NASH e NAFLD: la nuova epidemia

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Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE
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Centro Congressi Hotel Londra

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Abbvie: consultant fees

Allergan: consultant fees

Alfa-Wassermann: travel grants

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Ipsen: consultant fees

Intercept: speaker honoraria

Menarini: consultant fees

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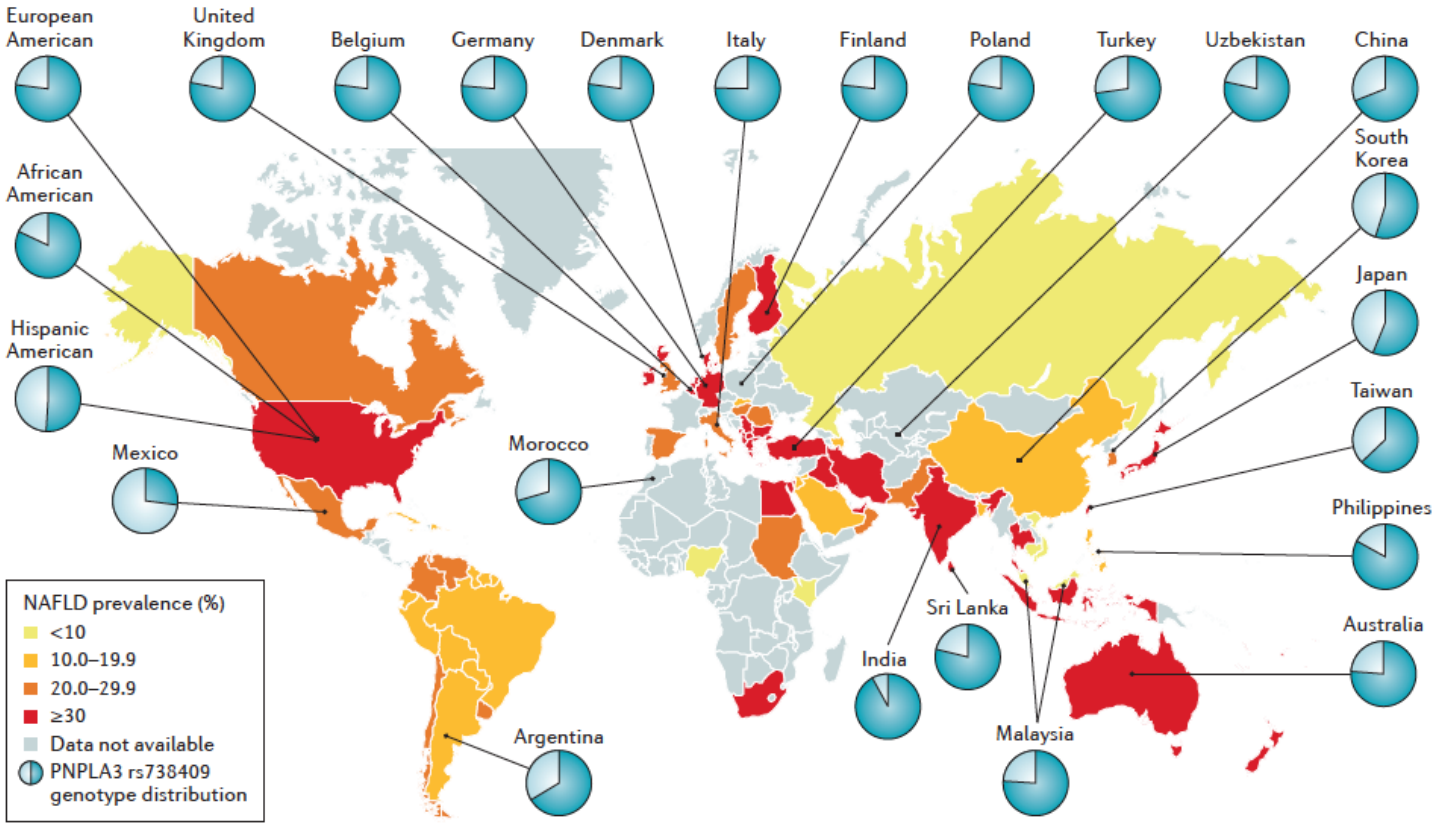
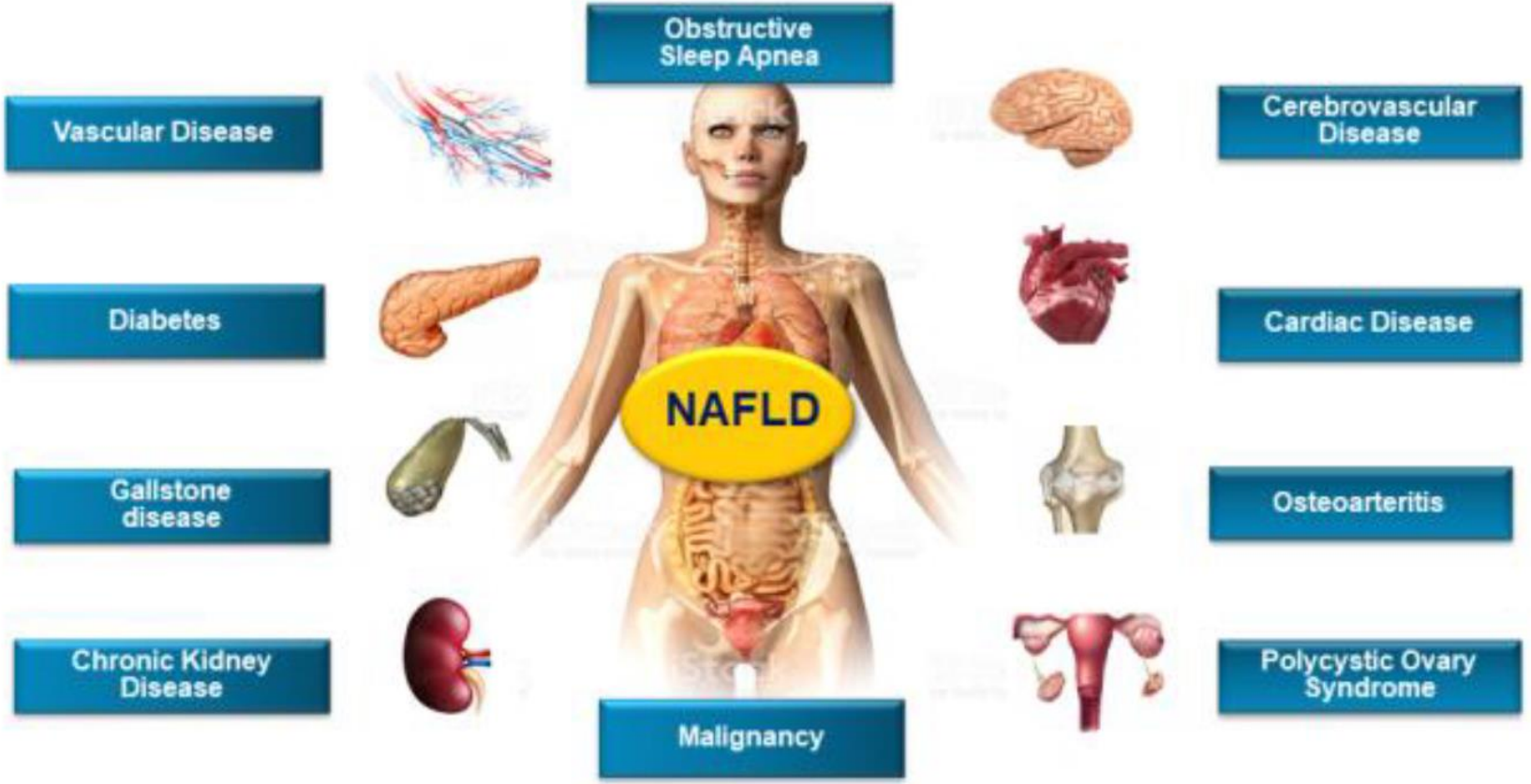
Global prevalence of NAFLD

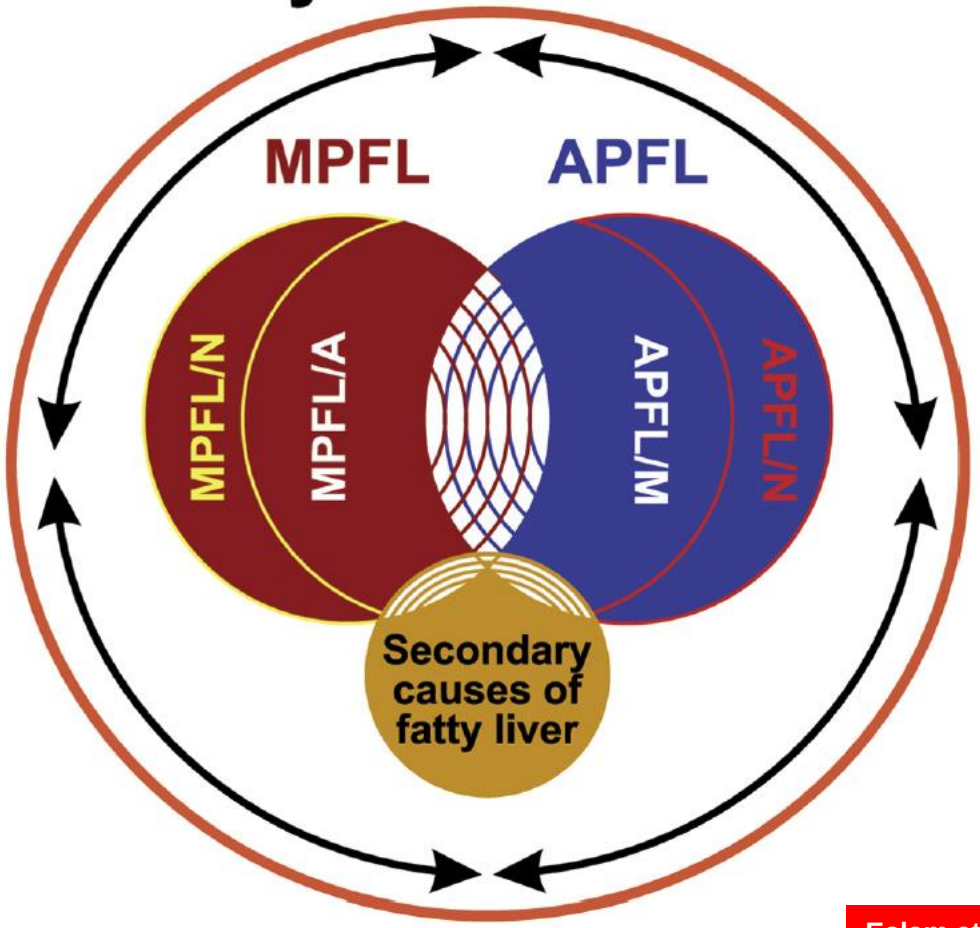


Younossi et al., Nat Rev Gastro Hep 2017



Younossi et al., Hepatology 2019

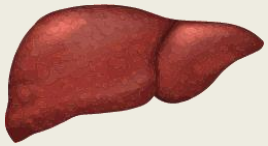
Fatty liver disease



Eslam et al., Gastroenterology 2019

NAFLD Disease Spectrum

NORMAL LIVER

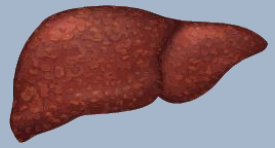


- Less than 5% fat

STEATOSIS

- T2DM
- Genetic factors
- Obesity
- Dyslipidemia

NASH



- Oxidative stress
- Lipotoxicity
- Inflammation
- Apoptosis

FIBROSIS

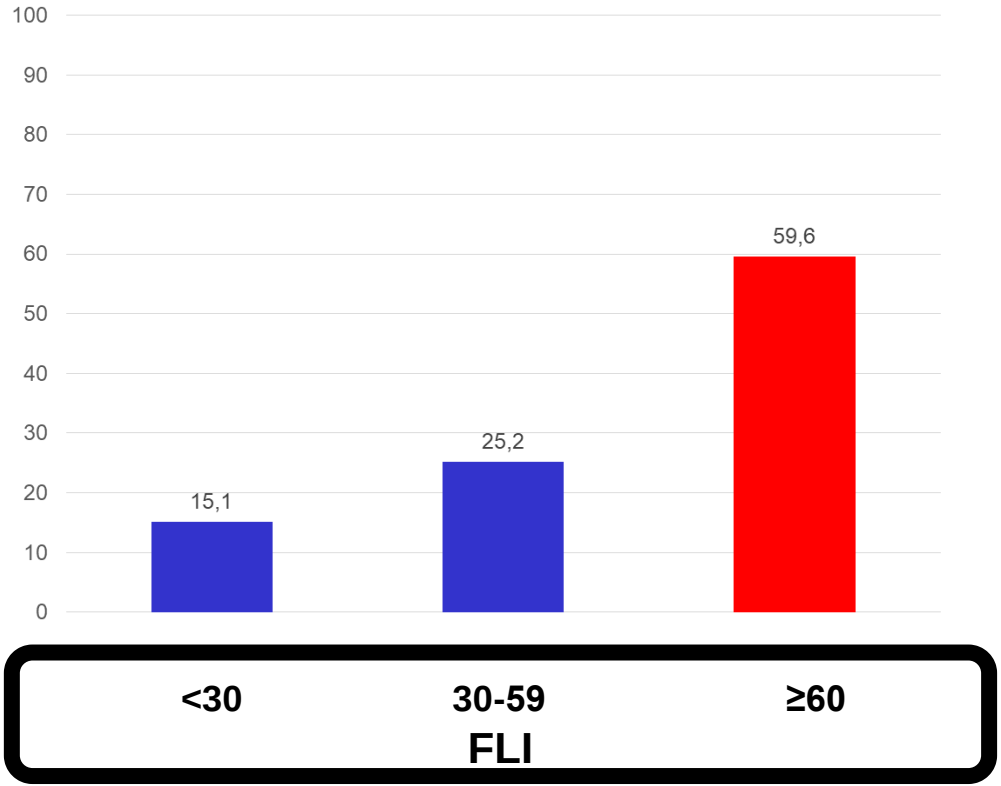
- Accumulation of scar tissue → cirrhosis

Severity

Schuppan &, Schattenberg *J Gastroenterol Hepatol*
Cusi. *Gastroenterology* 2012

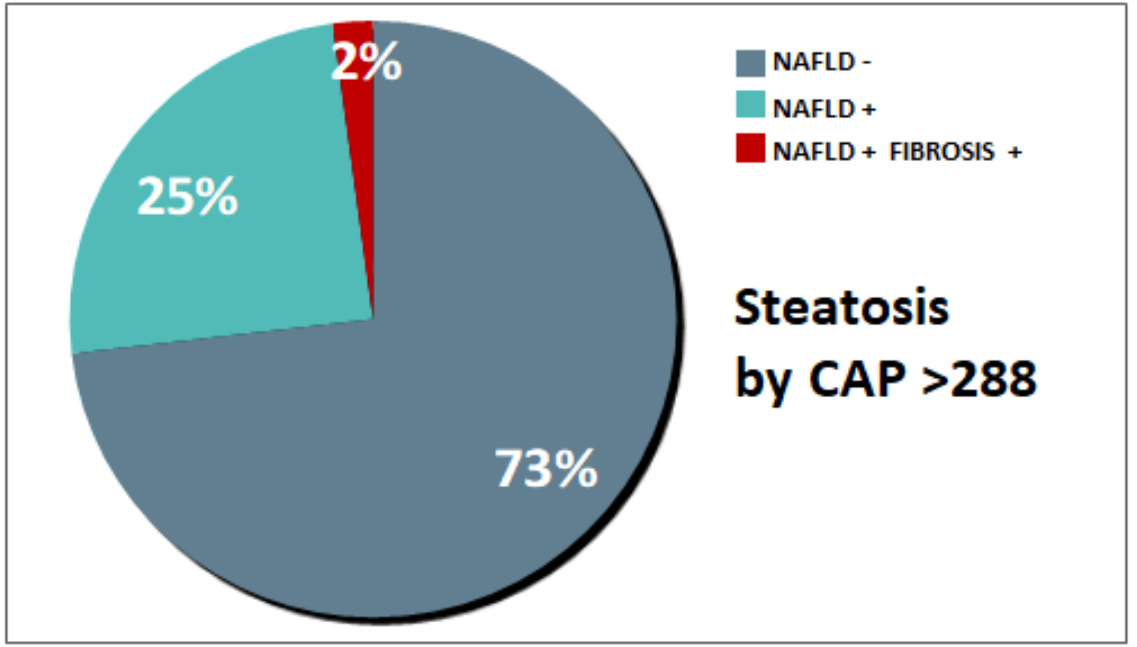
Steatosis Prevalence in T2DM in Italy

38,880 diabetic evaluated for steatosis by Fatty Liver Index >60



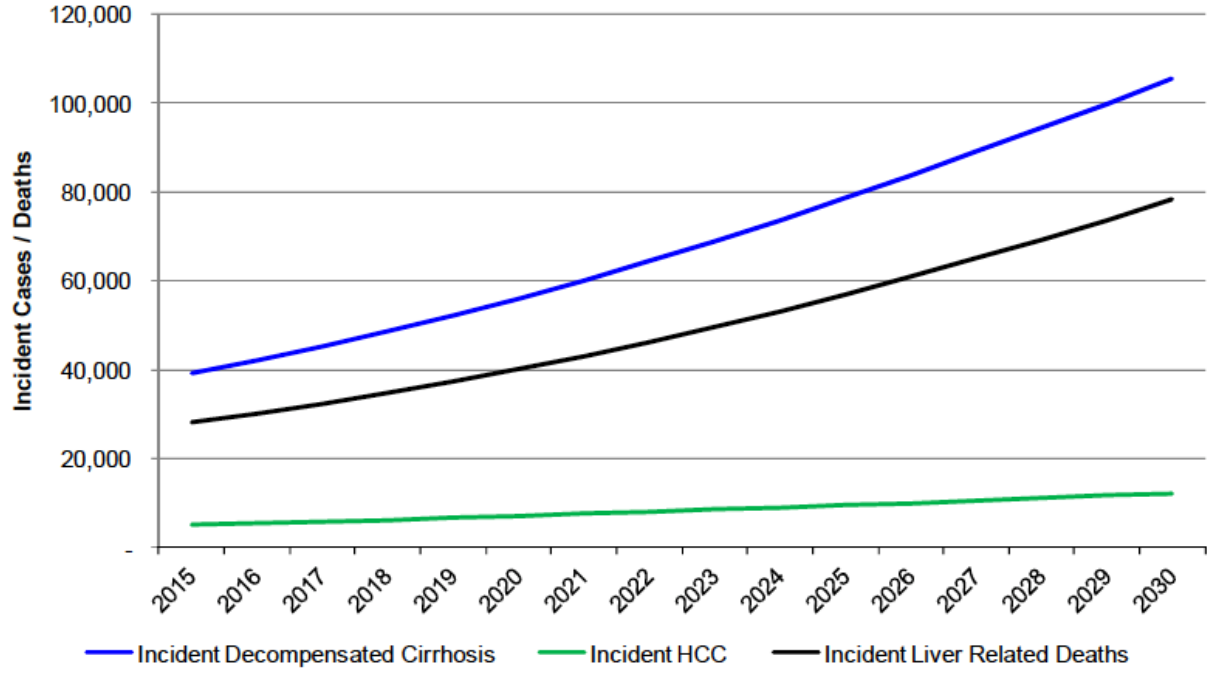
Forlani et al, J Diab Res 2016

The Epidemic of NAFLD: Data from General Population



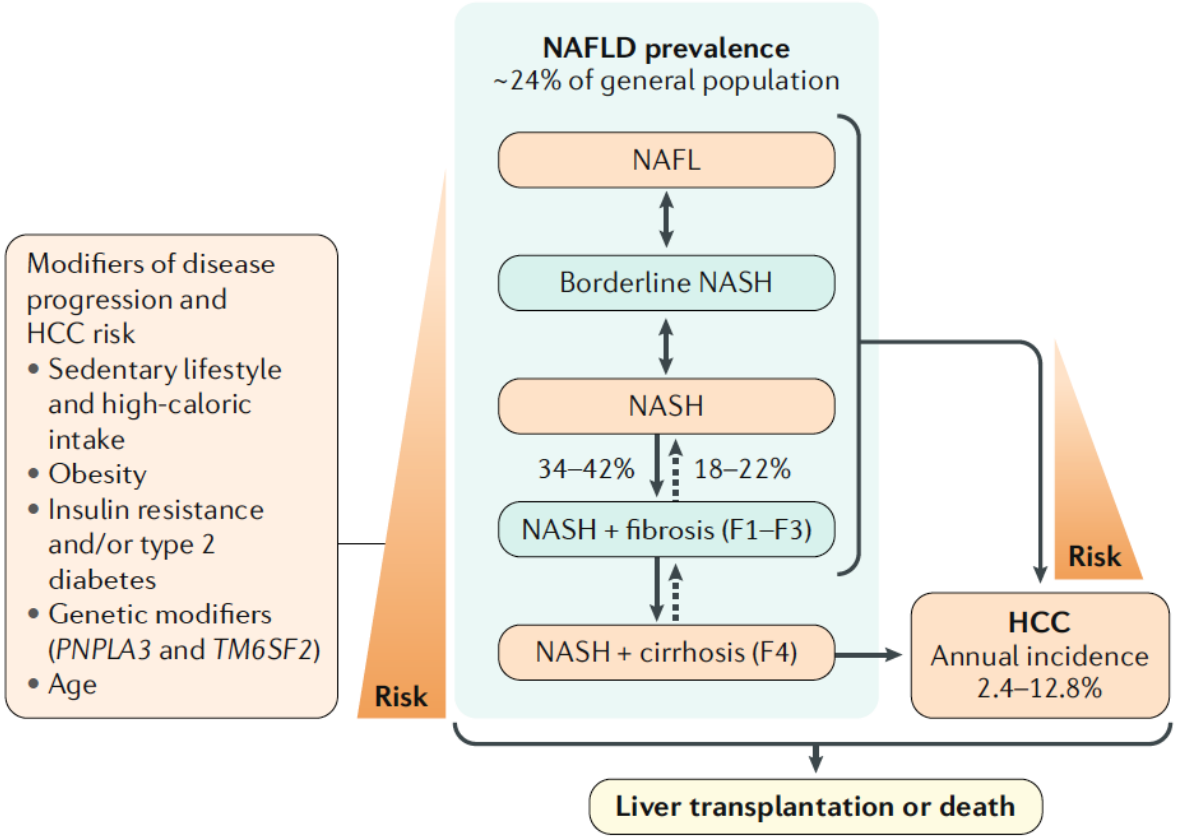
Petta S et al, Liv Int 2018

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



Estes et al., Hepatology 2017

Natural history of fatty liver



Anstee et al., Nat Rev Gastroenterol Hepatol 2019

NAFLD & mortality

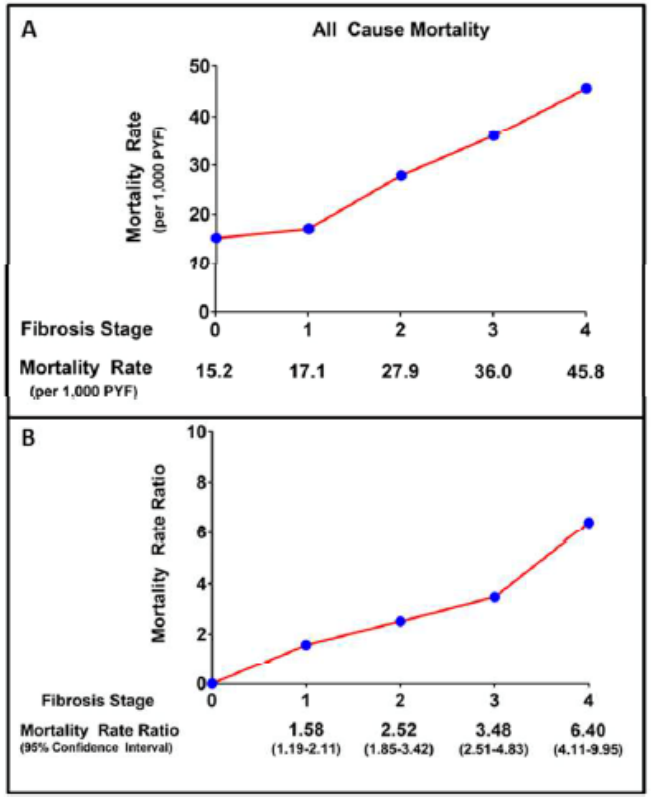
Cardiovascular (13-30%)
All cause malignancy (6-28%)

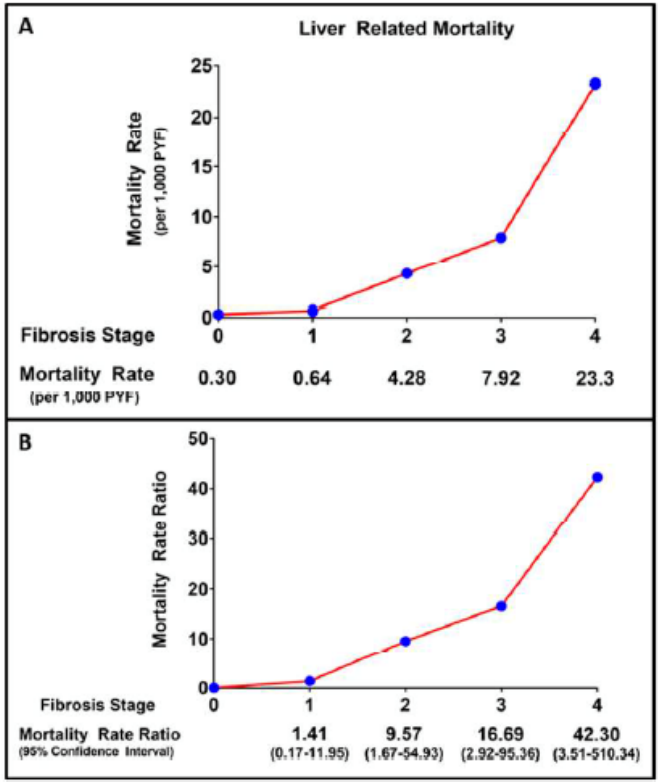
NAFLD & NASH

Liver-related death (3-19%)

NASH with fibrosis

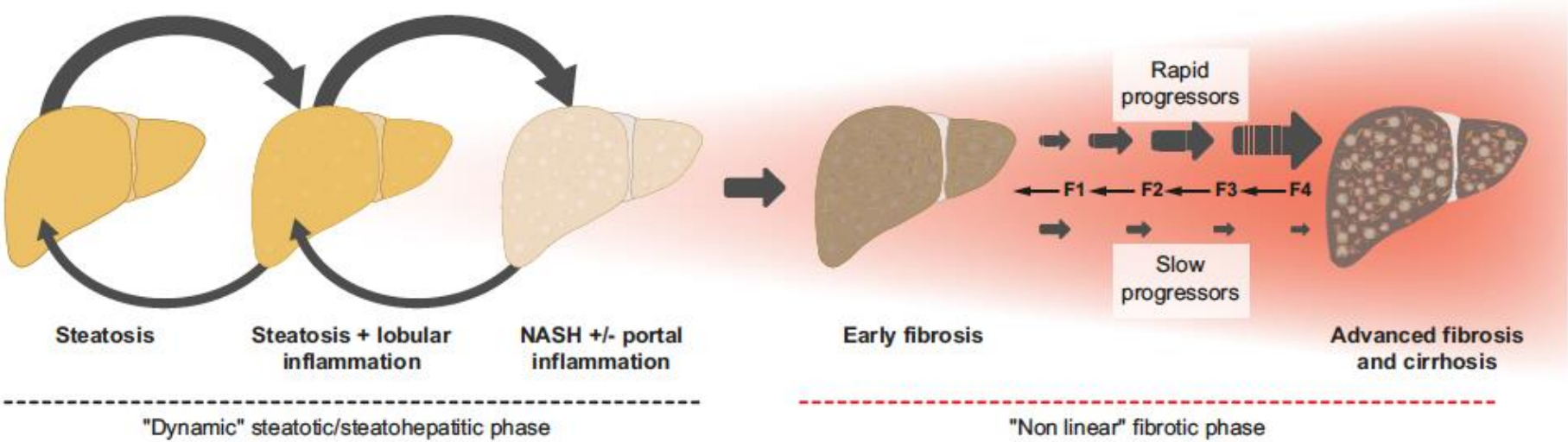
Fibrosis stage and mortality





Dulai et al., Hepatology 2017

The ‘dynamic’ natural history of NAFLD

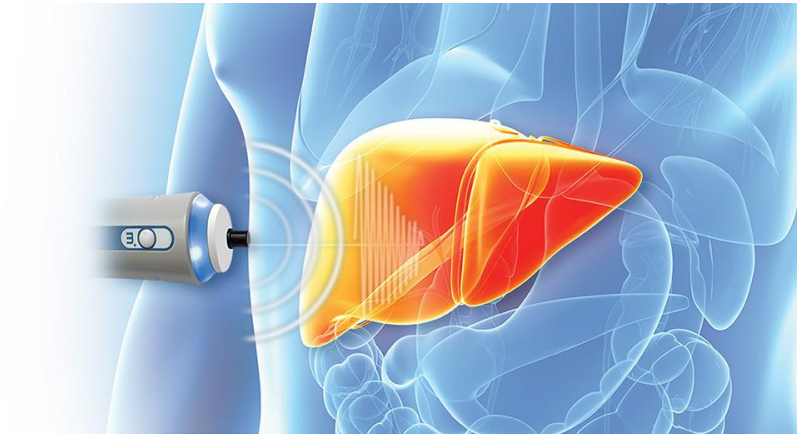


Rinella et al., J Hepatol 2019

Commonly used noninvasive tests for advanced fibrosis in NAFLD

FIB-4 → AST, ALT, Age, Platelet count

NFS → AST/ALT, IFG/T2DM, age, BMI, platelet count, albumin



Vibration-controlled transient elastography (**Fibroscan®**)

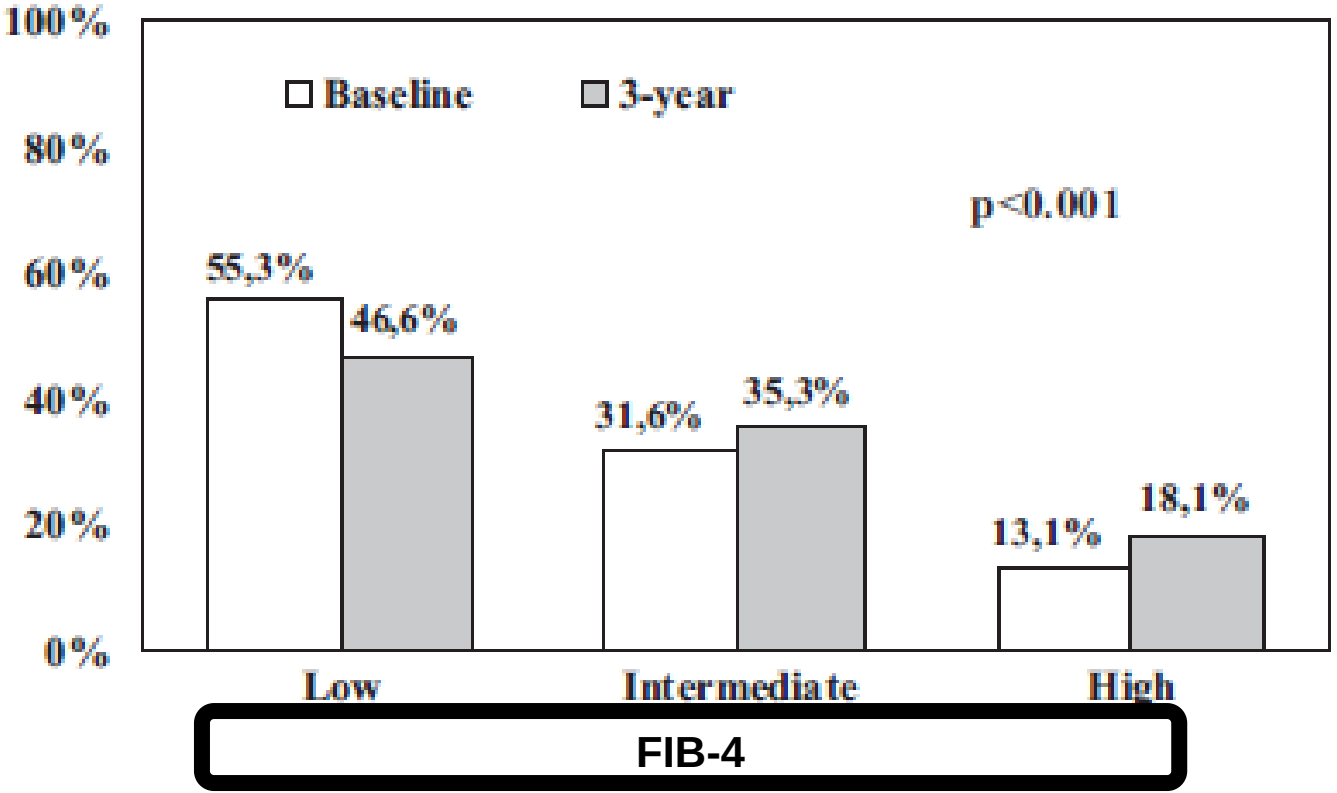
Liver fibrosis in the general population

Reference	Population	Age (yr)	Sample size	Non-invasive tool for screening	Prevalence of F ≥ 2	Prevalence of F ≥ 3	Prevalence of cirrhosis	Aetiology
Poynard et al.[25]	Walk-in primary care	>40	7463	FibroTest	2.8% (<0.48)	NA	0.3% (>0.75)	NAFLD
Roulot et al.[26]	Walk-in primary care	>45	1190	FibroScan	7.5% (>8 kPa)	NA	0.7% (>13 kPa)	NAFLD
Wong et al.[27]	Population based	>18	922	FibroScan	NA	3.7% (>9.6 kPa)	NA	NAFLD
Koehler et al.[24]	Population based	>45	3041	FibroScan	5.6% (>8 kPa)	NA	0.6% (>13 kPa)	NALFD
Harman et al.[30]	Risk-related lifestyle factors	>18	378	FibroScan	27% (>8 kPa)	NA	NA	NAFLD, ALD
Kwok et al.[29]	Type 2 Diabetics	>18	1918	FibroScan	NA	18% (>9.6 kPa)	11% (>11.5 kPa)	NAFLD

Castera Liver Int 2017

Liver Fibrosis Severity in T2DM in Italy

1,527 diabetic patients with Fatty Liver Index >60



Giorda et al, Diab Res Clin Pract 2018

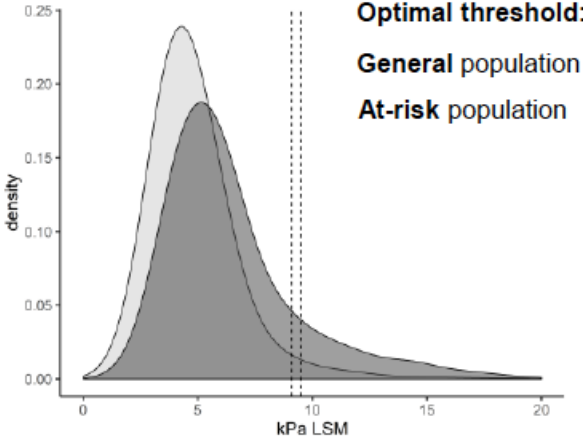
VCTE for F≥2 in NAFLD

Target population

General population ~ *3%*

At-risk population ~ *9% prevalence*

TE screening algorithm

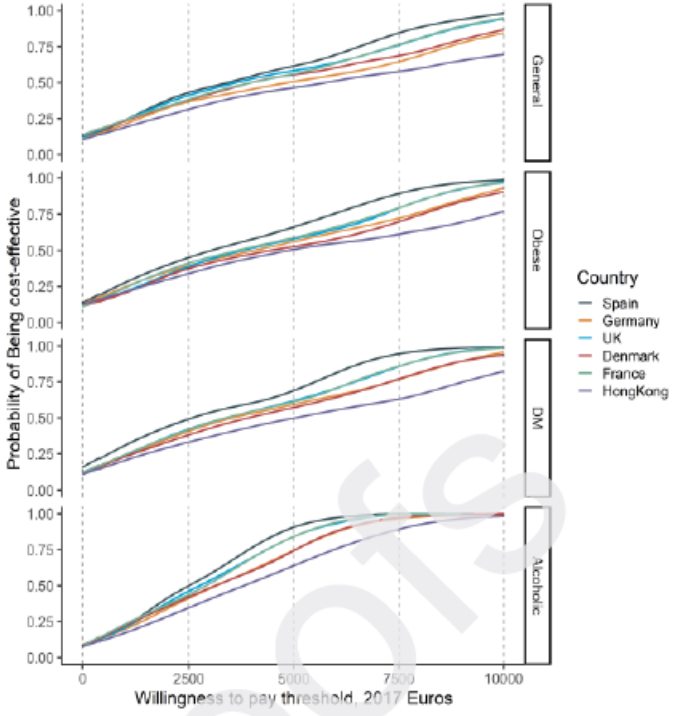


Optimal threshold:

General population ≥ 9.1 kPa

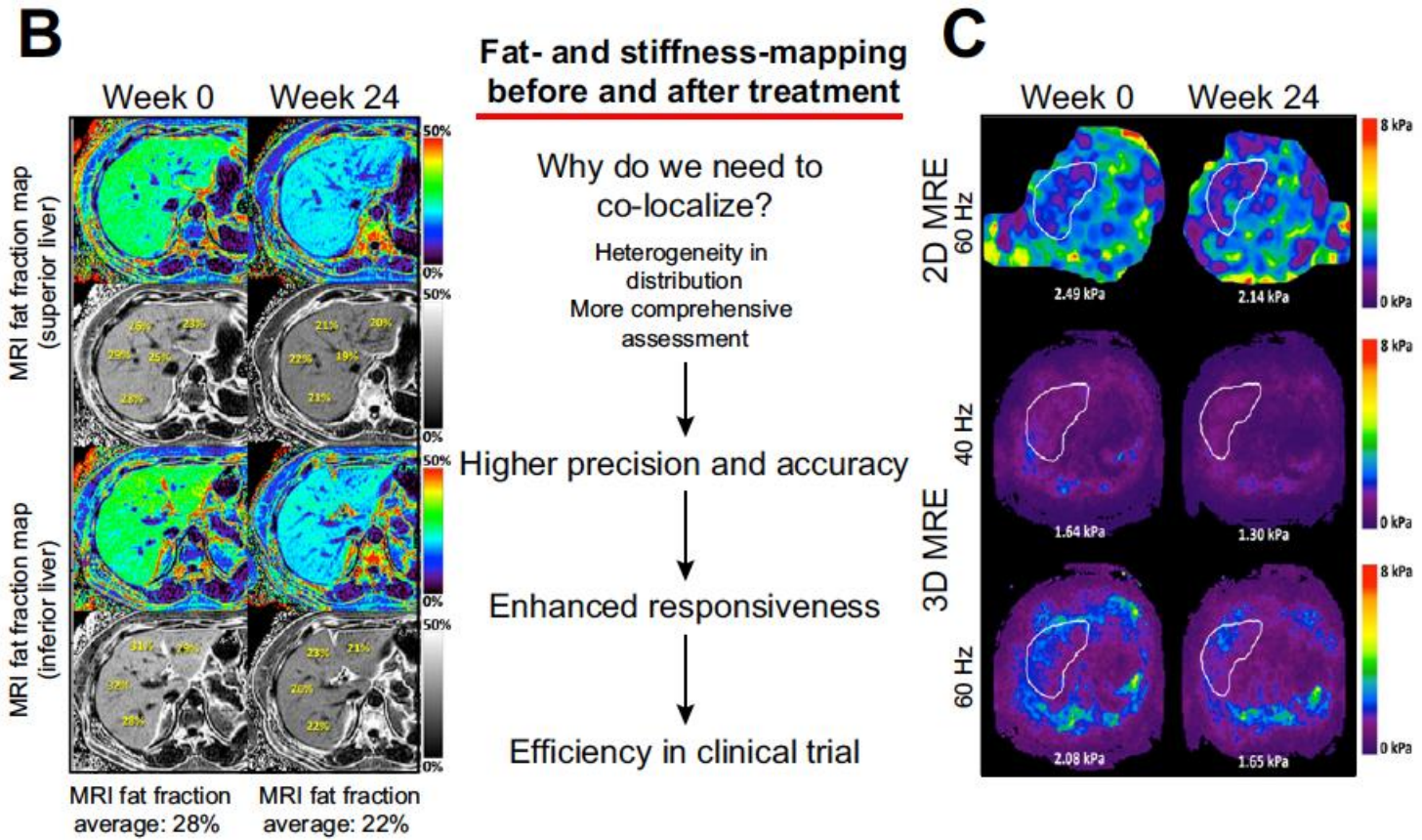
At-risk population ≥ 9.5 kPa

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



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

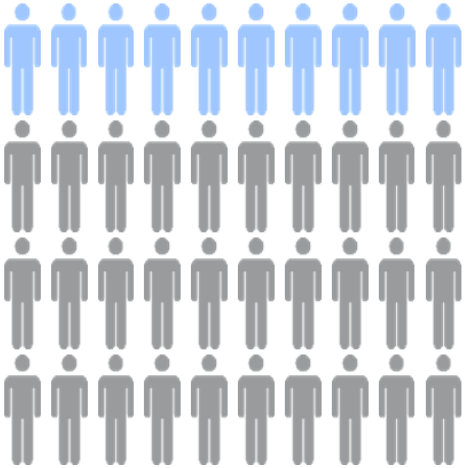
MRI and NAFLD



Dulai et al., J Hepatol 2016

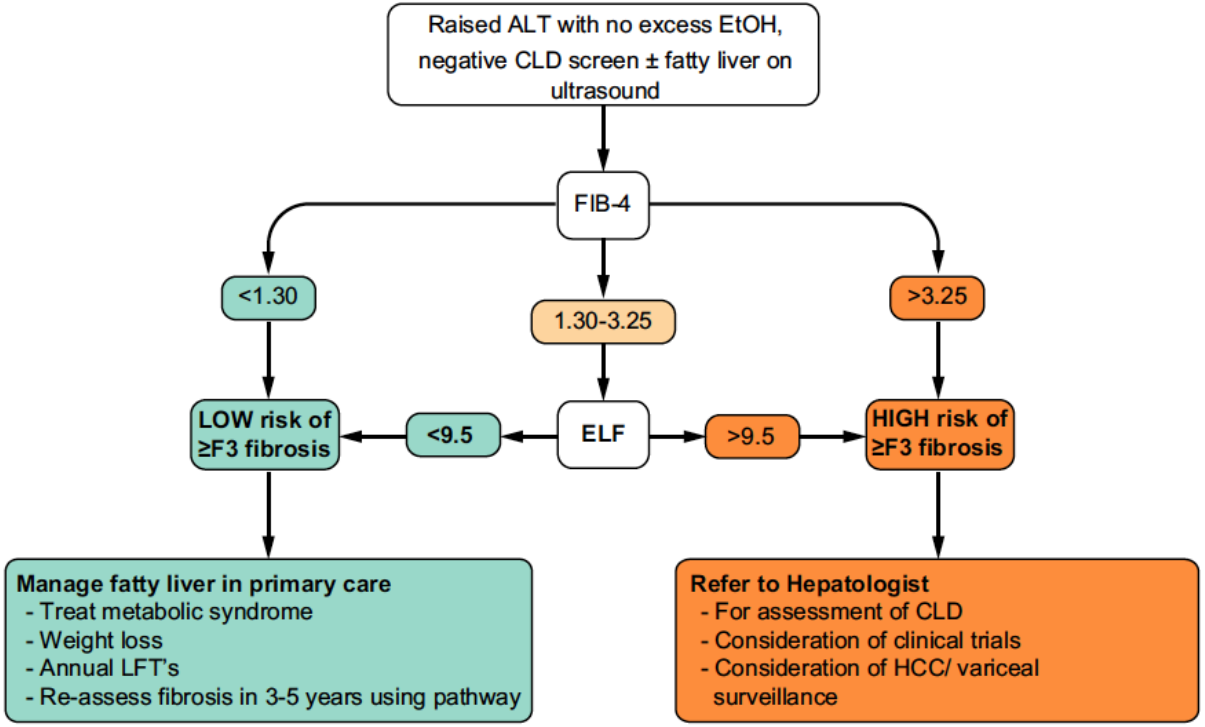
Identification of at risk patients

25% to 35% of general population has NAFLD



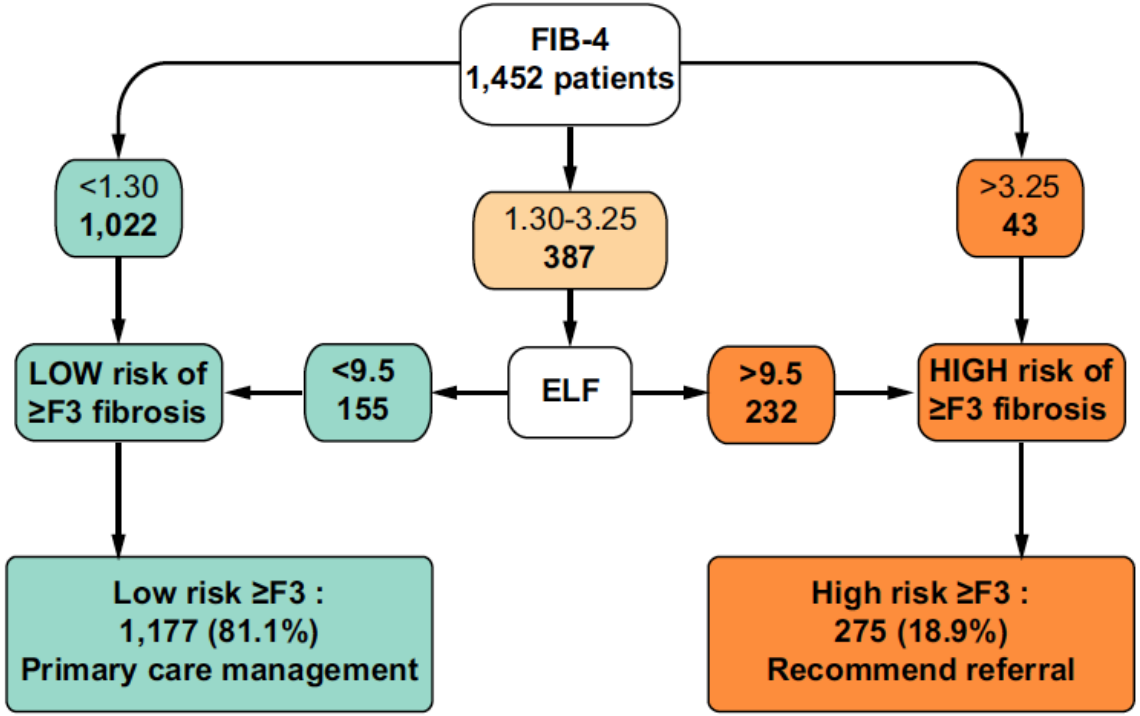
Only a minority will ever progress beyond NAFL

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

Fibrosis-4 (FIB-4) Calculator

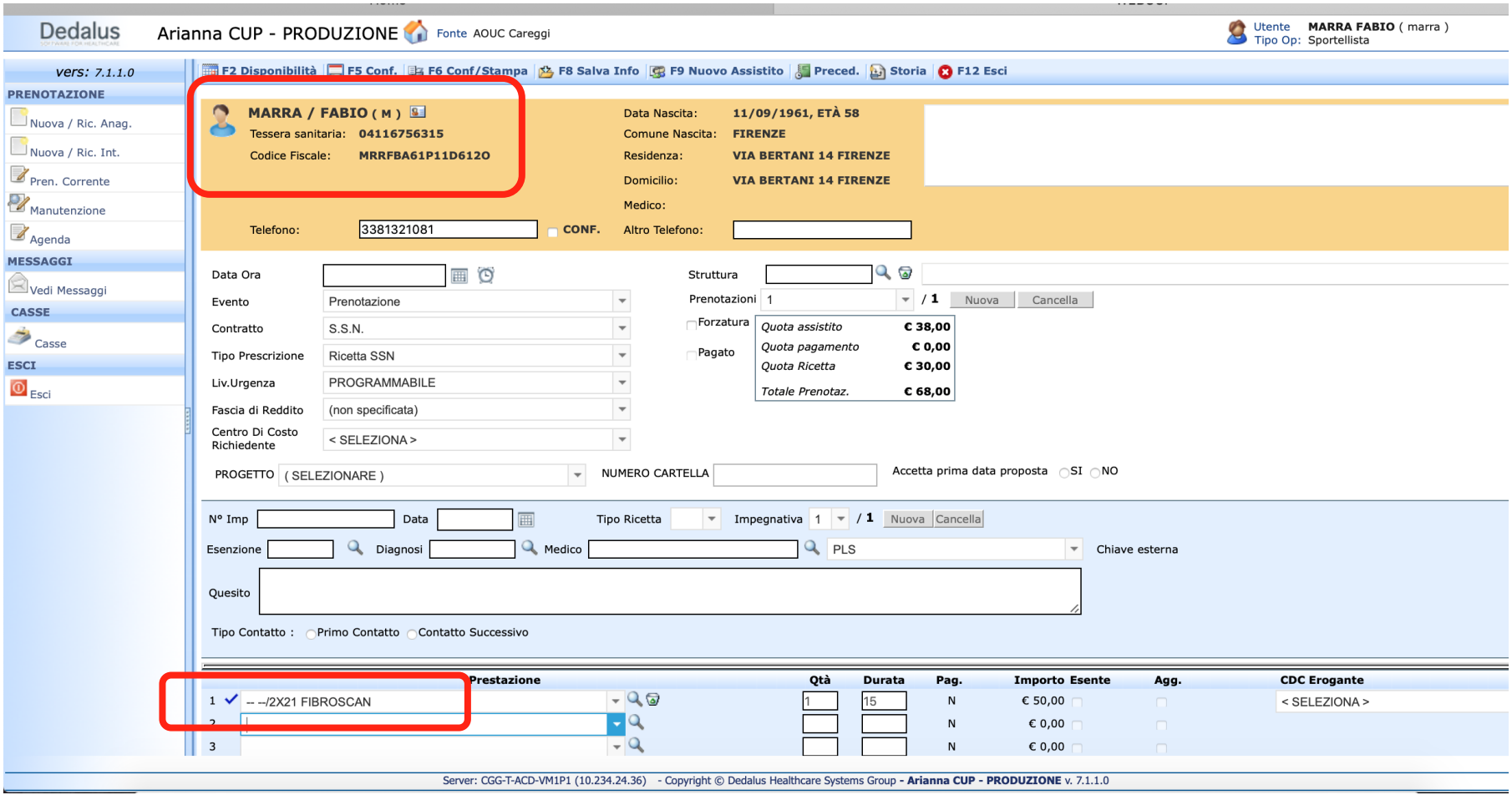
Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age } (\textit{years}) \times \text{AST Level } (\textit{U/L})}{\text{Platelet Count } (\textit{10}^9/\textit{L}) \times \sqrt{\text{ALT } (\textit{U/L})}} =$$

Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.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Arianna CUP - PRODUZIONE
Fonte AOUC Careggi
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F5 Conf.
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F8 Salva Info
F9 Nuovo Assistito
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Storia
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Comune Nascita: FIRENZE
Residenza: VIA BERTANI 14 FIRENZE
Domicilio: VIA BERTANI 14 FIRENZE
Medico:
Telefono: 3381321081
CONF.
Altro Telefono:
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Contratto S.S.N.
Tipo Prescrizione Ricetta SSN
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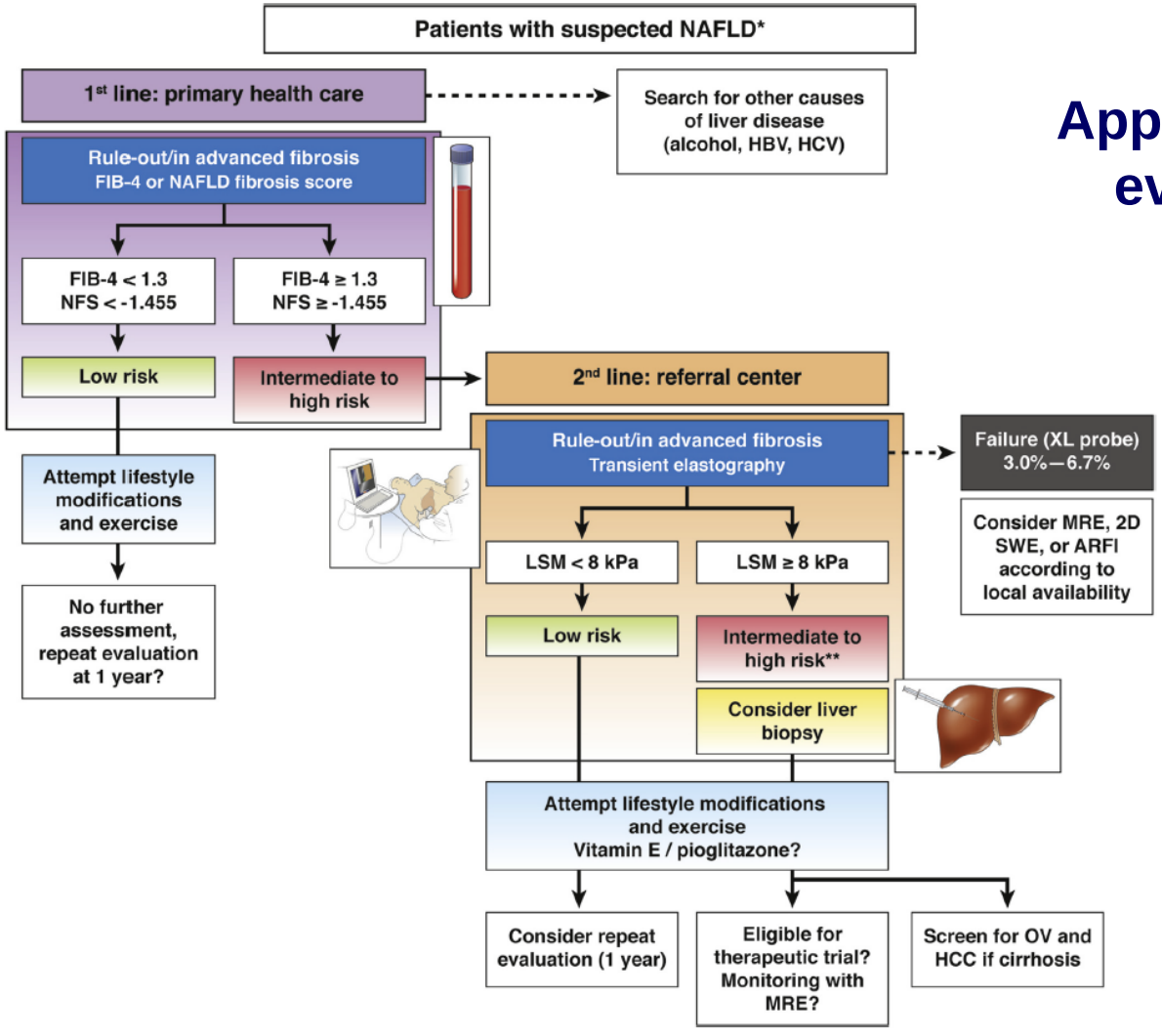
Approach to noninvasive evaluation of NAFLD

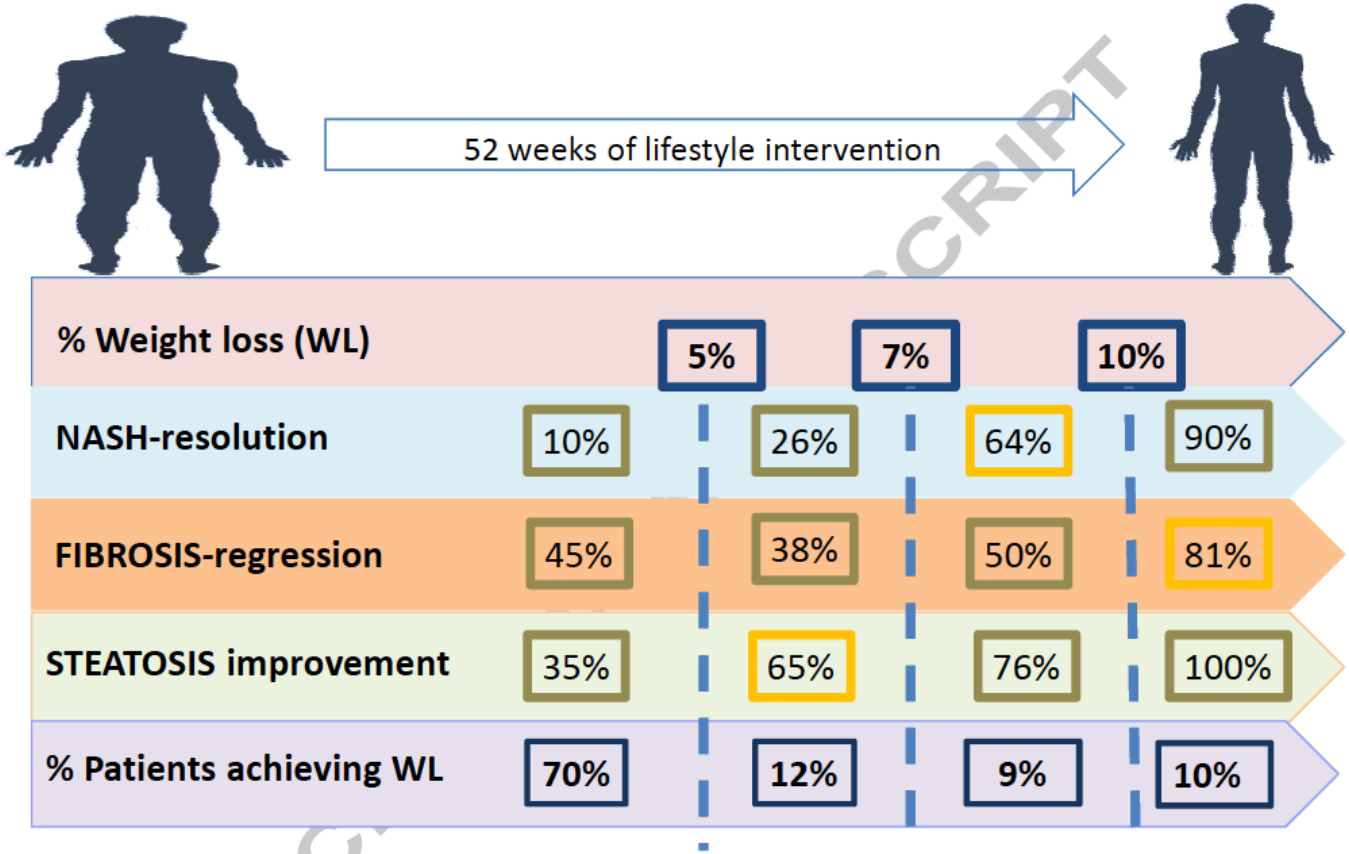


Castera et al., Gastroenterology 2019

Current situation in NASH treatment

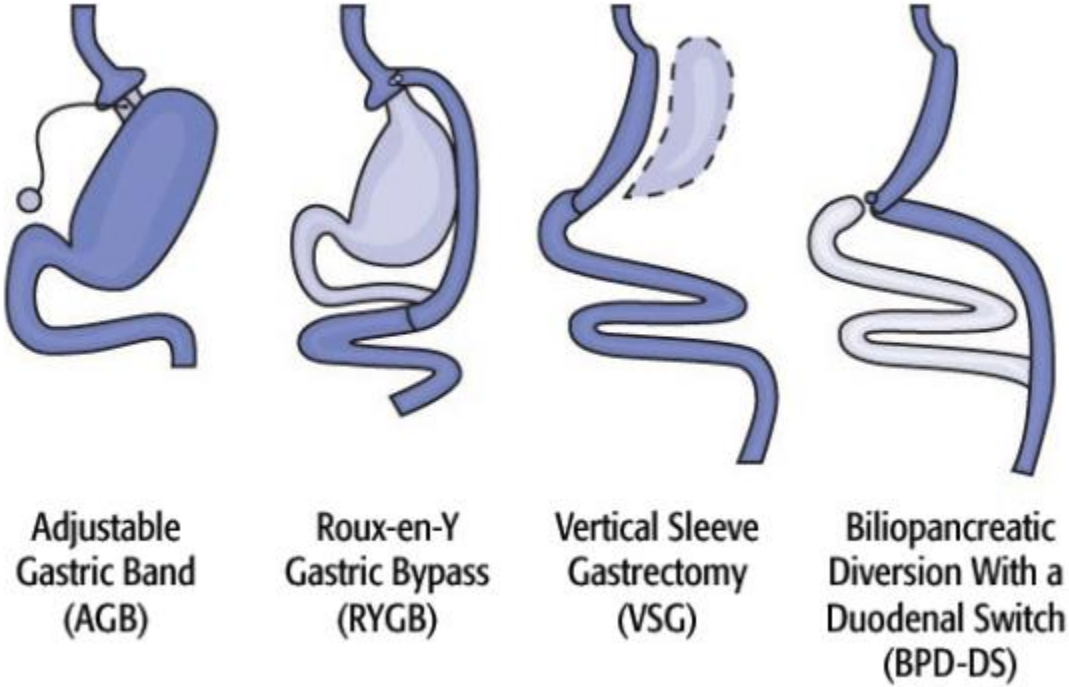
NASH: whom to treat

- Biopsy-proven NASH patients
- Presence of fibrosis ≥F2
- Early-stage NASH with risk of fibrosis progression
  (age >50 years; diabetes, MetS, increased ALT)
- Active NASH with high necroinflammatory activity
- NASH cirrhosis may be an indication for selected drugs



Data from Vilar-Gomez et al.

Bariatric surgery



Insulin sensitizers

Metformin

- No evidence of histological benefit
- Possible chemopreventive effects towards HCC

Thiazolidinediones

- PIVENS trial → improvement in histology except for fibrosis
- Prolonged treatement considered of scarce benefit
- Recurrence upon withdrawal
- Side effects
- May be used in patients with diabetes and NASH

Long-term pioglitazone in NASH

Primary outcome: reduction of ≥ 2 points in NAS in 2 histologic categories without worsening of fibrosis

Outcome	Placebo (n = 51)	Pioglitazone (n = 50)	Treatment Difference (95% CI)	P Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

Cusi et al., Ann Int Med 2016

Antioxidants

Vitamin E

- Used in the PIVENS trial → better than placebo in improving steatosis, inflammation and ballooning and ininducing NASH resolution
- Used at 800 IU/day
- Safety concerns (overall mortality, stroke, prostate cancer)
- Recent data supporting an effect on NASH progression

Ongoing phase 3 trials

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)

Effects of the PPARα/δ agonist elafibranor in NASH

Table 2. Response Rates and Main Analyses According to Protocol-Defined and the Modified Definitions of Response

NAS	n	Placebo, n (%)	Elafibranor 80 mg, n (%)	Elafibranor 120 mg, n (%)	OR (95% CI)[a]	*P* value[a]
Protocol-defined primary outcome						
Total	274	92 (17)	93 (23)	89 (21)	1.53 (0.70–3.34)	.280
NAS ≥4 (moderate and severe)	234	76 (11)	83 (20)	75 (20)	3.16 (1.22–8.13)	.018
NAS 3 (mild)	40	16 (50)	10 (40)	14 (29)		
Modified definition of response						
Total	274	92 (12)	93 (13)	89 (19)	2.31 (1.02–5.24)	.045
NAS ≥4 (moderate and severe)	234	76 (9)	83 (13)	75 (19)	3.52 (1.32–9.40)	.013
NAS 3 (mild)	40	16 (25)	10 (10)	14 (21)		

[a]Elafibranor 120 mg vs placebo, direct treatment effect.

Ratziu et al., Gastroenterology 2016

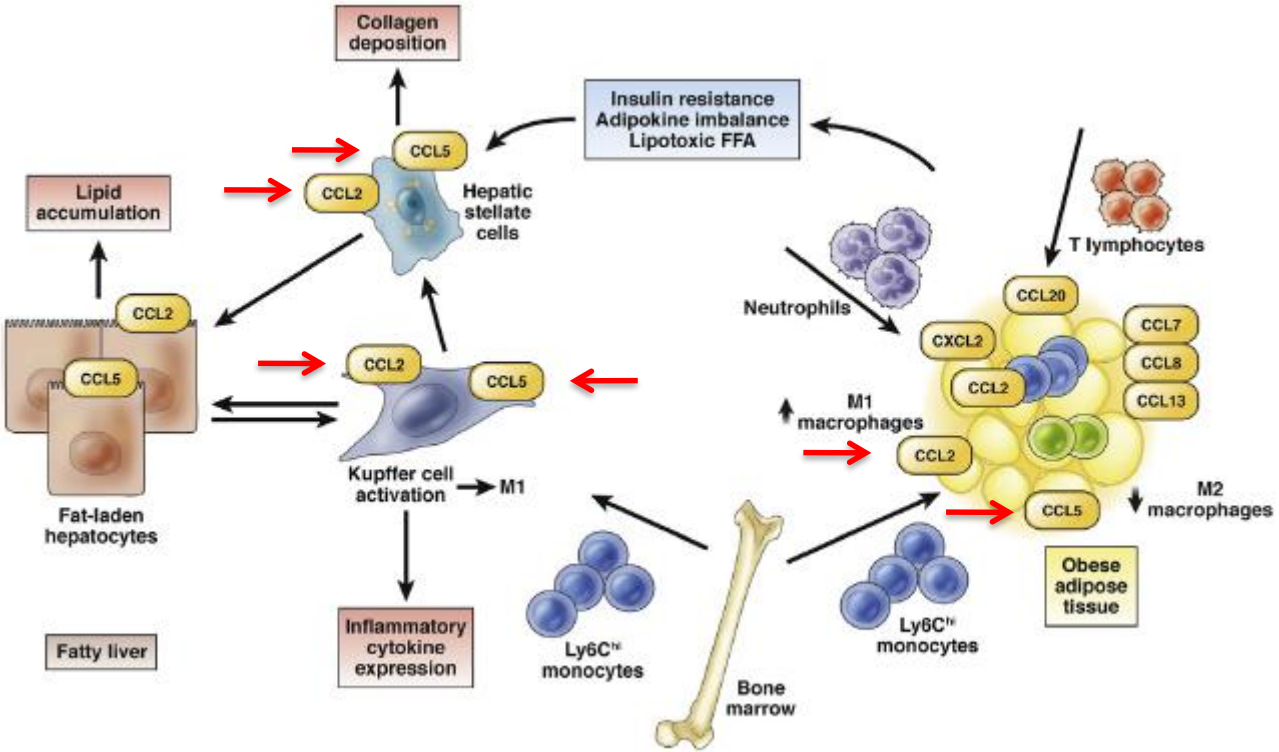
Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (NASH) (RESOLVE-IT)

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]

Chemokines and NASH progression



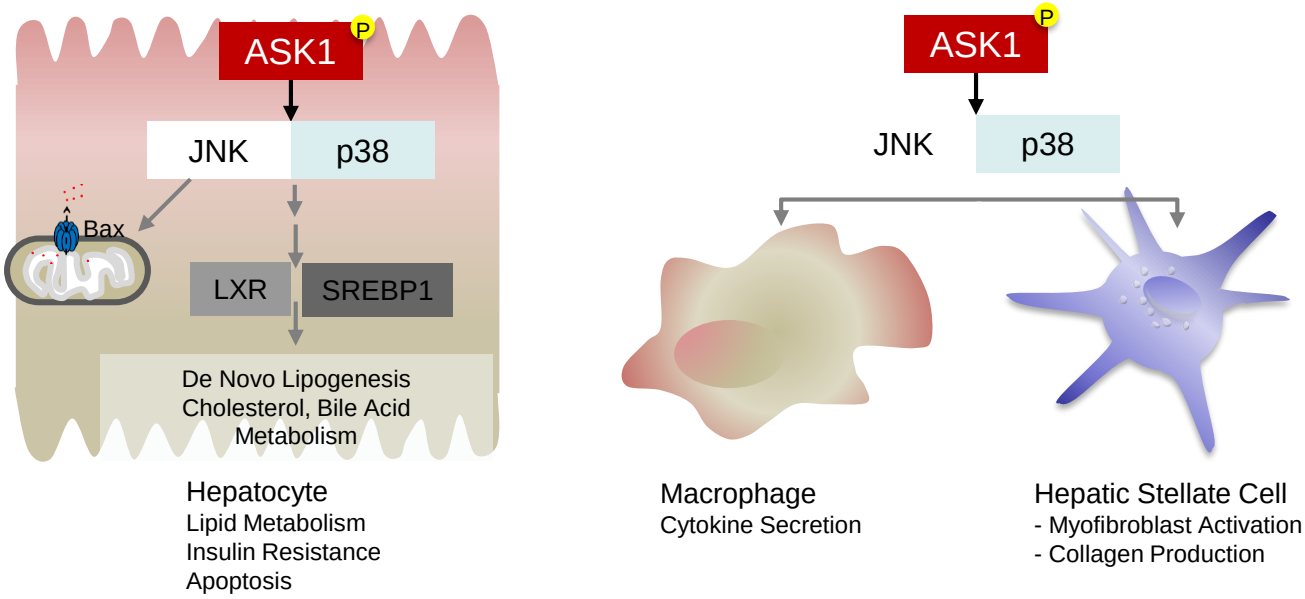
Marra & Tacke, Gastroenterology 2014

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]

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

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]

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.

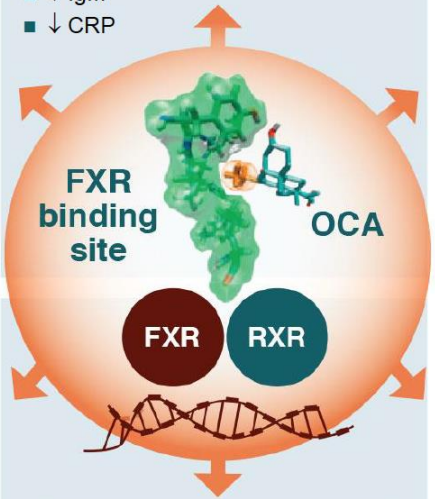
Multifunctional role of the Farnesoid X Receptor (FXR)

FIBROSIS

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

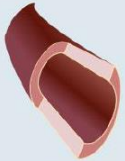
INFLAMMATION

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



GLUCOSE METABOLISM

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



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)

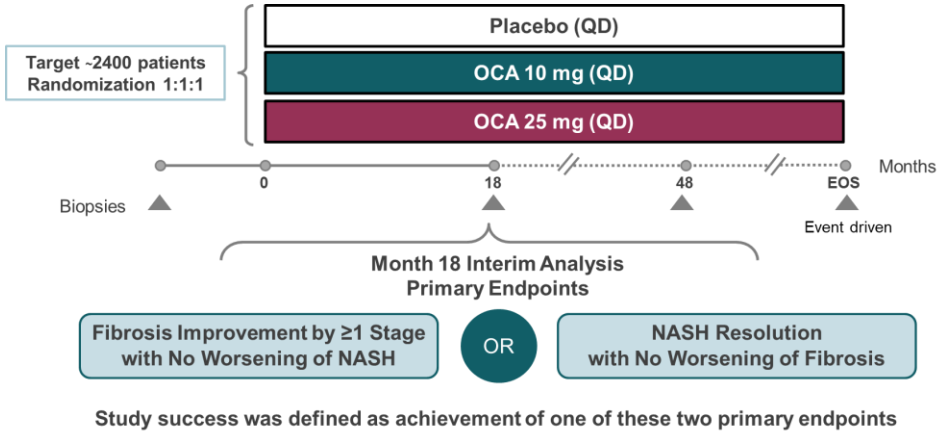
BILE ACID HOMEOSTASIS

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

Calkin & Tontonoz Nat Rev Mol Cell Biol 2013

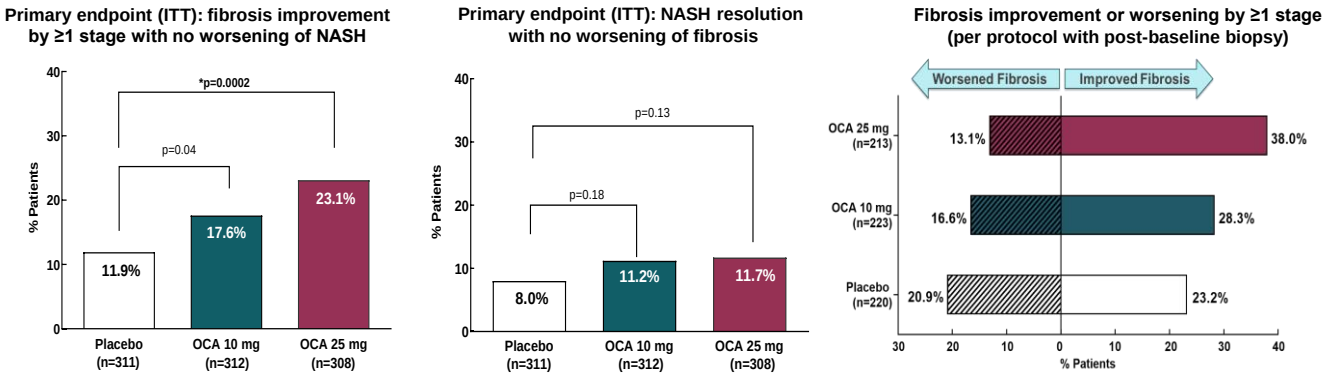
REGENERATE: a Phase 3 trial of obeticholic acid (OCA) for NASH

- 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



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

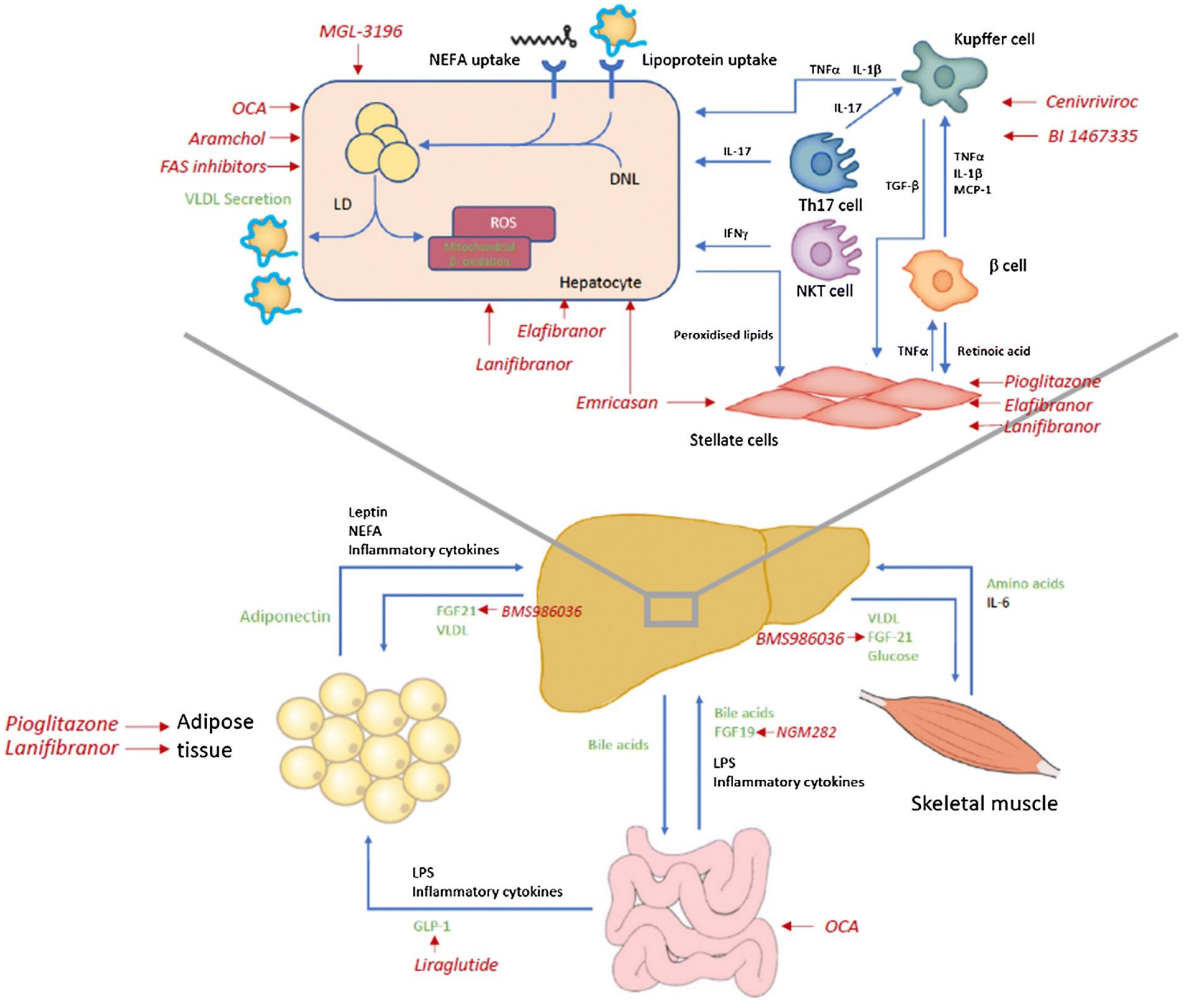
REGENERATE: a Phase 3 trial of obeticholic acid (OCA) for NASH

- 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



Francque & Vonghia, Adv Ther 2019