Therapy of Liver fibrosis: Where Do We Stand?

APASL Single Topic Conference

Cairo

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NASH Through the Ages

Kaaper, Chief Priest

Cairo Antiquities Museum
~ 2400 BC

Overview

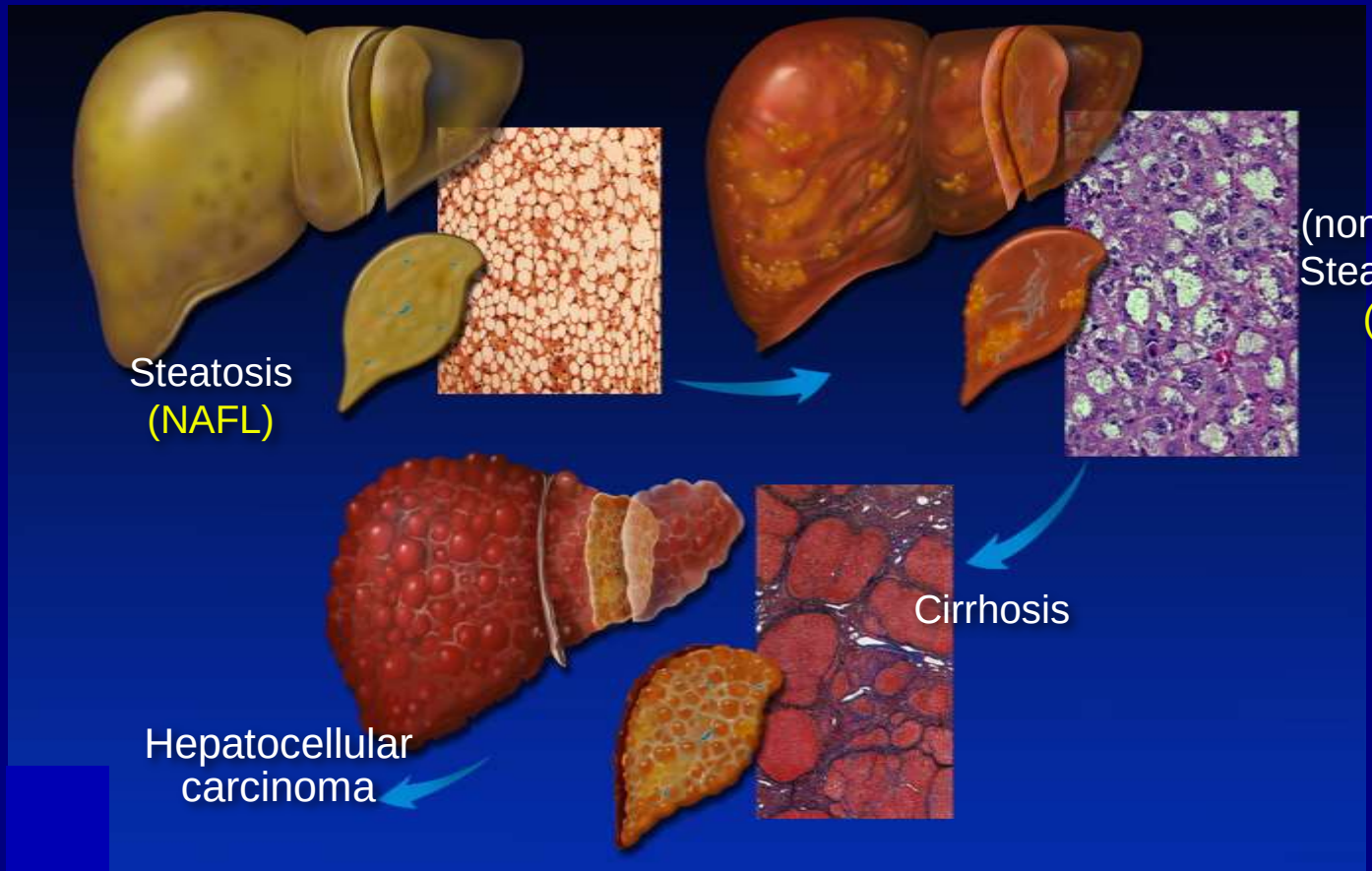
1. NAFLD/NASH definitions, features and epidemiology.

2. Hepatic fibrosis in NASH – implications and pathogenesis.

3. Diagnostic frontiers.

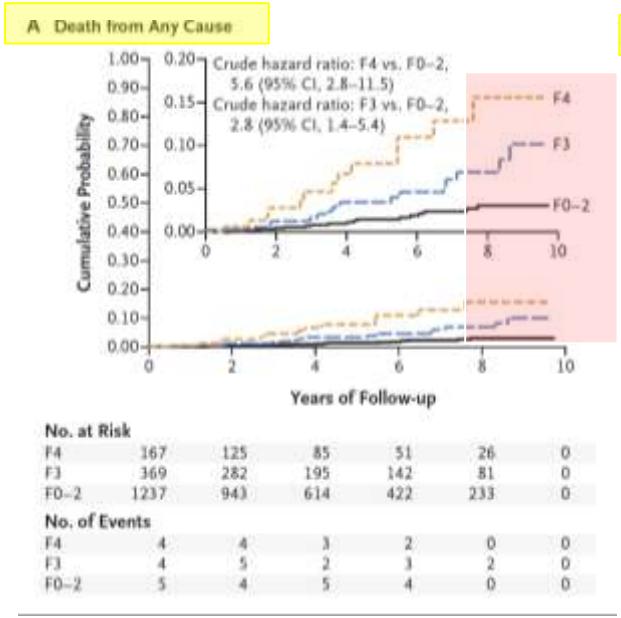
4. Therapeutic prospects.

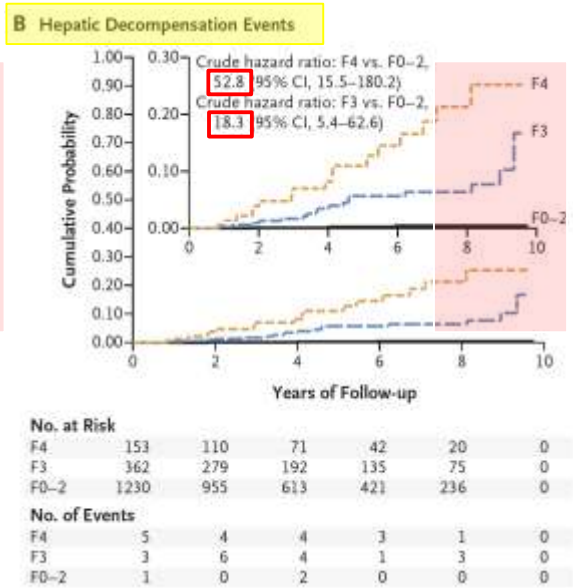
Progression of Hepatic Pathology in Non-Alcoholic fatty liver disease (NAFLD)

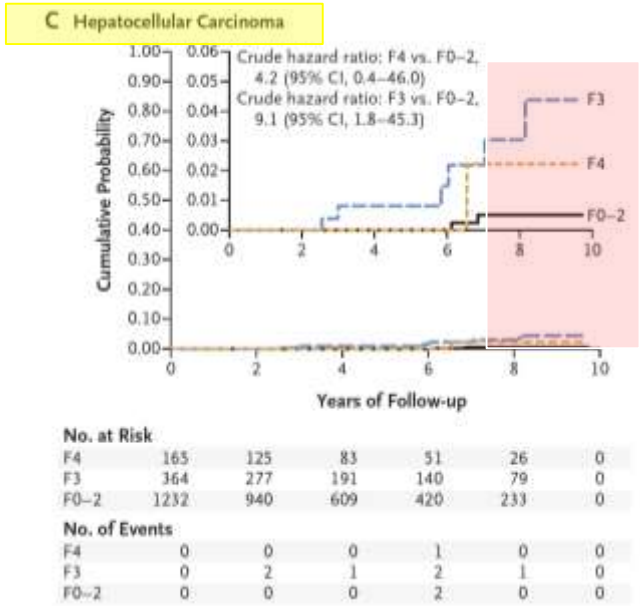


Fibrosis Drives Outcomes in NAFLD

NIDDK NASH CRN – 1773 patients followed for 10 years

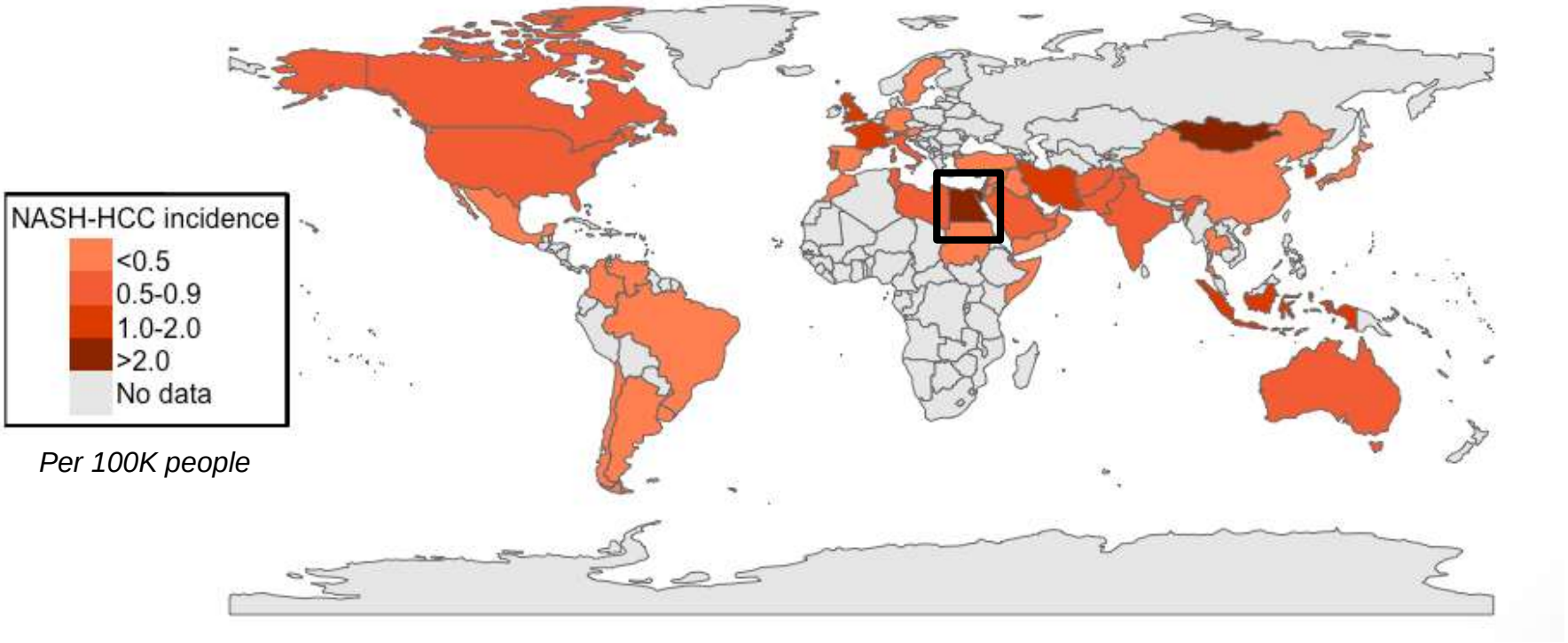






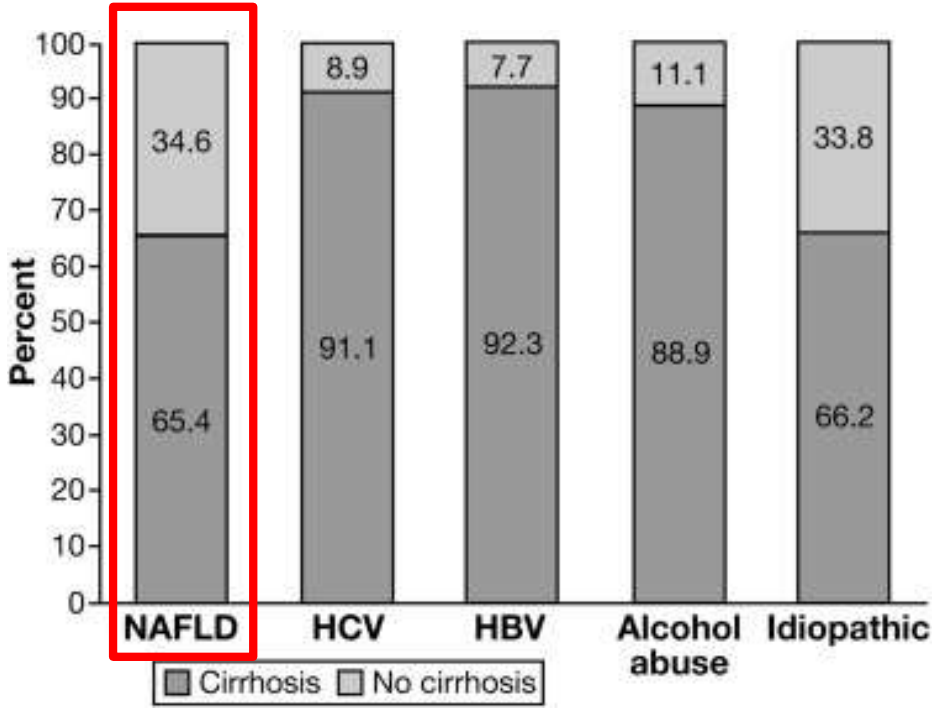
Sanyal A, et al., *NEJM, October 20, 2021*

The Global Incidence of NASH-HCC



Llovet, et al, *Nat Reviews Gastro & Hep,* 2022, in press

> 1/3 of HCCs in NAFLD Occur in Non-Cirrhotics in a VA Population



Mittal et al. Clinical Gastroenterology and Hepatology, 2016

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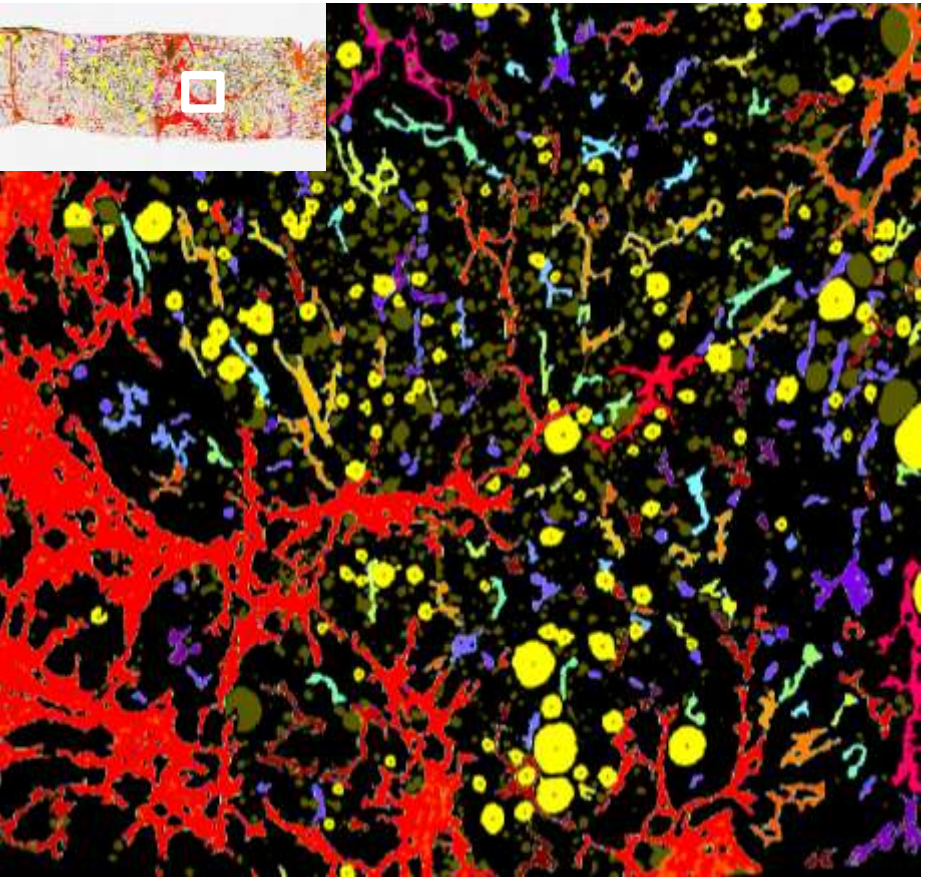
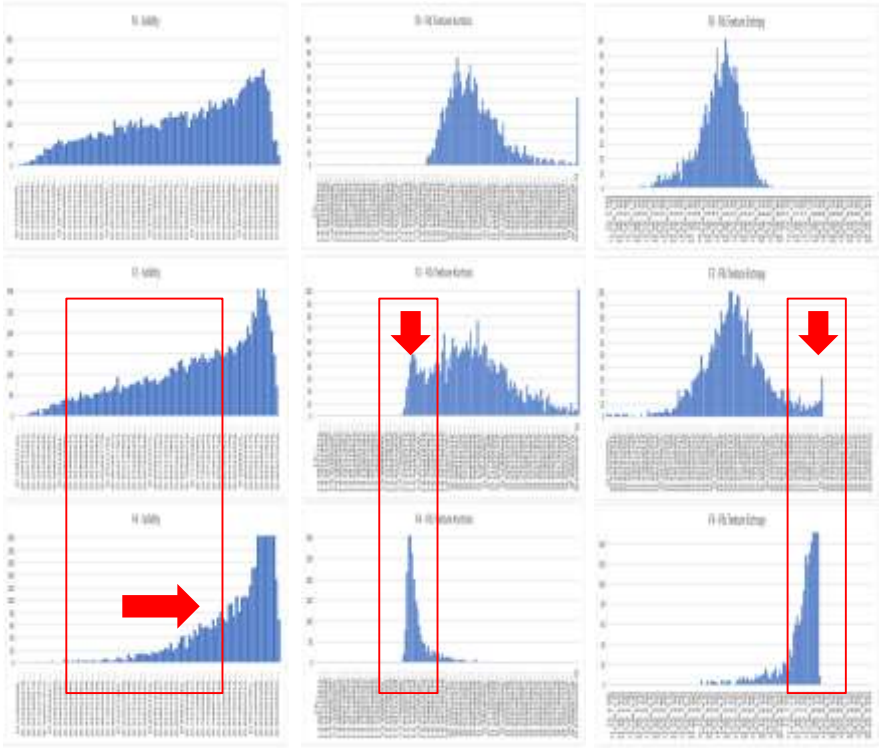
Fibrosis Diagnostics as Potential Endpoints in *Clinical trials*

- Biopsy
- Fibroscan
- MR Techniques
- HVPG
- Function tests

AI-based Analysis of Digital Pathology (Pharmnest)

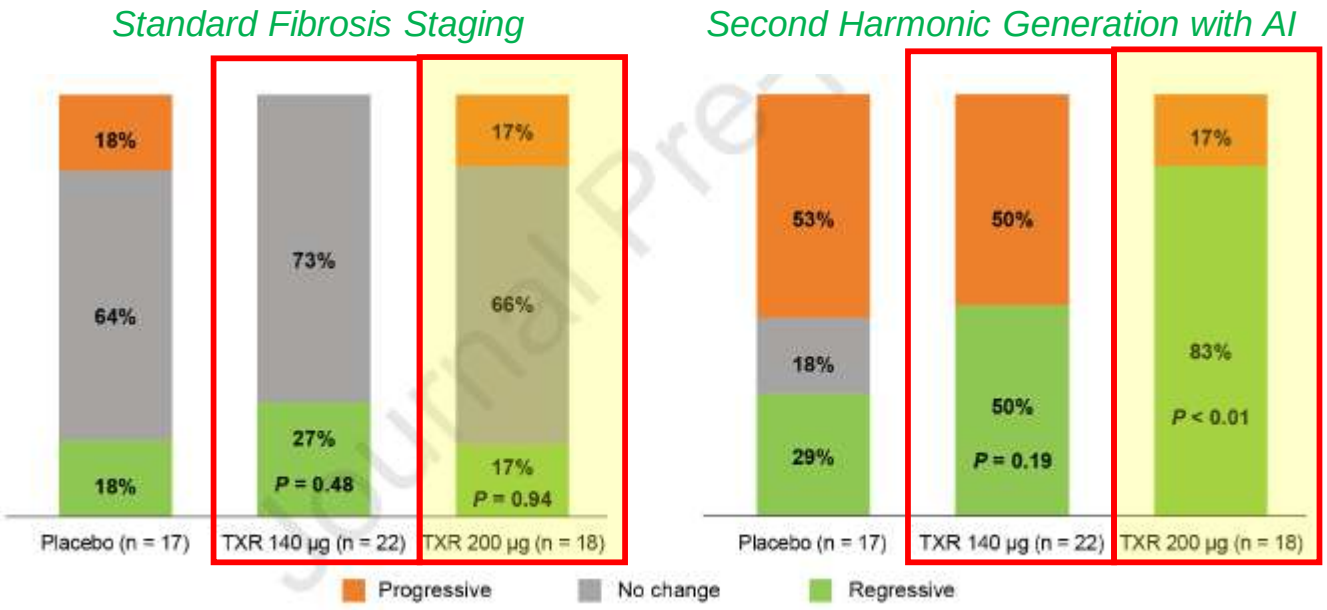


Disease Progression



Courtesy of
Matthieu Pettijean, Pharmanest

Digital Pathology Detects Fibrosis Regression that Conventional Liver Biopsies Miss



Naoumov et al, J Hepatology, 2022

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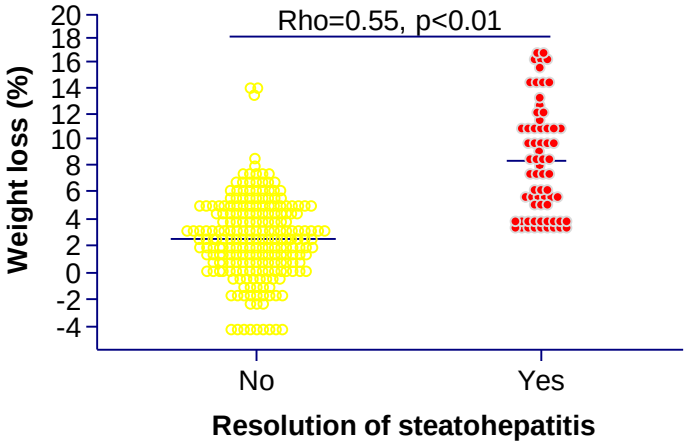
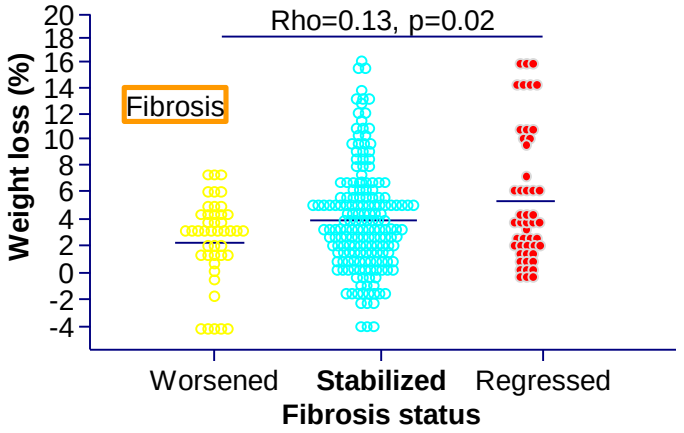
Weight loss Improves NASH Histology after 52 weeks of Lifestyle Modification

Correlations* between WL and steatohepatitis resolution



Correlations between WL and fibrosis status at the end of intervention

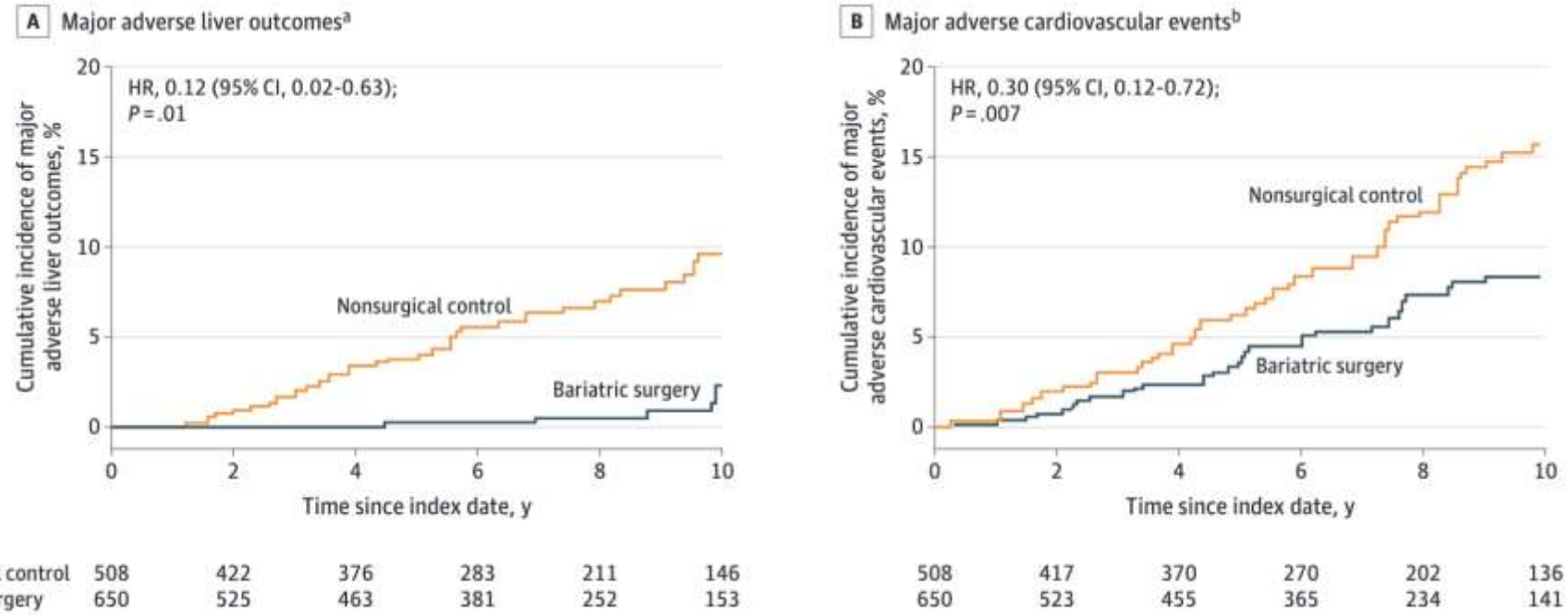


No significant correlation was found with changes in the physical activity score at the end of the intervention

- 5% weight loss improved steatosis
- 7% weight loss improved hepatocellular ballooning
- 10% weight loss needed for fibrosis improvement

Vilar-Gomez E, et al. Gastroenterology 2015

Bariatric Surgery Can Reduce Long-Term Liver and CV events in NASH Patients



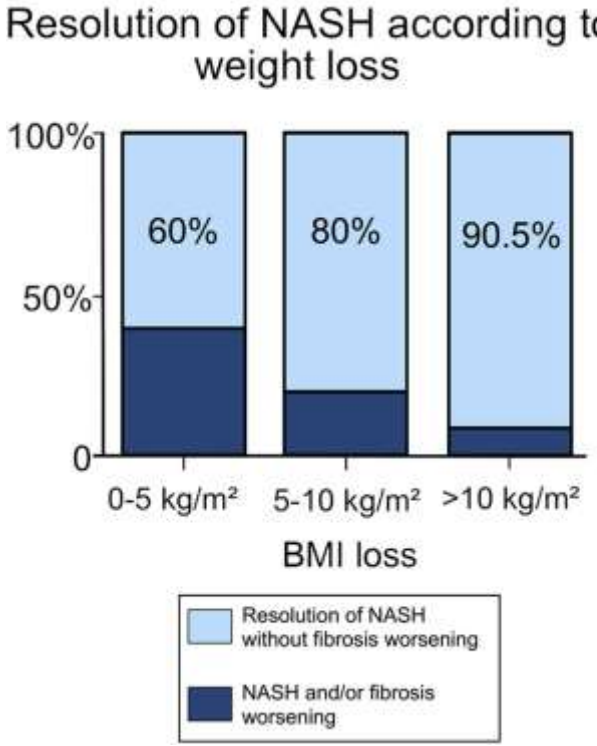
No. at risk						
Nonsurgical control	508	422	376	283	211	146
Bariatric surgery	650	525	463	381	252	153

508	417	370	270	202	136
650	523	455	365	234	141

Composite endpts; Fibrosis Stage 1-3; Retrospective; Mostly Roux-en-Y

Aminian et al, *JAMA*, 2021

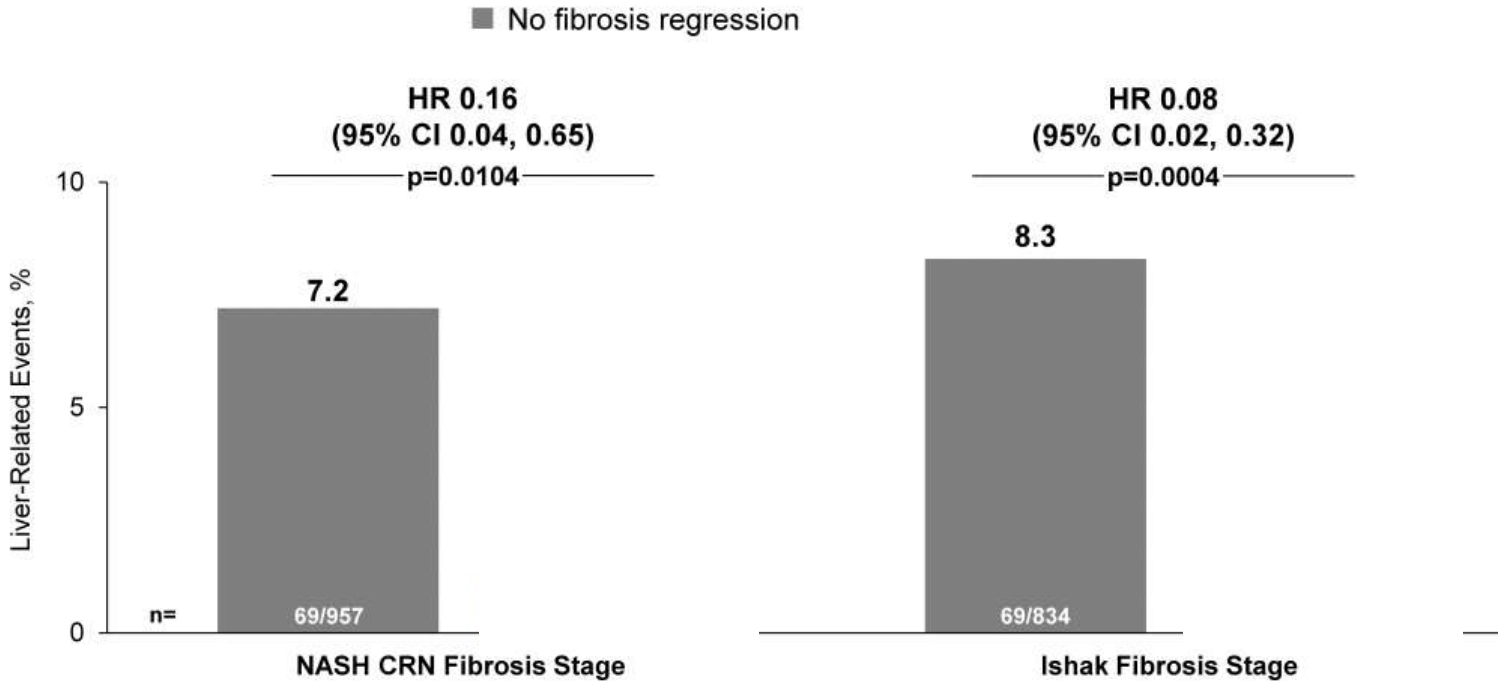
Fibrosis Resolution is Possible in NASH – *Success of Bariatric Surgery*



Lassailly et al, *Gastroenterology*, 2020

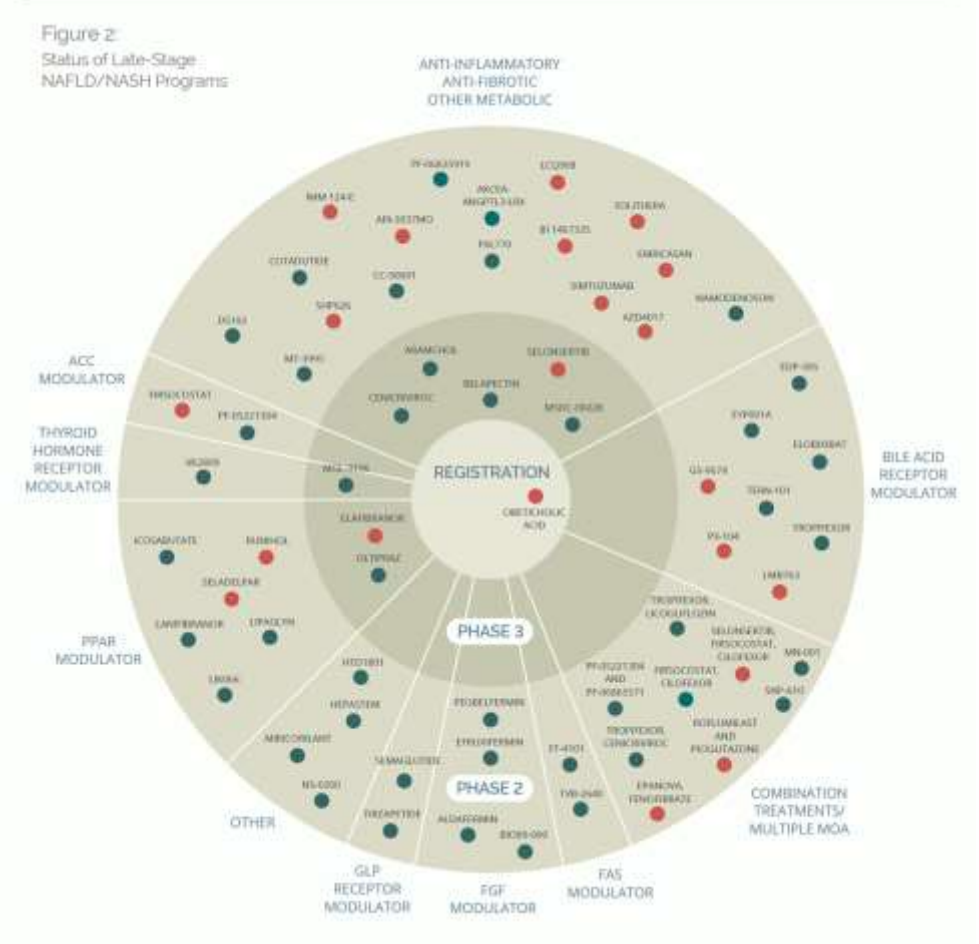
Fibrosis Regression Reduces Liver-related Clinical Events in Cirrhotics with NASH

1135 cirrhotic patients from 2 Gilead Trials: - 16% had fibrosis regression



Sanyal, et al. Hepatology, 2021

NASH Drugs in Phase 2 and 3 Trials



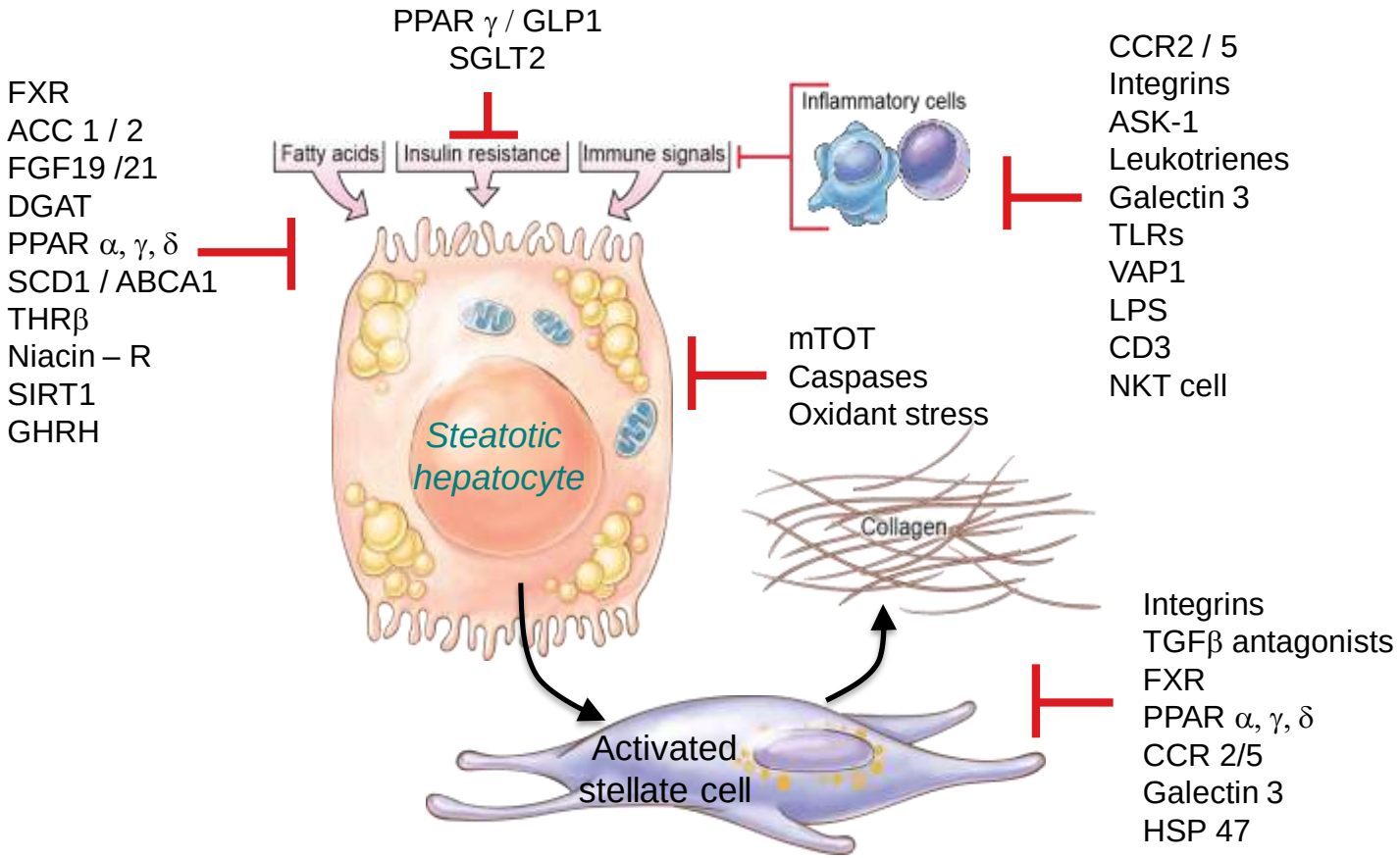
Number of drugs:
Phase 2 = 73
Phase 3 = 9

Number of approved drugs:
0

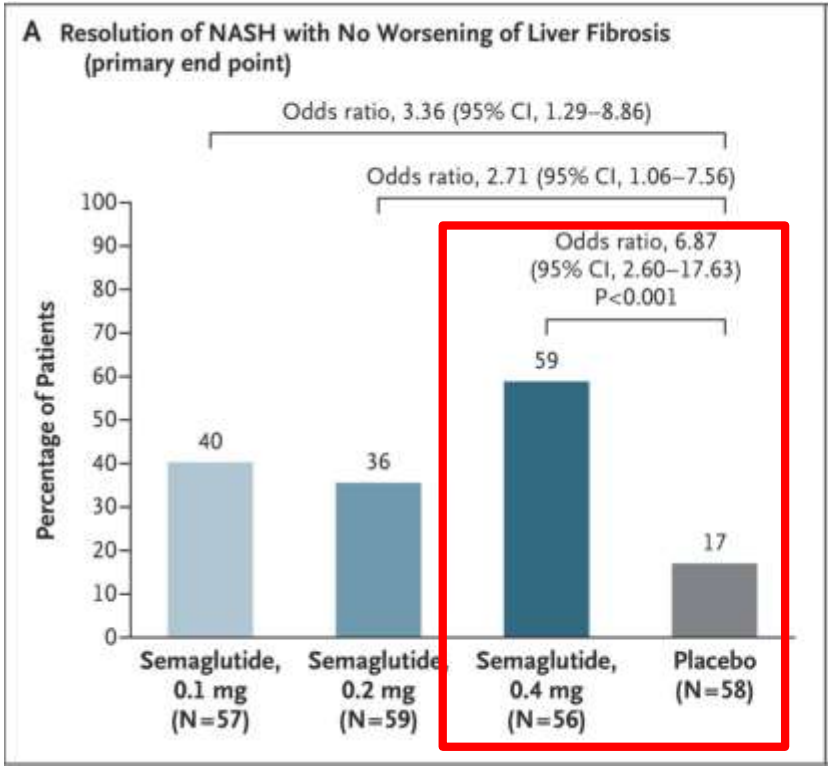
BACK BAY LIFE SCIENCE ADVISORS

Dec 2020

NASH Targets in Phase 2 or Phase 3 Trials



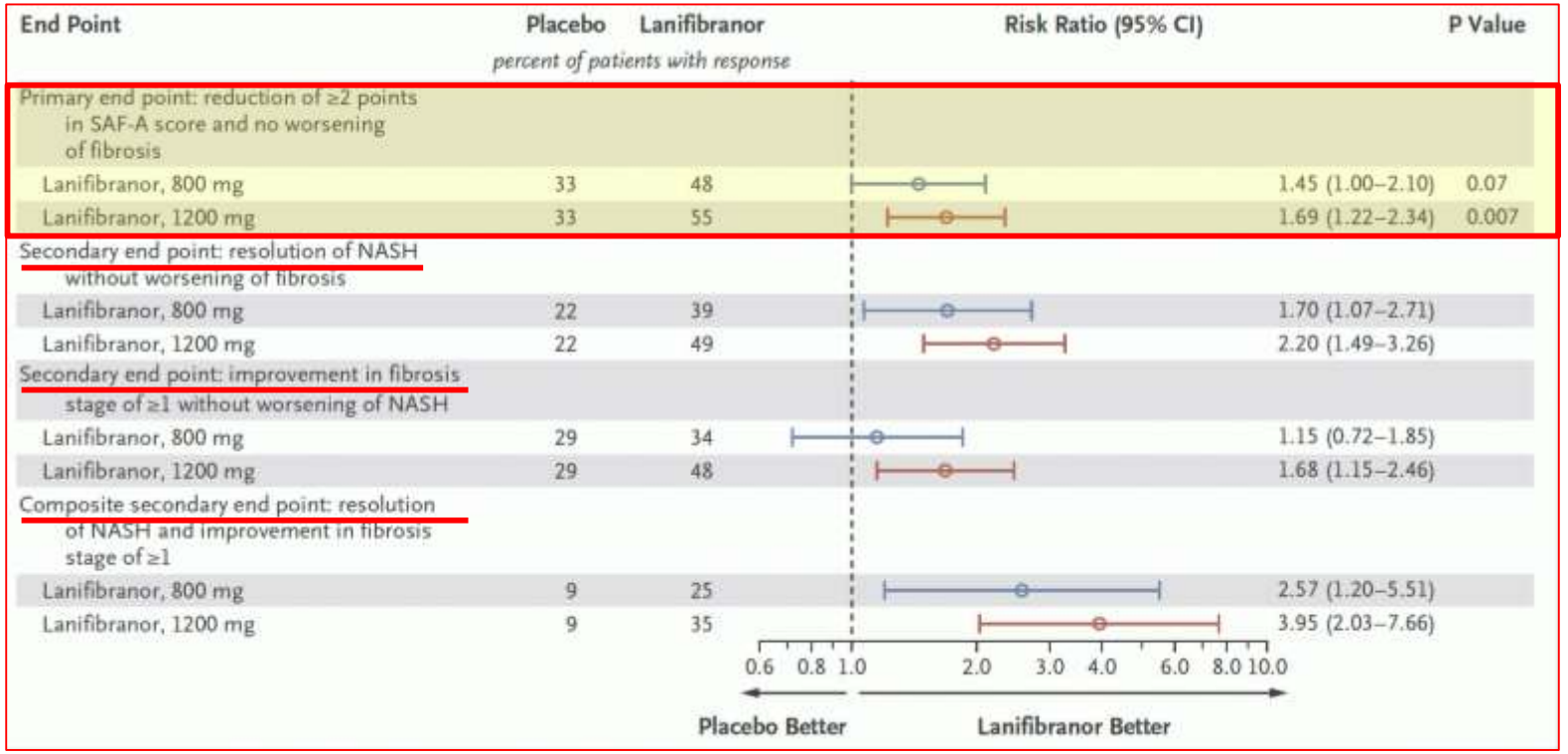
Semaglutide (GLP-1 agonist) Resolves NASH but does not Decrease Fibrosis in 72 Weeks



Phase 3 *REGENERATE* Trial of Obeticholic Acid for NASH

Endpoint	**Placebo (N=311)**	**OCA, 10 mg (n=312)**	**OCA, 25 mg (n=308)**
Fibrosis improvement (≥ 1 stage) with no NASH worsening	11.9%	**17.6%** **p=0.0446**	**23.1%** **p=0.0002**
ITT plus Stage 1 included	10.6% (n=407)	15.7% (n=407) p=0.0286	21.0% (n=404) p < 0.0001
NASH resolution with no worsening of fibrosis	8%	11.2% p=0.1814	11.7% p=0.1268
ITT plus Stage 1 included	7.9% (n=407)	11.3% (n=407) p=0.0903	14.9% (n=404) p =0.0013

Lanifibrinor (Pan PPAR agonist) Improves NASH Composite SAF Score after 24 weeks



Francque et al, *NEJM*, 2021

Unmet Needs – NASH Fibrosis 2022

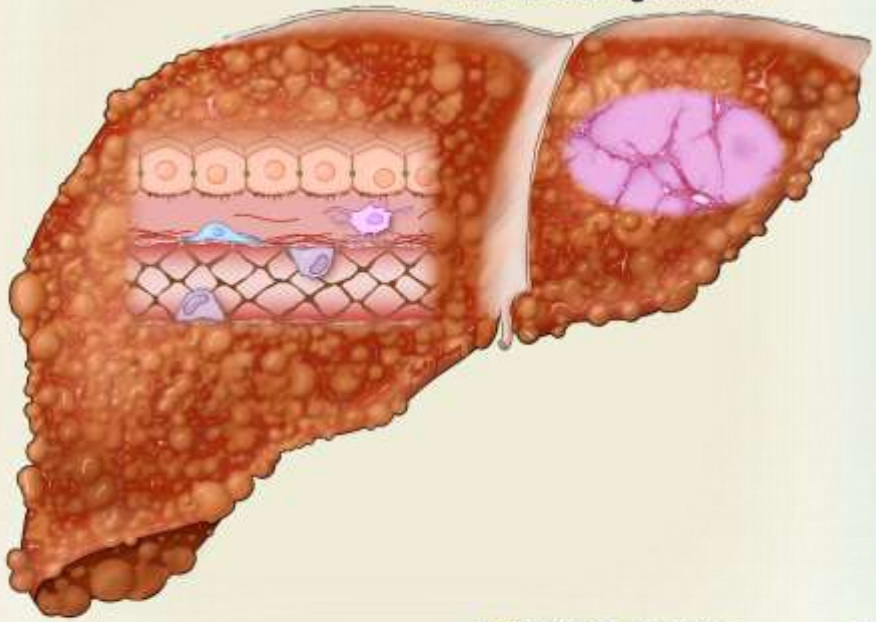
Basic → *Translational* → *Clinical*

Fibrotic microenvironment, cellular network beyond an HSC-centric view

ECM 3D-modeling of liver fibrosis

Fibrogenesis vs. fibrosis, angiogenesis, functional reserve and regeneration

Digital pathology, digital imaging and electronic patient records



Artificial intelligence to stratify cirrhosis

Etiology-specific matrisome drives fibrosis: new biomarkers

Disease-specific thresholds for clinically significant portal hypertension

Immune microenvironment of different chronic liver diseases

Metalloproteases and their regulation to maximize fibrosis regression

Data-driven rationales for combination therapies

Fibrosis regression: refine trial duration and end-points

Robust, efficient preclinical drug testing

Patient sub-grouping by using genetic, molecular and non-invasive markers

Hard end-points in clinical trials: does fibrosis regression translate into clinical benefit?

Summary: NASH Rx – Where do we stand?

1. Fibrosis drives outcomes in NASH and derives from activated hepatic stellate cells / myofibroblasts.

2. Biopsy is still the ‘gold standard’ but non-invasive dx’ics are improving, especially for screening and stratification.

3. Clinical translation is nearing reality, and drug approvals for NASH are coming soon. Combinations may be required to improve responses.