Inserm

unity
Addressing Unmet Needs through Innovation in hepatology and gastroenterology

OUTCOME IN NASH TRIALS:

From histology & “hard outcomes” to less invasive reliable surrogates

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Disclosures

- Speaking:
  - Abbvie, Echosens, Intercept, Gilead and Sirtex

- Consulting:
  - Allergan, Gilead, MSD, Pfizer and Servier

Outline

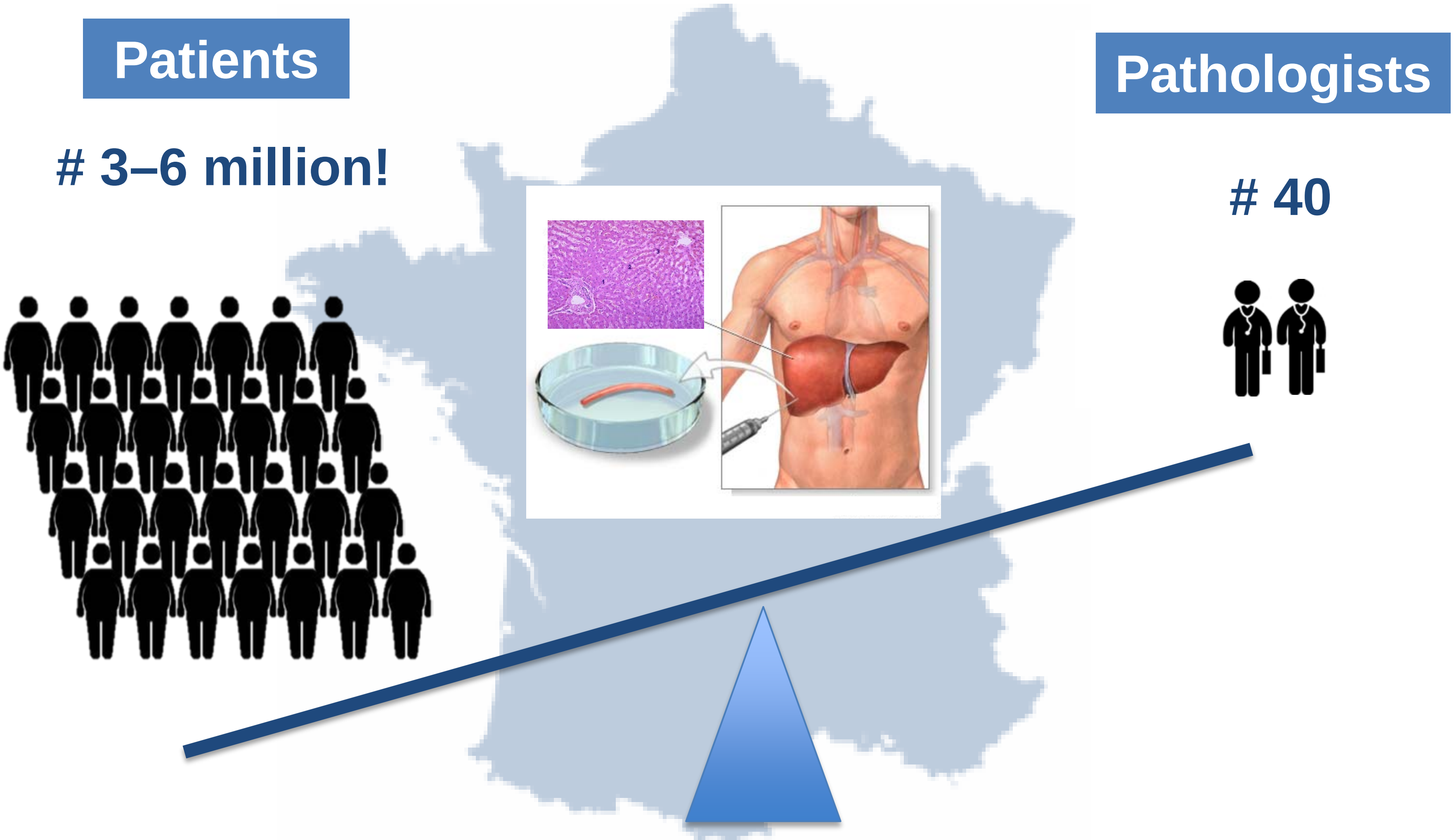
- **Enriching populations for clinical trials**
- **Surrogate endpoints for response to novel agents**

Current situation in clinical trials
Eligibility criteria

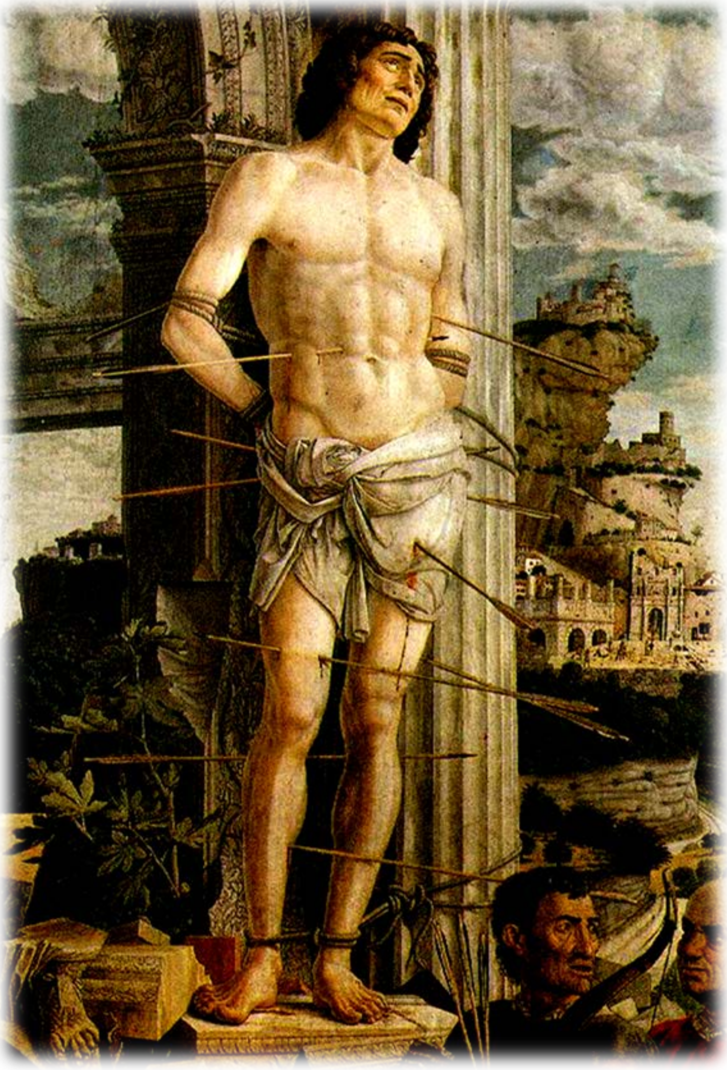
- Based on liver histology (<6-12 mo)
  - NASH defined by NAS ≥3-4
  - Fibrosis stage >1 targeting F3-F4

- High screening failure rate: 40 – 60%
  - Mainly related to liver histology

Diagnosing NAFLD with liver biopsy:
not realistic given the burden of disease!



The patient perspective !



Available non-invasive tests

2 different but complementary approaches

« Biological » approach

Non Specific

- AST/ALT ratio
- APRI
- FIB-4
- FibroTest®
- ELF®
- FibroMètre®
- Pro-C3®

Specific

- BARD score
- NAFLD score (NFS)

Serum Biomarkers

« Physical » approach

CAP / TE

PDFF / MRE

Castera L, Friedrich-Rust M, Loomba R. Gastroenterology; in revision

Non-Invasive Tests:
recommended by international guidelines

Clinical Practice Guidelines

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)

Clinical Practice Guidelines

Introduction

The Clinical Practice Guidelines propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the 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). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been retrieved by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities (Table 1) [2]. In particular, screening for NAFLD in the population at risk should be in the context of the available resources, considering the burden for the national health care systems and the currently limited effective treatments. The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults, with specific reference to paediatric NAFLD whenever necessary. The final purpose is to improve patient care and awareness of the importance of NAFLD, and to assist stakeholders in the decision-making process by providing evidence-based data, which also takes into consideration the burden of clinical management for the health-care system.

Definition

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) or quantitative fat/water selective magnetic resonance imaging (MRI). NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Table 2).

The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption ⩾30 g for men and ⩾20 g for women [1]. Alcohol consumption above these limits indicates alcoholic liver disease. The relationship between alcohol and liver injury depends on several cofactors (type of alcoholic beverage, drinking patterns, duration of exposure, individual/genetic susceptibility), rendering simple quantitative thresholds at least partly arbitrary. Specifically, patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors. Of note, the overall impact of metabolic risk factors on the occurrence of steatosis appears to be higher than that of alcohol in these patients [3]. The definitive diagnosis of NASH requires a liver biopsy.

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These Guidelines were developed by the EASL, EASD and the EASO, and are published simultaneously in the *Journal of Hepatology*, *Diabetologia* and *Obesity Facts*.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CCR, chemokine receptor; CK-18, cytokeratin-18 fragments; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; F, fibrosis stage; FIB-4, fibrosis 4 calculator; FLI, fatty liver index; HbA1c, glycosylated haemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IR, insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; OGTT, oral glucose tolerance test; PNHS, paediatric NAFLD histological score; PNPLA3, patatin-like phospholipase domain containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trials; SAF, steatosis, activity and fibrosis; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2; UDCA, ursodeoxycholic acid; US, ultrasound.

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Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

European Association for the Study of the Liver*, Asociación Latinoamericana para el Estudio del Hígado

Introduction

Liver fibrosis is part of the structural and functional alterations in most chronic liver diseases. It is one of the main prognostic factors as the amount of fibrosis is correlated with the risk of developing cirrhosis and liver-related complications in viral and non-viral chronic liver diseases [1,2]. Liver biopsy has traditionally been considered the reference method for evaluation of tissue damage such as hepatic fibrosis in patients with chronic liver disease. Pathologists have proposed robust scoring system for staging liver fibrosis such as the semi-quantitative METAVIR score [3,4]. In addition computer-aided morphometric measurement of collagen proportional area, a partly automated technique, provides an accurate and linear evaluation of the amount of fibrosis [5]. Liver biopsy gives a snapshot and not an insight into the dynamic changes during the process of fibrogenesis (progression, static or regression). However, immunohistochemical evaluation of cellular markers such as smooth muscle actin expression for hepatic stellate cell activation, cytokeratin 7 for labeling ductular proliferation or CD34 for visualization of sinusoidal endothelial capillarization or the use of two-photon and second harmonic generation fluorescence microscopy techniques for spatial assessment of fibrillar collagen, can provide additional "functional" information [6,7]. All these approaches are valid provided that the biopsy is of sufficient size to represent the whole liver [4,8]. Indeed, liver biopsy provides only a very small part of the whole organ and there is a risk that this part might not be representative for the amount of hepatic fibrosis in the whole liver due to heterogeneity in its distribution [9]. Extensive literature has shown that increasing the length of liver biopsy decreases the risk of sampling error. Except for cirrhosis, for which micro-fragments may be sufficient, a 25 mm long biopsy is considered an optimal specimen for accurate evaluation, though 15 mm is considered sufficient in most studies [10]. Not only the length but also the caliber of the biopsy needle is important in order to obtain a piece of liver of adequate size for histological evaluation, with a 16 gauge needle being considered as the most appropriate [11] to use for percutaneous liver biopsy. Interobserver variation is another potential limitation of liver biopsy which is related to the discordance between pathologists in biopsy interpretation, although it seems to be less pronounced when biopsy assessment is done by specialized liver pathologists [12]. Beside technical problems, liver biopsy remains a costly and invasive procedure that requires physicians and pathologists to be sufficiently trained in order to obtain adequate and representative results – this again limits the use of liver biopsy for mass screening. Last but not least, liver biopsy is an invasive procedure, carrying a risk of rare but potentially life-threatening complications [13,14]. These limitations have led to the development of non-invasive methods for assessment of liver fibrosis. Although some of these methods are now commonly used in patients for first line assessment, biopsy remains within the armamentarium of hepatologists when assessing the etiology of complex diseases or when there are discordances between clinical symptoms and the extent of fibrosis assessed by non-invasive approaches.

Methodological considerations when using non-invasive tests

The performance of a non-invasive diagnostic method is evaluated by calculation of the area under the receiver operator characteristic curve (AUROC), taking liver biopsy as the reference standard. However, biopsy analysis is an imperfect reference standard: taking into account a range of accuracies of the biopsy, even in the best possible scenario, an AUROC >0.90 cannot be achieved for a perfect marker of liver disease [15]. The AUROC can vary based on the prevalence of each stage of fibrosis, described as spectrum bias [16]. Spectrum bias has important implications for the study of non-invasive methods, particularly in comparison of methods across different study populations. If extreme stages of fibrosis (F0 and F4) are over-represented in a population, the sensitivity and specificity of a diagnostic method will be higher than in a population of patients that has predominantly middle stages of fibrosis (F1 and F2). Several ways of preventing the "spectrum bias" have been proposed including the adjustment of AUROC using the DANA method (standardization according to the prevalence of fibrosis stages that define advanced (F2–F4) and non-advanced (F0–F1) fibrosis) [17,18] or the Obuchowski measure (designed for ordinal gold standards) [19]. What really matters in clinical practice is the number of patients correctly classified by non-invasive methods for a defined endpoint according to the reference standard (i.e. true positive and true negative).

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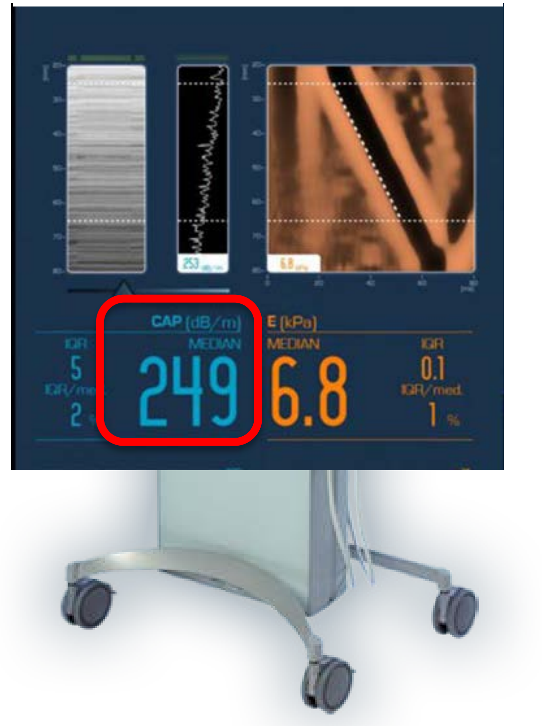
EASL CPG guidelines J Hep 2015: 63: 237-64

Can non-invasive tests detect and grade steatosis?

Currently available techniques

CAP

MRI- PDFF



VCTE

CAP *vs.* PDFF
Summary

CAP	PDFF

CAP

- **Advantages**
  - Point-of-care
  - Low cost & wide availability
  - Low Failure rate (XL probe)
  - Measurement of LS
- **Disadvantages**
  - Lower accuracy
  - No consensual cut-offs
  - Limited longitudinal data

PDFF

- **Advantages**
  - High accuracy
  - Gold standard
  - No failure
- **Disadvantages**
  - Cost & availability
  - Requires an MRI facility
  - Limited longitudinal data

Castera, Friedrich-Rust & Loomba. Gastroenterology; in revision

Can non-invasive tests differentiate NASH from simple steatosis?

Serum biomarkers for differentiating NASH from simple steatosis

Currently, none of the serum biomarkers available are sensitive and specific enough to differentiate NASH from simple steatosis

Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15

MRE and TE for diagnosing NASH

Author	Patients n	MRE/TE	NASH	F3-F4	Cut-offs (kPa)	Se / Sp (%)	Accuracy
Chen 2011	58	MRE	62%	19%	2.90	83 / 82	0.93
Loomba 2014	117	MRE	91%	19%	3.26	42 / 92	0.73
Loor							
Imaj							
Lee 2016	183	TE	51%	15%	7.0	86 / 58	0.75
Park 2017	104	MRE	73%	20%	2.53	64 / 68	0.70
		TE			5.6	61 / 59	0.35

Neither MRE or TE can reliably discriminate NASH from simple steatosis

Chen et al. Radiology 2011; Loomba et al. Hepatology 2014; Loomba et al. Am J Gastro 2016
Imajo et al. Gastro 2016; Lee et al. Plos One 2016; Park et al. Gastro 2017

Can non-invasive tests identify NAFLD patients with advanced fibrosis?

Serum biomarkers for advanced fibrosis non patented

Table 1 | Predicting advanced fibrosis* using routine clinical and laboratory variables in patients with NAFLD

Predictive score	Patients (n)	Variables/ formula [units]	AUROC (95% CI)	Cut-off points	PPV (%)	NPV (%)
NAFLD fibrosis score[8]	733	–1.675 + 0.037 × age [years] + 0.094 × BMI [kg/m²] + 1.13 × IFG/diabetes [yes = 1, no = 0]	0.88 (0.85–0.92)	≤–1.455 ≥0.676	56 90	93 85
BARD score[8]						96
FIB-4 s						90 83
FibroMeter™ NAFLD[89‡]	235	0.4184 glucose [mmol/l] + 0.0701 AST [U/l] + 0.00008 ferritin [µg/l] – 0.0102 platelet [g/l] – 0.0260 ALT [U/l] + 0.0459 body weight [kg] + 0.0842 age [years] + 11.6226	0.94	≤0.611 ≥0.715	NA 90	90 NA
Hepascore[91§]	242	Exp –4.185,818 – (0.0249 age) + (0.7 464 sex) + (1.30039 α2-macroglobulin) + (0.0302 hyaluronic acid) + (0.069 bilirubin) – (0.0012 GGT)	0.814 (0.73–0.90)	0.37	57.1	92.4

Better at ruling out than ruling in advanced fibrosis

Castera L, Vilgrain V & Angulo P. Nat Rev Gastro & Hepatol 2013; 10:666-75

Serum biomarkers for advanced fibrosis patented

Test	Description	Accuracy	Reproducibility	Responsiveness	Feasibility	Limitations
Specific fibro						
ELF						t sensitive early stages ibrosis; age, CD4⁺ T cell int and er factors affect ELF re results
FibroTest						optimal early-stage osis
FibroMeter NAFLD	fasting glucose	(Sn 27%, Sp 95%)				h cost

Lack of external validation

Slight improvement in accuracy but widespread application limited by cost and availability

Wong et al. Nat Rev Gastro & Hepatol 2018; 15:461-77

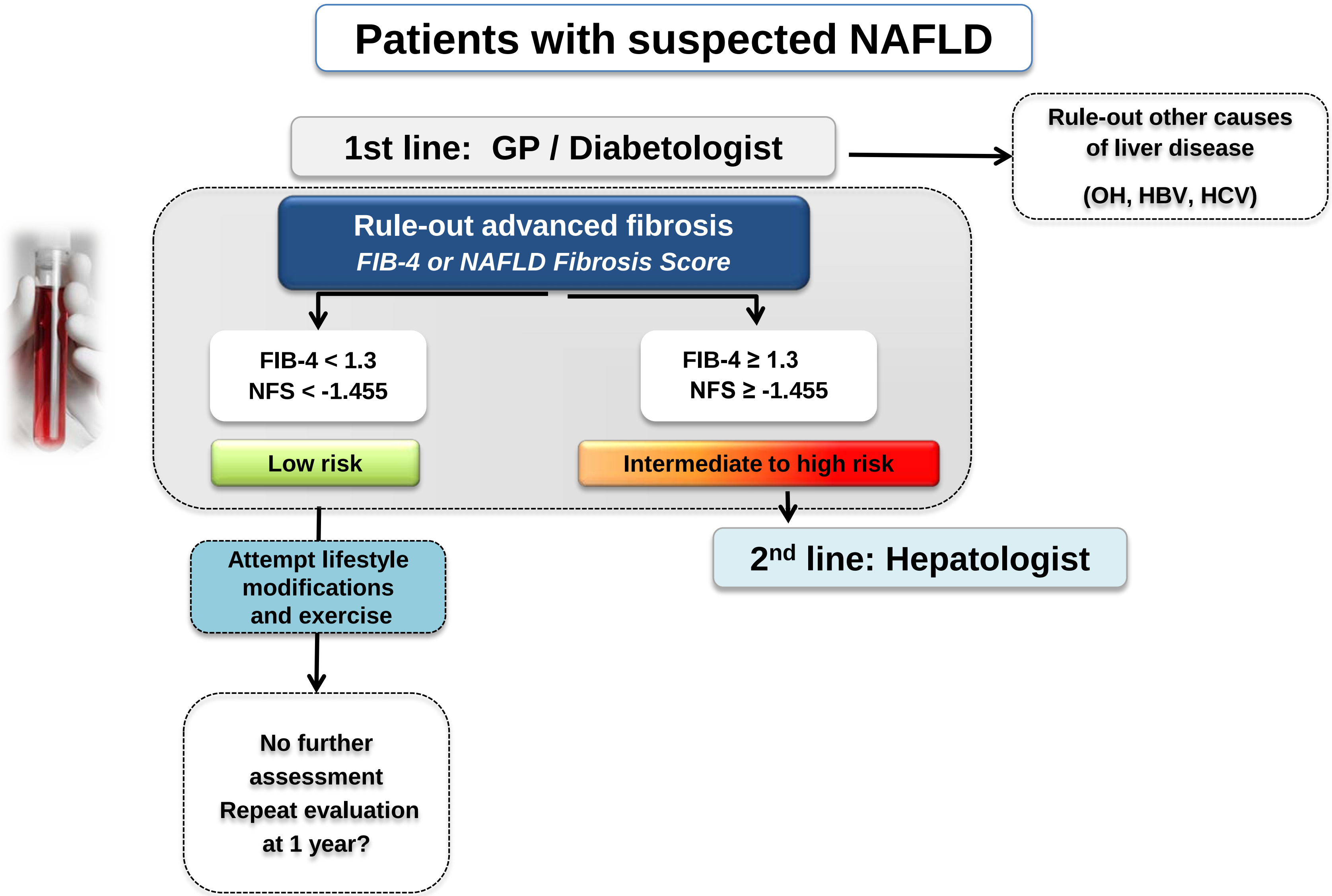
Serum biomarkers performance
meta-analysis

	No. of Studies (No. of Patients)	AUC Value (Mean)
APRI		
SF	11 (2352)	0.70
AF	29 (6746)	0.75
Cirrhosis	11 (2196)	0.75
Cirrhosis	5 (1263)	0.70
NAFLD score		
SF	11 (2098)	0.72
AF	38 (9245)	0.78
Cirrhosis	8 (1830)	0.83

NAFLD Fibrosis Score and FIB-4 are the most accurate and best validated

66 studies; n= 13046 patients

Xiao et al. Hepatology 2017; 66: 1486-501



Patients with suspected NAFLD
1st line: GP / Diabetologist
Rule-out other causes of liver disease
(OH, HBV, HCV)
Rule-out advanced fibrosis
FIB-4 or NAFLD Fibrosis Score
FIB-4 < 1.3
NFS < -1.455
FIB-4 ≥ 1.3
NFS ≥ -1.455
Low risk
Intermediate to high risk
2nd line: Hepatologist
Attempt lifestyle modifications and exercise
No further assessment
Repeat evaluation at 1 year?

TE for diagnosing F3-F4 in NAFLD

Meta-analysis

F3-F4

A: Significant Fibrosis

Sum AUROCS: 0.88

Sum

88

F4

Imajo K 2016

Sum AUROCS: 0.94

Kumar R 2013

p:

TE has high accuracy for F3-F4 evidence based on high number of patients (#4000)

DOR=44.0

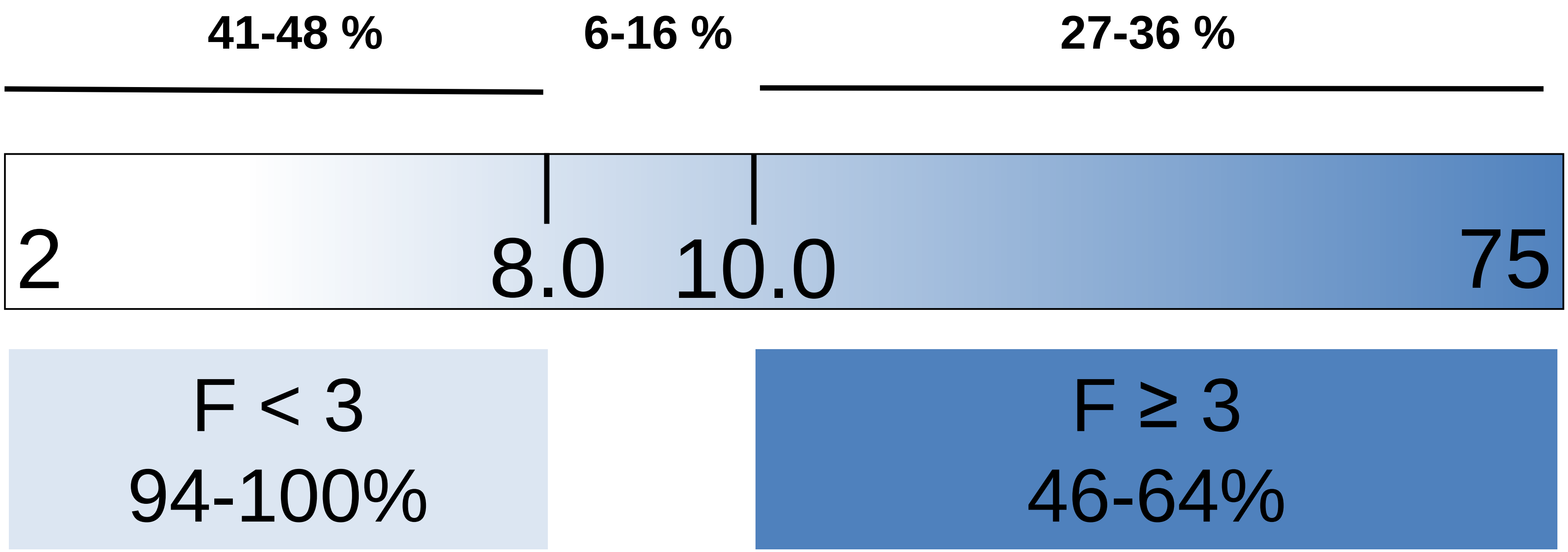
(C2)-FibroScan M

(A1)-APRI, DOR=5.0

23 studies; n= 3863 patients

Xiao et al. Hepatology 2017; 66: 1486-501

Which cut-off for advanced fibrosis?
Dual cut-off strategy



P ; N=164 NAFLD patients; M probe

R; N=761 NAFLD patients; XL probe

Tapper et al. Am J Gastroenterol 2016; 111: 677-84

Petta et al. APT 2017; 46 : 617-27

MRE for diagnosing F3-F4 in NAFLD

Author	Patients n	BMI	F3-F4	Cut-offs (kPa)	Se / Sp (%)	Accuracy	Failure (%)
Chen 2017	111	40.3	20%	3.6	84 / 83	0.92	4.5
Park 2017	104	30.4	17%	3.0	78 / 80	0.87	0
Loomba 2016	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Imajo 201[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Loomba 2014	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Cui 2015	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Total	**676**						

MRE has high accuracy for F3-F4 but evidence based on a limited number of patients (<700)

Chen et al. Radiology 2017; Park et al. Gastro 2017; Loomba et al. Am J Gastro 2016 Imajo et al. Gastro 2016; Loomba et al. Hepatology 2014; Cui et al. APT 2015

Comparison between TE and MRE for F3-F4 in NAFLD

Author	Patients	MRE/TE	BMI	F3-F4	Cut-offs (kPa)	Failure	Accuracy	p
Imajo 2016	142	MRE	28.1	32%	4.8	0%	0.89	NS
P								S
C								S
		(M/XL)						
Total	**357**							

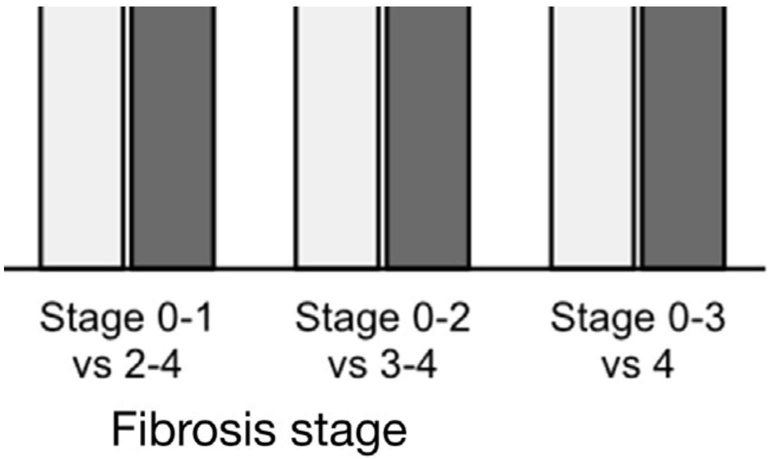
MRE and TE have similar accuracy

Less failure with MRE (0- 4.2 *vs* 6.7-18.2%)

Limited number of patients (#350)

Imajo et al. Gastro 2016; Park et al. Gastro 2017; Chen et al. Radiology 2017.

Comparison between TE and MRE in NAFLD meta-analysis



N=3 studies; 230 patients with biopsy-proven NAFLD

Hsu et al. CGH 2018; in press

TE *vs.* MRE

Advantages and limitations

Tech	Fat	Evidence in NAFLD	Counfounders			Quality criteria	Failure	Cost	POC
			Inflam	obesity	other				
TE	Yes CAP	N=25 3862	++	++ XL	Steatosis?	Well defined IQR/M<30%	3-27%	€	Yes
MRE	Yes PDFF	N=6 676	+	-	Iron	Not well defined	0-2%	€€€	No

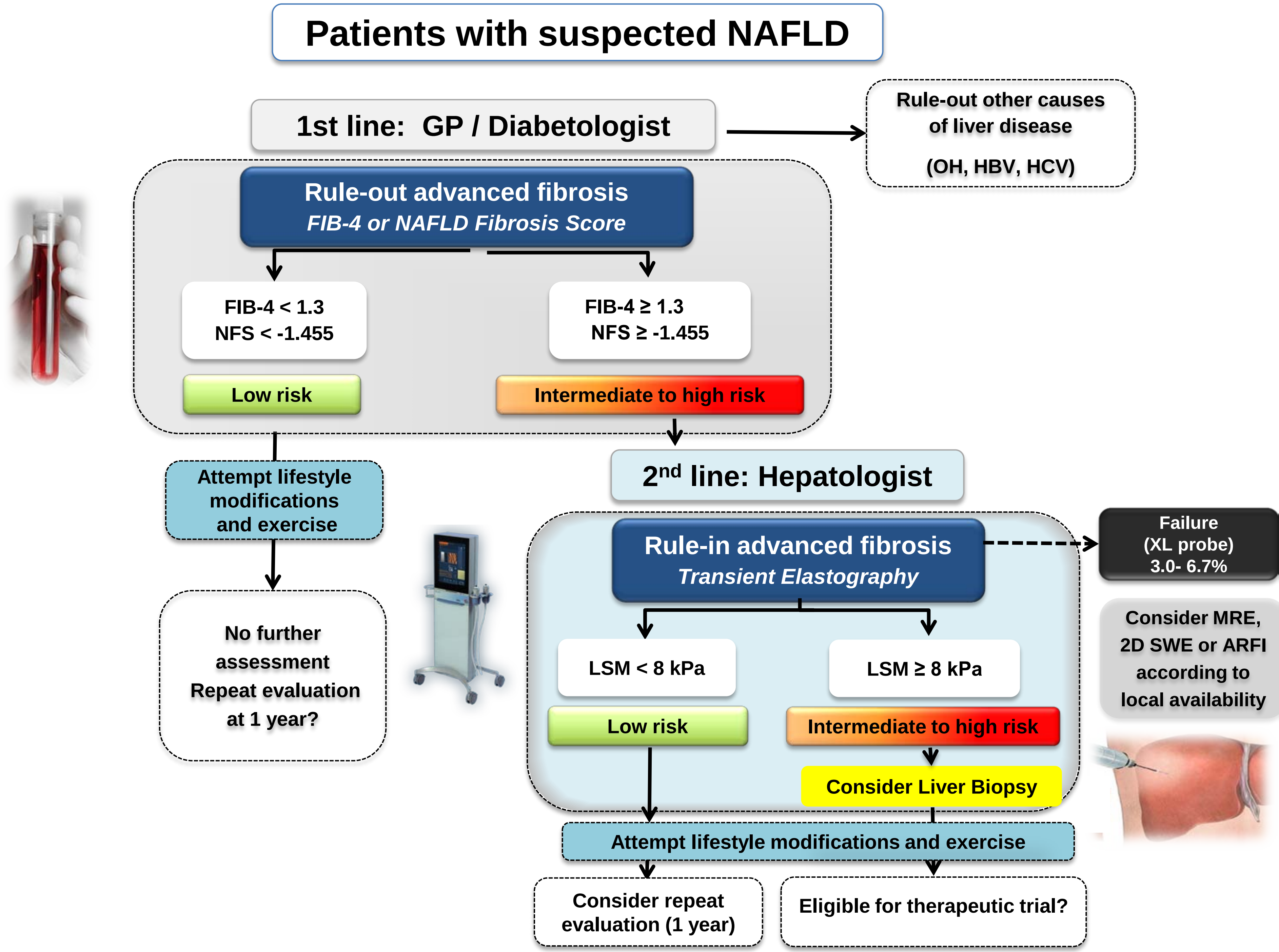
Adapted from Castera, Friedrich-Rust & Loomba. Gastroenterology; in revision

Screening patients for NASH trials
FS3 score = CAP + LSM + AST

Target = NASH patients with NAS≥4 and F≥2

	Derivation cohort		External validation cohorts			
	Development population	**Bootstrap validation**	**Malaysian NAFLD cohort**	**US screening cohort**	**French bariatric surgery cohort**	**Pooled**
N	**335**	**335**	**231**	**193**	**110**	**534**
Prevalence of NASH+NAS≥4 +F≥2	166 (**50**%)	(**44**%-**55**%)*	53 (**23**%)	24 (**12**%)	17 (**15**%)	96 (**18**%)
AUROC (95%CI)	**0.83** (0.78-0.87)	**0.83** (0.78-0.87)	**0.85** (0.80-0.91)	**0.91** (0.86-0.96)	**0.93** (0.89-0.98)	**0.88** (0.85-0.91)

Sasso et al. AASLD 2018



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NFS < -1.455
FIB-4 ≥ 1.3
NFS ≥ -1.455
Low risk
Intermediate to high risk
Attempt lifestyle modifications and exercise
No further assessment
Repeat evaluation at 1 year?
2nd line: Hepatologist
Rule-in advanced fibrosis
Transient Elastography
Failure
(XL probe)
3.0- 6.7%
Consider MRE, 2D SWE or ARFI according to local availability
LSM < 8 kPa
LSM ≥ 8 kPa
Low risk
Intermediate to high risk
Consider Liver Biopsy
Attempt lifestyle modifications and exercise
Consider repeat evaluation (1 year)
Eligible for therapeutic trial?

Use of TE / MRE in NAFLD

TE-CAP

Triage
in large
unselected
populations

MRE-PDFF

Assessment
& follow-up
In selected
populations in
clinical trials

Best used as an integrated system to allow more efficient evaluation of patients with NAFLD

Outline

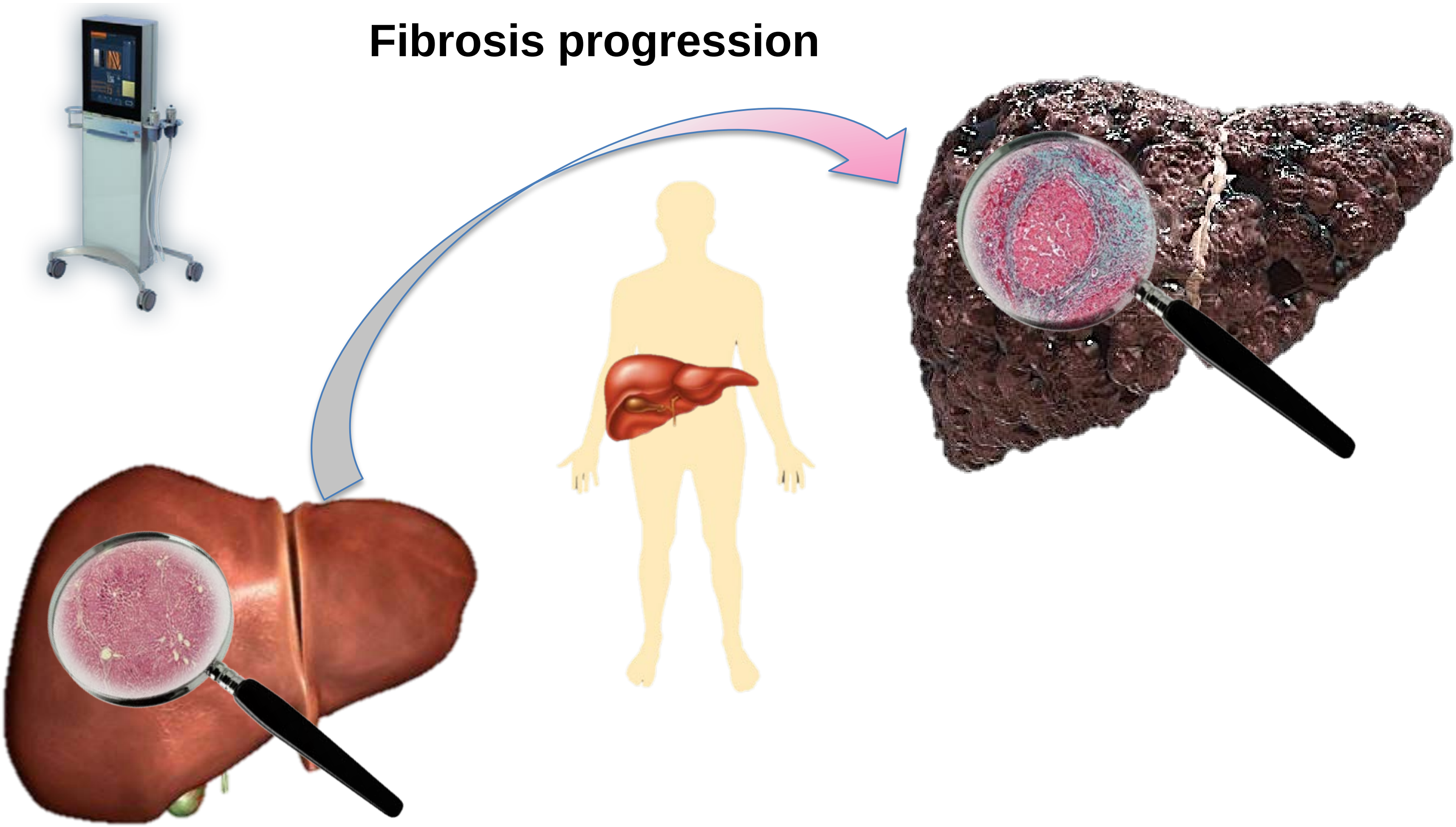
- Enriching populations for clinical trials

- **Surrogate endpoints for response to novel agents**

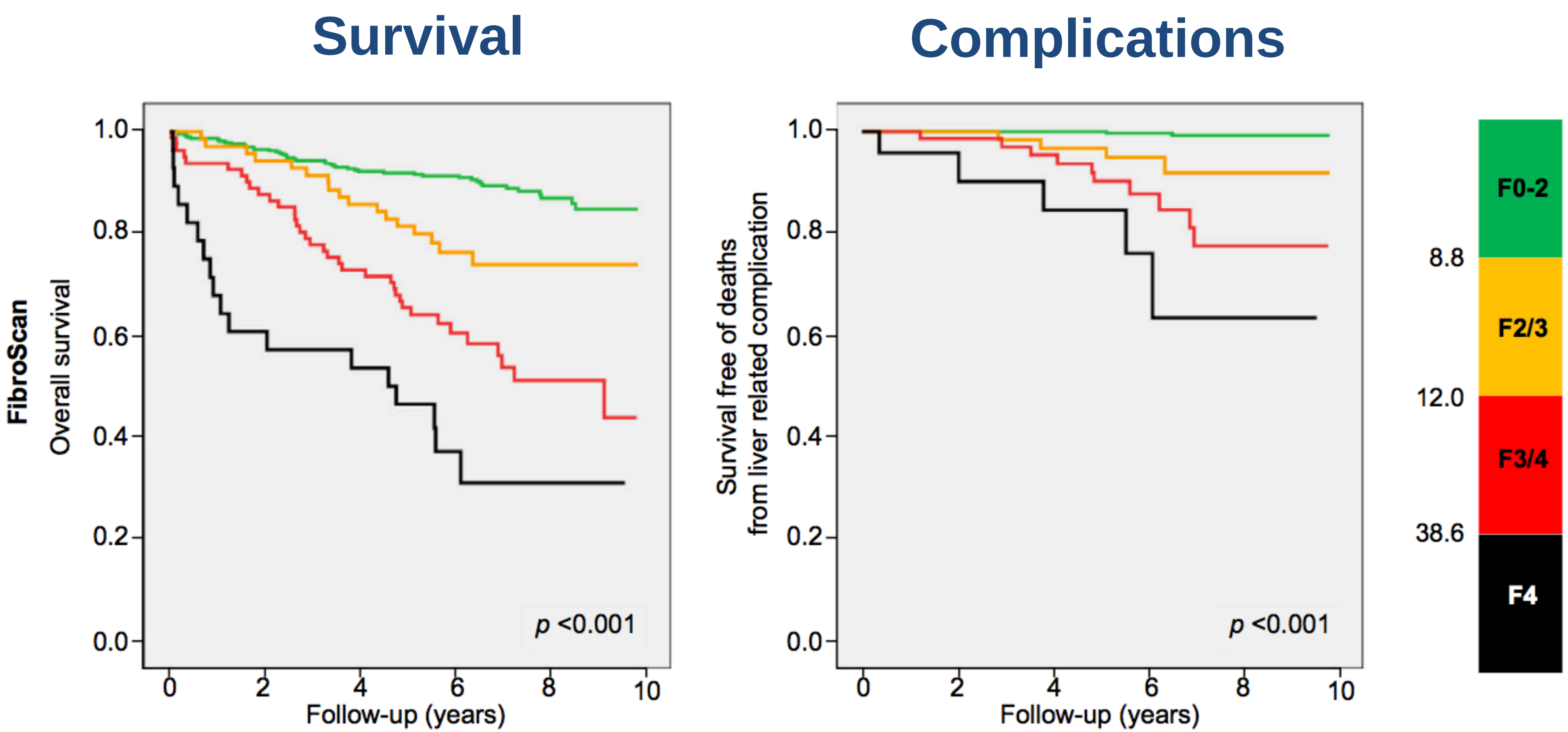
Endpoints in Clinical Trials

- Regression of fibrosis (at least 1 stage) without worsening of NASH is the usual primary endpoint In Phase 3 trials.

Liver stiffness for fibrosis progression



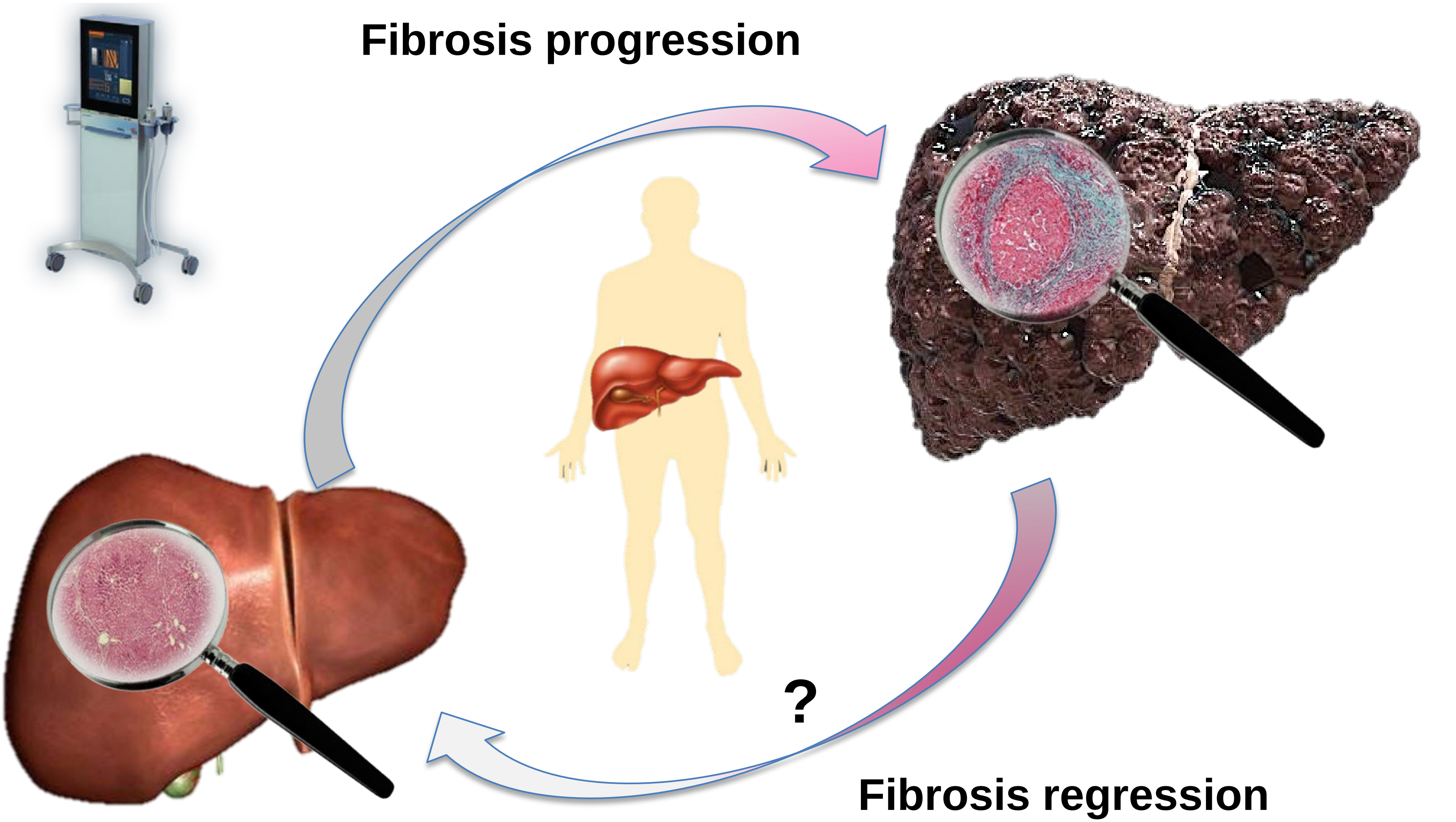
Liver stiffness (TE) has prognostic value in NAFLD



N= 360 NAFLD patients; f-up 6 yrs

Boursier et al. J Hepatol 2016; 65: 570-78

Is liver stiffness a good surrogate of fibrosis/cirrhosis regression ?



What have we learned from the Viral Hepatitis field ?

Liver stiffness (TE) decreases with SVR In HCV patients

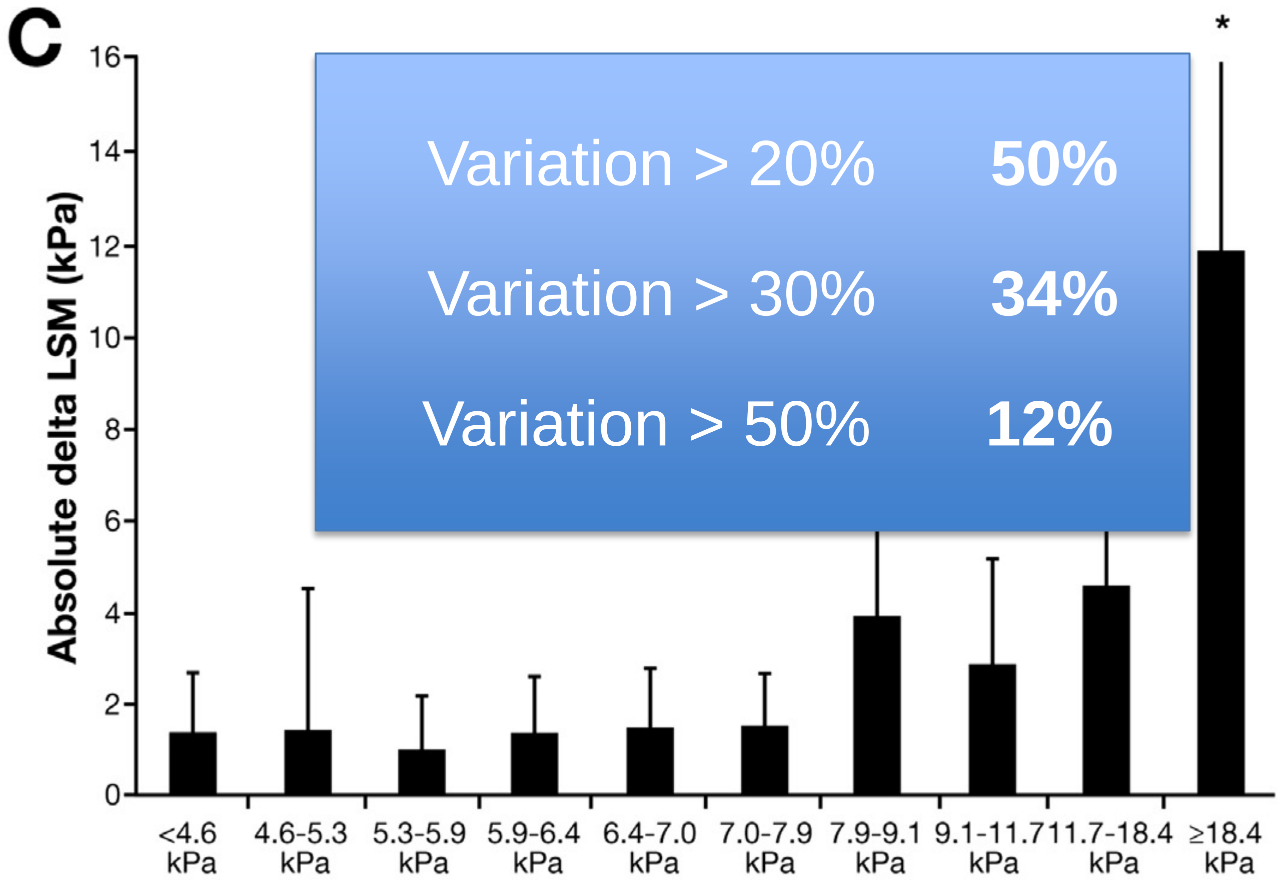
Caveats of available studies

- Mostly retrospective
- Small sample size
- Many IFN-based treatment
- Short follow-up
- No paired liver biopsy

Meta-analysis: 24 studies; N=2934 HCV patients; DAA n=10

Singh et al. Clin Gastroenterol Hepatol 2018; 16: 27-38

Variability of repeated TE measurements



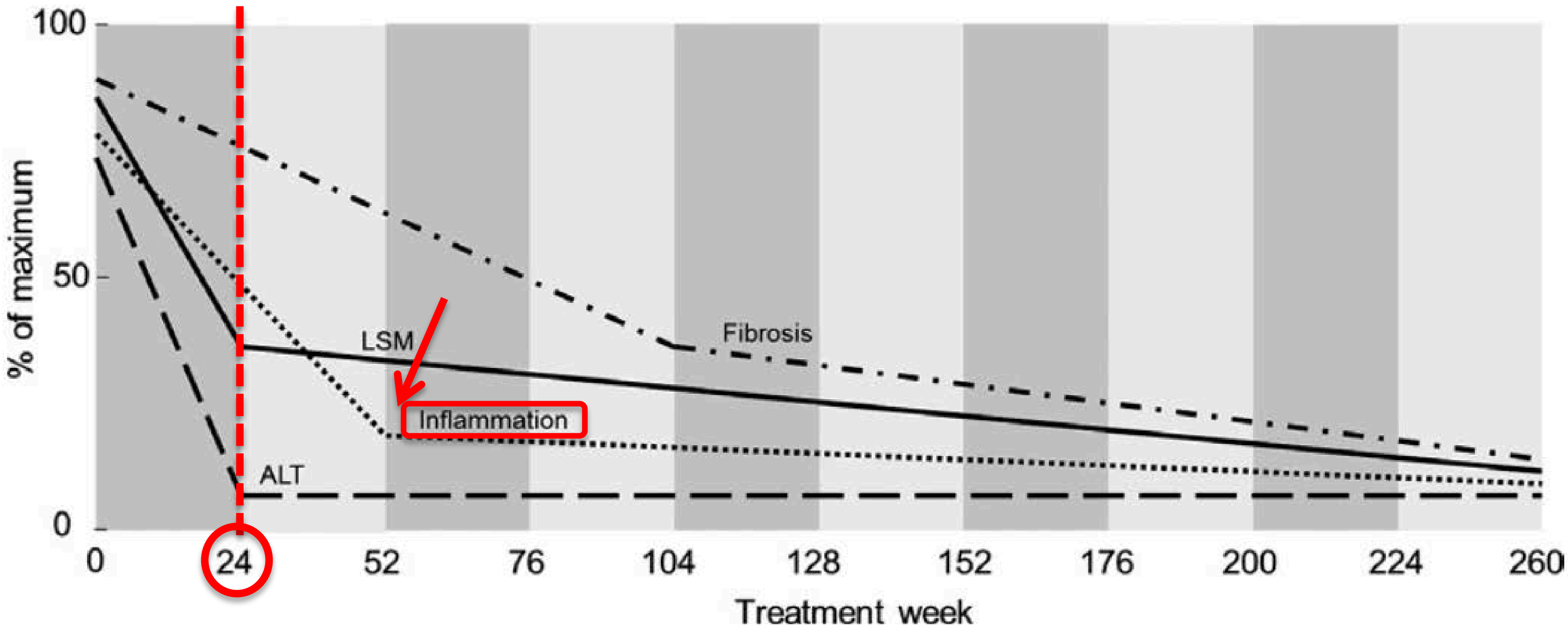
Variation > 20%	**50%**
Variation > 30%	**34%**
Variation > 50%	**12%**

531 paired liver stiffness measurements < 1 year from 452 patients

Nascimbeni et al. Clin Gastroenterol Hepatol 2015;13: 763-771.e6

2-phase decline of liver stiffness under NUC

Role of inflammation



N=534 HBV patients treated with telbivudine; 164 with paired biopsies

Liang et al. J Viral Hepat 2018; in press

Summary

- In viral hepatitis, eradication or virosupression is associated with decrease of liver stiffness over time.

- In the absence of paired liver biopsies, it is difficult to discriminate whether this is related to improvement in inflammation or fibrosis.

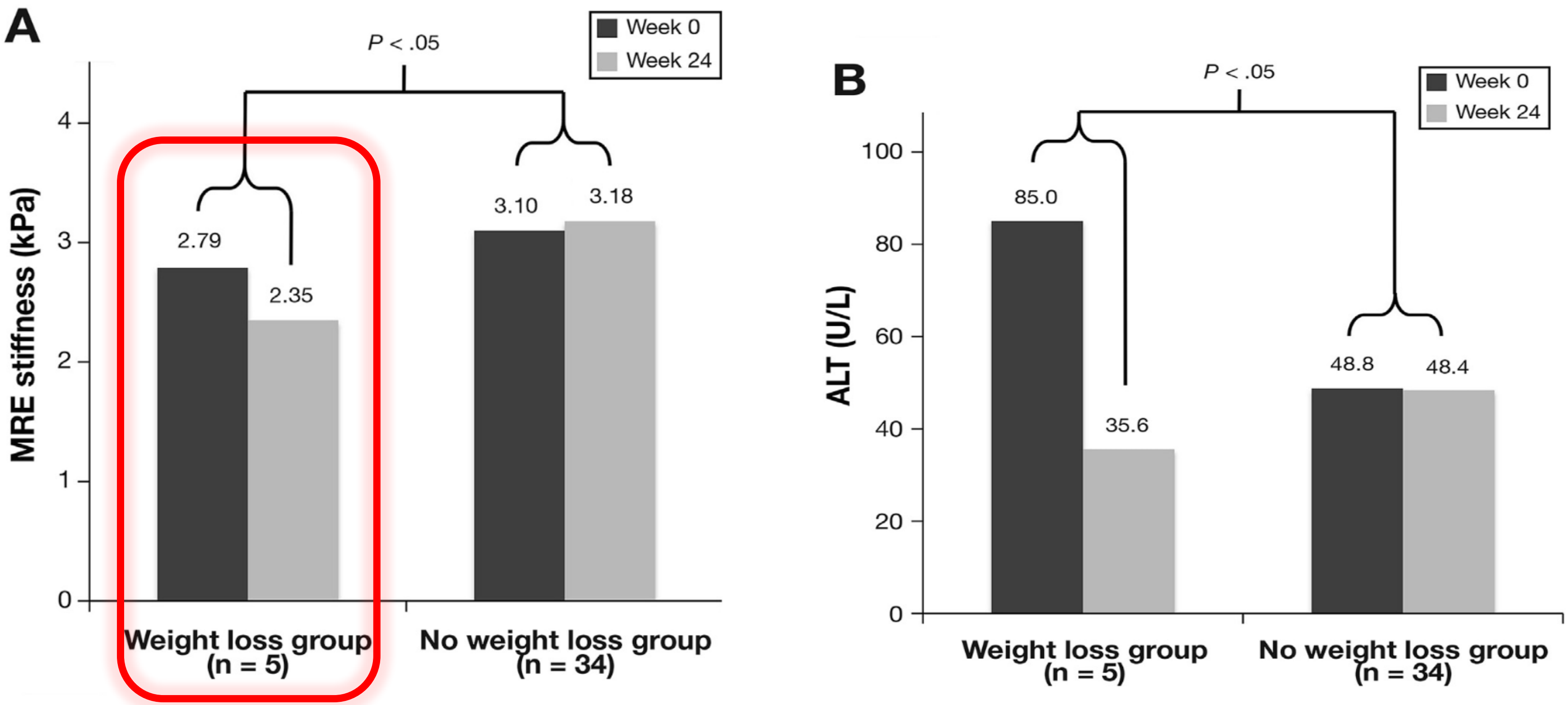
- Liver stiffness cannot be currently used as a good surrogate of cirrhosis regression.

- No standardized definition of liver stiffness improvement is available and no correlation with clinically relevant hard endpoints has been shown.

Liver stiffness decrease (MRE) with weight loss in NAFLD ?

Liver stiffness

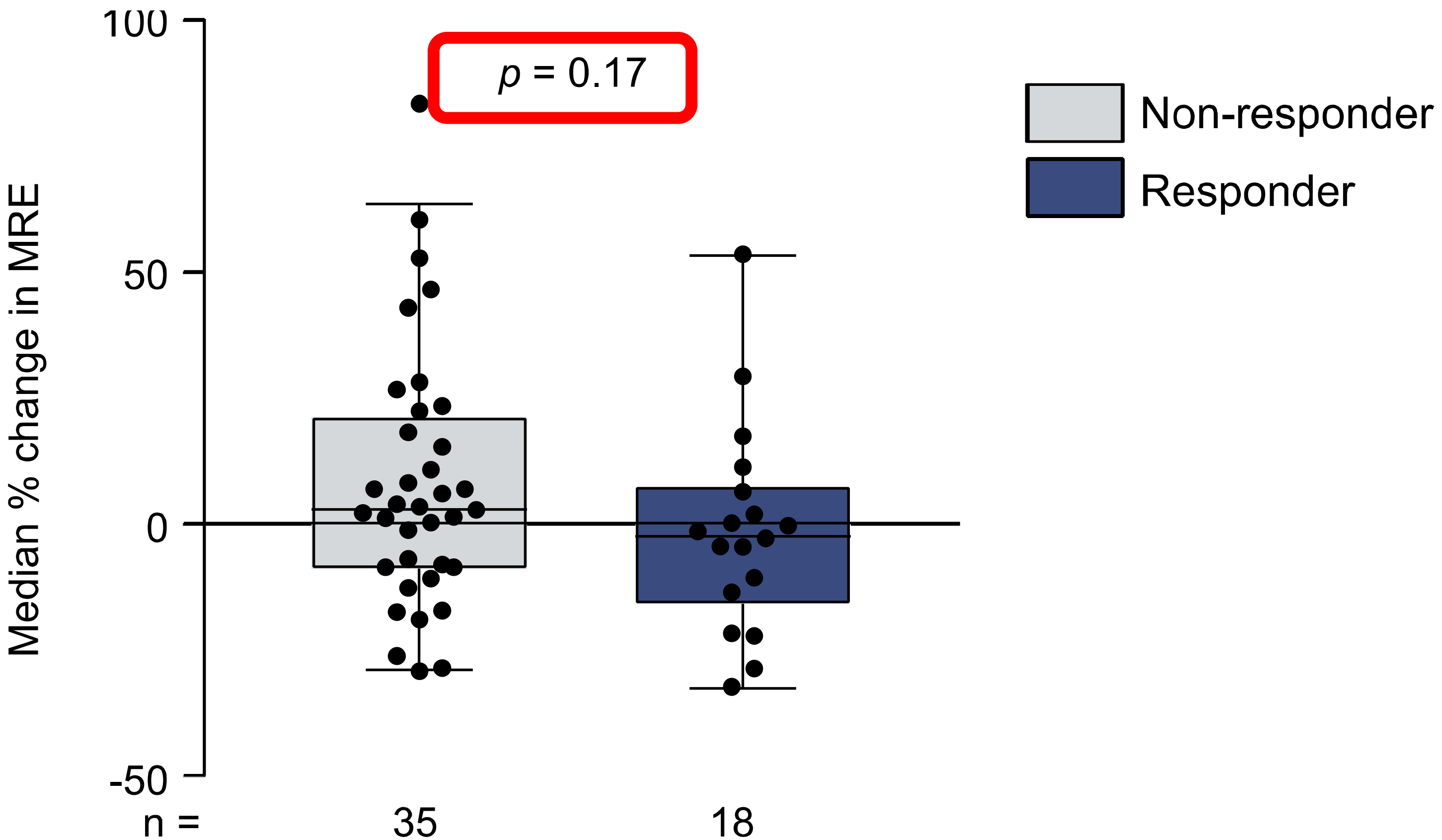
Transaminases



N= 39 treated NAFLD patients; MRE BL and 6 mo

Patel et al. CGH 2017; 15: 463-4

Liver stiffness decrease (MRE) according to fibrosis improvement (1 stage)

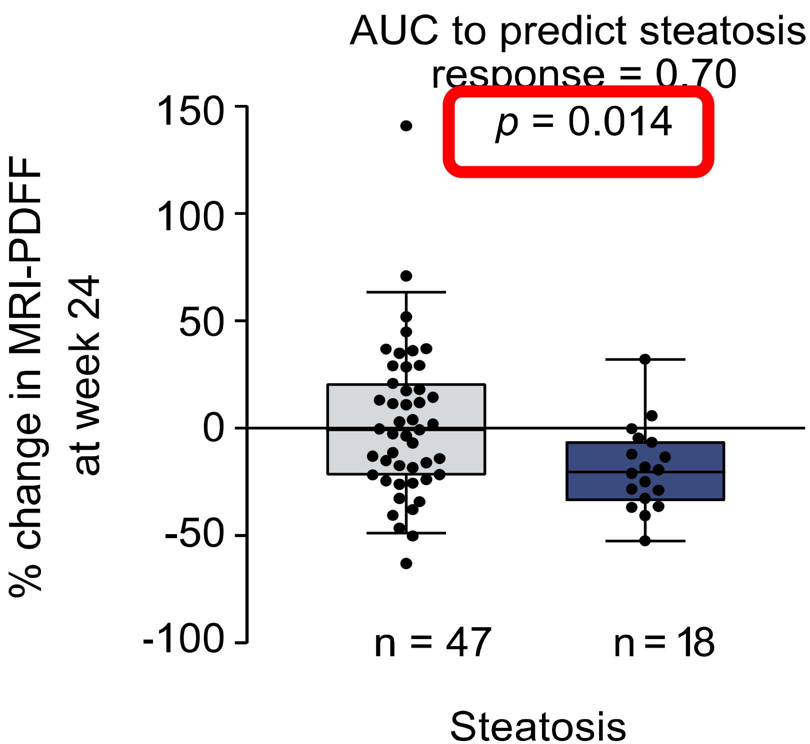


N= 54 NAFLD patients with MRE and biopsies at baseline and week 24

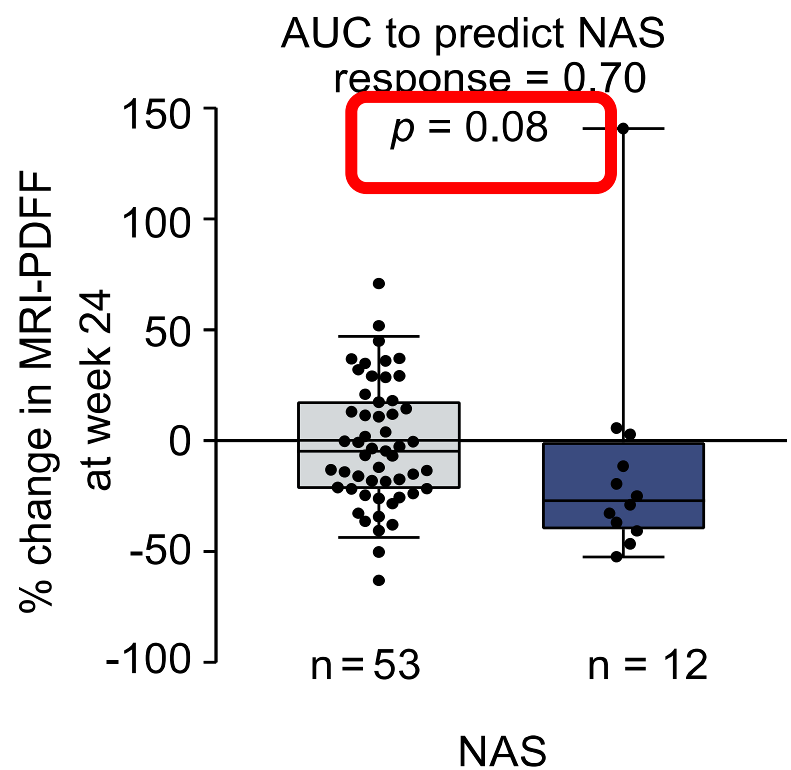
Jayakumar et al. J Hepatol 2018; in press

PDFF decrease according to NASH and steatosis improvement (1 stage)

Steatosis



NASH



N= 54 NAFLD patients with MRE and biopsies at baseline and week 24

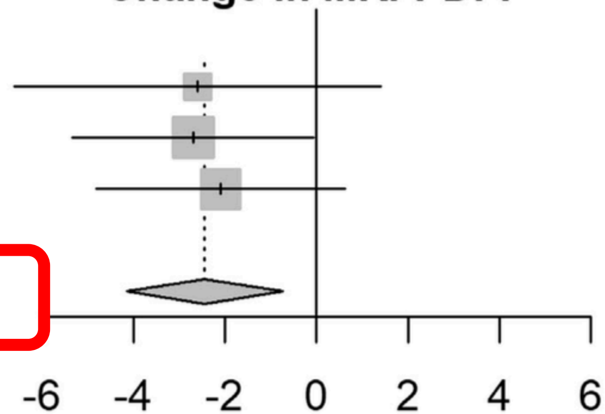
Jayakumar et al. J Hepatol 2018; in press

Changes in MRI-PDFF in placebo

Meta-analysis

Study	MD	95%-CI	Total	Weight
Cui, 2016	-2.60	[-6.61; 1.41]	17	18.3%
Le, 2012	-2.70	[-5.34; -0.06]	22	42.3%
Loomba, 2015	-2.10	[-4.83; 0.63]	22	39.5%
Random effects model	**-2.44**	**[-4.16; -0.73]**	**61**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .95$
Test for overall effect: $z = -2.79$ ($P < .01$)



N= 39 studies; 1463 patients NAFLD patients; 61 with MRI-PDFF

Han et al. CGH 2018; in press

Endpoints in early phase 2 development

Which MRI-PDFF cut-offs?

- **>5% absolute reduction ?**
- **>30 relative reduction ?**
- **Is it associated wih histological improvement?**

Take home messages (1)

- Serum biomarkers have limited value for enriching populations for clinical trials
- No highly sensitive and specific blood tests neither imaging modality can reliably discriminate NASH from simple steatosis
- TE is useful to identify NAFLD patients with advanced fibrosis, who are at the greatest risk of disease progression and appears as the method of choice
- The added value of CAP is currently under investigation

Take home messages (2)

- MRI-PDFF is the most accurate method for detection and grading of steatosis and seems sensitive to changes. Relevant cut-offs for steatosis improvement remain to be defined and validated

- MRE appears as the tool of choice for assessing treatment response but value of liver stiffness as a surrogate of fibrosis regression remains to be demonstrated

- Liver stiffness decrease needs to be correlated with hard clinical outcomes

Thank You !