Disparities in Test Performance: Imaging Biomarkers Risk Stratification of NASH in Different Parts of the World

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Disclosures

- **Consultant:** Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics
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Outline

- Assessment of hepatic fat
- Assessment of hepatic fibrosis
- Reason for disparities
- Methods to reduce disparities (imprecision)

Assessment of Liver Fat

Presence of NAFLD and Disparities in Detection

- **Liver biopsy assessment**
  - Clinical standard
  - Qualitative
- **Conventional ultrasound is routinely utilized**
  - Not sensitive and low negative predictive value
  - Qualitative rather than quantitative
  - Does not work in mild steatosis
- **CT scan is not favored**
  - Ionizing radiation
  - Inaccurate
  - Lacks sensitivity and specificity
- **MRI-PDFF and MRS**
  - Gold standard for fat quantification
  - Current non-invasive standard for non-invasive screening for NAFLD in epidemiologic and clinical studies

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Controlled Attenuation Parameter

United States

- CAP ≥ 288 db/min corresponds to MRI-PDFF ≥ 5%

Asia

- CAP ≥ 250 db/min corresponds to grade 1 steatosis

So, what is the truth and how do you eliminate/minimize imprecision?

Caussy et al. *Hepatology*. 2018; Chon et al. *Liver International*. 2014.

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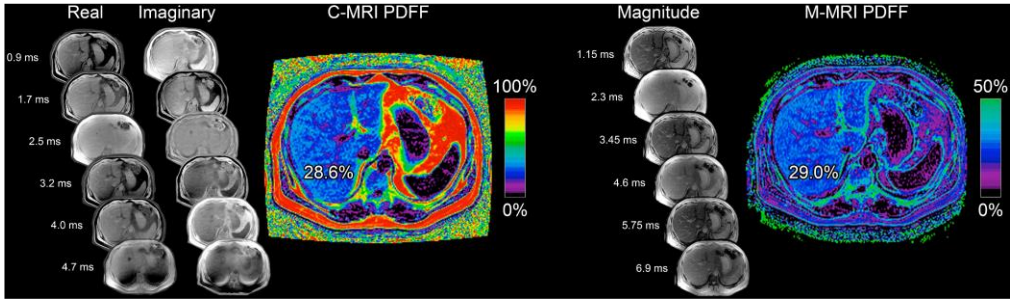
Assessing Liver Steatosis By MRI-PDFF

- Addresses confounding factors, unlike conventional in-phase and opposed-phase
- **Not** affected by
  - Scanner field strength
  - Patient factors: age, sex, BMI, etiology of liver disease
  - Concomitant liver abnormalities: iron overload, necroinflammation



BMI, body mass index; MRI, magnetic resonance imaging; PDFF, proton density fat fraction.

Yu H et al. *Magn Reson Med*. 2008; 60: 1122–34; Bydder M et al. *Magn Reson Imaging*. 2008; 26: 347–59; Bydder M et al. *Magn Reson Imaging*. 2010; 28: 767–76; Hansen. *MRI*. 2012; Kang BK et al. *Invest Radiol*. 2012; 47: 368–75; Kühn JP et al. *Radiology*. 2012; 265: 133–42; Tang A et al. *Radiology*. 2013; 267: 422–31; Dulai PS, Sirlin CB, and Loomba R. *J Hepatol*. 2016; 65: 1006–16.

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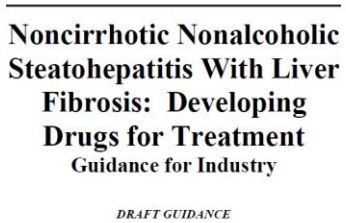
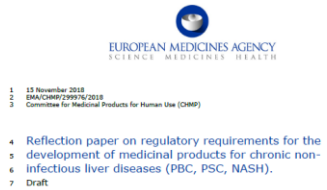
Organisations Are Currently Reflecting on the Future Use of Noninvasive Testing





However, more needs to be done!

EMA: European Medicines Agency;
FDA: Food and Drugs Administration

FDA. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: Developing drugs for treatment. Guidance for industry. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM627376.pdf (accessed April 2019).
EMA. Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH). Available at: https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-regulatory-requirements-development-medicinal-products-chronic-non-infectious-liver_en.pdf (accessed April 2019)

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Imaging-Based Fibrosis Assessment

Imaging Biomarkers

- Fibrosis has no molecular signature detectable by current imaging techniques
- Imaging attempts to detect fibrosis indirectly

- Many biomarkers proposed: stiffness, diffusion, perfusion, metabolites, image texture, etc.
- Leading biomarker is “stiffness” (or elasticity) and related parameters
- Rationale: fibrotic collagen deposition imparts parenchymal rigidity

Dulai PS et al. *J Hepatol*. 2016; 65: 1006–1016.

Differences in VCTE and SWE Cut-Points Between the West and the East

- In general, the cut-points for detection of fibrosis and advanced fibrosis are somewhat lower in the studies from Asia compared to studies conducted in US and Western population
- These cut-points are much for divergent for ultrasound-based methods versus MRI-based methods
- How have we minimized these and standardized them across geographic settings?
  - Standardizing the exam
  - Standardizing the conditions
  - Standardizing the review criteria
  - Pooled individual patient meta-analyses

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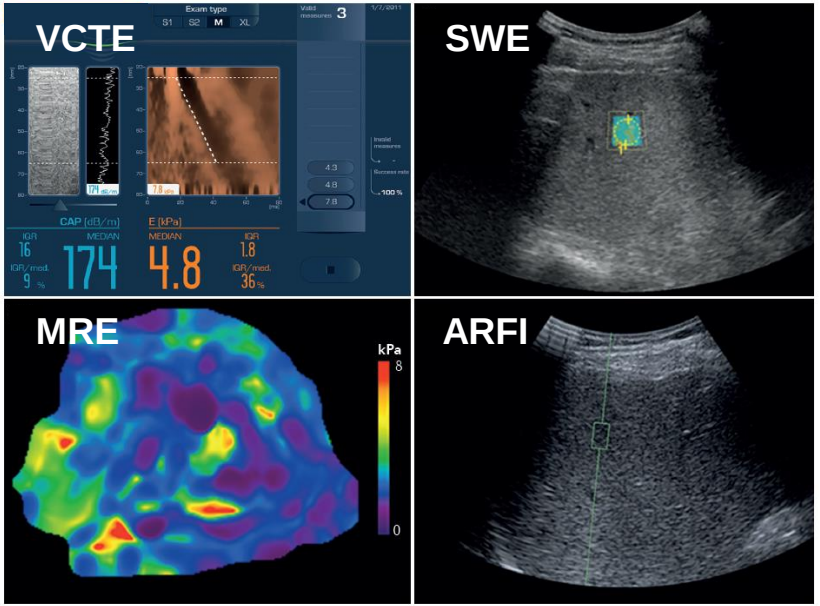
Non-invasive Assessment of Liver Fibrosis

Elastography-based Methods to Estimate Liver Stiffness

- VCTE (FibroScan) is most widely used
  - ≥ 10 images are required
  - Accurate for stages F3–4
  - Can estimate steatosis when used with CAP
- SWE/ARFI can be used to measure stiffness in a single ROI
- MRE measures stiffness across multiple ROIs



ARFI, acoustic radiation force impulse; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; ROI, region of interest; SWE, shear wave elastography; VCTE, vibration-controlled transient elastography.

Tapper EB and Loomba R. *Nat Rev Gastroenterol Hepatol.* 2018; 15: 274–282.

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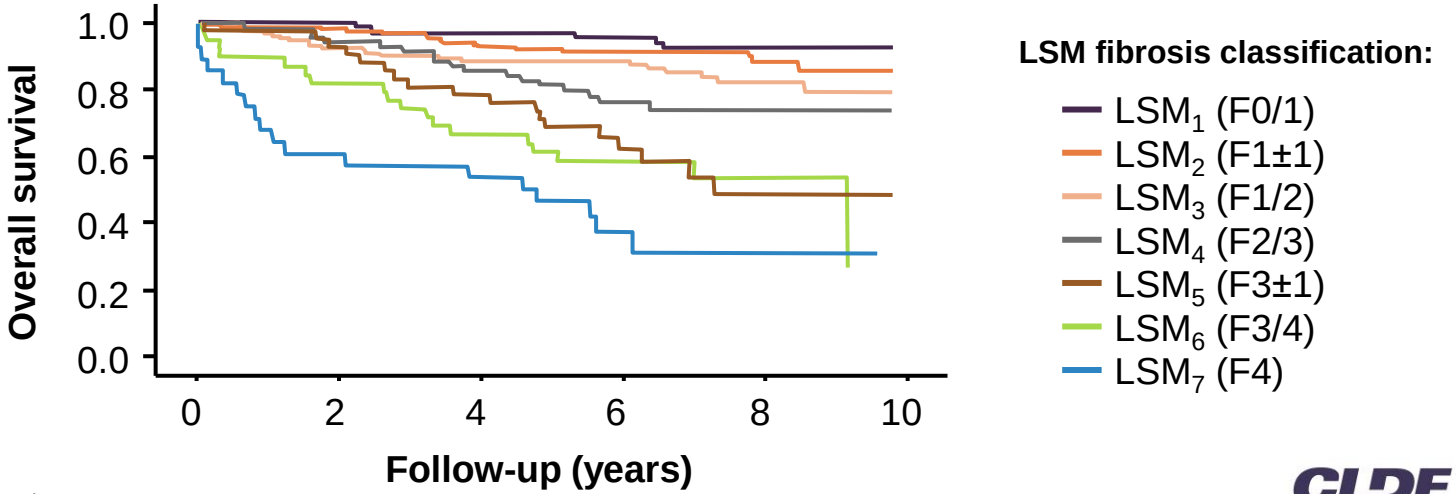
Liver Stiffness as a Non-invasive Biomarker of Fibrosis

A Cross-sectional Study of 452 Patients With Liver Biopsy

Fibrosis classification: (equivalence in fibrosis stage)



LSM, liver stiffness measurement.

Boursier J et al. *J Hepatol* 2016;65:570–578.

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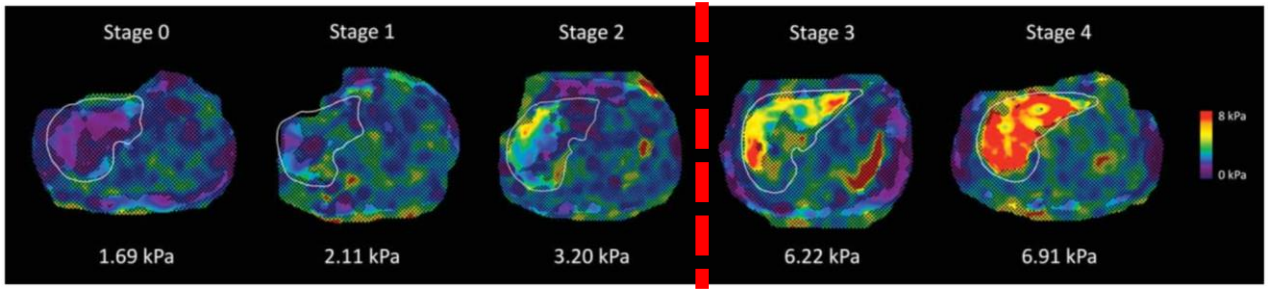
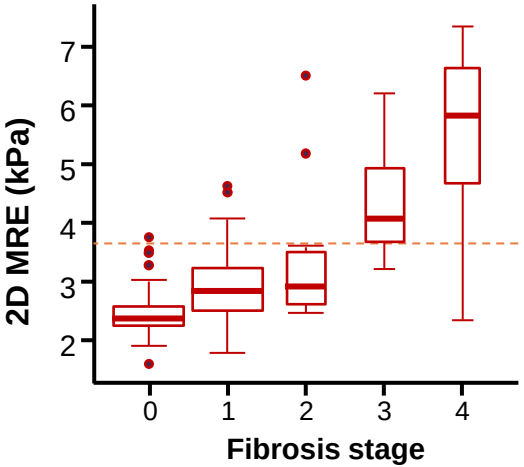
Validating MRE for Prediction of Advanced Fibrosis





"Stiffness" cutoff: 3.63 kPa
Sensitivity 0.86
Specificity 0.91

AUC for diagnosis of advanced fibrosis
0.924

AUC, area under the curve; MRE, magnetic resonance elastography.
Loomba R et al. *Hepatology*. 2014; 60(6): 1920–1928.

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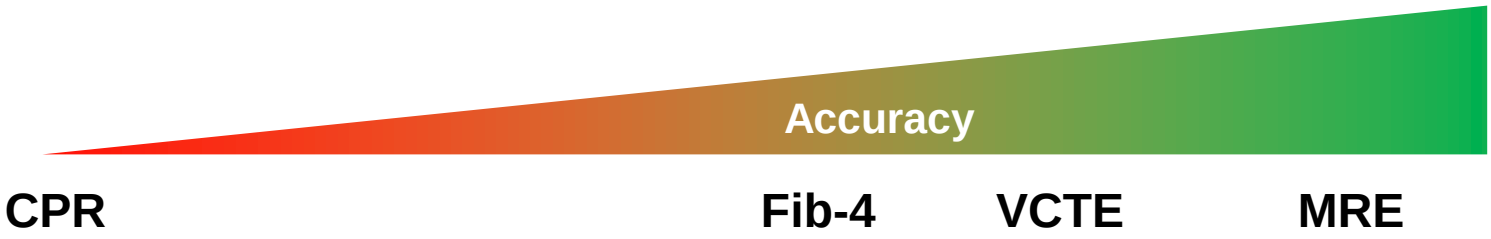
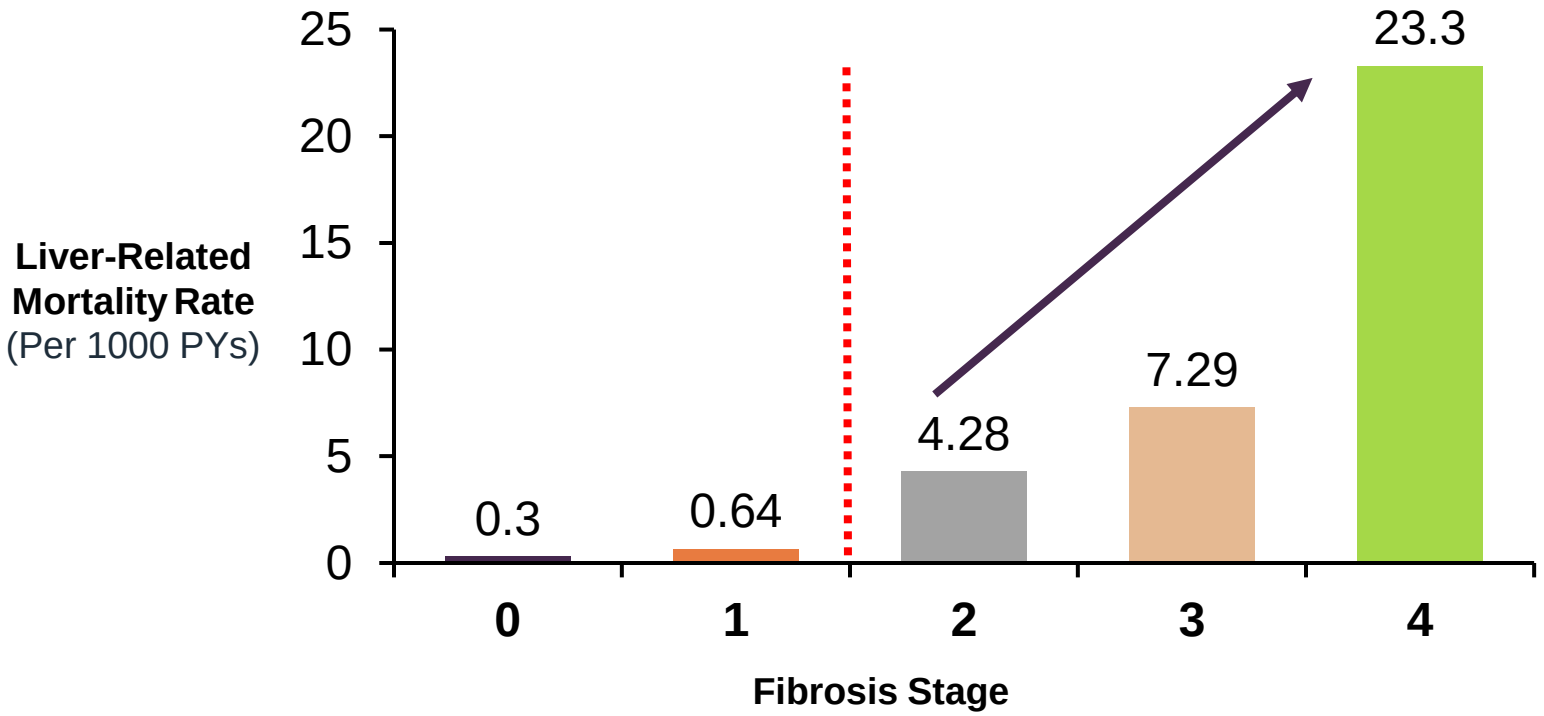
Hierarchy of Imaging-based Modalities Upon Evidence



Detection of “At Risk” NASH

Association Between Stage of Fibrosis and Risk of Liver-Related Mortality



Adapted from Dulai, 2017.

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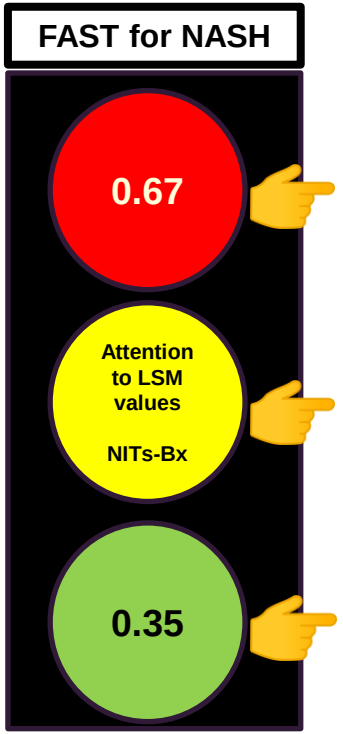
Role of FAST in Detection of High-risk NASH

	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)				Grey zone (FAST 0·35–0·67), n (%)	Rule-in zone (FAST ≥0·67)			
				n (%)	Sensitivity	Specificity	NPV		n (%)	Specificity	Sensitivity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)	113 (32%)	0·90 (157/174)	0·53 (93/176)	0·85 (93/110)	136 (39%)	101 (29%)	0·90 (159/176)	0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)	69 (63%)	1·00 (16/16)	0·73 (69/94)	1·00 (69/69)	22 (20%)	19 (17%)	0·93 (87/94)	0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28 (12%)	194 (80%)	0·64 (18/28)	0·86 (183/214)	0·95 (183/193)	39 (16%)	9 (4%)	0·99 (212/214)	0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36 (43%)	28 (34%)	0·94 (34/36)	0·55 (26/47)	0·93 (26/28)	29 (35%)	26 (31%)	0·89 (42/47)	0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9 (9%)	55 (53%)	0·89 (8/9)	0·56 (53/95)	0·98 (58/67)	37 (36%)	12 (11%)	0·92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)	67 (37%)	0·88 (69/78)	0·56 (58/104)	0·87 (58/67)	69 (38%)	46 (24%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)	78 (44%)	0·94 (34/36)	0·54 (75/140)	0·97 (75/77)	59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

FAST: CAP+LSM+AST
Main issue is low PPV: 0.33–0.83



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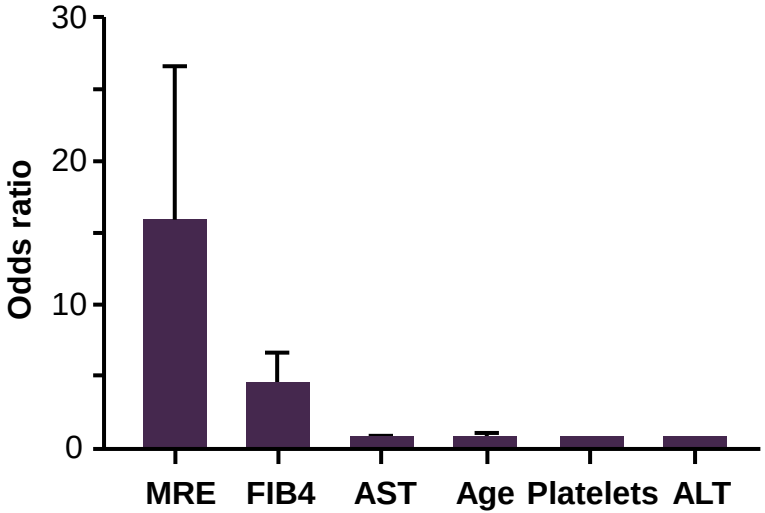
Newsome et al. *Lancet Gastro Hep*. 2020; Noureddin N, Alkhouri N et al. *Hepatology*. 2020.

Utility of Magnetic Resonance Elastography in Accurate Identification of Candidates for Pharmacologic Treatment of NASH Related Fibrosis: A Prospective Cohort Study

MRE has higher odds ratio in detecting **stage ≥ 2 fibrosis**



Combination of MRE and FIB-4 for ruling in ≥ stage 2 fibrosis

UCSD-NAFLD Cohort
(N = 238)

MRE ≥ 3.3kPa
PPV: 86.9

+

FIB-4 ≥ 1.6
PPV: 61.5

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 97.1

Japan-NAFLD Cohort
(N = 222)

MRE ≥ 3.3kPa + FIB-4 ≥ 1.6
PPV: 91.0

- Combination of imaging and serum markers (MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) yielded a high positive predictive value(97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in NAFLD

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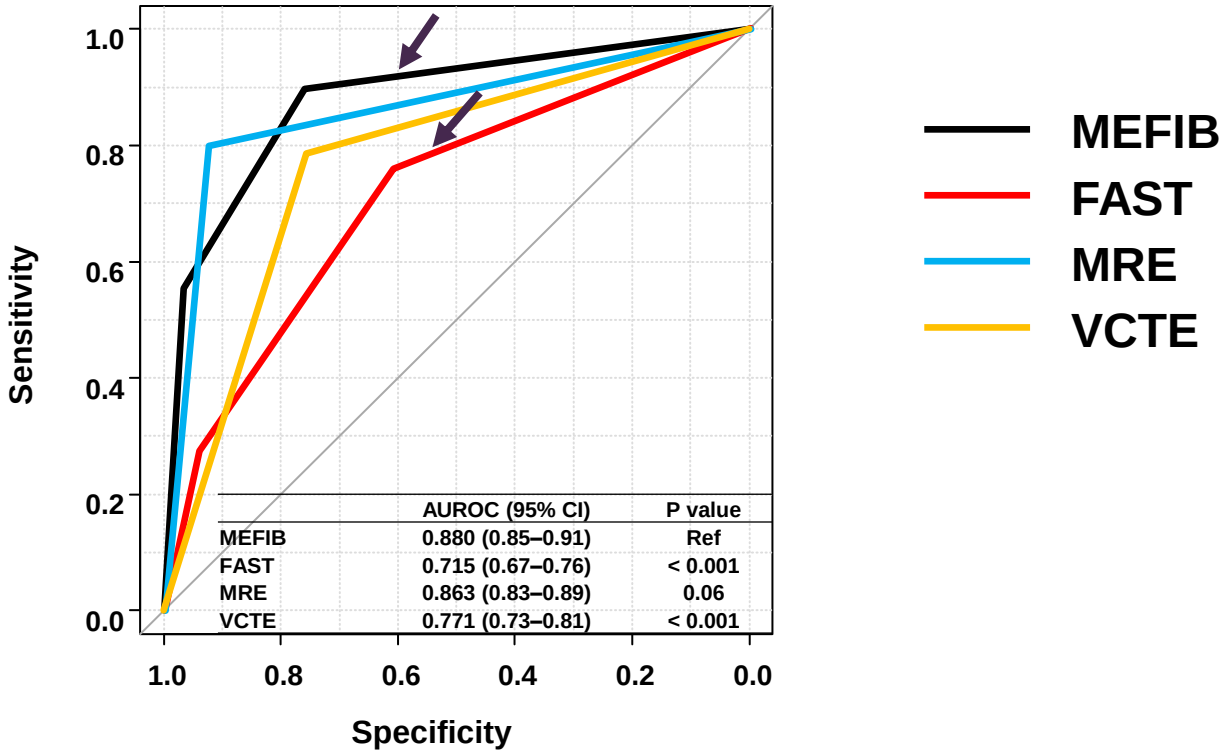
Jung J et al. *EASL*. dILC2020. #AS097; Jung J et al. *GUT*. 2020.

MEFIB Is Superior Than FAST in Detection of “At Risk” NASH Patients Among Patients With Biopsy-Proven NAFLD



Tamaki, Loomba et al. AASLD. 2021.

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Exploring Noninvasive Tests: Imaging Techniques

MRE ≤ 2.55 kPa	**Monitor in PCP clinic and no need for liver biopsy**	**VCTE** **LSM < 8 Kpa = low risk**
MRE > 2.99 kPa	**Monitor in hepatology clinic and may consider a liver biopsy**	
FIB-4 ≥ 1.6 **And** **MRE** ≥ 3.3 kPa	**Presence of ≥ stage 2 fibrosis with 90% PPV**	**LSM 8–12 Kpa = Fibrotic NAFLD**
MRE ≥ 3.63 kPa	**High risk for advanced fibrosis**	**LSM > 12 Kpa = high likelihood of Advanced fibrosis**

kPa: kilopascal; TE: transient elastography; VCTE: vibration controlled transient elastography.
Hsu C et al. *Clin Gastroenterol Hepatol.* 2019;17:630–7; Loomba R, et al. AASLD 2017 #2123.

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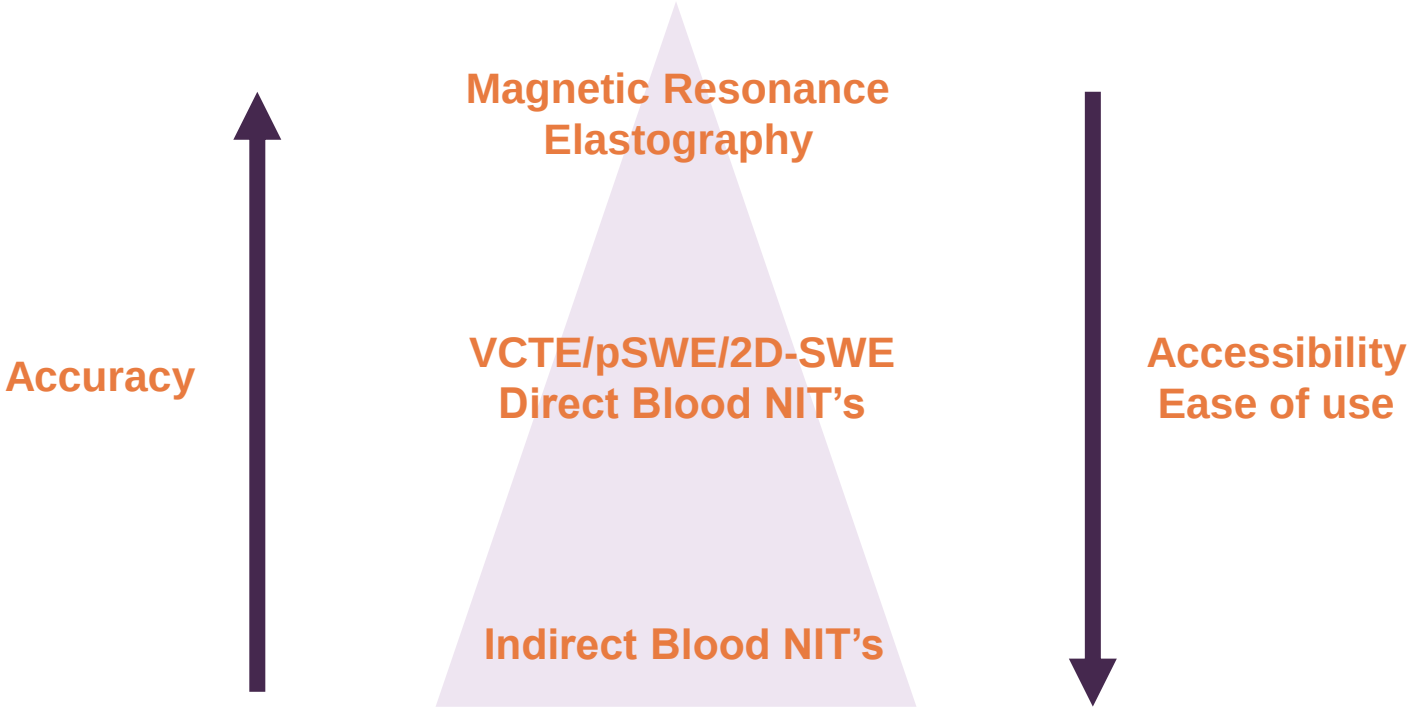
Comparative Accuracy and Accessibility of NITs



NITs = non-invasive fibrosis tests; pSWE = pulse shear wave elastography.
Loomba R, Adams LA. *Gut.* 2020; 69(7): 1343–1352.

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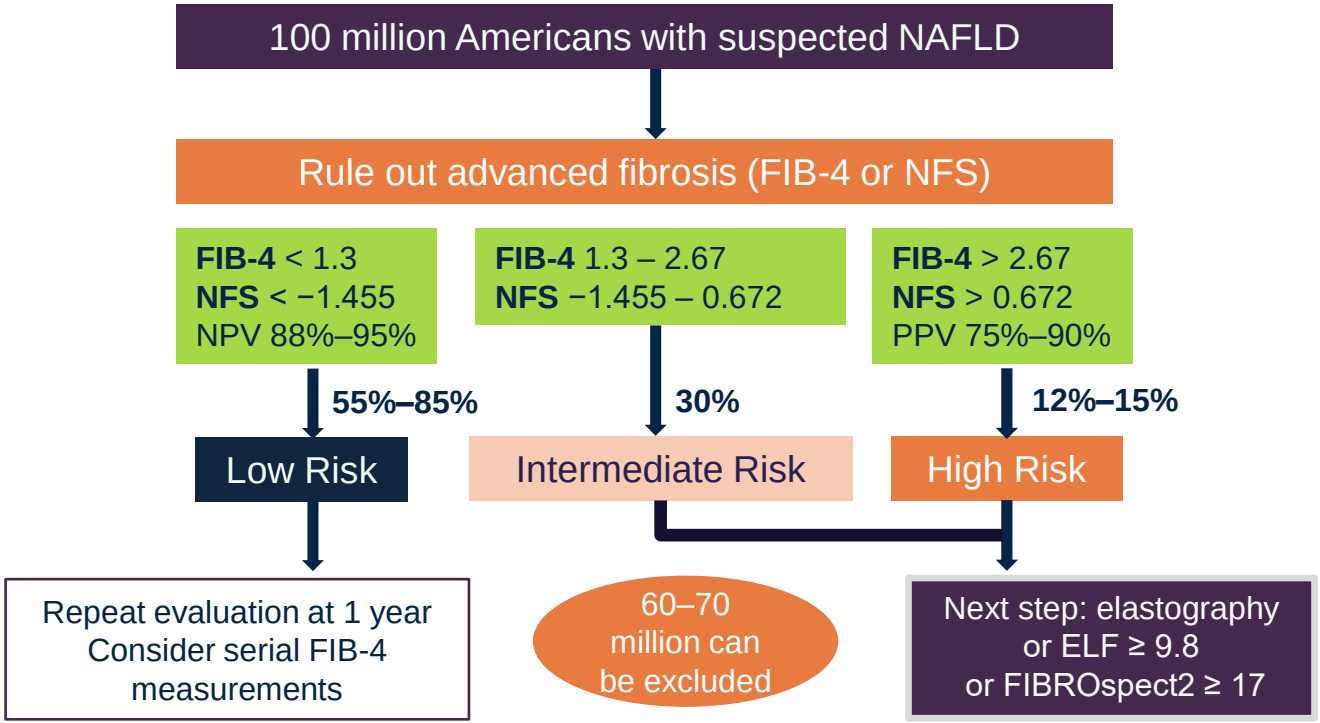
Optimizing Risk Management



ELF = enhanced liver fibrosis; NFS = NAFLD fibrosis score; NPV = negative predictive value; PPV = positive predictive value

Adapted from Castera L, Friedrich-Rush M, Loomba R. *Gastroenterology.* 2019; 156(5): 1264–1281.

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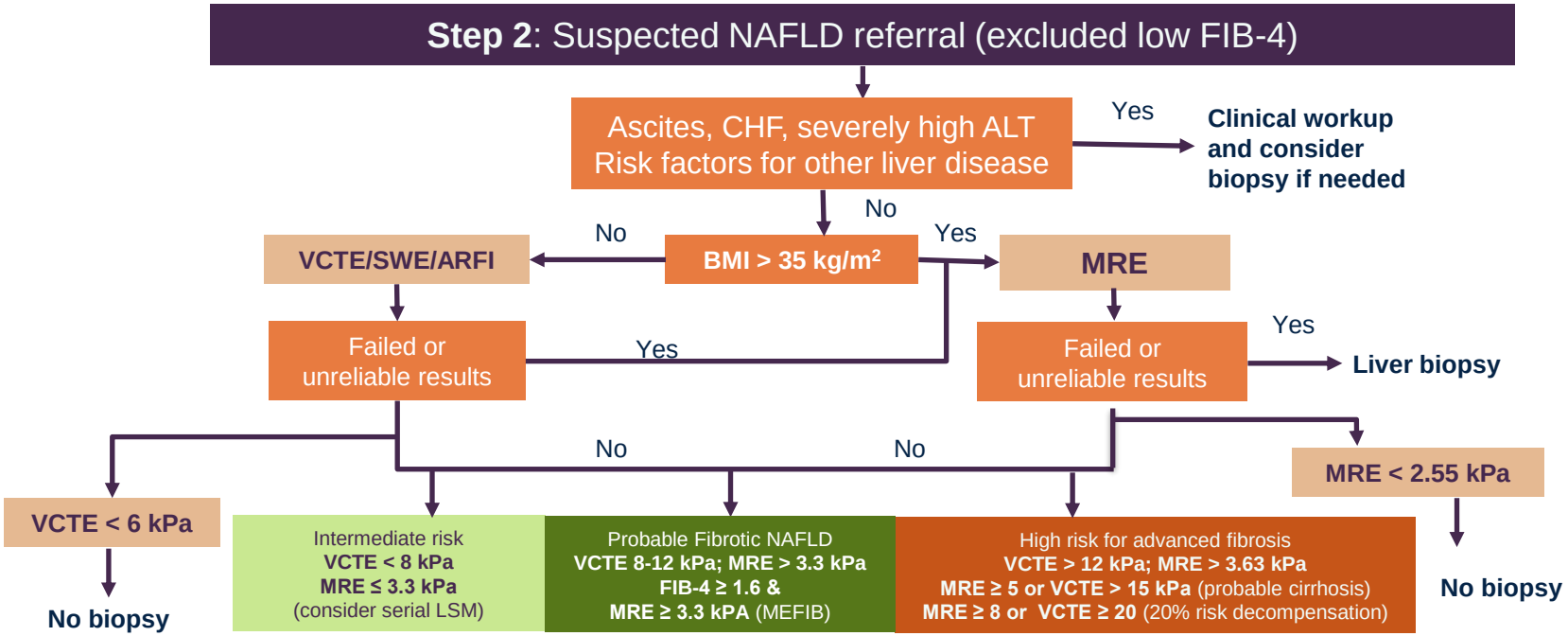
Elastography in Assessing Advanced Fibrosis



ARFI = acoustic radiation force impulse; ALT = alanine aminotransferase; BMI = body mass index; CHF = congestive heart failure; kPa = kilopascals; MRE = magnetic resonance elastography; SWE = shear-wave elastography; VCTE = vibration-controlled transient elastography.

Adapted from Tapper EB, Loomba R. *Nat Rev Gastroenterol Hepatol*. 2018;15:274-282;
Natarajan Y and Loomba R. *J Clin Transl Hepatol*. 2021. In press; Ajmera V and Loomba R. *Mol Metab.* 2021; 50: 101167.

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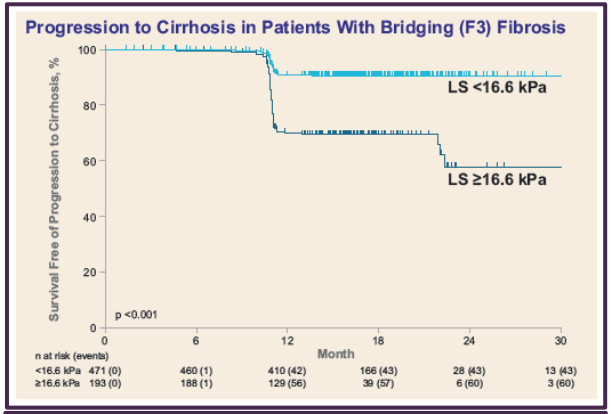
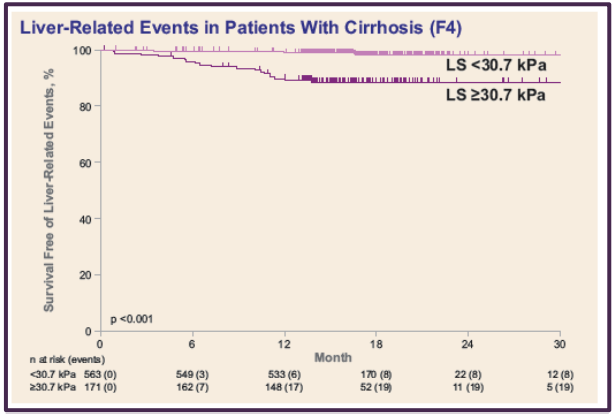
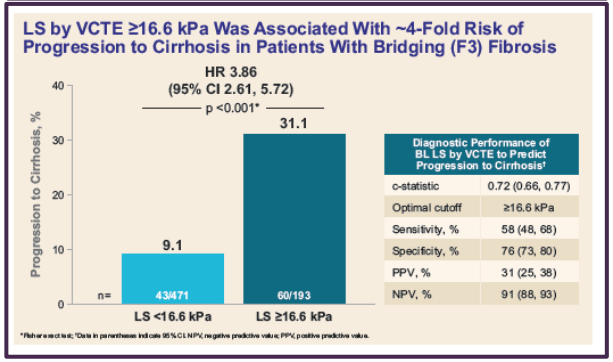
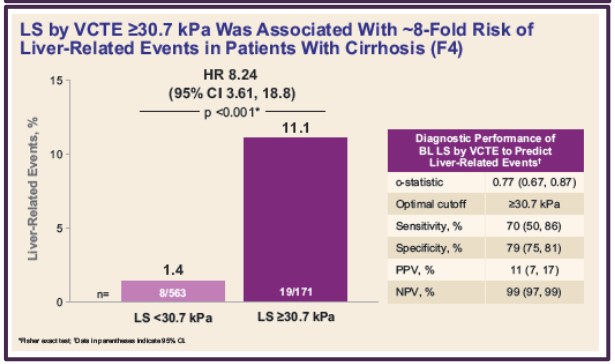
FibroScan Cut Points for Progression to Cirrhosis and for Those With Cirrhosis at Risk for Decompensation









Objective

To establish thresholds of LS by VCTE that predict clinical outcomes in patients with bridging fibrosis and cirrhosis due to NASH.

LS = liver stiffness

Loomba R et al. Presented at International Liver Congress. 2021.

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Summary

- Non-invasive assessment is taking the center stage in risk stratification, and we can use the cut-points using pooled estimates across geographic settings
- CAP and VCTE (or ultrasound-based modalities) may provide a lower value in Asian populations
- MRI-PDFF and MRS have no geographic differences
- MRE has higher precision compared to ultrasound-based modalities
- Gold-standard calibration and validation studies are helpful in improving precision, accuracy and reproducibility of imaging-based biomarkers

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Thank You

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