Advances in Understanding Hepatic Fibrosis and Chronic Liver Disease

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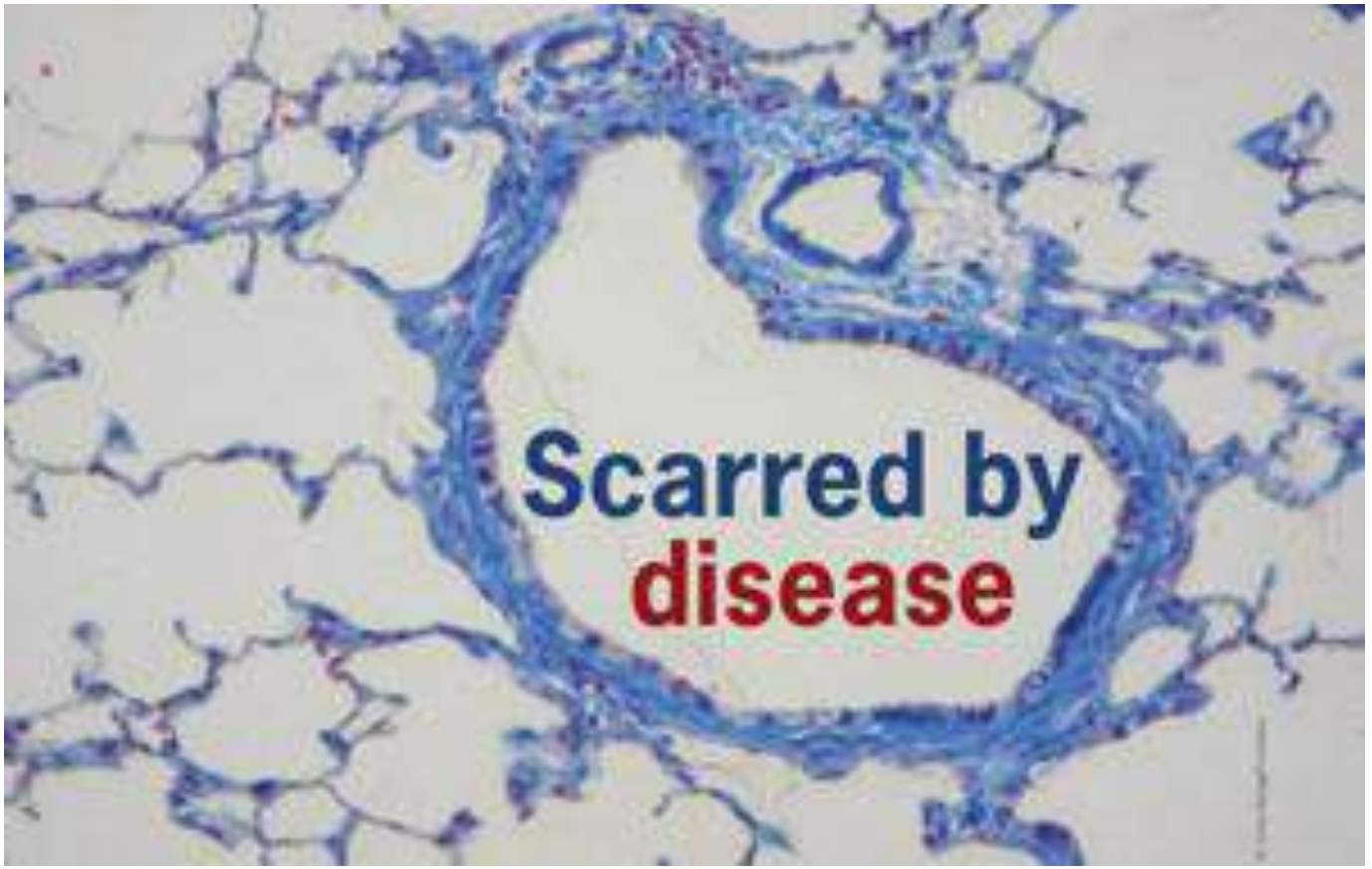
Mount Sinai

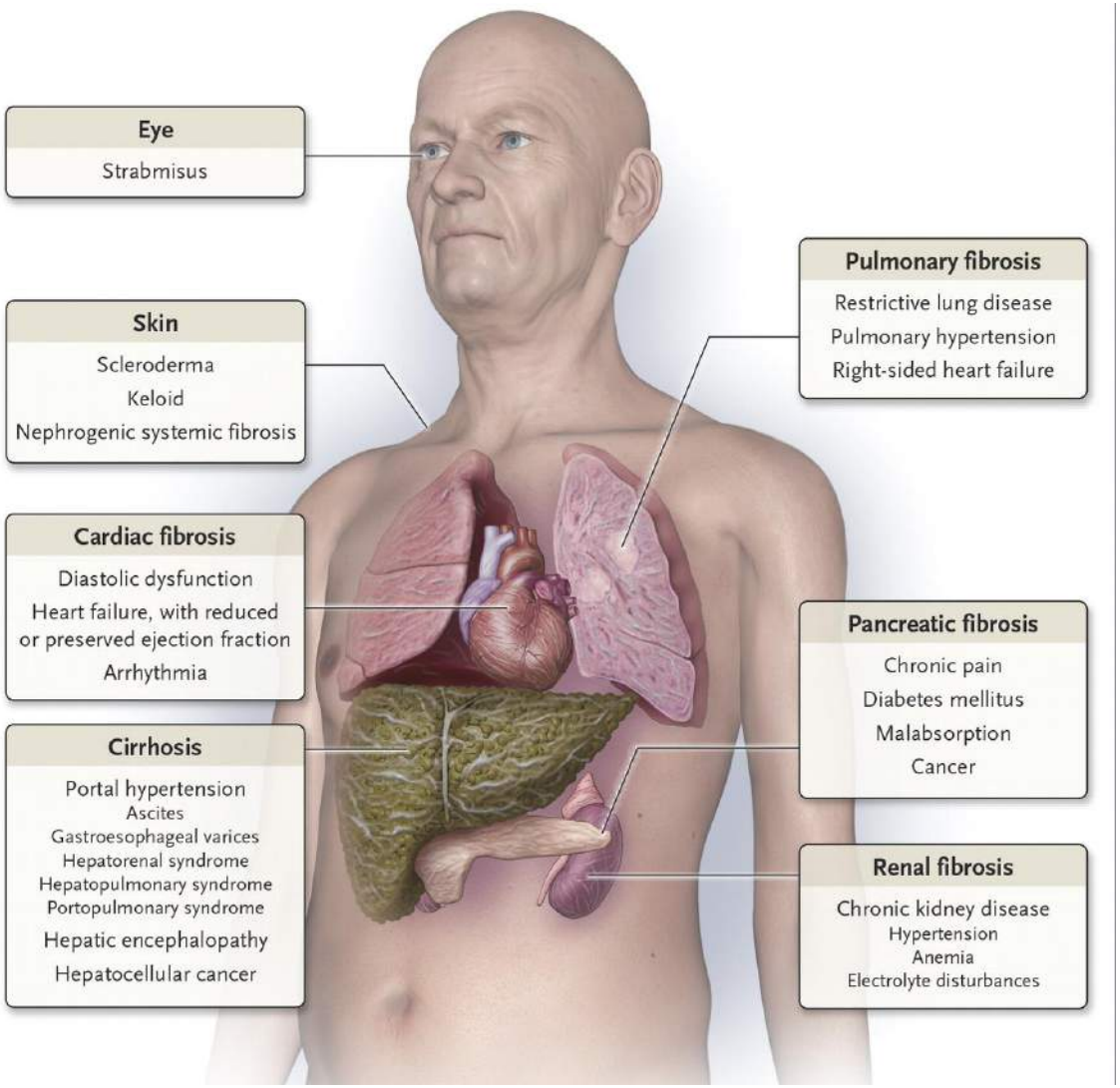
"Fibrosis accounts for ~45% of all deaths in industrialized nations"

-Wynn, T. J Pathol 214:199, 2008



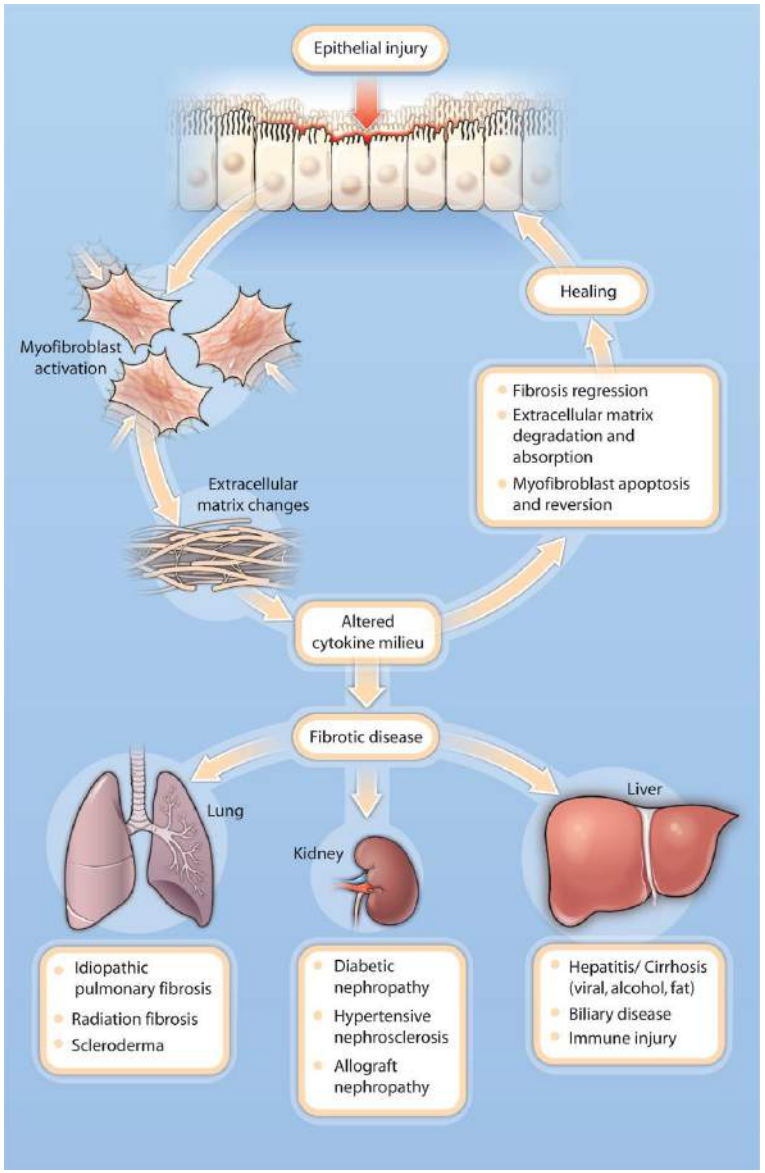
Nature Medicine, January 2011

Fibrosis Mechanisms are Similar in Different Organs



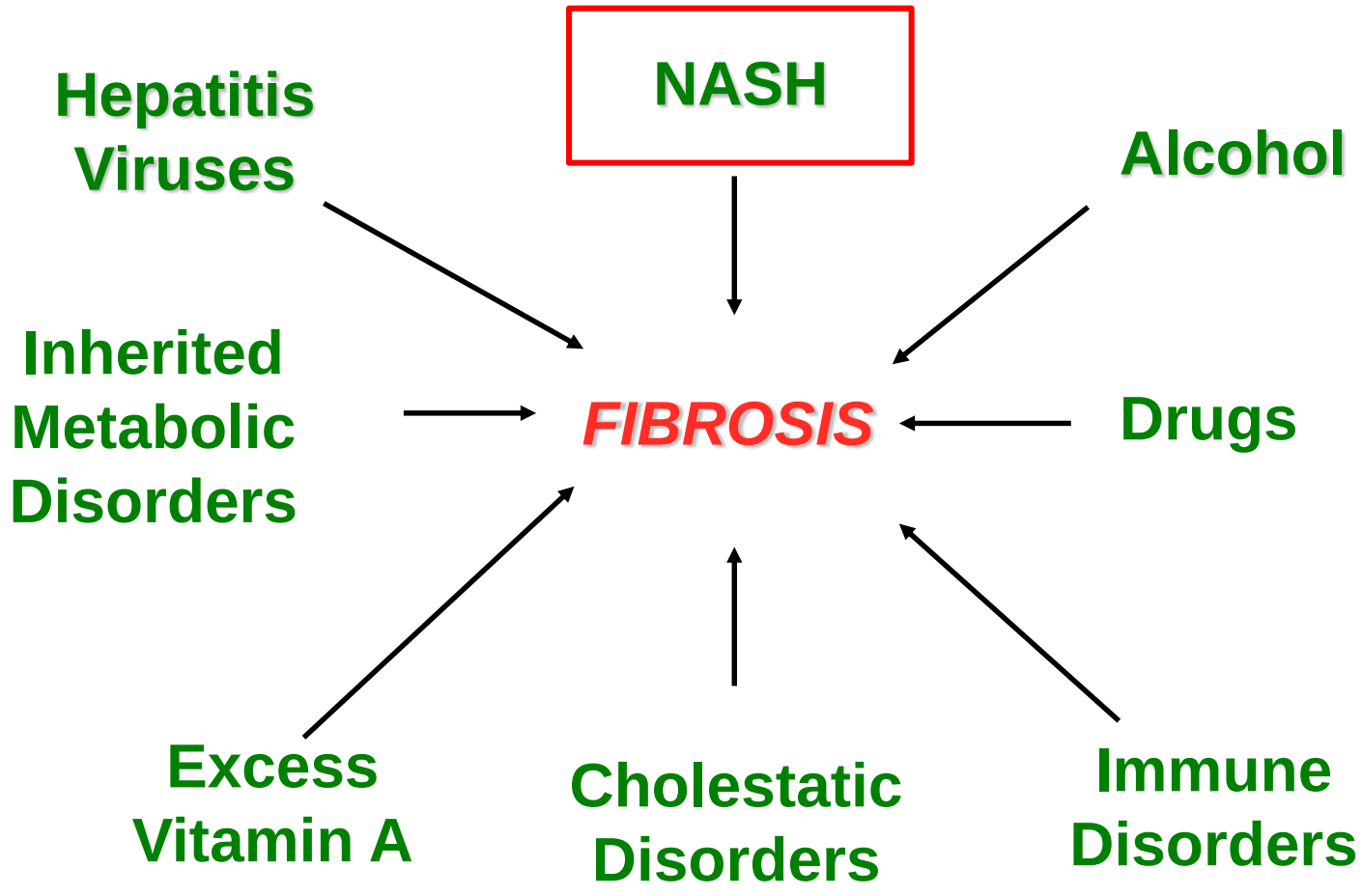
Rockey DC et al. N Engl J Med 2015;372:1138-1149.

Common Events in Fibrosis Progression and Regression Across Tissues

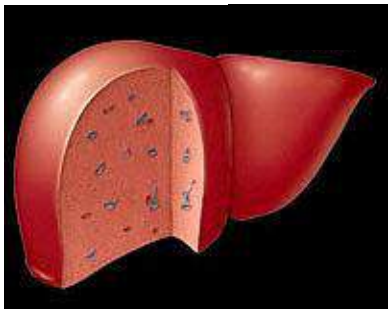


S. L. Friedman *et al.*,
***Sci Transl Med* 2013;5:167sr1-167sr1**

Fibrosis is a Common Pathway Among Different Etiologies of Liver Disease

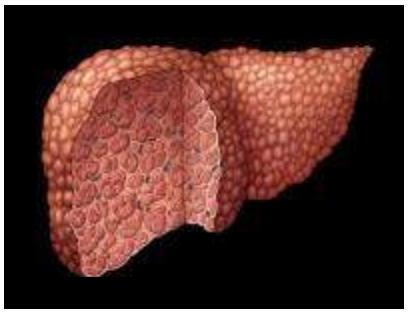


Natural History of Chronic Liver Disease



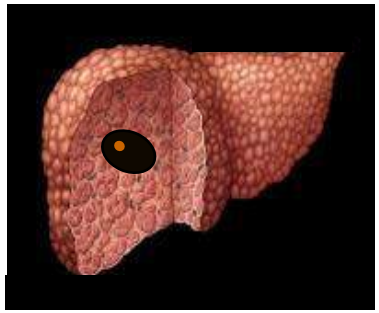
Normal liver

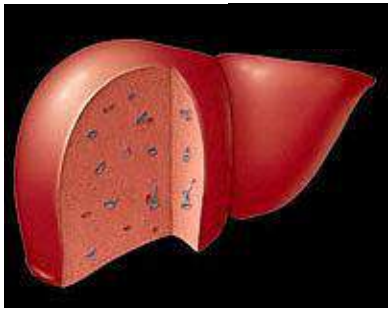
Chronic hepatitis with fibrosis
10-50 yrs



Cirrhosis

Hepatocellular Carcinoma

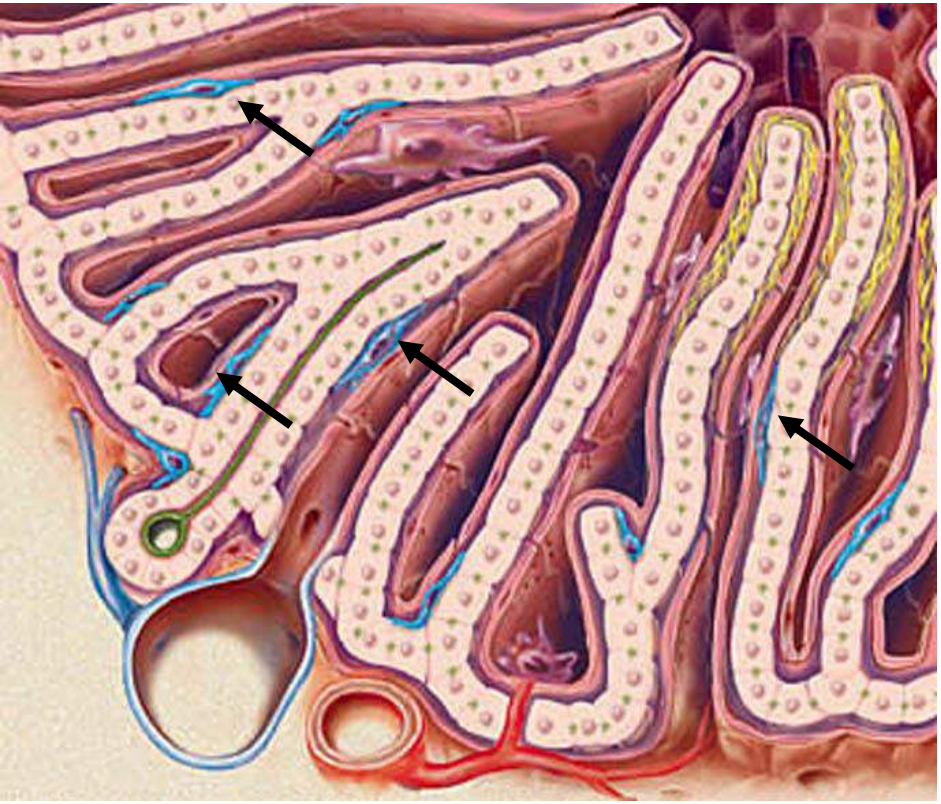


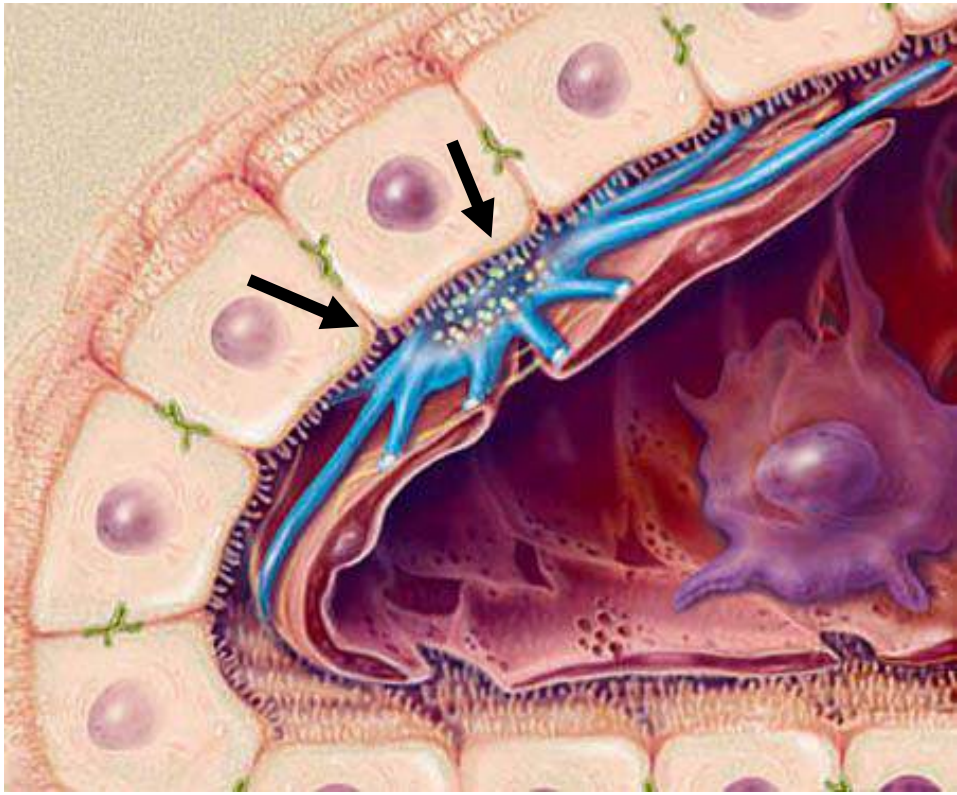


Liver Transplant

Chronic hepatitis - ~300 million worldwide
HCC - fastest rising tumor incidence

Hepatic Stellate cells - Perisinusoidal cells of Normal Liver

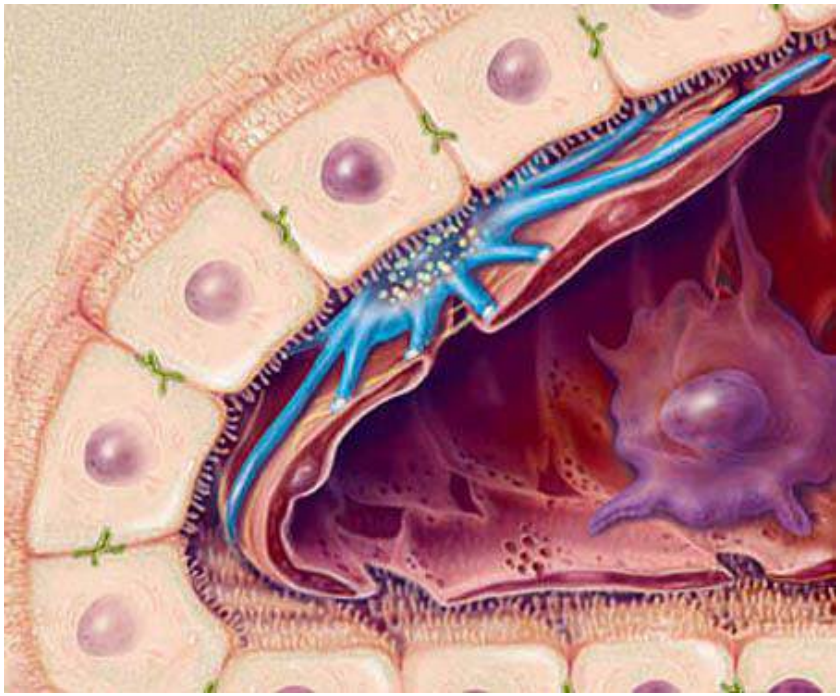




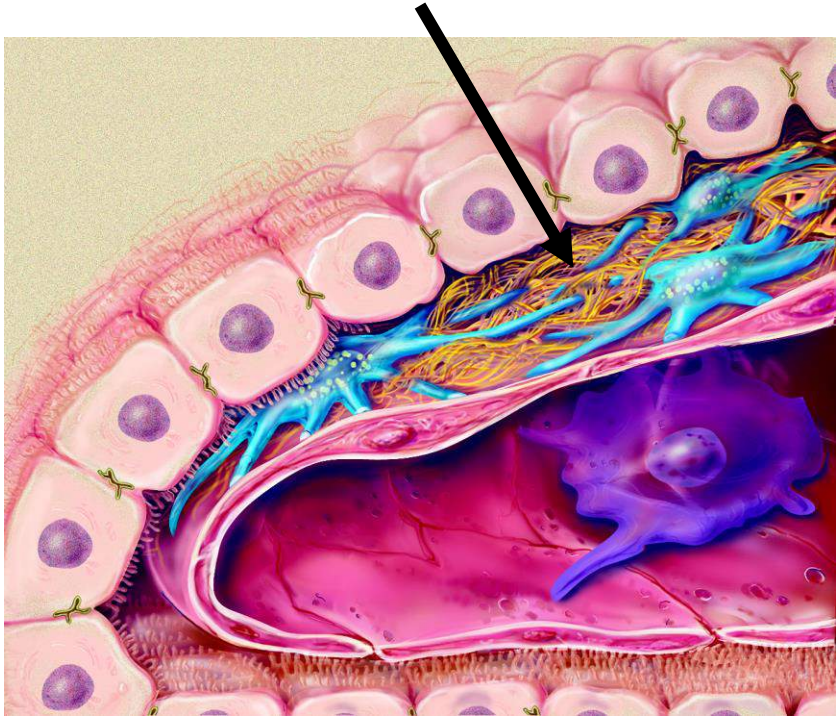
Friedman and Arthur, *Science & Medicine, 2002*

Hepatic Stellate cell Activation - *A Central Event in Liver Fibrosis*

Normal Liver

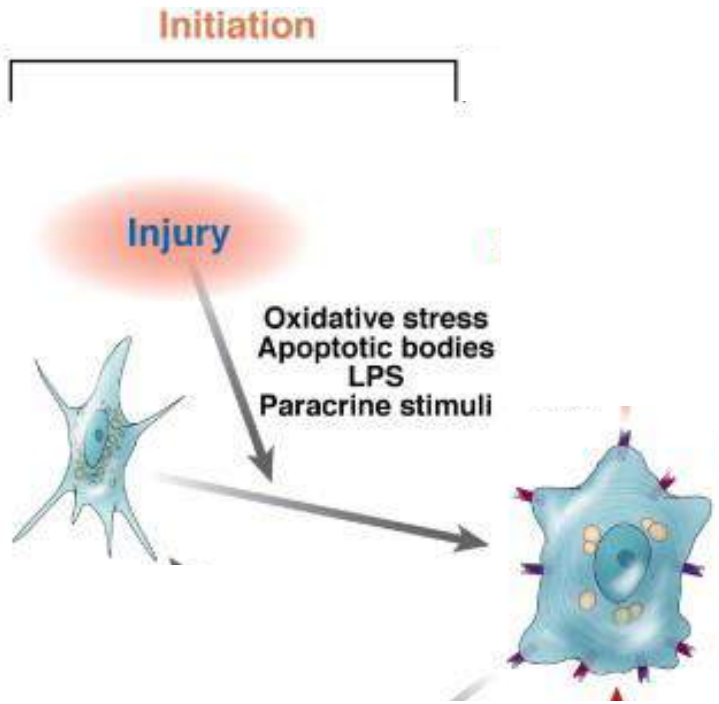


Activated HSC with Fibrosis

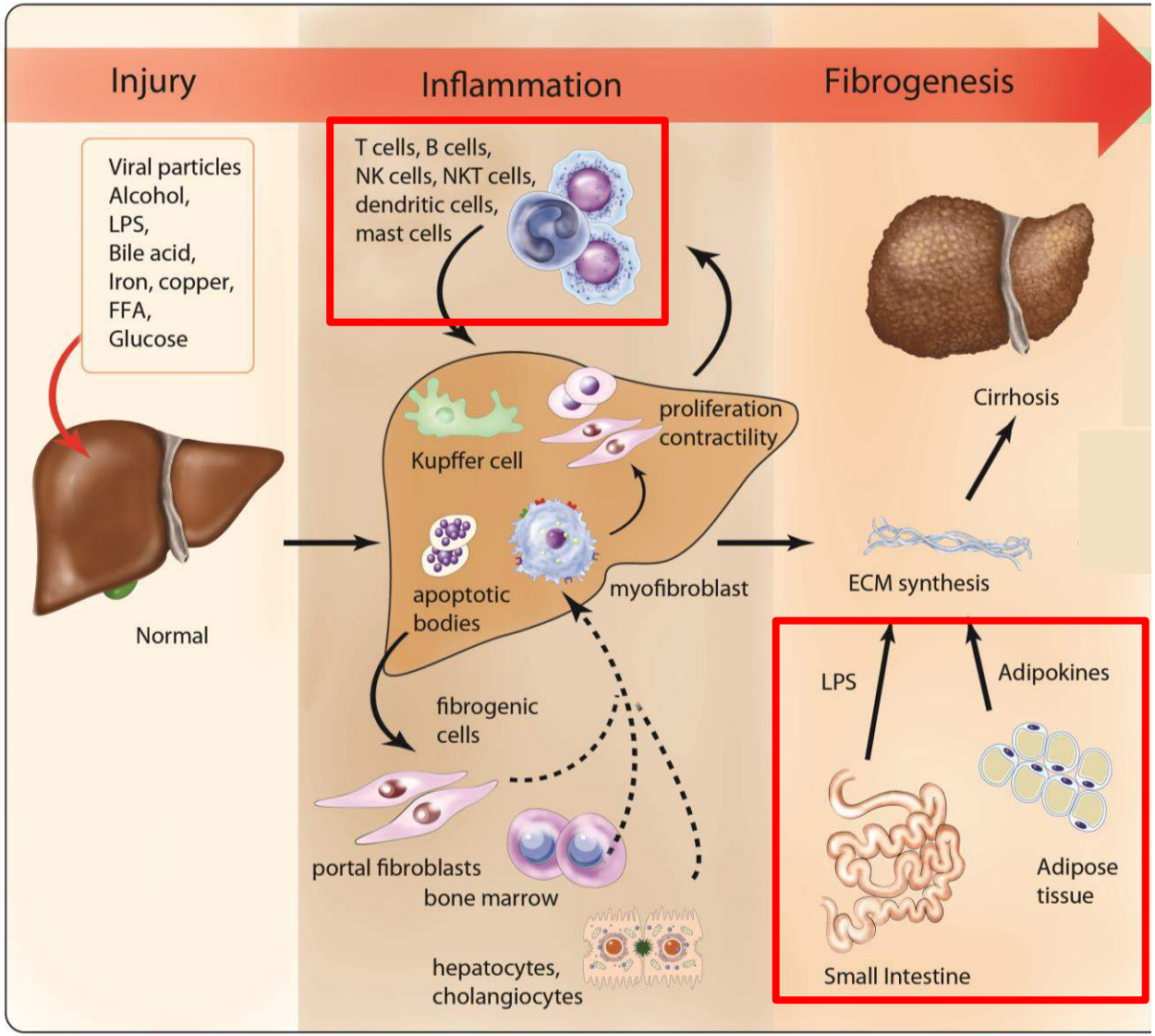


Friedman SL and Arthur, *Science and Medicine*, 2002

Pathways of Stellate cell Activation



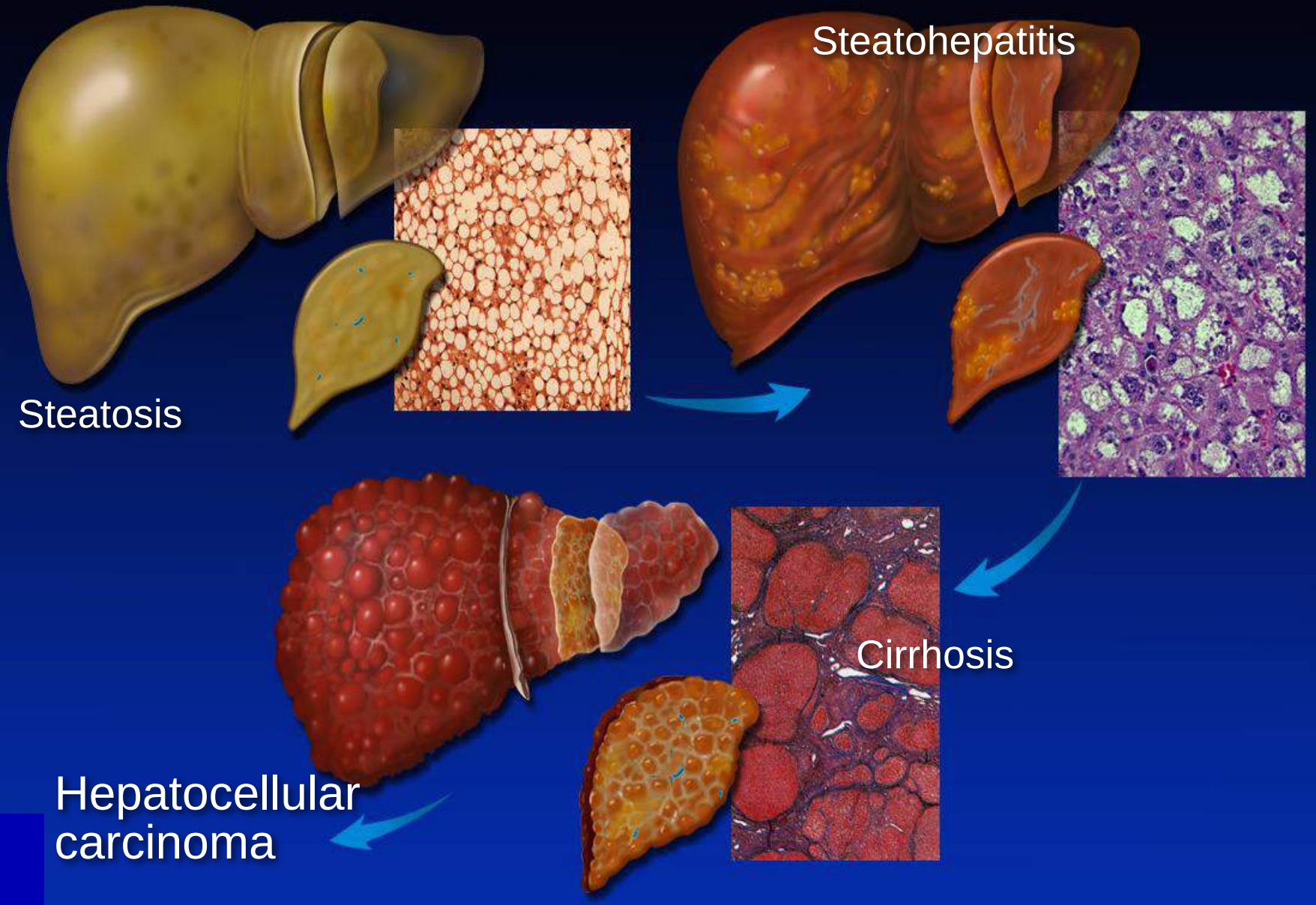
Pathogenesis of Hepatic Fibrosis - *Updates*



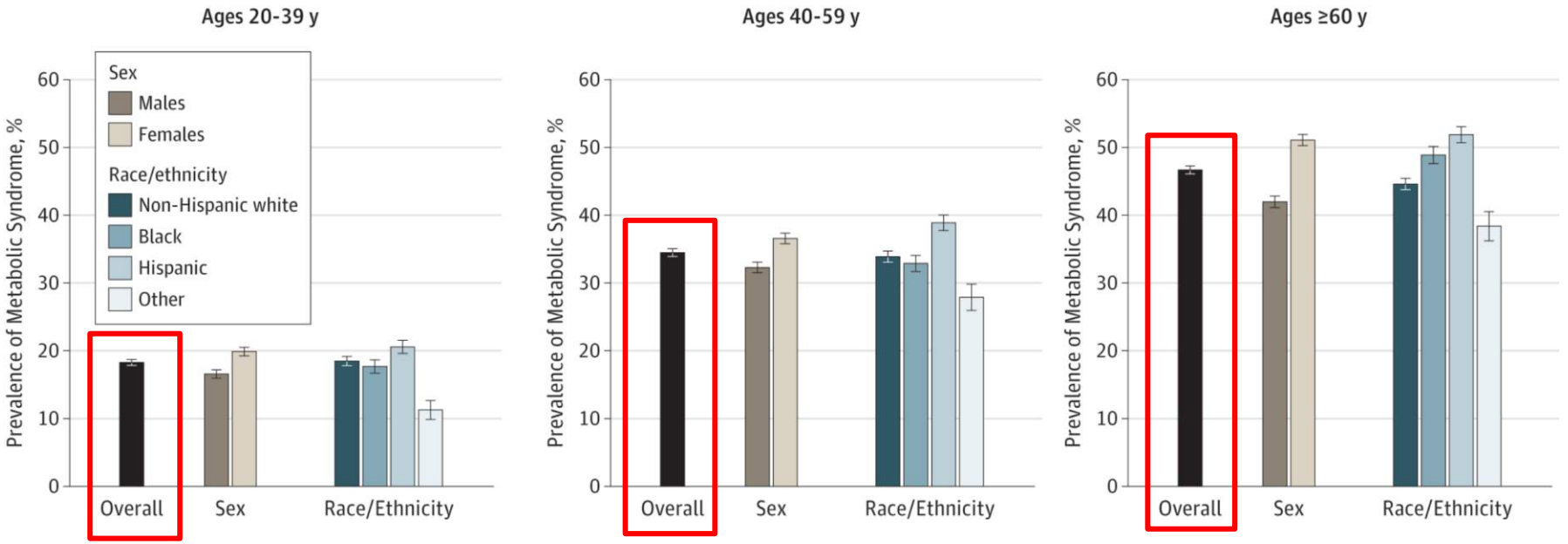
Cohen-Naftaly, Therapeutic Adv Gastro, 2012

Illustration by Alessandro Baliani (SAGE Publications Ltd)

NAFLD
Spectrum of Hepatic Pathology



Prevalence of the Metabolic Syndrome in the United States, 2003-2012, *NHANES data*



JAMA. 2015;313(19):1973-1974. doi:10.1001/jama.2015.4260

Prognostic Implications of NAFLD vs NASH

NAFLD

30% of population
10% of children

→ *> 10 years* → Cirrhosis 3%

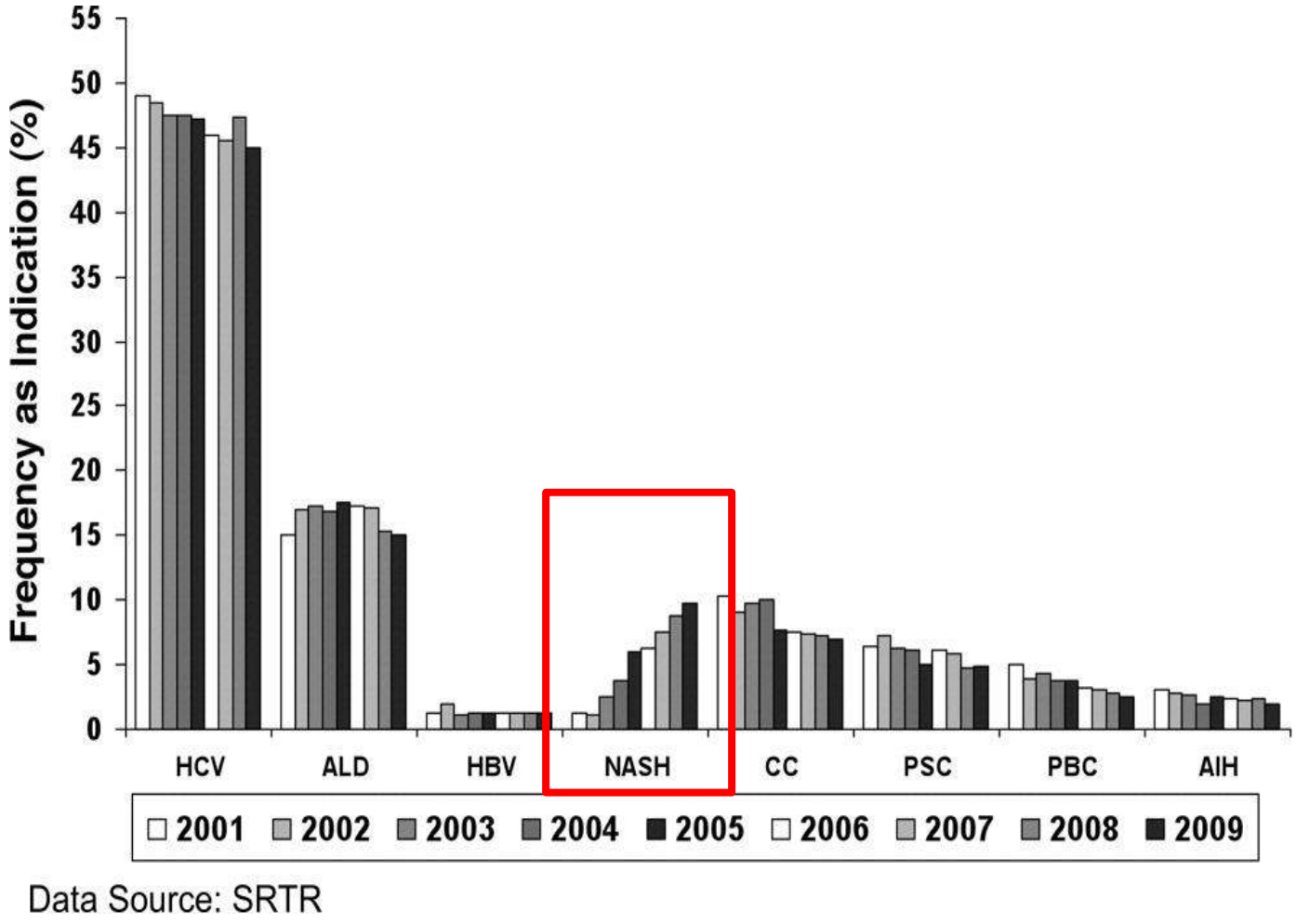
NASH + Fibrosis

7-8% of population

→ *5-10 years* → Cirrhosis 30%

More consistent and rapid progression to cirrhosis

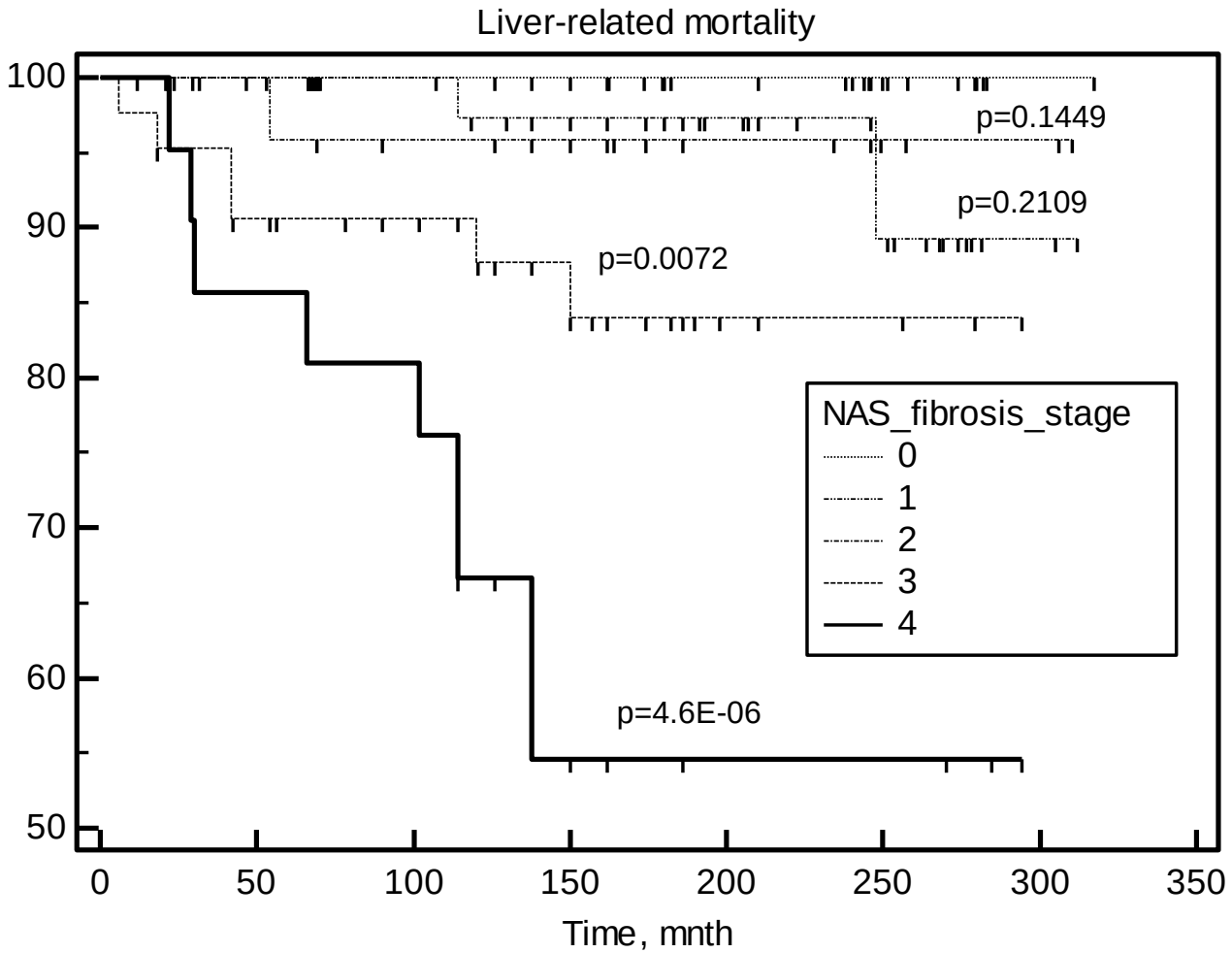
Changing Frequencies of HCV infection and NAFLD as Indications for Liver Transplantation in the U.S.



Charlton et al. Gastroenterology 141, 1249-1253, 2011

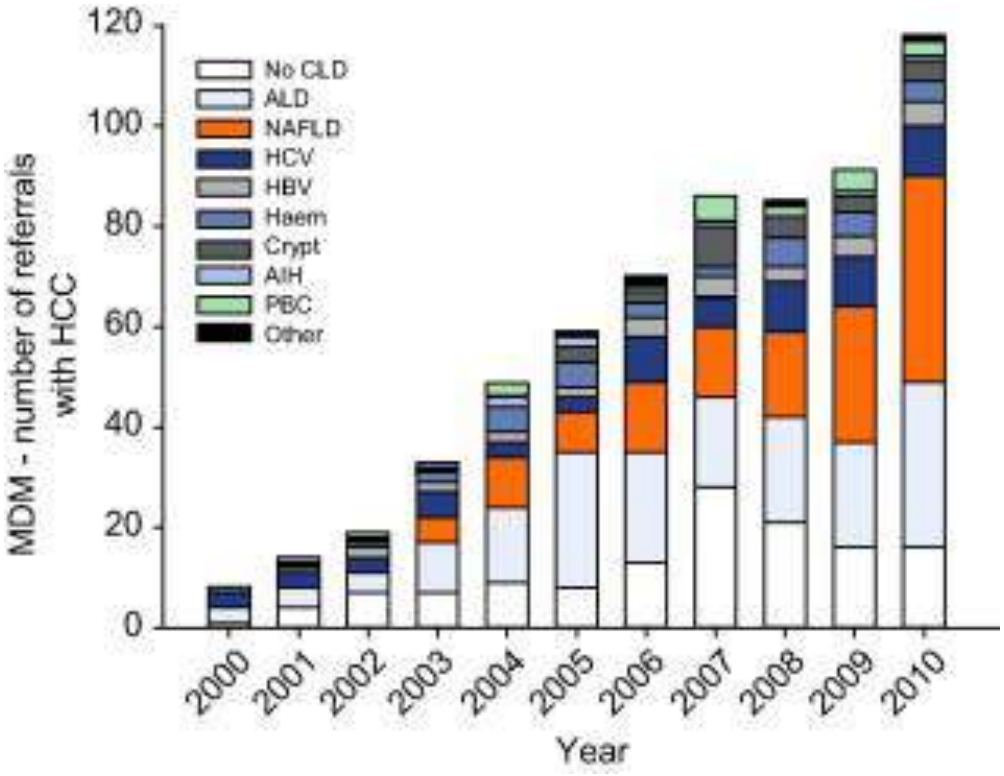
Fibrosis Drives Outcomes in NAFLD

Follow-up of 209 Patients – AFIP, 2010



Younossi Z, et al., *Hepatology* 53: 1874, 2011

Rising Contribution of NAFLD to HCC in Newcastle, UK



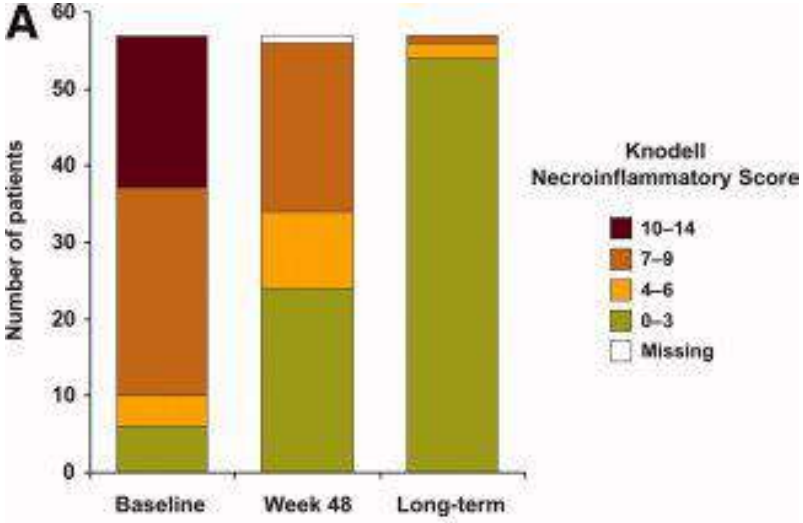
- NAFLD accounted for 34.8% of HCC
- 30% did not have cirrhosis

Dyson et al, *Journal of Hepatology*, Volume 60, 110 – 117, 2014

Hepatic Fibrosis is Reversible!

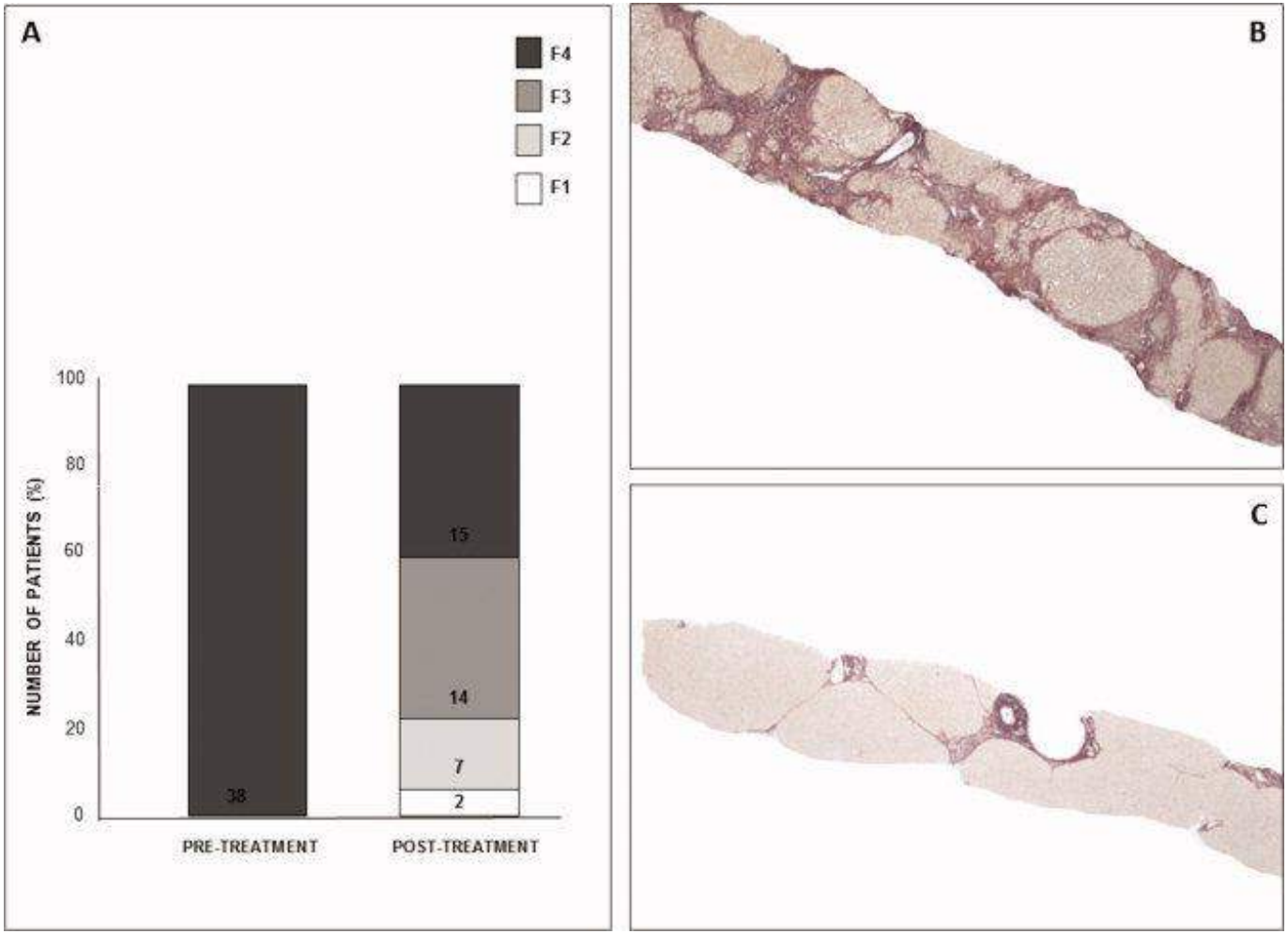
- There are no specific anti-fibrotic therapies yet, BUT
- Treatment of the underlying disease is often a very effective antifibrotic (e.g, HBV, HCV)
- These findings indicate that *the liver has innate pathways to resorb scar, providing clues to mimicking endogenous pathways with novel therapies*
- Recent pre-clinical and clinical data support that *cirrhosis* is also reversible

Improvement in Necroinflammation and Fibrosis from Long-term Entecavir Therapy



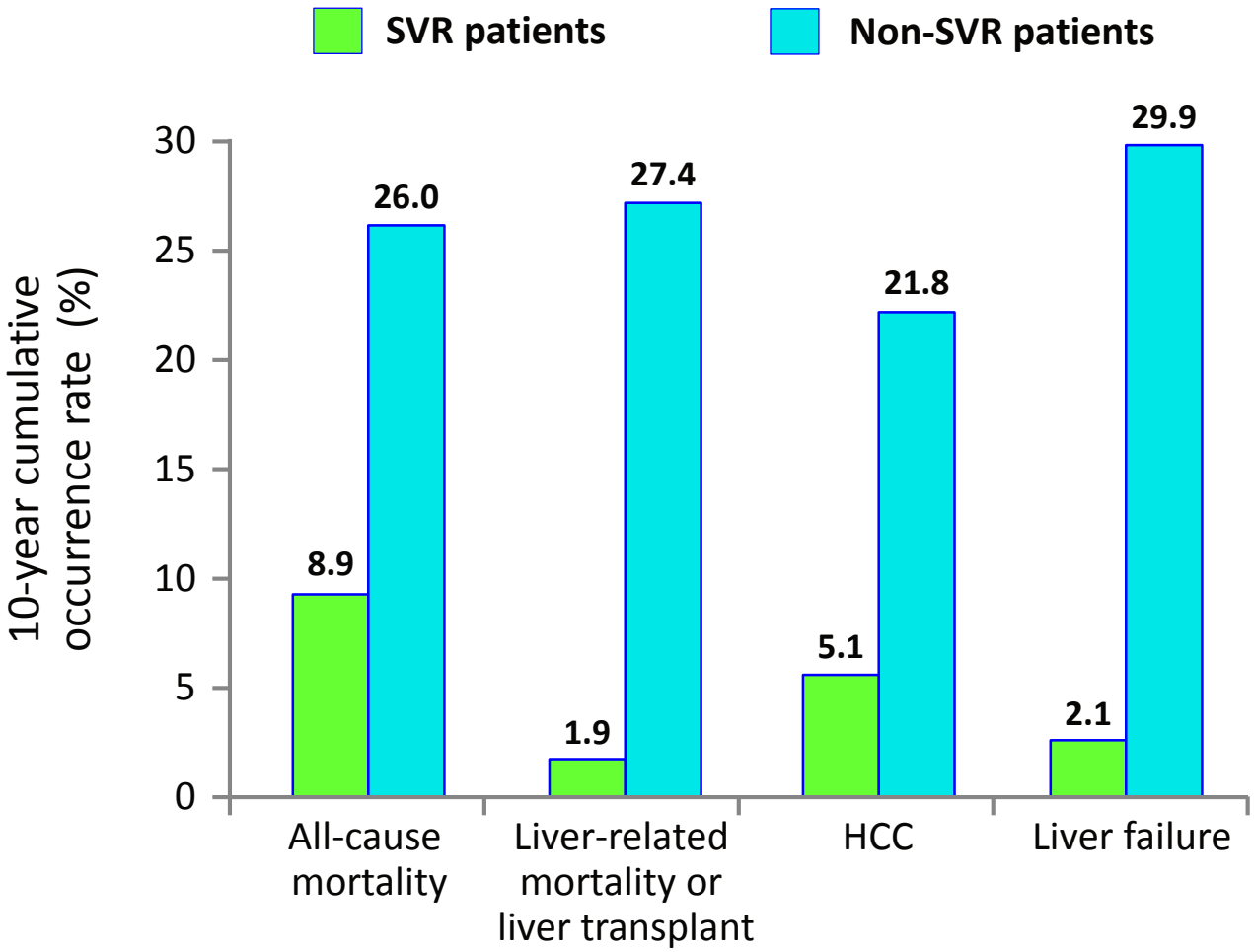
Chang, Hepatology , 2010

Cirrhosis Regression in HCV following Sustained Virologic Response



D'ambrosio et al. *Hepatology*, 56, (2): 532-543, 2012

SVR and All-cause Mortality in Chronic HCV Patients with Advanced Fibrosis



Baseline factors significantly associated with all-cause mortality:

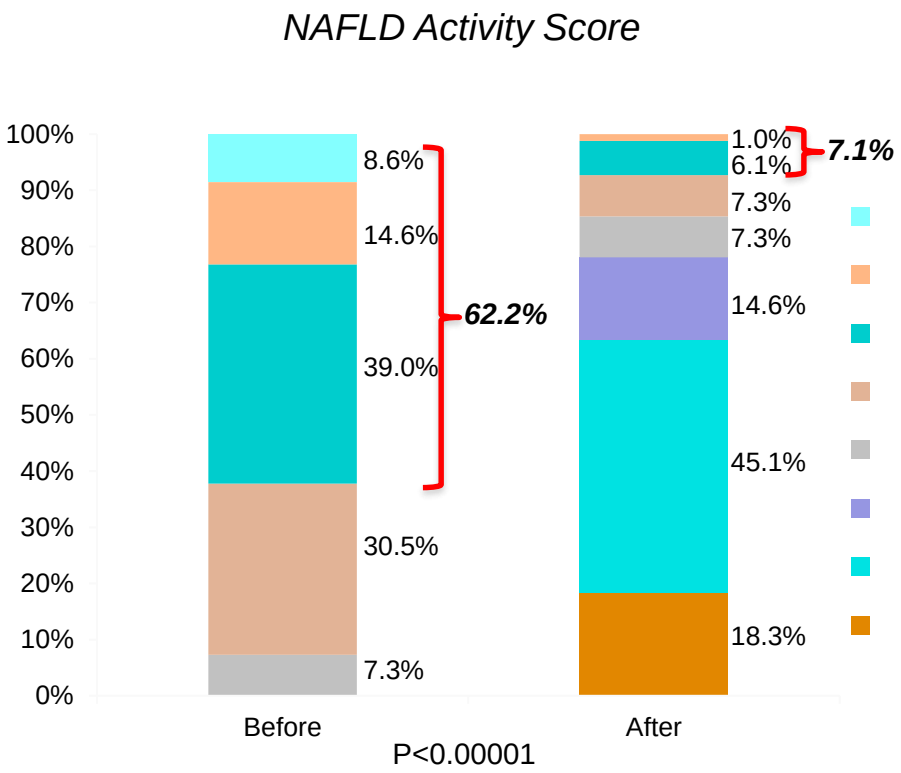
- Older age
- **Genotype 3 (2-fold increase in mortality and HCC)**
- Higher Ishak fibrosis score
- Diabetes
- Severe alcohol use

530 patients followed for a median of 8.4 years

Van der Meer A, *et al. JAMA* 2012; 308:2584–2593.

Effect of Bariatric Surgery on NASH

Impact on histology at 1 year after bariatric surgery (82 pts):



Lassailly , Mathurin et al, ***AASLD Abstract #213****, 2014.*

Determinants of Reversibility

Duration of injury and fibrosis:

- *More rapid onset ➔ more likely regression*

Extent and type of cellularity of the scar:

- *More cells ➔ more sources of proteases*

Cross-linking of the scar:

- *More cross-linking (lysyl oxidase, Ttg) ➔ more insoluble*

Thickness of the fibrotic bands:

- *Thicker septae ➔ more inaccessible to proteases*

Balance of proteases (MMPs) and inhibitors (TIMPs):

- *High TIMP levels may impede regression*

Other factors?

- *Genetic determinants of regression?*
- *Underlying etiology?*

Diagnostic Goals -
Establish Severity

Liver Biopsy remains the 'Gold standard'

- Use *Brunt/Kleiner NASH Activity Score (NAS)*:
  - steatosis
  - ballooning
  - lobular inflammation
  - (fibrosis)

BUT, sampling variability > 40% !

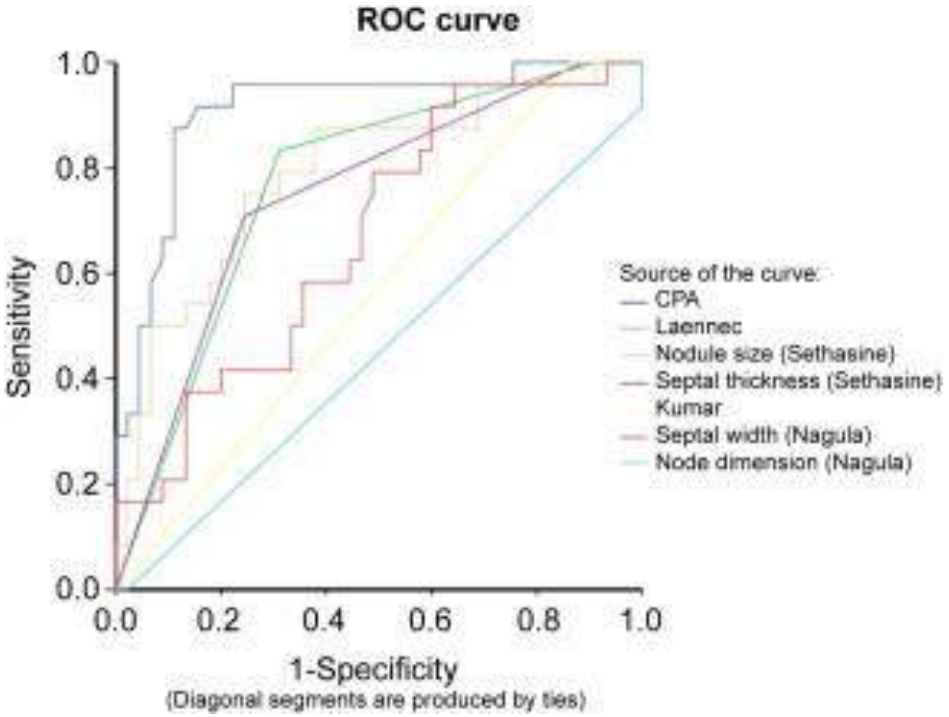
NAFLD Activity Score (NAS)

Item	Score	Extent
Steatosis	0	<5%
	1	5–33%
	2	>33–66%
	3	>66%
Lobular inflammation	0	No foci
	1	<2 foci/200x
	2	2–4 foci/200x
	3	>4 foci/200x
Hepatocyte ballooning	0	None
	1	Few balloon cells
	2	Many cells/prominent ballooning

Measuring Fibrosis – Collagen Proportionate Area (CPA)

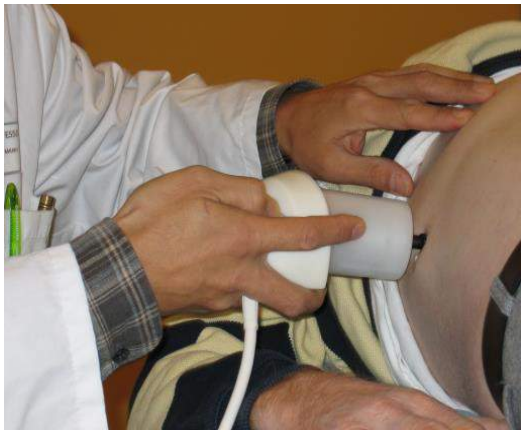
Without decompensation

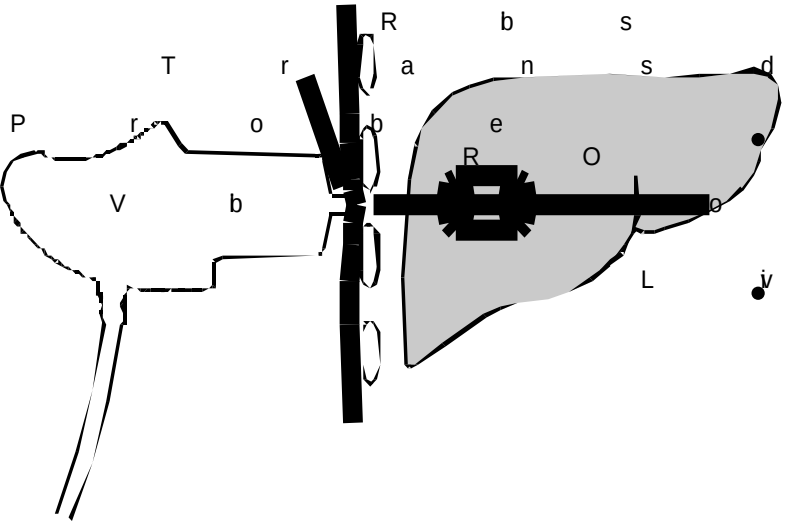
With decompensation



Tsochatzis et al, *Journal of Hepatology*, Volume 60: p. 948, 2014

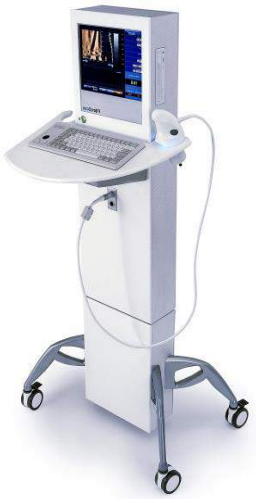
Fibrosis Assessment with Fibroscan®





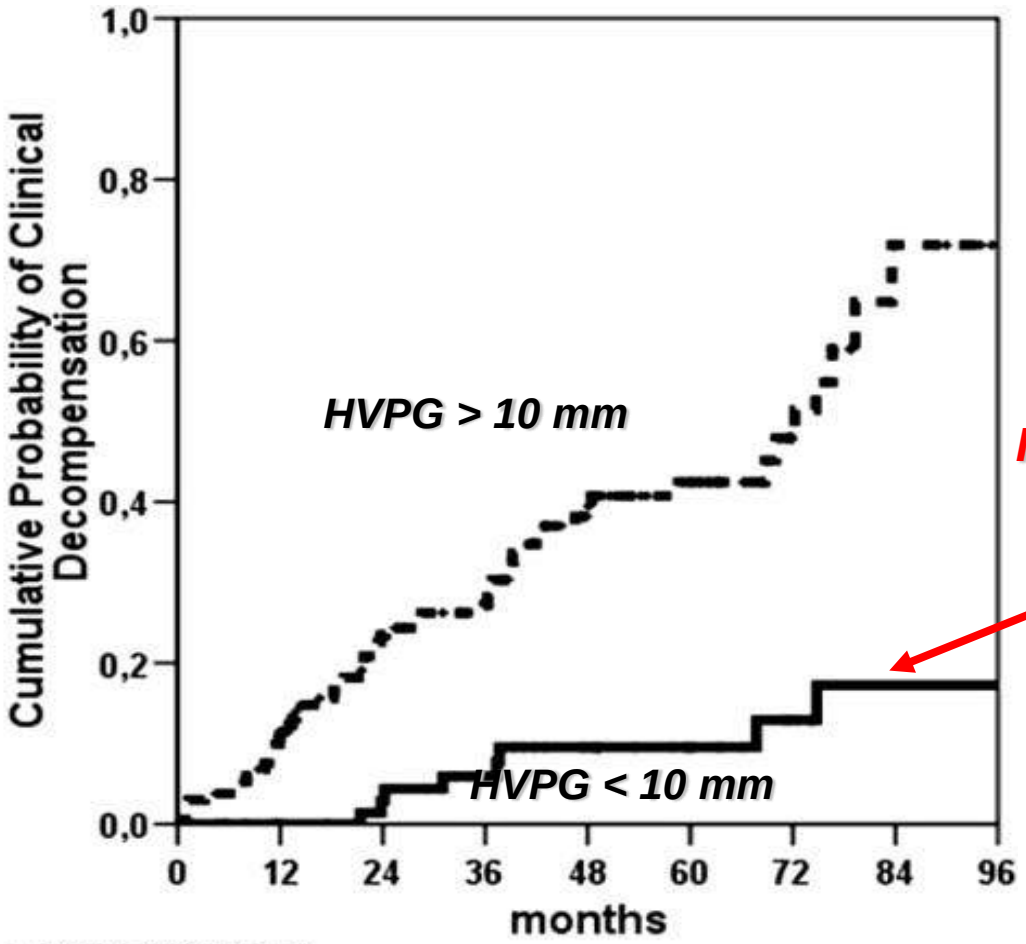
- Measurements are performed on the
- **right lobe** of the liver in **intercostal** position
- The **patient** is lying supine with the right arm placed behind his head
- Examination time is about **5 minutes**
- **Interobserver reproducibility**

  CVS < 10 %,



Courtesy of M. Ziol

HVPG Predicts Clinical Deterioration in Cirrhosis



HVPG <10 mmHg							
At risk	79	72	66	55	44	32	14
Events	0	0	2	4	6	6	8
HVPG ≥ 10 mmHg							
At risk	134	112	86	73	49	34	3
Events	0	15	29	33	44	47	54

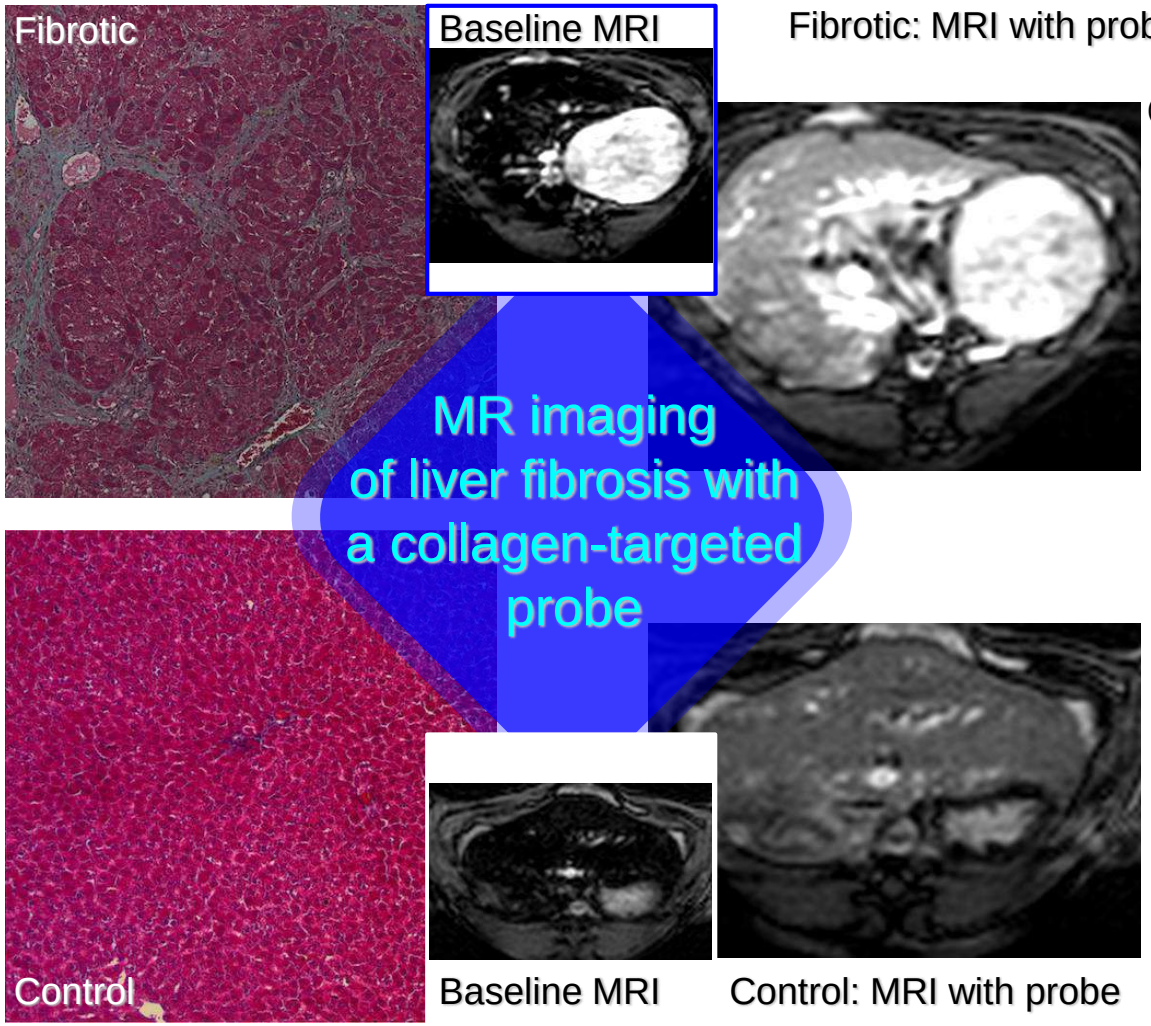
If HVPG < 10 mm, then only ~15% chance of decompensation over 8 yrs

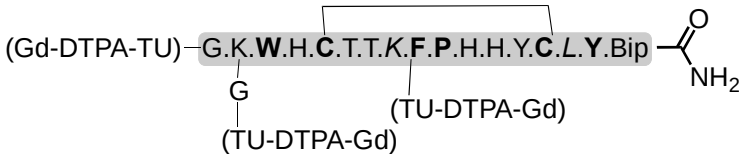
Ripoll et al, *Gastroenterology*, 2007

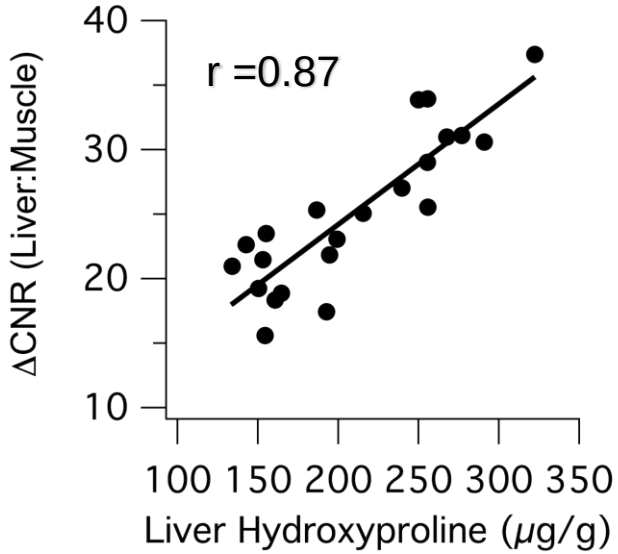
Quantitative Function Tests in Liver Disease - ? Correlation with HVPG

- Cholate clearance
- Indocyanine green clearance
- Methacetin breath test
- MEGX
- Galactose elimination
- Methionine breath test

MRI Quantification of Hepatic Fibrosis Using a Novel Collagen-Binding Probe







Peter Caravan

Polasek et al. J Hepatol. 2012, doi 10.1016/j.jhep.2012.04.035

Regulatory Challenges In Developing Novel Drugs for Inflammation and Fibrosis

1. Liver biopsy is the standard, but needs to be replaced or complemented by non-invasive markers.

2. Surrogate markers that correlate with clinical outcomes are sorely needed. These may include:
   - Functional tests (incl. HVPG, breath tests, cholate clearance)
   - Novel imaging tests that quantify collagen or fibrolytic enzymes (e.g., lysyl oxidase 2).
   - Tests to measure fat fraction (MR proton density, CAP)

3. Trials in non-cirrhotic patients cannot be powered for clinical outcomes as they will take too long.

How to Shorten the Path to New Anti-fibrotic Drugs?

- Re-purpose existing drugs:
  - Angiotensin receptor blockers
  - Tyrosine kinase inhibitors
  - Develop combination drug trials with new + existing agents
  - Other drugs: National Center for Advancing Translational Science (NCATS) repurposing initiative – *http://www.ncats.nih.gov*
- Identify new biomarkers that can reveal earlier evidence of activity
  - Serum markers (e.g, LOXL2)
  - MR imaging to quantify hepatic collagen
- Develop new clinical trial designs

What are the Features of an Ideal Antifibrotic Trial?

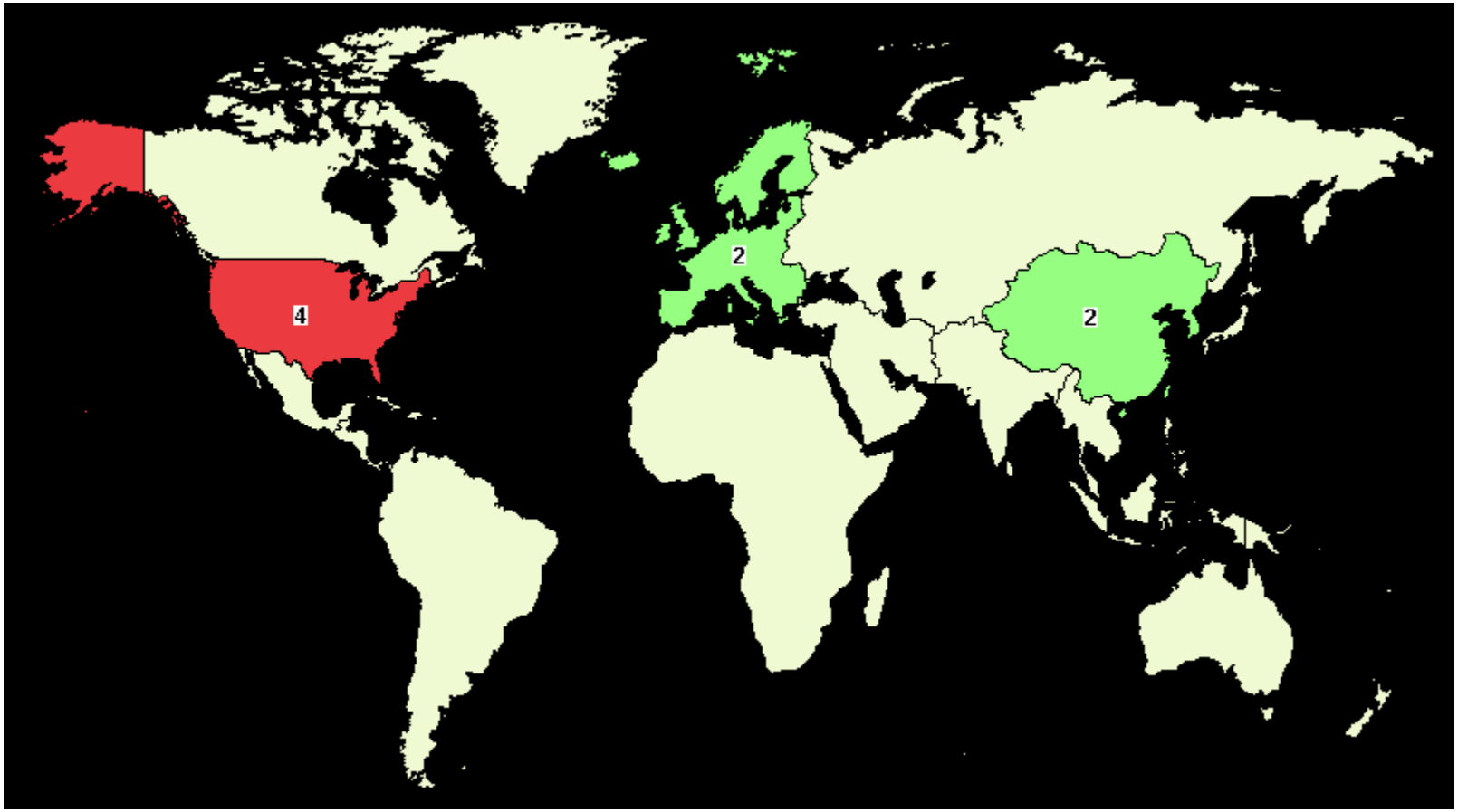
- Optimize selection of a treatment population
  - Use genetic markers to stratify based on risk of progression
  - Establish other markers of progression risk

- Attack molecular targets that are critical to disease pathogenesis
  - Strong validation in human liver
  - Relevant animal models that recapitulate features of human disease

- Establish and apply validated biomarkers that provide early and reliable readouts of drug efficacy

Therapeutic landscape for NASH: one year ago

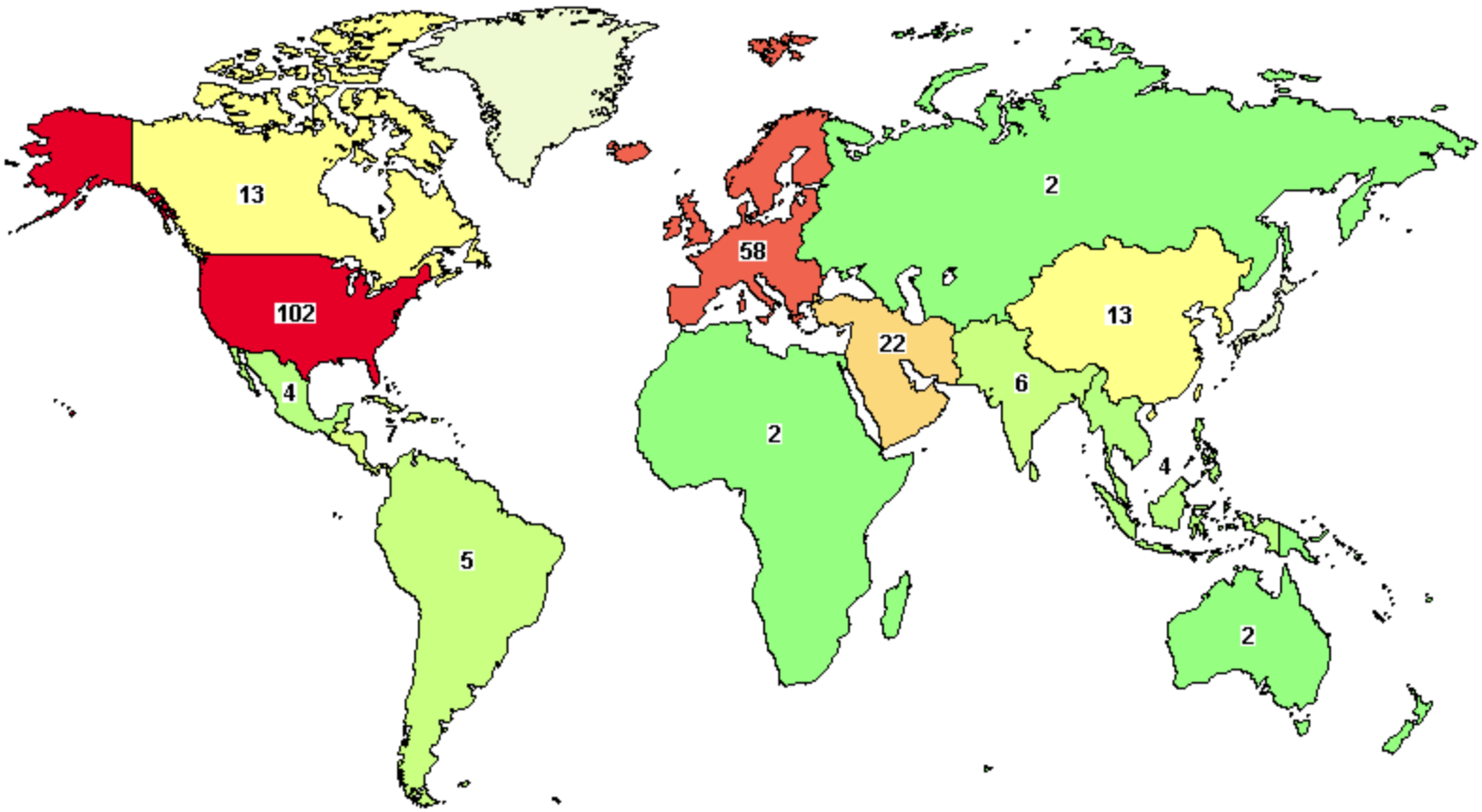
Actively recruiting Phase 2 trials for treatment of NASH



Clinical trials.gov on April 29, 2013

Therapeutic landscape for NASH: Now

Actively recruiting Phase 2 trials for treatment of NASH



Clinical trials.gov on Oct 22, 2014

Core vs. Regulatory Pathways

■ BENCH TO BEDSIDE

Expressway to the core of fibrosis

VOLUME 17 | NUMBER 5 | MAY 2011 NATURE MEDICINE

Wajahat Z Mehal, John Iredale & Scott L Friedman

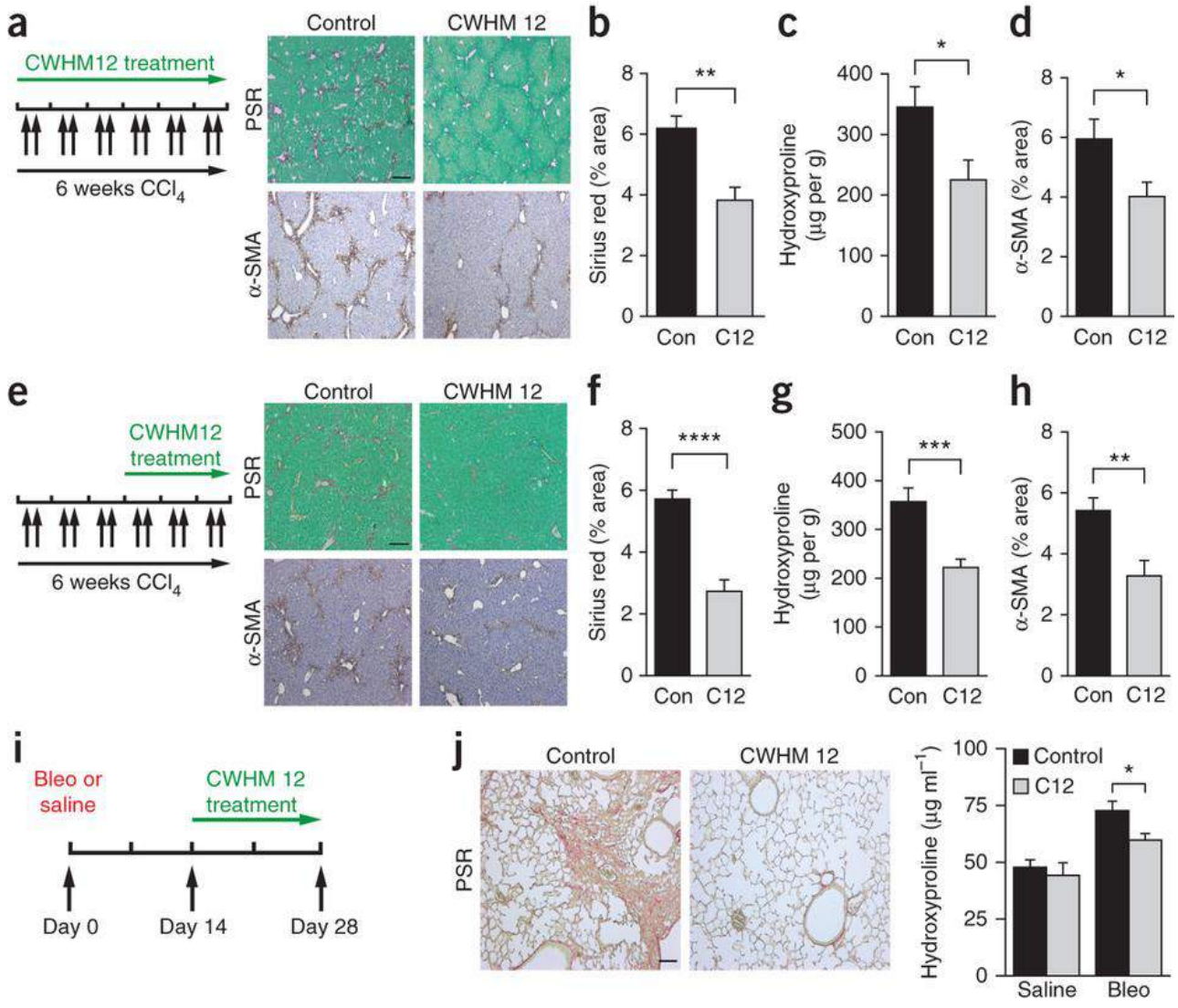
Core:

- common to ≥2 tissues and species
- earlier evolutionary role
- essential for fibrosis

Regulatory:

- affect fibrosis, but more variability between species and tissues

αv Integrin – A Core Pathway of Fibrosis



Blockade of αv integrins by a small molecule (CWHM 12) attenuates liver and lung fibrosis.

Henderson et al, Nature Med, 19, 1617–1624 (2013)

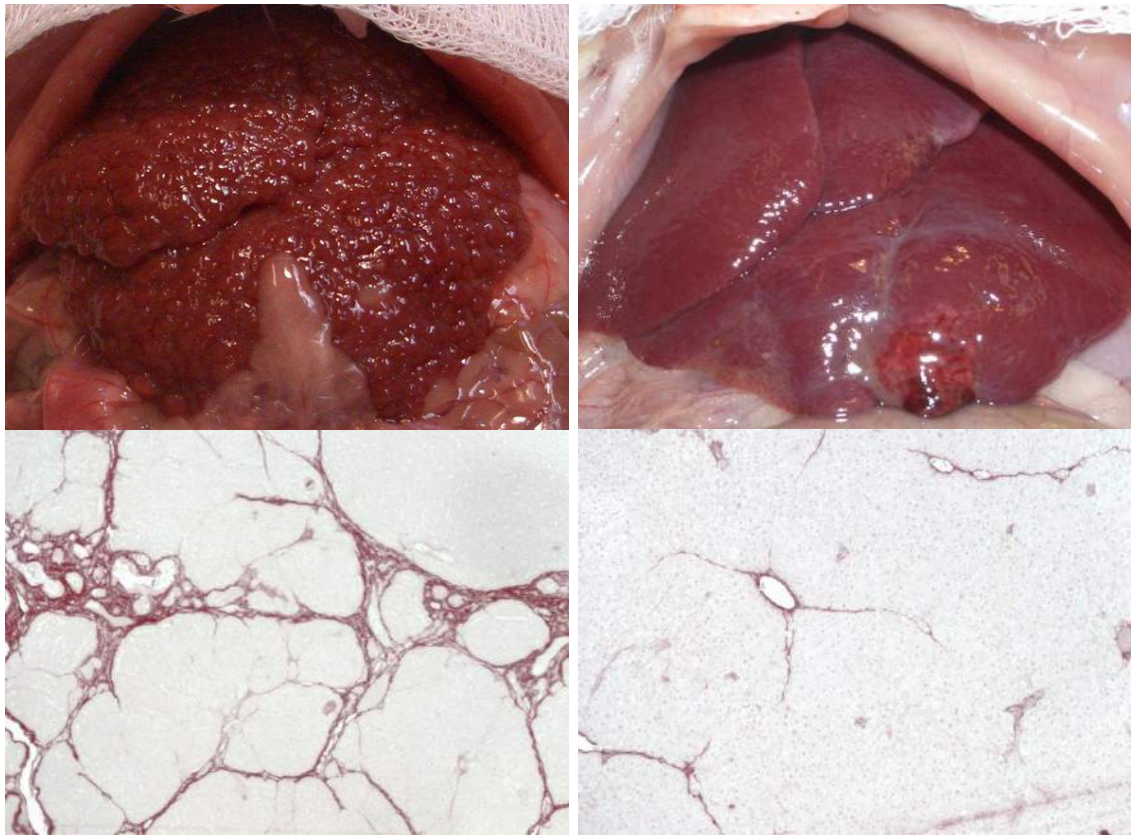
Therapies for Hepatic Fibrosis in Clinical Trials

1. Reduce primary disease (antivirals)
2. Reduce tissue injury and foster epithelial repair by:
   - Epithelial protectants (FXR ligands, HGF, antioxidants, PPAR α, δ, or γ agonists)
   - Anti-inflammatory agents (esp. chemokine antagonists)
   - Inflammatory cell modulation (macrophage polarization rx.)
3. Block myofibroblast proliferation, contractility & angiogenesis (tyrosine kinase antagonists)
4. Antagonize fibrogenic cytokines and signaling (TGFβ1, CTGF antagonism; si-HSP47; hedgehog antagonists)

   Promote apoptosis or reversion of myofibroblasts
6. Stimulate metalloprotease activity by:
   - Antagonize TIMPs (MoAb to TIMP-1)
   - Enhance MMP activity (block collagen cross linking by LOXL2)

FXR ligand (OCA) Reverses Fibrosis in TAA-Induced Liver Disease in Rats

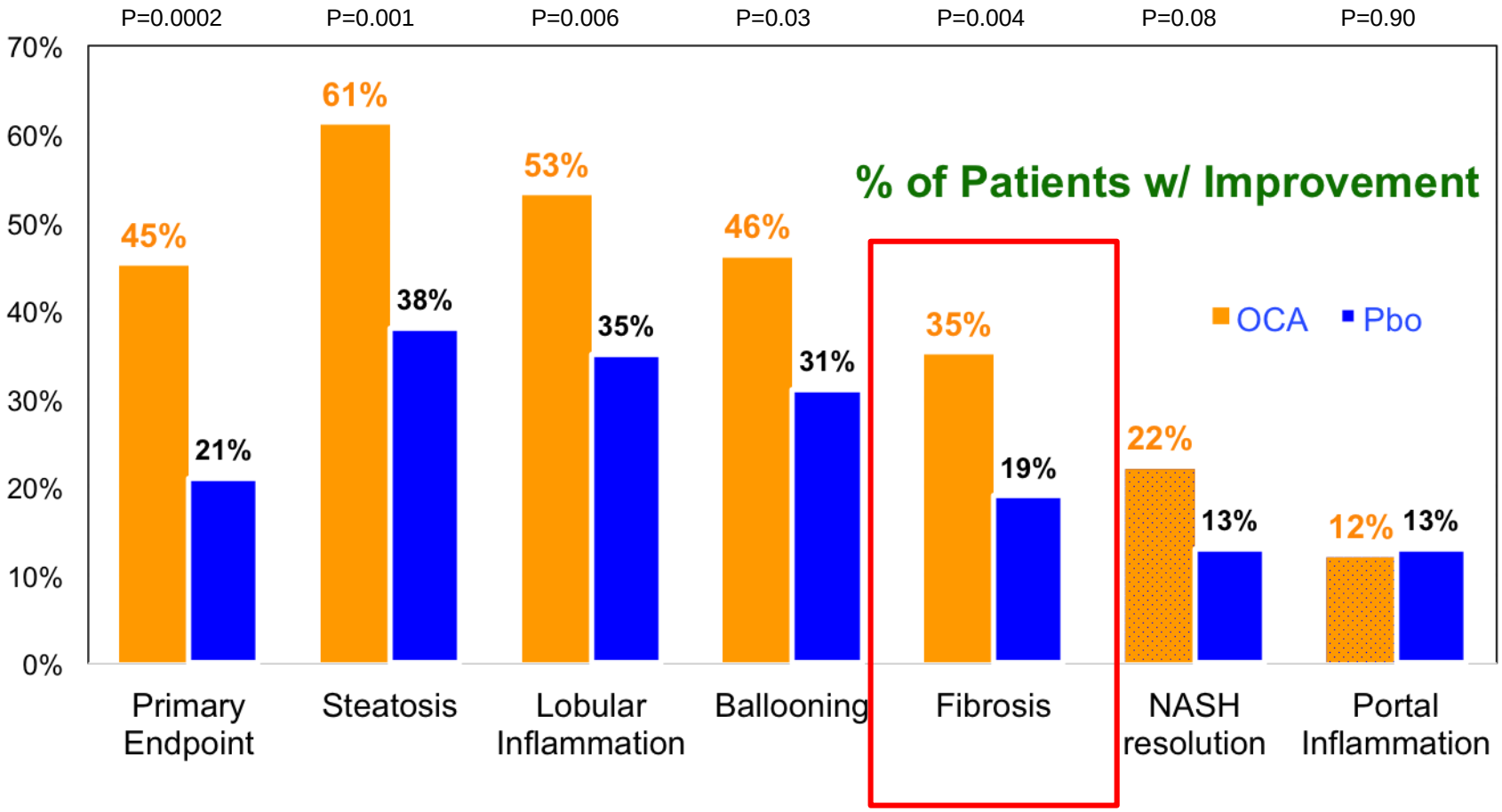
Untreated *OCA Treated*



- OCA lowered portal pressure, reduced fibrosis and decreased fibrotic marker expression in rats with TAA induced liver injury compared to control animals.

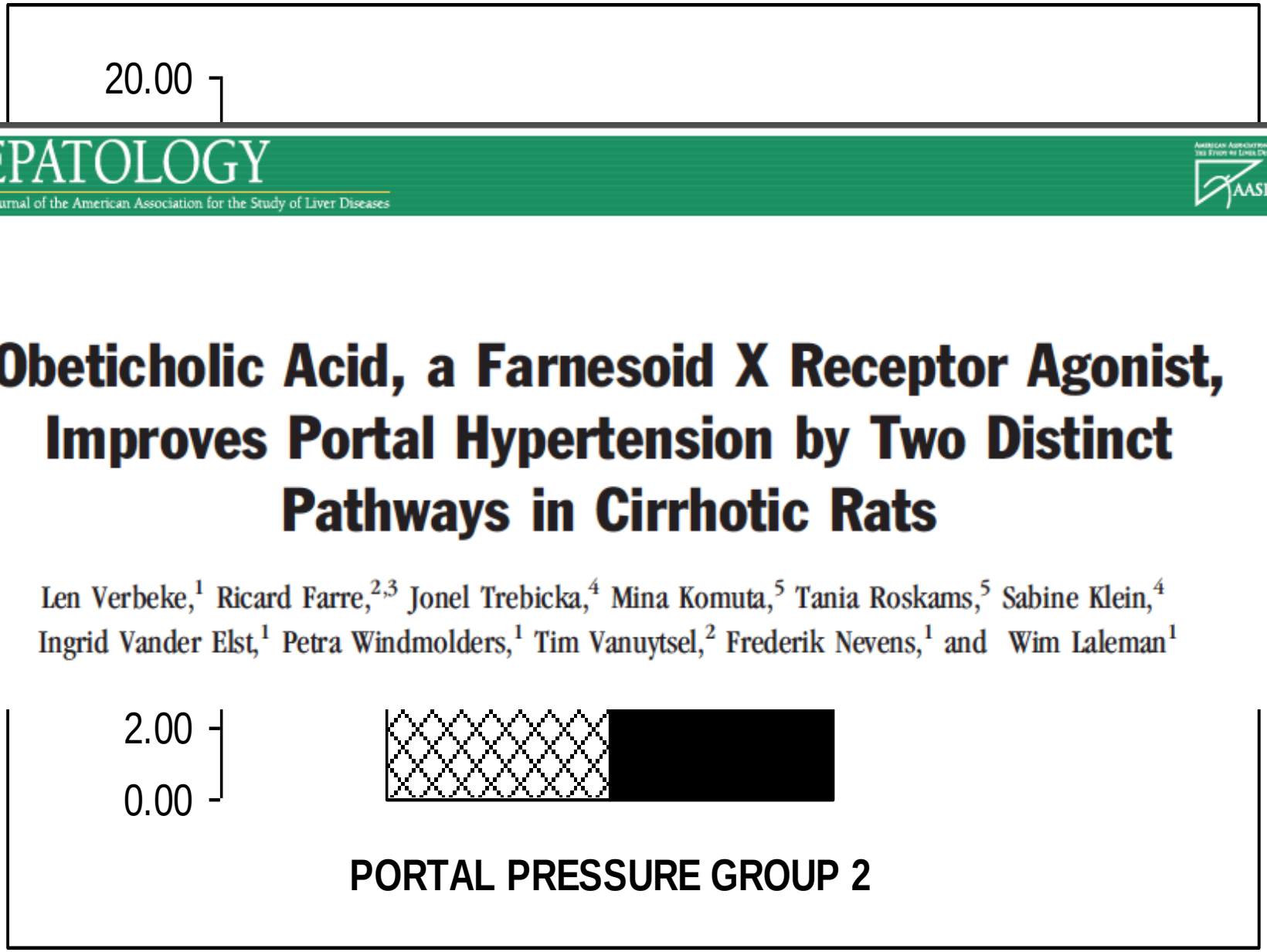
Source: Friedman et al. AASLD 2005.

FLINT: Primary and Secondary Histological Endpoints



1: Data from Tetri et al. *The Lancet*. Published online November 7, 2014.
2: All p-values compared to placebo.

Effect of Obeticholic Acid on Portal Hypertension



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Obeticholic Acid, a Farnesoid X Receptor Agonist, Improves Portal Hypertension by Two Distinct Pathways in Cirrhotic Rats

Len Verbeke,[1] Ricard Farre,[2,3] Jonel Trebicka,[4] Mina Komuta,[5] Tania Roskams,[5] Sabine Klein,[4] Ingrid Vander Elst,[1] Petra Windmolders,[1] Tim Vanuytsel,[2] Frederik Nevens,[1] and Wim Laleman[1]

Fibrosis Advances – *Summary*

1. Pathology remains the mainstay for liver disease dx, but will benefit from inclusion of quantitative, well validated measures that correlate with outcomes (e.g., CPA).

2. Current antifibrotic trials still need to include liver biopsy but promising biomarkers and imaging tests could shorten trial duration.

3. Lessons from other organs and novel trial designs can accelerate drug development.

4. We are reaching a ‘tipping point’ of interest and emerging clinical trials that will establish proof-of-principle for antifibrotic drugs