Provided by Clinical Care Options in collaboration with Global Liver institute

# NASH Core Curriculum: Imaging and Laboratory Tests for Diagnosis and Risk Stratification

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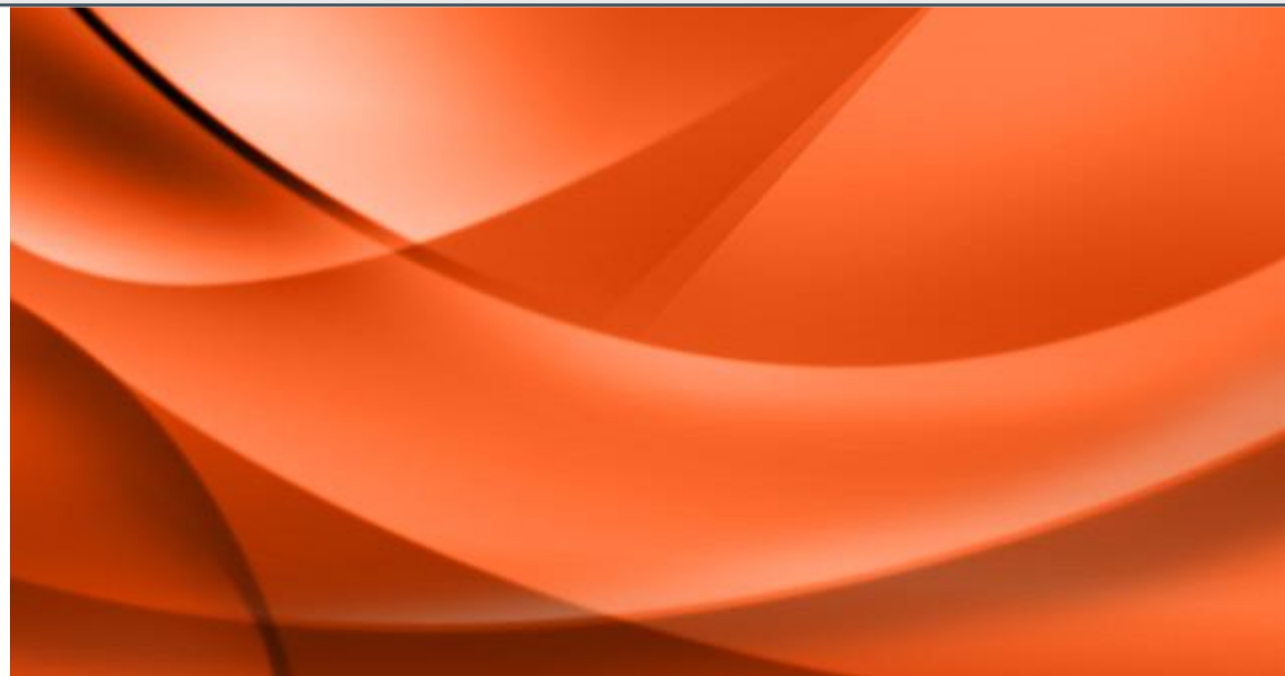
Supported by educational grants from
Gilead Sciences and Novo Nordisk Inc.



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# Faculty and Disclosures

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# Agenda

- Identifying Individuals With NAFLD
- Risk Stratifying NAFLD:
  Tests to Identify Significant or Advanced Hepatic Fibrosis
  - Clinical or Laboratory Scores
  - Imaging
  - Sequential Tests
- Summary

# Identifying Individuals With NAFLD

# NAFLD Presentation

## Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort

## Often an "incidental finding"

- Incidental abnormal LFTs
- Incidental "bright liver" on imaging
- Incidental hepatomegaly

## Common scenarios

- Statin monitoring
- "Annual reviews" in T2D/lipid/ hypertension clinics
- Medical insurance/occupational health checks

De Alwis. Dig Dis. 2016;34:19.

Slide credit: clinicaloptions.com

# Pragmatic First Steps in Suspected NAFLD

## 1. Risk Identification

- Metabolic syndrome or other high prevalence group, such as:
  - T2D
  - Metabolic risk factors (eg, BMI > 25, lipids, PCOS, OSA)
  - First-degree relative with NAFLD cirrhosis or HCC

## 2. History

- Alcohol intake (< 14/21 drinks/wk)
- No known preexisting liver disease

## 3. Tests

- Liver biochemistry (ALT, AST, etc)
- Exclude/identify other liver diseases:
  - Negative HBV and HCV serology
  - Negative autoantibodies (ANA, AMA, SMA, LKM1, ANCA)
  - Negative celiac serology
  - Normal immunoglobulins, ferritin, A1AT, Cu2+, etc
- Liver ultrasound: increased echogenicity (steatosis)

Chalasani. Hepatology. 2018;67:328.

Slide credit: clinicaloptions.com

# Liver Enzymes: Inadequate in Assessing NAFLD/NASH

- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage[3]:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT or AST not sensitive for NAFLD/NASH**

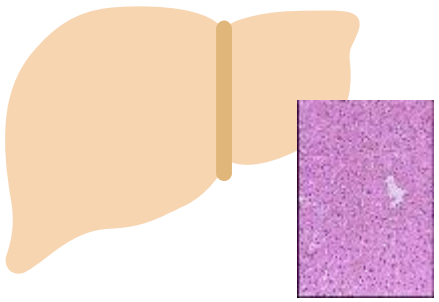
**Abnormal ALT may warrant workup for NAFLD,[4]**
**but is not sensitive to confirm, rule out, or characterize NAFLD**

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211.
3. Mofrad. Hepatology. 2003;37:1286. 4. Younossi. Am J Gastroenterol. 2020;00:1.

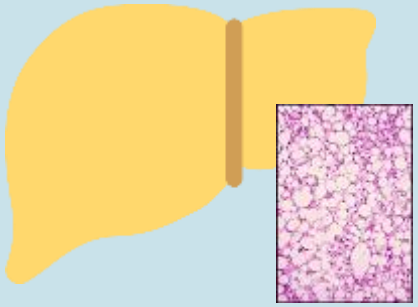
# Identifying NAFL: Ultrasound

**NAFLD**

**Normal Liver**

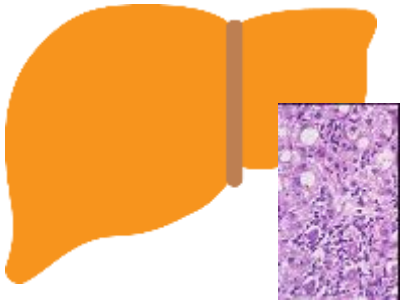


**Steatosis**
**"NAFL"**



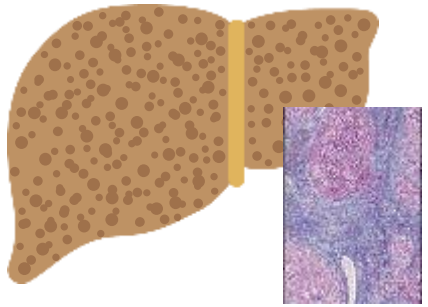
Fatty liver with trivial or no inflammation and no hepatocyte ballooning

**Steatohepatitis**
**"NASH"**



Fatty liver with significant inflammation and hepatocyte ballooning

**Cirrhosis**



Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

**Ultrasound can identify fatty liver (steatosis),**
**but cannot distinguish steatosis vs NASH vs fibrosis/early cirrhosis**

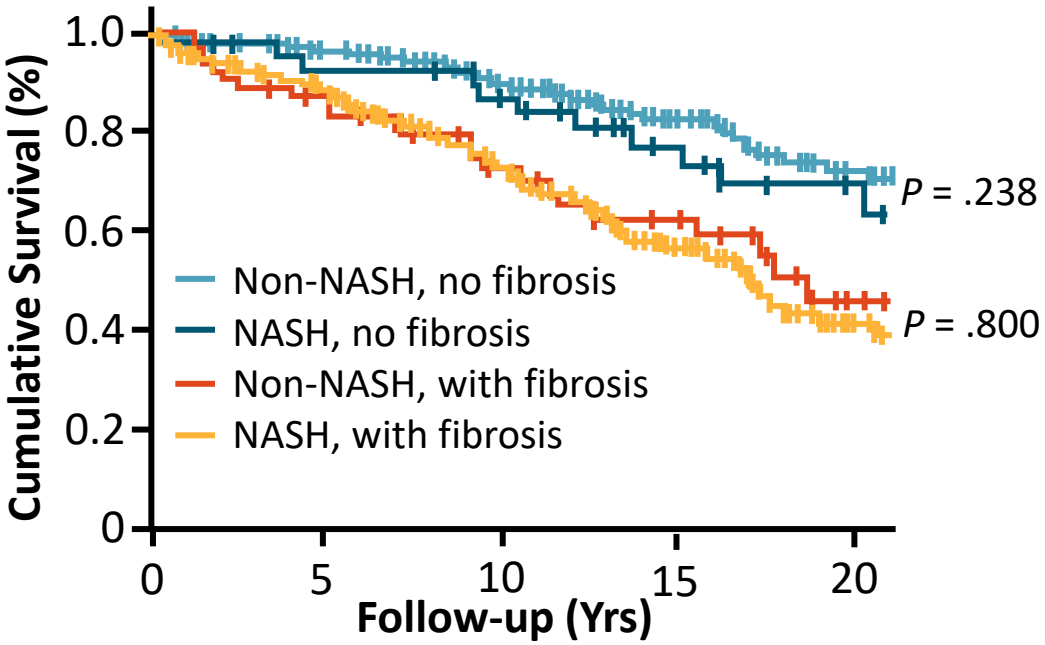
1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

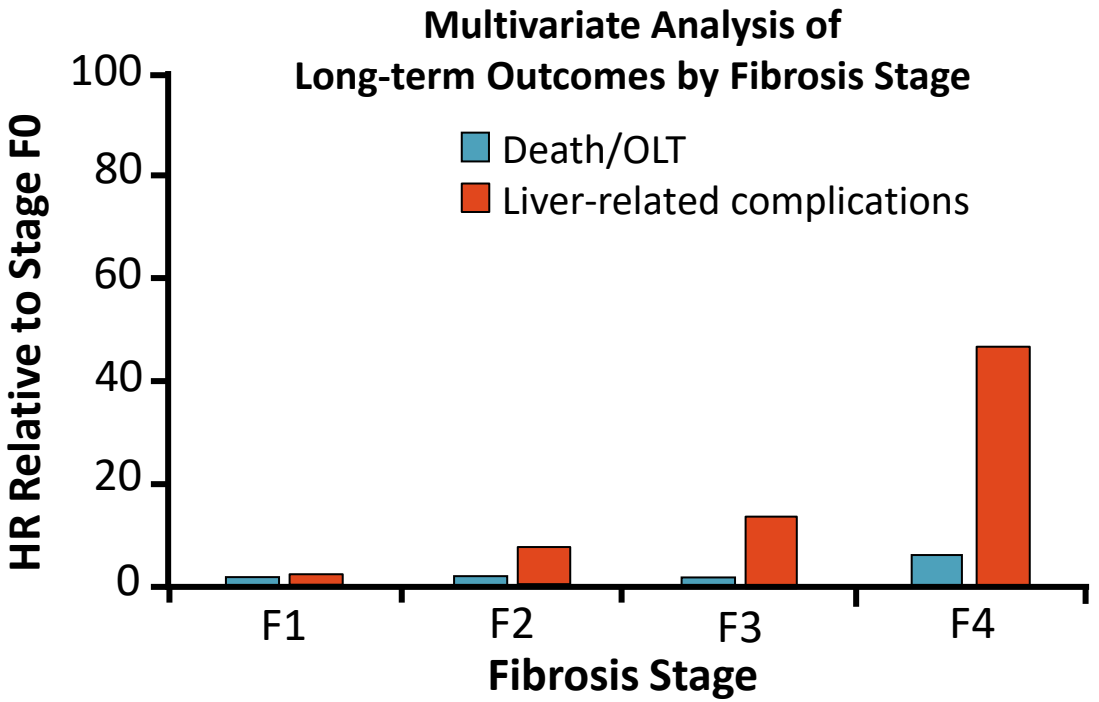
Slide credit: clinicaloptions.com

# Risk Stratifying NAFLD: Tools to Identify Significant or Advanced Hepatic Fibrosis

# PRELHIN Study: Hepatic Fibrosis Associated With Long-term Outcomes in Patients With NAFLD

- Retrospective analysis in patients with NAFLD (N = 619); median follow-up: 12.6 yrs (range: 0.3-35.1)



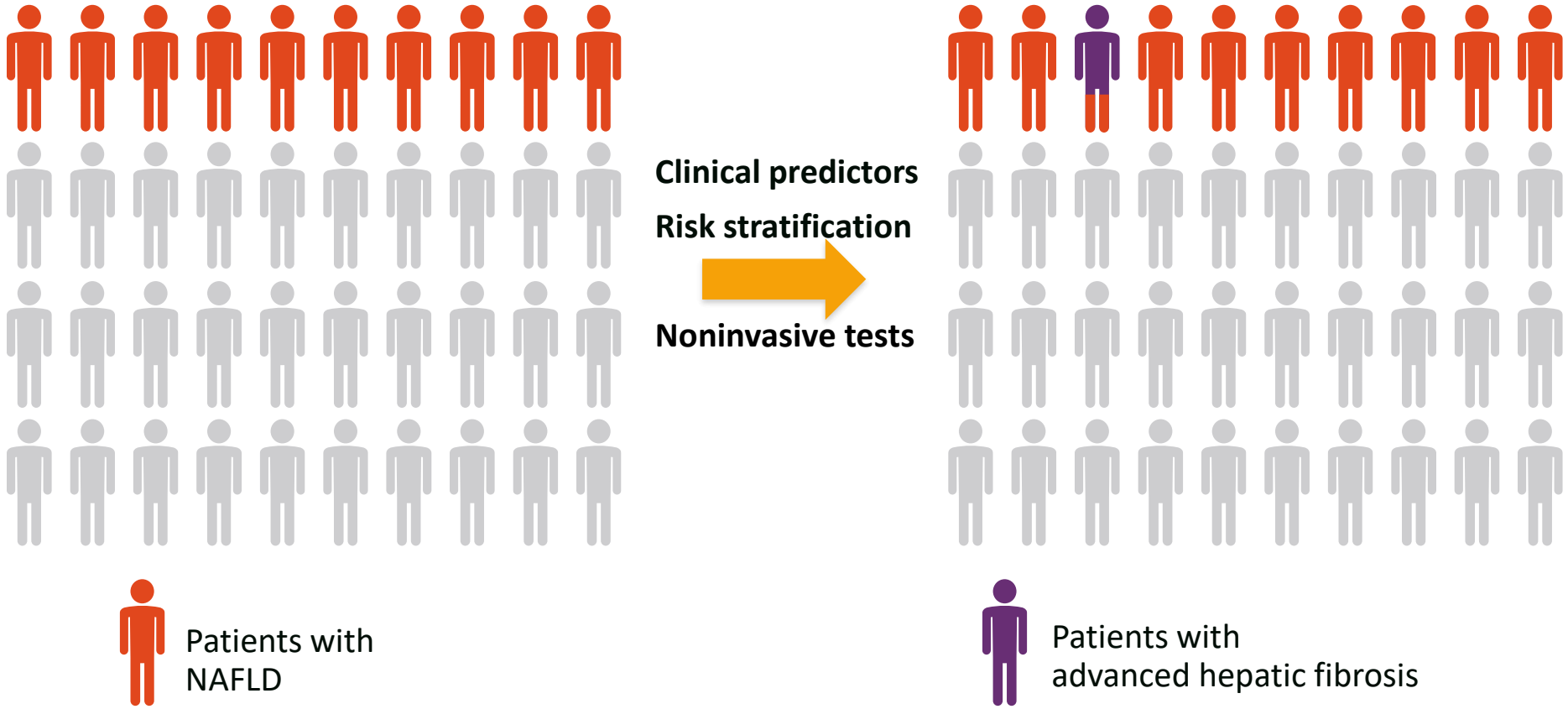

**Only fibrosis stage was associated with overall mortality, OLT, and liver-related events. Presence of NASH, NAS (or any of its components) had no independent prognostic effect.**

Angulo. Gastroenterology. 2015;149:389.

Slide credit: clinicaloptions.com

# Identifying Advanced Hepatic Fibrosis

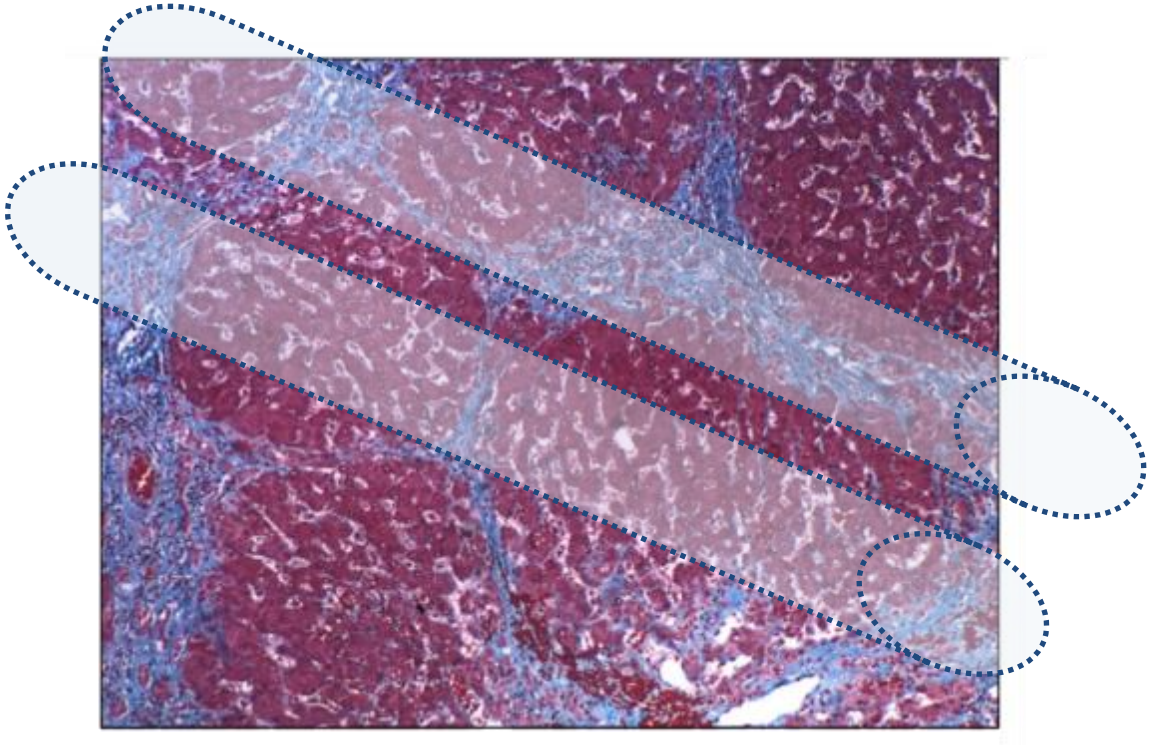
**Need to identify individuals at risk of progression BEFORE bad outcomes occur**




Slide credit: clinicaloptions.com

# Liver Biopsy: The Imperfect Gold Standard

- **Limitations**
  - Invasive
  - Painful
  - Expensive
  - Morbidity/mortality
  - Sampling variability
  - Observer variability
  - Expertise to perform
  - Impractical for population screening



**Sampling variability:**
Same biopsy may give
2 different grades of liver fibrosis

Rockey. Hepatology. 2009;49:1017. Kleiner. Hepatology 2005;41:1313.

Slide credit: clinicaloptions.com

# Commonly Used Noninvasive Tests

## Clinical or Laboratory Scores

### Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

### Proprietary

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

## Imaging

### Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

# Clinical or Laboratory Scores

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### Proprietary

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- *FibroSure*[1]

## Imaging

### Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1(*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

- Good negative predictive value for **ruling out** fibrosis
- Calculators freely available on the Internet

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

# NAFLD Fibrosis Score and FIB-4 Score: Online Calculators Easily Interpret Noninvasive Tests

- Based on age, platelet count, AST, ALT ± other lab values



Available at: https://www.mdcalc.com.

Slide credit: clinicaloptions.com

# Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4[1]

**Cutoff Scores for Measurement of Advanced Hepatic Fibrosis[2,3]**


1. Vallet-Pichard. Hepatology. 2007;46:32. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Shah. Clin Gastroenterol Hepatol. 2009;7:1104.

Slide credit: clinicaloptions.com

# ELF Test in NASH: Validation

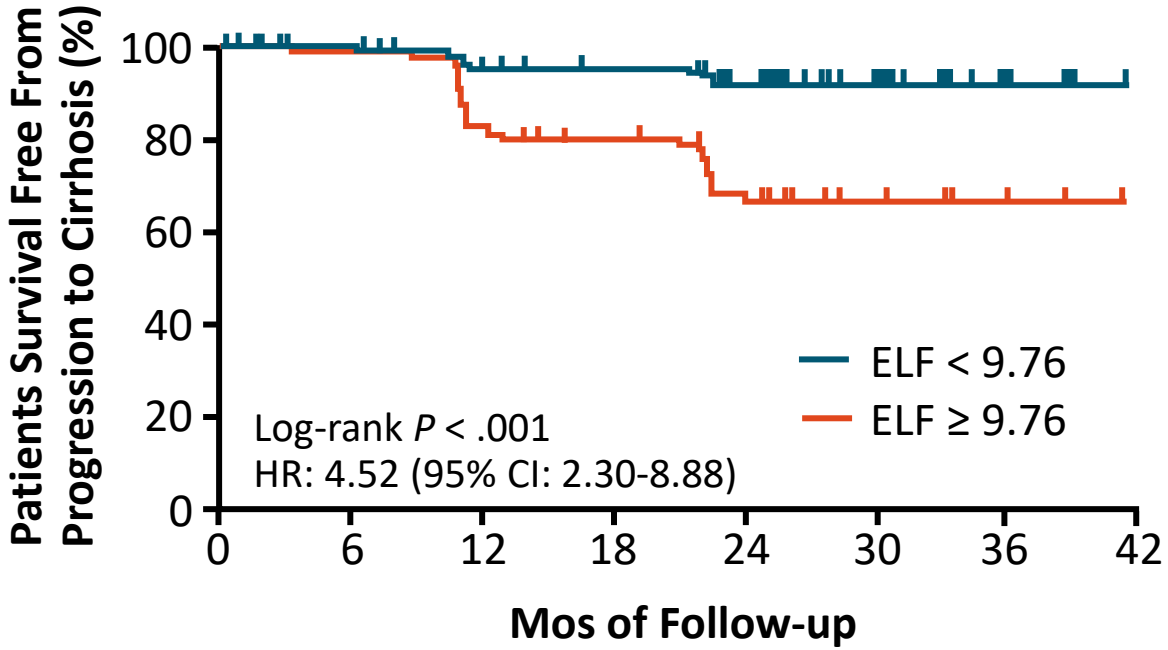
- Prospective study of adults with NASH and bridging fibrosis (n = 219) or compensated cirrhosis (n = 258) enrolled in 2 phase IIb simtuzumab clinical trials
- Liver biopsies staged according to Ishak scale at baseline, Wk 48, and Wk 96
- ELF score calculated at baseline and every 12 wks

Harrison. AASLD 2017. Abstr 2122.

Slide credit: clinicaloptions.com

# ELF Test in NASH Predicts Progression to Cirrhosis More Accurately Than Biopsy

**Progression to Cirrhosis by Baseline ELF**




**Predictors of Progression to Cirrhosis**

| Parameter | Adjusted HR (95% CI) | *P* Value |
|---|---|---|
| Baseline ELF | 3.20 (2.33-4.39) | < .001 |
| Change in ELF | 1.60 (1.19-2.16) | < .01 |
| Ishak stage 4 vs 3 | 0.87 (0.47-1.59) | .64 |

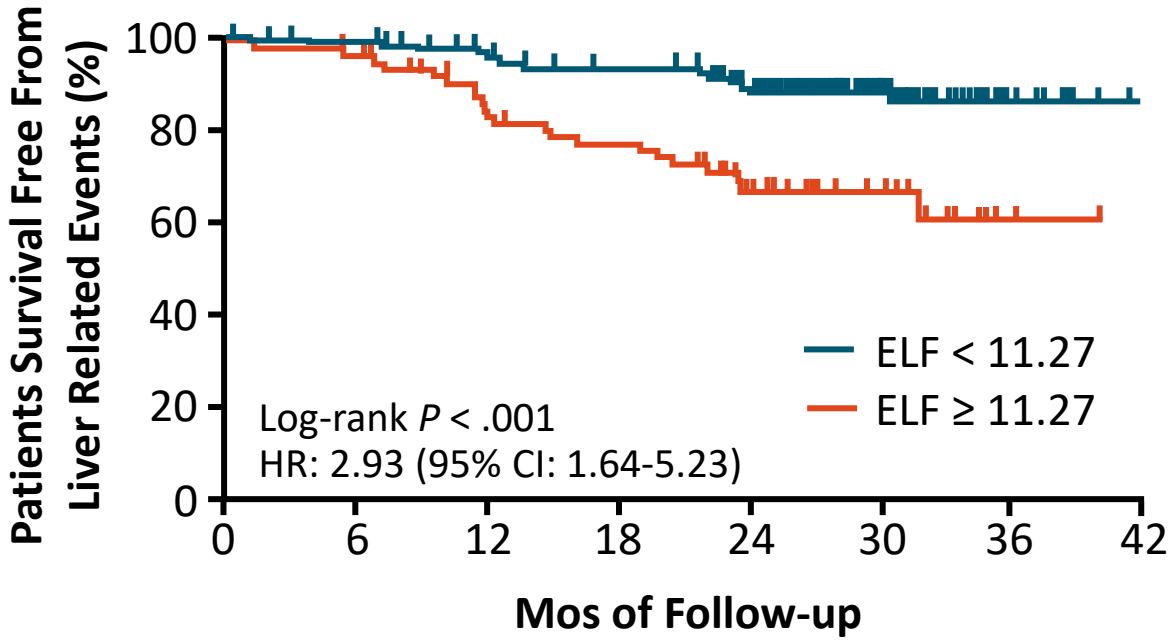
- Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)
- Higher baseline, greater change in ELF associated with increased risk of progression to cirrhosis

Harrison. AASLD 2017. Abstr 2122.

Slide credit: clinicaloptions.com

# ELF Test in NASH Predicts Liver-Related Clinical Events More Accurately Than Biopsy

**Liver-Related Clinical Events by Baseline ELF**




**Predictors of Liver-Related Clinical Events**

| Parameter | Adjusted HR (95% CI) | *P* Value |
|---|---|---|
| Baseline ELF | 2.40 (1.70-3.38) | < .001 |
| Change in ELF | 1.53 (1.09-2.14) | .01 |
| Ishak stage 6 vs 5 | 0.89 (0.47-1.68) | .71 |

- Optimal threshold of baseline ELF: 11.27 (sensitivity 56%, specificity 75%)
- Higher baseline ELF, greater change in ELF associated with liver-related clinical events

Harrison. AASLD 2017. Abstr 2122.

Slide credit: clinicaloptions.com

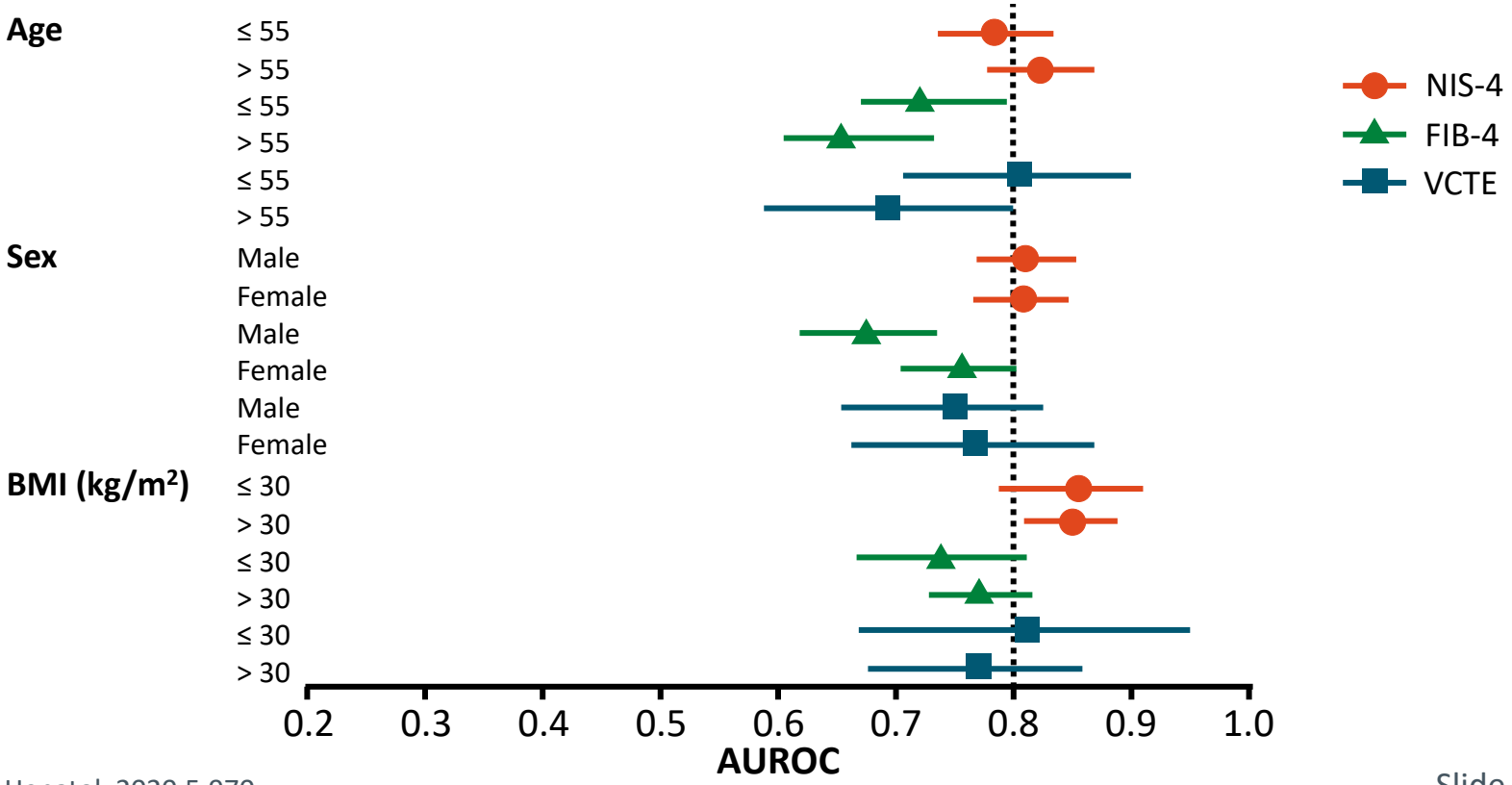
# NIS4: Detecting Active NASH and Significant Hepatic Fibrosis

- **NIS4:** score based on biomarkers miR-34a-5p, alpha-2-macroglobulin, YKL-40, and A1C used to detect patients with active NASH and significant hepatic fibrosis (NAS ≥ 4, fibrosis ≥ F2)
- Baseline data from GOLDEN-505 and RESOLVE-IT trials
  - Training set: 239 patients from "GOLDEN-505"
  - Validation set: first 475 patients screened for inclusion in "RESOLVE-IT," 227 patients with suspected NAFLD from "Angers" cohort

Harrison. Lancet Gastroenterol Hepatol. 2020;5:970.

# NIS4: Validation for Detecting NASH With NAS ≥ 4 and Significant Hepatic Fibrosis

- For pooled validation cohort, **NIS4 AUROC = 0.80** (95% CI: 0.77-0.84)
  - Consistently good performance across the clinical spectrum of NAFLD, regardless of age, sex, obesity, or aminotransferases




Harrison. Lancet Gastroenterol Hepatol. 2020;5:970.

Slide credit: clinicaloptions.com

# ADAPT/Pro-C3: Detecting Advanced Hepatic Fibrosis

- **ADAPT:** algorithm based on **age, diabetes, Pro-C3 (fibrogenesis marker), platelets**
  - Data derived from independent cohorts of NAFLD patients with liver biopsy
- **Pro-C3** independently associated with advanced hepatic fibrosis
  - **OR: 1.05** (95% CI: 1.02-1.08; *P* = .003)
- **ADAPT** accurately identified advanced hepatic fibrosis

| | Derivation Cohort (n = 150) | Validation Cohort (n = 281) |
|---|---|---|
| AUROC, % (95% CI) | 0.86 (0.79-0.91) | 0.87 (0.83-0.91) |

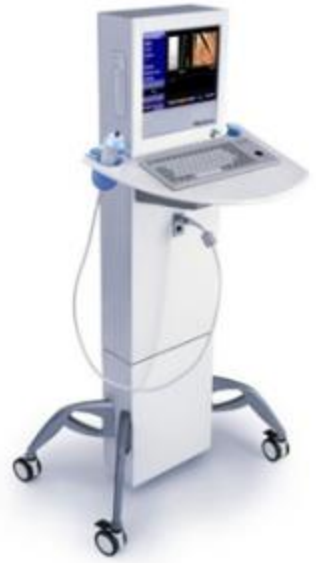
Daniels. Hepatology. 2019;69:1075

Slide credit: clinicaloptions.com

# Imaging

# Vibration-Controlled Transient Elastography

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience



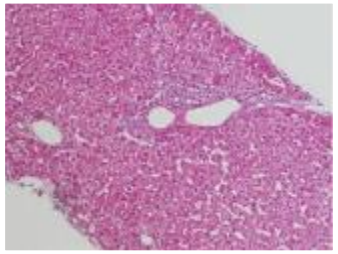

Sigrist. Theranostics 2017;7:1303.

Slide credit: clinicaloptions.com

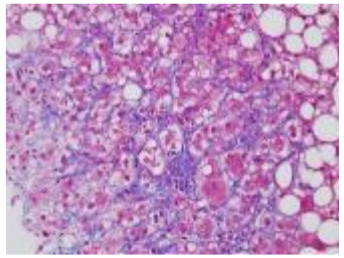
# VCTE for NASH Fibrosis

**Fibrosis Stage**

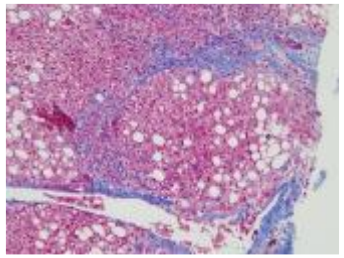
**F0**: Normal



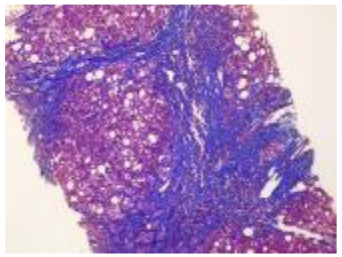
**F1/2:** Perisinusoidal ± Portal



**F3:** Bridging Fibrosis



**F4:** Cirrhosis



***FibroScan* Liver Stiffness (kPa)[1,2]**

**Increasing liver stiffness**

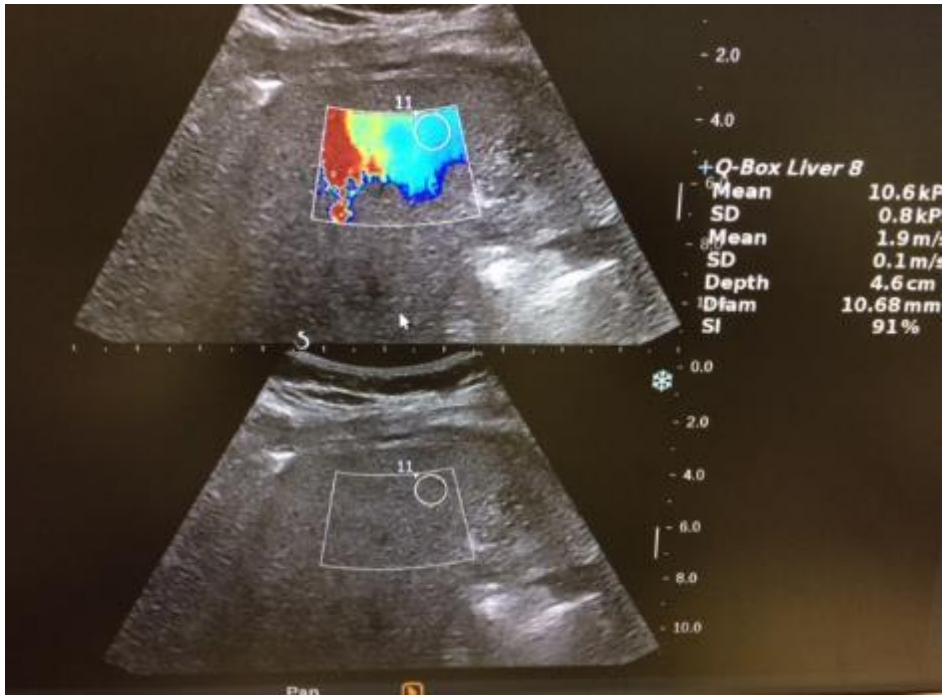
- Most reliable in **ruling out advanced hepatic fibrosis (NPV > PPV)**[2]
  - Fibrosis unlikely with low value (< 6 kPa)
- Higher values increase likelihood of more severe fibrosis, predicts risk of decompensation and complications[3]
- **Overestimation of fibrosis can occur** in cases of hepatitis, cholestasis, liver congestion, obesity, and if mass lesions are present in the liver[1,3]
- Correlates well with portal pressure (20+ kPa)[4]

1. Vuppalanchi. Hepatology. 2018;67:134. 2. Hashemi. Caspian J Intern Med. 2016;7:242.
3. Kemp. Australian Family Physician. 2013;42:468. 4. Robic. J Hepatol. 2011;55:1017.

Slide credit: clinicaloptions.com

# 2D Shear Wave Elastography

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness[1]
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys[1]
- May require radiologist/sonographer[1]
- Liver elasticity measurements can be obtained in challenging cases of obesity[1]



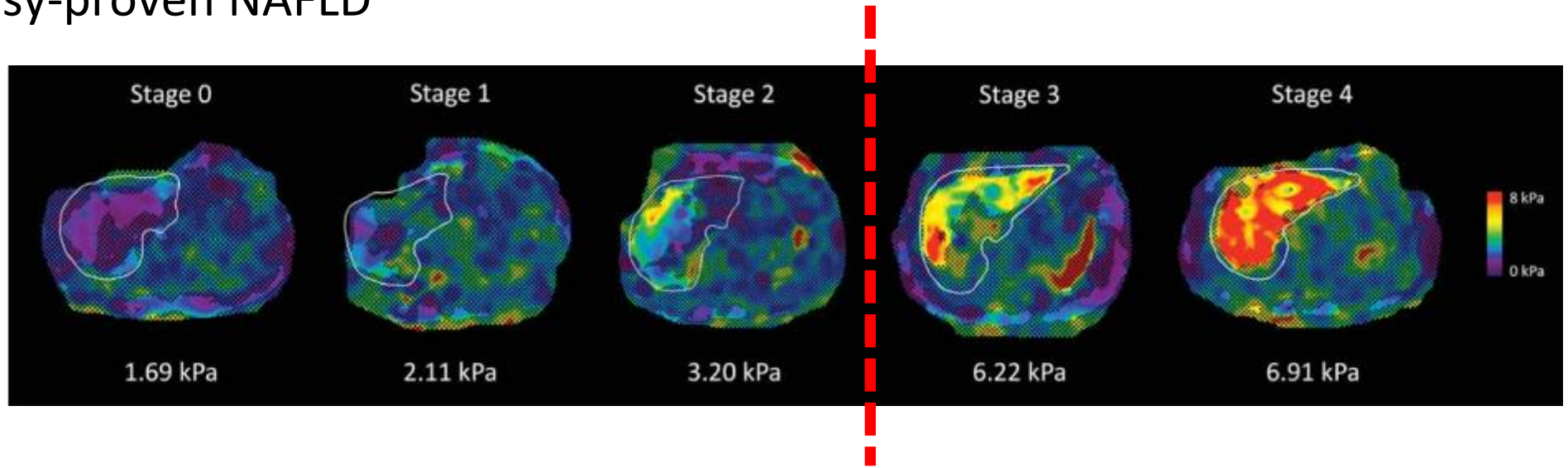

| Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 in HCV[2] | Sensitivity | Specificity | AUROC |
|---|---|---|---|
| 2D-SWE stiffness > 8.7 kPa | .973 | .951 | .98 |

1. Sigrist. Theranostics 2017;7:1303. 2. Ferraiolo. Hepatology 2012;56:2125.

Slide credit: clinicaloptions.com

# MRE: Detecting Advanced Hepatic Fibrosis in NAFLD

- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD




| Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 | Sensitivity | Specificity | AUROC |
|---|---|---|---|
| MRE stiffness > 3.63 kPa | .86 | .91 | .924 |

Loomba. Hepatology. 2014;60:1920.

Slide credit: clinicaloptions.com

# Common Imaging Tests for Hepatic Fibrosis: Summary

| Imaging | Comments |
|---|---|
| Vibration-controlled transient elastography – *FibroScan* | ▪ Can be point of care<br>▪ **Most reliable in ruling out advanced hepatic fibrosis (great NPV)** |
| MR elastography/MR spectroscopy/ *LiverMultiScan* | ▪ Requires radiology referral<br>▪ Most accurate of the imaging modalities |
| 2D shear wave elastography | ▪ May require radiology referral but can be point of care with minimal training |

**These imaging tests measure liver stiffness, which is an indirect measure of hepatic fibrosis and not hepatic fat content**

Slide credit: clinicaloptions.com

# FAST (VCTE + CAP + AST): Detecting Active NASH and Significant Hepatic Fibrosis

- Prospective, multicenter study of patients undergoing liver biopsy for suspected NASH
  - Derivation cohort: 350
  - Validation: 1026)
- **FAST:** Score based on **fibrosis, steatosis, and inflammation** (LSM, CAP, AST) to detect patients with active NASH and significant fibrosis (NAS ≥ 4, fibrosis level F ≥ 2)


Sasso. AASLD 2018. Abstr 140.

Slide credit: clinicaloptions.com

# Validation of the FAST Score in a US Cohort

- N = 585 adults with biopsy-confirmed NASH from the multicenter NASH CRN cohort
  - "At-risk" NASH defined as definite NASH with NAFLD Activity Score ≥ 4 and fibrosis stage ≥ 2
- 38% male, 79% White; 73% obese; mean age: 51 yrs; mean ALT: 68 U/L; mean AST: 53 U/L
- The prevalence of at-risk NASH was 37% (50% in the derivation population)

| Cut-off Criteria* | Cut-off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Rule out | 0.35 | 0.91 | 0.50 | 0.51 | 0.90 |
| Rule in | 0.67 | 0.51 | 0.87 | 0.69 | 0.76 |

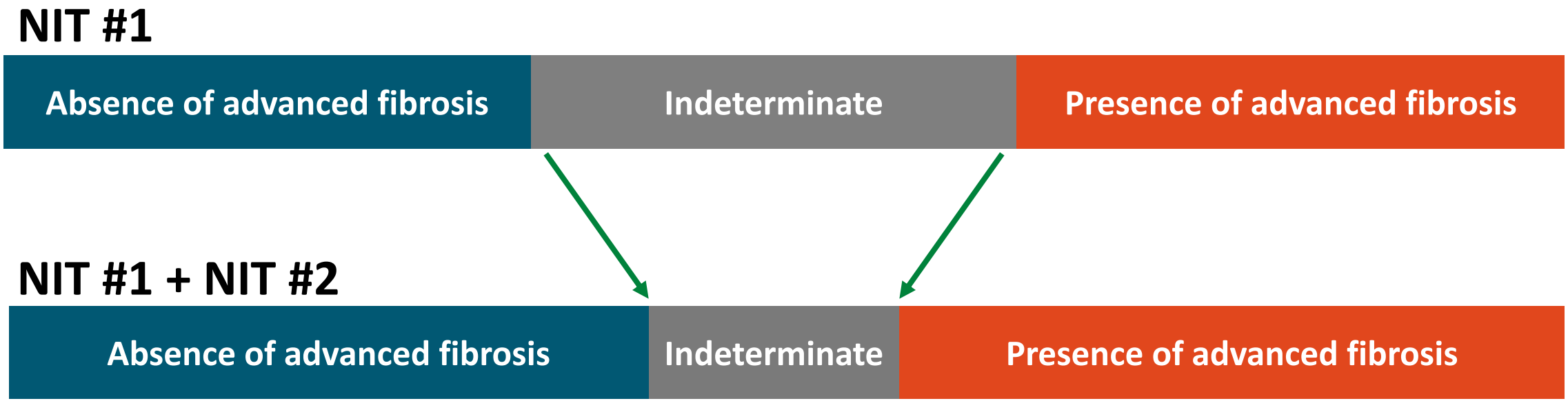
*From derivation cohort.

Woreta. EASL 2020. Abstr FRI-54.

Slide credit: clinicaloptions.com

# Sequential Tests

# Use of Sequential Noninvasive Tests Could Reduce the Number of Patients in the Indeterminate Zone




**The sequential use of NITs maintains sensitivity and specificity while enabling the classification of a larger proportion of patients**

Younossi. AASLD 2018. Abstr LB-10.

Slide credit: clinicaloptions.com

# Sequential Algorithms to Detect Advanced Hepatic Fibrosis due to NASH

- Study of baseline data from STELLAR trials (N = 3202) to determine performance of sequential combinations of noninvasive tests in diagnosing F3/F4 hepatic fibrosis
  - **Single tests** (either NFS, FIB-4, ELF, or VCTE) led to up to 50% indeterminate results
  - **Sequential tests** (FIB-4, then ELF or VCTE) led to up to 24% indeterminate results

| Outcome With Sequential Tests, % (95% CI)* | FIB-4, Then ELF (N = 3180) | FIB-4, Then VCTE (N = 3141) |
|---|---|---|
| Prevalence of F3/F4 | 71 | 71 |
| Sensitivity | 69 (67-71) | 77 (75-78) |
| Specificity | 92 (90-94) | 89 (87-91) |
| PPV | 96 (94-97) | 95 (93-96) |
| NPV | 55 (53-58) | 60 (58-63) |
| Indeterminate | 24 (23-26) | 20 (18-21) |
| Misclassified | 24 (23-26) | 20 (18-21) |

*Using published cutoffs: FIB-4 (1.30-2.67), ELF (9.8-11.3), VCTE (9.9-11.4 kPa).

Anstee. Hepatology. 2019;70:1521.

# Summary

# Summary

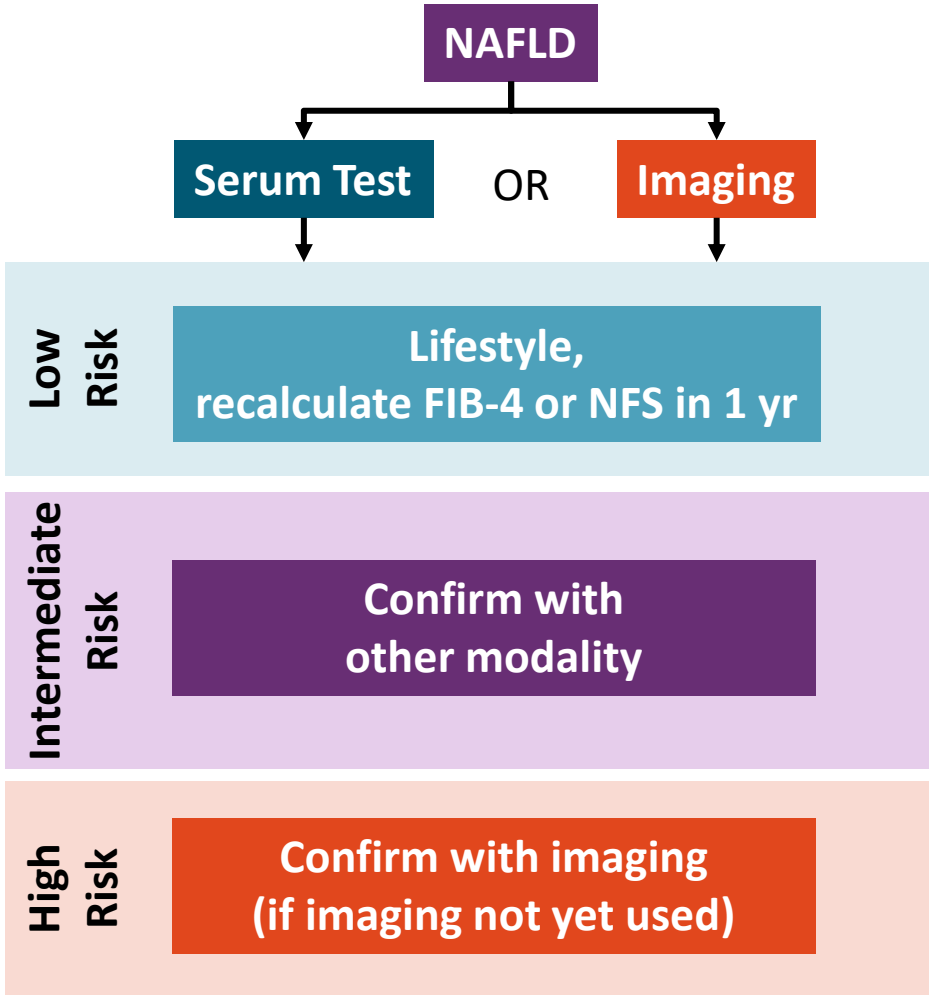
1. **Identify** NAFLD
2. If NAFLD/NASH is present, **stratify** according to **hepatic fibrosis**
   - A mix of approaches and sequential tests may help rule out or even rule in significant or advanced hepatic fibrosis

- Different approaches to assessing hepatic fibrosis
  - Simple and proprietary predictive scores quantify **biomarkers** in serum samples that have been shown to be associated with fibrosis stage
  - **Imaging** techniques measure liver stiffness

Slide credit: clinicaloptions.com

# Example of a Proposed Sequence of Testing in NAFLD

- If NAFLD, rule out low risk with either:
  - **Serum biomarker/algorithm** (FIB-4, NFS, ELF) or
  - **Imaging** (VCTE, MRE, or shear wave elastography)
- If low risk not ruled out, use the other modality to confirm intermediate or high risk




Younossi. Am J Gastroenterol. 2020;00:1.

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