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2021

INNOVAZIONE E RICERCA PER LA PRATICA CLINICA

XI Workshop Nazionale

TERAPIE INNOVATIVE
DELLE EPATITI CRONICHE VIRALI
E DELLE INFEZIONI VIRALI

Follow-up del paziente con NAFLD: un approccio multidisciplinare

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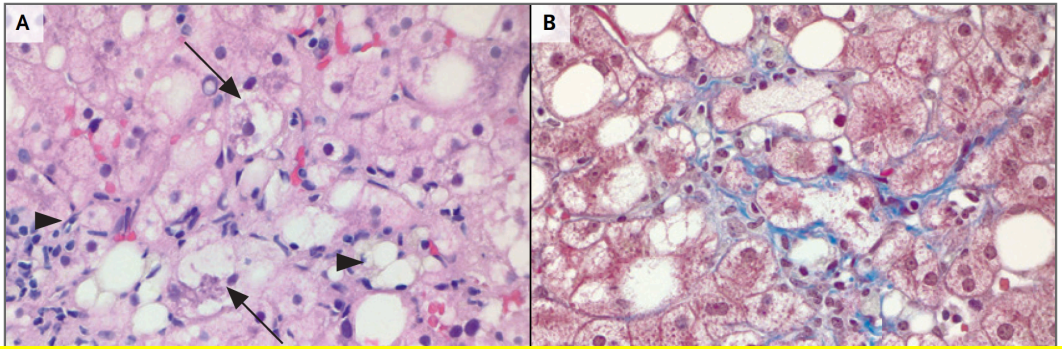
Disclosures

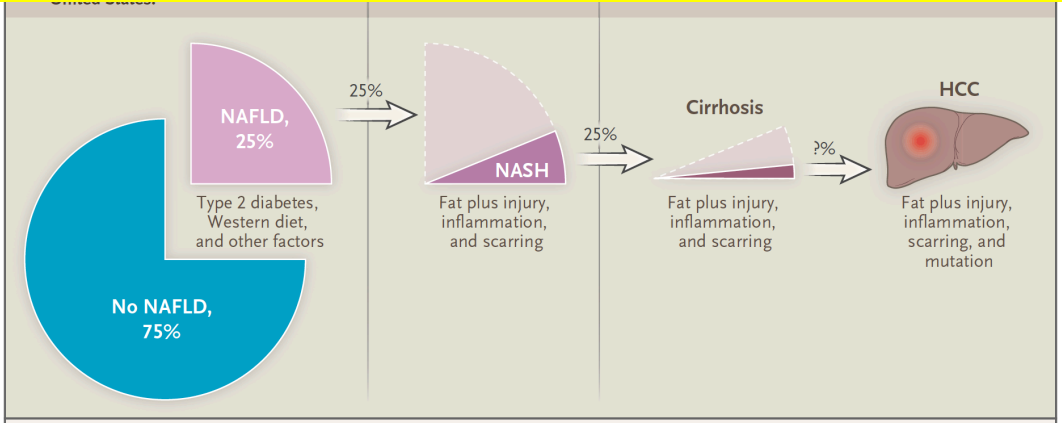
- **Abbvie**: consultant fees
- **Allergan:** consultant fees
- **Alfa-Wassermann:** travel grants
- **AstraZeneca:** consultant fees
- **Bayer:** speaker honoraria, consultant fees, travel grants
- **Gilead:** speaker honoraria, consultant fees
- **Ipsen:** consultant fees
- **Intercept:** speaker honoraria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

Definition and natural history

The spectrum of nonalcoholic steatosis

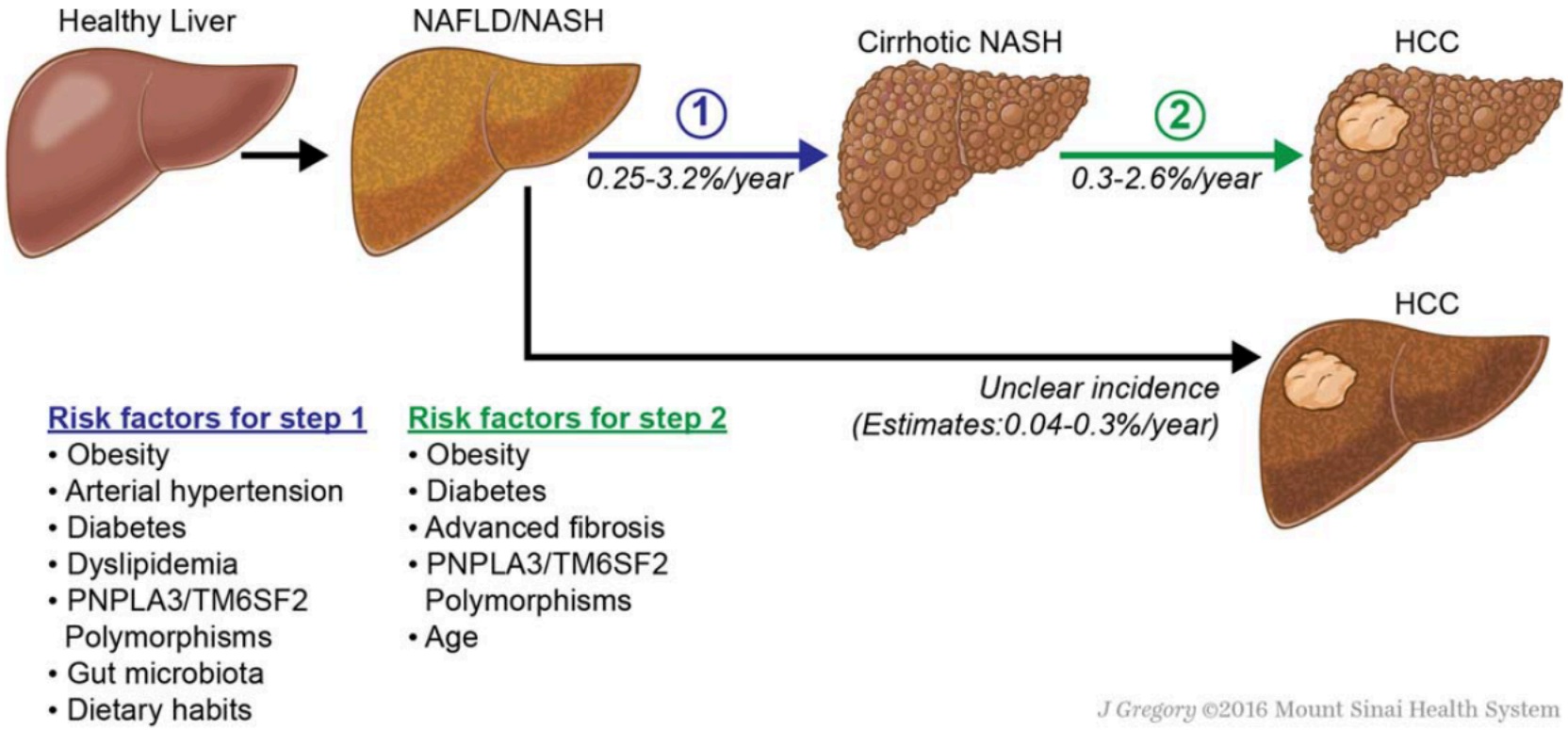


The hepatic manifestation of the metabolic syndrome



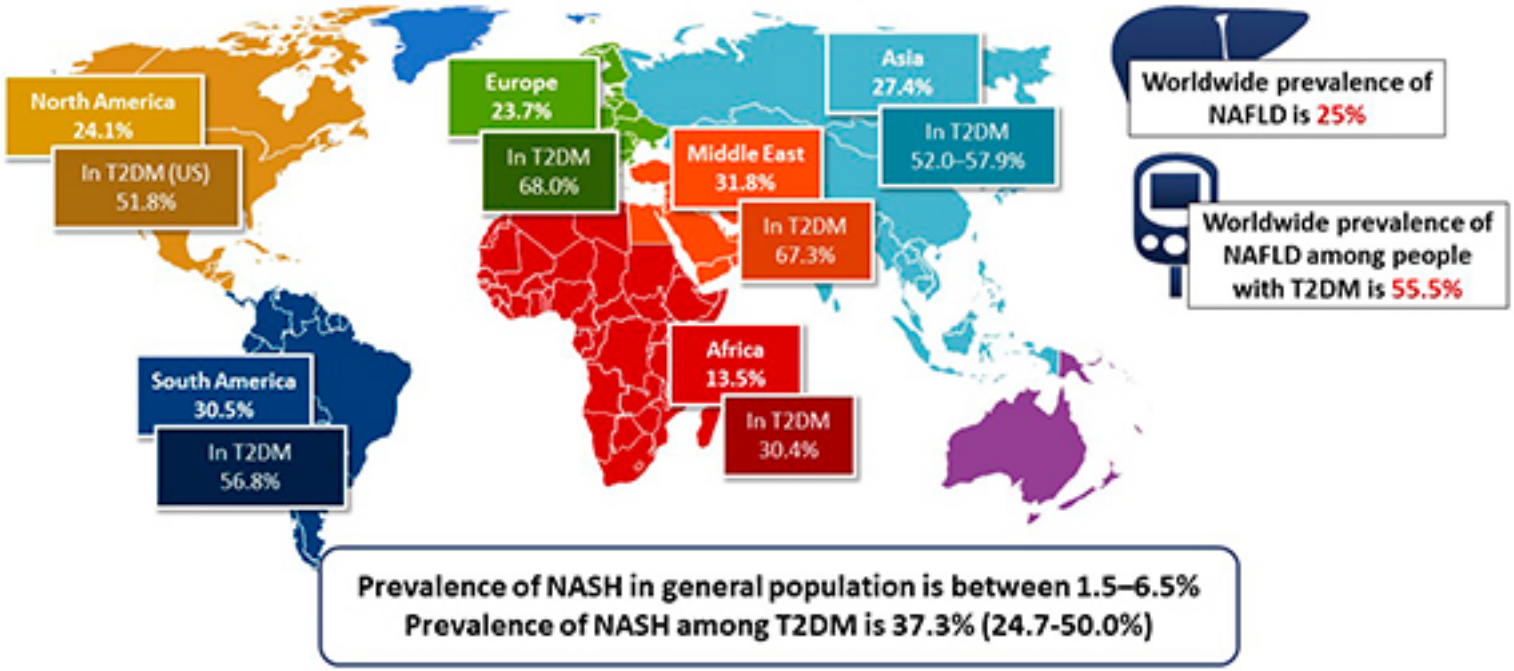
Diehl & Day NEJM 2017

Natural history of NAFLD



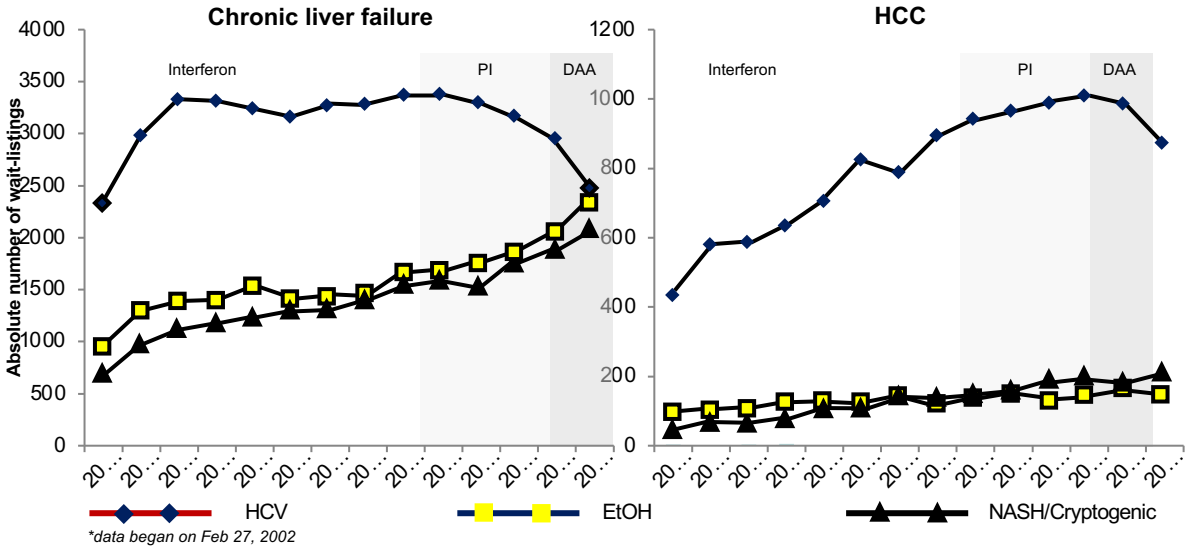
D'Avola et al., Clin Liver Dis 2016

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

Younossi et al., Hepatology 2019

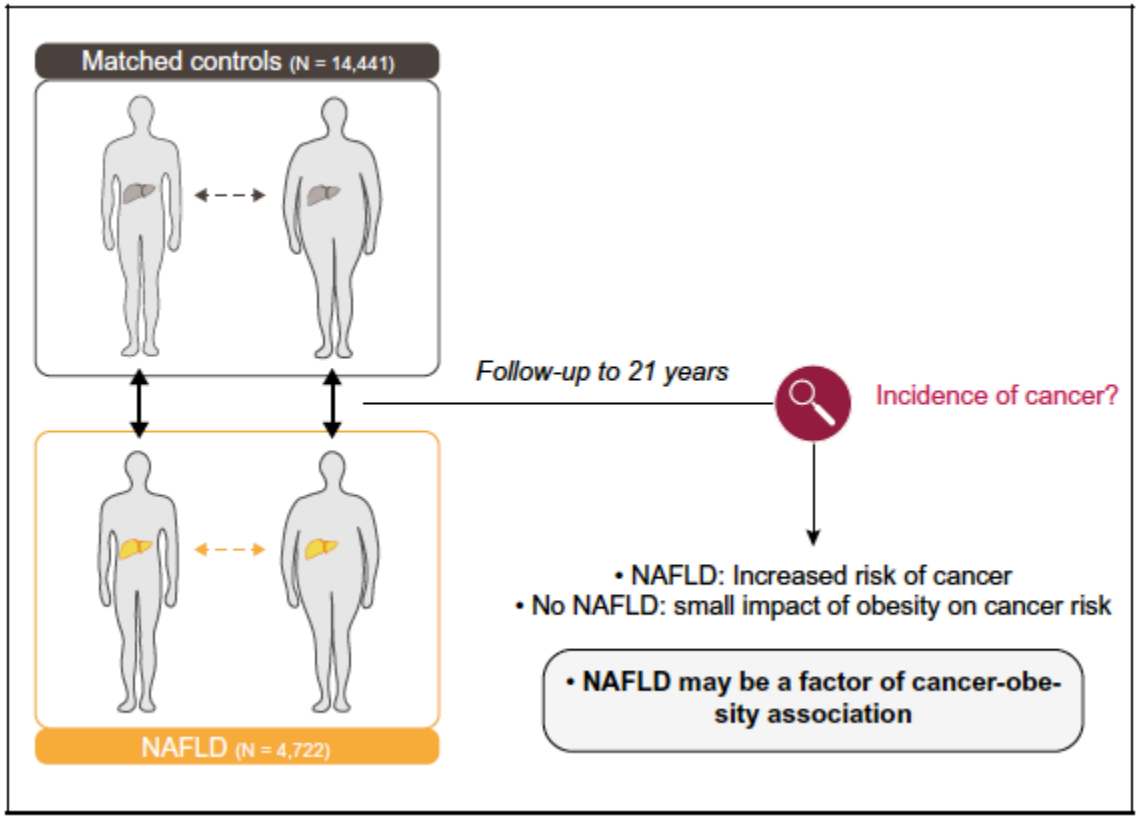
NAFLD & mortality

Cardiovascular (13-30%)

All cause malignancy (6-28%)

Liver-related death (3-19%)

The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity



Allen et al., J Hepatol 2020

Diagnostic strategies

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

Steatohepatitis as a phenotype determined by different types of injury

NASH

ASH

PNPLA3
PASH

Metabolic
MASH

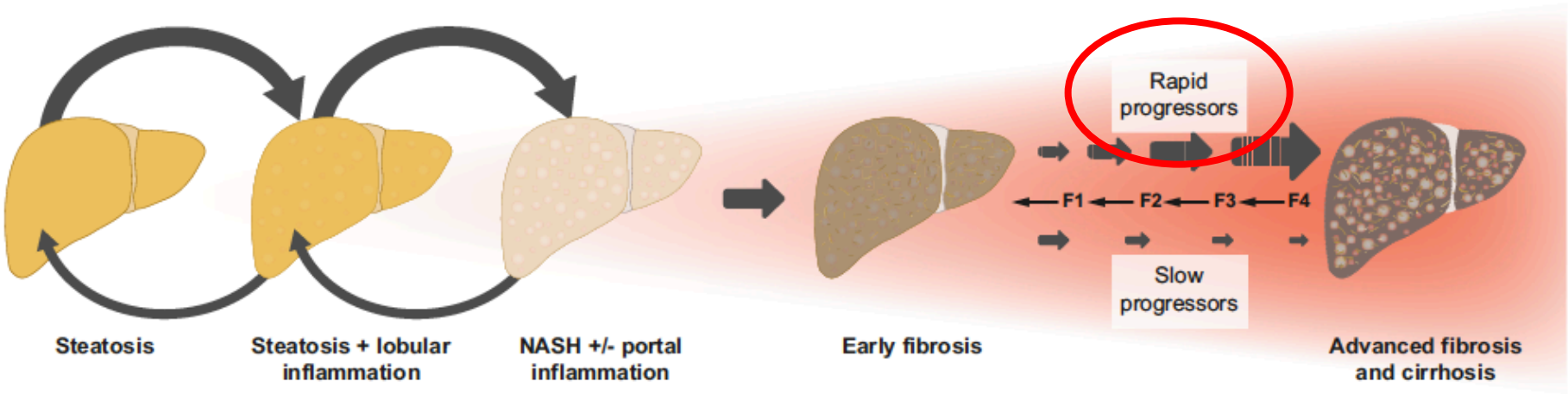
Toxic
TASH

Drug-induced
DASH

Chemotherapy
CASH

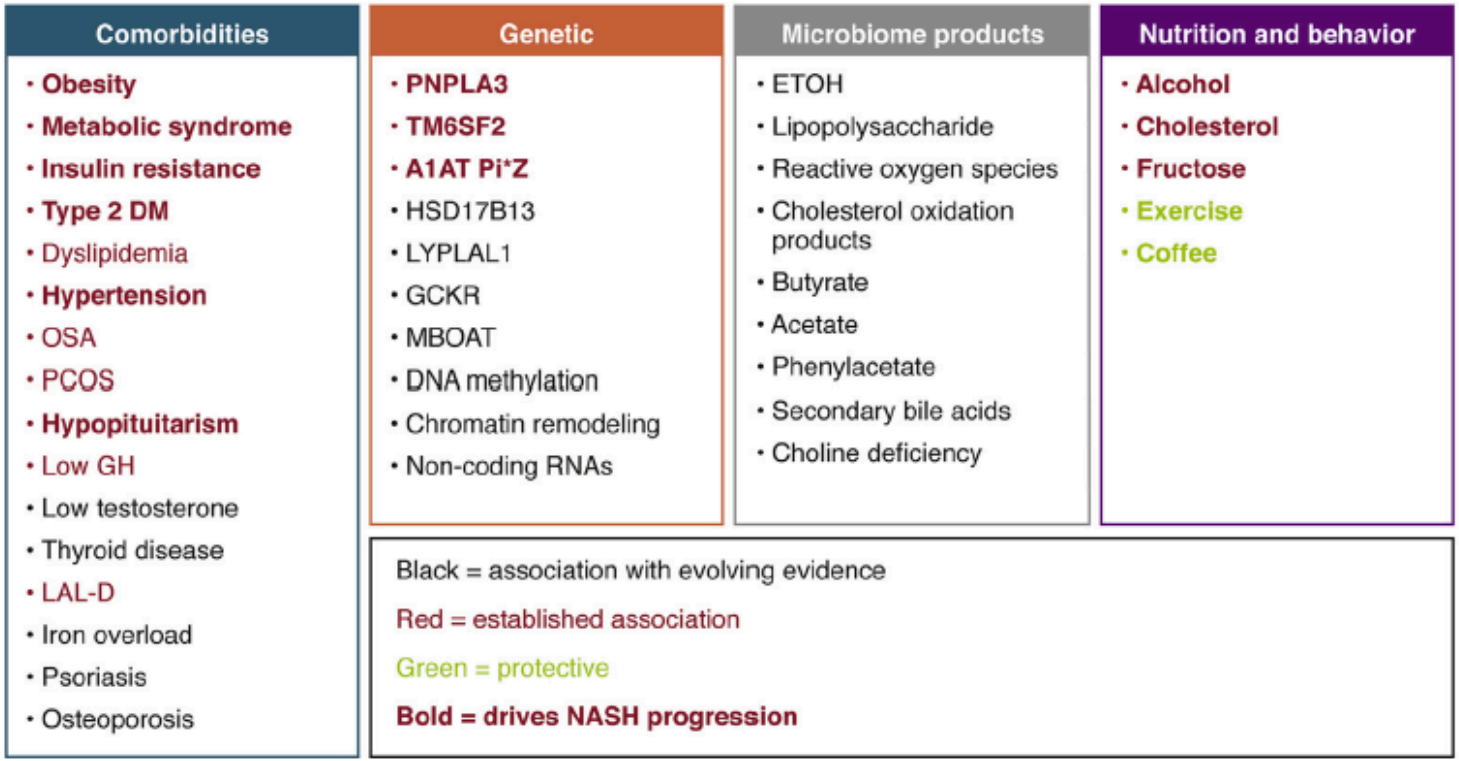
Both NASH-ASH
BASH

The ‘dynamic’ natural history of NAFLD



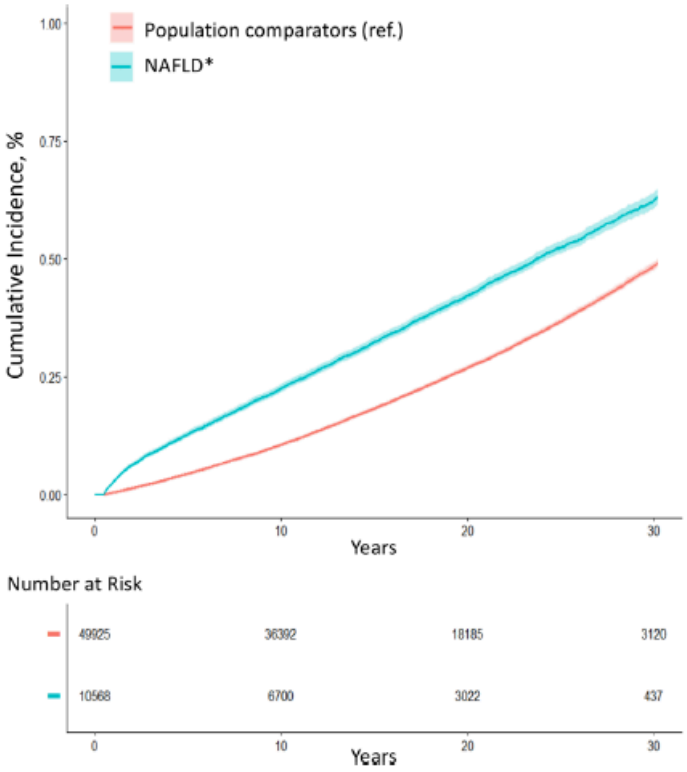
Rinella et al., J Hepatol 2019

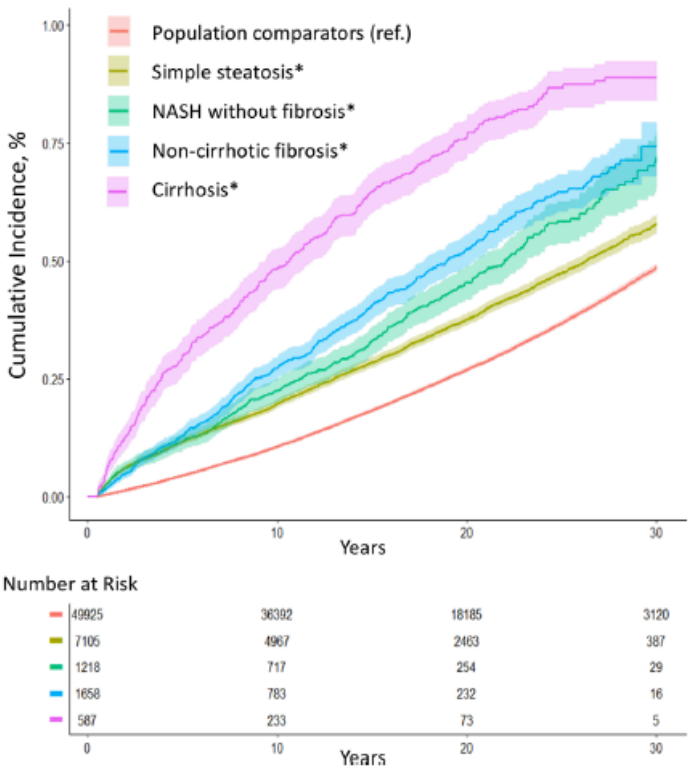
Modifiers of NASH



Cotter & Rinella, Gastroenterology 2020

All-cause mortality according to NASH and histological severity





Simon et al., Gut 2020

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

Noninvasive assessment of advanced fibrosis by serum markers

Model	Components and regression equation	Cut-offs for advanced fibrosis	Clinical benefits and limitations	
NAFLD fibrosis score	−1.675 + 0.037 × **Age** (yrs) + 0.094 × **BMI** (kg/m^2) + 1.13 × **IFG/diabetes** (yes = 1, no = 0) + 0.99 × **AST/ALT ratio** − 0.013 × **Platelet** (×10^9/L) −0.66 × **Albumin** (g/dl)	<−1.45 (low) – NPV: 88–93% >0.67 (high) – PPV: 78–90% Age >65 yrs <0.12 (low) – 81–98%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Yes Yes
FIB-4 index	**Age** (yrs) × **AST** [U/L]/(**Platelet** [10^9/L] × (**ALT** [U/L])$^{1/2}$)	<1.30 (low) – NPV: 90–95% >3.25 (high) – PPV: 75% Age >65 yrs <2.0 (low) – 82–98%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Yes Yes
BARD score	**AST/ALT ratio** ≥0.8 = 2 points **BMI** ≥28 = 1 point **Presence of diabetes** = 1 point Score ranges from 0 to 4 points	Single cut-off = 2 NPV: 95–97%, PPV: 27%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Low Unknown Yes
APRI	(AST [IU/L])/(AST upper limit of normal [IU/L])/(Platelet [10^9/L])	Single cut-off = 1 NPV: 84%, PPV: 37%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Low Unknown Yes
Hepascore	Y = exp [−4.185818 − (0.0249 × **Age**) + (0.7464 × **Sex**) + (1.0039 × **α2-macroglobulin**) + (0.0302 × **Hyaluronic acid**) + (0.0691 × **Bilirubin**) − (0.0012 × GGT)] *Hepascore* = Y/(1 + Y)	Single cut-off = 0.37 NPV: 92%, PPV: 57%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Unknown Yes

Vilar-Gomez & Chalasani, J Hepatol 2018

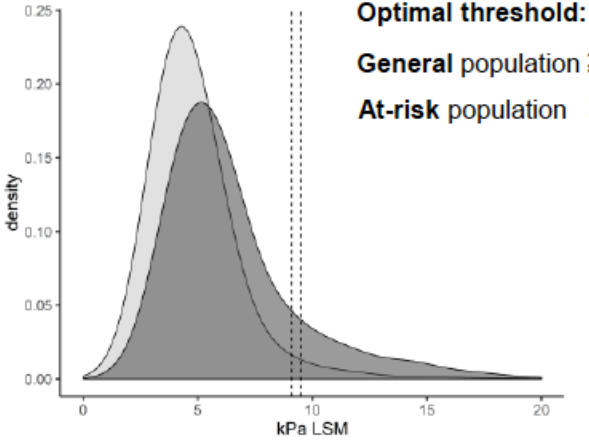
VCTE for F≥2 in NAFLD

Target population

General population ~ *3%*

At-risk population ~ *9% prevalence*

TE screening algorithm

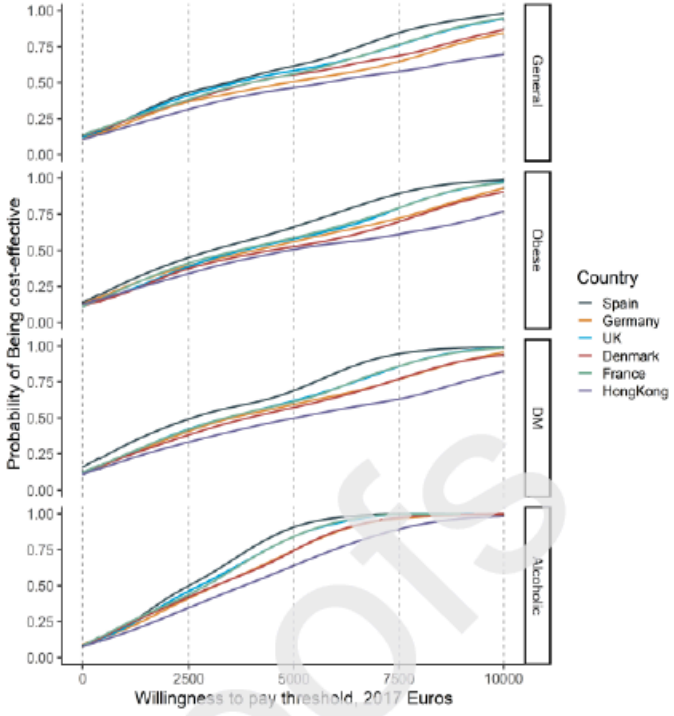


Optimal threshold:

General population ≥ 9.1 kPa

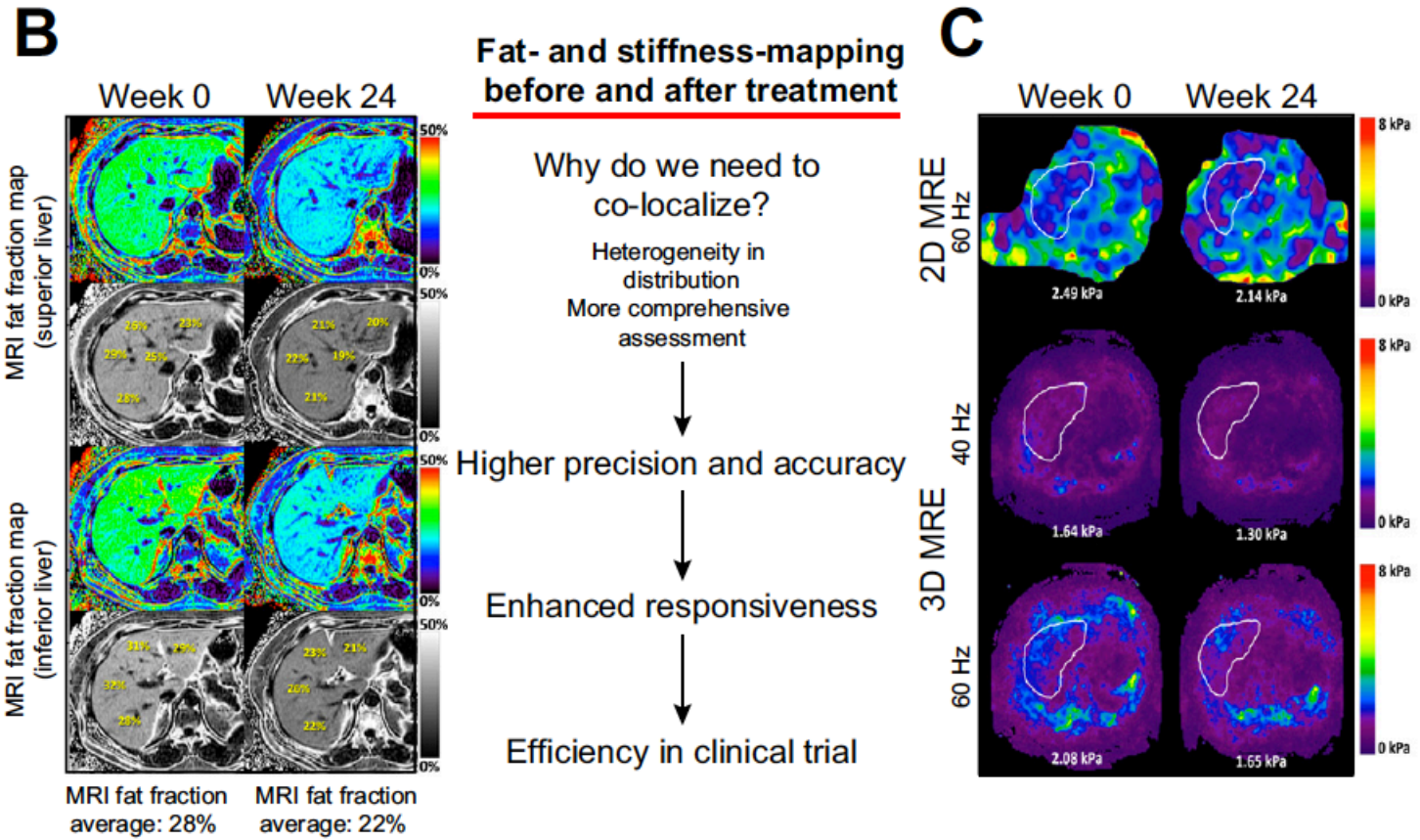
At-risk population ≥ 9.5 kPa

Cost-effectiveness acceptability curves by *Target population & Country*



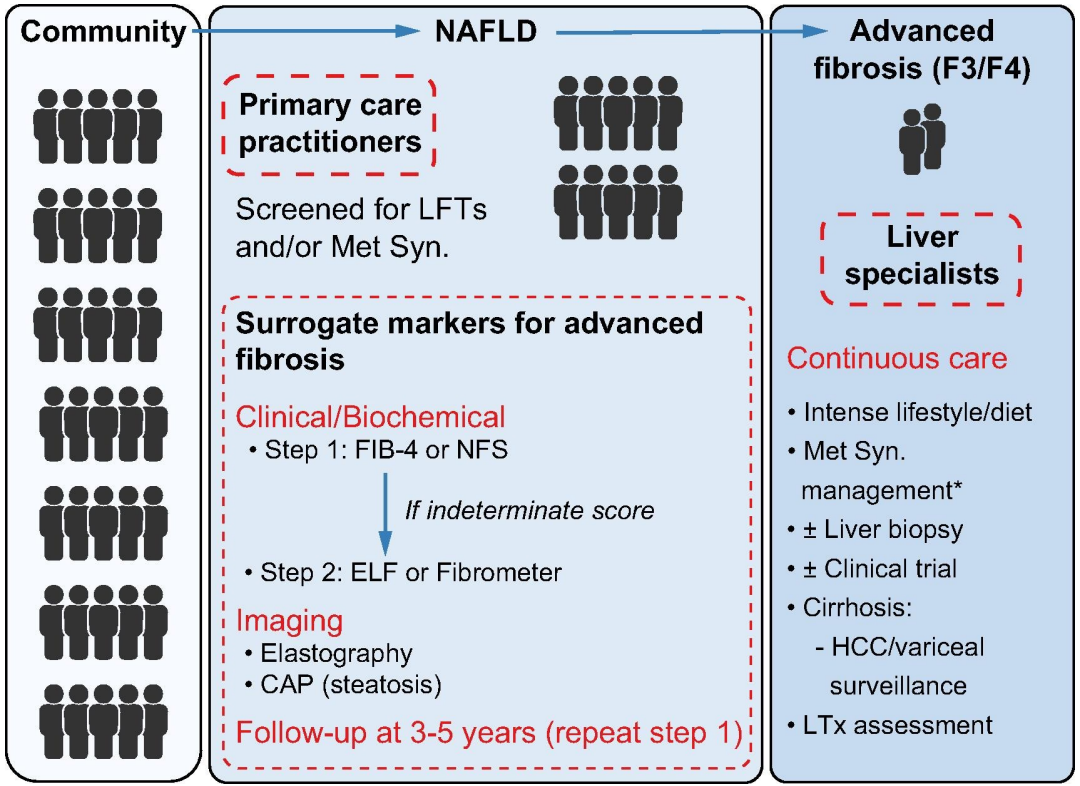
Serra-Burriel, Graupera et al., J Hepatol 2019

MRI and NAFLD



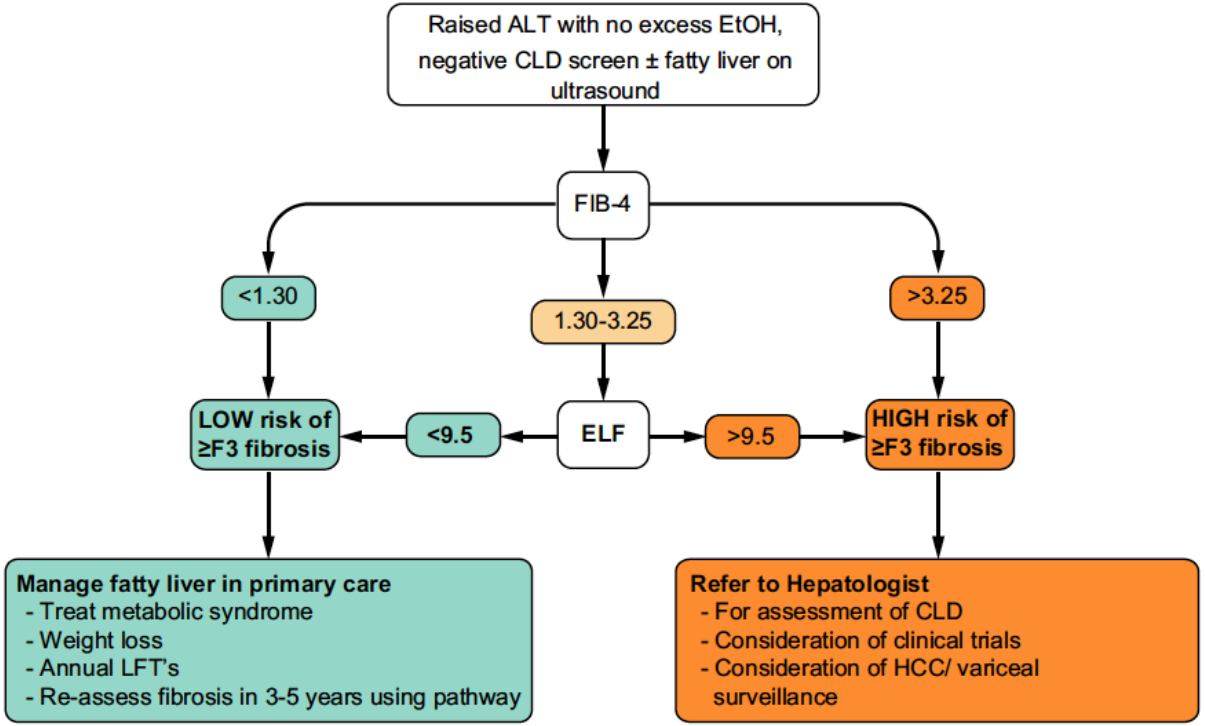
Dulai et al., J Hepatol 2016

Primary care/specialist interface in NAFLD



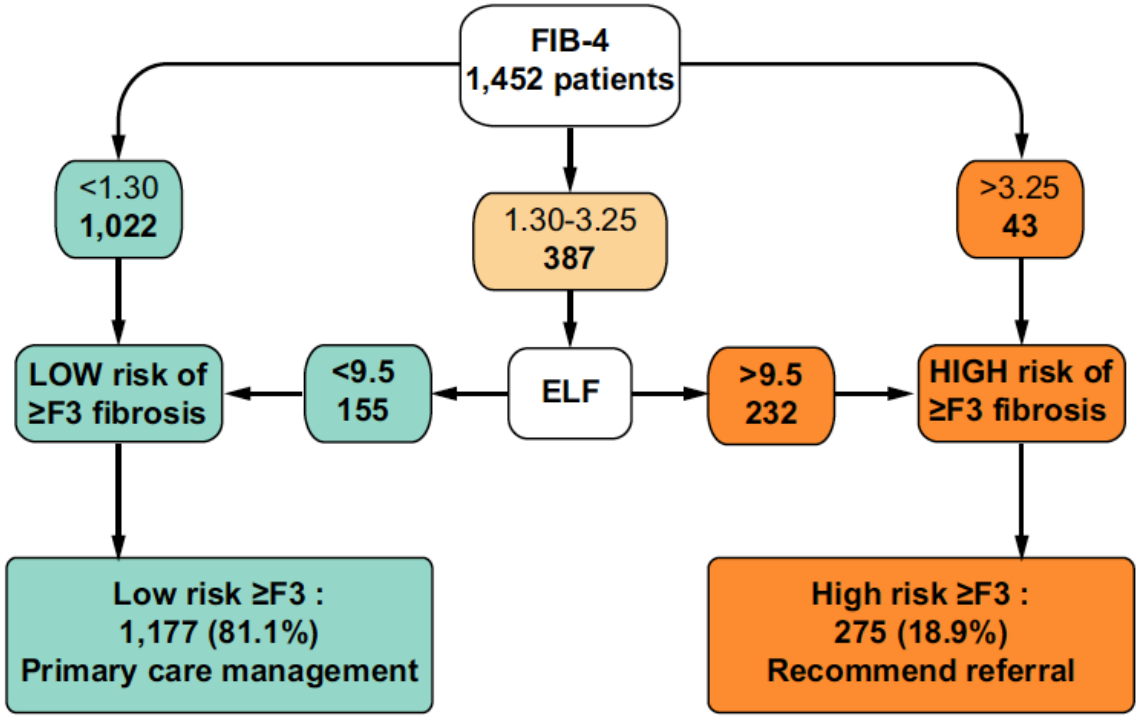
Marchesini & Armstrong,, J Hepatol 2019

Referral model from primary care in the UK



Srivastava et al., J Hepatol 2019

Referral model from primary care in the UK



Srivastava et al., J Hepatol 2019

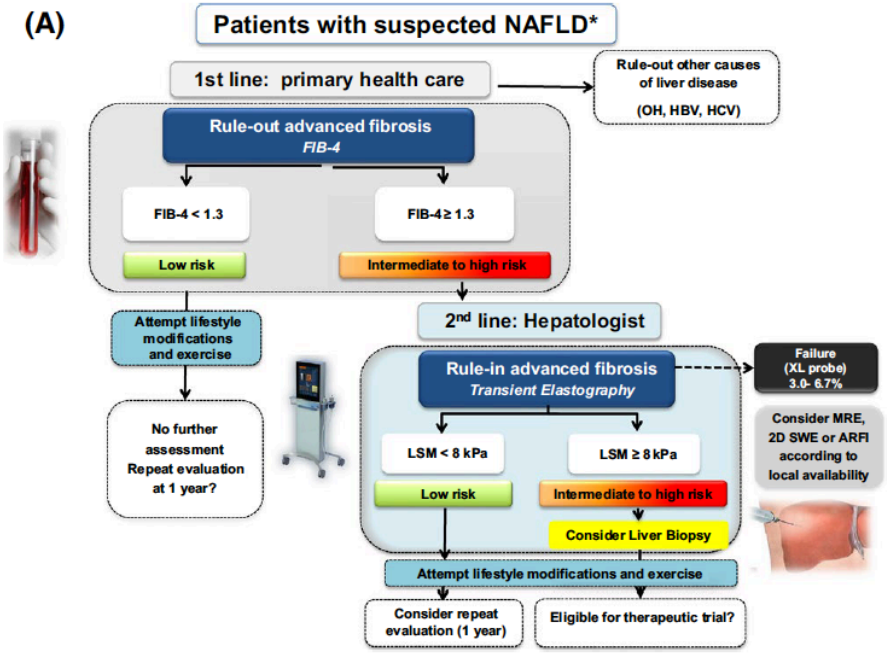
General population:
Advanced liver fibrosis (0·9–2·0%)
Cirrhosis (0·1–1·7%)

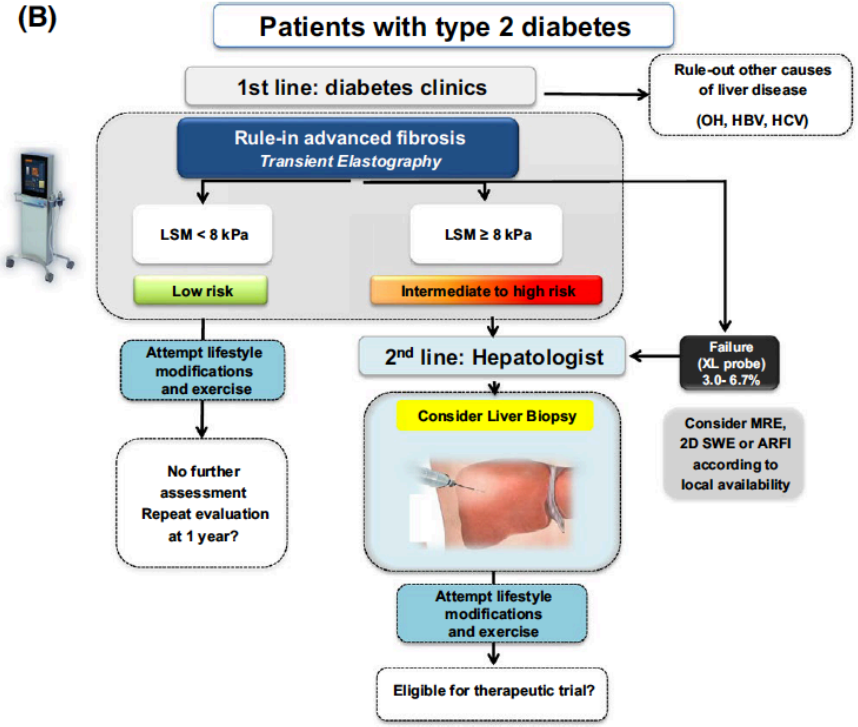
High-risk population:
Advanced liver fibrosis 0–27·9%
Cirrhosis 2·4–4·0%

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

Differential approach according to setting

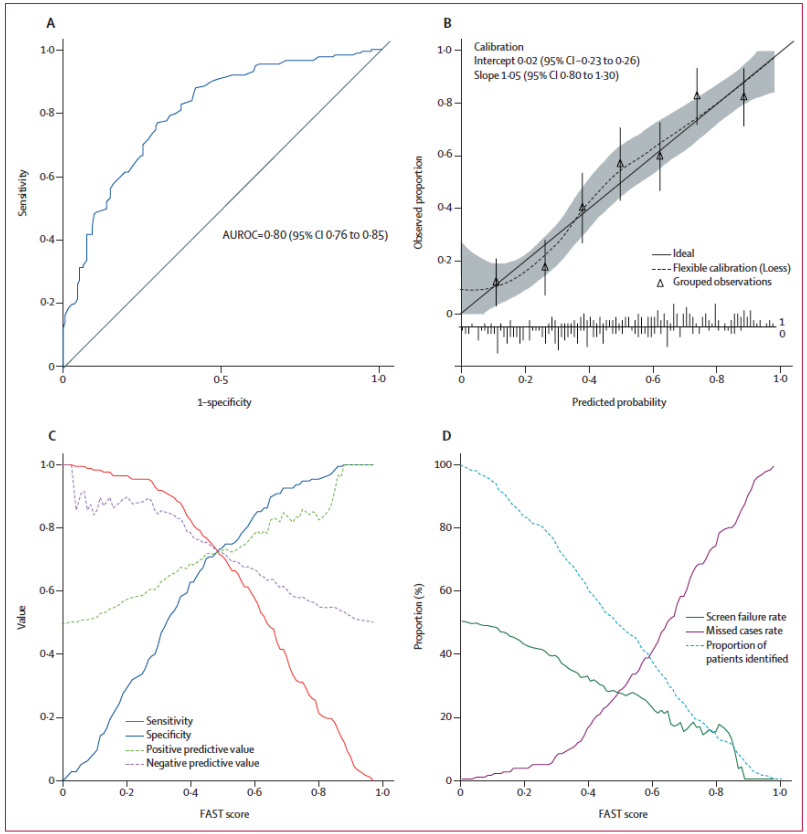
*Steatosis on ultrasound
OR Abnormal liver tests and metabolic risk factors





Castera, Liver Int 2020

The Fibroscan/AST (FAST) score for NASH + NAS ≥ 4 + F ≥ 2

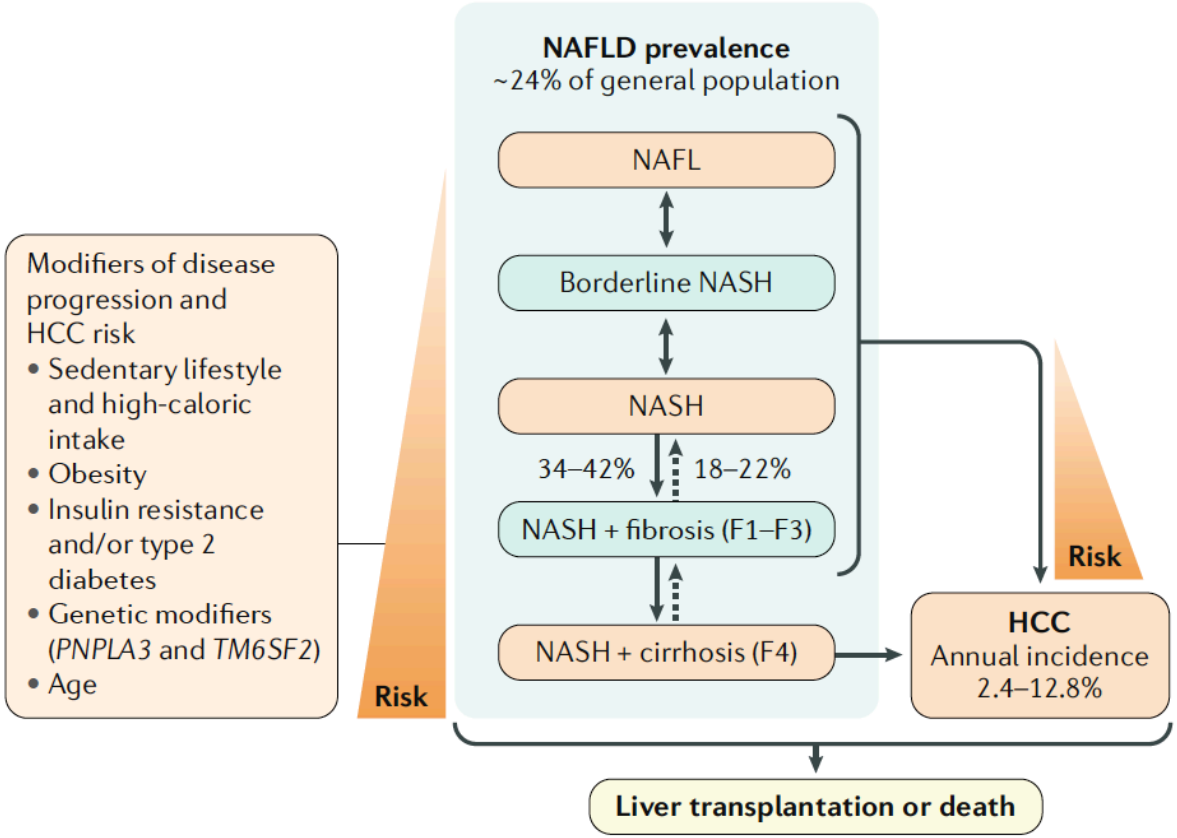


$$\mathrm{FAST} = \frac{e^{-1.65 + 1.07 \times \ln(\mathrm{LSM}) + 2.66 * 10^{-8} \times \mathrm{CAP}^3 - 63.3 \times \mathrm{AST}^{-1}}}{1 + e^{-1.65 + 1.07 \times \ln(\mathrm{LSM}) + 2.66 * 10^{-8} \times \mathrm{CAP}^3 - 63.3 \times \mathrm{AST}^{-1}}}$$

Newsome et al. Lancet Gastro Hep 2020

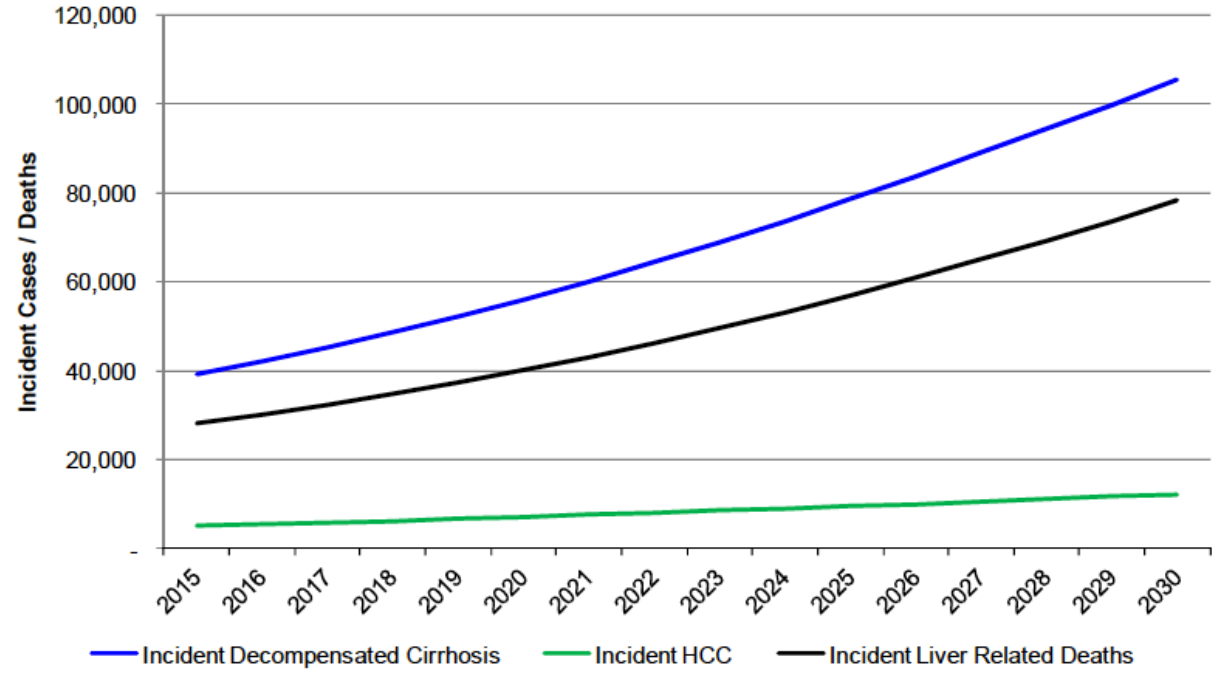
NAFLD and HCC

Natural history of fatty liver



Anstee et al., Nat Rev Gastroenterol Hepatol 2019

Figure 5. Incident Decompensated Cirrhosis, HCC and Liver-Related Deaths among Prevalent NAFLD Population – US, 2015-2030



Estes et al., Hepatology 2017

Comparison of HCC on NAFLD or HCV in an Italian cohort

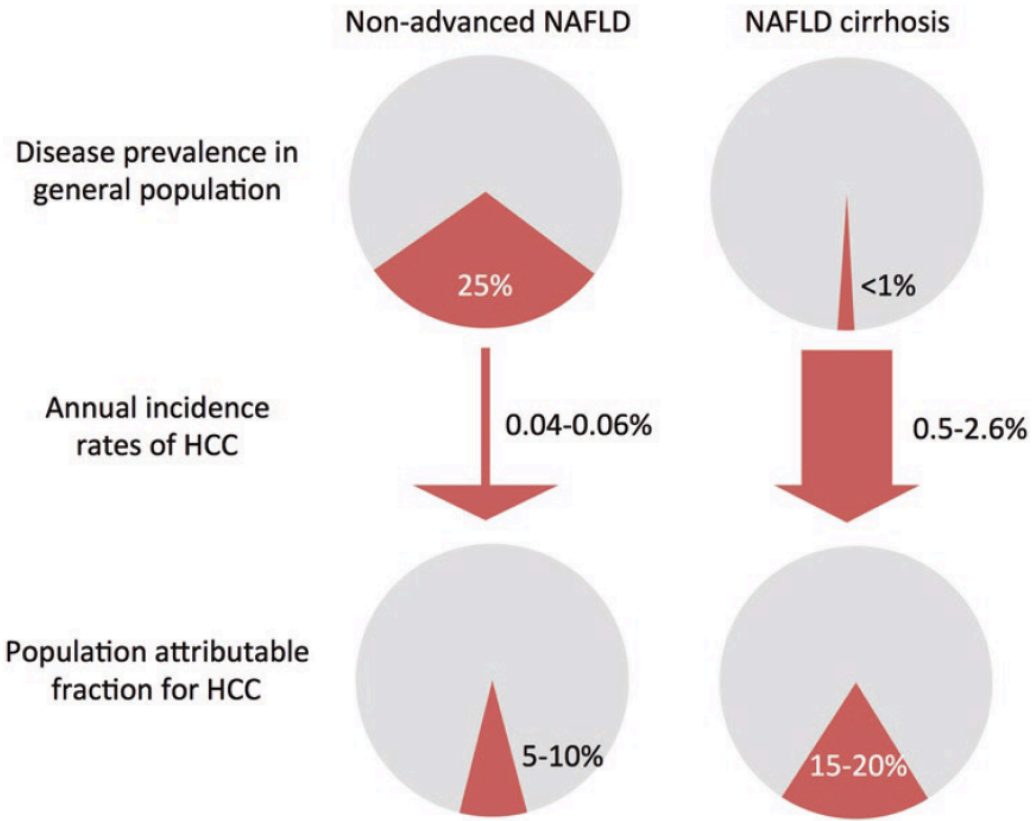
TABLE 2. Tumor Characteristics of the Study Population

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

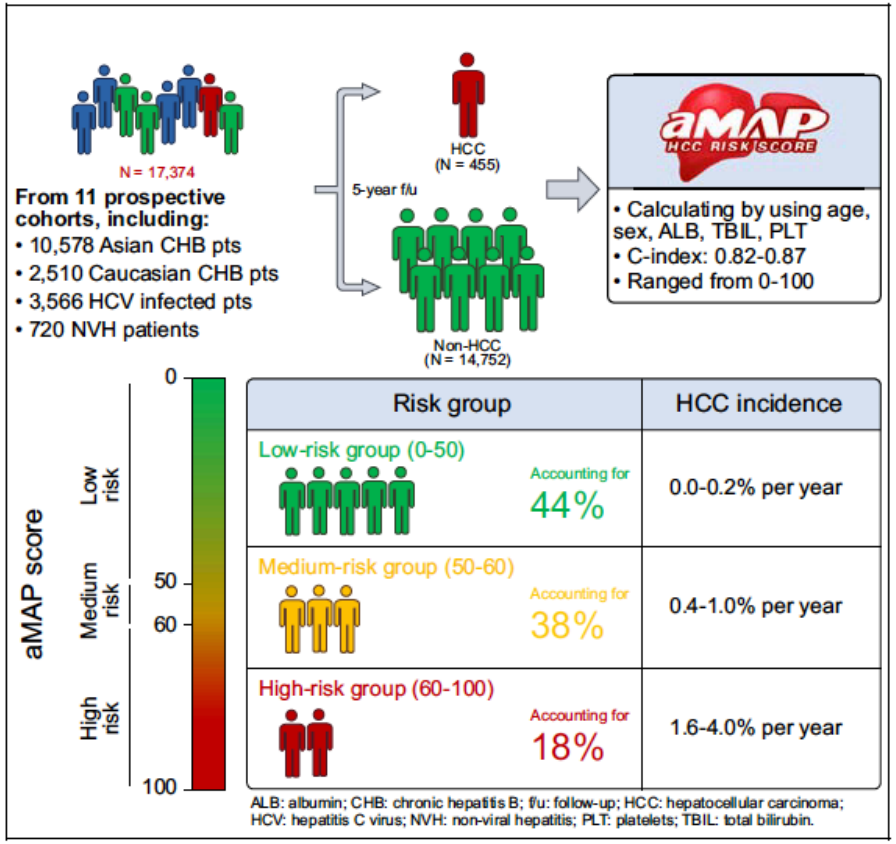
Piscaglia et al., Hepatology, 2016

NAFLD severity and the burden of HCC



Baffy, 2018

The aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis

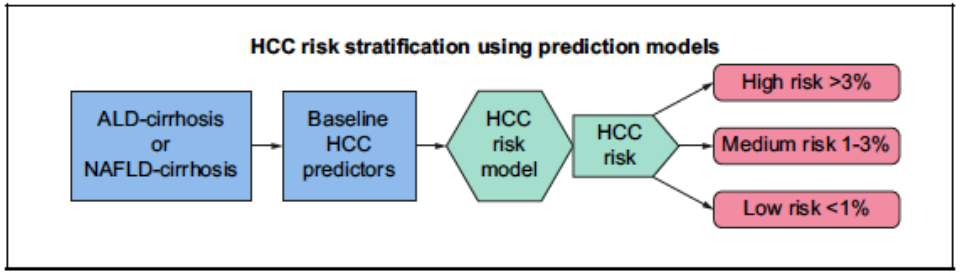


Fan et al., J Hepatol 2020

Models estimating risk of HCC in patients with alcohol or NAFLD-related cirrhosis

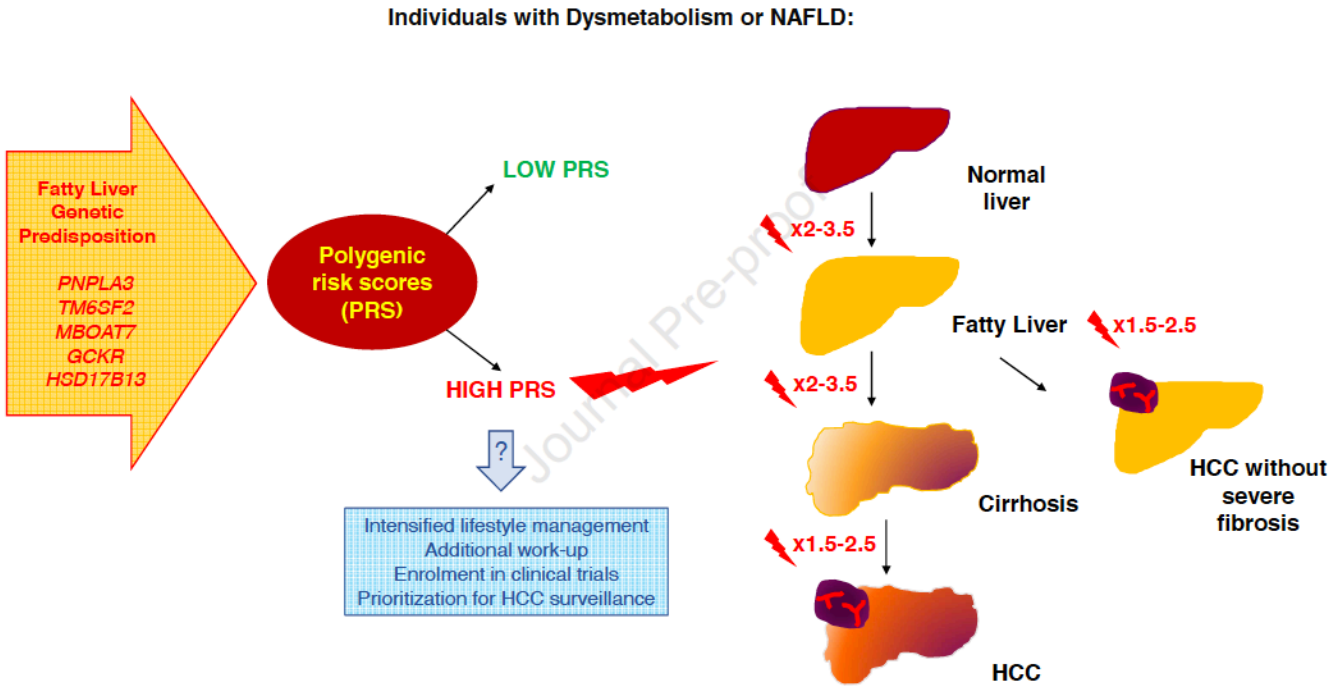
HCV	ALD - Cirrhosis	NAFLD - Cirrhosis
Age	__ Years	
Gender	Select	
BMI	__ kg/m²	
Diabetes	Select	
Platelet Count	__ x 10^9 per liter	
AST	__ u/L	
ALT	__ u/L	
Albumin	__ g/dL	
3-year HCC risk		
5-year HCC risk		

Calculate Reset



Ioannou et al., J Hepatol 2020

Non-invasive stratification of HCC risk in NAFLD using polygenic risk scores



Bianco et al., J Hepatol 2020

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

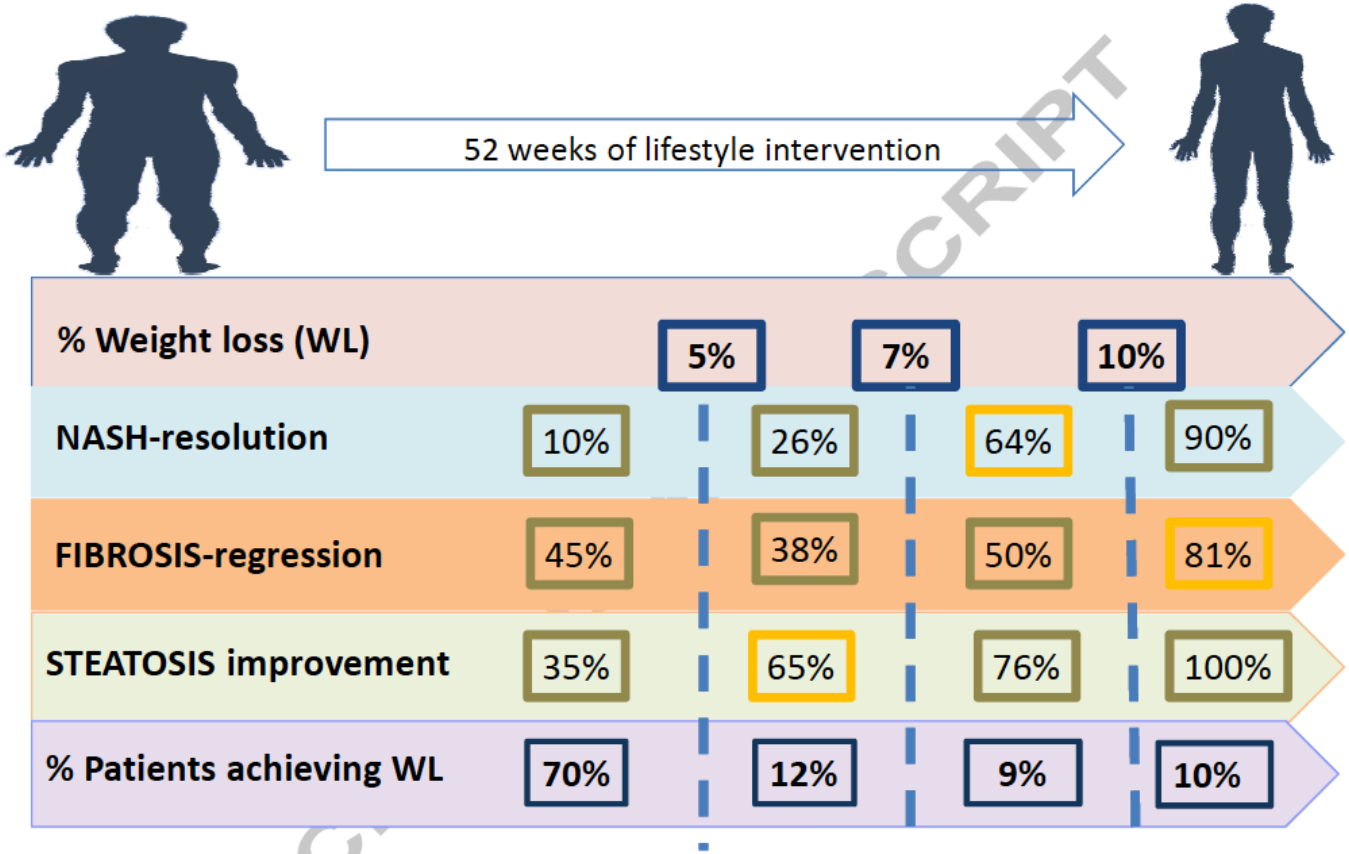
Best Practice Advice 3: Patients With Nonalcoholic Fatty Liver Disease in the Absence of Advanced Liver Fibrosis Should Not Be Routinely Considered for Hepatocellular Carcinoma Screening

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

Current situation in NASH treatment



Data from Vilar-Gomez et al.

Romero-Gomez et al., J Hepatol 2017

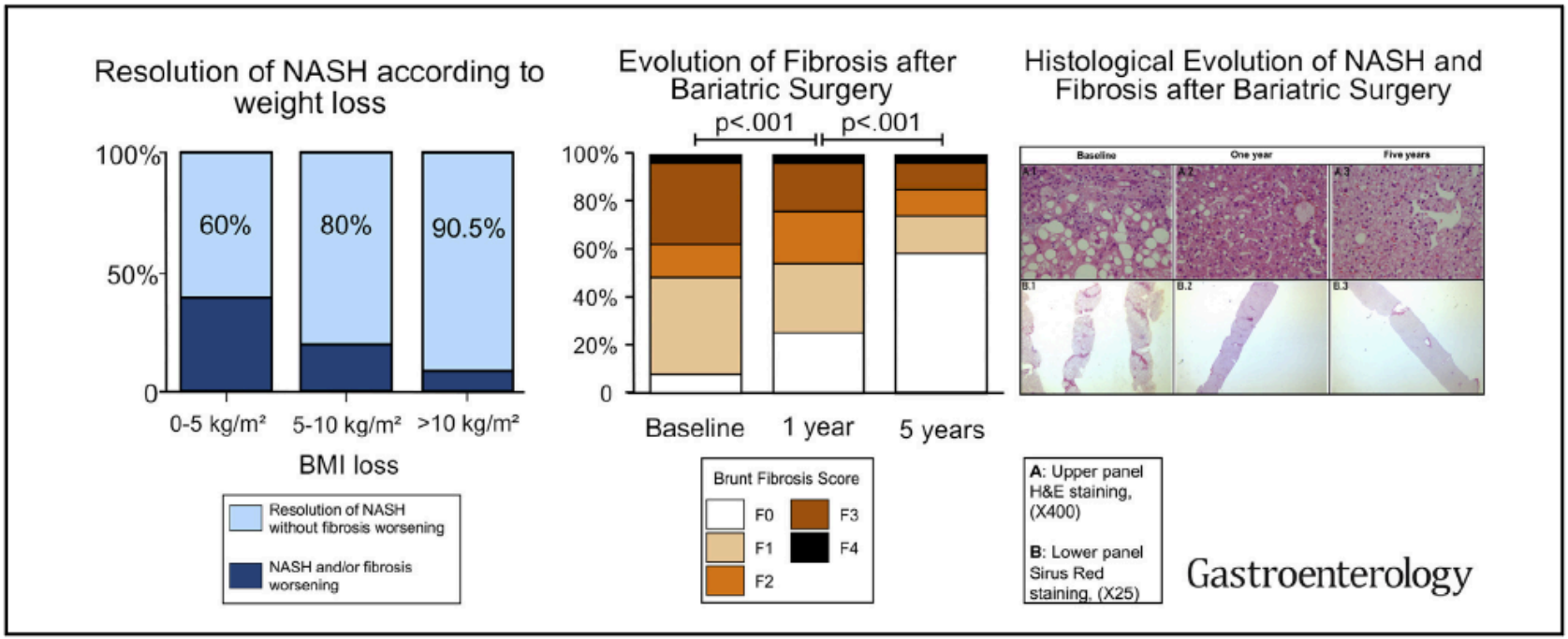
Gastroenterology 2020;■:1–7

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

Bariatric surgery provides resolution of NASH and regression of fibrosis



Lassailly et al., Gastroenterology 2020

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)

Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (NASH) (RESOLVE-IT)

Primary Outcome

Proportion of Elafibranor treated patients relative to placebo achieving resolution of NASH without worsening of fibrosis
[Time Frame: Measurement at 72 weeks]

All-cause mortality, cirrhosis, and liver-related clinical outcomes
[Time Frame: estimated to be 4 years]

(RESOLVE-IT) has been interrupted following interim results

Baseline characteristics

		Statistics	Elafibranor	Placebo	Overall
ITT Set (F2-F3)		N	717	353	1070
Age (Years)		Mean (SD)	54.35 (12.06)	55.04 (11.10)	54.58 (11.75)
Sex	Female	N(%)	283 (39.5)	137 (38.8)	420 (39.3)
	Male	N(%)	434 (60.5)	216 (61.2)	650 (60.7)
Fibrosis Stage	Stage 2	N (%)	338 (47.1)	167 (47.3)	505 (47.2)
	Stage 3	N (%)	379 (52.9)	186 (52.7)	565 (52.8)
Type 2 Diabetes	No	N (%)	361 (50.3)	178 (50.4)	539 (50.4)
	Yes	N (%)	356 (49.7)	175 (49.6)	531 (49.6)
NAS	4	N (%)	104 (14.5)	45 (12.7)	149 (13.9)
	5	N (%)	209 (29.1)	90 (25.5)	299 (27.9)
	6	N (%)	239 (33.3)	120 (34.0)	359 (33.6)
	7	N (%)	146 (20.4)	92 (26.1)	238 (22.2)
	8	N (%)	19 (2.6)	6 (1.7)	25 (2.3)

Interim efficacy results at week 72

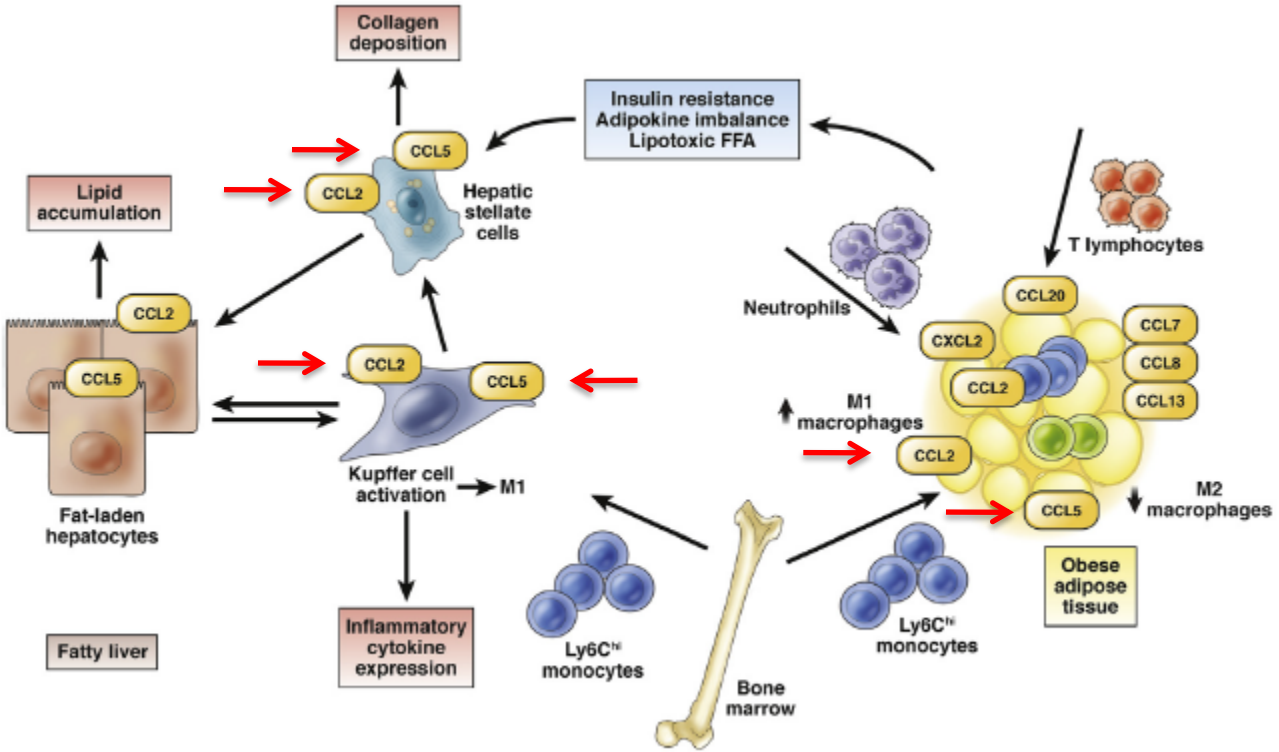
ITT (missing biopsy = non-responder)		Elafibranor 120mg N	Elafibranor 120mg %	*Placebo* N	*Placebo* %	*P-Value*
Primary Endpoint	NASH Resolution without worsening of fibrosis	138/717	19.2	52/353	14.7	0.0659
Key secondary Endpoint	Fibrosis improvement of at least one stage	176/717	24.5	79/353	22.4	0.4457

AURORA: Phase 3 Study for the Efficacy and Safety of cenicriviroc for the Treatment of Liver Fibrosis in Adults With NASH

Primary Outcome

- Superiority of CVC compared to placebo on liver histology at Month 12
- Proportion of subjects with improvement in fibrosis by at least 1 stage AND no worsening of steatohepatitis
- Superiority of CVC on progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality [End of Study, estimated to be 5 years]

Chemokines and NASH progression



Marra & Tacke, Gastroenterology 2014

Safety and Efficacy of Selonsertib in Adults With Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis (STELLAR 3)

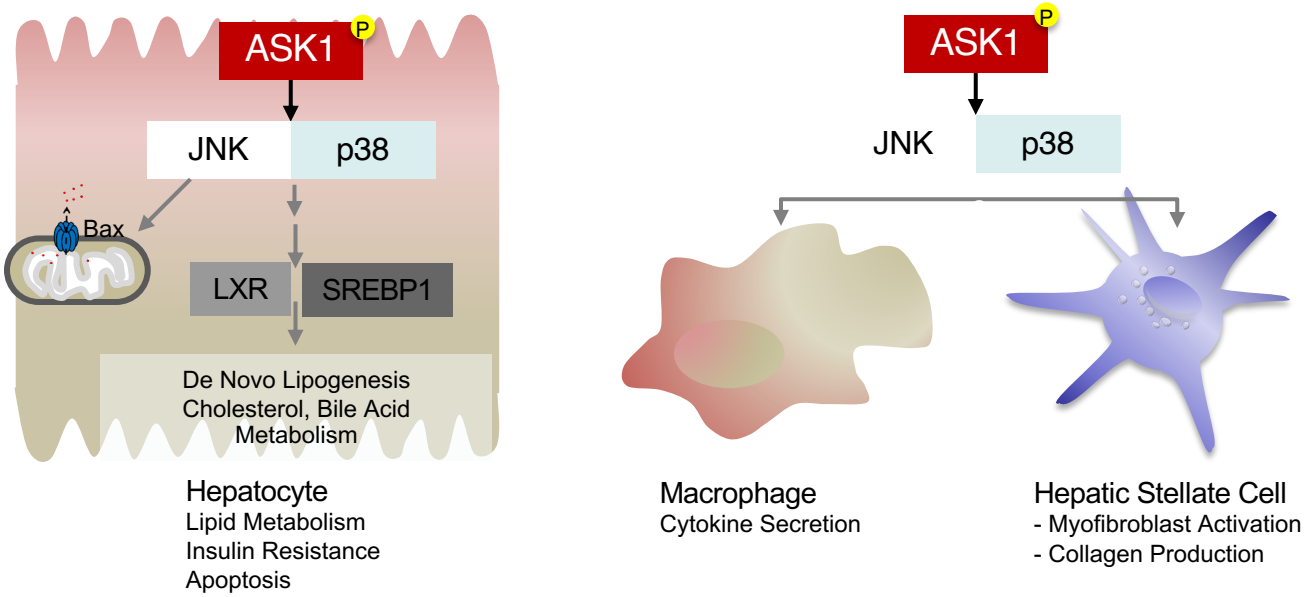
Compensated Cirrhosis (STELLAR 4)

Primary Outcome

≥ 1-Stage Improvement in Fibrosis Without Worsening of NASH [Time Frame: Week 48]

Event-Free Survival (EFS) at Week 240 as Assessed by Time to the First Clinical Event [Time Frame: Week 240]

Working Model for Role of ASK1 in NASH



Hepatocyte
Lipid Metabolism
Insulin Resistance
Apoptosis

Macrophage
Cytokine Secretion

Hepatic Stellate Cell
- Myofibroblast Activation
- Collagen Production

ASK1 = Apoptosis signal-regulating kinase 1

STELLAR studies have failed

February 11, 2019

Gilead Announces Topline Data From Phase 3 STELLAR-4 Study of Selonsertib in Compensated Cirrhosis (F4) Due to Nonalcoholic Steatohepatitis (NASH)

FOSTER CITY, Calif.–(BUSINESS WIRE)--Feb. 11, 2019-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that STELLAR-4, a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of selonsertib, an investigational, once-daily, oral inhibitor of apoptosis signal-regulating kinase 1 (ASK1), in patients with compensated cirrhosis (F4) due to nonalcoholic steatohepatitis (NASH), did not meet the pre-specified week 48 primary endpoint of a ≥ 1-stage histologic improvement in fibrosis without worsening of NASH.

In the study of 877 enrolled patients who received study drug, 14.4 percent of patients treated with selonsertib 18 mg (p=0.56 vs. placebo) and 12.5 percent of patients treated with selonsertib 6 mg (p=1.00) achieved a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH after 48 weeks of treatment, compared with 12.8 percent of patients who received placebo. Selonsertib was generally well-tolerated and safety results were consistent with prior studies.

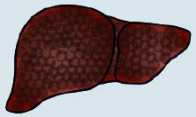
April 25, 2019

Gilead Announces Topline Data From Phase 3 STELLAR-3 Study of Selonsertib in Bridging Fibrosis (F3) Due to Nonalcoholic Steatohepatitis (NASH)

FOSTER CITY, Calif.–(BUSINESS WIRE)--Apr. 25, 2019-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that STELLAR-3, a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of selonsertib, an investigational, once daily, oral inhibitor of apoptosis signal-regulating kinase 1 (ASK1), for patients with bridging fibrosis (F3) due to nonalcoholic steatohepatitis (NASH), did not meet the pre-specified week 48 primary endpoint of a ≥ 1-stage histologic improvement in fibrosis without worsening of NASH.

In the study of 802 enrolled and dosed patients, 9.3 percent of patients treated with selonsertib 18 mg (p=0.42 versus placebo) and 12.1 percent of patients treated with selonsertib 6 mg (p=0.93) achieved a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH after 48 weeks of treatment, versus 13.2 percent with placebo. Selonsertib was generally well tolerated and safety results were consistent with prior studies.

Multifunctional role of the Farnesoid X Receptor (FXR)

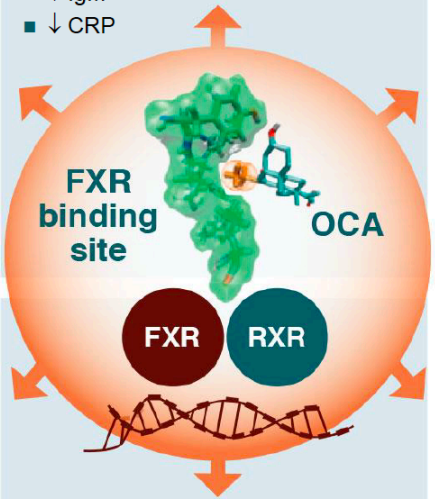


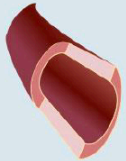
FIBROSIS

- ↓Stellate cell activation (PDGF)
- ↑Stellate cell apoptosis (TIMP-1)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

INFLAMMATION

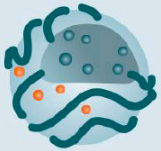
- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ, etc.
- ↓ IgM
- ↓ CRP





ATHEROSCLEROSIS

- ↑Vasodilation (eNOS)
- ↓Inflammation (COX-2, IL-1β, etc.)
- ↓Calcification (JNK)
- ↓Smooth muscle cell migration (PDGF)



LIPID METABOLISM

- ↓Triglyceride synthesis (SREBP-1c)
- ↑Triglyceride clearance (apoC-III)
- ↓VLDL formation (MTP)
- ↓HDL-C (SR-B1, CETP)
- ↑LDL-C (CETP)

GLUCOSE METABOLISM

- ↑ Insulin signaling (FGF19)
- ↑ Insulin sensitivity (IRS-1, IRS-2)
- ↑ Insulin production (KLF11, GLUT-2)
- ↓ Hepatic gluconeogenesis (PEPCK)

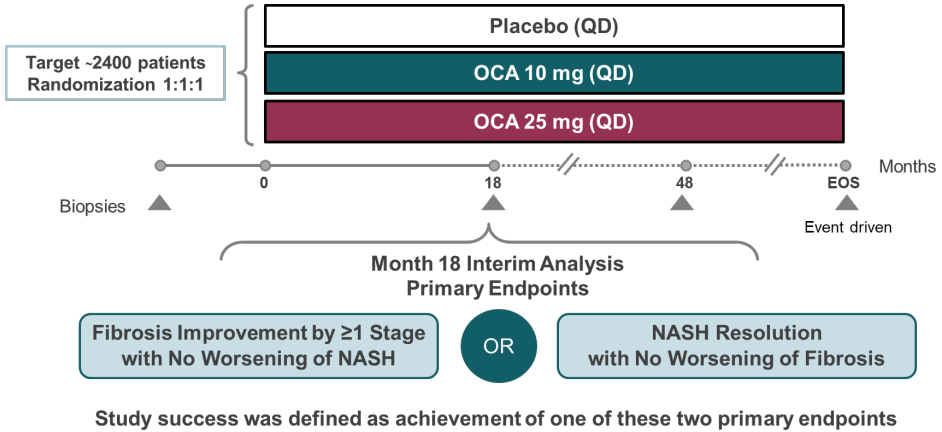
BILE ACID HOMEOSTASIS

- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (NTCP)
- ↑ Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

Calkin & Tontonoz Nat Rev Mol Cell Biol 2013

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

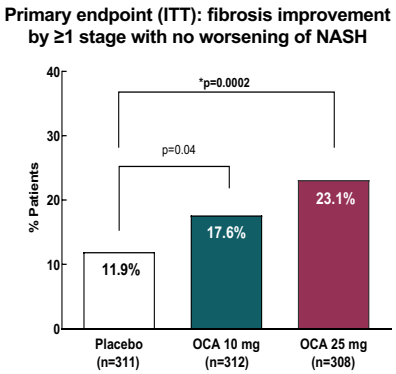
- In the Phase 2b FLINT study, the potent FXR agonist OCA 25 mg for 72 weeks improved fibrosis and other histological features of NASH
- Month 18 interim analysis of REGENERATE evaluated OCA on liver histology in NASH patients with F2/F3 fibrosis

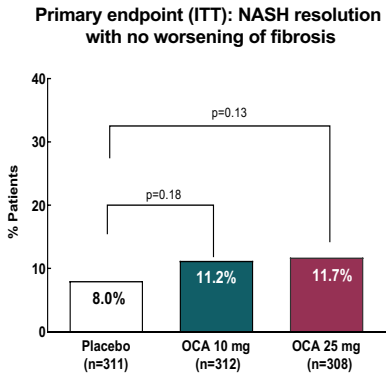


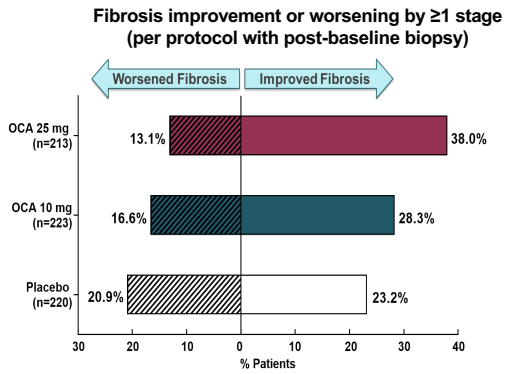
Study success was defined as achievement of one of these two primary endpoints

Younossi, EASL 2019

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

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

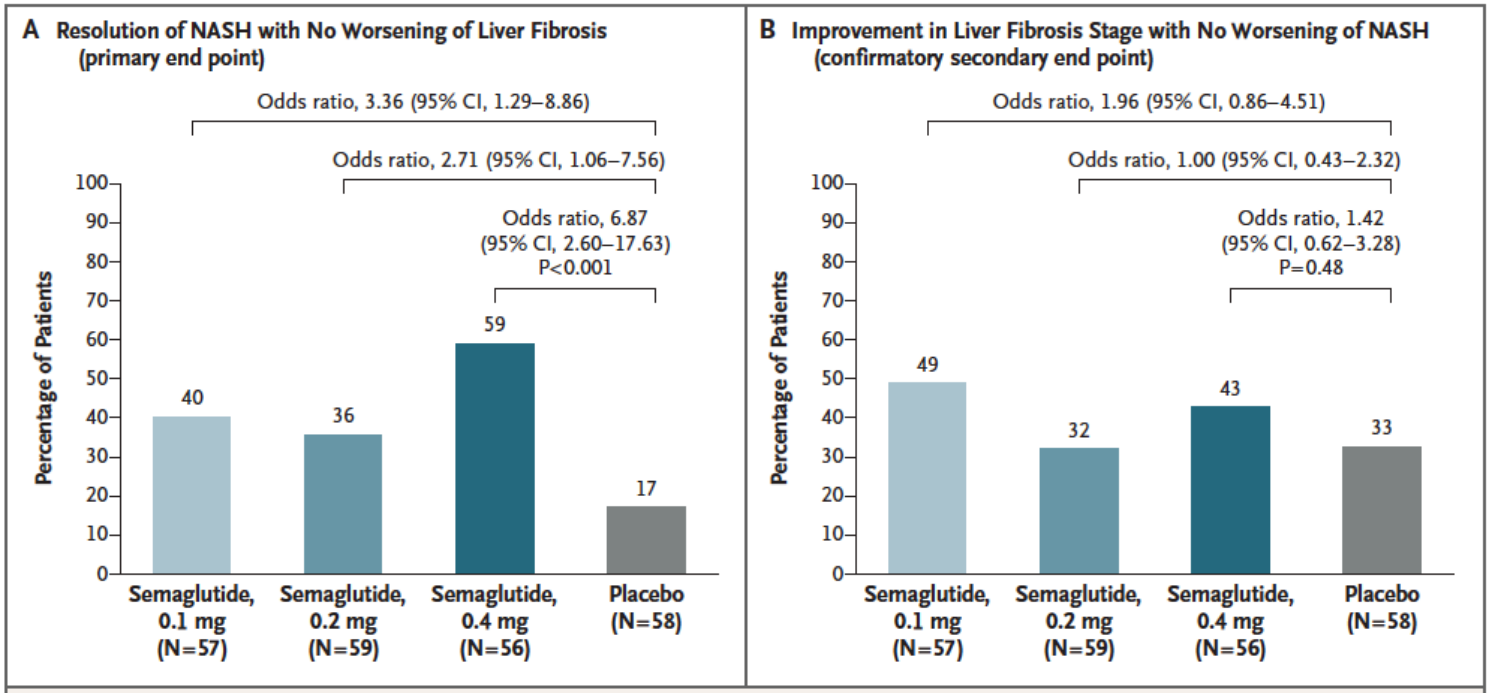
- 65.6% in OCA 25 mg **normalized ALT** vs. 37.3% in placebo
- **Safety**: Increase in LDL-C with both doses of OCA, with an eventual decrease over time
- **Treatment emergent AEs**: Pruritus was reported by 51% of patients with OCA 25 mg vs. 19% in the placebo group
- **Treatment discontinuation** was 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

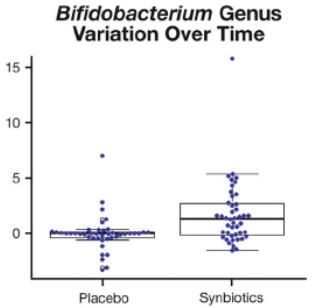
The GLP-1 agonist semaglutide induces NASH resolution but does not improve fibrosis

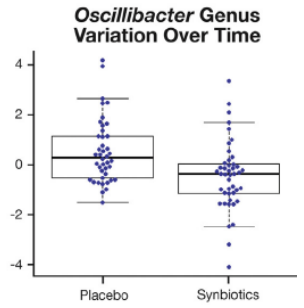


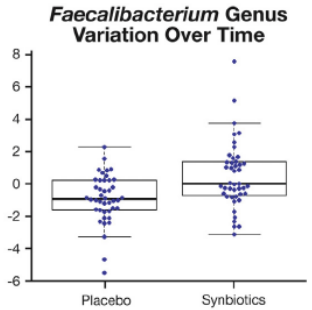
Newsome et al., NEJM 2020

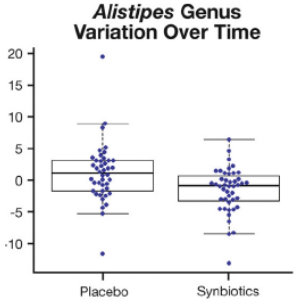
Synbiotics alter fecal microbiomes, but not liver fat or fibrosis, in patients with NAFLD

	Placebo		Synbiotic	
Primary outcomes	Baseline	End of study	Baseline	End of study
MRS-measured liver fat, %	22.9 (12.9 to 44.7)	21.4 (10.7 to 35.9)	26.9 (9.7 to 38.4)	23.7 (13.0 to 42.0)
ELF score	12.5 (0.7)	12.8 (0.8)	12.5 (0.9)	12.9 (0.8)
NAFLD fibrosis score	−1.2 (1.3)	−1.3 (1.3)	−1.3 (1.3)	−1.6 (1.4)









Scorletti et al., Gastroenterology 2020

Ongoing phase 3 trials for NASH

Pharmacologic agents	Mechanism of action	Trial identifier	Expected duration	Patient characteristics	Number	Primary endpoint	Latest results
Obeticholic acid	FXR agonist	REGENERATE (NCT02548351)	2015.9–2022.10	NASH fibrosis (F1-3[a])	2,480	1. Improvement of NASH without worsening of fibrosis or improvement of fibrosis without worsening of NASH 2. All-cause mortality and liver-related clinical outcomes	Interim 18 month analysis: improvement in fibrosis without worsening of NASH
		REVERSE (NCT03439254)	2017.8–2022.6	Compensated cirrhosis due to NASH	540	Percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH	Not available
Elafibranor	PPAR-α/δ agonist	RESOLVE-IT (NCT02704403)	2016.3–2021.12	NASH fibrosis (NAS score ≥ 4, F1-3)	2,000	1. Resolution of NASH without worsening of fibrosis 2. Composite long-term outcome of all-cause mortality, cirrhosis, and liver-related clinical outcomes	Not available
Cenicriviroc	CCR2/CCR5 inhibitor	AURORA (NCT03028740)	2017.4–2028.10	NASH fibrosis (F2-3)	2,000	1. Improvement of fibrosis without worsening of NASH 2. Composite long-term outcome of all-cause mortality, cirrhosis, and liver-related clinical outcomes	Not available
Resmetirom	Selective THR-β agonist	MAESTRO-NASH (NCT03900429)	2019.3–2024.3	NASH fibrosis (F2-3)	2,000	1. NASH resolution with at least 2 point reduction in NAS and no worsening of fibrosis 2. Composite long-term outcome of all-cause mortality, cirrhosis, and liver-related clinical outcomes	Not available
Aramchol	SCD1 inhibitor	ARMOR (NCT04104321)	2019.9–2024.12	NASH fibrosis (F2-3)	2,000	1. Resolution of NASH without worsening of fibrosis or improvement of fibrosis without worsening of NASH 2. Composite long-term outcome of all-cause mortality, liver transplant, cirrhosis, MELD >15, hospitalization due to hepatic decompensation events	Not available
Oltipraz	Liver X receptor-α inhibitor	NCT04142749	2019.11–2021.10	NAFLD (liver fat ≥ 20% on the MRS)	144	Variation of liver fat by MRS at 24 weeks compared to the baseline (%)	Not available
Dapagliflozin	SGLT2 inhibitor	DEAN (NCT03723252)	2019.3–2021.11	NASH and T2DM (HbA1c <9.5%)	100	Scored liver histological improvement	Not available

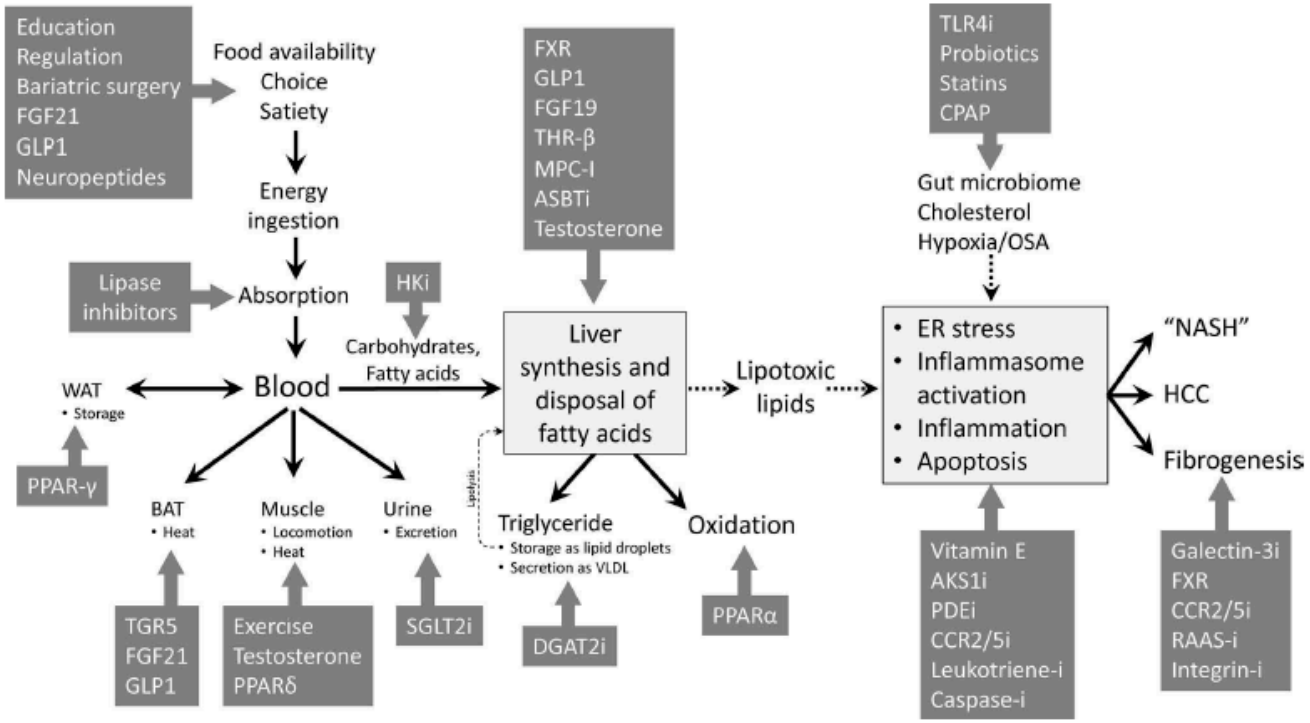
Jeong, Diabetes & Metabolism 2020

Pivotal phase 2 trials for NASH

Pharmacologic agents	Mechanism of action	Trial identifier	Expected duration	Patient characteristics	Number	Primary endpoint	Latest results
Tropifexor (LJN-452)	Non-bile acid FXR agonist	FLIGHT-FXR (NCT02855164)	2016.8–2020.4	NASH fibrosis (F1-3)	351	1. Adverse event profile of different doses of tropifexor 2. Change in transaminase levels 3. Change from baseline % of liver fat by MRI-PDFF	Interim analysis: relative decrease in liver fat content
Cilofexor (GS-9674)	Non-bile acid FXR agonist	NCT02854605	2016.8–2018.1	NASH without cirrhosis	140	Overall safety by percentage of treatment-emergent adverse events and percentage of treatment-emergent laboratory abnormalities	Significant reductions in steatosis, liver biochemistry, and serum bile acids [44]
NGM282	FGF19 analogue	NCT02443116	2015.5–2019.9	Biopsy proven NASH	250	Change in absolute liver fat content by MRI-PDFF from baseline to week 24	Not available
Pegbelfermin (BMS-986036)	Pegylated FGF21	FALCON 1 (NCT03486899)	2018.5–2020.11	NASH fibrosis (F3)	160	Proportion of participants who achieve ≥1 stage improvement in fibrosis without worsening of NASH or NASH improvement with no worsening of fibrosis	Not available
		FALCON 2 (NCT03486912)	2018.5–2021.10	NASH and cirrhosis	152	Proportion of participants who achieve ≥1 stage improvement in fibrosis without worsening of NASH	Not available
Lanifibranor (IVA337)	Pan-PPAR agonist	NATIVE (NCT03008070)	2017.2–2020.3	NASH without cirrhosis	247	Decrease from baseline of the SAF (steatosis: S, activity: A, and fibrosis: F) activity score	Not available
VK2809	THR-β agonist	VOYAGE (NCT04173065)	2019.11–2021.11	NASH fibrosis (F1-3) NAS score ≥4 MRI-PDFF ≥8%	337	Relative change in liver fat content by MRI-PDFF from baseline to week 12	Not available
Firsocostat (GS0976)	ACC inhibitor	NCT02856555	2016.8–2017.7	NASH fibrosis (F1-3)	126	Overall safety profile of GS-0976 assessed as the percentage of participants experiencing treatment-emergent adverse events	Reduction of hepatic steatosis, selected markers of fibrosis, and liver biochemistry [91]
MSDC-0602K	MPC inhibitor	EMMINENCE (NCT02784444)	2016.9–2019.6	NASH fibrosis (F1-3)	392	Hepatic histological improvement of ≥2 points in NAS with a ≥1-point reduction in either ballooning or lobular inflammation and no increase in fibrosis stage at 12 months	Not significant effect on liver histology, but improved glucose metabolism and liver enzyme [74]
Belapectin (GR-MD-02)	Galectin 3 antagonist	NCT02462967	2015.6–2017.10	NASH cirrhosis (HVPG ≥6 mmHg)	162	Change in HVPG (−28) at the end of the 52 week period compared with baseline	Not significant reduction in HVPG or fibrosis, but subgroup without esophageal varix reduce HVPG [99]
Semaglutide	GLP-1 analogue	SEMA-NASH (NCT02970942)	2016.11–2020.3	NASH fibrosis (F1-3)	320	NASH resolution without worsening of fibrosis	Not available
		NCT03987451	2019.6–2021.6	NASH fibrosis (F4)	65	At least 1 stage of liver fibrosis improvement with no worsening of NASH	Not available

Jeong, Diabetes & Metabolism 2020

Targets of therapies for NASH and NASH-induced fibrosis.



Qureshi & Neuschwander-Tetri, Exp Opin Invest Drugs 2020

COVIDO, ERGO ZOOM

René Descartes