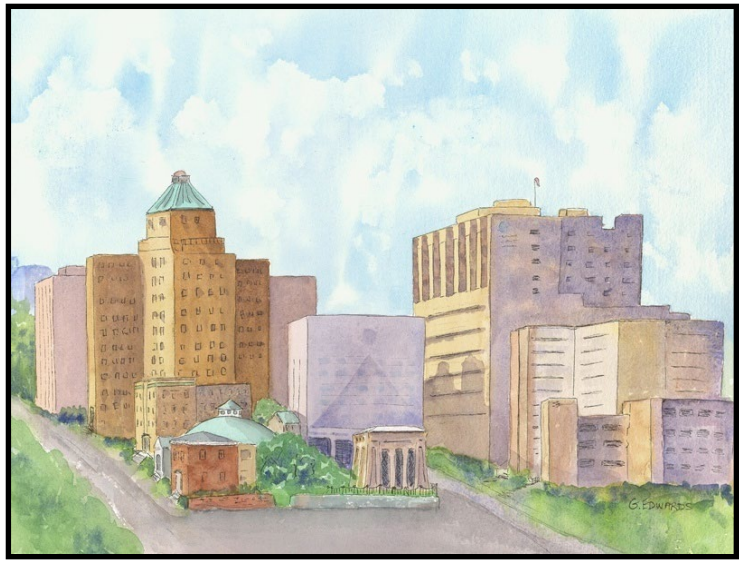
# Non-Invasive Diagnosis of Liver Fibrosis



M. Shadab Siddiqui, MD
Associate Professor of Medicine
Virginia Commonwealth University

Understanding Biomarker Principles

Clinical Prediction Models

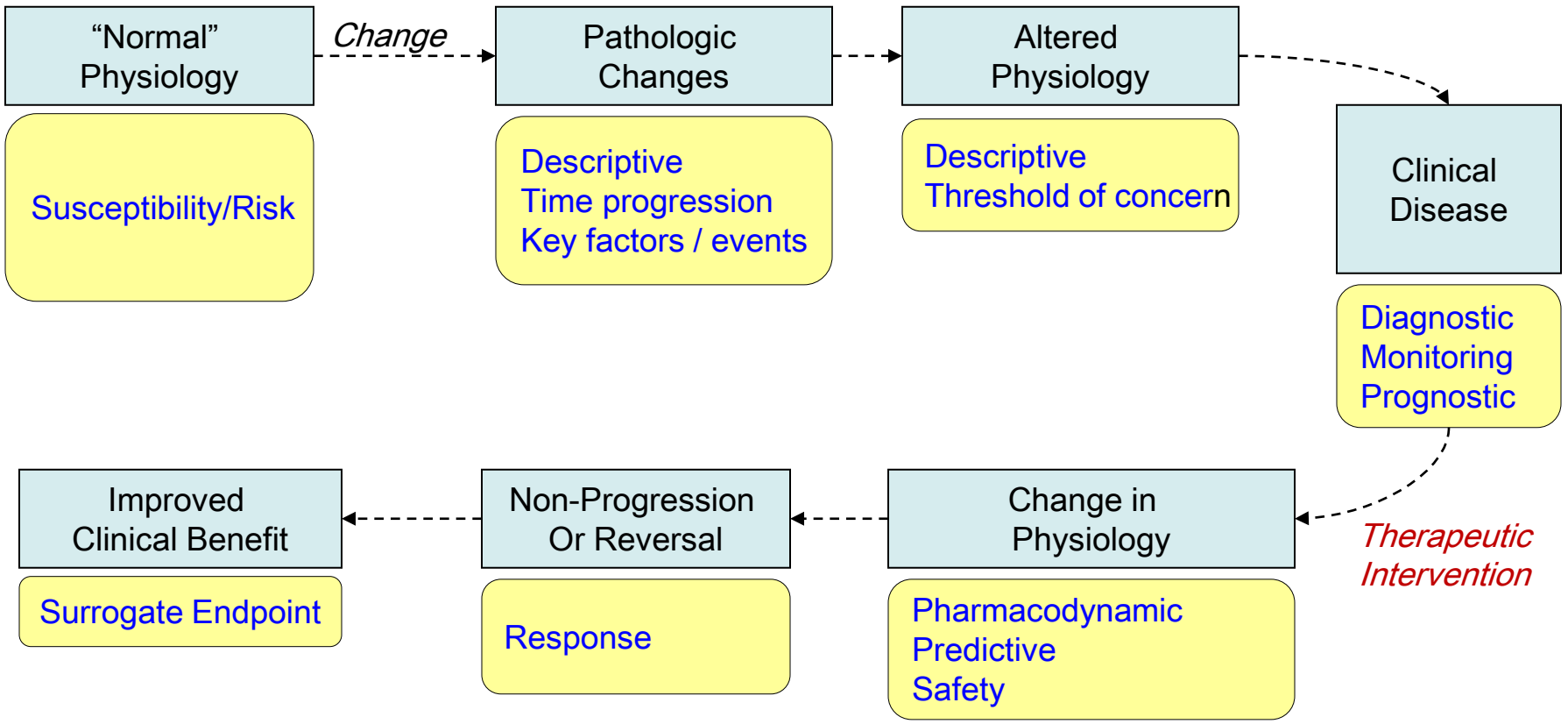
Imaging Based Biomarkers

Serum Based Biomarkers

# What is A Biomarker

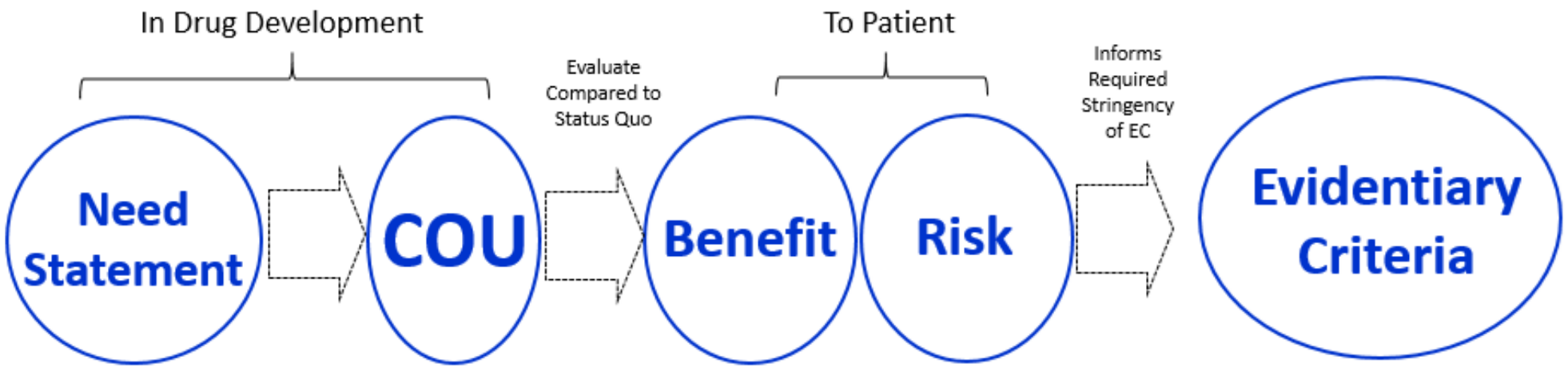
- *An objective patient characteristic that is measured as an indicator of:*
  - Normal biologic processes
  - Pathogenic processes (abnormal biologic processes)
  - Biological responses to a therapeutic intervention

# Biomarkers must be "Fit for Purpose"




Adapted from Chris Leptak…Liver Forum Biomarker Workshop 2017

# Steps For Biomarker Development



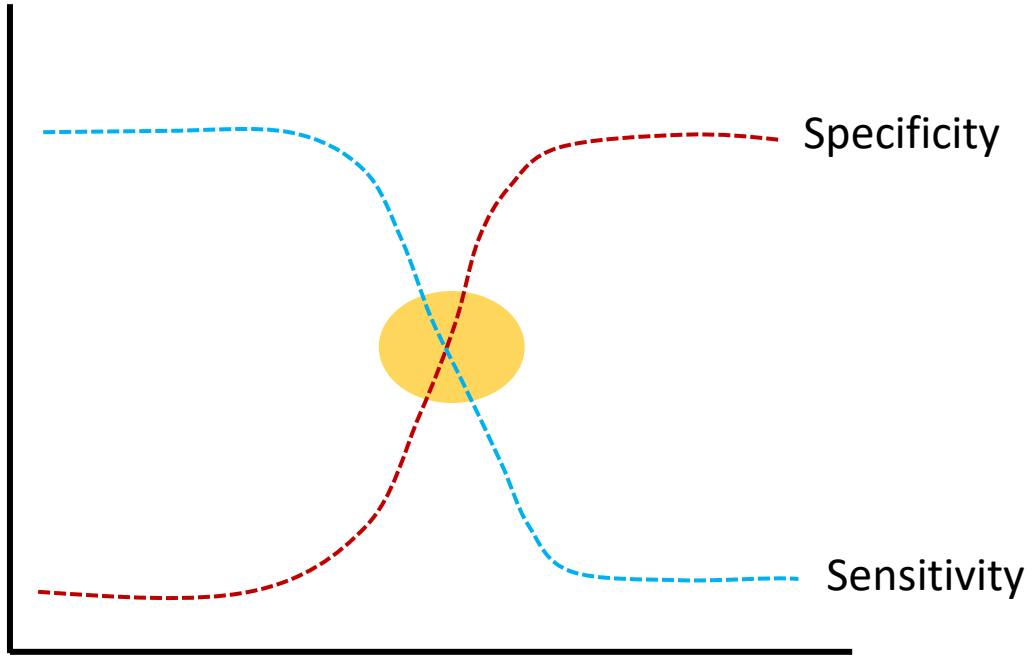

- *Class of Biomarker.*
- *What is the question the biomarker is addressing.*

- *Improved sensitivity*
- *Improved selectivity*
- *Mechanistic context*

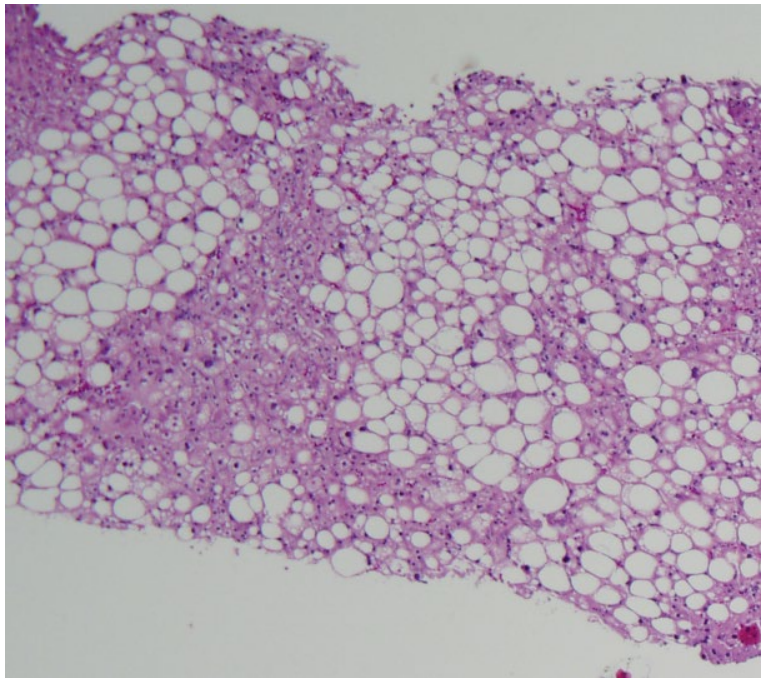
- *Consequence of false positive*
- *Consequence of false negative*

- *Characterization of Relationship Between the Biomarker and Clinical Outcome*
- *Biological Rationale for Use of Biomarker (If Known)*
- *Type of Data and Study Design (i.e. Prospective, Retrospective, etc.)*
- *Independent Data Sets for Qualification*
- *Comparison to current standard*
- *Assay performance*
- *Statistical Methods to Use*

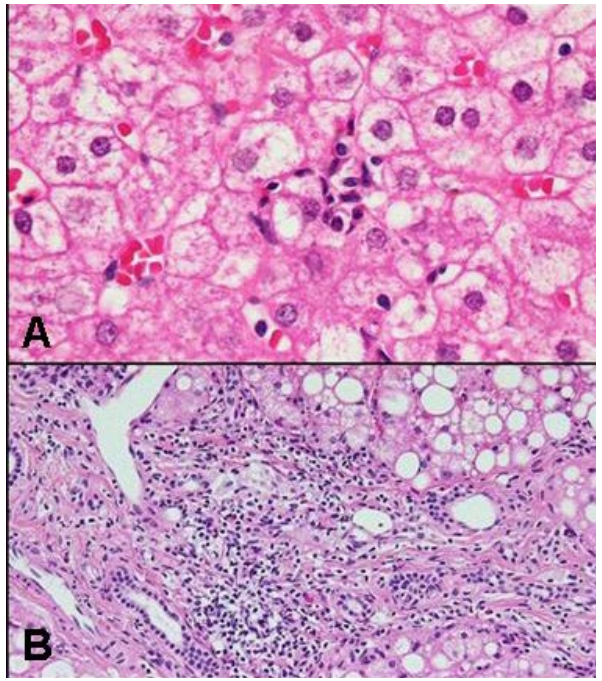
# Understanding Cut-Off Values in Clinical Practice



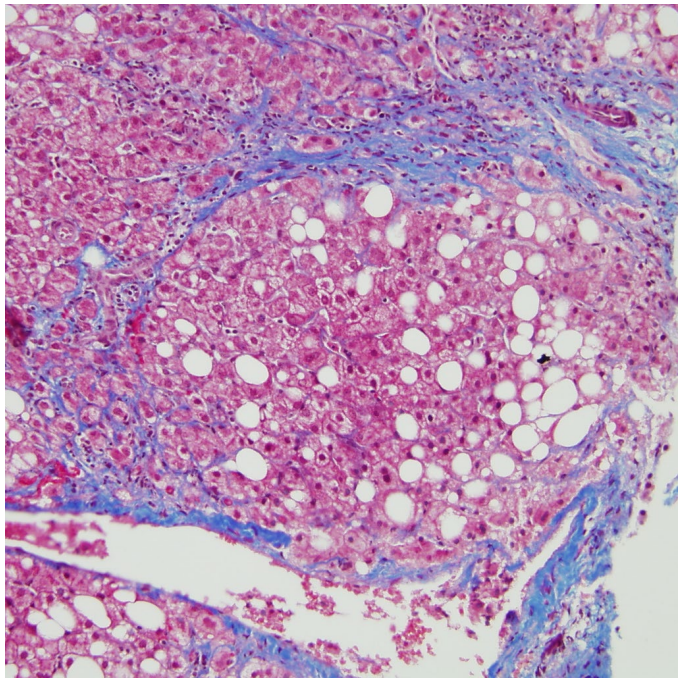
# Quantifiable Parameters on Biomarkers



**Steatosis**




**Inflammation**



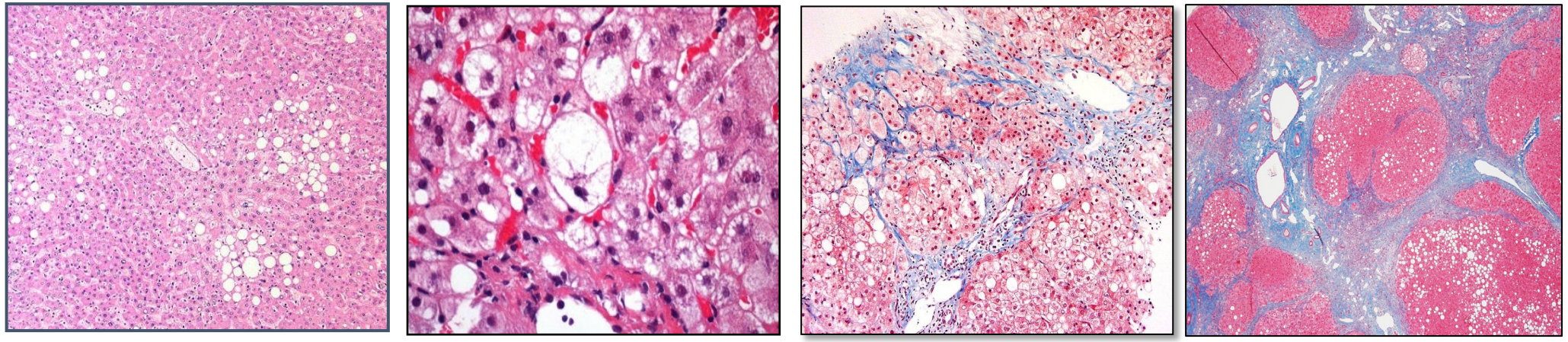
**Fibrosis**

# Priorities in Biomarker Development in NASH

Closest to cirrhosis
And most likely to benefit from prevention
Of progression

Closest to liver-related
Mortality

NAFL | NASH | NASH with fibrosis | NASH Cirrhosis



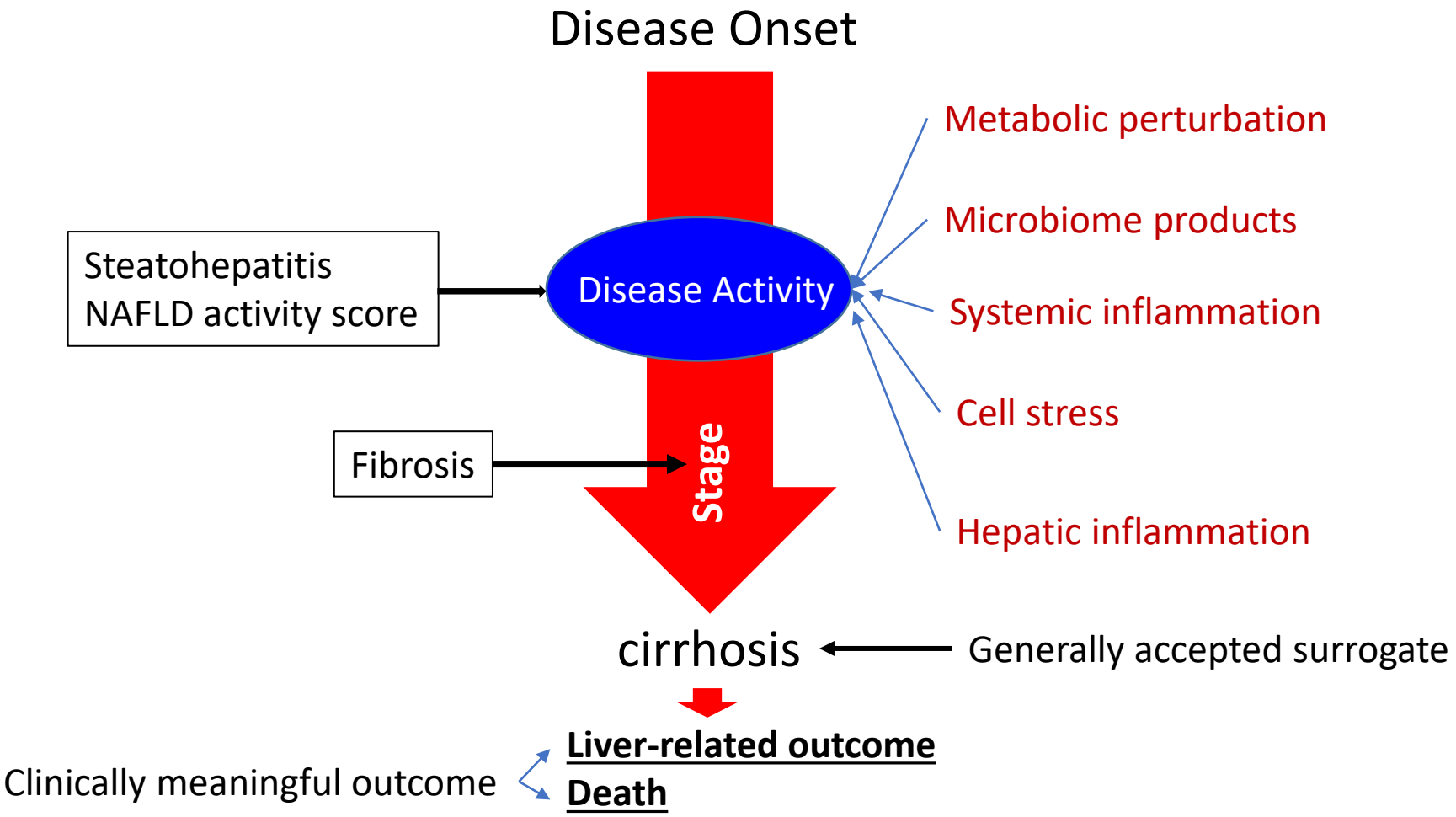
Cardiovascular, CKD and all-cause cancer outcomes

Liver decompensation

**Two Biomarker Priorities:**

1. *What is the risk of liver outcomes* – critical to determine who requires drug/surgical/endoscopic intervention
2. *Is disease trajectory changing* (with or without intervention): need to determine when to intervene, assess disease progression/regression and impact of therapy

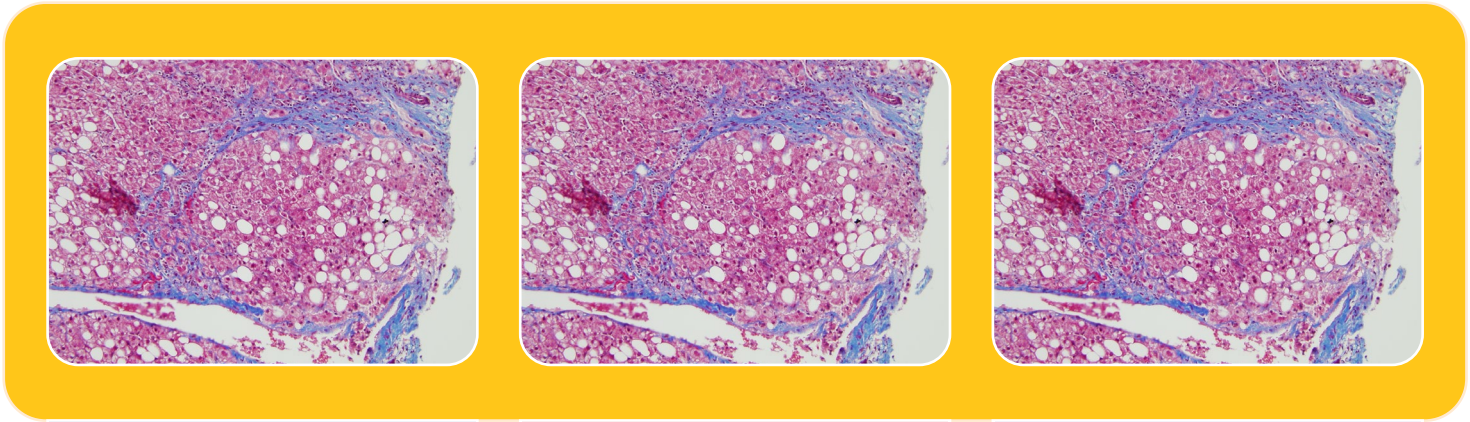
# Leveraging Pathophysiological Insights For Biomarker Development



# Summary and Conclusions

| Biomarker "fit for purpose" use | Impact | Rank order |
|---|---|---|
| Susceptibility | Low due to knowledge gaps and genetics based therapeutics | 5 |
| Is NAFLD present? | Low, can be easily predicted from clinical risk factor profile, does not correlate well with outcomes | 4 |
| What is the risk of liver outcome? | Very high- critical to determine who requires drug/surgical/endoscopic intervention | 1 |
| Can we match drug to patient? | Intermediate- more work needed to validate molecular classification | 3 |
| Is disease trajectory changing (with or without intervention) | High- needed to determine when to intervene, assess disease progression/regression and impact of therapy | 2 |

# Types of Fibrosis Models

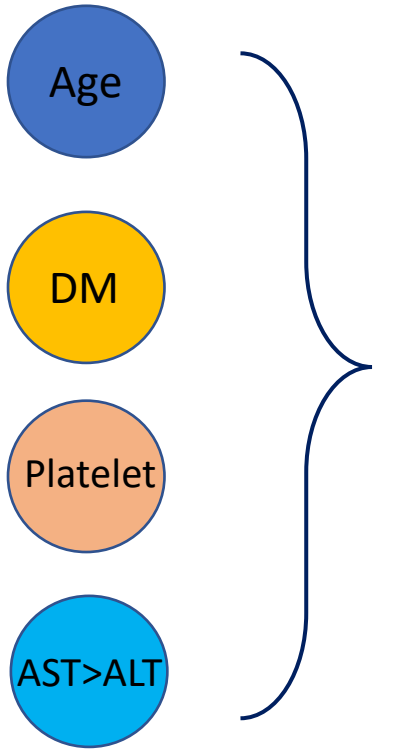


Clinical Prediction Models

Imaging Based

Serum Based

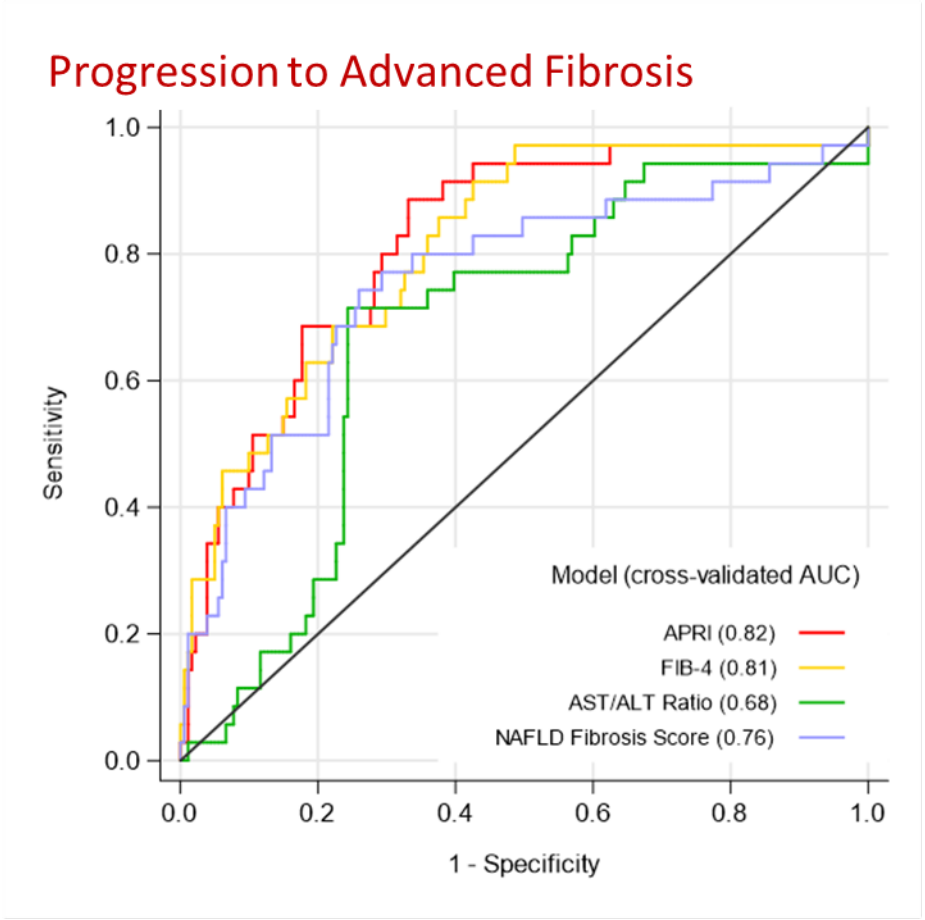
# Diagnostic Performance of Fibrosis Models




| Fibrosis Model | C-Statistic (95% CI) | PPV (%) | NPV (%) |
|---|---|---|---|
| **FIB-4** | 0.80 (0.78, 0.82) | 41 | 93 |
| **APRI** | 0.76 (0.74, 0.80) | 37 | 91 |
| **NAFLD Fibrosis Score** | 0.78 (0.76, 0.80) | 37 | 91 |
| **AST/ALT ratio** | 0.68 (0.66, 0.71) | 33 | 88 |

Siddiqui et. al. Clin Gastro Hep 2019

# CPM Can Predict Progression to Advanced Fibrosis

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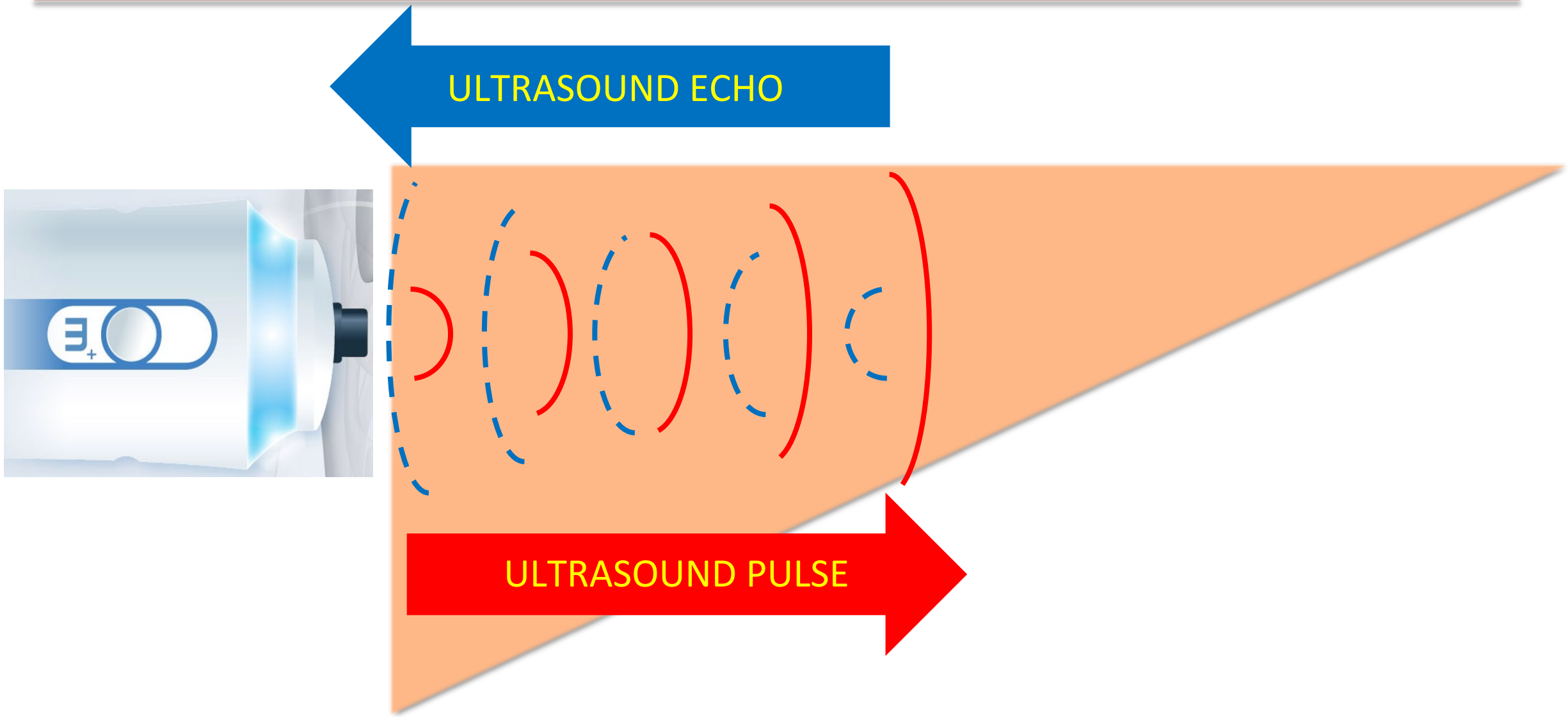
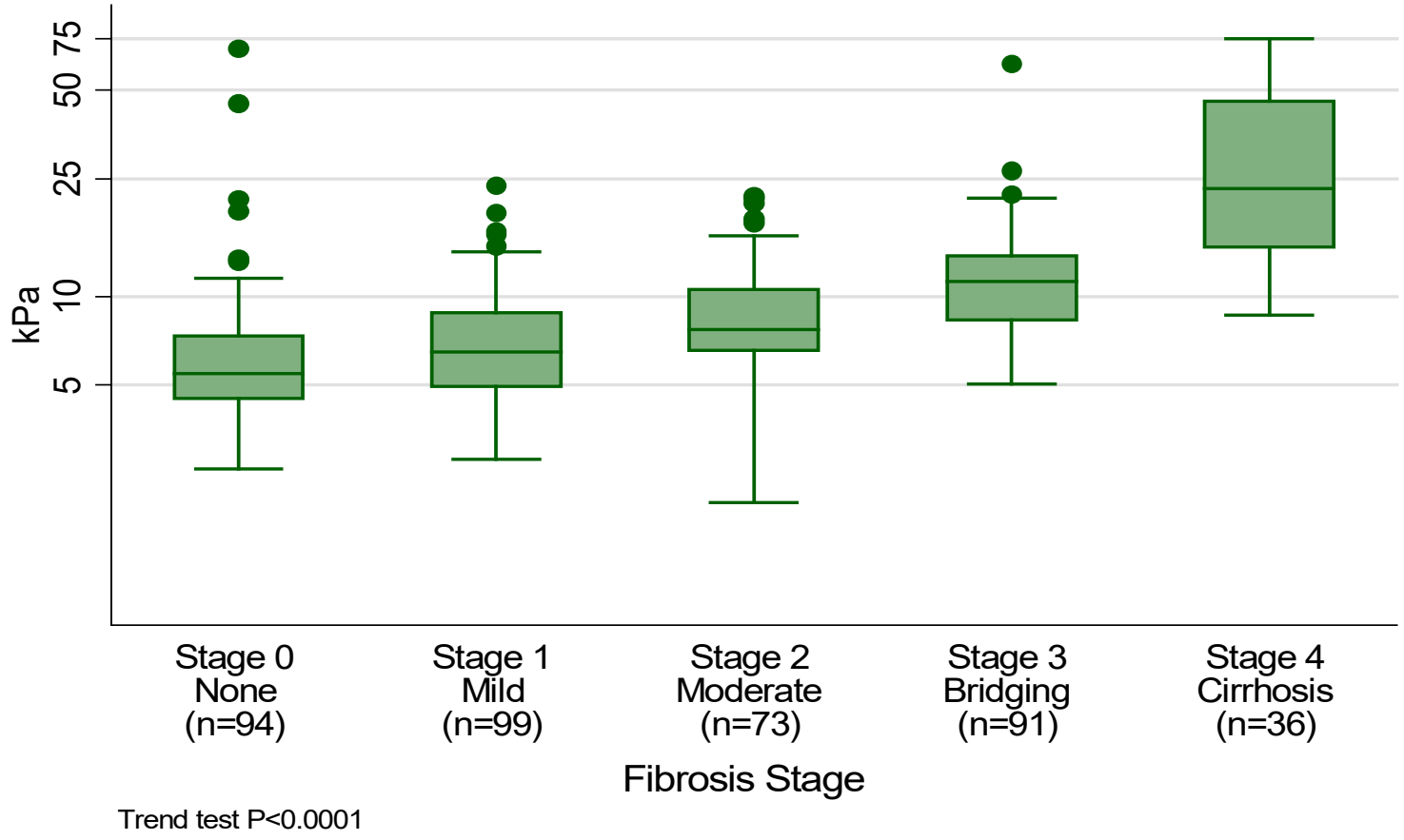
# Vibration Controlled Transient Elastography



# Median LSM Values Stratified by Fibrosis Stage




Siddiqui et. al. Clin Gastro Hep 2019

# Diagnostic Performance of VCTE

| Fibrosis stage | Cross-validated AUROC (95% CI) | Cutoff (kPa) | Sens | Spec | PPV | NPV |
|---|---|---|---|---|---|---|
| 0 vs 1-4 | 0.74 (0.68, 0.79) | 8.6 | 0.53 | 0.87 | 0.93 | 0.37 |
| 0-1 vs 2-4 | 0.79 (0.74, 0.83) | 8.6 | 0.66 | 0.80 | 0.78 | 0.70 |
| **0-2 vs 3-4** | 0.83 (0.79, 0.87) | 8.6 | 0.80 | 0.74 | 0.59 | 0.89 |
| **0-3 vs 4** | 0.93 (0.90, 0.97) | 13.1 | 0.89 | 0.86 | 0.39 | 0.99 |

Siddiqui et. al. Clin Gastro Hep 2018

# Diagnostic Performance of VCTE

| | Cutoff Values | No. of Studies (No. of Patients) | Summary PPV, % Mean (range) | Summary NPV, % Mean (range) |
|---|---|---|---|---|
| **Fibroscan –M probe** | | | | |
| Significant fibrosis | 7.25-11 | 8 (1110) | 75 (48-88) | 77 (66-91) |
| Advanced fibrosis | 9.6-11.4 | 5 (773) | 68 (57-75) | 93 (88-100) |
| Cirrhosis | 13.4-22.3 | 5 (518) | 60 (33-78) | 95 (78-100) |
| **Fibroscan XL probe** | | | | |
| Significant Fibrosis | 4.8-8.2 | 4 (654) | 66 (54-83) | 79 (72-84) |
| Advanced fibrosis | 5.7-9.3 | 3 (579) | 59 (45-71) | 89 (84-93) |
| Cirrhosis | 7.2-16 | 4 (654) | 40 (31-53) | 98 (95-100) |

Adapted from Xiao et. al. Hepatology 2017

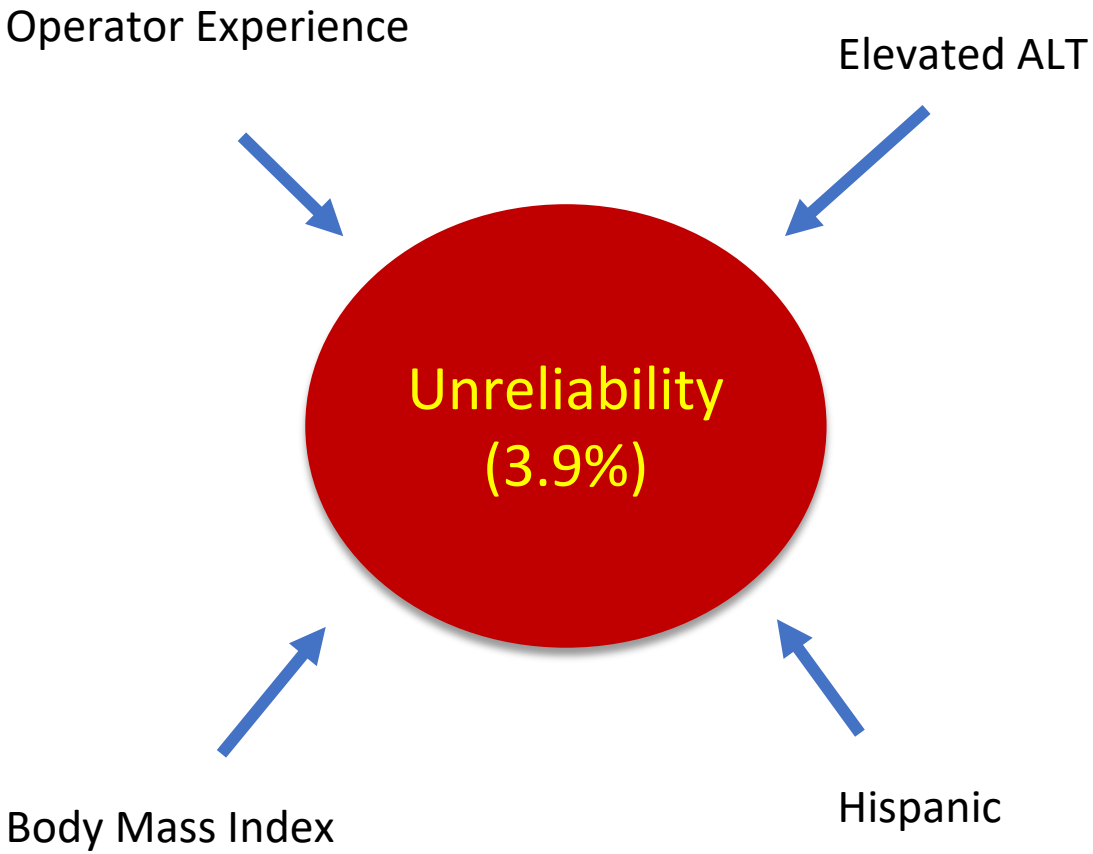
# Use of VCTE in Practice

| Fibrosis Stage | Cross-Validated AUROC (95% CI) | Sensitivity fixed at 0.90 | | | Specificity fixed at 0.90 | | |
|---|---|---|---|---|---|---|---|
| | | Cut-off (kPa) | PPV | NPV | Cut-off (kPa) | PPV | NPV |
| **0 vs 1-4** | 0.74 (0.68, 0.79) | 4.9 | 0.80 | 0.48 | 9.4 | 0.93 | 0.34 |
| **0-1 vs 2-4** | 0.79 (0.74, 0.83) | 5.6 | 0.62 | 0.80 | 11.9 | 0.80 | 0.59 |
| **0-2 vs 3-4** | 0.83 (0.79, 0.87) | 6.5 | 0.45 | 0.91 | 12.1 | 0.71 | 0.80 |
| **0-3 vs 4** | 0.93 (0.90, 0.97) | 12.1 | 0.34 | 0.99 | 14.9 | 0.41 | 0.97 |

# Technical Considerations with VCTE

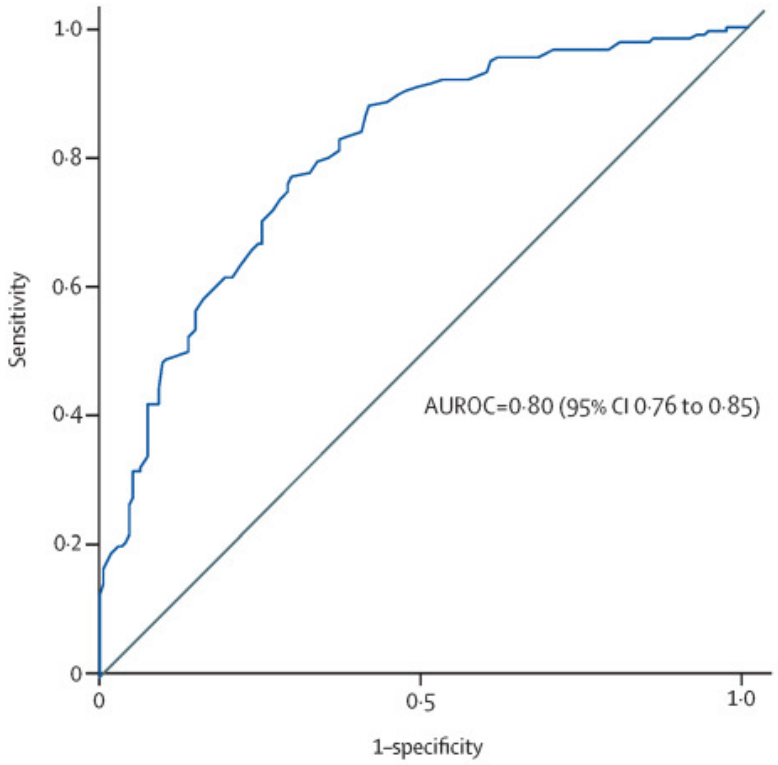
**Operating Parameters of VCTE:**

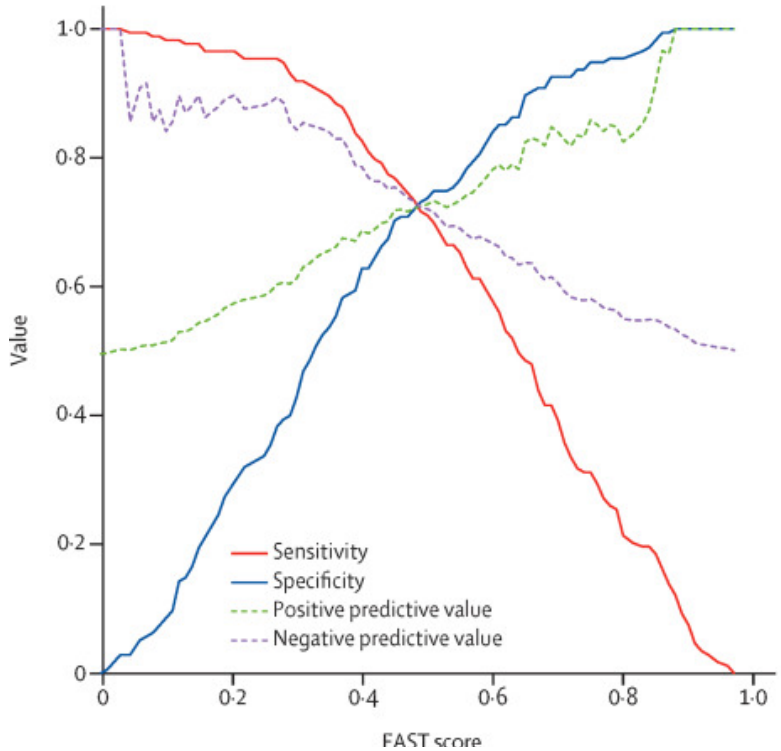
- Ten valid shots (>60% success rate)
- IQR-median LSM Ratio ≤ 30%




Vuppalanchi et. al. Hepatology 2017

# Fibroscan-AST (FAST) for NASH with Fibrosis

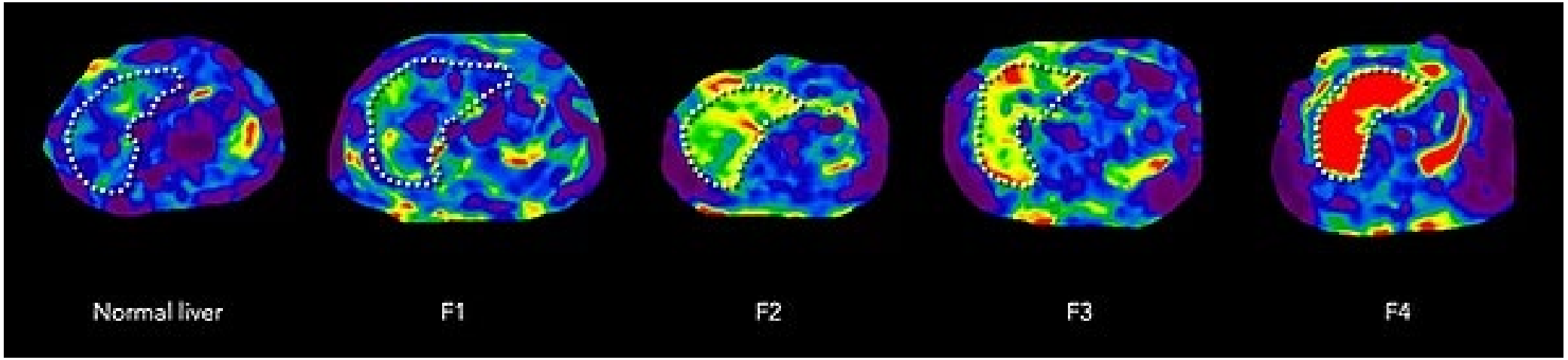


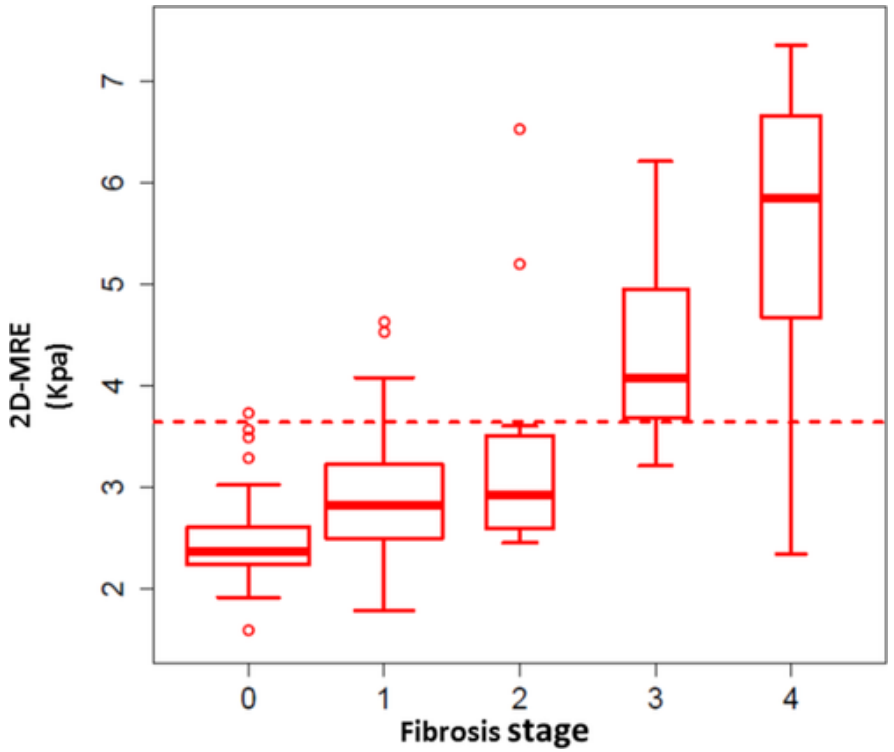

**Rule-out zone** (FAST≤0.35) NPV 85%; **Rule in zone** (FAST≥0.67) PPV 0.85

Newsome et. al. Lancet 2020

# Magnetic Resonance Elastography



# Diagnostic Performance of MRE in NAFLD

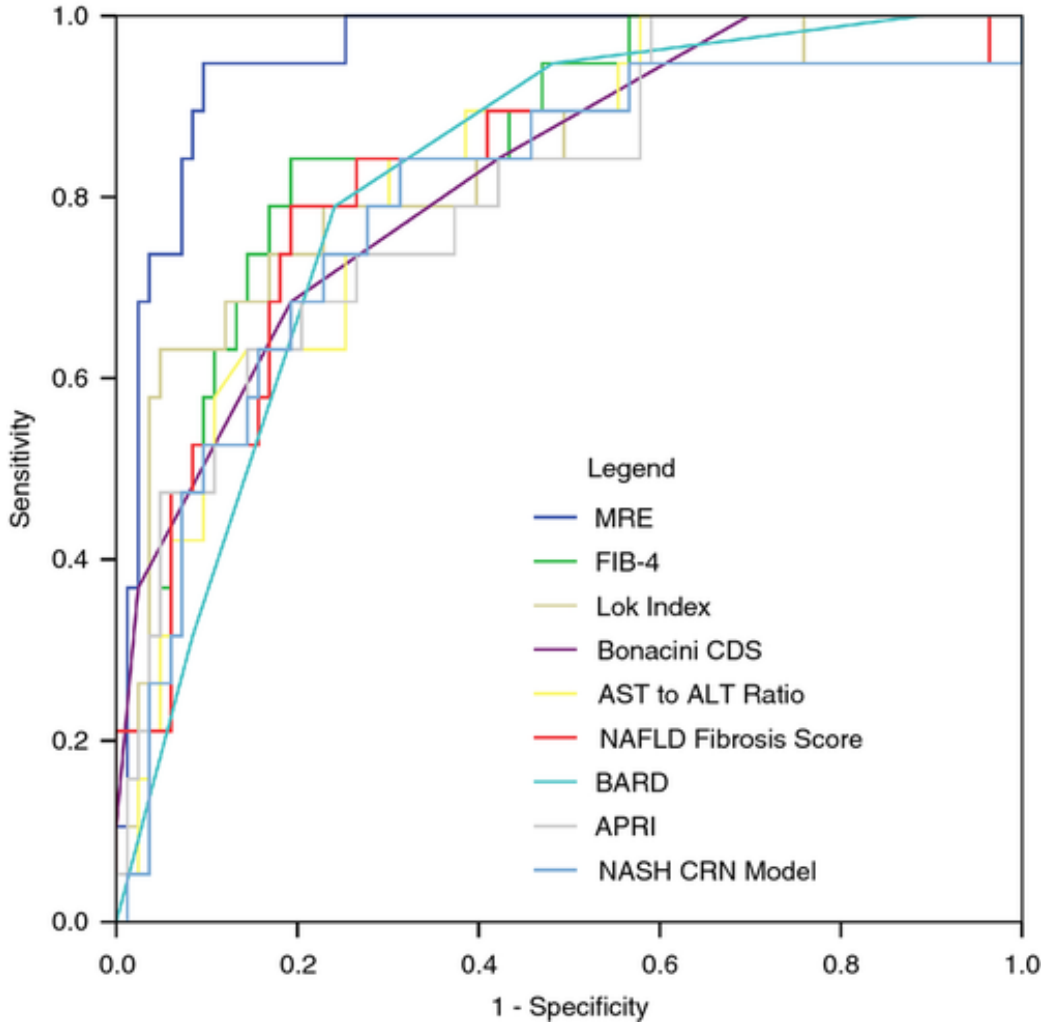



| | Cutoff Values | No. of Studies (No. of Patients) | Summary PPV, % Mean (range) | Summary NPV, % Mean (range) |
|---|---|---|---|---|
| **MRE** | | | | |
| Significant fibrosis | 3.4-3.62 | 3 (384) | 83 (77-88) | 86 (84-89) |
| Advanced fibrosis | 3.62-4.8 | 5 (628) | 71 (68-75) | 93 (81-98) |
| Cirrhosis | 4.15-6.7 | 3 (384) | 53 (44-58) | 99 (98-99) |

Loomba et. al. Hepatology 2014

Adapted from Xiao et. al. Hepatology 2017

# Diagnostic Performance of MRE vs. CPM (F≥3)




| | AUROC | AUROC of MRE vs. CPM |
|---|---|---|
| **2D-MRE** | 0.957 | ref |
| Clinical Prediction Models | | |
| FIB-4 | 0.861 | P=0.039 |
| AST:ALT Ratio | 0.825 | P=0.013 |
| NAFLD Fibrosis Score | 0.818 | P=0.013 |
| BARD | 0.816 | P=0.001 |
| APRI | 0.807 | P=0.006 |

Cui et. al. APT 2015

# Comparing Performance of MRE vs. VCTE

| | Stage 0 vs. Stage 1-4 | | Stage 0-1 vs. Stage 2-4 | | Stage 0-2 vs. Stage 3-4 | | Stage 0-3 vs. Stage 4 | |
|---|---|---|---|---|---|---|---|---|
| | AUROC | P-value vs MRE | AUROC | P-value vs MRE | AUROC | P-value vs MRE | AUROC | P-value vs MRE |
| **MRE** | 0.83 | 0.466 | 0.91 | 0.001 | 0.89 | 0.426 | 0.97 | 0.049 |
| **VCTE** | 0.78 | | 0.82 | | 0.88 | | 0.92 | |

Imajo et. al. Gastro 2015

# Factors Affecting MRE vs. VCTE Success Rates

| Factors | MR Elastography (n=110) | | | VCTE (n=97) | | |
|---|---|---|---|---|---|---|
| | Successful Examination (n=105) | Unsuccessful Examination (n=5) | P-value | Successful Examination (n=79) | Unsuccessful Examination (N=18) | P-value |
| Age (y) | 48 (46, 50) | 47 (23, 72) | 0.96 | 50 (47, 52) | 44 (39, 50) | 0.08 |
| Chest Cirucmference | 120 (117, 122) | 134 (117, 150) | 0.07 | 118 (116, 121) | 127 (121, 134) | 0.02 |
| Waist Circumference | 119 (116, 122) | 140 (124, 155) | 0.02 | 118 (115, 122) | 127 (120, 135) | 0.03 |
| Skin to capsule distance | 3.0 (2.7, 3.2) | 4.8 (0.2, 9.5) | 0.29 | 2.9 (2.6, 3.1) | 3.8 (2.8, 4.8) | 0.07 |
| BMI | 39.8 (37.7, 41.9) | 51 (39.3, 62.7) | 0.06 | 39.1 (37.4, 40.8) | 45.1 (40.8, 49.5) | 0.01 |
| Sex (Female) | 66 | 4 | 0.65 | 52 | 11 | 0.79 |

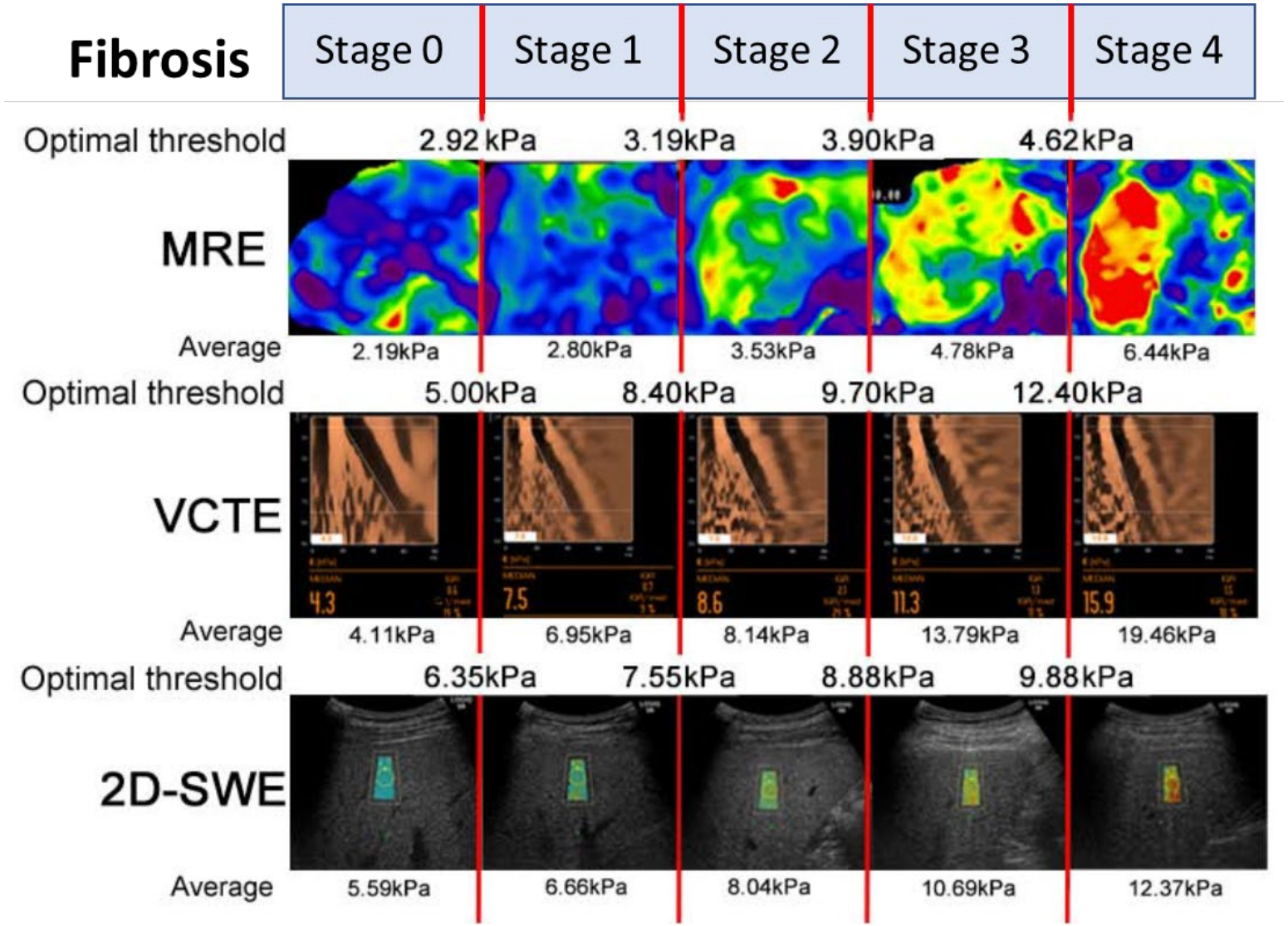
Imajo et. al. Gastro 2015

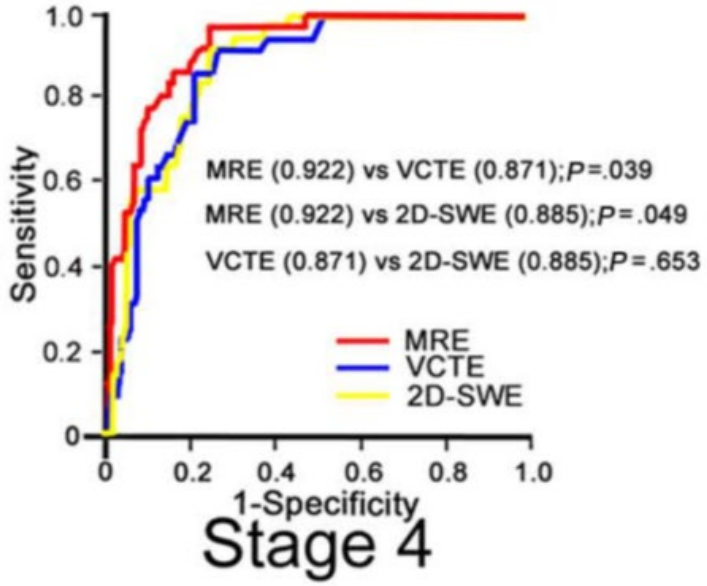
# Shear Wave Elastography


Point Shear Wave Elastography


2-D Shear Wave Elastography

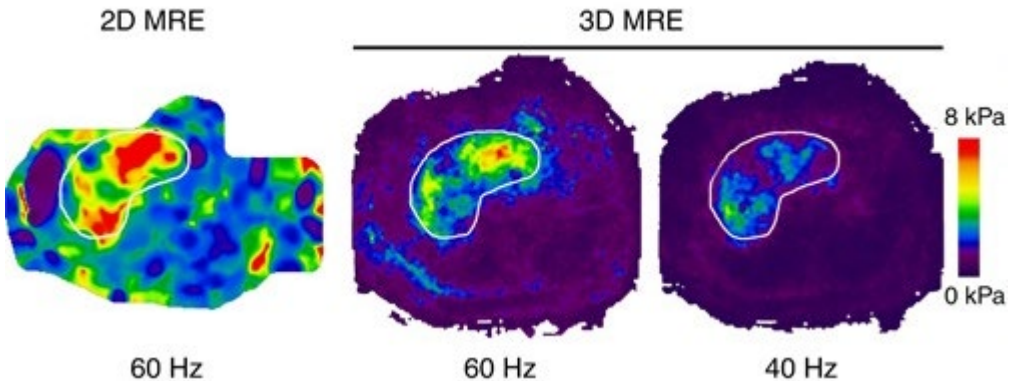
# 2D-Shear Wave Elastography



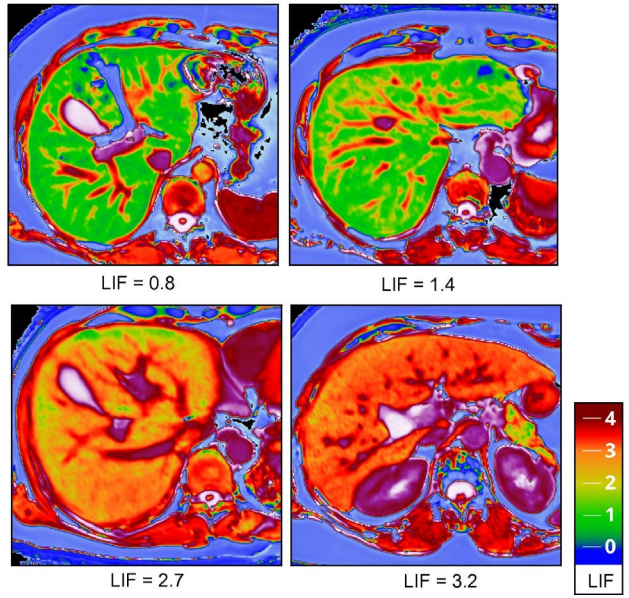




Imajo et. al. Clin Gastro Hepatol. 2020

# Emerging Imaging Biomarkers in NAFLD

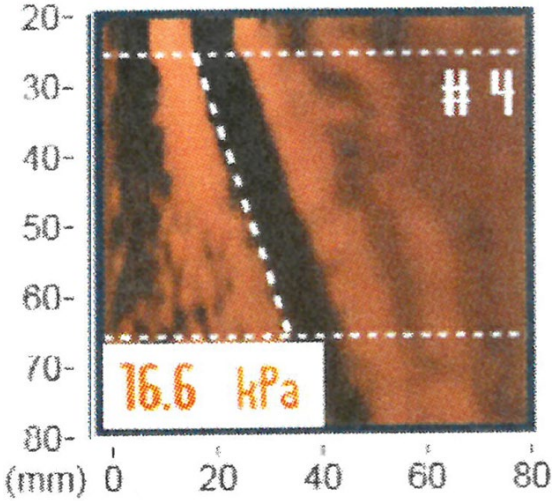



Loomba et. al. Am J Gastro 2016




Pavlides et. al. J Hepatol 2016

**FibroScan + AST (FAST) Score**

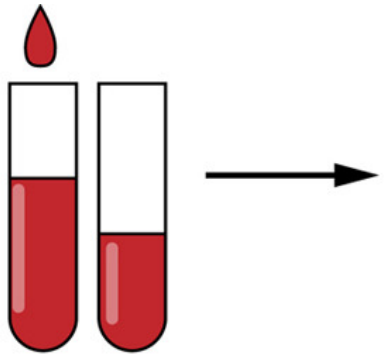



Newsome et. al. Lancet Gastro Hepatol 2020

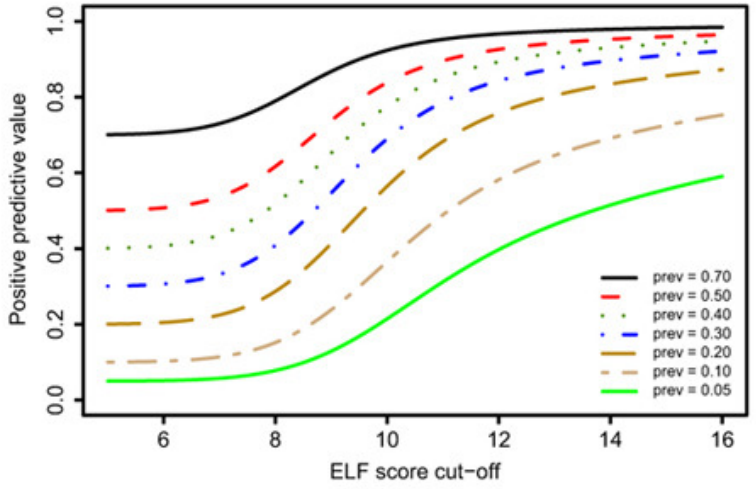
# Comparison of Imaging Biomarkers

| Technique | Performed by | Steatosis Grading | Quality Criteria | Failure Rate | Confounders | Cost | Point of Care |
|---|---|---|---|---|---|---|---|
| **TE** | Hepatologist Technician | Yes (CAP) | Well-defined | 3-27% | Inflammation Obesity Congestion | $ | Yes |
| **MRE** | Radiologist | Yes (PDFF) | Emerging | 0-2 | Iron overload | $$$ | No |
| **pSWE** | Radiologist Ultrasongrapher | No | Not well-defined | 2 | Limited data | $$ | No |
| **2D-SWE** | Radiologist Ultrasongrapher | No | Not well-defined | 13? | Limited Data | $$ | No |

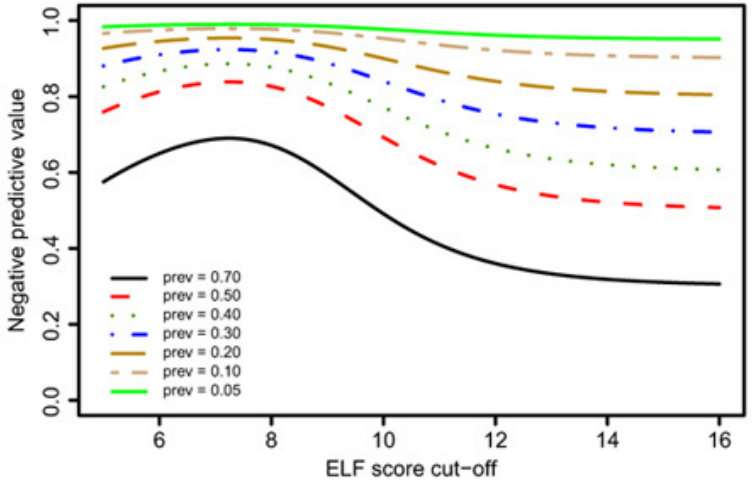
# Serum Based Biomarkers: ELF



Enhanced Liver Fibrosis test;
A blood based biomarker for diagnosis advanced fibrosis

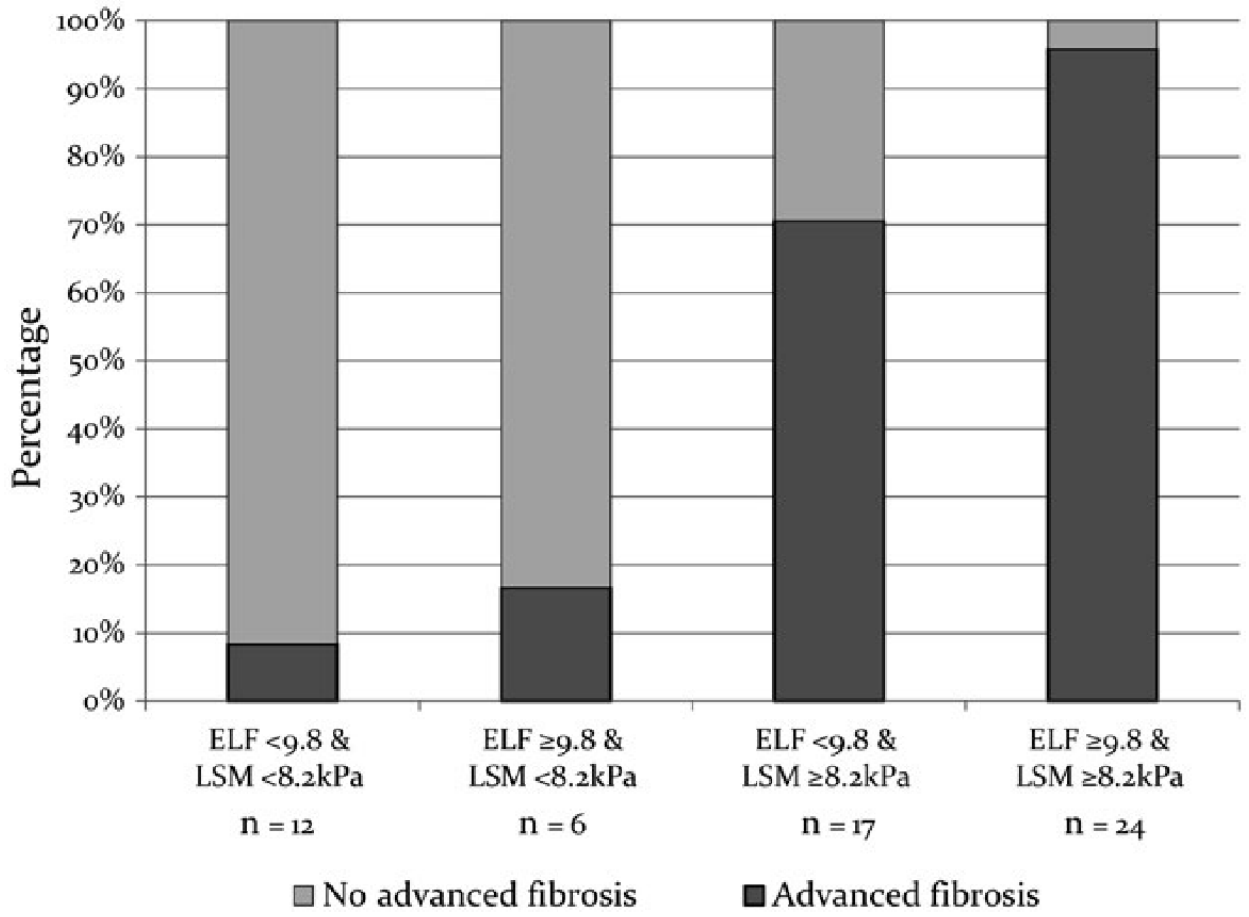



Corresponding PPV and NPV for different ELF cut-offs based on the multiple thresholds model




Vali et. al. J Hepatol 2020

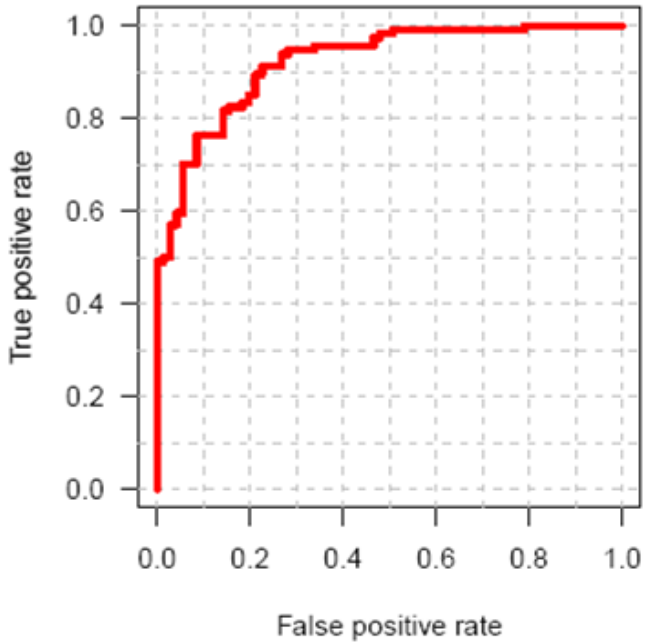
# ELF and LSM Identifies At Risk Diabetics



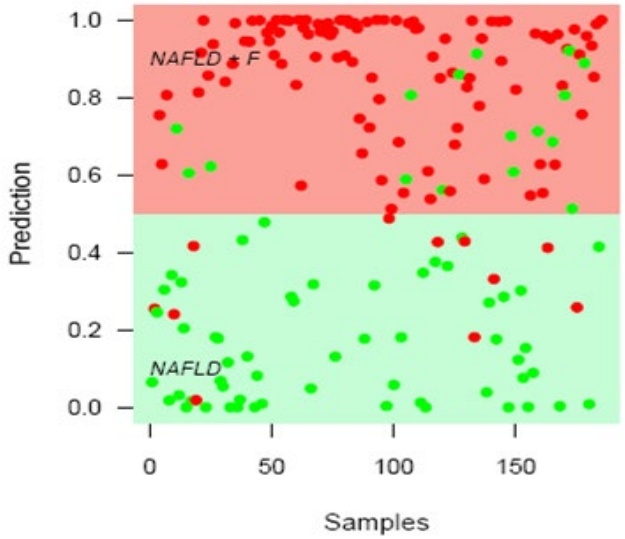

Patel et al, *Hepatology Communications* 2018;2:893-905

# Lipidomics To Identify NASH

- N=185; NAFL without (N=109) & NASH (N=76)
- 16 variables were included: phospholipids, triacylglycerols & non-esterified fatty acids



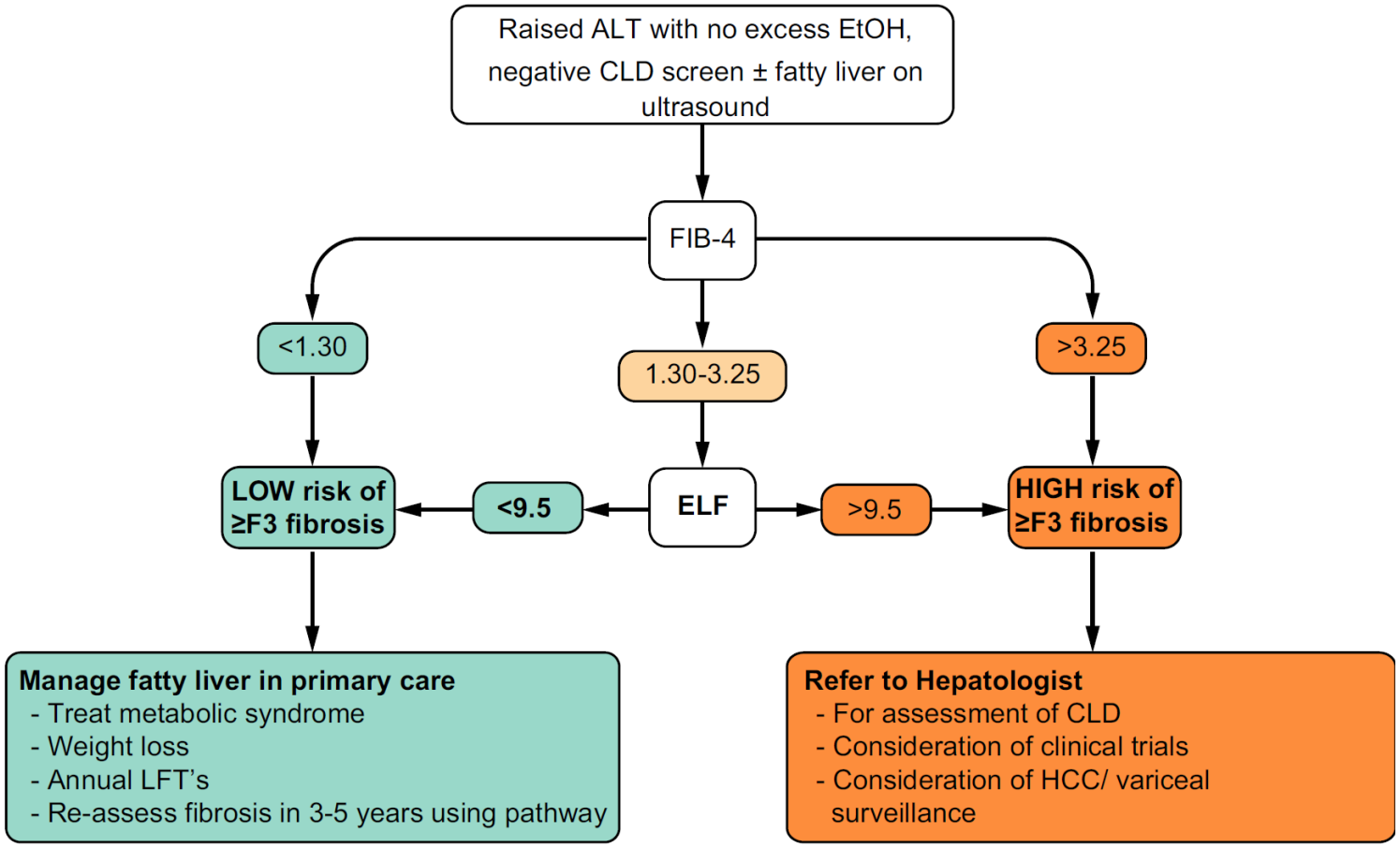

| | |
|---|---|
| **AUROC (se)** | **0.92 (0.02)** |
| **Accuracy** | 0.85 |
| **Sensitivity:** | 0.90 |
| **Specificity:** | 0.77 |
| **Pos Pred Value:** | 0.86 |
| **Neg Pred Value:** | 0.83 |




Leave One Out Cross Validation (LOOCV): AUROC = **0.85**, Accuracy = **0.78**

Mayo et al, Hepatology Communications 2018

# How Can Biomarkers Be Used In Primary Care




Reduced referrals to Hepatologists by 81%

Greater than 4-fold increase in detection of advanced fibrosis

Srivastava et. al. J Hepatol 2019

# Summary: Fibrosis Biomarkers in NAFLD

- Context of use
- Clinical use algorithm
- Disease monitoring
- Response to therapy
- Linking biomarker to clinical outcomes

# Thank you for your attention