Congresso Nazionale
AGGIORNAMENTI INFETTIVOLOGICI: HIV, EPATITI & …..
Firenze, 27-29 Gennaio 2025
Centro Congressi Hotel Albani

MASLD: Inquadramento diagnostico-terapeutico

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- **Alfasigma:** travel grants
- **AstraZeneca:** consultant fees
- **Biomarin:** consultant fees
- **Boehringer Ingelheim:** consultant fees
- **Gilead:** speaker honoraria, consultant fees
- **Gore:** speaker honoraria
- **Ipsen:** consultant fees
- **Madrigal:** consultant fees
- **MSD/Eisai:** consultant fees
- **Novo Nordisk:** consultant fees
- **Roche:** consultant fees, travel grants

Definition and (new) nomenclature

> Mayo Clin Proc. 1980 Jul;55(7):434-8.

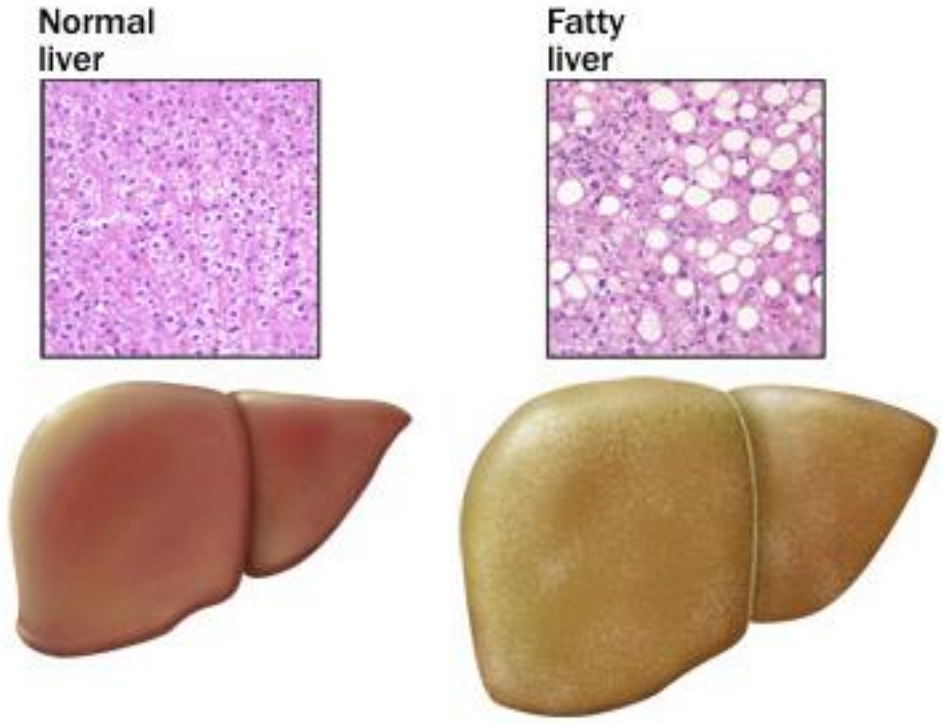
Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease

J Ludwig, T R Viggiano, D B McGill, B J Oh

PMID: 7382552

Abstract

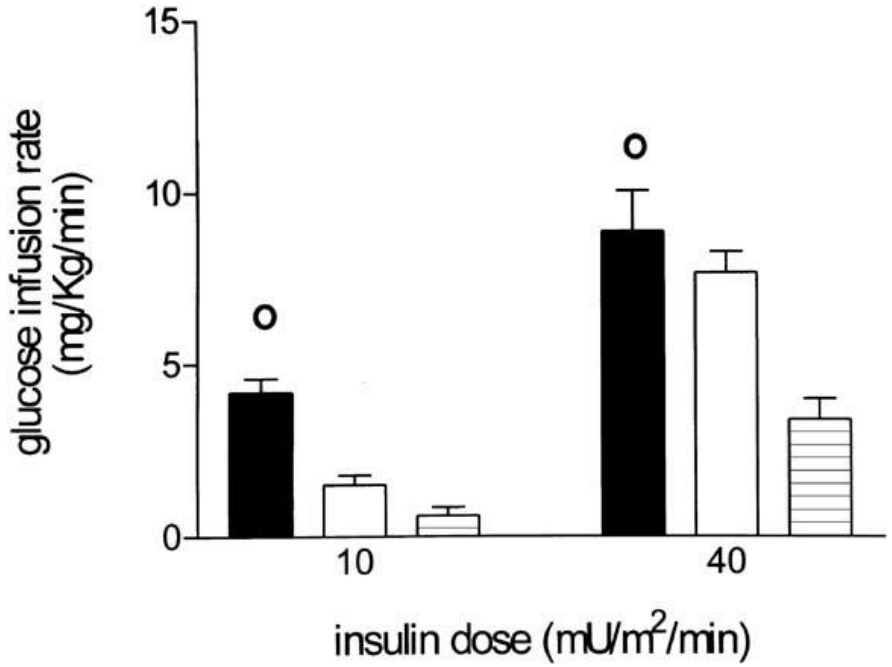
Nonalcoholic steatohepatitis is a poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Described here are findings in 20 patients with nonalcoholic steatohepatitis of unknown cause. The biopsy specimens were characterized by the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates, and, in most instances, Mallory bodies; Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings. Currently, we know of no effective therapy.

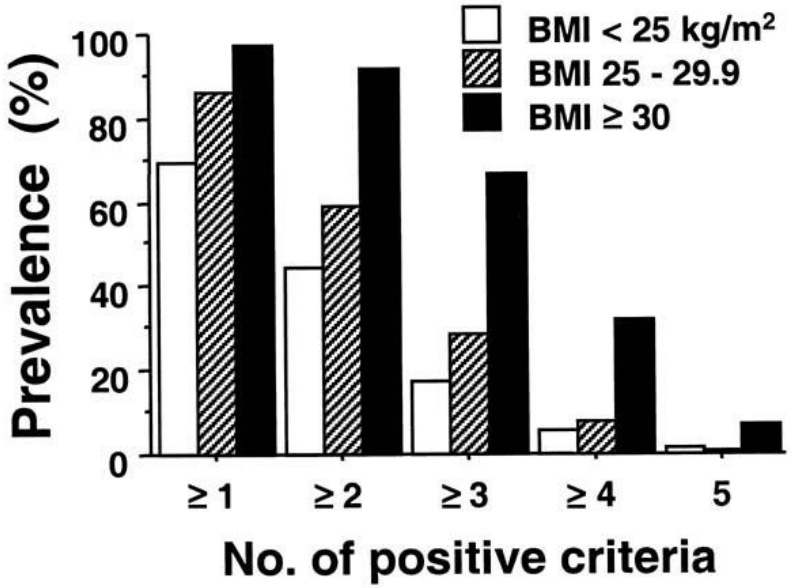


NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Steatosis (>5% of hepatocytes)
- Evidence for minimal (<20g/d) alcohol consumption
- Exclusion of other causes of liver disease

Insulin resistance and NAFLD





- Higher histopathologic grading
- More severe fibrosis

Sanyal et al., Gastroenterology 2001

Marchesini et al., Hepatology 2003

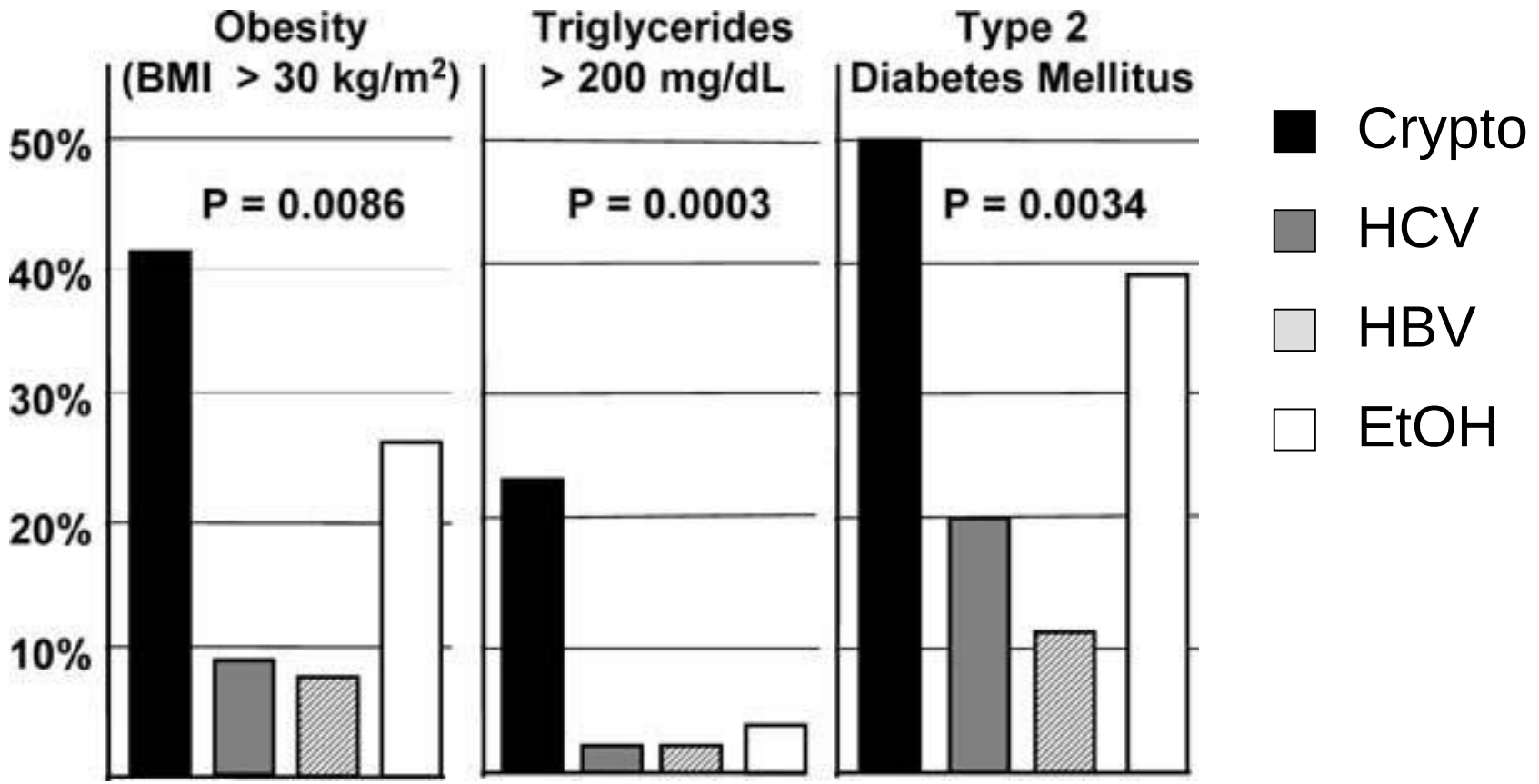
NASH as a cause of cryptogenic cirrhosis

TABLE 3. Comparison of Cryptogenic Patients With Controls

	Cryptogenic Cirrhosis	NASH	Nonalcoholic HCV Cirrhosis (Age ≥50)	AMA + PBC With Cirrhosis
N	70	50	39	33
Age	63 ± 11	49 ± 14	60 ± 7	54 ± 10
Female (%)	49 (70%)	28 (56%)	15 (36%)	33 (100%)
DM or obesity*	51 (73%)	35 (70%)	11 (28%)	8 (33%)
Diabetes (%)†	37 (53%)	21 (42%)	10 (25%)	5 (15%)
Marked obesity‡	33 (47%)	32 (64%)	1 (3%)	5 (15%)
AST (7-40 IU/L)	60 ± 54	70 ± 50	111 ± 83	83 ± 49
ALT (6-65 IU/L)	46 ± 37	88 ± 59	100 ± 78	76 ± 50
AST/ALT§	1.5 ± 0.9	0.9 ± 0.4	1.3 ± 0.5	1.3 ± 0.7
IgG (694-1,618 mg/dL)**	1,719 ± 704	1,375 ± 506	2,326 ± 549	1,873 ± 653
IgA (68-378 mg/dL)**	588 ± 405	359 ± 228	497 ± 282	368 ± 211
IgG/A ratio	3.6 ± 1.7	4.7 ± 2.4	5.2 ± 2.6	5.6 ± 2.3
Abn IgG (%)¶	26/52 (50%)	6/43 (14%)	17/18 (94%)	15/25 (60%)
Abn IgA (%)	32/52 (61%)	11/43 (26%)	9/18 (50%)	11/25 (44%)

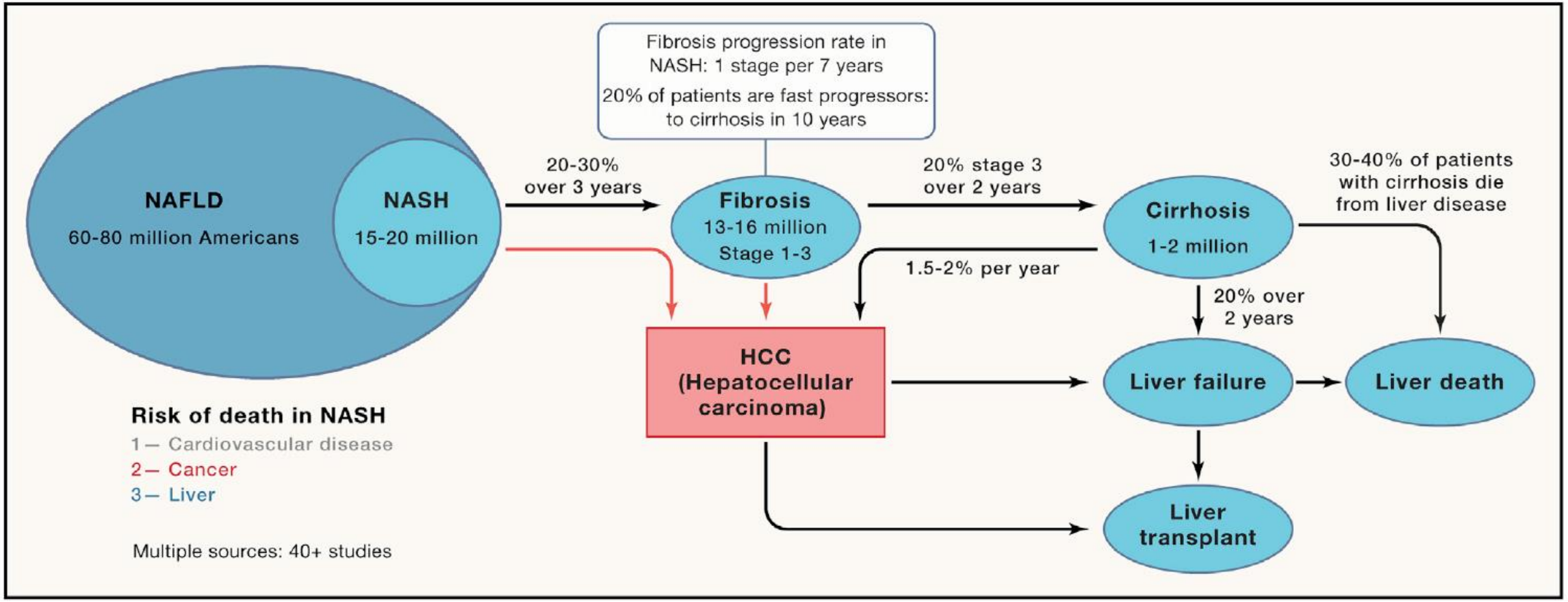
Caldwell et al., Hepatology 1999

NASH as a cause of hepatocellular carcinoma



Bugianesi et al., Gastroenterology, 2002

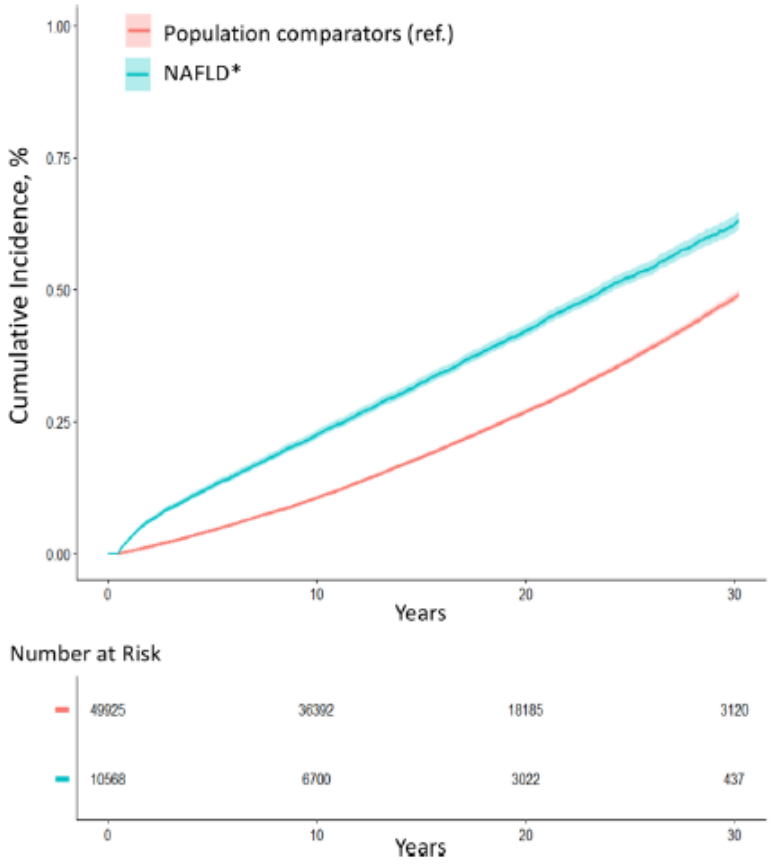
Natural history of NAFLD

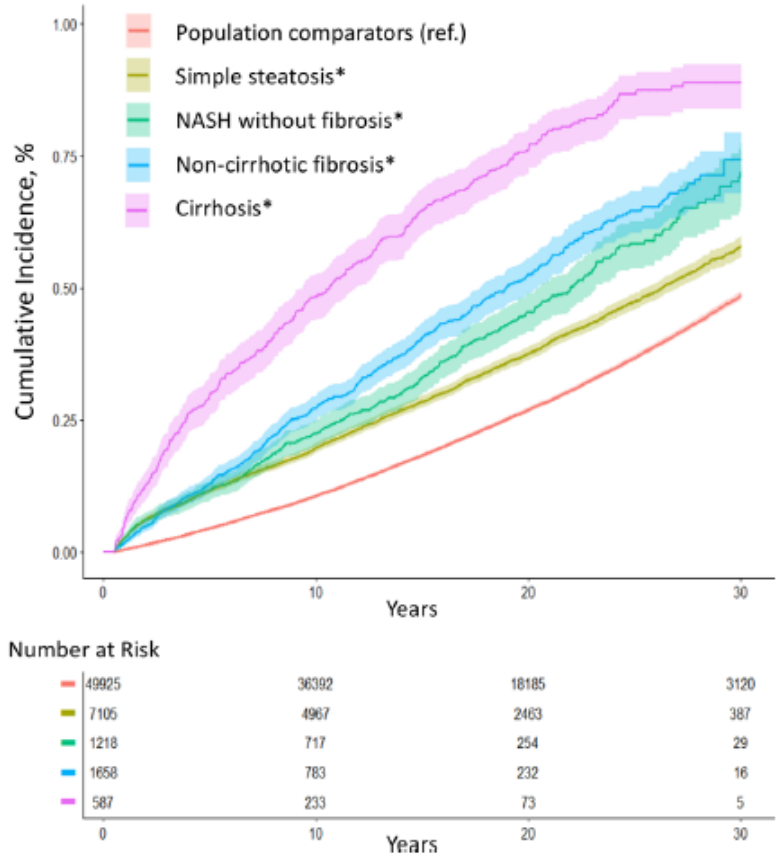


Loomba et al., Cell 2021

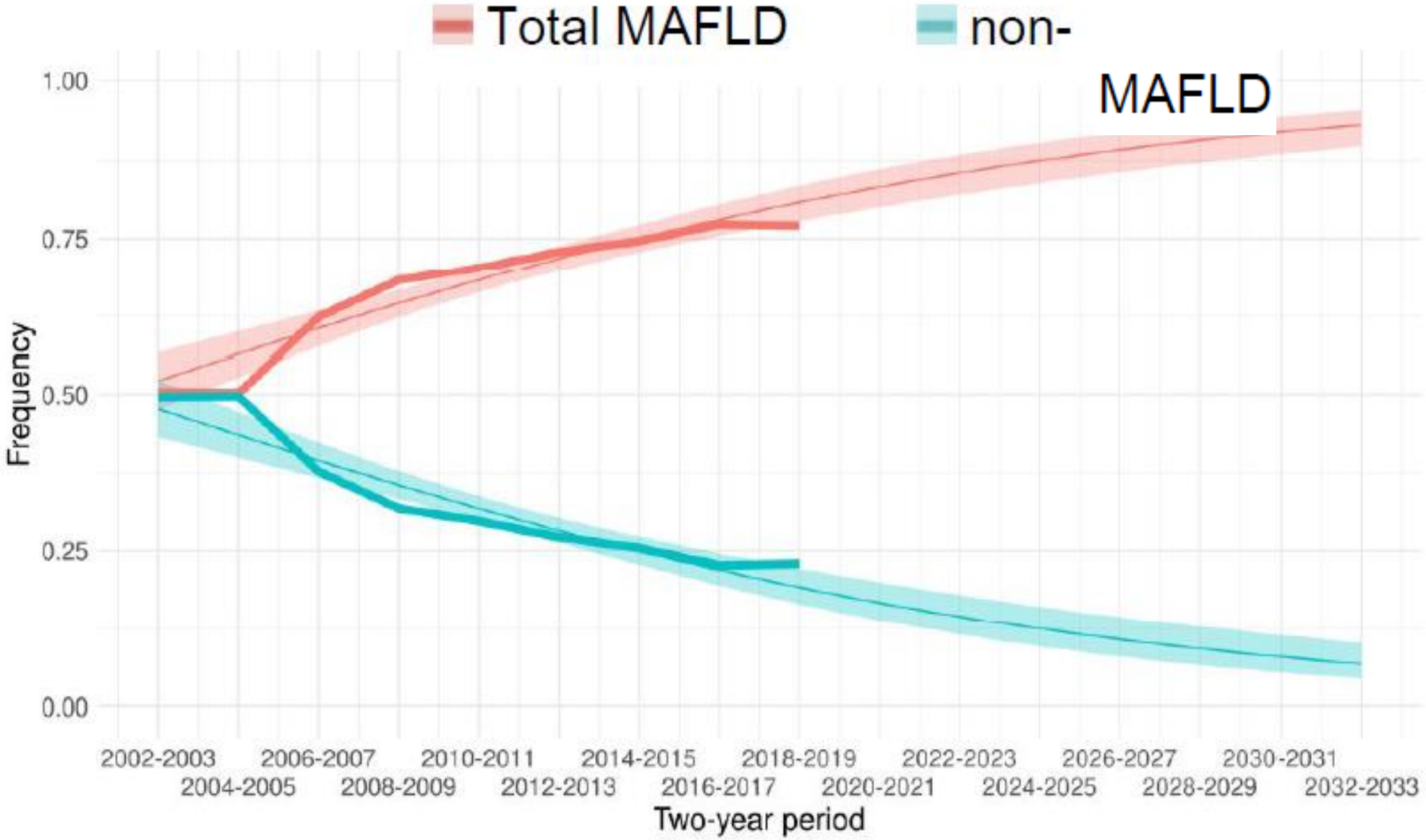
All-cause mortality according to NASH and histological severity

- Cardiovascular events
- Extrahepatic neoplasia
- Liver-related events





Simon et al., Gut 2020



Svegliati Baroni, Vitale et al., Gut 2022

Forms of NAFLD

✓ **"Primary" NAFLD: Associated with the metabolic syndrome**

✓ **"Secondary" NAFLD: Associated with different conditions**

Drugs: Steroids, Amiodarone, Tamoxifen, ART, chemotherapy

Metabolic or genetic alterations: Lipodystrophy, Dysbetalipoproteinemia, Weber-Christian disease

Nutritional: TPN, Rapid weight loss, Bariatric surgery, Starvation

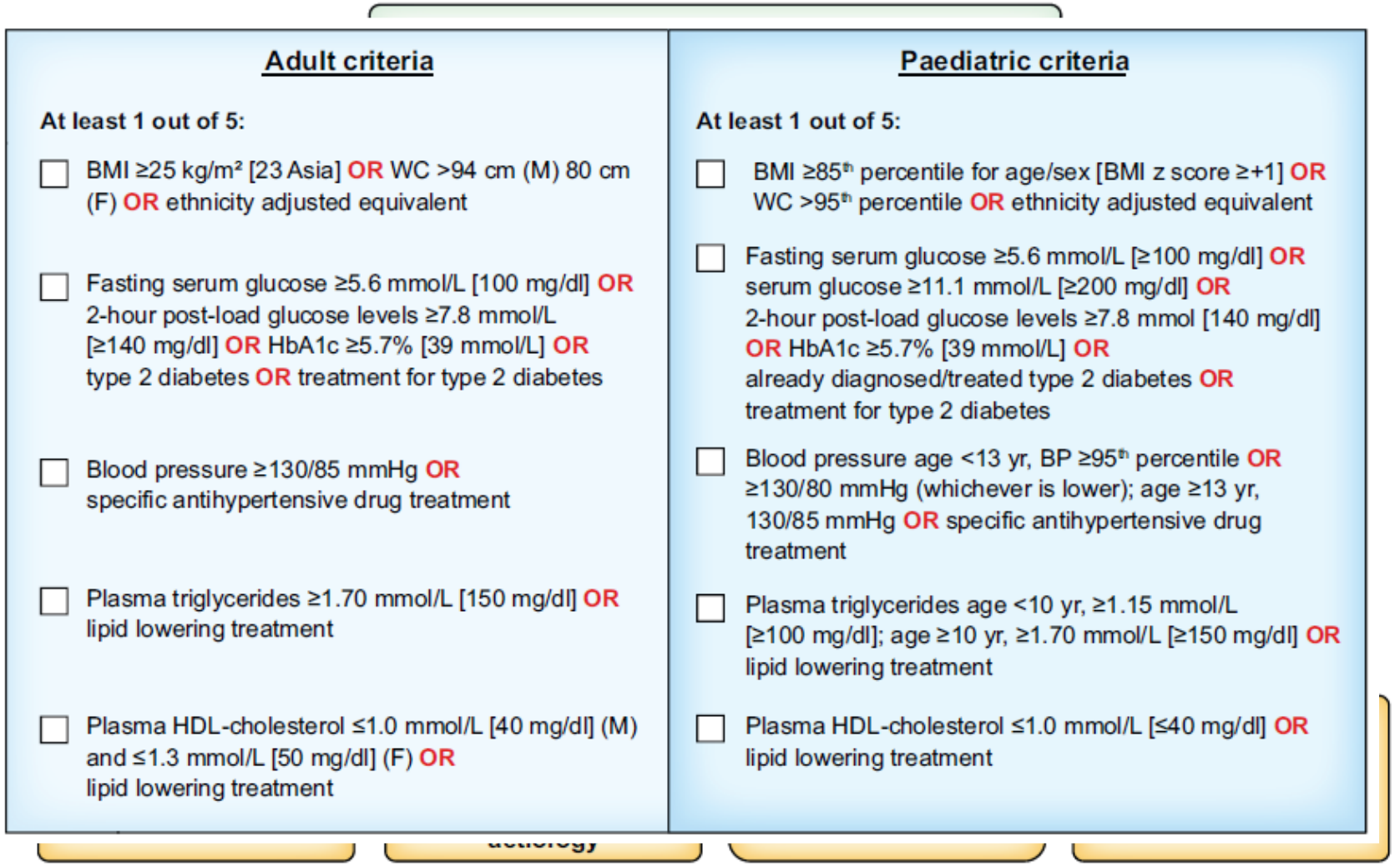
Small bowel diseases: IBD, Bacterial overgrowth

Environmental hepatotoxins: e.g. Petrochemicals

✓ **Steatosis accompanying other forms of liver disease**

HCV genotype 3, Wilson's disease, celiac disease

New nomenclature for steatosis



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 equivalent
- ☐ 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

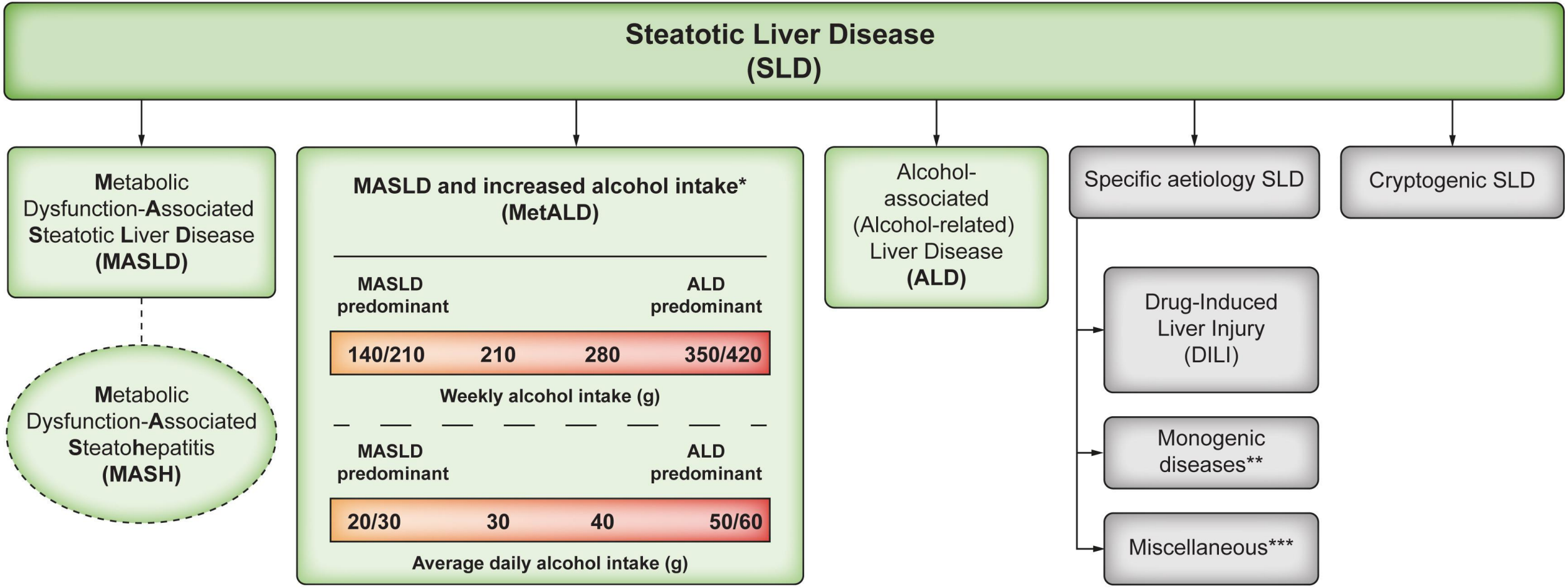
Paediatric criteria

At least 1 out of 5:

- ☐ BMI ≥85th percentile for age/sex [BMI z score ≥+1] OR WC >95th percentile OR ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥5.6 mmol/L [≥100 mg/dl] OR serum glucose ≥11.1 mmol/L [≥200 mg/dl] OR 2-hour post-load glucose levels ≥7.8 mmol [140 mg/dl] OR HbA1c ≥5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
- ☐ Blood pressure age <13 yr, BP ≥95th percentile OR ≥130/80 mmHg (whichever is lower); age ≥13 yr, 130/85 mmHg OR specific antihypertensive drug treatment
- ☐ Plasma triglycerides age <10 yr, ≥1.15 mmol/L [≥100 mg/dl]; age ≥10 yr, ≥1.70 mmol/L [≥150 mg/dl] OR lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤1.0 mmol/L [≤40 mg/dl] OR lipid lowering treatment

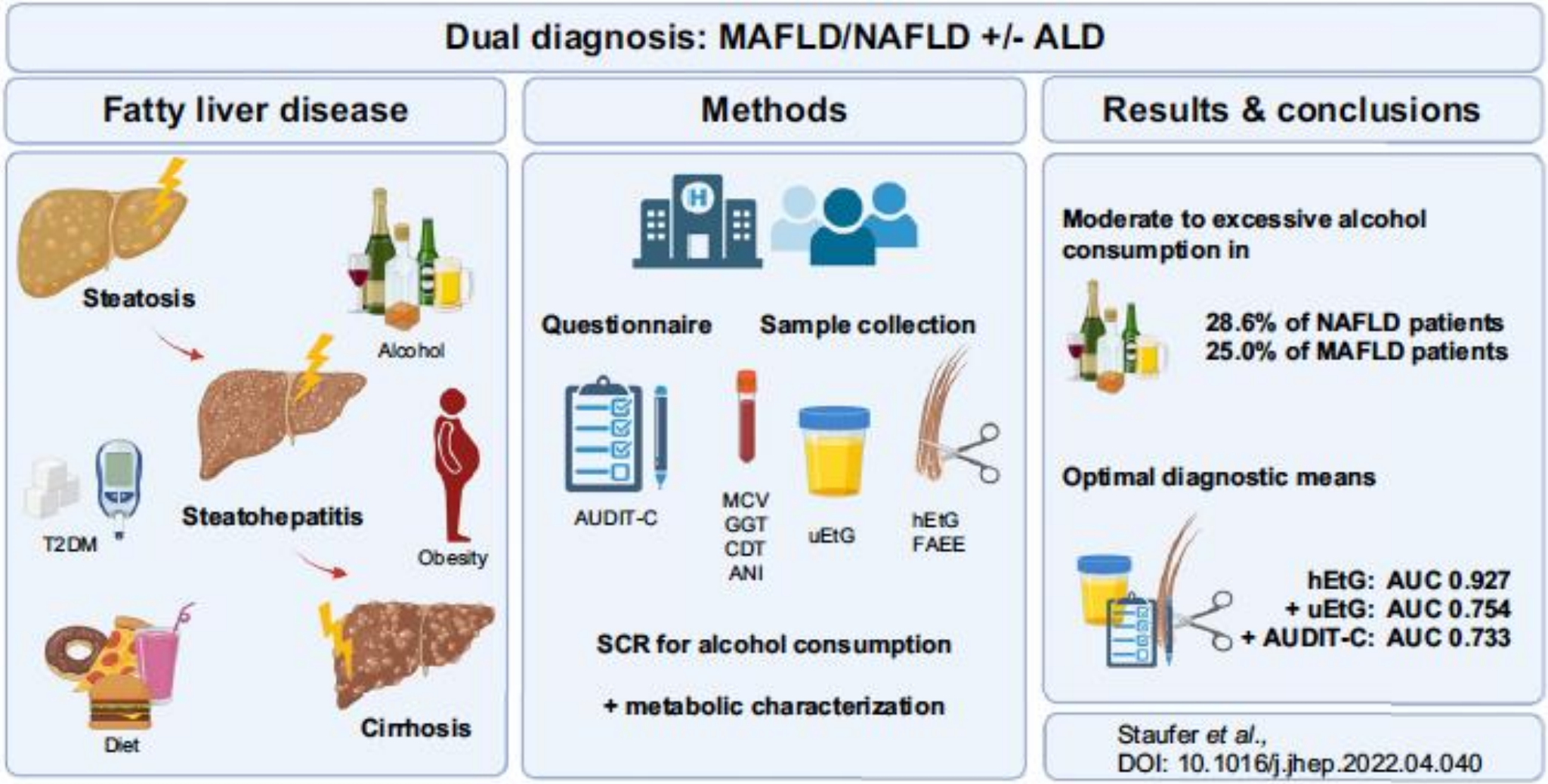
Rinella et al., J Hepatol 2023

New nomenclature for steatosis



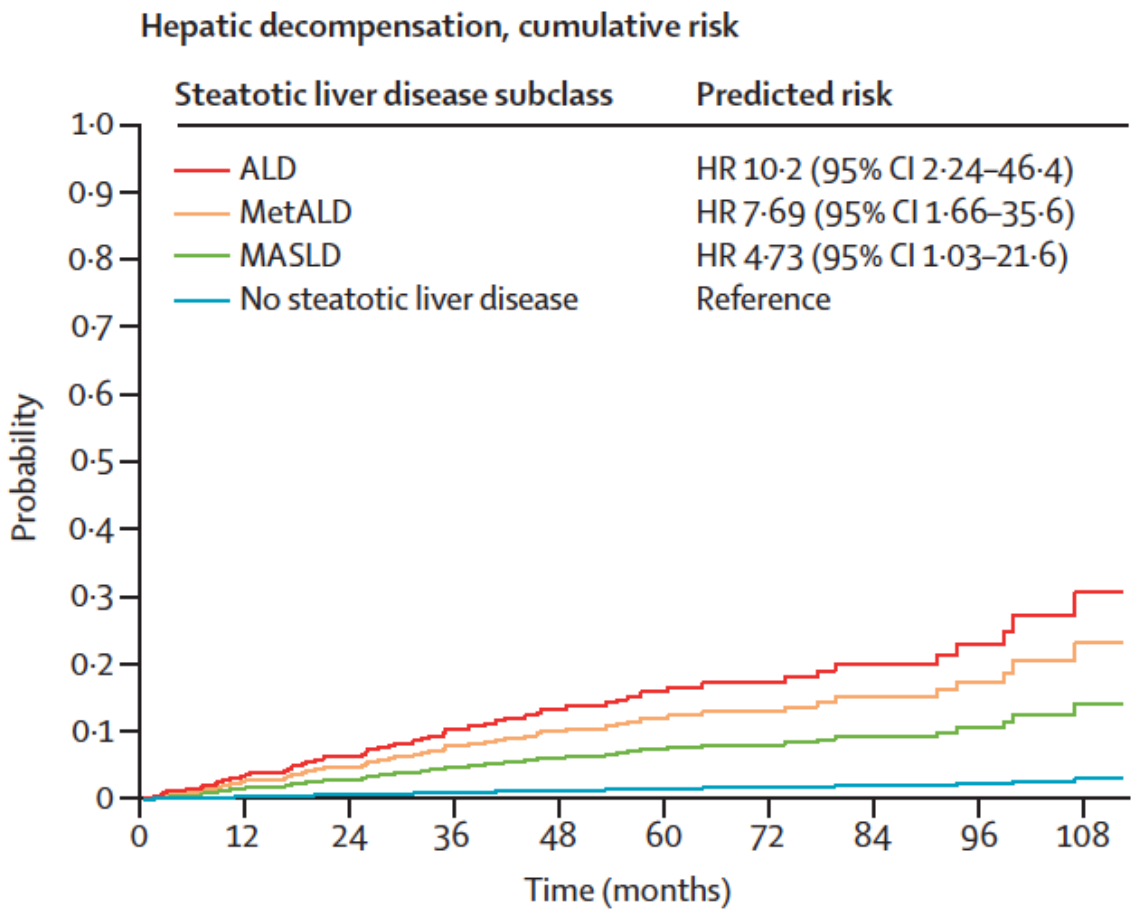
Rinella et al., J Hepatol 2023

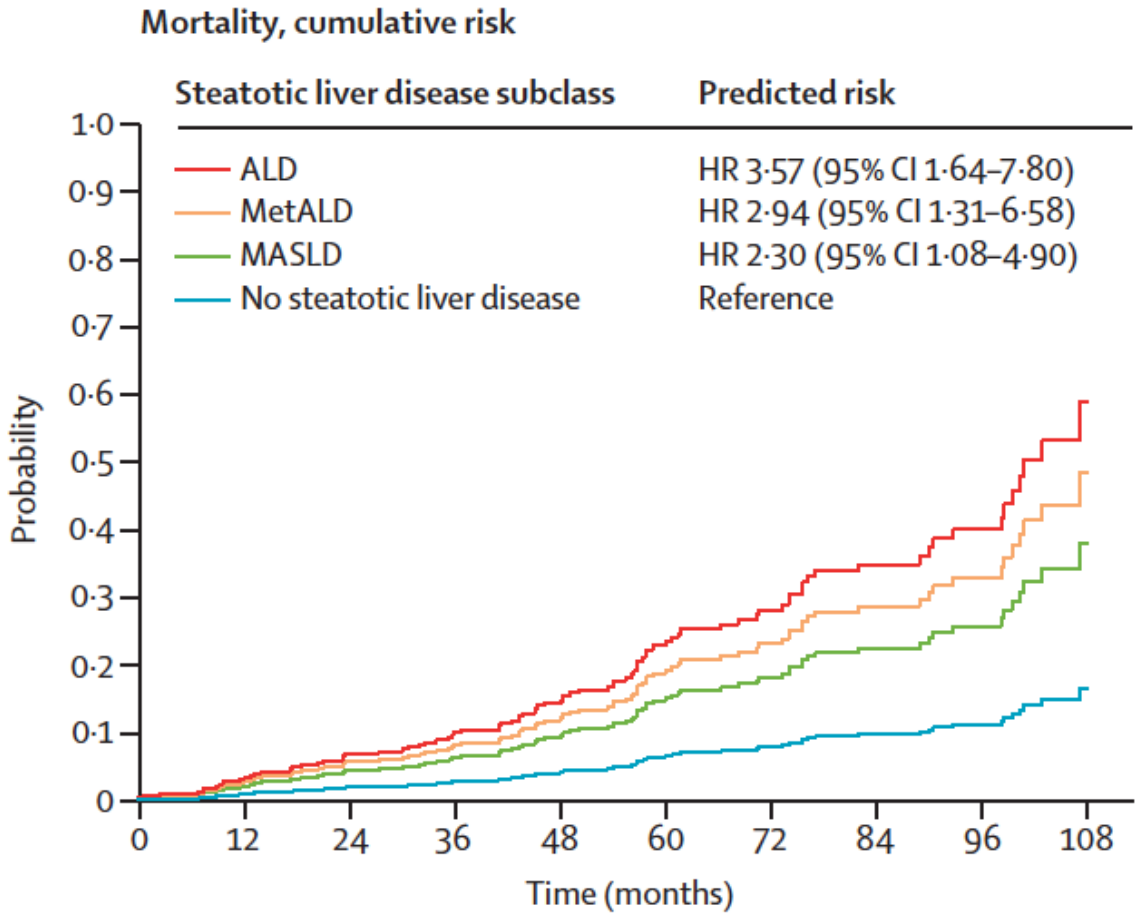
Alcohol consumption in presumed NAFLD



Staufer et al., J Hepatol 2022

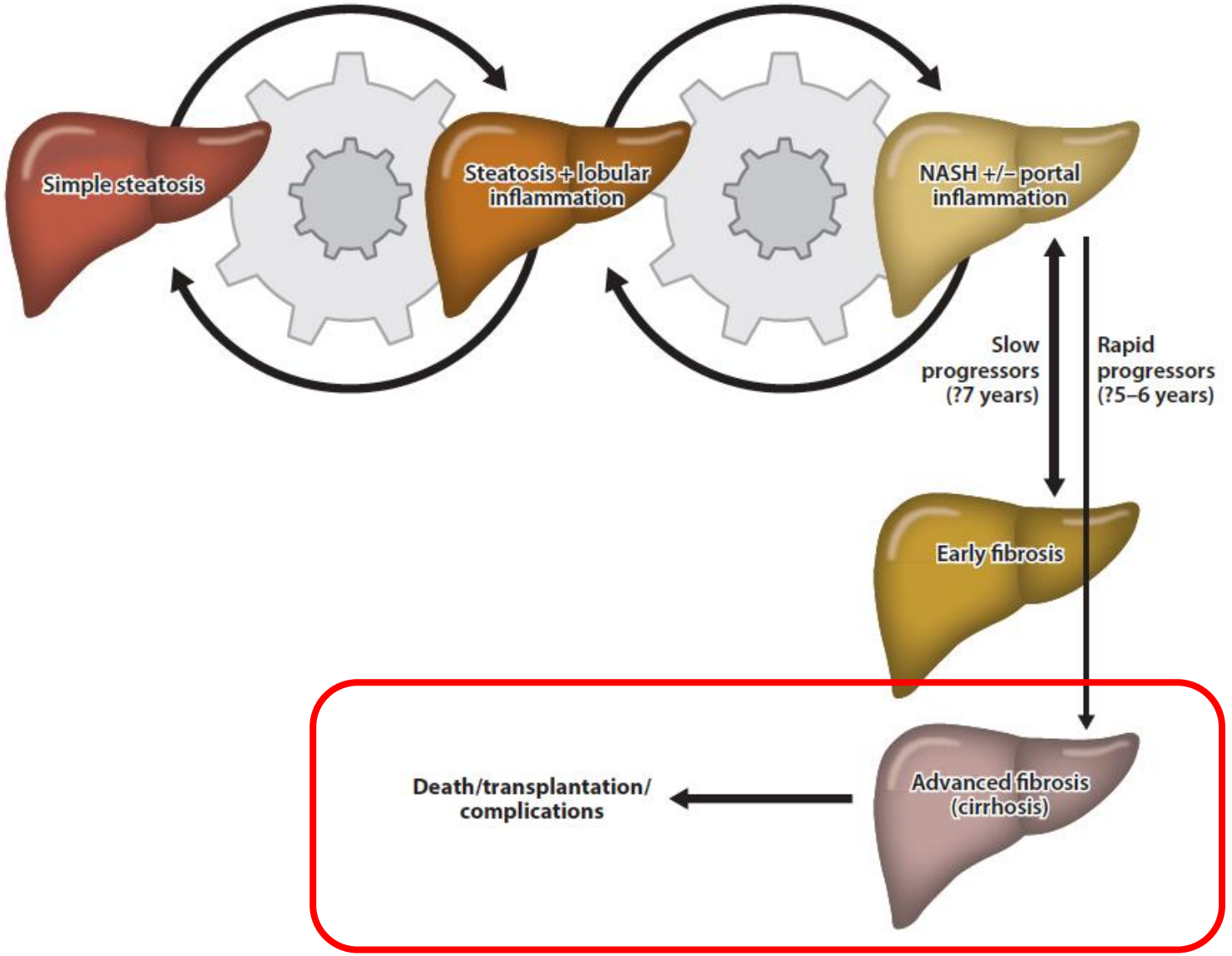
Distinct prognoses for the common subclasses of steatotic liver disease





Israelsen et al., Lancet 2024

Diagnostic strategies and referral



Hardy et al. Annu Rev Pathol 2017

Serum biomarkers

- AST/ALT ratio
- APRI
- FIB-4
- NAFLD fibrosis score (NFS)

Non Patented

- FibroTest®
- ELF™
- FibroMètre®
- Hepascore

Patented

Elastography techniques

TE | ARFI / 2D SWE | MRE

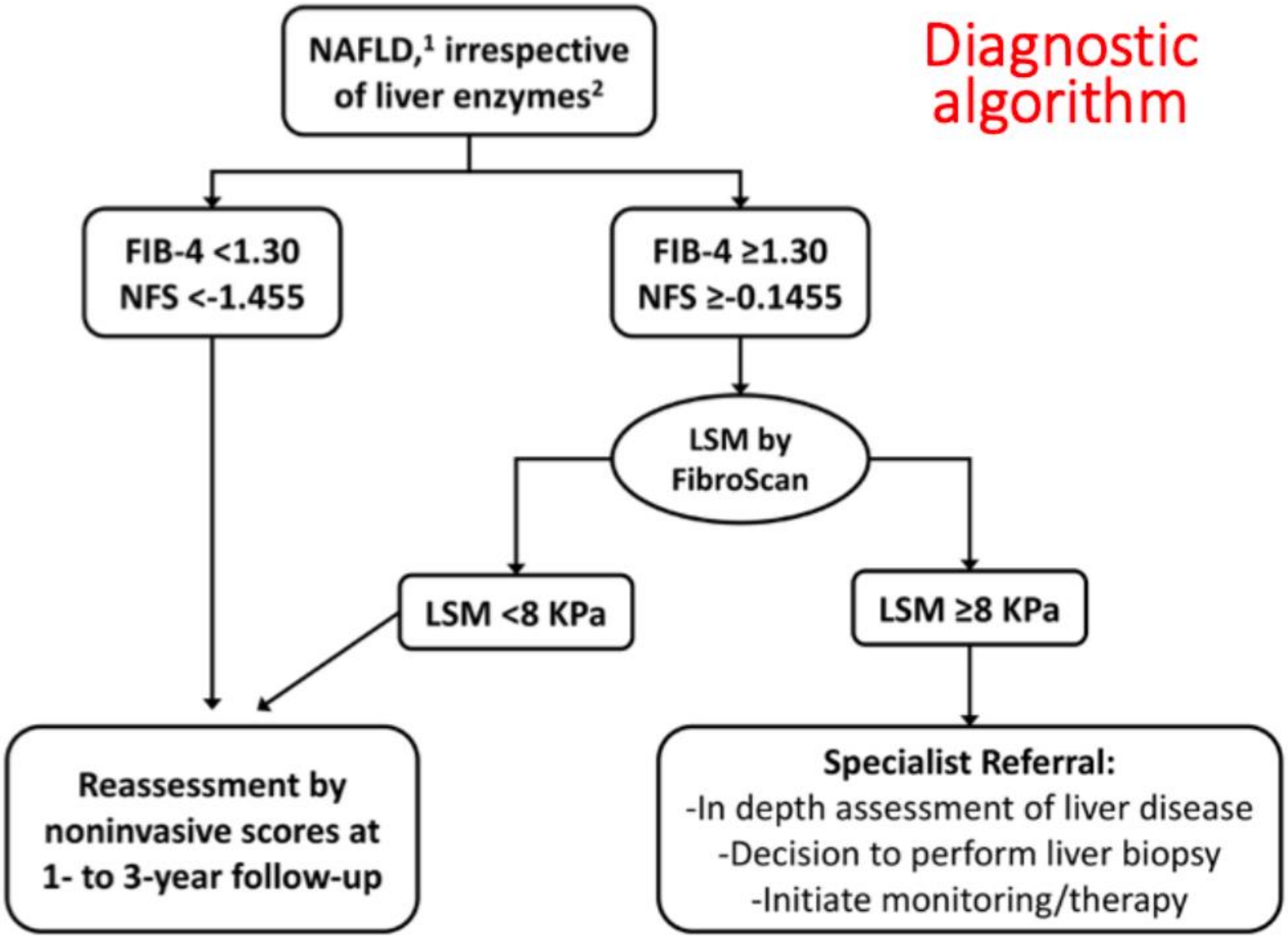
Availability

Cost

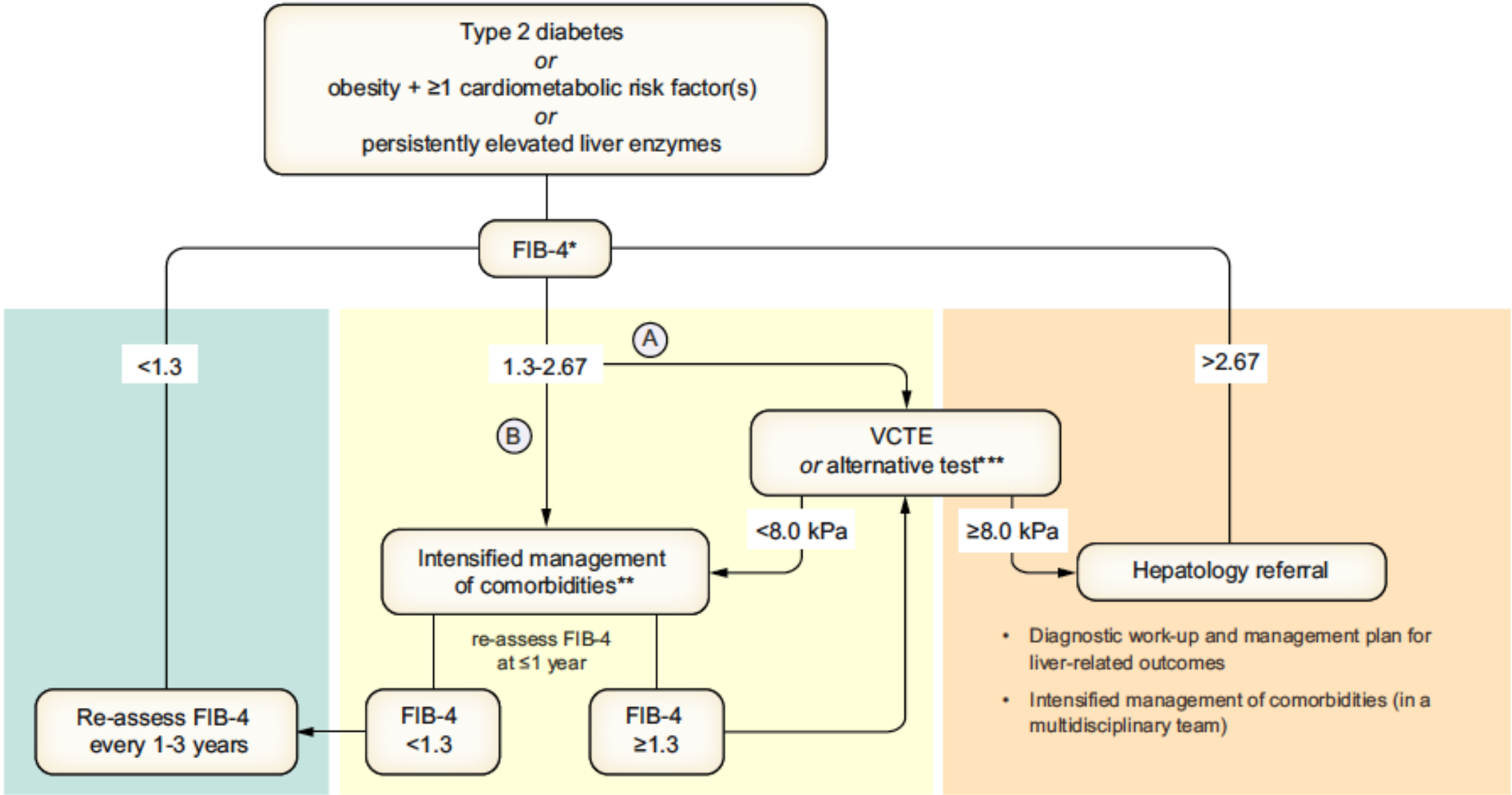
Primary care → Liver clinics

Castera, Liver Int 2020

Diagnostic algorithm



Italian NAFLD Guidelines, 2021

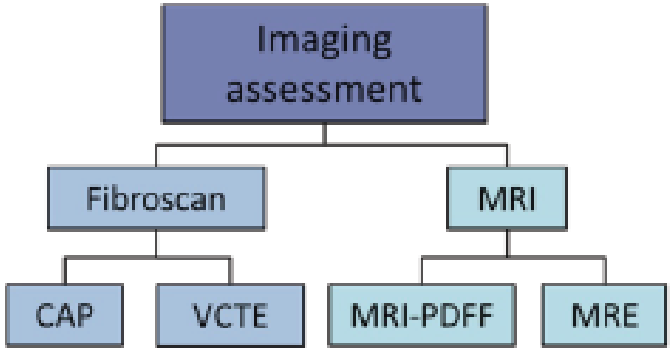


EASL guidelines 2024

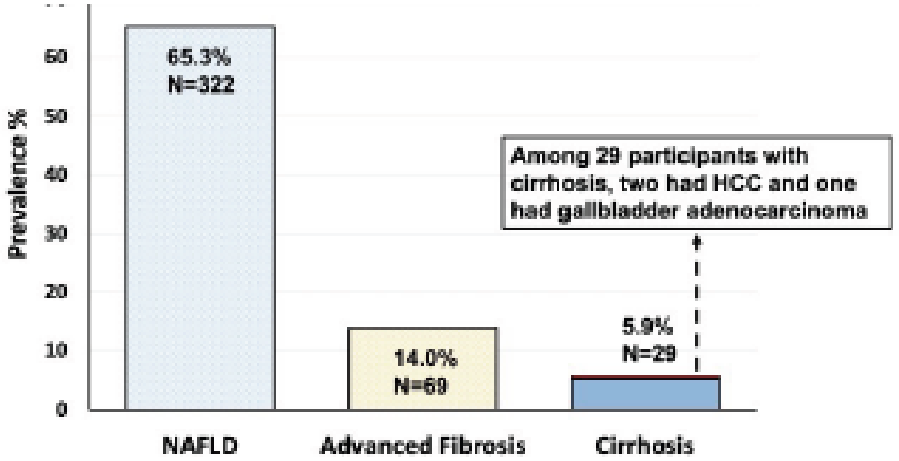
Prevalence of NAFLD, advanced fibrosis, cirrhosis and HCC in people with type 2 diabetes

Type 2 Diabetes
Age ≥ 50 years

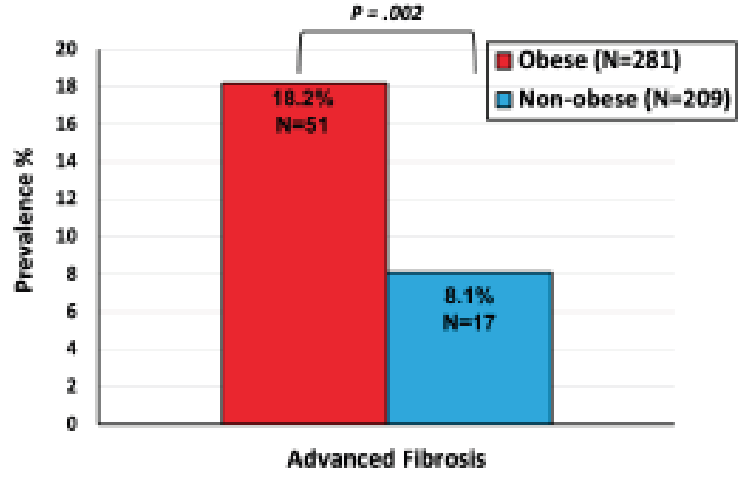
Prospectively recruited participants underwent a research examination with laboratory and clinical assessment to rule out other causes of liver disease.



The prevalence of NAFLD, advanced fibrosis and cirrhosis were 65%, 14% and 6% respectively.

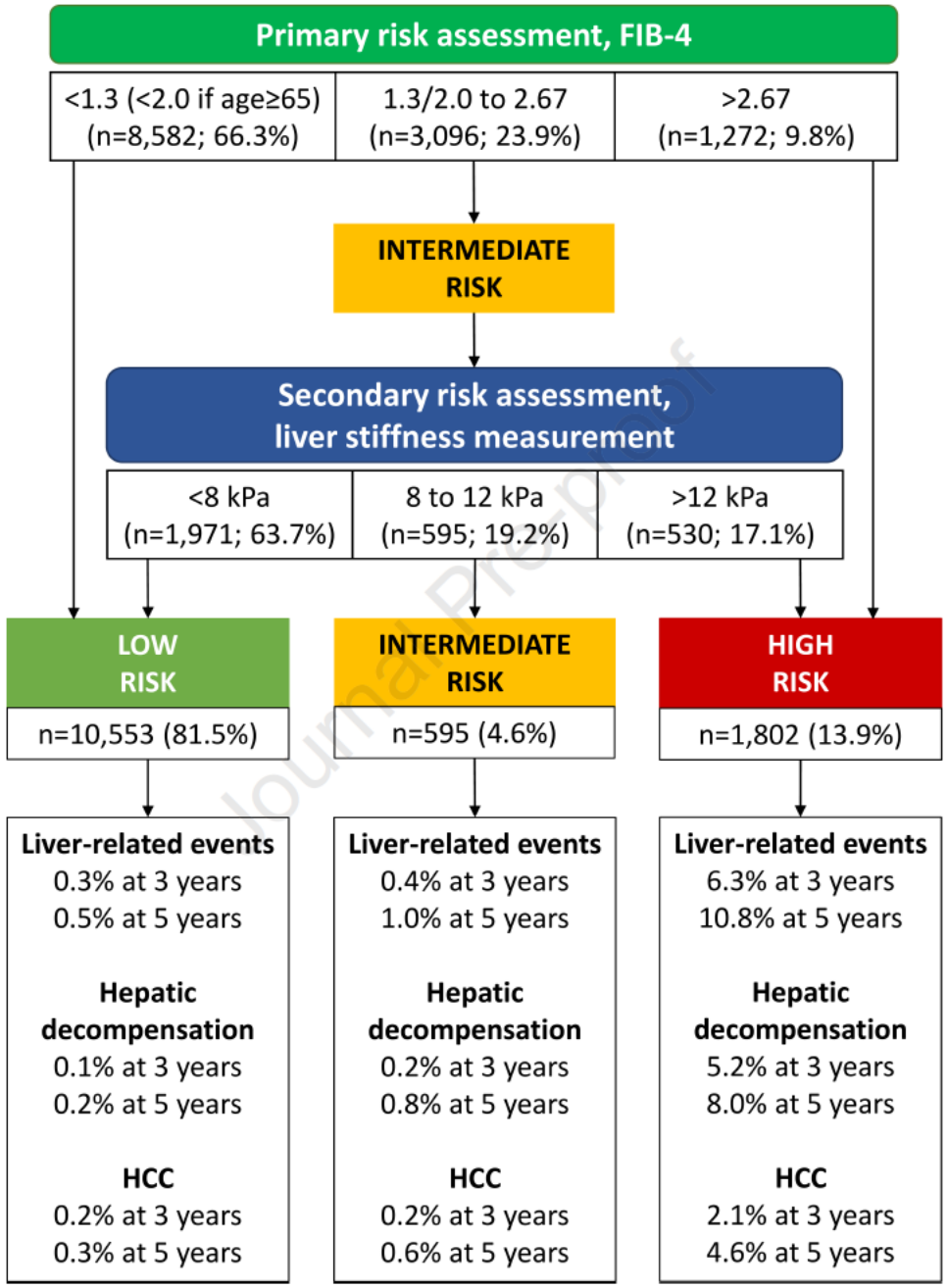


Obesity significantly increased the risk of advanced fibrosis



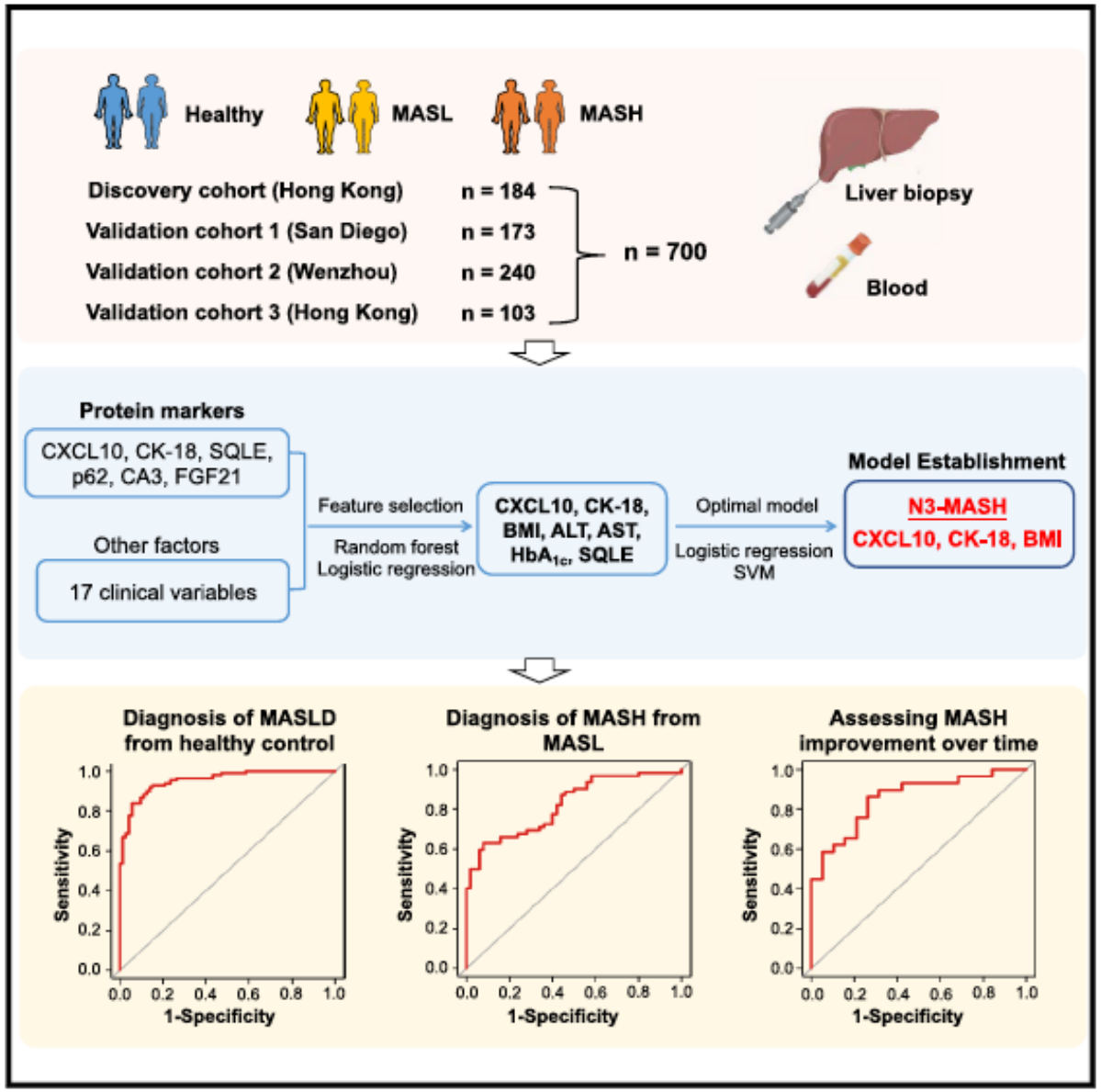
Ajmera et al., J Hepatol 2022

Prognostic performance of the two-step clinical care pathway



Cheuk-Fung Yip et al, J Hepatol 2025

A blood-based biomarker panel for non-invasive diagnosis of MASLD



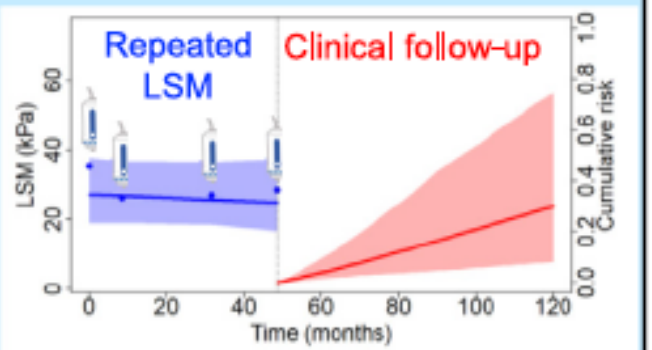
Zhang et al., Cell Metab 2024

Dynamics in liver stiffness measurements predict outcomes in advanced chronic liver disease

Cohort

- **2508** patients (757 cACLD)
- **8561** single reliable liver stiffness measurements (LSM)
- **71 months** of clinical follow-up

Joint modeling
updated risk assessment



LSM-dynamics in cACLD

20% increase → 50% increased risk

20% decrease → 50% decreased risk

✓ **Superior** to **single LSM**

✓ **Superior** to **FIB-4** & **MELD dynamics**

Decrease to <20kPa → favorable outcome

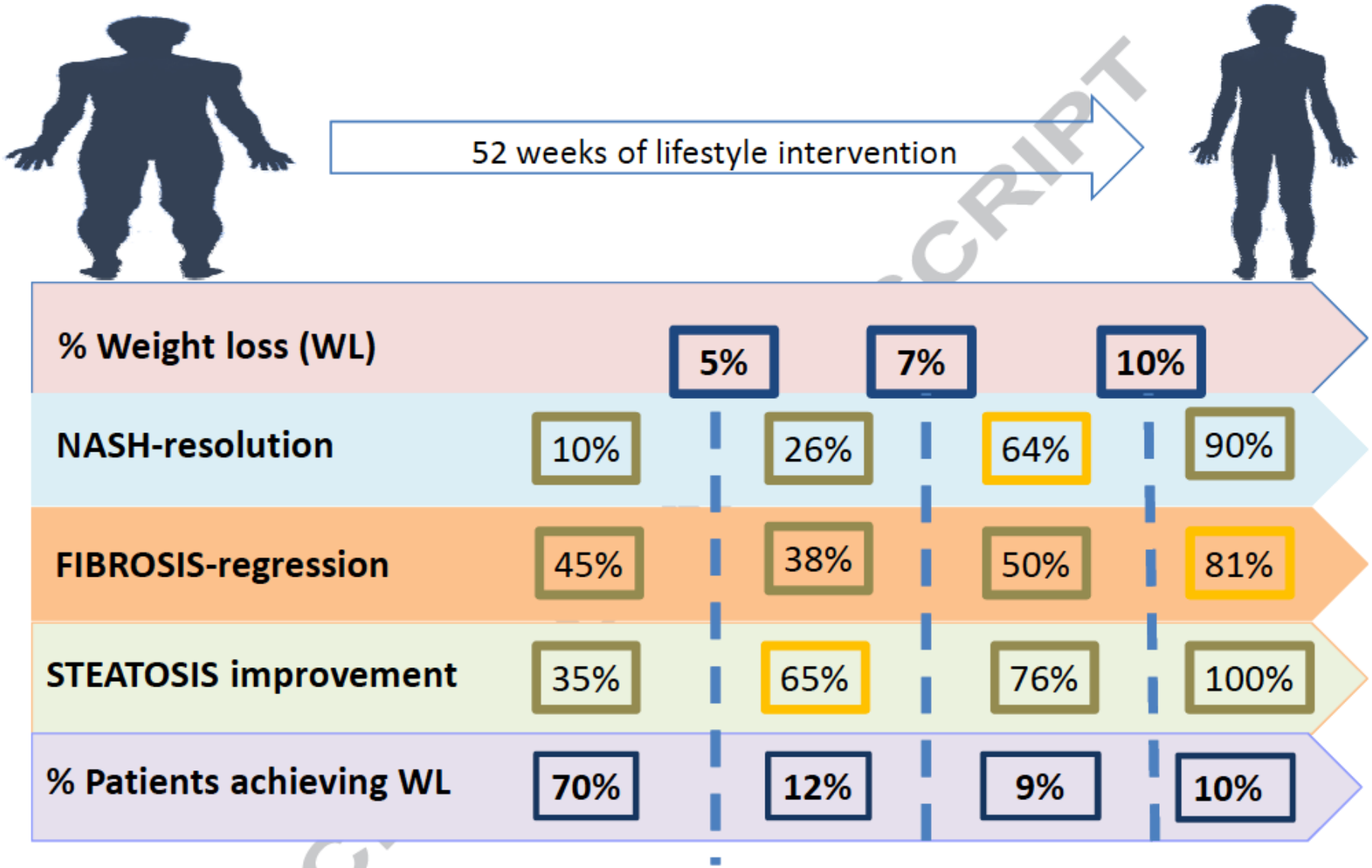
Repeat LSM

- ☑ **to monitor progression** (nonACLD)
- ☑ **to predict outcome** (cACLD + dACLD)

Gastroenterology

Semmler et al., Gastroenterology 2023

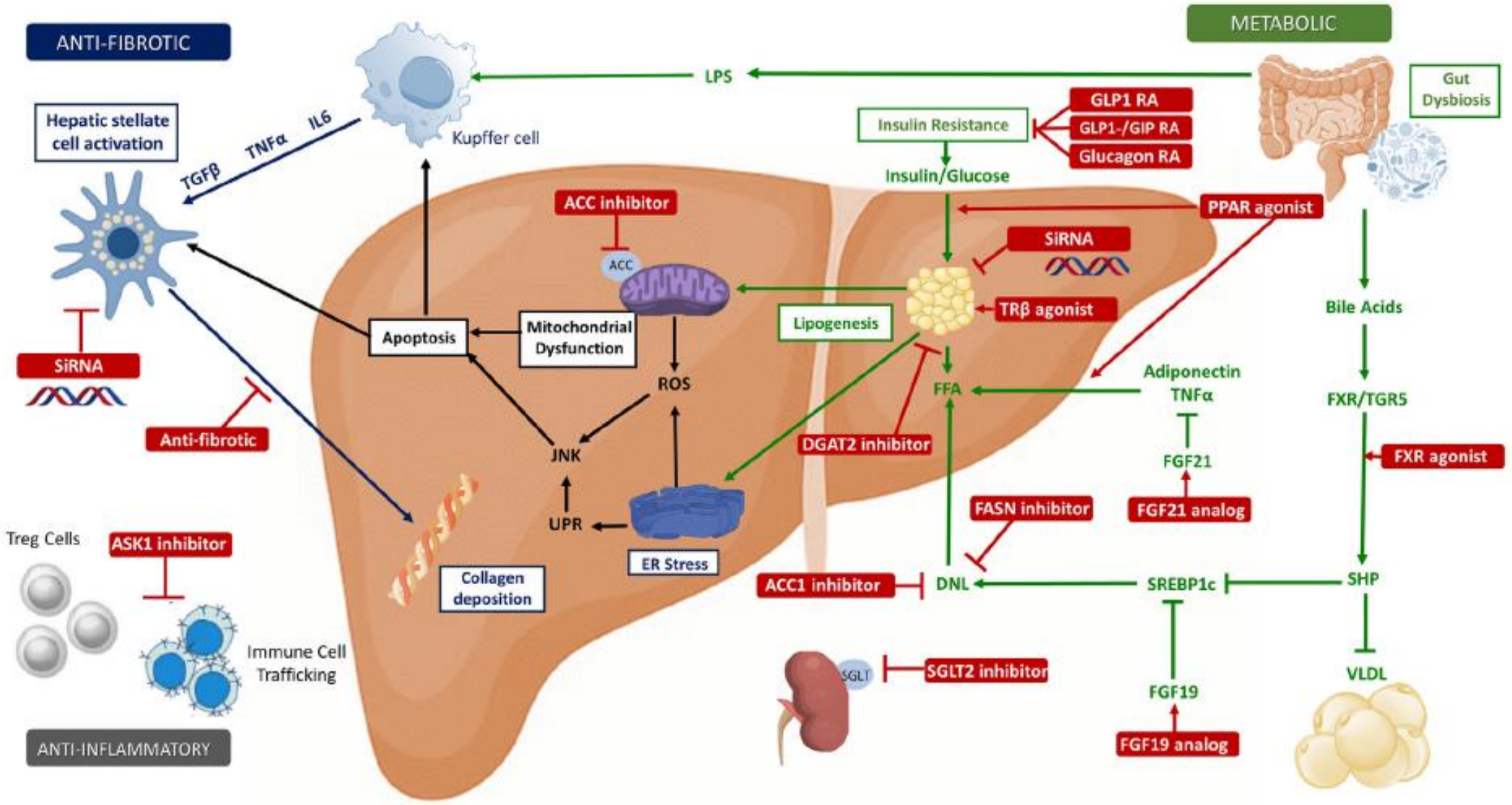
Current situation in NASH treatment



Data from Vilar-Gomez et al.

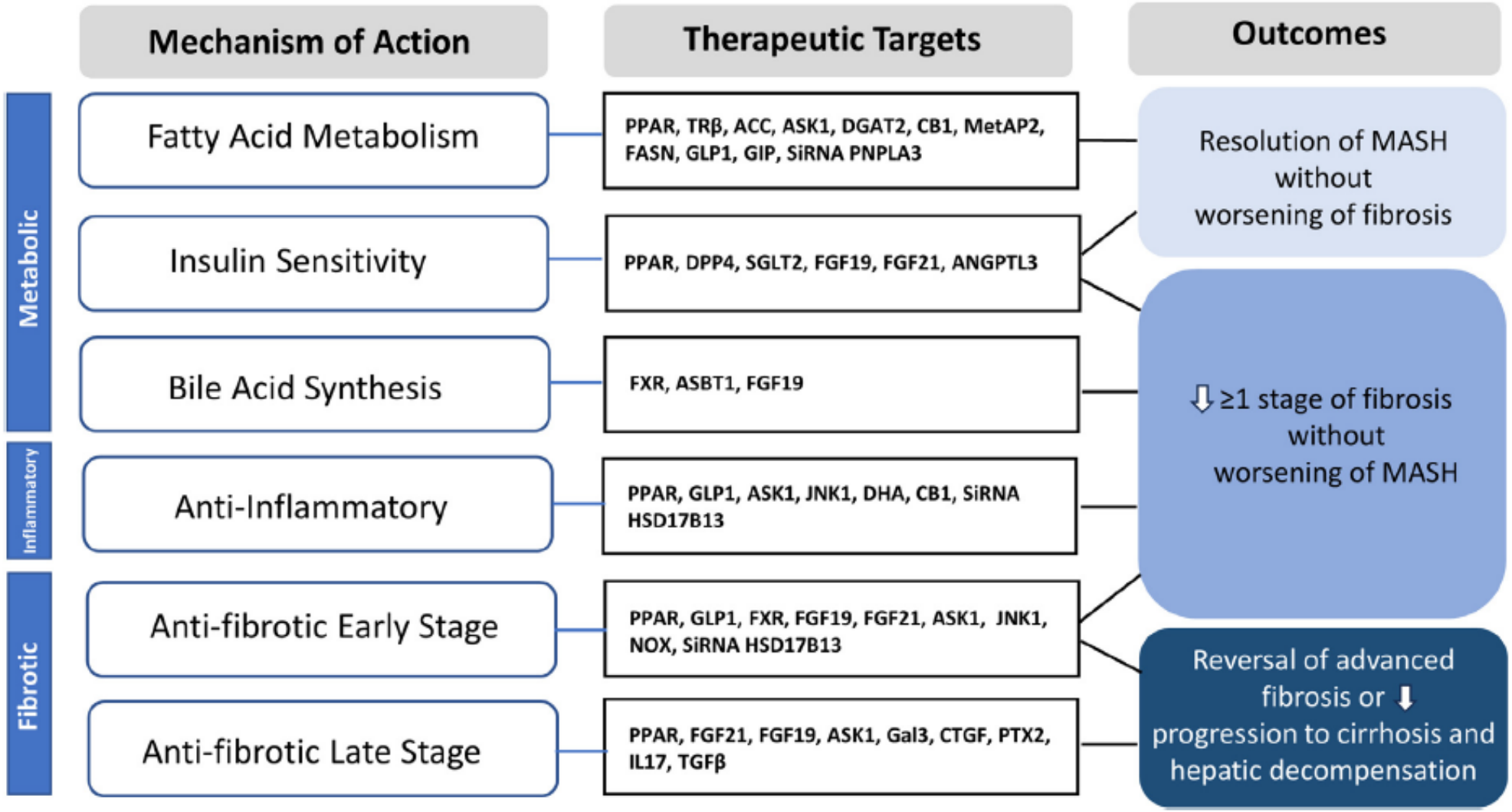
Romero-Gomez et al., J Hepatol 2017

Pathogenesis of MASH and MoA of emerging therapies



Tincopa et al., Cell Metab 2024

Endpoints in MASH trials



Tincopa et al., Cell Metab 2024

FDA NEWS RELEASE

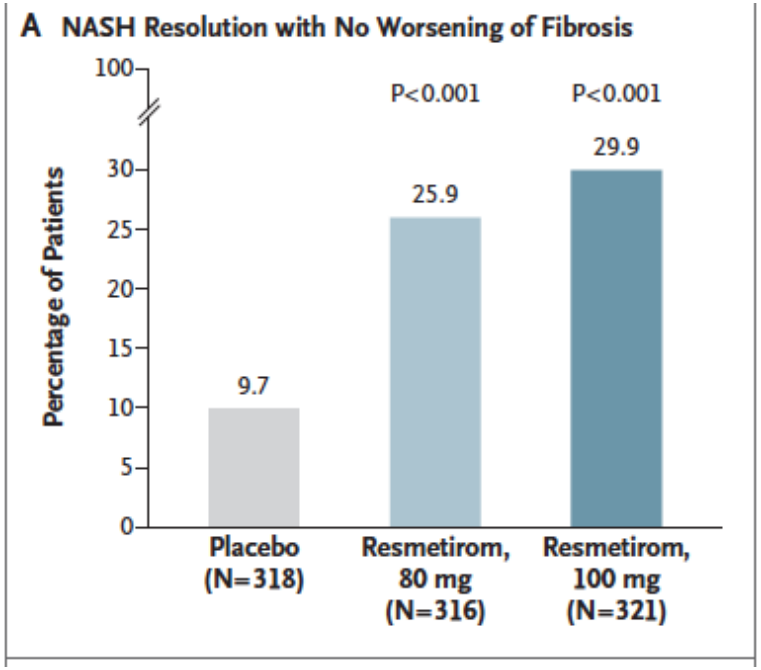
FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

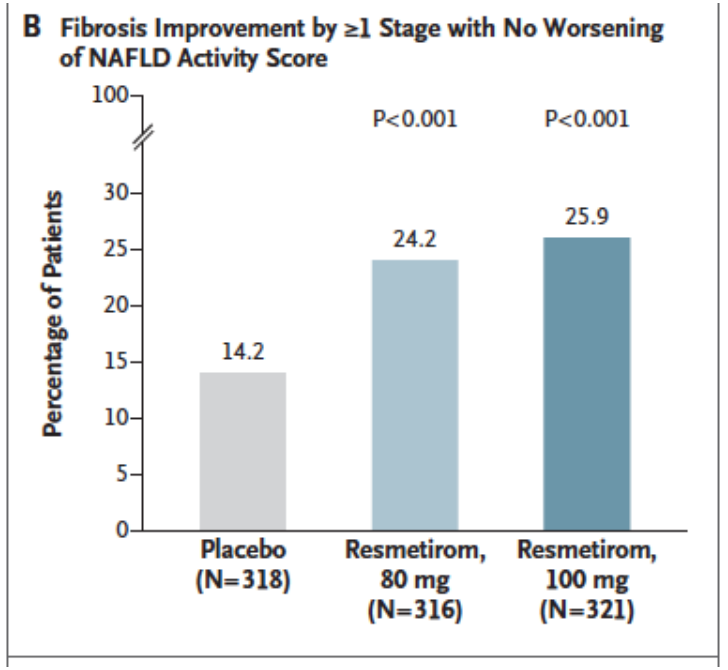
For Immediate Release: March 14, 2024

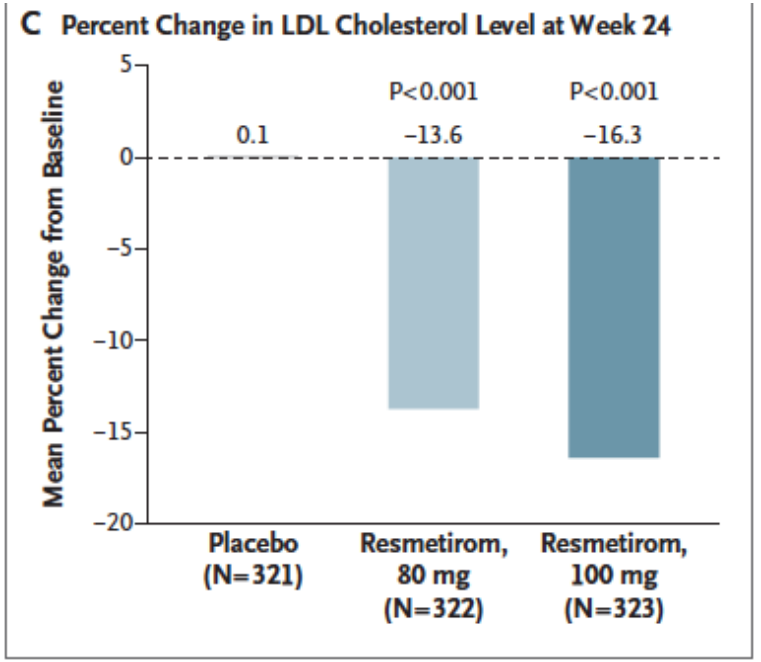
Content current as of:
03/14/2024

Regulated Product(s)

Resmetirom for the treatment of MASH: the MAESTRO-NASH study

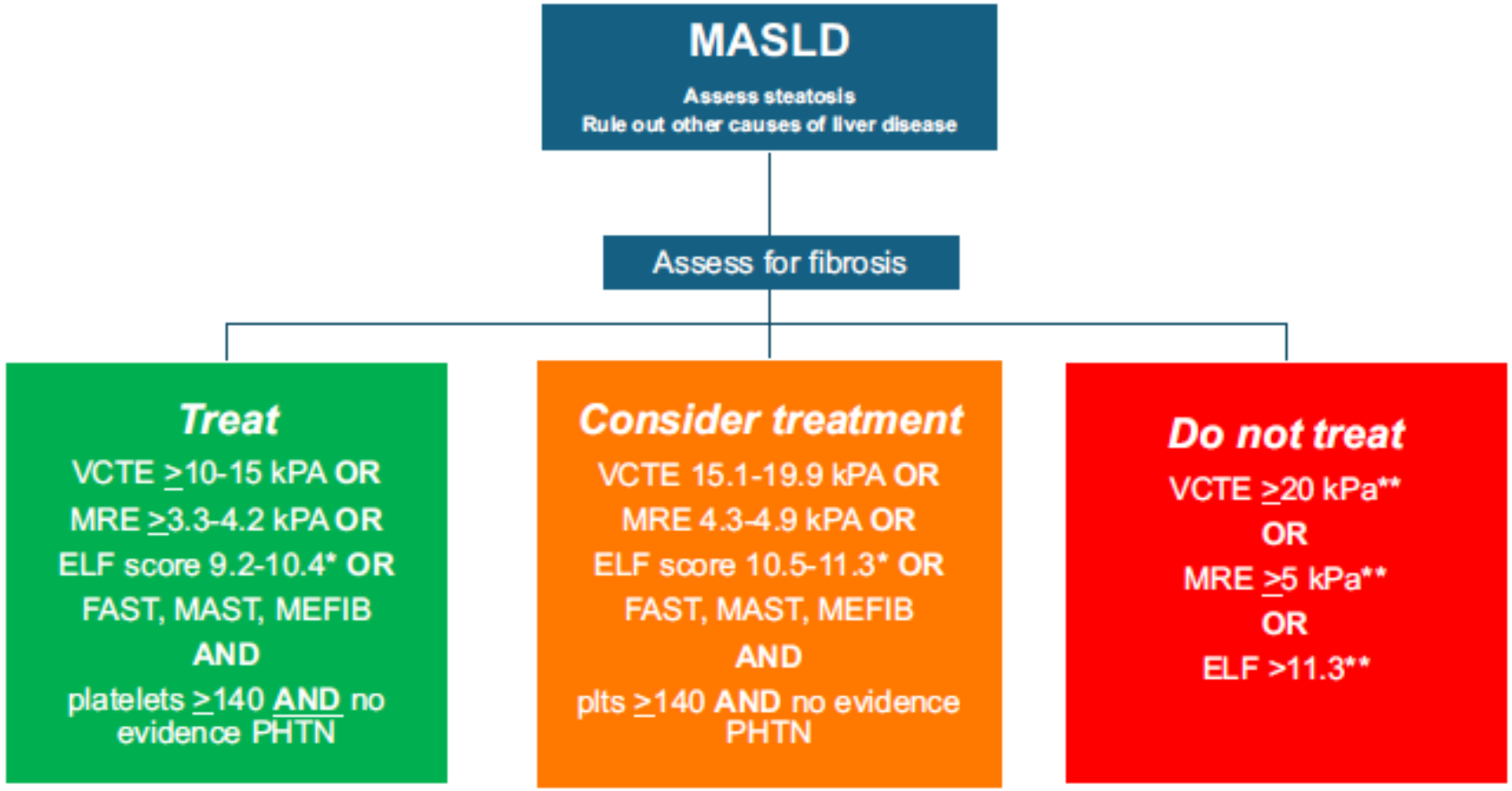






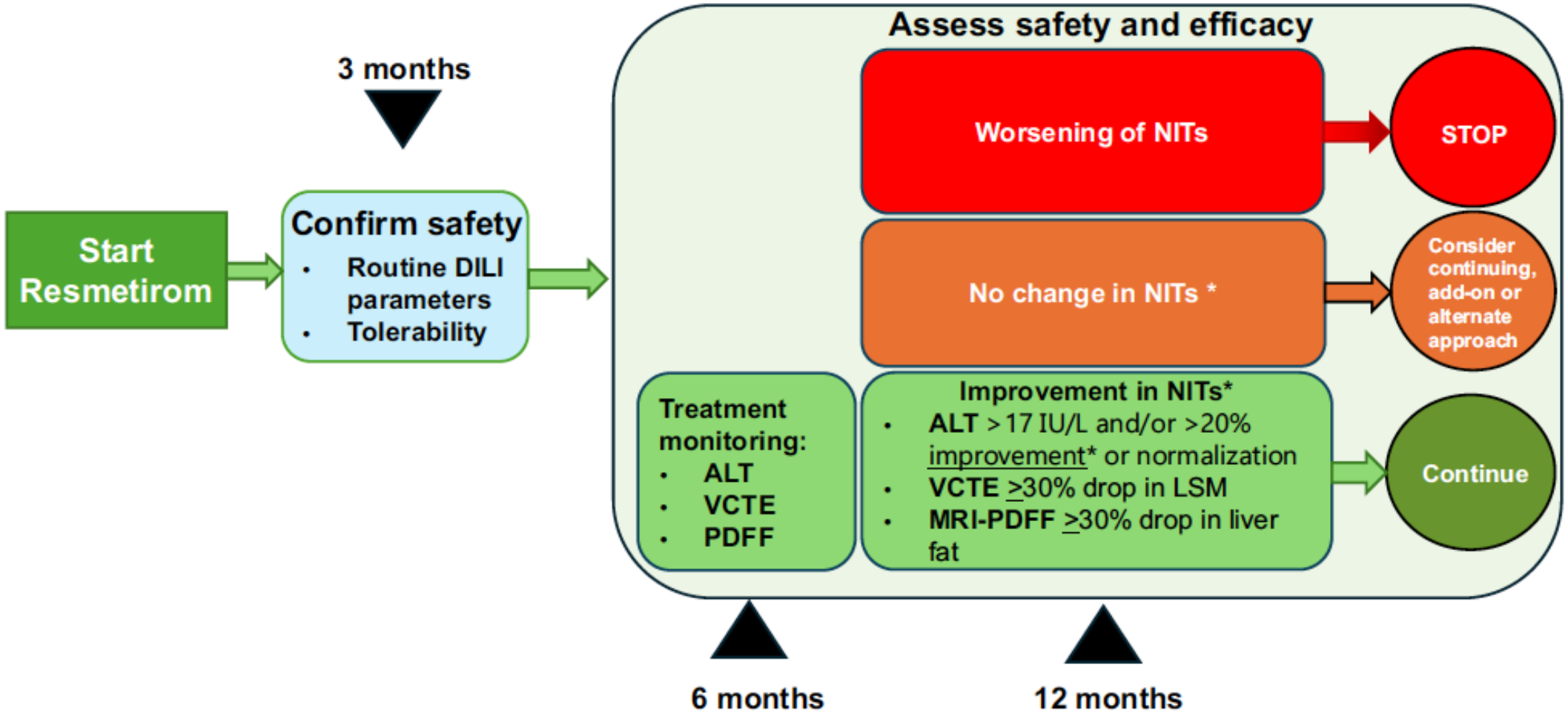
Harrison et al, NEJM 2024

Patient selection for resmetirom treatment



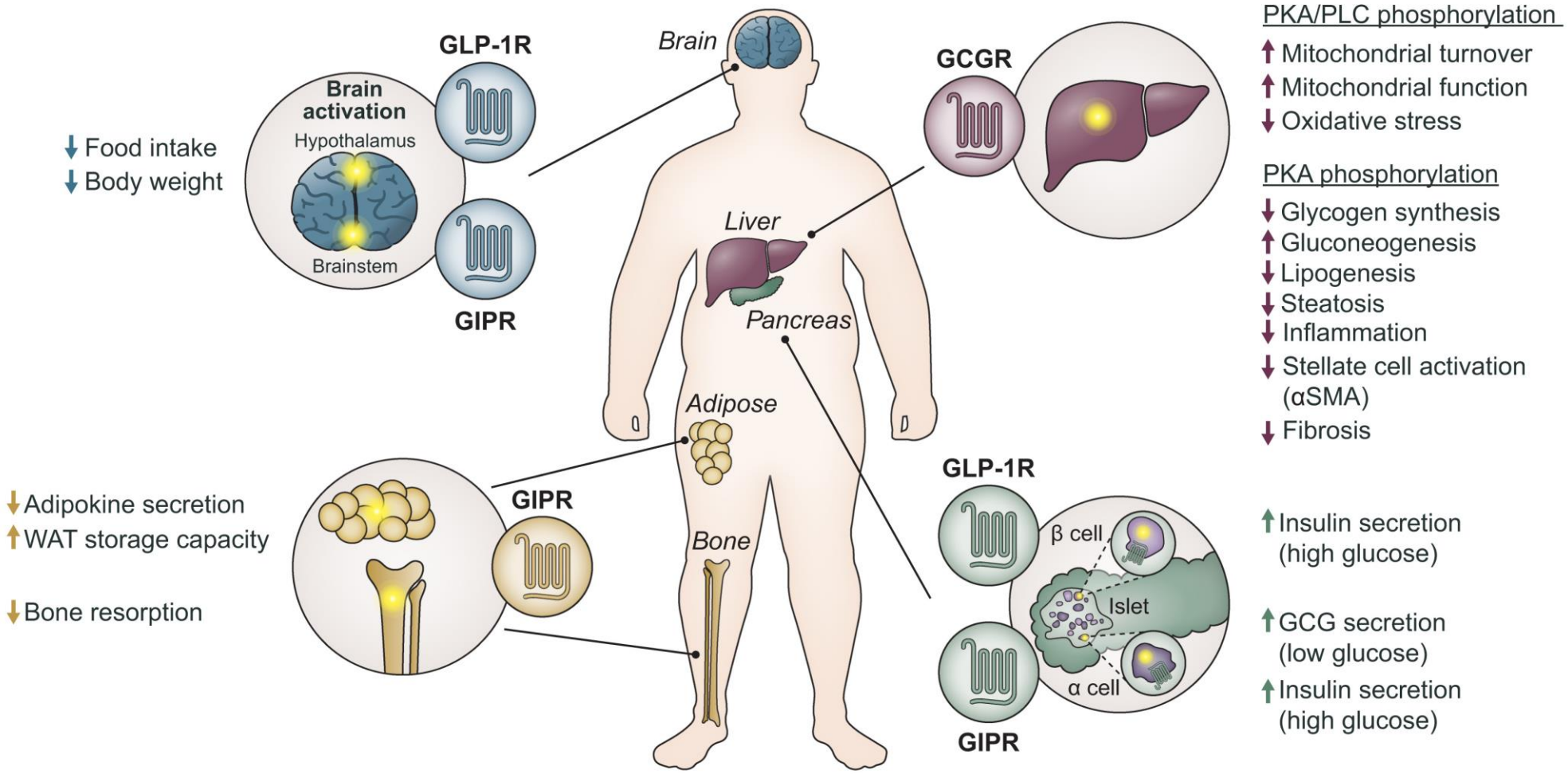
Noureddin et al., Clin Gastroenterol Hepatol 2024

Assessment of treatment response to resmetirom



Noureddin et al., Clin Gastroenterol Hepatol 2024

Incretins and MASLD



Newsome & Ambery, J Hepatol 2023

company announcement

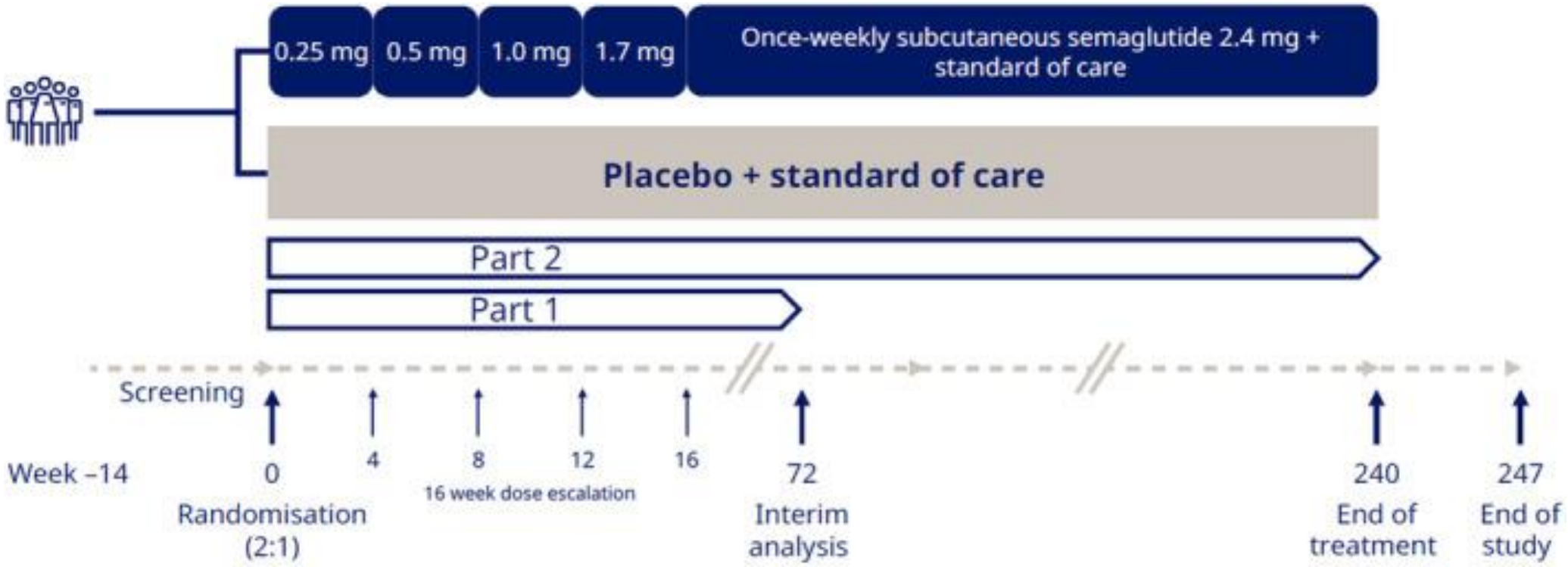
Semaglutide 2.4 mg demonstrates superior improvement in both liver fibrosis and MASH resolution in the ESSENCE trial

Bagsværd, Denmark, 1 November 2024 – Novo Nordisk today announced the headline results from part 1 of the ongoing ESSENCE trial, a pivotal phase 3, 240-week, double-blinded trial in 1,200 adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate to advanced liver fibrosis (stage 2 or 3)[1]. Part 1 of the ESSENCE trial evaluated the effect of once-weekly semaglutide 2.4 mg on liver tissue (histology) compared to placebo on top of standard of care for the first 800 randomised people at 72 weeks.

The trial achieved its primary endpoints by demonstrating a statistically significant and superior improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis with semaglutide 2.4 mg compared to placebo. At week 72, 37.0% of people treated with semaglutide 2.4 mg achieved improvement in liver fibrosis with no worsening of steatohepatitis compared to 22.5% on placebo[2]. 62.9% of people treated with semaglutide 2.4 mg achieved resolution of steatohepatitis[3] with no worsening of liver fibrosis compared to 34.1% on placebo[2].

In the trial, semaglutide 2.4 mg appeared to have a safe and well-tolerated profile in line with previous semaglutide 2.4 mg trials.

Semaglutide in MASH with fibrosis: the ESSENCE study



Dual GLP-1/GIP agonists for MASH and fibrosis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

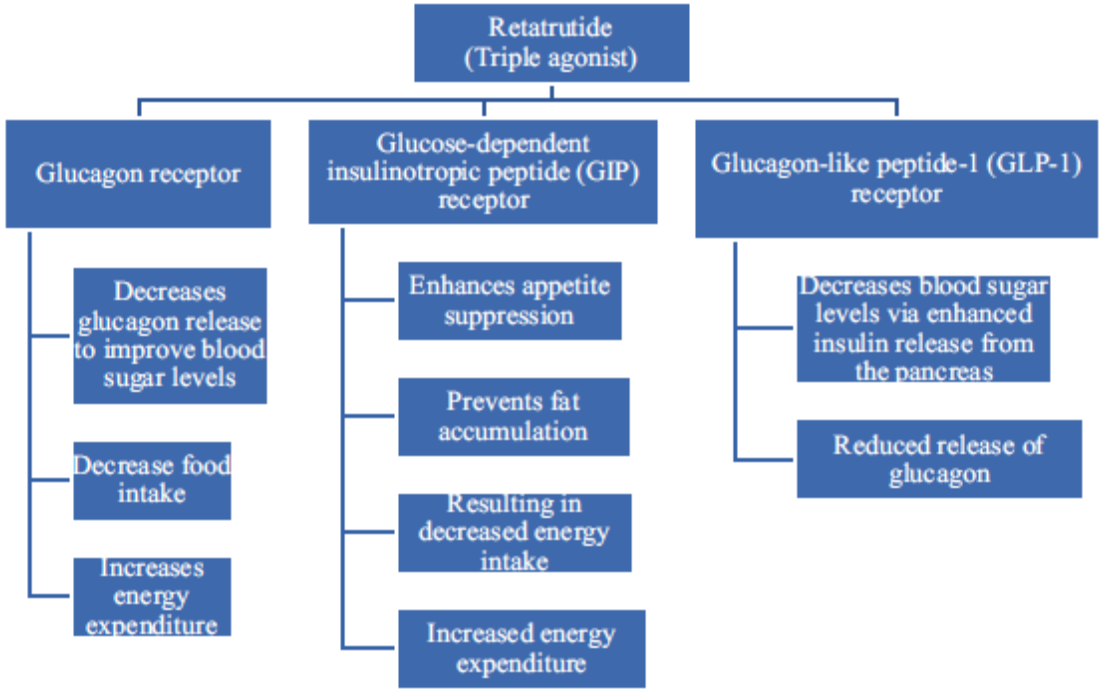
R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

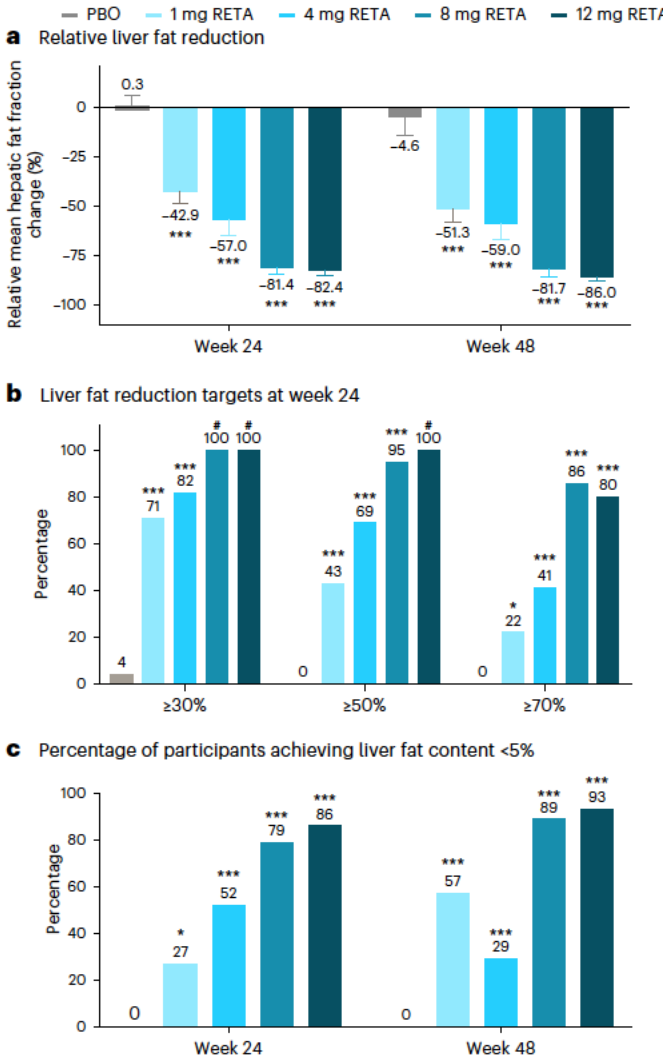
ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., Samina Ajaz Hussain, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Vlad Ratziu, M.D., Azadeh Hosseini-Tabatabaei, Pharm.D., Ph.D., Jörn M. Schattenberg, M.D., Mazen Noureddin, M.D., M.H.Sc., Naim Alkhouri, M.D., and Ramy Younes, M.D., Ph.D., for the 1404-0043 Trial Investigators*

Retatrutide, a triple agonist, reduces liver fat

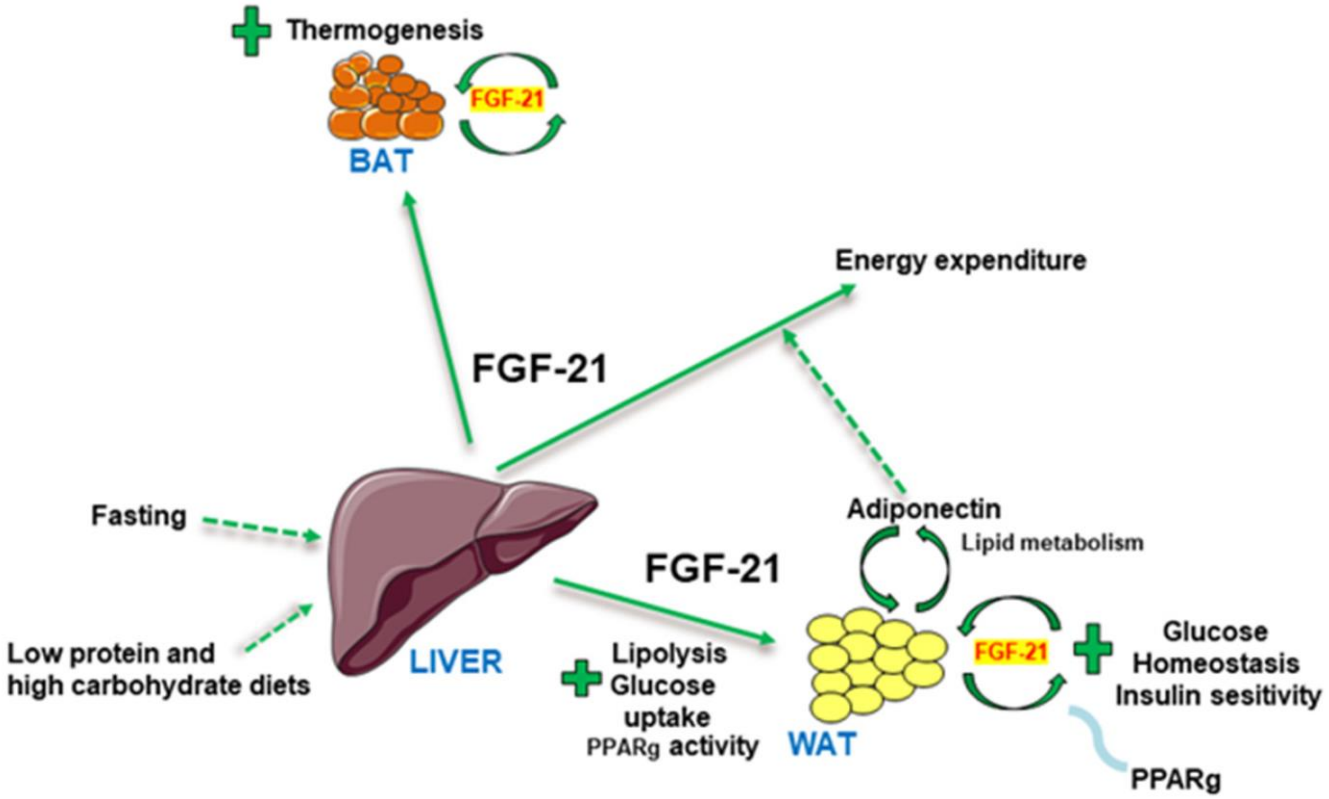


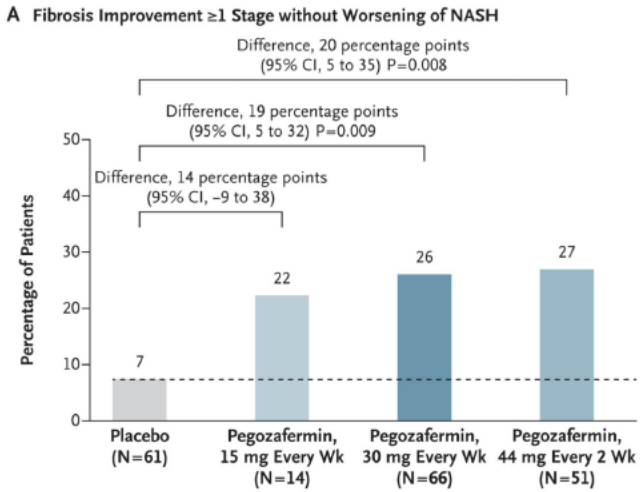


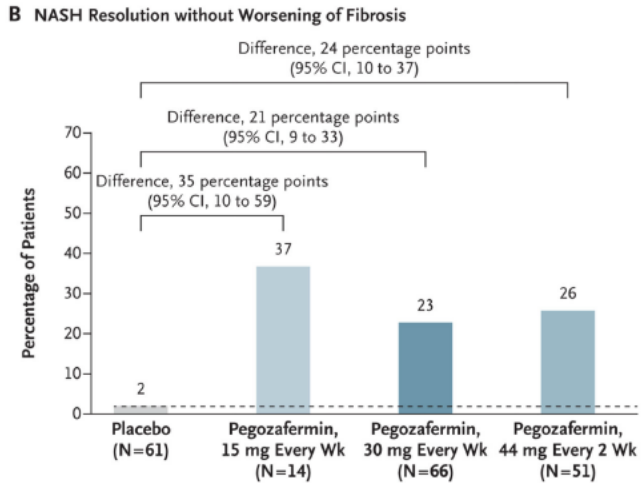
Kaur & Misra Eur J Clin Pharmacol 2024

Sanyal et al., Nat Med 2024

The FGF-21 agonist pegozafermin in MASH







Loomba et al. NEJM 2023

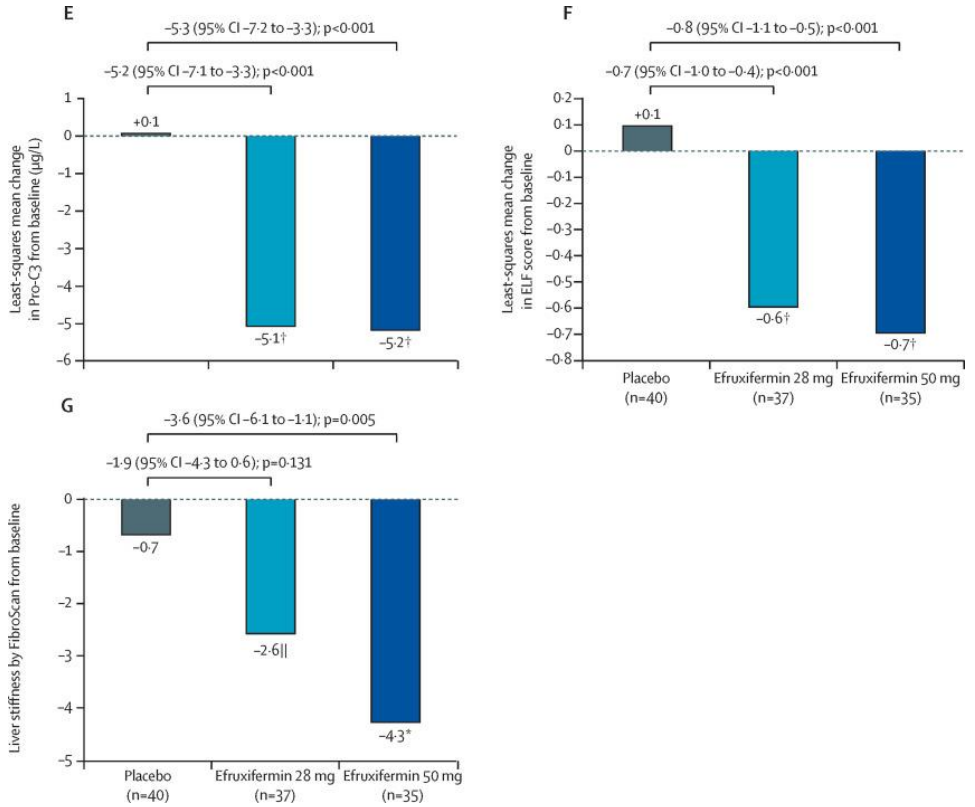
Efruxifermin and MASH

» Evaluating EFRUXIFERMIN (EFX), An Fc-FGF21 Fusion Protein

akero

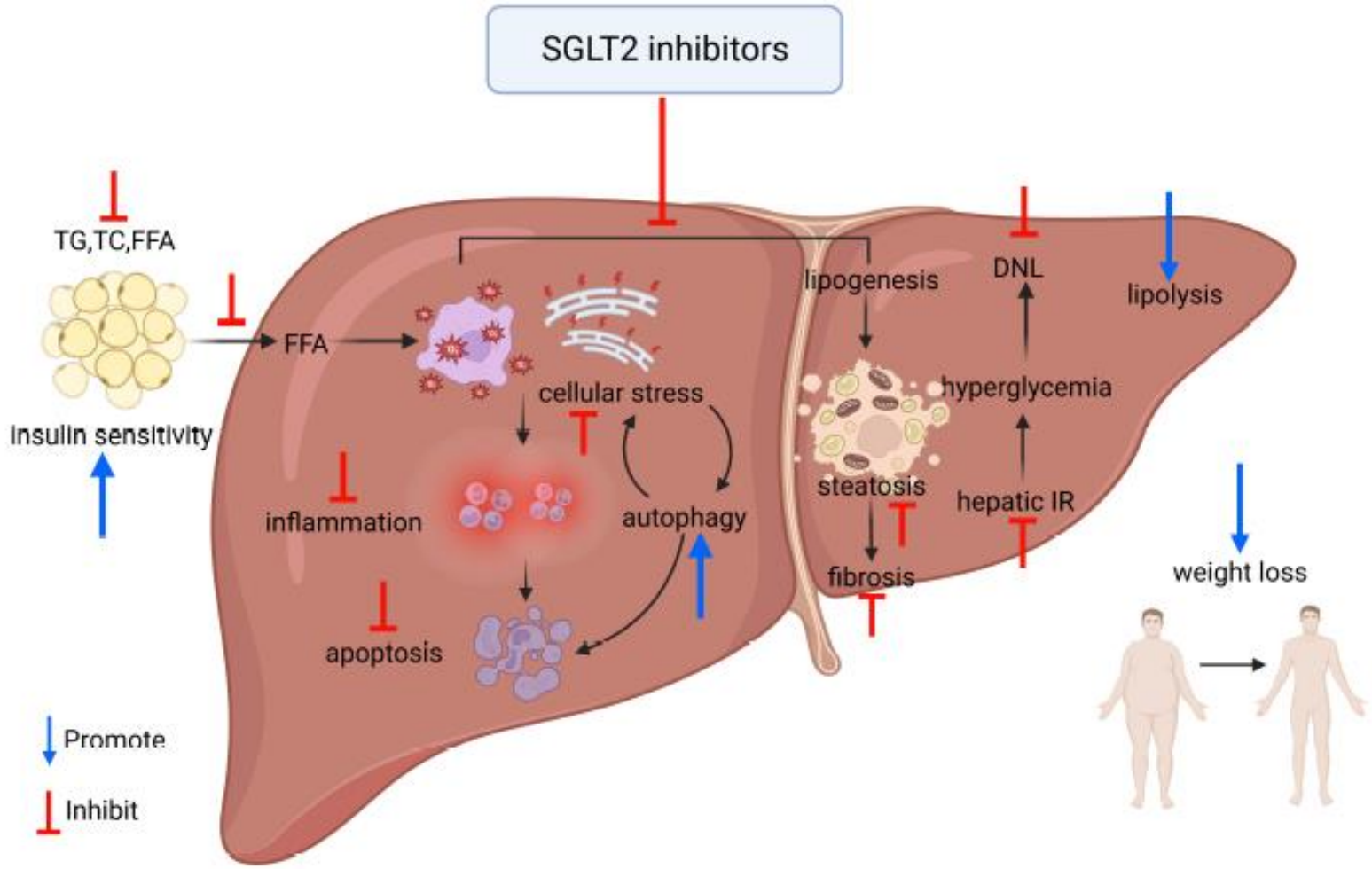
HARMONY

STATISTICALLY SIGNIFICANT EFFECTS AFTER 24 WEEKS

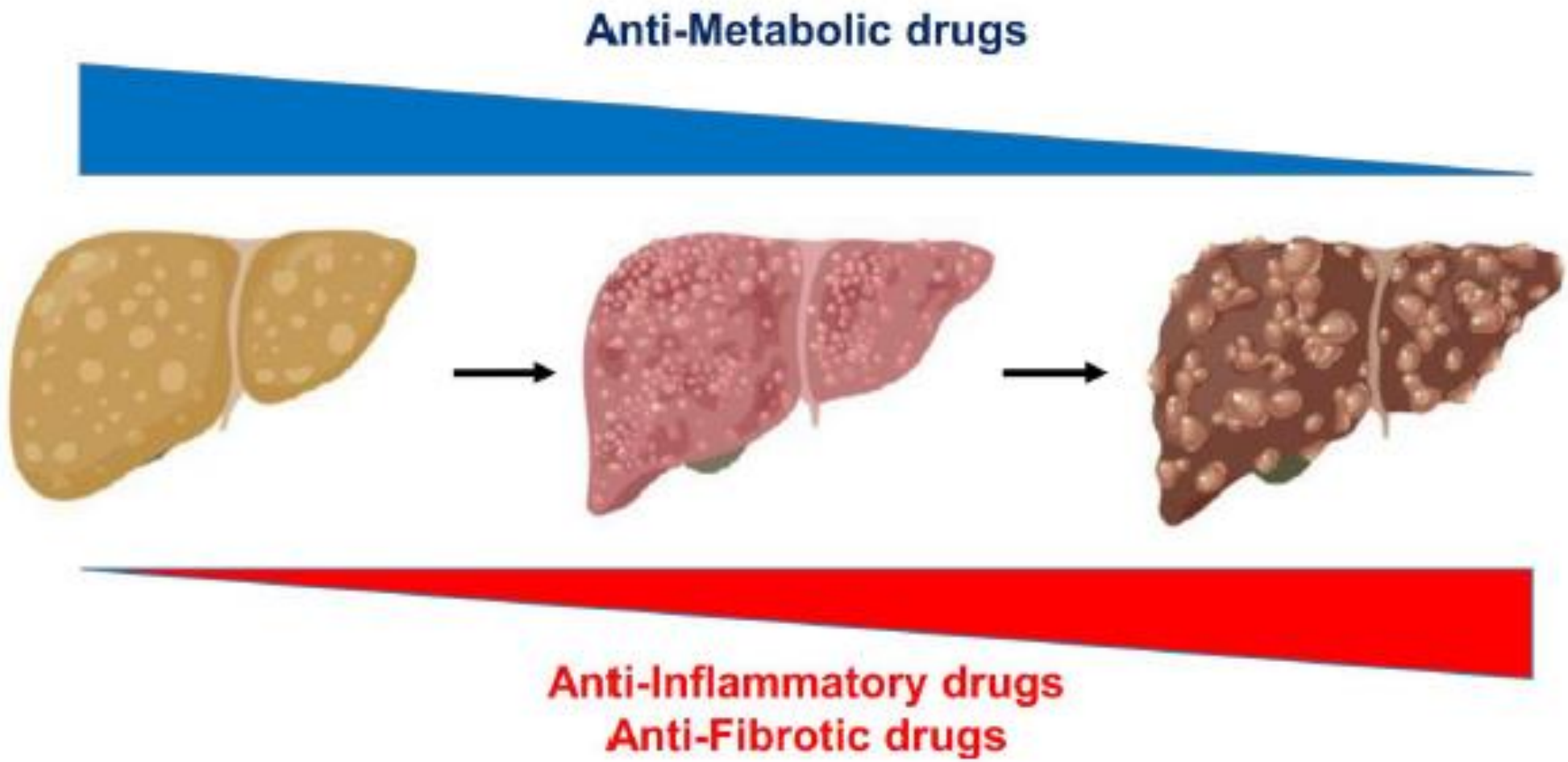


Harrison et al., Lancet Gastro Hep 2023

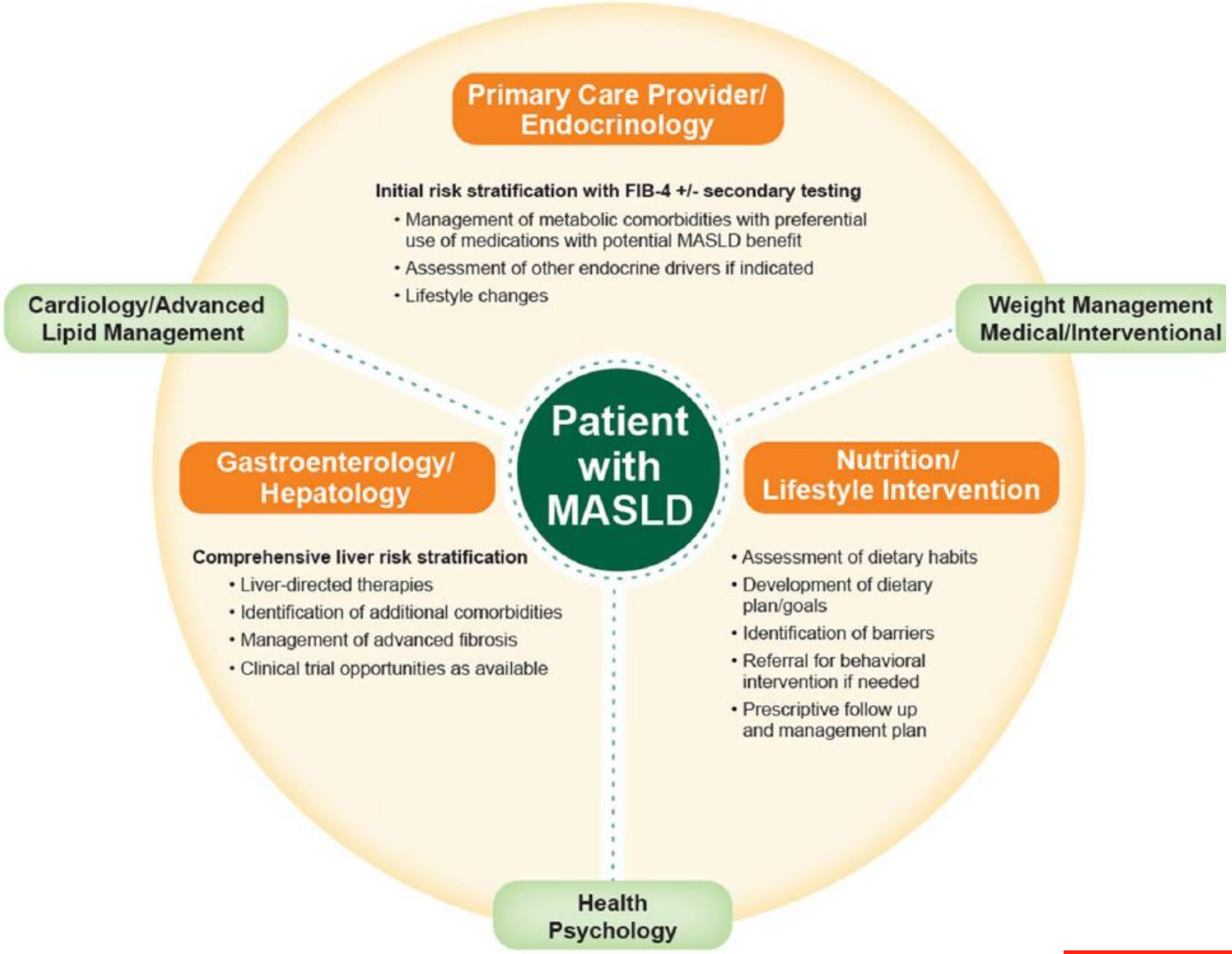
SGLT2 inhibitors and the treatment of MASLD



Xu et al., Front Biosci 2023



Ciardullo et al., Gastroenterol Hepatol 2024



Kanwal et al., Hepatology 2023

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