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Addressing Unmet Needs through Innovation
In hepaTology and gastroenterologY

Non-invasive Tests in NAFLD

Creating Pathways between Primary Care and Liver Clinics

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Speaker's name : Laurent CASTERA, Clichy

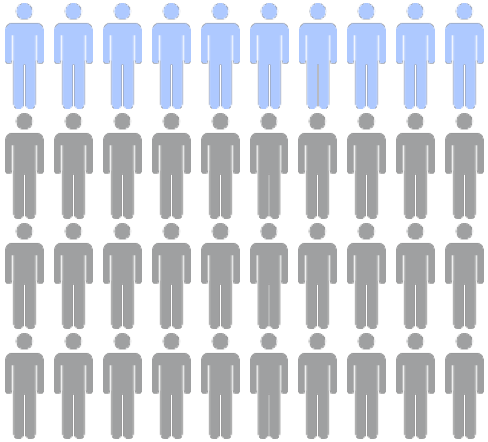
 I have the following potential conflicts of interest to report:

Speaker’s bureau: Allergan, Gilead, Intercept, Merck, Novo Nordisk, Pfizer, Servier

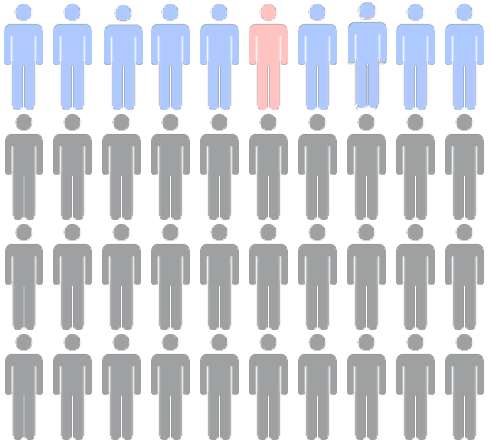
Honoraria : Abbvie, echosens, intercept, Gilead

The challenge is to identify patients with NASH and advanced fibrosis

20–30% of general population has NAFLD

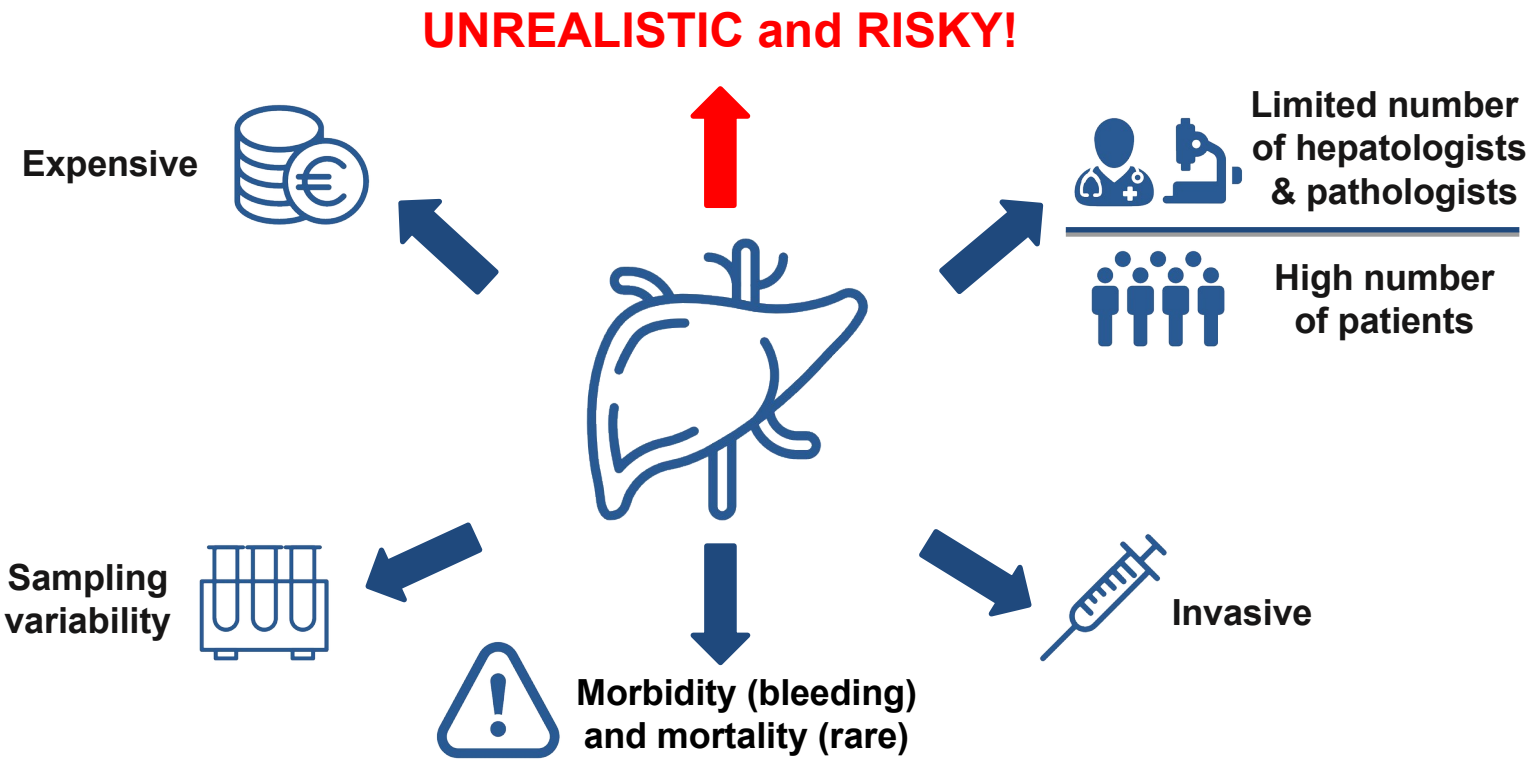


Only a minority will ever progress beyond NAFL



The challenge is to identify patients most at risk of complications, especially those with advanced fibrosis, and link them to care

Liver biopsy is impractical and has many limitations



Outline

- Critical issues when using non-invasive tests
- Evidence in NAFLD
- Referral pathways

Available non-invasive tests:
two different but complementary approaches

« Biological » approach

- AST/ALT ratio
- APRI
- FIB-4
- NFS

Non-patented

- FibroTest®
- ELF™
- FibroMètre®
- Hepascore

Patented

« Physical » approach

VCTE **ARFI / 2D SWE** **MRE**

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

Critical issues when using non-invasive tests

1. Availability
2. Cost
3. Applicability
4. Context of use

Available non-invasive tests:
Availability and cost

« Biological » approach

- AST/ALT ratio
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VCTE **ARFI / 2D SWE** **MRE**

Availability

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

Applicability of non-invasive tests

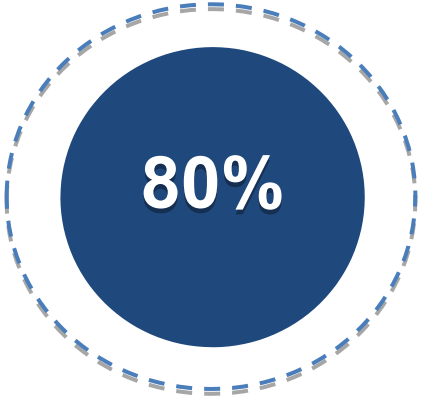
= reliability + failure rate

FibroTest

N= 342,346

Poynard et al. BMC Gastroenterol 2011

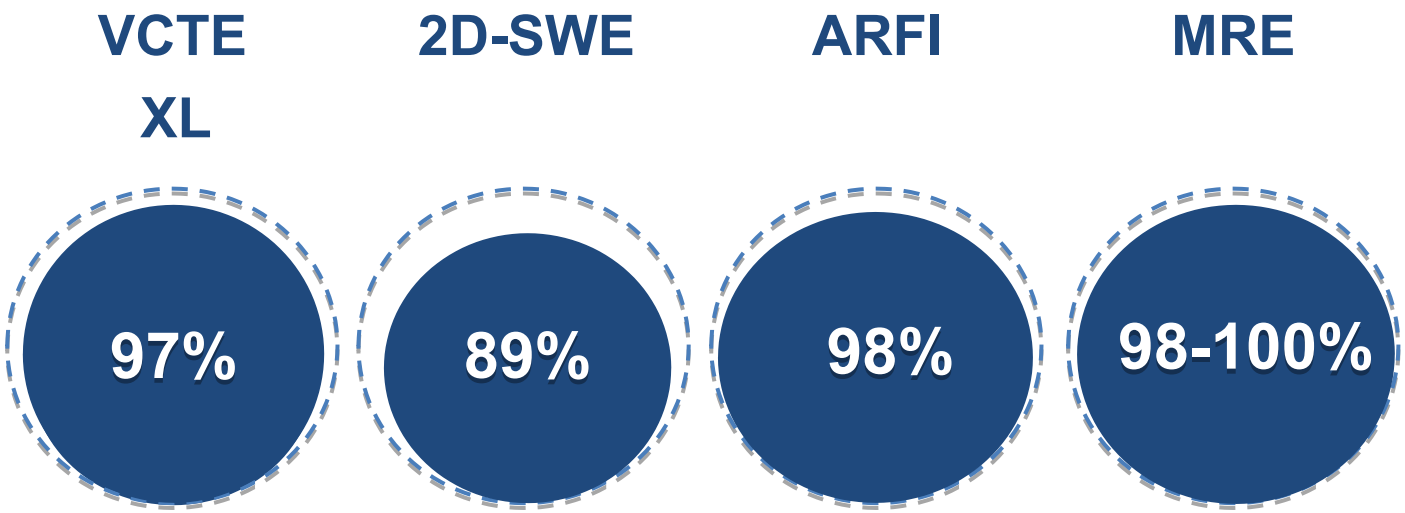
FibroScan



N= 13,669

Castera et al. Hepatology 2010

Applicability of elastography techniques



Castera L, Friedrich-Rust M, Loomba R. Gastroenterology 2019; 156: 1264-81

Available non-invasive tests:
Context of use

« Biological » approach

- AST/ALT ratio
- APRI
- FIB-4
- NFS

Non-patented

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« Physical » approach

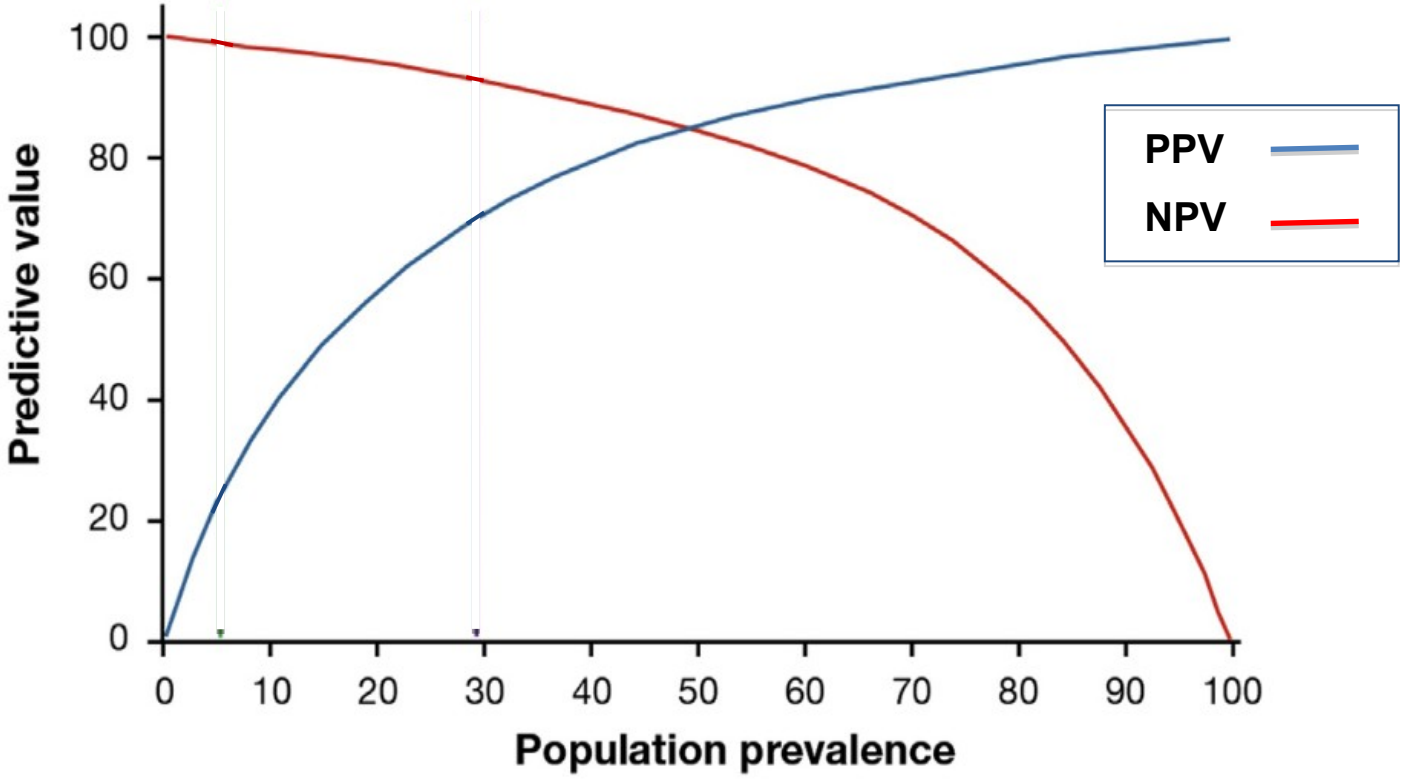
VCTE | **ARFI / 2D SWE** | **MRE**

Availability

Primary care → **Tertiary care**

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

Importance of context of use

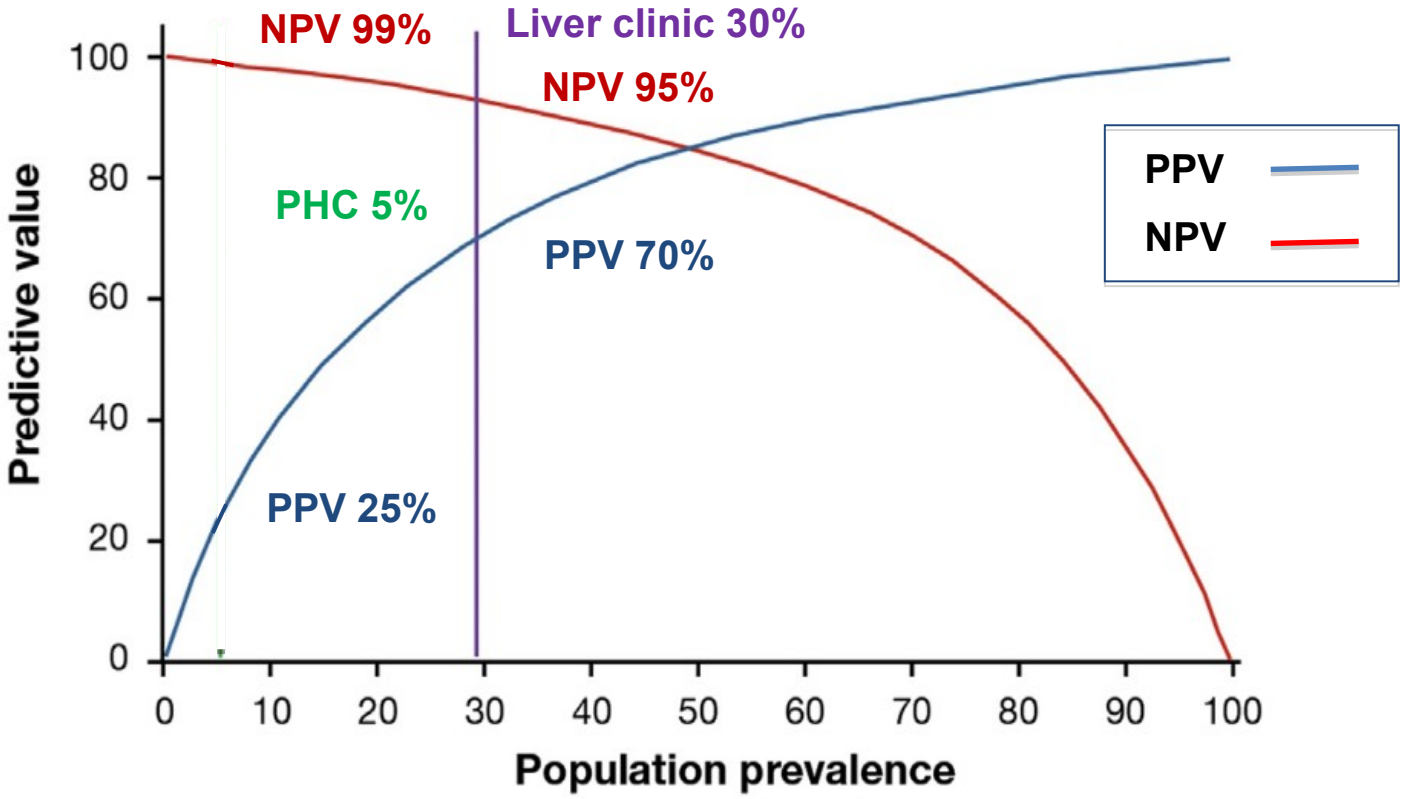


Prevalence of advanced fibrosis according to the target population

	NAFLD (%)	F3–F4 (%)
Liver clinic	100	20–25
Diabetes clinic	73	17
General population	25	2.5

Kwok R et al. Gut 2016;65:1359–68; Younossi ZM et al. Hepatology 2016;64:73–84

Importance of context of use



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FIB-4 and NFS are the most validated serum scores

	Number of studies (number of patients)	AUC value (mean)
APRI Advanced fibrosis	29 (6,746)	0.75
FIB-4 Advanced fibrosis	34 (8,245)	0.80
NFS Advanced fibrosis	38 (9,245)	0.78
BARD score Advanced fibrosis	30 (7,791)	0.73

Meta-analysis of 64 studies; N=13,046 patients

Xiao G et al. Hepatology 2017;66:1486–501

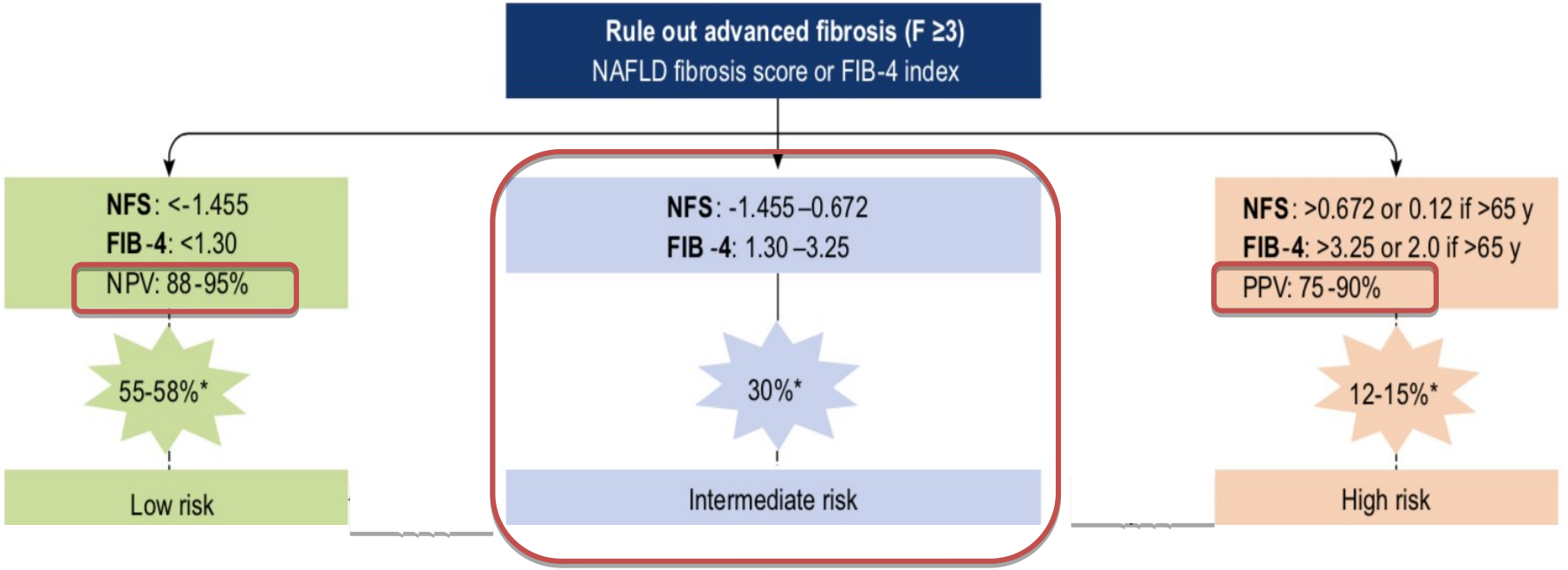
Head-to-head comparison: FIB-4, NFS and ELF™

	Number of patients	AUC value (mean)
FIB-4 Advanced fibrosis	3,123	0.78
NFS Advanced fibrosis	2,417	0.74
ELF™ Advanced fibrosis	3,173	0.80

ELF™ performance is similar to that of FIB-4, but widespread application is limited by cost and availability

Anstee QM et al. Hepatology 2019.

FIB-4 *vs.* NFS



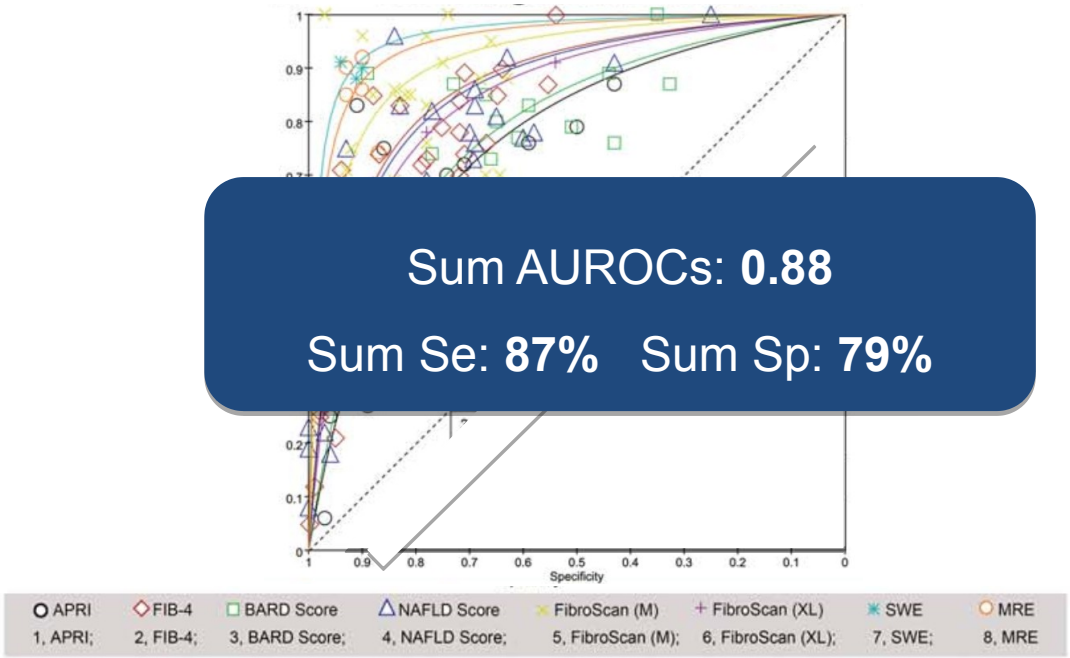
Sterling RK et al. Hepatology 2006;43:1317–25; Angulo P et al. Hepatology 2007;45:846–54

Elastography techniques in NAFLD
Summary

Technique	Evidence in NAFLD	Fat Detection & quantification	Failure rate	Point-of-Care	Availability	Cost
VCTE	N=25 3862	Yes CAP	<7% XL probe	Yes	+++	€
pSWE/ARFI	N=8 834	No	2%	No	++	€€
2D-SWE	N=2 447	No	13%	No	+	€€
MRE	N=6 676	Yes PDFF	0-2%	No	+	€€€

Castera L, Friedrich-Rust M, Loomba R. Gastroenterology 2019; 156: 1264-81

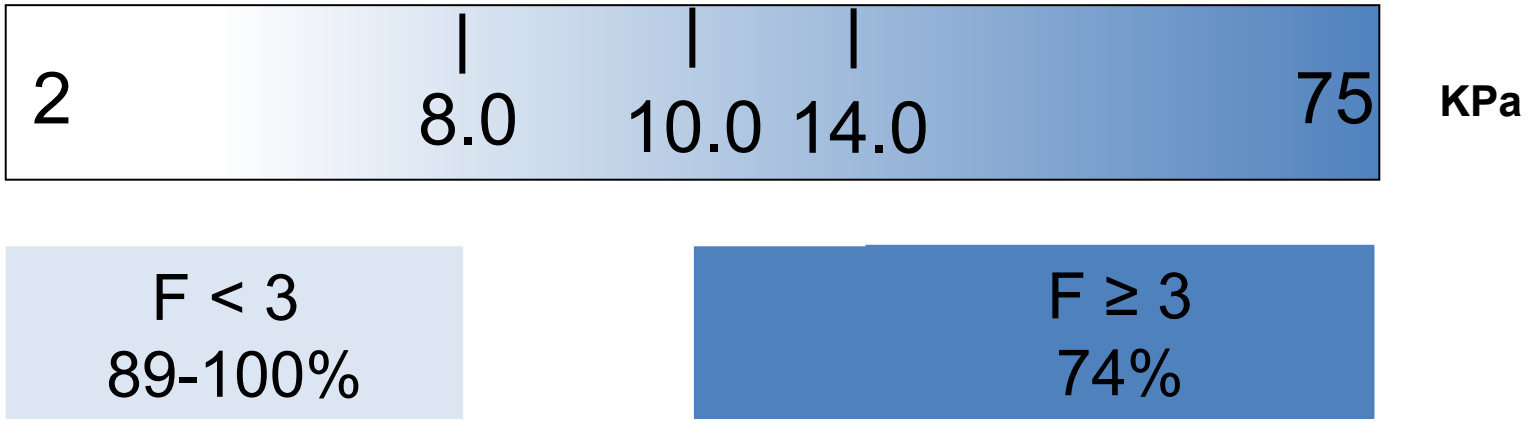
VCTE has high diagnostic accuracy



Meta-analysis; 17 studies; N=2,642 NAFLD patients with F3-F4

Xiao G et al. Hepatology 2017;66:1486–501

VCTE has high NPV but suboptimal PPV for F3-F4 in NAFLD



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

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

Siddiqui et al. CGH 2019;17:156–163

Eddowes PJ et al. Gastroenterology 2019; 156: 1717-30

Outline

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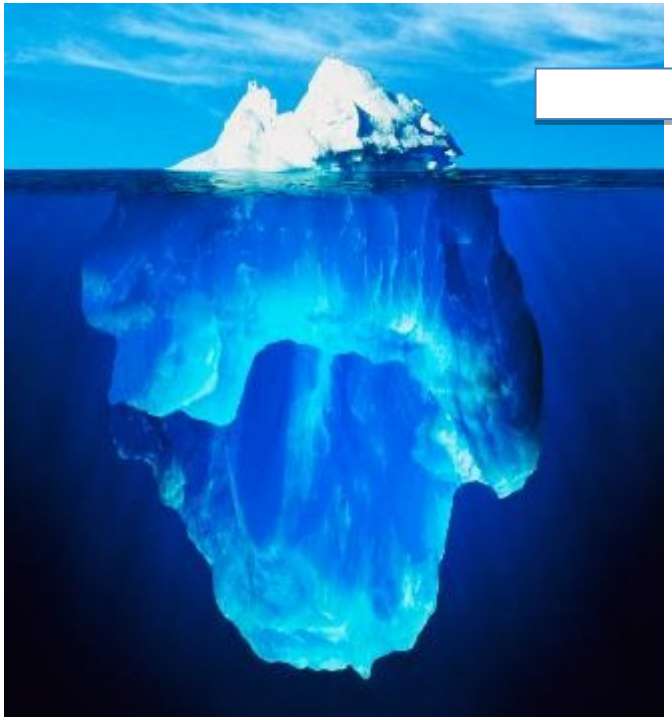
NAFLD: an under-recognised disease in Primary Health Care

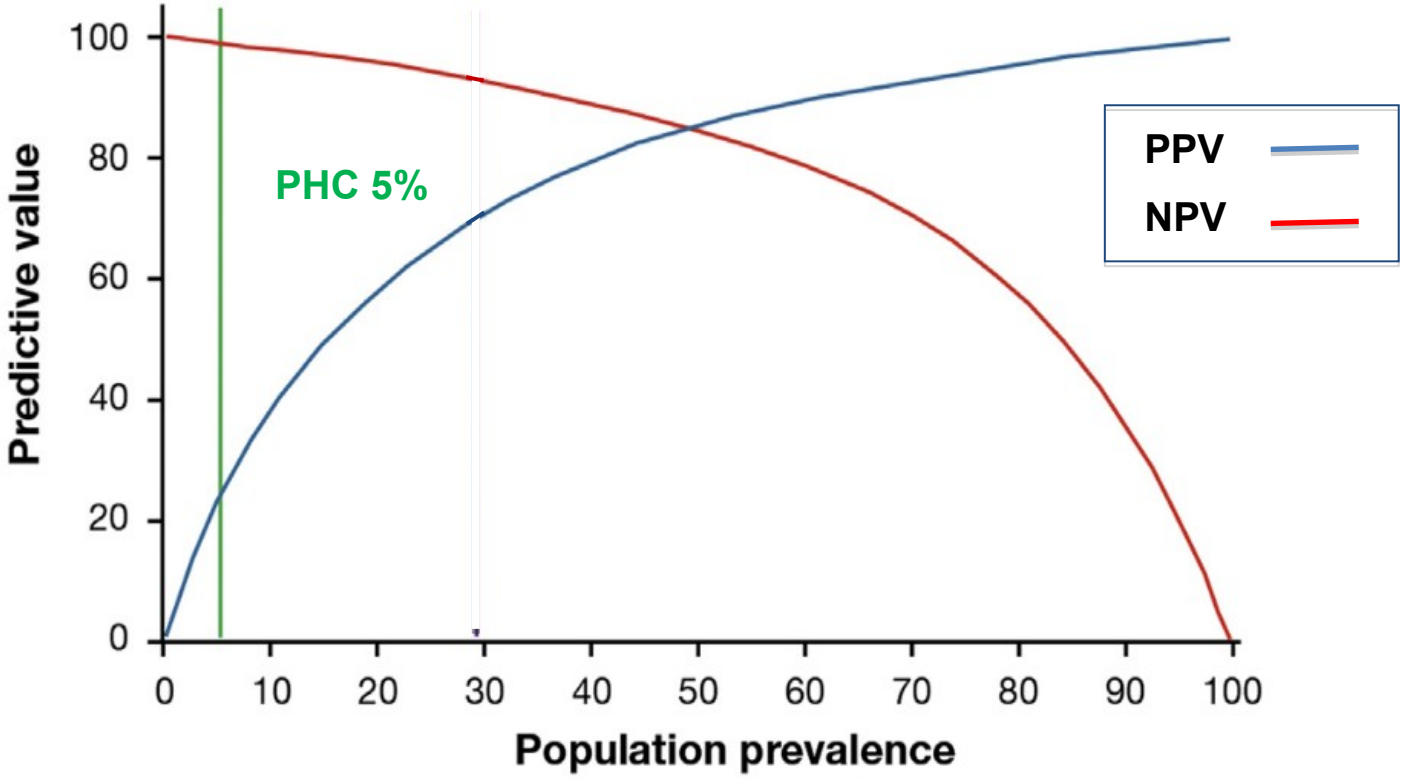


Referral to specialist <10%

- No symptoms
- No simple diagnostic marker
- Lack of awareness of most GP

Blais P et al. Am J Gastroenterol 2015;110:10–14

High prevalence, low severity (F3-F4 <5%)



Simple serum scores should be used as first-line

FIB-4 *vs.* NFS

FIB-4

Age *(years)* AST level *(U/L)*

× √

NFS

Age *(years)*

BMI *(kg/m²)*

Platelets *(x10⁹/L)*

Albumin *(g/L)*

calculate score

FIB-4 is the most suited for primary health care

Sterling RK et al. Hepatology 2006;43:1317–25; Angulo P et al. Hepatology 2007;45:846–54

FIB-4 and NFS performance according to context of use

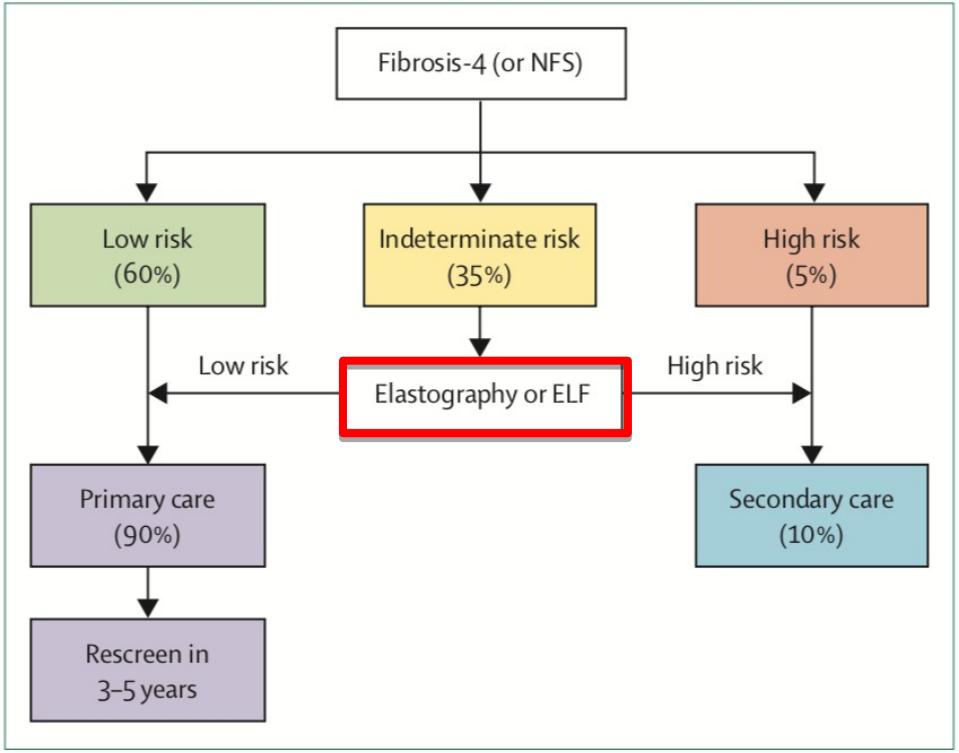
F3-F4 prevalence	50 %
FIB-4 (1.45 - 3.25) *NPV*	64
PPV	
NFS (-1.455 – 0.675) *NPV*	62
PPV	94

High NPV but poor PPV

N= 759 NAFLD patients 10 centers in Asia

Chan et al. GCH 2019; 17: 2570-80

Need for a second test



Tsochatzis & Newsome. Lancet GH 2018; 3: 509-17

Combination: what is the best strategy?

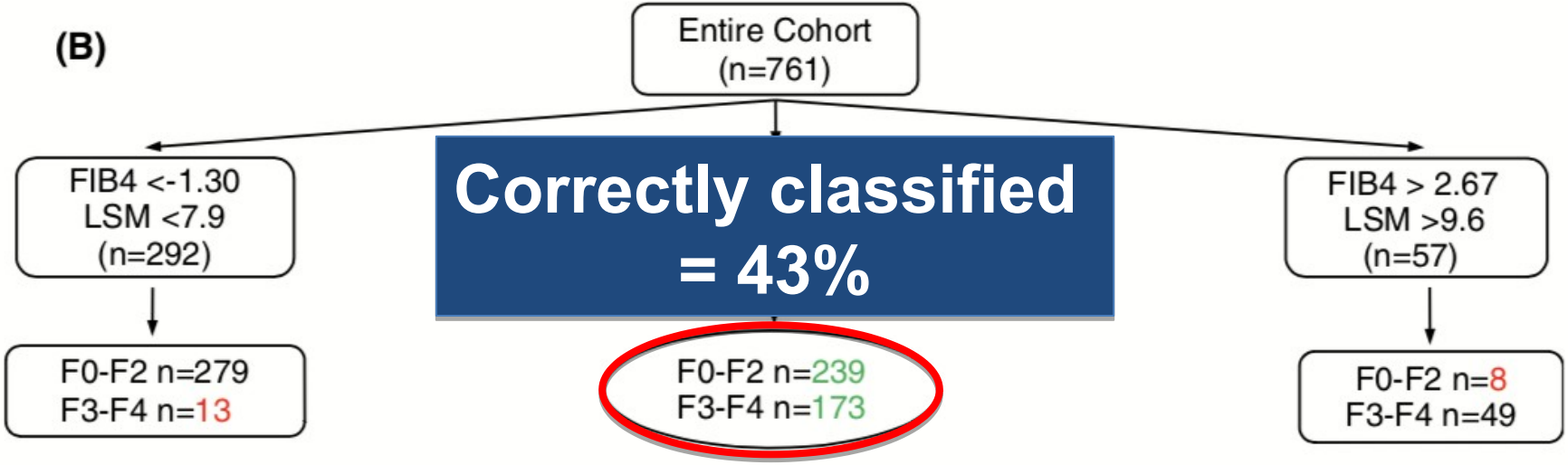
Paired

+

or

Sequential

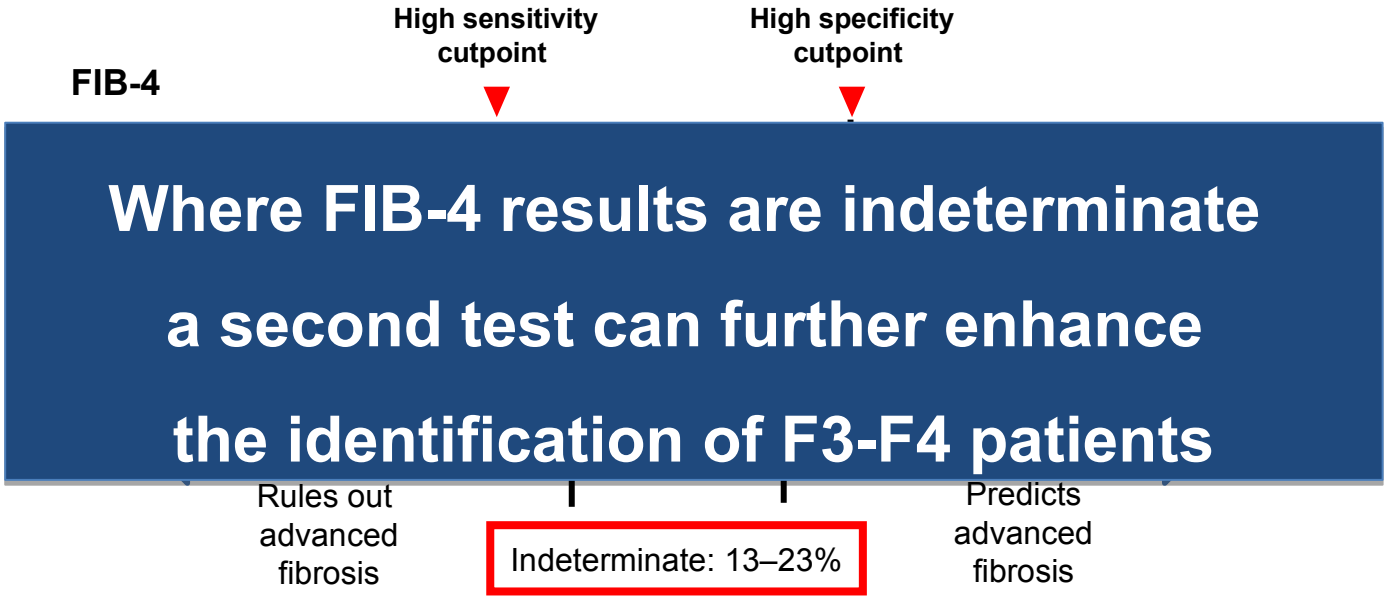
Paired combination



N= 741 NAFLD patients ; tertiary referral center

Petta et al. APT 2017

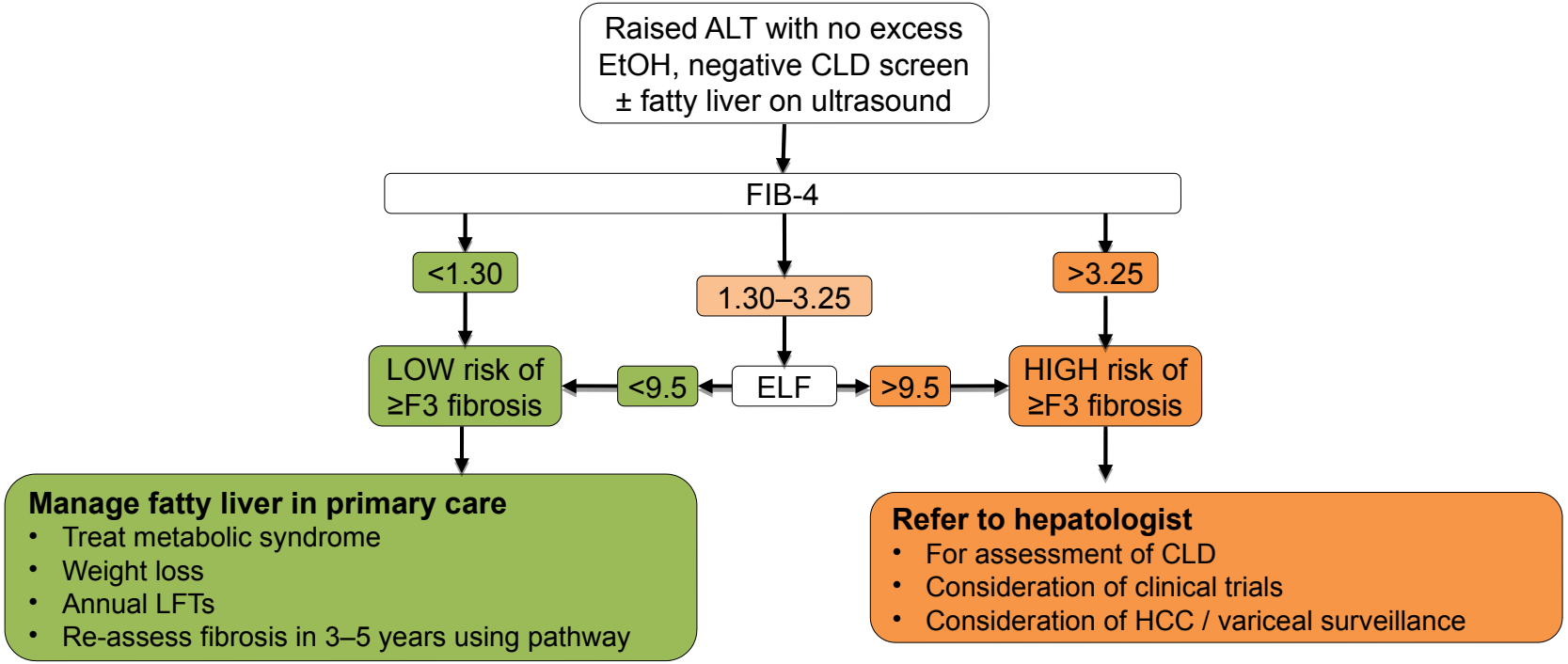
Sequential combination



N= 3,200 NAFLD patients ; tertiary referral centers; 71% F3-F4

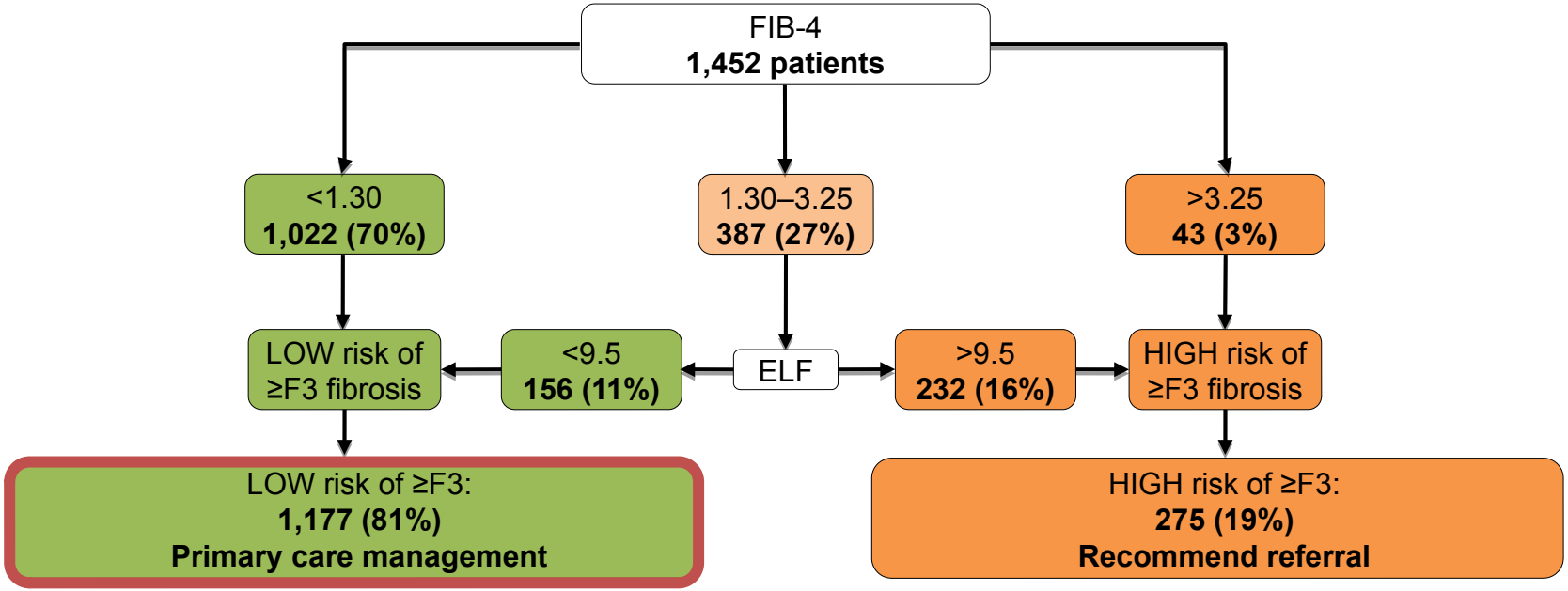
Anstee QM et al. Hepatology 2019.

From selected patients to real-life populations the Camden-Islington algorithm



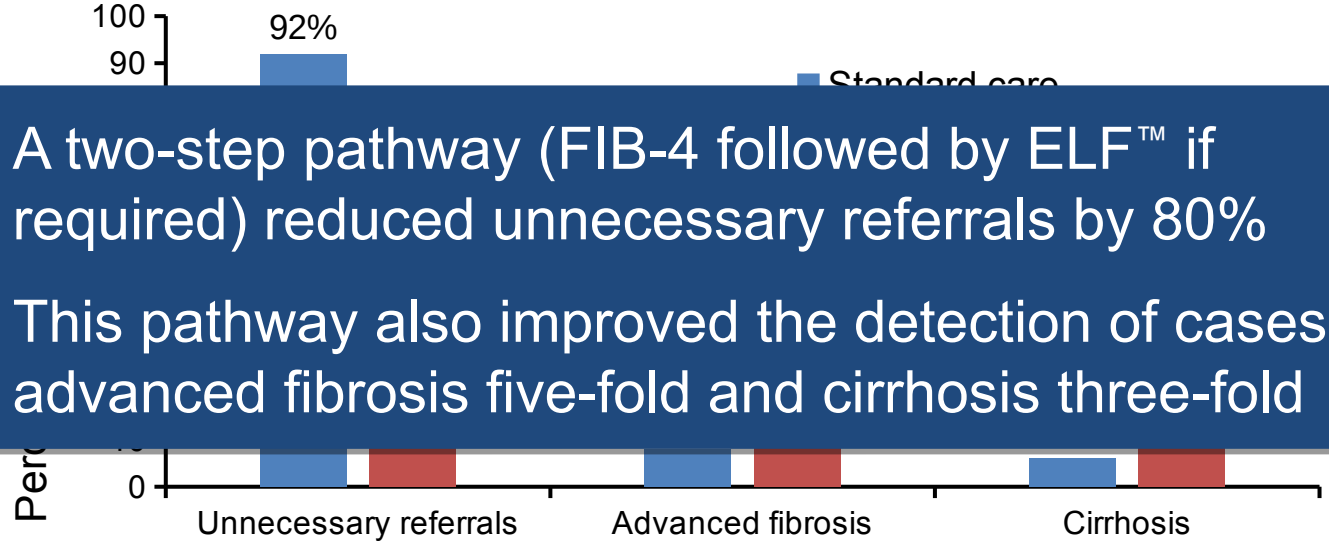
Srivastava A et al. J Hepatol 2019;71:371–8

From selected patients to real-life populations the Camden-Islington algorithm



Srivastava A et al. J Hepatol 2019;71:371–8

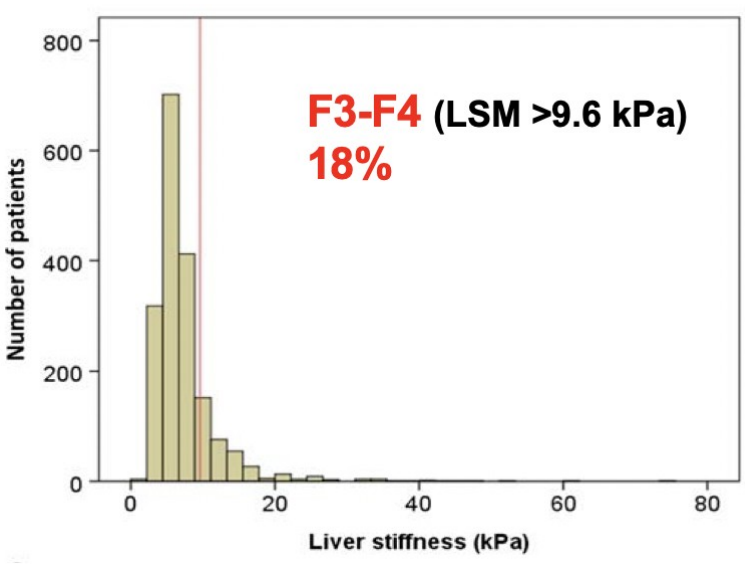
Impact on referrals



- A two-step pathway (FIB-4 followed by ELF™ if required) reduced unnecessary referrals by 80%
- This pathway also improved the detection of cases of advanced fibrosis five-fold and cirrhosis three-fold

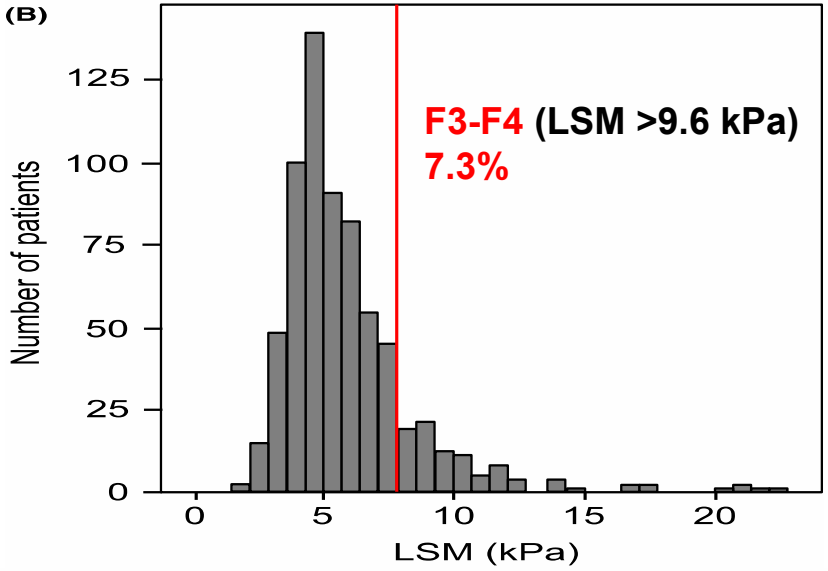
Srivastava A et al. J Hepatol 2019;71:371–8

Screening type 2 Diabetics with VCTE



N= 1918 Chinese diabetics patients

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



N= 435 French diabetics patients

Roulot et al. Liver Int 2017; 37: 1897-06

Use in clinical practice

Patients in Primary Health Care

1st line: General practitioner

Rule-out advanced fibrosis
FIB-4

- FIB-4 < 1.3 → Low risk
- FIB-4 ≥ 1.3 → Intermediate to high risk

Low risk → Attempt lifestyle modifications and exercise → No further assessment Repeat evaluation at 1 year?

2nd line: Hepatologist

Rule-in advanced fibrosis
Transient Elastography

- LSM < 8 kPa → Low risk
- LSM ≥ 8 kPa → Intermediate to high risk → Consider Liver Biopsy

Failure (XL probe) 3.0- 6.7% → Consider MRE, 2D SWE or ARFI according to local availability

Low risk / Consider Liver Biopsy → Attempt lifestyle modifications and exercise

- Consider repeat evaluation (1 year)
- Eligible for therapeutic trial?

Patients with type 2 diabetes

1st line: diabetes clinics

Rule-in advanced fibrosis
Transient Elastography

LSM < 8 kPa

Low risk

Attempt lifestyle modifications and exercise

No further assessment Repeat evaluation at 1 year?

LSM ≥ 8 kPa

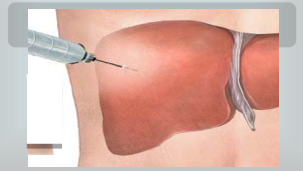
Intermediate to high risk

2nd line: Hepatologist

Failure (XL probe) 3.0- 6.7%

Consider MRE, 2D SWE or ARFI according to local availability

Consider Liver Biopsy



Attempt lifestyle modifications and exercise

Eligible for therapeutic trial?

Take Home messages

- VCTE, FIB-4, and NAFLD fibrosis score are the most widely used and best validated tests
- Availability, cost, applicability and context of use are critical issues when using non-invasive tests
- The optimal way to identify F3-F4 NAFLD patients is the sequential use of FIB-4/NFS then VCTE to select those who should be considered for LB
- The next step is to establish effective pathways from primary health care and/or diabetes clinics where most NAFLD patients are seen in order to identify those who need to be referred to liver clinics for further assessment