XV Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI

Firenze, 9-10 Gennaio 2023

Centro Congressi Hotel Albani

Steatosi epatica, NASH, NAFLD: inquadramento diagnostico-terapeutico

Fabio Marra

Dipartimento di Medicina Sperimentale e Clinica

Università di Firenze

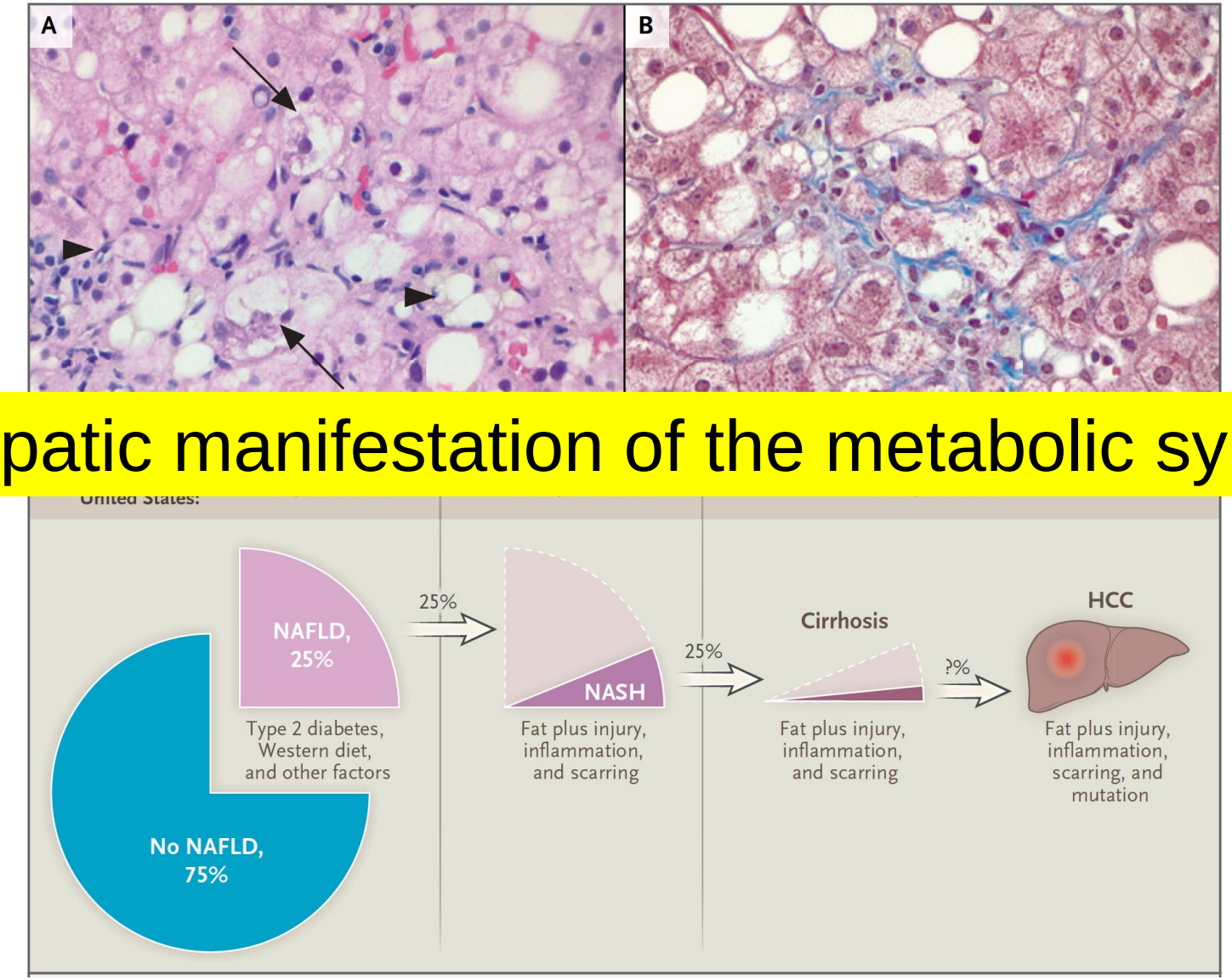
fabio.marra@unifi.it

Disclosures

- **Alfasigma:** 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
- **Roche:** consultant fees

Definition and natural history

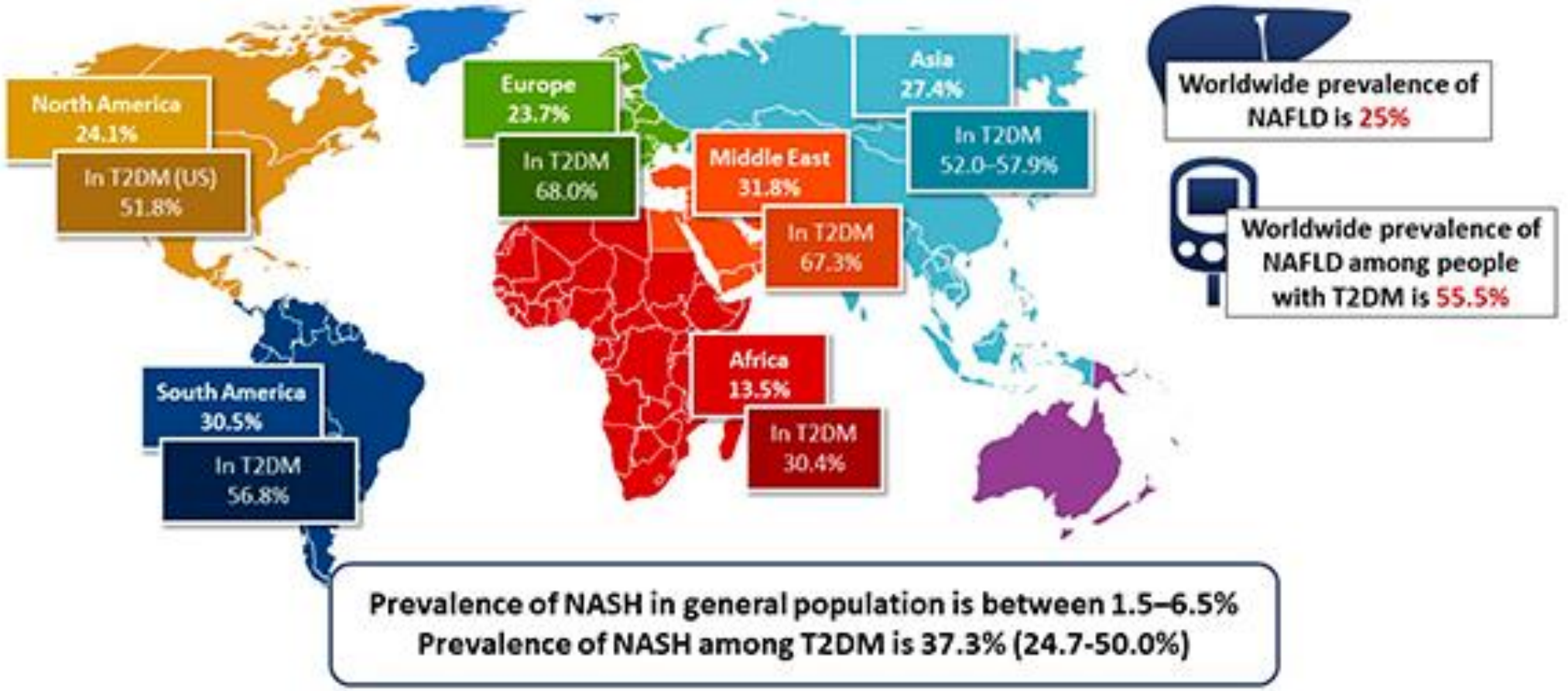
The spectrum of nonalcoholic steatosis



The hepatic manifestation of the metabolic syndrome

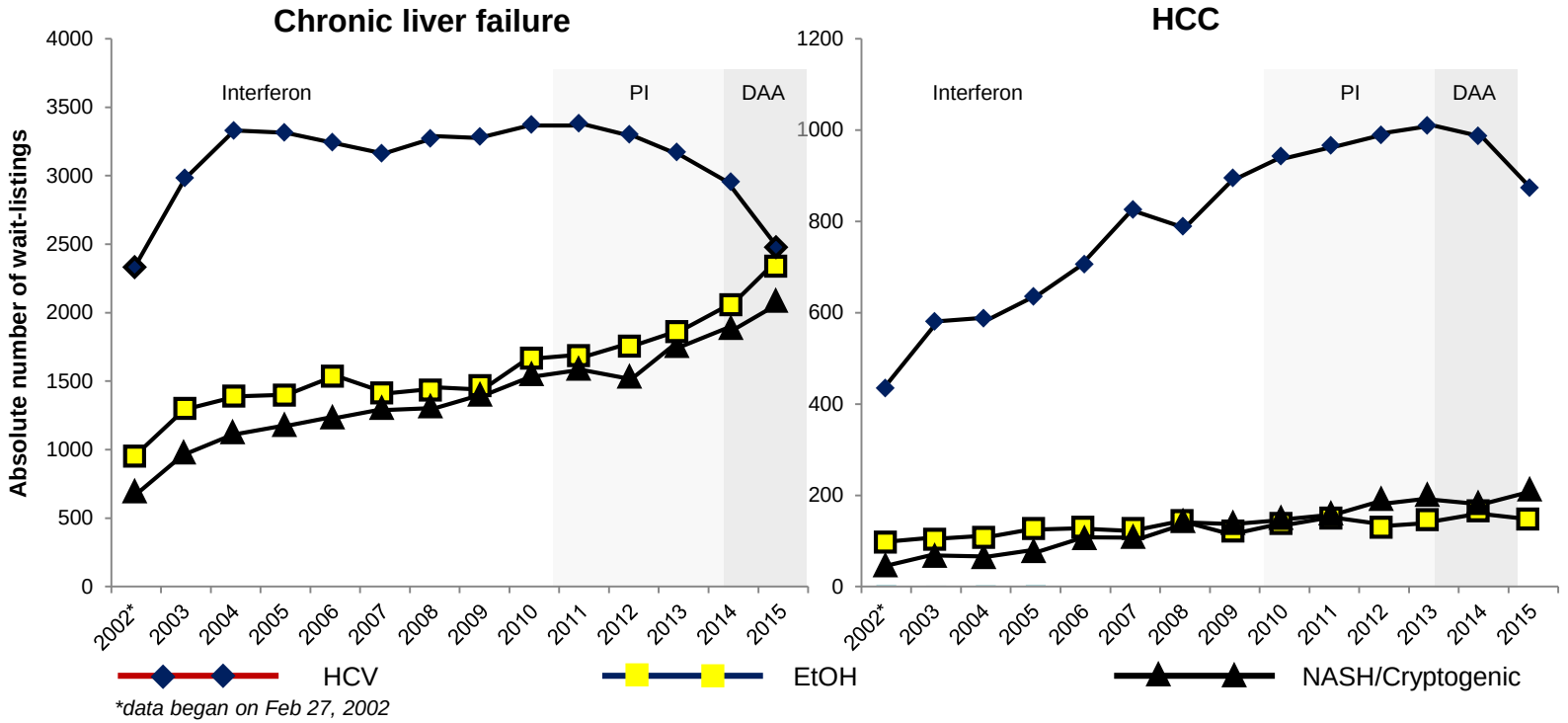
Diehl & Day NEJM 2017

Global prevalence of NAFLD



Younossi et al Hepatology 2016

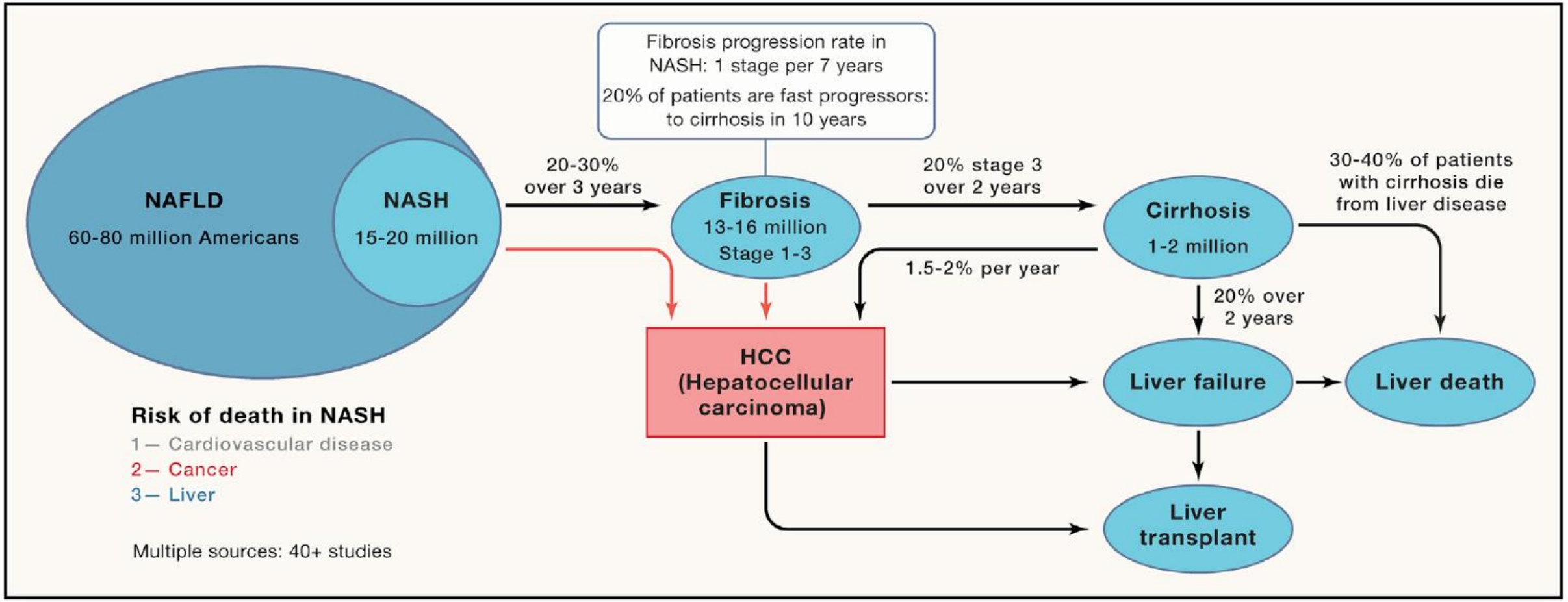
Rise in Liver Transplant Waiting list for NASH



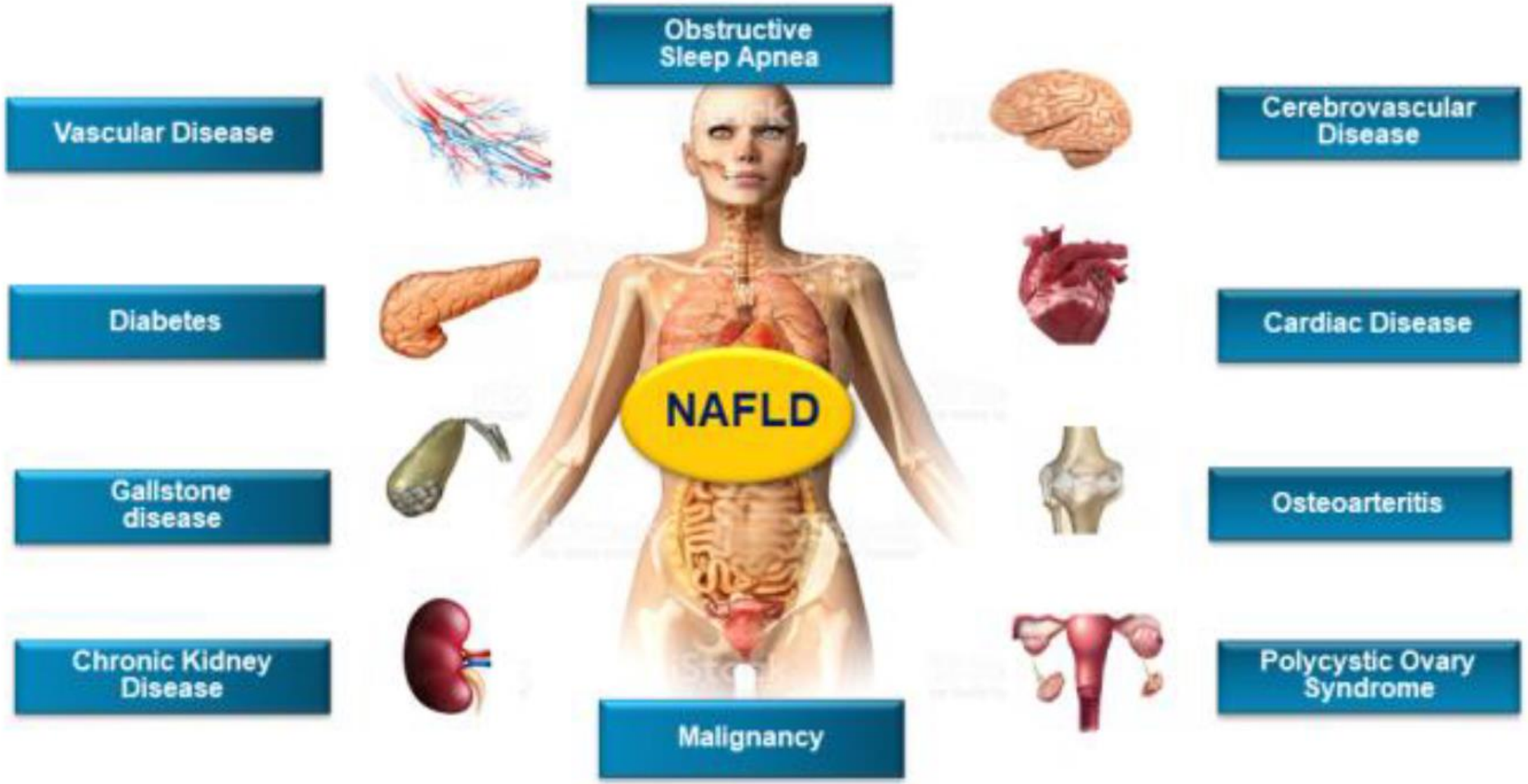
Liver transplant wait-listing for NASH continues to rise and expected to surpass HCV within 2 years

Goldberg et al. Gastroenterology 2017

Natural history of NAFLD

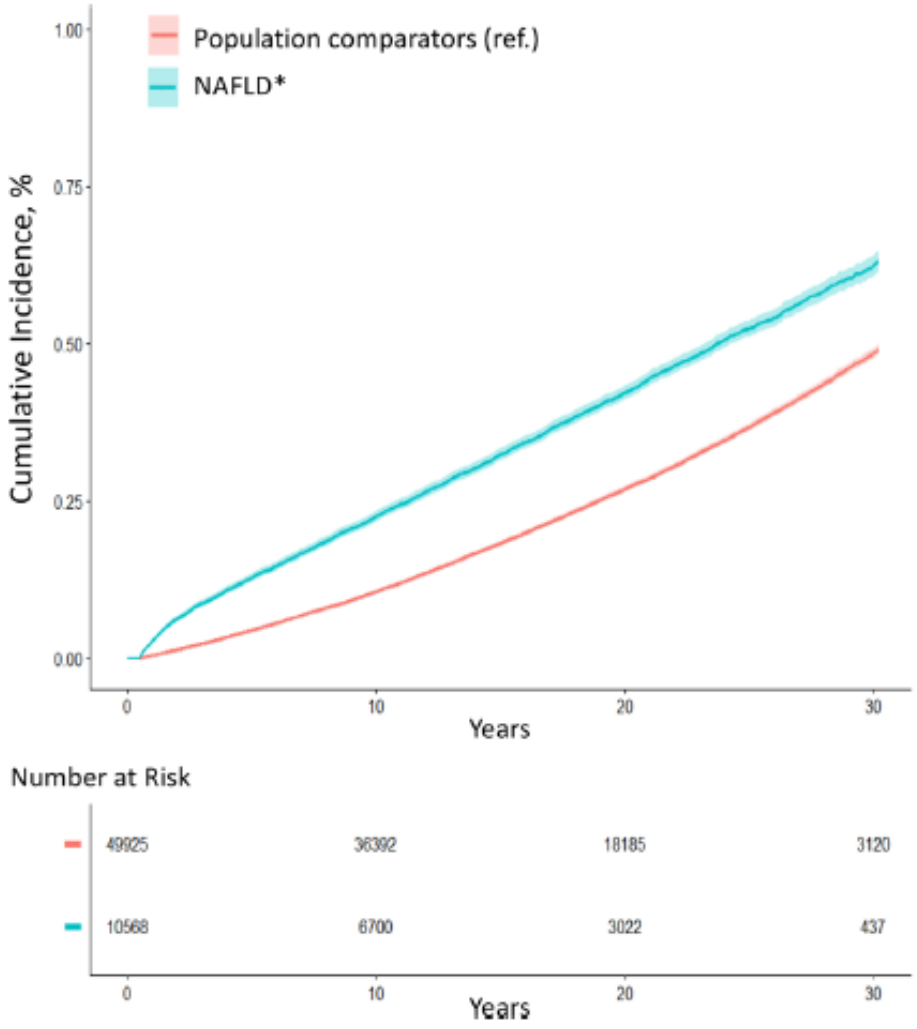


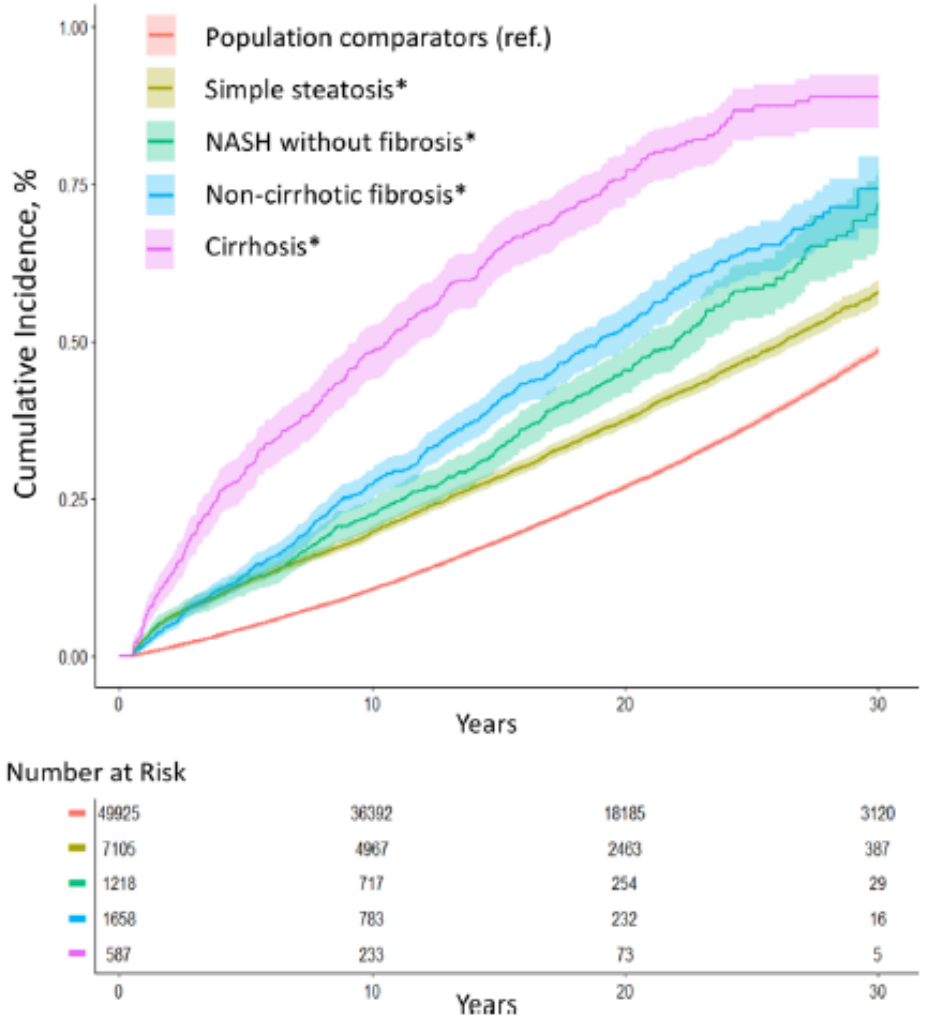
Loomba et al., Cell 2021



Younossi et al., Hepatology 2019

All-cause mortality according to NASH and histological severity



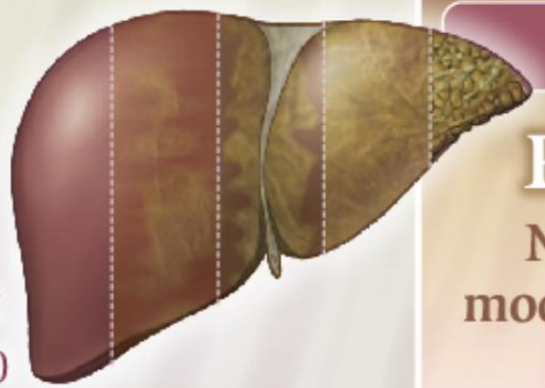


Simon et al., Gut 2020

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

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

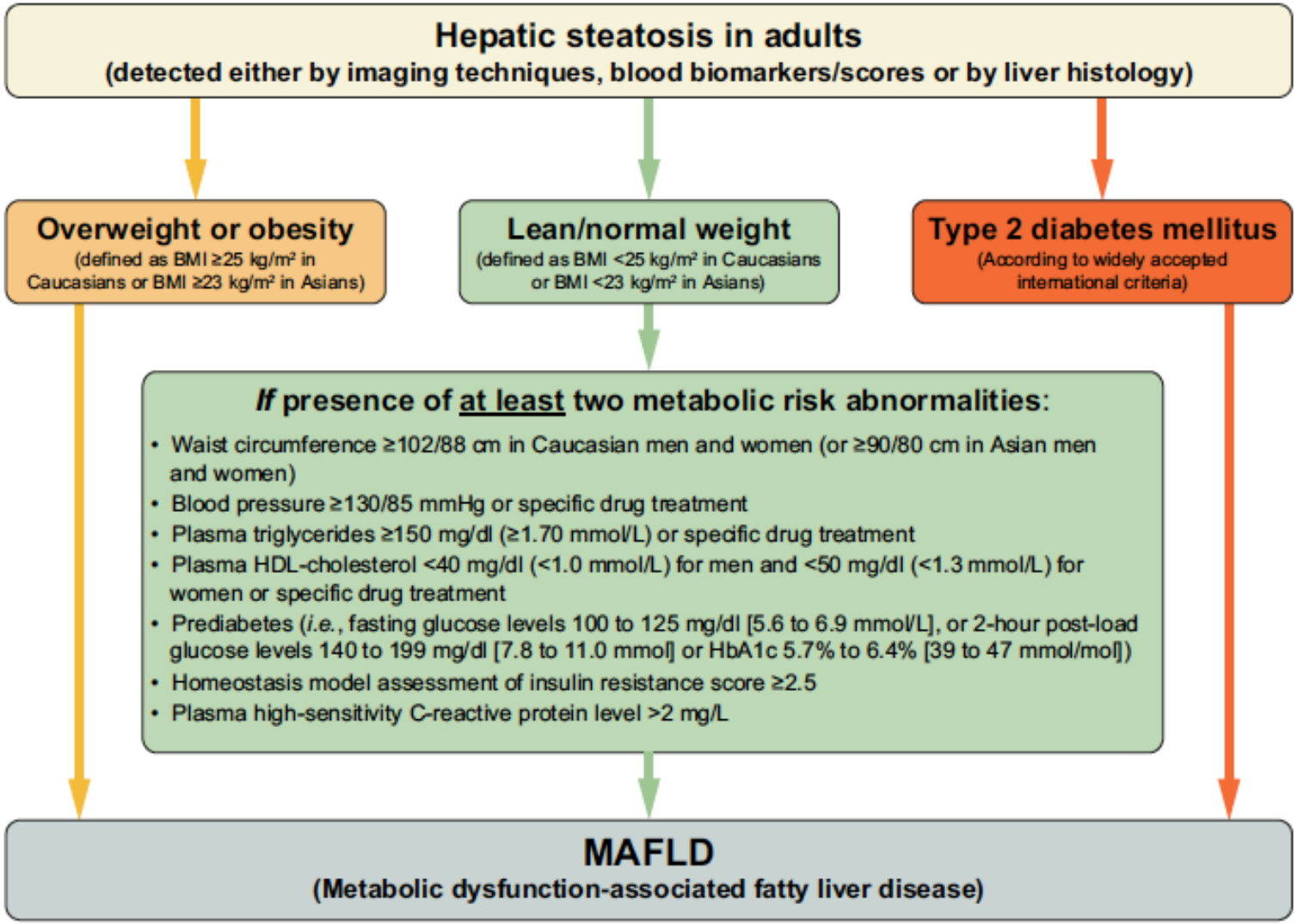
Small bowel diseases: IBD, Bacterial overgrowth

Environmental hepatotoxins: e.g. Petrochemicals

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

HCV genotype 3, Wilson's disease, celiac disease

‘Positive’ diagnostic criteria for MAFLD



Eslam et al., J Hepatol 2020

Steatohepatitis as a phenotype determined by different types of injury

NASH

ASH

PNPLA3
PASH

Metabolic
MASH

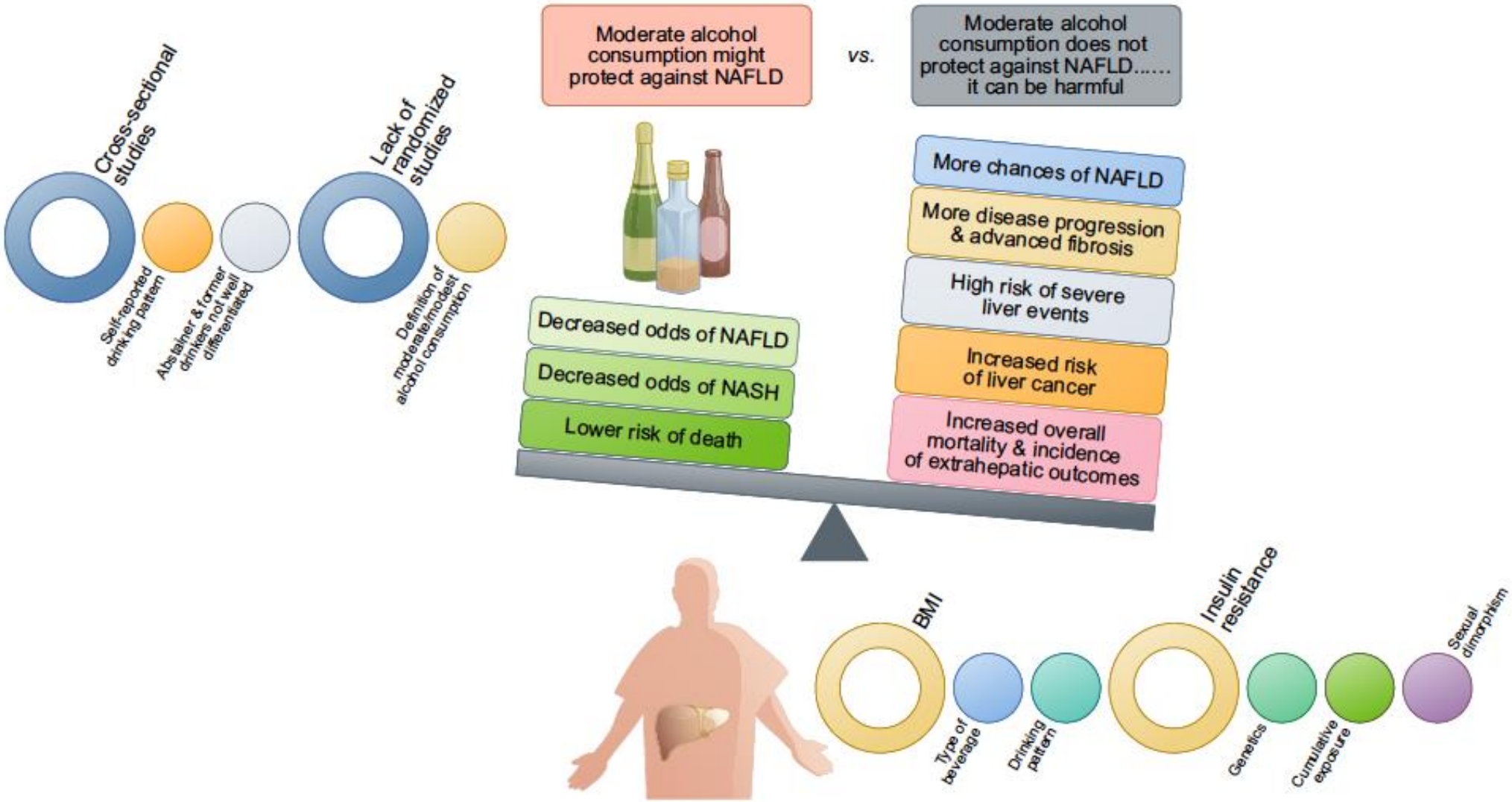
Toxic
TASH

Drug-induced
DASH

Chemotherapy
CASH

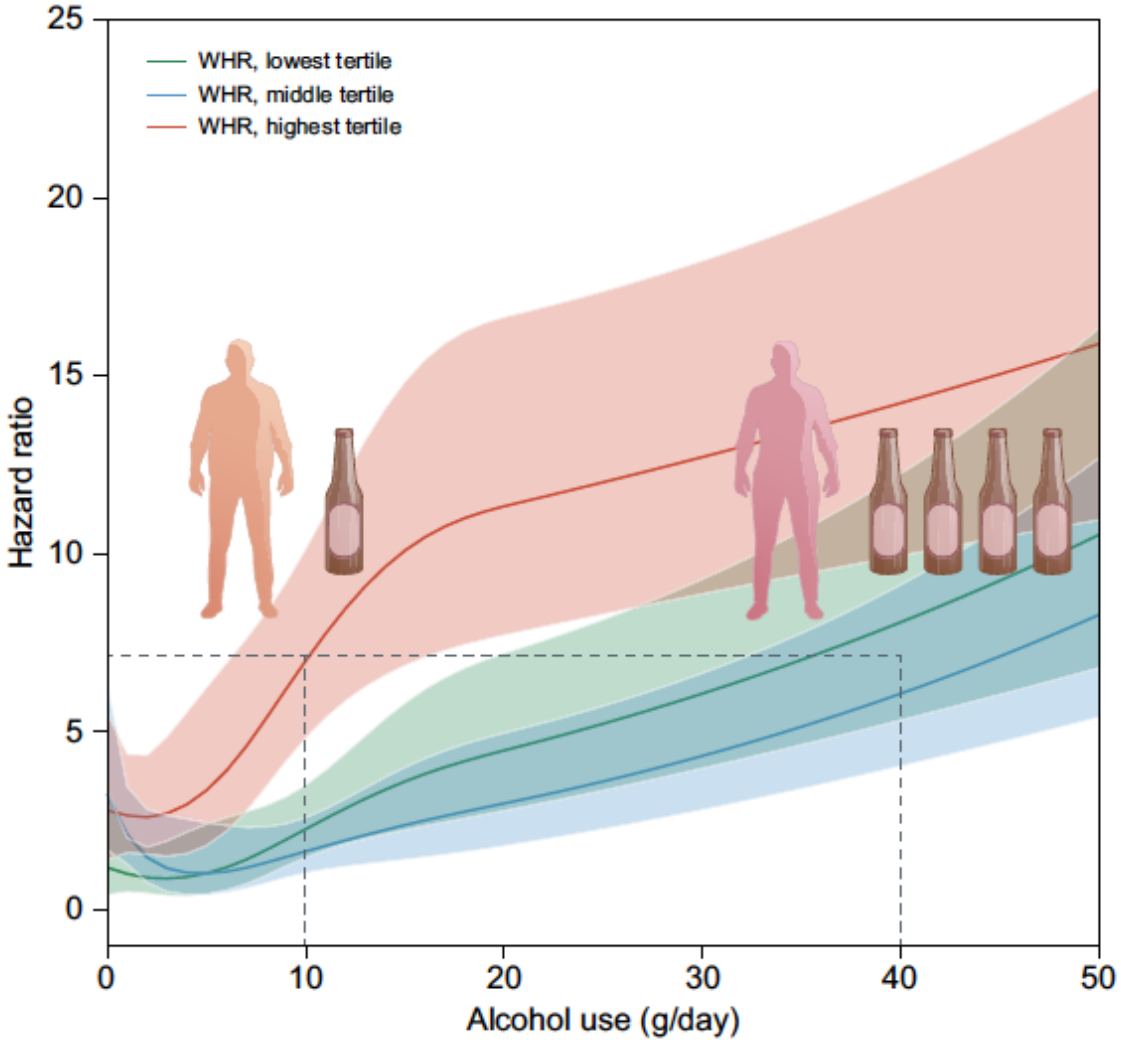
Both NASH-ASH
BASH

Alcohol consuption and the metabolic syndrome



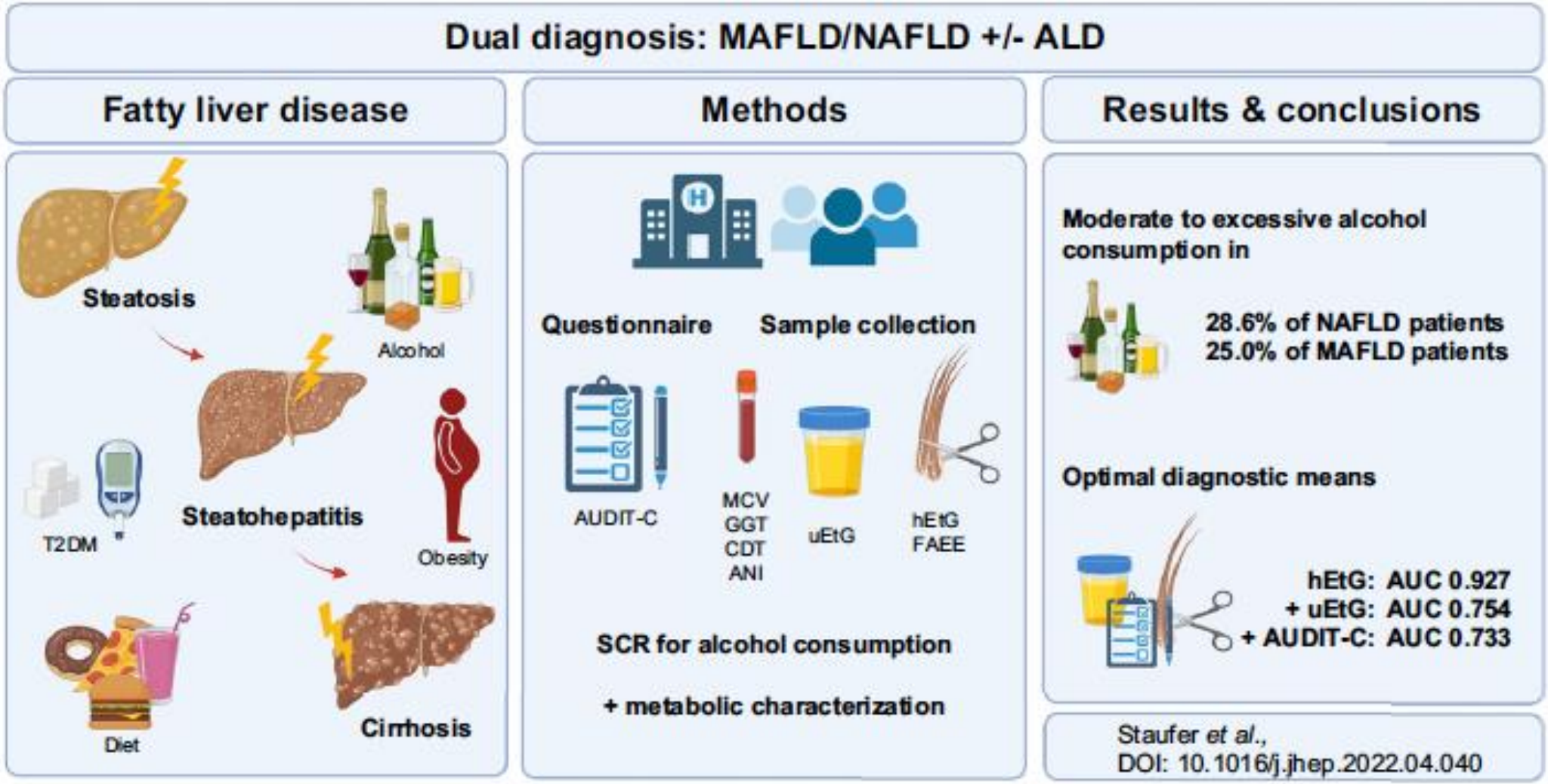
Aberg et al., J Hepatol 2023

Obesity increases alcohol toxicity



Aberg et al., J Hepatol 2023

Alcohol consumption in presumed NAFLD



Staufer et al., J Hepatol 2022

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

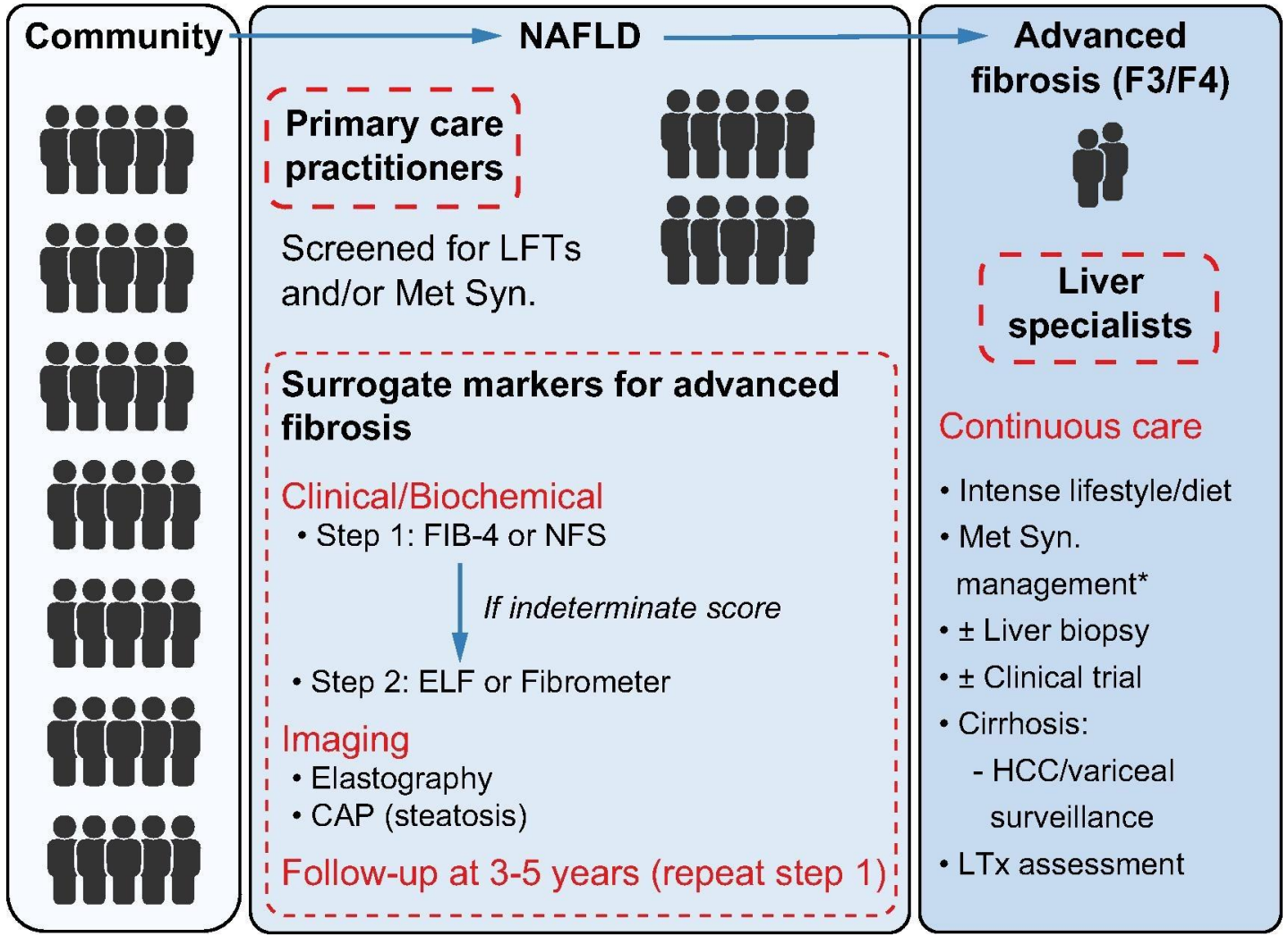
Availability

Cost

Primary care → Liver clinics

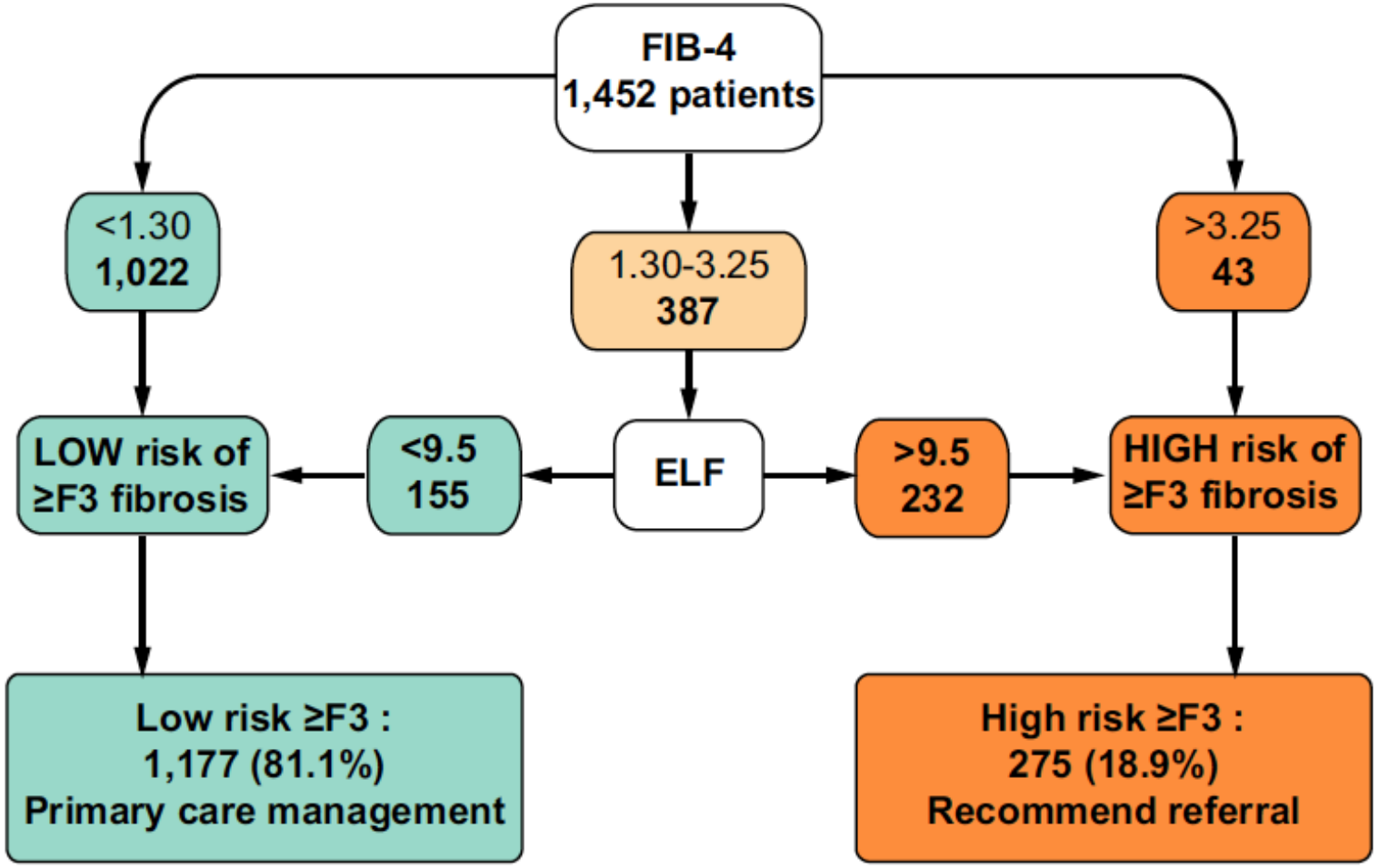
Castera, Liver Int 2020

Primary care/specialist interface in NAFLD



Marchesini & Armstrong,, J Hepatol 2019

Referral model from primary care in the UK



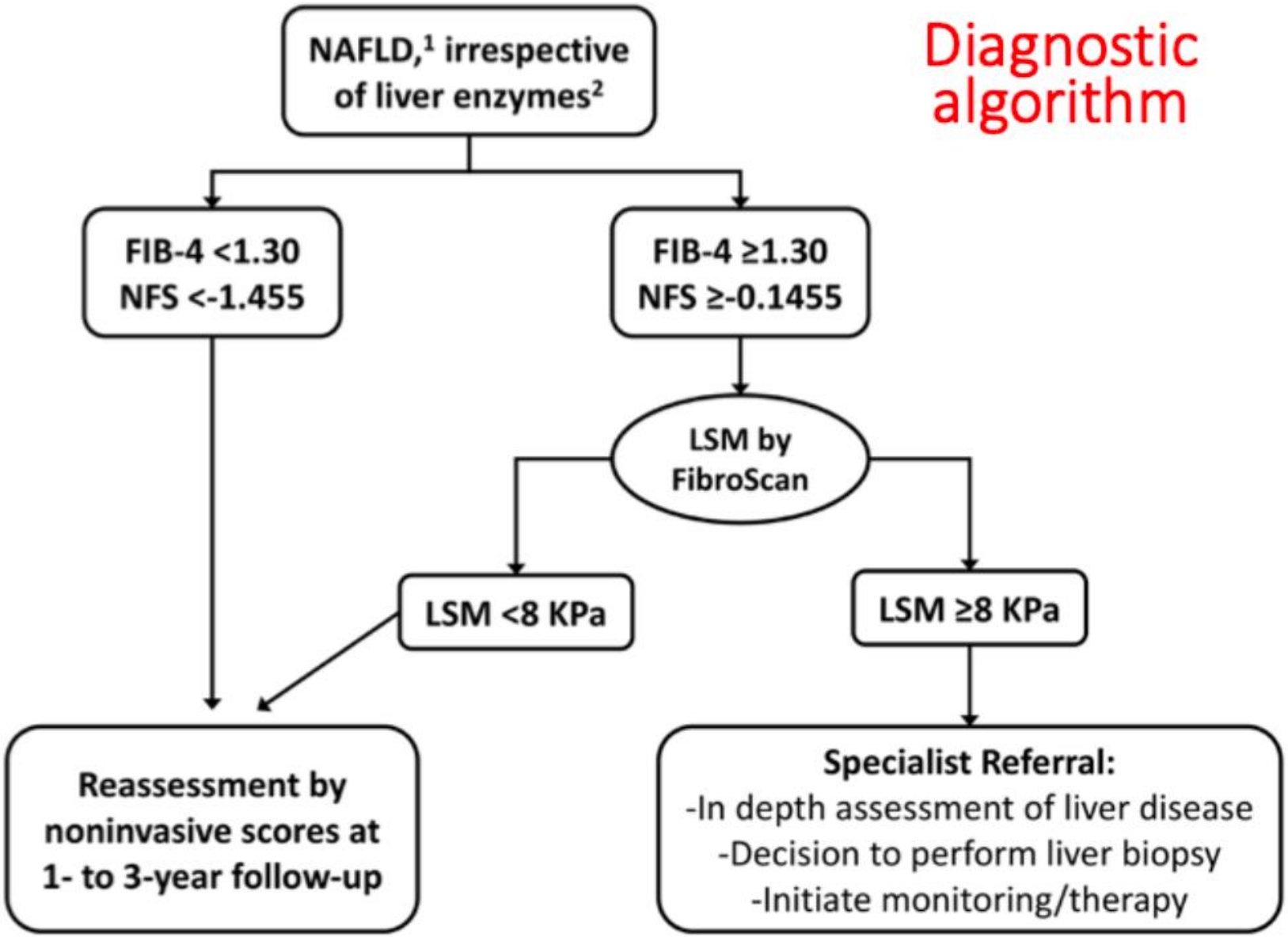
Srivastava et al., J Hepatol 2019

General population:
Advanced liver fibrosis (0·9–2·0%)
Cirrhosis (0·1–1·7%)

High-risk population:
Advanced liver fibrosis 0–27·9%
Cirrhosis 2·4–4·0%

Reliance on abnormal liver function tests will miss most patients with significant liver injury.

Diagnostic algorithm

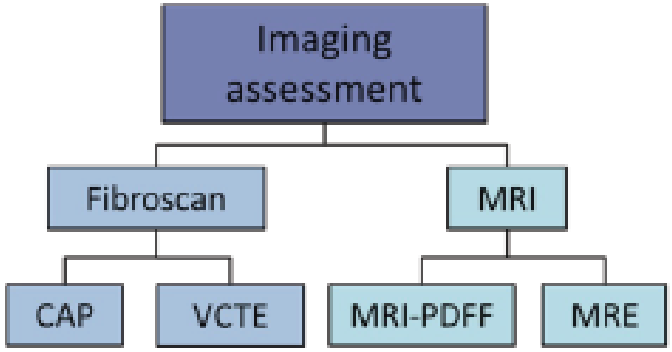


Italian NAFLD Guidelines, 2021

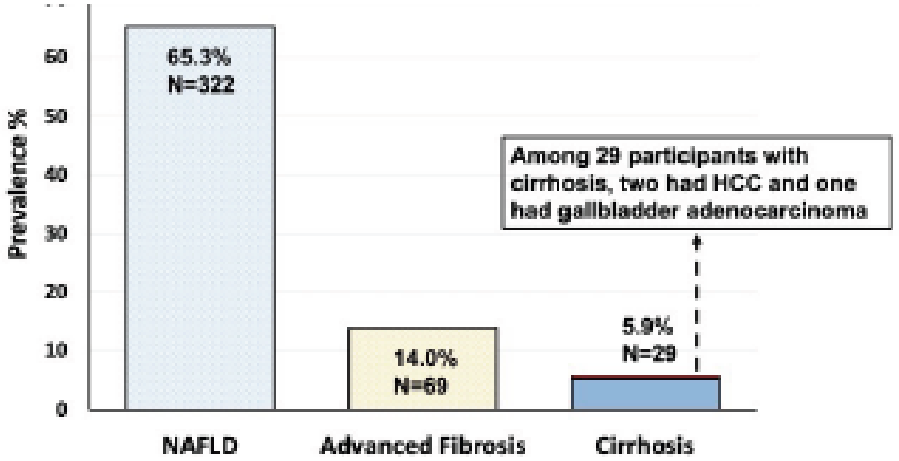
Prevalence of NAFLD, advanced fibrosis, cirrhosis and HCC in people with type 2 diabetes

Type 2 Diabetes
Age ≥ 50 years

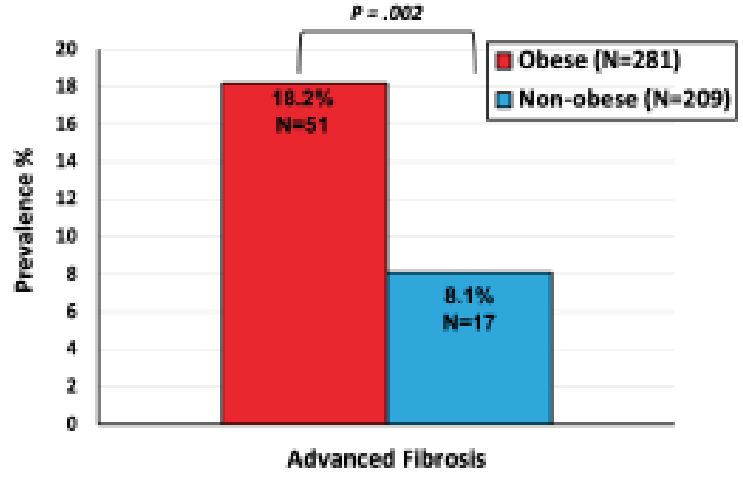
Prospectively recruited participants underwent a research examination with laboratory and clinical assessment to rule out other causes of liver disease.



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



Obesity significantly increased the risk of advanced fibrosis

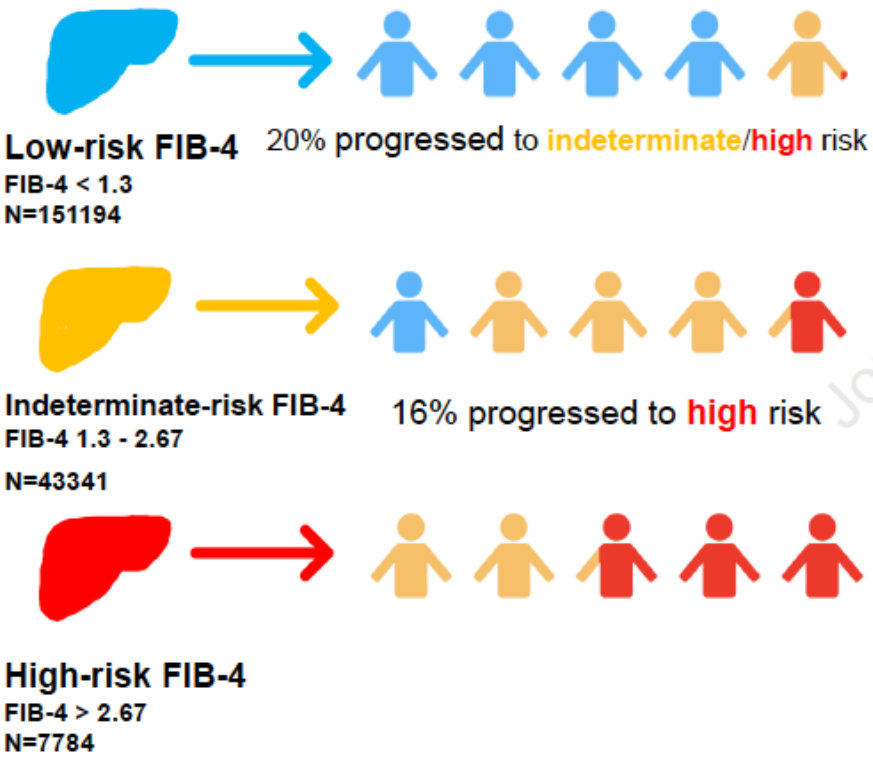


Journal Pre-proof

Ajmera et al., J Hepatol 2022

Longitudinal changes in fibrosis markers and the risk of cirrhosis and HCC

Change in FIB-4 Risk Group from baseline and at 3 year from NAFLD diagnosis



Low-risk FIB-4
FIB-4 < 1.3
N=151194

20% progressed to indeterminate/high risk

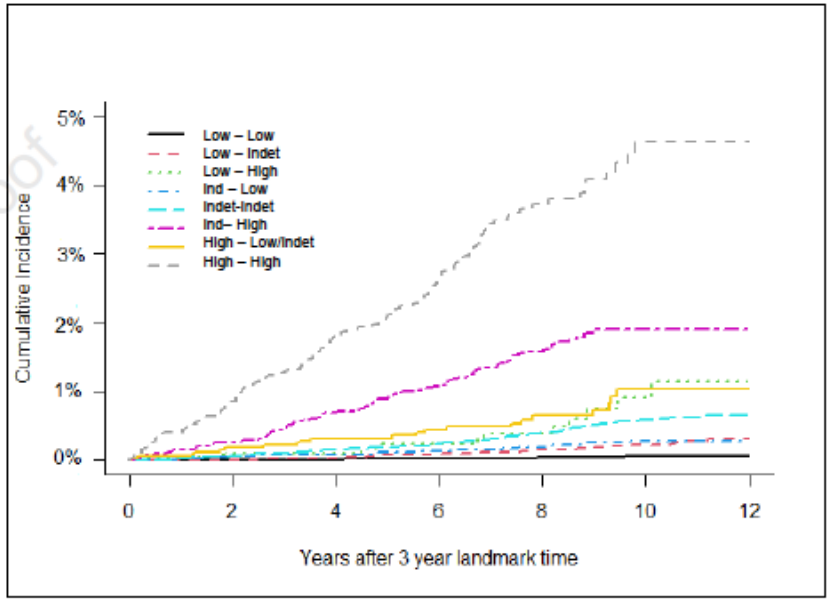
Indeterminate-risk FIB-4
FIB-4 1.3 - 2.67
N=43341

16% progressed to high risk

High-risk FIB-4
FIB-4 > 2.67
N=7784

HCC Risk

HCC risk after change in FIB-4 at 3 years



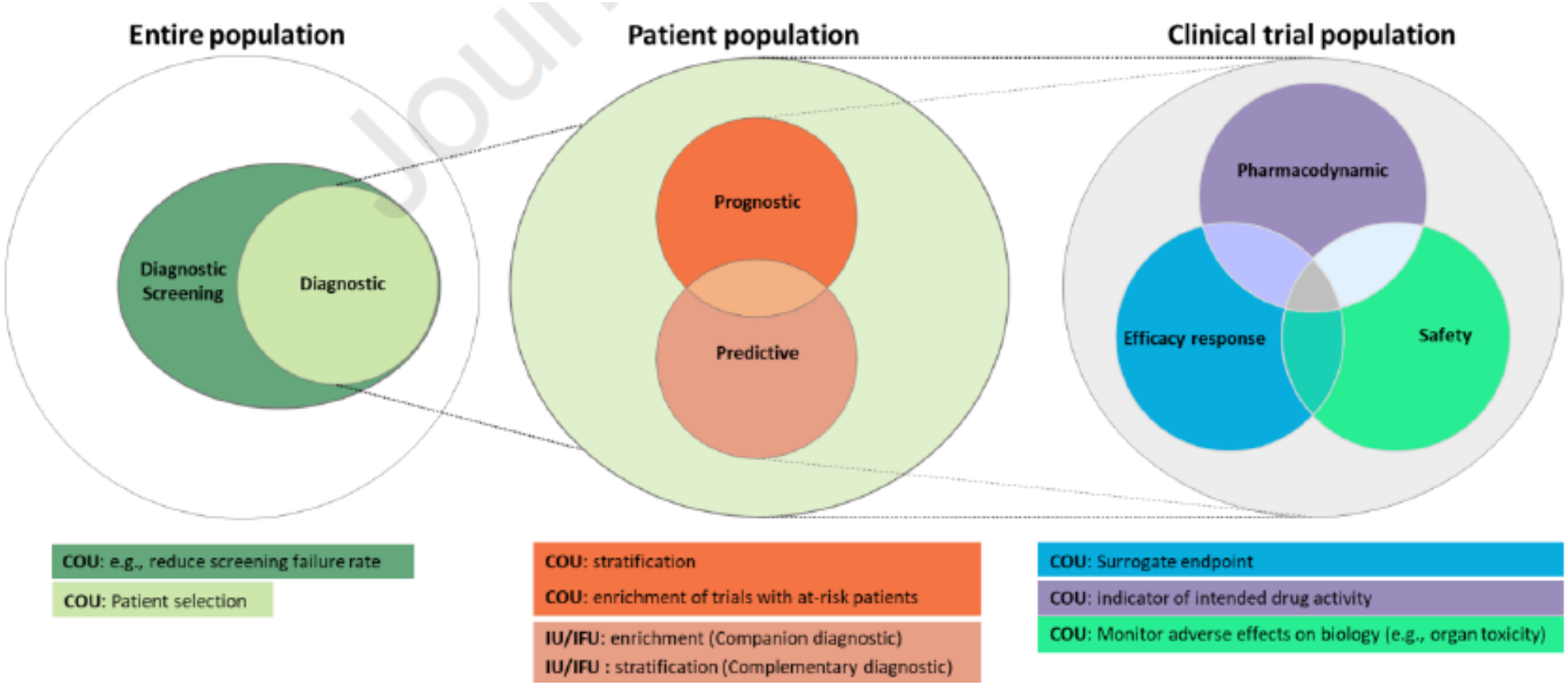
Annual IR for HCC per 1,000 PY
Low-Low 0.05 per 1,000 PY (reference)
Low-Indeterminate 0.21 per 1,000 PY, adjusted HR 3.45
Indet-Indet 0.53 per 1,000 PY, adjusted HR 7.96
Indet-High 1.90 per 1,000 PY, adjusted HR 26.52
High-High 4.56 per 1,000 PY, adjusted HR 57.69

Risk of developing cirrhosis or HCC corresponded to a subsequent increase or decline in FIB-4 over 3 years

Journal Pre-proof

Cholankeril et al., J Hepatol 2022

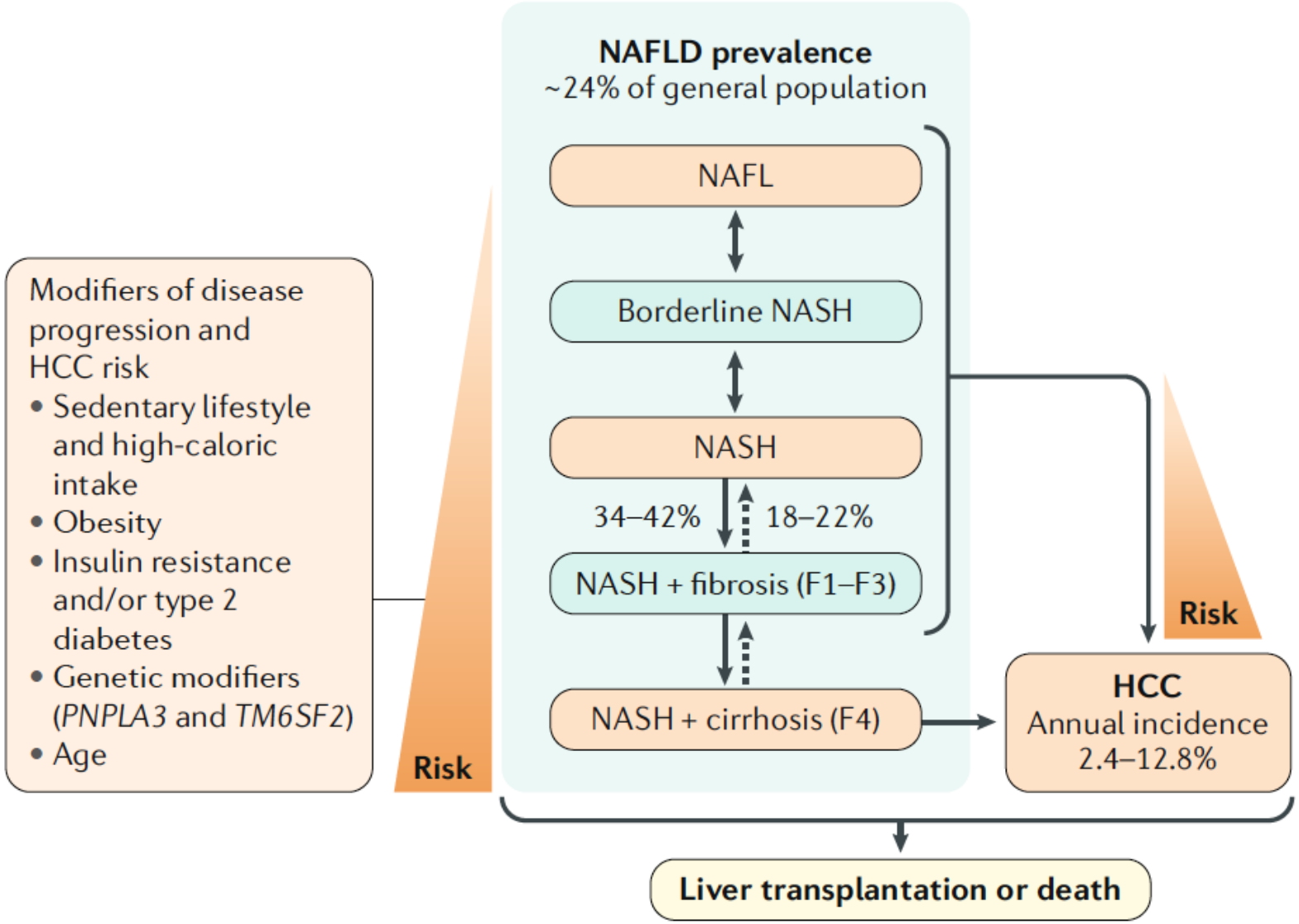
Biomarker categories in drug development



Rasmussen et al., J Hepatol 2023

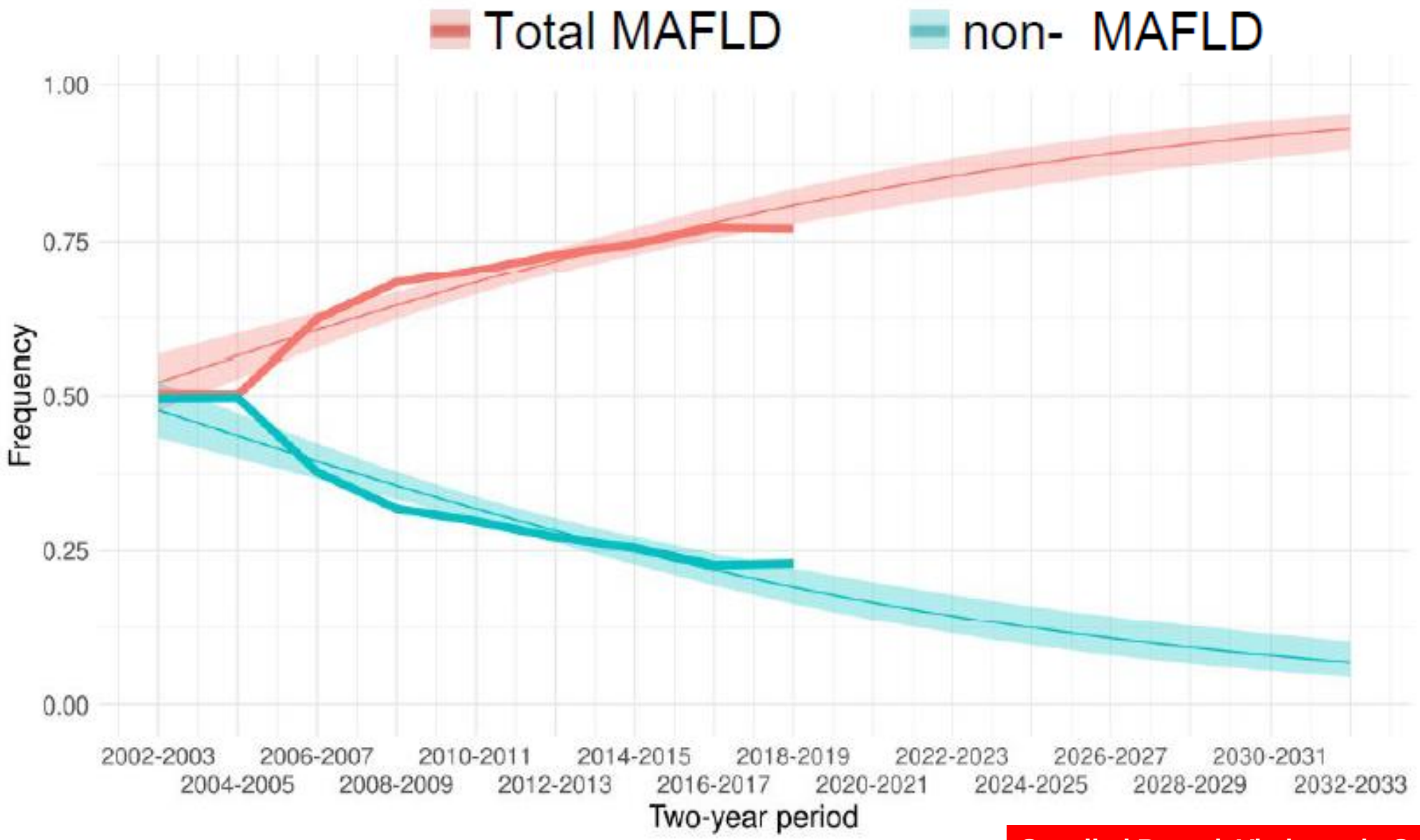
NAFLD and HCC

Natural history of fatty liver



Anstee et al., Nat Rev Gastroenterol Hepatol 2019

Trends in HCC etiology



Svegliati Baroni, Vitale et al., Gut 2022

Comparison of HCC on NAFLD or HCV in an Italian cohort

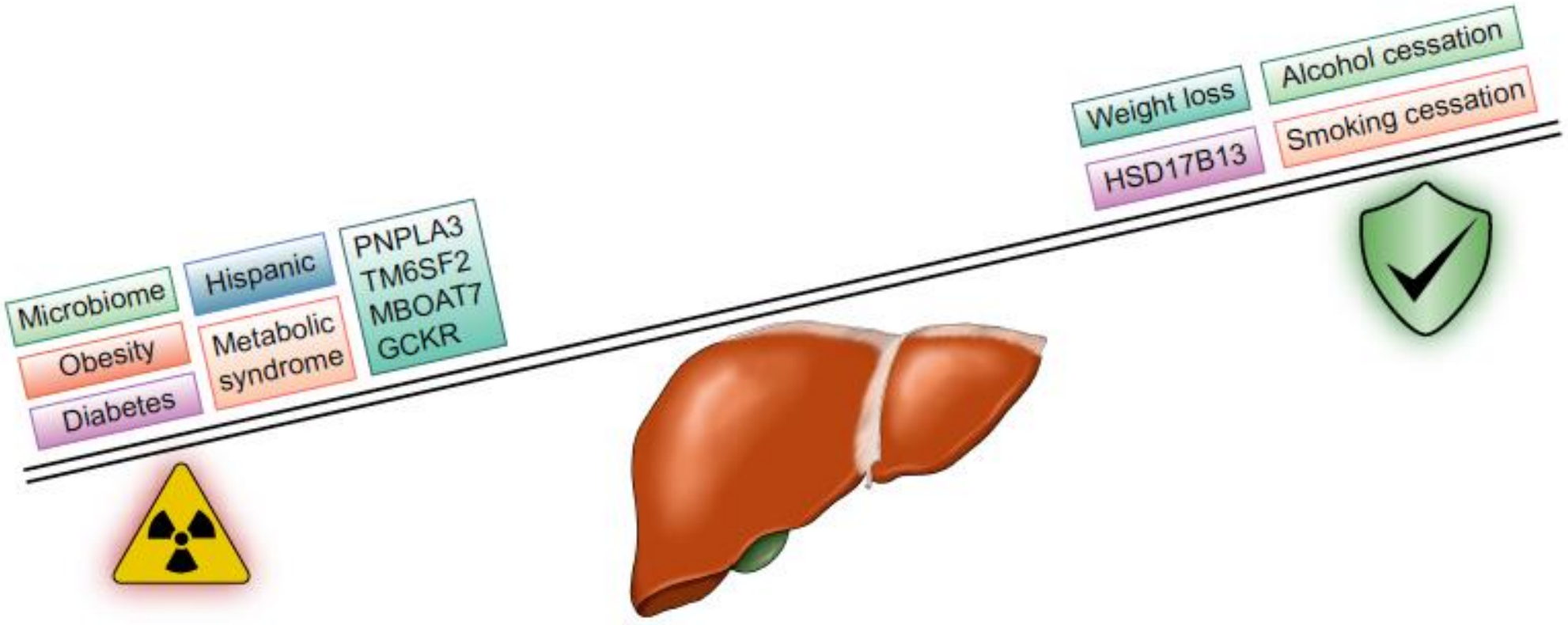
TABLE 2. Tumor Characteristics of the Study Population

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	P
Modality of initial tumor detection			
Surveillance (n and percent of patients)	69 (47.6%)	387 (63.3%)	0.001
Case findings (n and percent of patients)	56 (38.6%)	150 (24.6%)	0.001
Symptomatic (n and percent of patients)	20 (13.8%)	45 (7.4%)	0.056
Not specified			
Tumor characteristics at observat			
Size of largest tumor (cm; me			0.003
Number of nodules (mean and			0.080
Milan In (n and percentage of patients)	80 (55.2%)	418 (68.4%)	0.005
Milan Out (n and percentage of patients)	65 (44.8%)	193 (31.6%)	0.005
Barcelona Clinic Liver Cancer			
Stage 0	0	68 (11.1%)	<0.0001
Stage A	62 (42.8%)	256 (42.9%)	0.925
Stage B	28 (19.3%)	89 (14.6%)	0.201
Stage C	48 (33.1%)	146 (23.9%)	0.033
Stage D	3 (2.1%)	30 (4.9%)	0.174
Infiltrative (n and percent of patients)*	21 (15.4%)	21 (4.0%)	<0.0001
Extrahepatic metastasis (n and percent of patients)*	13 (9.3%)	105 (17.2%)	0.020
Macrovascular infiltration (n and percent of patients)*	25 (17.5%)	87 (14.7%)	0.436
Alpha-fetoprotein (ng/dL; median and range)	7.13 (1.5-83110.2)	20.4 (1-267912)	0.001

49% without cirrhosis

Piscaglia et al., Hepatology, 2016

Risk and protective factors for NAFLD-related HCC



Shah et al., Hepatology 2022

Article

Gut bacteria alleviate smoking-related NASH by degrading gut nicotine

https://doi.org/10.1038/s41586-022-05299-4

Received: 16 July 2021

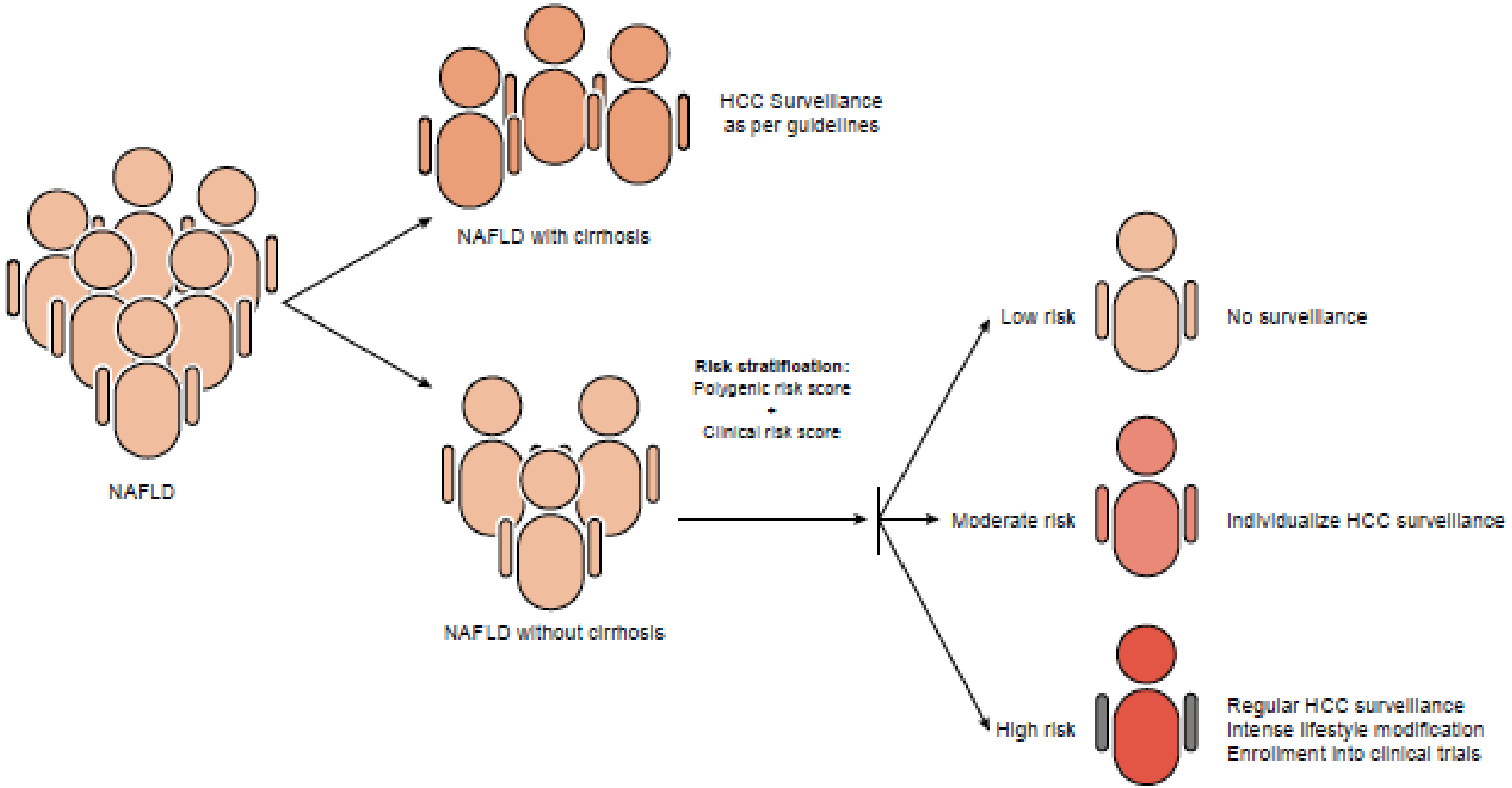
Accepted: 31 August 2022

Published online: 19 October 2022

Bo Chen[1,2,3,4,12], Lulu Sun[5,12], Guangyi Zeng[1,2,3,4,12], Zhe Shen[6,12], Kai Wang[1,2,3,4,12], Limin Yin[7,12], Feng Xu[1,2,3,4], Pengcheng Wang[1,2,3,4], Yong Ding[1,2,3,4], Qixing Nie[1,2,3,4], Qing Wu[1,2,3,4], Zhiwei Zhang[1,2,3,4], Jialin Xia[1,2,3,4], Jun Lin[1,2,3,4], Yuhong Luo[5], Jie Cai[5], Kristopher W. Krausz[5], Ruimao Zheng[8], Yanxue Xue[9], Ming-Hua Zheng[10,11]✉, Yang Li[7]✉, Chaohui Yu[6]✉, Frank J. Gonzalez[5]✉ & Changtao Jiang[1,2,3,4]✉

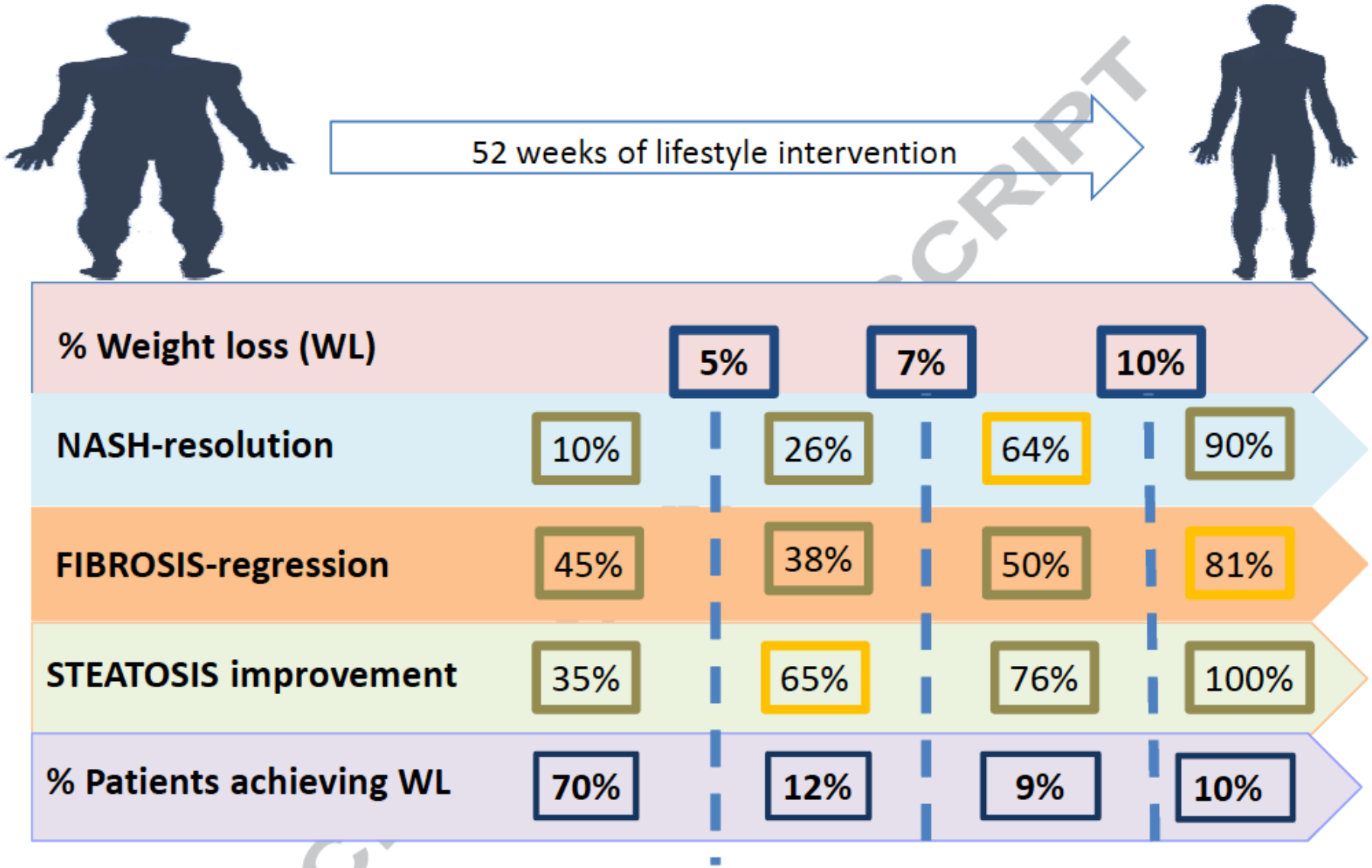
Nature 2022

Surveillance strategies in NAFLD



Shah et al., Hepatology 2022

Current situation in NASH treatment



Data from Vilar-Gomez et al.

Romero-Gomez et al., J Hepatol 2017

Ongoing phase 3 trials

Population:

- ❑ Biopsy-proven NASH patients
- ❑ Presence of fibrosis ≥F2

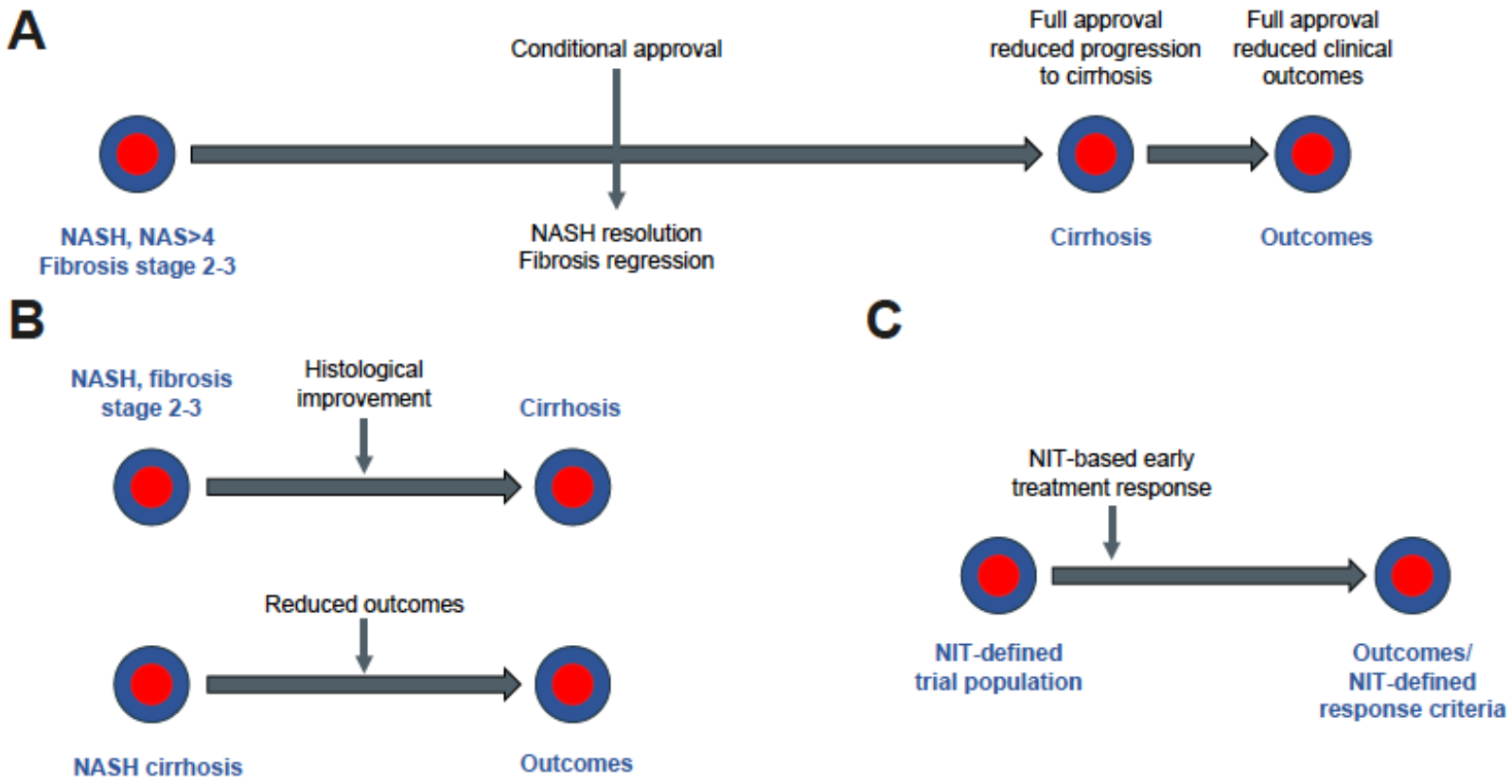
Outcomes:

- Resolution of NASH without worsening of fibrosis

And/or

- Improvement of at least one stage in fibrosis without worsening of NASH
- Long-term prevention of hard endpoints (death, decompensation, OLT)

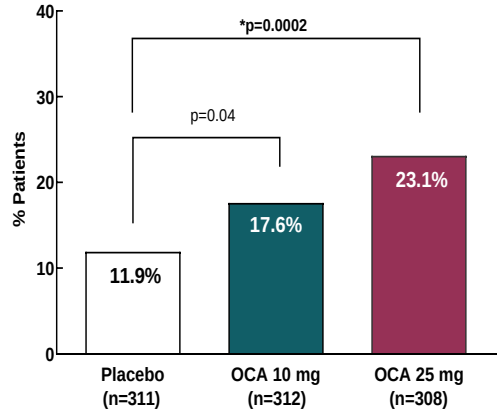
Regulatory requirements for approval of NASH medications



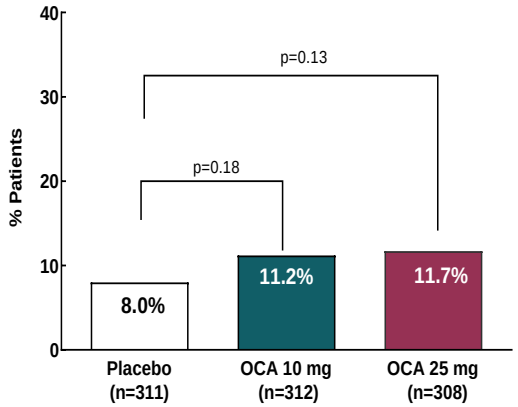
Ratziu et al., J Hepatol 2022

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

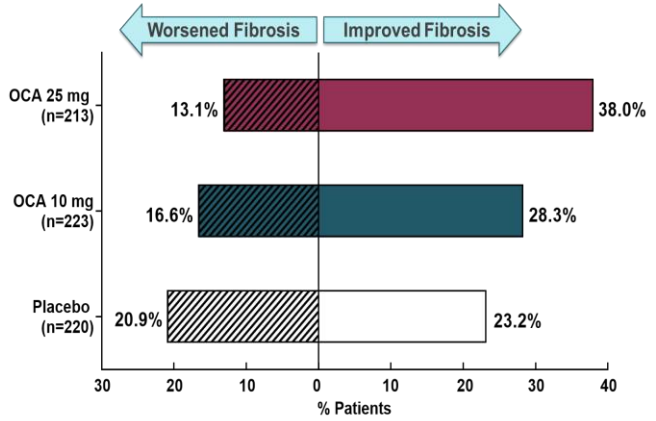
Primary endpoint (ITT): fibrosis improvement by ≥1 stage with no worsening of NASH



Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



Fibrosis improvement or worsening by ≥1 stage (per protocol with post-baseline biopsy)



- 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

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

- 65.6% in OCA 25 mg **normalized ALT** vs. 37.3% in placebo
- **Safety**: Increase in LDL-C with both doses of OCA, with an eventual decrease over time
- **Treatment emergent AEs**: Pruritus was reported by 51% of patients with OCA 25 mg vs. 19% in the placebo group
- **Treatment discontinuation** was similar in the three groups. More patients in the OCA 25 mg group (9%) discontinued due to pruritus.

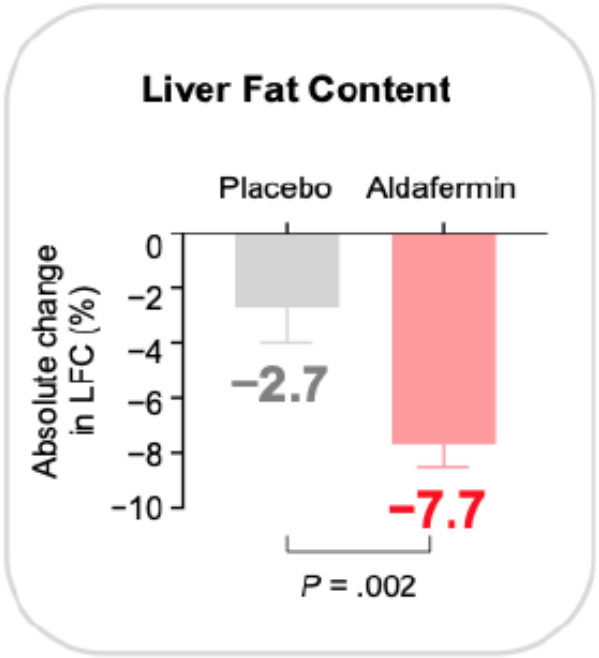
First successful phase 3 trial in patients with NASH

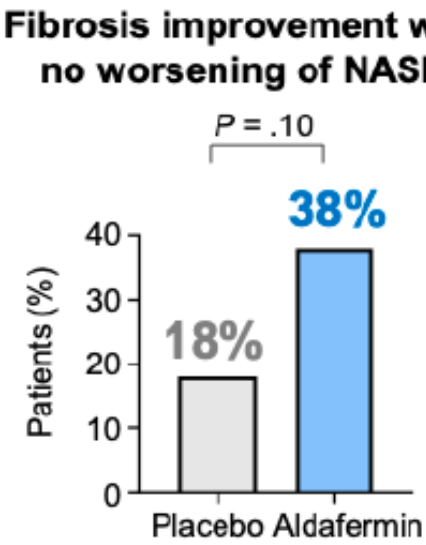
Study is ongoing to confirm benefit on clinically relevant outcomes

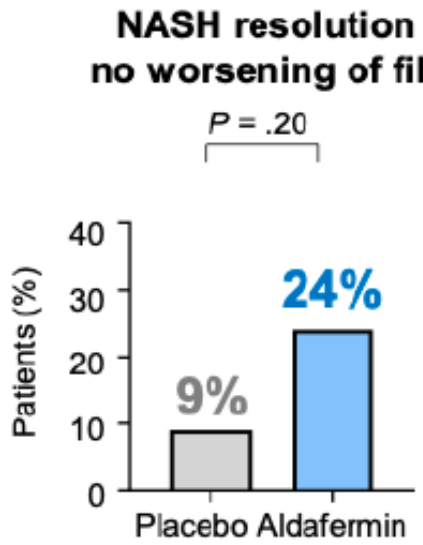
Younossi, EASL 2019

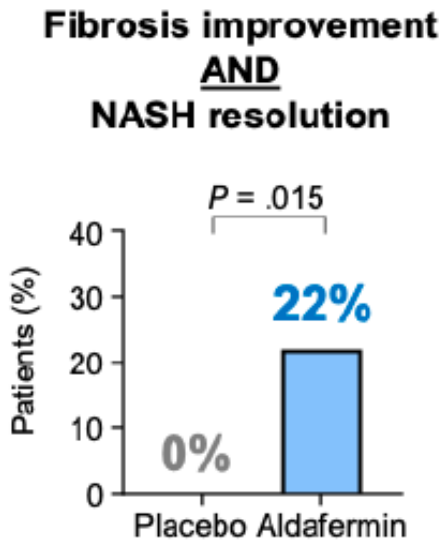
Aldafermin, a FGF-19 analog, in patients with NASH

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)

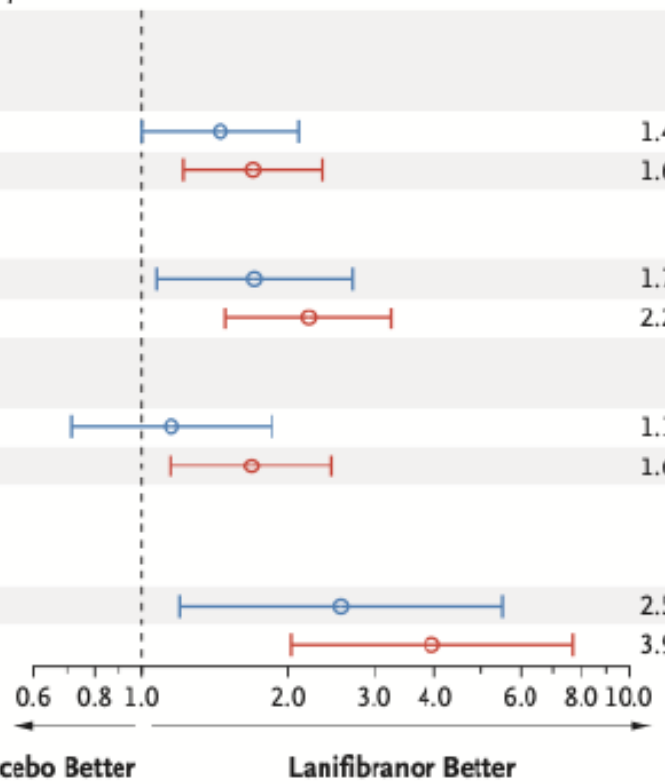
Gastroenterology

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)	

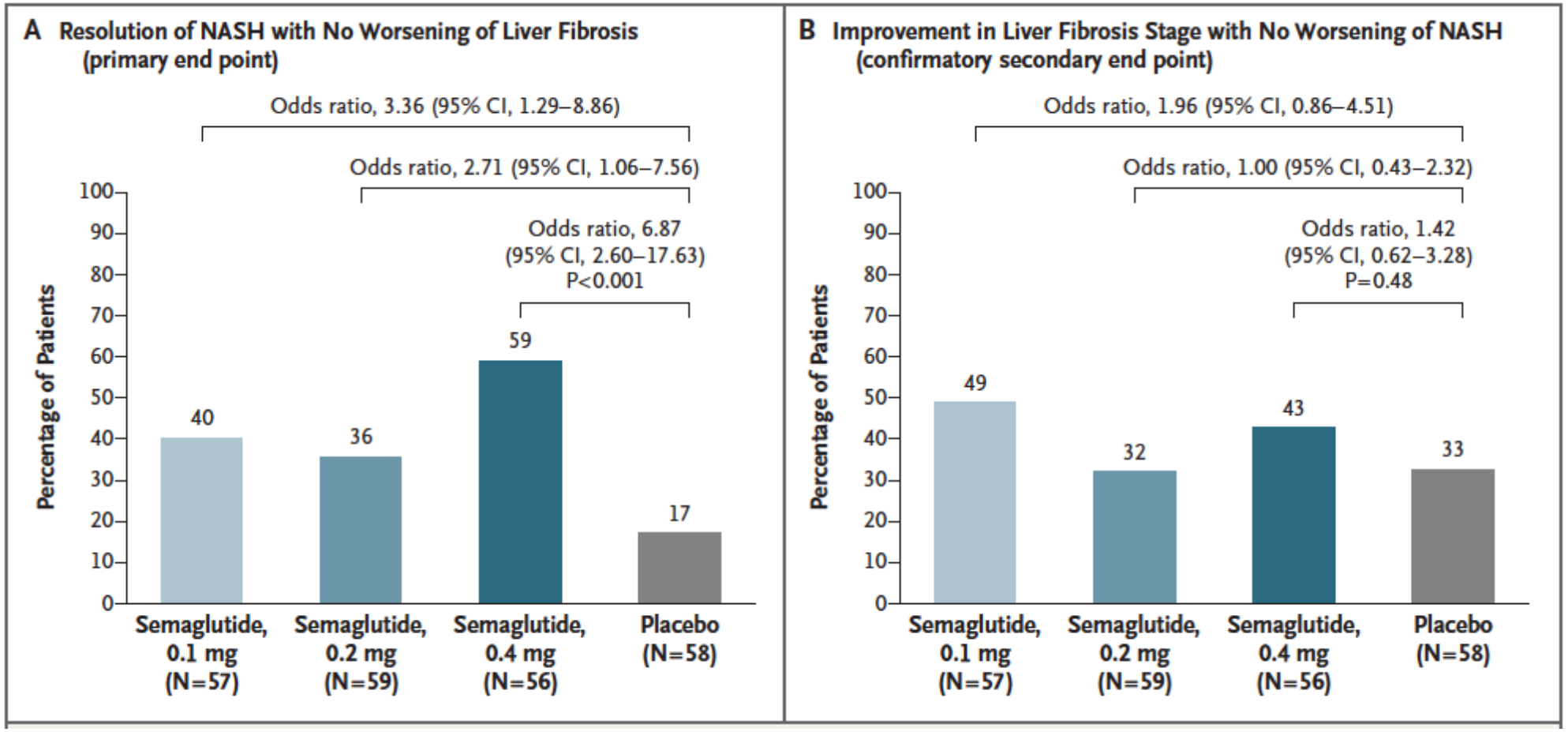


Primary end point:
- decrease of at least 2 points in the SAF-A score (ballooning and inflammation) without worsening of fibrosis

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

Francque et al., NEJM 2021

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



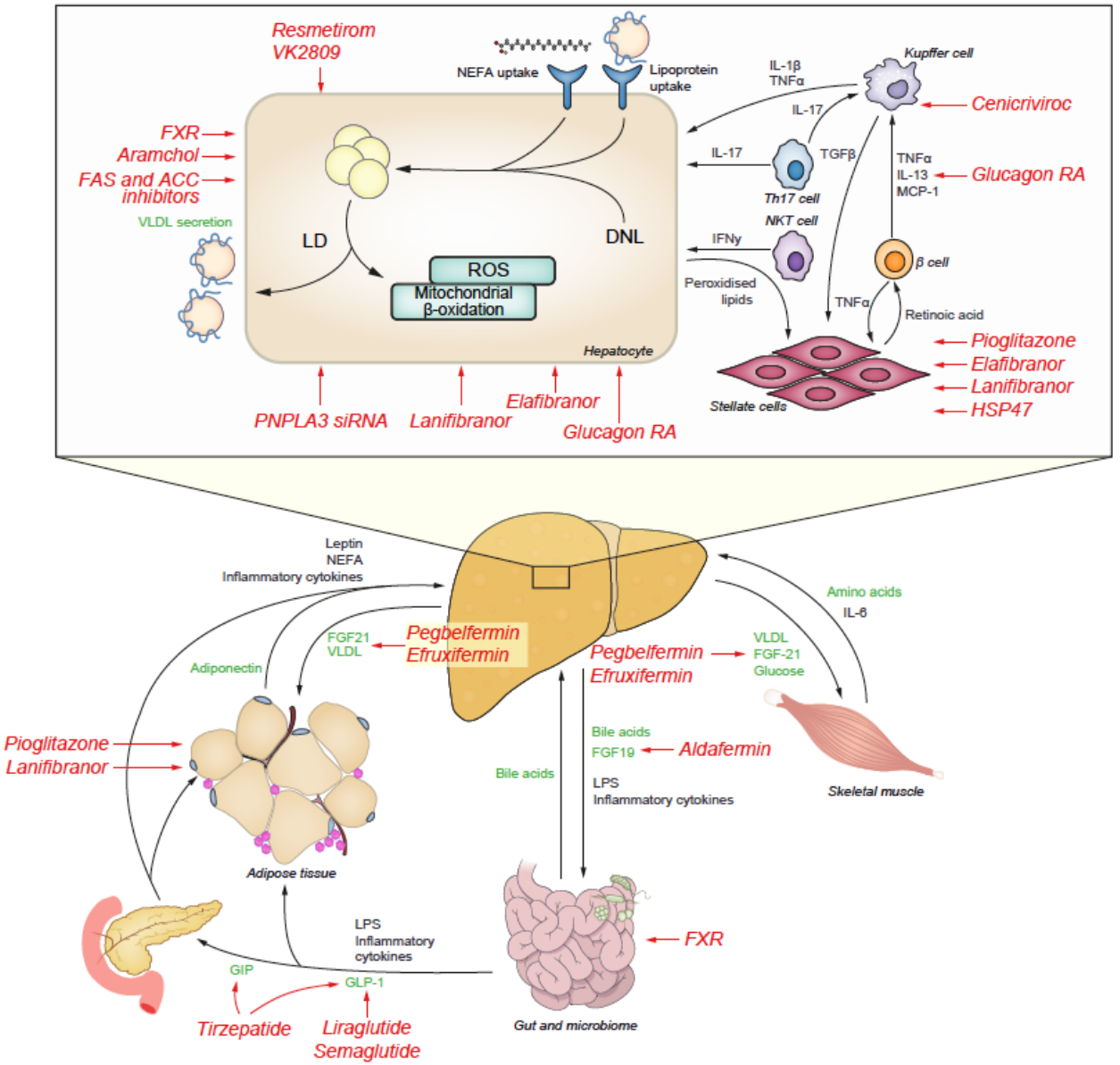
Newsome et al., NEJM 2020

Madrigal Announces Additional Positive Results from the Pivotal Phase 3 MAESTRO-NASH Clinical Trial of Resmetirom for the Treatment of NASH with Liver Fibrosis

January 6, 2023

Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	26%	<0.0001	30%	<0.0001	10%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	0.0002	26%	<0.0001	14%

Current therapeutic targets in NASH



Ratziu et al., J Hepatol 2022

Francesco Vizzutti
Umberto Arena
Davide Roccarina

Valentina Adotti
Silvia Aspite
Claudia Campani
Chiara Di Bonaventura
Martina Rosi