

Non-invasive markers of fibrosis in NASH

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Disclosures

Scientific Consulting:

Intercept Pharmaceuticals, Gilead Sciences, NGM Biopharmaceuticals, Enanta, Immuron, Fractyl, Prociento, Gelesis, Merck, Bristol-Myers Squibb, Metacrine, Viking Therapeutics, Allergan, Cymabay, Boehringer Ingelheim and Novartis.

CLDF, Global NASH Forum

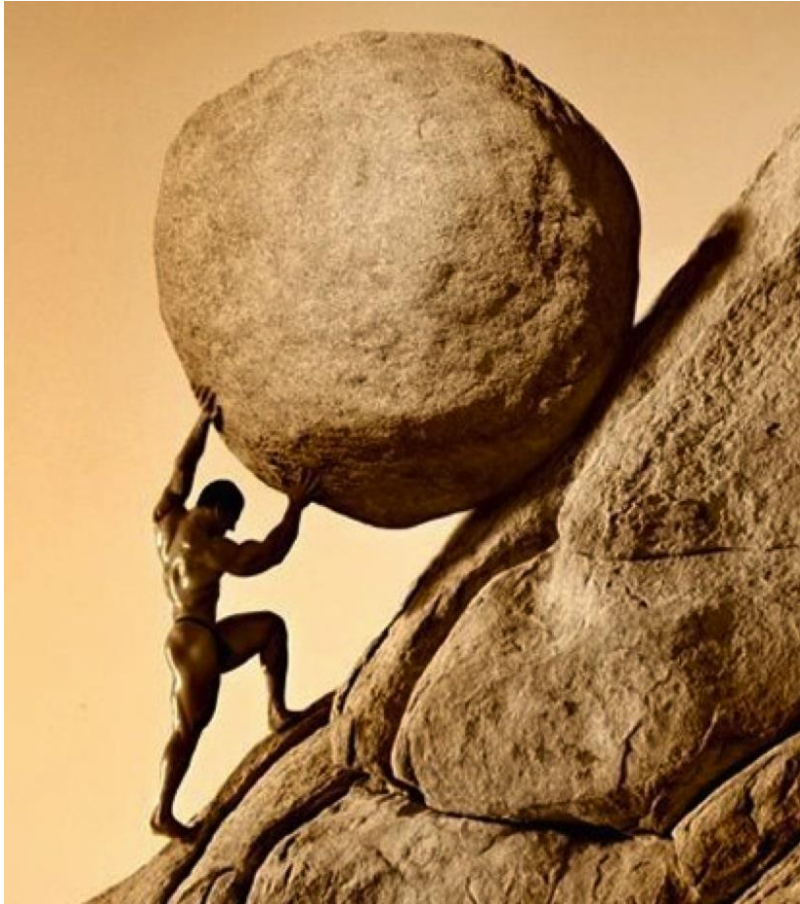
Editorial:

- Associate Editor *Hepatology, Seminars in Liver Disease*

Research support:

- Novartis (individual grant)
- Multiple Phase 2 and 3 clinical trials

Barriers to NASH cure



No ideal biomarker

Reference standard is flawed

NASH activity dynamic

+

*Disease heterogeneity – no
NASH ‘phenotypes’*



Modest efficacy

The ideal biomarker

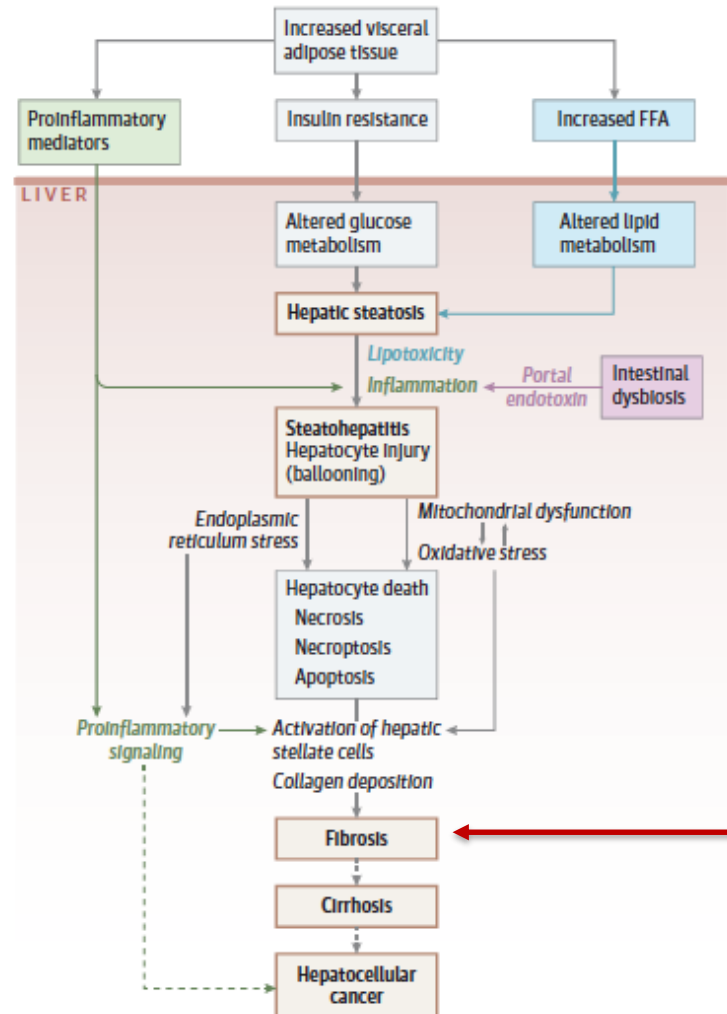
- ✓ Biologically plausible, accurate and reproducible
- ✓ Rapid, inexpensive, non-invasive, readily available
- ✓ Suitable for screening, diagnosis and monitoring
- ✓ Correlates with disease activity and fibrosis stage
- ✓ Capable of detecting treatment effects
- ✓ Predictive of outcomes

Biomarkers for NAFLD

- **Steatosis** – mostly in context of response to therapy
- **Extent of fibrosis/cirrhosis** – Assess urgency for therapy, determine prognosis, alter approach
- **Identification of NASH** – Assess need for treatment, distinguish from other etiologies
- **Predict outcomes**

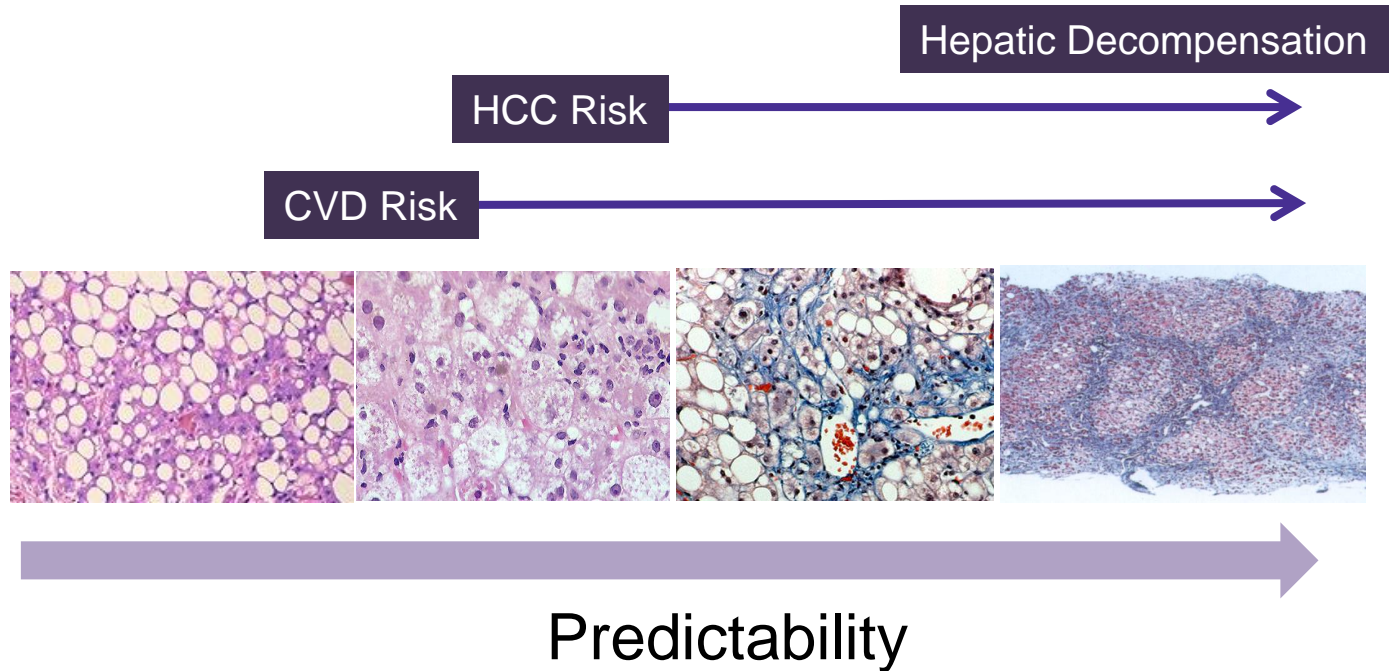
Multiple
metabolic
factors
driving
disease
progression

Adverse
hepatic
outcomes



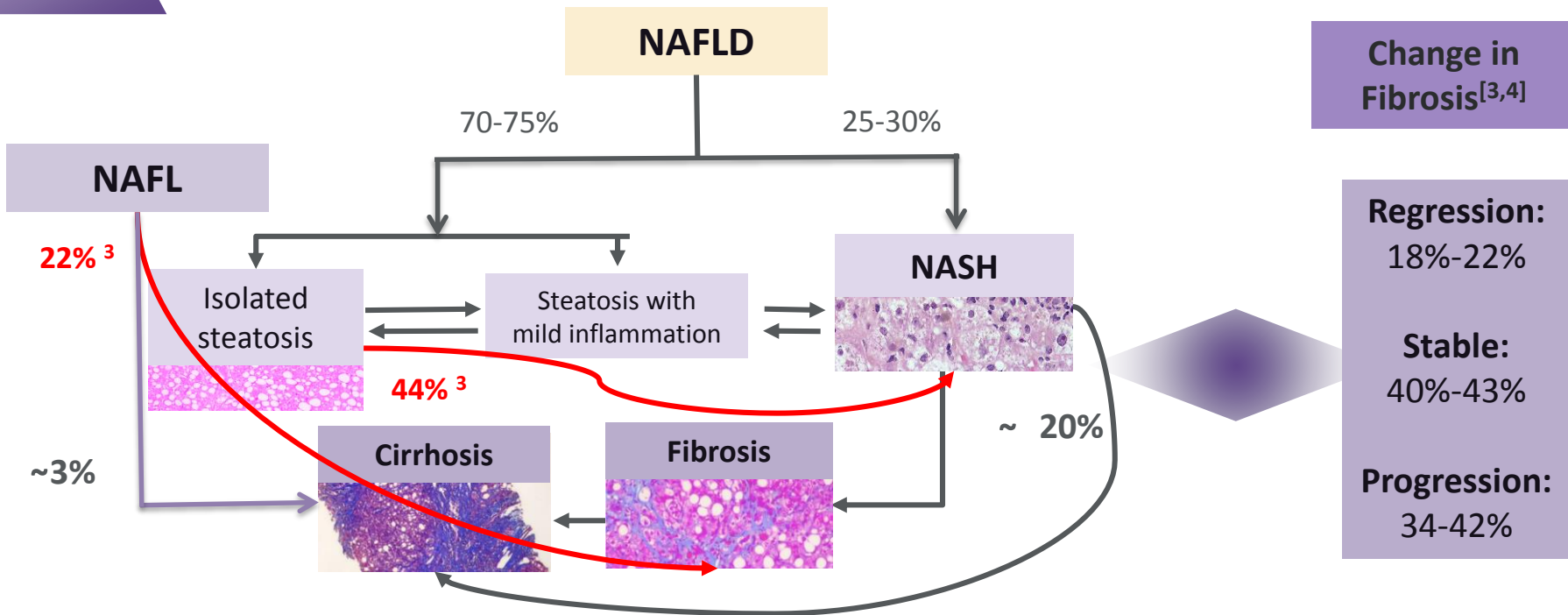
Rinella JAMA 2015

Outcomes are Associated with the Presence and Extent of Fibrosis



Angulo, et al. Gastroenterology 2015; Ekstedt et al. 2015; Hagstrom et al. 2017

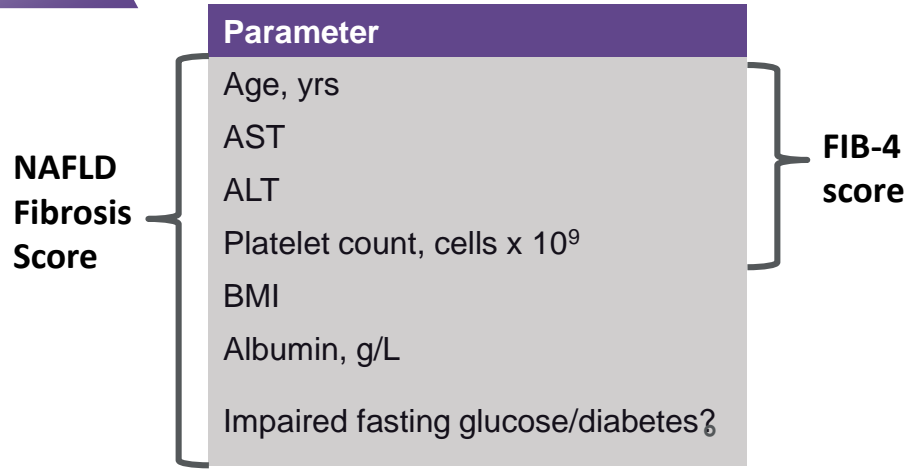
NAFLD disease progression – A moving target



1. Ludwig J, et al. Mayo Clin Proc. 1980;55(7):434-438.
2. Kleiner DE, et al. Hepatology. 2005;41(6):1313-1321.
3. McPherson S, et al. J Hepatol. 2015;62:1148-1155.
4. Singh S, et al. Clin Gastroenterol Hepatol. 2015 Apr;13(4):643-54

*N = 108 pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).³

CPRs identify those with fibrosis and predict outcomes



Negative Predictive Value:

NAFLD Fib Score <1.455 : 88-93%
FIB-4 <1.3 : 95%

Positive Predictive Value*:

NAFLD Fib Score >0.676 : 88-93%
FIB-4 >3.25 : 70%

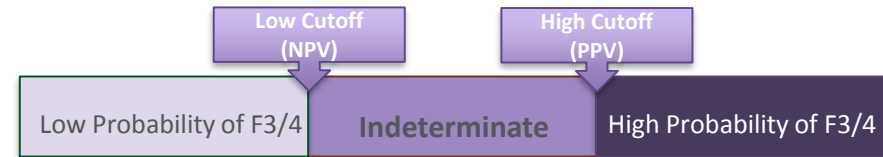
Limitations:

Most useful in excluding advanced disease

*Performance characteristics vary with age

Less accurate in diabetic patients

May underestimate disease in leaner patients



‘Wet’ Fibrosis biomarkers

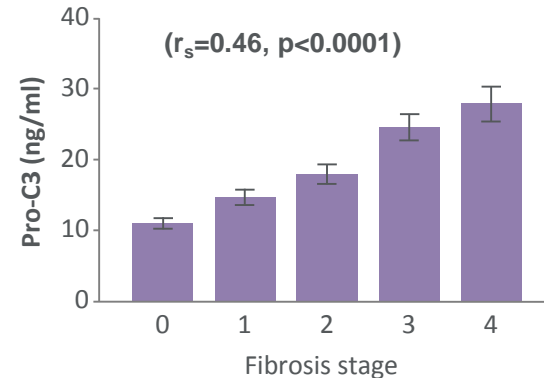
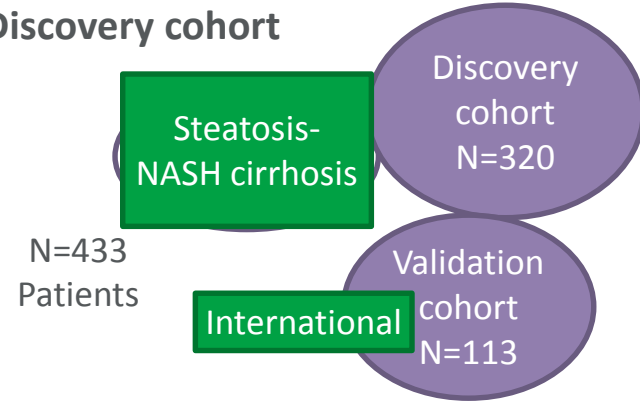
Pro-C3 “FIB-C3 score” for detection and staging of advanced NAFLD

Pro-C3: Direct marker of fibrogenesis released by ADAMTS2 during collagen type III maturation



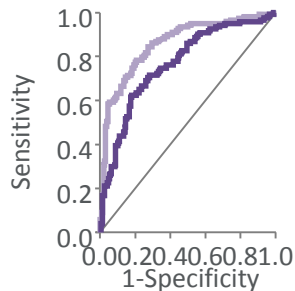
- **Pro-C3 correlates with clinical outcomes in HCV and T2DM**
- **Relative reductions of >15% ? meaningful**

Discovery cohort



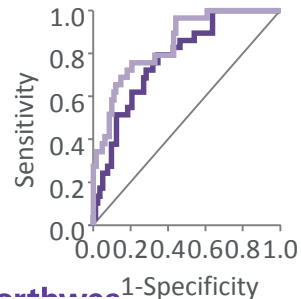
Pro-C3 'FIB-C3 score' for detection and staging of advanced NAFLD

Discovery cohort
(n=320)



FIB-4 0.77
FIB-C3 0.86
CI: 0.817–0.903,
p<0.0001

Validation cohort
(n=113)



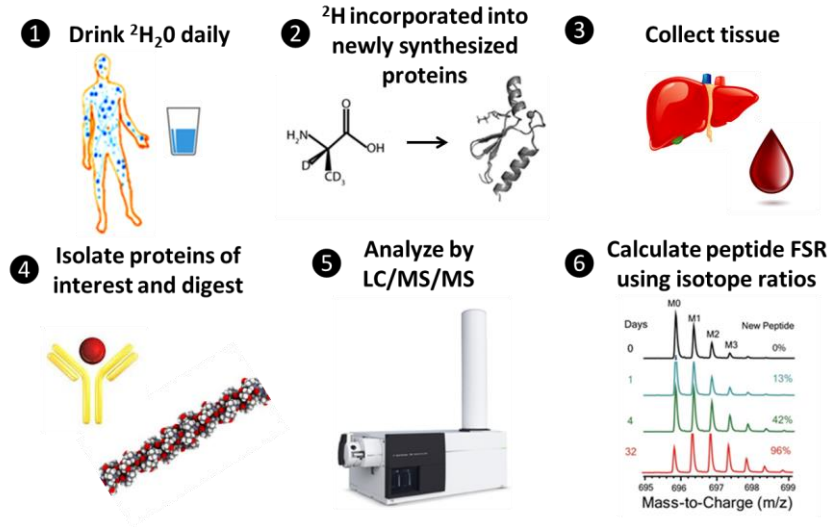
FIB-4 0.78
FIB-C3 0.847
CI: 0.769–0.924,
p<0.0001

Test	Cohort	SEN % (95% CI)	SPEC% (95% CI)	PPV % (95% CI)	NPV % (95%CI)
FIB-4 (≥2.67)	Discov (n=320)	25.2 (17.9–33.7)	91.1 (86.3–94.7)	64.0 (51.0–75.2)	66.1 (63.6–68.5)
FIB-C3 (≥-0.29)		77.0 (68.7–84.0)	80.4 (74.1–85.8)	71.8 (65.4–77.5)	84.3 (79.5–88.2)
FIB-4 (≥2.67)	Validat (n=113)	29.0 (14.2–48.0)	86.8 (78.1–93.0)	42.9 (25.9–61.6)	78.2 (73.9–82.0)
FIB-C3 (≥-0.29)		76.7 (57.7–90.1)	75.9 (65.3–84.6)	53.5 (42.8–63.9)	90.0 (82.3–94.6)

- The combination of FIB-4 with Pro-C3 (FIB-C3 score) may improve predictive power

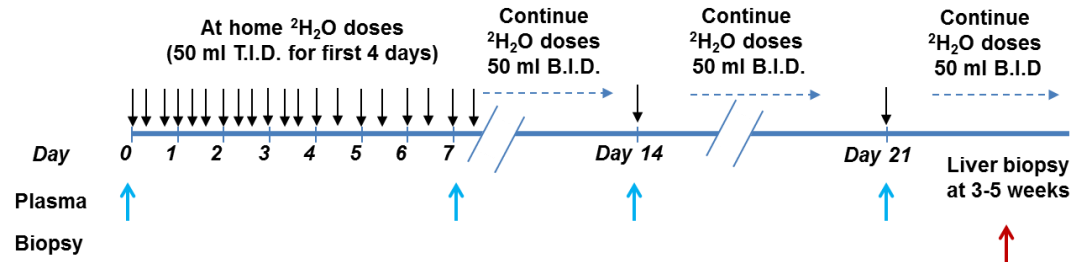
Kinetic biomarkers of fibrosis in NAFLD

A

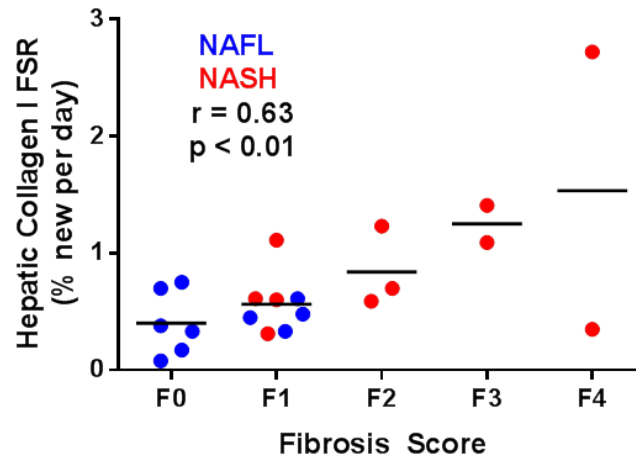
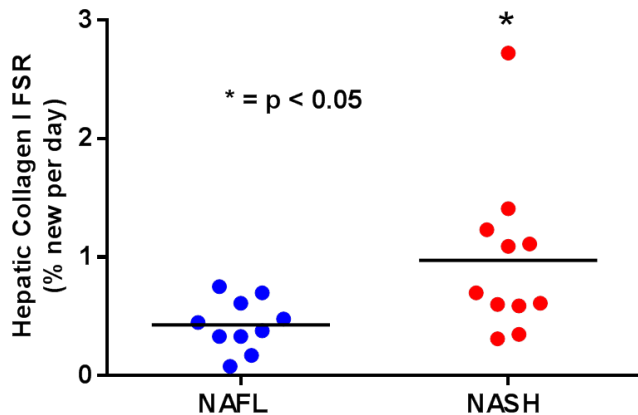


Liver collagen fractional synthesis rate (FSR) and plasma lumican FSR were measured based on ^2H labeling using tandem mass spectrometry

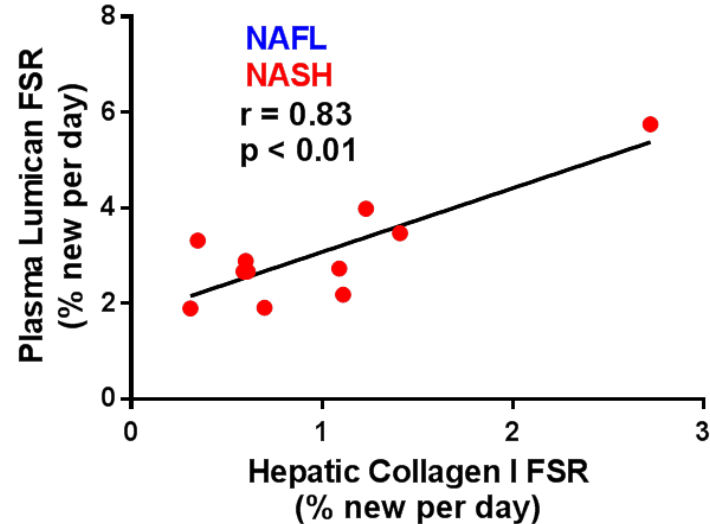
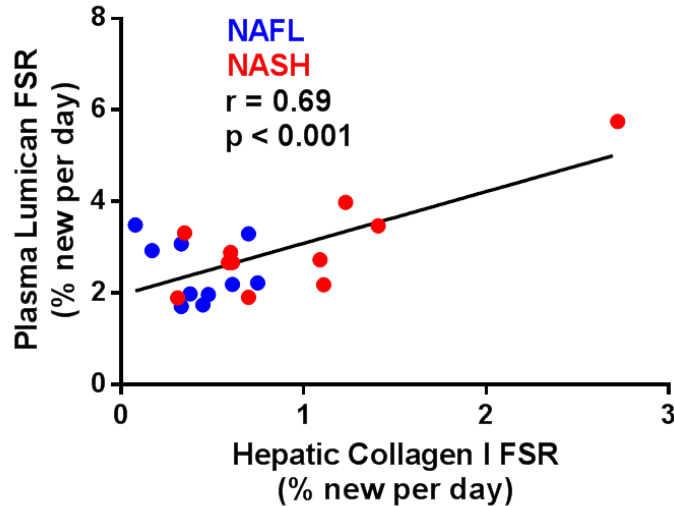
B



Hepatic collagen FSR identifies NASH and fibrosis stage



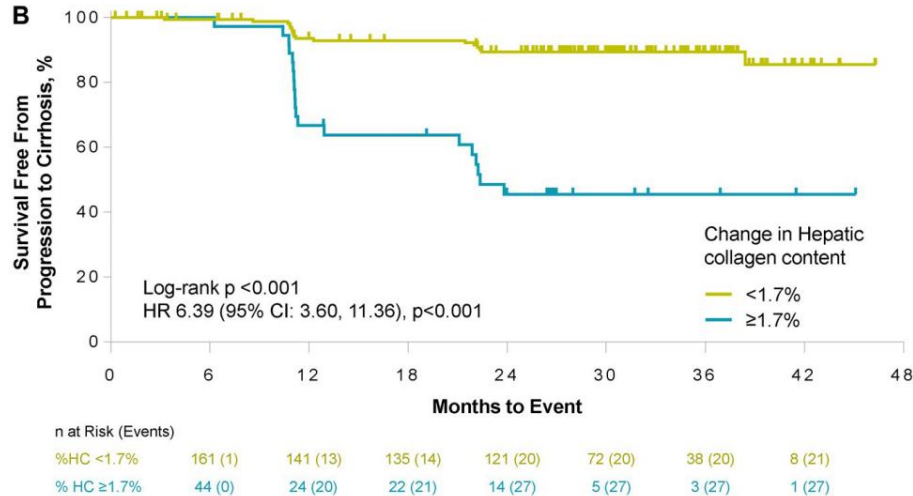
Plasma lumican FSR correlates with hepatic collagen FSR



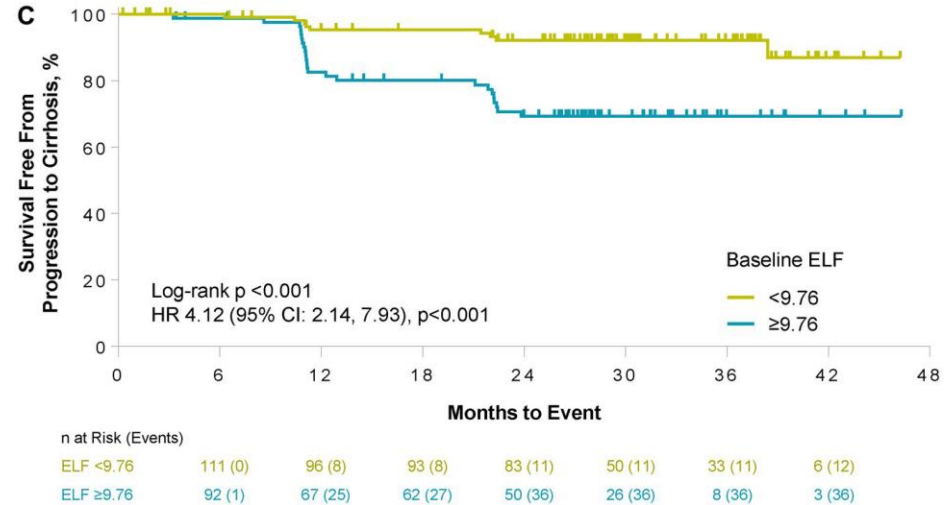
Progression to cirrhosis

Bridging Fibrosis

Change in hepatic collagen content



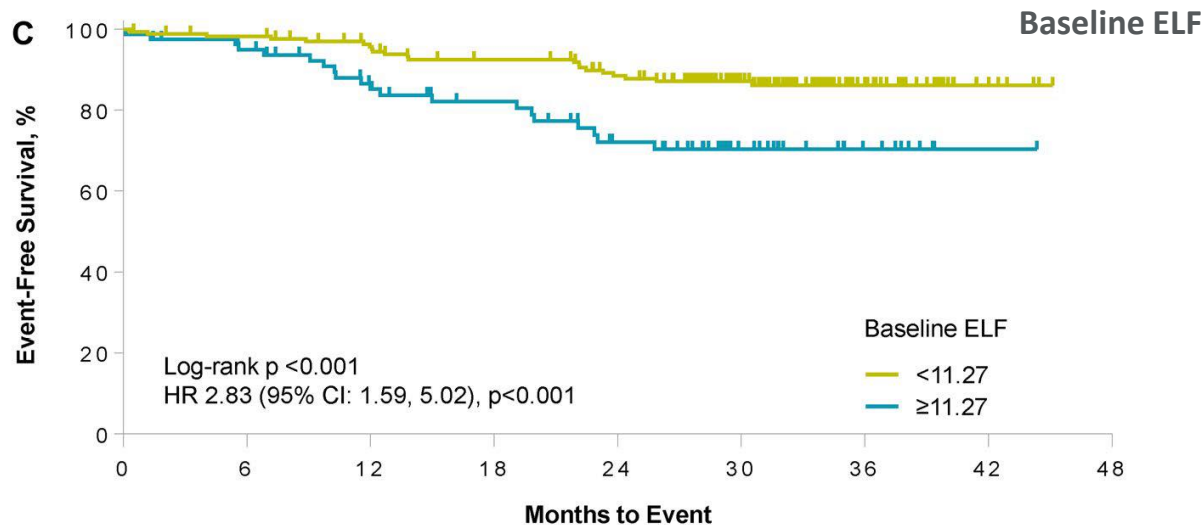
ELF



- Median follow-up 24.9 months (range, 0.3–41.4)

- 47 patients (21.5%) progressed to cirrhosis
 - 89% (n=42) histologic progression
 - 11% (n=5) clinical events

Liver related clinical events in patients with cirrhosis



n at Risk (Events)

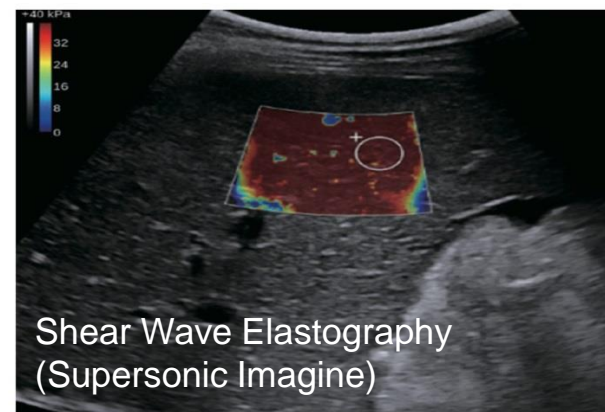
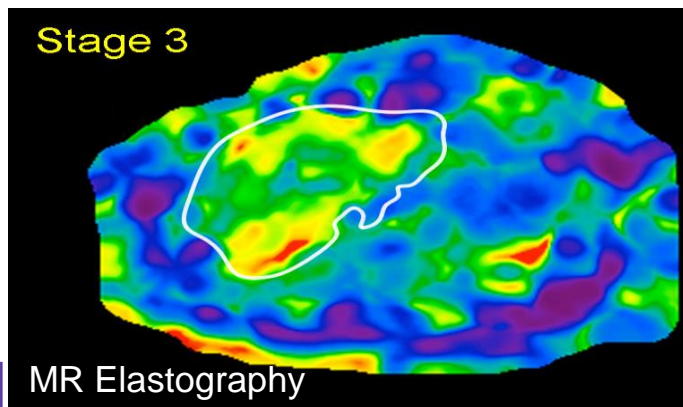
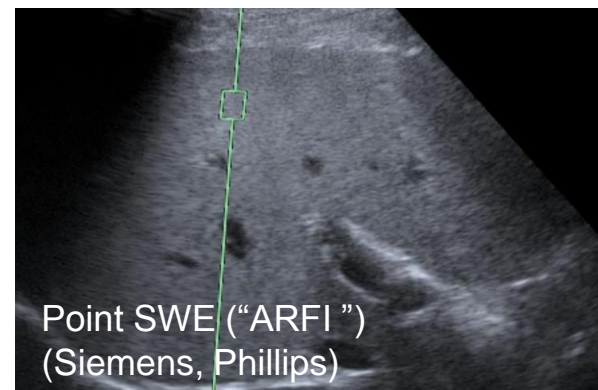
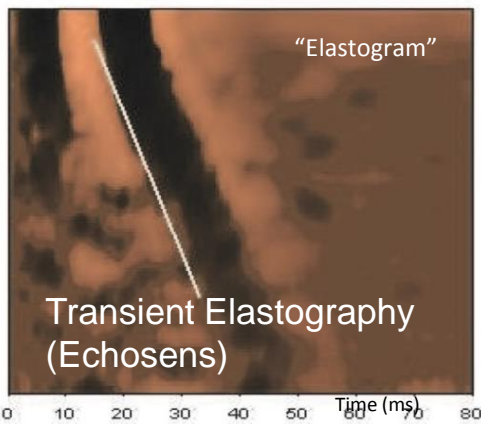
ELF <11.27	164 (3)	154 (7)	144 (12)	130 (20)	85 (22)	28 (23)	6 (23)
ELF ≥ 11.27	72 (4)	59 (12)	51 (17)	40 (23)	21 (23)	9 (24)	1 (24)

- Median follow-up 24.9 months (range, 0.3–41.4)

- Ascites (n=19)
- Encephalopathy (n=13)
- Variceal hemorrhage (n=6)
- Newly-diagnosed varices (n=4)
- ≥ 2 -point increase in Child-Pugh score and/or MELD ≥ 15 (n=6)
- Death (n=1)

Imaging biomarkers of fibrosis

Imaging assessment of liver stiffness



Liver Fibrosis or Liver Stiffness?

Obtain a quality scan

>100

Experienced operator

performed >100 exams

≥10 measurements
IQR < 30%



Obesity

Use an XL
probe at BMI ≥ 30

Know what impacts liver stiffness



Nonfasting

Have patients fast
for 3 hours

Congestion

Examine for right
heart failure



ALP

Cholestasis

Know the alkaline phosphatase

Alcohol

Determine drinking status



Pearls

Cutoffs not uniform across
populations

Different cutoffs should be used
tailored to question (e.g. identify or
exclude advanced fibrosis)

VCTE Early Fibrosis Assessment

393 Biopsy-Proven NAFLD Subjects

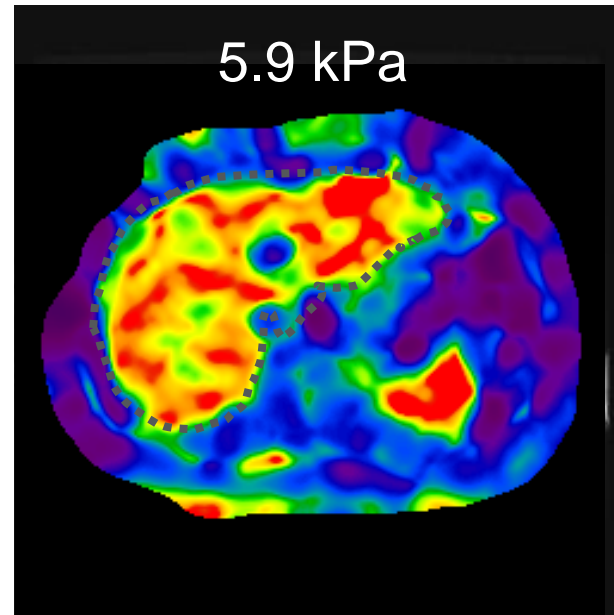
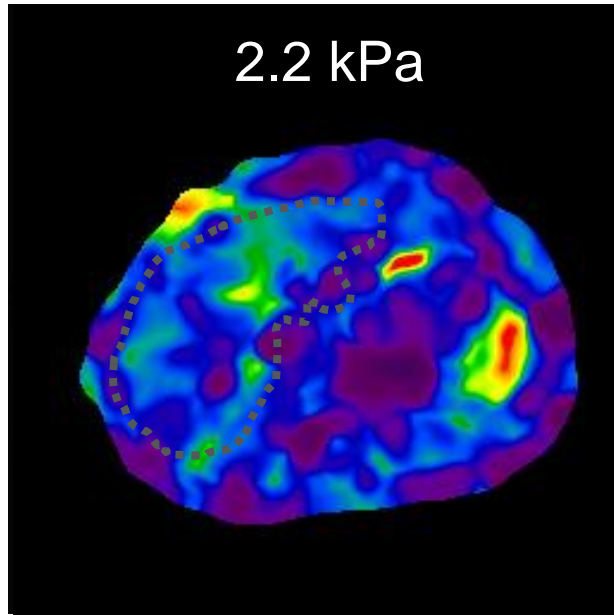
Fibrosis Stage	AUROC	Threshold Priority	Threshold (kPa)	Sensitivity	Specificity	PPV	NPV
F0-1 vs F2-4	0.74	Sensitivity Priority	5.6	0.90	0.44	0.62	0.81
		Balanced Priority	8.6	0.66	0.80	0.78	0.70
		Specificity Priority	11.9	0.40	0.90	0.80	0.59

VCTE Based Cirrhosis Assessment

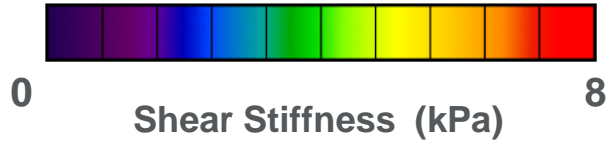
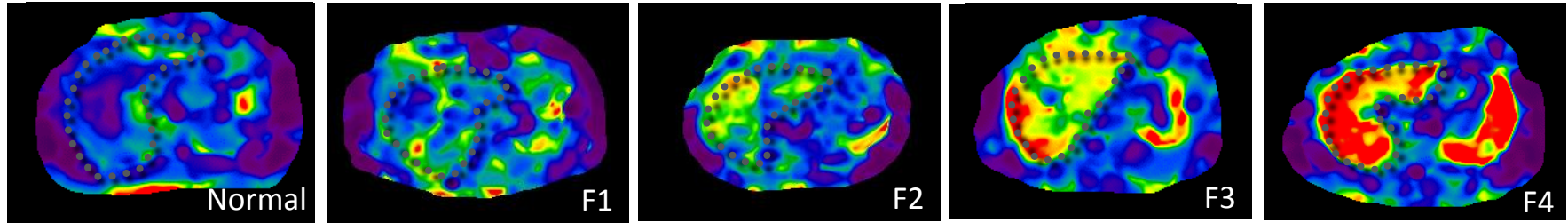
393 Biopsy-Proven NAFLD Subjects

Fibrosis Stage	AUROC	Threshold Priority	Threshold (kPa)	Sensitivity	Specificity	PPV	NPV
F0-3 vs F4	0.93	Sensitivity Priority	12.1	0.90	0.82	0.34	0.99
		Balanced Priority	13.1	0.89	0.86	0.39	0.99
		Specificity Priority	14.9	0.69	0.90	0.41	0.97

Two Patients with Chronic Liver Disease: Is Hepatic Fibrosis Present?



Magnetic resonance elastography



AUROC: 0.924
for 0-2 vs. 3-4

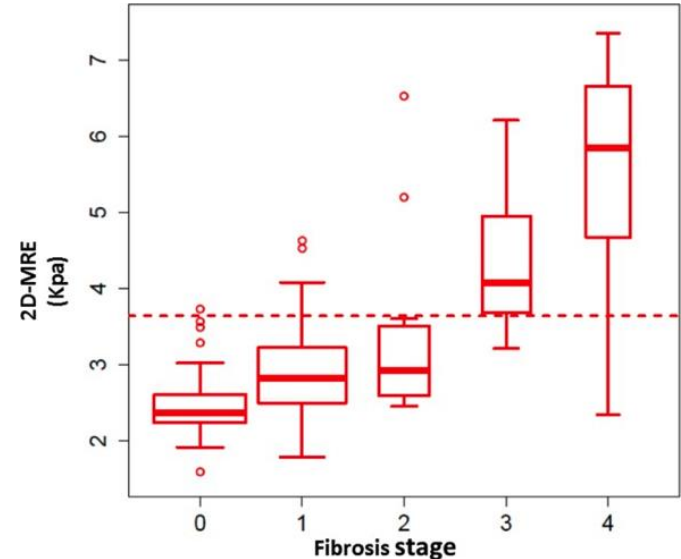
3.63 kPa:

Sensitivity: 0.86 (95% [CI]: 0.65-0.97)

Specificity: 0.91 (95% CI: 0.83-0.96)

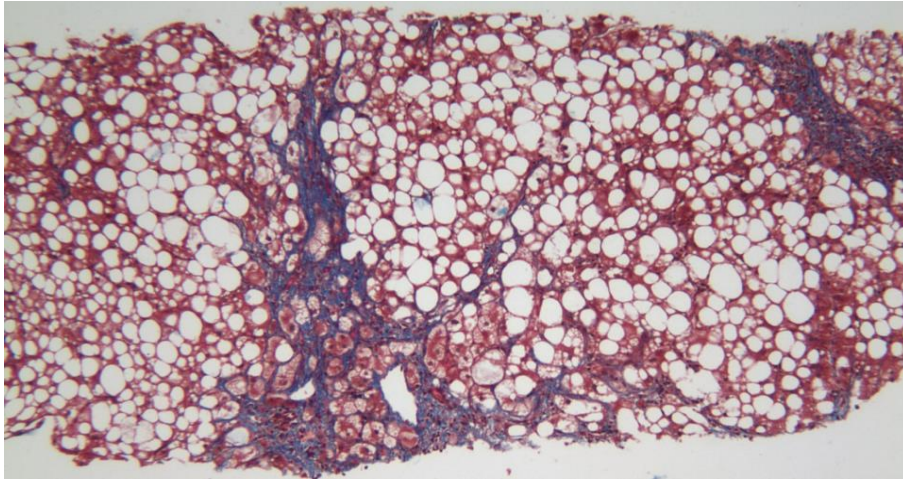
PPV: 0.68 (95% CI: 0.48-0.84)

NPV: 0.97 (95% CI: 0.91-0.99)

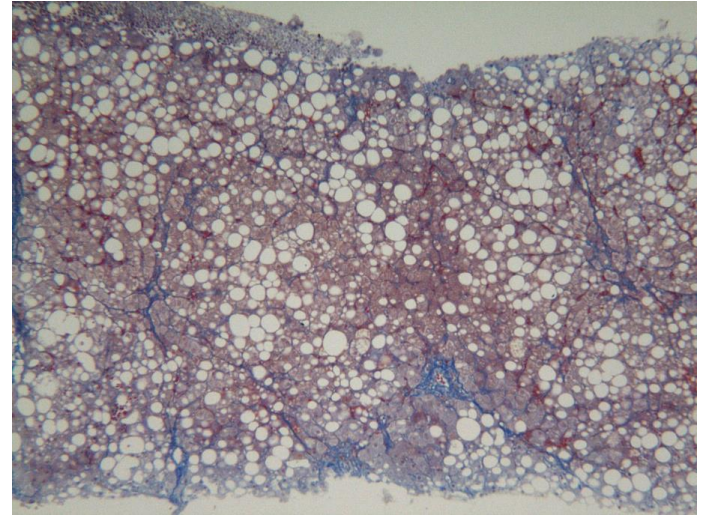


Variability in collagen burden within fibrosis stage

Baseline

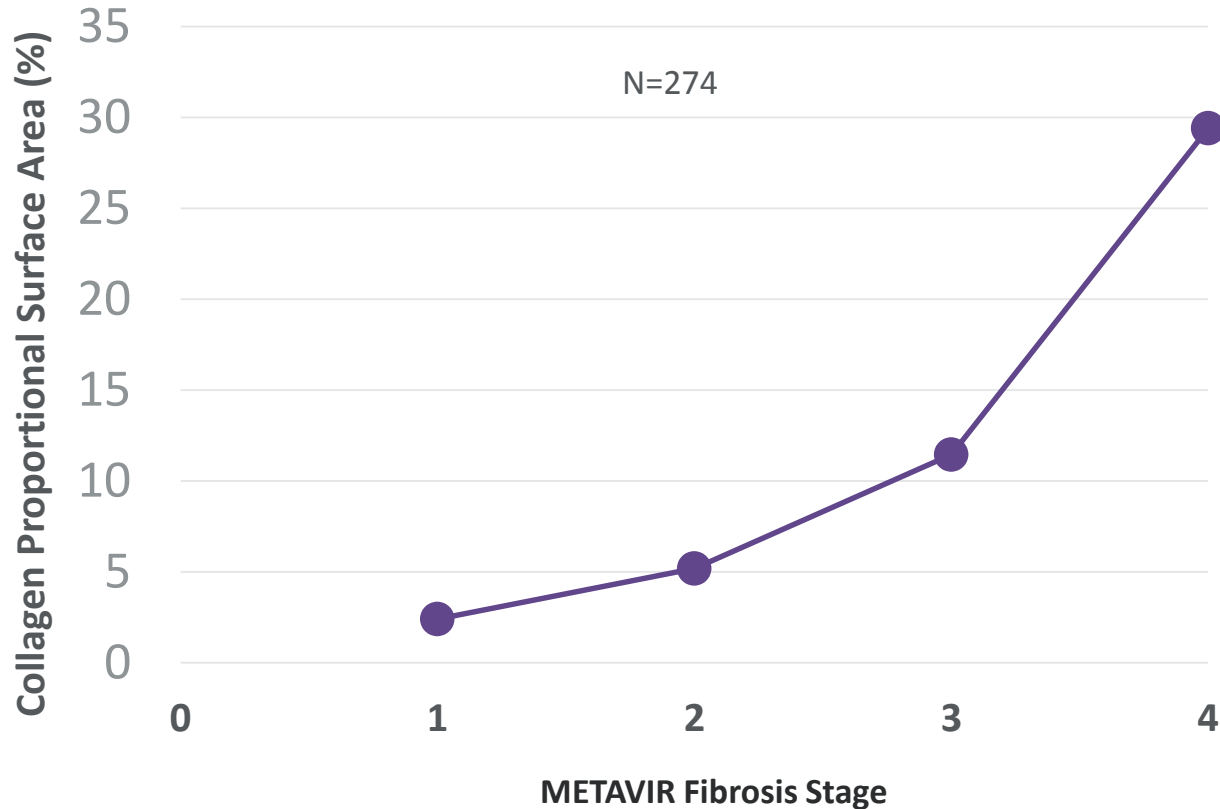


Post-treatment

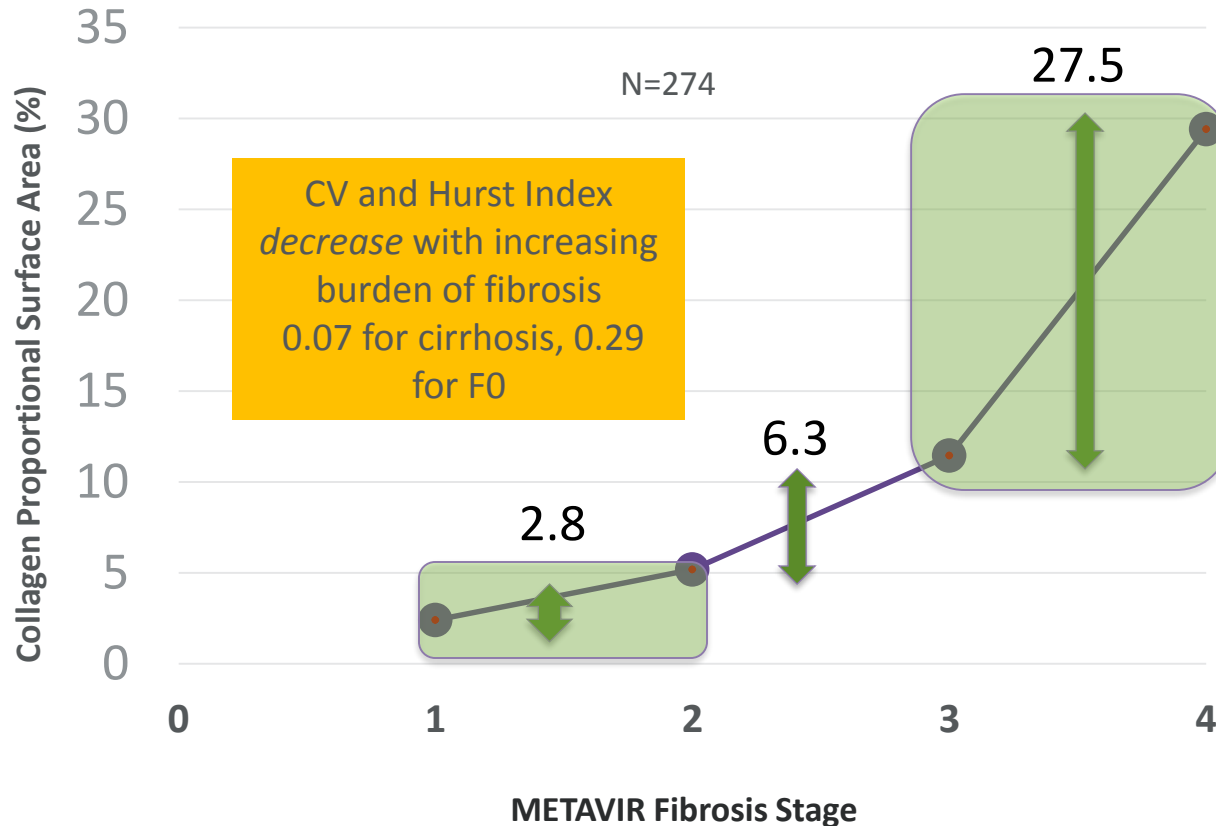


Both are technically stage 3 fibrosis

Liver Collagen Burden is not Linear Across Fibrosis Stages

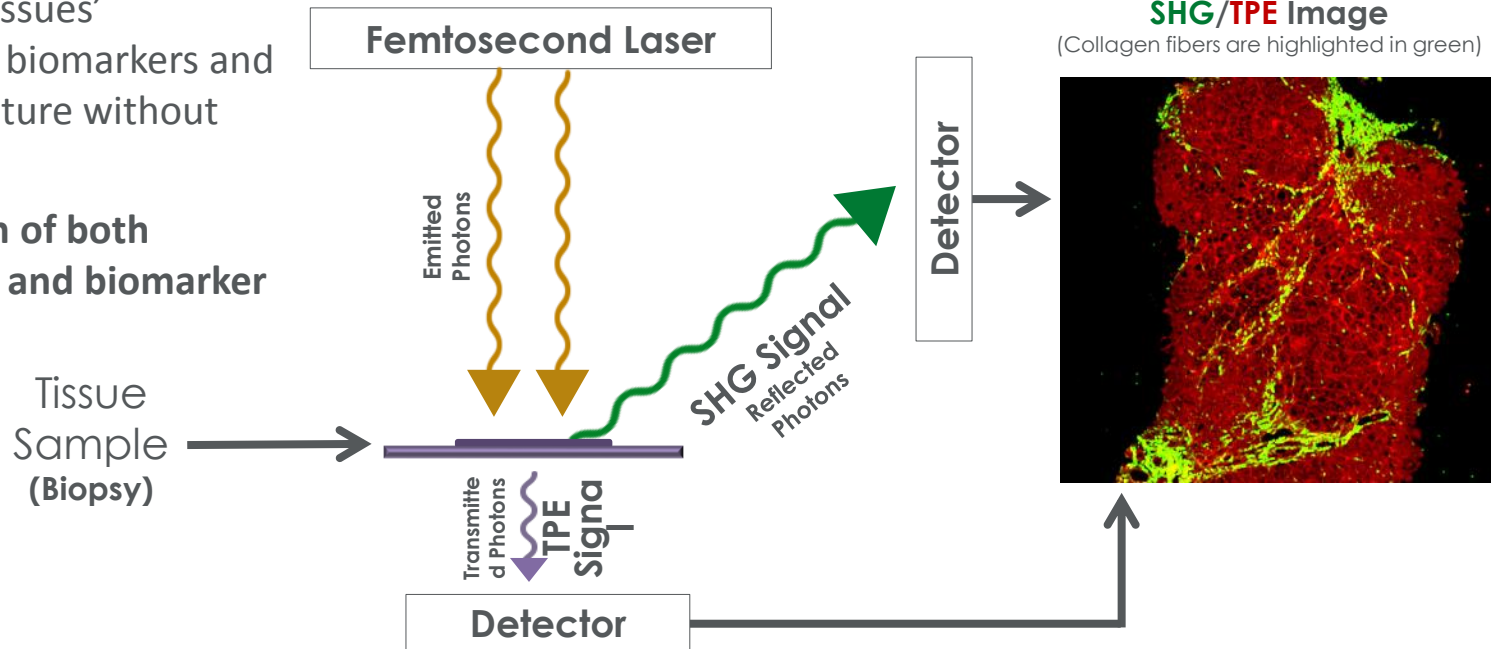


Liver Collagen Burden is not Linear Across Fibrosis Stages



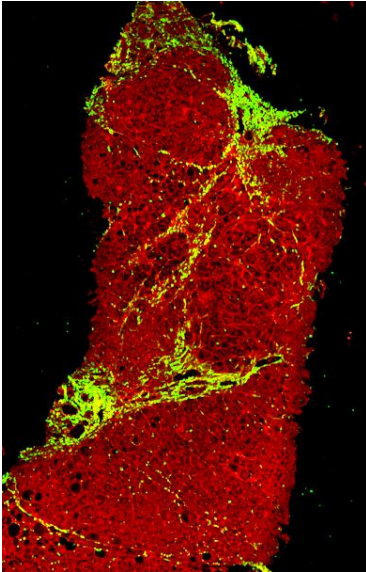
SHG/TPEF Non-Staining Imaging System

- Reading of tissues' endogenous biomarkers and unique signature without staining
- Combination of both morphology and biomarker information

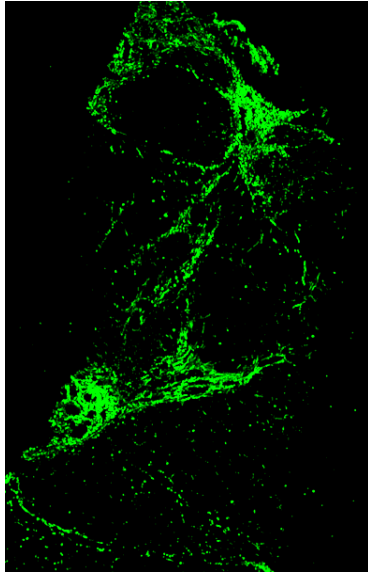


Total Quantification and Positioning of Fibrosis, Steatosis, Ballooning & Inflammation (qFIBS)

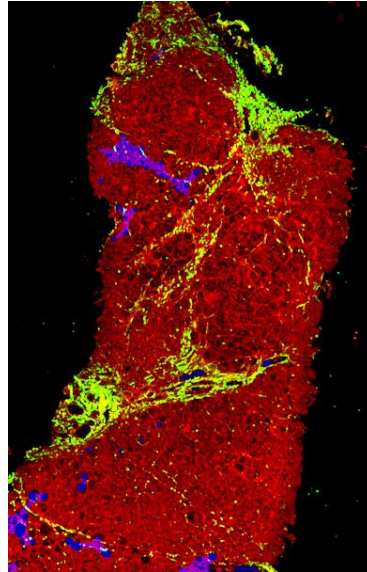
SHG/TPE image



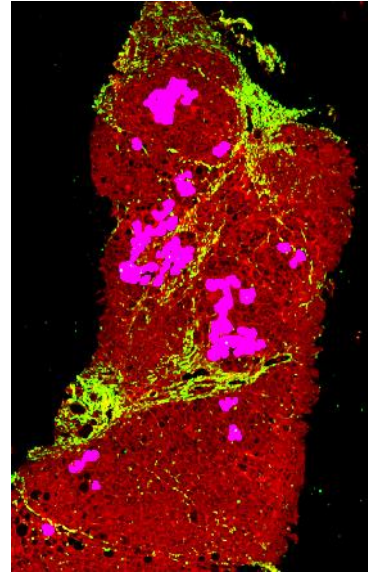
Fibrosis



Steatosis



Ballooning



Inflammation

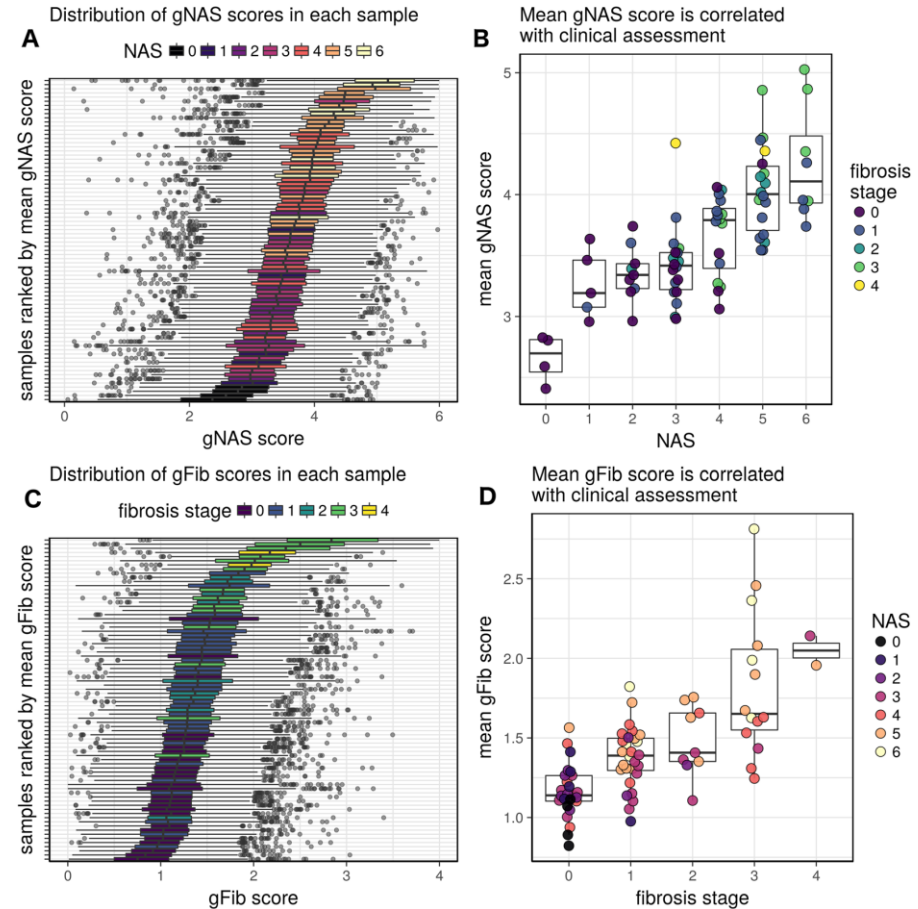


Improved discrimination across fibrosis stages

	AUROC	95% CI	Sensitivity	Specificity
<i>qFibrosis</i>				
F0 vs F1/2/3/4	0.851	0.776-0.926	68.8%	92.3%
F0/1 vs F2/3/4	0.904	0.844-0.963	84.8%	84.2%
F0/1/2 vs F3/4	0.905	0.846-0.965	72.7%	90.0%
F0/1/2/3 vs F/4	0.915	0.851-0.979	84.6%	86.7%
<i>qSteatosis</i>				
0 vs 1/2/3	0.957	0.914-0.999	93.0%	100%
0/1 vs 2/3	0.938	0.894-0.982	85.5%	93.8%
0/1/2 vs 3	0.908	0.830-0.986	90.9%	82.7%
<i>qBallooning</i>				
0 vs 1/2	0.831	0.744-0.919	61.5%	95.0%
0/1 vs 2	0.855	0.775-0.935	76.7%	88.3%
<i>qInflammation</i>				
0 vs 1/2/3	0.853	0.784-0.923	84.0%	100%
0/1 vs 2/3	0.858	0.786-0.930	86.4%	75.0%
0/1/2 vs 3	0.872	0.771-0.973	90.0%	79.6%

Gene scores to predict disease activity and severity

- Coordinated regulation of genes and pathways that change over the course of disease
- Expression levels of 20 genes can infer disease severity
- gScores for NAS and fibrosis



Glympse – liquid biopsy



- Urine diagnostic test measuring hepatic protease activity
- Nanosensors injected that sense proteases involved in inflammation and fibrosis, amplified by hepatic enzymatic activity and concentrated in urine, measured by mass spec

State of biomarkers in August 2019

- We can accurately measure fat and assess dynamic change, not changes in fibrosis yet
- We can noninvasively rule-out advanced fibrosis and rule in cirrhosis
- Some available biomarkers can predict long-term outcomes NFS, FIB-4 and ELF
- More granularity needed to distinguish fibrosis stages

Obrigada pela
sua atenção

