4 (3.4%) discontinued for ↑CK (none in placebo)

- 2 were on statin
- 1 had CKD
- 1 had autoimmune thyroiditis

2 of the 4 had myalgias

All cases of ↑ ALT were reversible after discontinuation

advanced cirrhosis and concomitant statin

2 deaths receiving elafibranor (1.9%)

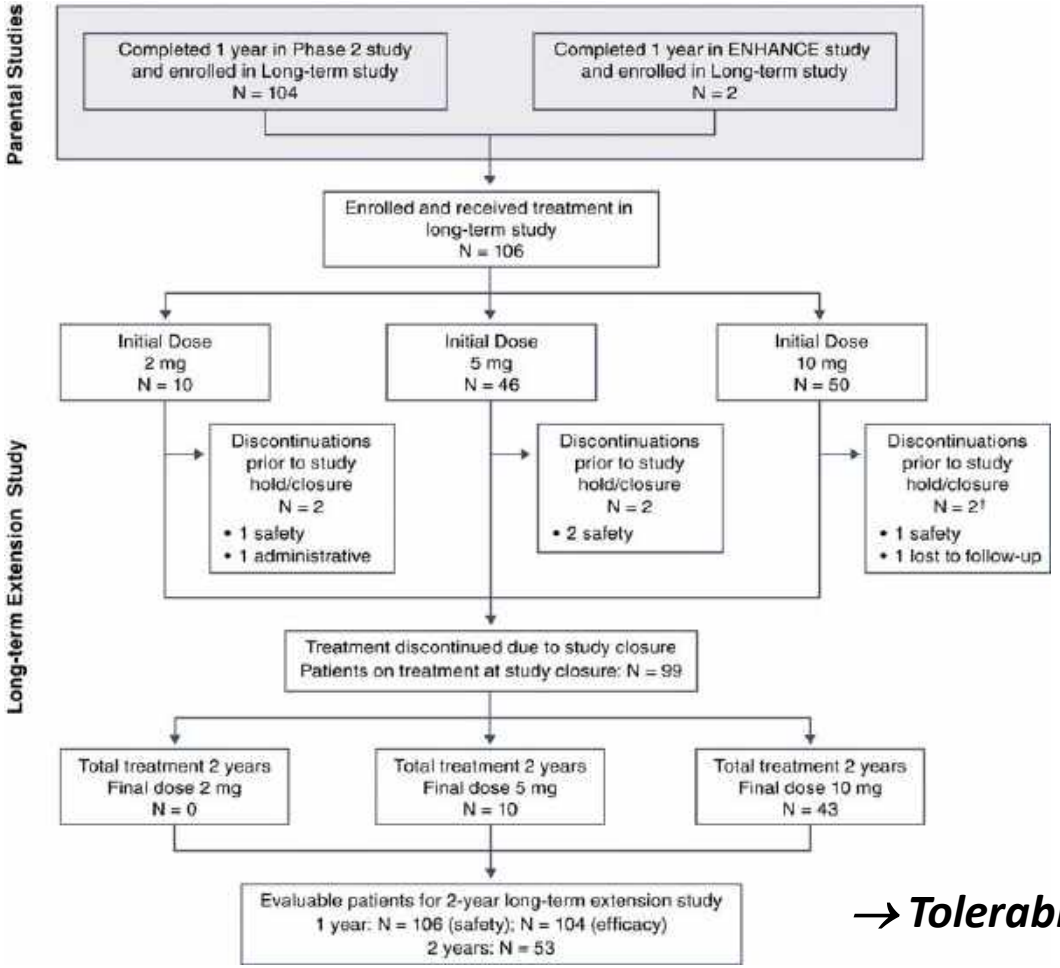
- 1 postoperative complications
- 1 biliary sepsis and acute kidney injury (had cirrhosis)

Table S6. Summary of all serious treatment-emergent adverse events*

Preferred Term	Elafibranor (N=108)	Placebo (N=53)
	n (%)†	
Acute kidney injury	3 (2.8)	1 (1.9)
Hip fracture	2 (1.9)	0 (0)
Abdominal hernia	1 (0.9)	0 (0)
Appendicitis	1 (0.9)	0 (0)
Ascites	1 (0.9)	0 (0)
Asthma	1 (0.9)	0 (0)
Biliary sepsis	1 (0.9)	0 (0)
Blood bilirubin increased	1 (0.9)	0 (0)
Cardiac arrest	1 (0.9)	0 (0)
Cardiac failure	1 (0.9)	0 (0)
Cholecystitis acute	1 (0.9)	0 (0)
Crohn's disease	1 (0.9)	0 (0)
Edema peripheral	1 (0.9)	0 (0)
Hemorrhagic stroke	1 (0.9)	0 (0)
Hypervolemia	1 (0.9)	0 (0)
Multiple fractures	1 (0.9)	0 (0)
Multiple organ dysfunction syndrome	1 (0.9)	0 (0)
Osteonecrosis	1 (0.9)	0 (0)
Parkinsonism	1 (0.9)	0 (0)
Pneumonia	1 (0.9)	0 (0)
Pulmonary embolism	1 (0.9)	0 (0)
Pulseless electrical activity	1 (0.9)	0 (0)
Rhabdomyolysis	1 (0.9)	0 (0)
Retroperitoneal hematoma	1 (0.9)	0 (0)
Sudden hearing loss	1 (0.9)	0 (0)
Tremor	1 (0.9)	0 (0)
Anxiety	0 (0)	1 (1.9)
Cataract	0 (0)	1 (1.9)
COVID-19	0 (0)	1 (1.9)
Invasive ductal breasts carcinoma	0 (0)	1 (1.9)
Pain	0 (0)	1 (1.9)
Papillary thyroid cancer	0 (0)	1 (1.9)
Procedural pain	0 (0)	1 (1.9)
Syncope	0 (0)	1 (1.9)
Urinary tract infection	0 (0)	1 (1.9)

Kowdley KV et al. N Engl J Med. 2023 Nov 13

7.Safety and Tolerability Data from LTSE



During 2nd year of LTSE

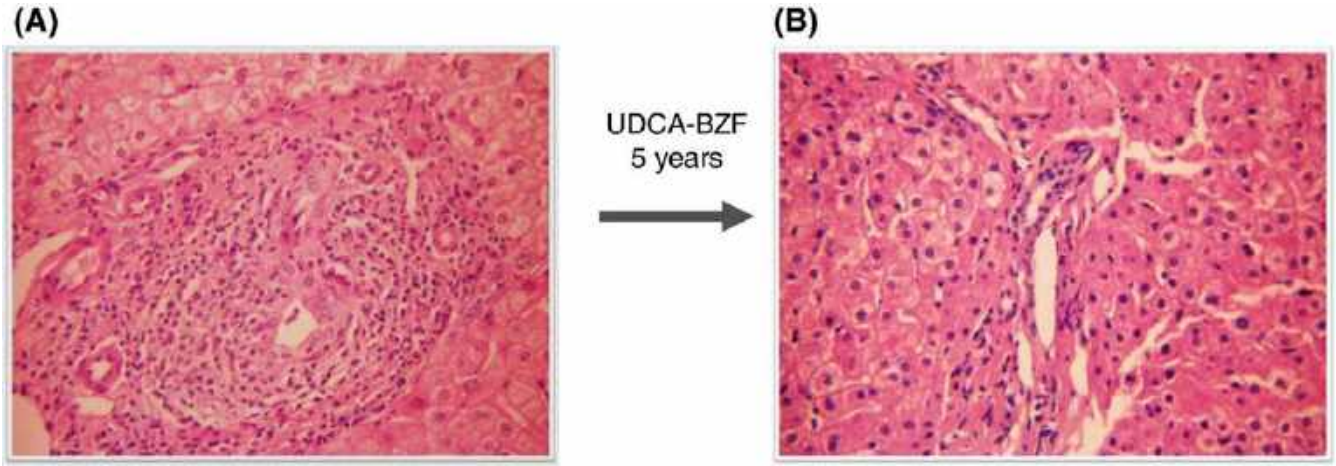
4 subjects **discontinued** due to safety

- 1 subject met treatment discontinuation criteria due to progression of PBC (severe ductopenia noted on a post-treatment biopsy)
- 1 subject had grade 2 increase in total bilirubin and AST but causality attributed to rheumatoid arthritis and NSAIDs. Abnormalities resolved upon discontinuation of seladelpar

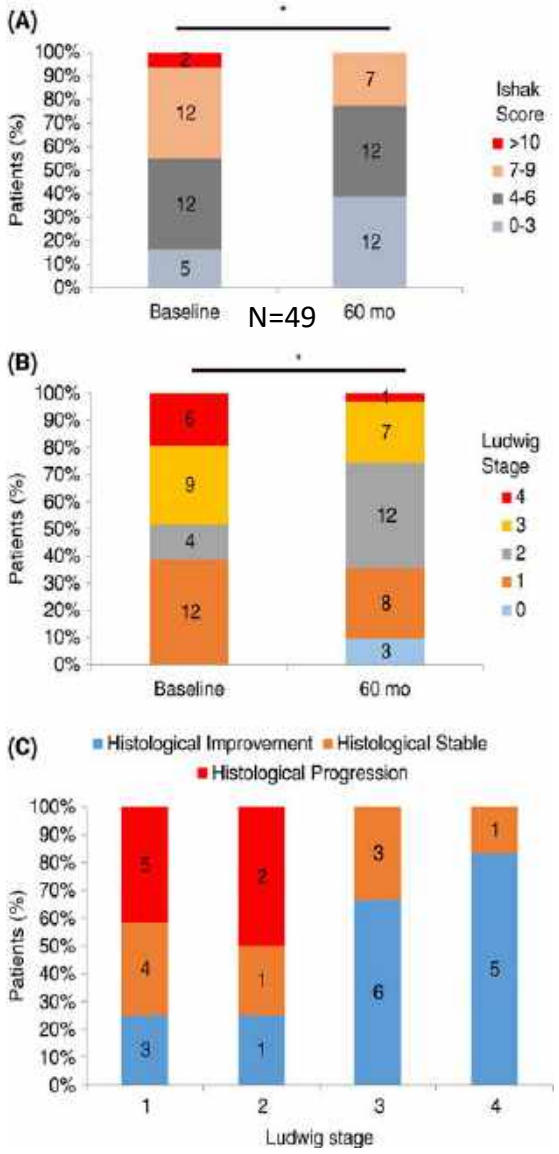
→ ***Tolerabililty- not much of a concern***

Mayo M et al. Aliment Pharmacol Ther. 2024;59:186-200

8. Regression of fibrosis



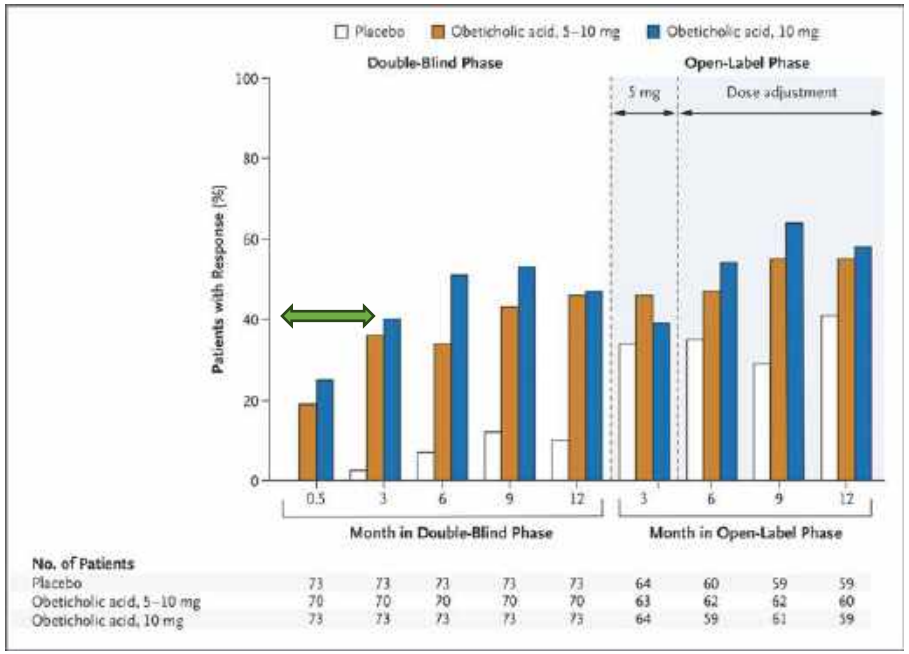
Currently, elafibranor and seladelpar do not have histology as part of phase 3 or open label clinical trial LTSE

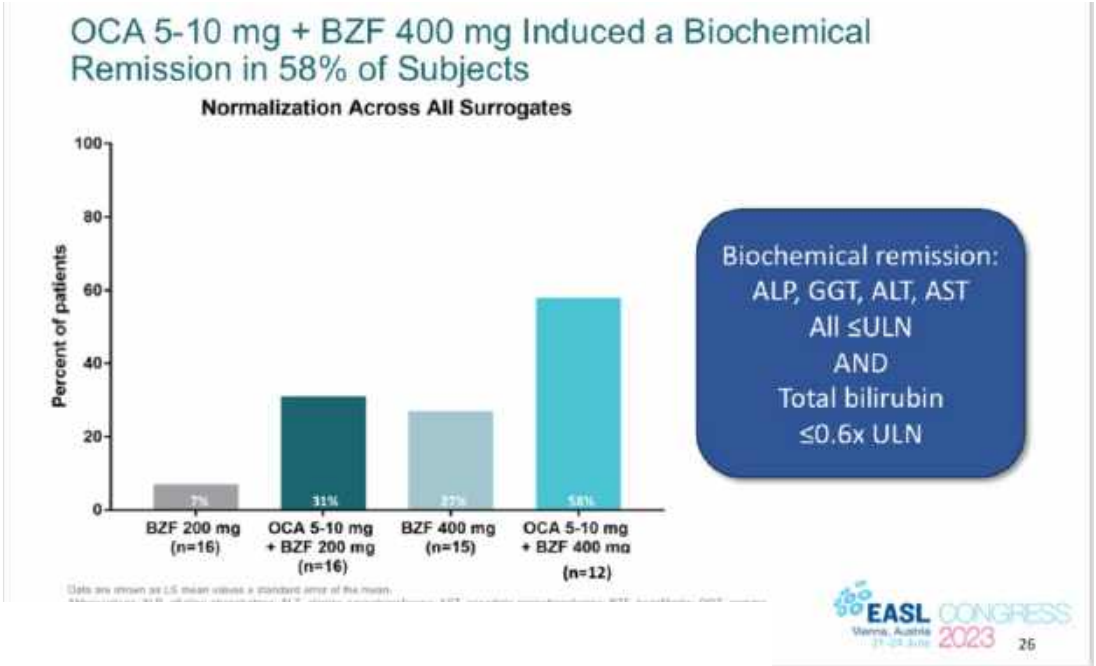


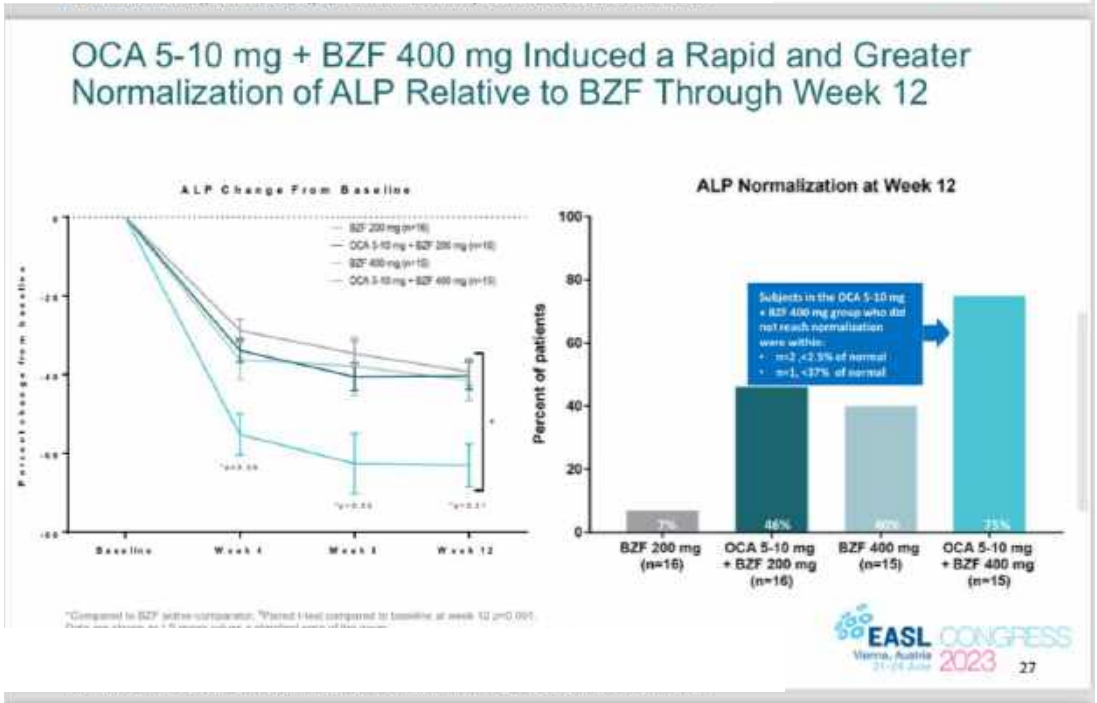
Bezafibrate therapy in primary biliary cholangitis refractory to ursodeoxycholic acid: a longitudinal study of paired liver biopsies at 5 years of follow up. APT 2021 Nov;54(9):1202-1212

9. OCA + BZF Combination

- Increased efficacy
- Requires 400mg BZF
- No OCA arm







9. OCA + BZF Combination

- Increased tolerability
- Improved lipid effect
- BZF 400 mg

Summary of Adverse Events Through Week 12

All groups have comparable adverse event rates

	BZF 200 mg (n=16) N (%)	OCA 5-10 mg + BZF 200 mg (n=16) N (%)	BZF 400 mg (n=15) N (%)	OCA 5-10 mg + BZF 400 mg (n=15) N (%)
Subjects with TEAE	**8** (50.0)	**11** (68.8)	**12** (80.0)	**9** (60.0)
Pruritus	**4** (25.0)	**4** (25.0)	**3** (20.0)	**2** (13.3)
Serious TEAEs	0	0	0	**1** (6.7)[a]
TEAE leading to discontinuation	0	0	0	**1** (6.7)[a]
TEAEs leading to death	0	0	0	0

- Pruritus event rate in the combination groups of OCA 5-10 mg + BZF was 19.4%
- No difference in Gastrointestinal or Musculoskeletal adverse events between groups

[a]1 event of pruritus led to discontinuation from the study.

Abbreviations: BZF, bezafibrate; OCA, obeticholic acid; TEAEs, treatment-emergent adverse events.

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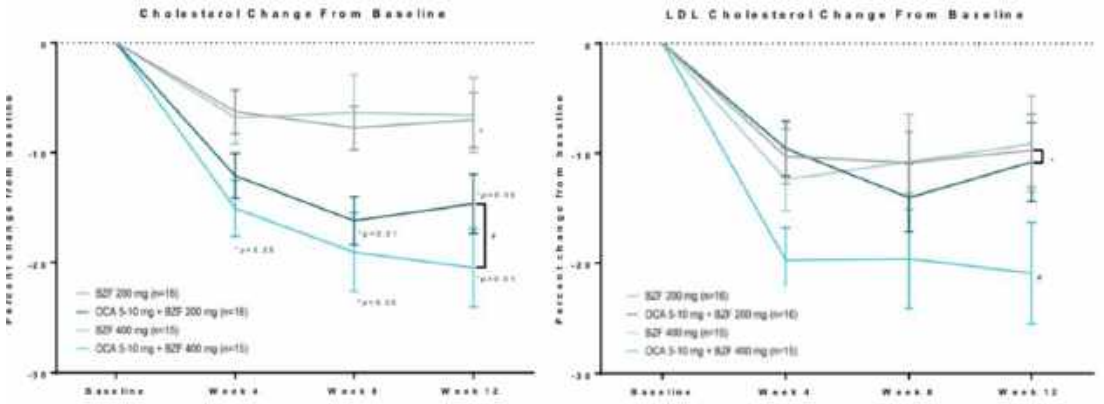
OCA 5-10 mg + BZF 400 mg Induced a Rapid and Greater Change in Cholesterol and LDL Cholesterol Relative to BZF Through Week 12



*Compared to BZF active-comparator; †Paired t-test compared to baseline at week 12 p<0.001; ‡Paired t-test compared to baseline at week 12 p<0.05.
Data are shown as LS mean values ± standard error of the mean.
Abbreviations: BZF, bezafibrate; LS, least-squares; OCA, obeticholic acid.

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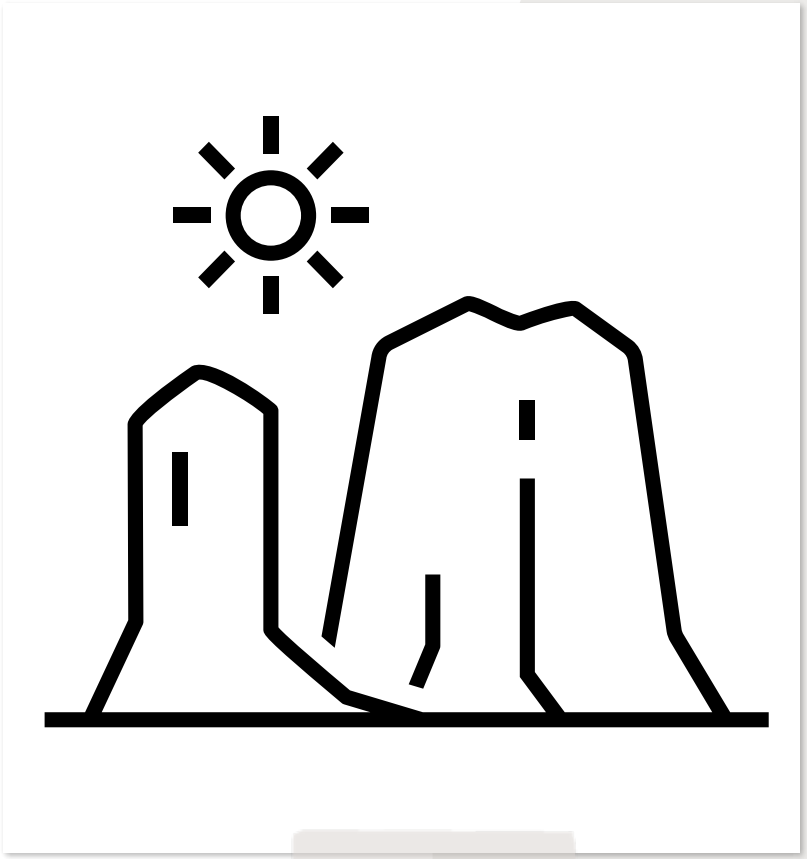
Key Takeaways

- Robust options for 2nd line treatment
- Efficacy probably in the similar range
- Safety signals emerging
  - Myalgias and rhabdomyolysis
    - in those with cirrhosis | CKD | concomitant statin
  - Hepatotoxicity -- jury is out there
- Field is moving
  - from POISE criteria to complete normalization of ALP
  - from “not worsening pruritus” to “improvement in pruritus”
  - non-cirrhotic to compensated cirrhosis
  - improvement in sleep and quality of life



2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

Genetic Cholestasis for the Adult Provider

- **Naim Alkhouri, MD**
- Chief Medical Officer
- Director of the Steatotic Liver Program
- Arizona Liver Health (ALH)
- Chandler, AZ

ARIZONA LIVER HEALTH™

Objectives

- Describe the spectrum of PFIC in adults and the clinical presentations
- Discuss the role of genetic testing/Cholestasis Panel in adult patients with unexplained cholestatic liver disease.
- Discuss new therapeutic options for pruritus for patients with genetic cholestasis.
- @AlkhouriNaim 

There is More to Chronic Cholestatic Liver Diseases than PBC and PSC

Defective hepatic bile formation leads to intrahepatic cholestasis, a group of heterogeneous liver diseases[1]

- Commonly recognized forms of intrahepatic cholestasis include primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC); however, in many patients, a clear diagnosis is difficult to confirm[2]

Progressive familial intrahepatic cholestasis (PFIC) is a severe form of cholestatic liver disease caused by genetic variants that affect the transport of biliary components and canalicular membrane stability[1,2]

- The estimated incidence of PFIC is 1 in every 50,000 to 100,000 births[3]

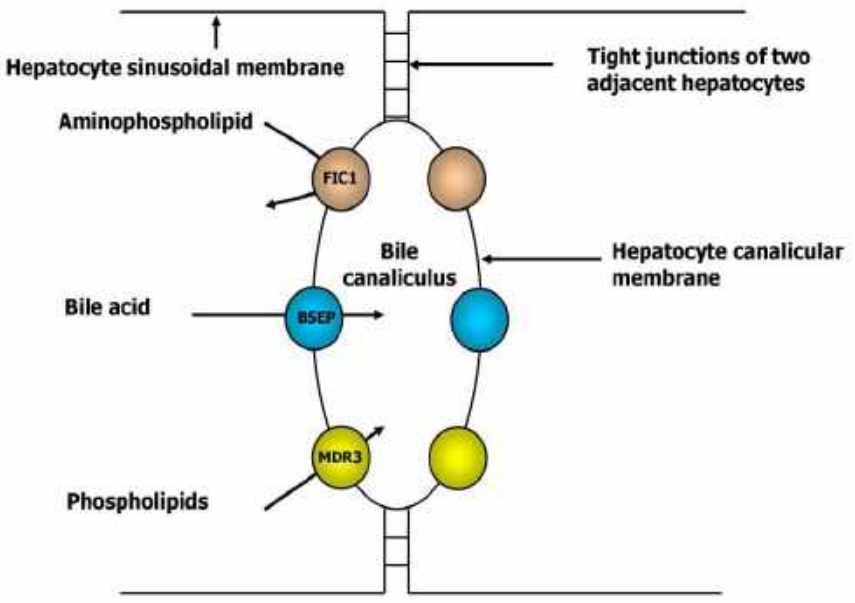
While PFIC commonly presents in the first months of life, it is now evident that variants in PFIC genes *ABCB4*, *ABCB11*, and *ATP8B1* can contribute to later onset forms of the disease[1,2]

- *ABCB4*/MDR3-related disease can present in adulthood as late-onset PFIC 3 with biliary fibrosis and cirrhosis[1]

1. Dröge C et al. *Explor Dig Dis*. 2023;2:34-43. 2. Nayagam JS et al. *Hepatol Commun*. 2022;6(10):2654-2664.

Progressive Familial Intrahepatic Cholestasis: PFIC

- Heterogenous group of recessive disorders
- PFIC1: FIC1 deficiency
  - Important for PL and bile salt transport/ regulate expression of other transporters (BSEP)
- PFIC2: BSEP deficiency
  - Main transporter for bile salts
- PFIC3: MDR3 deficiency



Key Clinical Features

	PFIC1	PFIC2	PFIC3
Feature	**ATP8B1**	**ABCB11**	**ABCB4**
Direct hyper bilirubinemia	Birth – 6m	Birth – 6m	Birth – adulthood
GGT	**LOW**	**LOW**	**HIGH**
Earliest time to cirrhosis	Late childhood and adolescence	Early infancy	Any age
Extrahepatic Sx	**Diarrhea**, Hearing Loss, Pancreatitis, Pneumonia	NO	NO
Pruritus	**YES**	**YES**	YES/NO
Cholelithiasis	NO	YES	YES (**Intrahepatic**)
Cancer	?	**HCC**	**HCC & CCA (teens +)**

Adapted from: Morotti RA, Suchy FJ, Magid MS. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis*. 2011 Feb;31(1):3–10.

The Long and Difficult Diagnostic Journey for Some Adults with PFIC

Female patient with no family history of gallstone disease, ICP, or liver disease

Age 20

First experienced cholestatic liver disease symptoms, namely **abdominal pain,** which was **diagnosed as gallstones**

Mid-30s

- Underwent **cholecystectomy** due to recurrent symptoms
- **Hereditary disease not suspected.** No regular follow-ups implemented

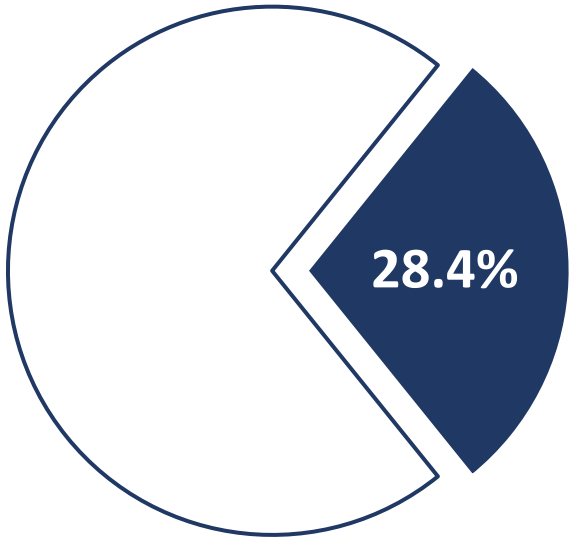
~Age 60: PFIC diagnosis

- **Abnormal labs: elevated sBA** (2.3x ULN), **ALT** (1.9x ULN), **AST** (1.5x ULN), **GGT** (7.4x ULN), and **ALP** (1.7x ULN)
- Bilirubin and liver function tests normal
- Viral hepatitis, autoimmune liver disease, PSC, PBC excluded. **Hereditary cholestasis suspected**
- 40 years after symptom onset, whole-exome sequencing showed **heterozygous missense *ABCB4* variant**, with clinical phenotype of *ABCB4*/MDR3-related low phospholipid-associated cholelithiasis (LPAC)

Dröge C et al. *Explor Dig Dis*. 2023;2:34-43.

PFIC Variants are Frequently Identified in Adults with Unexplained Liver Disease

A large cohort of 356 patients with adult-onset liver disease and a suspected genetic contribution were screened for 3 PFIC genes



of patients had **≥1 potentially pathogenic variant** in genes coding for the proteins FIC1, BSEP, or MDR3

	FIC1 *(ATP8B1)*	BSEP *(ABCB11)*	MDR3 *(ABCB4)*
CLINICAL PRESENTATION*	Chronic liver disease, liver disease of alternate cause	Pregnancy-associated liver dysfunction, acute/episodic cholestasis	Chronic liver disease, pregnancy-associated liver dysfunction
HISTOLOGY			
Number of histological samples	16	12	20
Biliary disease, n (%)	7 (44%)†	4 (33%)	16 (80%)†
Acute or cholestatic hepatitis, n (%)	4 (25%)‡	7 (58%)‡	3 (15%)
Advanced fibrosis, n (%)	10 (63%)	1 (8%)	9 (45%)

Nayagam JS et al. *Hepatol Commun*. 2022;6(10):2654-2664.

Case 2: 28-Year-Old Female With Elevated Liver Enzymes and history of ICP/Cholelithiasis

HPI: 28 y.o. F presented with elevated liver enzymes.

PE: Unremarkable

PMHx:

- 2016: Elevated liver enzymes and RUQ pain → Dx of NAFLD and biliary sludge.
- 2018: Elevated liver enzymes and severe pruritus during pregnancy. Elevated serum BAs → Diagnosis of ICP → Labor induction.
- 2019: Episodes of severe pruritus, no relief with cholestyramine → Lap. chole.
- 2020-2022: Several episodes of pruritus.

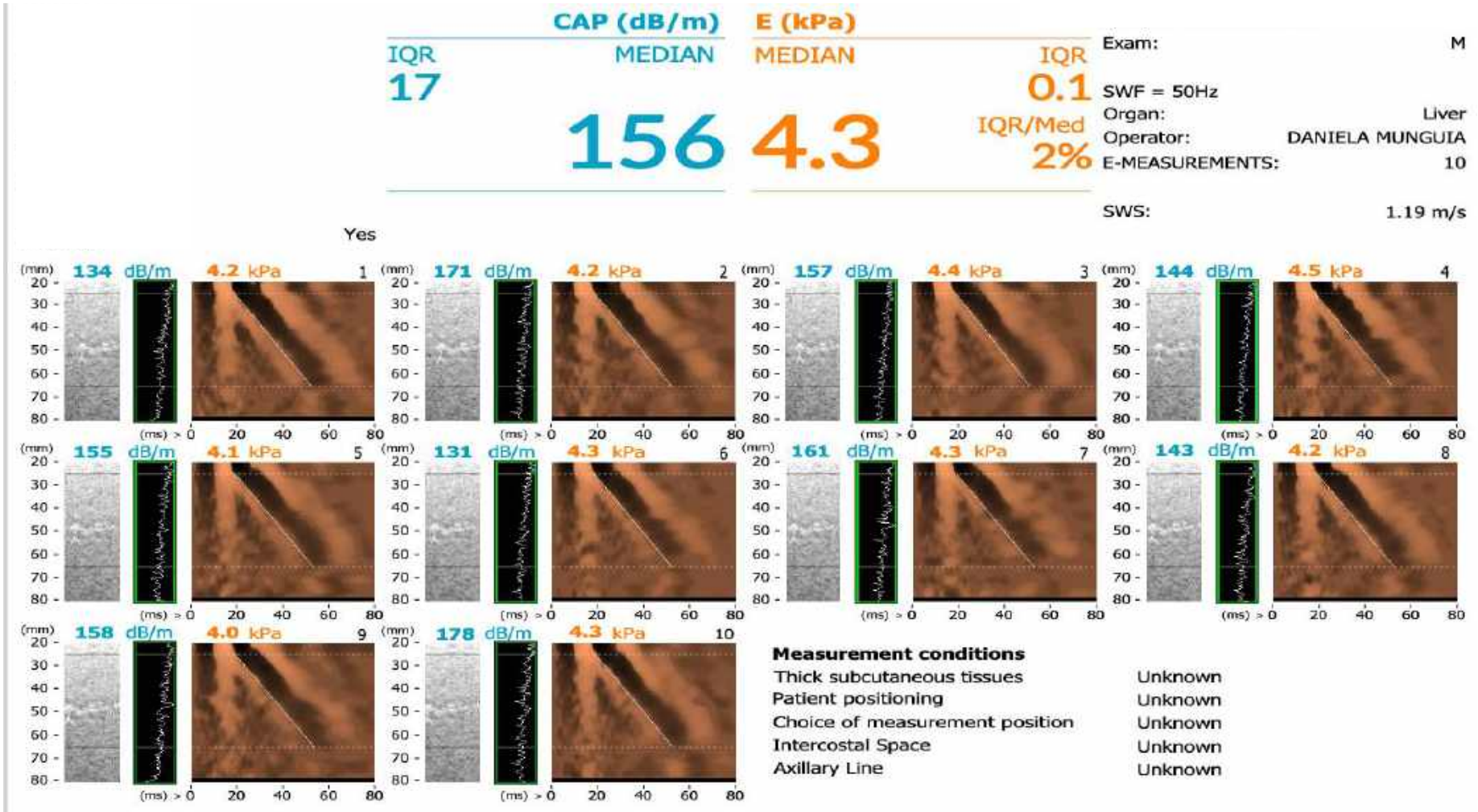
LABS:

Conj. bilirubin	**1.1**
Total bilirubin	**1.8**
ALT	**127**
AST	**66**
GGT	**122**
Hb	**13**
WBC	**7**
Plts	**306k**
ALK PHOS	**197**
Albumin	**4.0**

Viral/ autoimmune/ metabolic liver disease work up negative

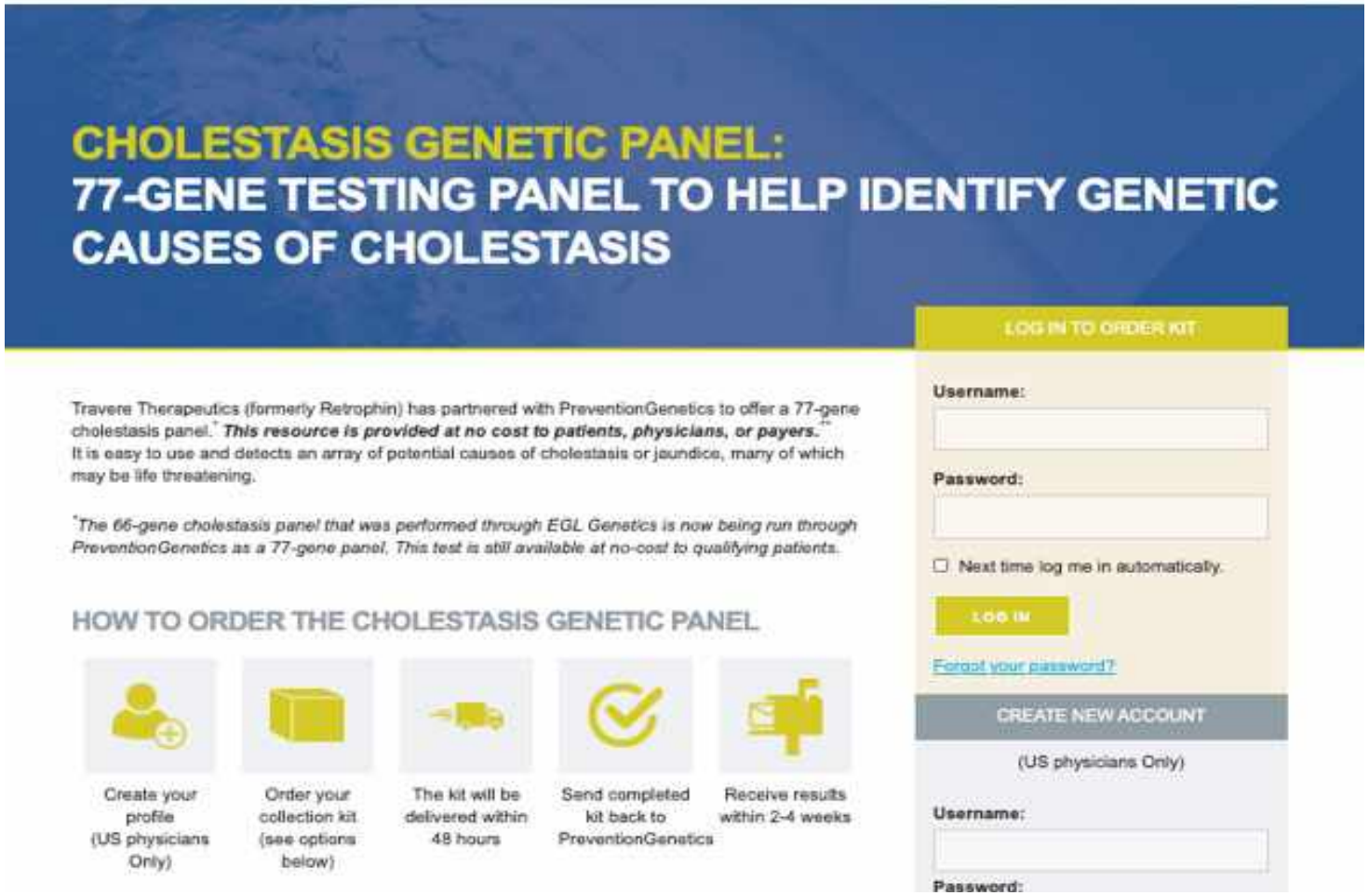
RAD: U/S – Normal. S/p cholecystectomy

VCTE: LSM (kPa) and CAP (dB/m)



Utilization of Genetic Testing in Hepatology

- Roles for Panels & Whole Exome Sequencing
- VOUS are common and may be significant
- Compound heterozygous and modifier genes
- Human variant databases are open, global & growing
- New diseases are being discovered through NGS
- Timely genetic testing may be cost effective and lead to early implementation of effective therapies



Test Code: 13371 77 Genes

ABCB11, ABCB4, ABCC2, ABCG5, ABCG8, ACOX2, AKR1C4, AKR1D1, ALDOB, AMACR, ATP8B1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCDC2, DGUOK, DHCR7, EHHADH, FAH, GNAS, GPBAR1, HNF1B, HSD17B4, HSD3B7, INVS, JAG1, KMT2D, LIPA, MKS1, MPV17, MYO5B, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PKD1L1, PKHD1, POLG, SCP2, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SLC51A, SLC51B, SLCO1B3, SMPD1, TALDO1, TJP2, TMEM216, TRMU, UGT1A1, UTP4, VIPAS39, VPS33B

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Genetic Testing Results

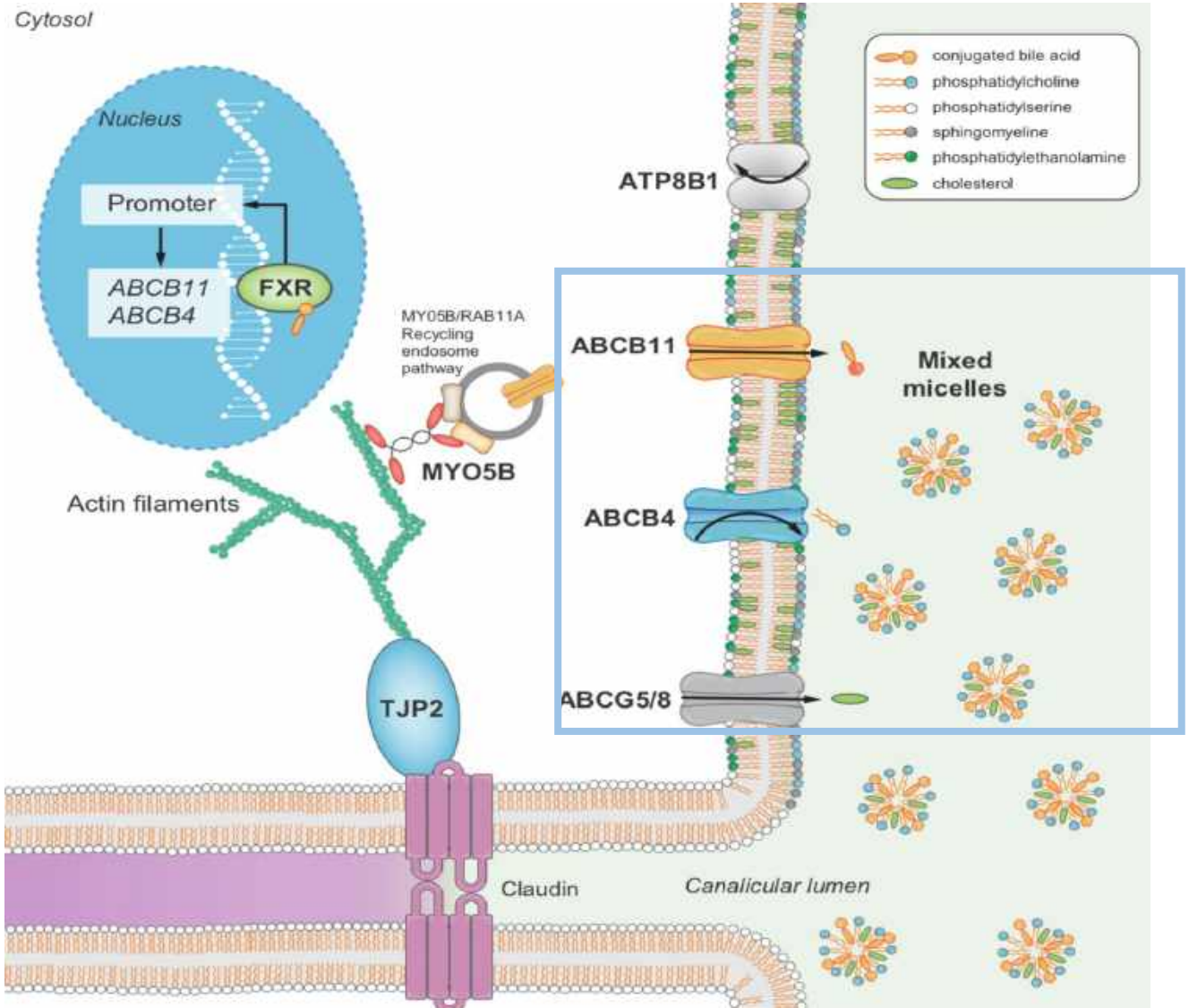
Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
ABCB4, NM_000443.3	AD, AR, 171060	c.1634G>A, p.Arg545His, Heterozygous	Not listed in ClinVar	Not Present	Damaging	LIKELY PATHOGENIC

***ABCB4* VARIANT INFORMATION:**

This patient is heterozygous in the *ABCB4* gene for a sequence variant defined as c.1634G>A, which is predicted to result in the amino acid substitution p.Arg545His. This variant was reported in the heterozygous state, compound heterozygous state and homozygous state in patients with low phospholipid associated cholelithiasis, intrahepatic cholestasis of pregnancy or progressive familial intrahepatic cholestasis (Poupon et al 2013. PubMed ID: 23533021; Wang Z et al 2016. PubMed ID: 26796082; Dröge C et al 2017. PubMed ID:

Molecular Mechanisms Underlying Cholestasis and Lithogenecity Associated with ABCB4



Disease Manifestations Associated with Heterozygous ABCB4 Variants

	LPAC	ICP
Underlying genetic defect in *ABCB4*	Heterozygous	Heterozygous
Age at presentation	Early adulthood (<40 years)	Pregnancy (2^{nd}/3^{rd} trimester)
Clinical presentation	Cholelithiasis, biliary colic	Gestational pruritus
Disease course	Benign	Benign
Complications	Jaundice, cholangitis, biliary pancreatitis, intrahepatic stones	Premature birth, foetal asphyxia, meconium-stained amniotic fluid
Treatment	UDCA, cholecystectomy	UDCA
Differential diagnosis	Primary sclerosing cholangitis, Caroli's disease (congenital dilation of intrahepatic bile ducts)	Acute fatty liver of pregnancy, HELLP syndrome, Budd-Chiari-syndrome

Transporter Variants → Hepatotoxicity

Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury

Carmen Lang[a,*], Yvonne Meier[a,*], Bruno Stieger[a], Ulrich Beuers[c], Thomas Lang[d], Reinhold Kerb[d], Gerd A. Kullak-Ublick[a,b], Peter J. Meier[a] and Christiane Pauli-Magnus[a]

Objectives Increasing evidence suggests that a genetically determined functional impairment of the hepatocellular efflux transporters bile salt export pump (BSEP, *ABCB11*) and multidrug resistance protein 3 (MDR3, *ABCB4*) play a pathophysiological role in the development of drug-induced liver injury. The aim of this study was therefore to describe the extent of genetic variability in *ABCB11* and *ABCB4* in patients with drug-induced liver injury and to *in vitro* functionally characterize newly detected *ABCB11* mutations and polymorphisms.

hepatocellular injury patients and healthy controls, respectively; $P<0.05$). The in-vitro transport activity of the V444A and the D676Y BSEP constructs was similar, whereas the G855R mutation was nonfunctional.

Conclusion In summary, our data support a role of *ABCB11* and *ABCB4* mutations and polymorphisms in drug-induced cholestasis. Genotyping of selected patients with acquired cholestasis might help to identify individuals with a genetic predisposition. *Pharmacogenetics and Genomics* 17:47–60 © 2007 Lippincott Williams & Wilkins.

Wide Spectrum of ABCB4 (MDR3) Deficiency

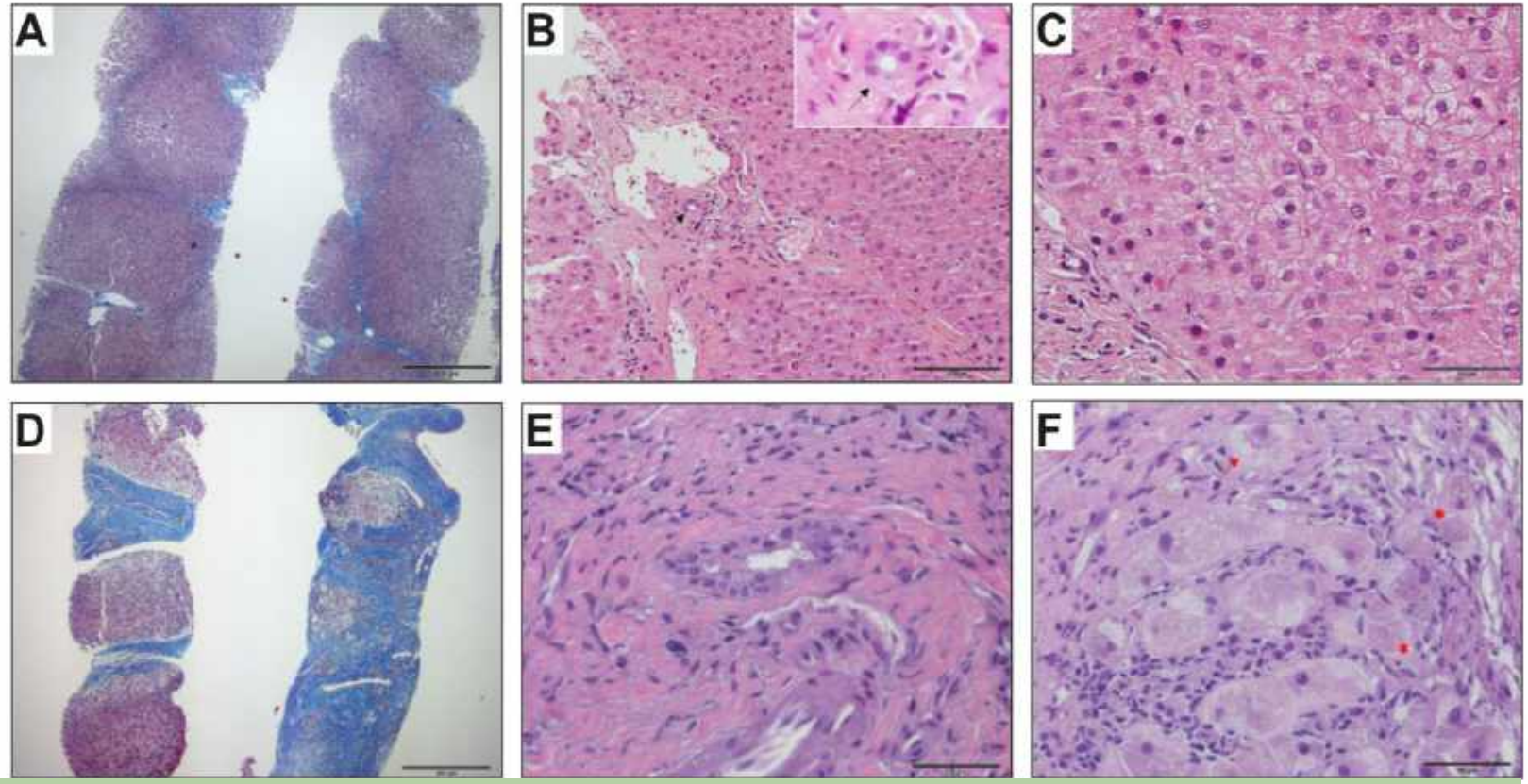
- 20 patients from 12 families were included.
- 5 were homozygotes
- 10 were heterozygotes (one mutation)
- 5 were compound-heterozygotes (two mutations)

PatientN°	Family Relationshipto index case	Gender	Age (years)	LPA Csyndrome	Cholecystectomy (years)	ICP(N° of episodes)	DILI
P1	A Index case	F	46	Yes	17	2	Yes
P2	A Brother	M	49	Yes	44	-	No
P3	A Mother	F	69	No	No	No	No
P4	A Daughter	F	23	No	No	-	No
P5	A Daughter	F	21	No	No	-	No
P6	A Niece	F	23	No	No	-	No
P7	A Niece	F	17	No	Waiting for surgery	-	No
P8	B Index case	F	38	Yes	23	2	No
P9	B Brother	M	34	Yes	22	-	No
P10	C Index case	F	74	Yes	33	1	No
P11	D Index case	F	35	Yes	23	2	No
P12	E Index case	F	51	No	No	1	No
P13	F Index case	F	57	No	No	-	Yes
P14	G Index case	M	42	No	No	-	No
P15	G Uncle	M	74	No	No	-	No
P16	H Index case	F	65	Yes	40	No	No
P17	I Index case	F	23	Yes	17	No	No
P18	J Index case	M	48	No	No	-	No
P19	K Index case	M	62	No	No	-	No
P20	L Index case	F	32	No	29	No	No

Falcao D, et al. Dig Liver Dis. 2022 Feb;54(2):221-227.

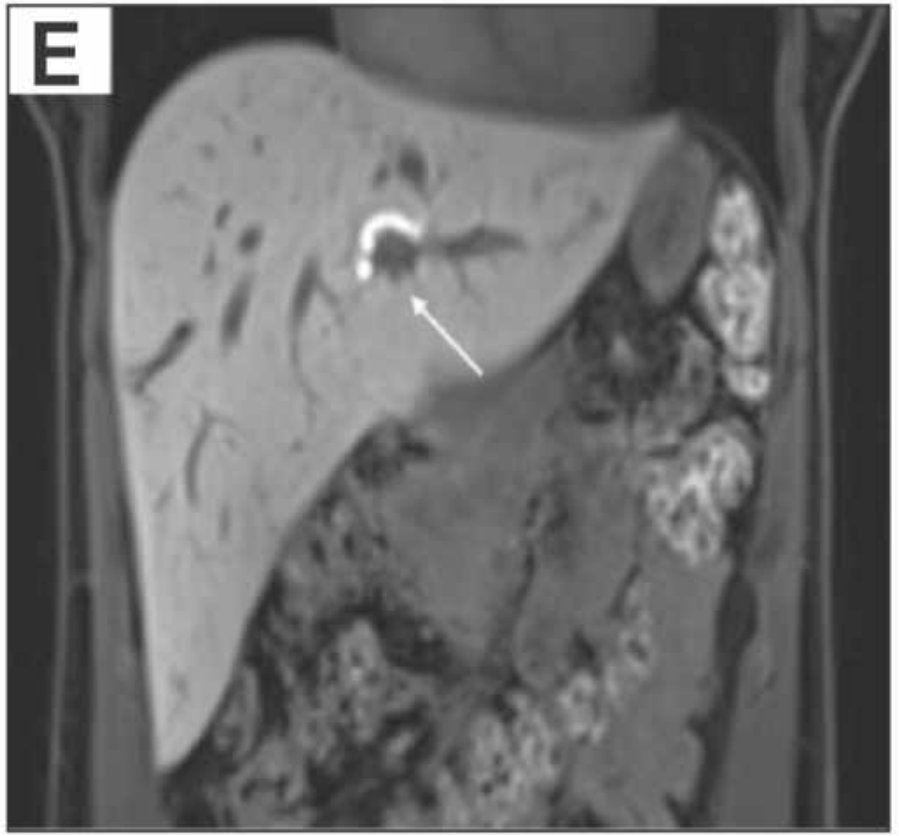
Wide Spectrum of ABCB4 (MDR3) Deficiency

19 y.o. M. presented with elevated liver tests (cholestatic pattern)
→ Negative w/u, was started on Urso and lost to f/u



18 years later presented w decompensation → Homozygous variant in exon 28 of ABCB4 – c.3768_3769delAG

40 y.o. asymptomatic sister with intrahepatic cholestasis (LPAC)



Stättermayer AF et al. J of Hep. 2020 vol 73. 651–663

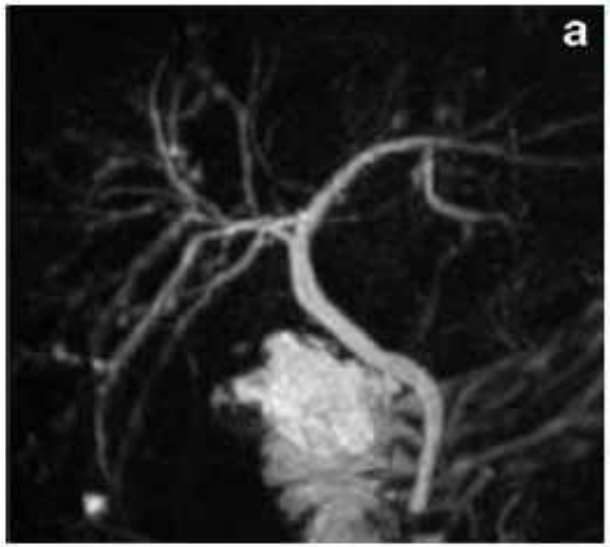
Wide Spectrum of ABCB4 (MDR3) Deficiency

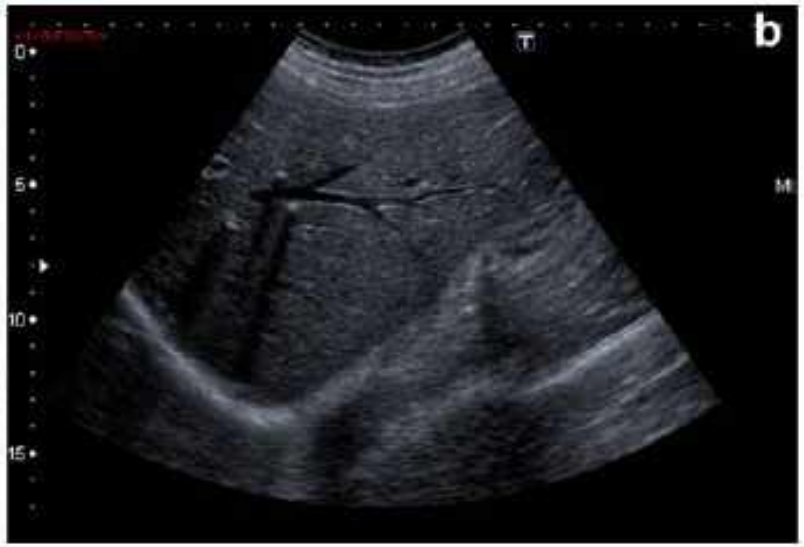
GASTROENTEROLOGY 2001;120:1448–1458

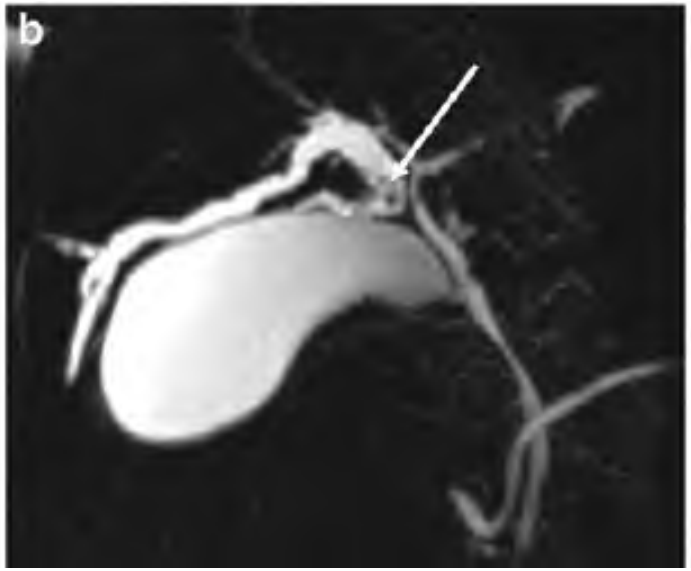
The Wide Spectrum of Multidrug Resistance 3 Deficiency: From Neonatal Cholestasis to Cirrhosis of Adulthood

EMMANUEL JACQUEMIN,* J. MARLEEN L. DE VREE,† DANIÈLE CRESTEIL,* ETIENNE M. SOKAL,§ EKKEHARD STURM,‖ MICHELINE DUMONT,¶ GEORGE L. SCHEFFER,# MARIANNE PAUL,† MARTIN BURDELSKI,‖ PITER J. BOSMA,† OLIVIER BERNARD,* MICHELLE HADCHOUEL,* and RONALD P. J. OUDE ELFERINK†

*Hepatology Unit, Department of Pediatrics, and INSERM U 347, Hôpital de Bicêtre, Le Kremlin Bicêtre, France; †Department of Gastroenterology and Liver Diseases, Academic Medical Center, and #Department of Pathology, Free University, Amsterdam, The Netherlands; §Department of Pediatrics, Université Catholique de Louvain, Cliniques St Luc, Bruxelles, Belgium; ‖Department of Pediatric Gastroenterology and Nutrition, Children's Hospital, University Hospital Eppendorf, Hamburg, Germany; and ¶INSERM U 481, Hôpital







MRCP: Intrahepatic stone

MRCP- Diffuse abnormalities

Certain patient presentations of progressive cholestasis Should Make You Test for PFIC with the Genetic Cholestasis Panel

Idiopathic cholestasis

Consider reassessing your patient if signs of cholestasis manifest without apparent cause[1,2]

Cholestasis with pruritus or unusual presentation

Consider reassessing if your patient is receiving care for another liver disease but has unusual symptoms, including

- Small duct PSC[3]
- AMA negative PBC[4,5]
- MASLD with pruritus[6]*
- Lean MASLD without metabolic syndrome[6]*
- Lean MASH with pruritus and without metabolic syndrome[6]*

Secondary cholestasis triggered by liver issue

Consider reassessing if symptoms of cholestatic pruritus arise in patients who have recently experienced liver issues, including

- All women with history of ICP[3]
- Drug-induced cholestasis[3]
- Hormone-induced cholestasis triggered by birth control, menopause, etc[3,7]

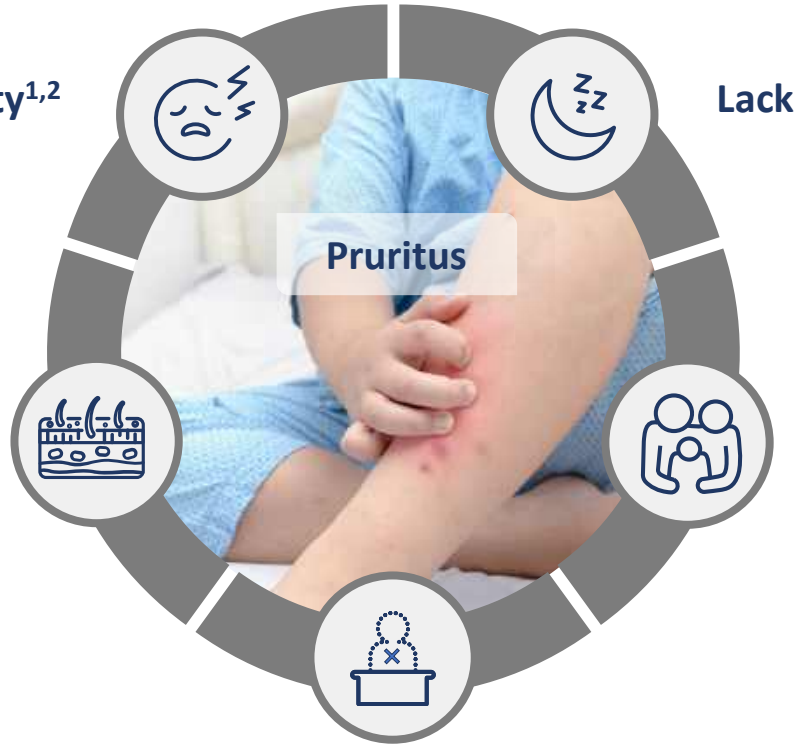
History of complicated gallstones

Consider reassessing if your patient has a complicated history of gallstones, including

- Intrahepatic gallstones[3]
- Very strong family history of gallstones and incident at a young age[8,9]
- LPAC leading to stones in the gallbladder or liver[10]

1. Vitale G et al. *J Gastroenterol*. 2018;53(8):945-958. **2.** Aamann L et al. *Scand J Gastroenterol*. 2018;53(3):305-311. **3.** Hilscher MB et al. *Mayo Clin Proc*. 2020;95(10):2263-2279. **4.** Chascsa DM et al. *Clin Liver Dis.* 2018;22(3):589-601. **5.** Zen Y et al. In: Burt AD et al, eds. *MacSween's Pathology of the Liver*. 7th ed. 2018:515-593. **6.** Boehlig A et al. *Biomedicines*. 2022;10(2):1-10. **7.** Zu Y et al. *Front Pharmacol.* 2021;12:761255.
8. Sarin SK et al. *Hepatology*. 1995;22(1):138-141. **9.** Hsing AW et al. *Int J Cancer*. 2007;121(4):832-838. **10.** Goubault P et al. *J Visc Surg*. 2019;156(4):319-328.

Pruritus in patients with PFIC can be debilitating and affect many aspects of life[1,2]



Even when liver function is satisfactory, the debilitating nature of cholestatic pruritus may necessitate transplant

1. Srivastava A. *J Clin Exp Hepatol*. 2014;4(1):25-36. **2.** Mehl A et al. *World J Transplant*. 2016;6(2):278-290

Historic Treatment Options for Pruritus Caused by Cholestatic Liver Diseases

Goals of Treatment[1,2]

- Provide relief from cholestatic pruritus
- Improve nutritional status and correct vitamin deficiencies
- Manage advanced disease complications to help delay liver transplant

Nutritional support, vitamin and fatty acid supplementation[1]

Symptomatic relief of PFIC, including[2-4]

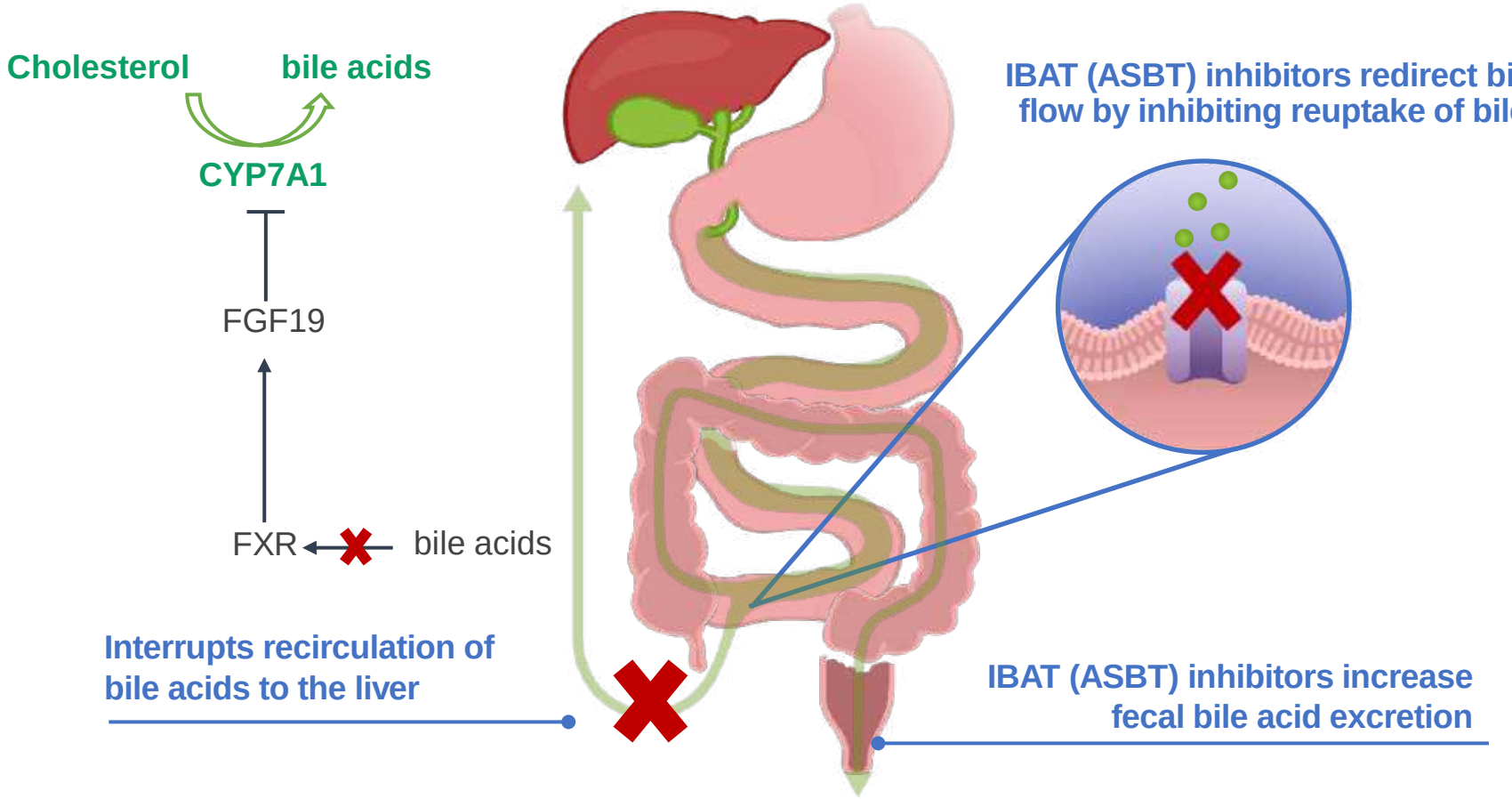
- Hydrophilic bile acids
- Antimycobacterials
- Antihistamines
- Opiate antagonists
- Bile acid sequestrants

Surgical therapy[2]

- Biliary diversion
- Liver transplantation

1. Srivastava A. *J Clin Exp Hepatol.* 2014;4(1):25-36. 2. Gunaydin M, Bozkurter Cil AT. *Hepat Med*. 2018;10:95-104.

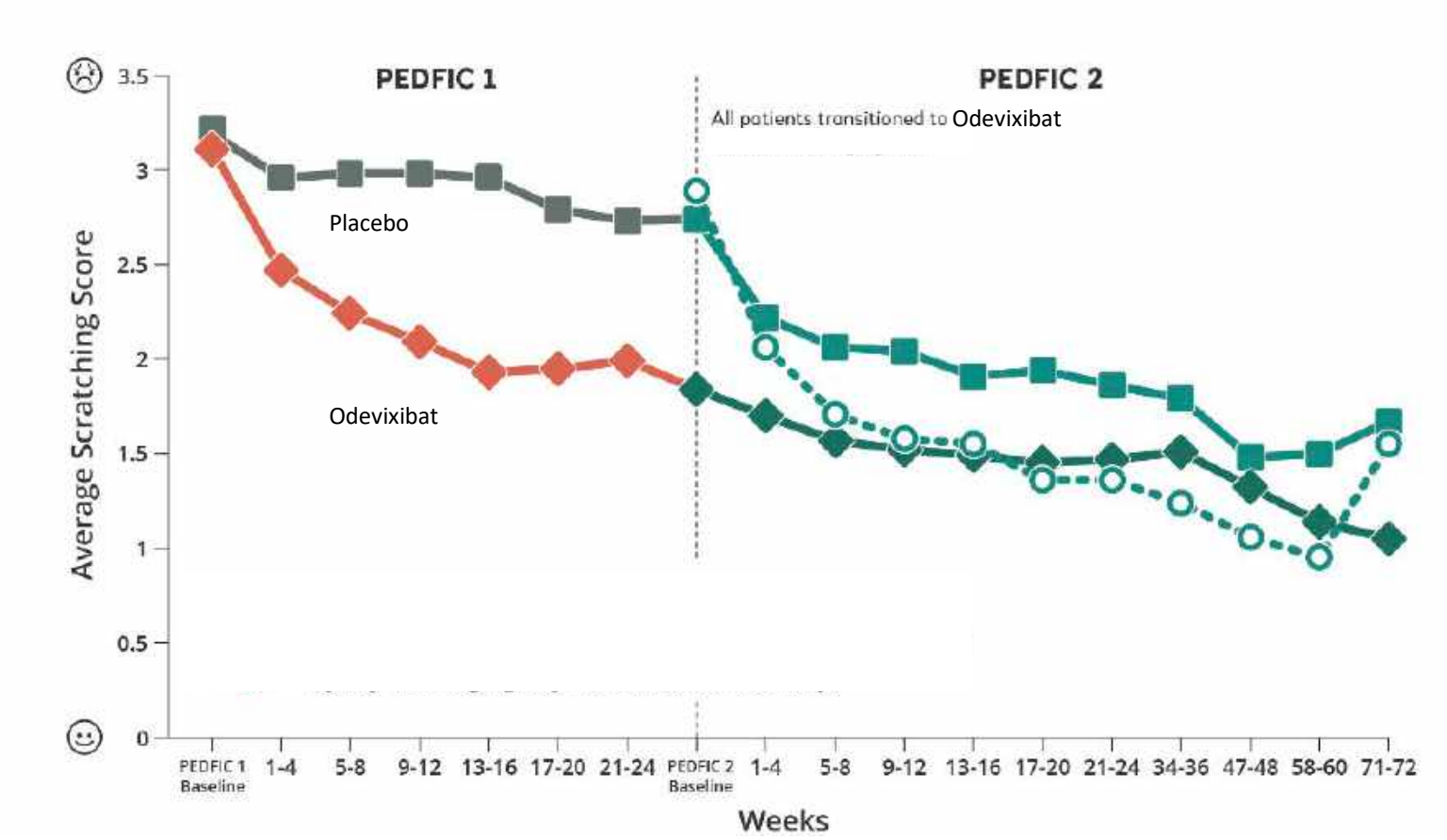
Novel Treatment Strategies – Pharmacologic Interruption of Enterohepatic Circulation



ASBT, apical sodium-dependent bile acid transporter; CYP7A1, cholesterol 7a-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor.

1. Keller B, et al. Poster 55 presented at the Falk Symposium 194. Oct 8–9, 2014. Freiburg, Germany;
2. Al-Dury S, et al. *Sci Rep.* 2018; **8**:6658; 3. Hegade VS, et al. *Lancet.* 2017; **389**:1114–23;
4. Mayo MJ, et al. *Hepatol Commun.* 2019; **3**:365–81; 5. Shneider BL, et al. *Hepatol Comms.* 2018; **2**:1184–98.

Change in Scratching Score with Odevixibat: PEDFIC 1 and PEDFIC 2 Trials



Thompson RJ et al. *Lancet Gastroenterol Hepatol*. 2022;7(9):830-842.

Take Home Messages

- The spectrum of PFIC in adults is wide and should be considered in any cases of unexplained liver disease.
- Have a low threshold to obtain Genetic testing/Cholestasis Panel is available for free to our patients.
- Novel therapeutic agents for cholestatic pruritus are now available and FDA-approved.
- @AlkhouriNaim 

2024
DESERT LIVER CONFERENCE
PHOENIX, ARIZONA

Genetic Cholestasis for the Adult Provider

- **Naim Alkhouri, MD**
- Chief Medical Officer
- Director of the Steatotic Liver Program
- Arizona Liver Health (ALH)
- Chandler, AZ

ARIZONA LIVER HEALTH™

Objectives

- Describe the spectrum of PFIC in adults and the clinical presentations
- Discuss the role of genetic testing/Cholestasis Panel in adult patients with unexplained cholestatic liver disease.
- Discuss new therapeutic options for pruritus for patients with genetic cholestasis.
- @AlkhouriNaim 

There is More to Chronic Cholestatic Liver Diseases than PBC and PSC

Defective hepatic bile formation leads to intrahepatic cholestasis, a group of heterogeneous liver diseases[1]

- Commonly recognized forms of intrahepatic cholestasis include primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC); however, in many patients, a clear diagnosis is difficult to confirm[2]

Progressive familial intrahepatic cholestasis (PFIC) is a severe form of cholestatic liver disease caused by genetic variants that affect the transport of biliary components and canalicular membrane stability[1,2]

- The estimated incidence of PFIC is 1 in every 50,000 to 100,000 births[3]

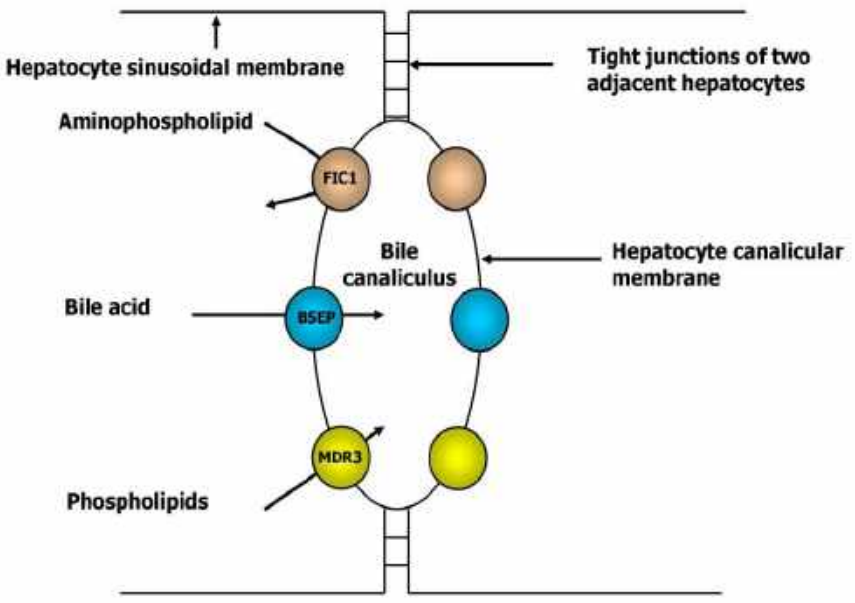
While PFIC commonly presents in the first months of life, it is now evident that variants in PFIC genes *ABCB4*, *ABCB11*, and *ATP8B1* can contribute to later onset forms of the disease[1,2]

- *ABCB4*/MDR3-related disease can present in adulthood as late-onset PFIC 3 with biliary fibrosis and cirrhosis[1]

1. Dröge C et al. *Explor Dig Dis*. 2023;2:34-43. 2. Nayagam JS et al. *Hepatol Commun*. 2022;6(10):2654-2664.

Progressive Familial Intrahepatic Cholestasis: PFIC

- Heterogenous group of recessive disorders
- PFIC1: FIC1 deficiency
  - Important for PL and bile salt transport/ regulate expression of other transporters (BSEP)
- PFIC2: BSEP deficiency
  - Main transporter for bile salts
- PFIC3: MDR3 deficiency



Key Clinical Features

	PFIC1	PFIC2	PFIC3
Feature	**ATP8B1**	**ABCB11**	**ABCB4**
Direct hyper bilirubinemia	Birth – 6m	Birth – 6m	Birth – adulthood
GGT	**LOW**	**LOW**	**HIGH**
Earliest time to cirrhosis	Late childhood and adolescence	Early infancy	Any age
Extrahepatic Sx	**Diarrhea**, Hearing Loss, Pancreatitis, Pneumonia	NO	NO
Pruritus	**YES**	**YES**	YES/NO
Cholelithiasis	NO	YES	YES (**Intrahepatic**)
Cancer	?	**HCC**	**HCC & CCA (teens +)**

Adapted from: Morotti RA, Suchy FJ, Magid MS. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis*. 2011 Feb;31(1):3–10.

The Long and Difficult Diagnostic Journey for Some Adults with PFIC

Female patient with no family history of gallstone disease, ICP, or liver disease

Age 20

First experienced cholestatic liver disease symptoms, namely **abdominal pain,** which was **diagnosed as gallstones**

Mid-30s

- Underwent **cholecystectomy** due to recurrent symptoms
- **Hereditary disease not suspected.** No regular follow-ups implemented

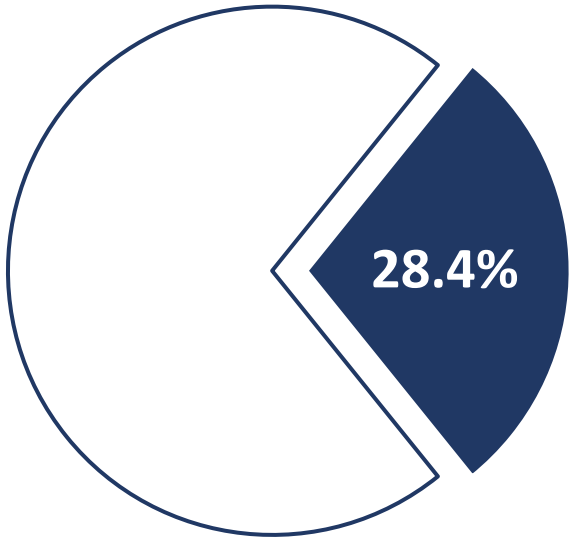
~Age 60: PFIC diagnosis

- **Abnormal labs: elevated sBA** (2.3x ULN), **ALT** (1.9x ULN), **AST** (1.5x ULN), **GGT** (7.4x ULN), and **ALP** (1.7x ULN)
- Bilirubin and liver function tests normal
- Viral hepatitis, autoimmune liver disease, PSC, PBC excluded. **Hereditary cholestasis suspected**
- 40 years after symptom onset, whole-exome sequencing showed **heterozygous missense *ABCB4* variant**, with clinical phenotype of *ABCB4*/MDR3-related low phospholipid-associated cholelithiasis (LPAC)

Dröge C et al. *Explor Dig Dis*. 2023;2:34-43.

PFIC Variants are Frequently Identified in Adults with Unexplained Liver Disease

A large cohort of 356 patients with adult-onset liver disease and a suspected genetic contribution were screened for 3 PFIC genes



of patients had **≥1 potentially pathogenic variant** in genes coding for the proteins FIC1, BSEP, or MDR3

	FIC1 *(ATP8B1)*	BSEP *(ABCB11)*	MDR3 *(ABCB4)*
CLINICAL PRESENTATION*	Chronic liver disease, liver disease of alternate cause	Pregnancy-associated liver dysfunction, acute/episodic cholestasis	Chronic liver disease, pregnancy-associated liver dysfunction
HISTOLOGY			
Number of histological samples	16	12	20
Biliary disease, n (%)	7 (44%)†	4 (33%)	16 (80%)†
Acute or cholestatic hepatitis, n (%)	4 (25%)‡	7 (58%)‡	3 (15%)
Advanced fibrosis, n (%)	10 (63%)	1 (8%)	9 (45%)

Nayagam JS et al. *Hepatol Commun*. 2022;6(10):2654-2664.

Case 2: 28-Year-Old Female With Elevated Liver Enzymes and history of ICP/Cholelithiasis

HPI: 28 y.o. F presented with elevated liver enzymes.

PE: Unremarkable

PMHx:

- 2016: Elevated liver enzymes and RUQ pain → Dx of NAFLD and biliary sludge.
- 2018: Elevated liver enzymes and severe pruritus during pregnancy. Elevated serum BAs → Diagnosis of ICP → Labor induction.
- 2019: Episodes of severe pruritus, no relief with cholestyramine → Lap. chole.
- 2020-2022: Several episodes of pruritus.

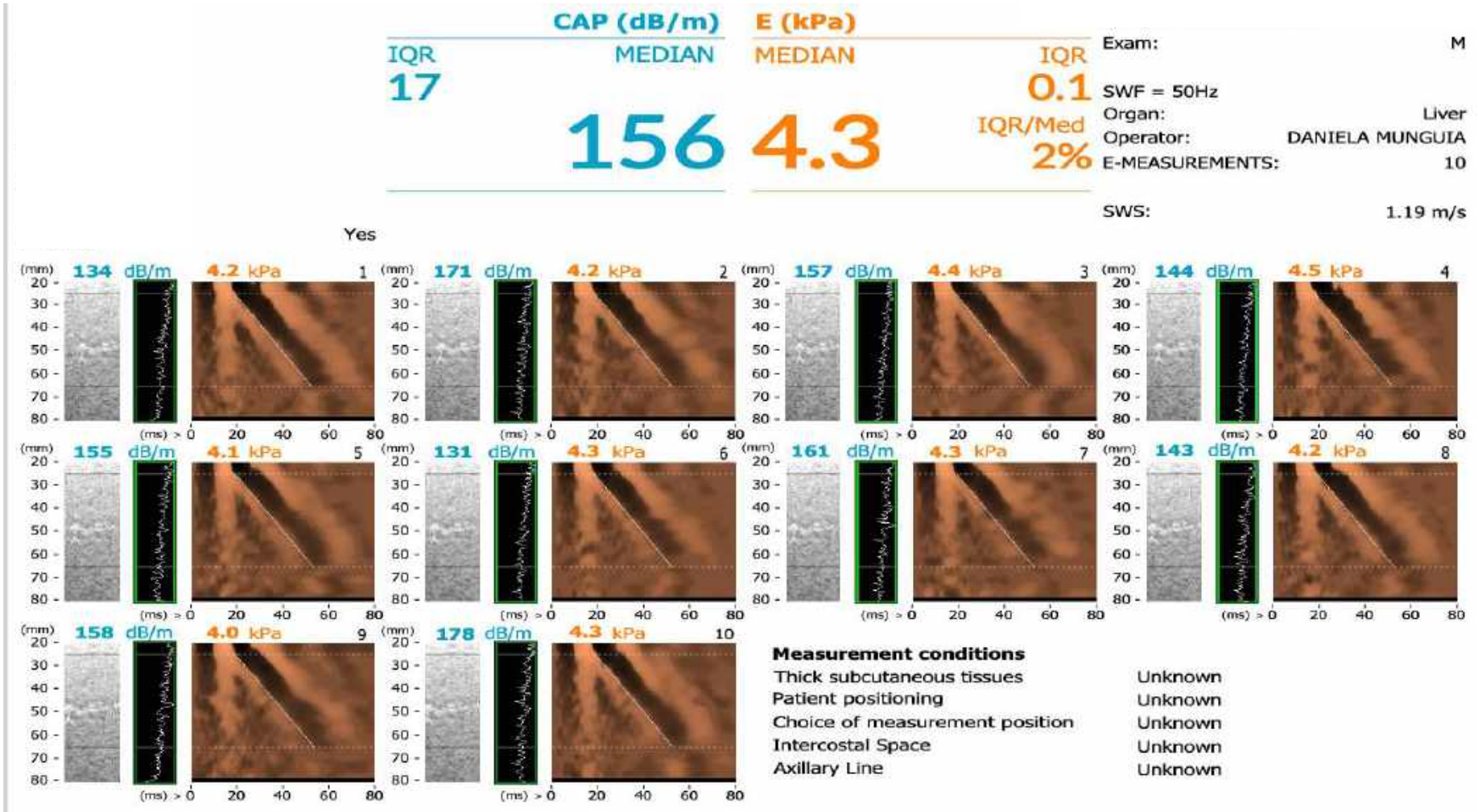
LABS:

Conj. bilirubin	**1.1**
Total bilirubin	**1.8**
ALT	**127**
AST	**66**
GGT	**122**
Hb	**13**
WBC	**7**
Plts	**306k**
ALK PHOS	**197**
Albumin	**4.0**

Viral/ autoimmune/ metabolic liver disease work up negative

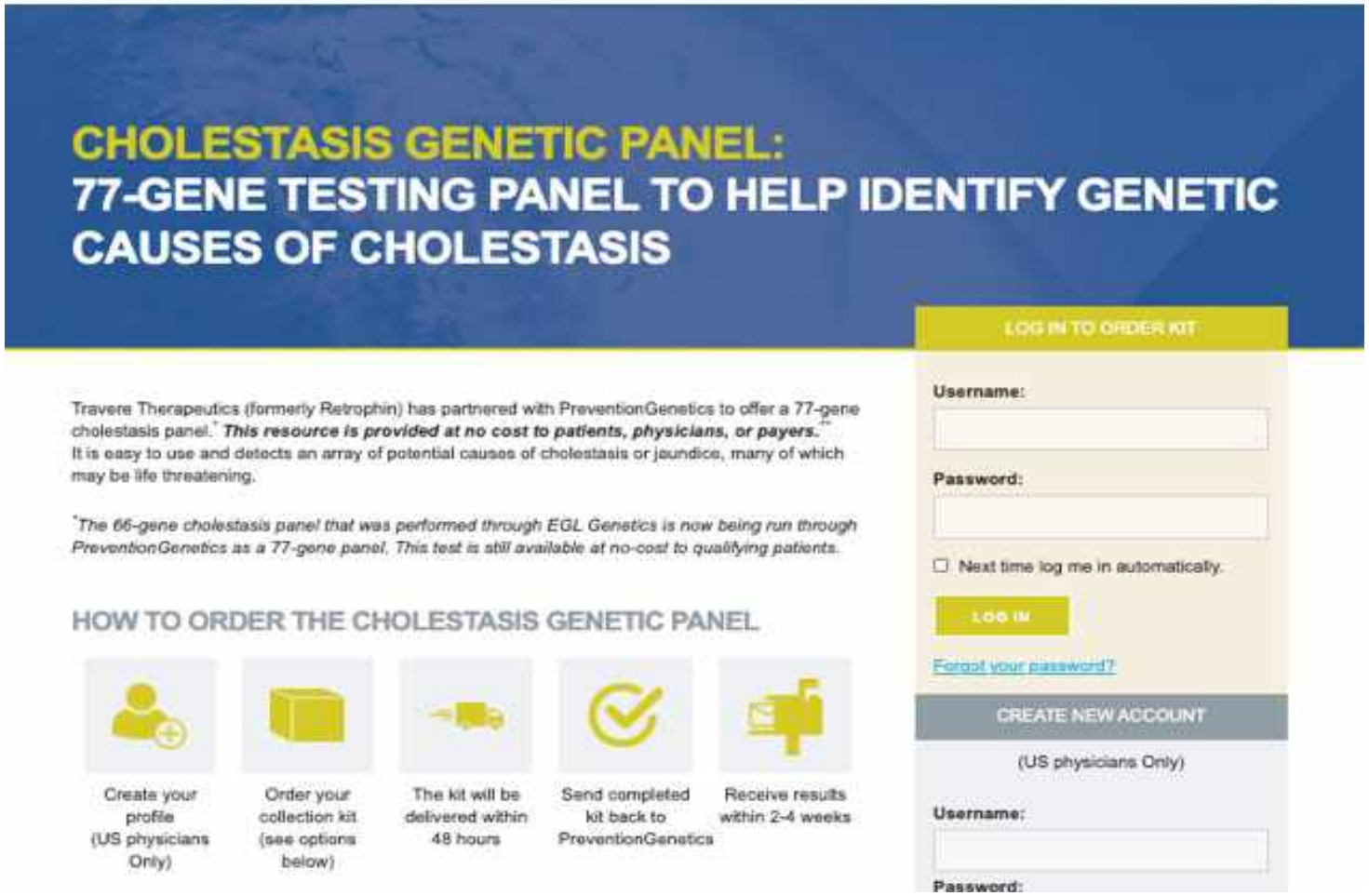
RAD: U/S – Normal. S/p cholecystectomy

VCTE: LSM (kPa) and CAP (dB/m)



Utilization of Genetic Testing in Hepatology

- Roles for Panels & Whole Exome Sequencing
- VOUS are common and may be significant
- Compound heterozygous and modifier genes
- Human variant databases are open, global & growing
- New diseases are being discovered through NGS
- Timely genetic testing may be cost effective and lead to early implementation of effective therapies



Test Code: 13371 77 Genes

ABCB11, ABCB4, ABCC2, ABCG5, ABCG8, ACOX2, AKR1C4, AKR1D1, ALDOB, AMACR, ATP8B1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCDC2, DGUOK, DHCR7, EHHADH, FAH, GNAS, GPBAR1, HNF1B, HSD17B4, HSD3B7, INVS, JAG1, KMT2D, LIPA, MKS1, MPV17, MYO5B, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PKD1L1, PKHD1, POLG, SCP2, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SLC51A, SLC51B, SLCO1B3, SMPD1, TALDO1, TJP2, TMEM216, TRMU, UGT1A1, UTP4, VIPAS39, VPS33B

www.testcholestasis.com

Genetic Testing Results

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Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
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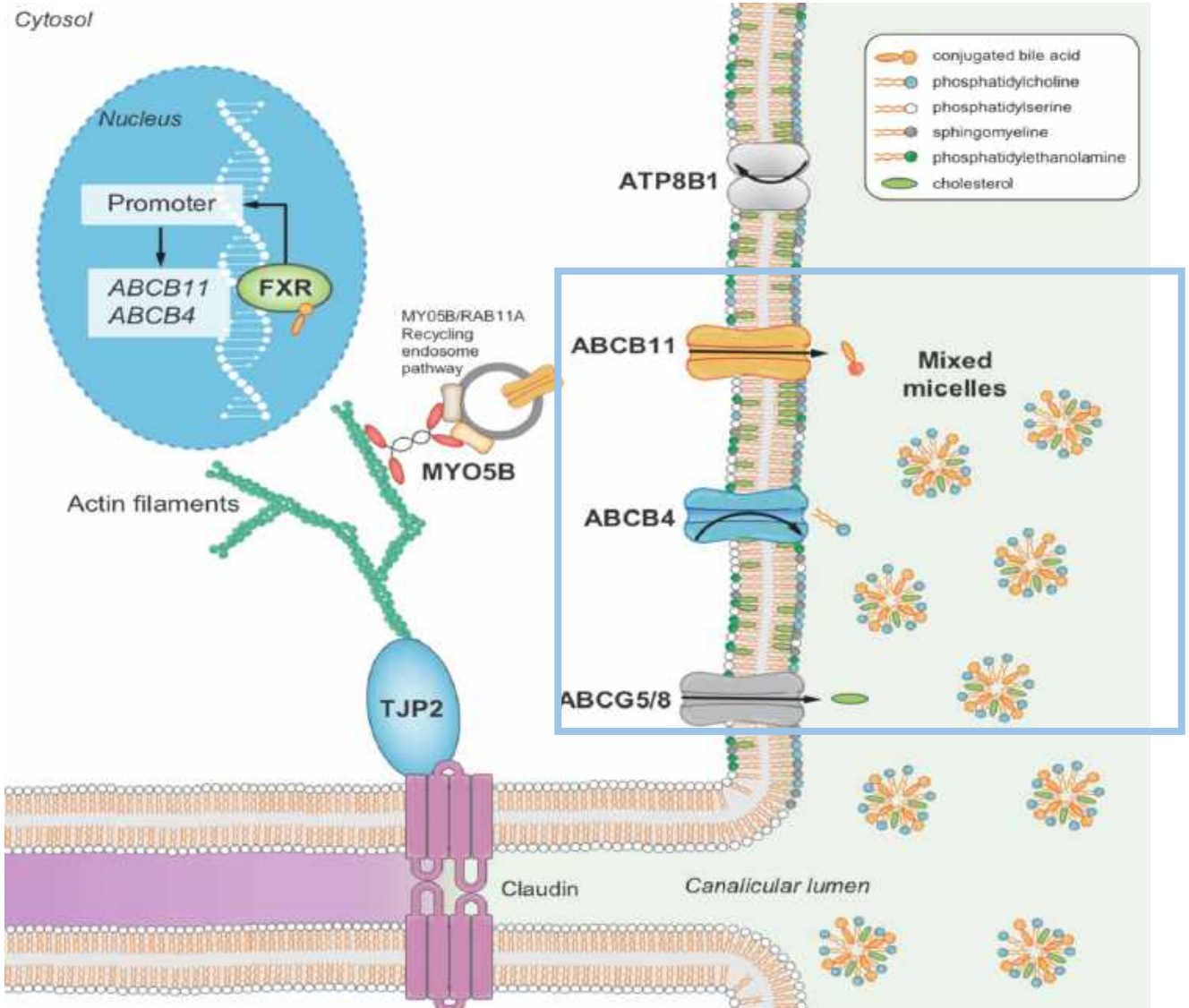
This patient is heterozygous in the *ABCB4* gene for a sequence variant defined as c.1634G>A, which is predicted to result in the amino acid substitution p.Arg545His. This variant was reported in the heterozygous state, compound heterozygous state and homozygous state in patients with low phospholipid associated cholelithiasis, intrahepatic cholestasis of pregnancy or progressive familial intrahepatic cholestasis (Poupon et al 2013. PubMed ID: 23533021; Wang Z et al 2016. PubMed ID: 26796082; Dröge C et al 2017. PubMed ID:

Molecular Mechanisms Underlying Cholestasis and Lithogenecity Associated with ABCB4



Disease Manifestations Associated with Heterozygous ABCB4 Variants

	LPAC	ICP
Underlying genetic defect in *ABCB4*	Heterozygous	Heterozygous
Age at presentation	Early adulthood (<40 years)	Pregnancy (2^{nd}/3^{rd} trimester)
Clinical presentation	Cholelithiasis, biliary colic	Gestational pruritus
Disease course	Benign	Benign
Complications	Jaundice, cholangitis, biliary pancreatitis, intrahepatic stones	Premature birth, foetal asphyxia, meconium-stained amniotic fluid
Treatment	UDCA, cholecystectomy	UDCA
Differential diagnosis	Primary sclerosing cholangitis, Caroli's disease (congenital dilation of intrahepatic bile ducts)	Acute fatty liver of pregnancy, HELLP syndrome, Budd-Chiari-syndrome

Transporter Variants → Hepatotoxicity

Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury

Carmen Lang[a,*], Yvonne Meier[a,*], Bruno Stieger[a], Ulrich Beuers[c], Thomas Lang[d], Reinhold Kerb[d], Gerd A. Kullak-Ublick[a,b], Peter J. Meier[a] and Christiane Pauli-Magnus[a]

Objectives Increasing evidence suggests that a genetically determined functional impairment of the hepatocellular efflux transporters bile salt export pump (BSEP, *ABCB11*) and multidrug resistance protein 3 (MDR3, *ABCB4*) play a pathophysiological role in the development of drug-induced liver injury. The aim of this study was therefore to describe the extent of genetic variability in *ABCB11* and *ABCB4* in patients with drug-induced liver injury and to *in vitro* functionally characterize newly detected *ABCB11* mutations and polymorphisms.

hepatocellular injury patients and healthy controls, respectively; $P<0.05$). The in-vitro transport activity of the V444A and the D676Y BSEP constructs was similar, whereas the G855R mutation was nonfunctional.

Conclusion In summary, our data support a role of *ABCB11* and *ABCB4* mutations and polymorphisms in drug-induced cholestasis. Genotyping of selected patients with acquired cholestasis might help to identify individuals with a genetic predisposition. *Pharmacogenetics and Genomics* 17:47–60 © 2007 Lippincott Williams & Wilkins.

Wide Spectrum of ABCB4 (MDR3) Deficiency

- 20 patients from 12 families were included.
- 5 were homozygotes
- 10 were heterozygotes (one mutation)
- 5 were compound-heterozygotes (two mutations)

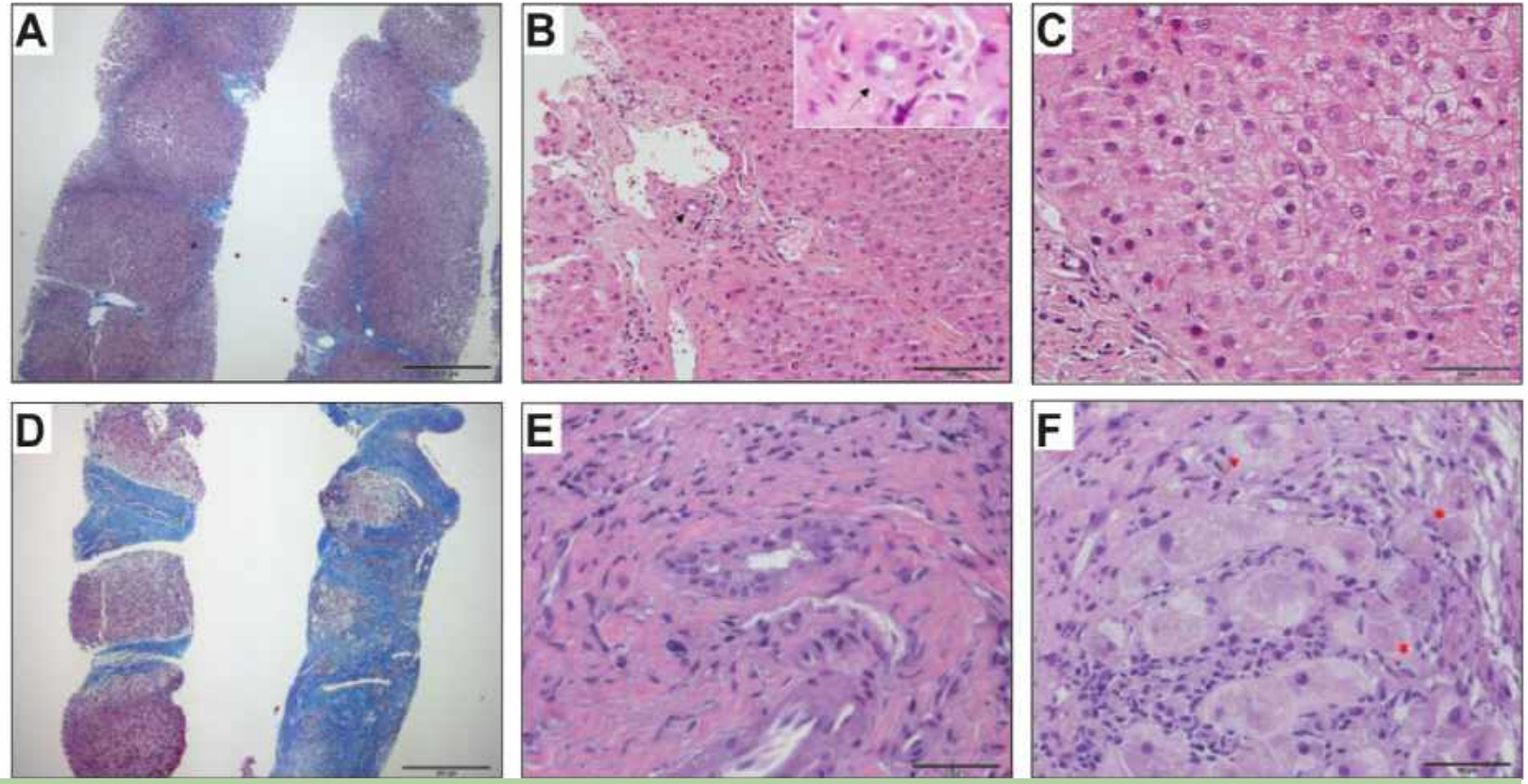
PatientN°	Family Relationshipto index case	Gender	Age (years)	LPA Csyndrome	Cholecystectomy (years)	ICP(N° of episodes)	DILI
P1	A Index case	F	46	Yes	17	2	Yes
P2	A Brother	M	49	Yes	44	-	No
P3	A Mother	F	69	No	No	No	No
P4	A Daughter	F	23	No	No	-	No
P5	A Daughter	F	21	No	No	-	No
P6	A Niece	F	23	No	No	-	No
P7	A Niece	F	17	No	Waiting for surgery	-	No
P8	B Index case	F	38	Yes	23	2	No
P9	B Brother	M	34	Yes	22	-	No
P10	C Index case	F	74	Yes	33	1	No
P11	D Index case	F	35	Yes	23	2	No
P12	E Index case	F	51	No	No	1	No
P13	F Index case	F	57	No	No	-	Yes
P14	G Index case	M	42	No	No	-	No
P15	G Uncle	M	74	No	No	-	No
P16	H Index case	F	65	Yes	40	No	No
P17	I Index case	F	23	Yes	17	No	No
P18	J Index case	M	48	No	No	-	No
P19	K Index case	M	62	No	No	-	No
P20	L Index case	F	32	No	29	No	No

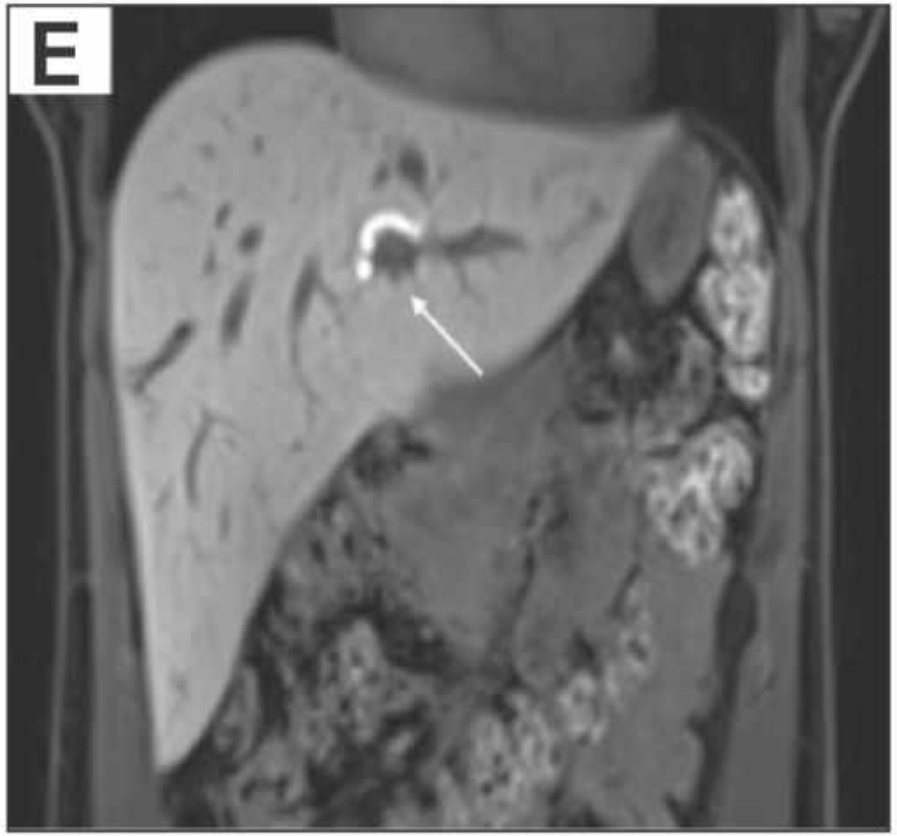
Falcao D, et al. Dig Liver Dis. 2022 Feb;54(2):221-227.

Wide Spectrum of ABCB4 (MDR3) Deficiency

19 y.o. M. presented with elevated liver tests (cholestatic pattern)
→ Negative w/u, was started on Urso and lost to f/u

40 y.o. asymptomatic sister with intrahepatic cholestasis (LPAC)





18 years later presented w decompensation → Homozygous variant in exon 28 of ABCB4 – c.3768_3769delAG

Stättermayer AF et al. J of Hep. 2020 vol 73. 651–663

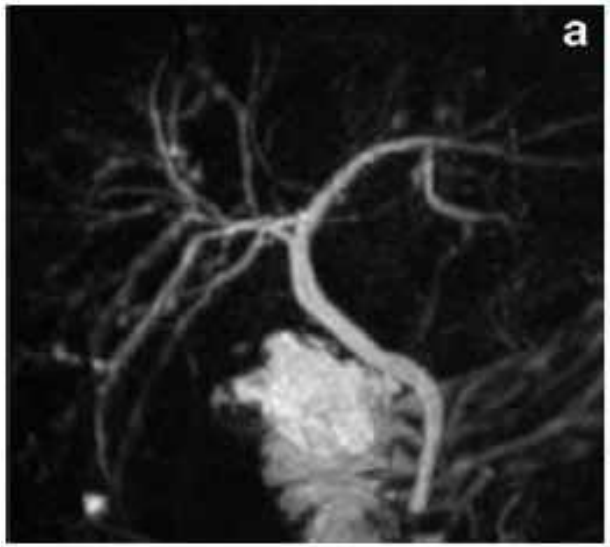
Wide Spectrum of ABCB4 (MDR3) Deficiency

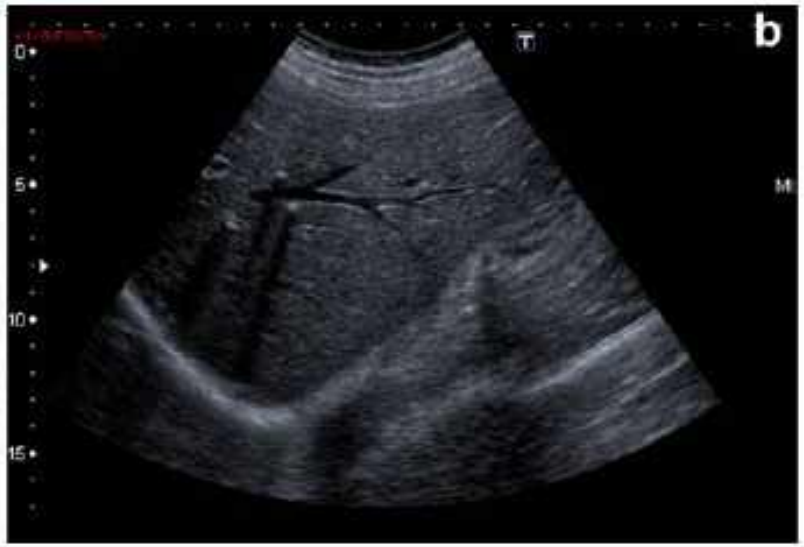
GASTROENTEROLOGY 2001;120:1448–1458

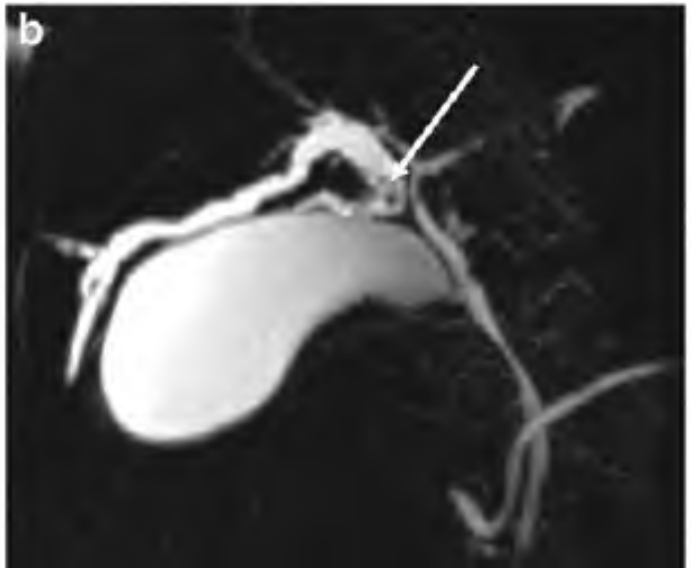
The Wide Spectrum of Multidrug Resistance 3 Deficiency: From Neonatal Cholestasis to Cirrhosis of Adulthood

EMMANUEL JACQUEMIN,* J. MARLEEN L. DE VREE,† DANIÈLE CRESTEIL,* ETIENNE M. SOKAL,§ EKKEHARD STURM,‖ MICHELINE DUMONT,¶ GEORGE L. SCHEFFER,# MARIANNE PAUL,† MARTIN BURDELSKI,‖ PITER J. BOSMA,† OLIVIER BERNARD,* MICHELLE HADCHOUEL,* and RONALD P. J. OUDE ELFERINK†

*Hepatology Unit, Department of Pediatrics, and INSERM U 347, Hôpital de Bicêtre, Le Kremlin Bicêtre, France; †Department of Gastroenterology and Liver Diseases, Academic Medical Center, and #Department of Pathology, Free University, Amsterdam, The Netherlands; §Department of Pediatrics, Université Catholique de Louvain, Cliniques St Luc, Bruxelles, Belgium; ‖Department of Pediatric Gastroenterology and Nutrition, Children's Hospital, University Hospital Eppendorf, Hamburg, Germany; and ¶INSERM U 481, Hôpital







MRCP: Intrahepatic stone

MRCP- Diffuse abnormalities

Certain patient presentations of progressive cholestasis Should Make You Test for PFIC with the Genetic Cholestasis Panel

Idiopathic cholestasis

Consider reassessing your patient if signs of cholestasis manifest without apparent cause[1,2]

Cholestasis with pruritus or unusual presentation

Consider reassessing if your patient is receiving care for another liver disease but has unusual symptoms, including

- Small duct PSC[3]
- AMA negative PBC[4,5]
- MASLD with pruritus[6]*
- Lean MASLD without metabolic syndrome[6]*
- Lean MASH with pruritus and without metabolic syndrome[6]*

Secondary cholestasis triggered by liver issue

Consider reassessing if symptoms of cholestatic pruritus arise in patients who have recently experienced liver issues, including

- All women with history of ICP[3]
- Drug-induced cholestasis[3]
- Hormone-induced cholestasis triggered by birth control, menopause, etc[3,7]

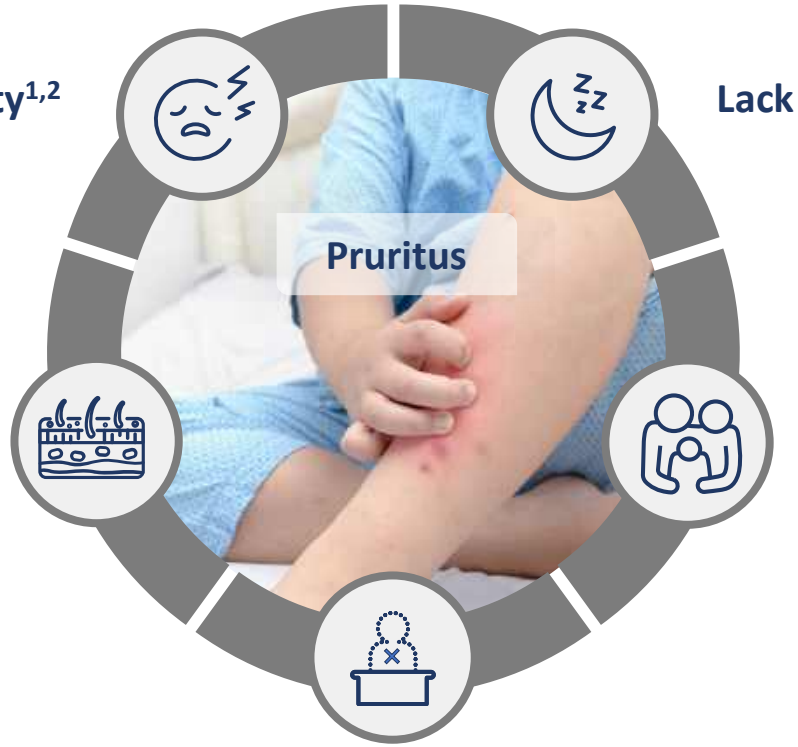
History of complicated gallstones

Consider reassessing if your patient has a complicated history of gallstones, including

- Intrahepatic gallstones[3]
- Very strong family history of gallstones and incident at a young age[8,9]
- LPAC leading to stones in the gallbladder or liver[10]

1. Vitale G et al. *J Gastroenterol*. 2018;53(8):945-958. **2.** Aamann L et al. *Scand J Gastroenterol*. 2018;53(3):305-311. **3.** Hilscher MB et al. *Mayo Clin Proc*. 2020;95(10):2263-2279. **4.** Chascsa DM et al. *Clin Liver Dis.* 2018;22(3):589-601. **5.** Zen Y et al. In: Burt AD et al, eds. *MacSween's Pathology of the Liver*. 7th ed. 2018:515-593. **6.** Boehlig A et al. *Biomedicines*. 2022;10(2):1-10. **7.** Zu Y et al. *Front Pharmacol.* 2021;12:761255.
8. Sarin SK et al. *Hepatology*. 1995;22(1):138-141. **9.** Hsing AW et al. *Int J Cancer*. 2007;121(4):832-838. **10.** Goubault P et al. *J Visc Surg*. 2019;156(4):319-328.

Pruritus in patients with PFIC can be debilitating and affect many aspects of life[1,2]



Even when liver function is satisfactory, the debilitating nature of cholestatic pruritus may necessitate transplant

1. Srivastava A. *J Clin Exp Hepatol*. 2014;4(1):25-36. **2.** Mehl A et al. *World J Transplant*. 2016;6(2):278-290

Historic Treatment Options for Pruritus Caused by Cholestatic Liver Diseases

Goals of Treatment[1,2]

- Provide relief from cholestatic pruritus
- Improve nutritional status and correct vitamin deficiencies
- Manage advanced disease complications to help delay liver transplant

Nutritional support, vitamin and fatty acid supplementation[1]

Symptomatic relief of PFIC, including[2-4]

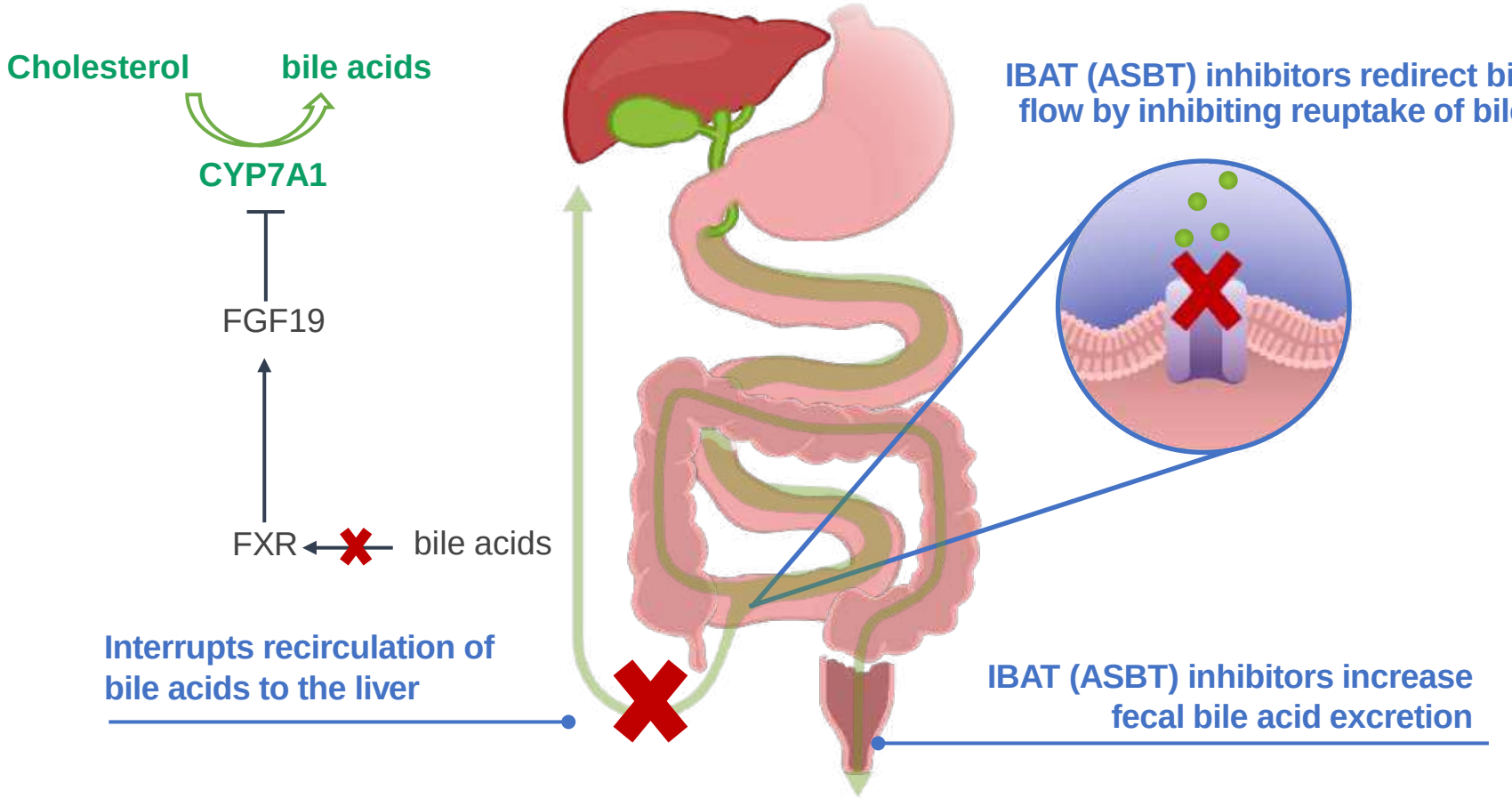
- Hydrophilic bile acids
- Antimycobacterials
- Antihistamines
- Opiate antagonists
- Bile acid sequestrants

Surgical therapy[2]

- Biliary diversion
- Liver transplantation

1. Srivastava A. *J Clin Exp Hepatol.* 2014;4(1):25-36. 2. Gunaydin M, Bozkurter Cil AT. *Hepat Med*. 2018;10:95-104.

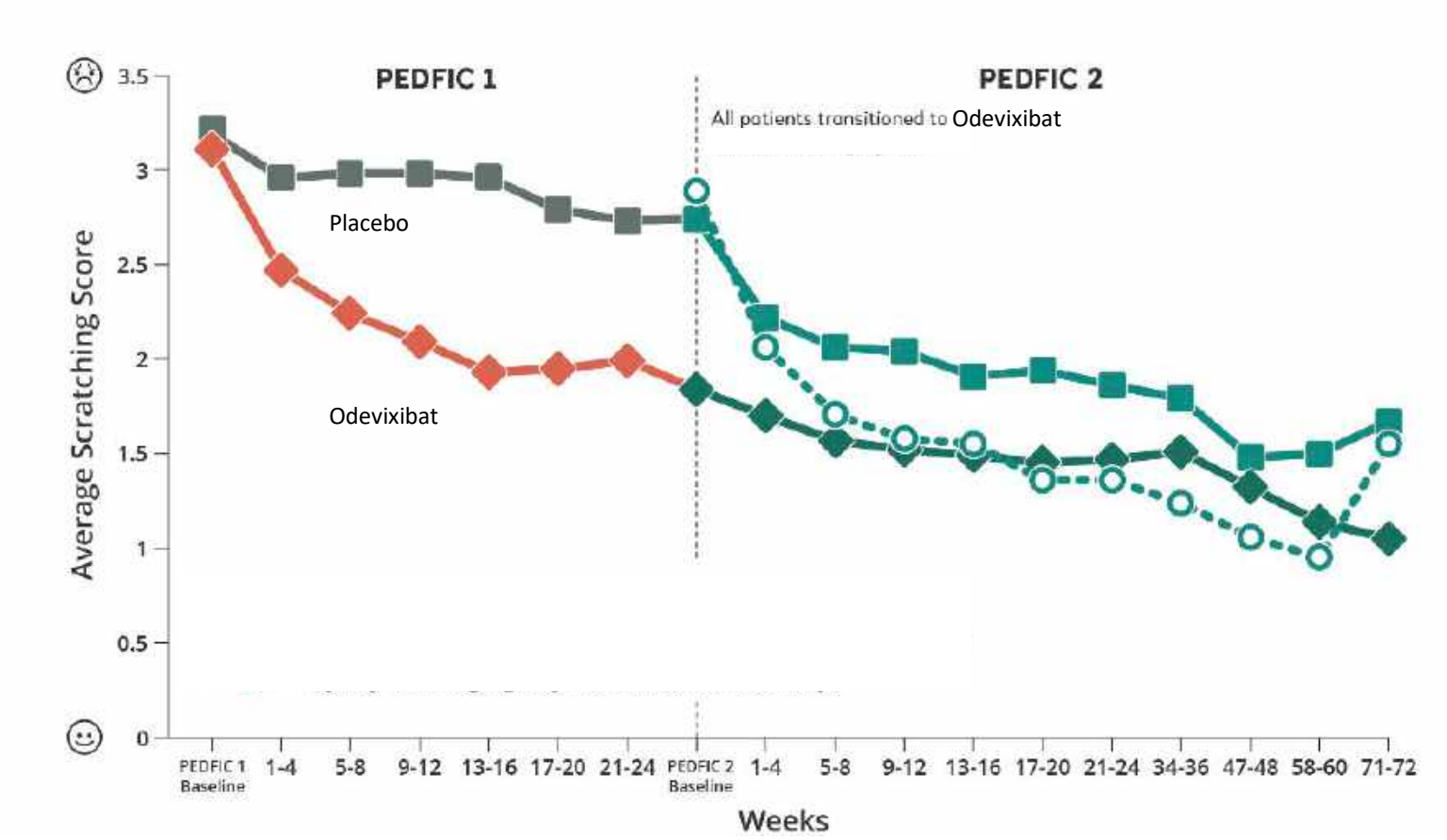
Novel Treatment Strategies – Pharmacologic Interruption of Enterohepatic Circulation



ASBT, apical sodium-dependent bile acid transporter; CYP7A1, cholesterol 7a-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor.

1. Keller B, et al. Poster 55 presented at the Falk Symposium 194. Oct 8–9, 2014. Freiburg, Germany;
2. Al-Dury S, et al. *Sci Rep.* 2018; **8**:6658; 3. Hegade VS, et al. *Lancet.* 2017; **389**:1114–23;
4. Mayo MJ, et al. *Hepatol Commun.* 2019; **3**:365–81; 5. Shneider BL, et al. *Hepatol Comms.* 2018; **2**:1184–98.

Change in Scratching Score with Odevixibat: PEDFIC 1 and PEDFIC 2 Trials



Thompson RJ et al. *Lancet Gastroenterol Hepatol*. 2022;7(9):830-842.

Take Home Messages

- The spectrum of PFIC in adults is wide and should be considered in any cases of unexplained liver disease.
- Have a low threshold to obtain Genetic testing/Cholestasis Panel is available for free to our patients.
- Novel therapeutic agents for cholestatic pruritus are now available and FDA-approved.
- @AlkhouriNaim 

Panel Discussion

Moderator: Anita Kohli, MD

Julio Gutierrez, MD

Raj Vuppalanchi, MD

Naim Alkhouri, MD, FAASLD, ABOM

Cholestasis Case Studies

Case Study # 1

HPI: 39 y.o. presented with elevated liver enzymes.

PE: Unremarkable

PMHx: update for pt

- 2009 dx ICP treated with Urso 300mg bid and delivery early
- Has continued on Urso since pregnancy with sx of itching and fatigue
- 2017 had liver bx- mild chronic hepatitis and mild fibrosis. No features suggestive of PBC or AIH observed. No granulomas.
- Viral/ autoimmune/ metabolic liver disease work up negative. MRI/MRCP was negative.

LABS:

Total bilirubin	**0.5**
ALT	**30**
AST	**18**
Alk Phos	**156**
GGT	**141**
Hb	**12.1**
WBC	**8.5**
Plts	**274**
Albumin	**4.7**

Fibroscan: CAP 178 kPa 6.1

Cholestatic Genetic Testing Results

SUMMARY OF RESULTS: **Heterozygous for Pathogenic Variants in *ABCB4* and *SERPINA1*; Heterozygous for a Variant of Uncertain Significance in *JAG1***

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
ABCB4, NM_000443.3	AD, AR, 171060	c.1768C>T, p.Arg590*, Heterozygous	Not listed in ClinVar	Not Present	Not Applicable	PATHOGENIC
SERPINA1, NM_000295.4	AR, 107400	c.1096G>A, p.Glu366Lys, Heterozygous	17967	1.8% European (Non-Finnish)	Damaging	PATHOGENIC
JAG1, NM_000214.2	AD, 601920	c.3257T>C, p.Val1086Ala, Heterozygous	Not listed in ClinVar	0.000885% European (Non-Finnish)	Conflicting	UNCERTAIN

Case study # 2

HPI: 34 y.o. F presented with elevated liver enzymes (ALT 33)

PE: Unremarkable

PMHx:

- Liver enyzmes elevated during pregnancy in 2016. Dx ICP. Was delivered 3 weeks early.
- Itching continued x 1 year after pregnancy and then only gets itching when she eats a lot of sugar.

Fibroscan CAP 329, kPa 4.9

LABS:

ALT	**25**
AST	**16**
ALK PHOS	**62**
GGT	**172**
Total bilirubin	**0.6**
Albumin	**4.9**
Hgb	**13**
WBC	**5.4**
Plts	**304**

Viral/ autoimmune/ metabolic liver disease work up negative

RAD: U/S – Normal. S/p cholecystectomy

Cholestatic Genetic Testing Results

SUMMARY OF RESULTS: **Indeterminate**

Sequence Variant(s):

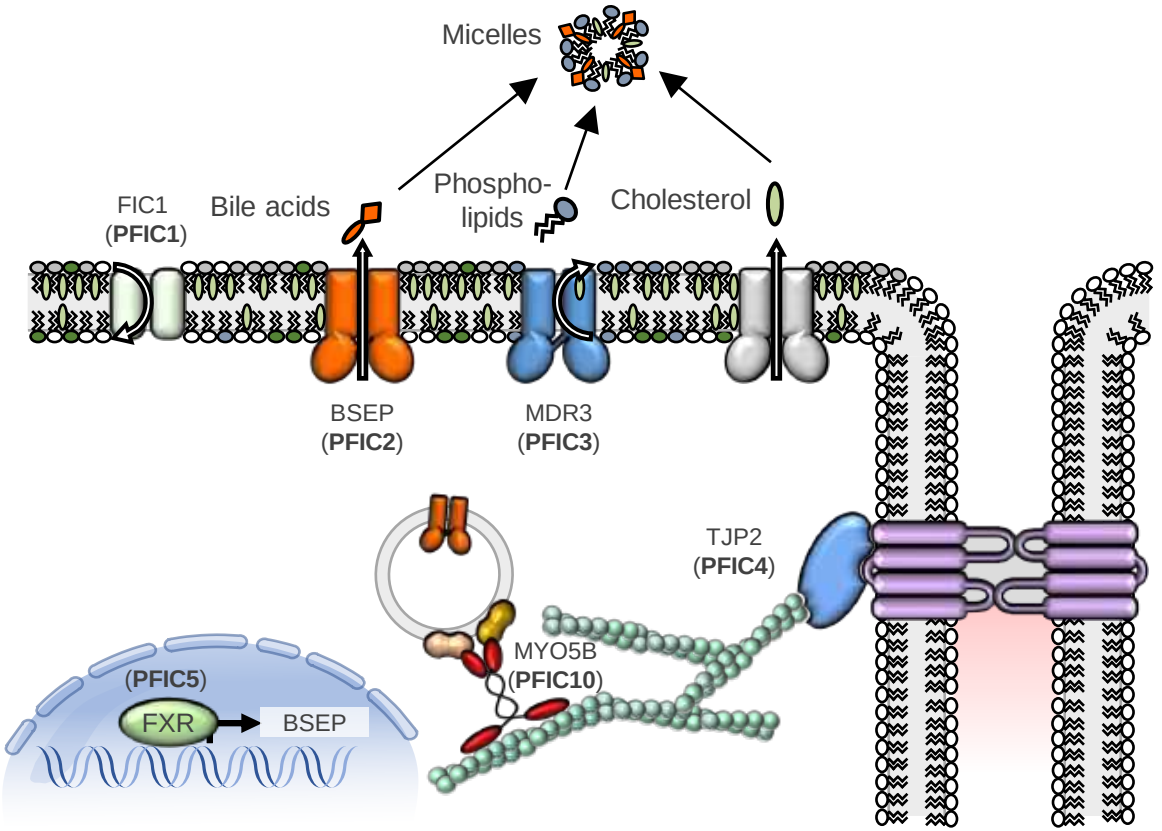
Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
MYO5B, NM_001080467.2	AR, 606540	c.115C>T, p.Gln39*, Heterozygous	Not listed in ClinVar	0.0100% Ashkenazi Jewish	Not Applicable	LIKELY PATHOGENIC
MYO5B, NM_001080467.2	AR, 606540	c.1392G>T, p.Gln464His, Heterozygous	Not listed in ClinVar	0.0029% Latino	Damaging	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599).

PFIC type is determined by genetic changes related to the hepatocellular transport system

There are several types of PFIC, each characterized by proteins with diverse functions[1]

- **The most common types of PFIC** are **PFIC 1** (FIC1), **PFIC 2** (BSEP), and **PFIC 3** (MDR3)[1]
  - **PFIC 1** is detected in ~10% to ~38% of patients
  - **PFIC 2** is detected in ~38% to ~91% of patients
  - **PFIC 3** is detected in ~28% to ~38% of patients
- Additional PFIC types include PFIC 4 (TJP2), PFIC 5 (FXR), and PFIC 10* (MYO5B)[2-4]
- Potential mutations in other genetic loci have also recently been identified[5,6]



Adapted with permission from Verena Keitel-Anselmino (Marburg University Clinic) and Jan Stindt (Düsseldorf University Clinic)

1. Baker A et al. *Clin Res Hepatol Gastroenterol*. 2019;43(1):20-36. **2.** Bull LN, Thompson RJ. *Clin Liv Dis*. 2018;22(4):657-669. **3.** Goldberg A, Mack CL. *Clin Liver Dis (Hoboken).* 2020;15:105-109. **4.** OMIM.org. 2023. Accessed January 17, 2023. **5.** Maddirevula S et al. *Genet Med*. 2019;21(5):1164-1172. **6.** Wu S-H et al. *Hepatology*. 2019;70(6):2221-2224.

Summary of affected proteins and genes in select PFIC types*

PFIC Type	Affected Protein/Gene	Description
PFIC 1	FIC1 (*ATP8B1)*	An altered cell membrane structure may impair activity of proteins such as BSEP, possibly leading to the retention of bile acids in the liver[1,2]
PFIC 2	BSEP (*ABCB11*)	Bile acids accumulate in hepatocytes, leading to hepatocellular damage and cholesterol may crystallize into stones, obstructing small bile ducts and damaging liver structures[1-4]
PFIC 3	MDR3 (*ABCB4)*	Micelle formation is impaired, and excess unsequestered bile acids can damage cholangiocytes, increasing risk of cholesterol stones[1,5]
PFIC 4	TJP2 (*TJP2*)	Compromised cellular junctions may allow the spillover of bile acids, damaging hepatocytes and cholangiocytes[4]
PFIC 5	FXR (*NR1H4*)	Key transporters encoded by *ABCB11* and *ABCB4* are not produced, leading to the intracellular accumulation of bile acids[6]
PFIC 10	MYO5B (*MYO5B*)	A possible decreased targeting of BSEP and other proteins to the membrane leads to reduced export and retention of bile acids in hepatocytes[1]

Numerous causative mutations have also been identified in PFIC genes, for example dozens of mutations in *ATP8B1* in PFIC 1 patients and >200 in *ABCB11* in PFIC 2[7]

1. Bull LN, Thompson RJ. *Clin Liv Dis*. 2018;22(4):657-669. **2.** Vitale G et al. *Dig Liver Dis*. 2019;51(7):922-933. **3.** Goldberg A, Mack CL. *Clin Liver Dis (Hoboken).* 2020;15(3):105-109. **4.** Amirneni S et al. *World J Gastroenterol*. 2020;26(47):7470-7484. **5.** Srivastava A. *J Clin Exp Hepatol.* 2014;4(1):25-36. **6.** Bosma et al. *Int J Mol Sci*. 2021;22(1):1-13. **7.** Henkel SAF et al. *World J Hepatol*. 2019;11(5):412-488.

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Break & Exhibits

3:40 PM – 3:55 PM

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CME University

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- Form is in your Folder
- Virtual Attendance – link will be sent to you via email

Cirrhosis & Portal HTN Update: From HRS to HCC

Jacqueline G. O'Leary, MD MPH
Chief of Hepatology, Dallas VA Medical Center
Professor of Medicine, UTSW

Outline

- AKI in Cirrhosis
- Treatment of HRS-AKI
- Preventing Decompensation
  - NSBB
  - Statin therapy
- HCC

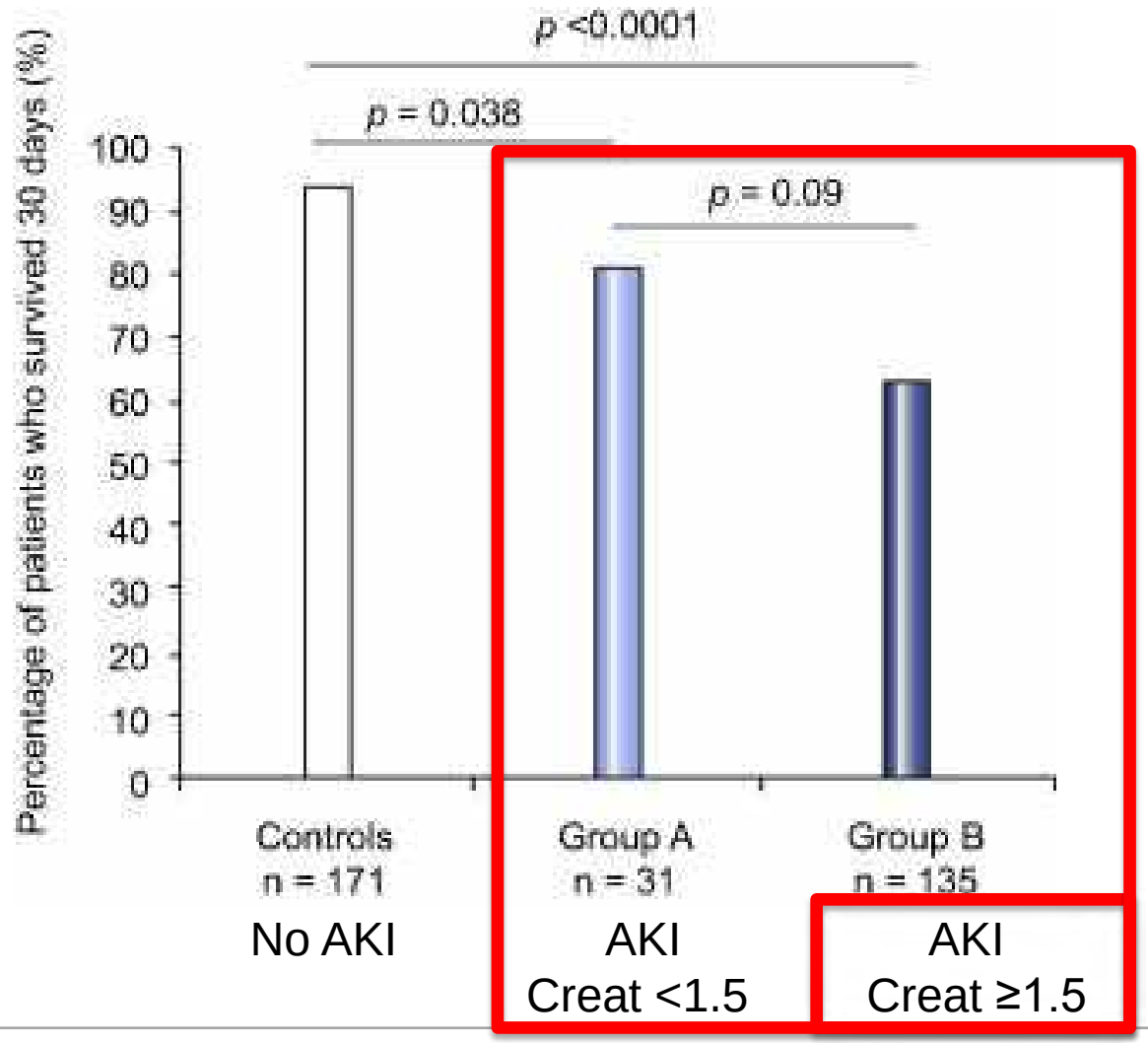
Diagnosis

- International Ascites Club

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or, • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	• **Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline • **Stage 2**: increase in sCr >2-fold to 3-fold from baseline • **Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy		
Progression of AKI	**Progression** Progression of AKI to a higher stage and/or need for RRT	**Regression** Regression of AKI to a lower stage	
Response to treatment	**No response** No regression of AKI	**Partial response** Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value	**Full response** Return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value

Angeli P, et al. J Hepatology 2015

AKI Impacts Survival Regardless of Peak Serum Creatinine



Wong F, et al. Journal of Hepatology 2015

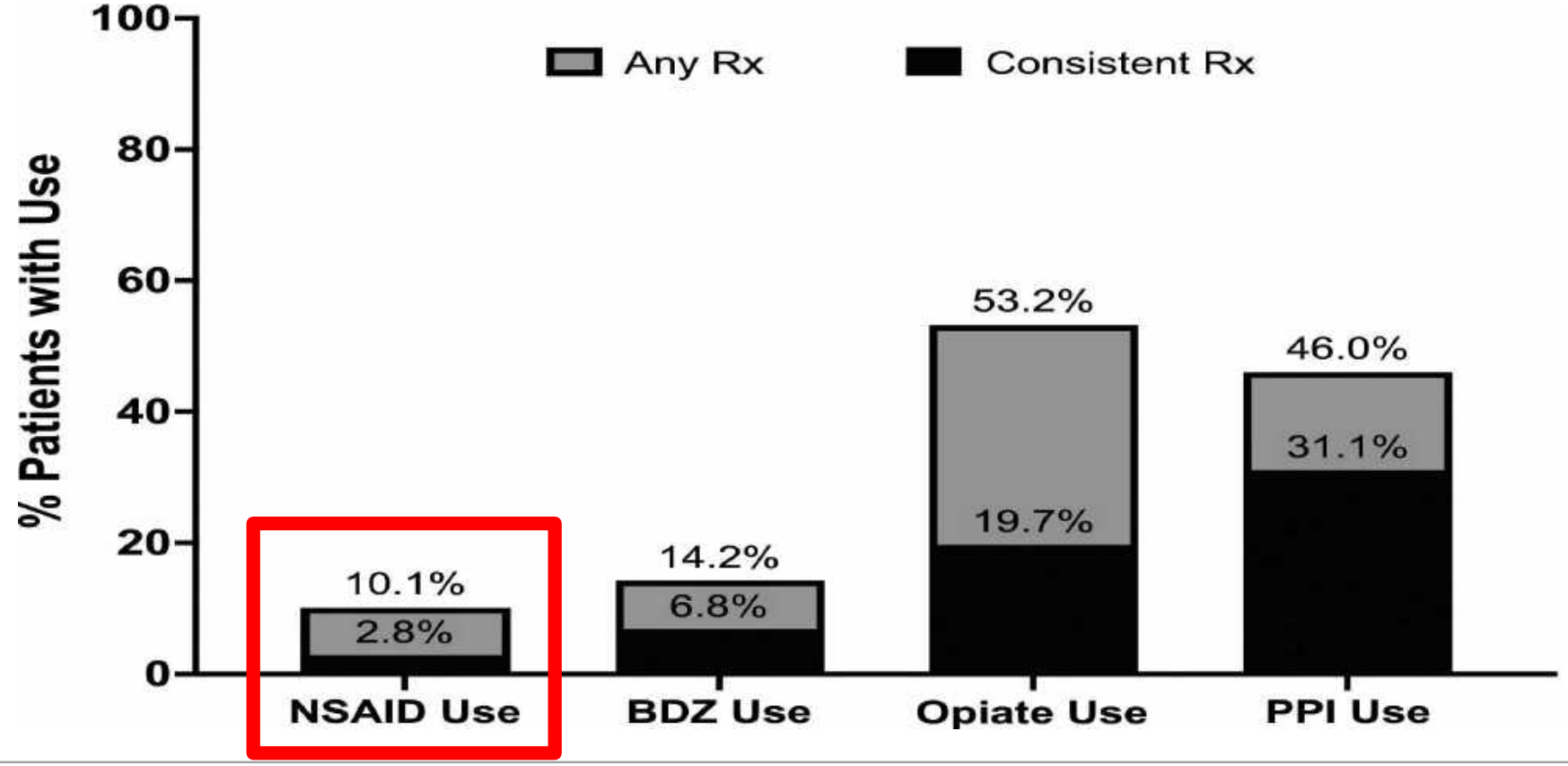
Prevention of AKI is Critical

- Infection prevention is critical
  - Secondary SBP prophylaxis
  - GI bleeding antibiotic prophylaxis
  - D/C PPI in cirrhotic patients when possible
  - Only use Foley catheters for approved indications
- Expeditious antibiotic therapy in patients w/ suspected infections.
  - For every hour delay there is an increased risk of death.
- Use of IV albumin
  - SBP
  - Prevent post-paracentesis circulatory dysfunction
    - >5L in all patients
    - All LVPs in ACLF patients
  - AKI…

Kumar A, et al. Crit Care Med 2006. Guevara M, et al. J Hepatology 2012

Risk Factors – Easy to Remove

- Retrospective review of outpatient pharmacy claims -- managed care organization
- Included 12,621 pts with decompensated cirrhosis



Thompson M, et al. Hepatology 2020

UT Southwestern Medical Center

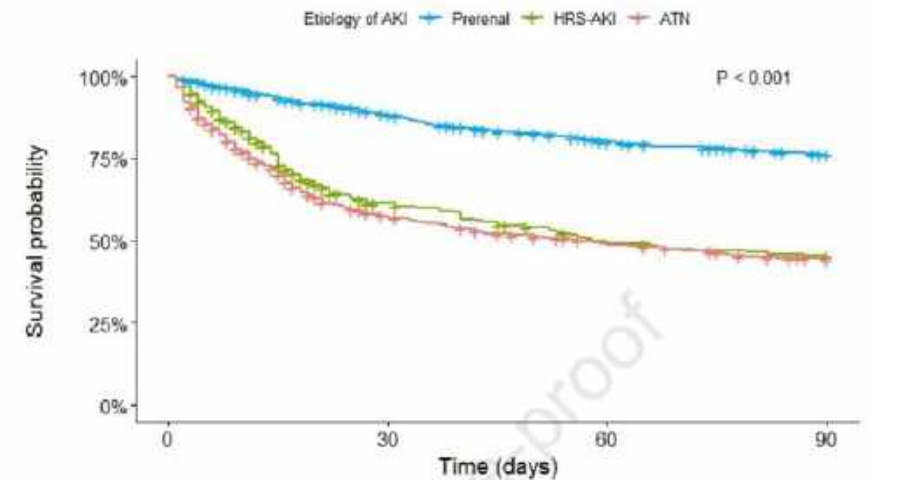
Differential Diagnosis

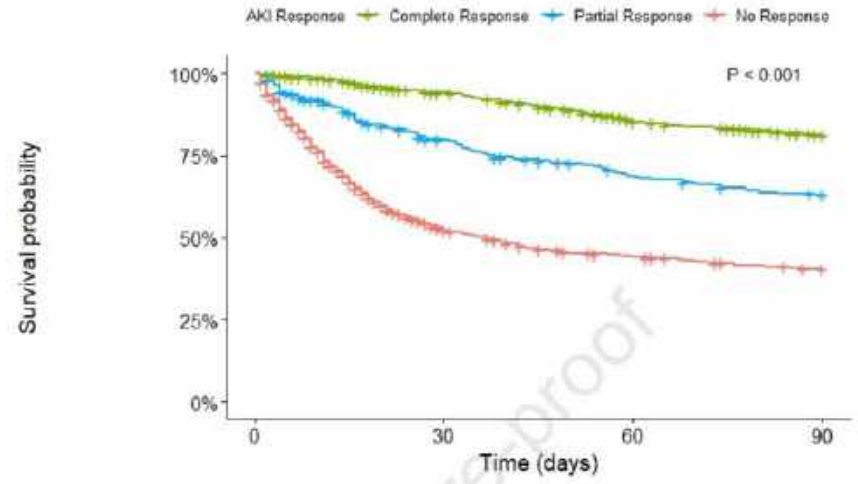
- Post-renal (not this talk)
- Structural Renal Disease (not this talk)
  - Don’t forget - IgA nephropathy in ETOH liver disease..
- Medication induced:
  - NSAIDS, contrast, some antibiotics
- Functional Renal Disease
  - Pre-renal (low Urine Na, normal UA)
    - Hypovolemia
    - HRS-AKI
  - ATN (high Urine Na, casts on UA)

AKI Etiology & Mortality

- 90-day mortality based on etiology of AKI

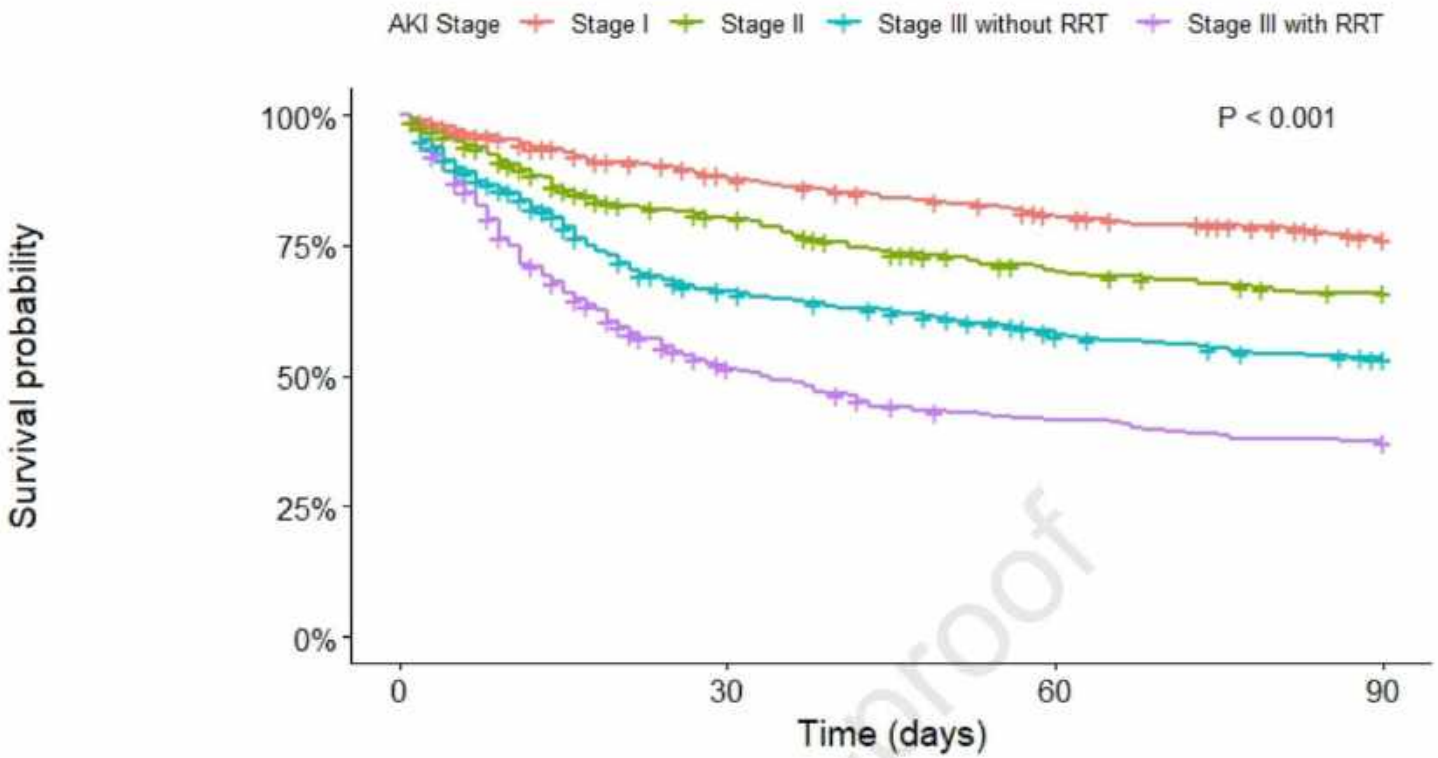
Etiology, Stage & Response Matter





Number of participants entering intervals

Complete Response	863	753	666	608
Partial Response	300	219	180	162
No Response	883	415	336	299



Number of participants entering intervals

Stage I	700	564	504	456
Stage II	471	344	289	267
Stage III without RRT	501	302	252	223
Stage III with RRT	374	177	137	123

Pre-proof

Patidar KR, et. al. J Hepatology 2023

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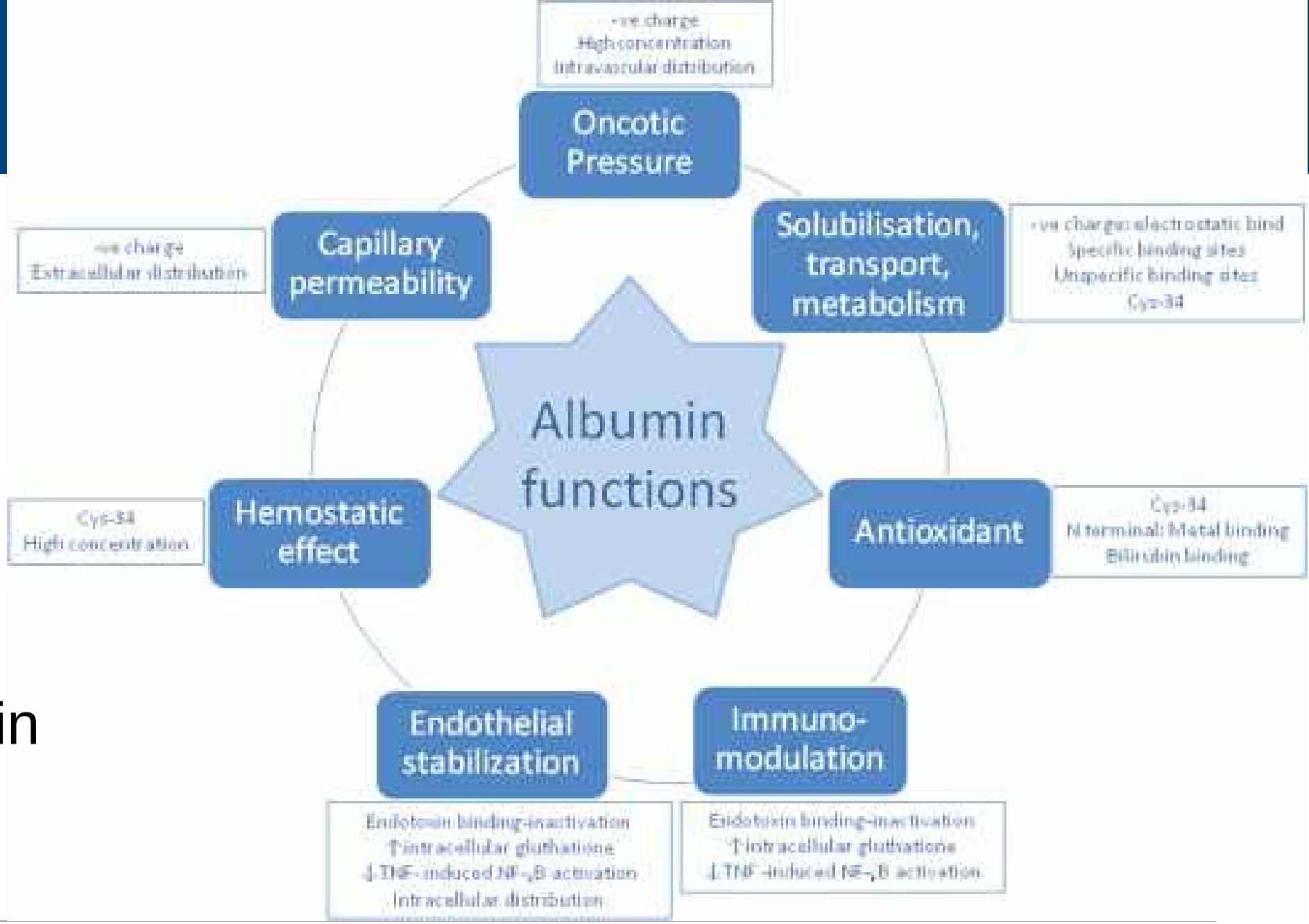
Albumin

- Albumin is a drug

Serum albumin concentration

≠

Effective albumin concentration



Garcia-Martinez R, et al. Hepatology 2013

Diagnosis HRS-AKI

TABLE 11. Diagnosis of HRS-AKI

Diagnosis of HRS-AKI*
Cirrhosis with ascites
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

Biggins SW, et al. Hepatology 2021

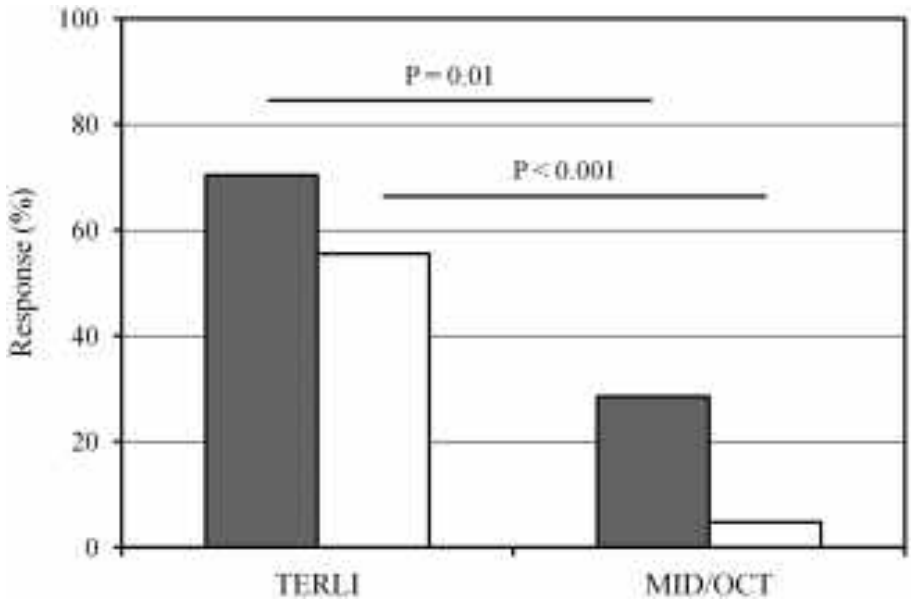
Treatment HRS-AKI

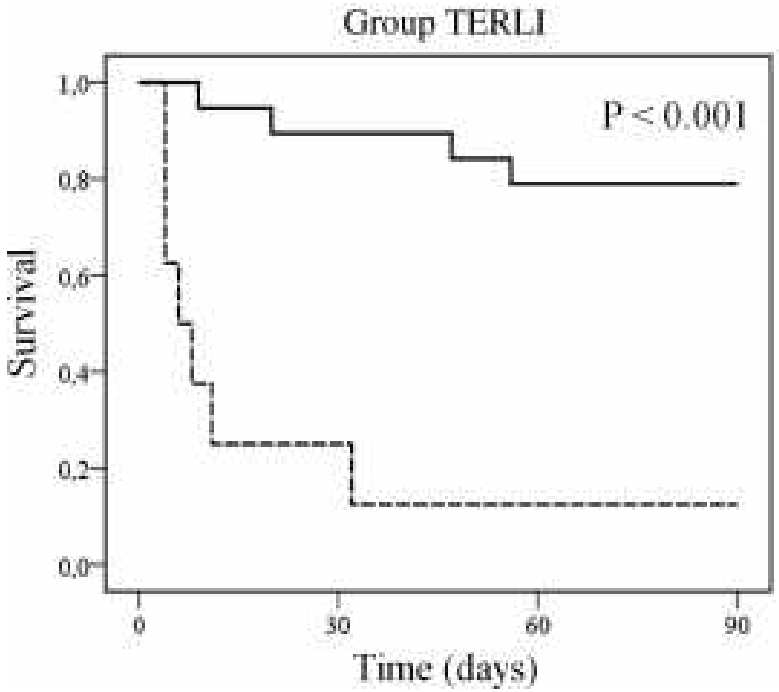
- **Transplant**
- **TIPS**
- **Norepinephrine (MAP ≥10 mmHg) + IV albumin**
- **Terlipressin +/- Albumin**

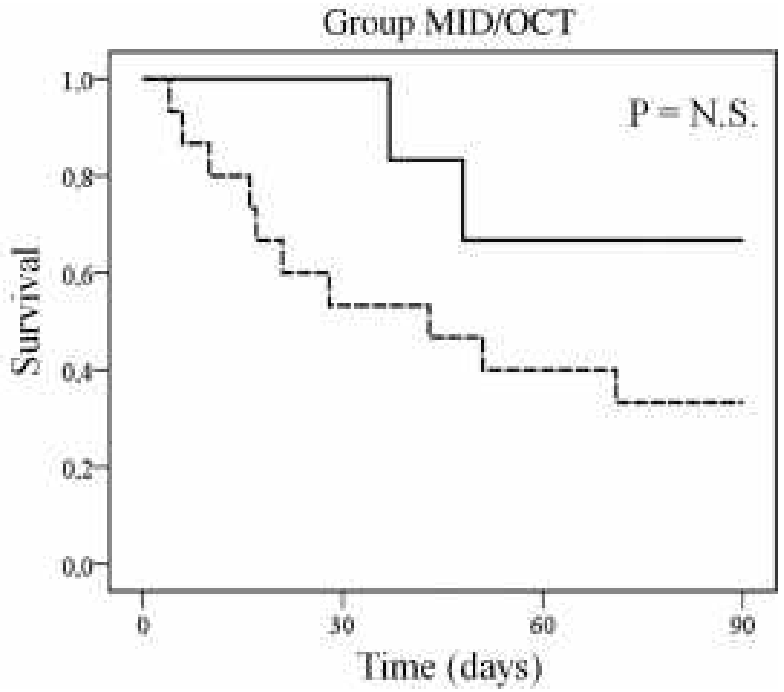
Terlipressin

- Mechanism = vasopressin analog
  - Relatively selective for V1
  - Relative specificity for splanchnic circulation – reduces splanchnic vasodilation
    - Reduces portal pressure
  - Increased peripheral vasoconstriction
- Improves renal perfusion

Treatment HRS-AKI







Complete or partial response

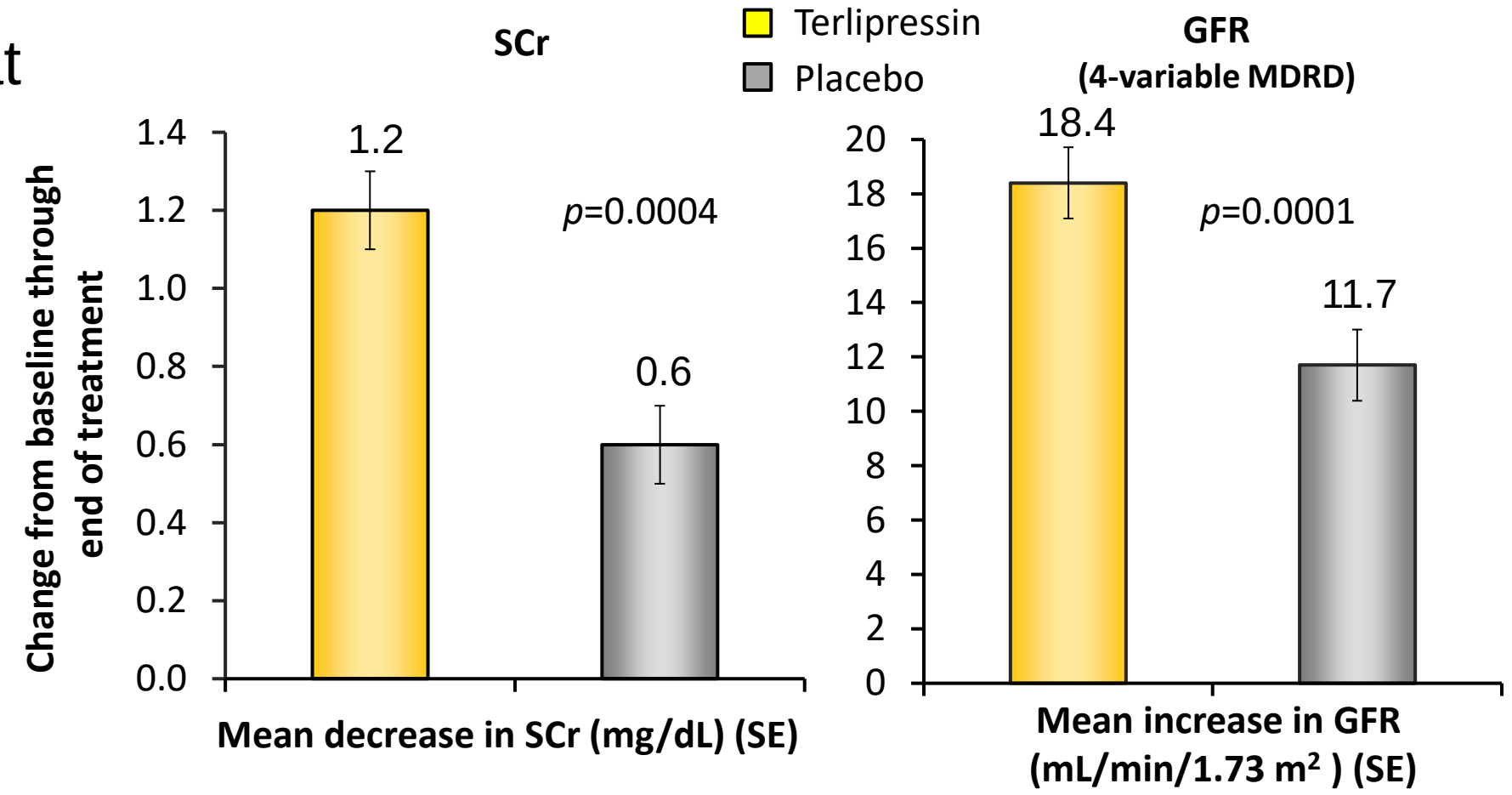
Complete response

Rossle M & Gerbes AL. Gut 2010

UT Southwestern Medical Center

Terlipressin

- REVERSE Trial
- Terlipressin to treat HRS-AKI



Boyer TD, et al. Gastroenterology 2016

Terlipressin

- CONFIRM Trail
- Terlipressin to treat HRS-AKI

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
Secondary end points included in multiplicity adjustment			
HRS reversal§			<0.001
Clinical success	78/199 (39)	18/101 (18)	
Clinical failure	105/199 (53)	79/101 (78)	
Competing event‡			
Liver transplantation	11/199 (6)	4/101 (4)	
Death	5/199 (3)	0/101	
HRS reversal with no renal-replacement therapy through 30 days			0.001
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
Competing event‡			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	

Wong F, et al. NEJM 2021

Terlipressin

- CONFIRM Trail

- **Terlipressin is contraindicated**
- ACLF-3
- Respiratory compromise
- Creatinine >5.0 mg/dL

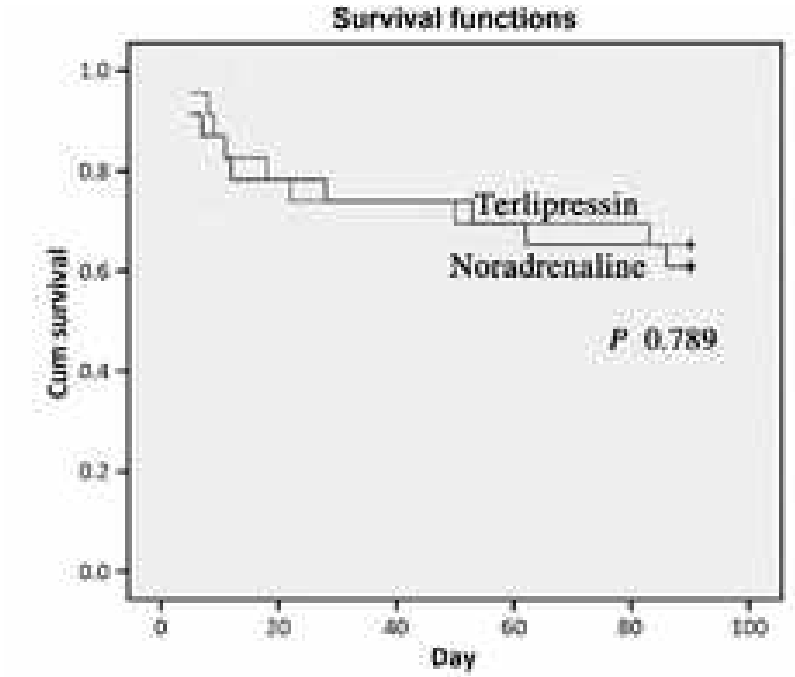
Table 4. Adverse Events in the Safety Population.*

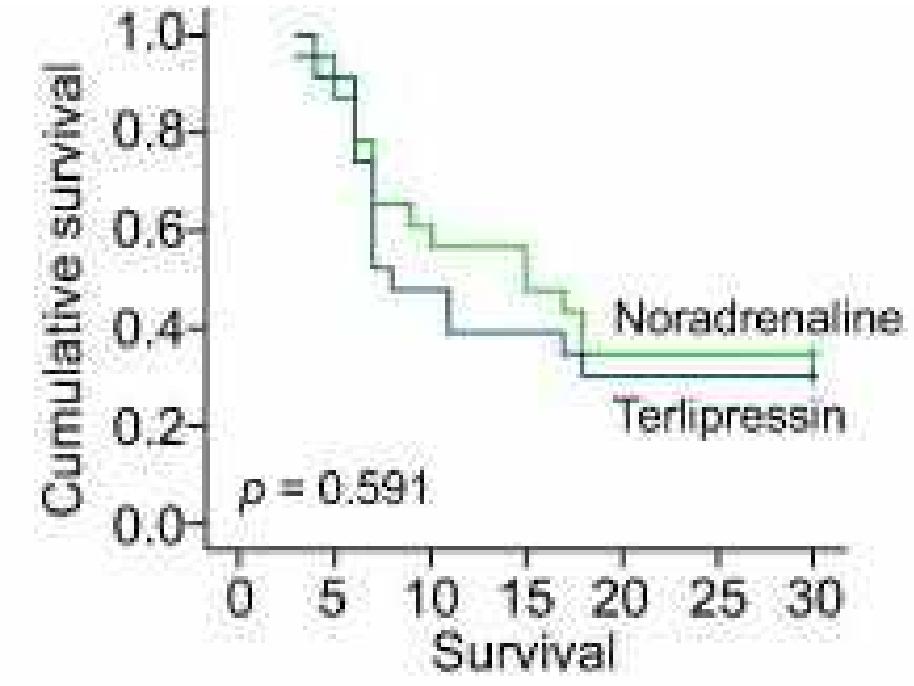
Event	Terlipressin (N=200)	Placebo (N=99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)

Wong F, et al. NEJM 2021

Terlipressin vs. Norepinephrine

When terlipressin is contraindicated:



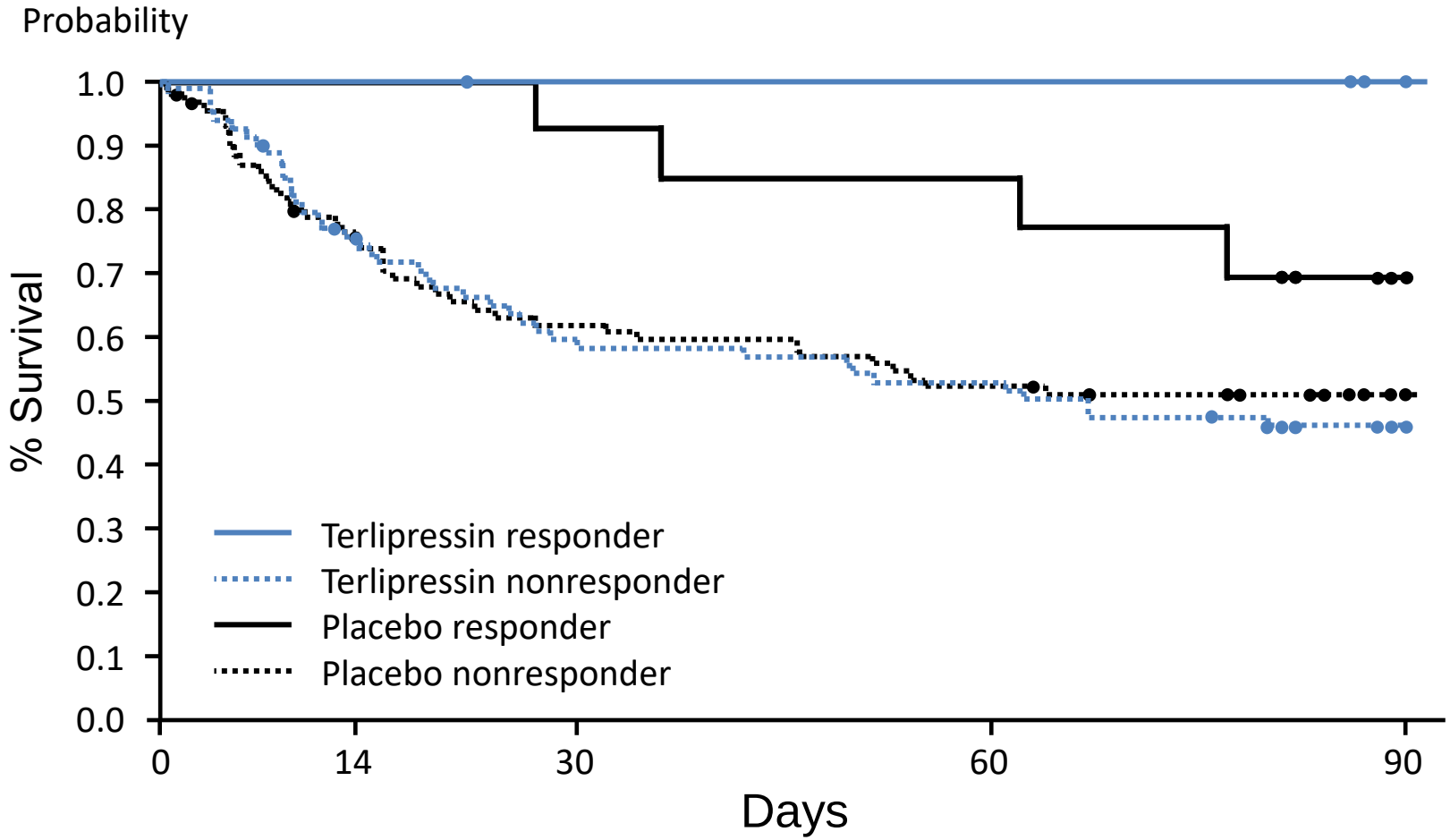


Norepinephrine use – inferior data

Requires: central line & ICU monitoring

Singh V, et al. J Hepatology 2012. Ghosh S, et al. Liver International 2013

Survival is Based on Response

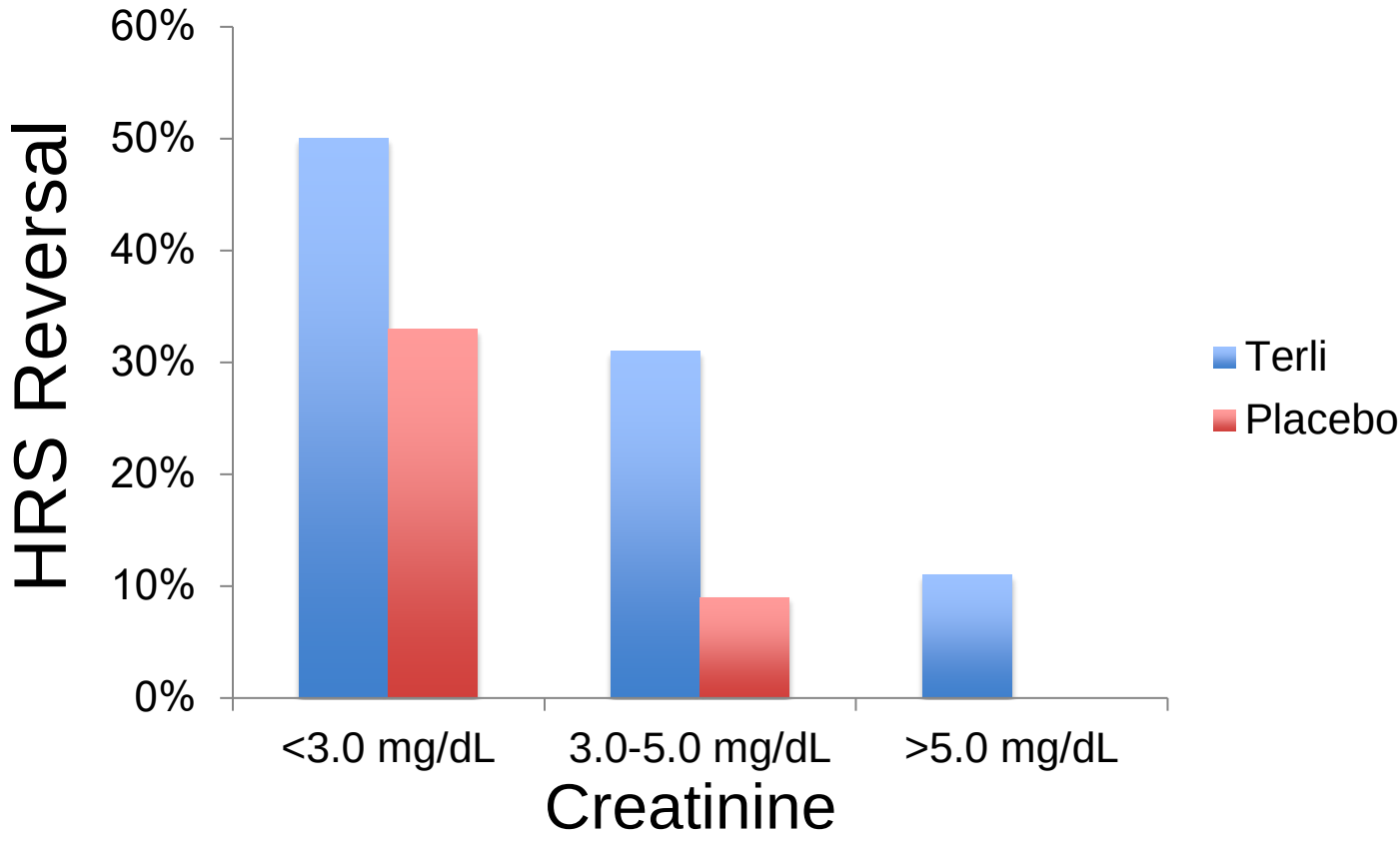


ITT population stratified by qualifying SCr and alcoholic hepatitis.

Boyer TD, et al. Gastroenterology 2016

Predictors of Response

- Predictors of response
  - Starting Creatinine
  - Rise in MAP ≥ 5 on day 3
  - Bilirubin <10 mg/dL
- Start Early



Boyer TD, et al. J Hepatology 2011. Nazar A, et al. Hepatology 2010

Guideline Statements

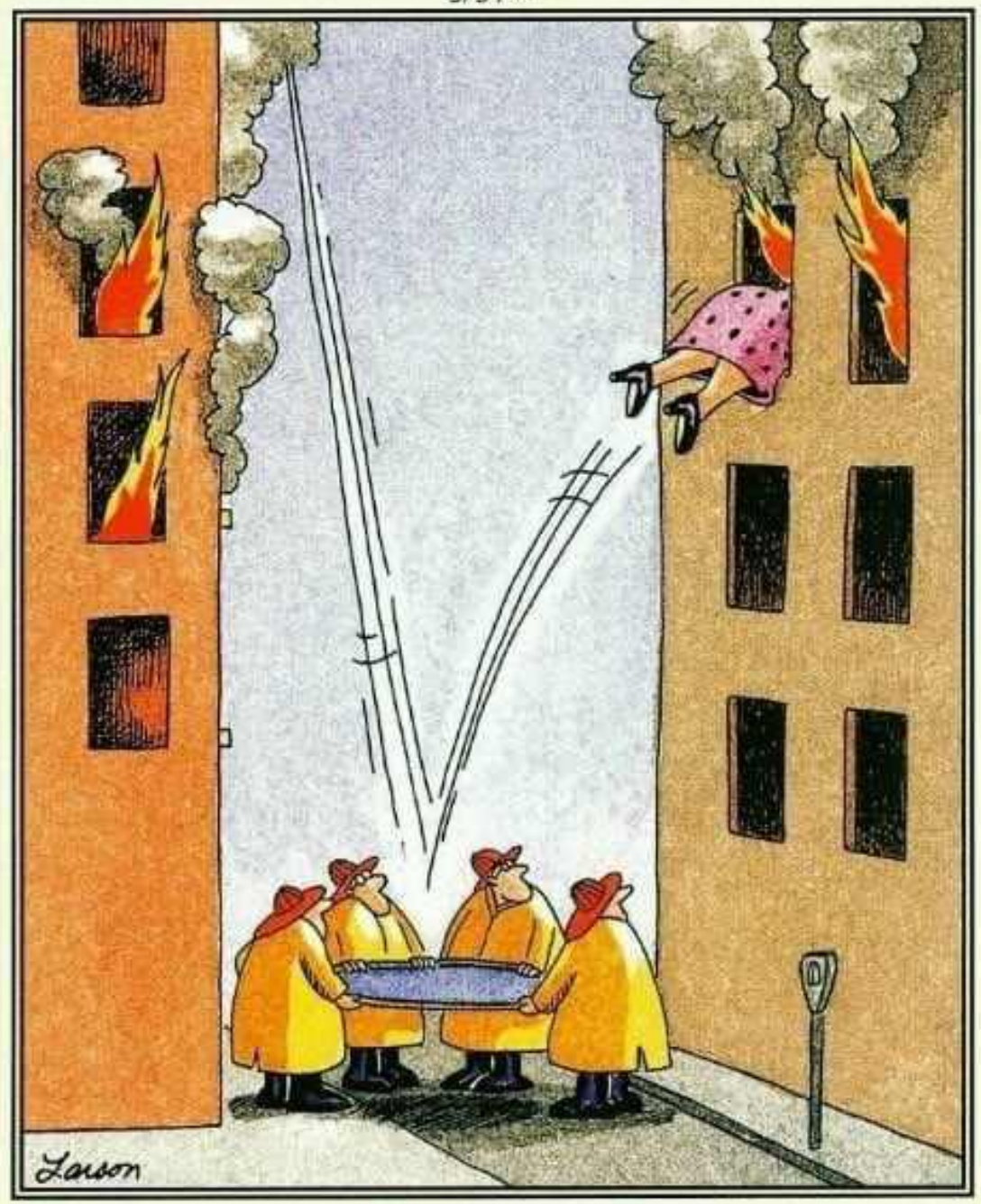
Guidance Statement

- The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin. The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.

4. In hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or disease, we suggest terlipressin (moderate quality, conditional recommendation) or norepinephrine (low quality, conditional recommendation) to improve renal function.

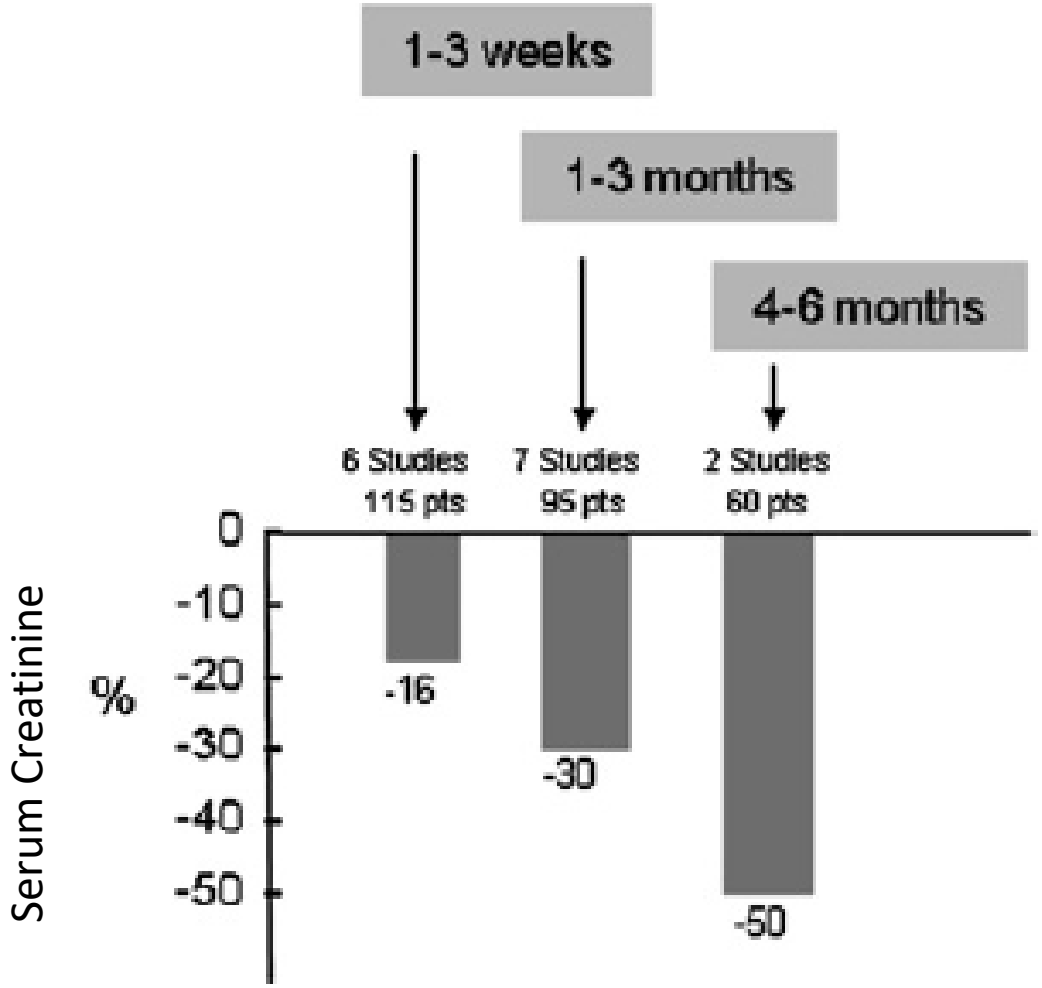
Biggins SW, et al. Hepatology 2021. Bajaj JS, O'Leary JG, et al. AJG 2022

3/31/81



TIPS HRS-AKI

- TIPS has been studied but has limited application because MELD predicts death.
  - Patients with HRS tend to have high MELD
- TIPS can be considered:
  - After HRS reversal
  - In patients with low bilirubin



Rossle M & Gerbes AL. Gut 2010

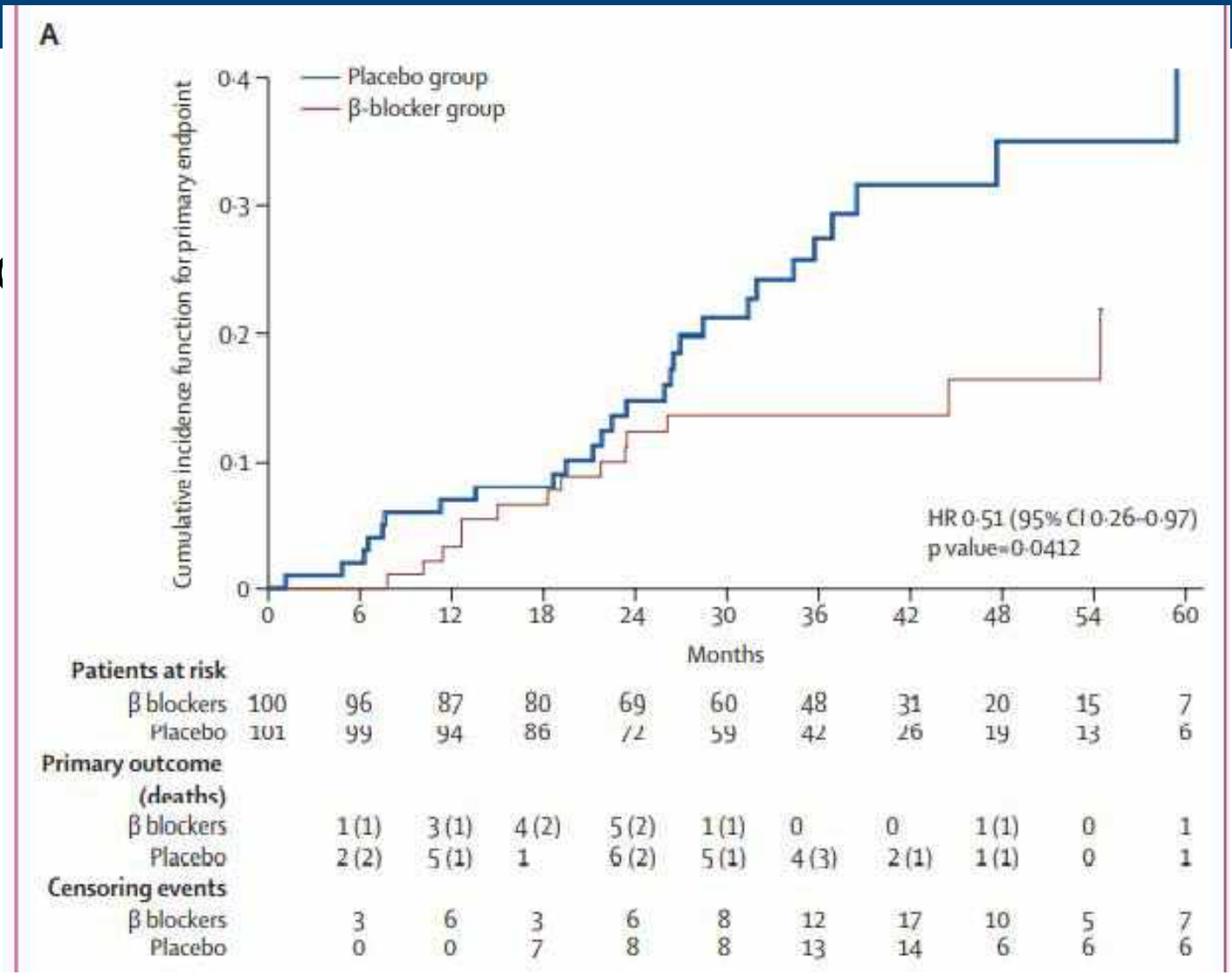
AKI Conclusions

- **Renal dysfunction terminology has changed.**
  - Facilitate easier diagnosis
  - Earlier treatment
- **Small changes (≥0.3 mg/dL) in baseline creatinine affect mortality & long-term renal function.**
- **Treatment options for HRS-AKI include:**
  - Terlipressin + albumin
  - Norepinephrine
- **Prevention is the best option.**

"I'll have an ounce of prevention."

NSBBs Prevent Decompensation

- 201 patents:
  - Compensated CTP-A cirrhosis
  - Grade 0-1 varices on screening E
  - Portal hypertension by HVPG
- Patients were randomized:
  - Propranolol (if >10% decrease)
  - Carvedilol
- Primary endpoint: **Risk for decompensation**



Villanueva C, et al. Lancet 2019

Which NSBB?

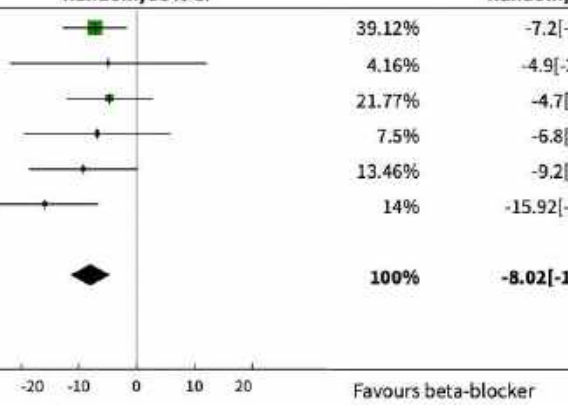
- Meta-analysis of 4 trials of carvedilol vs placebo:
  - Risk of decompensation sHR = 0.51
  - Risk of death sHR = 0.42
- Meta-analysis of 6 trials of carvedilol vs. other NBB

Analysis 1.15. Comparison 1 Carvedilol versus non-selective beta-blockers, Outcome 15 Reduction in hepatic venous pressure gradient (%) (overall).

Study or subgroup	Carvedilol N	Carvedilol Mean(SD)	Traditional, beta-blocker N	Traditional, beta-blocker Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bañares 2002	24	-19.2 (9.8)	22	-12 (9.4)		39.12%	-7.2[-12.74,-1.66]
De 2002	17	-28.2 (29.1)	16	-23.3 (20.2)		4.16%	-4.9[-21.91,12.11]
Gupta 2016	29	-27.1 (15.2)	28	-22.4 (13.4)		21.77%	-4.7[-12.13,2.73]
Hobolth 2012	14	-19.3 (16.1)	12	-12.5 (16.7)		7.5%	-6.8[-19.47,5.87]
Kim 2016	55	-20.3 (21.6)	55	-11.1 (28.5)		13.46%	-9.2[-18.65,0.25]
Mo 2014	48	-28.3 (22.2)	48	-12.4 (24.1)		14%	-15.92[-25.19,-6.65]
Total ***	**187**		**181**			**100%**	**-8.02[-11.49,-4.55]**

Heterogeneity: $Tau^2=0$; $Chi^2=3.87$, df=5(P=0.57); $I^2=0\%$

Test for overall effect: Z=4.53(P<0.0001)



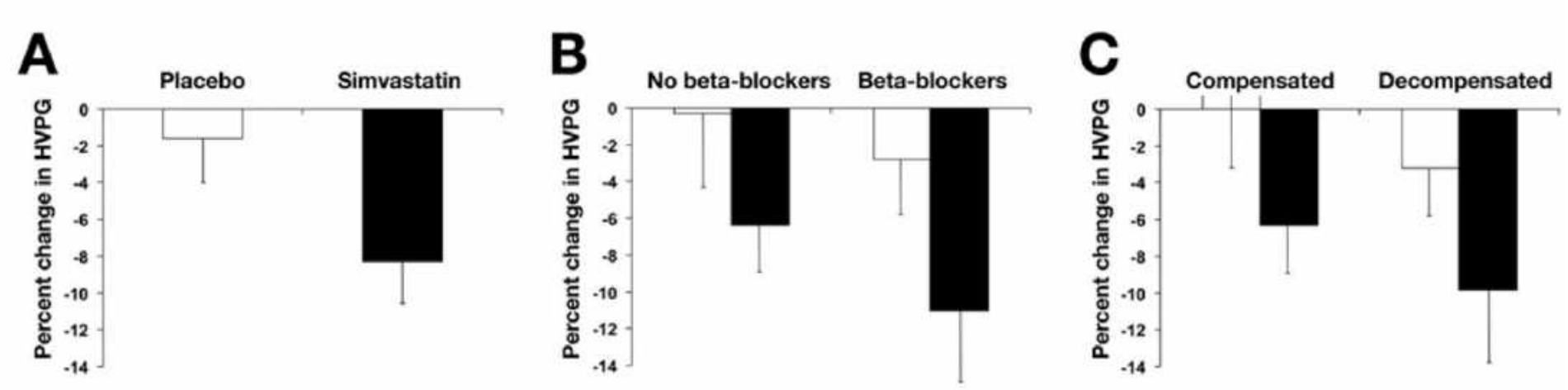
Carvedilol is preferred in compensated cirrhosis.

Villanueva C, et al. J Hep 2022

Zacharias AP, et al. Cochrane Database of Systematic Reviews 2018

What Else Lowers Portal Pressures?

- Simvastatin lowers portal pressure
  - Additive to NSBB
  - Compensated & decompensated patients



P=0.04 **P=0.03** **P=0.04**

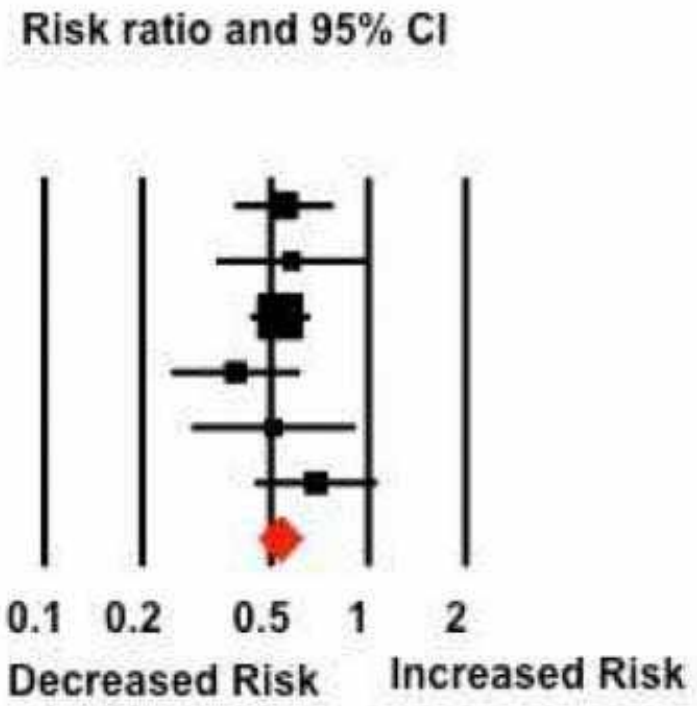
Abraldes JG, et. al. Gastroenterology 2009

Statin Use ↓ Risk of Decomp

- Meta-analysis shows reduced risk of decompensation:

Statin Exposure and Risk of Decompensation of Cirrhosis

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Mohanty 2015 - HCV	0.55	0.39	0.78	0.00
Kumar 2014 - Mixed	0.58	0.34	0.98	0.04
Huang 2016 - HBV	0.53	0.43	0.66	0.00
Chang 2017 - HBV	0.39	0.25	0.61	0.00
Chang 2017 - HCV	0.51	0.28	0.91	0.02
Chang 2017 - EtOH	0.69	0.45	1.06	0.09
	0.54	0.46	0.62	0.00



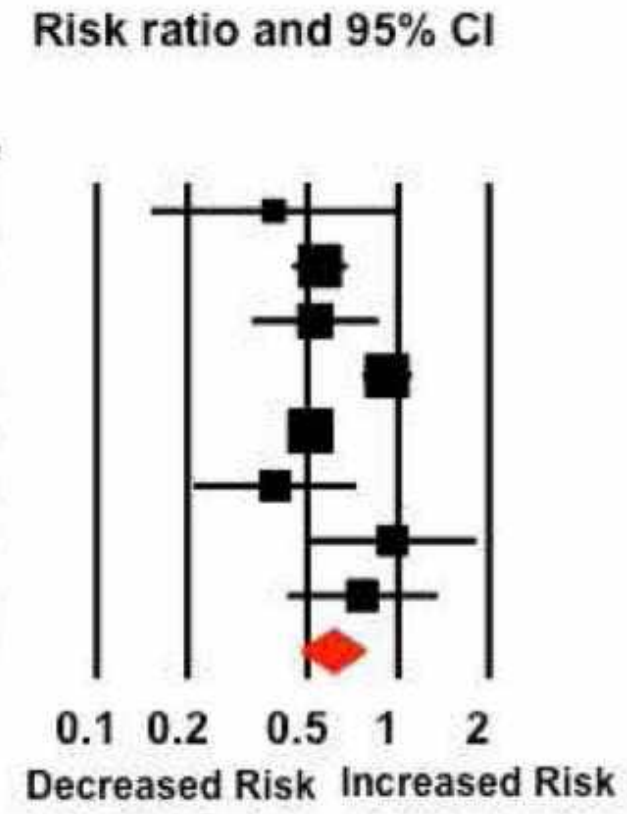
Kim RG, et al. Clinical Gastro & Hep 2017

Statin Use ↓ Mortality

- **Meta-analysis shows reduced risk of mortality:**

Statin Exposure and Risk of All-Cause Mortality

Study name	Risk ratio	Lower limit	Upper limit	p-Value
Abraldes 2016 - Mixed	0.39	0.15	0.99	0.05
Mohanty 2015 - HCV	0.55	0.45	0.68	0.00
Kumar 2014 - Mixed	0.53	0.33	0.86	0.01
Hsiang 2015 - HBV	0.92	0.76	1.11	0.39
Bang 2016 - EtOH	0.51	0.44	0.59	0.00
Chang 2017 - HBV	0.39	0.21	0.72	0.00
Chang 2017 - HCV	0.96	0.51	1.80	0.90
Chang 2017 - EtOH	0.76	0.43	1.35	0.35
	0.61	**0.48**	**0.78**	**0.00**



- HR = 0.24 for PVT
  - 2785 pts – matched

De Franchis R, et al. J of Hepatology 2021
Amjad M, Clinical Gastro & Hep 2024 ePub

Statin Use & Risk for HCC

- **Meta-analysis of lipophilic statins shows reduced risk of HCC:**

	No. of studies	Sample size	HR	95% confidence interval	*p* value	I^2 (%)	*p* value for Cochran Q test of heterogeneity	Subgroup difference
Statins								
Overall	10	1,774,476	0.52	0.37–0.72	**<0.01***	97.80	<0.01	
Cirrhosis	3	21,584	0.95	0.91–0.99	**0.04***	90.20	<0.01	
Hepatitis B	5	152,716	0.53	0.32–0.88	**0.01***	96.70	<0.01	
Hepatitis C	3	16,058	0.79	0.64–0.99	**0.04***	81.70	<0.01	
NAFLD	2	242,751	0.68	0.59–0.77	**<0.01***	90.80	<0.01	
Accounted for competing risk of death without HCC	5	980,486	0.51	0.32–0.81	**<0.01***	97.50	<0.01	
Statin type								
Lipophilic	3	1,083,952	0.46	0.37–0.57	**<0.01**	64.00	0.06	0.93
Hydrophilic	3	1,083,952	0.48	0.18–1.27	0.14	99.10	<0.01	
Accounted for concurrent use of aspirin, NSAIDs and metformin								
Yes	9	1,534,926	0.52	0.37–0.75	**<0.01***	98.10	<0.01	

Zeng RW, et al. Alimentary Pharmacology & Therapeutics 2023

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PRACTICE GUIDANCE

AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma

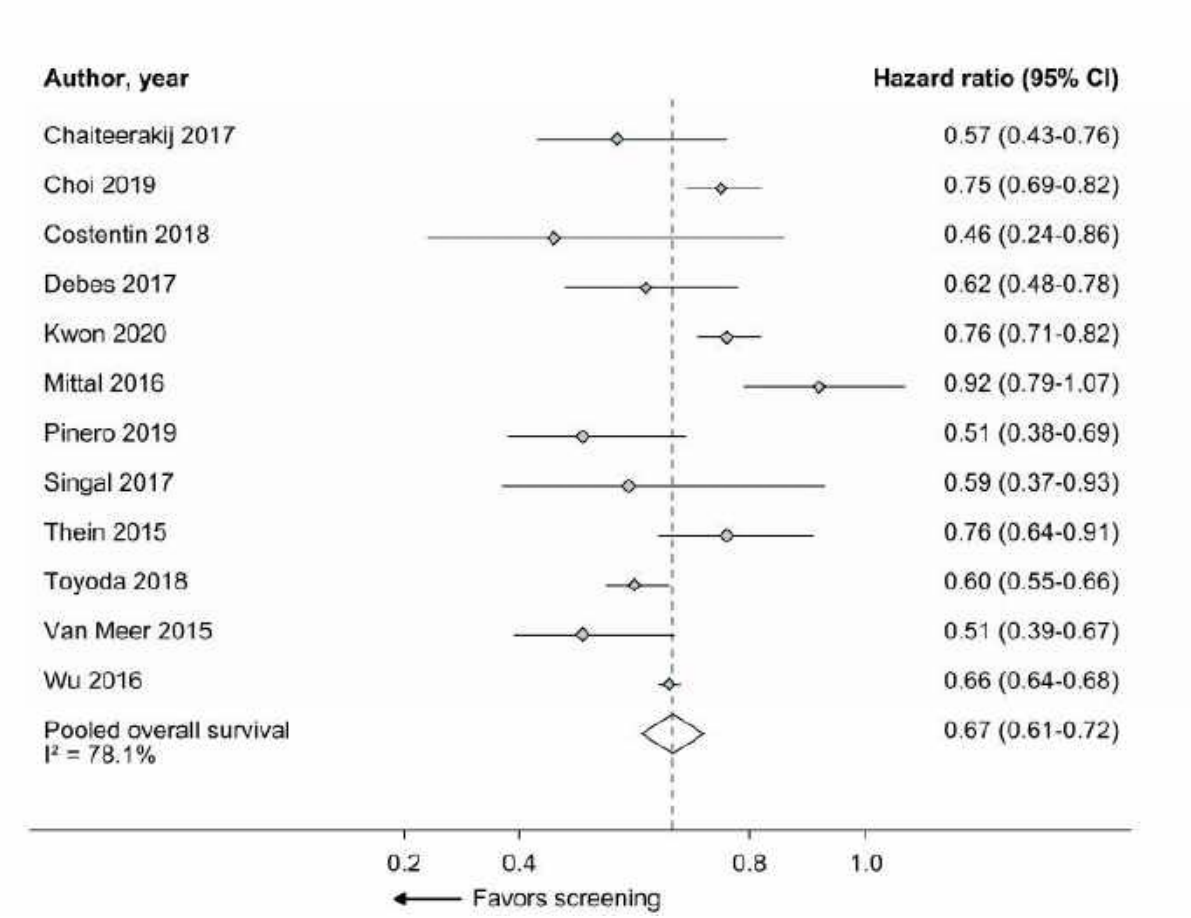
Amit G. Singal[1] | Josep M. Llovet[2,3,4] | Mark Yarchoan[5] | Neil Mehta[6] | Julie K. Heimbach[7] | Laura A. Dawson[8] | Janice H. Jou[9] | Laura M. Kulik[10] | Vatche G. Agopian[11] | Jorge A. Marrero[12] | Mishal Mendiratta-Lala[13] | Daniel B. Brown[14] | William S. Rilling[15] | Lipika Goyal[16] | Alice C. Wei[17] | Tamar H. Taddei[18,19]

HCC Screening

- US + AFP
- Who to screen?

Population group	Incidence of HCC
Sufficient risk to warrant surveillance	
Child-Pugh A–B cirrhosis, any etiology Hepatitis B Hepatitis C (viremic or post-SVR) Alcohol associated cirrhosis Nonalcoholic steatohepatitis Other etiologies	≥ 1.0% per year
Child-Pugh C cirrhosis, transplant candidate	
Non-cirrhotic chronic hepatitis B Man from endemic country[a] age > 40 y Woman from endemic country[a] age > 50 y Person from Africa at earlier age[b] Family history of HCC PAGE-B score ≥ 10[c]	≥ 0.2% per year
Insufficient risk and in need of risk stratification models/biomarkers	
Hepatitis C and stage 3 fibrosis	< 0.2% per year
Noncirrhotic NAFLD	

- Screening improves survival



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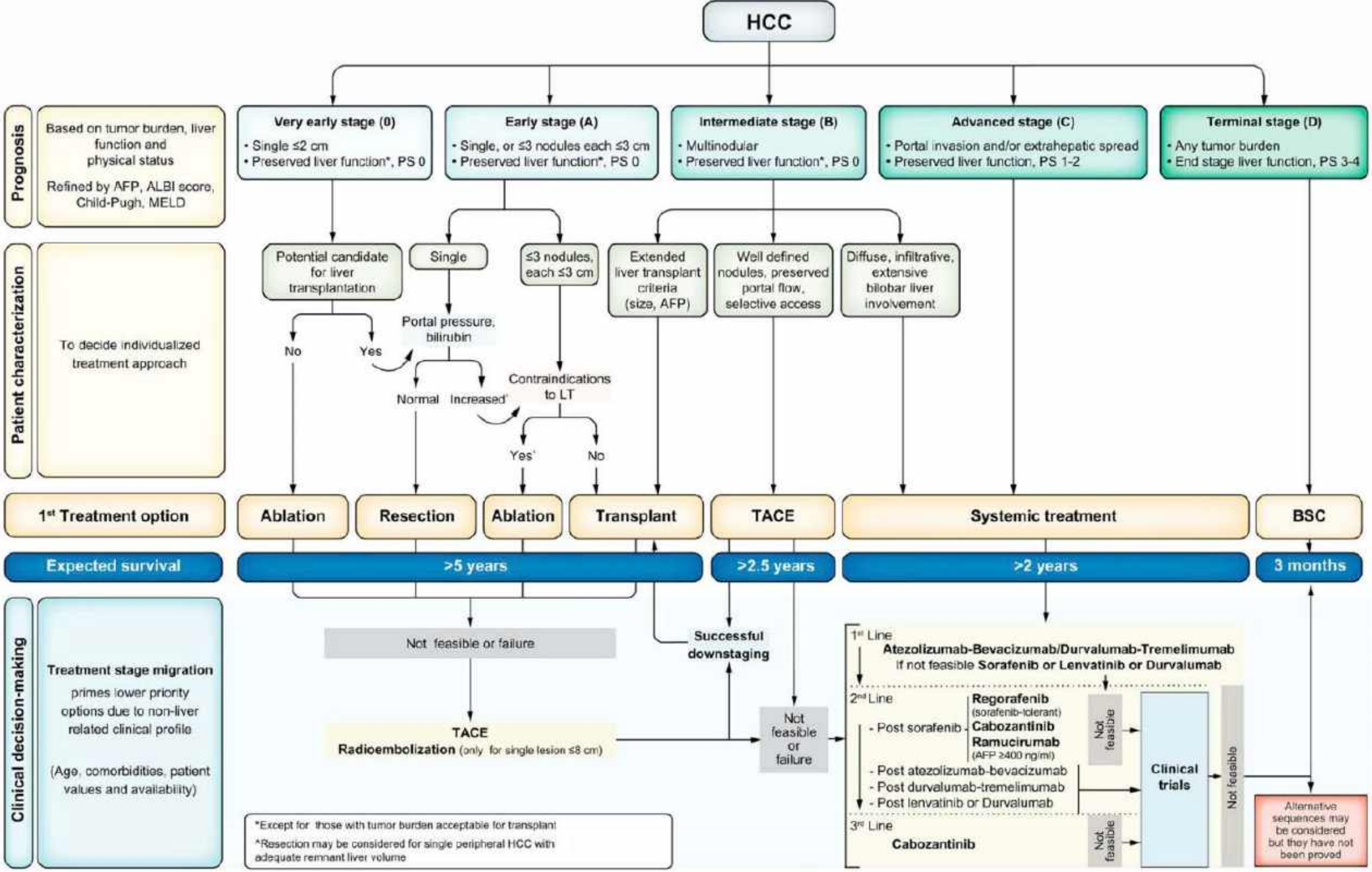
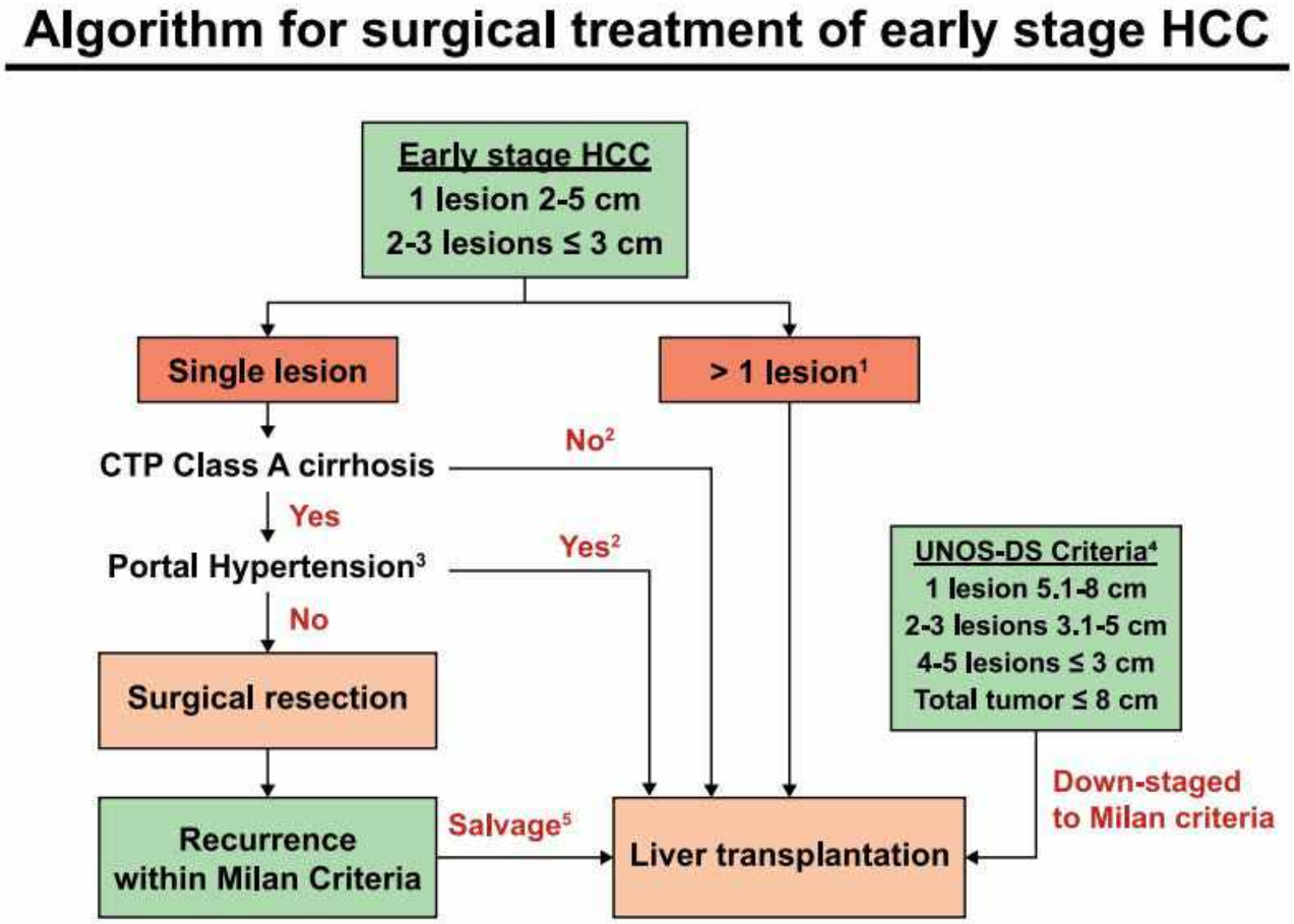
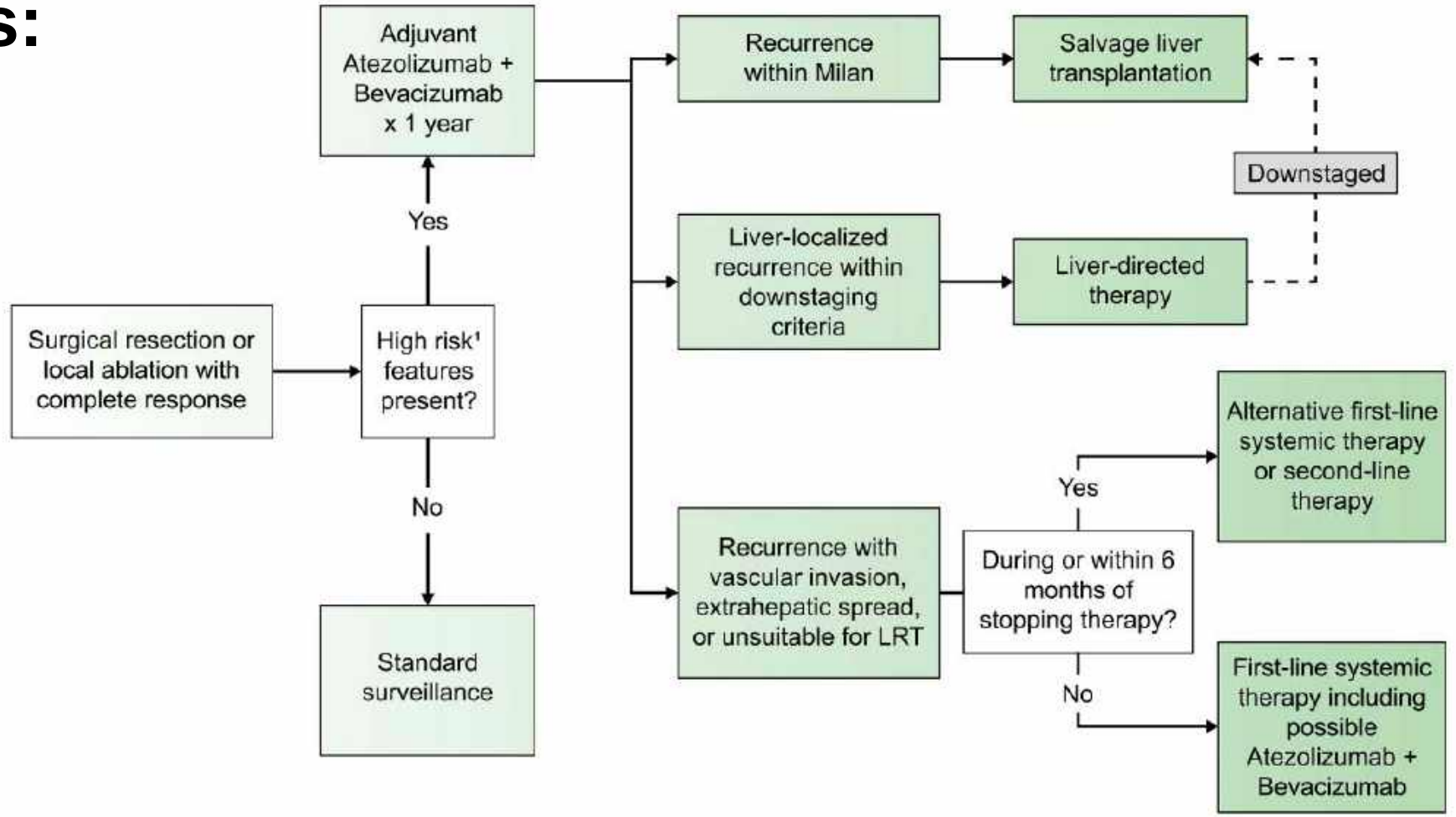

HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased'
Contraindications to LT
Yes'
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib (sorafenib-tolerant)
Cabozantinib
Ramucirumab (AFP ≥400 ng/ml)
Not feasible
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
3rd Line
Cabozantinib
Not feasible
Clinical trials
Not feasible
Alternative sequences may be considered but they have not been proved
*Except for those with tumor burden acceptable for transplant
'Resection may be considered for single peripheral HCC with adequate remnant liver volume

Surgical Resection for HCC

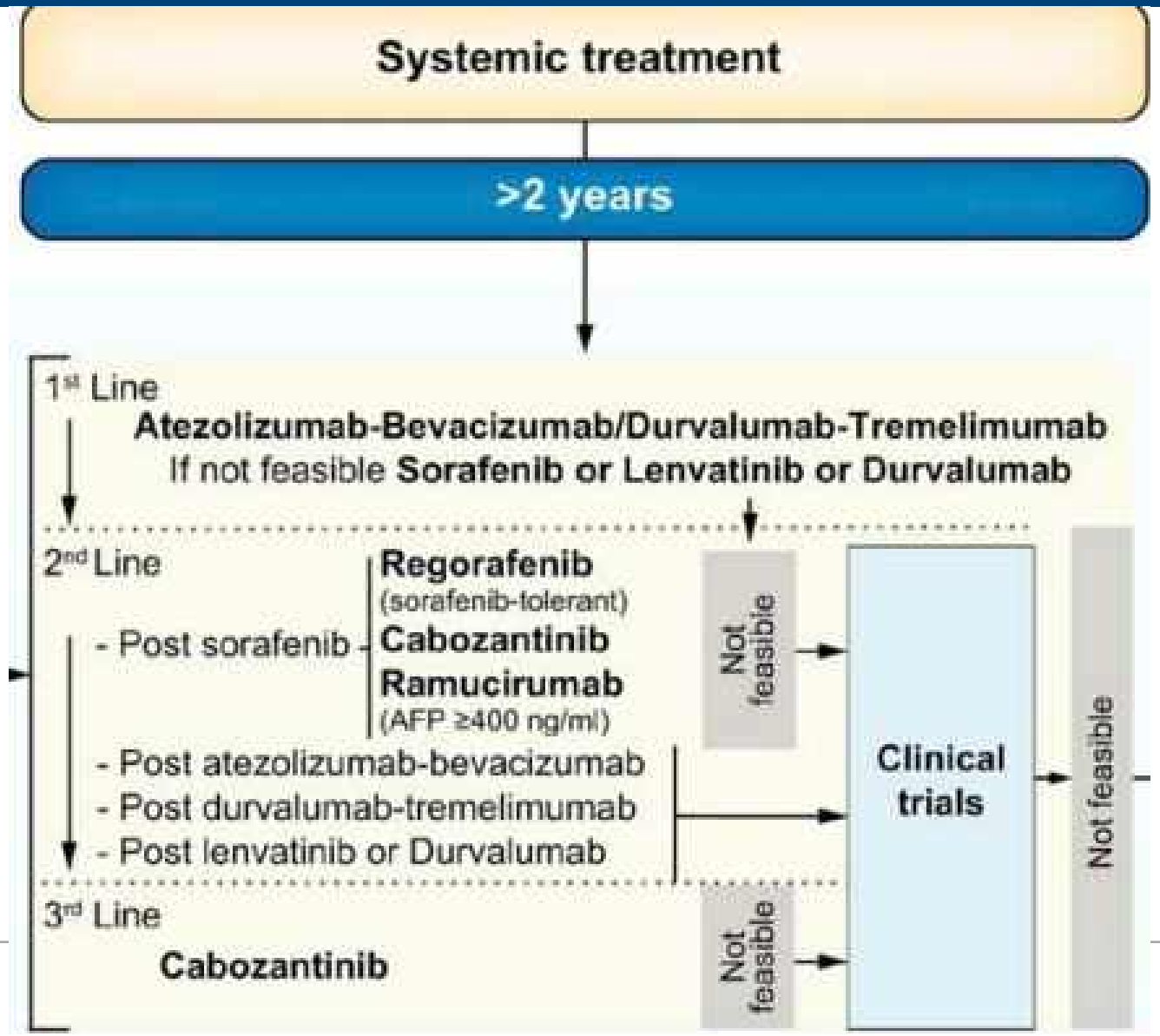


Adjuvant Therapy for HCC

- **High risk features:**
  - **Size >5cm**
  - **>3 lesions**
  - **Poor tumor differentiation**
  - **Macro- or microvascular tumor invasion**



Metastatic HCC Treatment Options



HCC Conclusions

- **HCC screening improves survival.**
  - US (LIRADS) + AFP is recommended
  - CTP-C patients who are NOT transplant candidates do not benefit
- **Resection remains the best option for HCC**
- **Adjuvant immunotherapy is now recommended in patients with high-risk features after resection or ablation**
- **Systemic options for HCC therapy have improved dramatically.**

Conclusions

- **Prevent AKI**
- **Terlipressin treats HRS-AKI**
- **NSBB:**
  - Carvedilol decreases the risk for decompensation
  - Carvedilol is the NSBB of choice
- **Statins:**
  - Lower portal pressures
  - Decrease risk for decompensation
  - Lower HCC risk
  - May prevent PVT
  - Lower all cause mortality

2024

DESERT LIVER CONFERENCE

PHOENIX, ARIZONA

The "Big Three" of Genetic Liver Diseases:

Hemochromatosis

Alpha 1 Antitrypsin Disease

Wilson Disease

Richard A. Manch MD, FAASLD, FACP, FACG

Director of Hepatology

Arizona Liver Health

Clinical Professor of Medicine

University of Arizona

The Big Three of Genetic Liver Diseases

- All genetic based disorders
- All etiologically related to single point gene mutations
- Several pathogeneses now explained by abnormal or absent function of mutated gene product
- Unpredictable genotype-phenotype correlations
- Included in work-up of unexplained liver disease

Prevalence

Hemochromatosis	1:300 – 500
Wilson Disease	1:30,000
A1AD	1:3000-5000

MASLD	1:3 – 1:4
MASH	1:20-1:50
HCV	1:100

The Big Three of Genetic Liver Diseases

Hemochromatosis

Wilson Disease

Alpha 1-antitrypsin deficiency

Iron Overload States: Classification

1. Hereditary hemochromatosis (HH)
2. Acquired hemochromatosis (Secondary iron overload)
3. Miscellaneous iron overload states

Normal Iron Balance

Ingested

10-20 mg/day

Absorbed

1-2 mg/day

Lost

Gut, skin, urine - 1-2 mg/day

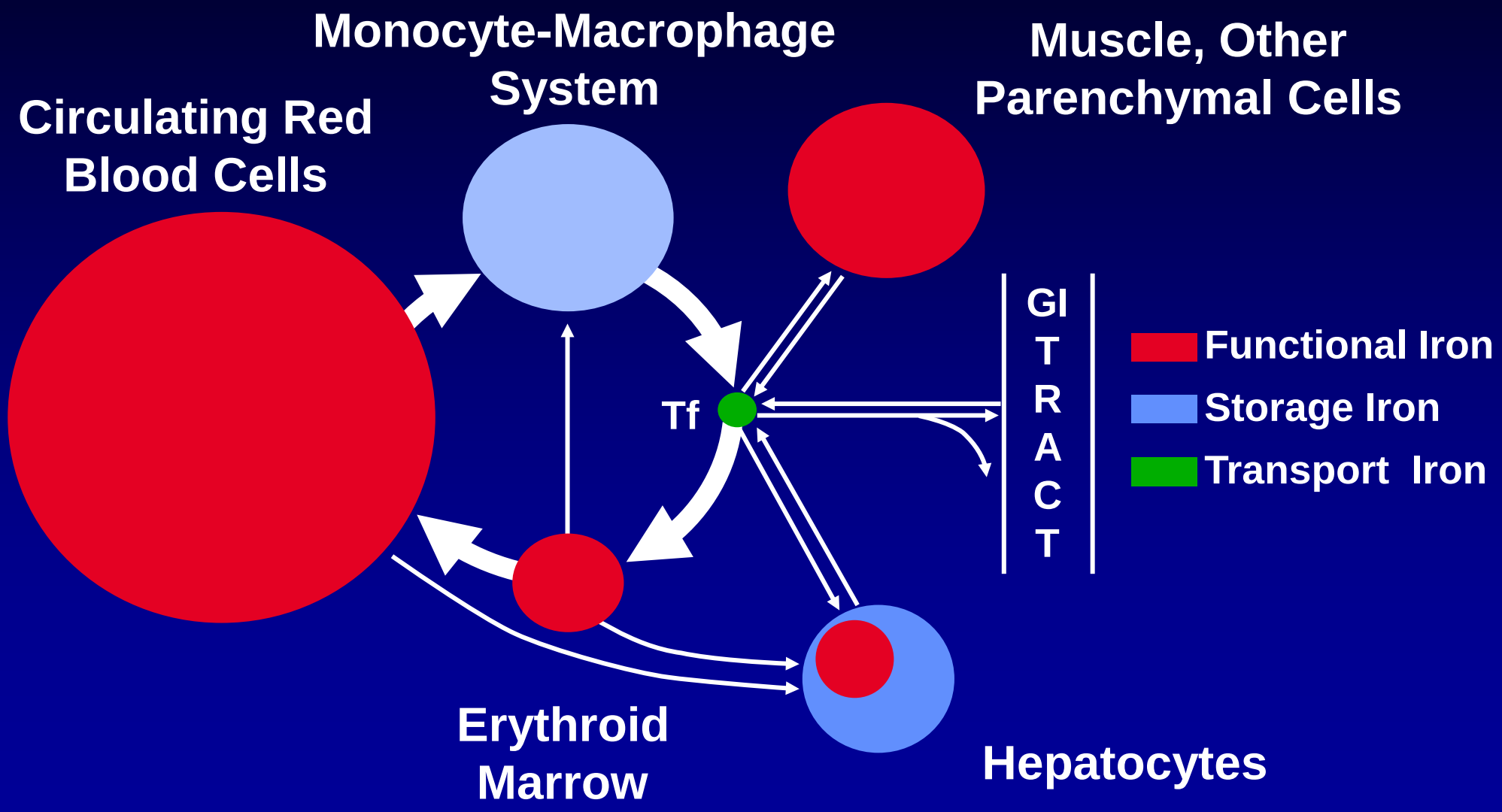
Andrews NC, N Engl J Med 1999; 341:1986

Iron Overload and the Liver

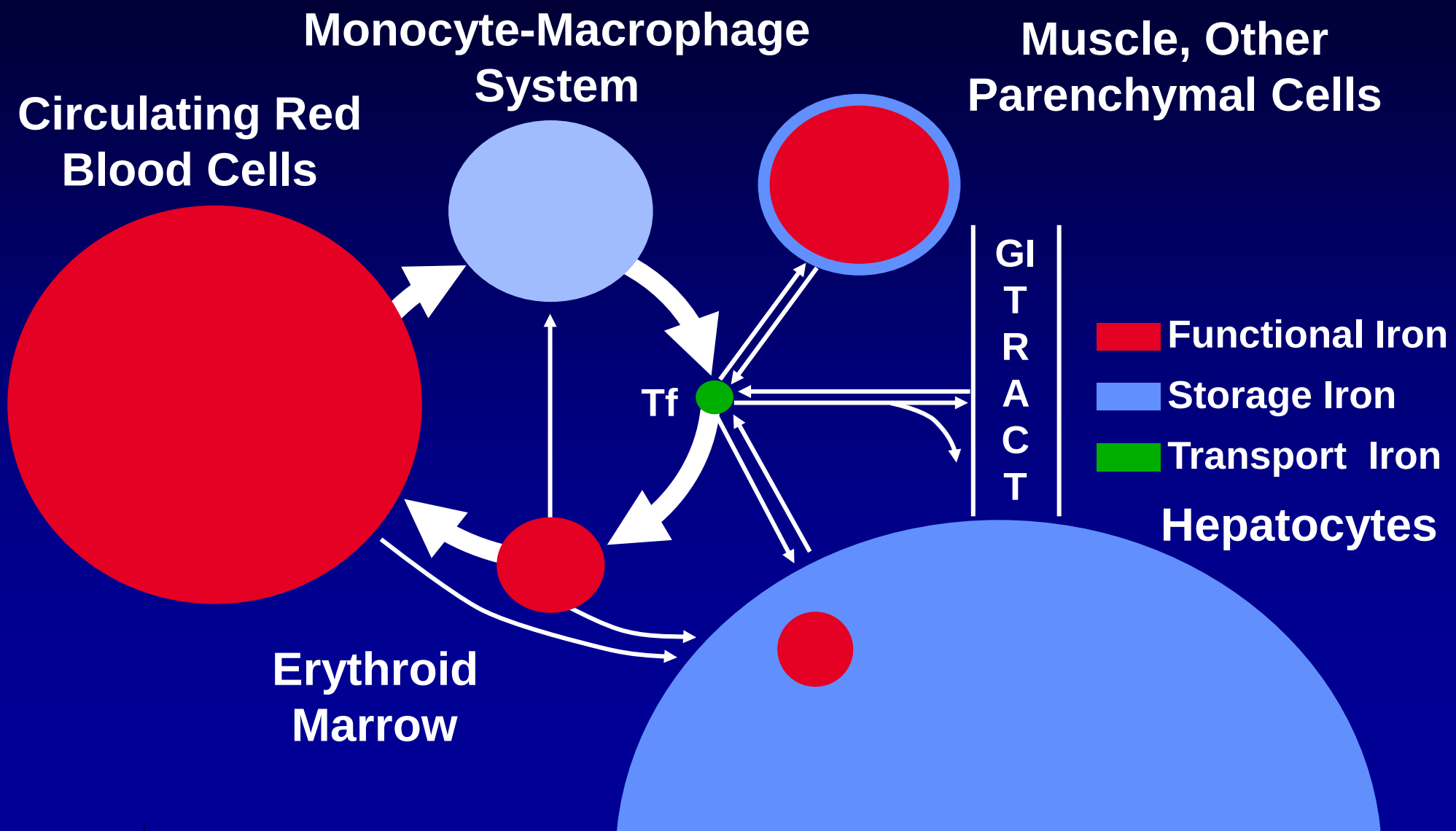
Hereditary Hemochromatosis

- ***Type 1:HFE* associated (90% of total HH)**
- ***Type 2:Juvenile hemochromatosis***
  - *Hemojuvelin (HJV) (Type 2A)*
  - *Hepcidin (HAMP) (Type 2B)*
- ***Type 3:TfR2 mutation***
- ***Type 4: Ferroportin mutation (autosomal dominant)***

Iron Metabolism: Normal



Hereditary Hemochromatosis: Massive Iron Excess



Hereditary Hemochromatosis (HH) Pathogenetic Mechanisms

- Genetic factors
  - Autosomal recessive, gene frequency 5%
  - Gene location, chromosome 6
  - *HFE* mutation homozygous C282Y leading to underexpression of hepcidin (the inhibitory protein for iron transport) synthesized in the liver
- Pathophysiology
  - Inappropriate intestinal iron absorption
  - 2-4 mg/day - net accumulation 1000 mg/yr
- Iron toxicity

  - Parenchymal iron toxic

  - Correlation between iron and fibrosis

Hereditary Hemochromatosis

- Four stages of disorder
  - Genetic predisposition without iron overload
  - Early iron overload (2-5g, up to 20 yrs)
  - Moderate iron overload (5-10g, 20-40 yrs)
  - Heavy iron overload (>10g, >40 yrs)

Disease

But now it is recognized only 10-15% of genetic C282Y homozygotes develop clinical disease

HFE Gene Mutations

Lead to deficient liver hepcidin production & failure of intestinal ferroportin inactivation

Increased intestinal iron absorption

Iron-induced tissue injury and fibrogenesis

Hereditary Hemochromatosis

Pigmentation **Cirrhosis** **Diabetes**

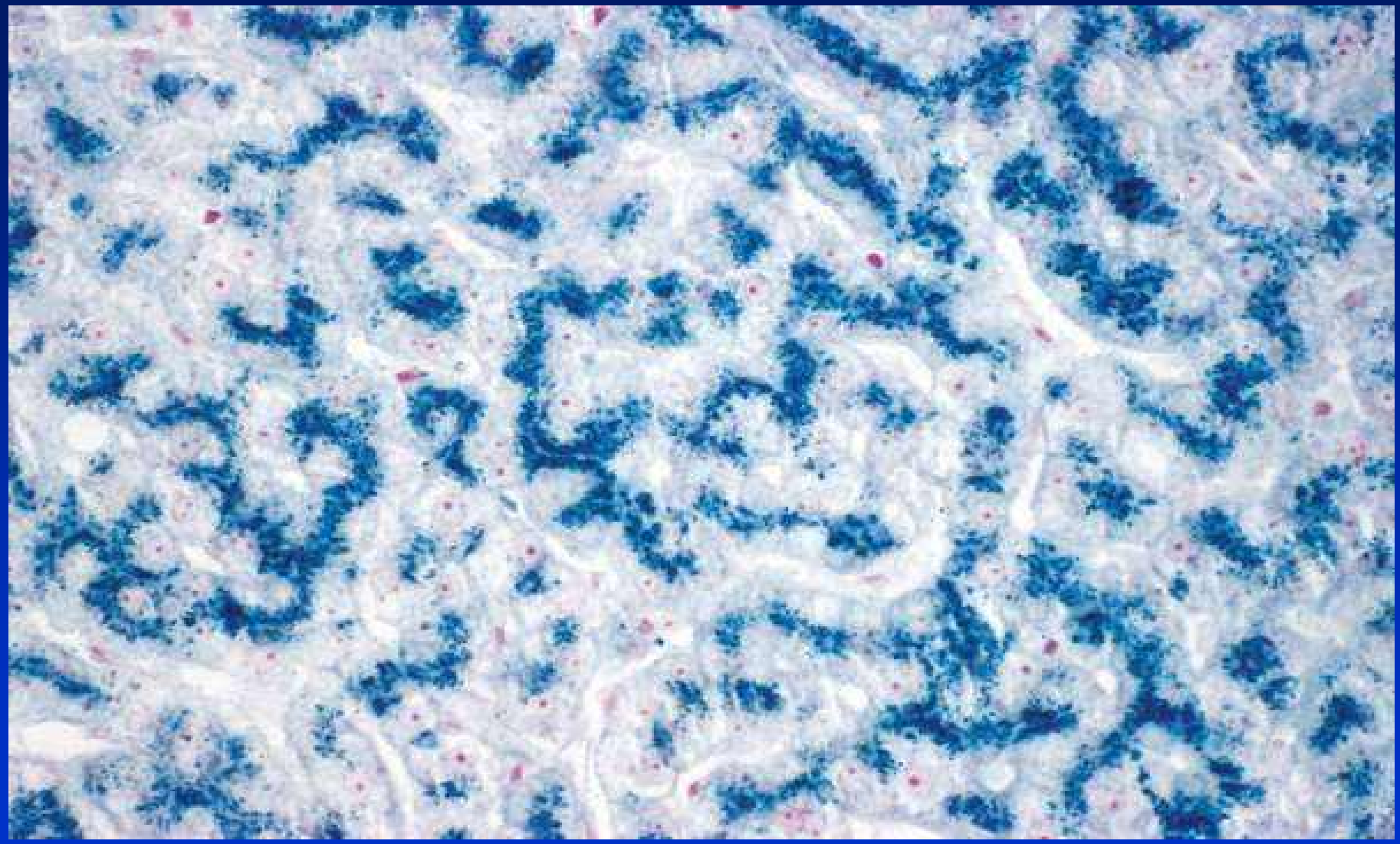
Malaise Weight loss Abdominal pain

Hypogonadism Arthropathy Cardiac failure

HOW IS IRON OVERLOAD IDENTIFIED?

- Clinical
- Blood testing
  - Transferrin saturation
  - Ferritin levels
  - Association with *HFE* mutation
- Phlebotomy requirements
- Liver biopsy
- Non-invasive imaging
  - MRI

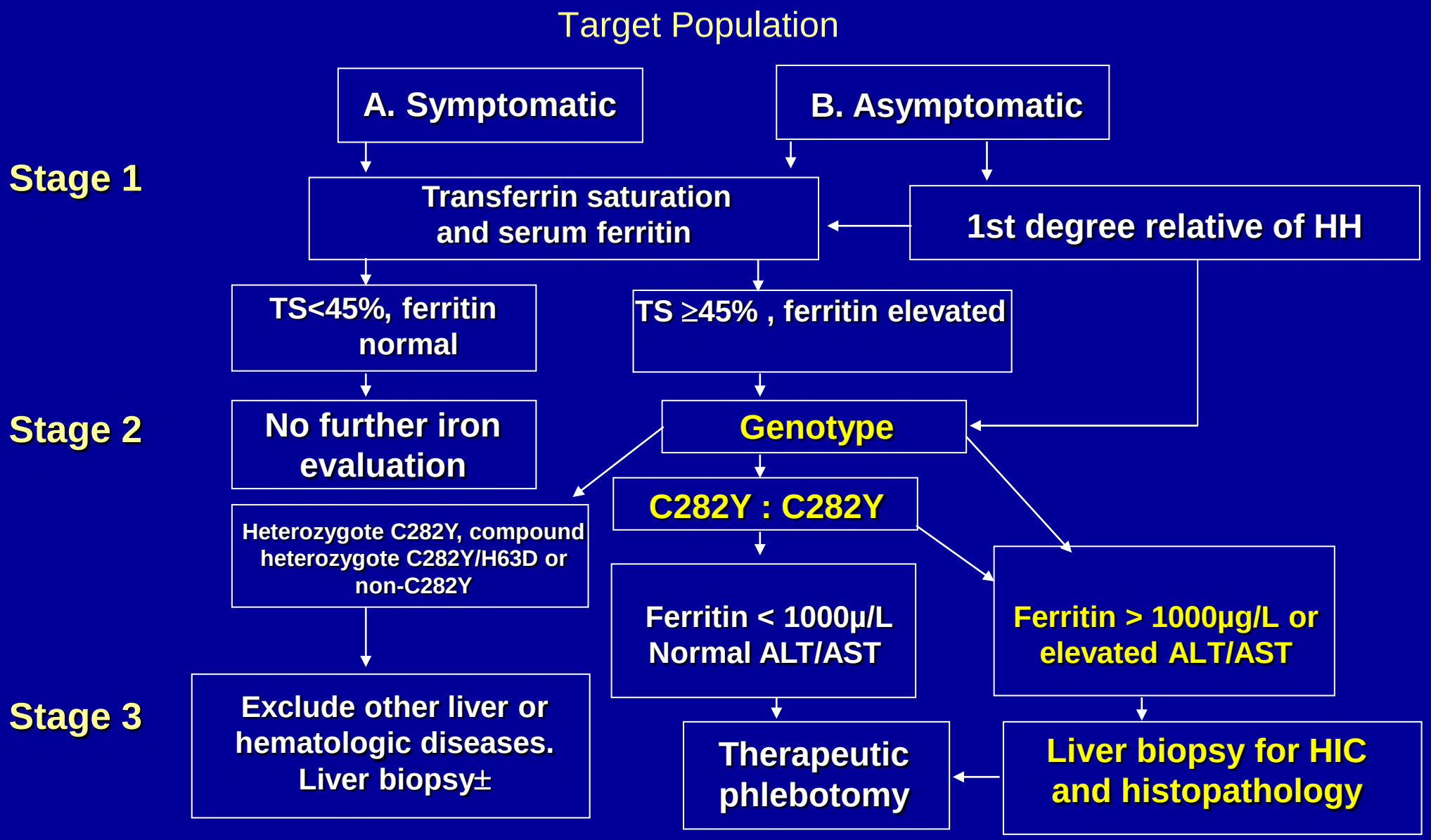
Hemochromatosis



Hepatocytes showing iron overload, stained blue color in perl's prussian blue stain. Note **the inflammation characteristically absent**.

Algorithm for Diagnosis and Treatment of HH

(2011 Practice Guideline by the AASLD. Hepatology 2011;54:328-343)



Hemochromatosis - Management Objectives

- Early diagnosis to prevent organ damage
- Early detection to promote longevity
  - In first degree relatives of probands
  - In higher risk general population
  - Males may present earlier than females
- **Optimal treatment of probands and detected cases**
  - Rapid and safe iron removal to reach **ferritin of 50 µg/L**
- Appropriate follow-up and maintenance treatment
  - Monitor for cirrhosis and HCC

The Big Three of Genetic Liver Diseases

Hemochromatosis

Wilson Disease

Alpha 1-antitrypsin deficiency

Wilson Disease

[MARCH, 1912.]

BRAIN.

PART IV., VOL. 34.

Original Articles and Clinical Cases.

PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

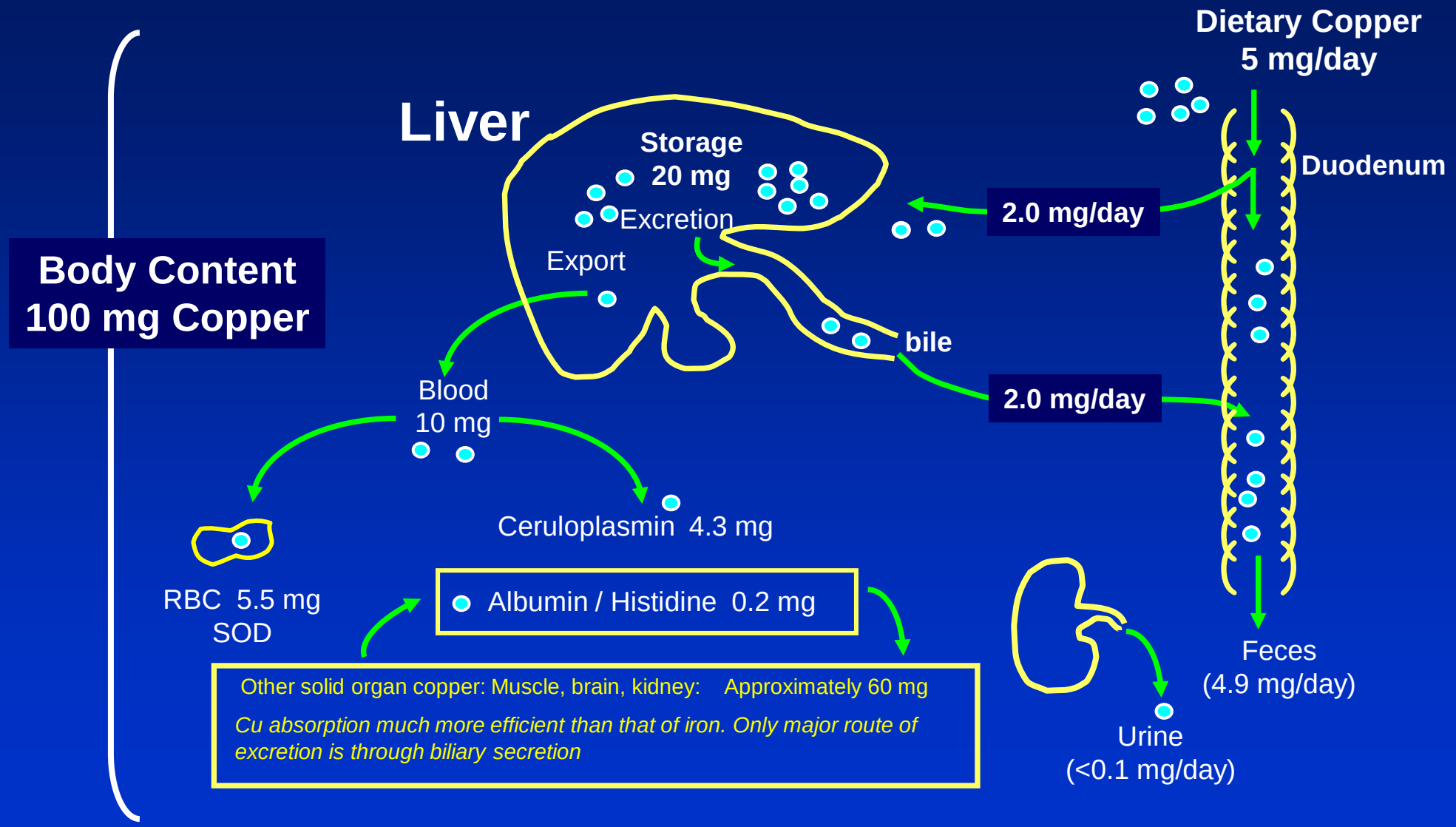
BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.

Registrar to the National Hospital, Queen Square, London.

(*From the Laboratory of the National Hospital, Queen Square.*)

DR. KINNIER WILSON

Human Copper Metabolism



Wilson Disease

= Hepatolenticular degeneration

- Pathogenesis
  - Genetic
    - Mutant regulator gene
      - Ceruloplasmin degradation increased
      - **Biliary copper excretion reduced**
    - Hepatic copper metabolism
      - Defective vesicular trafficking
    - Tissue toxicity of copper
      - Liver, brain, kidney, RBCs

Genetics of Wilson Disease

- Autosomal recessive
- Carrier rate ~ 1:90
- Prevalence of disease ≥ 1:30,000
- Defect on chromosome 13

Wilson Disease

- Initial Clinical Presentation
  - Hepatic 42%
  - Neurologic 34%
  - Psychiatric 10%
  - Hematologic & miscellaneous 13%
  - Renal & metabolic 1%

Note: In 25% more than one organ system is involved.

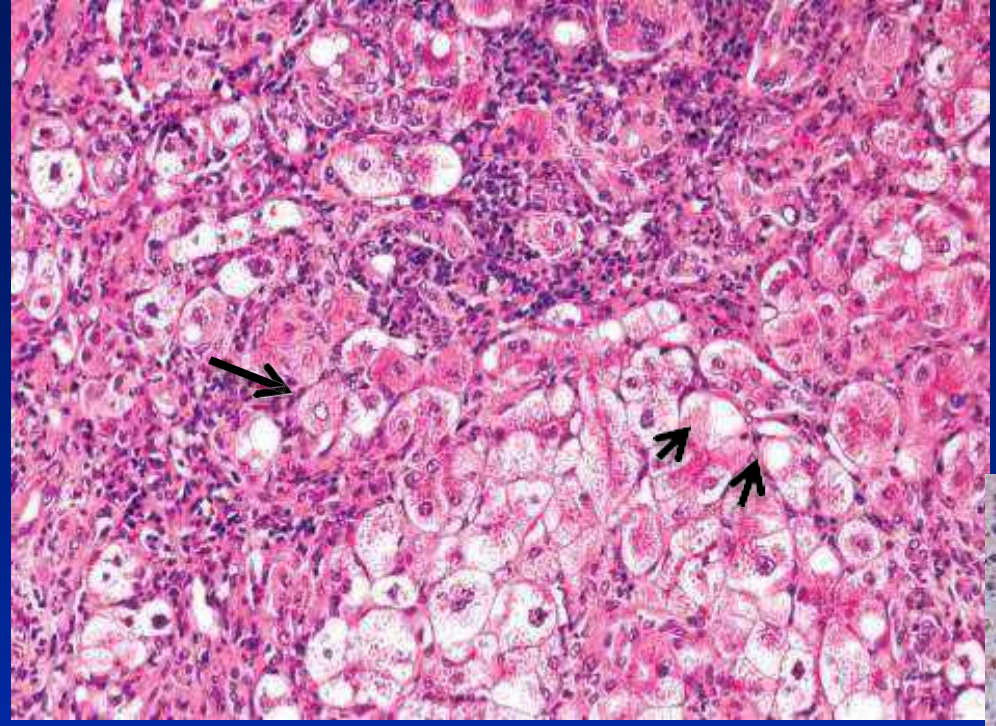
Wilson Disease

- Hepatic disease (6 - 35+ years)
  - Acute hepatitis with resolution
  - Fulminant hepatitis with rapid progression
  - Chronic active hepatitis
  - Cirrhosis without previous hepatic manifestations

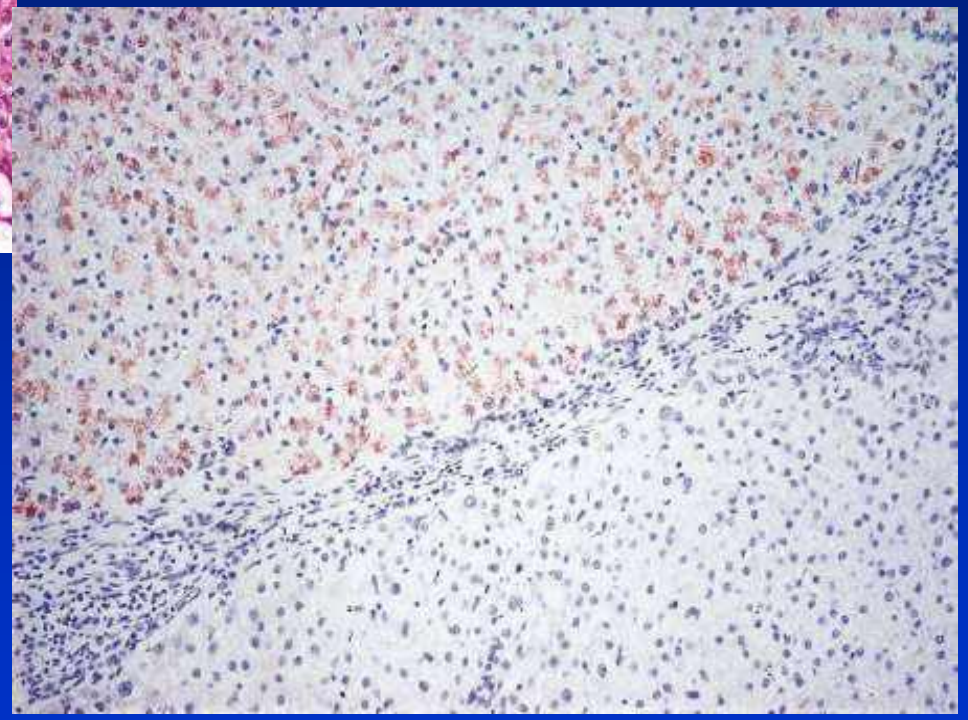
Wilson Disease

- Hepatic pathology
  - Steatosis
  - Necroinflammation
  - Portal & lobular fibrosis
  - Mallory bodies
  - Micro-macronodular cirrhosis

Wilson Disease



Fatty change, mild to moderate hepatocytic necrosis, with inflammatory infiltrate, intranuclear glycogen inclusions also seen.



The upper nodule is strongly positive for copper, stained orange-red. The lower nodule is completely negative. (Wedge biopsy, Rhodanine Stain)

Wilson Disease

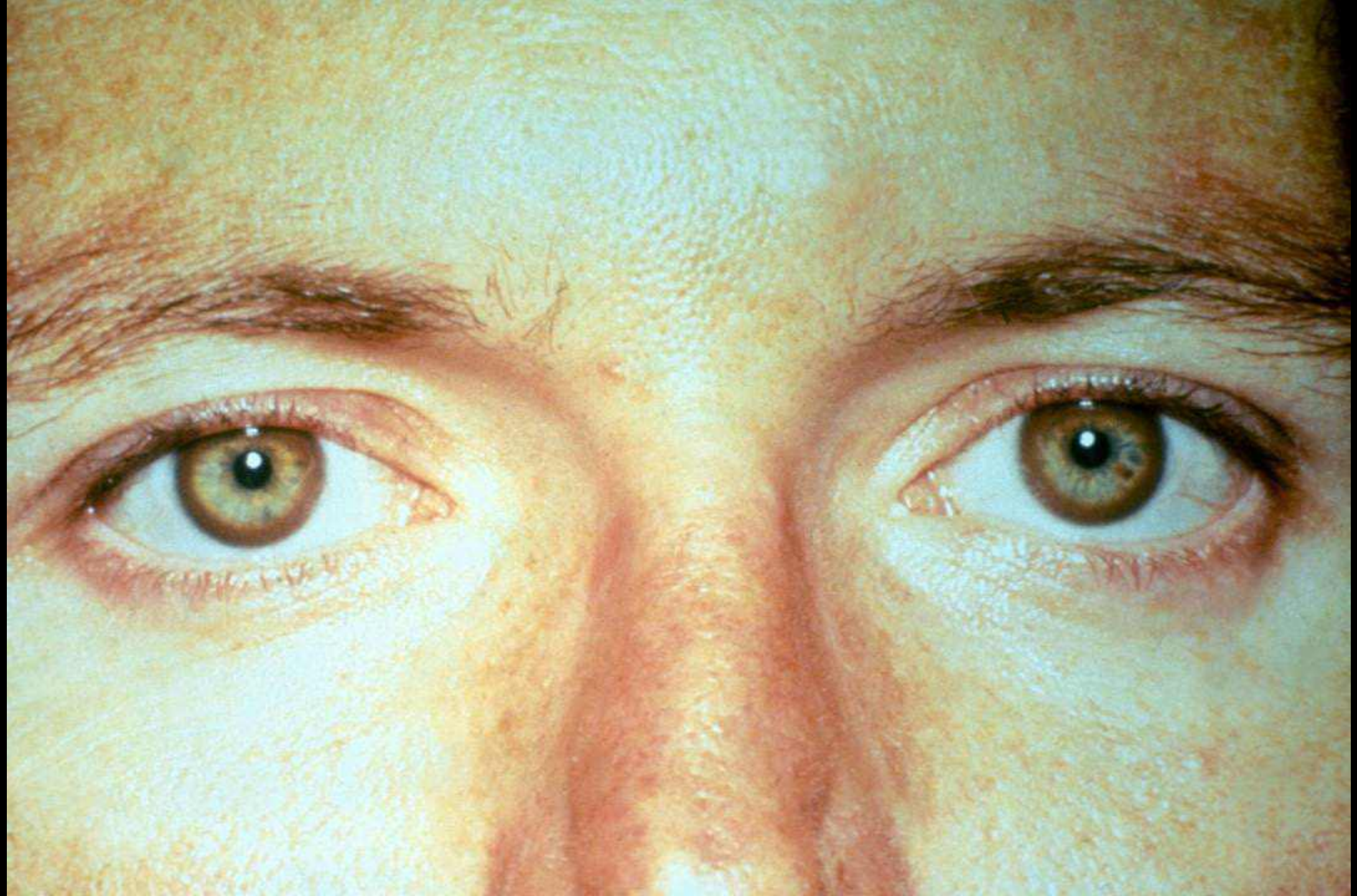
- Neurologic disease (12- 40 yrs)
  - (Associated cirrhosis & K.F. rings)
    - Tremor and ataxia
    - Choreiform movements
    - Dysarthria, dystonia
    - Slow movements
    - Behavioral problems
    - Rigidity and drooling

Wilson Disease

- Miscellaneous abnormalities
  - Hemolytic anemia (Coombs negative)
  - Renal tubular dysfunction
    - Aminoaciduria
    - Glucosuria
    - Uricosuria
    - Defective bicarbonate reabsorption
    - Hyperphosphaturia
    - Hypercalciuria (nephrocalcinosis)
  - Bone and joint disease
    - Osteomalacia
    - Osteochondritis dissecans
    - Chondrocalcinosis

Wilson Disease

- Ophthalmologic manifestations
  - Kayser-Fleischer rings
  - Sunflower cataracts



Wilson Disease

Representative copper measurements

	Normal	W.D.
Plasma ceruloplasmin (mg/dL)	20-40	< 20
Urine copper (μg/24 hr)	< 40	100-1000
Liver copper (μg/g dry weight)	15-55	250-3000

Wilson Disease

- Management (lifelong)
  - D-penicillamine 500 mg t.i.d.

    (Reduced to 375 mg b.i.d.)+pyridoxine
  - Trien (triethylene tetramine,trientene) in intolerant patient
  - Reduced doses in pregnancy,surgery
  - Zinc (150 mg daily) as maintenance
  - Avoid high copper foods (shellfish, nuts, mushrooms, chocolate & liver)

Wilson Disease

Indications for Hepatic Transplantation

- Features of fulminant hepatitis
  - Initial presentation or following discontinuation of D-penicillamine
- Decompensated cirrhosis
  - Despite adequate chelation and supportive measures

The Big Three of Genetic Liver Diseases

Hemochromatosis

Wilson Disease

Alpha 1-antitrypsin deficiency


Conditions Associated with
Alpha-1 Antitrypsin Deficiency
Skin
- Necrotising Panniculitis
- Systemic Vasculitis
- Psoriasis
- Urticaria
-angioedma
Liver
- Cirrhosis
- Neonatal Hepatitis
- Hepatocellular Carcinoma
Kidneys
- Proliferative Glomerulonephritis
- IgA Nephropathy
Intestines
- Inflammatory Bowel Disease
Lungs
- Chronic Obstructive Pulmonary Disease (Panacinar Emphysema)
- Bronchiectasis
- Asthma
Vascular
- ANCA-positive Vasculitis
- Abdominal and Intracranial aneurysms
- Arterial fibromuscular Dysplasia

Pathophysiology of α1-AT deficiency

- α1-AT is a serine protease inhibitor (serpin) whose role is to inactivate neutrophil elastase (and others) to maintain protease-antiprotease balance
- Produced in endoplasmic reticulum of the liver, and subsequently undergoes foldings and insertions of carbohydrate side chains.
- Defect is deficient secretion from liver to circulation
- Diffuses from circulation to lung, but insufficient available to protect lung from neutrophil elastases

Alpha 1-AT: Pi types

Pi type	Plasma α 1-AT level	(nl 200-300 mg/dL)
	Percent	Prevalence (%)
PiMM	100	80-95
PiMZ	57.5	0.5-0.7
PiSS	60	0.1-1.6
PiSZ	37.5	0.1-0.2
PiMnull	50	v.rare
PiZZ	15	0.1-0.6
PiNull-Null	0	v.rare

Clinical manifestations

- Lung
  - Emphysema and bronchiectasis
- Liver
  - Chronic hepatitis, cirrhosis, HCC
- Skin
  - panniculitis
- Vasculitis
  - ANCA positive disease such as Wegener's granulomatosis
- Most common causes of death
  - Respiratory failure (50-72%)
  - Complications of cirrhosis (10-13%)

Alpha 1-antitrypsin Deficiency

- Hepatic manifestations
  - Neonatal hepatitis
    - In only 15% of PiZZ homozygotes
  - Childhood cirrhosis
    - 50% give no history of neonatal hepatitis
  - Adult cirrhosis
    - rare *de novo* presentation of PiZZ phenotype
  - Hepatocellular carcinoma
    - Odds ratio increased by PiZ allele

Alpha 1-Antitrypsin Deficiency

- Diagnostic evaluation

  Low α-1 AT concentration or trypsin inhibitory activity

  -misleading due to acute phase response

  Pi genotype defines specific phenotype

  -PiZZ, PiMZ etc.

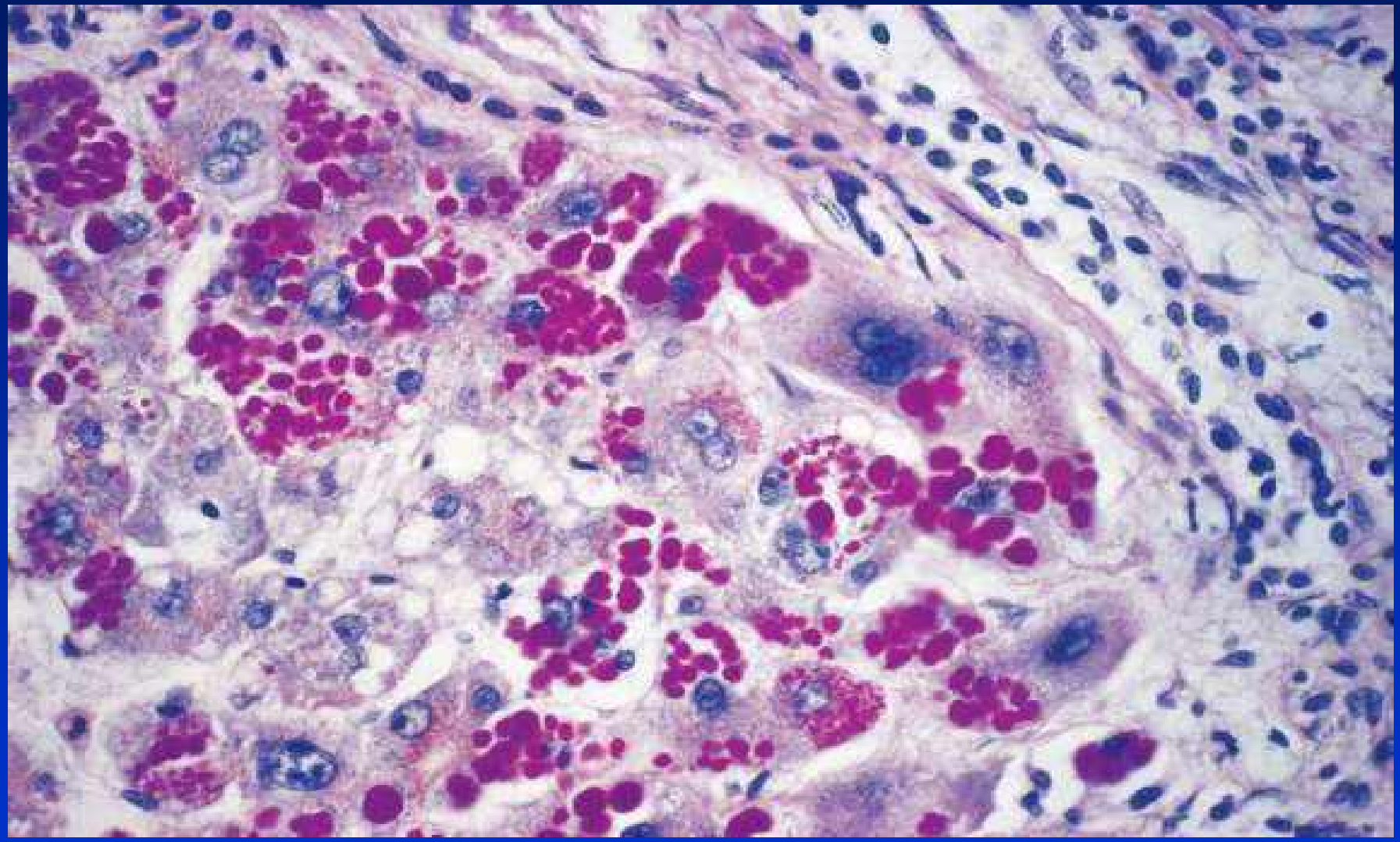
  Liver biopsy (also defines stage)

  -PAS-diastase positive inclusions

  -immunoperoxidase

  -electron microscopy

α1- Antitrypsin deficiency



Hepatocytes near periportal region contain mutated proteins, and stained magenta color for PAS+diastase. May also show steatosis, necrosis and fibrosis.

Pathophysiology

- Mechanism of liver disease
  - Loop sheet polymers of α1-AT in the ER of the hepatocyte cannot complete the secretory pathway
  - Liver disease depends on balance of synthesis, intracellular degradation, and cellular export. Degradation separates those ZZ who develop liver disease from those who are spared
  - S allele inherited with M or with S has some retention, but less polymerization, and does not cause liver disease
  - SZ can cause liver disease

Diagnosis

- Concentration of α-1AT in serum
  - but α-1AT is an acute phase reactant and may be spuriously elevated

- Therefore phenotype/genotype
  - Phenotype will not identify Pi Null
  - Genotype identifies Pi S and Pi Z
  - Genotype will miss rare alleles

Diagnosis – Who to test?

- COPD or asthma with irreversible airflow obstruction
  - Especially early onset (<45 yrs), or with strong family history of COPD
- Unexplained liver disease (any age)
- Necrotizing panniculitis
- c-ANCA positive vasculitis

Treatment – Liver Disease

- Treat all complications of cirrhosis
- Replacement therapy with α-1AT concentrate will not benefit liver disease but may protect lung elastic tissue
- Liver transplant **corrects metabolic disorder**
  - Recipients acquire donor phenotype
  - Unknown outcomes regarding onset or progression of lung disease
  - Excellent outcomes for liver, similar to that of other indications for OLT

2024
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PHOENIX, ARIZONA

Thank you!

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Director of Hepatology
Arizona Liver Health
Clinical Professor of Medicine
University of Arizona

Panel Discussion

Moderator: Jacqueline O'Leary, MD MPH

Richard Manch, MD, FAASLD, FACP, FACG

Naim Alkhouri, MD, FAASLD, ABOM

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Closing Remarks

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