3RD ANNUAL NCSCG POST-AASLD SYMPOSIUM

Rehoboth McKinley Christian Health Care Services

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Northern California Society for Clinical Gastroenterology

Noninvasive Measurement Of Hepatic Fibrosis:

It's here, are we ready?

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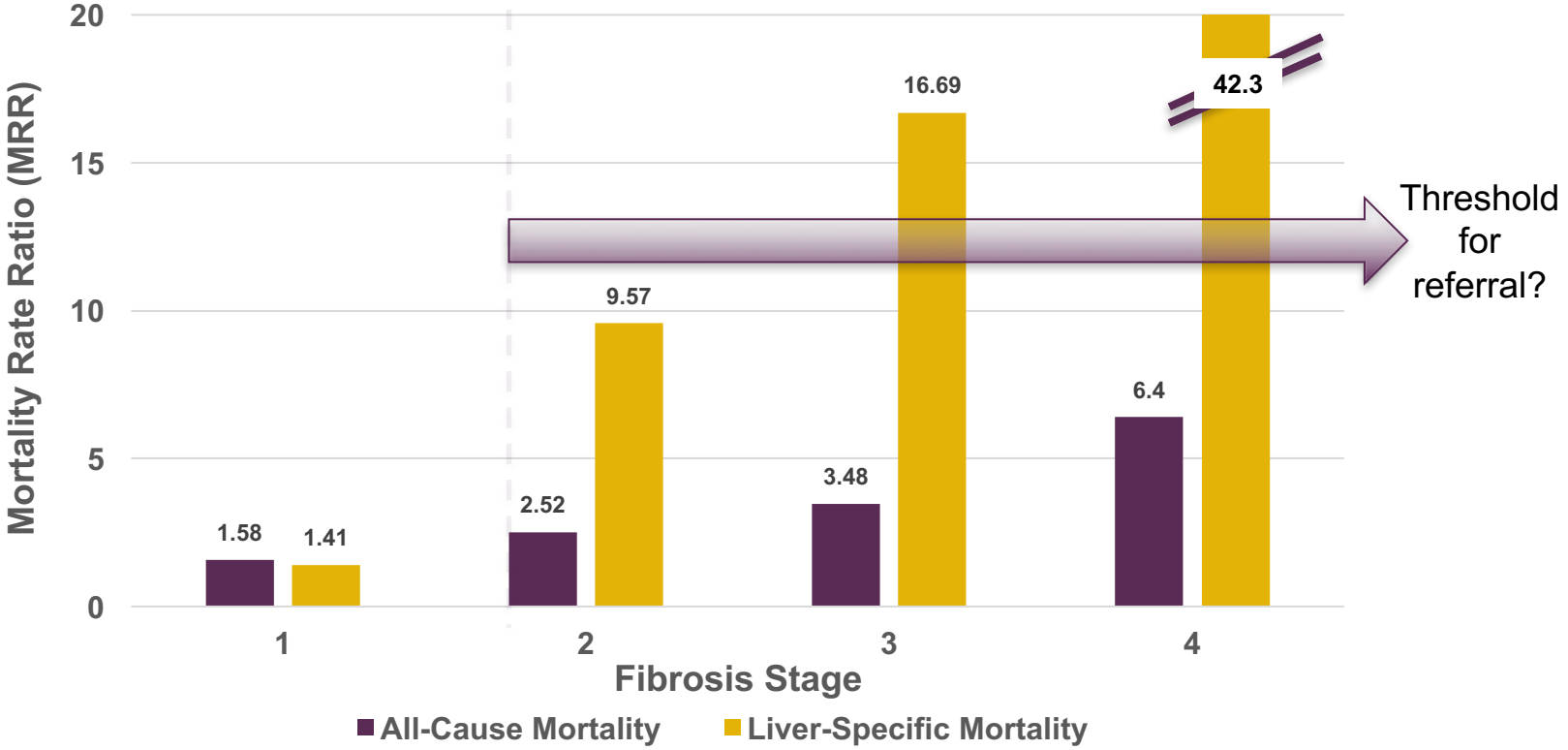
Disclosures

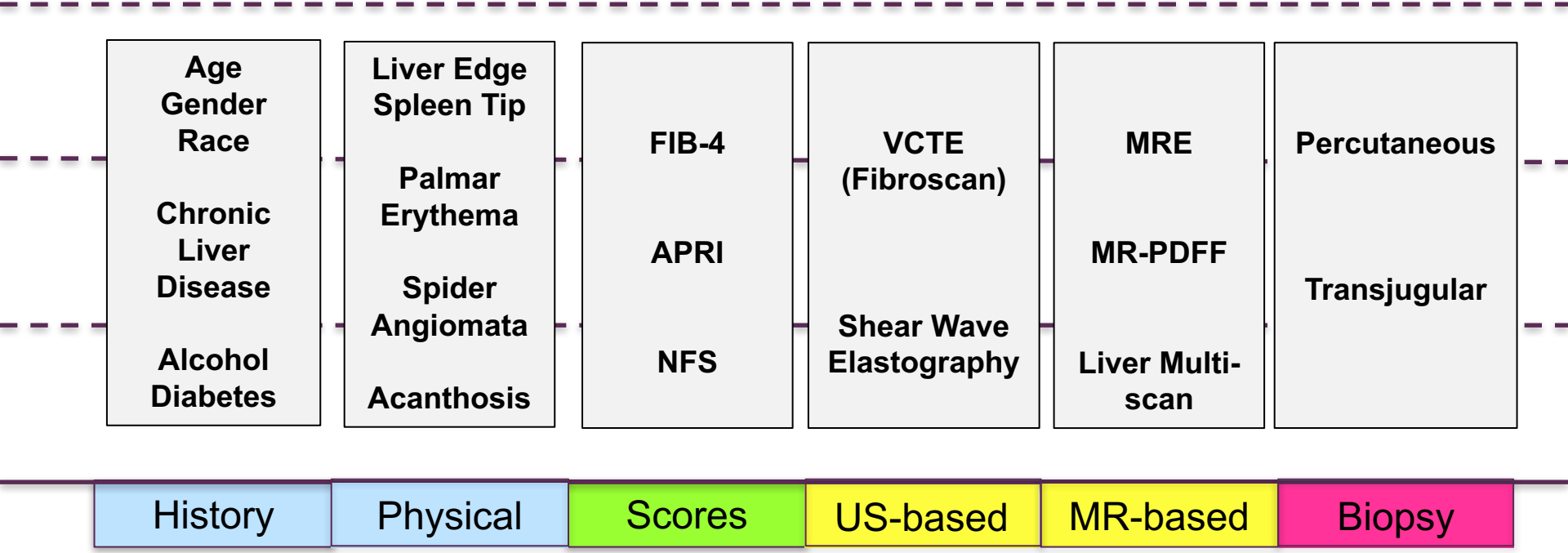
- No relevant financial relationships to disclose

Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis

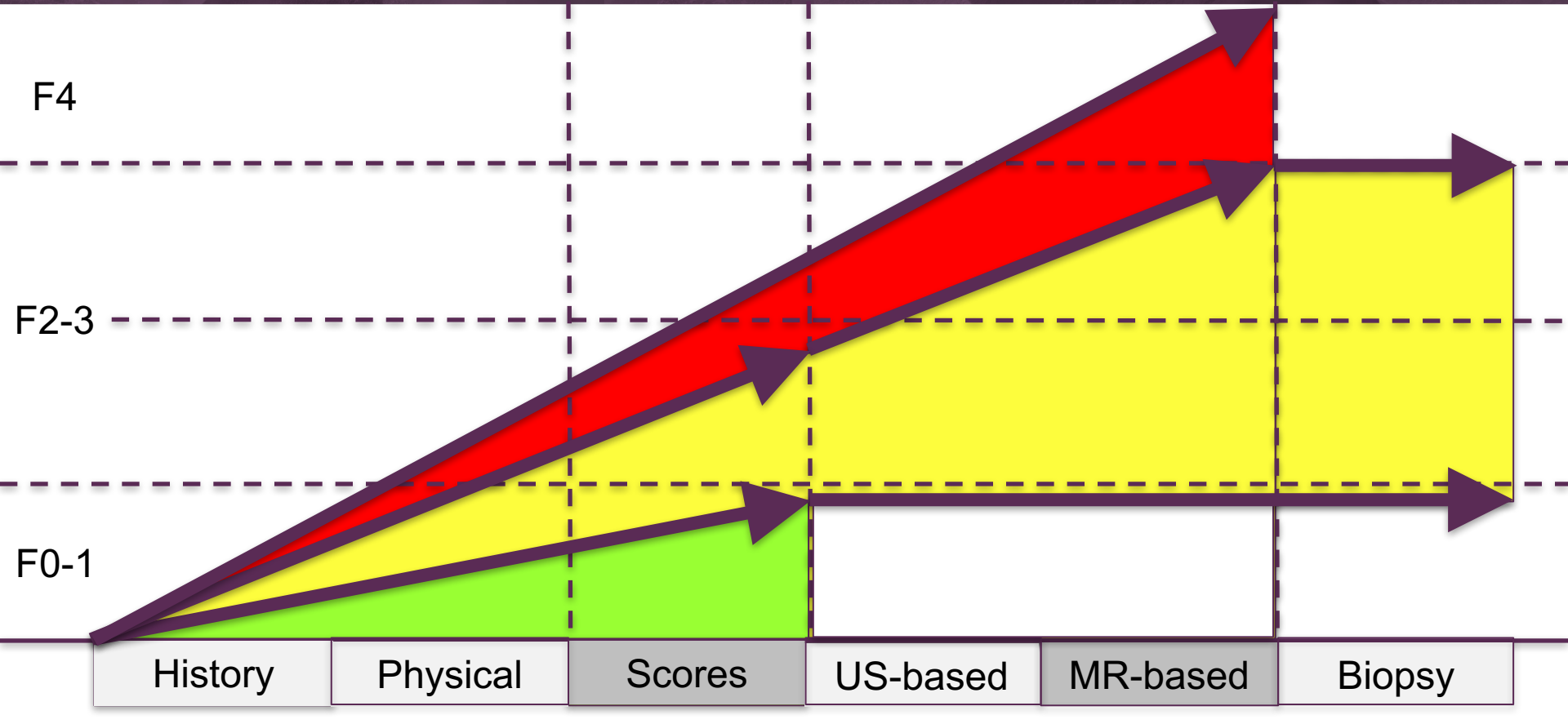


Dulai PS, *Hepatology* 2017;65:1557-65.

Tools to estimate fibrosis stage



Clinical use of tools to estimate fibrosis stage



Outline

I. **Serum scores & commercial biomarker assays**
   A. **NFS, FIB4 & APRI**
   B. **ELF**
   C. **FIB-C3**

II. Ultrasound-based tests (elastography)
   A. VCTE
   B. SWE

III. MR-based tests
   A. MRE
   B. MR-PDFF

Serum-based assessment of liver fibrosis

- You are talking to a primary care physician about a mutual patient when, at the end of the conversation, the physician asks you about a couple of patients with NAFLD.

- “The ultrasound showed fatty liver. Should I be referring these patients?” the PCP asks.

Serum-based assessment of liver fibrosis

- Retrospective review of ~33,000 patients with steatosis on imaging between 01/2006 and 08/2016
- After exclusions 410 had data to calculate NAFLD Fibrosis Score (NFS) within 3 months of imaging
- 196 (48%) were at high risk for advanced fibrosis with NFS >0.675
- 32.6% given lifestyle recommendations, 22.4% referred to a nutritionist, 9.1% referred to a hepatologist

Izzy MJ, et. al. Evaluation of access to NAFLD-related care offered by primary providers: single center experience. AASLD 2017 abstract 583. *Hepatology* 2017;66(suppl):318A.

Serum-based assessment of liver fibrosis

NFS

-1.65 + (0.037 x **age**) + (0.094 x **BMI**) + (1.13 x **IFG/DM**, yes=1, no=) + (0.99 x **AST/ALT** ratio) – (0.013 x **platelets**) – (0.66 x **alb**)

< -1.455 = F0-2

-1.455 – 0.675=indeterminate

> 0.675 = F3-4

FIB4

$$\frac{\textbf{Age} \times \textbf{AST}}{\textbf{Plt} \times \sqrt{(\textbf{ALT})}}$$

<1.45 = F0-2

1.45-3.25 = indeterminate

>3.25 = F3-4

APRI

$$\frac{\textbf{AST} \text{ / ULN AST}}{\textbf{Platelet} \text{ count}} \times 100$$

≤0.5 = F0-2

0.5-1.5 = indeterminate

>1.5 = F3-4

1. Angulo P, *Hepatology* 2007;45:846-54. 2. Vallet-Pichard A, *Hepatology* 2007;46:32-6. 3. Wai C, *Hepatology* 2003;38:518-26.

Serum-based assessment of liver fibrosis

- In a retrospective case-cohort study using data collected within 8 weeks of liver biopsy in a non-transplant population, noninvasive scores evaluated for their ability to predict advanced fibrosis (F3-4):

Score	Disease	AUROC	Sens	Spec	Accuracy
FIB4	NAFLD	0.887	94%	89%	91.5%
	HCV	0.831	85.2%	67%	76.1%
NFS	NAFLD	0.826	84%	67%	75.5%
APRI	NAFLD	0.810	67%	81%	74%

Schmoyer C, et. al. Diagnostic accuracy of non-invasive test of hepatic fibrosis in liver transplant recipients. AASLD 2017 abstract 1708. *Hepatology* 2017;66(suppl):913A.

How good is liver biopsy, anyway?

- 124 patients with chronic HCV had laparoscopic liver biopsies from both lobes. Staging was discrepant (F0-2 vs. F3-4) in 12 of 124 cases.
- 50 were graded *twice* by 2 pathologists. Pathologists re-staged the biopsies the same in 47/50 and 45/50 cases.

Biopsy	Accuracy
Left lobe vs. Right lobe	90.3%
Re-read by the same pathologist	92%

Regev A, et. al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-18.
Schmoyer C, et. al. Diagnostic accuracy of non-invasive test of hepatic fibrosis in liver transplant recipients. AASLD 2017 abstract 1708. *Hepatology* 2017;66(suppl):913A.

Commercial serum-based assays: ELF

- Enhanced Liver Fibrosis (ELF, Siemens) test uses 3 markers of stellate cell activation – involved in the synthesis and degradation of the extracellular matrix – to predict fibrosis:
  - hyaluronic acid (HA)
  - procollagen III N-terminal peptide (PIIINP, a.k.a. Pro-C3)
  - tissue inhibitor of matrixmetaloproteinase (TIMP1)
- $2.494 + 0.846 \ln(C_{HA}) + 0.735 \ln(C_{PIIINP}) + 0.391 \ln(C_{TIMP\text{-}1})$

Commercial serum-based assays: ELF

- ELF score compared to staging biopsy (Ishak F0-6) in 79 subjects with HCV and 400 healthy controls
  - For advanced fibrosis (F3-6), ELF cutoff of 9.8 yielded
    - sens 84.6%, spec 75.8%, acc 80.2%, AUROC 0.90 ± 0.04
  - For ‘cirrhosis’ (F5-6), ELF cutoff of 11.3 yielded
    - sens 82.8%, spec 96.6%, acc 89.7%, AUROC 0.95 ± 0.03

Lichtinghagen R, et. al. The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values. J Hepatol 2013;59:236-42.

Commercial serum-based assays: ELF

- Prospective validation of ELF for prediction of NASH progression as part of simtuzumab (Gilead) phase 2b trial (stopped early at 96 wks).
- 477 adult subjects (45.9% bridging, 54.1% cirrhosis)
  - F3 → F4 in 47 (21%) and F4 → clinical event in 49 (19%)

Group	HR for progression (with higher baseline ELF)	ELF cutoff	Sensitivity (for progression)	Specificity (for progression)	Accuracy (for progression)
F3	3.13 [2.31-4.22]	≥9.76	77%	66%	71.5%
F4	2.37 [1.69-3.31]	≥11.27	56%	75%	65.5%

Harrison S, et. al. Prospective validation of the Enhanced Liver Fibrosis (ELF) test for the prediction of disease progression in patients with nonalcoholic steatohepatitis (NASH) and advanced fibrosis. AASLD 2017 abstract 2122. *Hepatology* 2017;66(suppl):1120A.

A Combined Approach: FIB-C3

- 433 NAFLD patients with prior biopsy had Pro-C3 levels determined using competitive ELISA
- Pro-C3 was combined with *age*, *BMI*, *T2DM* (y/n) and *platelets* to create FIB-C3 score.
- Optimal threshold of FIB-C3 ≥ -0.28 was found to predict advanced fibrosis in NAFLD (F3-4 of 4)

Boyle MP, et. al. Development and validation of the collagen neo-epitope biomarker Pro-C3 “FIB-C3” Score for detection and staging of advanced non-alcoholic fatty liver disease in a large international multi-centre patient cohort. AASLD 2017 abstract 1793. *Hepatology* 2017;66(suppl):54A.

A Combined Approach: FIB-C3

Test	Cohort	Sensitivity	Specificity	Accuracy	PPV	NPV	AUROC
FIB4 ≥2.76	Discovery (n=320)	25.2%	91.1%	58.2%	64.0%	66.1%	
FIB-C3 ≥-0.28		77.0%	80.4%	78.7%	71.8%	84.3%	0.86
FIB4 ≥2.76	Validation (n=113)	29.0%	86.8%	57.9%	42.9%	78.2%	
FIB-C3 ≥-0.28		76.7%	75.9%	76.3%	53.5%	90.0%	0.85

Boyle MP, et. al. Development and validation of the collagen neo-epitope biomarker Pro-C3 “FIB-C3” Score for detection and staging of advanced non-alcoholic fatty liver disease in a large international multi-centre patient cohort. AASLD 2017 abstract 1793. *Hepatology* 2017;66(suppl):54A.

Serum-based assessment of liver fibrosis

- “The ultrasound showed fatty liver. Should I be referring these patients?” the PCP asks.
  - No, not the ones with non-invasive tests that suggest F0-2.
  - FIB4 & NFS are fast, free and practically universally available, have high sensitivities (& high NPV’s) and can be used to identify patients at low risk of fibrosis who do not need further workup.
  - There is not convincing evidence that commercial-based assays are consistently more sensitive.

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   A. VCTE
   B. SWE

III. MR-based tests
   A. MRE
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Ultrasound-based assessment of liver fibrosis

- You are talking to a primary care physician about a mutual patient when, at the end of the conversation, the physician asks you about a couple of patients with NAFLD.

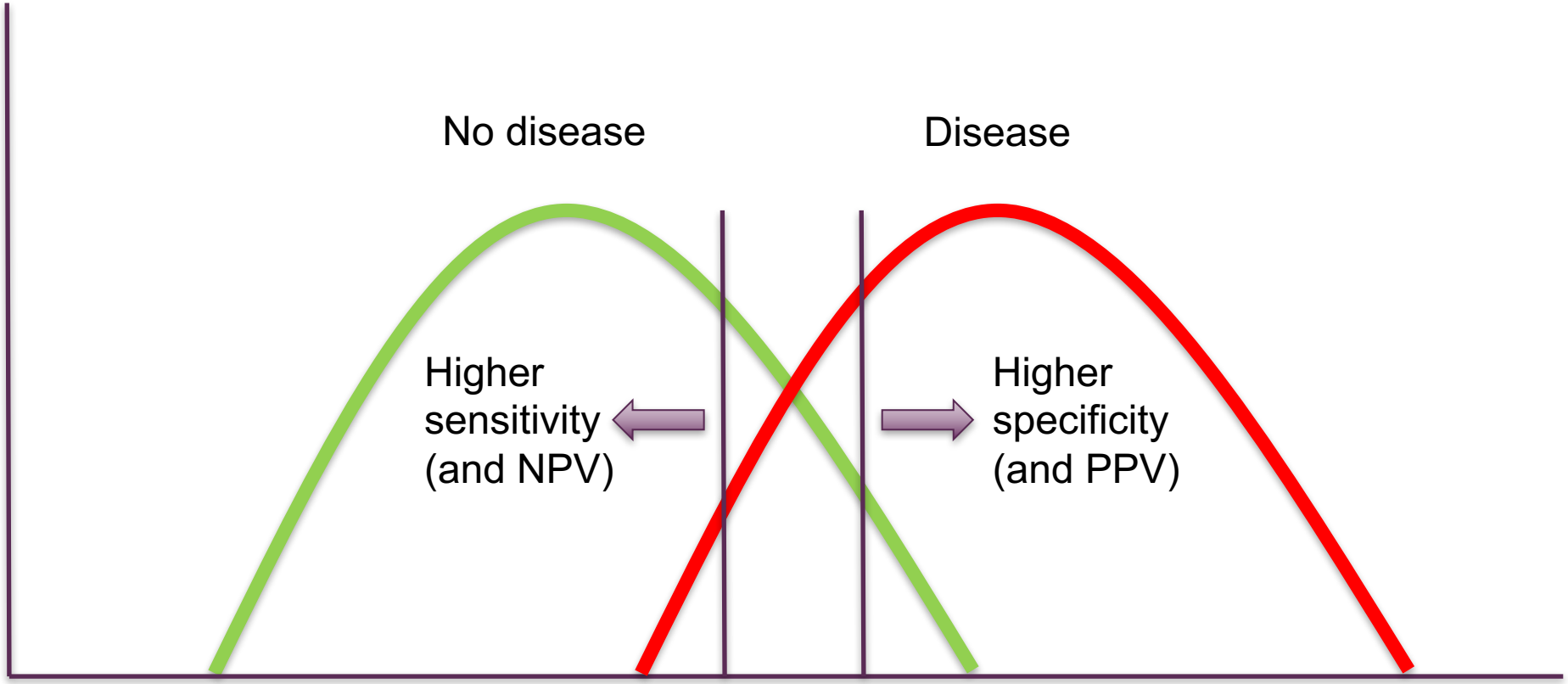
- “The NAFLD Fibrosis Scores were indeterminate, should I be referring these patients?” the PCP asks.

Vibration Controlled Transient Elastography

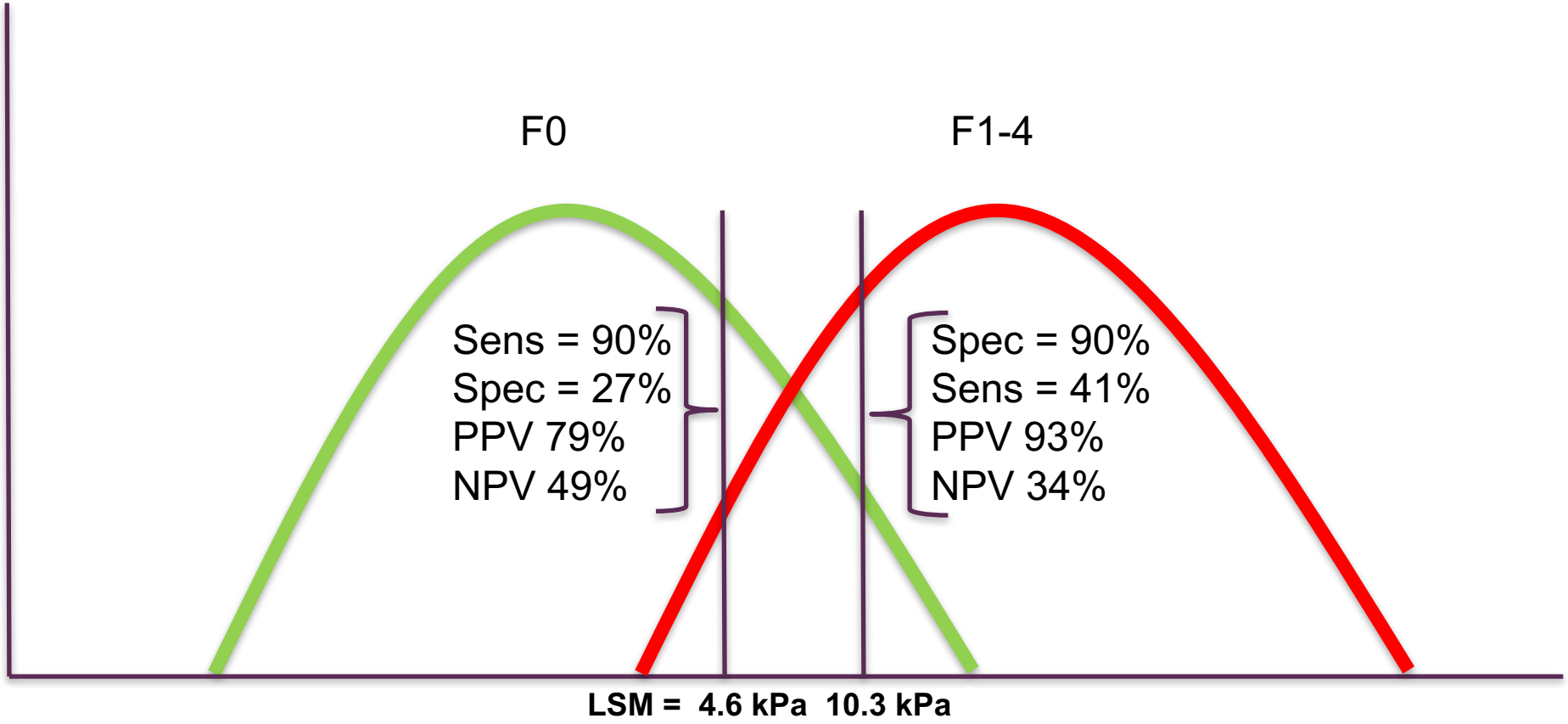
- Aim: to evaluate the performance of Fibroscan in grading steatosis and staging fibrosis in patients with NAFLD
- Methods: In 292 adults with Fibroscan and biopsy within the preceding 12 months (median 36 days), CAP and LSM measurements were compared to histologic steatosis grade and fibrosis stage.

Siddiqui M, et al. Accuracy of vibration controlled transient elastography (VCTE) in grading steatosis and staging fibrosis in patients with nonalcoholic fatty liver disease (NAFLD): a prospective multicenter study. AASLD 2017 abstract 183. *Hepatology* 2017;66(suppl):105A.

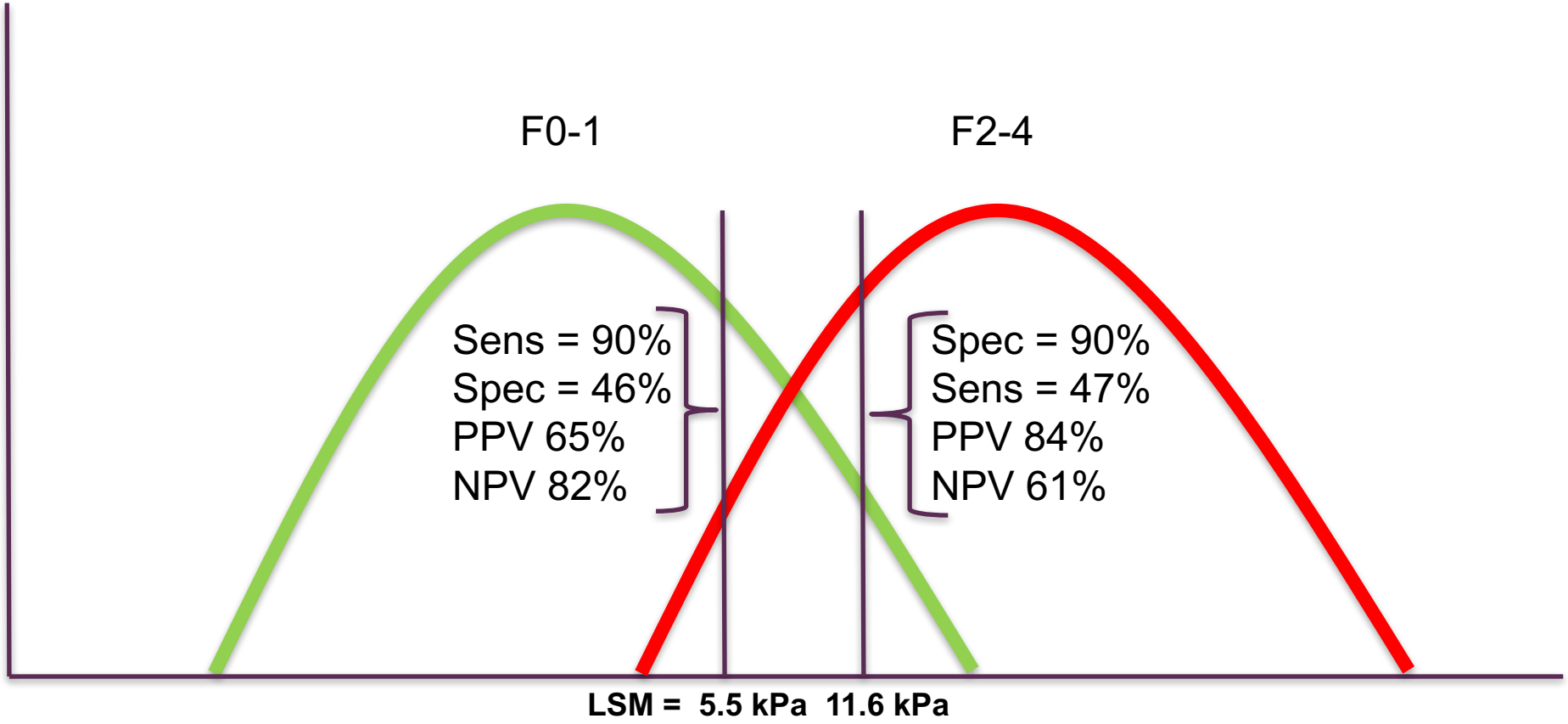
Test Characteristics



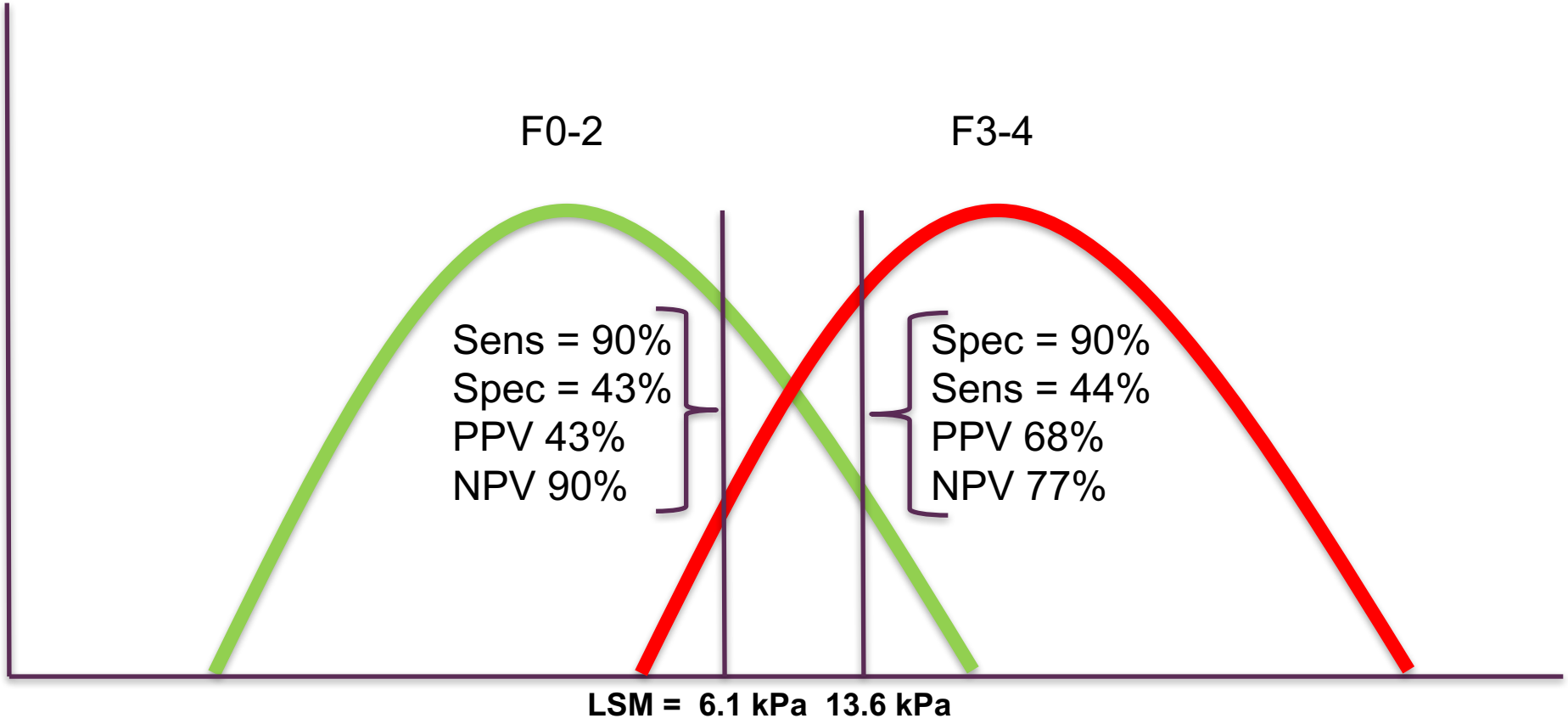
VCTE for Predicting Hepatic Fibrosis



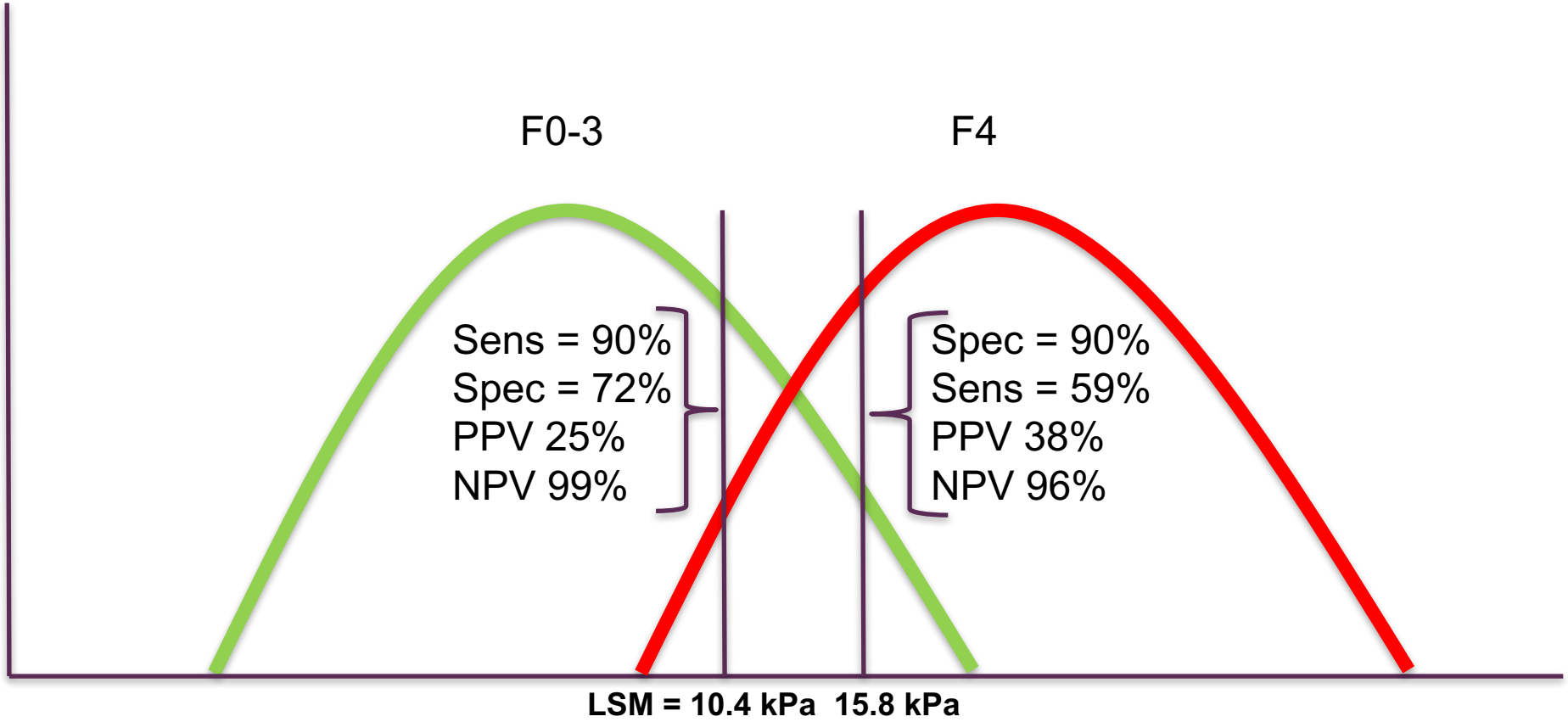
VCTE for Predicting Hepatic Fibrosis



VCTE for Predicting Hepatic Fibrosis



VCTE for Predicting Hepatic Fibrosis



VCTE and Clinically Significant Portal HTN

- Aim: to examine the accuracy of liver stiffness measurement by VCTE for identifying clinically significant portal hypertension (CS-PHTN = HVPG ≥10)
- In 133 patients with 193 paired PPM and VCTE procedures, CS-PHTN was present in 66.7%.
- AUROC of LSM for CS-PHTN was 0.79 (discovery dataset) and 0.77 (validation dataset)

Vuppalanchi R, et al. Liver stiffness measured by vibration controlled transient elastography is an excellent surrogate for identifying clinically significant portal hypertension in patients with compensated NASH cirrhosis. AASLD 2017 abstract 446. *Hepatology* 2017;66(suppl):245A.

VCTE and Clinically Significant Portal HTN

Discovery cohort:

Cut-off levels (kPa)	Sensitivity	Specificity	PPV	NPV	LR	Accuracy
Optimal cut-off: 19.6	85%	68%	86%	67%	35.2	80.3%
90% Sensitivity: 17.0	90%	46%	79%	65%	18.2	76.4%
90% Specificity: 27.9	47%	91%	91%	42%	17.6	59.8%

Validation cohort:

Cut-off levels (kPa)	Sensitivity	Specificity	PPV	NPV	LR	Accuracy
Optimal cut-off: 19.6	89%	[illegible]	[illegible]	71%	13.8	77.2%
90% Sensitivity: 17.0	93%	46%	77%	77%	13.3	77.3%
90% Specificity: 27.9	59%	86%	90%	51%	13.5	68.1%

Vuppalanchi R, et al. Liver stiffness measured by vibration controlled transient elastography is an excellent surrogate for identifying clinically significant portal hypertension in patients with compensated NASH cirrhosis. AASLD 2017 abstract 446. *Hepatology* 2017;66(suppl):245A.

Shear Wave Elastography

- Aim: evaluate the accuracy of VCTE, shear wave elastography (SWE) and MRE compared to NFS in determining fibrosis stage
- Methods: 48 prospectively enrolled patients with NAFLD had liver biopsy NFS and each imaging modality. AUROC was calculated for the ability of each test to predict advanced fibrosis on biopsy.

Furlan A, et al. A prospective evaluation of noninvasive modalities of liver fibrosis assessment in biopsy-proven nonalcoholic fatty liver disease. AASLD 2017 abstract 2189. *Hepatology* 2017;66(suppl):1158A.

Shear Wave Elastography

- For detection of significant fibrosis (F2-4)

	NFS (n=47)	VCTE (n=47)	SWE (n=48)	MRE (n=45)
AUROC	0.727	0.674	0.703	0.758

- For detection of advanced fibrosis (F3-4)

	NFS (n=47)	VCTE (n=47)	SWE (n=48)	MRE (n=48)
AUROC	0.739	0.872	0.820	0.927

Furlan A, et al. A prospective evaluation of noninvasive modalities of liver fibrosis assessment in biopsy-proven nonalcoholic fatty liver disease. AASLD 2017 abstract 2189. *Hepatology* 2017;66(suppl):1158A.

Ultrasound-based assessment of liver fibrosis

- “The NAFLD Fibrosis Scores were indeterminate, should I be referring these patients?” the PCP asks.
  - VCTE and SWE give a more detailed assessment of liver fibrosis than non-invasive serum-based scores:
    - Detect significant fibrosis (F2) vs. no fibrosis (F0-1)
    - Distinguish between advanced fibrosis (F3) & cirrhosis (F4)
  - Variability in results with VCTE and SWE require familiarity and clinical context for interpretation

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MR-based assessment of liver fibrosis

- You are talking to a primary care physician about a mutual patient when, at the end of the conversation, the physician asks you about a patient with NAFLD.
- “Shear wave said the patient has cirrhosis but I don’t believe it. Should I send this patient for biopsy?” the PCP asks.

MR-based assessment of liver fibrosis

- Aim: analyze the ability of MR, TE and biomarkers to predict liver histology.
- 35 patients with biopsy-proven NAFLD underwent MRI (mDIXON, MRS, MRE), TE and Luminex Multiplex Assay

Lee Y, et al. Assessing the severity of liver fibrosis and steatosis in biopsy-proven NAFLD patients using MR imaging, transient elastography and serum biomarker. AASLD 2017 abstract 2111. *Hepatology* 2017;66(suppl):104A.

MR-based assessment of liver fibrosis

- For detection of advanced fibrosis (F3-4)

	VCTE	MRE
AUROC	0.83	0.89

- For detection of severe steatosis (S2-3)

	CAP	mDIXON	MRS
AUROC	0.7	0.83	0.82

Lee Y, et al. Assessing the severity of liver fibrosis and steatosis in biopsy-proven NAFLD patients using MR imaging, transient elastography and serum biomarker. AASLD 2017 abstract 2111. *Hepatology* 2017;66(suppl):104A.

MR-based assessment of liver fibrosis

- Serum biomarker analysis
  - Resistin predicted S2-3 vs. S0-1, **OR 1.44**, p=0.11
  - IFN-γ predicted severe inflammation (grade 2-3 vs. grade 0-1), **OR 1.36**, p=0.04)
  - Total PA-I associated with NASH, **OR 1.063**, p=0.07

Lee Y, et al. Assessing the severity of liver fibrosis and steatosis in biopsy-proven NAFLD patients using MR imaging, transient elastography and serum biomarker. AASLD 2017 abstract 2111. *Hepatology* 2017;66(suppl):104A.

Serum biomarkers

- Resistin – modulates inflammation, regulates stellate cell function
- IFN-γ – recruits & modulates lymphocytes, participates in direct cell killing
- PA-I (plasminogen activator inhibitor) – maintains tissue homeostasis; promotes collagen accumulation

MR-based assessment of liver fibrosis

- Aim: to examine the role of MR in the detection of NASH before the onset of fibrosis
- 83 patients scheduled for bariatric surgery (with liver biopsy) had multifrequency MRE & MR-PDFF
  - MRE at frequency of 30 Hz correlated with lobular inflammation
  - MRE at frequency of 60 Hz correlated with ballooning
  - MR-PDFF correlated with steatosis

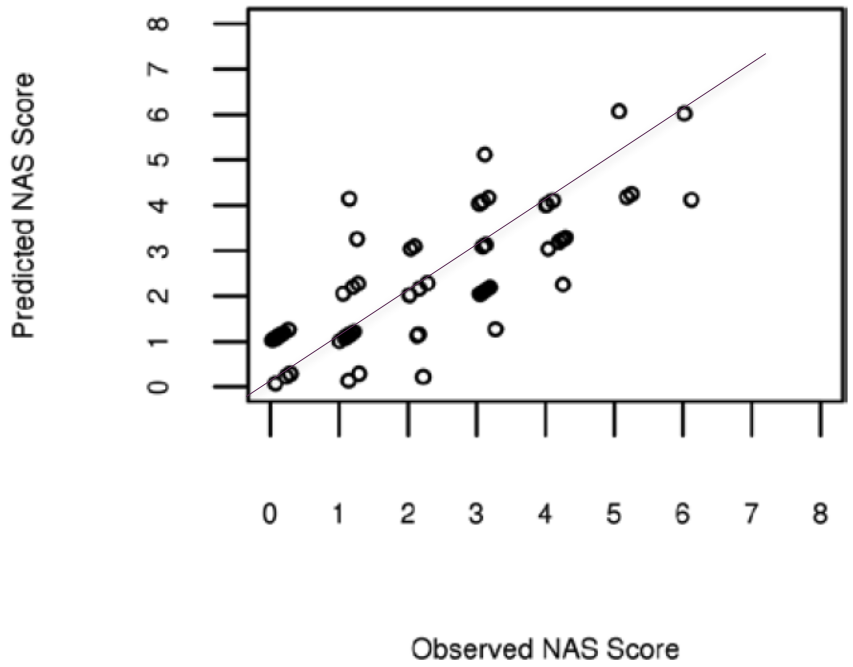
Allen AM, et al. Novel multiparametric magnetic resonance elastography (MRE) protocol accurately predicts early NASH and disease activity. AASLD 2017 abstract 181. *Hepatology* 2017;66(suppl):104A.

MR-based assessment of liver fibrosis

- MRE at 30 Hz, MRE at 60 Hz and MR-PDFF were fit into a general model that predicted NASH on biopsy
  - (NAS 0-2: ‘not NASH’; NAS 3-4: borderline NASH; NAS 5-8: definite NASH)
  - AUROC 0.89
  - Sensitivity 68%, Specificity 85%, Accuracy 76.5%
  - PPV 72%, NPV 82%

Allen AM, et al. Novel multiparametric magnetic resonance elastography (MRE) protocol accurately predicts early NASH and disease activity. AASLD 2017 abstract 181. *Hepatology* 2017;66(suppl):104A.

MR-based assessment of liver fibrosis

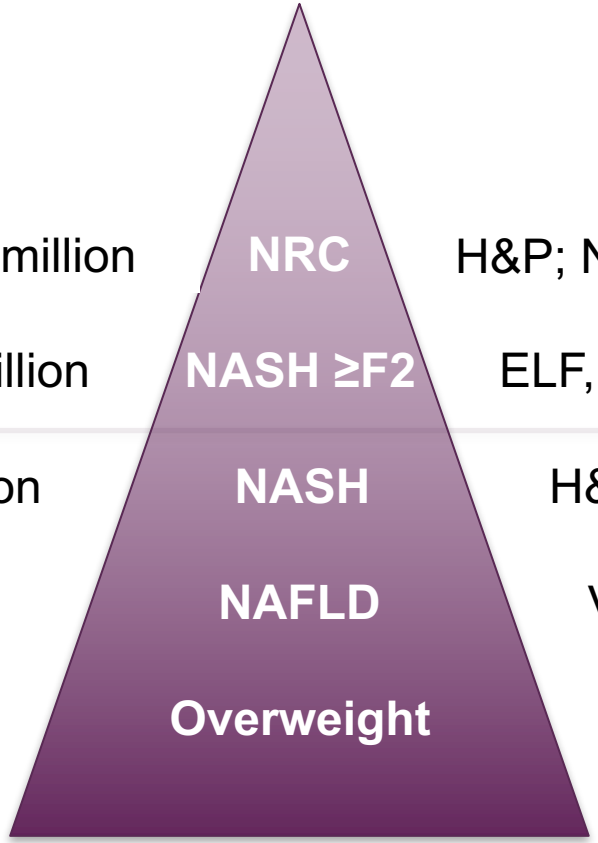


Furlan A, et al. Novel Multiparametric Magnetic Resonance Elastography (MRE) Protocol Accurately Predicts Early NASH and Disease Activity AASLD 2017 abstract 2189. *Hepatology* 2017;66(suppl):1158A.

MR-based assessment of liver fibrosis

- “Shear wave said the patient has cirrhosis but I don’t believe it. Should I send this patient for biopsy?” the PCP asks.
  - For fibrosis assessment of, MRE (if available) is nearly as good as liver biopsy, confers a lower risk to the patient and *may be* less subject to sampling error
  - MRE and MR-PDFF – still largely for research – will likely replace biopsy for NASH staging in the future

Summary



~1 million	NRC	H&P; NFS, FIB4, ELF, VCTE, SWE, MRE
7-10 million	NASH ≥F2	ELF, FIB-C3, VCTE, SWE, MRE, biopsy
15-20 million	NASH	H&P, multifrequency MRE, biopsy
60-80 million	NAFLD	VCTE, Ultrasound, MRI, MR-PDFF
~200 million	Overweight	H&P