Il paziente con NAFLD: inquadramento e ruolo del CAP

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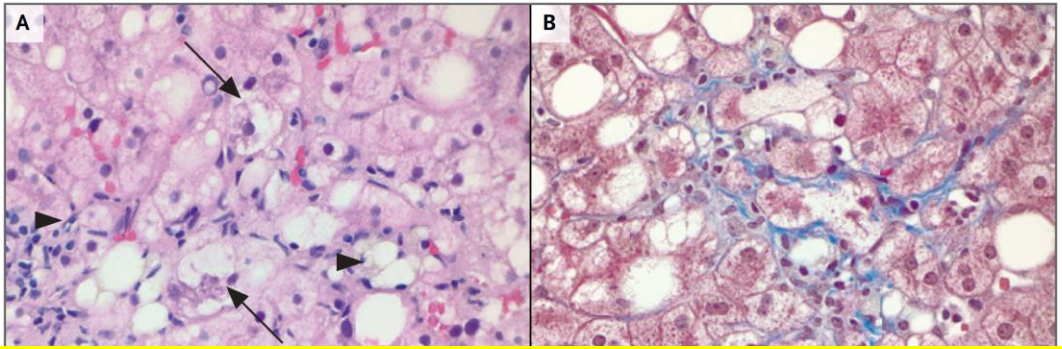
Disclosures

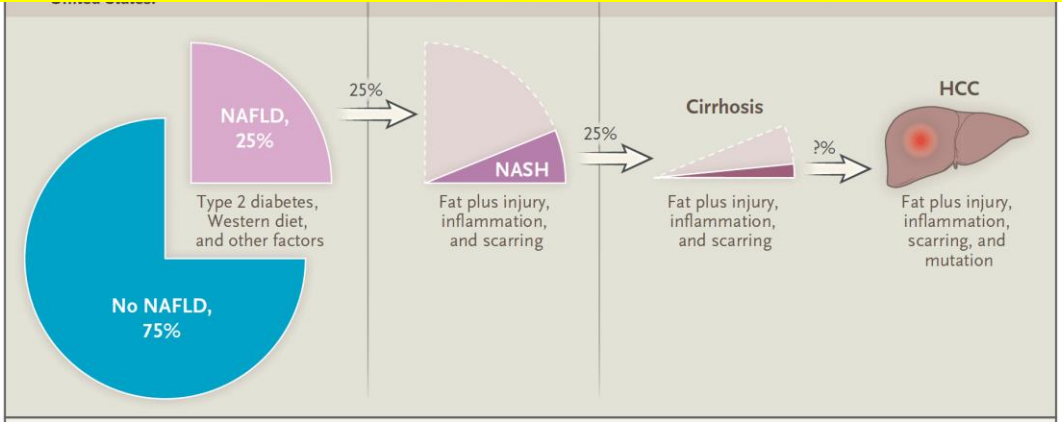
- **Abbvie**: consultant fees, travel grants
- **Allergan:** consultant fees
- **Alfa-Wassermann:** travel grants
- **AstraZeneca:** consultant fees
- **Bayer:** speaker honoraria, consultant fees, travel grants
- **Gilead:** speaker honoraria, consultant fees
- **Ipsen:** consultant fees
- **Intercept:** speaker honoraria
- **MSD/Eisai:** consultant fees
- **Menarini:** consultant fees
- **Novartis:** consultant fees
- **Novo Nordisk:** consultant fees

Definition and natural history

The spectrum of nonalcoholic steatosis

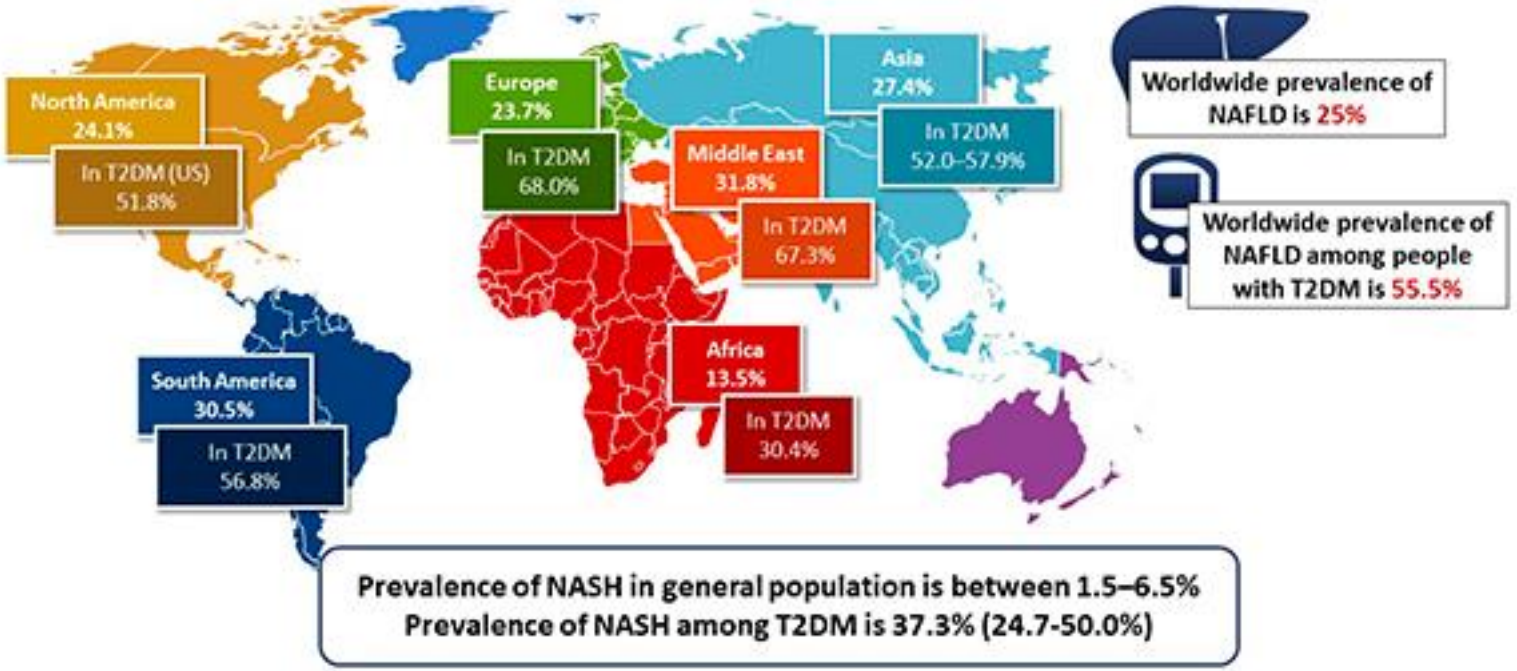


The hepatic manifestation of the metabolic syndrome

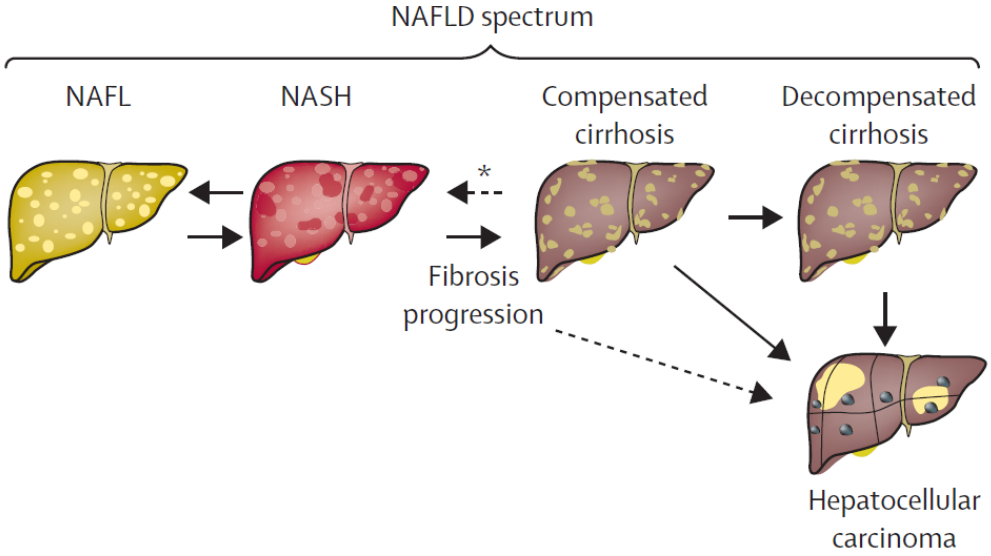


Diehl & Day NEJM 2017

Global prevalence of NAFLD



Younossi et al Hepatology 2016



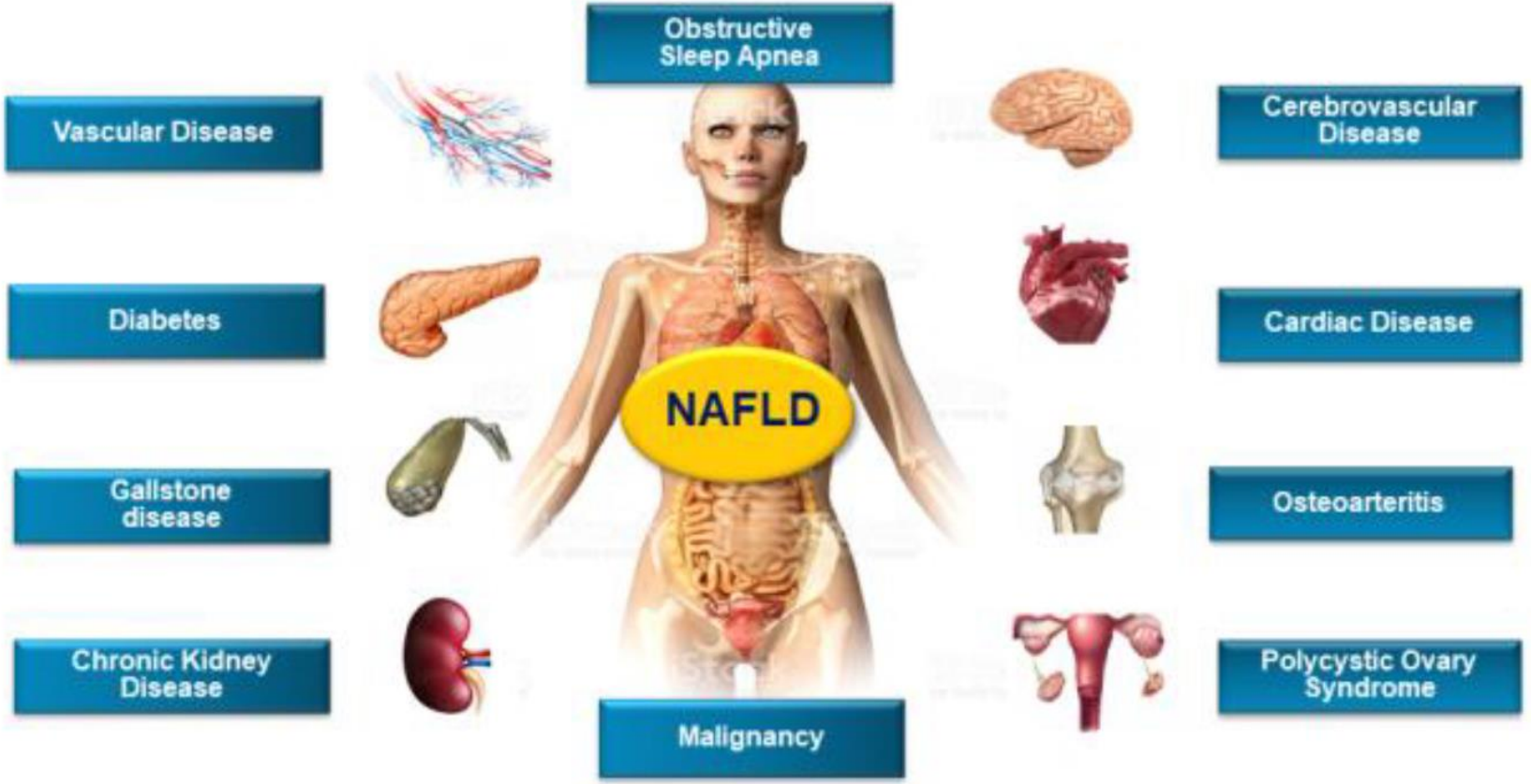
Factors associated with NAFLD and NASH progression

Comorbid illness
- Type 2 diabetes
- Insulin resistance
- Dyslipidaemia
- Obesity
- Hypertension
- Hypopituitarism

Genetic factors
- *PNPLA3*
- *TM6SF2*
- *GCKR*
- *MBOAT7*
- ***HSD17B13***

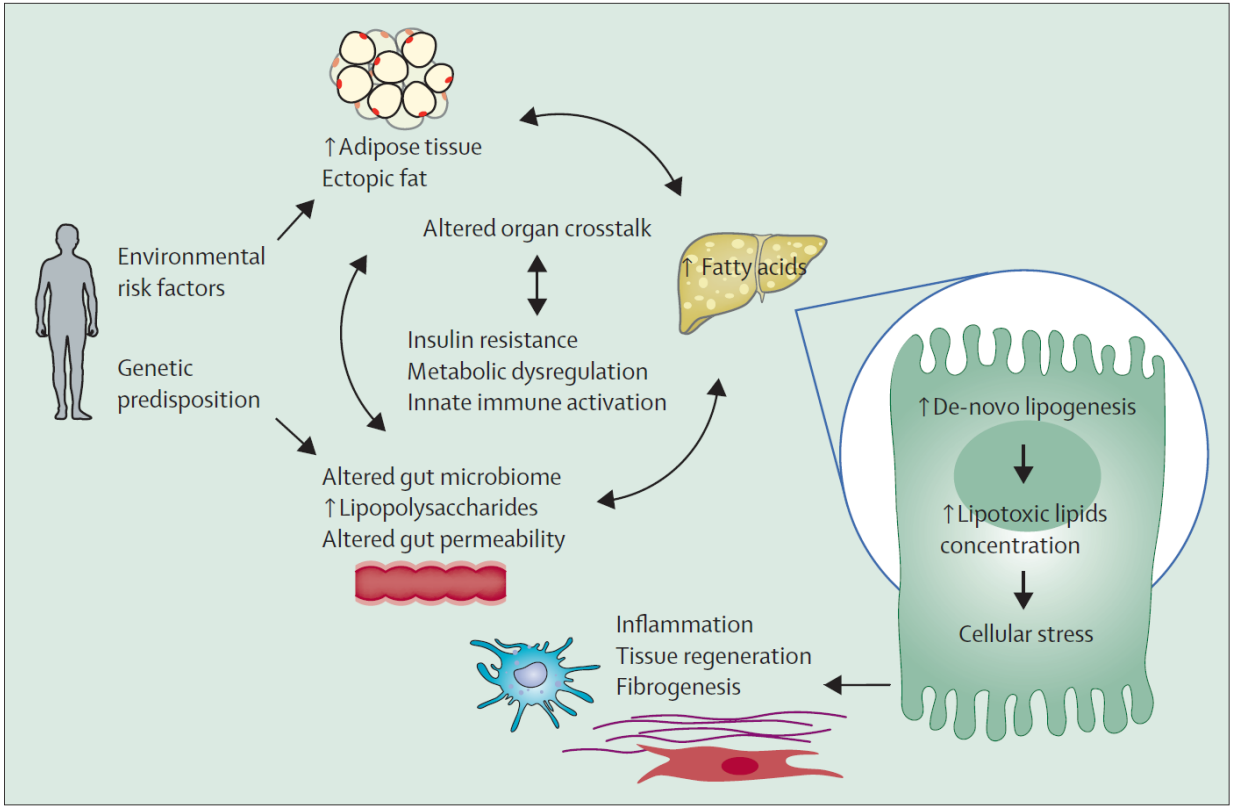
Environmental factors
- Fructose
- Cholesterol
- Alcohol
- **Exercise**
- **Coffee**

Powell et al., Lancet 2021



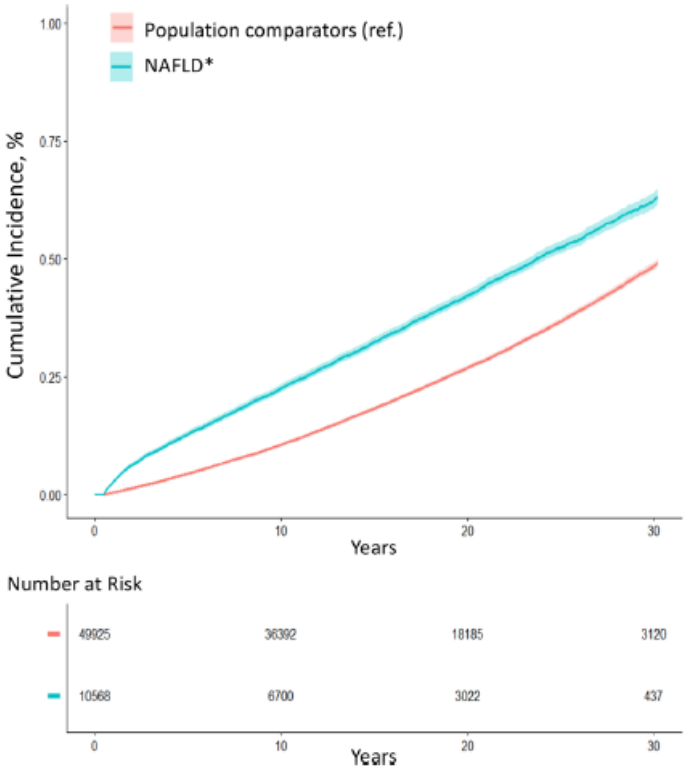
Younossi et al., Hepatology 2019

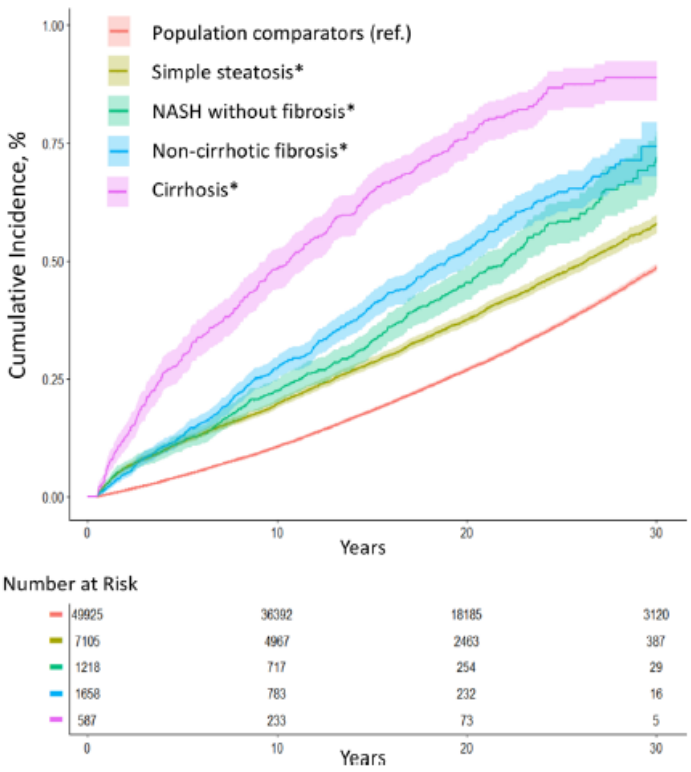
Multiple pathways and interactions between different organs, affect the pathogenesis of NAFLD



Powell et al., Lancet 2021

All-cause mortality according to NASH and histological severity





Simon et al., Gut 2020

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

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

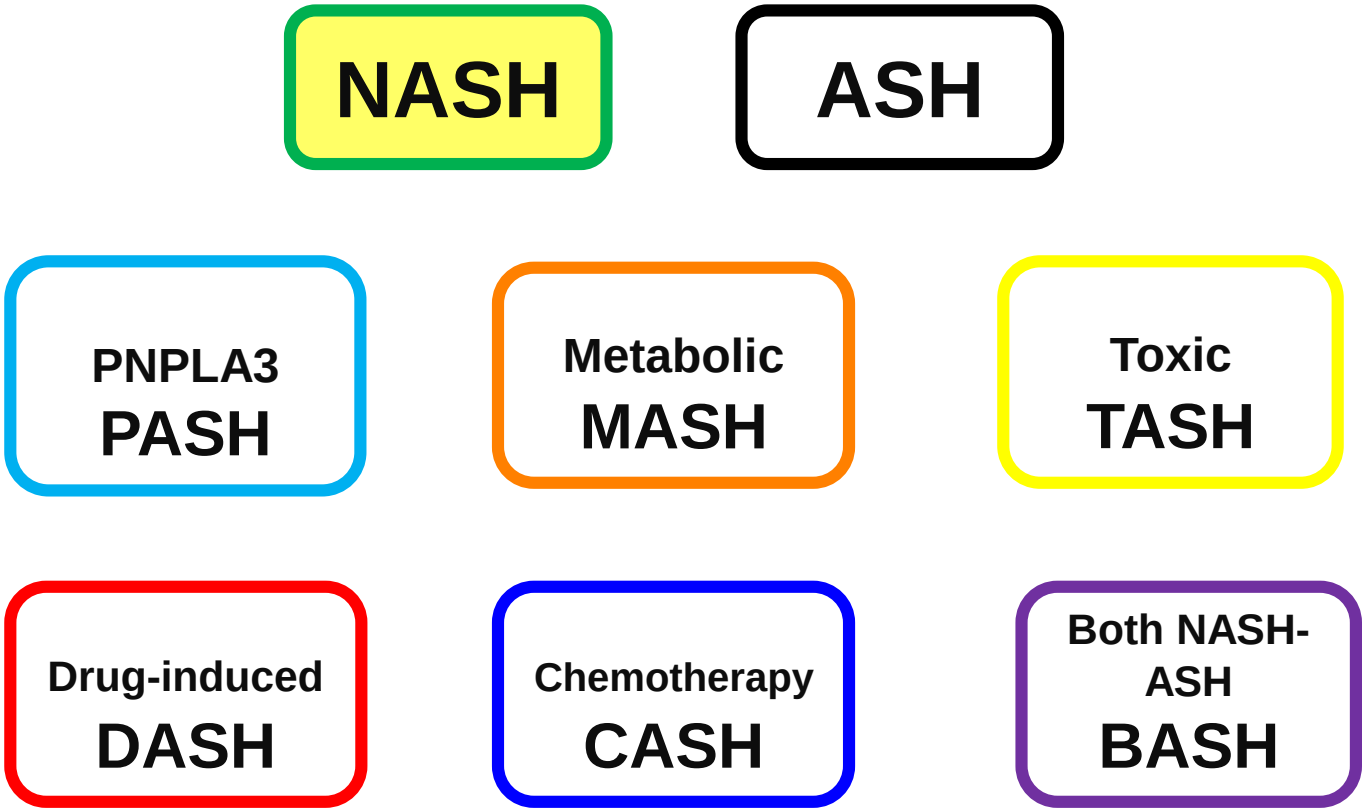
	Fibrosis Stage		
	F0 to F2 No, mild, or moderate fibrosis N=1237	**F3** Bridging fibrosis N=369	**F4** Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from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

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

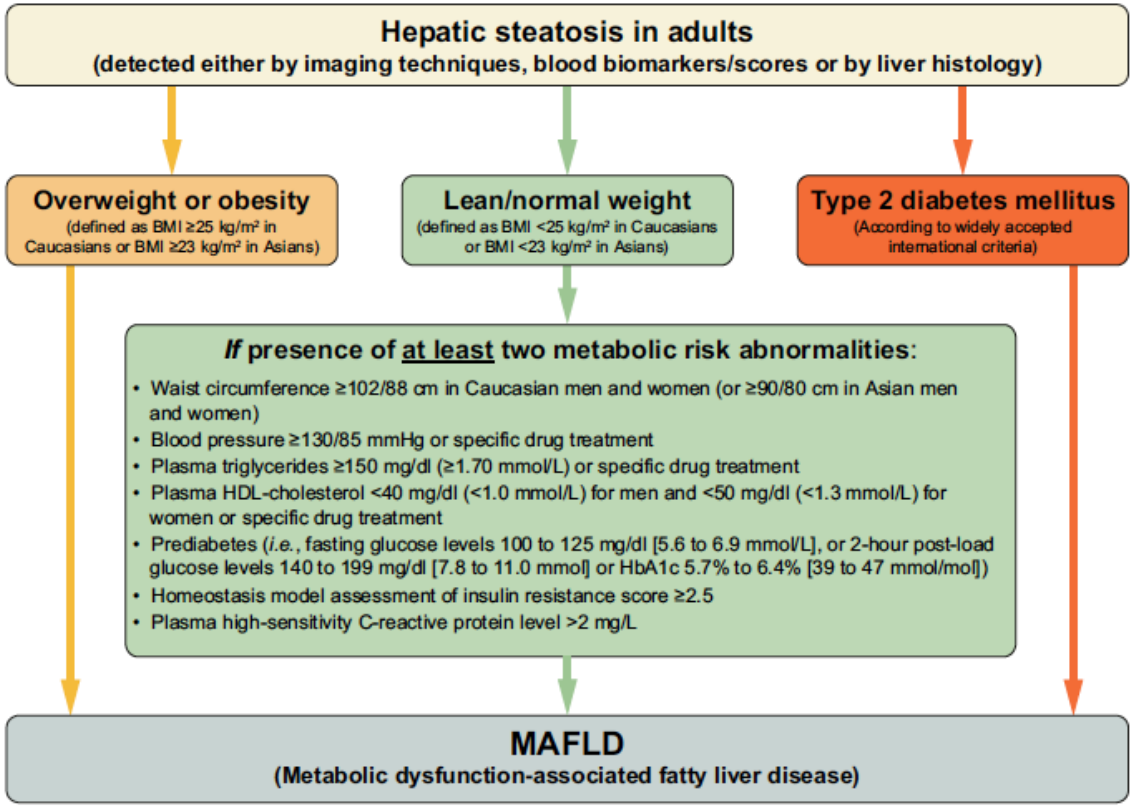
Sanyal et al., N Engl J Med 2021

Diagnostic strategies and referral

Steatohepatitis as a phenotype determined by different types of injury

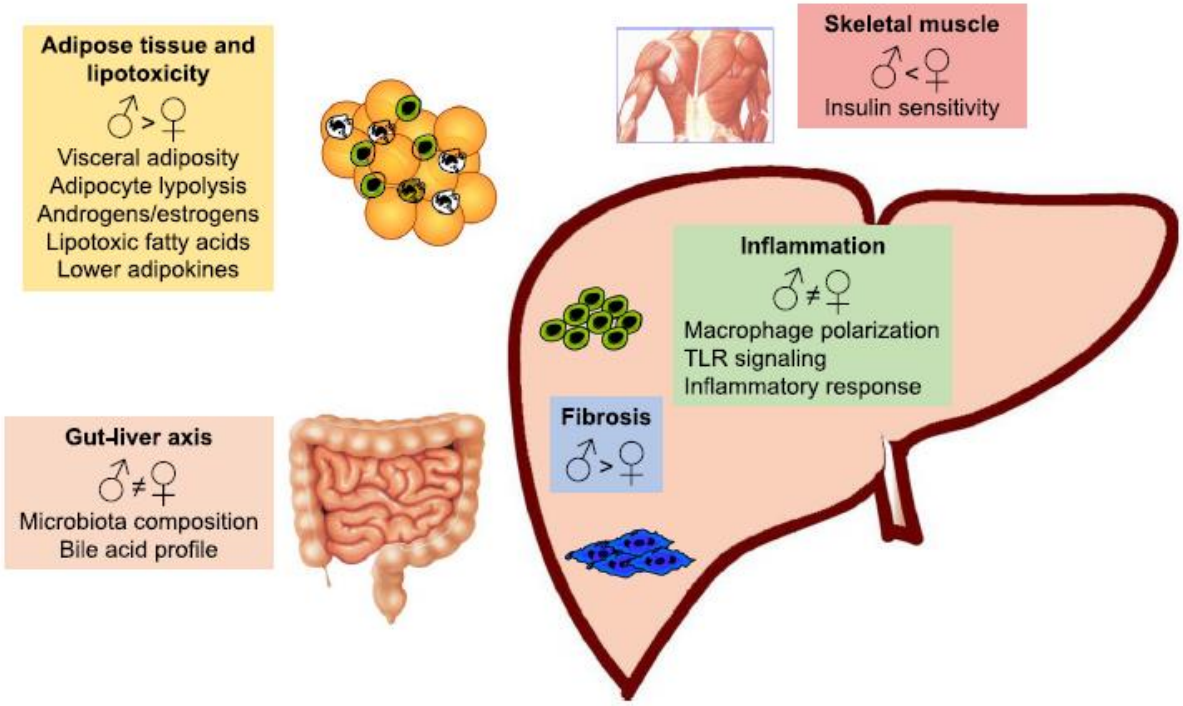


‘Positive’ diagnostic criteria for MAFLD



Eslam et al., J Hepatol 2020

Sexual dimorphism in NAFLD



Burra et al., Liver Int 2021

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

Accuracy of CAP and stiffness measurement in in patients with Nonalcoholic Fatty Liver Disease

> 450 patients with suspicion of NAFLD prospectively recruited

> Underwent liver biopsy within 2 weeks of FibroScan
(M or XL probe according to the automatic probe recommendation tool)

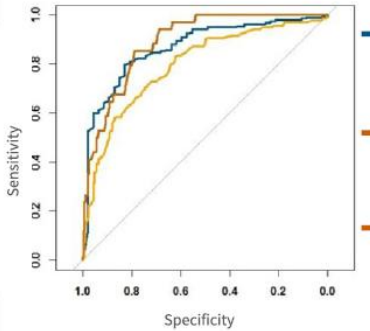
Steatosis

Fibrosis

CAP (dB/m)

LSM (kPa)

> Results and conclusions



CAP for steatosis (S≥1):
> AUC = 0.87 (0.82-0.92)

LSM for advanced fibrosis (F≥3):
> AUC = 0.80 (0.75-0.84)

LSM for cirrhosis (F=4):
> AUC = 0.89 (0.84-0.93)

> Steatosis or probe type had no impact on LSM (multivariable analysis)

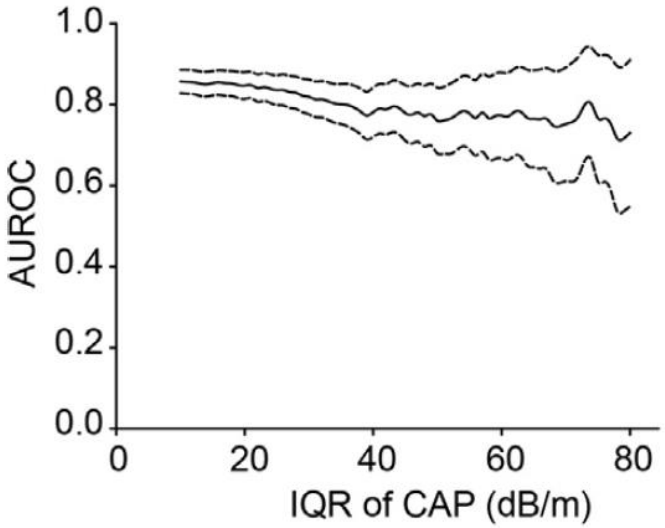
>>> CAP and LSM by FibroScan are reliable biomarkers to non-invasively assess liver steatosis and fibrosis respectively in NAFLD

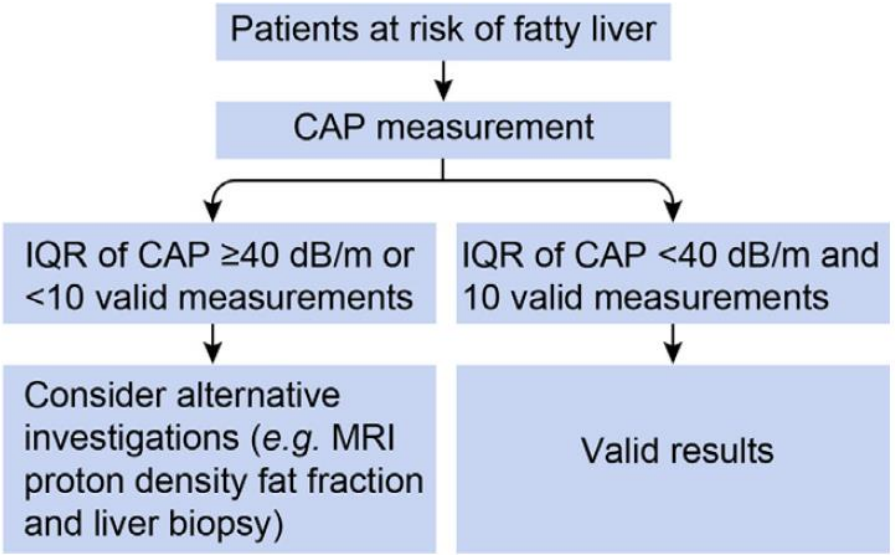
Gastroenterology

Eddowes et al., Gastroenterology 2019

Validity criteria for the diagnosis of fatty liver by controlled attenuation parameter

The interquartile range (IQR) reflects the variability of controlled attenuation parameter (CAP) measurement. A wide IQR was associated with a decline in the accuracy of CAP for the detection of fatty liver.





Wong et al., J Hepatol 2017

Received: 26 July 2019 | Revised: 29 November 2019 | Accepted: 7 December 2019

DOI: 10.1111/liv.14325

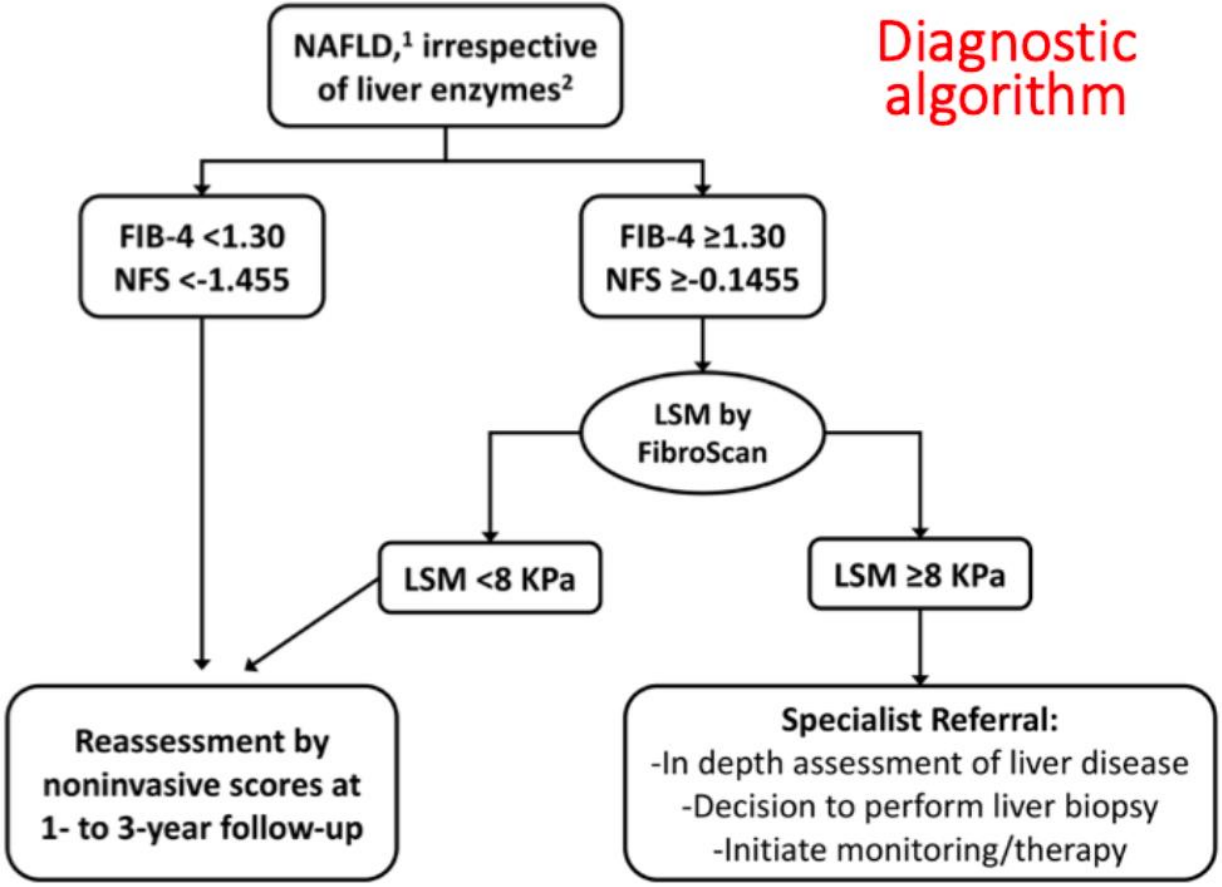
ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Controlled attenuation parameter reflects steatosis in compensated advanced chronic liver disease

Rosangela Piccinni[1] | Susana G. Rodrigues[1] | Matteo Montani[2] | Giuseppe Murgia[1] | Maria G. Delgado[1] | Stefania Casu[1] | Guido Stirnimann[1] | Nasser Semmo[1] | Andrea De Gottardi[1] | Jean-François Dufour[1] | Annalisa Berzigotti[1]

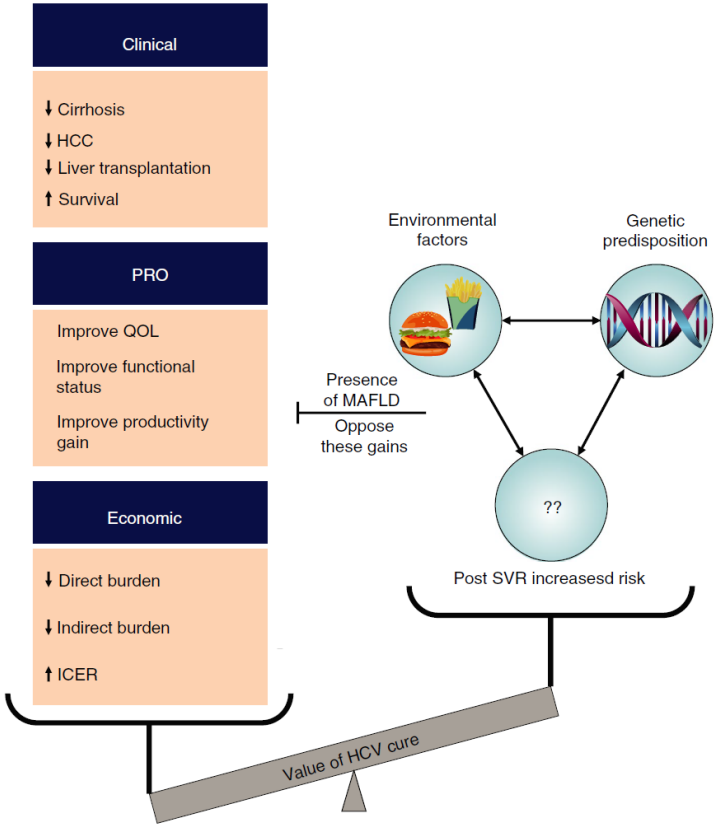
Diagnostic algorithm



Italian NAFLD Guidelines, 2021

NAFLD and HCV

Negative impact of MAFLD in the SVR population



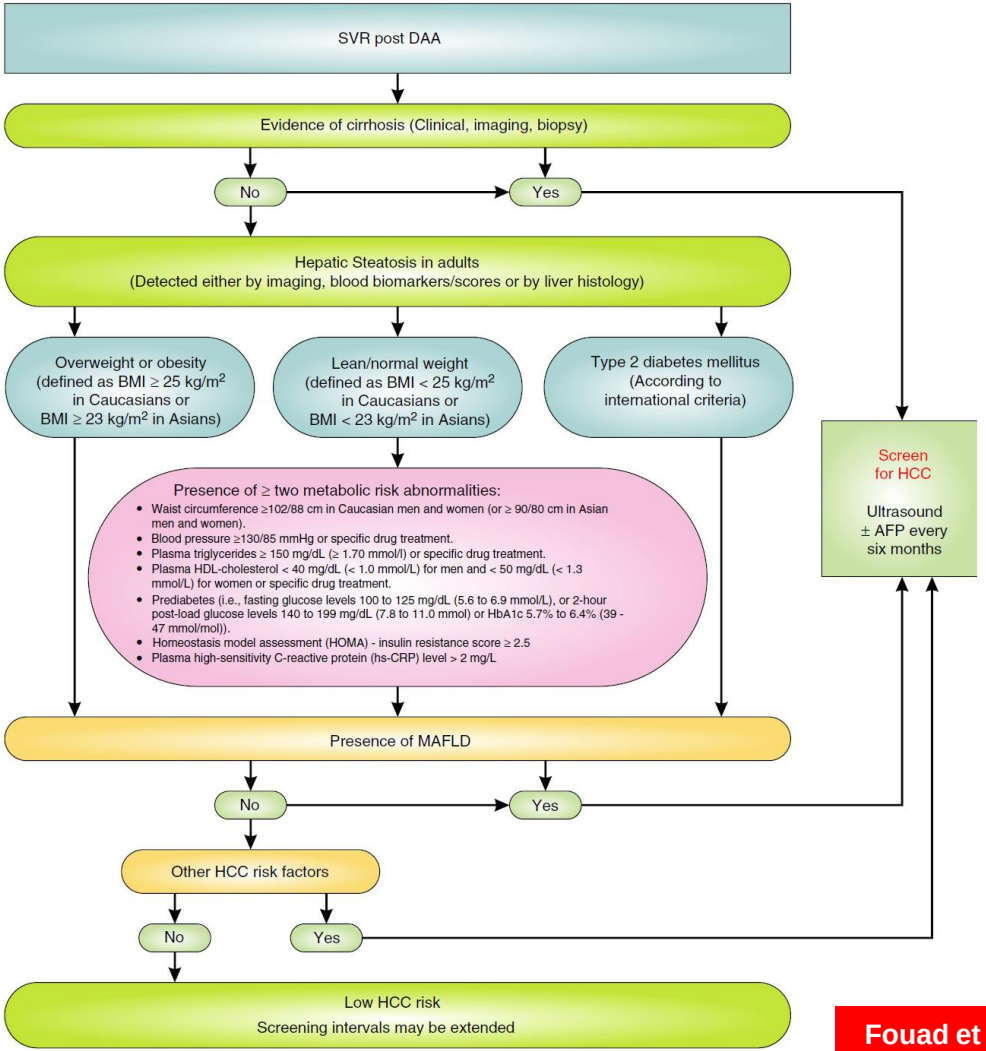
Fouad et al., Aliment Pharm Ther 2021

- MAFLD should be incorporated to the glossary of liver diseases either as a specific liver disease or as comorbid or superimposed disease (with viral hepatitis, hemochromatosis and PBC among others).

- Patients cured of CHC with MAFLD need monitoring given their risks of adverse outcomes, including increased risk for new diagnosis of cirrhosis, development of liver-related complications and HCC as well as extrahepatic-related complications

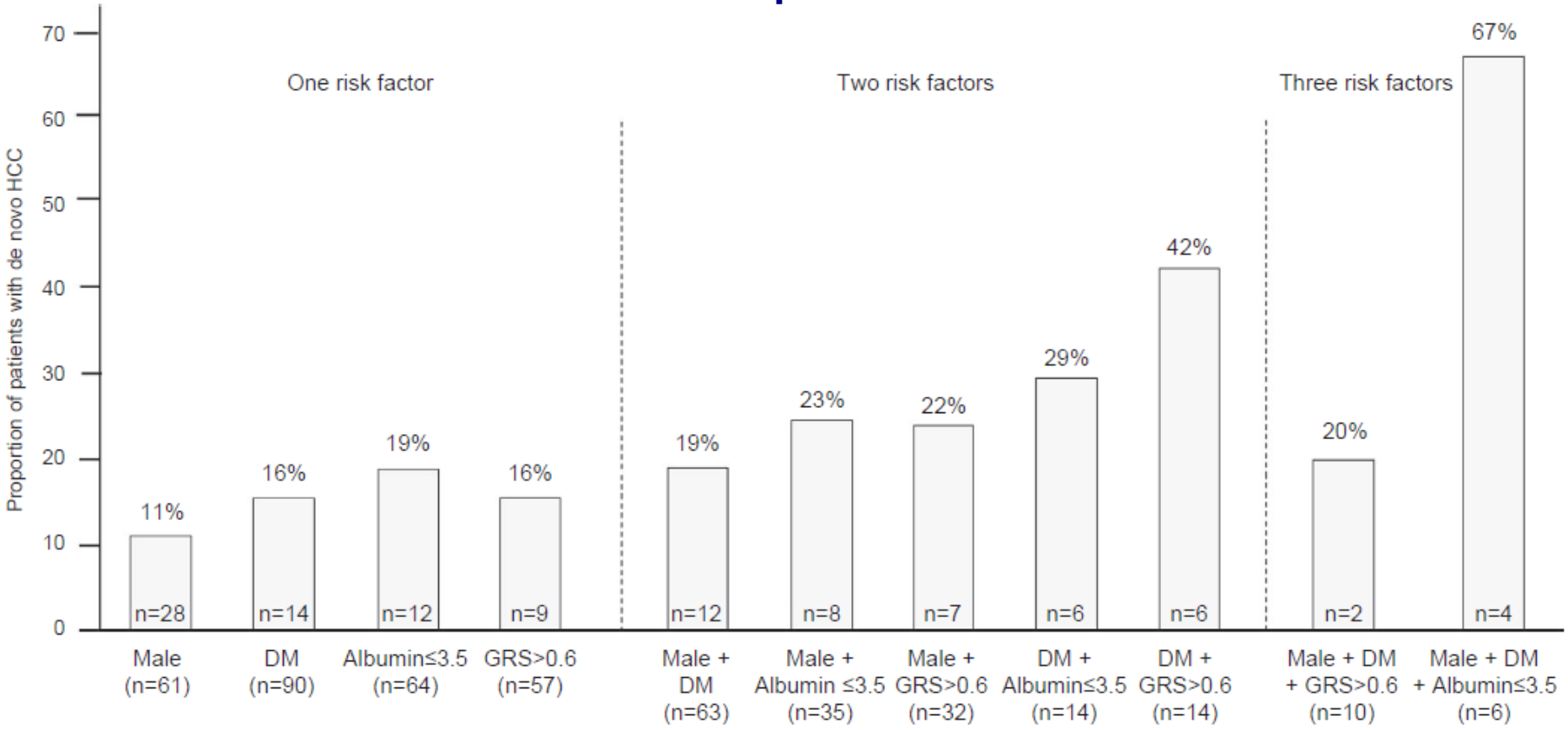
- The simplicity of the diagnostic criteria of MAFLD will help raise clinical awareness and should facilitate the monitoring process. However, the exact monitoring parameters remain undefined

Modified from: Fouad et al., Aliment Pharm Ther 2021



Fouad et al., Aliment Pharm Ther 2021

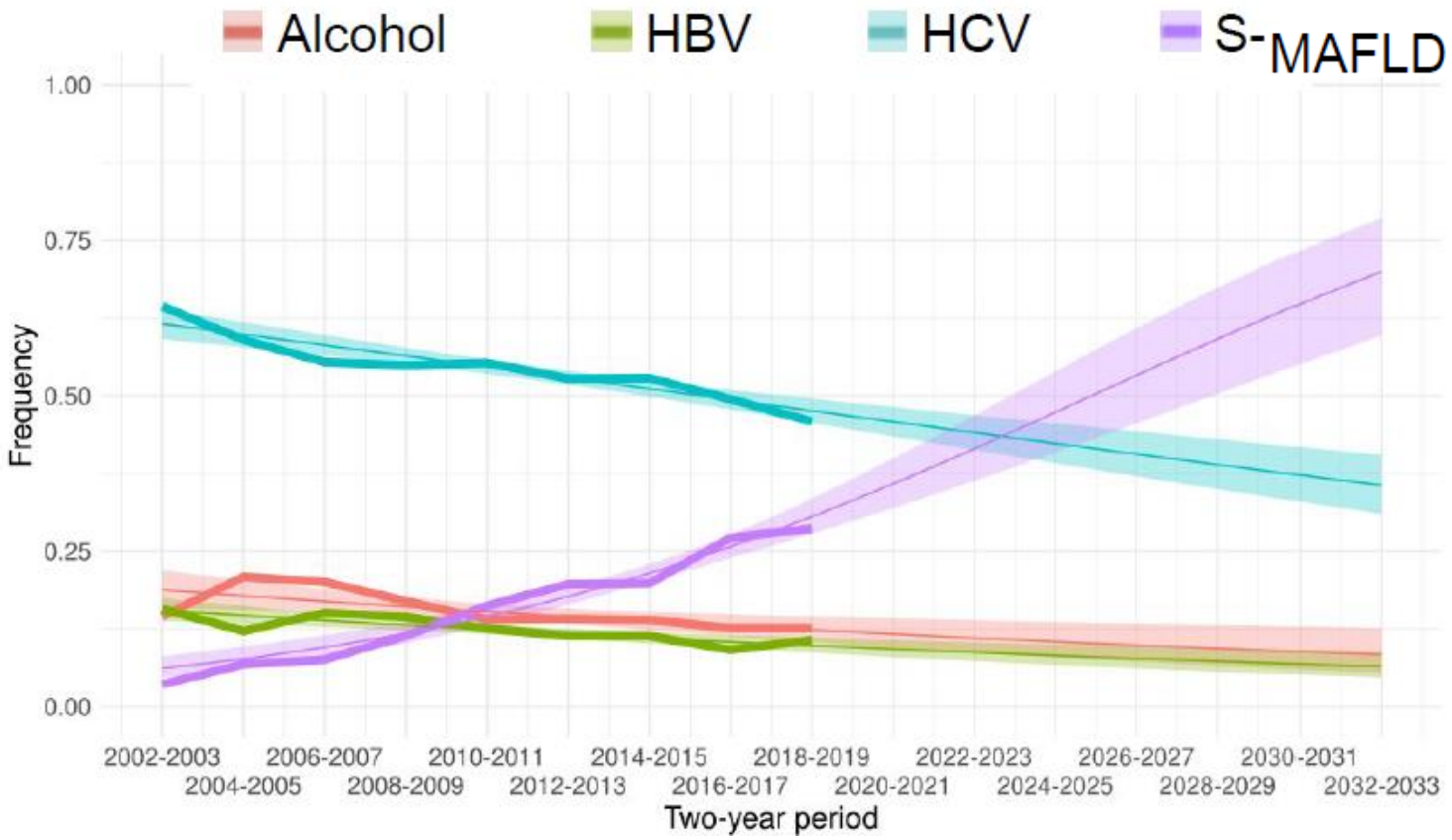
Proportion of patients with de novo HCC according to a combination of independent risk factors



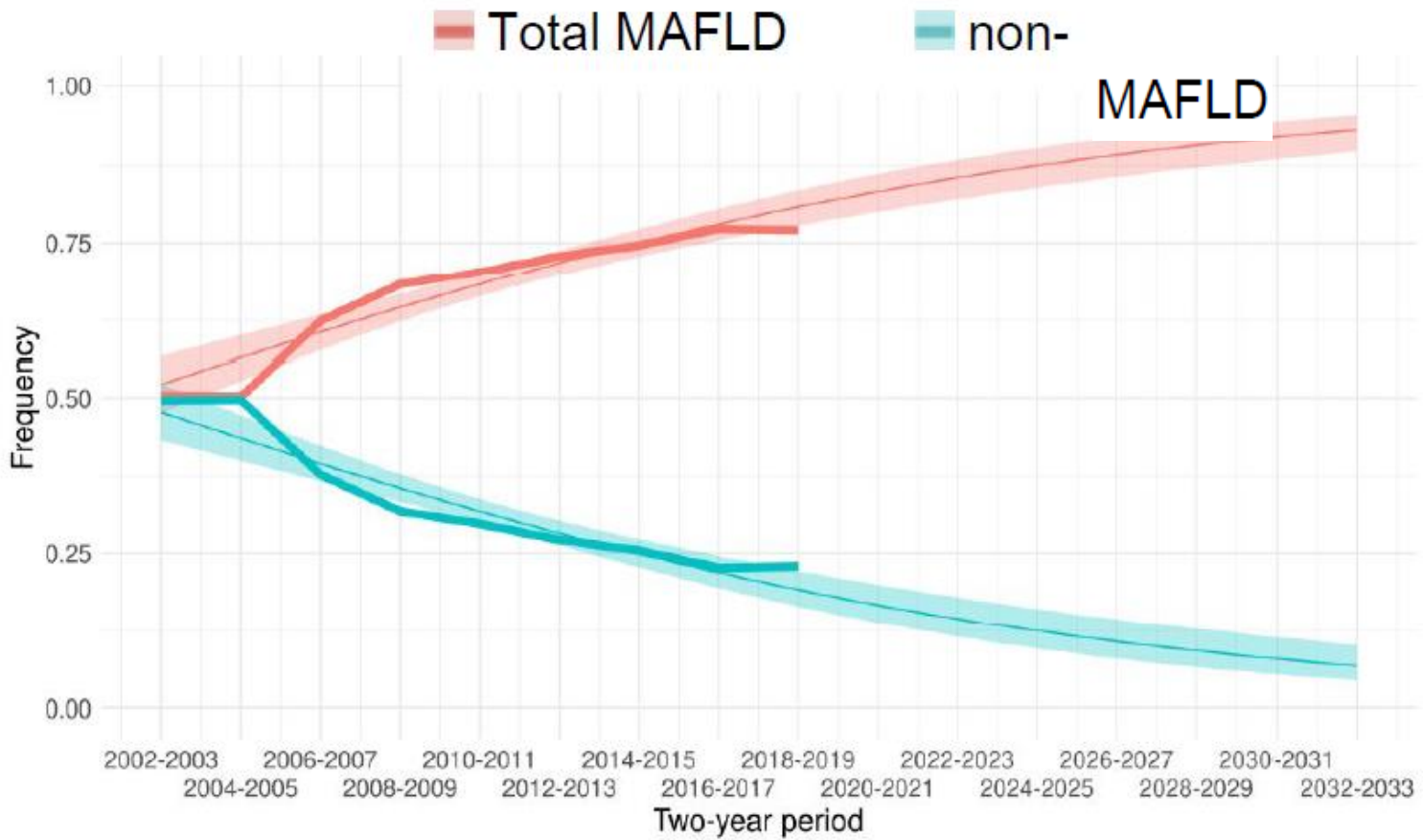
Degasperi et al., Hepatology 2020

NAFLD and HCC

Trends in HCC etiology



Svegliati Baroni, Vitale et al., Gut 2022



Svegliati Baroni, Vitale et al., Gut 2022

AGA clinical practice update on screening and surveillance for HCC in patients with NAFLD

Best Practice Advice 1: Screening for Hepatocellular Carcinoma Should Be Considered in All Patients With Cirrhosis Due to Nonalcoholic Fatty Liver Disease

Best Practice Advice 2: Patients With Nonalcoholic Fatty Liver Disease With Noninvasive Markers Showing Evidence of Advanced Liver Fibrosis or Cirrhosis Should Be Considered for Hepatocellular Carcinoma Screening

Best Practice Advice 3: Patients With Nonalcoholic Fatty Liver Disease in the Absence of Advanced Liver Fibrosis Should Not Be Routinely Considered for Hepatocellular Carcinoma Screening

Best Practice Advice 4: Adequacy of Ultrasound in Assessing the Liver Parenchyma for Mass Lesions Should Be Documented When Used for Hepatocellular Carcinoma Screening in Patients With Cirrhosis Due to Nonalcoholic Fatty Liver Disease

Best Practice Advice 5: When the Quality of Ultrasonography Is Suboptimal for Screening of Hepatocellular Carcinoma (eg, Due to Obesity) Future Screening Should Be Performed by Either Computed Tomography or Magnetic Resonance Imaging Scan, With or Without α-Fetoprotein, Every 6 Months

Loomba et al., Gastroenterology 2020

NASH and immunotherapy

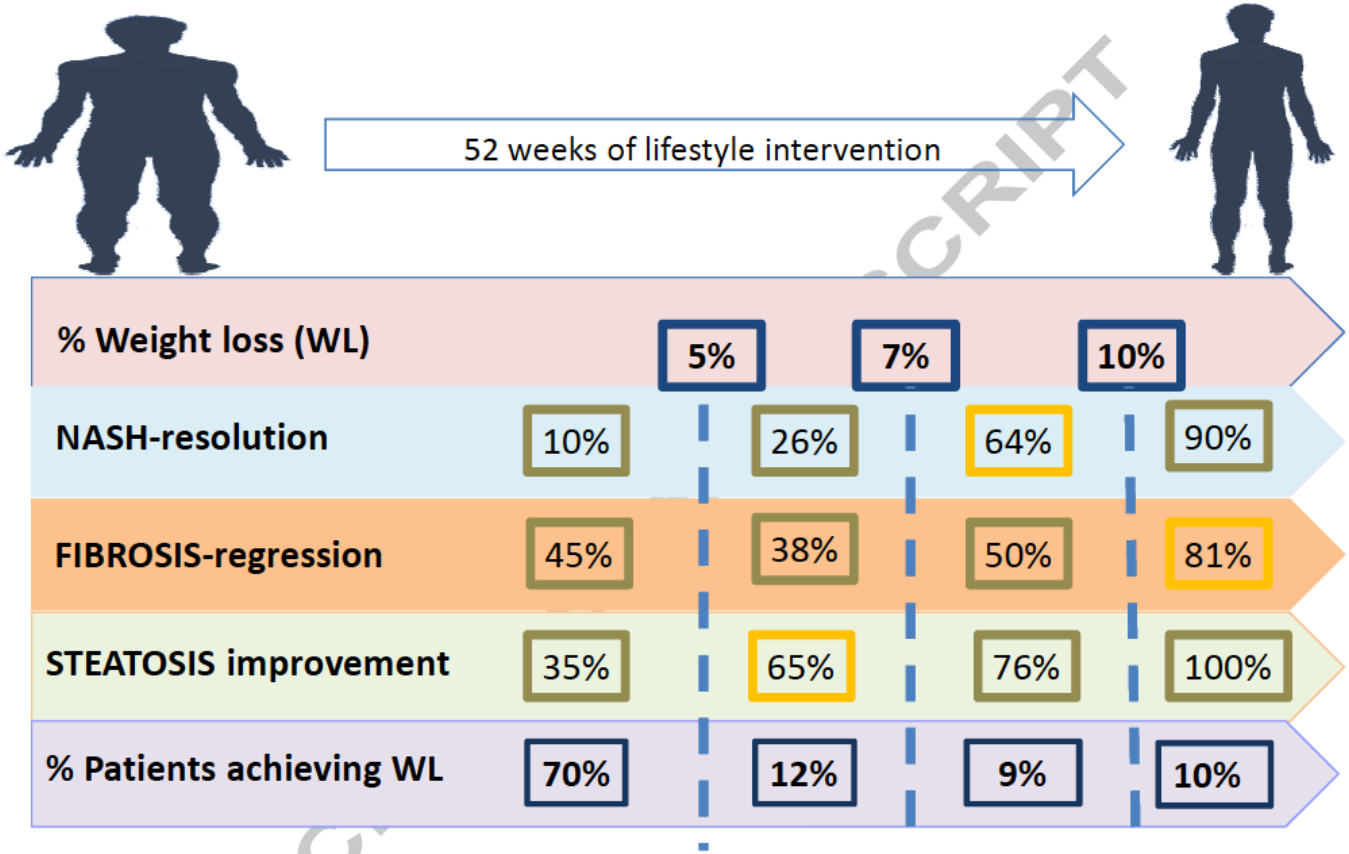
Article

NASH limits anti-tumour surveillance in immunotherapy-treated HCC

Dominik Pfister[1,82], Nicolás Gonzalo Núñez[2], Roser Pinyol[3], Olivier Govaere[4], Matthias Pinter[5,6], Marta Szydlowska[1], Revant Gupta[7,8], Mengjie Qiu[9], Aleksandra Deczkowska[10], Assaf Weiner[10], Florian Müller[1], Ankit Sinha[11,12], Ekaterina Friebel[2], Thomas Engleitner[13,14,15], Daniela Lenggenhager[16], Anja Moncsek[17], Danijela Heide[1], Kristin Stirm[1], Jan Kosla[1], Eleni Kotsiliti[1], Valentina Leone[1,18], Michael Dudek[19], Suhail Yousuf[9], Donato Inverso[20,21], Indrabahadur Singh[1,22], Ana Teijeiro[23], Florian Castet[3], Carla Montironi[3], Philipp K. Haber[24], Dina Tiniakos[4,25], Pierre Bedossa[4], Simon Cockell[26], Ramy Younes[4,27], Michele Vacca[28], Fabio Marra[29], Jörn M. Schattenberg[30], Michael Allison[31], Elisabetta Bugianesi[27], Vlad Ratziu[32], Tiziana Pressiani[33], Antonio D'Alessio[33], Nicola Personeni[33,34], Lorenza Rimassa[33,34], Ann K. Daly[4], Bernhard Scheiner[5,6], Katharina Pomej[5,6], Martha M. Kirstein[35,36], Arndt Vogel[35], Markus Peck-Radosavljevic[37], Florian Hucke[37], Fabian Finkelmeier[38], Oliver Waidmann[38], Jörg Trojan[38], Kornelius Schulze[39], Henning Wege[39], Sandra Koch[40], Arndt Weinmann[40], Marco Bueter[41], Fabian Rössler[41], Alexander Siebenhüner[42], Sara De Dosso[43], Jan-Philipp Mallm[44], Viktor Umansky[45,46], Manfred Jugold[47], Tom Luedde[48], Andrea Schietinger[49,50], Peter Schirmacher[51], Brinda Emu[1], Hellmut G. Augustin[20,21], Adrian Billeter[52], Beat Müller-Stich[52], Hiroto Kikuchi[53], Dan G. Duda[53], Fabian Kütting[54], Dirk-Thomas Waldschmidt[54], Matthias Philip Ebert[55], Nuh Rahbari[56], Henrik E. Mei[57], Axel Ronald Schulz[57], Marc Ringelhan[58,59,60], Nisar Malek[61], Stephan Spahn[61], Michael Bitzer[61], Marina Ruiz de Galarreta[24,62], Amaia Lujambio[24,62,63], Jean-Francois Dufour[64,65], Thomas U. Marron[24,66], Ahmed Kaseb[67], Masatoshi Kudo[68], Yi-Hsiang Huang[69,70], Nabil Djouder[23], Katharina Wolter[71,72], Lars Zender[71,72,73], Parice N. Marche[74,75], Thomas Decaens[74,75,76], David J. Pinato[77,78], Roland Rad[13,14,15], Joachim C. Mertens[17], Achim Weber[16,79], Kristian Unger[18], Felix Meissner[11], Susanne Roth[9], Zuzana Macek Jilkova[74,75,77], Manfred Claassen[7,8], Quentin M. Anstee[4,80], Ido Amit[10], Percy Knolle[19], Burkhard Becher[2], Josep M. Llovet[3,24,81] ✉ & Mathias Heikenwalder[1] ✉

Nature 2021

Current situation in NASH treatment



Data from Vilar-Gomez et al.

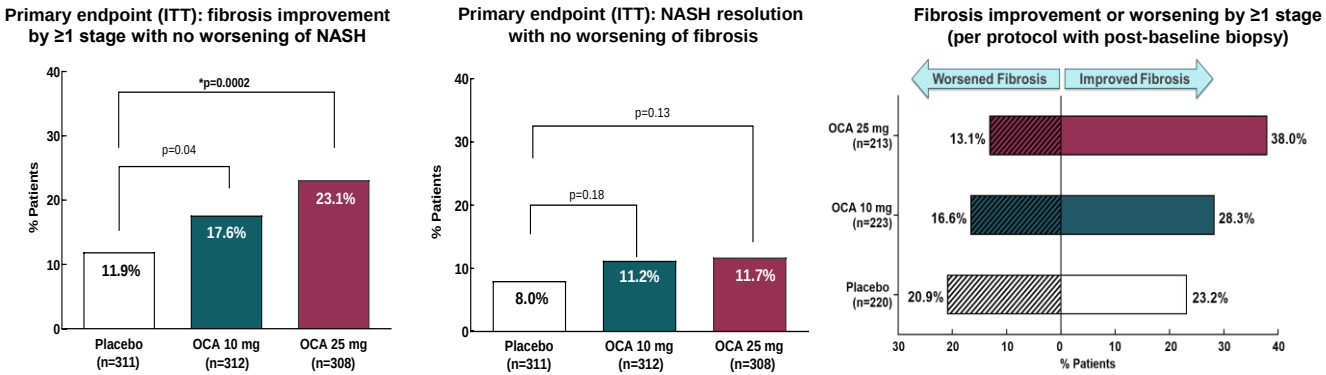
Gastroenterology 2020;■:1–7

AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review

Zobair M. Younossi,[1,2,*] Kathleen E. Corey,[3,*] and Joseph K. Lim[4]

[1]Center for Liver Diseases and Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, Virginia; [3]Liver Center, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; and [4]Yale Liver Center and Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut

REGENERATE: a Phase 3 trial of obeticholic acid (OCA) for NASH

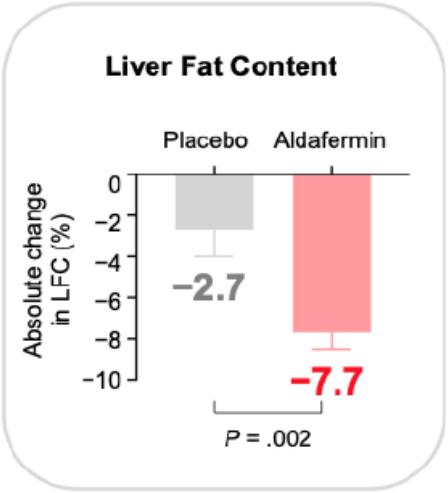


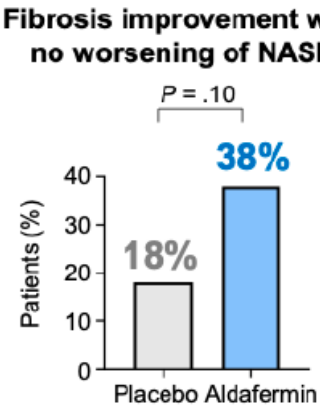
- OCA 25 mg QD **met the primary endpoint of improvement in liver fibrosis** with no worsening of NASH
- Although **the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met**, resolution of NASH based on the overall pathologist's assessment was more frequent with OCA 25 mg

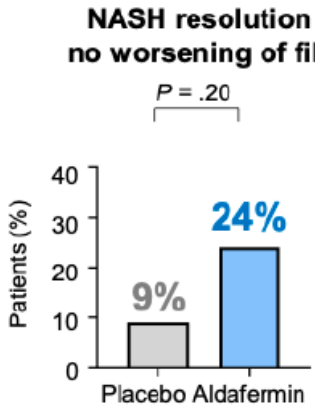
Younossi, EASL 2019

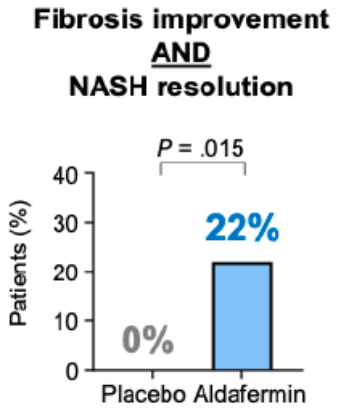
Aldafermin, a FGF-19 analog, in patients with NASH

24- week, phase 2 study, in 78 patients with biopsy-proven NASH. Key inclusion criteria were NAS score ≥4, stage 2 or 3 fibrosis, and absolute liver fat content ≥8%, measured by MRI-PDFF. Patients were randomly assigned to s.c PL or aldafermin 1 mg daily for 24 weeks. The primary outcome was change in liver fat content by week 24. Secondary outcomes were serum markers, fibrosis improvement and NASH resolution.









Trial population: NAS ≥4, stage 2 or 3 fibrosis
Trial arms: placebo (n=25), aldafermin 1 mg (n=53)

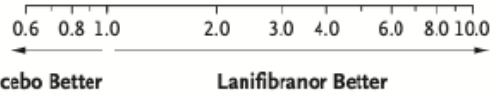
Gastroenterology

Harrison e tal., Gastroenterology 2021

The pan-PPAR agonist lanifibranor in NASH

Phase 2b, double-blind, RCT in 247 patients with noncirrhotic, highly active NASH assigned to 1200 or 800 mg of lanifibranor or PL once daily for 24 weeks. 103 (42%) had T2D and 188 (76%) had significant or advanced fibrosis.

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	

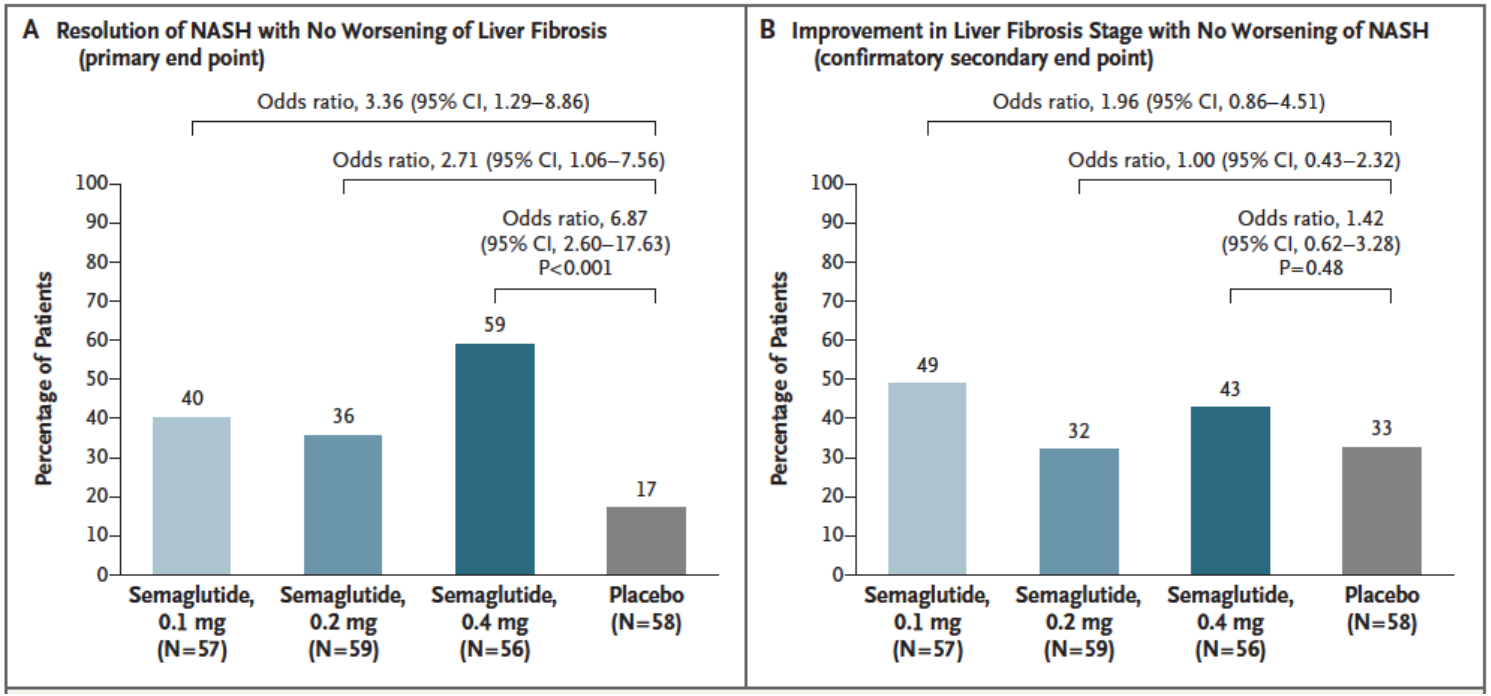


Primary end point:
- decrease of at least 2 points in the SAF-A score (ballooning and inflammation) without worsening of fibrosis

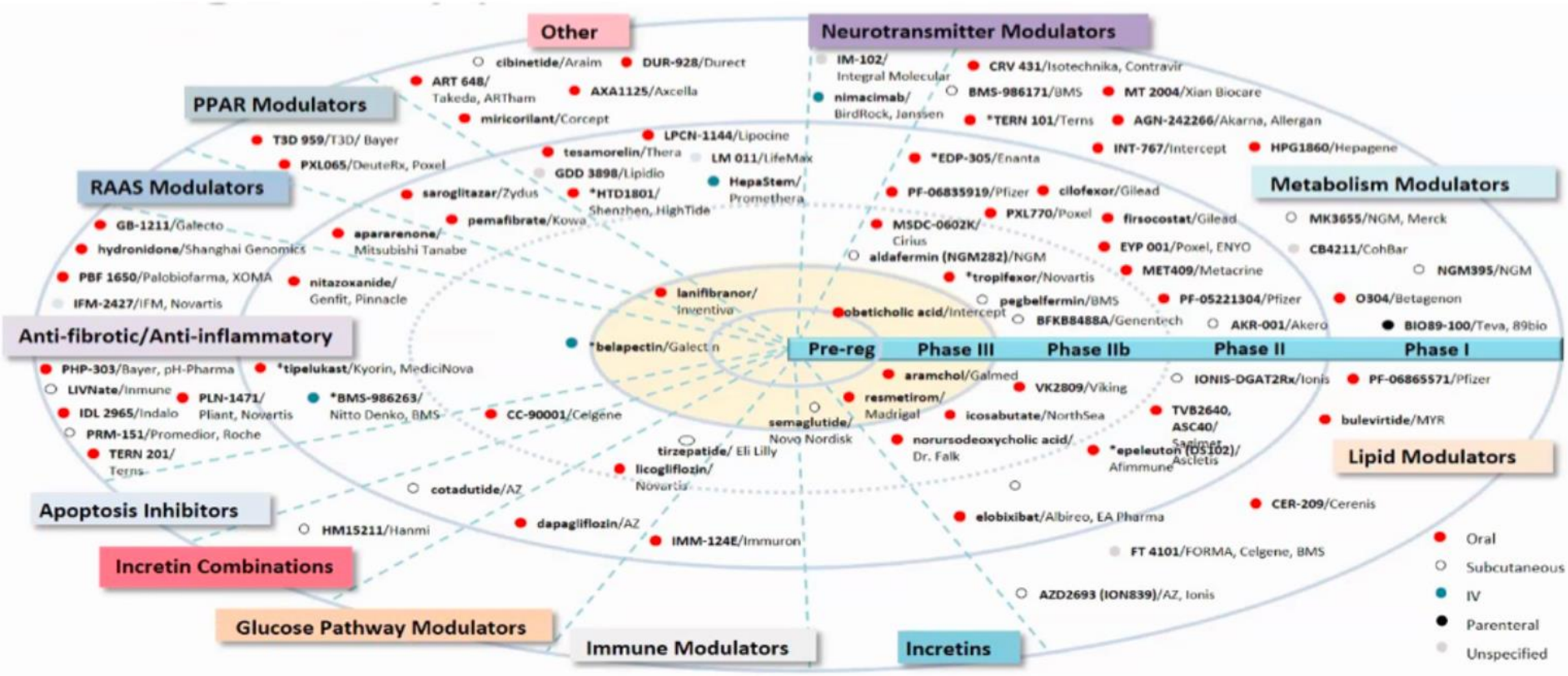
Secondary end points:
- surrogate biomarkers, resolution of NASH and regression of fibrosis.

Francque et al., N Engl J Med 2021

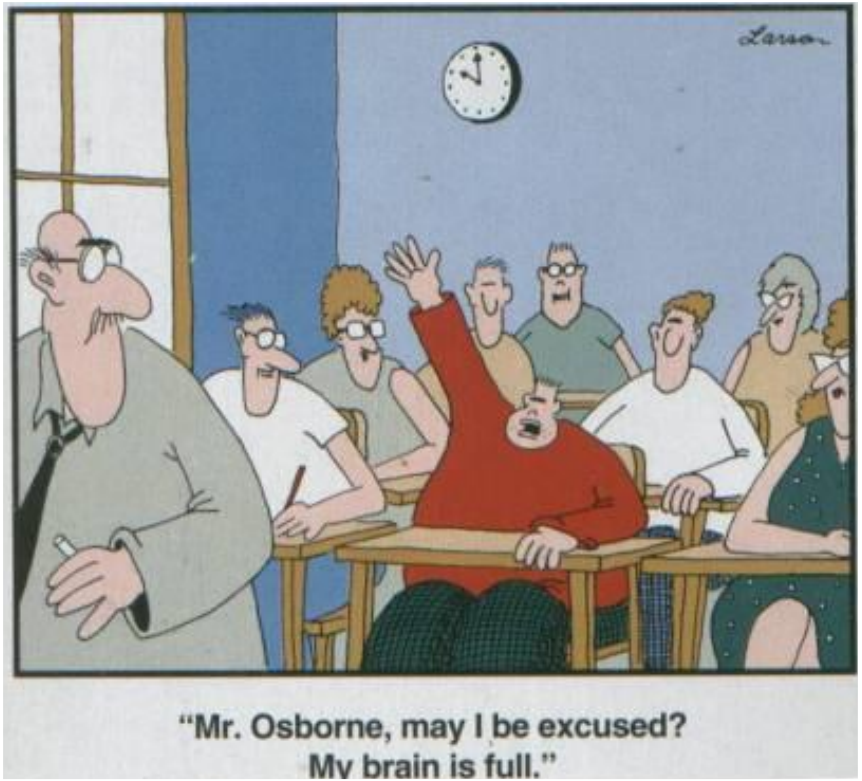
The GLP-1 agonist semaglutide induces NASH resolution but does not improve fibrosis



Newsome et al., NEJM 2020



Courtesy of Prof. Marchesini Reggiani



THANK YOU!