Mr N… 55 yrs

- Referred for hyperferritinemia
- Type 2 diabetes
- Alcohol intake 50 g/day
- Weight 90 Kg; height 170 cm
- Physical examination: no signs of liver disease

Lab tests

- AST: 250 (ULN 40 IU/L)
- ALT: 200 (ULN 50 IU/L)
- Gamma GT: 450 (ULN 50 IU/L)
- Alkaline phosphatase: 100 (ULN 130 IU/L)
- Total Bilirubin: 15 (<17 µmol/L)
- Prothrombin Time: 75%
- Ferritin 1139 µg/ L; Transferrin saturation: 30%
- Platelet count: 140 000 /mm3

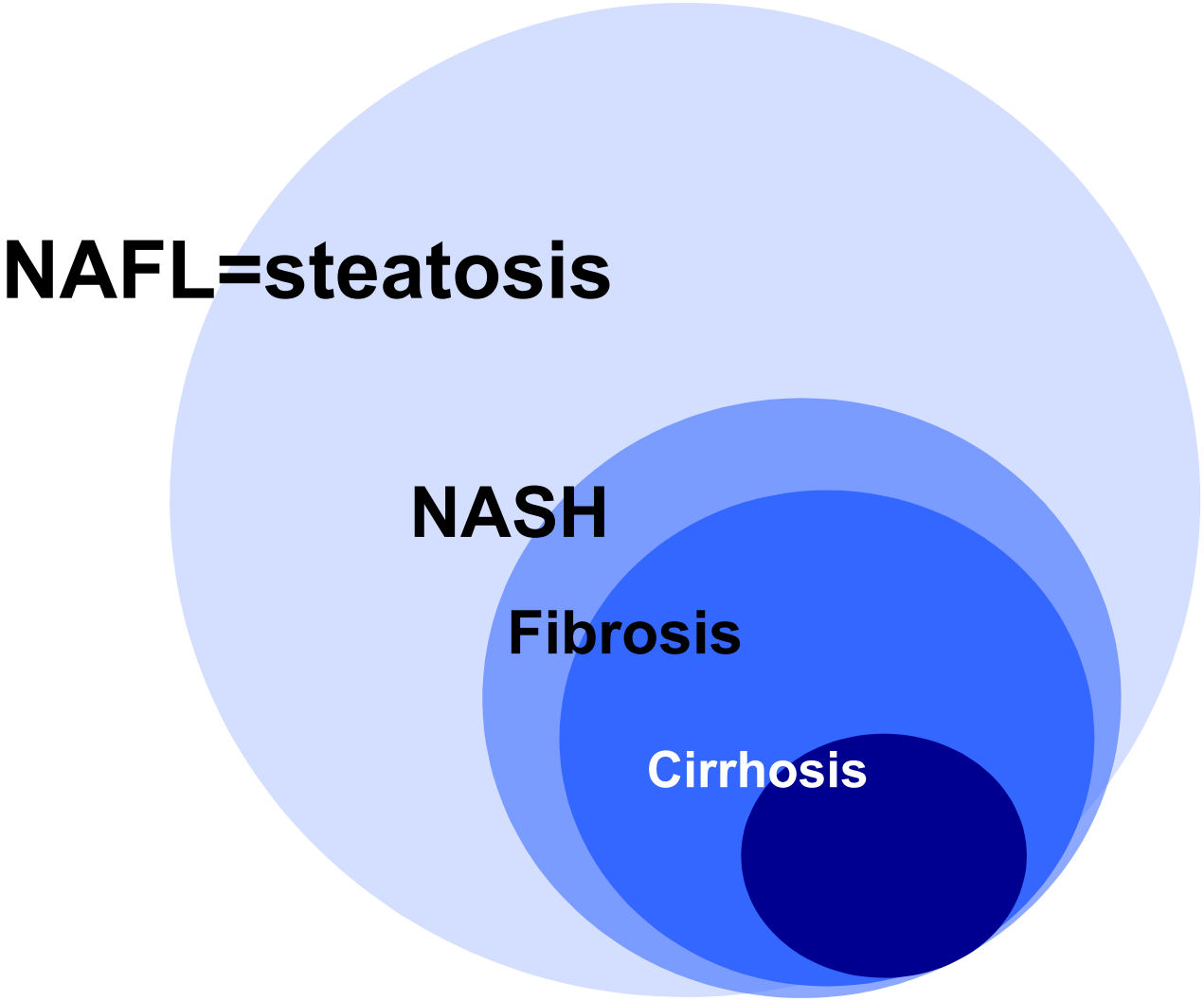
Imaging

- Ultrasound: bright liver
- CAP: 310 dB/m
- Liver stiffness: 26 kPa (IQR 4.5)

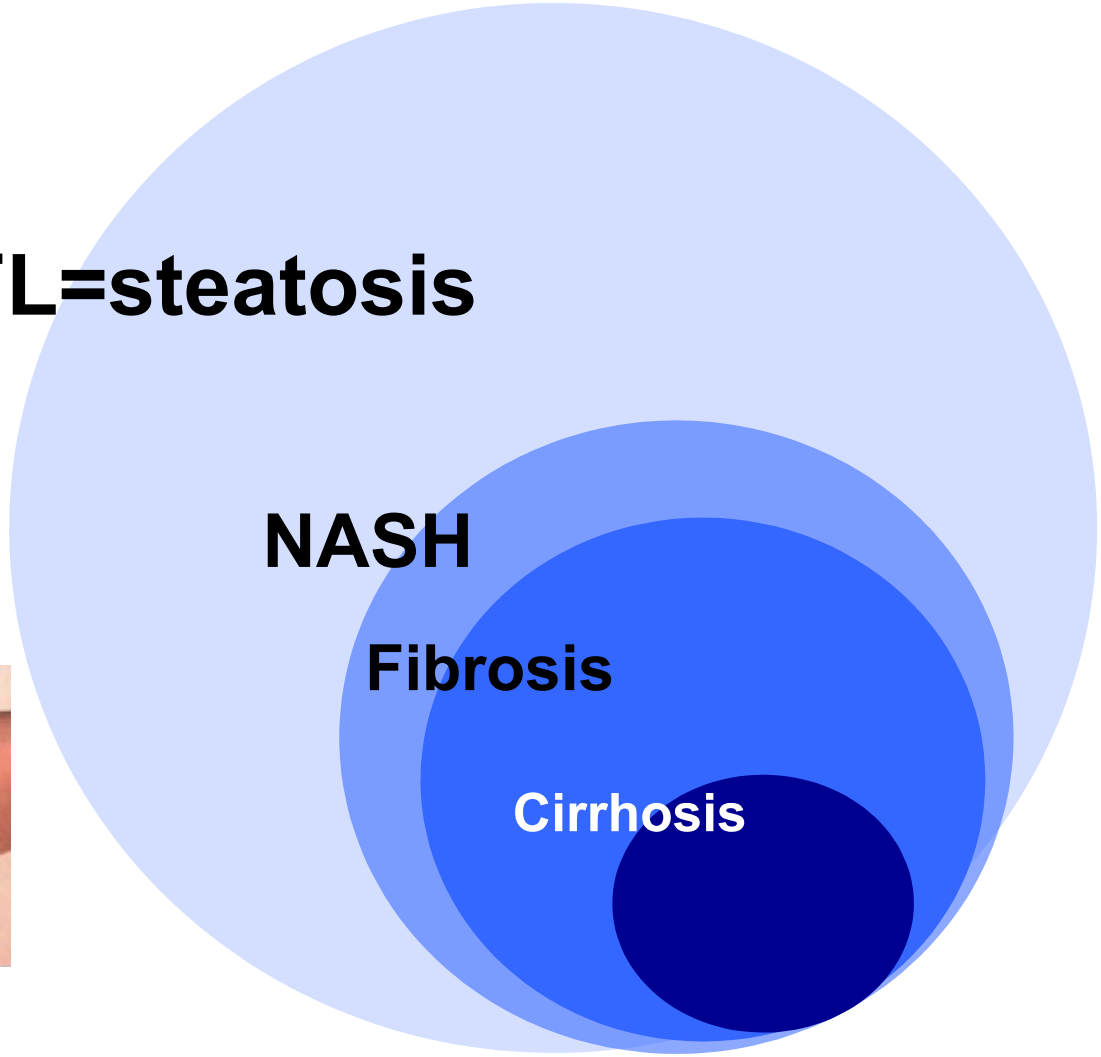
Do you need further exams for the diagnosis?

1. Serum markers
2. Liver biopsy
3. None or other

NAFLD: wide spectrum & lack of standardized definition



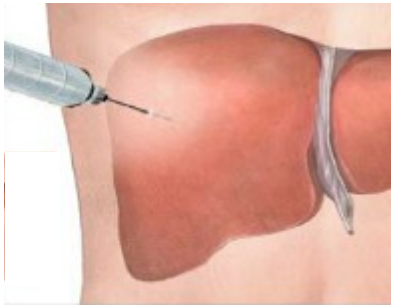
NAFLD: variable definition according to diagnostic tools



ALT

US

LB



NAFLD: diagnostic strategy

Hepatitis C

HCV RNA by PCR

NAFLD

Transaminases

Steatosis

NAFLD: diagnostic strategy

Patients at risk

- *Obesity*
- *Type 2 Diabetes*
- *↗ ALT unexplained*

Imaging

No Steatosis

Steatosis **= NAFLD**

Ultrasound

Advantages

- Simplicity
- Availability
- Inocuity
- Low cost
- Good specificity

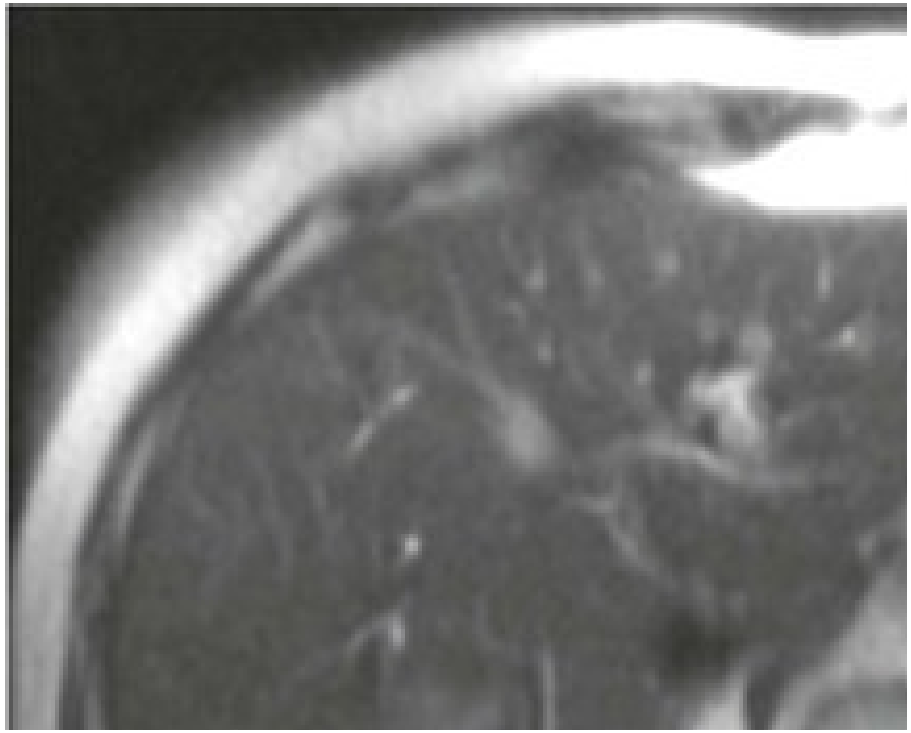
Disadvantages

- Low sensitivity
- Sensitivity↘ in obese
- Operator-dependent ++
- No quantification

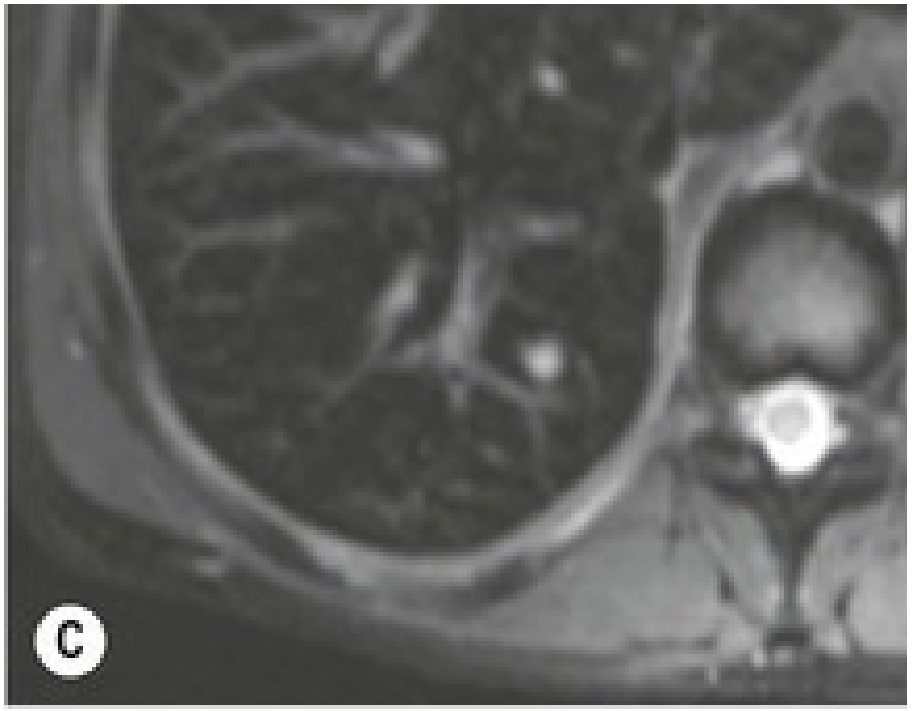
Schwenzer et al. J Hepatol 2009;51:433-45

MRI
Iron quantification

Normal liver



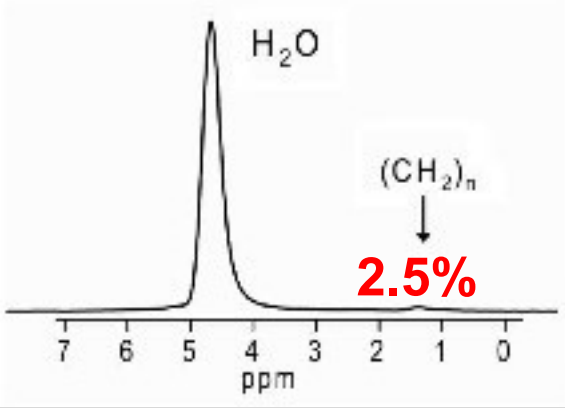
Increased hepatic iron



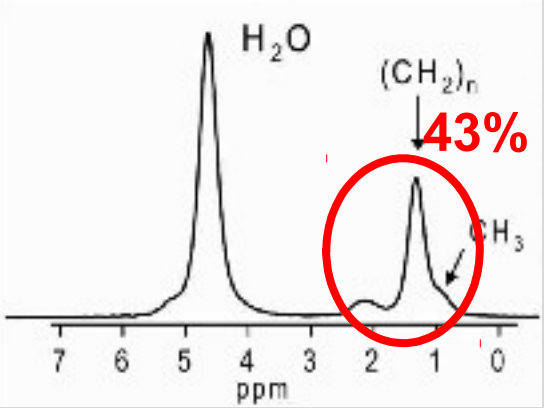
Gandon P, et al. Lancet 2004

MRI
Spectroscopy (1H MRS) / PDFF

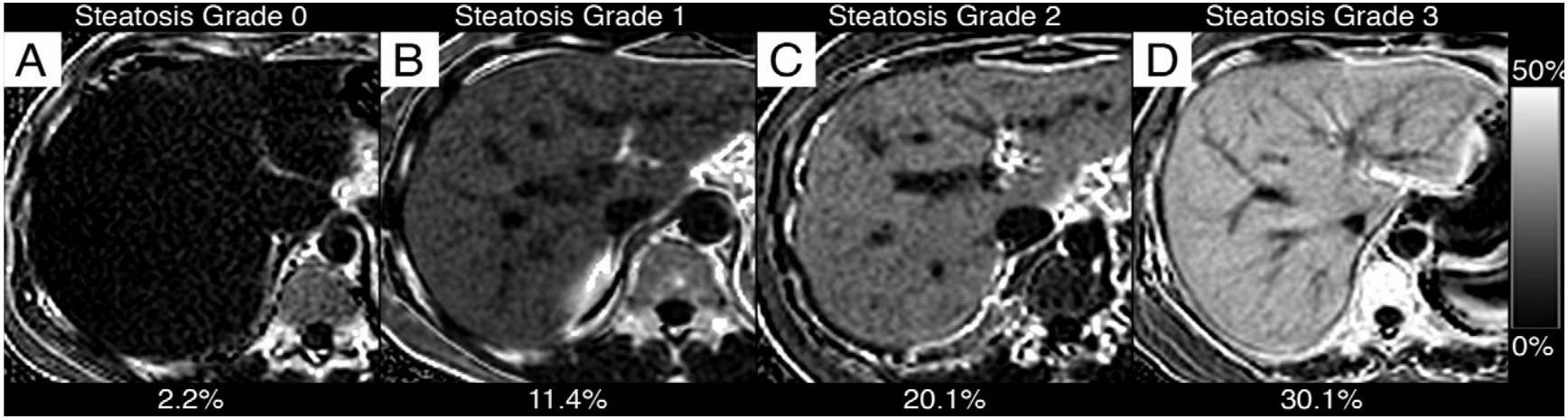
Healthy subject without steatosis



Obese with severe steatosis



Proton Density Fat Fraction (PDFF)



Dulai P, Sirlin C, Loomba R. J Hepatol 2016;65:1006-16

MRI

Spectroscopy (1H MRS) / PDFF

Advantages

Highly sensitive

Highy specific

Precise quantification

Inocuity

Disadvantages

Operator expertise

Reproductibility

Availability

High Cost

Dulai P, Sirlin C, Loomba R. J Hepatol 2016;65:1006-16

NAFLD: diagnostic strategy

Patients at risk

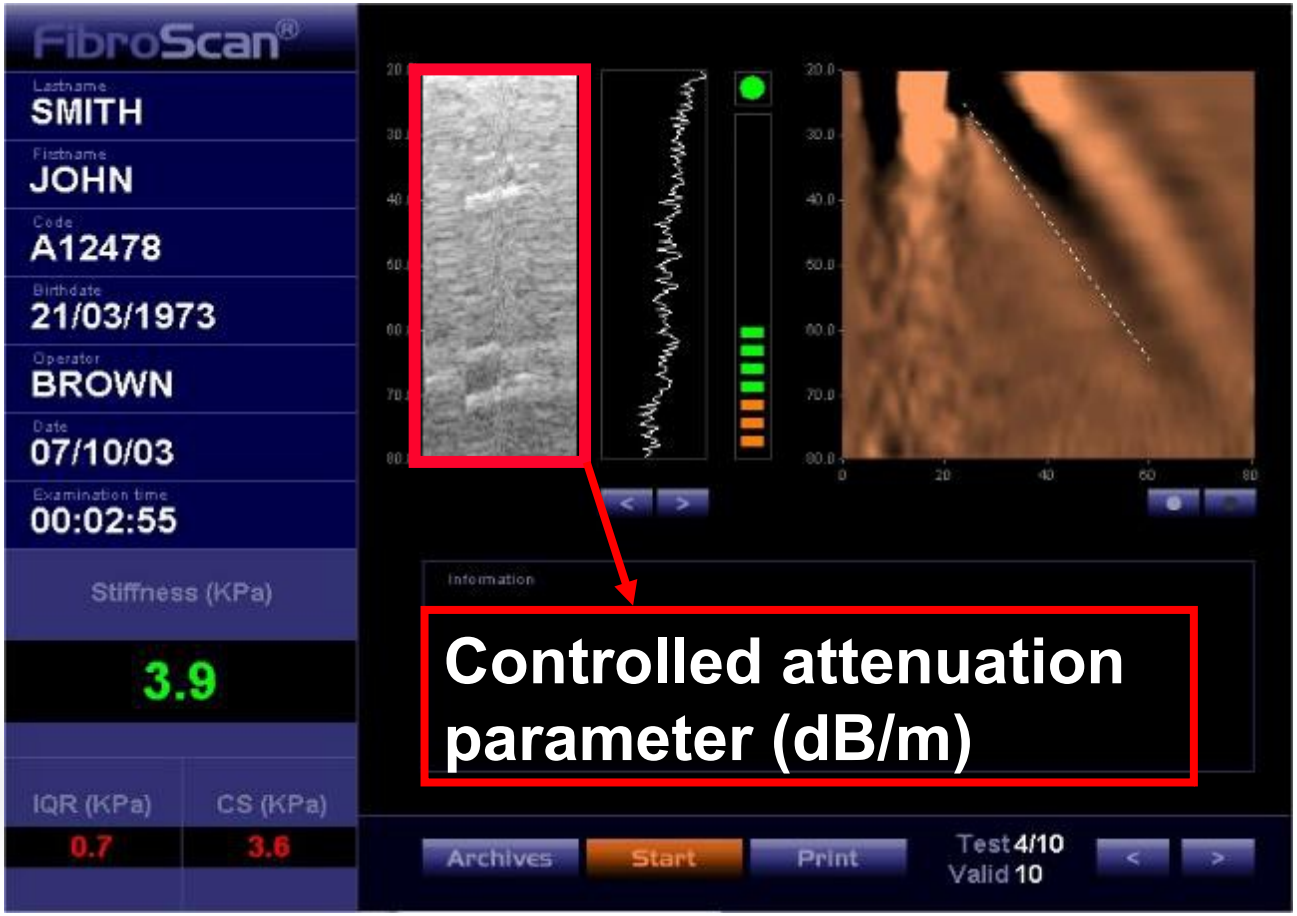
- *Obesity*
- *Type 2 Diabetes*
- *↗ ALT unexplained*

Imaging
Non-invasive tests?

No Steatosis

Steatosis **= NAFLD**

CAP (FibroScan)



Sasso et al. Ultrasound in Med & Biol 2010; 36: 1825-35

CAP diagnostic performance
summary

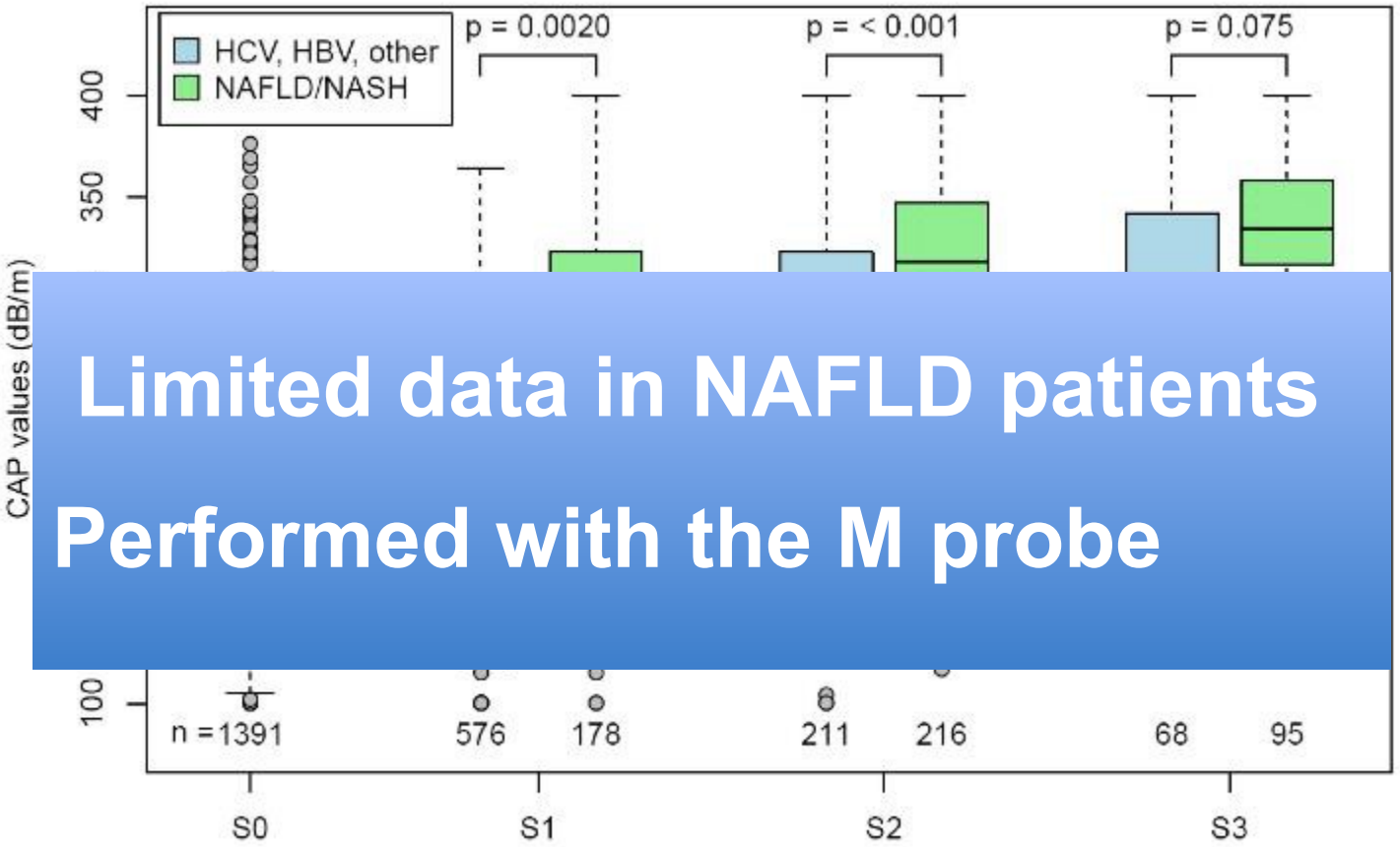
Authors	Year	Patients Total/NAFLD (n)	Etiologies	Steatosis Grading	Steatosis Prevalence (%)	Cut-off (dB/m)	AUC	Se (%)	Sp (%)	CC (%)
Sasso et al.	2010	115 / 17	Mixed	**≥11%**	58	238	0.91	91	81	-
				≥33%	39	259	0.95	89	86	-
									78	-
de Ledinghen et al.									85	77
									94	82
									91	91
Myers et al.									79	77
									62	70
									47	52
Sasso et al.	2012	615 / 0	HCV	**≥11%**	31	222	0.80	76	71	72
				≥33%	13	233	0.86	87	74	76
				≥66%	1	290	0.88	78	93	93
Friedrich-Rust et al.	2012	46 / 46	NAFLD	**≥11%**	98	-	-	-	-	-
				≥33%	74	245	0.78	97	67	-
				≥66%	46	301	0.72	76	68	-

Limited data in NAFLD patients

No consensual cut-offs

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

CAP diagnostic performance
meta-analysis



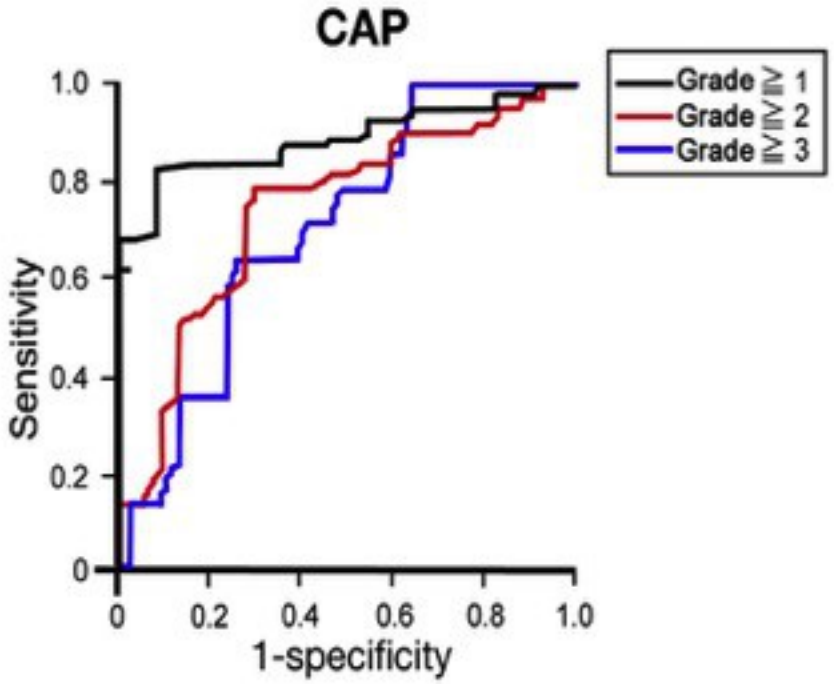
Limited data in NAFLD patients

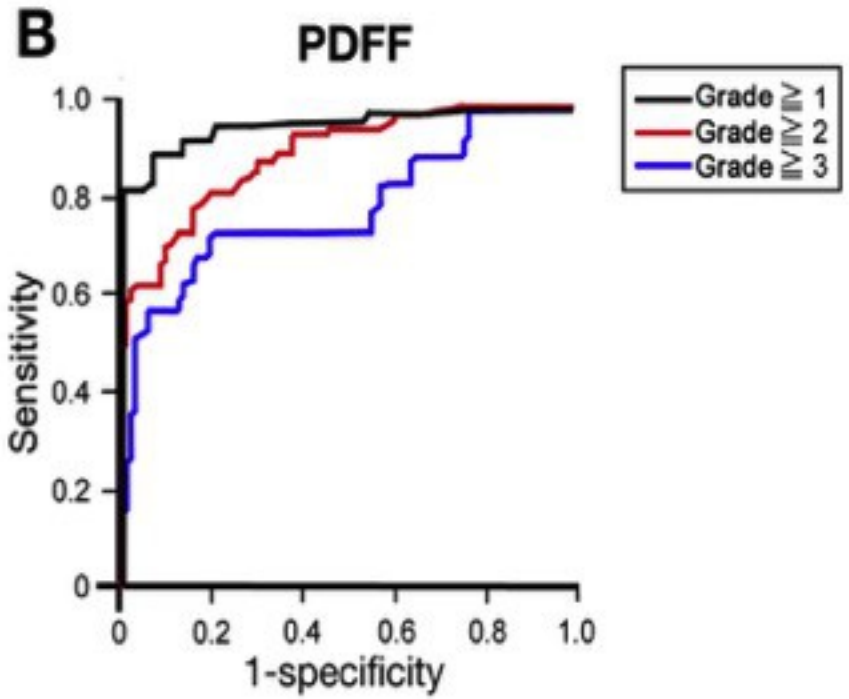
Performed with the M probe

N=2735 patients; 20% with NAFLD, S1S2S3: 27%/16%/6%

Karlas T et al. J Hepatol 2017; in press

CAP *vs.* MRI





N= 127 Japanese NAFLD patients

Imajo et al. Gastroenterology 2016; 150: 626-37

CAP *vs.* MRI

	CAP		MRI-PDFF		
Steatosis grade	Cutoff level, *dB/m*	AUROC	Cutoff level, %	AUROC	vs PDFF *P* value
≥1	236	0.88	5.2	0.96	.048[a]
≥2	270	0.73	11.3	0.90	<.001[a]
≥3	302	0.70	17.1	0.79	.015[a]

N= 127 Japanese NAFLD patients

Imajo et al. Gastroenterology 2016; 150: 626-37

Park et al. Gastroenterology 2017; in press

Summary

- CAP is promising but needs to be better validated in patients with NAFLD (no consensual cut-offs)
- CAP needs to be compared to ultrasound that, despite its limitations, remains the most widely used tool for steatosis assessment.
- CAP is now implemented with the XL probe but most studies have been performed with M probe
- Quality criteria not well defined
- MRI outperforms CAP

Serum scores of steatosis

Tests	Year	Components	Patients	Reference	AUROC
SteatoTest®	2005	FibroTest, CT, TG,BMI, glycemia	884	LB	0.72-0.86
Fatty (FLI)					84
NAFL Score					87
Hepat index					81
Lipid Accumulation Product (LPA)	2010	Sex, WC, TG	388	US	0.80

Serum scores have been designed

With different gold standards (US or LB)

And populations

Poynard et al. Comp Hepatol 2005; Bedogni et al. BMC Gastroenterol 2006; Kotronen et al. Gastro 2009; Lee et al. Dig Liver Dis 2010; Bedogni et al. BMC Gastroenterol 2010

Recommendations

Recommendations

- US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information (**A1**)
- Whenever imaging tools are not available or feasible (e.g. large epidemiological studies), serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis (**B2**)
- A quantitative estimation of liver fat can only be obtained by ^{1}H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting (**A1**)

EASL-EASD-EASO Clinical practice Guidelines. J Hepatol 2016; 64: 1388-402.

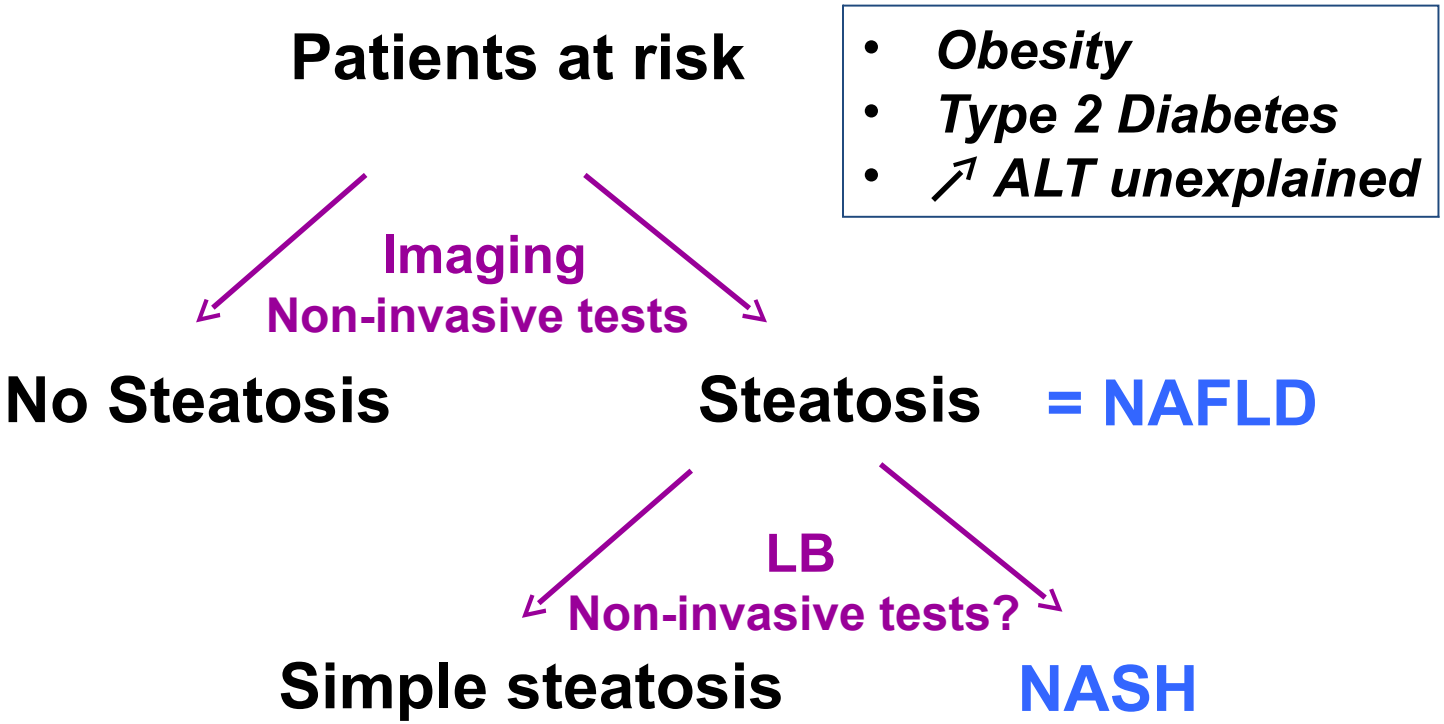
Mr N… 55 yrs

- Steatosis very likely

Do you need further exams for the diagnosis?

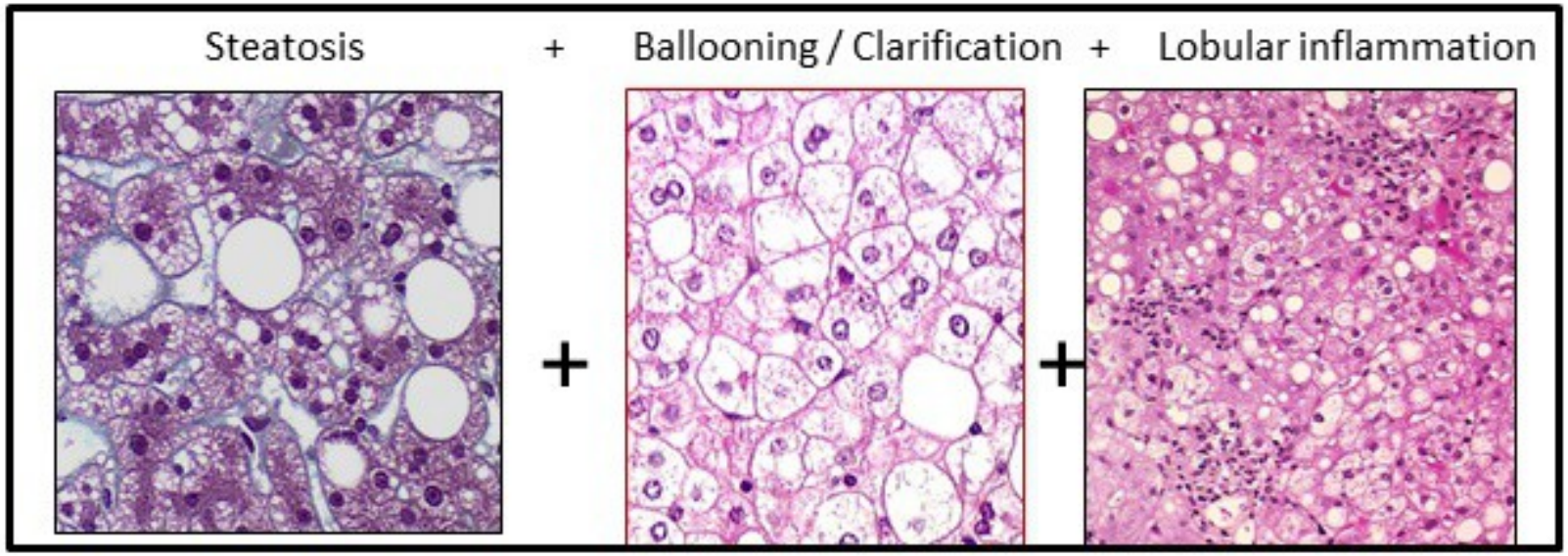
1. Serum markers
2. Liver biopsy
3. None or other

NAFLD: diagnostic strategy



NASH = histologic definition

> 5% steatosis
+ ballooning / clarification hepatocytes
+ lobular inflammation



Sanyal A et al. Hepatology 2011; 54: 344-53

NASH non-invasive diagnosis : CLA score

Risk stratification	CLA score	Scoring			NASH in each score (%)
		By CAP values (>250 dB/m)	By LS value (>7 kPa)	By ALT level (>60 IU/L)	
Low risk	0	0	0	0	5.0
Interm					
risk					
High r					
		0	1	2	
	4	1	1	2	84.6

No reliable non-invasive test for NASH

N= 183 patients with suspected NAFLD; 51% NASH

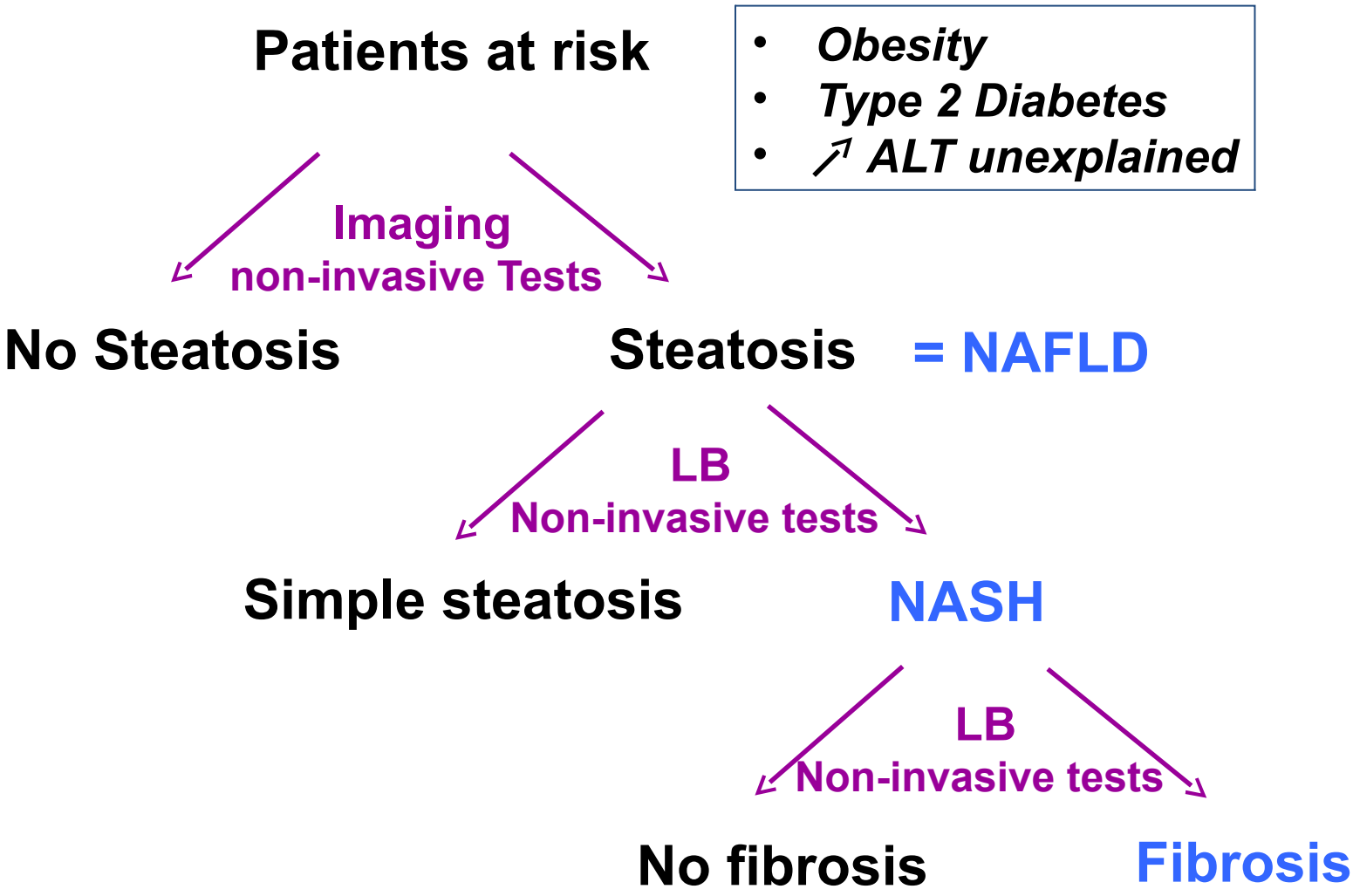
Lee et al. PlosOne 2016;

Mr N… 55 yrs

- Steatosis very likely
- Not keen for a liver biopsy
- Liver stiffness: 26 kPa (IQR 4.5)

How important is it to diagnose NASH?

NAFLD: diagnostic strategy



TE has high accuracy for cirrhosis

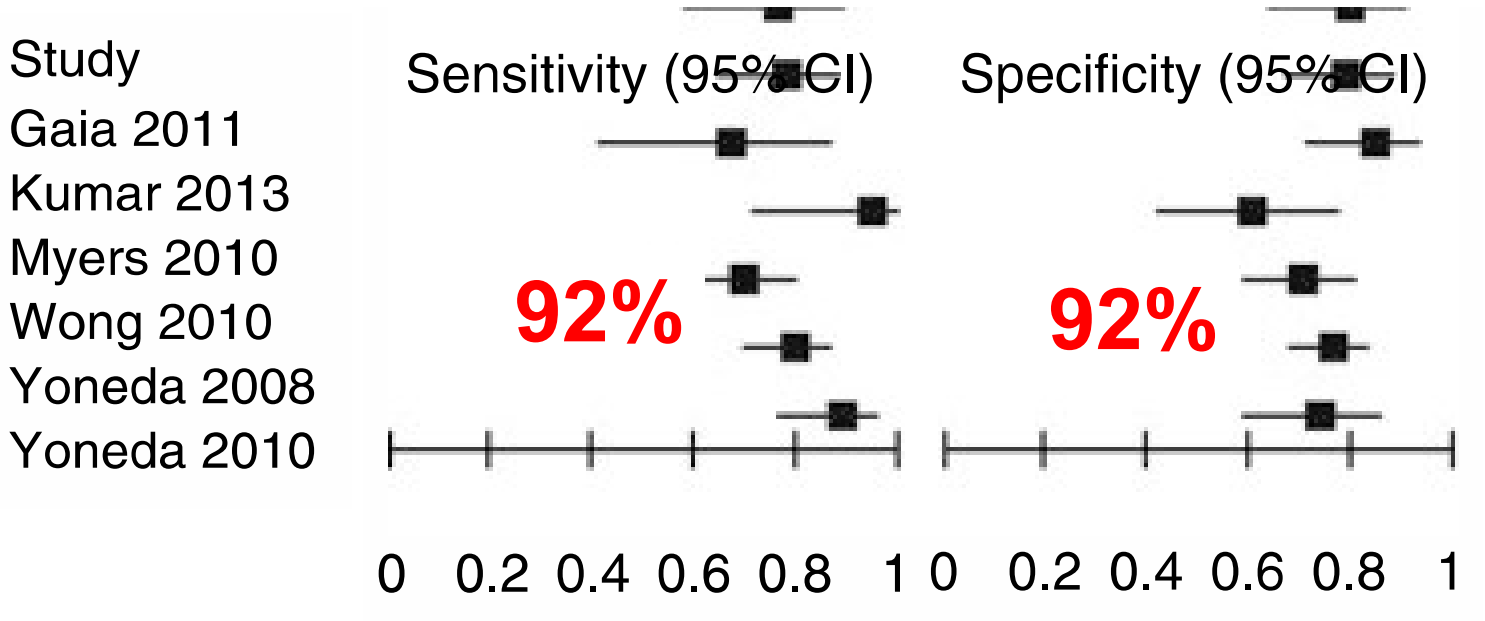
meta-analyses

	Number of included studies	Number of included subjects for analysis	AUROC
			F4
Talwalkar[15]	9	2,083	0.957
Stebbing[16]	22	4,760	0.94
Fredrich-rust et al[17]	50	8,206	0.94
Tsochatzis et al[18]	40	7,723	N/A
Chon et al	18	2,772	**0.929**

Talwalkar et al. CGH 2007 *Friedrich-Rust et al. Gastroenterology 2008*
Stebbing et al. APT 2010 *Tsochatzis et al. J Hepatol 2011* *Chon et al. PLoS ONE 2012*

TE has high diagnostic accuracy for NAFLD cirrhosis

Meta-analysis



6 studies; n= 639 patients

Kwok et al. Aliment Pharmacol Ther 2014; 39: 254-69

Recommendations
interpretation of TE results

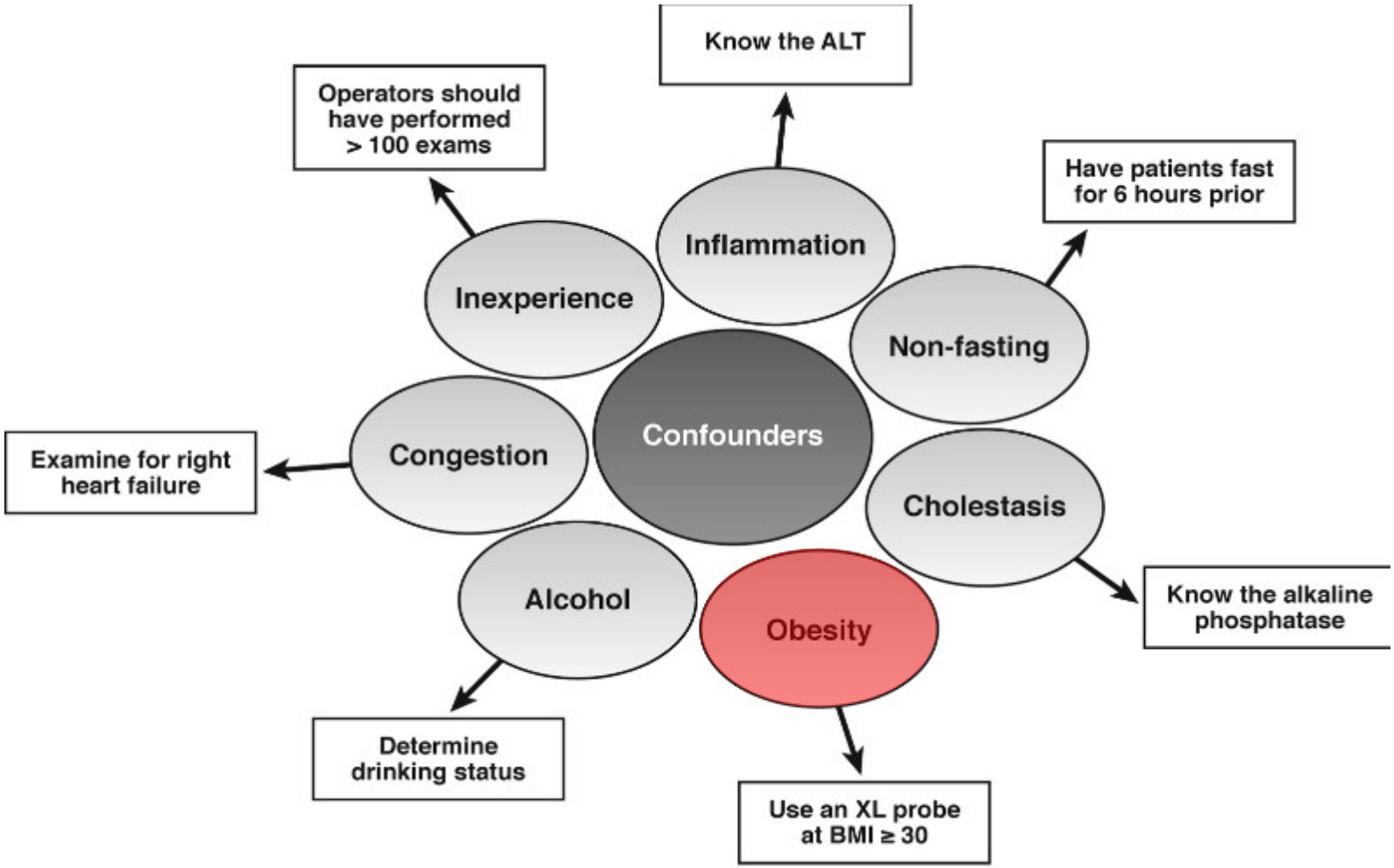
- Correct interpretation of TE results in clinical practice must consider the following parameters:
  - IQR/ median value (<30%),
  - Serum aminotransferases levels (<5 x ULN),
  - BMI (use XL probe above 30 kg/m^2 or if skin-to-capsule distance is >25 mm),
  - Absence of extra-hepatic cholestasis,
  - Absence of right heart failure, or other causes of congestive liver
  - Absence of ongoing excessive alcohol intake

  (**A1**)

EASL-ALEH Clinical practice Guidelines. J Hepatol 2015; 63: 237-64.

Confounders of liver stiffness

summary for clinical practice



Tapper, Castera & Afdhal. Clin Gastroenterol Hepatol 2015; 13:60-7

FibroScan and NAFLD
Comparison M & XL probe

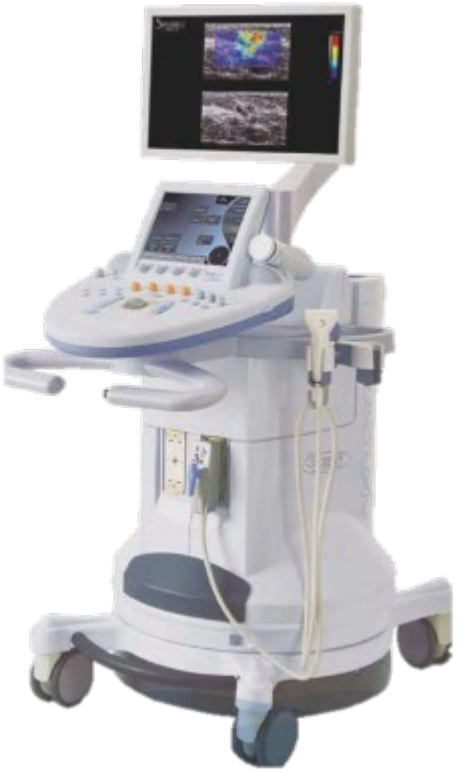
Parameters	M probe	XL probe	p
Failure	10%	2%	0.002
Reliable result	67%	75%	0.093

N= 193 NAFLD patients

Wong et al. Am J Gastroenterol 2012; 107: 1862-71.

What about Novel techniques ?

ARFI



SWE

Novel techniques
Advantages & disavantages

ARFI

- **Advantages**
  - Can be implemented on a regular US machine
  - Good applicability
  - Performance equivalent to TE
- **Disadvantages**
  - Results in meters/sec
  - Narrow range of values
  - Quality criteria not well defined

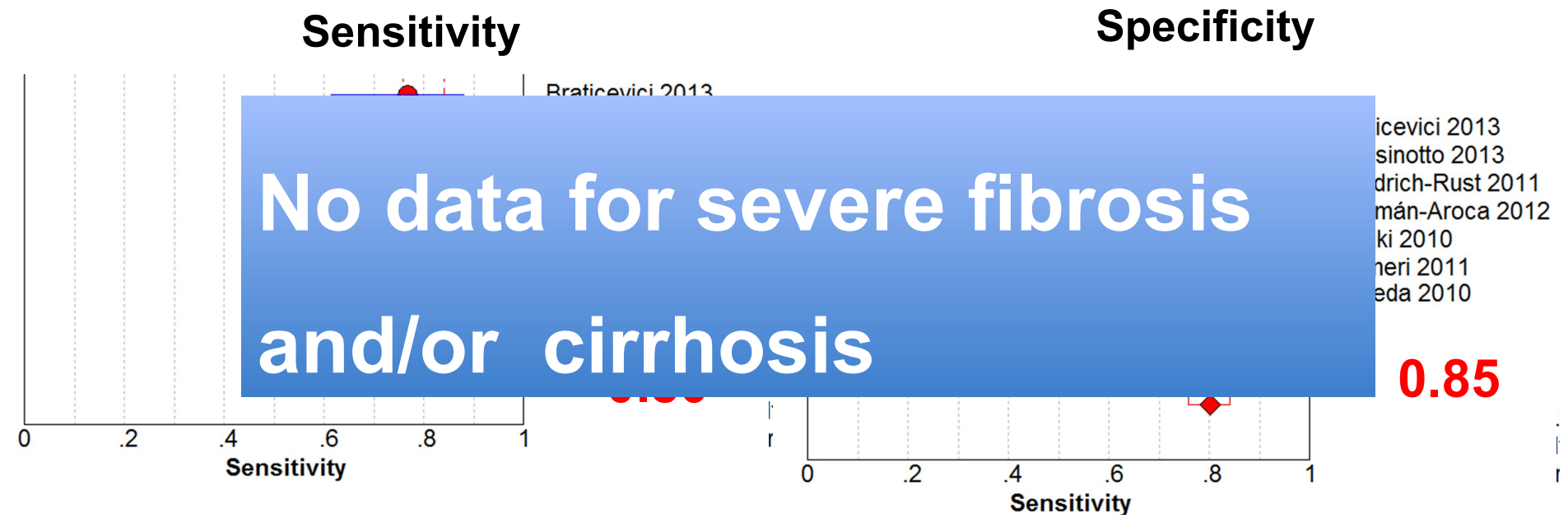
SWE

- **Advantages**
  - Can be implemented on a regular US machine
  - High range of value (2-150 kPa)
  - Performance equivalent toTE
- **Disadvantages**
  - Less well evaluated
  - Quality criteria not well defined

Friedrich-Rust, Poynard & Castera. Nat Rev Gastroenterol Hepatol 2016; 13; 402-11

Performance of ARFI in NAFLD
meta-analysis

Significant fibrosis



No data for severe fibrosis and/or cirrhosis

7 studies; n = 723 patients

Liu et al. PlosOne 2015

Comparison between SWE, TE & ARFI NAFLD

SWE outperformed TE and ARFI for F≥2 only

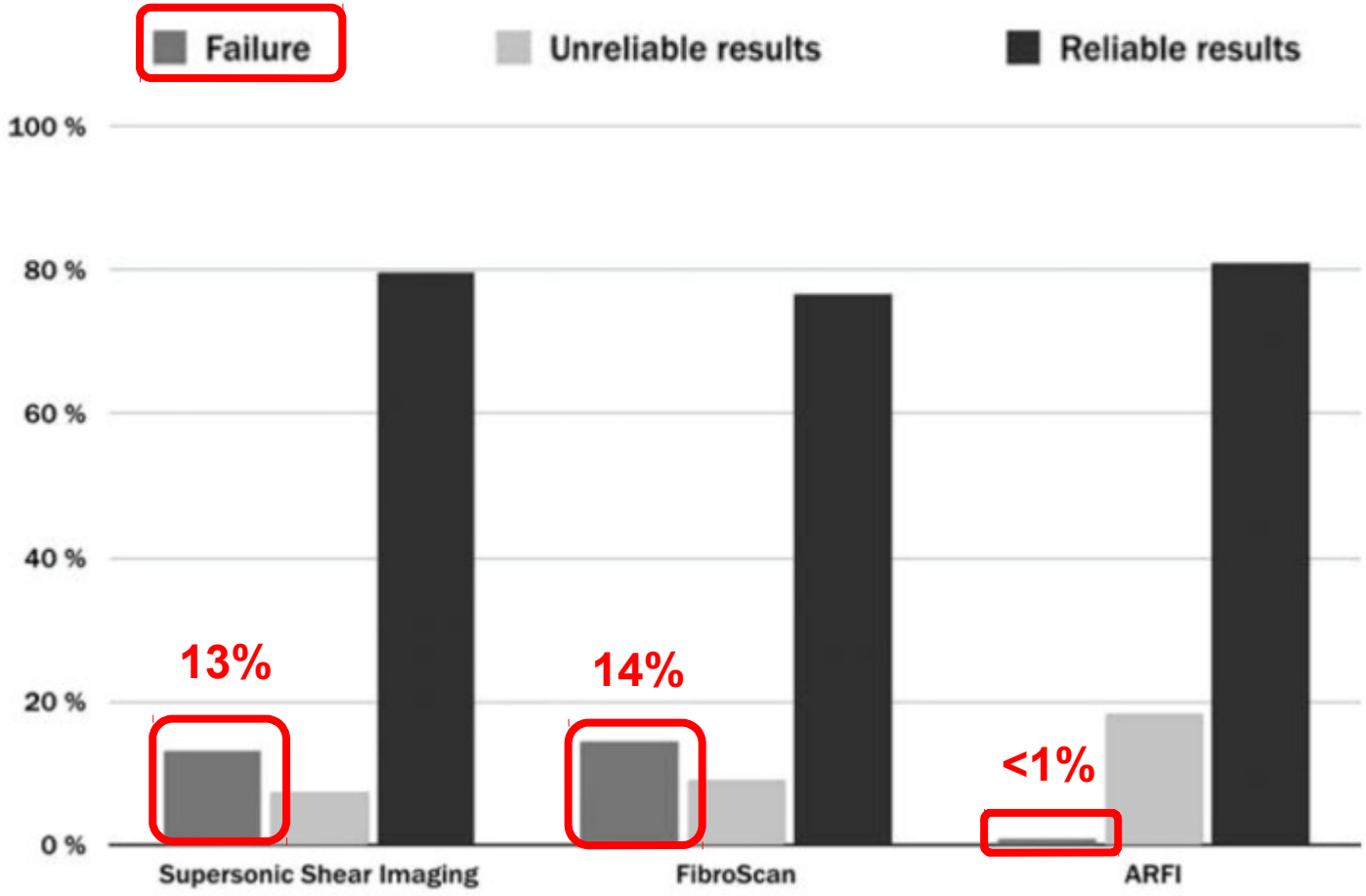
P=0.004

Fibrosis Stage	AUROC (95% CI)	Fibrosis Stage	AUROC (95% CI)	Fibrosis Stage	AUROC (95% CI)
SSI, kPa		FibroScan, kPa		ARFI, m/s	
≥F2	0.86 (0.79-0.90)	≥F2	0.82 (0.76-0.87)	≥F2	0.77 (0.70-0.83)
≥F3	0.89 (0.83-0.92)	≥F3	0.86 (0.80-0.90)	≥F3	0.84 (0.78-0.89)
F4	0.88 (0.82-0.92)	F4	0.87 (0.79-0.92)	F4	0.84 (0.78-0.89)

N= 291 NAFLD patients

Cassinotto et al. Hepatology 2016; 63: 1817-27

Comparison between SWE, TE & ARFI
Failure, unreliable results



N= 291 NAFLD patients

Cassinotto et al. Hepatology 2016; 63: 1817-27

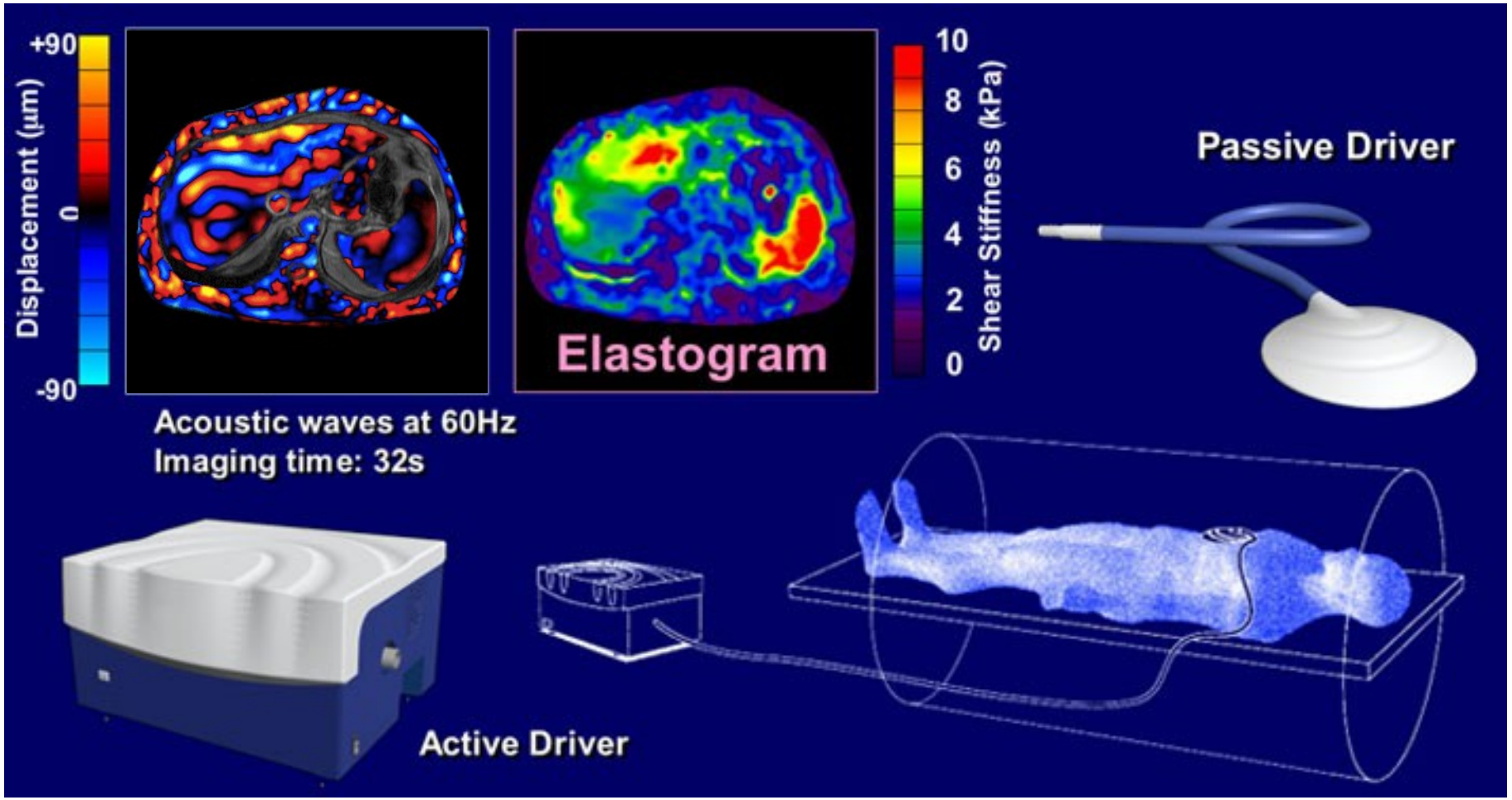
Novel techniques ?

Insufficient data in NAFLD

ARFI

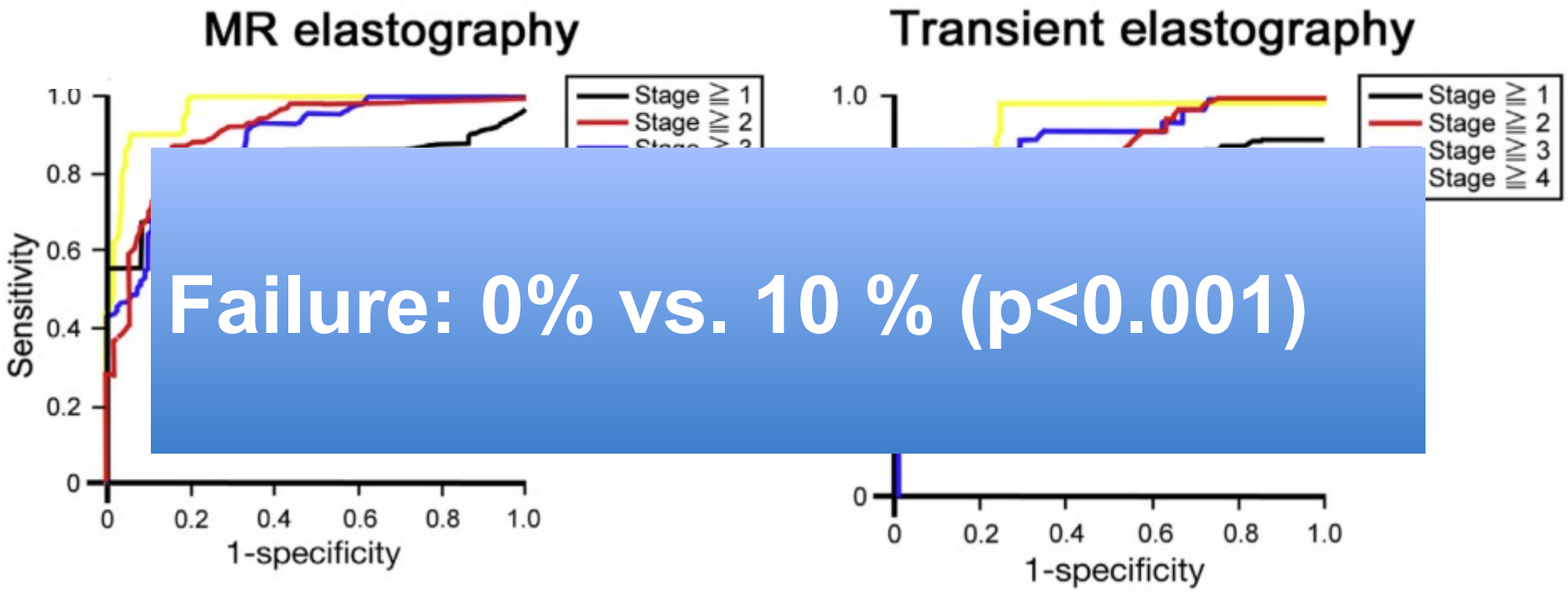
SWE

Magnetic resonance elastography



Muthupillai et al. Science 1995; 269: 1854-7

Diagnostic performance in NAFLD
MR elastography *vs.* TE



Failure: 0% vs. 10 % (p<0.001)

N= 142 Japanese NAFLD patients

Imajo et al. Gastroenterology 2016; 150: 626-37

Diagnostic performance in NAFLD
MR elastography *vs.* TE

Modality	Stage 0 vs stage 1–4 AUROC	95% CI	*P* value	vs MRE *P* value	Stage 0–1 vs stage 2–4 AUROC	95% CI	*P* value	vs MRE *P* value
MRE	0.83	0.72–0.93	.003		0.91	0.86–0.96	<.001	
TE	0.78	0.70–0.87	.003	.466	0.82	0.74–0.89	<.001	.001[a]

Modality	Stage 0–2 vs stage 3–4 AUROC	95% CI	*P* value	vs MRE *P* value	Stage 0–3 vs stage 4 AUROC	95% CI	*P* value	vs MRE *P* value
MRE	0.89	0.83–0.94	<.001		0.97	0.94–1.00	<.001	
TE	0.88	0.79–0.97	<.001	.426	0.92	0.86–0.98	<.001	.049[a]

N= 142 Japanese NAFLD patients

Imajo et al. Gastroenterology 2016; 150: 626-37

MR elastography *vs.* TE
critical analysis

Cuf-offs

Fibrosis stage	TE (n Cut-off level, *kPa*	
≥1	7.0	0.78
≥2	11.0	0.82
≥3	11.4	0.88
≥4	14.0	0.92

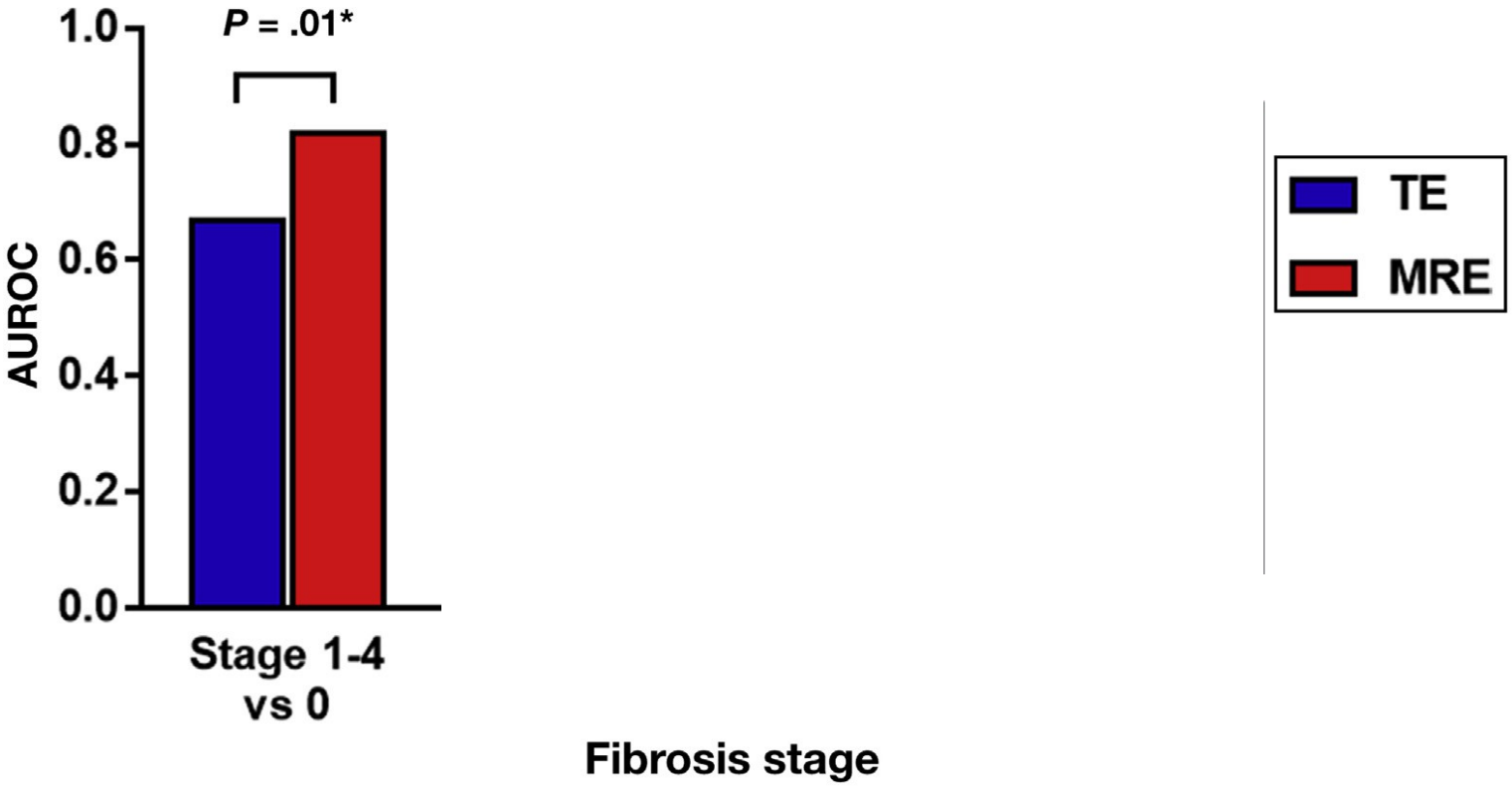
External validation needed with XL probe

Cost

		US dollars) TE
		65
USA	2871	137
United Kingdom	335	216
France	363	29

Imajo et al. Gastroenterology 2016; 150: 626-37

Diagnostic performance in NAFLD
MR elastography *vs.* TE



N= 104 American NAFLD patients

Park et al. Gastroenterology 2017; in press

What about Serum biomarkers? comparison with TE

Fibrosis test	AUROC	
	F ≥3	F4
BARD	0.695 ± 0.024	0.694 ± 0.031
NFS	0.732 ± 0.024	0.766 ± 0.032
FibroMeter^{NAFLD}	0.759 ± 0.023	0.779 ± 0.029
APRI	0.754 ± 0.023	0.767 ± 0.034
FIB4	0.780 ± 0.022	0.777 ± 0.033
Fibrotest	0.736 ± 0.024	0.761 ± 0.034
Hepascore	0.778 ± 0.022	0.807 ± 0.034
FibroMeter^{V2G}	0.817 ± 0.020	0.824 ± 0.029
LSM	0.831 ± 0.019	0.864 ± 0.024

N= 360 NAFLD patients

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

Take Home messages

- .CAP is promising tool for non-invasive diagnosis of steatosis

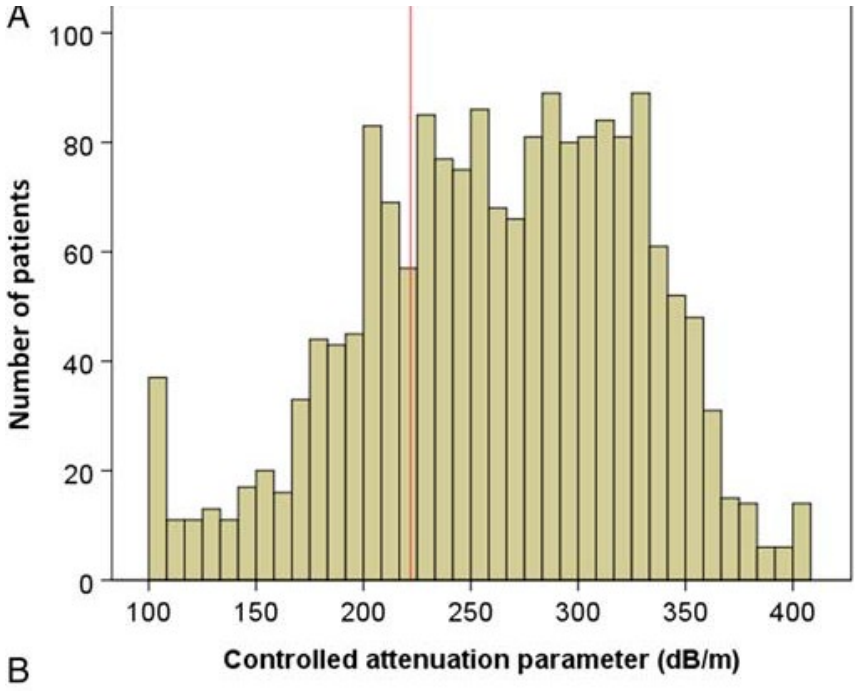
- .MRI-PDFF is currently the best tool but not ready for routine use

- .There is currently no validated tool for non-invasive diagnosis of NASH and LB remains the reference standard.

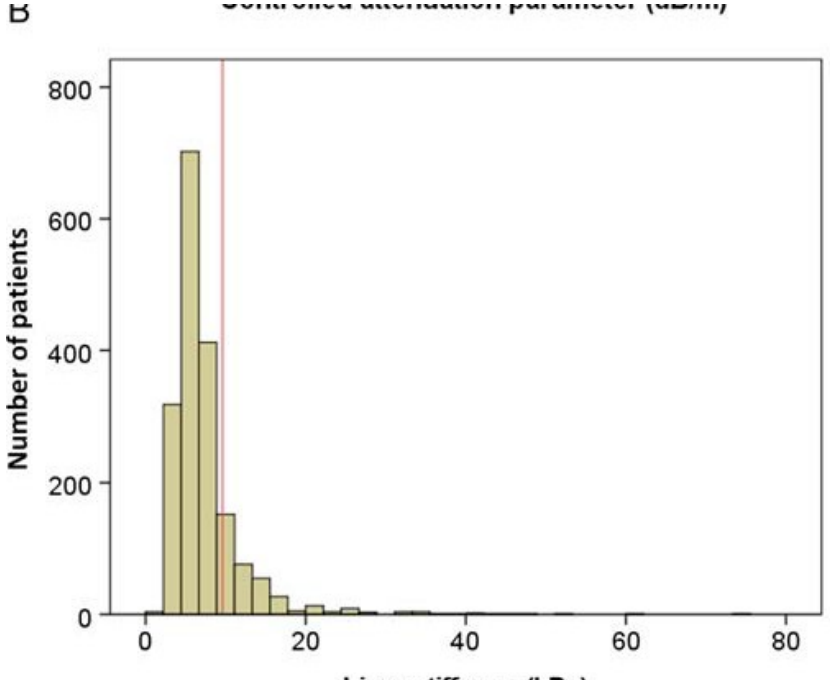
- .Non-invasive tests, particularly transient elastography, are accurate for diagnosing severe fibrosis / cirrhosis.

Screening diabetics for NAFLD

CAP >222db/m 73%



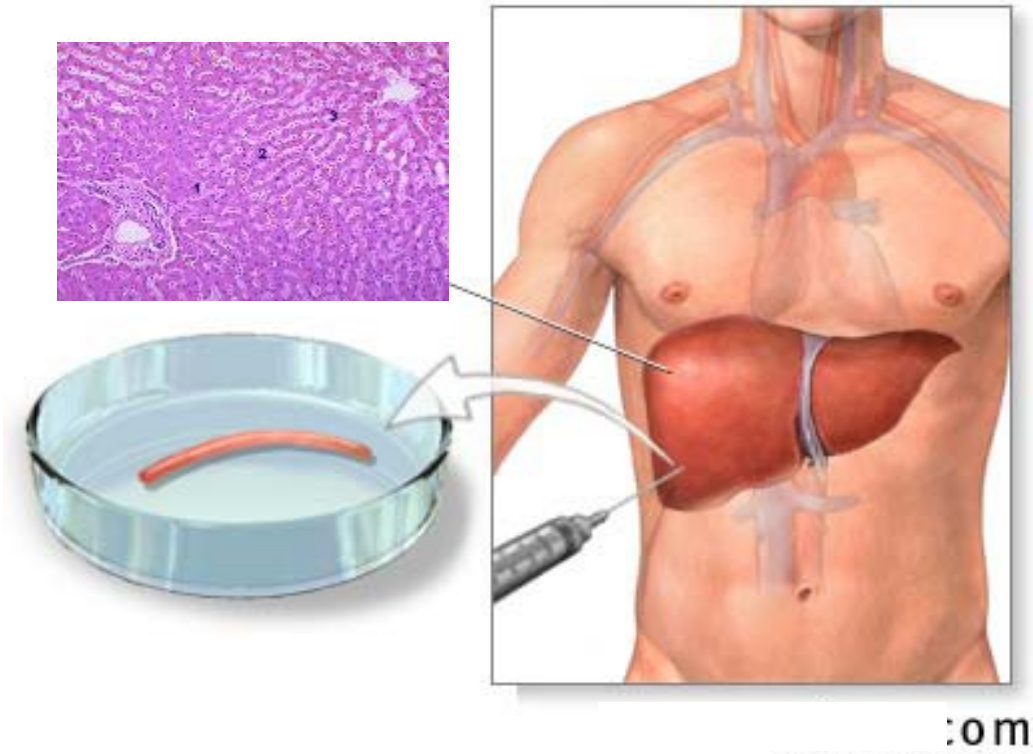
LSM >9.6kPa 18%



N= 1918 diabetics Chinese patients

Kwok et al. Gut 2016; 65: 1359-65

Screening diabetics for NAFLD



NASH: 56%

F3-F4: 50%

N= 94 liver biopsies

Kwok et al. Gut 2016; 65: 1359-65