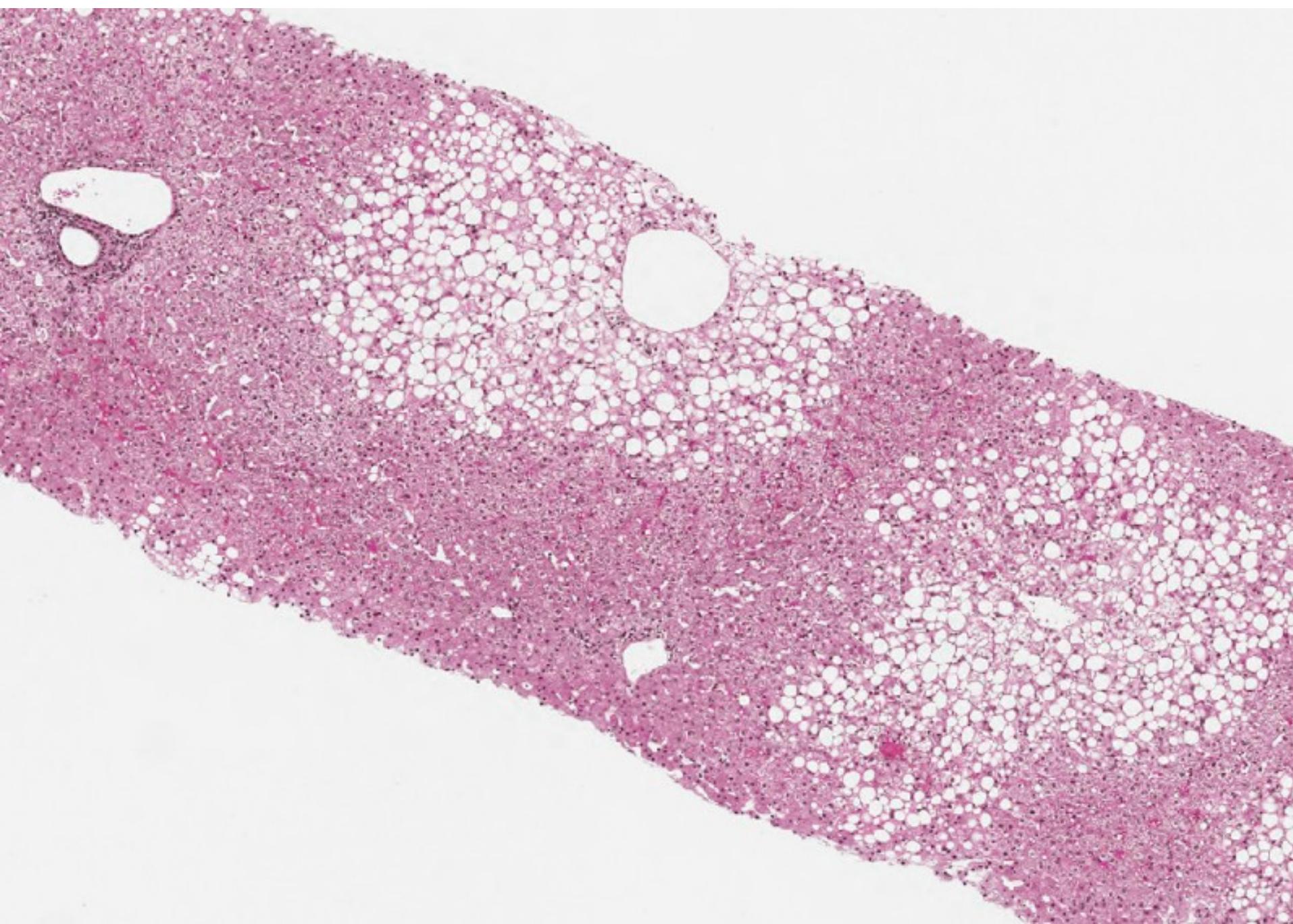


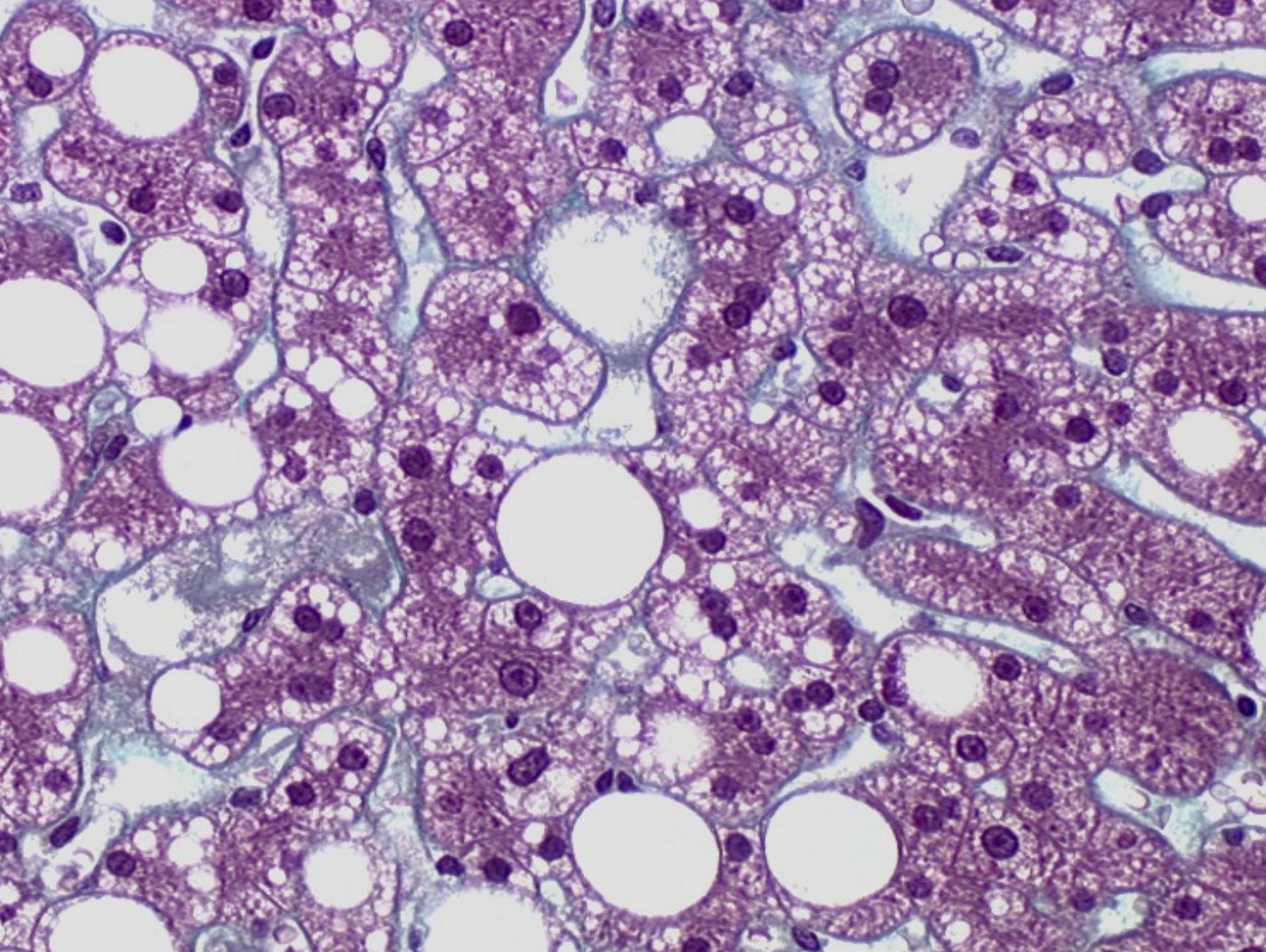
LIVER BIOPSY IN NAFLD

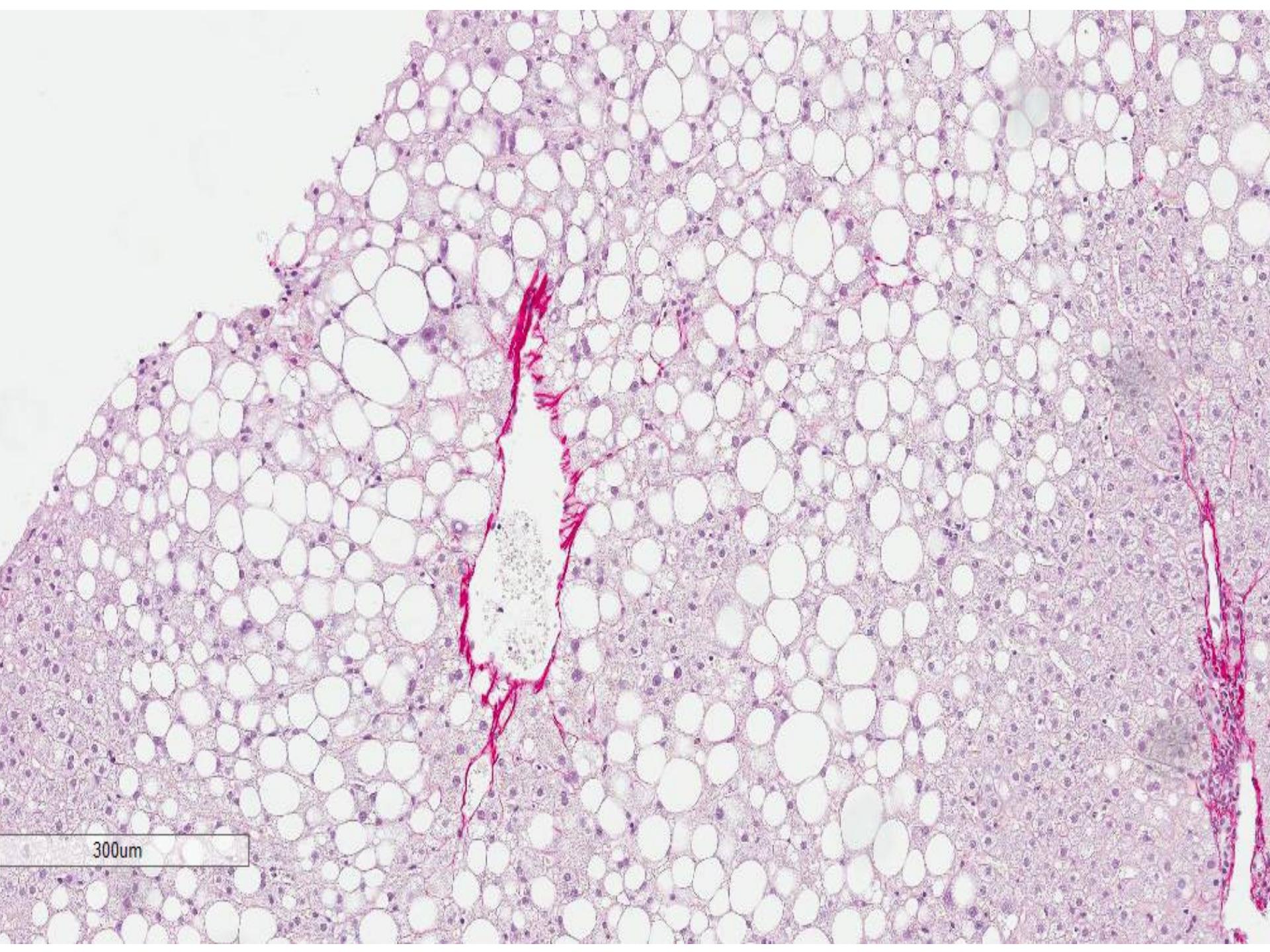
CASE 1

- 45 yrs old male
- Overweight (95kg, BMI = 35)
- Alcohol intake (?)
- Hepatomegaly
- ALT = NI, AST = NI
- No Insulin Resistance
- VCTE (Fibroscan) = 8 kpa

→ Liver biopsy







300um

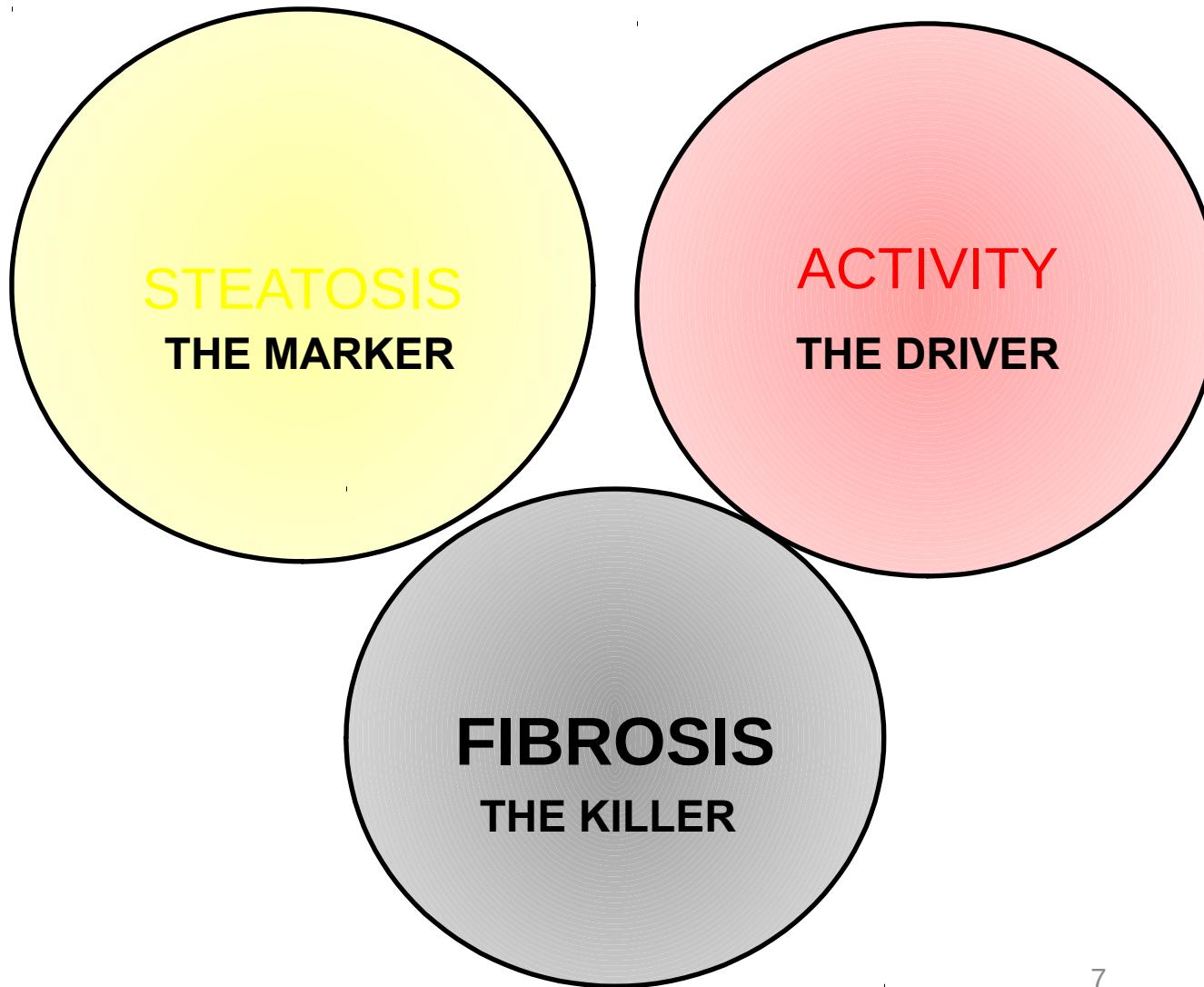
DIAGNOSIS

- STEATOSIS (macrovesicular, ~ 50%, zone 3)
- NO HEPATOCELLULAR DEGENERATION
- NO INFLAMMATION
- NO SIGNIFICANT FIBROSIS

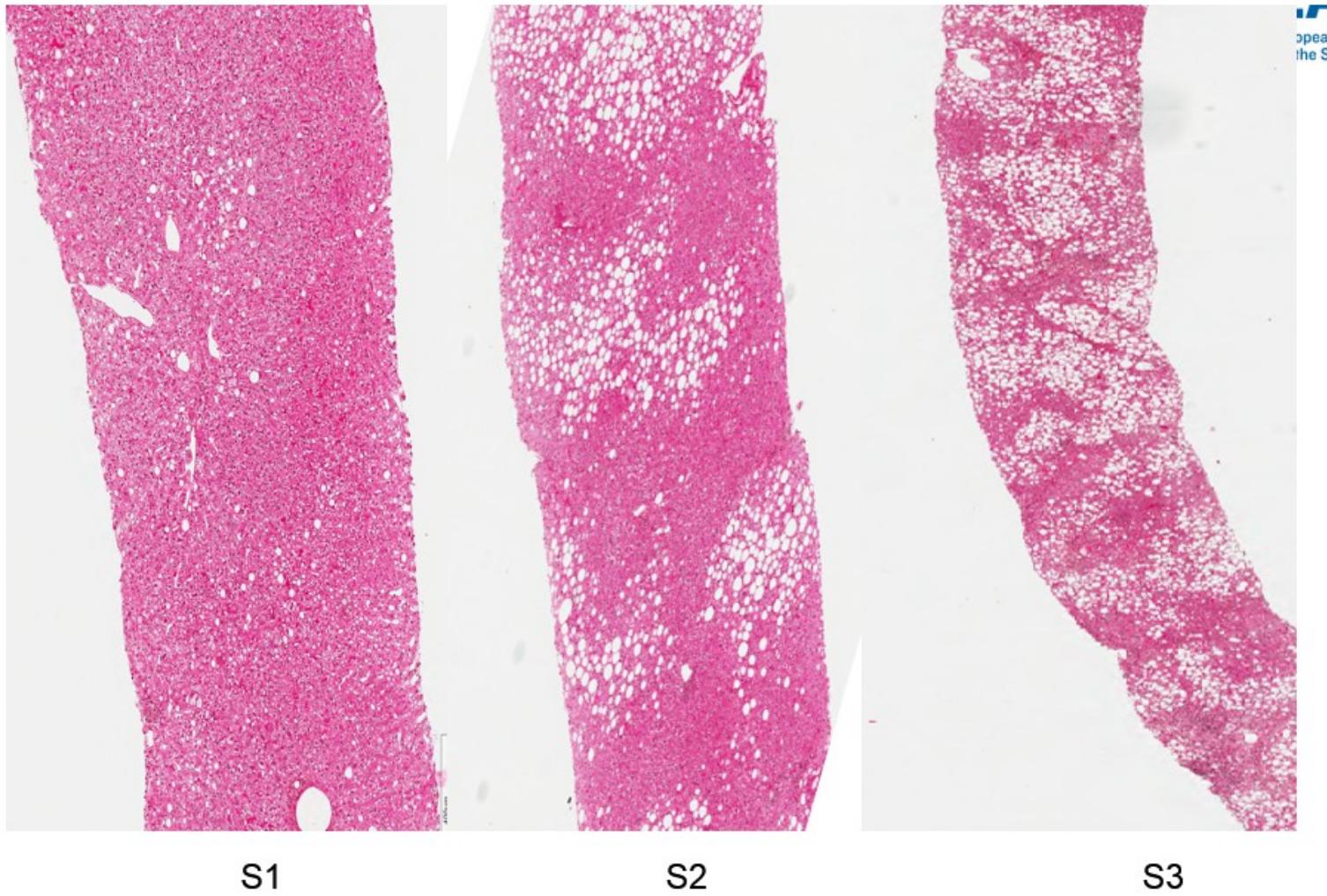
**NON ALCOHOLIC FATTY LIVER (NAFL)
STEATOSIS**

UNDER THE LENS : THE 3 HISTOLOGICAL COMPONENTS OF NAFLD

FLIP consortium, Hepatology 2012, Hepatology 2014



- **Steatosis (0-3)** 0 = <5%, 1 = 5-33%, 2 = 34-66%, 3 = >66%



STEATOSIS / Serum Markers

STEATOSIS > 30%	AUROC (95% CI)	Sensitivity (%)	Specificity (%)
Fatty liver index (FLI)	0.65 (0.59-0.71)	59	69
Hepatic steatosis index (HSI)	0.59 (0.52-0.66)	74	41
NAFLD-liver fat score (LFS)	0.72 (0.66-0.77)	78	59
Visceral adiposity index (VAI)	0.59 (0.52-0.65)	58	58
Triglyceride x glucose index (TyG)	0.65 (0.58-0.70)	59	68

NOT ENOUGH ACCURATE

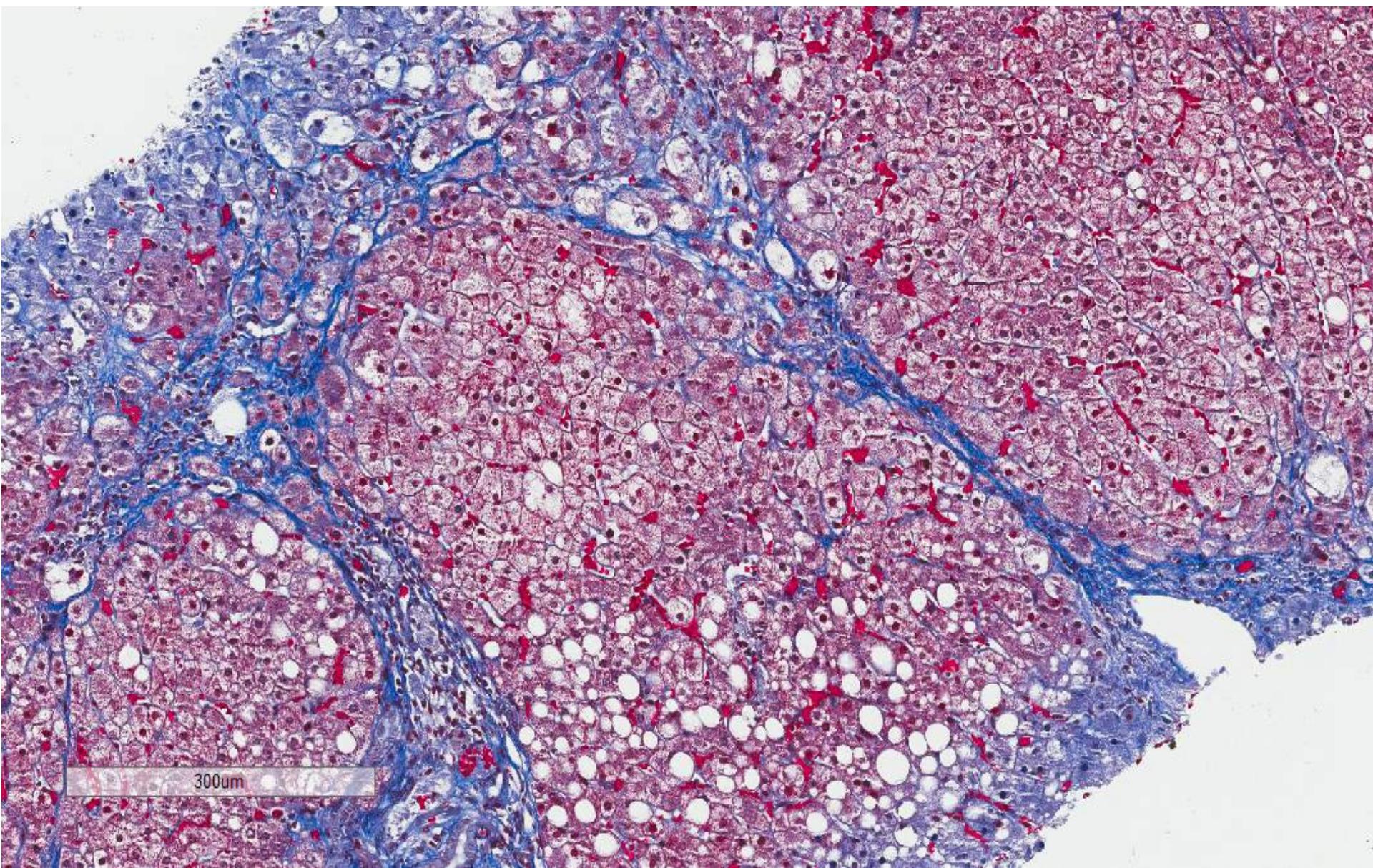
STEATOSIS / Imaging Markers

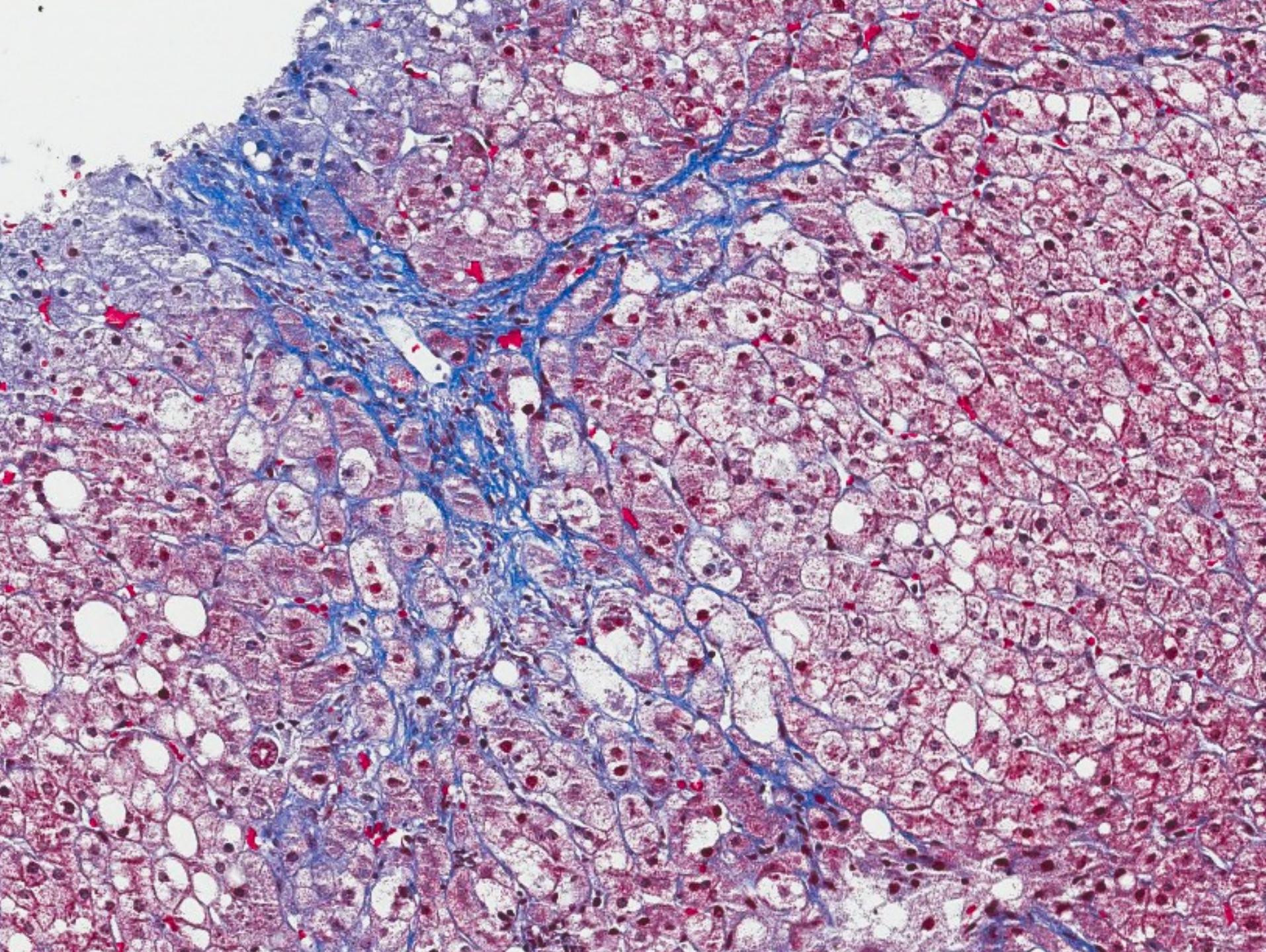
- **Ultrasound:** Sensitivity ↘ if Steatosis < 20%
- **Fibroscan :** Controlled Attenuation parameter (CAP)
 - For $S \geq 1$; Se = 82% , Sp= 91%
- **MR-Spectroscopy (MR-PDFF)**
 - Se = 90%, Sp=93% (any steatosis)
 - Accurate and sensitive method for steatosis quantification

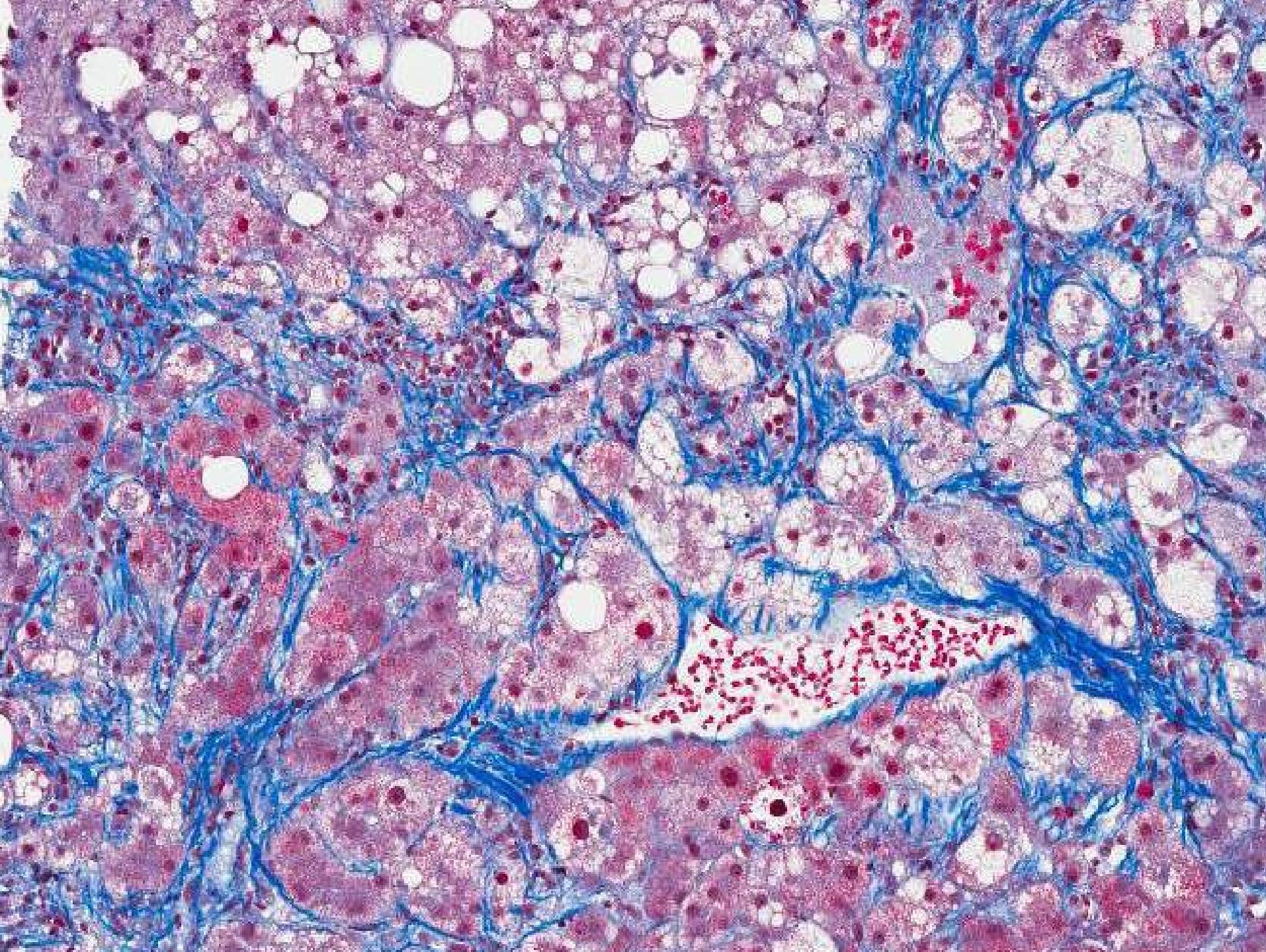
CASE 2

- 62 yrs old female
- T2D
- Overweight
- HTA
- ALT=2N, AST=N, Pal=N!
- Potentially eligible for clinical trial

→ Liver biopsy







DIAGNOSIS

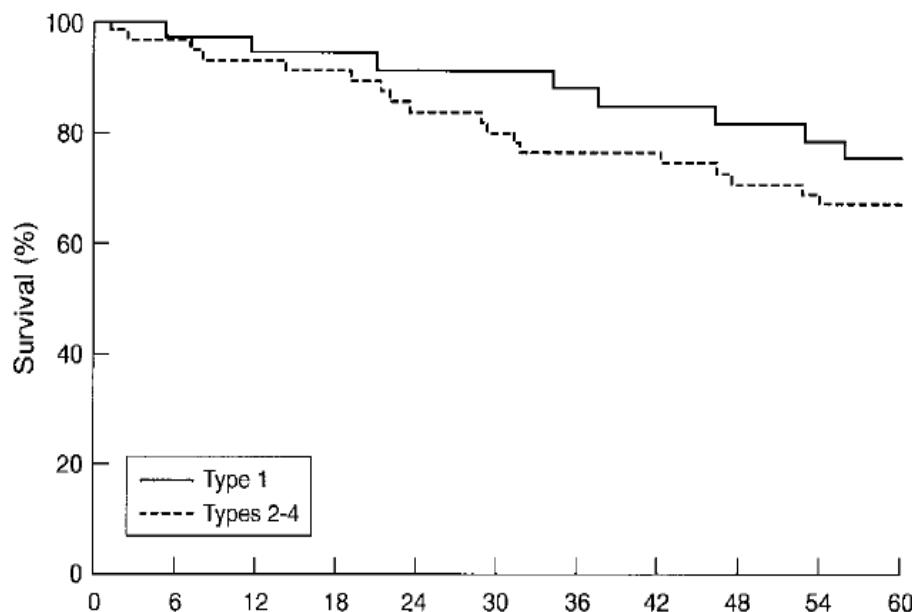
- STEATOSIS (macrovesicular, ~ 30%)
- LIVER CELL BALLOONING
- LOBULAR INFLAMMATION
- SEPTAL / PERISINUSOIDAL FIBROSIS

NON ALCOHOLIC STEATOHEPATITIS
(NASH)

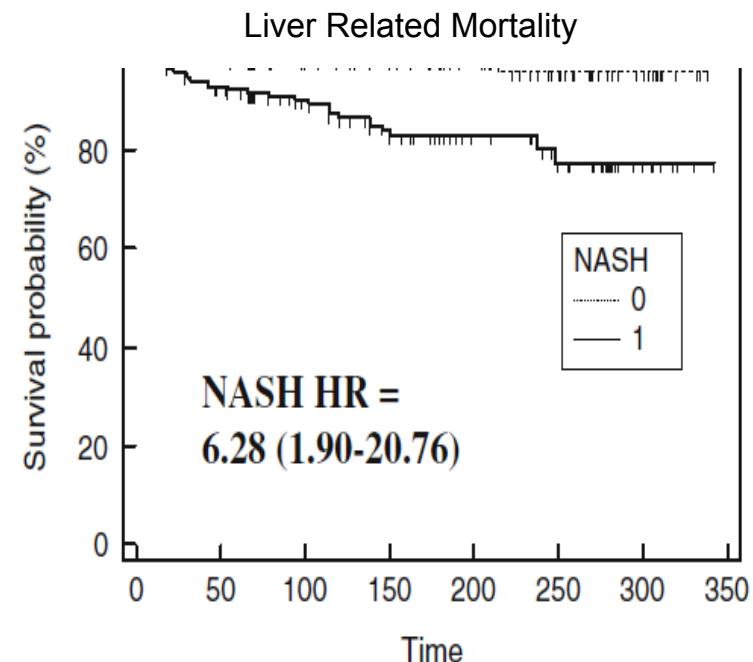
SEPTAL FIBROSIS (Stage 3)

PROGNOSIS : NAFL vs NASH

Overall survival in patients with steatosis (Type I) and NASH (Type 2-4), $p<0.01$



Liver related mortality in patients with and without NASH



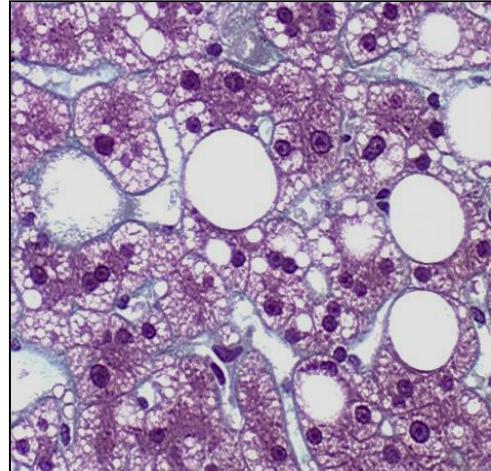
Matteoni CA, Younossi, Z, Gralich T et al. Gastro, 1999

Stepanova M, Rafiq N, Makhlouf H et al. Dig Dis Sci 2013

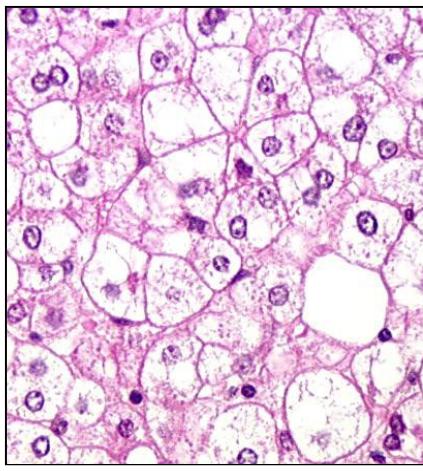
HISTOLOGIC CRITERIA FOR NASH DIAGNOSIS

An association of features

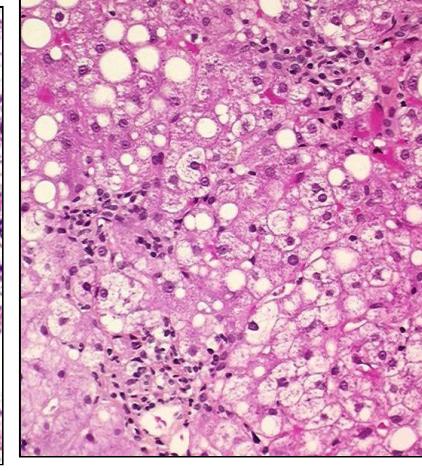
Steatosis



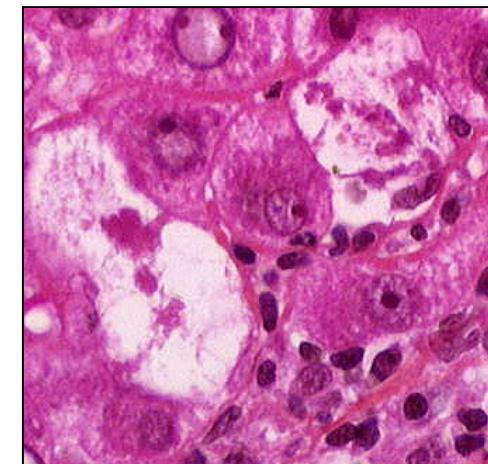
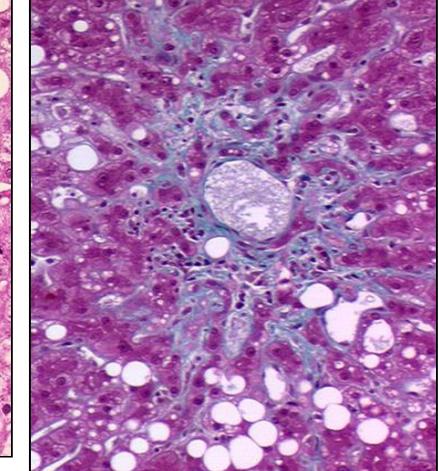
Ballooning/clarification



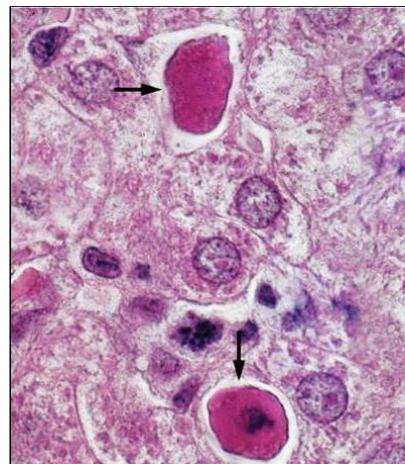
Lobular inflammation



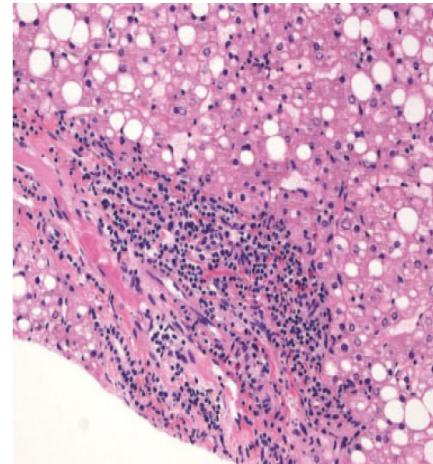
Perisinusoidal Fibrosis



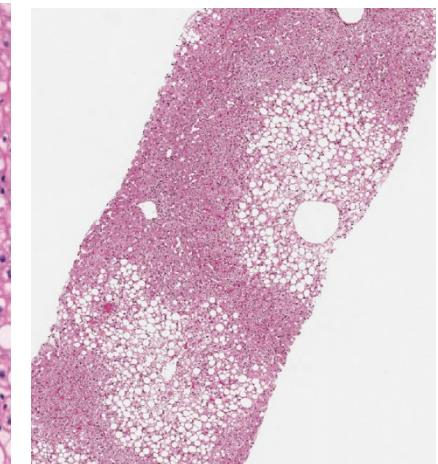
Mallory Denk body



Apoptotic body



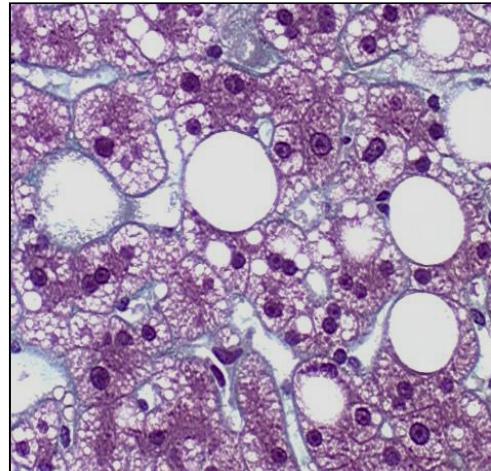
Portal Inflammation



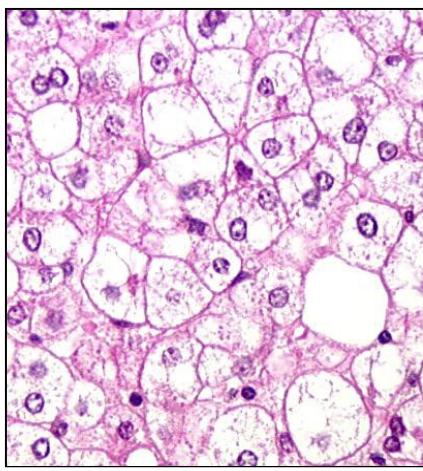
Zone 3 localisation

HISTOLOGIC CRITERIA FOR NASH DIAGNOSIS

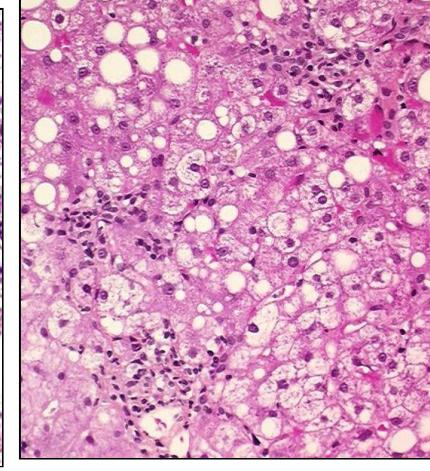
Steatosis



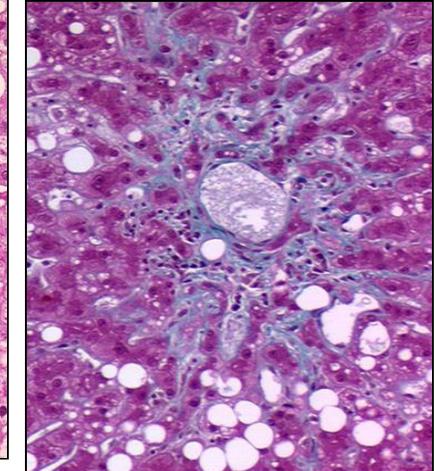
Ballooning/clarification



Lobular inflammation



Perisinusoidal Fibrosis



NOT CONSTANT

Mallory Denk body



Apoptotic body



Portal Inflammation



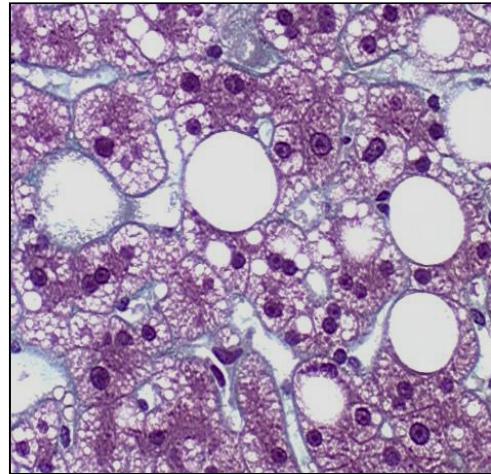
18

Zone 3 localisation

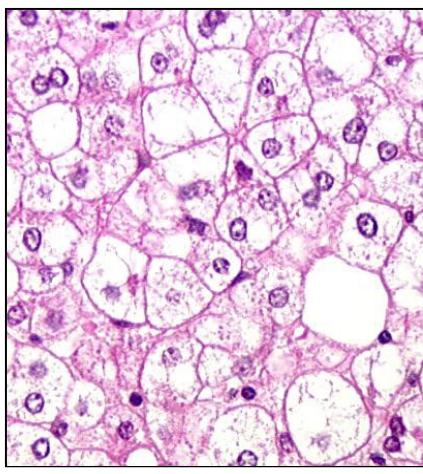


HISTOLOGIC CRITERIA FOR NASH DIAGNOSIS

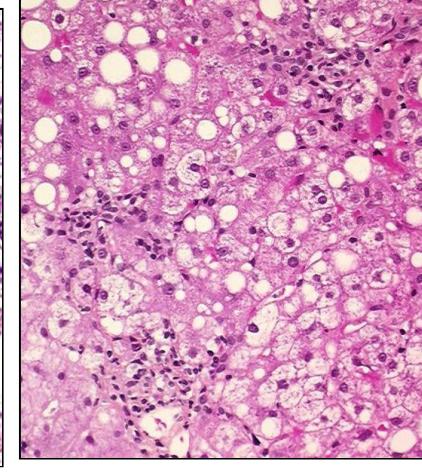
Steatosis



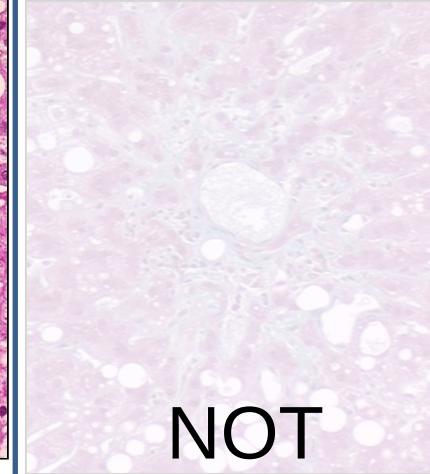
Ballooning/clarification



Lobular inflammation

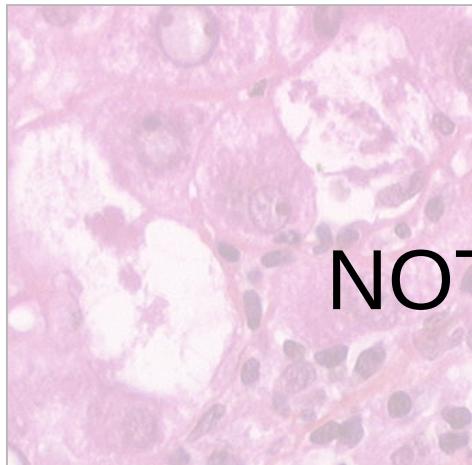


Perisinusoidal Fibrosis

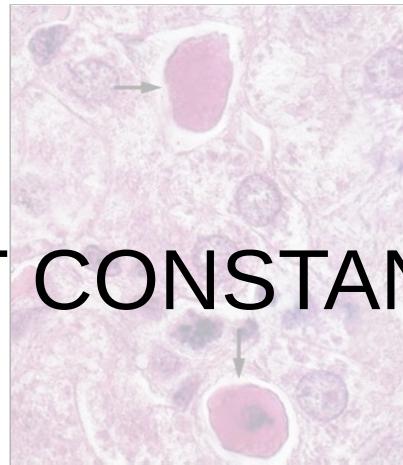


NOT CONSTANT

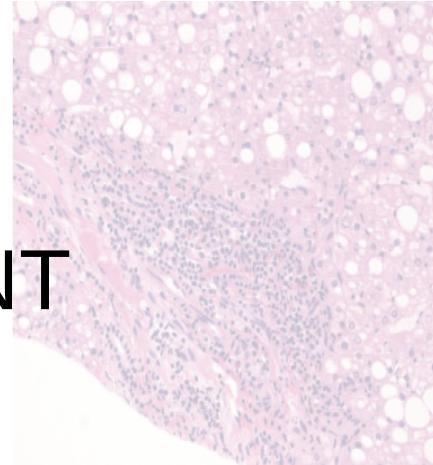
Mallory Denk body



Apoptotic body



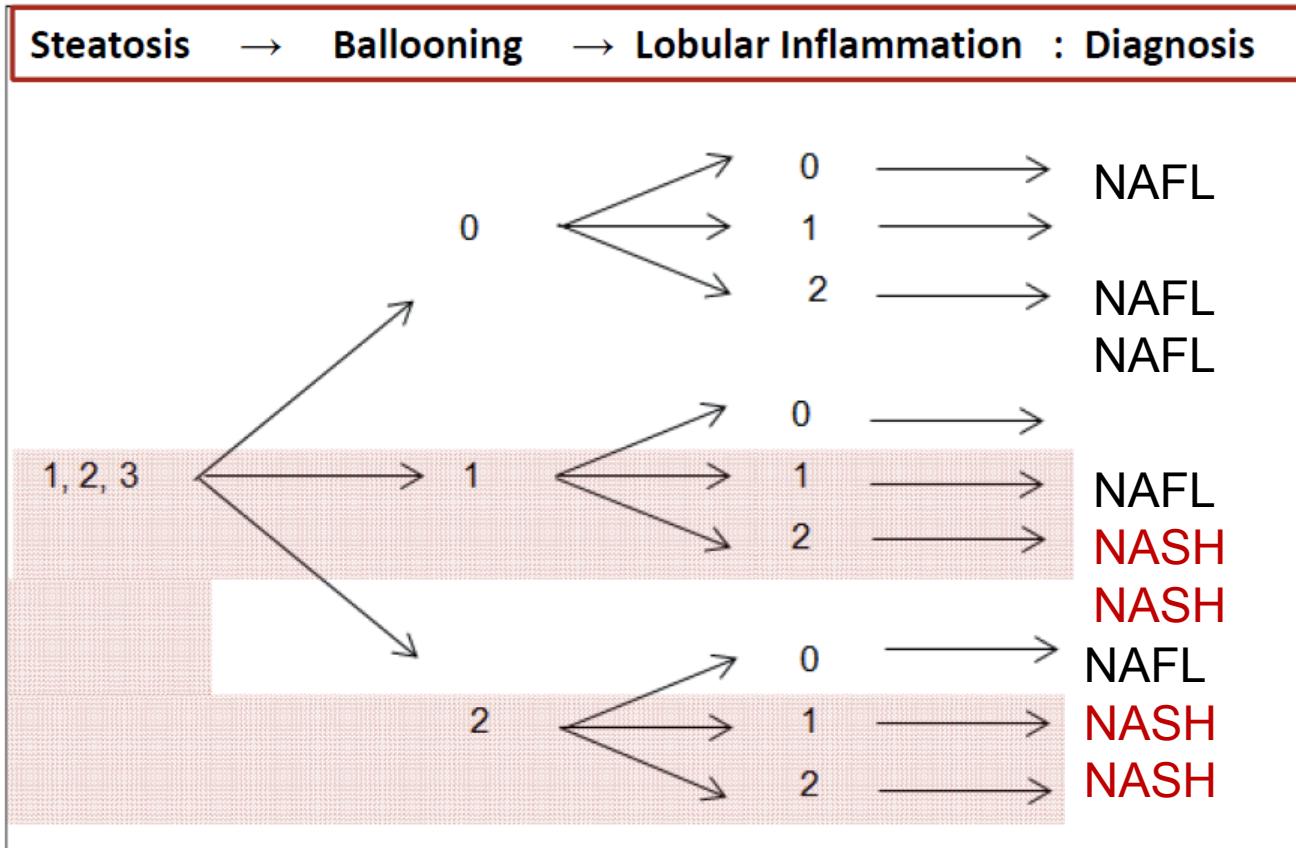
Portal Inflammation



NOT
SPECIFIC

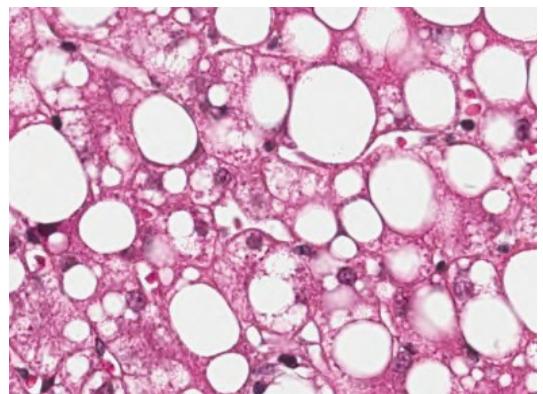
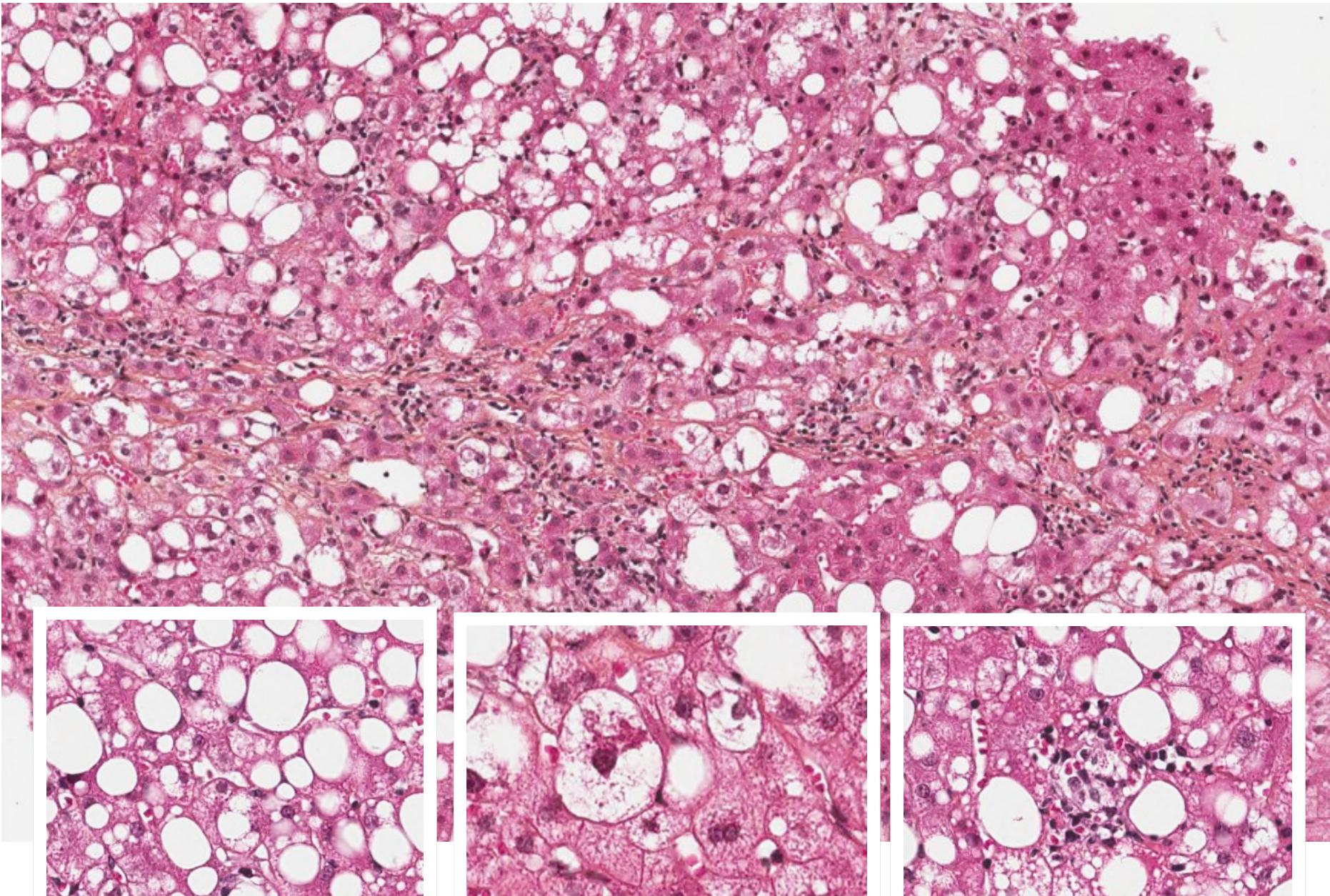
Zone 3 localisation

The FLIP algorithm

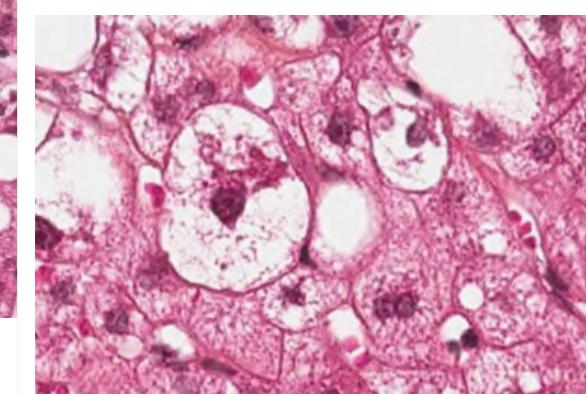


Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Hepatology. 2012 Nov;56(5):1751-9

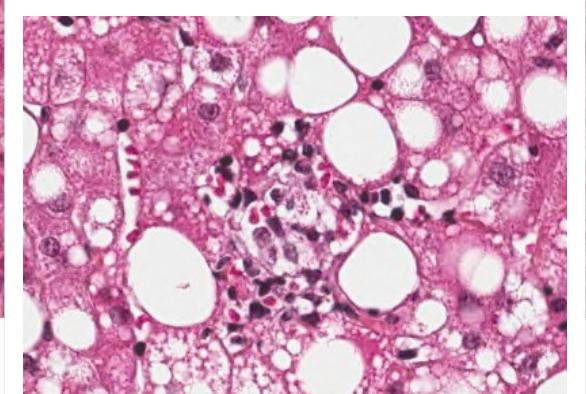
STEATOHEPATITIS (NASH)



Stéatose



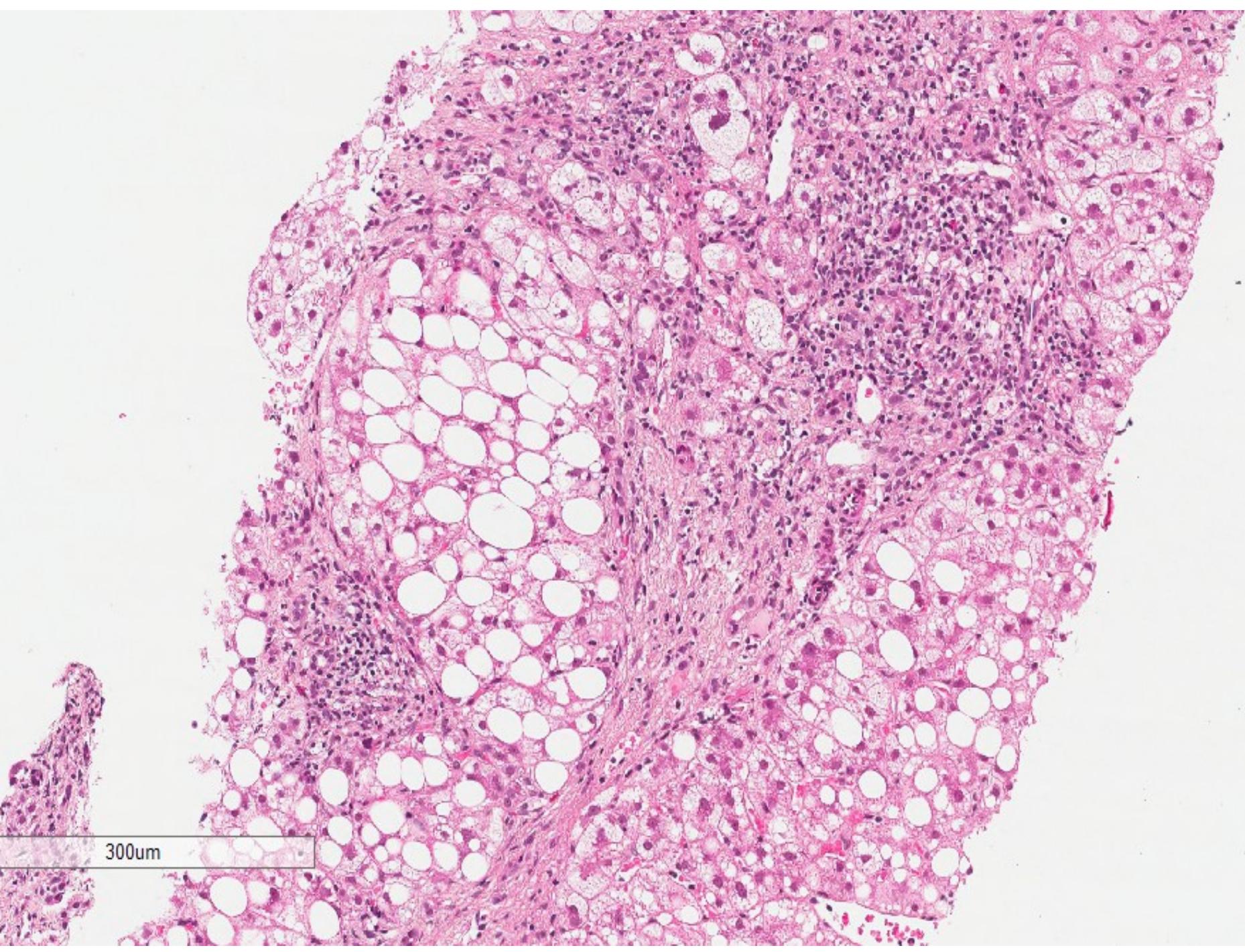
Lésions hépatocytaires



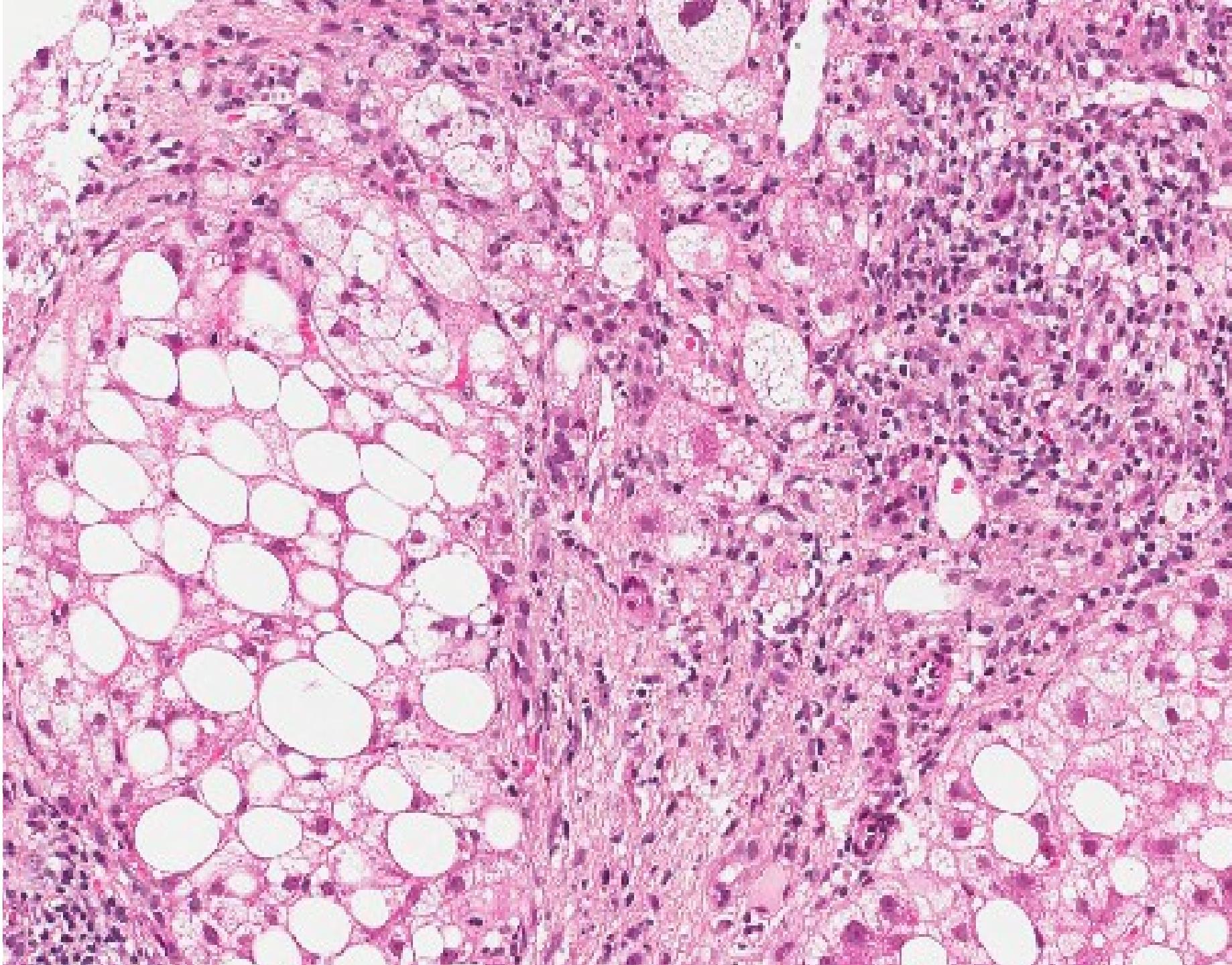
Inflammation

CASE 3

- 64 yrs old male
- T2D
- HTA
- ALT=2N, AST=3N, Platelet count=100.000 mm³/l
- Endoscopical Varices, Splenomegaly
- Fibroscan = 14 kpa
→ Transjugular Liver biopsy (HVPG=21 mm Hg)



300um



DIAGNOSIS

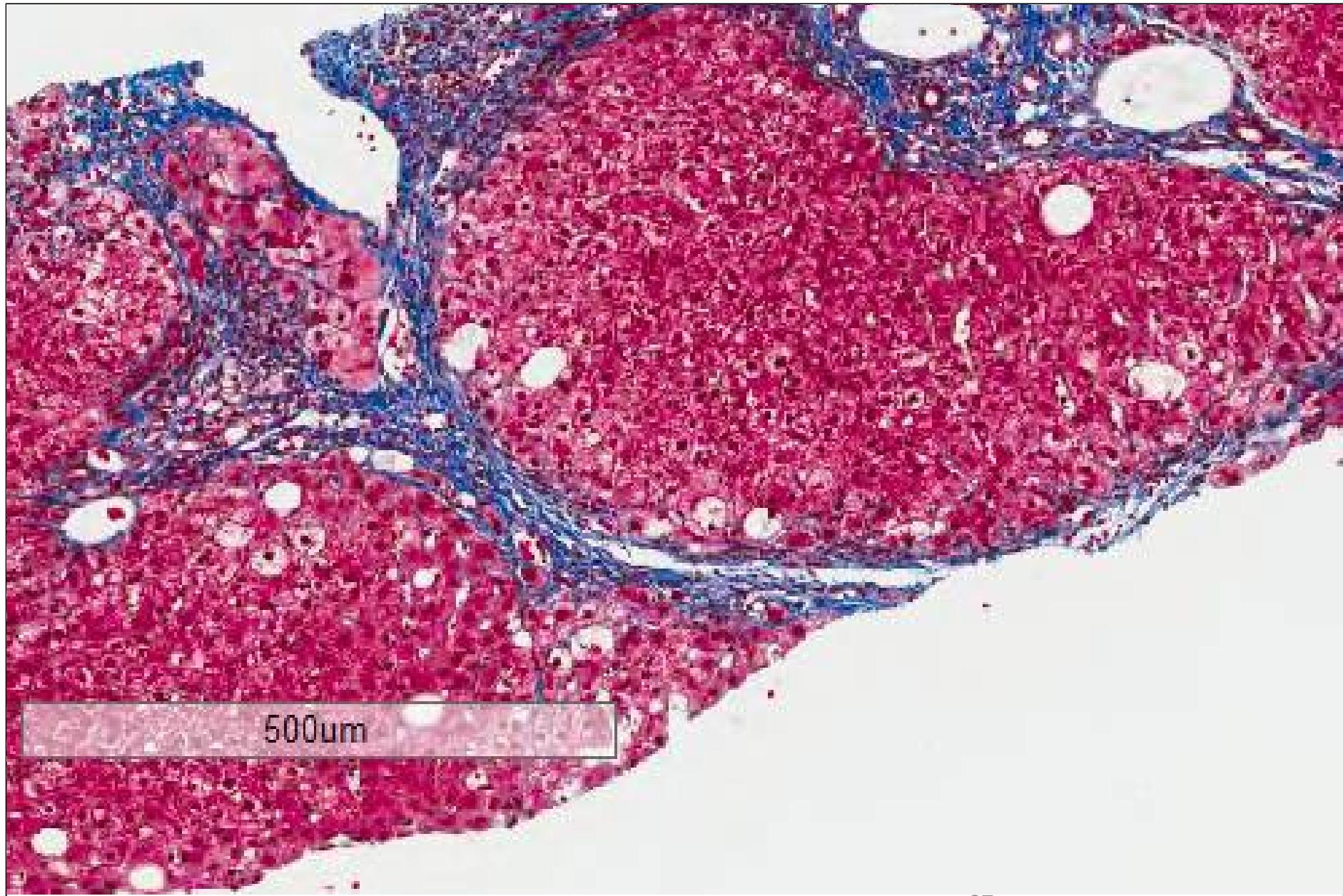
- CIRRHOSIS
- STEATOSIS
- LIVER CELL BALLOONING +++
- LOBULAR INFLAMMATION +++

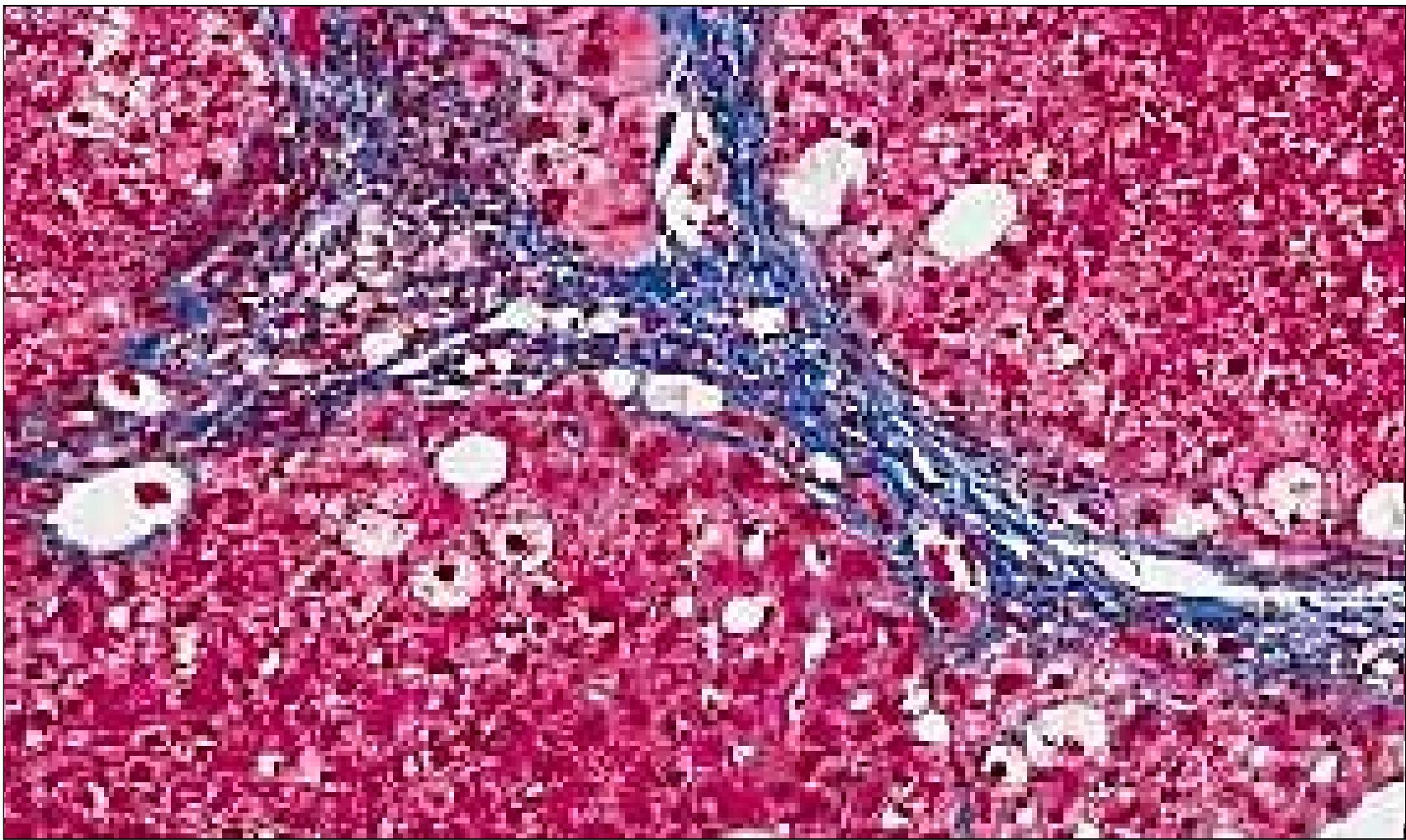
NASH CIRRHOSIS

CASE 4

- 72 yrs old male
- No past history of liver disease
- No alcohol or other cause of CLD
- ICU for oesophagal haemorrhage
- Endoscopy: Grade 2 varices
- ALT=N, AST=N

→ Transjugular Liver biopsy





DIAGNOSIS

- CIRRHOSIS
- STEATOSIS < 5%
- HEPATOCYTE BALLOONING (rare)
- NO LOBULAR INFLAMMATION

CRYPTOGENIC / NASH CIRRHOSIS

NASH and FIBROSIS / Non Invasive Markers

- NASH (Yes/no) : No NI marker with high enough accuracy
- NASH + Fibrosis
 - APRI, Fibrotest, Fibrometer, NAFLD Fibrosis score
 - High NPV (exclude F3-F4)
- VCTE / MRE : high diagnostic accuracy for Dc of advanced fibrosis / cirrhosis
- None of them are enough accurate to follow-up histological evaluation (clinical trials)

Not one fits for all
No NASH (Activity) marker
Quantitative

Non Invasive
Accessibility for «dry»
markers

All in one

Semiquantitative
Unsuspected associated
lesions
Comorbidities
Invasive (harmful)

Accessibility (pathologist)
(Sampling and observer
variability)

NI markers are urgently needed but still an unmet need

Liver biopsy in 2017 : when ?

- Anytime accurate evaluation of liver damages is needed
- Comorbidities, unclear situation...
- Clinical trial (baseline and follow-up)



THE LIVER FORUM INITIATIVE

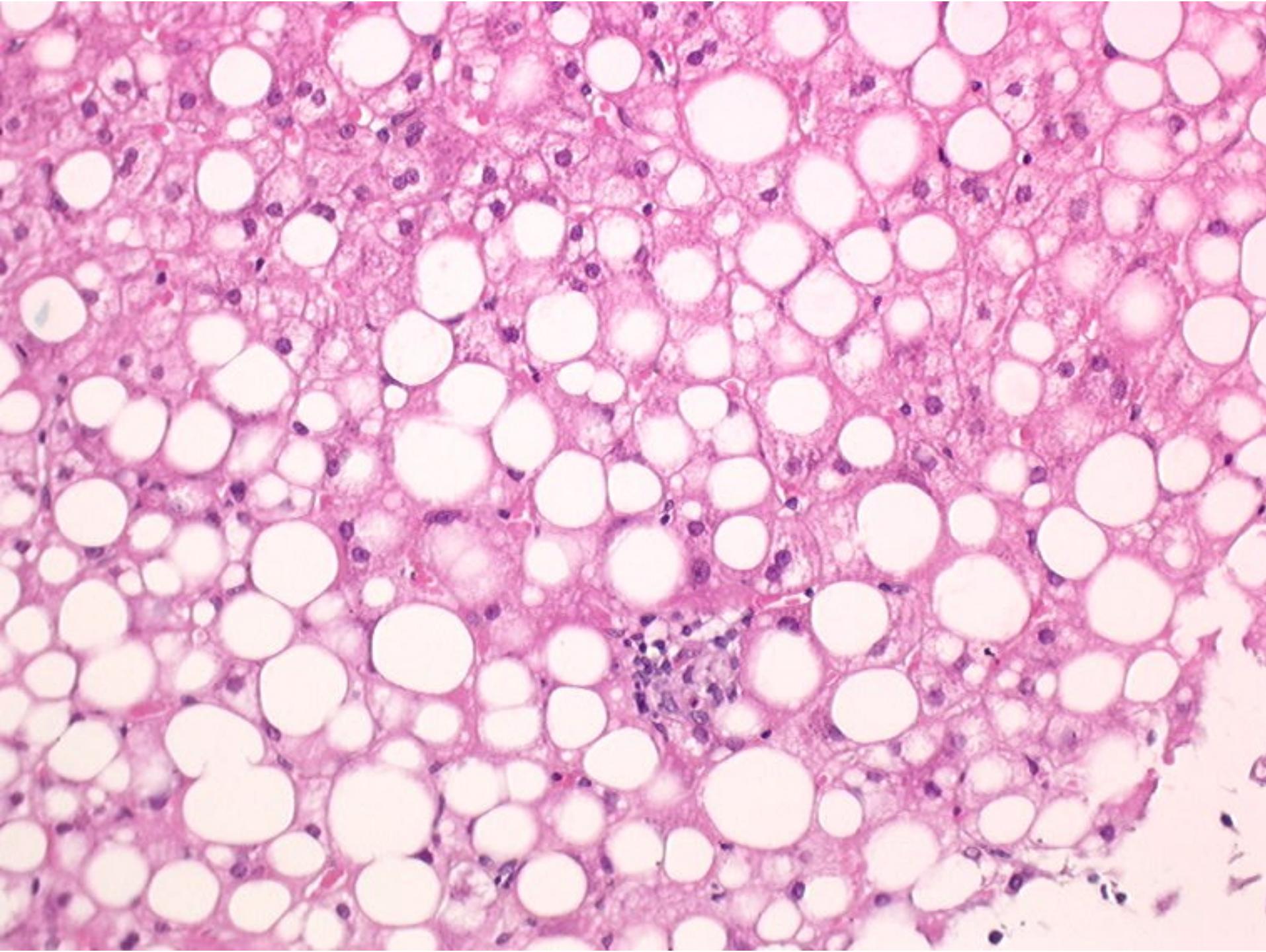
- A multi-stakeholder initiative:
 - US and EU Regulatory agencies
 - Academic investigators
 - Industry
 - Patient and professional organizations
- WP/ Provide a consensual case definitions based on :
 - Histology
 - Clinical Phenotype
 - Non Invasive tools

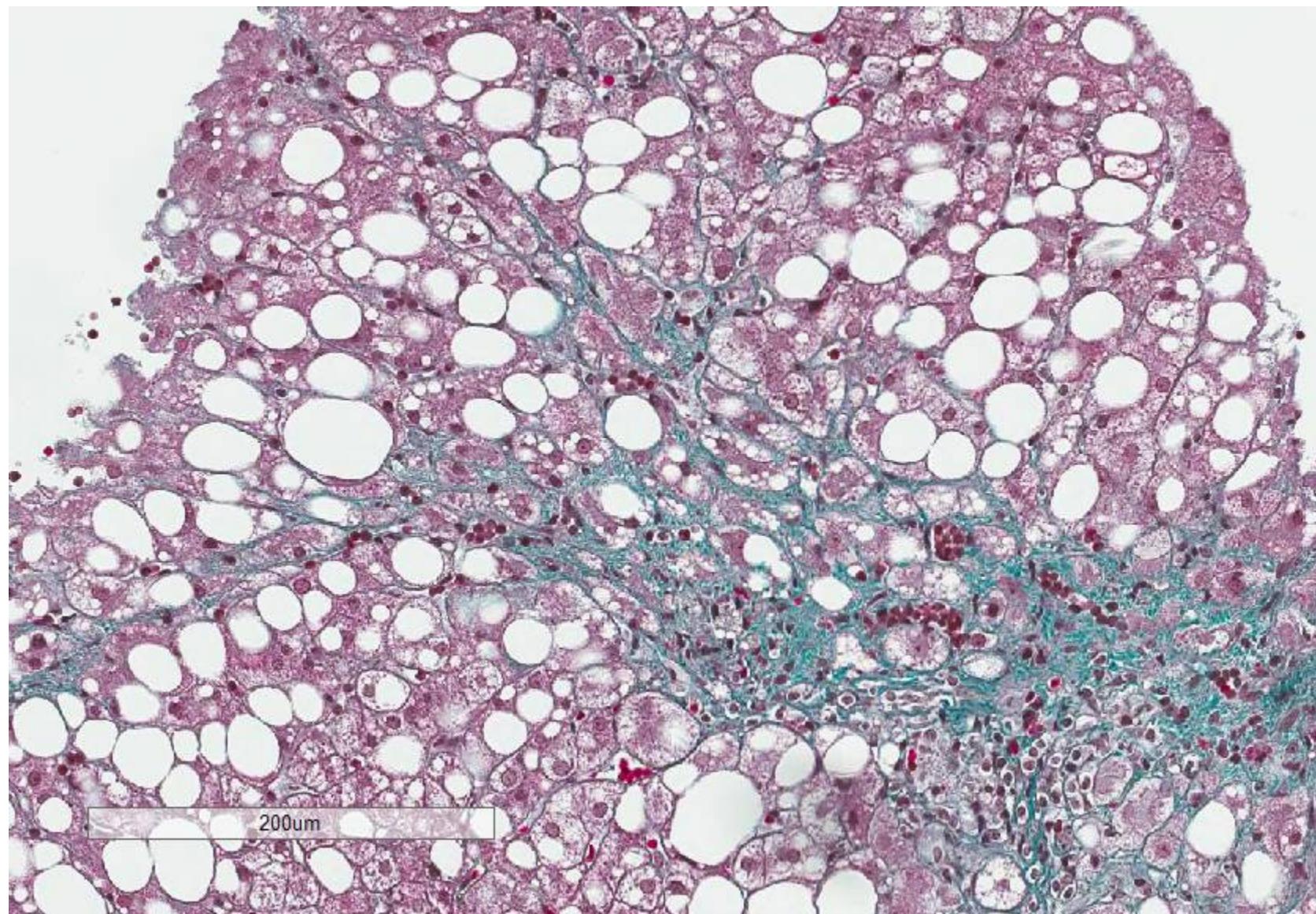
3 CATEGORIES

1. NAFL (FATTY LIVER)
2. NASH
3. NASH CIRRHOSIS

NAFL (FATTY LIVER) CATEGORY

CATEGORY	SUBCATEGORY	HISTOLOGY	CLINICAL PHENOTYPE	PROGNOSIS
NAFL	FATTY LIVER	Steatosis > 5%	NONE	BENIGN
	INDETERMINATE NASH	Borderline NASH Fat + Inflammation liver cell injury	METAB SYNDROME None, One, Several	?
	STEATOSIS WITH FIBROSIS	Fat + Fibrosis	INSULIN RESISTANCE: No, Yes	?





NASH CATEGORY

CATEGORY	HISTOLOGY	CLINICAL PHENOTYPE	SUBCATEGORY
NASH	<p>STEATOSIS + BALLOONING + INFLAMMATION (+) (Zone 3 / NASH CRN)</p> <p>Activity SCORE NAS / SAF</p>	<p>No highly specific feature</p> <p>AGE BMI IR / DIABETES OBESITY</p>	<p>+ NO FIBROSIS</p> <p>+ EARLY FIBROSIS</p> <p>+ BRIDGING FIBROSIS</p>

NASH CIRRHOSIS

CATEGORY	HISTOLOGY	NON INVASIVE PARAMETER (cirrhosis)	SUBCATEGORIES
NASH CIRRHOSIS	ANNULAR FIBROSIS and ARCHITECTURAL DISRUPTION + either NASH / STEATOSIS / NONE	VCTE LSM > 14 kpa or MRE LSM > 6.7 kpa + Collateral, nodular liver, splenomegaly (imaging or endoscopy) Or HVPG > 6mm Hg AST:ALT >1 Platelet < 150.000/mm³	COMPENSATED
			DECOMPENSATED

THANK YOU FOR YOUR ATTENTION !