

2023 SCSG LGI SYMPOSIUM



NASH: Use of Non-Invasive Testing

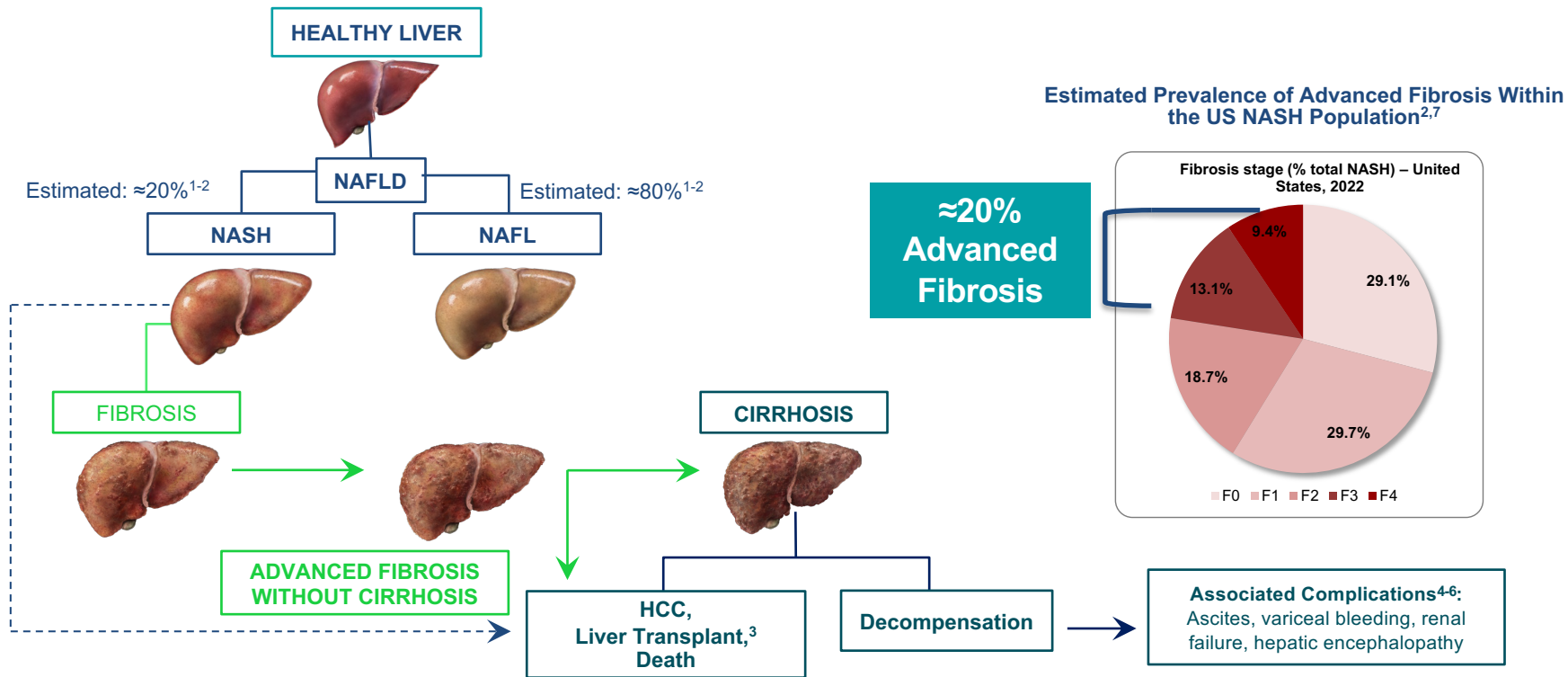
Sherona Bau, ACNP
Pfleger Liver Institute

University of California, Los Angeles
Los Angeles, CA

Disclosures of Financial Relationships

- Samantha Ramirez
 - No relevant financial relationships to disclose
- Sherona Bau
 - No relevant financial relationships to disclose

Prevalence of NASH



1. Torres DM. *Clin Gastro Hepatol.* 2012;10:837-858. 2. Estes C, et al. *Hepatology.* 2018;67(1):123-133. 3. Younossi ZM et al. *Clin Gastroenterol Hepatol.* 2021 Mar;19(3):580-589. 4. Nusrat S, et al. *World J Gastroenterol.* 2014;20(18):5442-5460. 5. Bittencourt PL, et al. *World J Hepatol.* 2015;7(21):2336-2343. 6. Li et al. *Can J Gastroenterol Hepatol.* 2018; 2018: 2784537. 7. Razavi H. Presented at: NASH 2022. Paris, France.

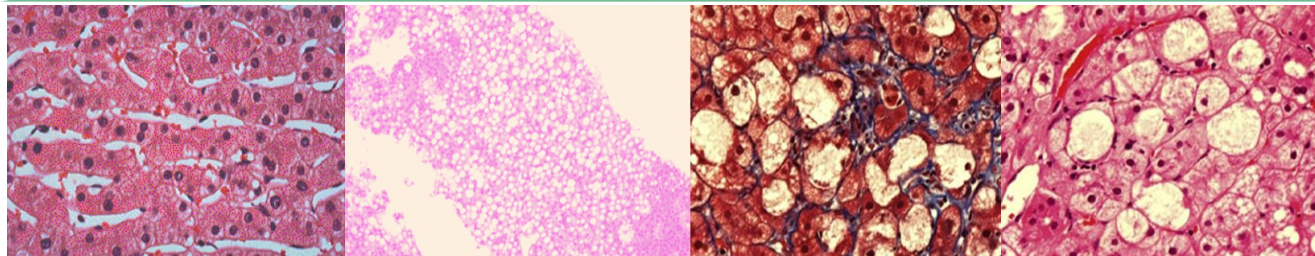
NAFLD: Definitions

- NAFLD: Histology of >5% macrovesicular steatosis in individual without significant EtOH use (<30 g men; <20g women)
- NASH (Non-Alcoholic Steatohepatitis): histologic evidence of steatosis, cellular ballooning degeneration, and lobular inflammation

NAFLD Encompasses the Entire Spectrum of Fatty Liver Disease

NAFLD

Disease of hepatic fat accumulation, absent alcohol consumption, hereditary disorders, or steatogenic medication use



Normal

NAFL

- >5% hepatic steatosis
- No evidence of hepatocyte injury (ballooning) or fibrosis

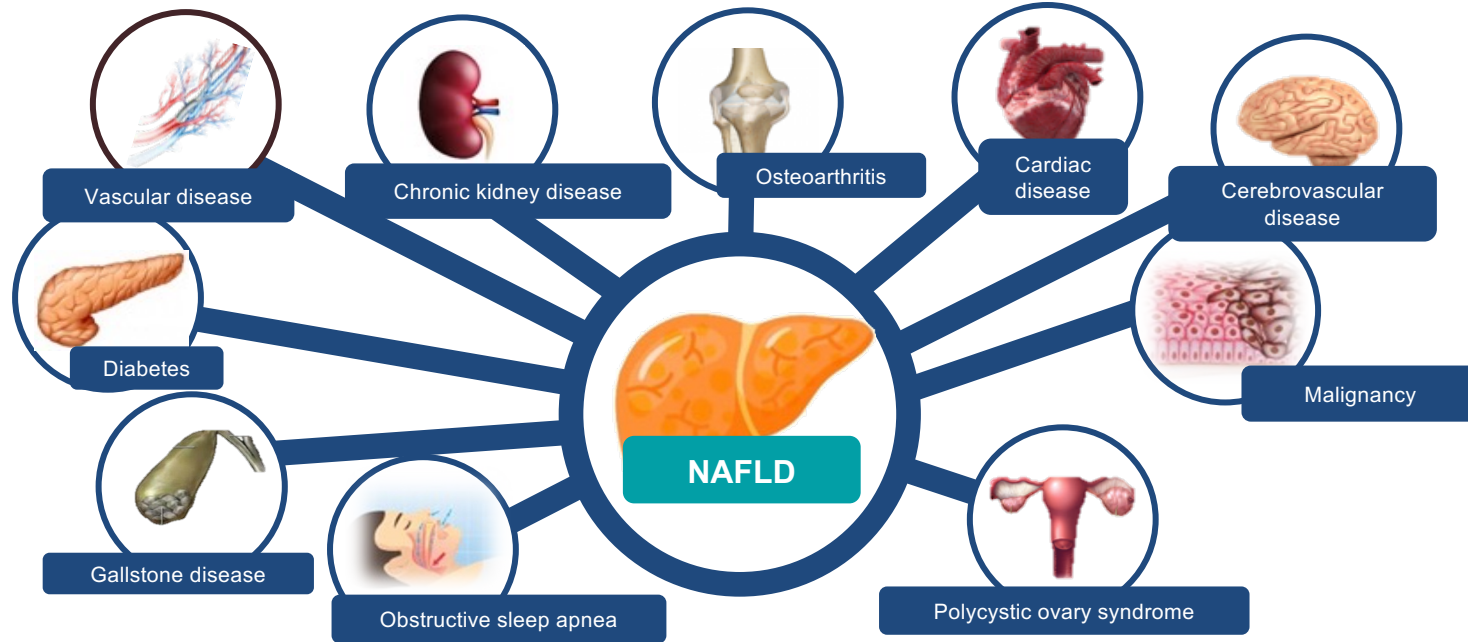
NASH

- Progressive type of NAFLD
- >5% hepatic steatosis ± inflammation with hepatocyte injury (ballooning) ± fibrosis

NASH Cirrhosis

Cirrhosis + current or previous histological evidence of steatosis

Not to Forget NASH as a Part of a Multisystem Disorder



Identification of Patients at Risk for NASH

RISK FACTORS for NASH

- Age >50
- BMI >30
- Elevated Liver enzymes
(AST >20 U/L, AST/ALT ≥ 1)
- Diabetes
- Hypertension
- Dyslipidemia
- Metabolic Syndrome
- Fatty liver on ultrasound
- Historical Fibroscan >8 kpa, CAP >280

Highest risk profile:
Post-menopausal, obese,
diabetic, Hispanic, female

NASH: Mortality

- Fibrosis stage strongest predictor of mortality
- C-V disease: 13-30%
- All cause malignancy: 6-28%
- Liver related death: 2.8-19%



Question

How can we identify patients at risk for NASH?

The Challenge: Diagnosing a Silent Disease Using Liver Biopsy

- Liver biopsy is the ‘gold standard’ tool for the diagnosis and staging of chronic liver disease
- However, the limitations are widely acknowledged
 - **Painful, invasive procedure**
 - High-cost, with **significant risk** of complications;
 - Complications in 1 in 1,000; Mortality Rate 1 in 5,000
- Therefore, liver biopsy is a Diagnostic of ‘Last Resort’
 - Only 60K biopsies annually performed for 64M patients with non-alcoholic fatty liver disease in the US

Most patients not diagnosed, and if found, are found late



“Novel strategies are needed to move the field forward”

**Pierre Bedossa,
Department of Pathology,
INSERM**

Routine Clinical Biochemistry (LFTs)

- NAFLD is the most common diagnosis in patients with 'incidental' abnormal LFTs
- **Liver enzymes may be normal in up to 80% of NAFLD patients**
 - Transaminases are not a sensitive test for NAFLD/NASH
 - Poor correlation between ALT and histology
 - **ALT typically falls with advanced fibrosis**
 - **ALT > AST → ALT < AST**
- Severity of histology in NAFLD with normal LFTs no different from those with abnormal LFTs

Grade/Stage of NAFLD with normal LFTs no different from those with abnormal LFTs

Pattern	Normal ALT (n = 51)	Abnormal ALT (n = 50)	P Value
Fat alone, n	8	10	NS
Fat + scattered inflammation, n	8	10	NS
Fat + ballooning ± inflammation, n	13	11	NS
Fat + ballooning ± Mallory hyaline ± pericellular fibrosis, n	22	19	NS

Routine LFTs do not differentiate Steatosis/NASH or Stage of fibrosis

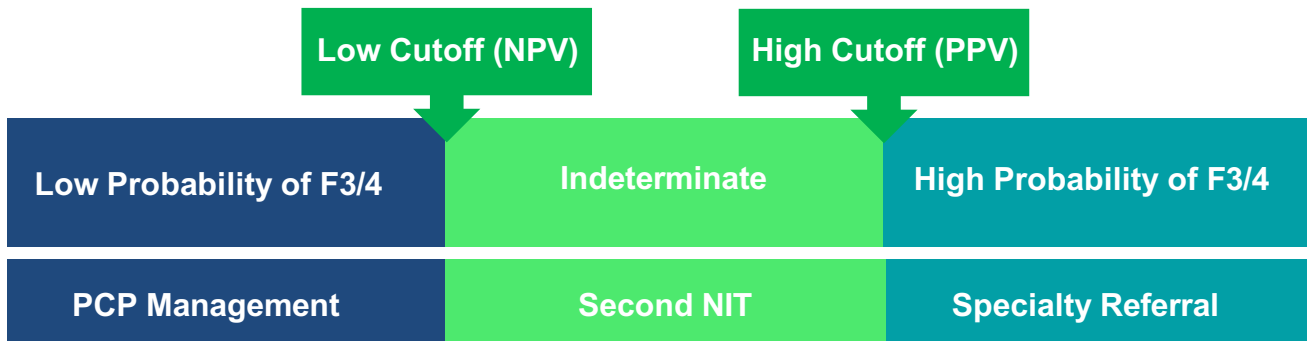
“Simple Scores” for Predicting Advanced (F3-4) Fibrosis

NAFLD Fibrosis Score

- $= -1.675 + 0.037 \times \text{Age} + 0.094 \times \text{BMI} + 1.13 \times \text{IFG/diabetes} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{Platelets} - 0.66 \times \text{Albumin}$.
- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%).

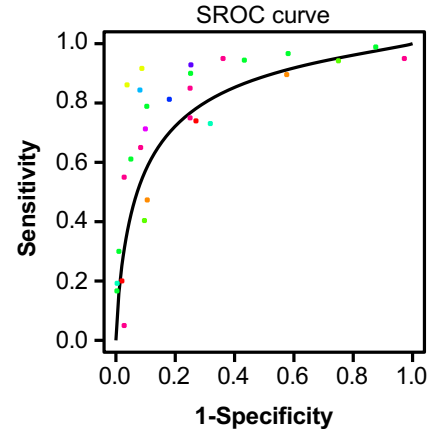
FIB-4 Score

- $= (\text{Age} * \text{AST}) / (\text{Platelets} * \text{Sqrt}(\text{ALT}))$
- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)



Enhanced Liver Fibrosis (ELF) Score

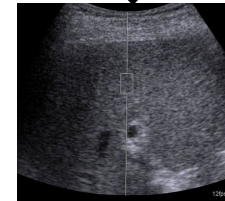
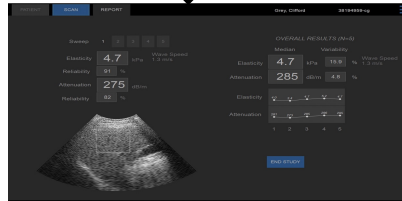
- **Hyaluronic acid (HA)**
- **Procollagen III amino terminal peptide (PIIINP)**
- **Tissue inhibitor of metalloproteinase 1 (TIMP-1)**



11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

- Meta-analysis of 11 studies
- ELF test had a sensitivity of >0.90 for excluding fibrosis at a threshold of 7.7
- To achieve a specificity of 0.90 for advanced and significant fibrosis, thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55) were required, respectively

Available US-Based Radiologic Tests



	Transient Elastography (kPa) (FibroScan)	Velacur™ (kPa) (Point of Care Ultrasound)	ARFI (m/s) – SSW (kPa)
Advantages	<ul style="list-style-type: none"> Can be performed in clinic with real-time results 	<ul style="list-style-type: none"> Can be performed in clinic with real-time results 	<ul style="list-style-type: none"> Can be integrated into a conventional ultrasound
Disadvantages	<ul style="list-style-type: none"> Increased failure rate with obesity Expensive device <ul style="list-style-type: none"> Cutoff values with XL probe are slightly different from M probe 	<ul style="list-style-type: none"> More time consuming than TE (although time can be reduced significantly with training) <ul style="list-style-type: none"> Limited availability 	<ul style="list-style-type: none"> Increased failure rate with obesity Cutoff values for advanced fibrosis vary significantly

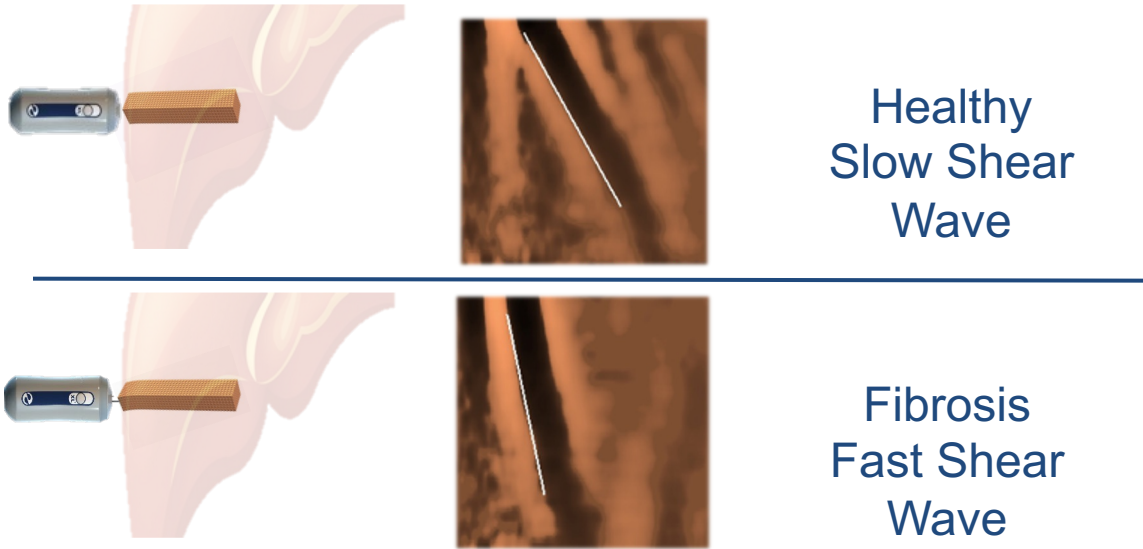
Vibration-Controlled Transient Elastography VCTE/ FibroScan Technology Overview

Non-invasive quantification of two physical biomarkers of the liver within a 10-minute examination:

Liver Stiffness	Controlled Attenuation Parameter (CAP)
<ul style="list-style-type: none">• Obtained through a VCTE measurement• Correlated to extent of fibrosis	<ul style="list-style-type: none">• Quantification of ultrasound attenuation obtained in VCTE measurement• Correlated to liver steatosis

Both biomarkers can be used to assess disease severity in different etiologies including NASH

Liver Stiffness Correlates to Fibrosis Level



VCTE Range: 2.5-75 kPa

Sample VTCE Report

SAMPLE
Normal

CAP (dB/m)

MEDIAN

179

E (kPa)

MEDIAN

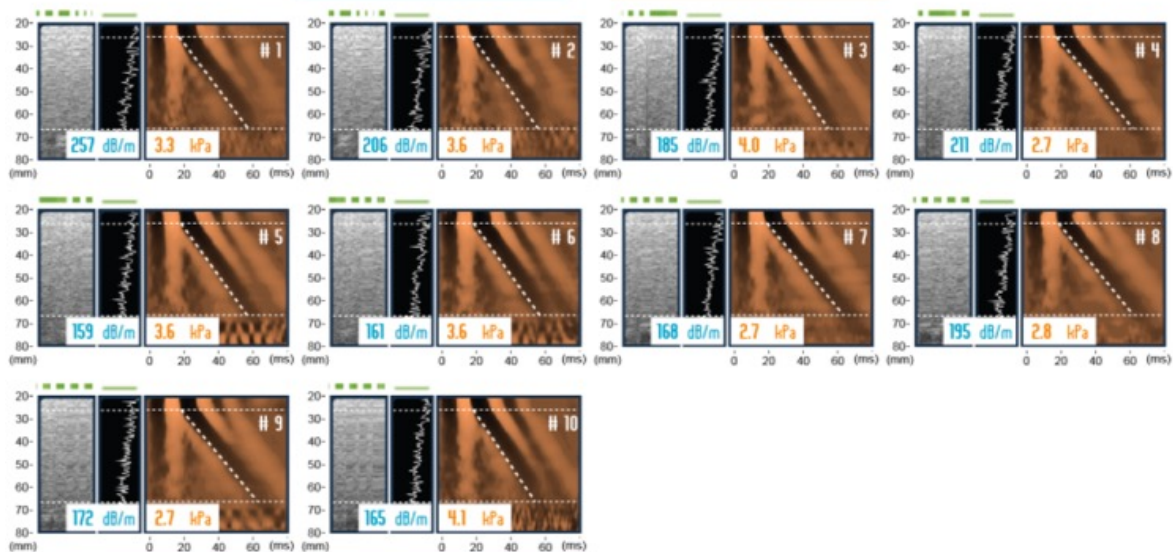
3.5

QR/med.
26%

Exam M (Liver)

Valid measurements: 10

Total measurements: 10



NITs to Predict Response to Treatment FDA Efficacy Endpoints for Phase 3 Trials: Liver

Histologic Improvement

NASH Resolution

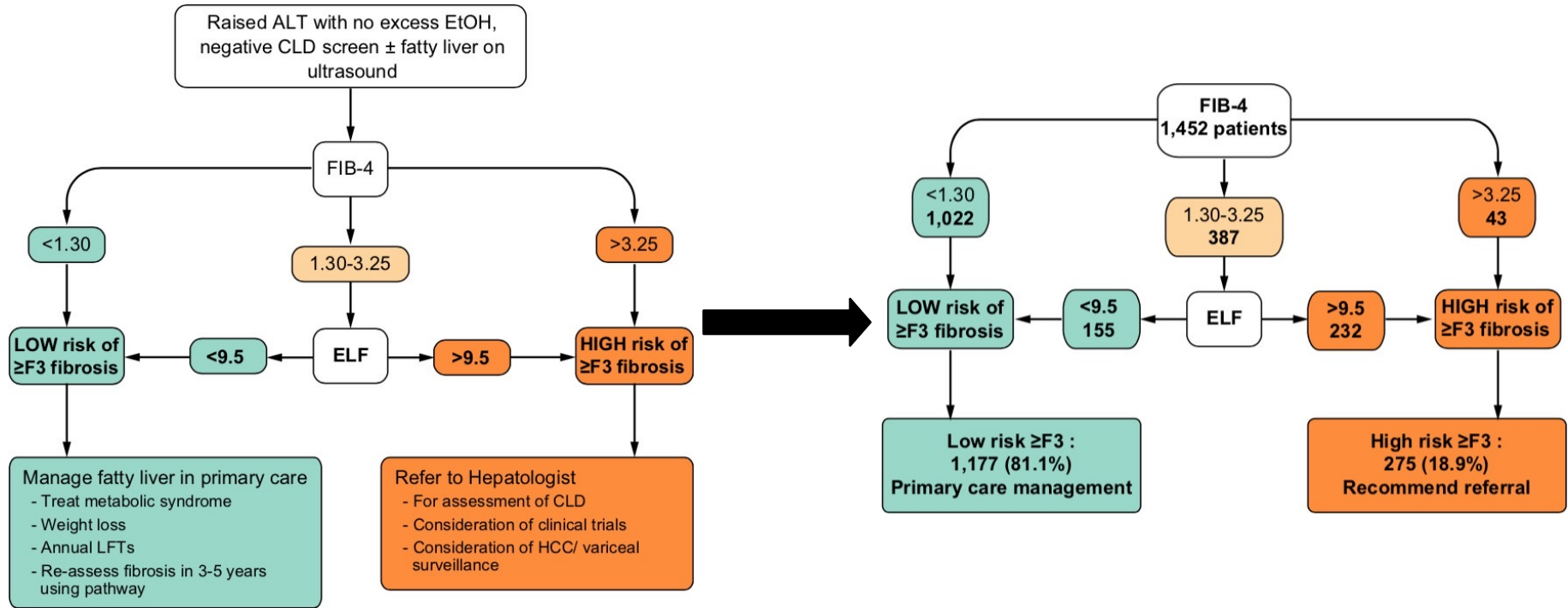
- Resolution of steatohepatitis on overall histopathologic reading
and
- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage
and
- No worsening of steatohepatitis

OR BOTH

Prospective Evaluation of a Primary Care Referral Pathway



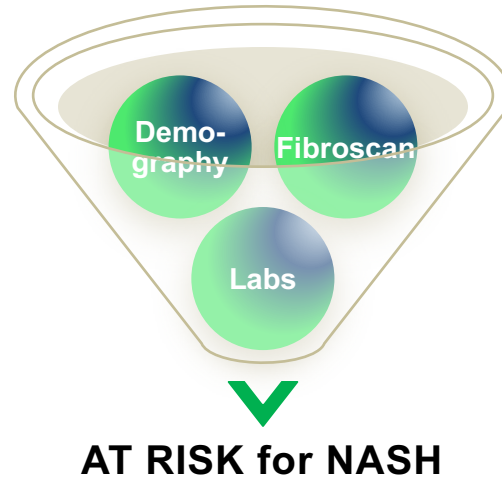
Non-Invasive Tests (NITs)

PROPER USE OF NITs HELP RISK-STRATIFY SUBJECTS

“At Risk for NASH” Criteria

- Demography
- VCTE
- Labs
- Imaging

Detect population with advanced disease
(F2/F3 fibrosis)



Conclusions

- NAFLD is a silent and progressive disease that, if left uncontrolled, can lead to a more severe form called NASH
- Common comorbidities (e.g. Metabolic syndrome) are bi-directionally associated with NAFLD and contribute to the growing prevalence
- Fibrosis (F2-F4) is the most important histological feature of NASH associated with long-term mortality

Conclusions (Cont'd)

- Liver biopsy is the gold standard for diagnosing NASH, but is met with many disadvantages
- Noninvasive biomarkers (i.e. serum and imaging) are being used more frequently
- NASH is an exploding area of clinical research



Q&A

Thank you.

Sherona Bau, ACNP
Pfleger Liver Institute
University of California, Los Angeles
Los Angeles, CA