

**GASTROENTEROLOGY
AND
HEPATOLOGY
CLINICAL RESEARCH
UPDATE**

ANTONIO SANCHEZ, M.D.

DIRECTOR OF HEPATOLOGY

**CLINICAL PROFESSOR OF MEDICINE
DIVISION OF GASTROENTEROLOGY
AND HEPATOLOGY**

UNIVERSITY OF IOWA HEALTH CARE

I , Antonio Sanchez, MD, disclose the following financial relationships with manufacturers of health care products:

Grant/Research Support:

**Merck, Inventiva, GSK, Escient, Mirum ,Calliditas,
Boehringer-Ingelheim, Gilead, Salix**

Clinical Trials – UIHC

GI/HEPATOLOGY - Clinical Research Unit

Inflammatory Bowel Disease

Motility studies

Eosinophilic esophagitis / Celiac Disease

Liver Studies

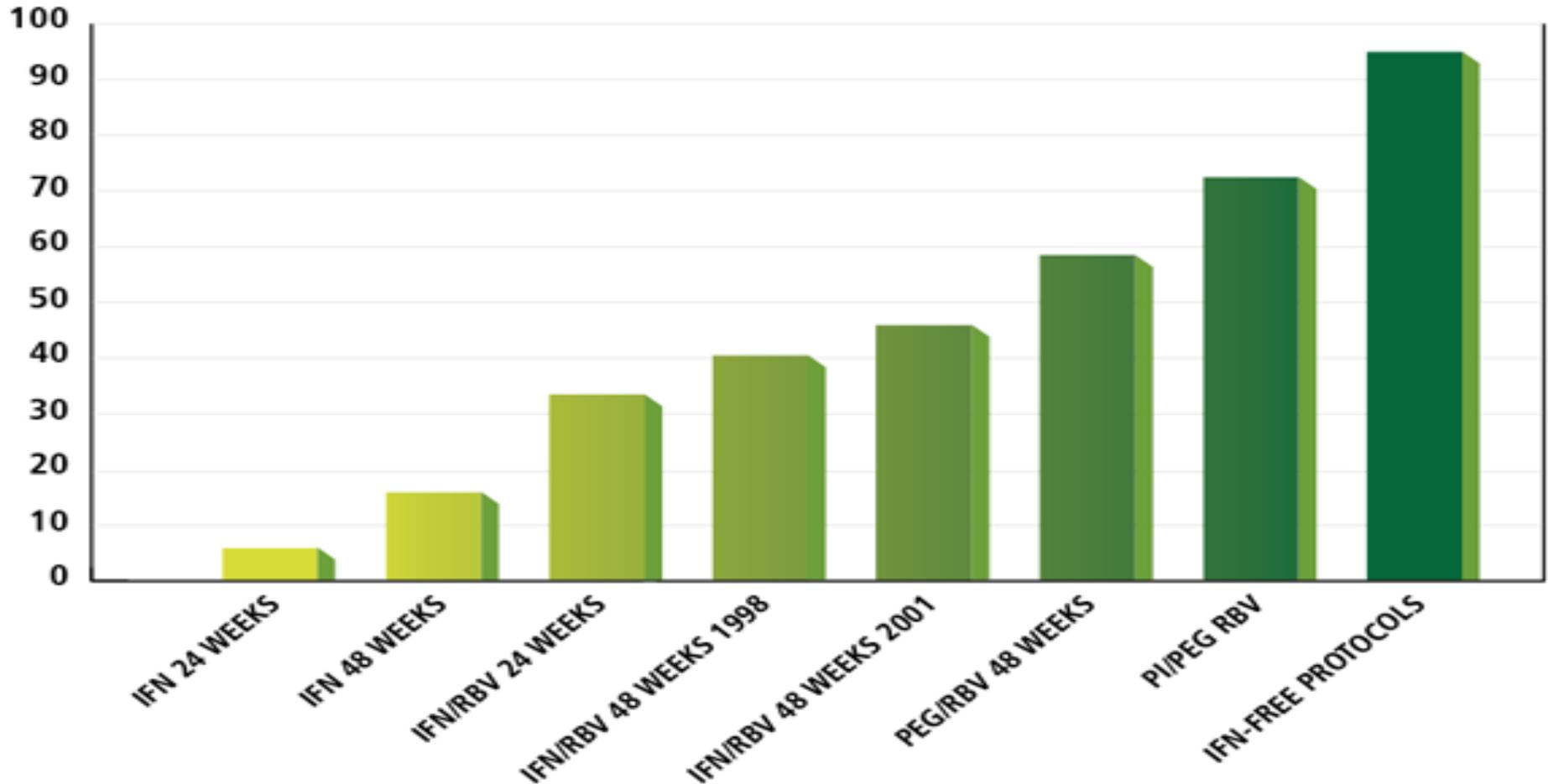
Clinical Trials in Hepatology – UIHC

Liver Studies

- MASLD
- PRIMARY BILIARY CHOLANGITIS / PSC
- HEPATITIS B and C
- ALPHA 1 ANTITRYPSIN DEFICIENCY
- LIVER TRANSPLANTATION

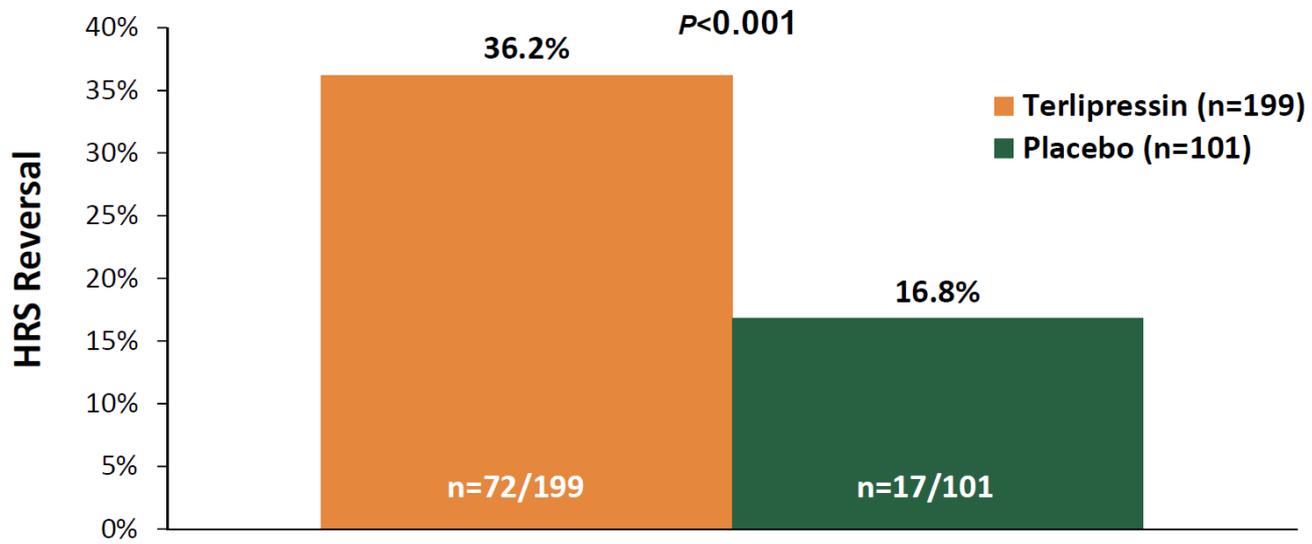
Therapeutic options - Hepatitis C treatment in 2024

EVOLUTION OF HCV THERAPY

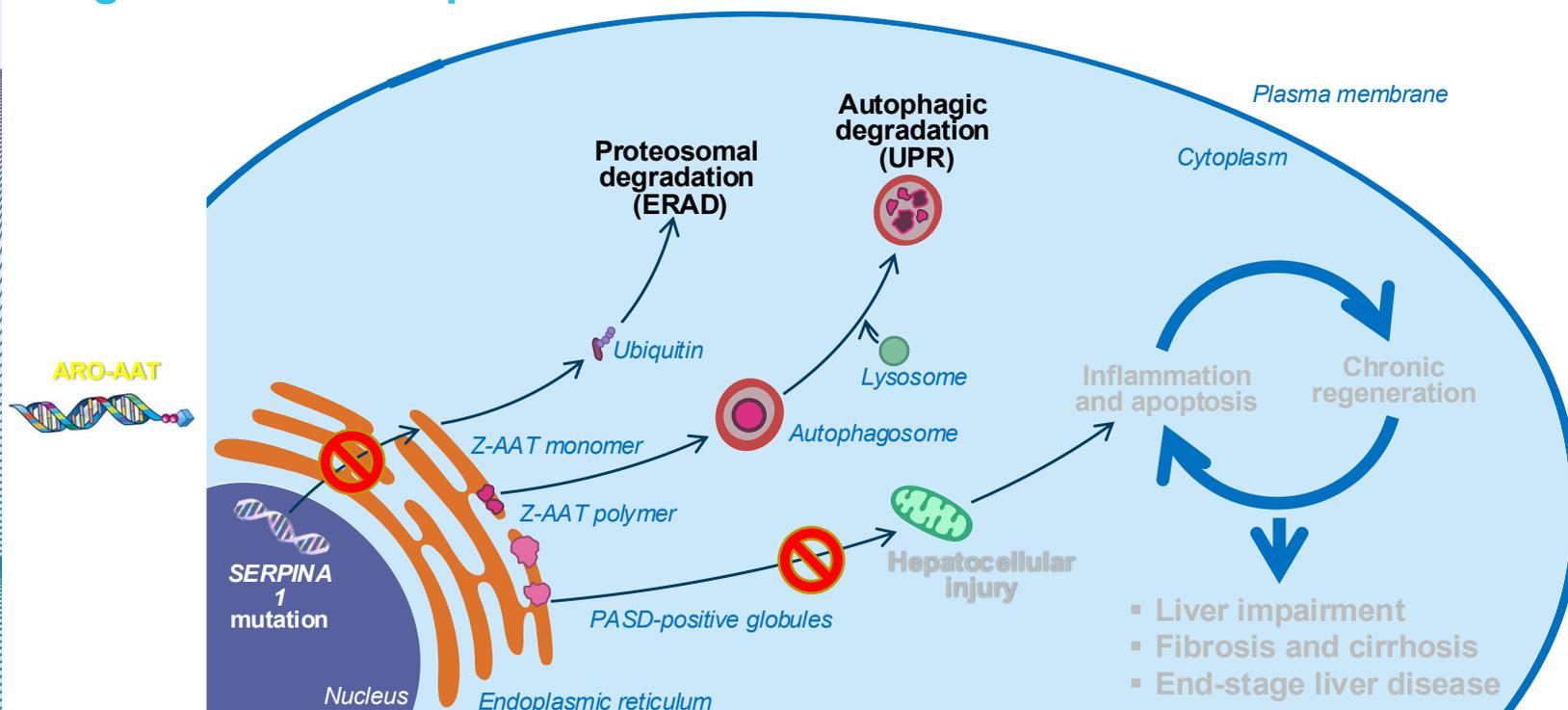


THE CONFIRM STUDY: A NORTH AMERICAN RANDOMIZED CONTROLLED TRIAL (RCT) OF TERLIPRESSIN PLUS ALBUMIN FOR THE TREATMENT OF HEPATORENAL SYNDROME TYPE 1 (HRS-1)

The CONFIRM Study: HRS Reversal (HRSR)



Fazirsiran (ARO-AAT) is an RNA interference therapeutic that inhibits Z-AAT expression to allow clearance of polymers and globules and improvement in liver health



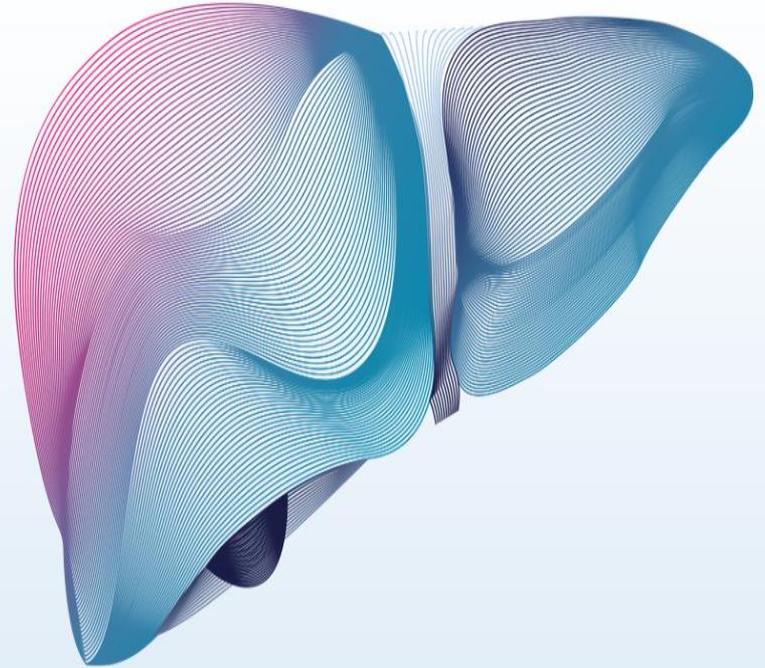
AAT, alpha-1 antitrypsin; ERAD, endoplasmic-reticulum-associated protein degradation; PASD, periodic acid Schiff plus diastase; UPR, unfolded protein response



EASL CONGRESS

Vienna, Austria
21-24 June 2023

The International Liver Congress™



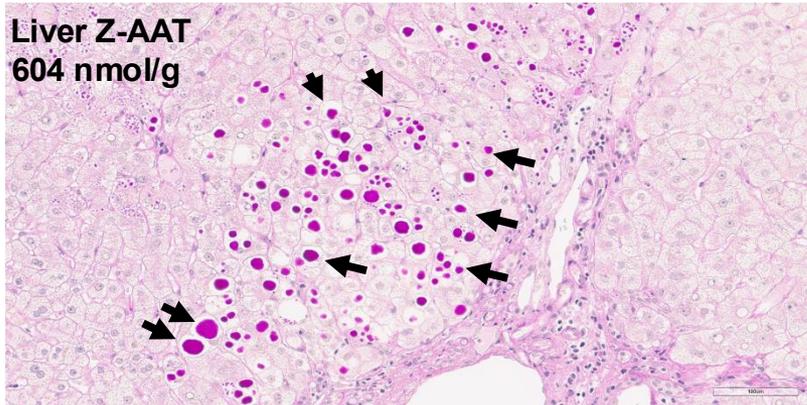
Fazirsiran reduces liver Z-alpha-1 antitrypsin synthesis, decreases globule burden and improves histological measures of liver disease in adults with alpha-1 antitrypsin deficiency: a randomized placebo-controlled phase 2 study

Virginia Clark,¹ Charlton Strange,² Pavel Strnad,³ Antonio J Sanchez,⁴ Paul Kwo,⁵ Vitor Magno Pereira,⁶ Bart van Hoek,⁷ Igor Barjaktarevic,⁸ Angelo Guido Corsico,⁹ Mònica Pons,¹⁰ Monica Goldklang,¹¹ Meagan Gray,¹² Brooks Kuhn,¹³ Hugo E Vargas,¹⁴ John M Vierling,¹⁵ Raj Vuppalanchi,¹⁶ Mark Brantly,¹ Naomi Kappe,⁷ Ting Chang,¹⁷ Thomas Schluep,¹⁷ Rong Zhou,¹⁷ James Hamilton,¹⁷ Javier San Martin,¹⁷ Rohit Loomba¹⁸

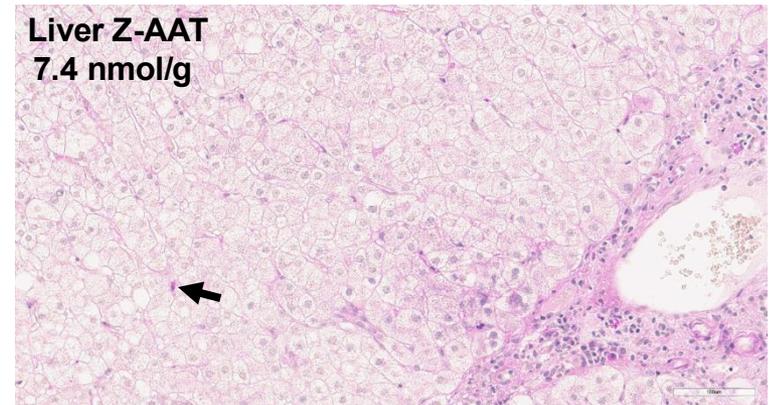
¹University of Florida, Gainesville, FL, USA; ²Medical University of South Carolina, Charleston, SC, USA; ³University Hospital Aachen, Aachen, Germany; ⁴University of Iowa, Iowa City, IA, USA; ⁵Stanford University, Stanford, CA, USA; ⁶Funchal Central Hospital, Funchal, Madeira, Portugal; ⁷Leiden University Medical Center, Leiden, Netherlands; ⁸University of California, Los Angeles, CA, USA; ⁹Foundation IRCCS San Matteo Hospital and Pavia University, Pavia, Italy; ¹⁰Vall d'Hebron University Hospital, Barcelona, Spain; ¹¹Columbia University Irving Medical Center, New York, NY, USA; ¹²University of Alabama at Birmingham, Birmingham, AL, USA; ¹³UC Davis Medical Center, Sacramento, CA, USA; ¹⁴Mayo Clinic in Arizona, Phoenix, AZ, USA; ¹⁵Baylor College of Medicine, Houston, TX, USA; ¹⁶Indiana University School of Medicine, IN, USA; ¹⁷Arrowhead Pharmaceuticals, Pasadena, CA, USA; ¹⁸UC San Diego Medical Center, San Diego, CA, USA

Fazirsiran consistently reduced hepatic globule burden

Screening



Post-dose biopsy



Mean (SD) PASD-positive globule burden

	Placebo (n = 9)	Pooled fazirsiran (n = 16)
Baseline	6.9 (1.76)	5.9 (2.24)
Post-baseline	6.6 (2.13)	2.3 (2.24)
Median % change	-3%	-68%

Patients with change in PASD-positive globule burden

PASD-positive globule burden	Placebo (n = 9)	Pooled fazirsiran (n = 16)
≥ 1-point improvement*	4/9 (44%)	16/16 (100%)
No change	1/9 (11%)	0/16 (0%)
≥ 1-point worsening**	4/9 (44%)	0/14 (0%)

*A baseline minimum severity score of 0, as assessed by the central read, was ineligible for assessment of improvement.

**A baseline maximum severity score, as assessed by the central read, was ineligible for assessment of worsening.

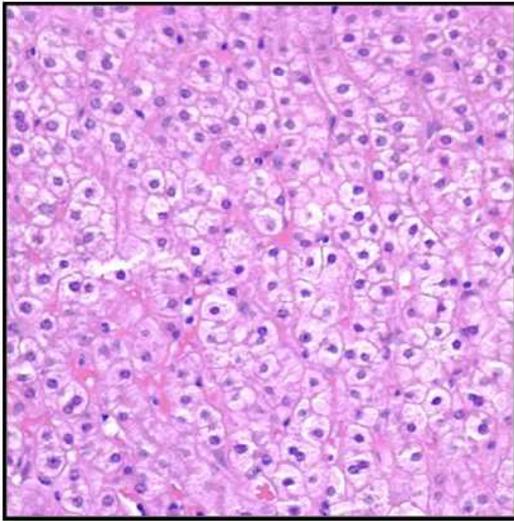
Multi-Society Expert Panel Consensus Guidance Regarding Clinical Assessment and Clinical Trial Endpoints in Adults With α -1 Antitrypsin Deficiency—Associated Liver Disease

Rohit Loomba, Virginia C. Clark, Mattias Mandorfer, Marc Miravittles
Mark Brantly, Saul J. Karpen, Aleksander Krag, Paul Y. Kwo, Don C.
Rockey, Mark W. Russo, Antonio J. Sanchez, Scott Santarella,
Suzanne R. Sharpton, Charlie Strange, Jeffrey H. Teckman, Alice M.
Turner, Hugo Vargas, and Pavel Strnad

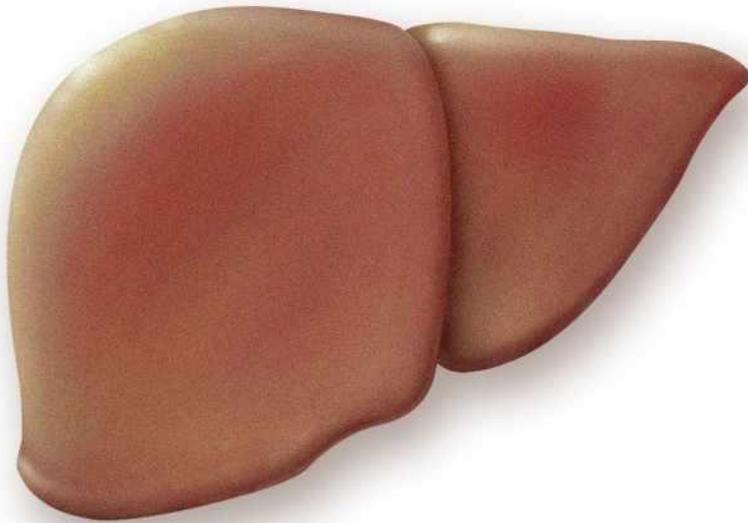
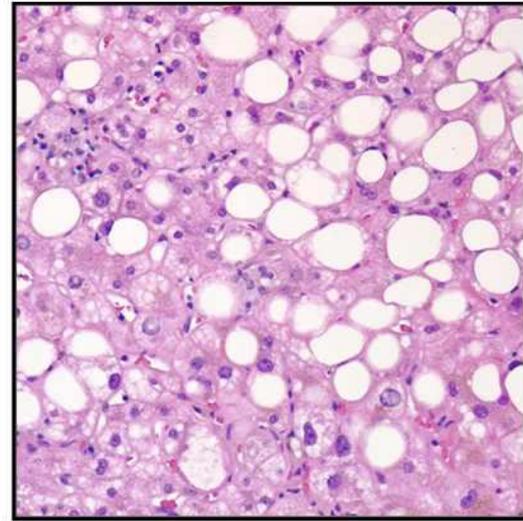
Research Projects Gastroenterology and Hepatology

- MASLD
- COMPLICATIONS OF CIRRHOSIS/PORTAL HYPERTENSION
- ALPHA 1 ANTITRYPSIN DEFICIENCY
- LIVER TRANSPLANTATION

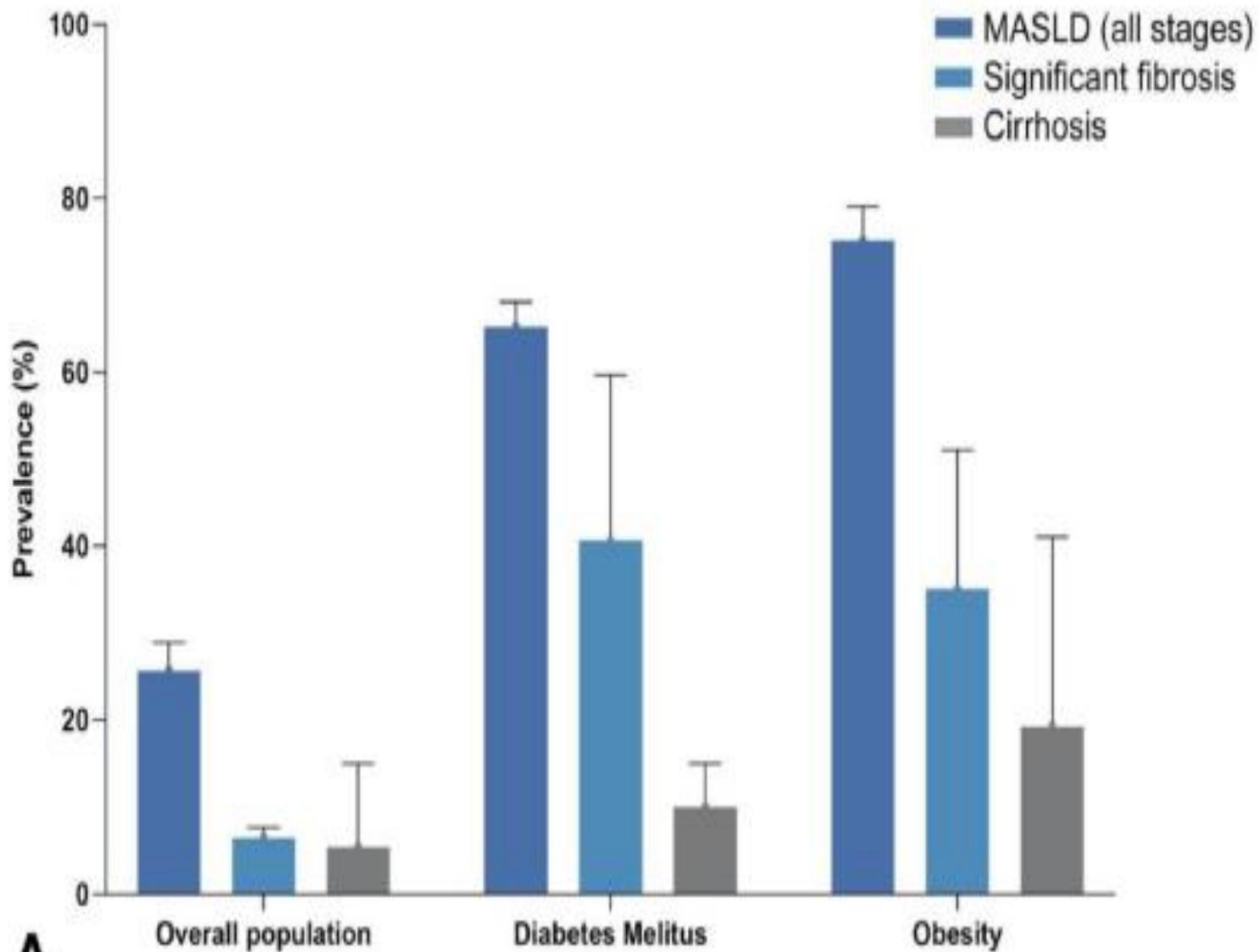
Normal liver



Fatty liver

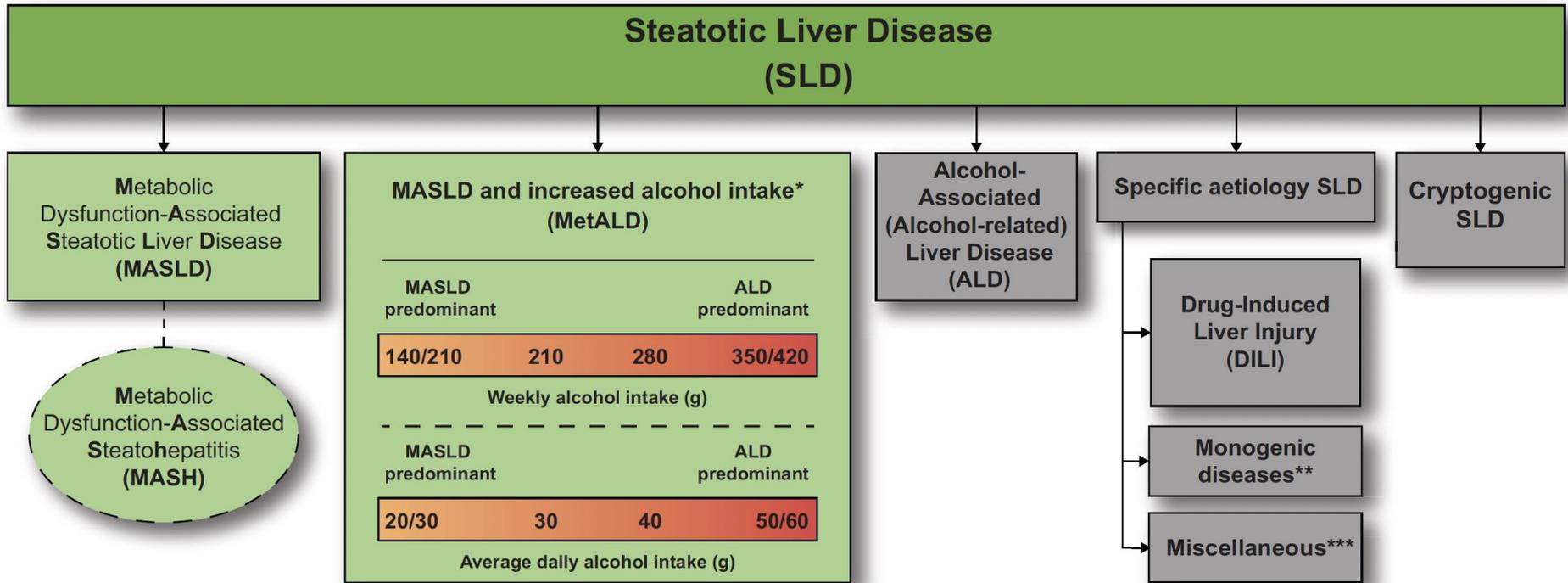


Global Estimated Prevalence of MASLD



A

Consensus Nomenclature



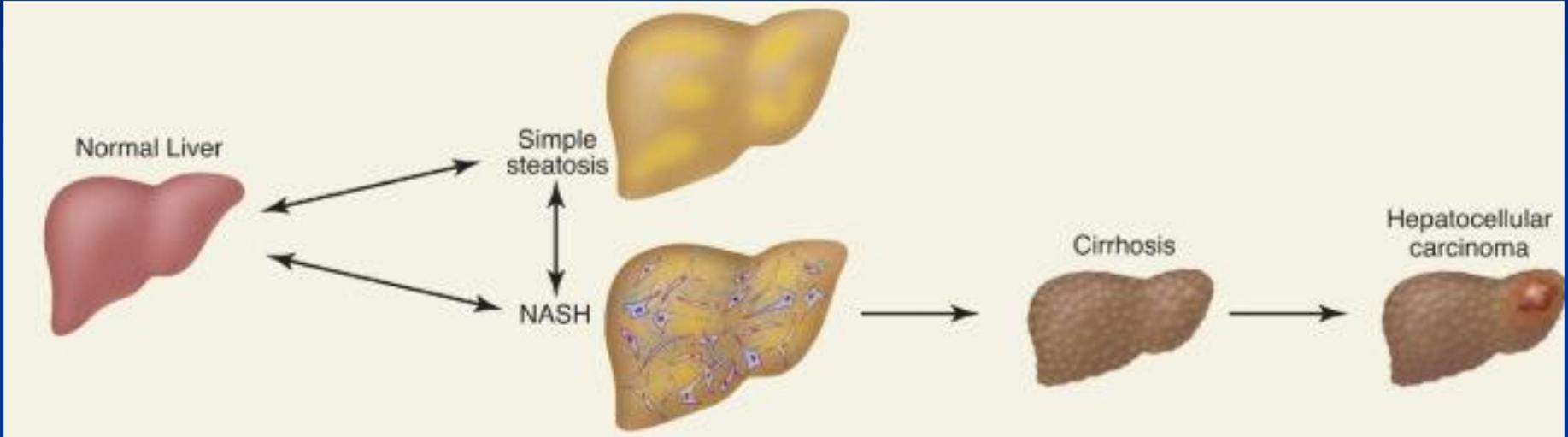
*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

**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)

The NAFLD nomenclature is changing

Natural History of MASLD

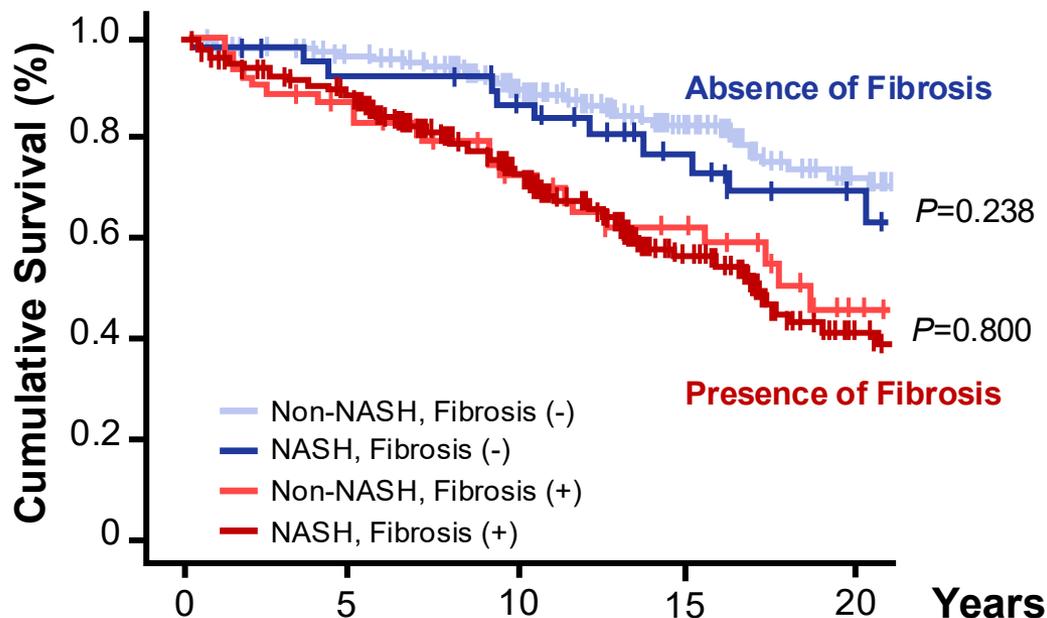


Hepatic manifestation of the metabolic syndrome.

Strongly associated with insulin resistance

Fibrosis Was the Only Independent Predictor of Clinical Outcomes

NAS Does not Predict Mortality



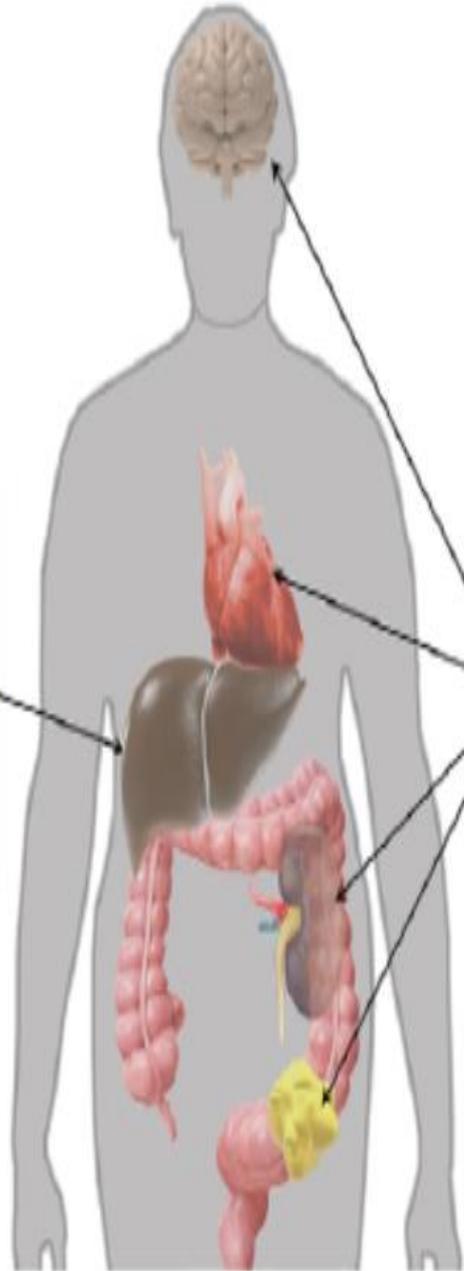
NAS score ≥ 5 was used as a surrogate for the histologic diagnosis of NASH

Fibrosis Predicts Morbidity

Fibrosis Stage	Liver-related Events	Hazard Ratio (95% CI)
0	1.6%	1.0 (reference)
1	2.8%	2.4 (0.6-8.9)
2	7.1%	7.5 (2.3-24.9)
3	13.7%	13.8 (4.4-43.7)
4	23.5%	47.5 (11.9-188.6)

Liver-related events were gastroesophageal varices with/without bleeding, ascites, portosystemic encephalopathy, HCC, and hepatorenal syndrome.

International cohort of biopsy proven 619 NAFLD patients followed for a median of 12.6 years (range: 0.3–35.1)



Patients with at-risk MASH

Liver-Related Outcomes:

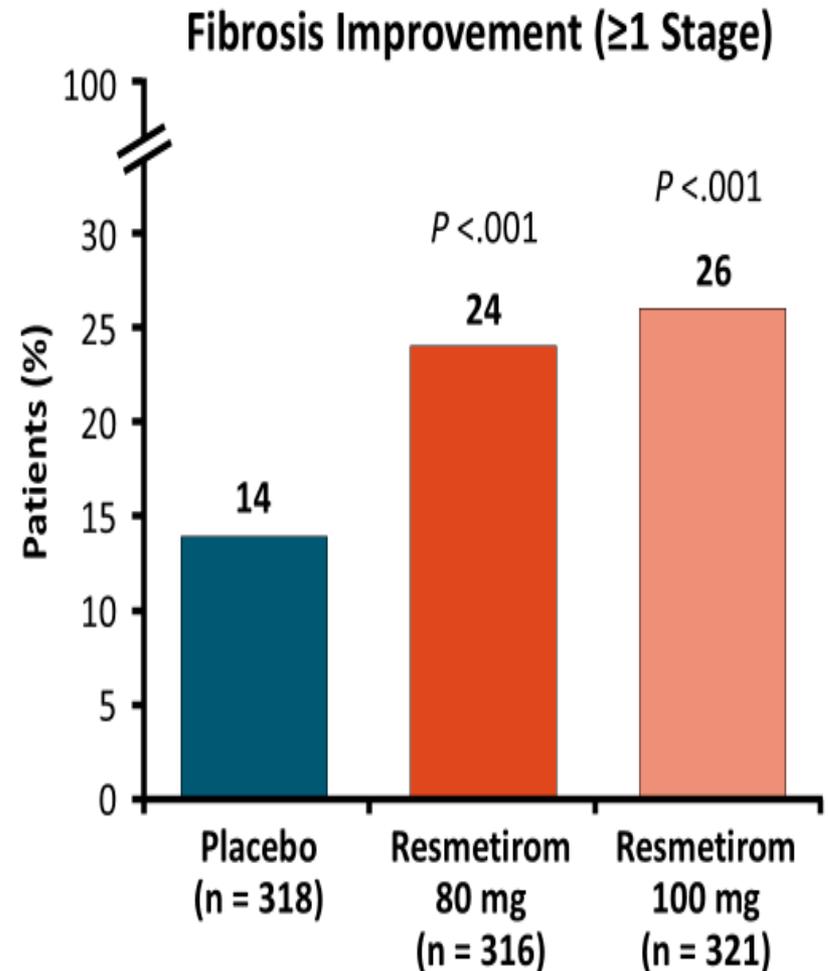
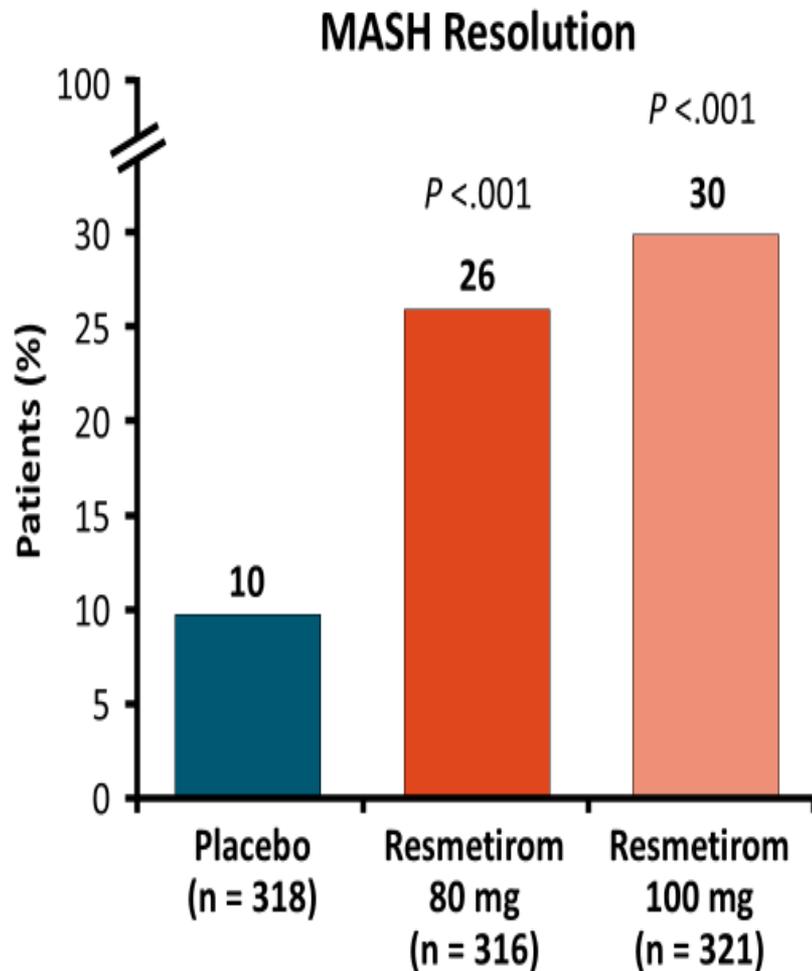
- Cirrhosis
- Hepatic Decompensation
- Liver Cancer

All patients with MASLD

Systemic Outcomes:

- Cardiovascular Disease
- Cerebrovascular Disease
- Diabetes Mellitus
- Chronic Kidney Disease
- Extrahepatic Cancers

MAESTRO-NASH: Phase III Trial With Resmetirom Liver Biopsy at Wk 52

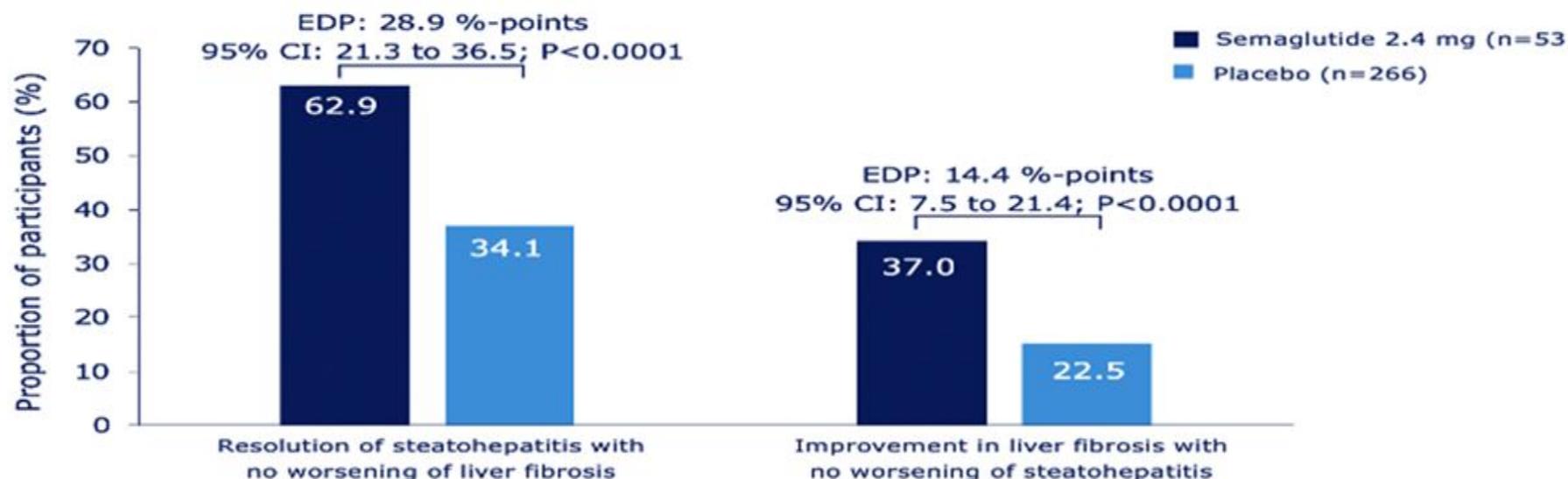


Baseline characteristics

Characteristic	Semaglutide 2.4 mg (N=534)	Placebo (N=266)
Age, years, mean (SD)	56.3 (11.4)	55.4 (12.0)
Sex, female, n (%)	313 (58.6)	144 (54.1)
Type 2 diabetes, n (%)	296 (55.4)	151 (56.8)
HbA _{1c} %, mean (SD)	6.6 (1.1)	6.4 (1.0)
HbA _{1c} %, mean (SD) — with type 2 diabetes	7.2 (1.1)	6.9 (1.0)
Body mass index, kg/m ² , mean (SD)	34.3 (7.2)	35.0 (7.1)
Alanine aminotransferase, U/L, mean (SD)	67.8 (42.3)	67.9 (44.7)
Fibrosis stage 3, n (%)	365 (68.4)	185 (69.5)
Liver stiffness by VCTE, kPa, mean (SD)	12.8 (6.6)	12.9 (7.6)
ELF score, mean (SD)	10.0 (0.9)	10.0 (1.0)
PRO-C3, ng/ml, mean (SD)	52.9 (24.9)	52.9 (28.1)

ELF, Enhanced Liver Fibrosis; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; PRO-C3, N-terminal type III collagen; SD, standard deviation; VCTE, vibration-controlled transient elastography.

Primary endpoints (ITT population)



CI, confidence interval; EDP, estimated difference in responder proportions; ITT, intention-to-treat.

Research Projects Gastroenterology and Hepatology

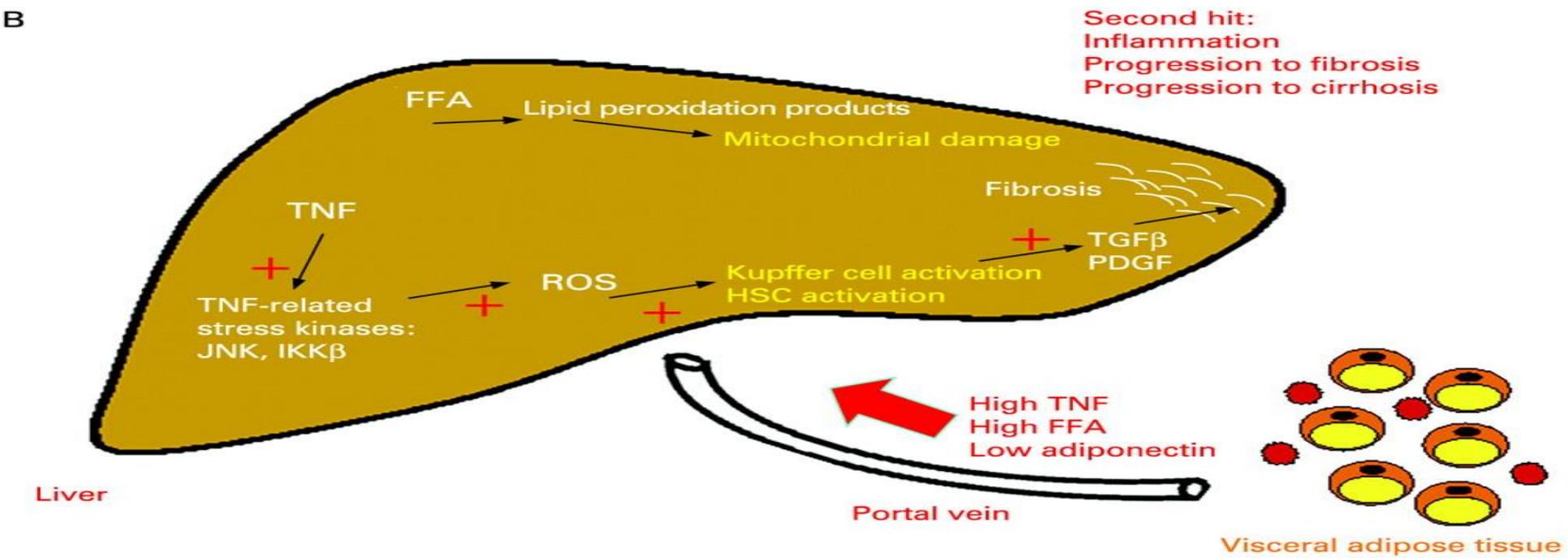
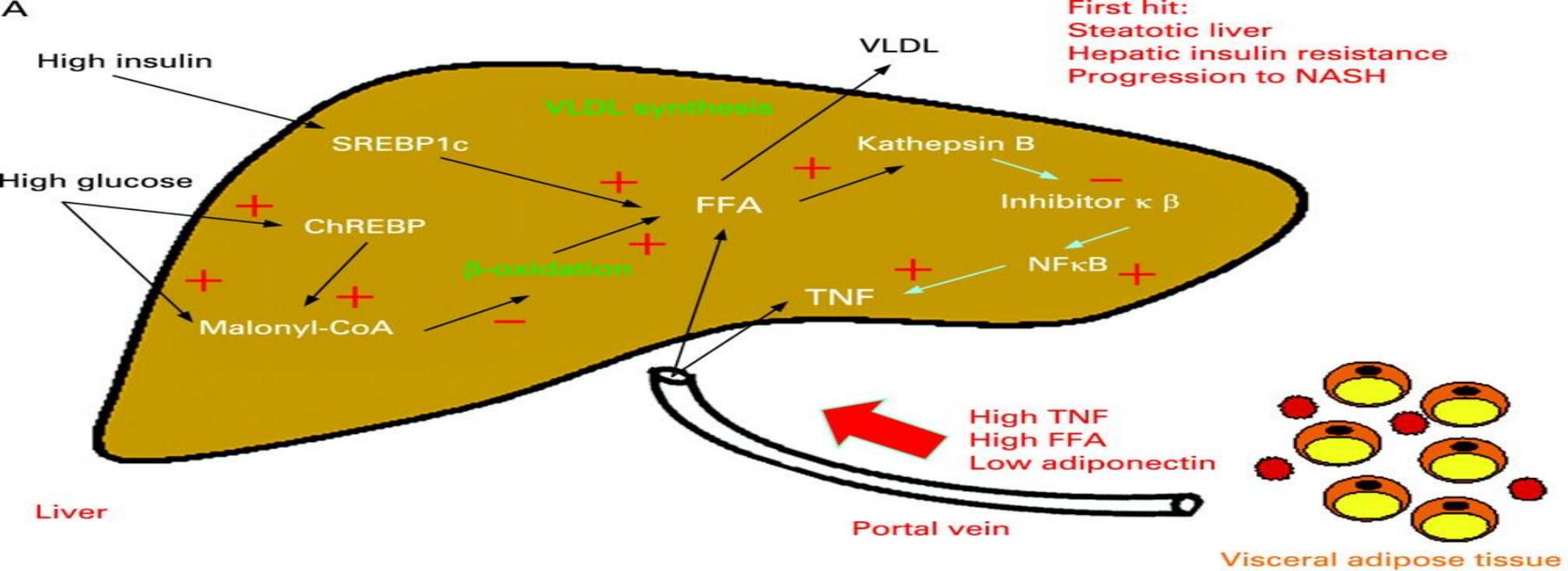
- MASLD

- Laderian B, Murali A, Sanchez AJ. Outcomes of Patients with Nonalcoholic Steatohepatitis with Cirrhosis and Low Model for End Stage Liver Disease Score. American Journal of Gastroenterology: October 2019
- Ahmed HS, Gangasani N, Jayanna M, Long M, Sanchez AJ, Murali A. The NAFLD Decompensation Risk Score: External Validation and Comparison to Existing Models to Predict Hepatic Events in a Retrospective Cohort Study. Journal of Clinical and Experimental Hepatology. Volume 13, Issue 2, 2023.
- Ahmed H, N. Murali, Sanchez AJ. Time to Development of Hepatic Events in Patients with Non-Alcoholic Fatty Liver Disease.
- Taiwo A, Merrill, R, Wendt L, Sanchez AJ, et al. Non-alcoholic Fatty Liver Disease (NAFLD), A Silent But Emerging Problem In Type 1 Diabetes. J Endocr Soc. 2023 Oct 5
- Chrysostome ML, Prakash S, Sanchez, AJ Nonalcoholic Fatty Liver Disease Is Associated With An Increased Risk Of Heart Block And Hepatic Events.
- Aslam, A; Kahveci, A; Garza, A; Sanchez, AJ Patterns of Practice for Screening and Management of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). Report of a Global Survey.

Research Projects Gastroenterology and Hepatology

MASLD, AA1AA def and Portal Hypertension

- Murali A, Prakash S, Sanchez AJ. Alpha-1-Antitrypsin Pi*MZ variant increases risk of developing hepatic events in nonalcoholic fatty liver disease patients. Clinics and Research in Hepatology and Gastroenterology, Volume 47, Issue 2, 2023, 102066.
- Wadle, R; Rustam, L; Sanchez, AJ;. Management and Outcomes of Gastric Varices: A Retrospective Study Presented at the World Congress of Gastroenterology. American College of Gastroenterology. (ACG) 2024.
- Safety and Outcomes of GLP-1 Receptor Agonists in Patients With Cirrhosis: A MELD-Matched Real-World Cohort Study- Submitted to EASL 2026
- Safety Of Resmetirom in MASLD: A Propensity Score-matched Real-world Cohort Analysis
- Submitted to EASL 2026



NASH - PILOT TRIAL

The aim of this study is to investigate the potential metabolic effects of resveratrol and NMN on **reversing mitochondrial defects** that develop in patients with fatty liver disease.

The hypothesis is that resveratrol plus NMN will enhance mitochondrial efficiency and electron transport improving fatty acid metabolism and one carbon metabolism. This will give insights into the **metabolic pathways** that could play a role in the progression of fatty liver disease.

NASH - PILOT TRIAL

Change from baseline to after treatment with C 13
breath testing for Mitochondrial Function,
comparing patients receiving:

Resveratrol plus NMN

Fat mass, fat free mass, percent fat of liver tissue
per MRI

antonio-sanchez@uiowa.edu

Projects in Hepatology

Real world Use of Anti-obesity Medications, and its effects in MASLD outcomes

Alpha 1 antitrypsin deficiency MZ - Predictors of disease progression, correlation with other liver diseases, and risk of liver cancer

antonio-sanchez@uiowa.edu

Projects in Hepatology (Portal HTN)

Pre-emptive TIPS:

- Retrospective review of all admissions for acute variceal hemorrhage.
- Assess whether indication for pre-emptive TIPS was present, and whether it was inserted.
- Identify reasons/risk factors for not inserting pre-emptive TIPS if indicated.

marta-tejedorbravo@uiowa.edu

Projects in Hepatology (MASLD)

Quality improvement project:

-Longitudinal study

-Provide written and audiovisual information to MASLD patients through MyChart, via a novel tool the University is implementing.

-Assess patient's outcomes and experience measures,

marta-tejedorbravo@uiowa.edu

Projects in Hepatology (CF- BM)

Cystic fibrosis related liver disease

MASLD in bone marrow transplant patients

sara-naimimohasses@uiowa.edu

Projects In Liver Transplantation

Transplant registry data (UNOS Star SAF)

Sex and body size disparities under MELD 3.0:
Evaluation of persisting gaps in liver transplant
access

tomohiro-tanaka@uiowa.edu

Projects in Metabolism

Understanding the mechanism of energy regulation and weight balance within the brain

Gut- brain axis cross talk in regulation metabolism

The role of the circadian molecular Clock in glucose and energy metabolism

Understanding the underlying mechanism of bariatric surgery on metabolism

Role of Toll-like receptor-4 and innate immune system in cardiac and metabolic function

mohamad-mokadem@uiowa.edu

Projects in IBD

Intestinal graft versus host disease

Graft versus tumor response

Inflammatory bowel disease

Role of microbiota and T helper 2 response in these pathologies

nedim-ince@uiowa.edu

Projects in IBD

Dr. Polyak will consider starting up any clinical IBD research project if there are interested residents.

steven-polyak@uiowa.edu

Projects in GI Motility

The mechanism of the motility and dysmotility of esophagus, stomach, and colon

The role of a novel population of subepithelial cells, subepithelial PDGFR α + cells (SPAC) in the mucosal homeostasis and immunity.

masaaki-kurahashi@uiowa.edu

GI/Hepatology Research Team

Jessica Valestin, B.S.

Clinical Research Manager

Division of GI/Hepatology | Digestive Health Center

Phone: 319.353.4574

Email:

antonio-sanchez@uiowa.edu

jessica-valestin@uiowa.edu

