NAFLD/NASH

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Disclosures

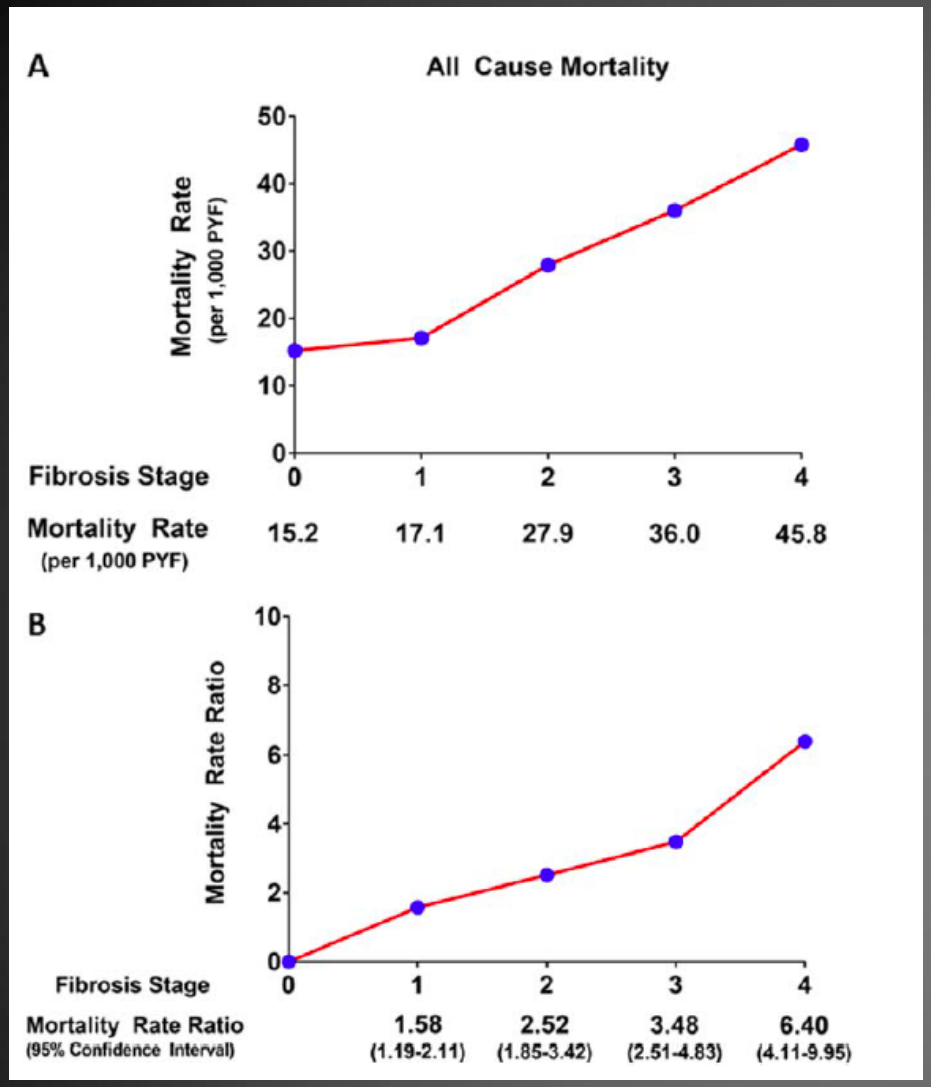
consultancy and/or speaker for Gilead, MSD, BMS, Roche, Bayer, Aktelion, Janssen, Intercept, Genfit, Inventiva, GSK, Boehringer Ingelheim, Galmed, Genentech, Galapagos, Aligos.

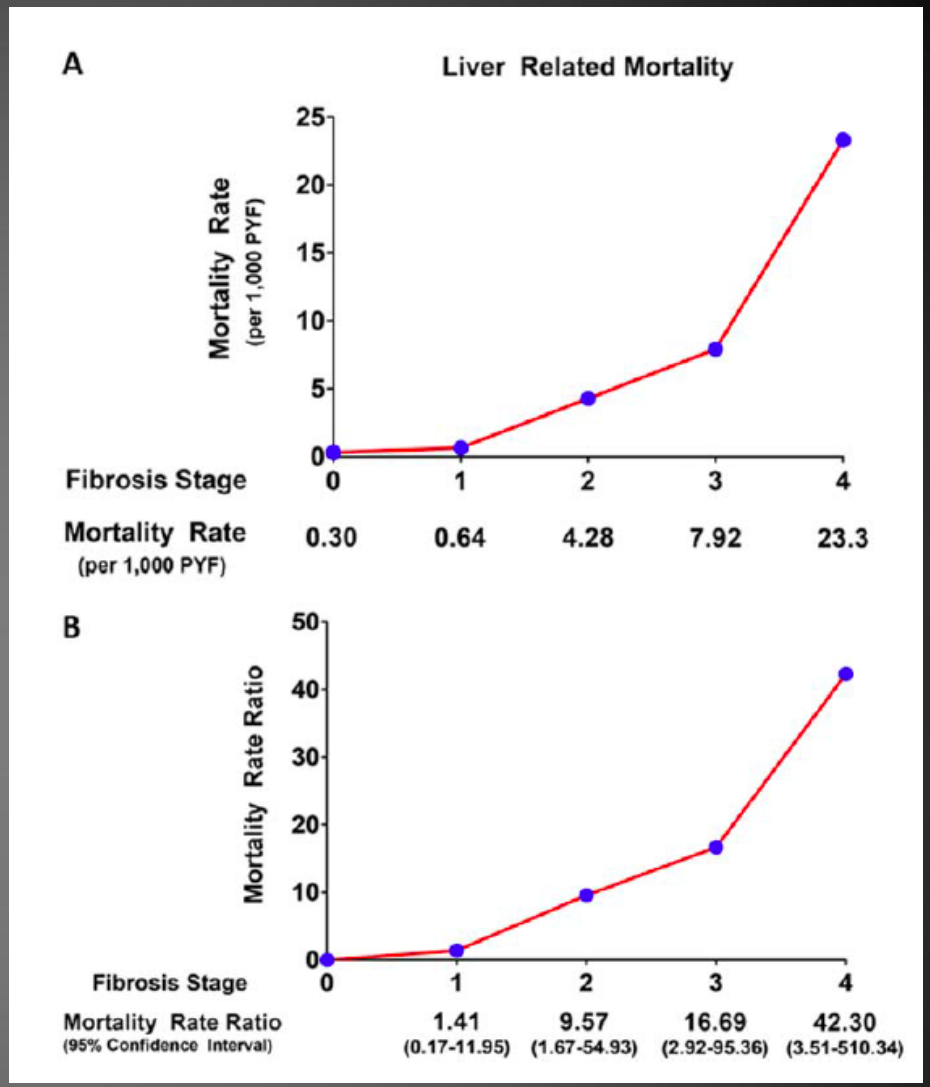
Screening?

- You must be able to identify patient at risk in an early phase of the disease of which the natural history is known
- You must have an acceptable tool to make the accurate diagnosis
- You must have a treatment to offer
- Successful treatment should offer a benefit
- All this should be cost-effective.

1968 Wilson and Jungner criteria
2008 WHO revision and extension.

Who to screen and what to screen for?





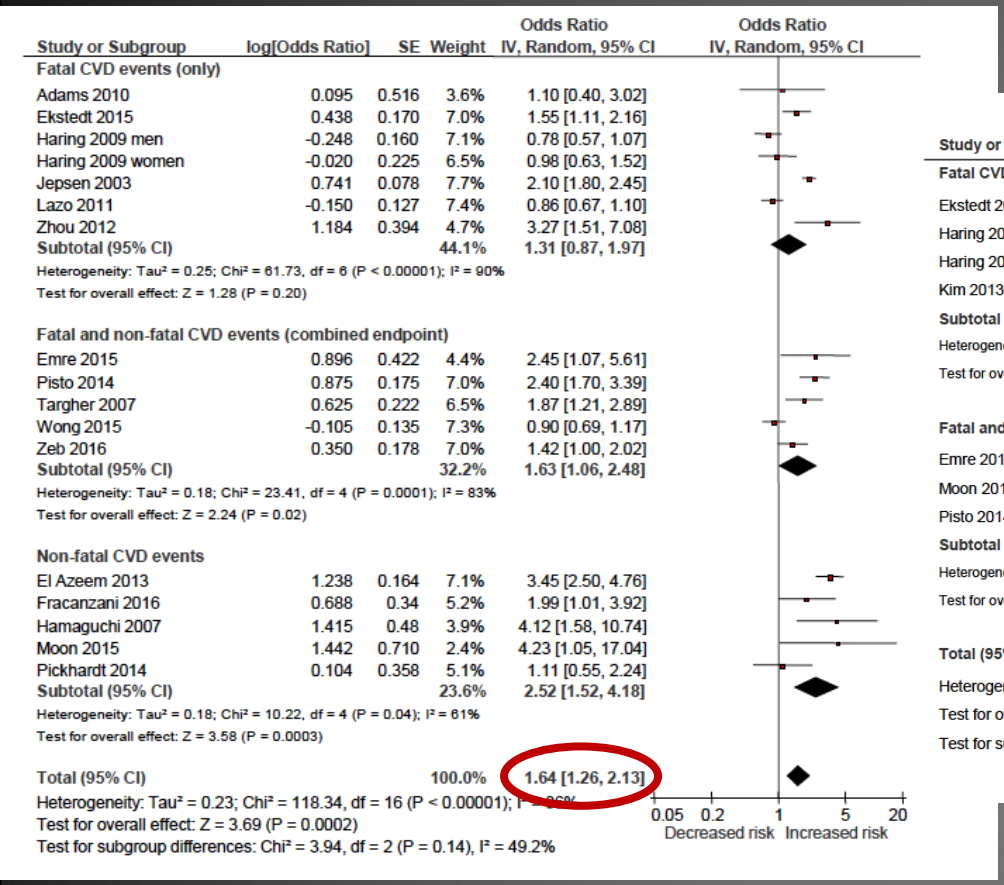
Dulai *et al*. Hepatology 2017

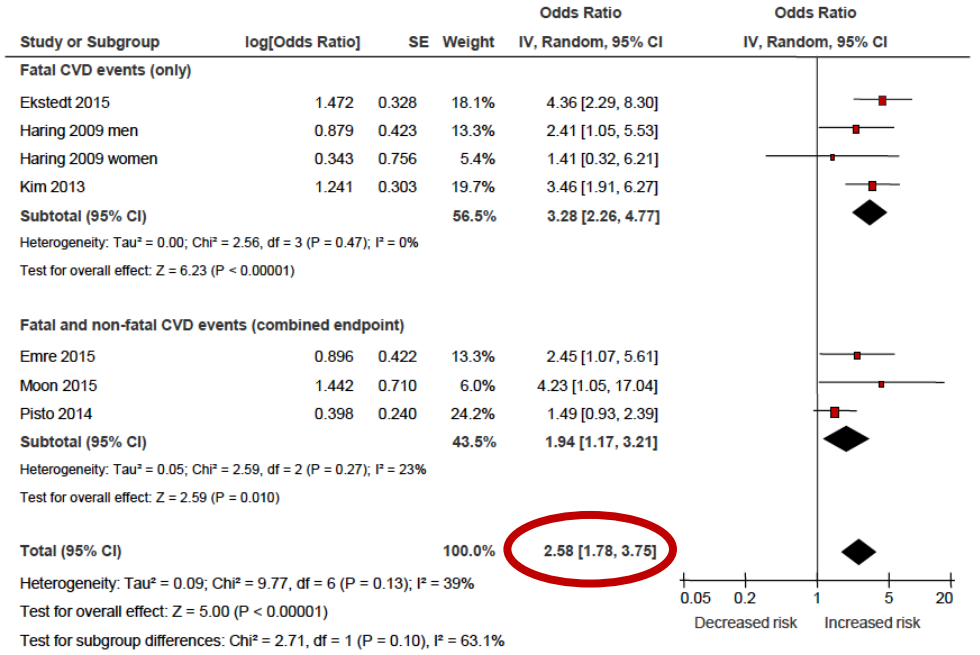
Table 3. Overall FPR by Baseline Fibrosis Stage in Patients With NAFLD, NAFL Alone, and NASH Alone

		Final fibrosis stage					Total stages of fibrosis progressed	Person-years of follow-up evaluation	FPR (95% CI)	Time taken to progress by 1 stage (95% CI)
NAFLD (11 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (131)	79	28	13	7	4	+91	968	0.13 (0.07–0.18)	7.7 (5.5–14.8)
	1 (119)	26	44	32	15	2	+43	628.4	0.10 (0.04–0.16)	10.0 (6.2–25.0)
	2 (61)	9	17	14	13	8	−6	331.8	NA	-
	3 (34)	2	5	10	7	10	−16	153.4	NA	-
	4 (21)	0	0	1	6	14	−8	63.8	NA	-
	Overall (366)						+104	2145.4	NA	-
	Stage 0 plus stage 1 fibrosis (250)						+134	1596.4	0.12 (0.07–0.16)	8.3 (6.2–14.3)
NAFL (6 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (81)	52	16	8	4	1	+48	751.3	0.07 (0.02–0.11)	14.3 (9.1–50.0)
	1 (39)	6	13	14	6	0	+20	112.6	0.15 (-0.09 to 40)	NA
	2 (13)	2	3	5	2	1	−3	40.7	NA	-
	3 (0)	0	0	0	0	0	0	0	NA	-
	4 (0)	0	0	0	0	0	0	0	NA	-
	Overall (133)						+75	904.6	NA	-
	Stage 0 plus stage 1 fibrosis (120)						+68	863.9	0.09 (0.04–0.14)	11.1 (7.1–25.0)
NASH (7 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (21)	10	7	2	1	1	+18	115.5	0.14 (0.07–0.21)	7.1 (4.8–14.3)
	1 (49)	9	25	9	5	1	+13	396.6	0.08 (-0.01 to 0.17)	NA
	2 (25)	3	10	4	4	4	−4	222.3	NA	
	3 (16)	0	4	4	2	6	−6	95.8	NA	
	4 (5)	0	0	0	1	4	−1	12.6	NA	
	Overall (116)						+20	842.8	NA	
	Stage 0 plus stage 1 fibrosis (70)						+31	512.1	0.10 (0.03–0.17)	10.0 (5.9–33.3)

NOTE. If the lower limit of the 95% CI for FPR was negative (ie, the lower limit suggested there could be net regression of fibrosis stage), then the time taken to progress to fibrosis by 1 stage was not calculated.

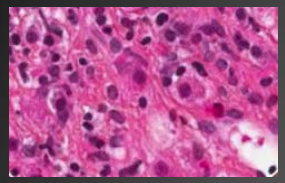
Singh *et al*. Clin Gastroenterol Hepatol 2015





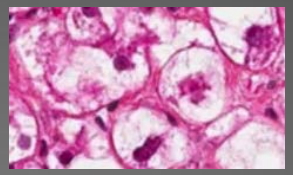
Targher *et al*. J Hep 2016

NASH is a driver of fibrogenesis



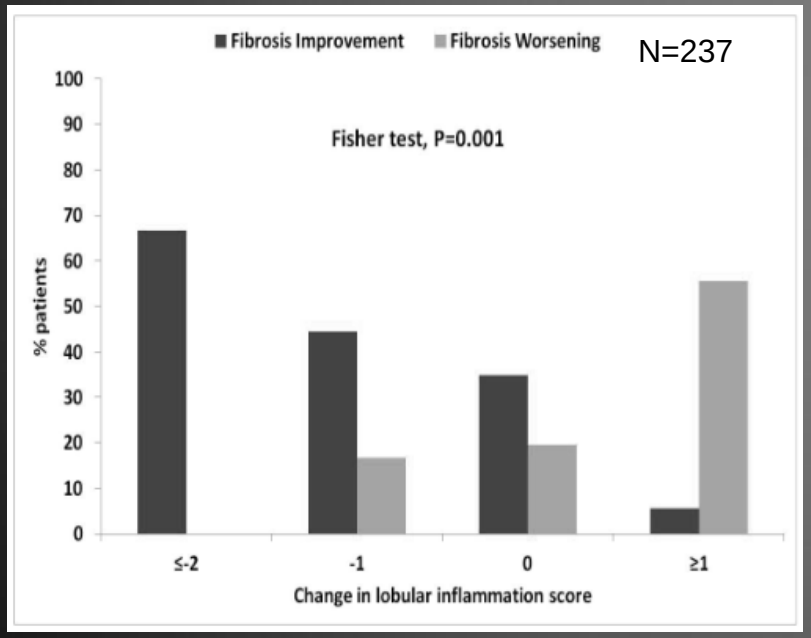
Inflammation

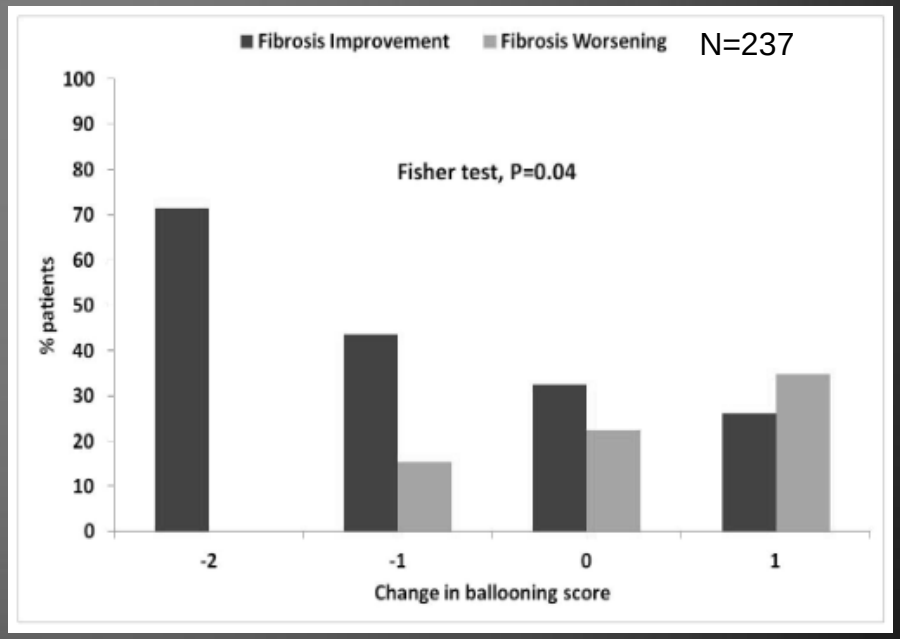
Change in lobular inflammation score and fibrosis evolution



Ballooning

Change in hepatocyte ballooning score and fibrosis evolution





Ratziu V, Francque S, Harrison SH, Anstee QM, Bedossa P, Hum DW, et al.Improvement in NASH histological activity highly correlates with fibrosisregression. Hepatology 2016;64:LB21, Suppl 1.

- Fibrosis is most important predictor of prognosis
  - Reflects longstanding disease activity vs. defective repair
- NASH is the driver of disease progression and adverse outcomes
- Patients to treat?

Treatment indication

NASH

±

Some degree of activity?

(NAS ≥ 4?, A3?)

+

Some degree of fibrosis

F ≥ 2

or

F1 + risk factors (NAS ≥ 5, DM2, obesity,…)

In patients who have otherwise been optimised cardiometabolically

Sanyal *et al*. Hepatology 2015
EASL-EASD-EASO practice guideline. J Hep 2016
Chalasani *et al*. AASLD Practice guidance. Hepatology 2017
Francque *et al*. Acta Gastroenterol Belg 2018

EASL | JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

- All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screene
  main reason for u
  (**A1**)
- In subjects with ob
  by liver enzymes a
  routine work-up. In
  years, T2DM, Met
  (i.e. NASH with fib

- In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (**A1**) and if available by the standardized 75 g OGTT in high-risk groups (**B1**)
- In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (**A2**)

The Belgian Association for Study of the Liver Guidance Document on the Management of Adult and Paediatric Non-Alcoholic Fatty Liver Disease

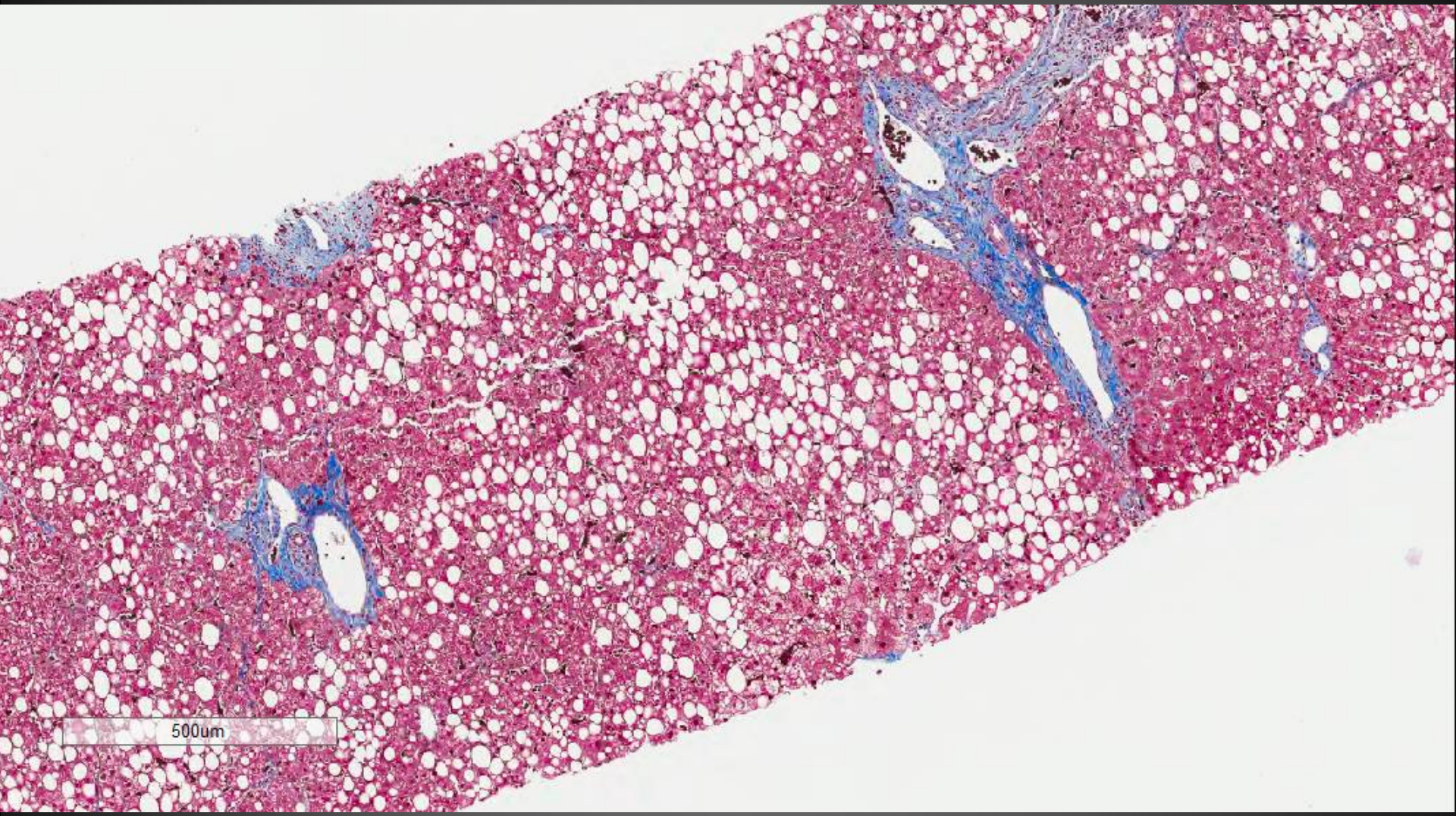
S. Francque[1,2], N. Lanthier[3], L. Verbeke[4], H. Reynaert[5], C. van Steenkiste[6,7], L. Vonghia[1,2], W. J. Kwanten[1,2], J. Weyler[1,2], E. Trépo[8], D. Cassiman[5], F. Smets[9], M. Komuta[10], A. Driessen[11], E. Dirinck[2,12], E. Danse[13], B. Op de Beeck[14], E. van Creanenbroeck[15], Y. Van Nieuwenhove[16], G. Hubens[17], A. Geerts[4*], C. Moreno[8*]

Guidance statement : The following populations are at high risk for NAFLD and should be screened by their general practitioner or the specialists involved: presence of the metabolic syndrome or its components, patients with obesity (BMI ≥ 30 kg/m²), patients with DM2 or patients with a history of ischemic CVD.

Francque *et al*. Acta Gastroenterol Belg 2018

Take home messages 1

- Case finding recommended in populations at risk
- Identifying active NASH with some degree of fibrosis



Courtesy P. Bedosssa

How to select patients that qualify for a liver biopsy?

How to increase pre-test probability of the biopsy to diagnose significant lesions?

ALT cut-off values

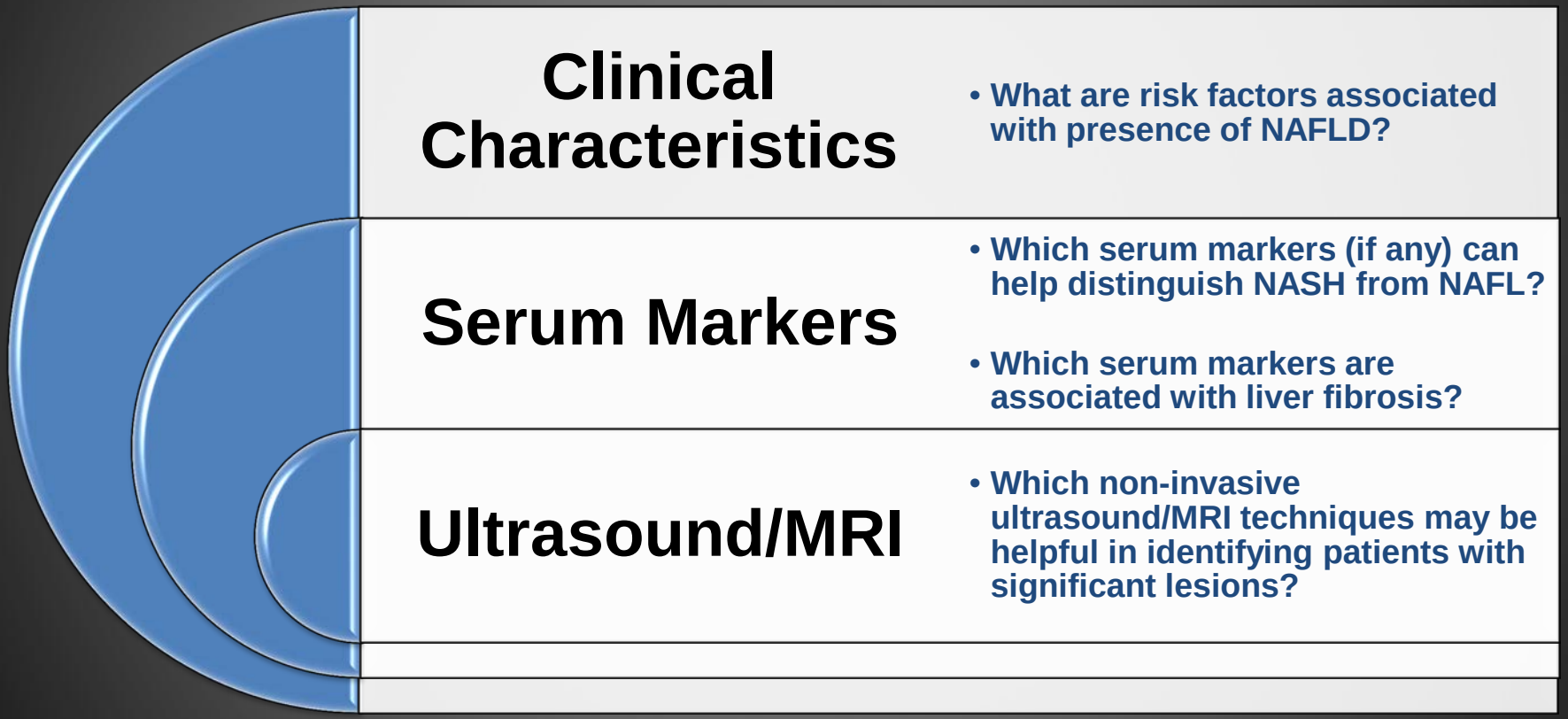
- Male:
  - ALT 29-33 U/L
- Female
  - ALT 19-25 U/L

ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

Am J Gastroenterology 2016

How to enrich for patients with high likelihood of having significant lesions?



Clinical Risk Factors Associated with Fatty Liver Disease

- Presence of multiple features of the metabolic syndrome
  - Abdominal obesity: a waist circumference ≥102 cm (40 in) in men and ≥ 88 cm (35 inches) in women.
    For Asian Americans, the cutoff values are ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.
  - Serum triglycerides ≥ 150 mg/dl
  - HDL cholesterol ≤40mg/dl in men and ≤50mg/dl in women
  - Blood pressure of ≥ 130/85
  - Fasting blood glucose of ≥ 100 mg/dl
- Presence of type 2 diabetes mellitus (T2DM)
- Persistently elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
- Increasing age
- Increasing BMI

Non-invasive assessments of clinically significant fatty liver disease such as NASH and liver fibrosis

- Serum Markers
  - APRI, FIB-4, AST/ALT ratio
  - Enhanced liver fibrosis score (ELF)
  - NAFLD fibrosis score (NFS)
  - FibroTest® (FibroSure®)
  - CK-18
  - HepaScore®
- Liver ultrasound elastography and imaging methods
  - Ultrasound Transient Elastography (TE) / Controlled Attenuation Parameter (CAP®)
  - Magnetic Resonance (MR) Elastography (MRE)
  - Acoustic radiation ARFI
  - MR spectroscopy for Proton Density Fat Fraction (PDFF)

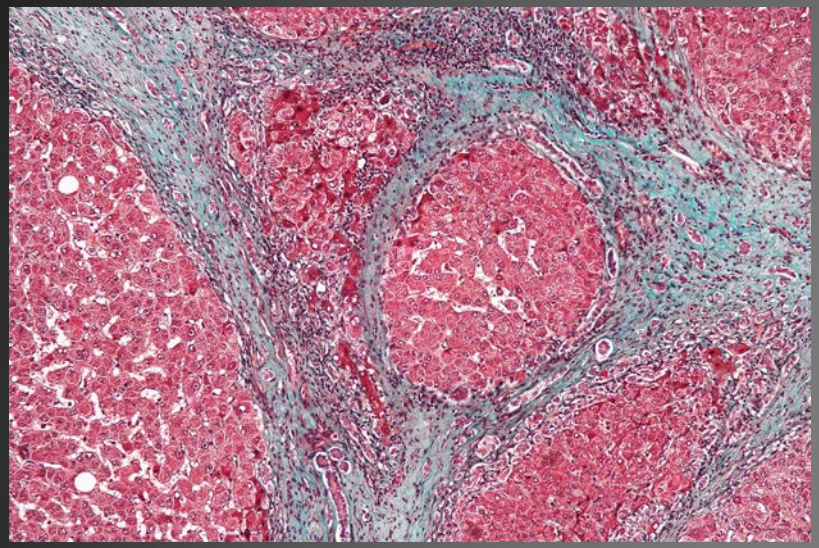
Non-invasive scoring systems

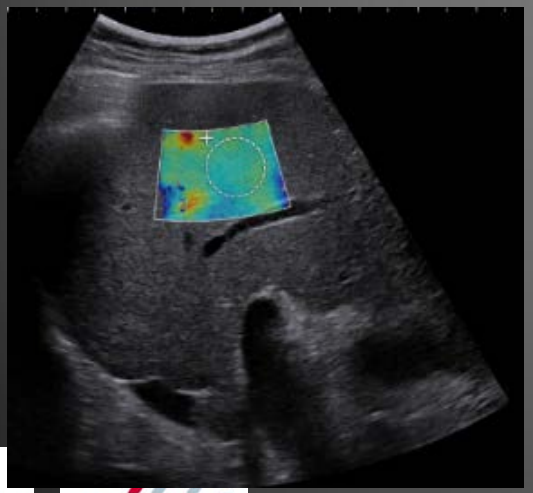
- Fatty Liver Index
  - BMI, age, AST,ALT
- NAFLD Fibrosis Score
  - Age, BMI, IFG/2DM, AST/ALT, platelets, albumin
- Fib-4
  - Age, AST, platelet count, ALT

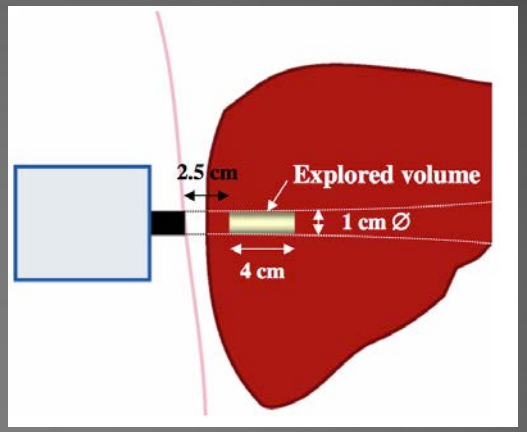
- Low PPV but **high NPV**

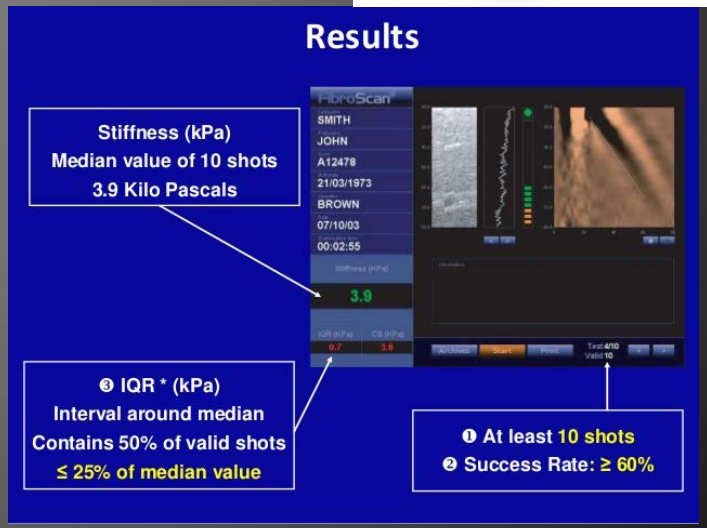
Bedogni G. *et al*, BMC Gastroneterol 2006
Angulo P. *et al*, Gastronetrology 2007
McPherson S. *et al*, Gastroenterology 2010

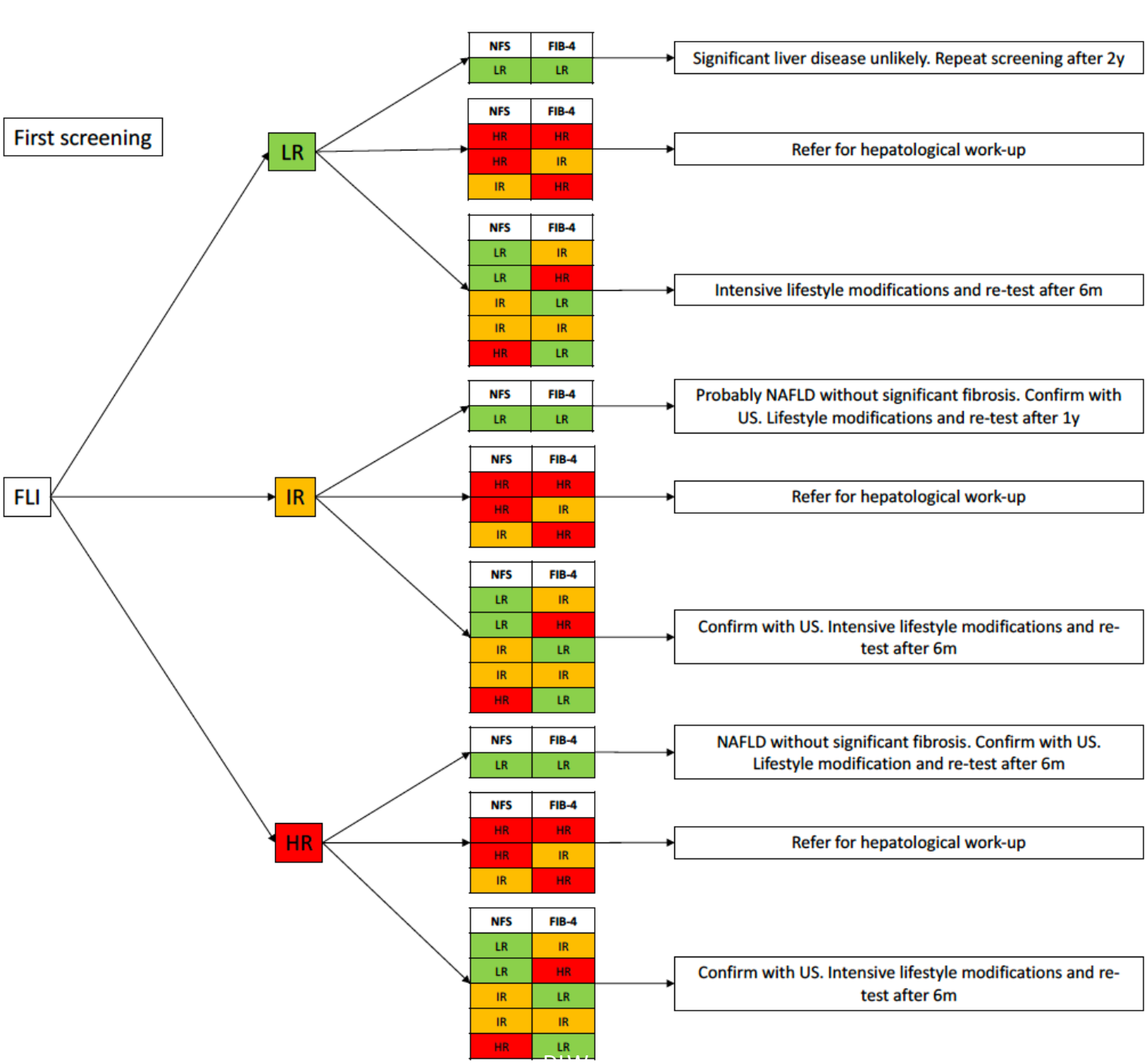
Liver stiffness measurement

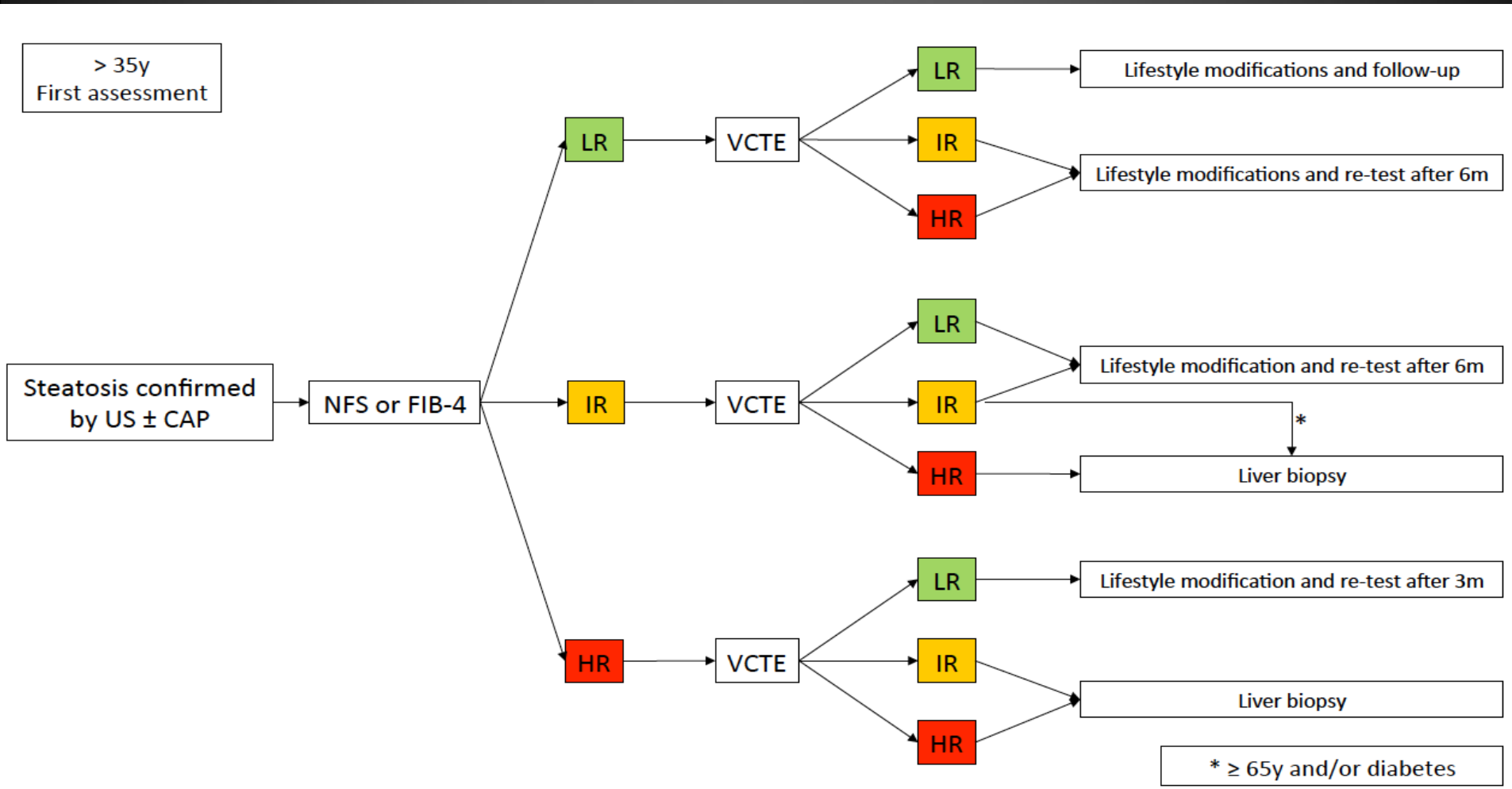




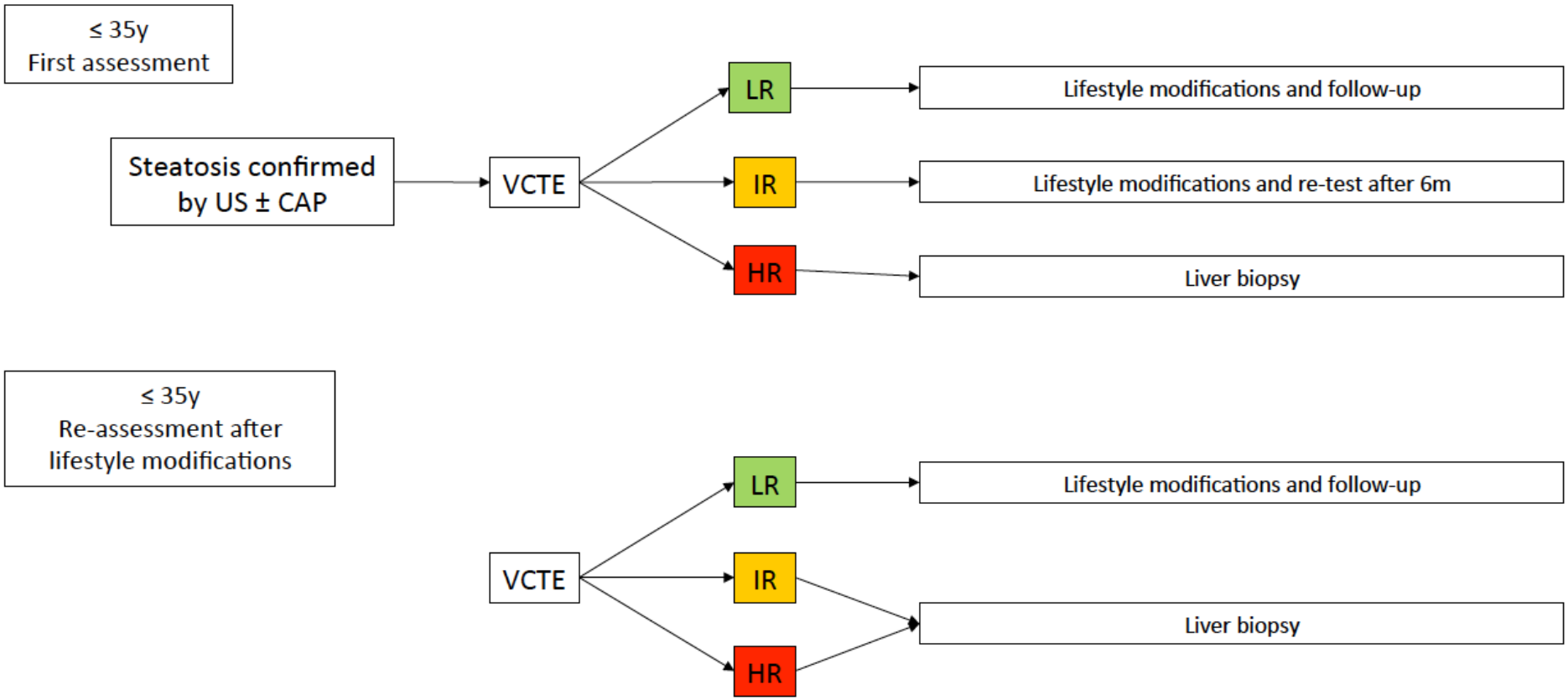





First screening
FLI
LR
IR
HR
NFS
FIB-4
LR
LR
Significant liver disease unlikely. Repeat screening after 2y
HR
HR
IR
HR
Refer for hepatological work-up
LR
IR
LR
HR
IR
LR
IR
IR
HR
LR
Intensive lifestyle modifications and re-test after 6m
Probably NAFLD without significant fibrosis. Confirm with US. Lifestyle modifications and re-test after 1y
Refer for hepatological work-up
Confirm with US. Intensive lifestyle modifications and re-test after 6m
NAFLD without significant fibrosis. Confirm with US. Lifestyle modification and re-test after 6m
Refer for hepatological work-up
Confirm with US. Intensive lifestyle modifications and re-test after 6m



Cut-off values		
Age ≤ 35 y:	the NFS and FIB-4 are unreliable and an alternative method (*e.g.* elastometry) should be used to screen for fibrosis	
Age 35-65y:	NFS	LR < -1.455 < IR < 0.676 < HR
	FIB-4	LR < 1.30 < IR < 2.67 < HR
Age ≥ 65 y:	NFS	LR < 0.120 < IR < 0.676 < HR
	FIB-4	LR < 2.00 < IR < 2.67 < HR
All ages:	FLI	LR < 30 < IR < 60 < HR



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Age 35-65y:	NFS	LR < -1.455 < IR < 0.676 < HR
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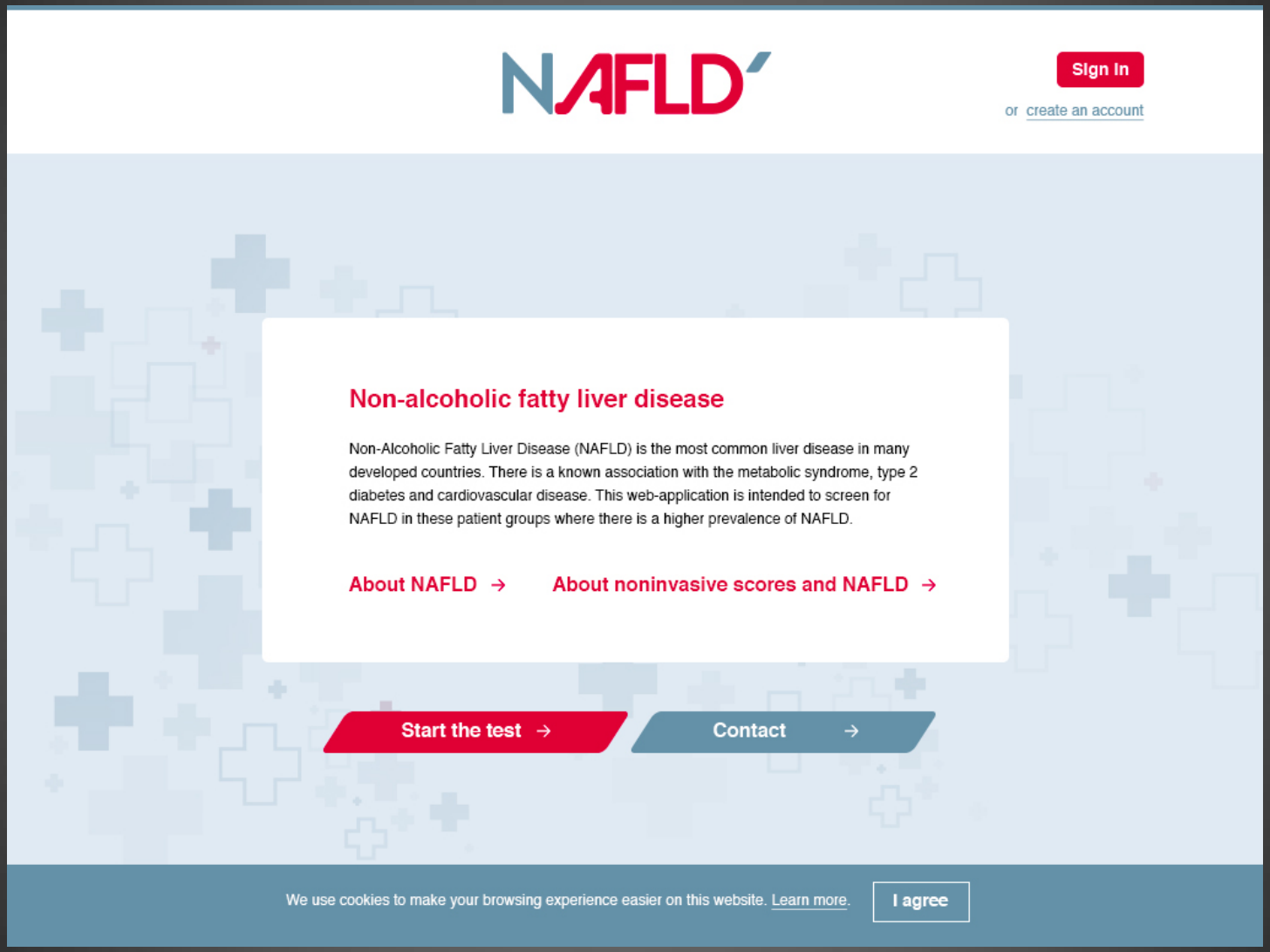
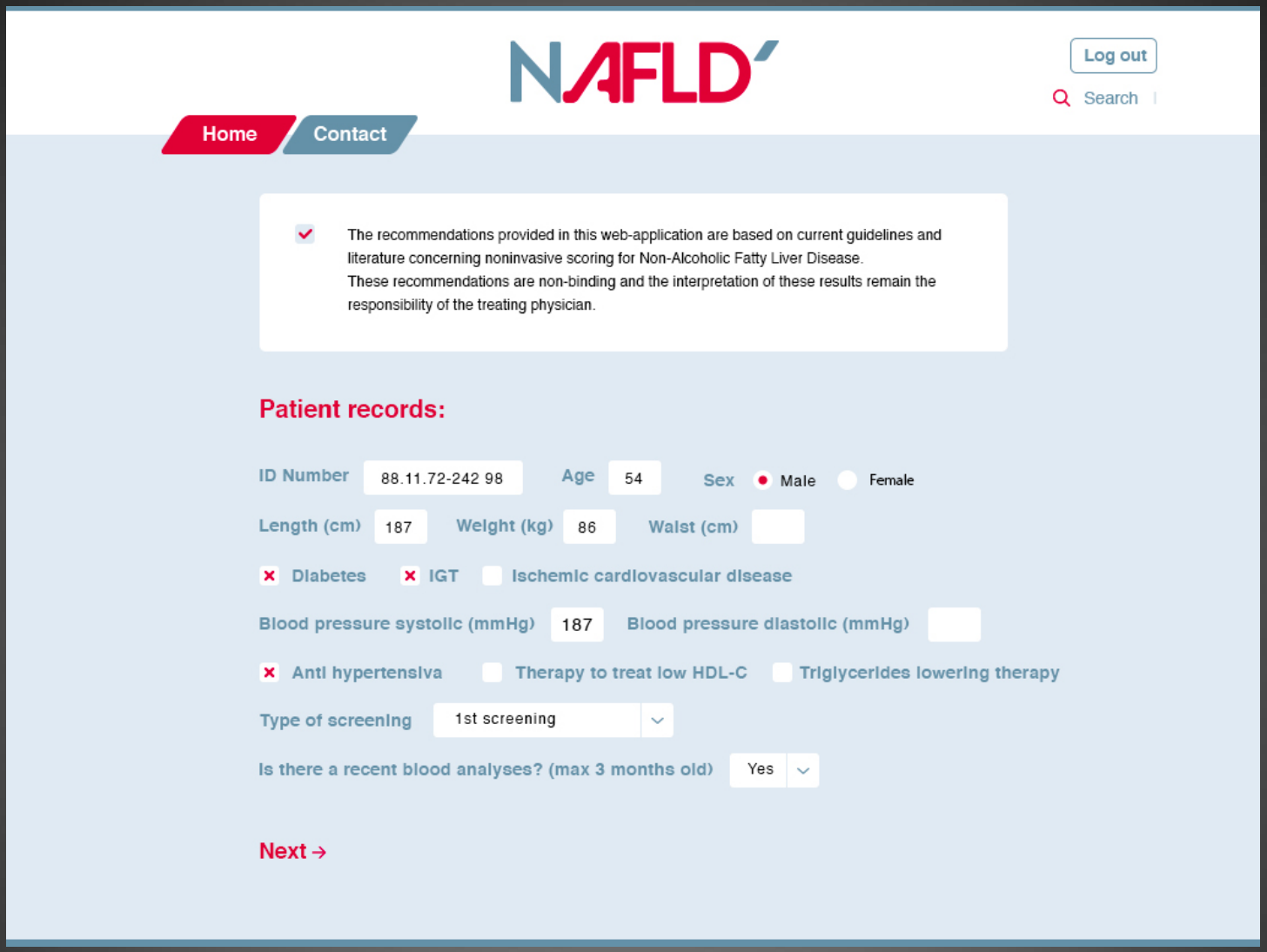
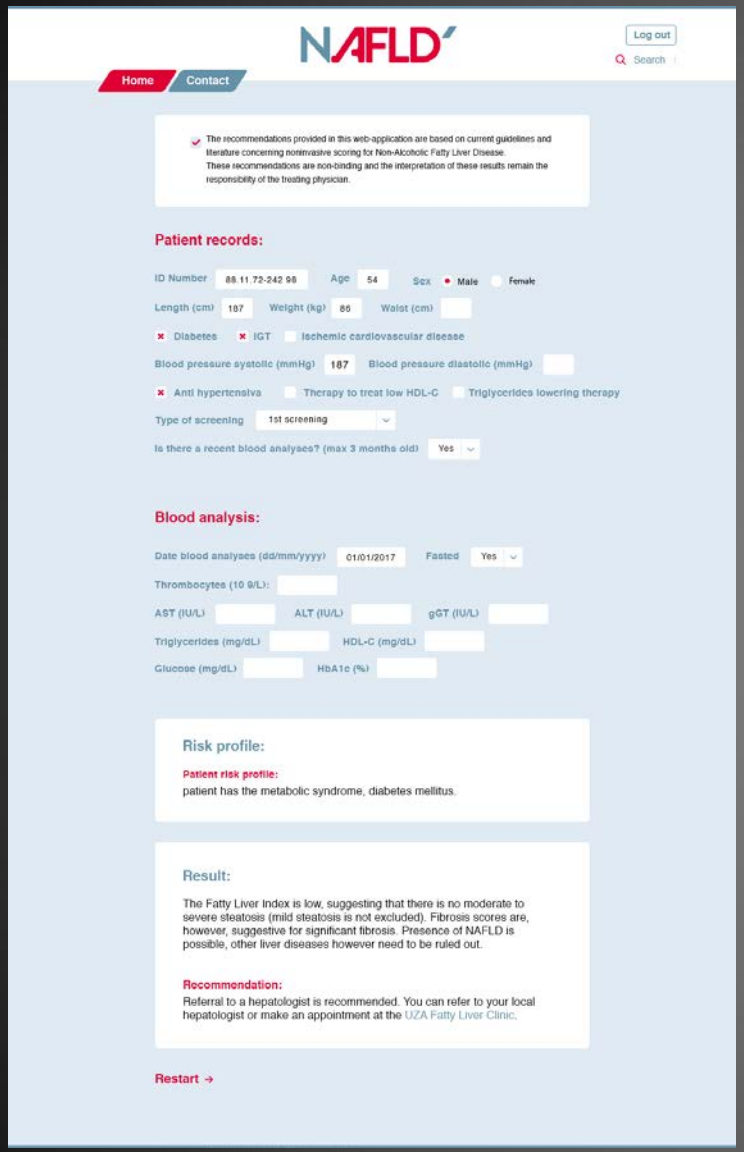
Age ≥ 65 y:	NFS	LR < 0.120 < IR < 0.676 < HR
	FIB-4	LR < 2.00 < IR < 2.67 < HR
Fibroscan® :	M-probe	LR < 7.9 kPa < IR < 9.6 kPa < HR
	XL-probe	LR < 7.2 kPa < IR < 9.3 kPa < HR

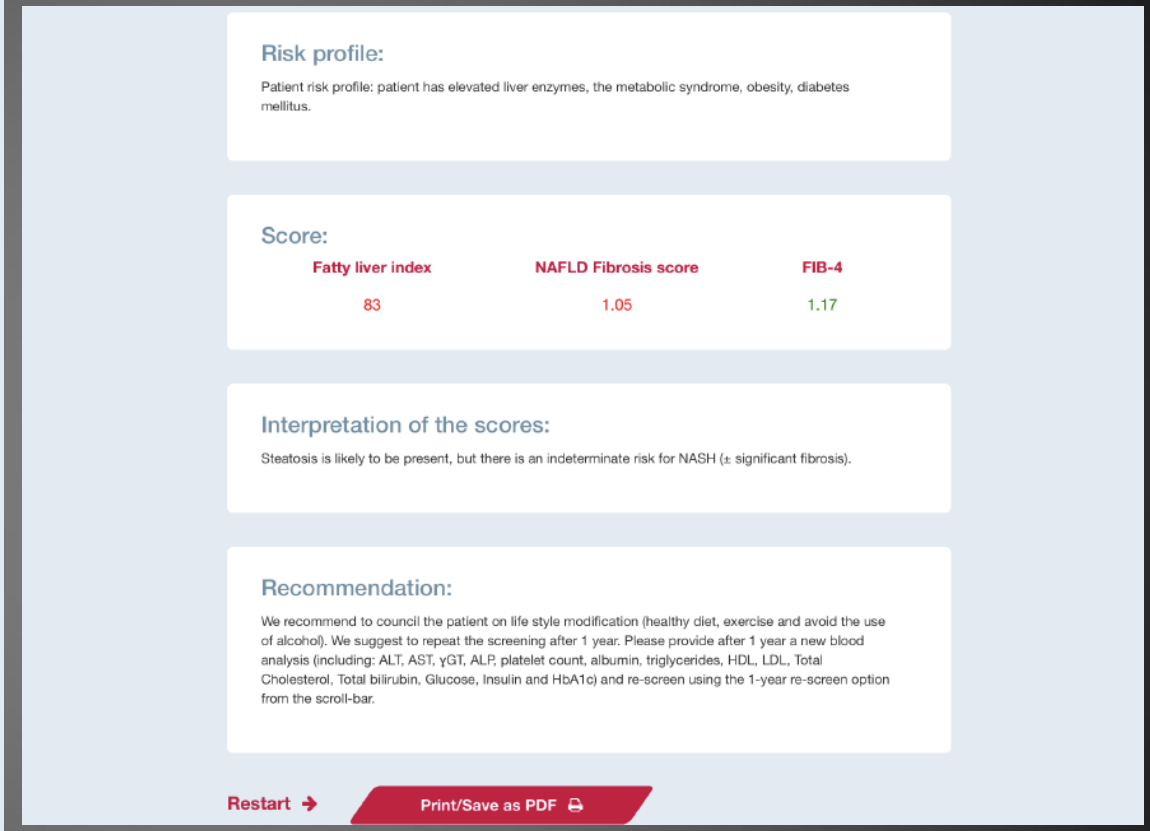
Francque *et al*. Acta Gastroenterol Belg 2018


NAFLD
Sign In
or create an account
Non-alcoholic fatty liver disease
Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common liver disease in many developed countries. There is a known association with the metabolic syndrome, type 2 diabetes and cardiovascular disease. This web-application is intended to screen for NAFLD in these patient groups where there is a higher prevalence of NAFLD.
About NAFLD →
About noninvasive scores and NAFLD →
Start the test →
Contact →
We use cookies to make your browsing experience easier on this website. Learn more.
I agree



www.antwerpnafldguide.com





www.antwerpnafldguide.com

Risk profile:

Patient risk profile: patient has elevated liver enzymes, the metabolic syndrome, obesity, diabetes mellitus.

Score:

Fatty liver index	NAFLD Fibrosis score	FIB-4
99	3.541	8.06

Interpretation of the scores:

There is a high likelihood for the presence of significant NASH (± significant fibrosis).

Recommendation:

Referral to a hepatologist is recommended. Anternatively you can click on the link to make an appointment at the University Hospital of Antwerp (by clicking on the link a work-up will be scheduled and sent to the patient; work-up consists of a blood analysis and an ultrasound with elastography).

Restart → Print/Save as PDF

thebmj Visual summary

Testing for non-alcoholic fatty liver disease

The term "Non-alcoholic fatty liver disease" (NAFLD) encompasses a spectrum of pathologic conditions, ranging from non-alcoholic fatty liver (NAFL) to steatohepatitis (NASH), fibrosis, and cirrhosis. This flow diagram offers a pragmatic approach to the diagnosis and monitoring of NAFLD in asymptomatic adult patients.

Abnormal liver function tests

+

Alcohol consumption within recommended amounts

Recommended amounts are less than 14 units for both men and women, spread over a week, with 2–3 alcohol-free days every week

History and examination

Consider alternative diagnoses such as effects of medication, infection, or nutritional problems.

Red flags: Consider admission or urgent referral

- Suspected malignancy
- Ascites
- Jaundice
- Encephalopathy
- Sepsis
- Evidence of disordered clotting
- Haematemesis
- ALT or ALP very high (5x upper limit of normal)
- Persistently low albumin or platelets
- Rapid deterioration

Drug-induced liver injury

Consider referral to hepatology if patient has a history of drug exposure, such as:

- Valproic acid
- Oestrogens
- Tamoxifen
- Tetracycline
- Amiodarone
- Perhexiline maleate
- Methotrexate
- 4,4'-diethylaminoethoxyhexesterol
- Chloroquine
- L-asparaginase
- Corticosteroids

Non-invasive liver screen (NILS)

- Liver ultrasound
- Blood tests

Undertaking a liver biopsy is a risky, potentially painful procedure. Non-invasive techniques can be used to assess the presence of both hepatic steatosis and fibrosis.

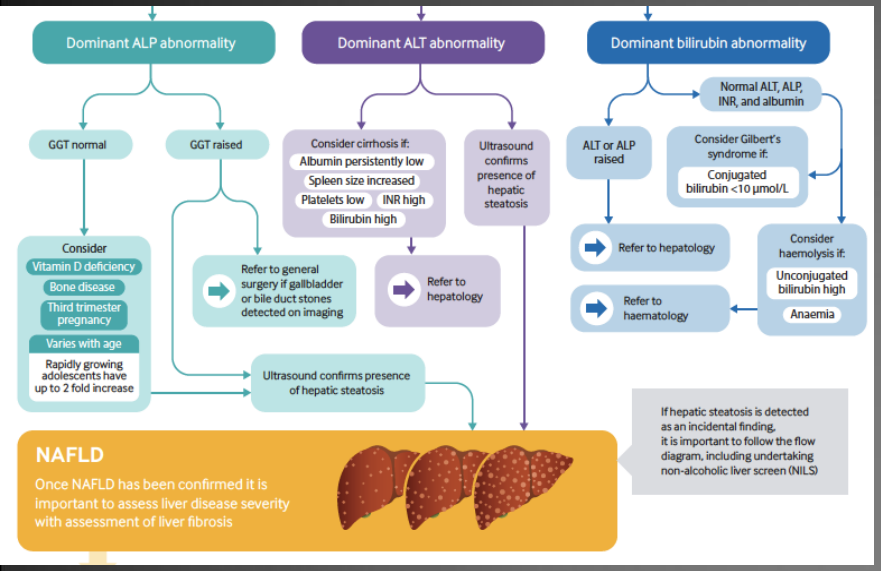
Refer to Hepatology if NILS tests yield positive results for:

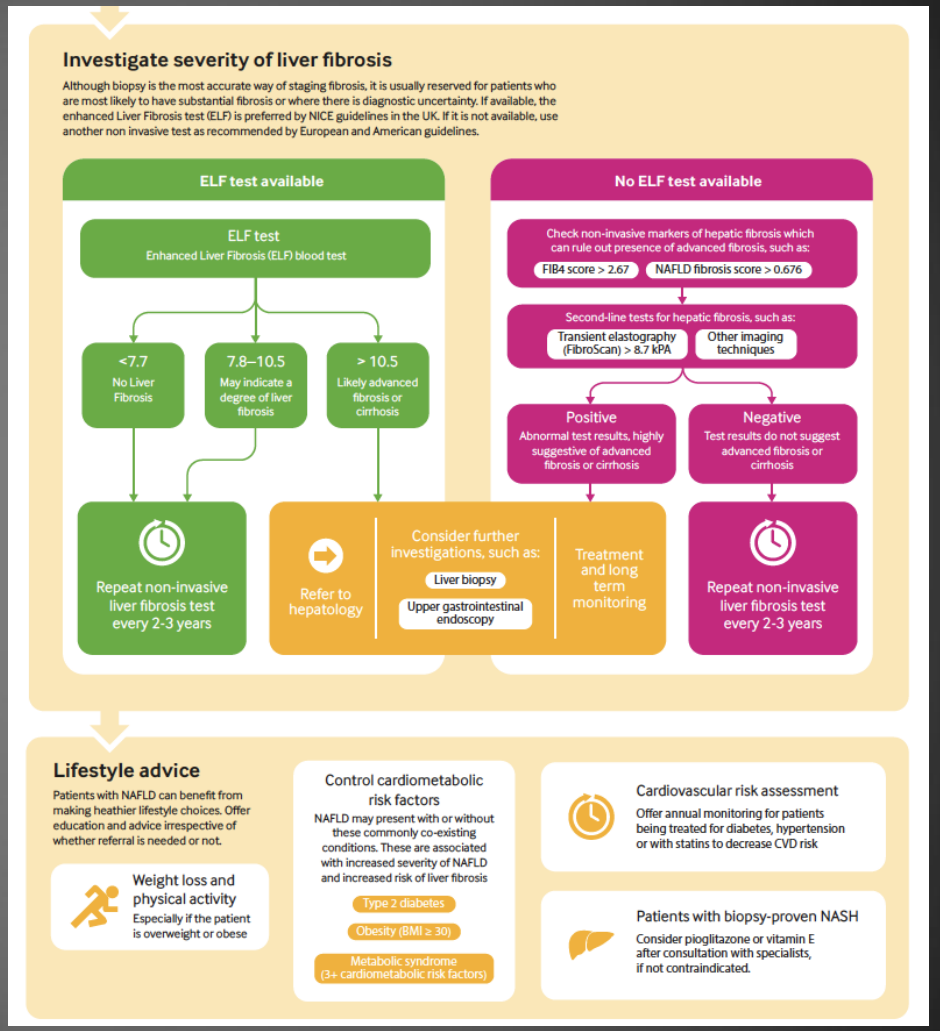
- Immunoglobulins raised
- Hepatitis B or C
- High ferritin and high transferrin saturation
- Autoimmune liver screen (Primary biliary cholangitis)
- Low caeruloplasmin
- Low alpha 1 anti-trypsin protein

Consider non-hepatic causes for raised ALT:

- Thyroid diseases
- Coeliac disease
- Muscle diseases, such as polymyositis, heavy exercise

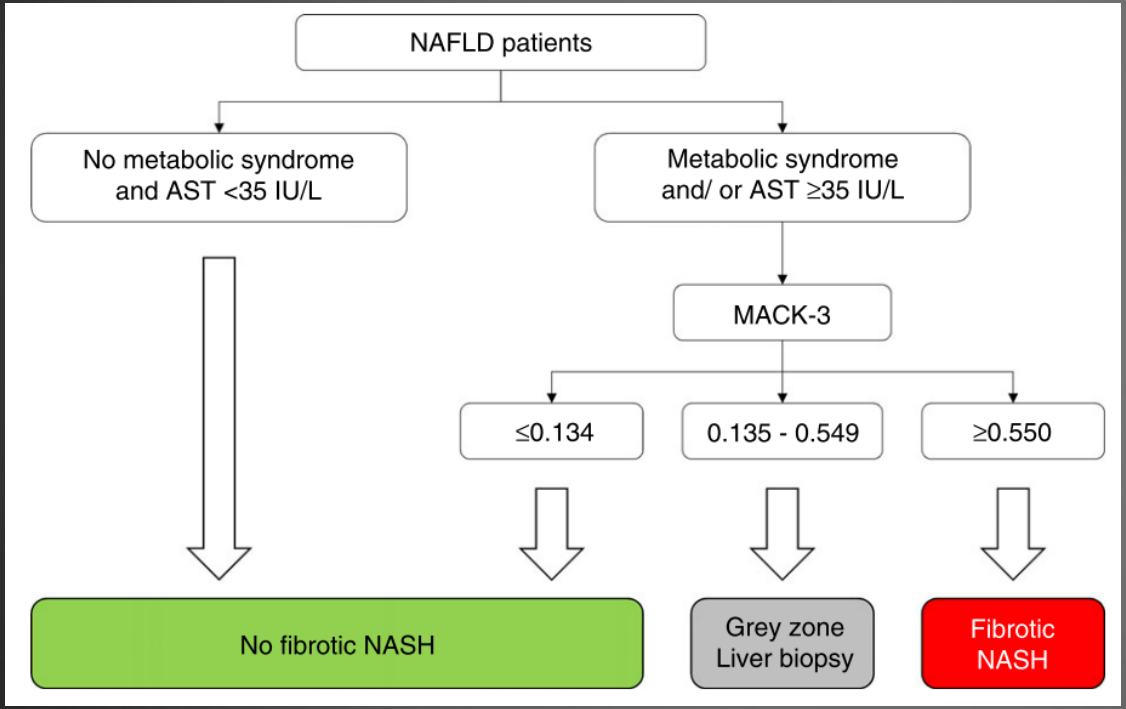
Byrne *et al*. BMJ 2018





Byrne *et al*. BMJ 2018

Non-invasive diagnosis of fibrotic NASH



Diagnosis of fibrotic NASH

- MACK-3

AST + HOMA + CK-18
AUROC = 0.85

- Algorithm

93.2% well classification

Boursier, Francque *et al*. Aliment Pharmacol Ther 2018

ALGORITHM TO IDENTIFY PATIENTS WITH A SAF ACTIVITY SCORE > 2 IN TYPE 2 DIABETIC PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) - DEVELOPMENT IN A LARGE PROSPECTIVE MULTICENTER UK STUDY

P.J. EDDOWES[1], M. ALLISON[2], E. TSOCHATZIS[3], Q.M. ANSTEE[4], D. SHERIDAN[5], I.N. GUHA[6], J.F. COBBOLD[7], V. PARADIS[8], P. BEDOSSA[8], P.N. NEWSOME[1]

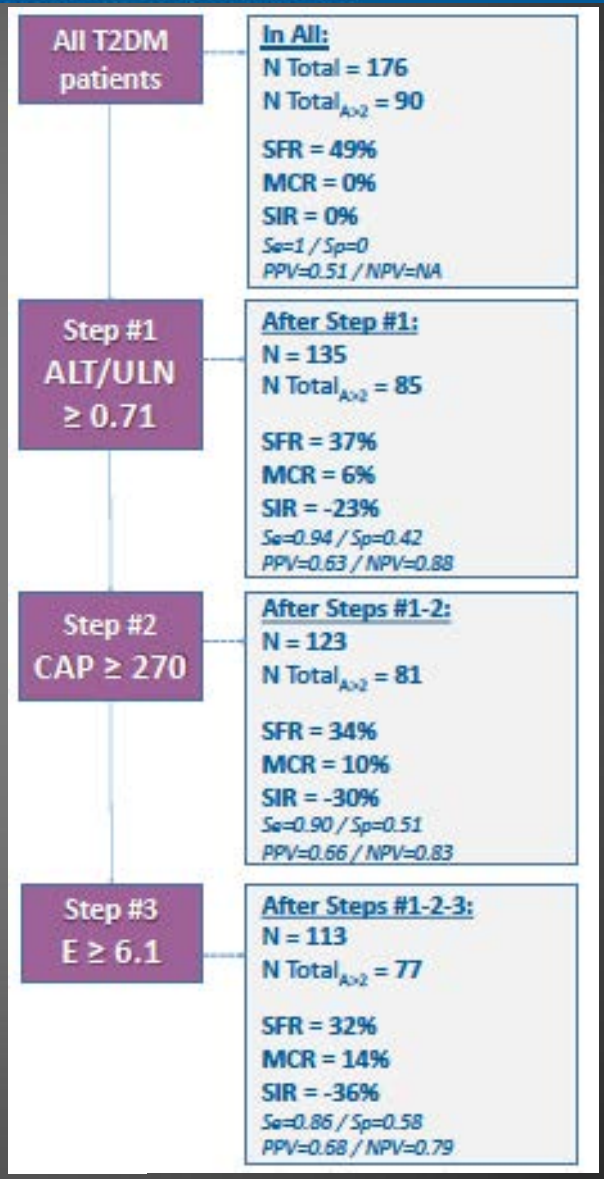
An algorithm was devised with the 3 optimally determined parameters:

- ALT normalized by the upper limits of normal (ULN)

- CAP
- E

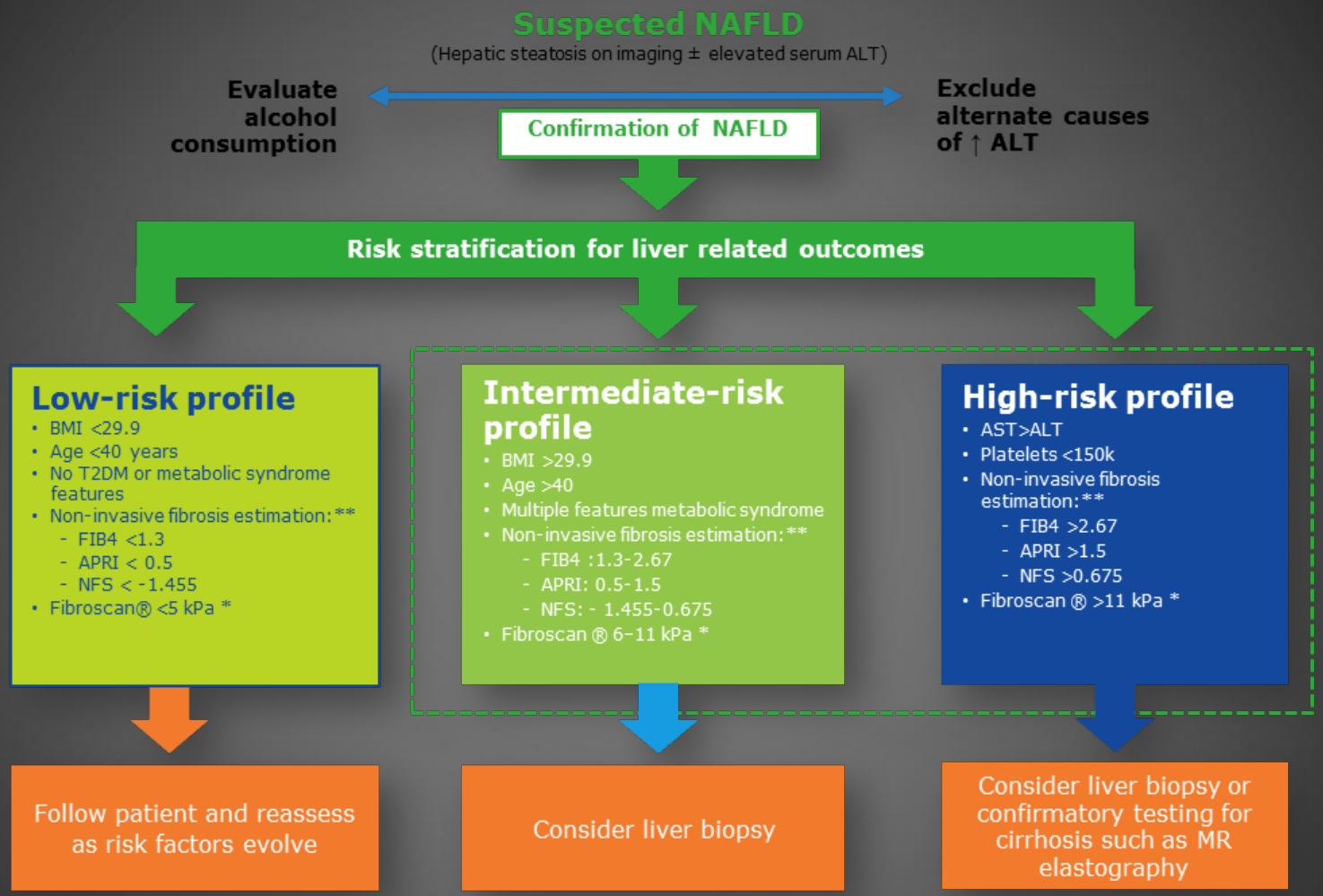
Parameters calculated:

- ***SFR (screen failure rate): 1-PPV***
  [Proportion of "improperly" screened/biopsied patients]
- ***MCR (missed cases rate): 1-Se***
  [Proportion of initial target patient who wouldn't have been "biopsied"]
- ***SIR (screening improvement rate): $[N\text{-}N_{total}] / N_{total} * 100$***
  [Proportion of "saved" LB in comparison if all patient would have underwent LB]



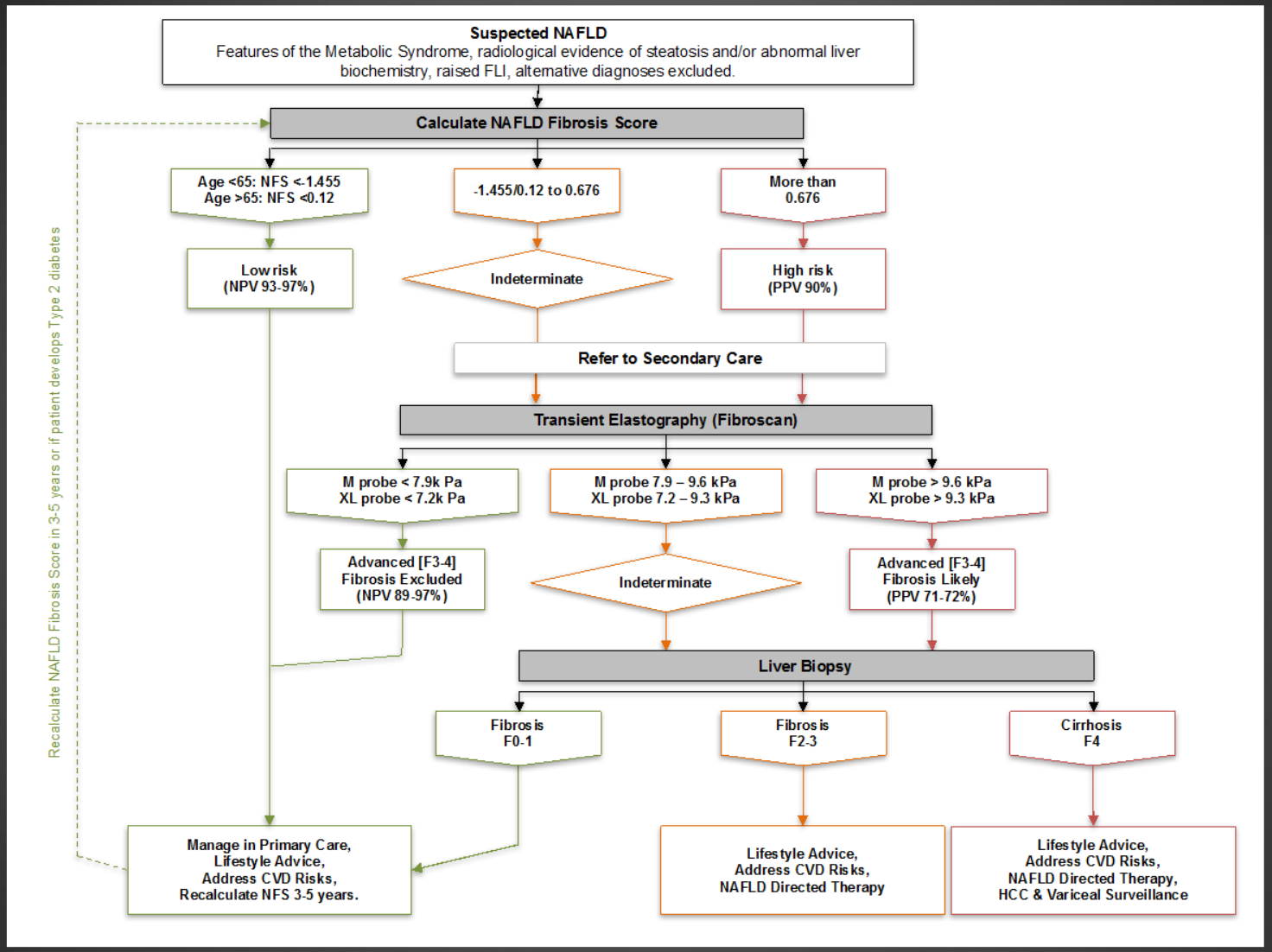
Newsome *et al*. ILC 2018

Risk Assessment Algorithm – Focus on Liver Biopsy



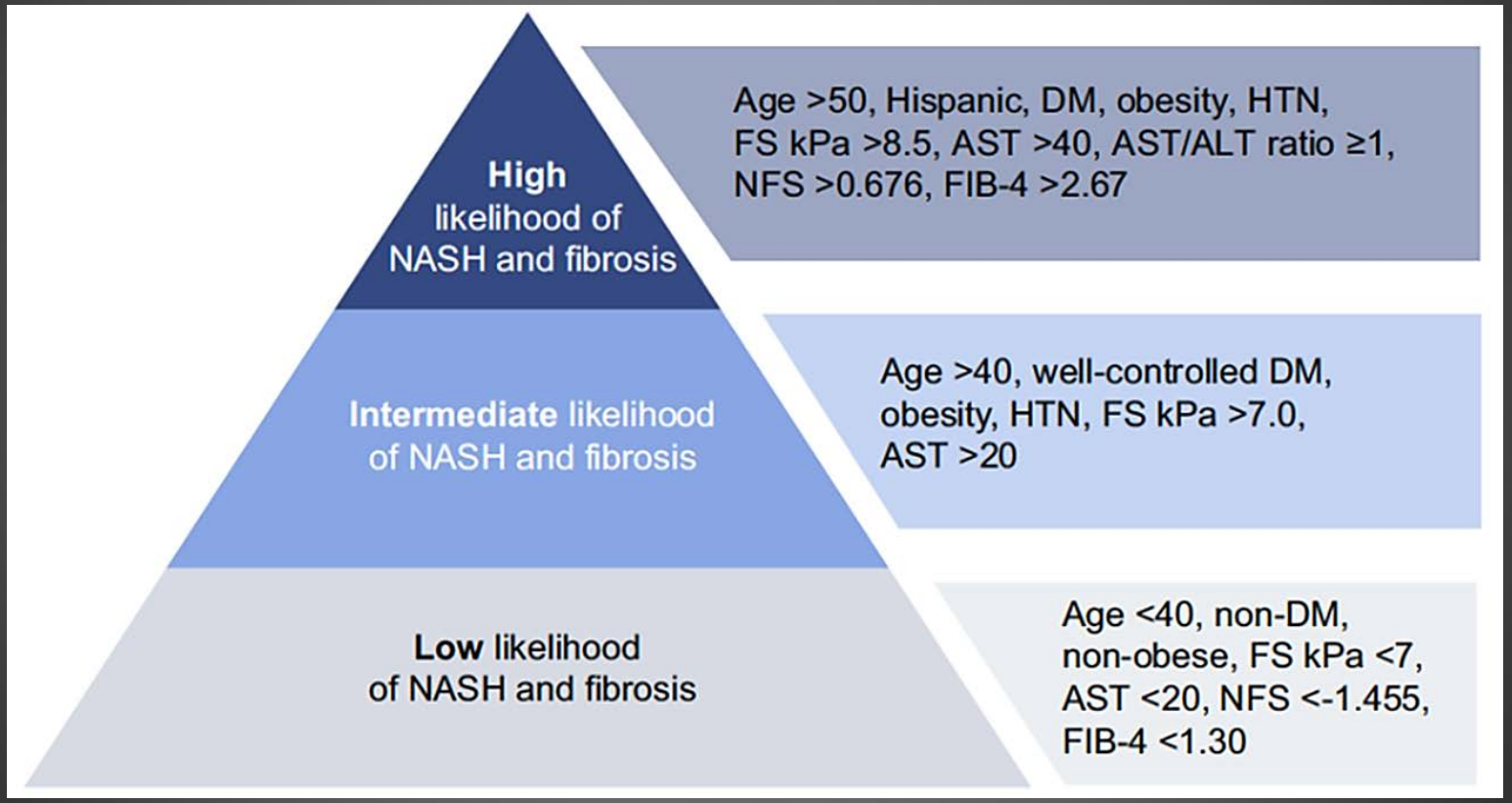
Rinella M and Sanyal A. Nat Rev Gastroenterol Hepatol 2016

Risk Assessment Algorithm – Focus on Liver Biopsy



Courtesy of Q. Anstee

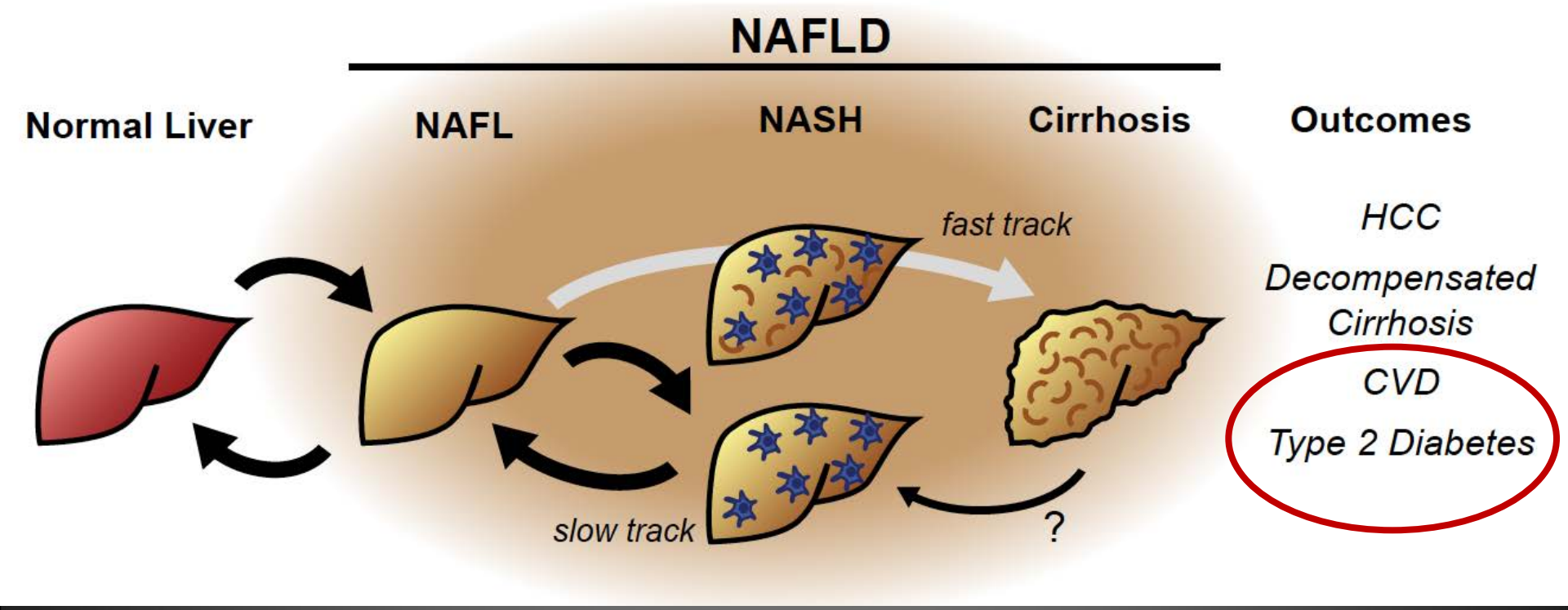
Clinical phenotypes & associated NASH/fibrosis risk



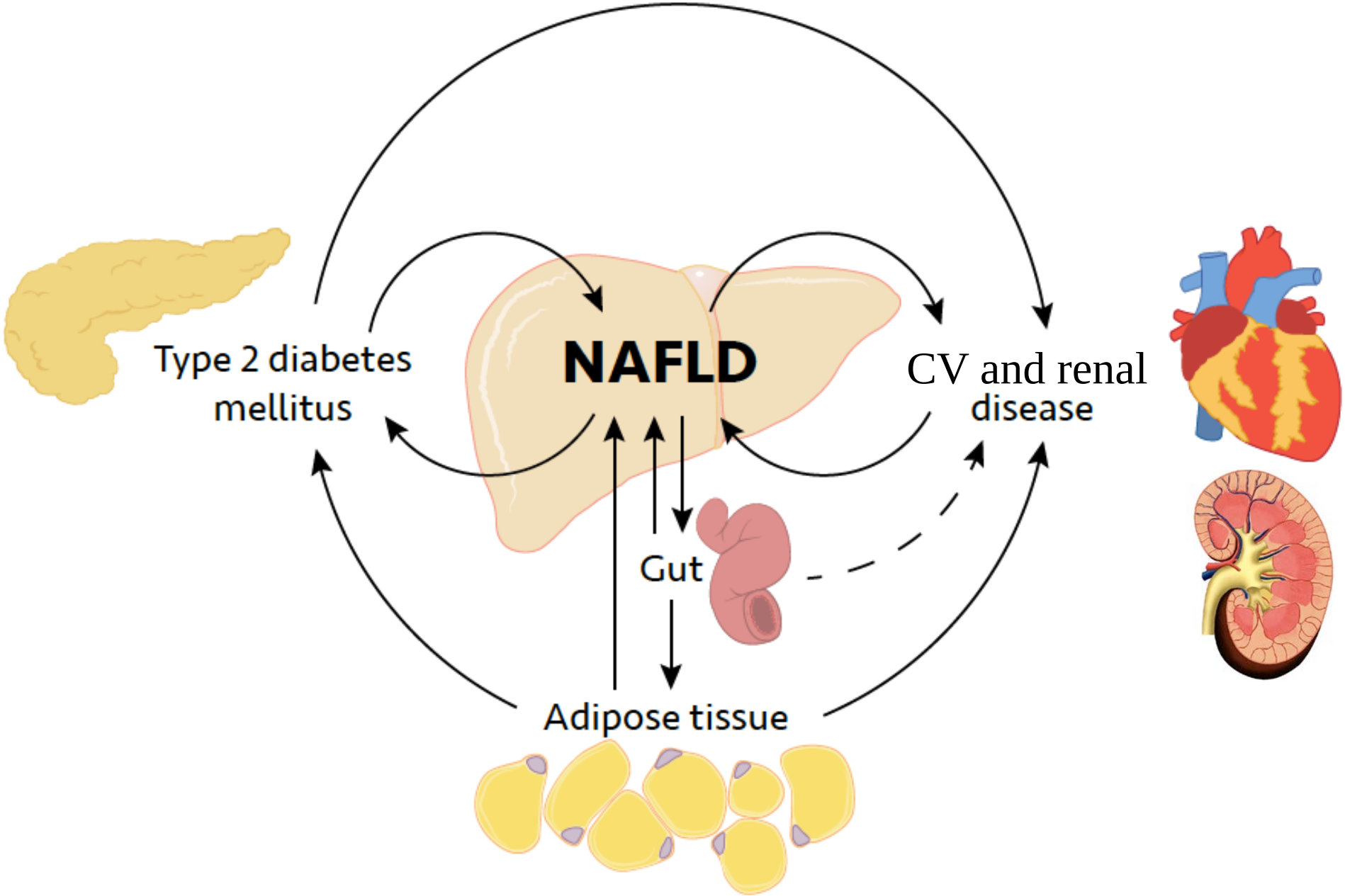
Konerman et al. J Hepatol 2018; 68(2): 362-375.

Take home messages 2

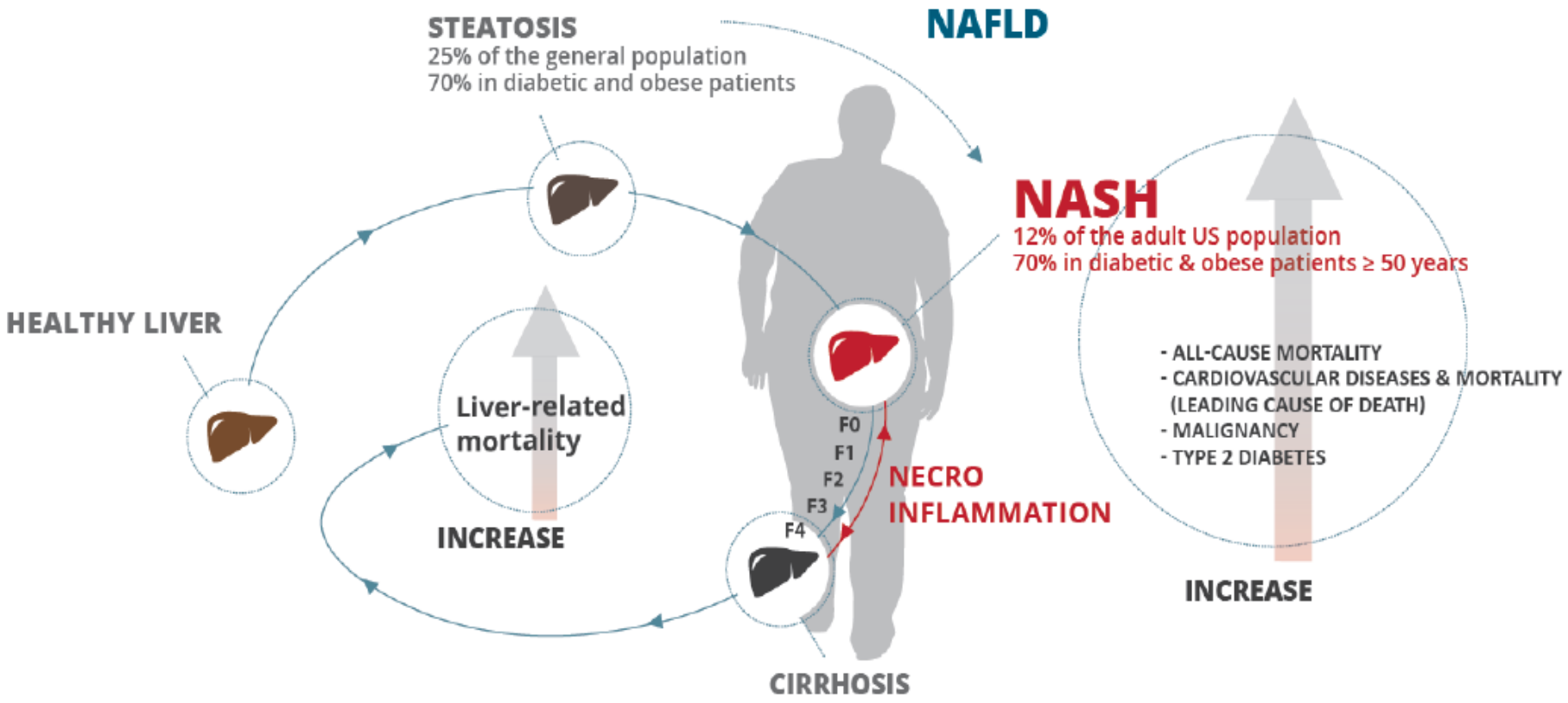
- Pre-screening strategies
  - with a combination of clinical, biochemical and imaging parameters
- Increases
  - pre-test probability of having the desired criteria
- Mainly because of their high NPV
- Several strategies possible
  - Choose one based on local availablility of techniques and own experience



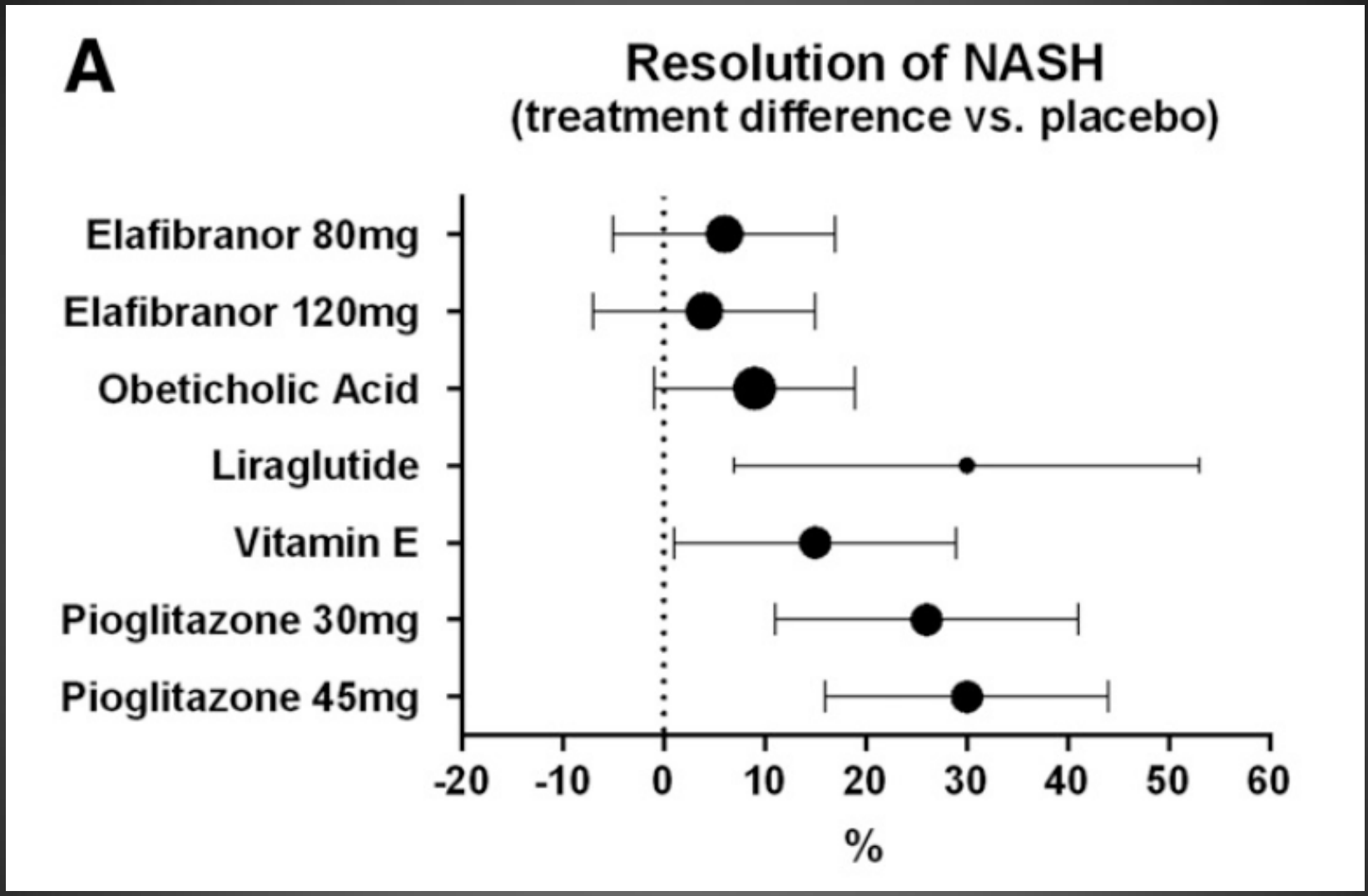
Haas, Francque & Staels. Ann Rev Physiol, submitted



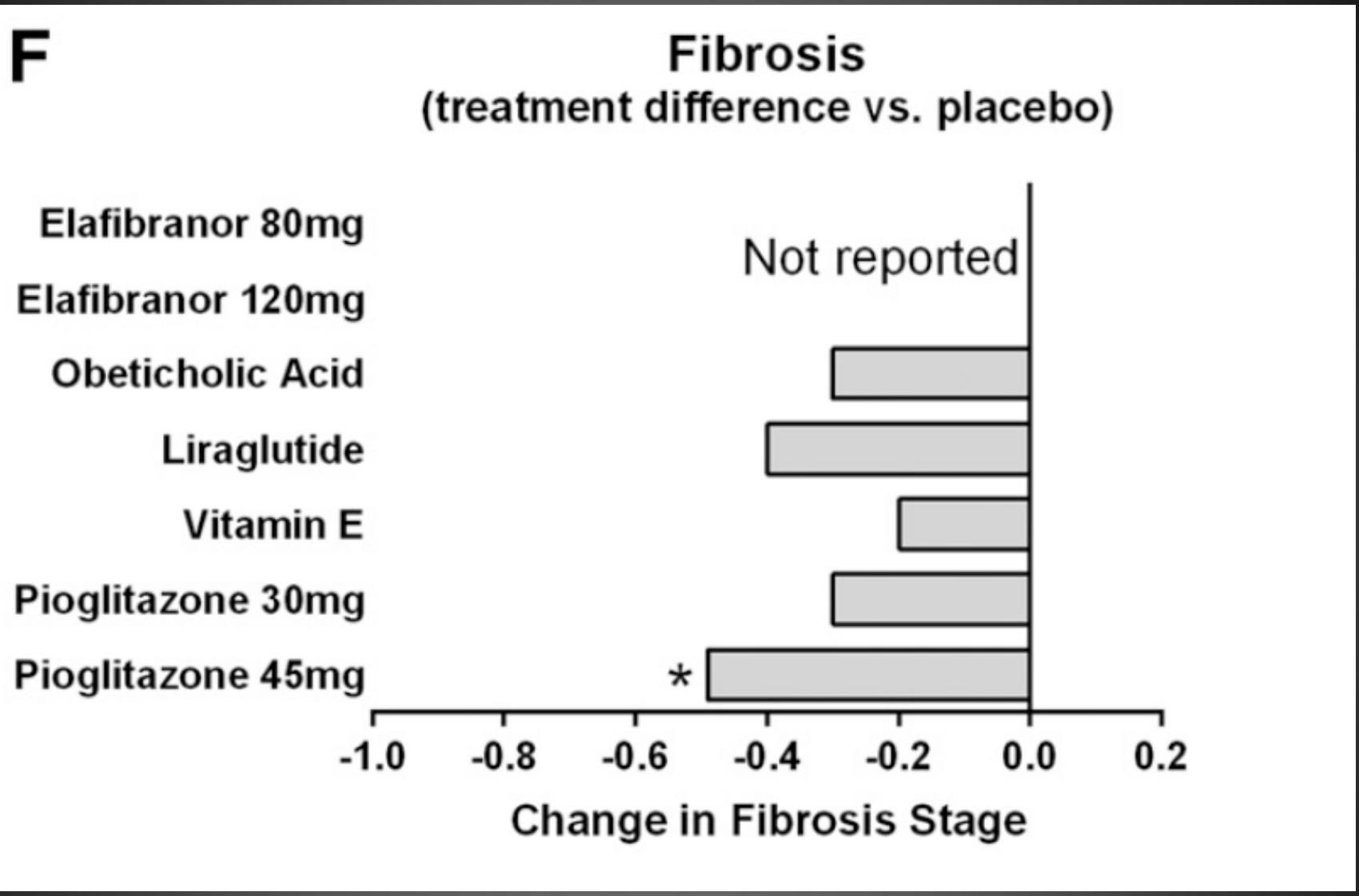
Adapted from Francque *et al*, J Hep 2016



Vanni *et al*, Dig Liv Dis 2010
Targher *et al*, NEJM 2010
Ekstedt *et al*, Hepatology 2006
Anstee *et al*, Nature Reviews 2013
Ballestri *et al*, WJG 2014
Yki-Järvinen, Lancet 2014

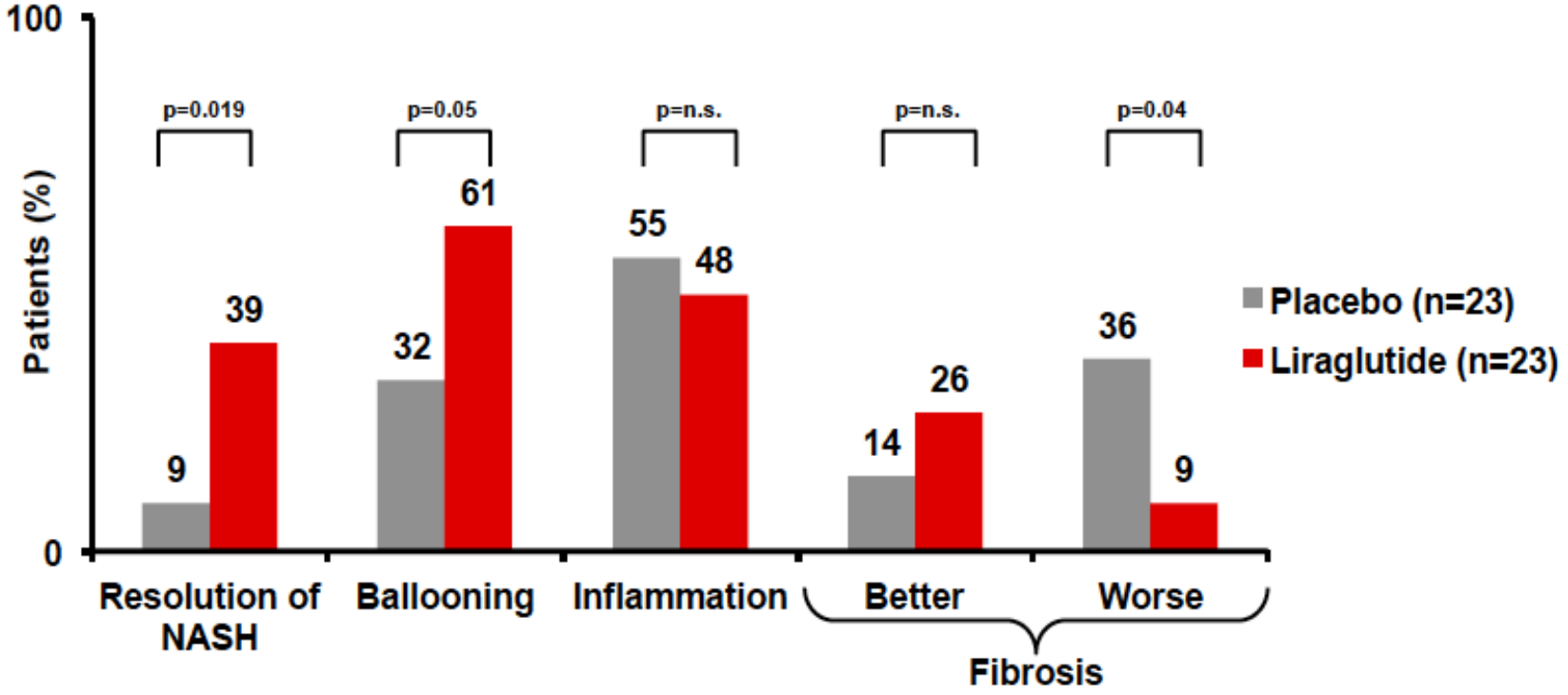


Bril & Cusi. Diabetes Care 2017



Bril & Cusi. Diabetes Care 2017

The LEAN 1 year trial of liraglutide: Histological improvement



Armstrong MJ, et al. Lancet. 2016;387:679-90

REGENERATE
NASH FIBROSIS STUDY

Positive Results From REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH

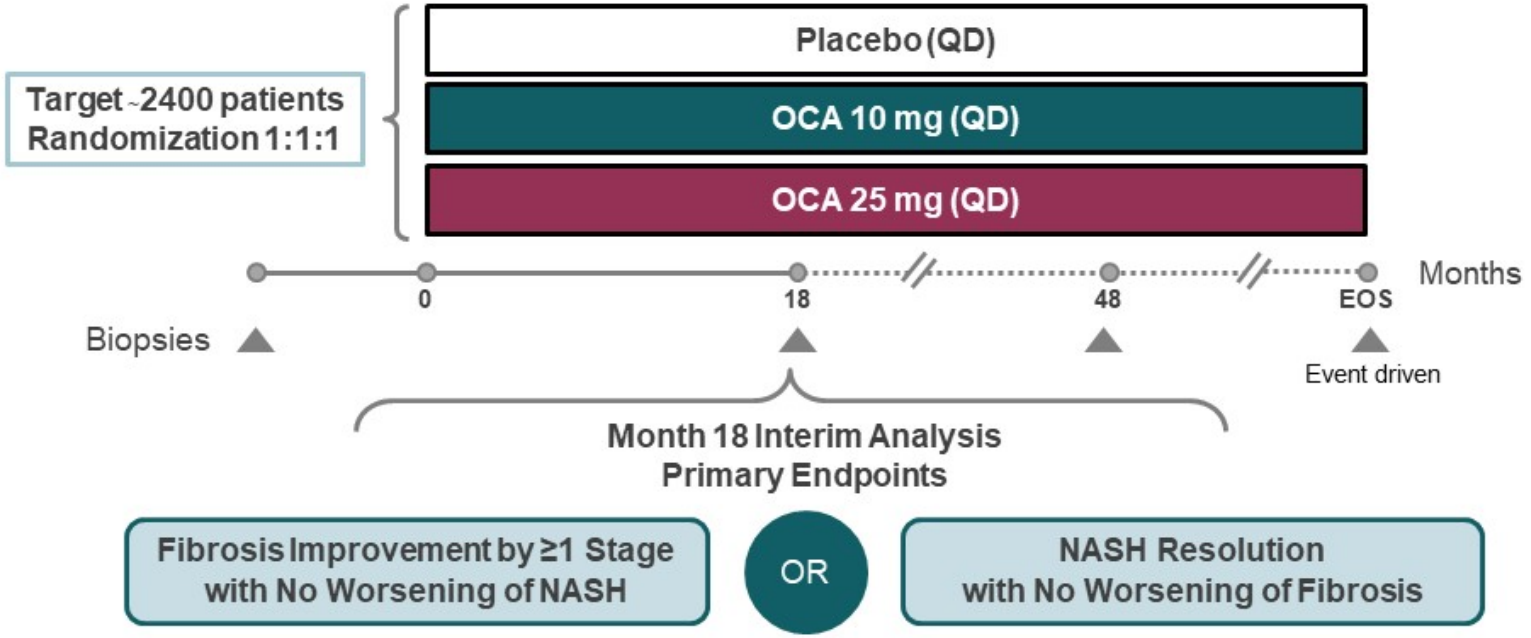
Zobair M. Younossi, Vlad Ratziu, Rohit Loomba, Mary Rinella, Quentin M. Anstee, Zachary Goodman, Pierre Bedossa, Andreas Geier, Susanne Beckebaum, Philip Newsome, David Sheridan, James Trotter, Whitfield Knapple, Eric Lawitz, Kris Kowdley, Aldo Montano-Loza, Jerome Boursier, Philippe Mathurin, Elisabetta Bugianesi, Giuseppe Mazzella, Antonio Olveira, Helena Cortez-Pinto, Isabel Graupera, David Orr, Lise Lotte Gluud, Jean-Francois Dufour, David Shapiro, Jason Campagna, Luna Zaru, Leigh MacConell, Reshma Shringarpure, Stephen Harrison, Arun J. Sanyal on behalf of the REGENERATE Study Investigators

Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Intercept

UZA
kennis / ervaring / zorg

REGENERATE Study Design



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

The interim analysis was conducted after 931 randomized patients with stage 2 or 3 liver fibrosis had or would have reached their actual/planned Month 18 visit (ITT population).
EOS analysis of clinical outcomes to confirm clinical benefit.
EOS, end of study; ITT, intent to treat; PBO, placebo; QD, once a day.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Study Eligibility Criteria

KEY INCLUSION CRITERIA

- Biopsy-confirmed NASH
- Fibrosis stage 2 or 3 (NASH CRN)
  - Exploratory cohort with fibrosis stage 1 and concomitant risk factors*
- NAFLD activity score (NAS) ≥4

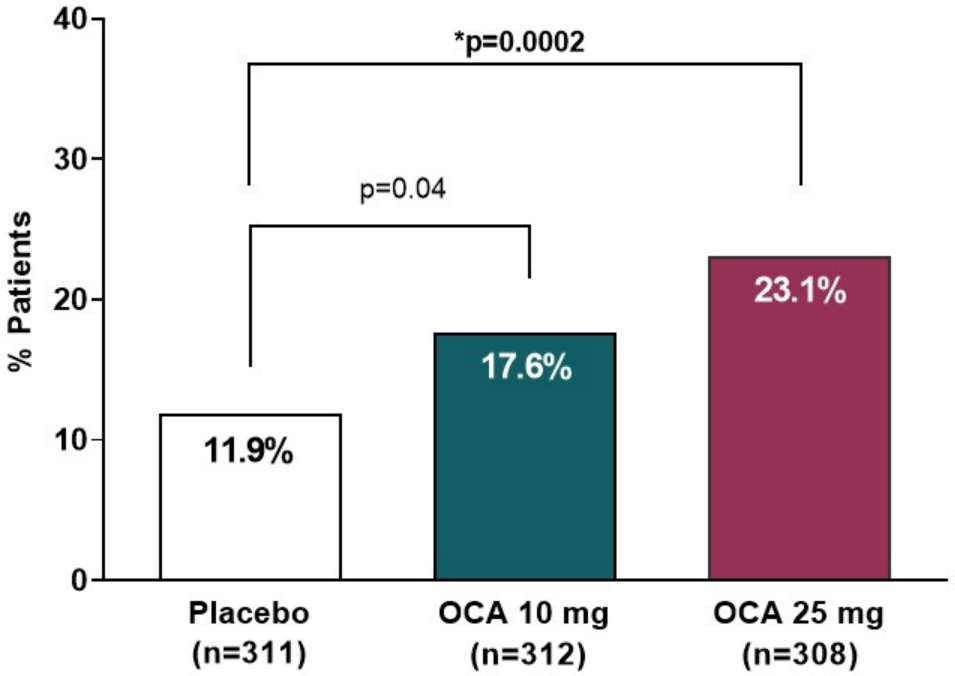
KEY EXCLUSION CRITERIA

- Evidence of other chronic liver disease
- Histologic presence of cirrhosis
- Total bilirubin >1.5 mg/dL
- ALT ≥10 × ULN
- HbA1c >9.5%
- Significant alcohol consumption**

All biopsies were read centrally and Month 18 biopsy slides were pair-read ensuring that pathologists were blinded to both treatment assignment and biopsy sequence

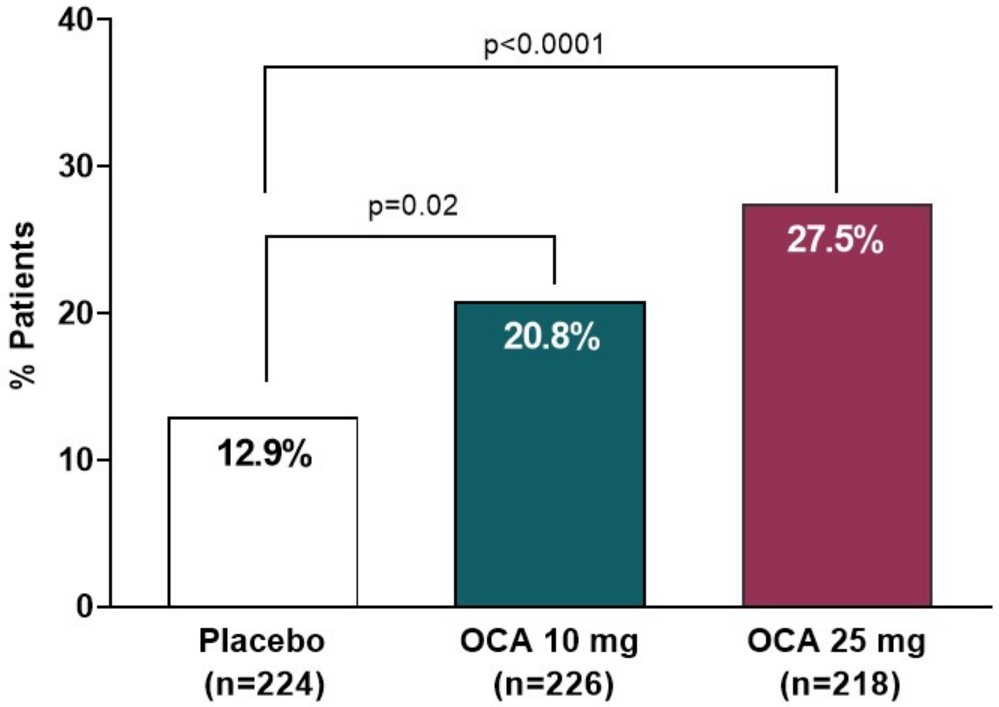
*Risk factors included type 2 diabetes, obesity (BMI ≥30 kg/m^2) or ALT >1.5 × ULN.
**Defined as >2 units/day for females and >4 units/day for males for >3 months within 1 year before screening.
ALT, alanine aminotransferase; BMI, body mass index; CRN, clinical research network; HbA1c, glycated hemoglobin; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; ULN, upper limit of normal.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
Primary Endpoint: ITT Population, N=931



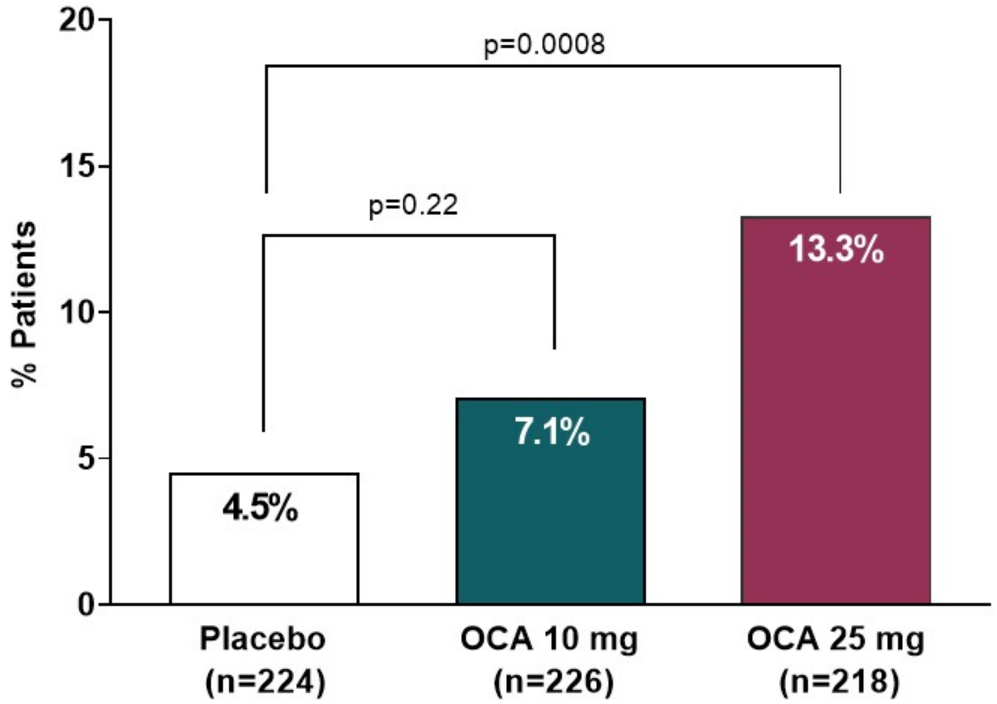
Primary endpoint definition: fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation or steatosis).
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.
*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
Primary Endpoint: Per Protocol Population, N=668



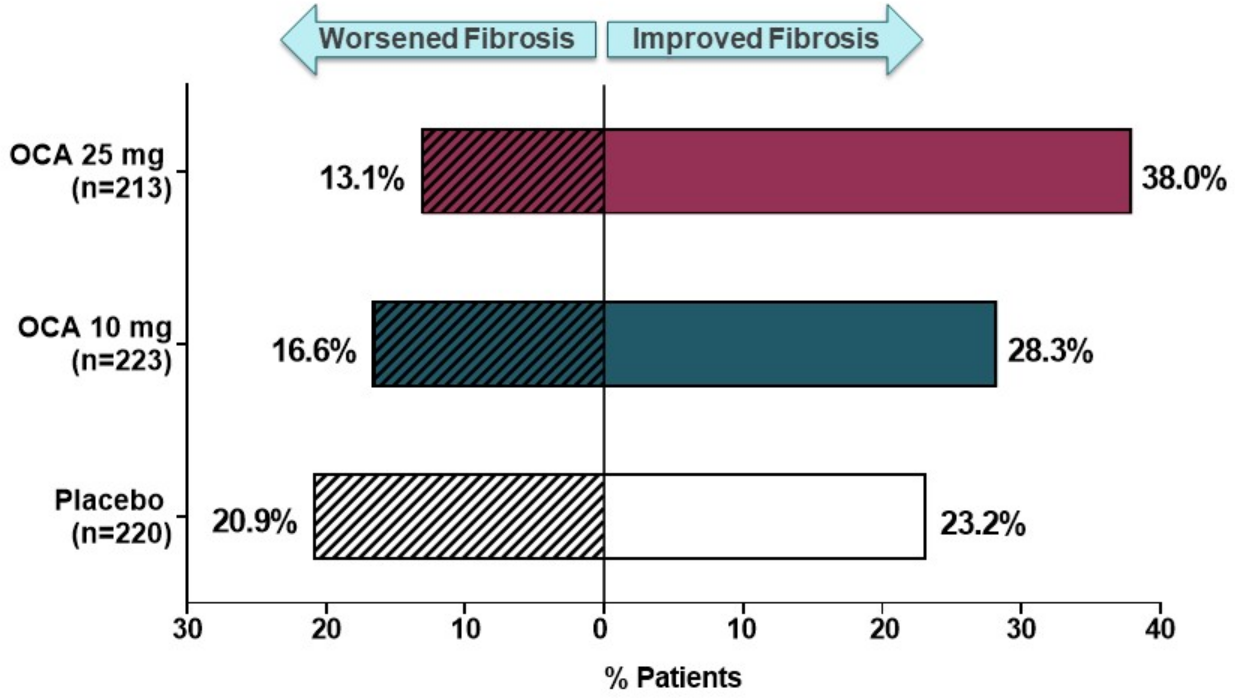
Primary endpoint definition: fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation or steatosis).
Per protocol population defined as all patients from the ITT population who completed ≥15 months of treatment and had a Month 18/EOT biopsy, were on treatment for at least 30 days immediately preceding the biopsy, and did not have any major protocol deviation.
P values are nominal.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Fibrosis Improvement by ≥2 Stages
Per Protocol Population



P values are nominal.
Per protocol population (N=668).
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Regression or Progression of Fibrosis by ≥1 Stage
*Per Protocol Population**



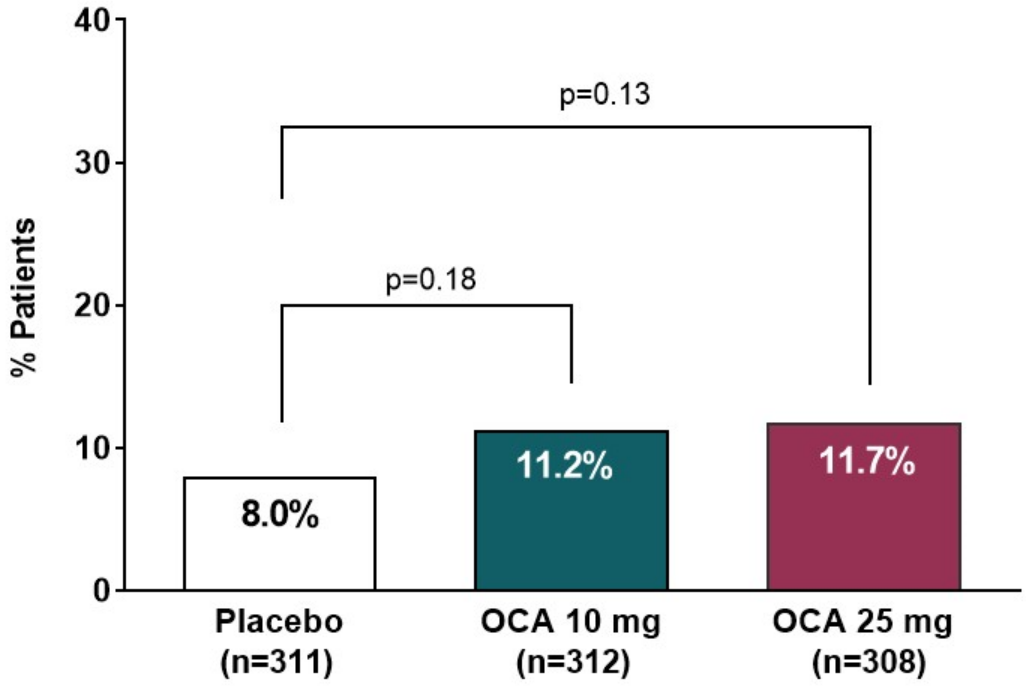
*Per protocol population with available fibrosis stage data at Month 18/EOT (n=656).
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
Subgroup Analyses: Per Protocol Population

Subgroups	OCA : Placebo Response Ratio (95% CI)	P value
Fibrosis Stage 2		
25 mg (n=101)	1.87 (1.08, 3.24)	0.02
10 mg (n=91)	1.73 (0.97, 3.07)	0.06
Fibrosis Stage 3		
25 mg (n=117)	2.36 (1.32, 4.20)	0.003
10 mg (n=135)	1.56 (0.84, 2.88)	0.15
NAS ≥6		
25 mg (n=144)	2.45 (1.52, 3.95)	0.0001
10 mg (n=152)	1.76 (1.06, 2.92)	0.03
NAS <6		
25 mg (n=74)	1.55 (0.74, 3.24)	0.24
10 mg (n=74)	1.36 (0.61, 3.04)	0.45
Type 2 Diabetes		
25 mg (n=119)	2.22 (1.14, 4.35)	0.02
10 mg (n=121)	2.07 (1.05, 4.11)	0.03
No Type 2 Diabetes		
25 mg (n=99)	2.10 (1.28, 3.44)	0.002
10 mg (n=105)	1.32 (0.76, 2.28)	0.32

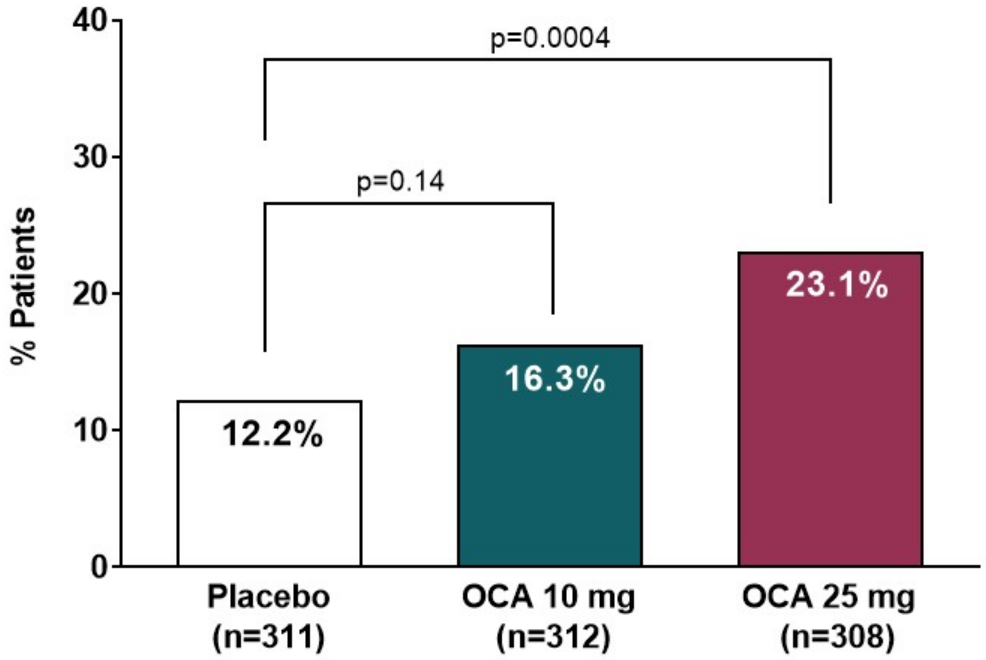
Per protocol population (N=668). P values are nominal.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

NASH Resolution with No Worsening of Fibrosis
Additional Primary Endpoint: ITT Population, N=931



Primary endpoint definition:
(i) overall pathologist assessment of "no steatohepatitis"; and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

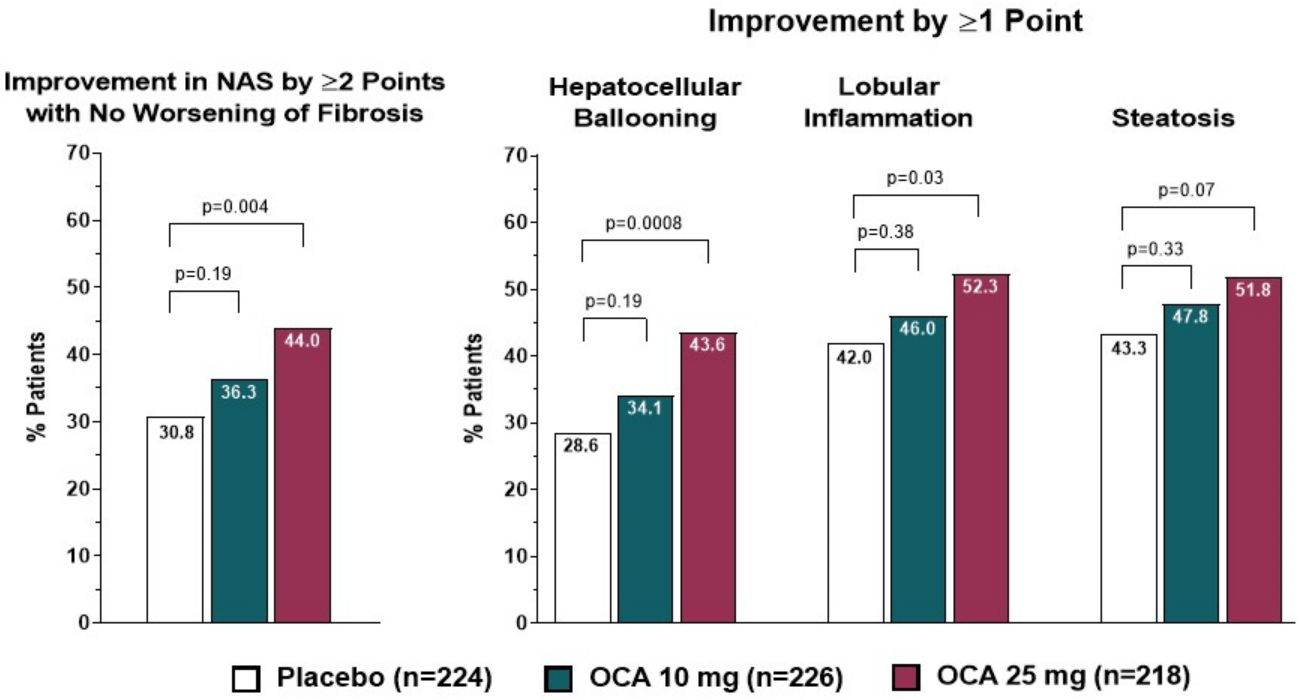
Resolution of Definite NASH with No Worsening of Fibrosis
*Overall Pathologist Assessment: ITT Population**



*Post-hoc analysis with endpoint defined as: (i) overall pathologist assessment of "no steatohepatitis"; and (ii) no increase in fibrosis stage from baseline. P values are nominal.

Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

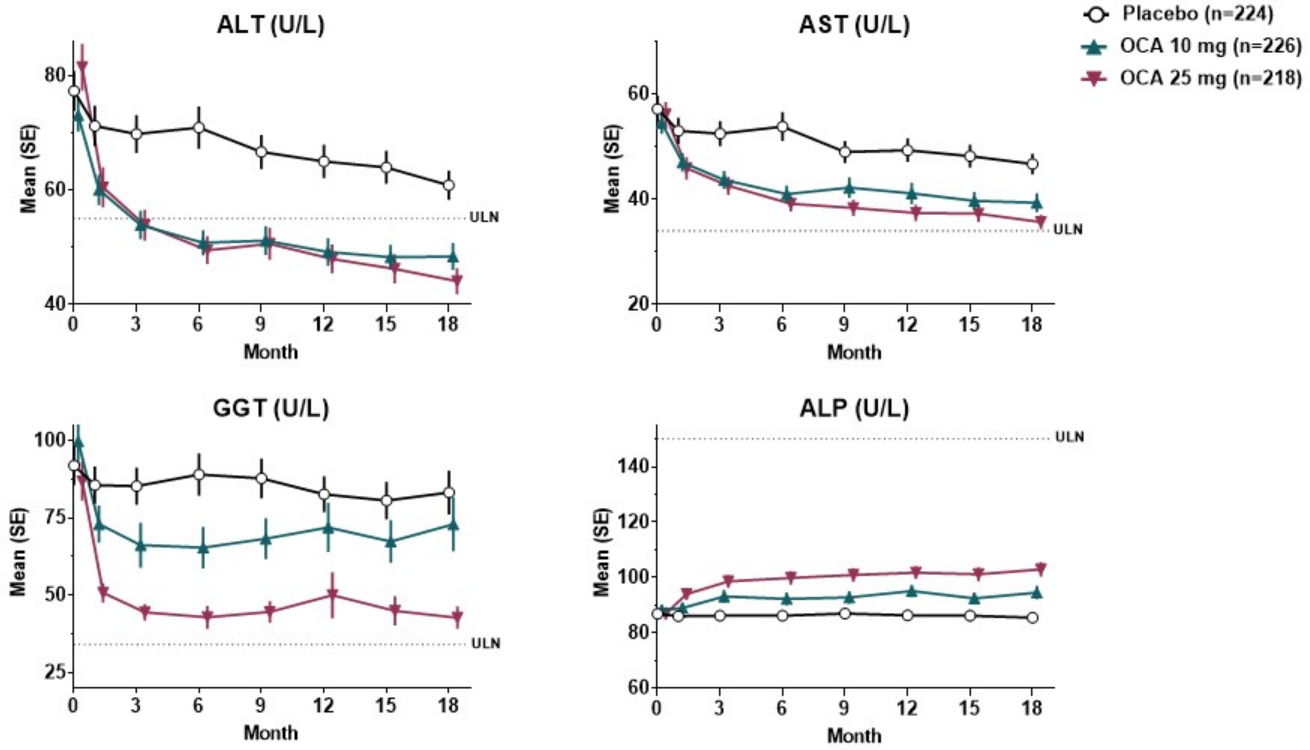
Improvement in NAS ≥2 with No Worsening of Fibrosis and NAS Parameters ≥1: *Per Protocol Population*



P values are nominal.
Per protocol population (N=668).
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Changes in Liver Biochemistry Over Time

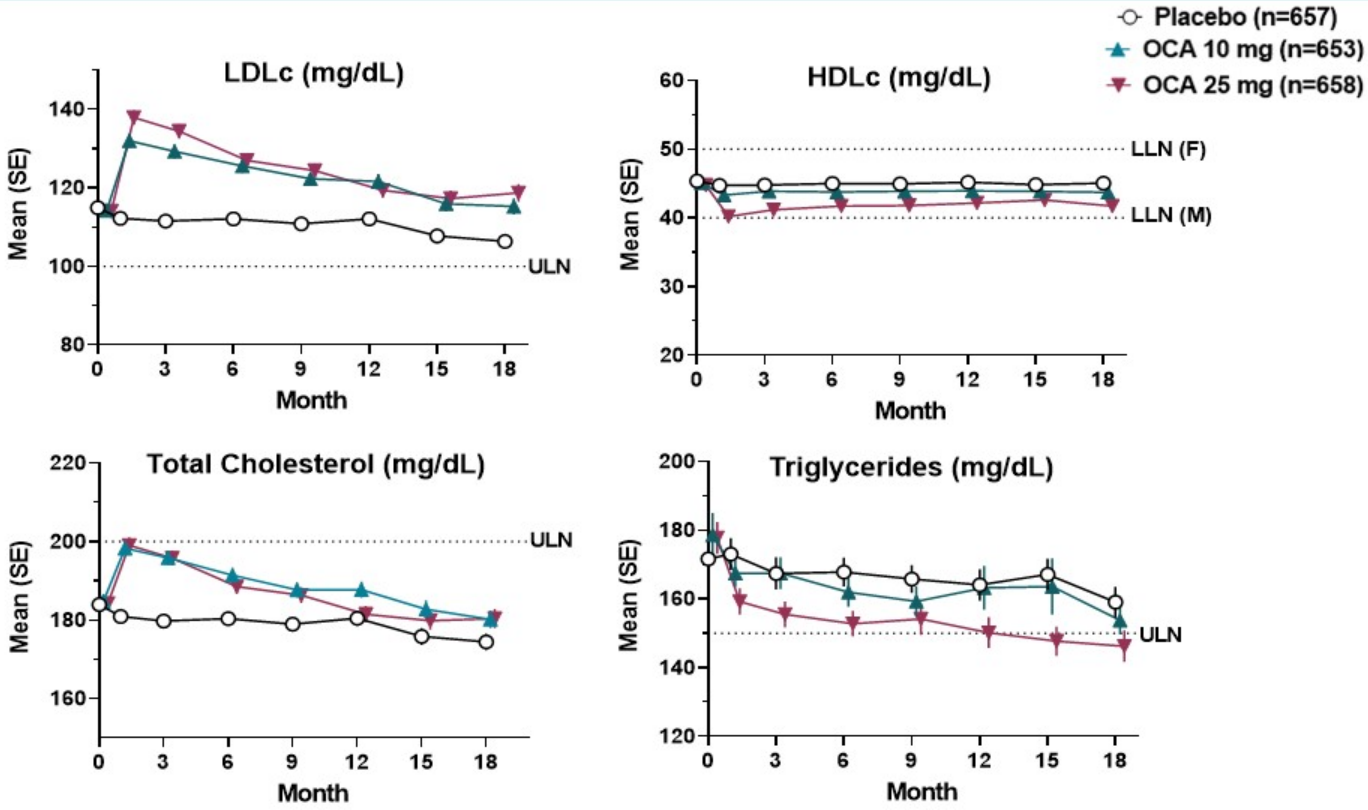
Per Protocol Population



Per protocol population (N=668).
SE, standard error.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Changes in Lipid Parameters Over Time

Safety Population, N=1968



Safety population defined as all randomized patients with stage 1, 2 or 3 fibrosis who received at least 1 dose of study treatment.
LDLc, low density lipoprotein cholesterol; HDLc, high density lipoprotein cholesterol.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Most Frequent Treatment-Emergent Adverse Events

Safety Population: Events Occurring in ≥10% of Patients in Any Treatment Group

n (%)	Placebo (n=657)	OCA 10 mg (n=653)	OCA 25 mg (n=658)
Pruritus (all pooled terms)	123 (19)	183 (28)	336 (51)
LDL increased	47 (7)	109 (17)	115 (17)
Nausea	77 (12)	72 (11)	83 (13)
Fatigue	88 (13)	78 (12)	71 (11)
Constipation	36 (5)	65 (10)	70 (11)
Abdominal pain	62 (9)	66 (10)	67 (10)
Diarrhea	79 (12)	44 (7)	49 (7)

Most frequent TEAEs were mostly mild to moderate in severity and consistent with the known profile of OCA

Data are presented in decreasing order of occurrence in the OCA 25 mg group. All data are based on investigator-reported events.
Safety population (N=1968).
LDL, low density lipoprotein.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).

Additional Safety and Tolerability Information
Safety Population

Pruritus

- Incidence was highest in the first 3 months and decreased thereafter
- In patients on OCA 25 mg reporting pruritus, 93% of events were mild to moderate
- 9% of patients on OCA 25 mg discontinued due to pruritus: more than half of these were protocol mandated and overall discontinuation rates were similar across the treatment arms

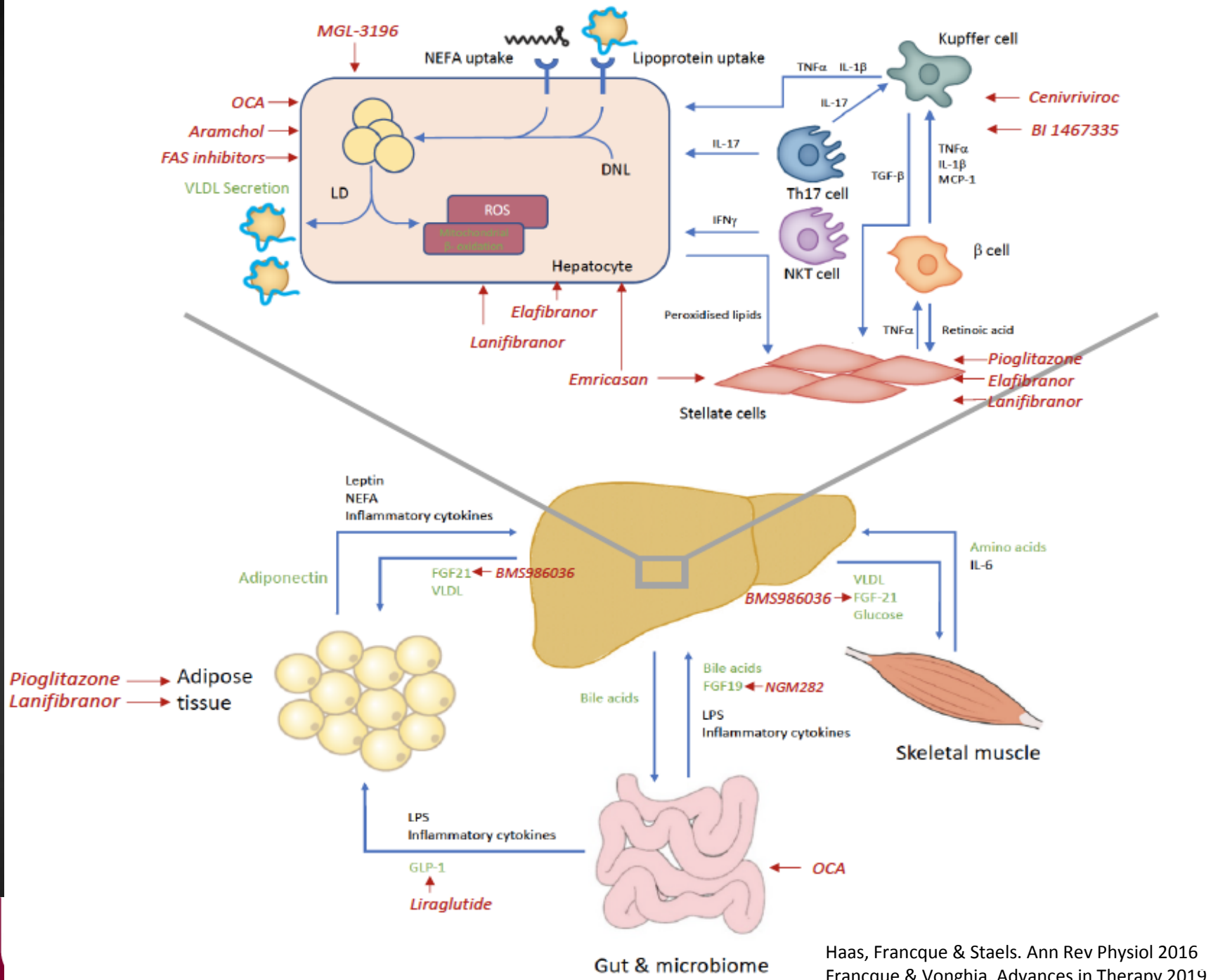
Hepatobiliary

- Hepatic TEAEs were balanced across treatment groups (Placebo, 13%; OCA 10 mg, 13%; OCA 25 mg, 11%)
- Hepatic SAEs were rare (<1% in all treatment groups): more occurred in the OCA 25 mg group with no pattern attributable to OCA (based on eDISH and case review)
- Incidence of cholelithiasis or cholecystitis AEs* was low (Placebo, <1%; OCA 10 mg, 1%; OCA 25 mg, 3%)

Cardiovascular

- Incidence of CV** SAEs was low and balanced across groups (Placebo, 2%; OCA 10 mg, 1%; OCA 25 mg, 2%)

*Gallbladder SMQ includes TEAEs and SAEs.
**By SMQ and preferred term.
CV, cardiovascular; eDISH, Evaluation of Drug-Induced Serious Hepatotoxicity; SMQ, standardized MedDRA queries.
Younossi Z, et al. Presented at EASL, 2019; Vienna, Austria. Oral (GS-06).



Haas, Francque & Staels. Ann Rev Physiol 2016
Francque & Vonghia. Advances in Therapy 2019

Take home messages 3

- NAFLD/NASH is part of a multisystemic disease
  - Complex multidirectional interactions
  - Need for multidisciplinary approach
- Therapy
  - Optimisation of co-morbid conditions
  - Drugs with proven efficacy but not licensed
  - OCA first topline Phase 3 results
  - Large pipeline

1st International NASH Day

June 12, 2018

https://www.international-nash-day.com https://www.the-nash-education-program.com

MORNING CONFERENCE

JUNE 12TH 2019

THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE

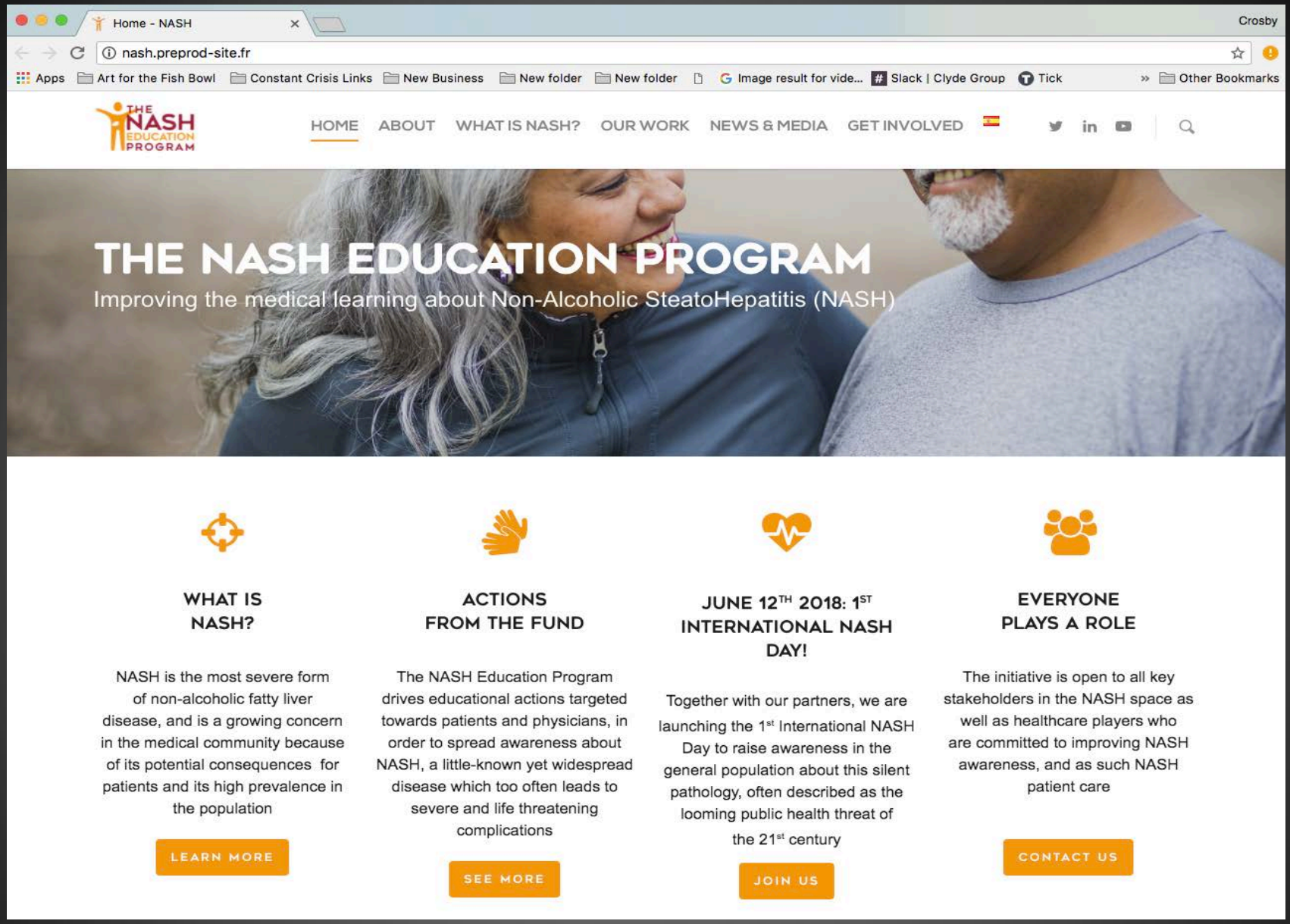
9:00 - 13:00

Hilton Brussels Grand Place,
Carrefour de l'Europe 3,
1000 Brussels

NASH*, A LOOMING PUBLIC HEALTH CRISIS: WHAT ARE THE CHALLENGES FOR HEALTH AUTHORITIES AND MEDICAL COMMUNITY?

- NASH, a looming public health crisis
- Challenges to raise public awareness
- Challenges for the medical community

UZA
kennis / ervaring / zorg


Home - NASH
Crosby
nash.preprod-site.fr
Apps
Art for the Fish Bowl
Constant Crisis Links
New Business
New folder
New folder
Image result for vide...
Slack | Clyde Group
Tick
Other Bookmarks
THE NASH EDUCATION PROGRAM
HOME
ABOUT
WHAT IS NASH?
OUR WORK
NEWS & MEDIA
GET INVOLVED
THE NASH EDUCATION PROGRAM
Improving the medical learning about Non-Alcoholic SteatoHepatitis (NASH)
WHAT IS NASH?
NASH is the most severe form of non-alcoholic fatty liver disease, and is a growing concern in the medical community because of its potential consequences for patients and its high prevalence in the population
LEARN MORE
ACTIONS FROM THE FUND
The NASH Education Program drives educational actions targeted towards patients and physicians, in order to spread awareness about NASH, a little-known yet widespread disease which too often leads to severe and life threatening complications
SEE MORE
JUNE 12TH 2018: 1ST INTERNATIONAL NASH DAY!
Together with our partners, we are launching the 1st International NASH Day to raise awareness in the general population about this silent pathology, often described as the looming public health threat of the 21st century
JOIN US
EVERYONE PLAYS A ROLE
The initiative is open to all key stakeholders in the NASH space as well as healthcare players who are committed to improving NASH awareness, and as such NASH patient care
CONTACT US

THE NASH EDUCATION PROGRAM

NASH:

Een handleiding voor patiënten en hun families

NIET-ALCOHOLISCHE STEATOHEPATITIS (NASH)
BETER BEGRIJPEN

Take home messages 4

- Increase disease awareness
  - Patients
  - GPs
  - Diabetologists, cardiologists, obesity physicians…
  - Gastroenterologists/hepatologists…
- Educational material and websites available
- International NASH Day and other initiatives

International NASH Day

June 12