THE BURDEN OF NASH IN PATHOLOGY.
HOW TO RECOGNIZE AND HOW TO SCORE ?

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FRANCE

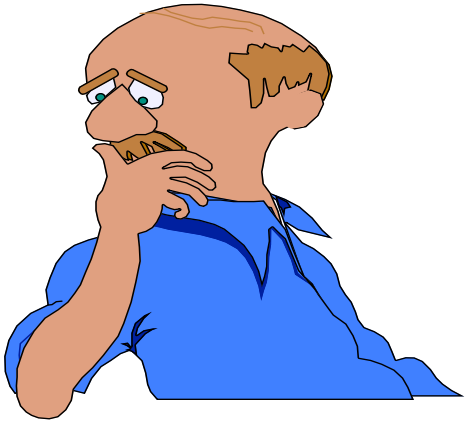
THE BURDEN OF NASH IN PATHOLOGY.
HOW TO RECOGNIZE AND HOW TO SCORE ?

- NASH : a risk factor for development of liver fibrosis, liver-related mortality and overall mortality.
- Non Invasive markers for steatosis and advanced fibrosis but not for NASH
- Liver biopsy remains the only reliable tool for diagnosis of NASH.

THE BURDEN OF NASH IN PATHOLOGY.

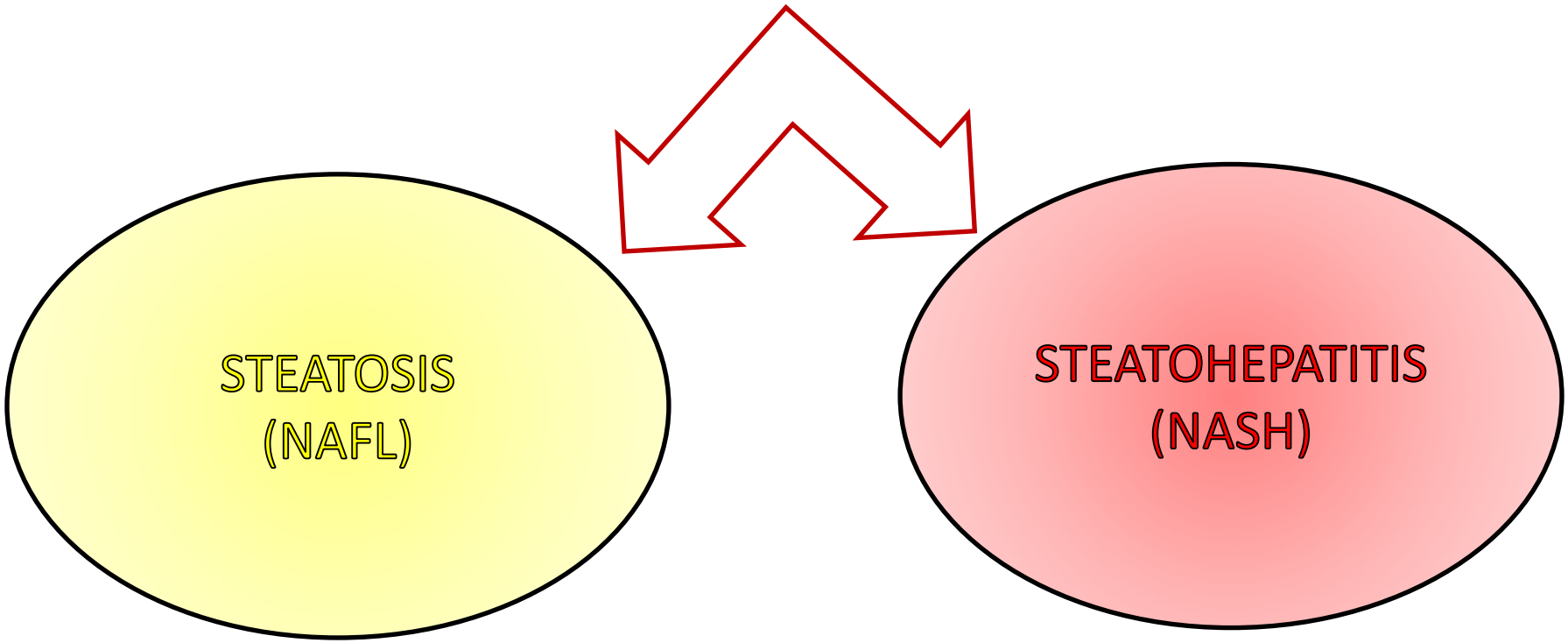
HOW TO RECOGNIZE AND HOW TO SCORE ?

1- NASH: HOW TO RECOGNIZE ?



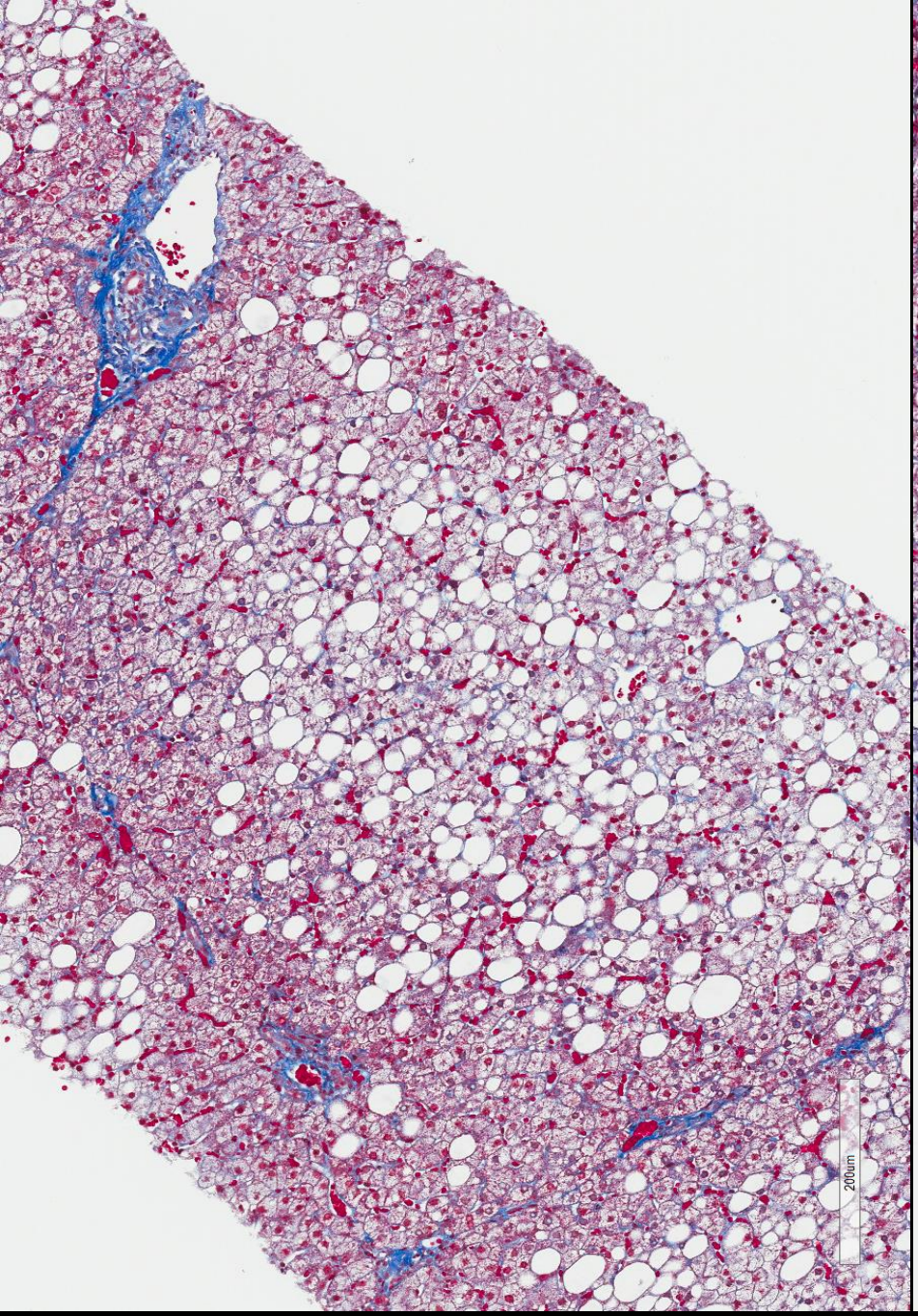
QUESTION TO PATHOLOGIST : IS IT A NASH ?

NAFLD: A DICHOTOMOUS CLASSIFICATION

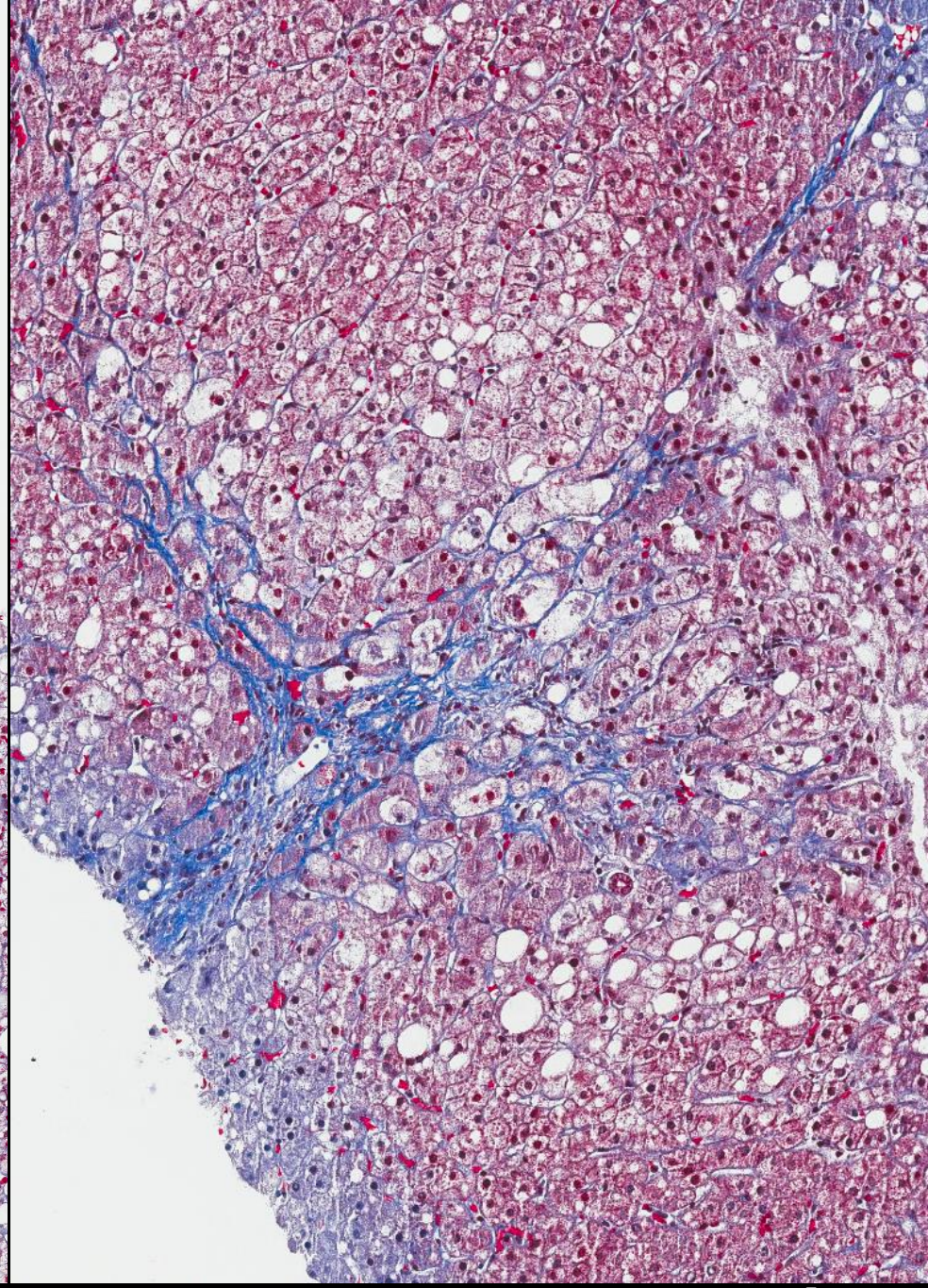


HISTORICAL LANDMARKS :

- Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Ludwig J, et al. Mayo Clin Proc. 1980
- Brunt E. et al. Am J Gastroenterol 1999
- Matteoni et al. Gastroenterology 1999

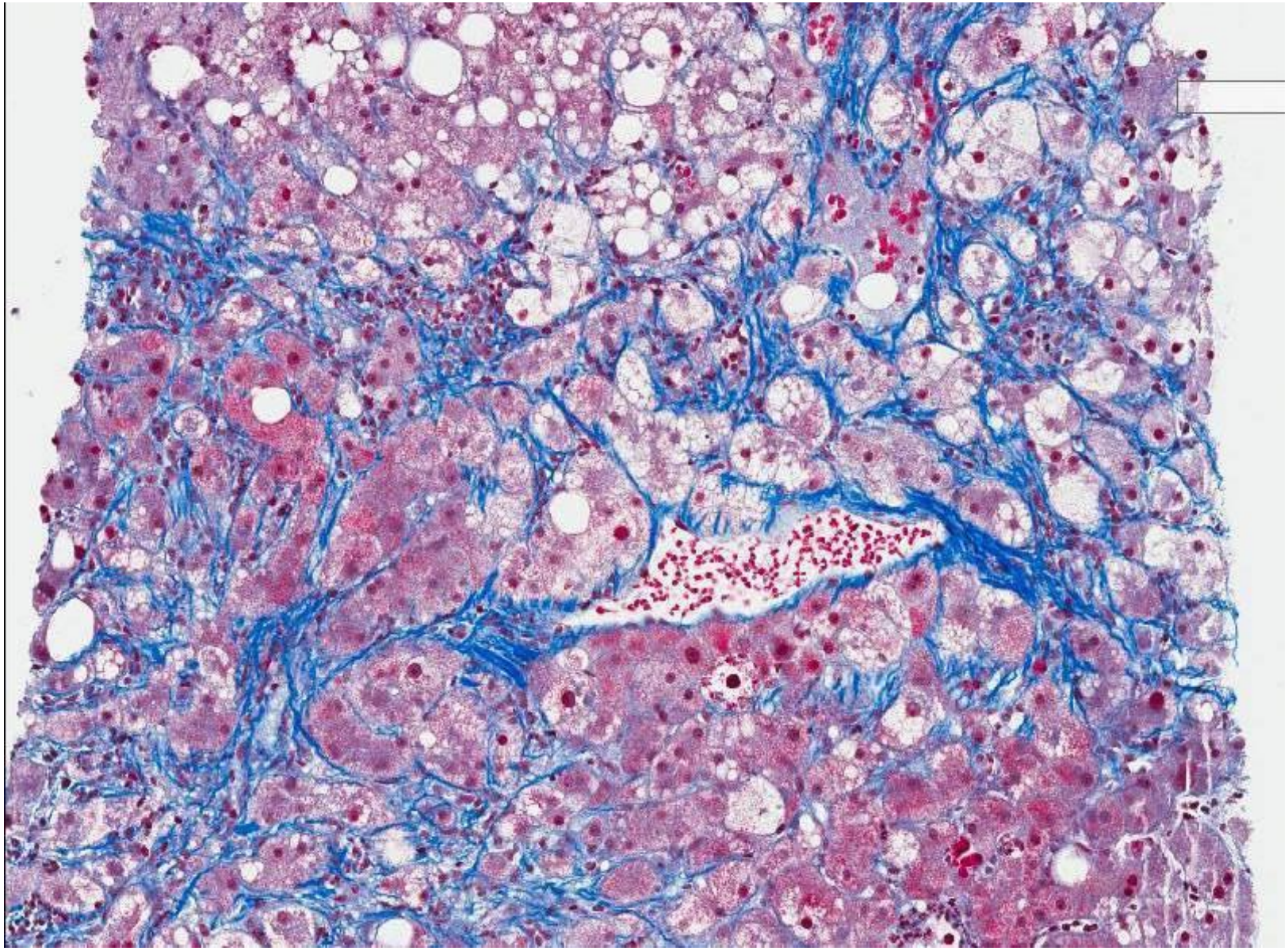


STEATOSIS (NAFL)



STEATOHEPATITIS (NASH)

DEFINITION : AN HISTOLOGICAL PATTERN

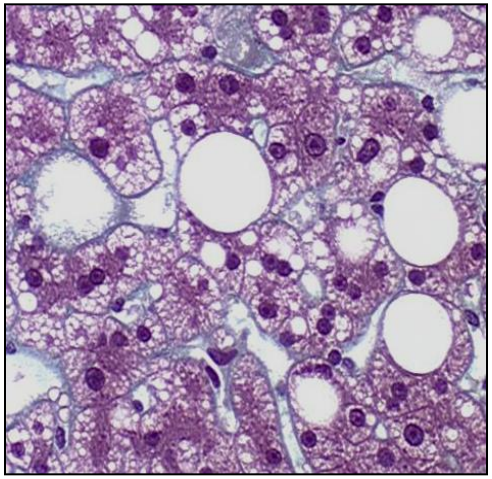


STEATOHEPATITIS (NASH)

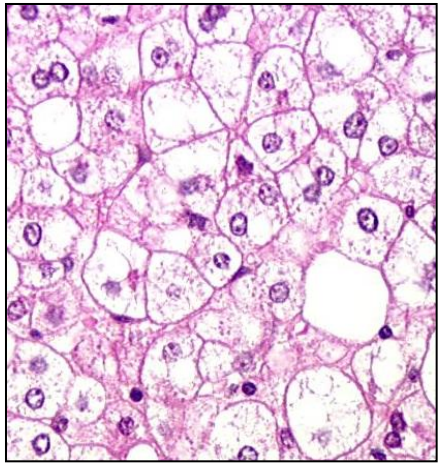
DEFINITION : AN HISTOLOGICAL PATTERN

DEFINITION : AN ASSOCIATION OF 3 FEATURES

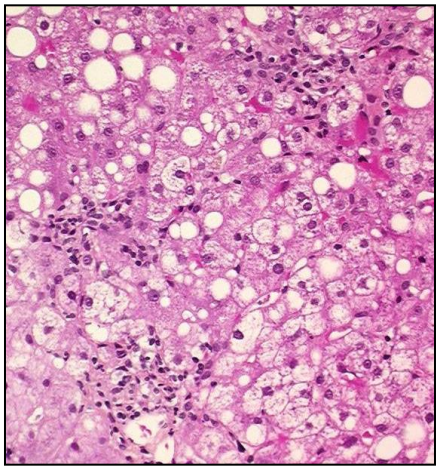
Steatosis



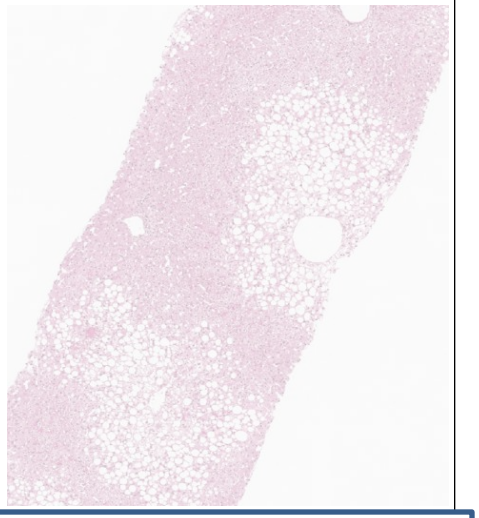
Ballooning/clarification



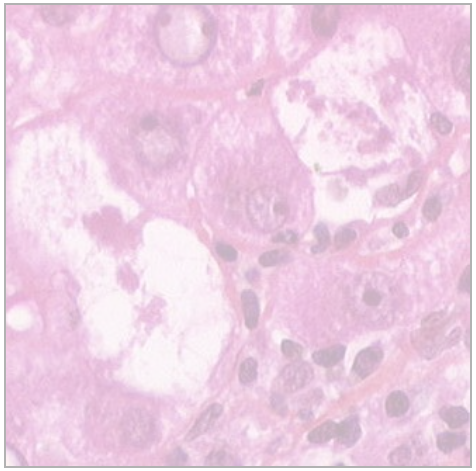
Lobular inflammation



Zone 3

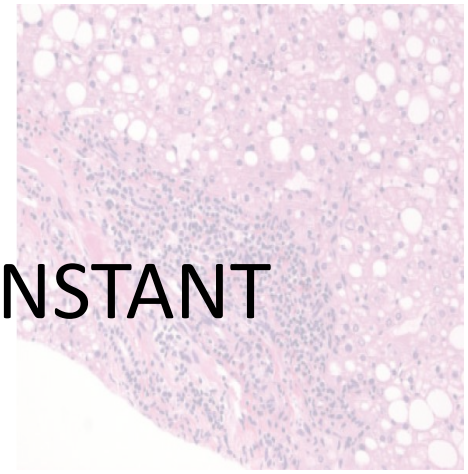


NOT CONSTANT

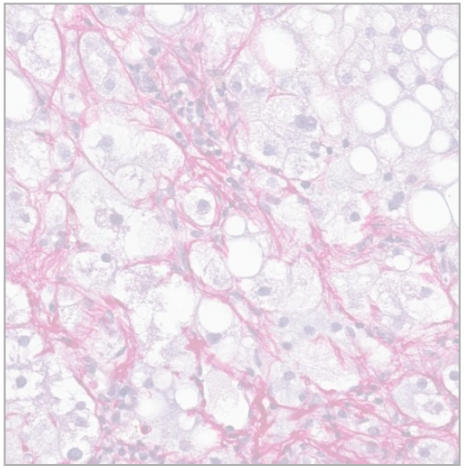


Mallory Denk body

Apoptotic body

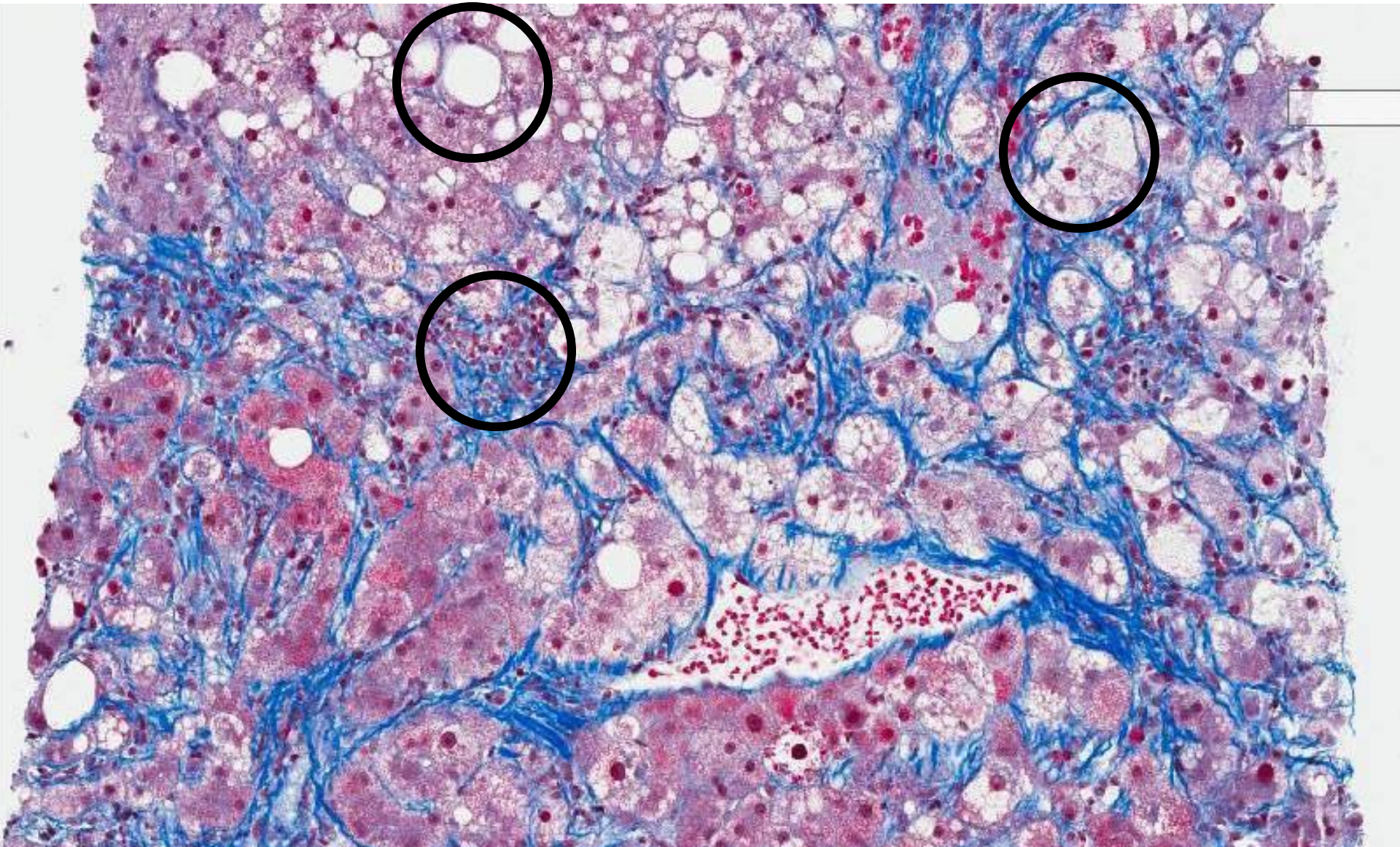


Portal Inflammation



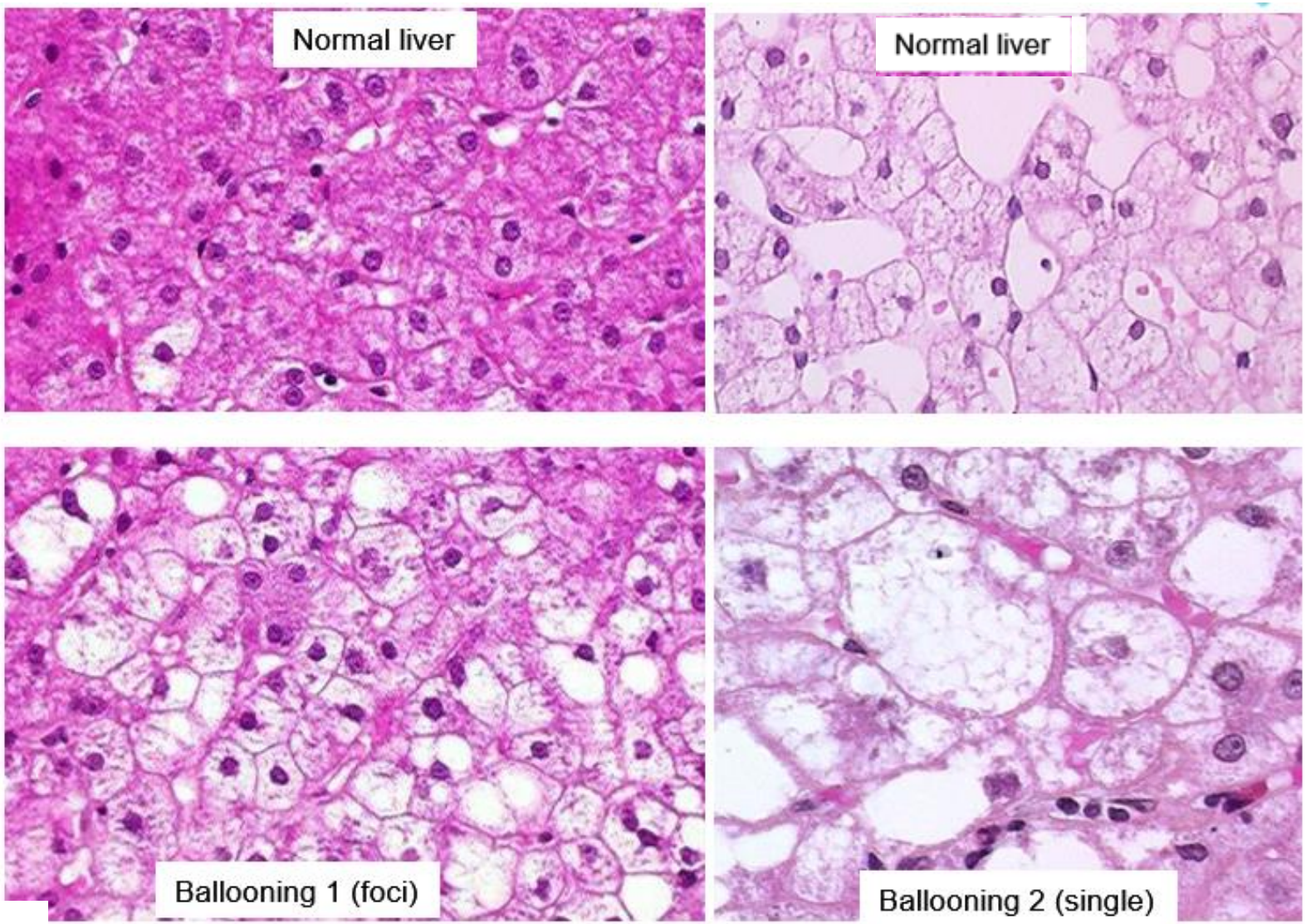
Perisinusoidal fibrosis

HISTOLOGIC CRITERIA FOR NASH DIAGNOSIS
An association of 3 elementary features



HEPATOCELLULAR BALLOONING: THE HALLMARK OF NASH

SHAPE + COLOR + SIZE



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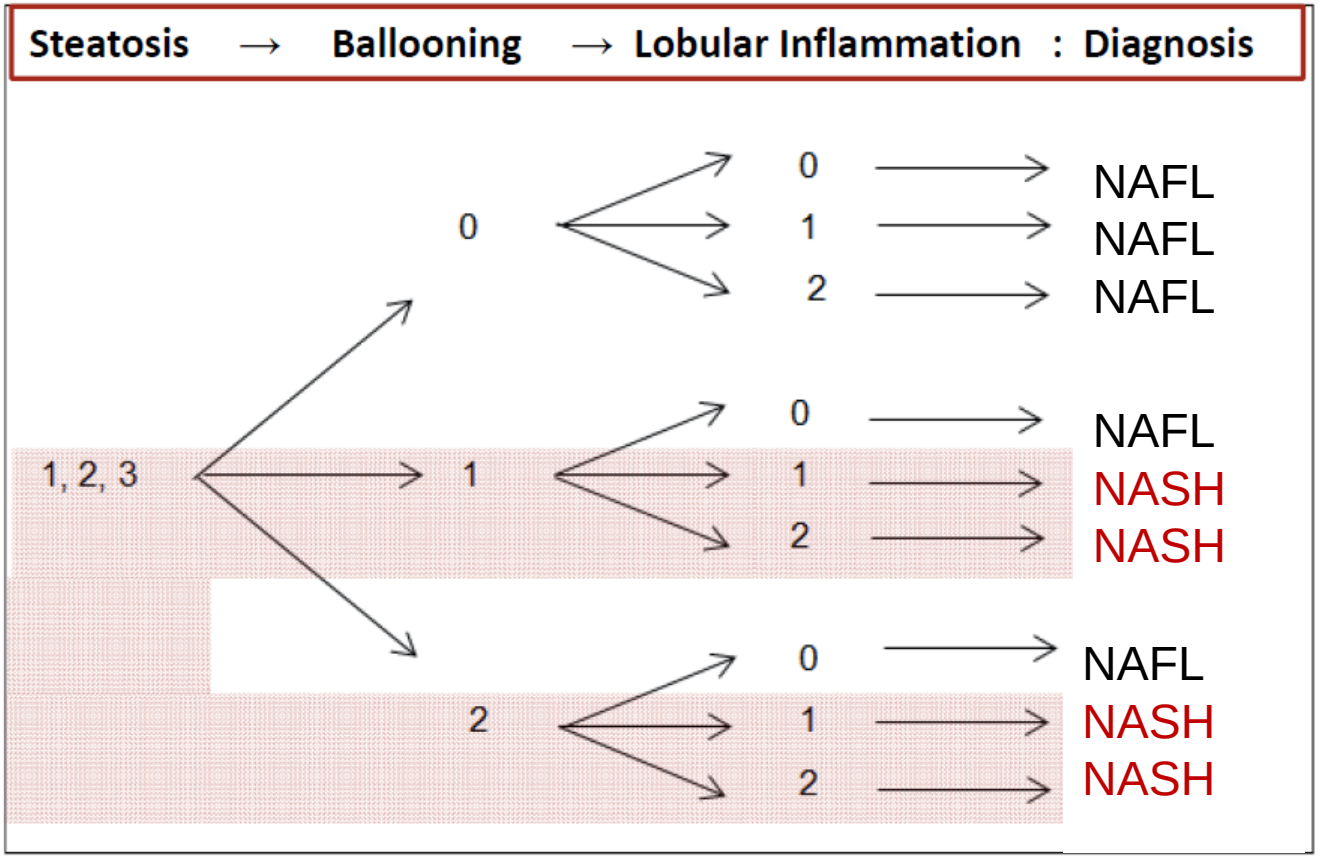
The FLIP algorithm



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

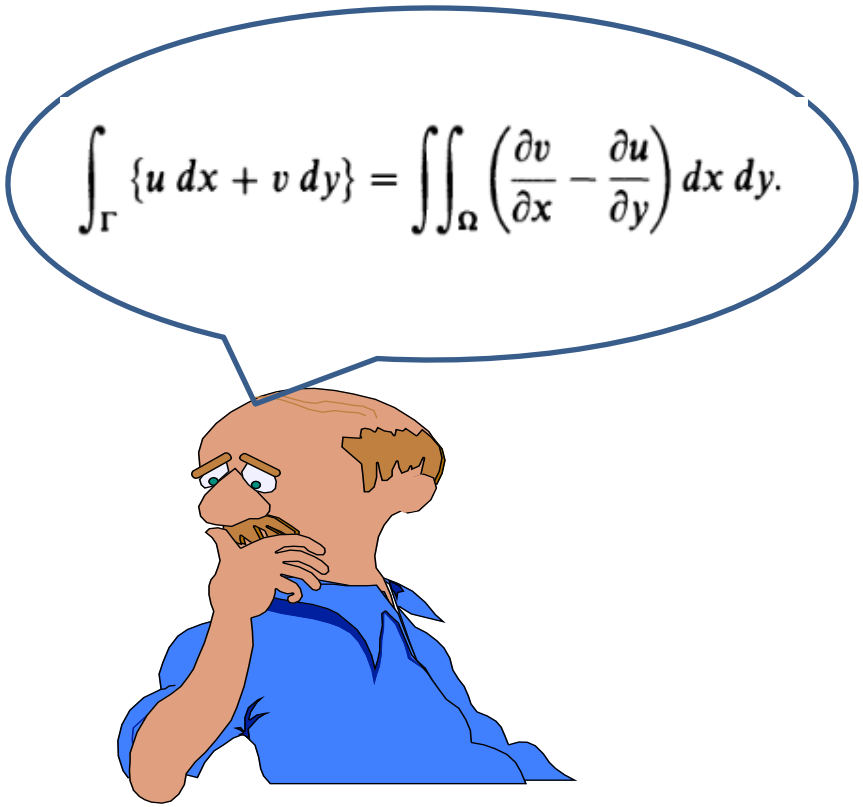
REPRODUCIBILITY OF DIAGNOSIS OF NASH WITH FLIP ALGORITHM

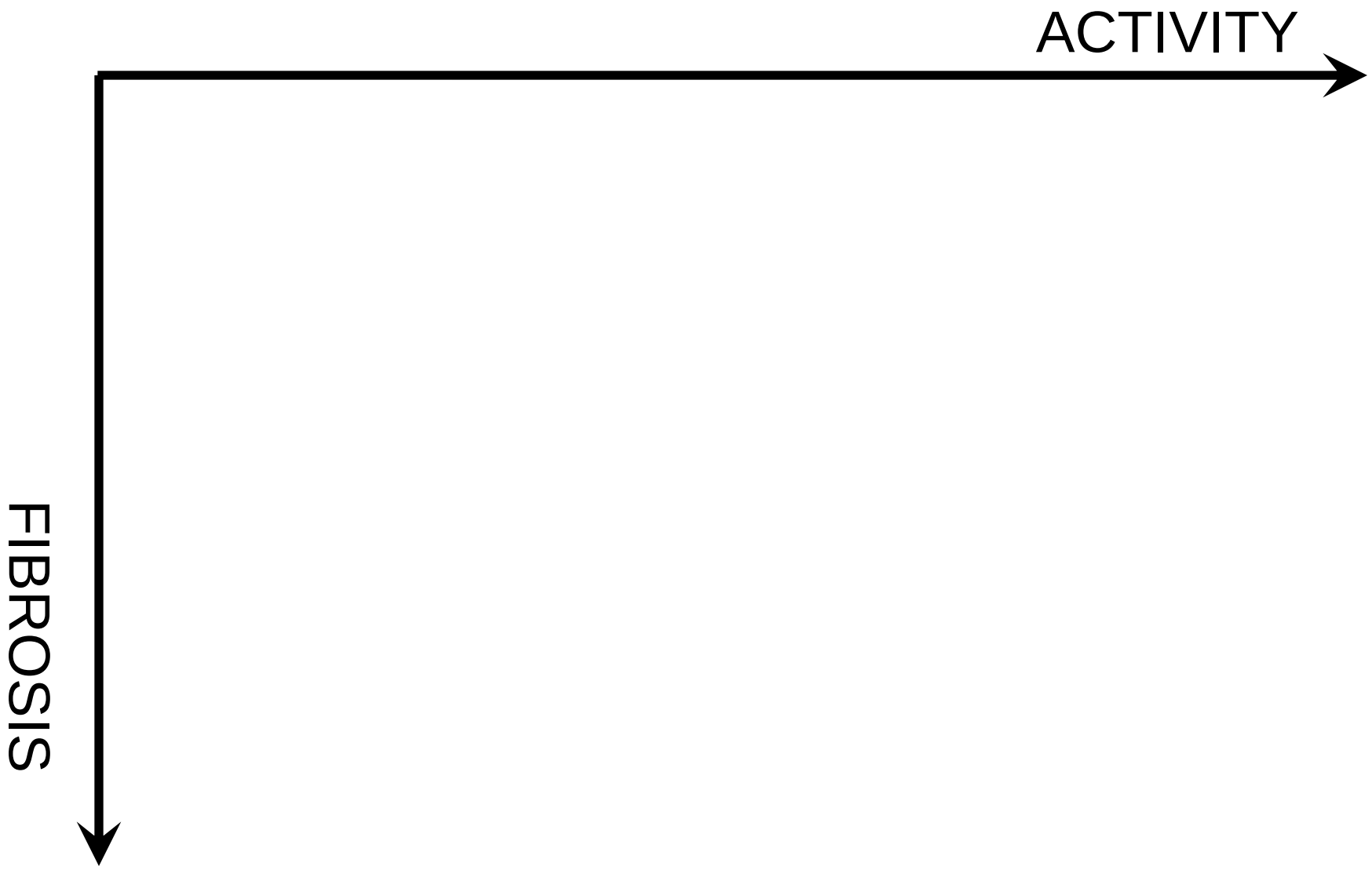
40 biopsies (Steatosis, NASH)	1st session (unsupervised)		2nd session (with classifier)
Liver Pathologists (n=6)			
• **κ score**	**0.54 (moderate)**	➡	**0.66 (substantial)**
• Nbr of biopsies with agreement between all pathologists	26/40 (65 %)	➡	34/40 (85 %)
General Pathologists (n=10)			
• κ score	0.35 (fair)	➡	**0.70 (substantial)**
• Nbr of biopsies with agreement between all pathologists	18/40 (45 %)	➡	34/40 (85 %)

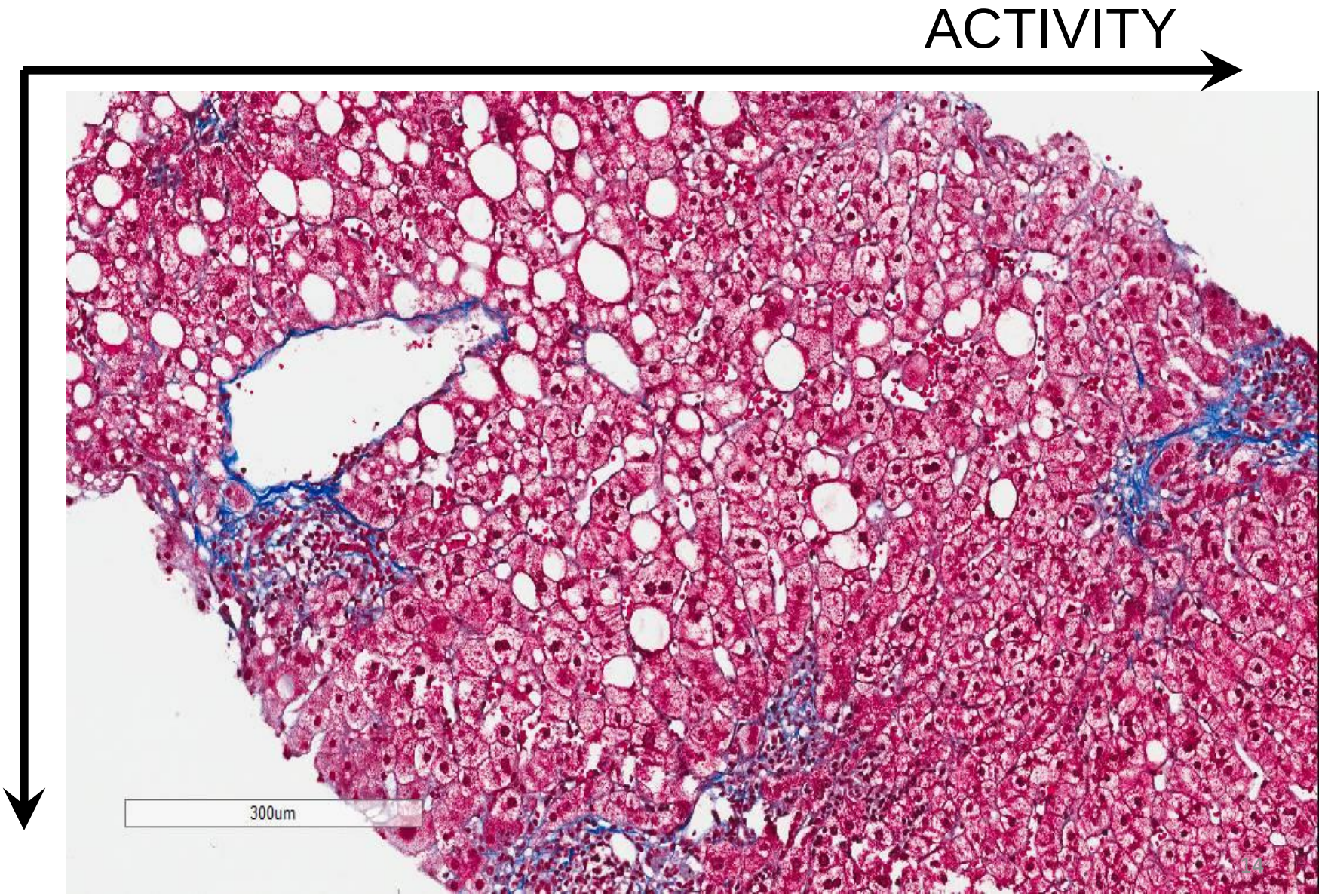
The FLIP Pathology consortium, Hepatology 2014

The definition of NASH by an association of 3 features and a clear definition of each of them make the diagnosis of NASH strongly reproducible

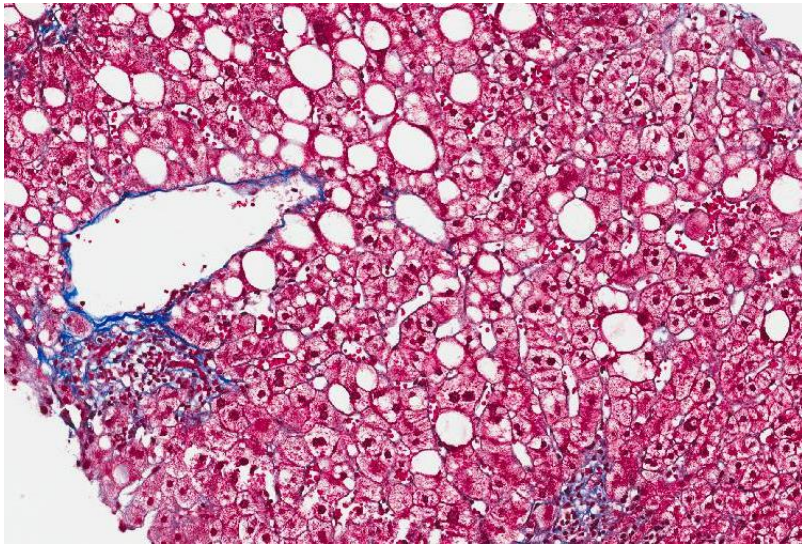
NASH: **HOW TO SCORE** ?



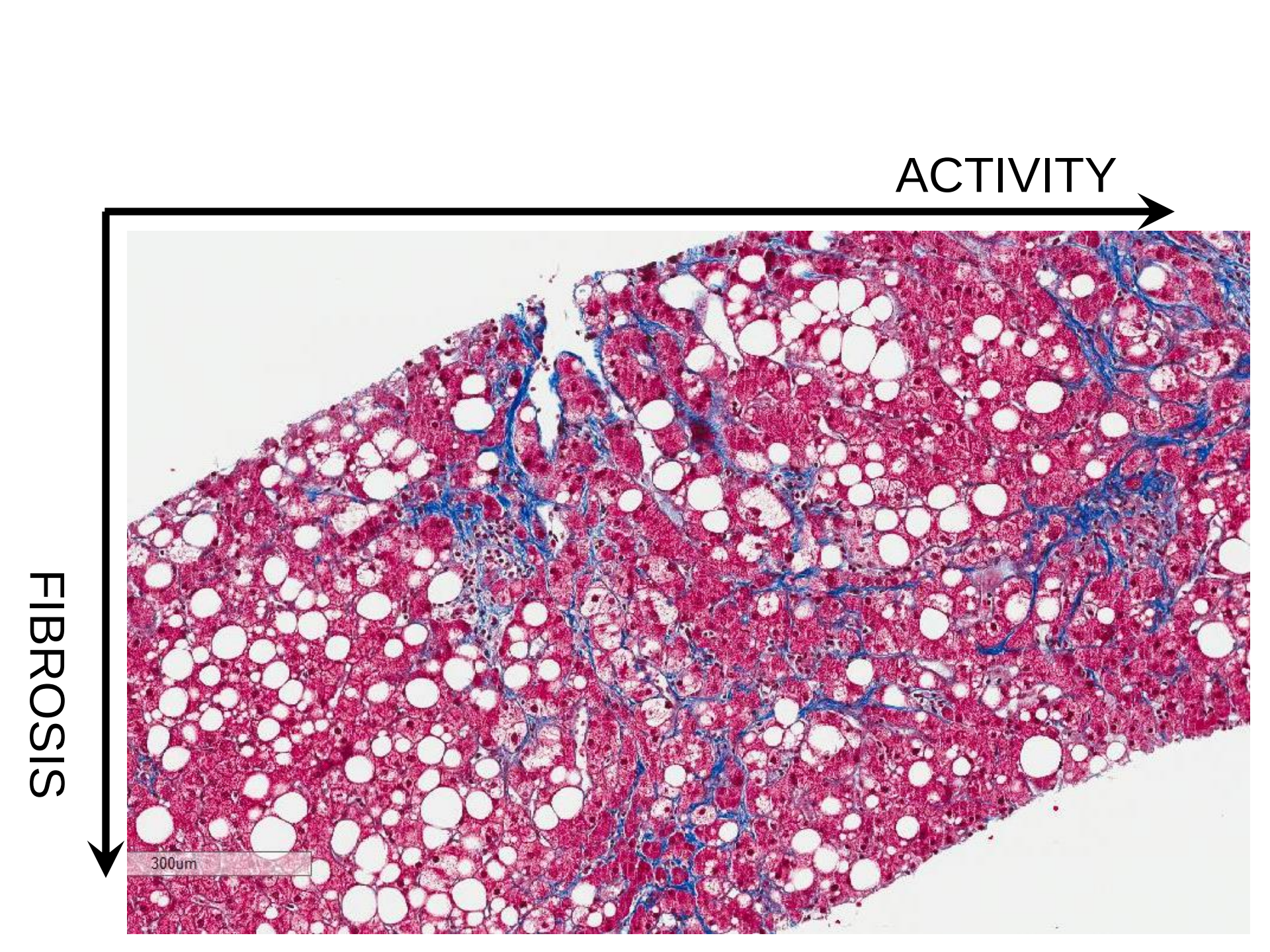

ACTIVITY
FIBROSIS


ACTIVITY
FIBROSIS
300um

ACTIVITY

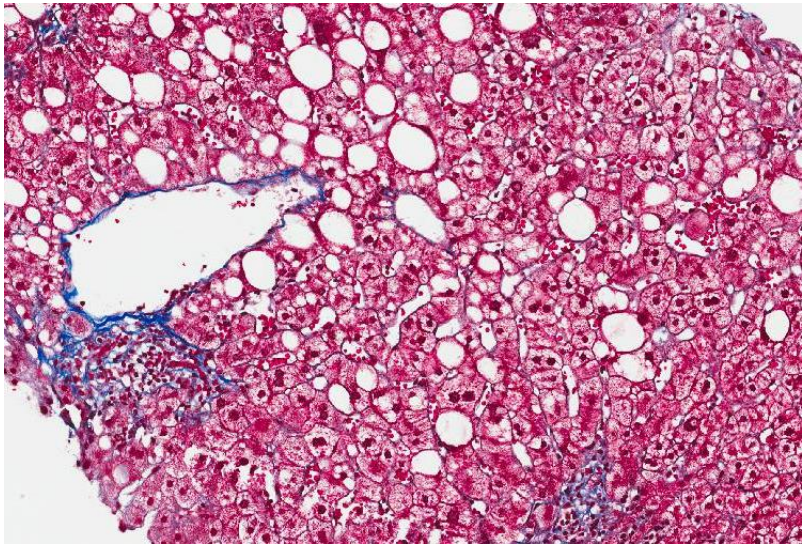


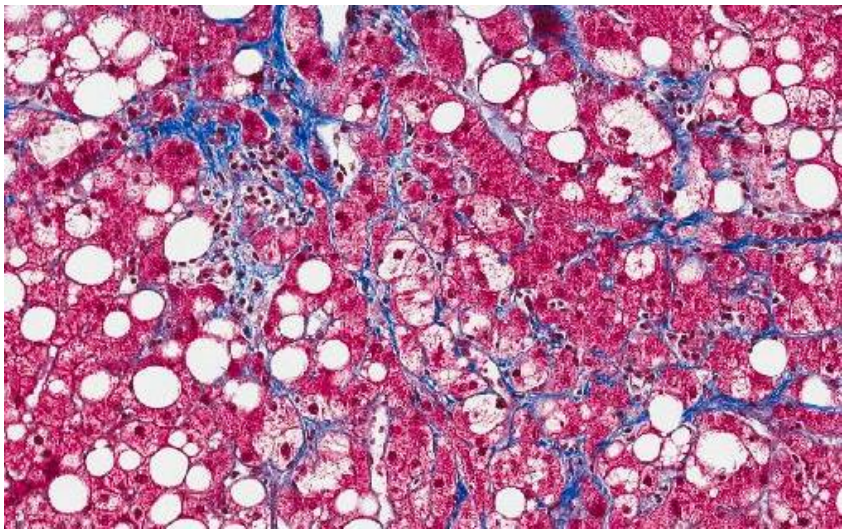
FIBROSIS


ACTIVITY
FIBROSIS
300um

ACTIVITY

FIBROSIS





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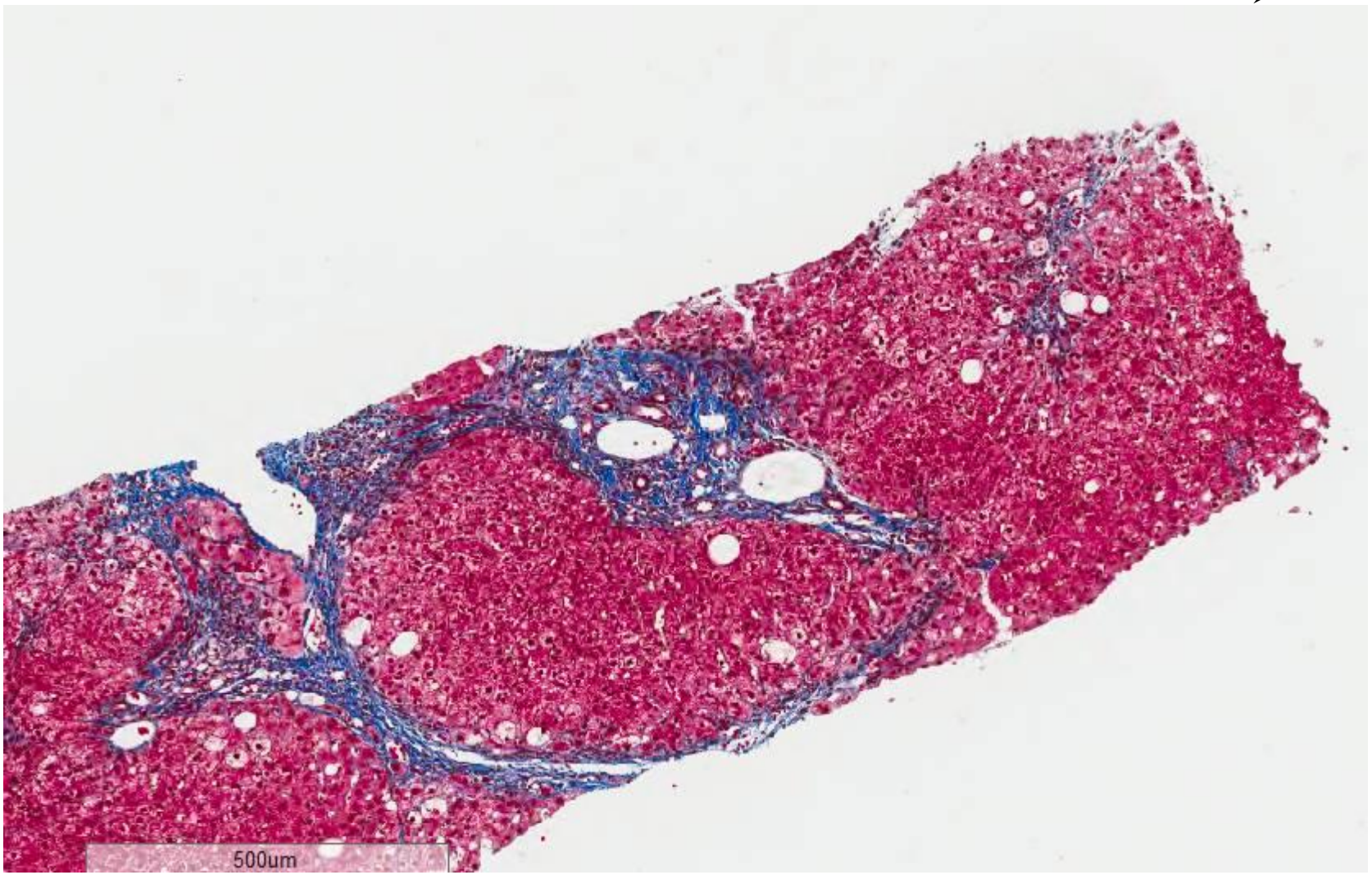

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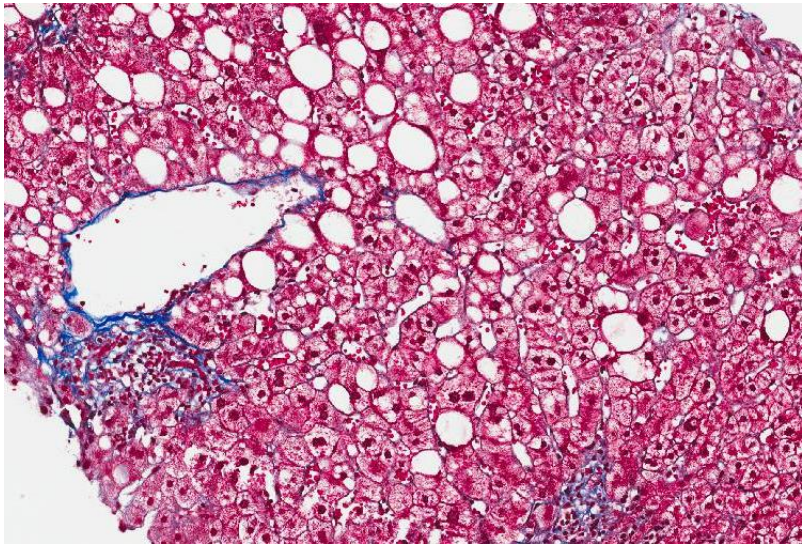
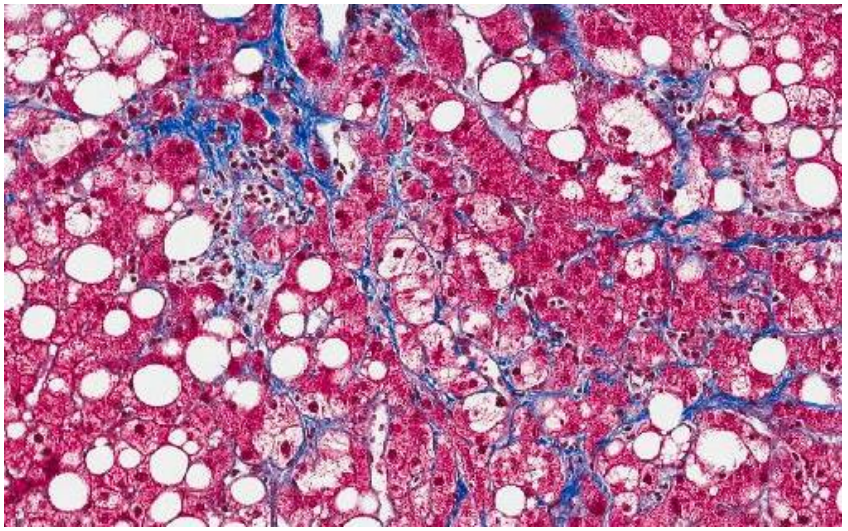
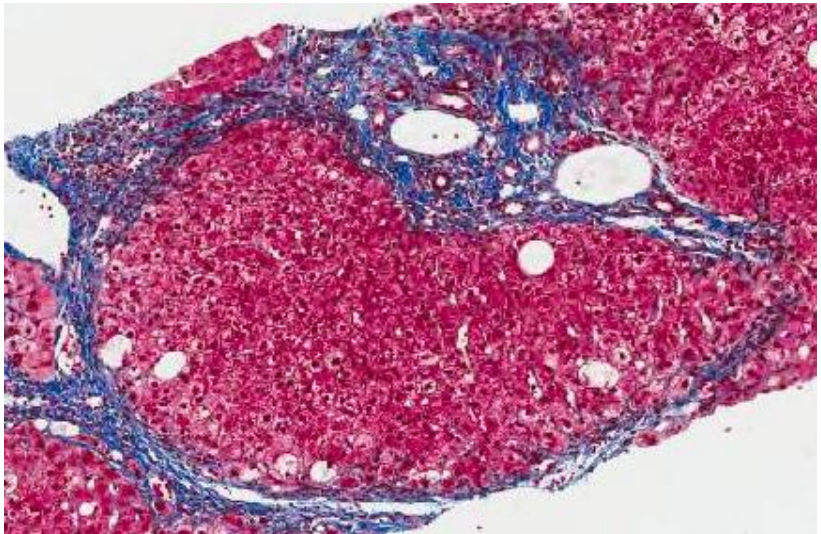
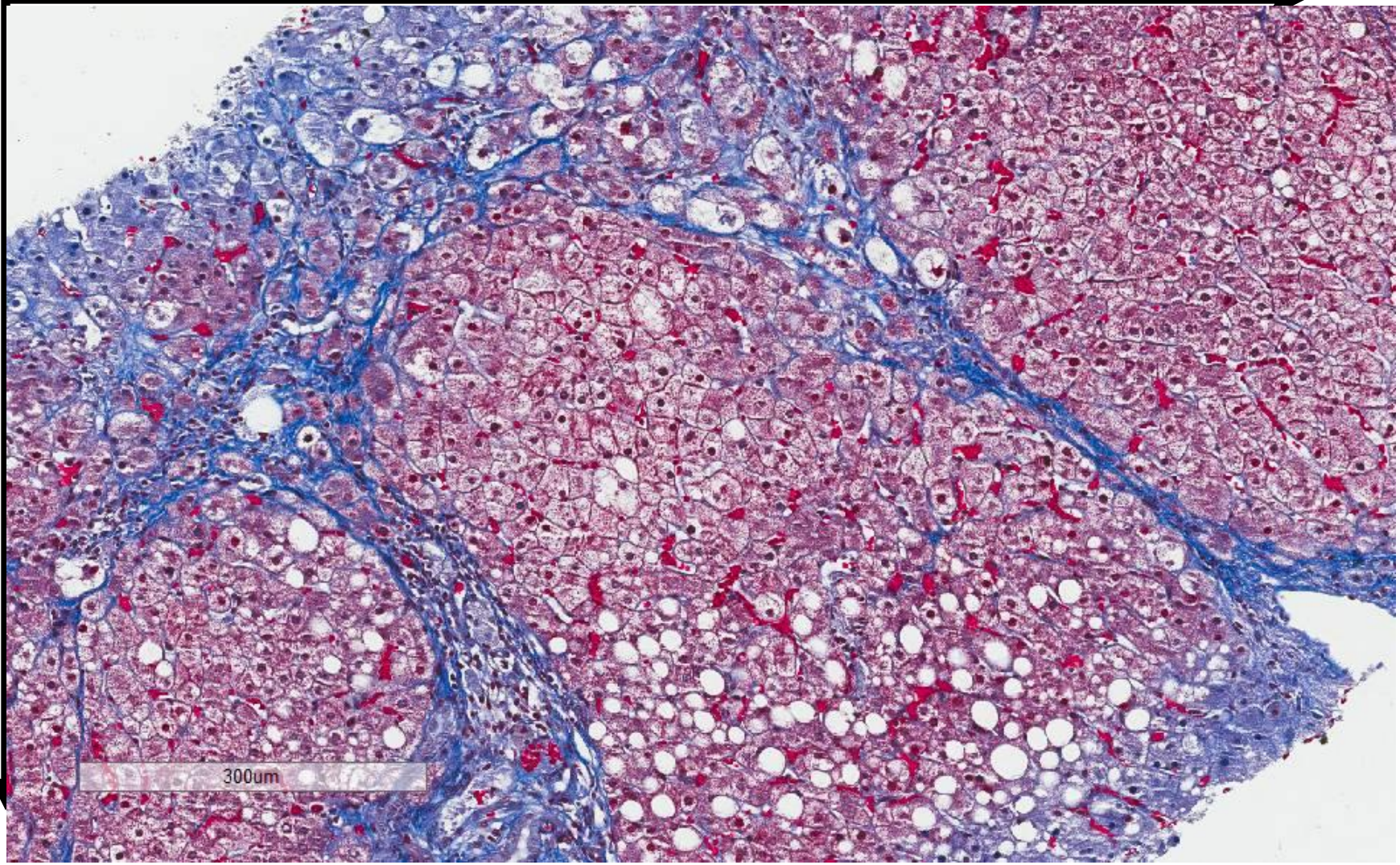






ACTIVITY

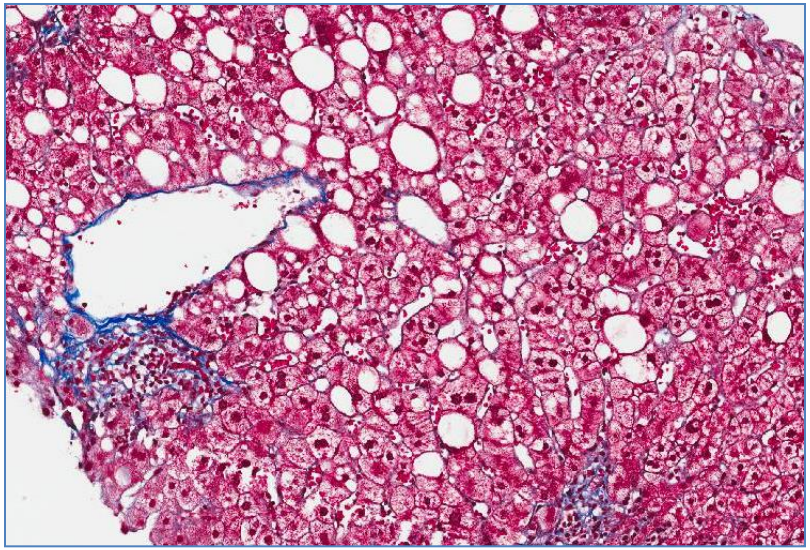
FIBROSIS

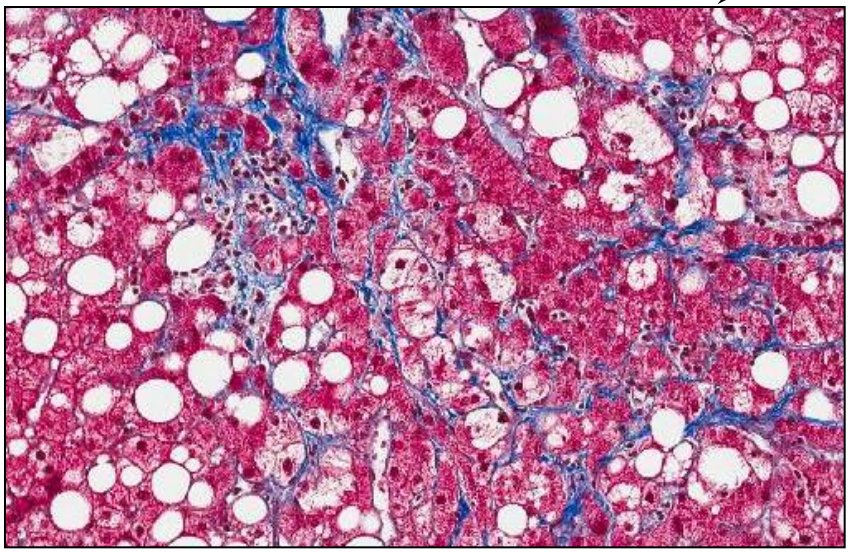


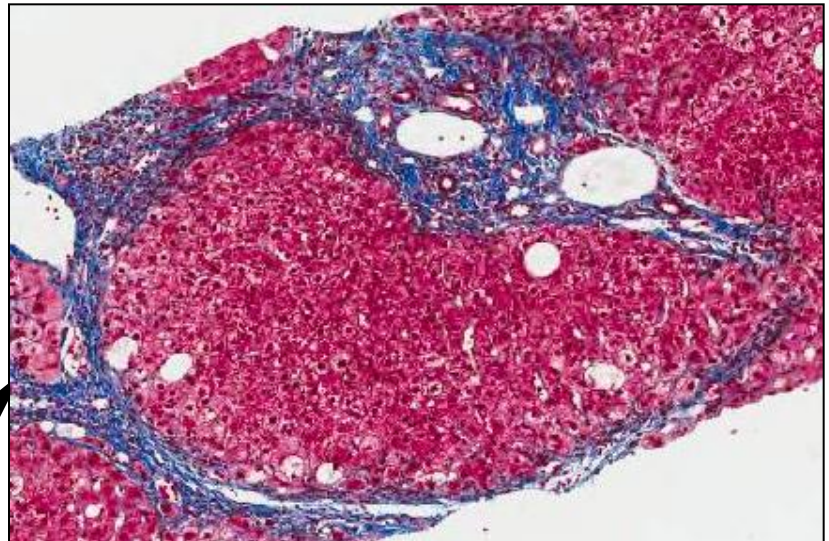
MANY SHADES OF NASH

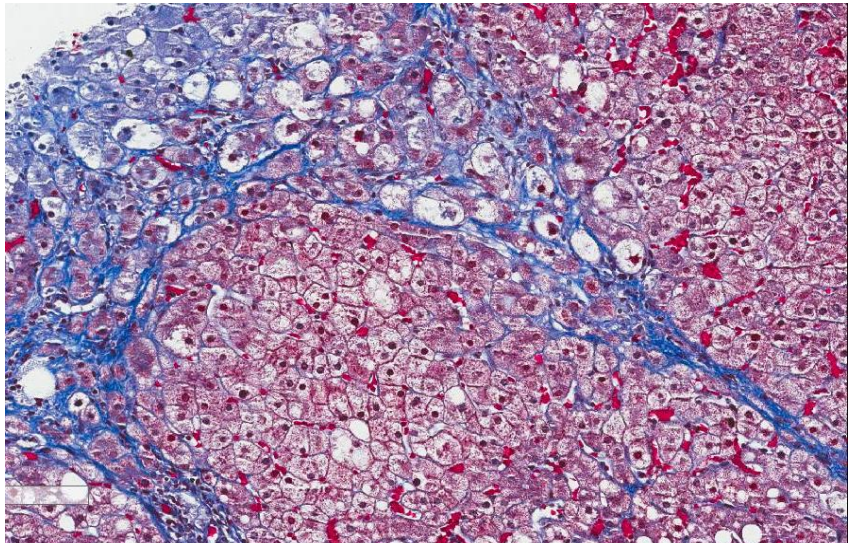
ACTIVITY

FIBROSIS









SCORING SYSTEM FOR NAFLD

NAFLD ACTIVITY SCORE - NAS (NASH CRN)

ADDITIVE SCORING SYSTEM

Steatosis	0-3
	+
Ballooning	0-2
	+
Inflammation	0-3

NAS (0-8)

SAF SCORE (FLIP)

DESCRIPTIVE SCORING SYSTEM

Steatosis	(0–3)
Activity	(0–4)

Ballooning (0-2) + Inflammation (0-2)

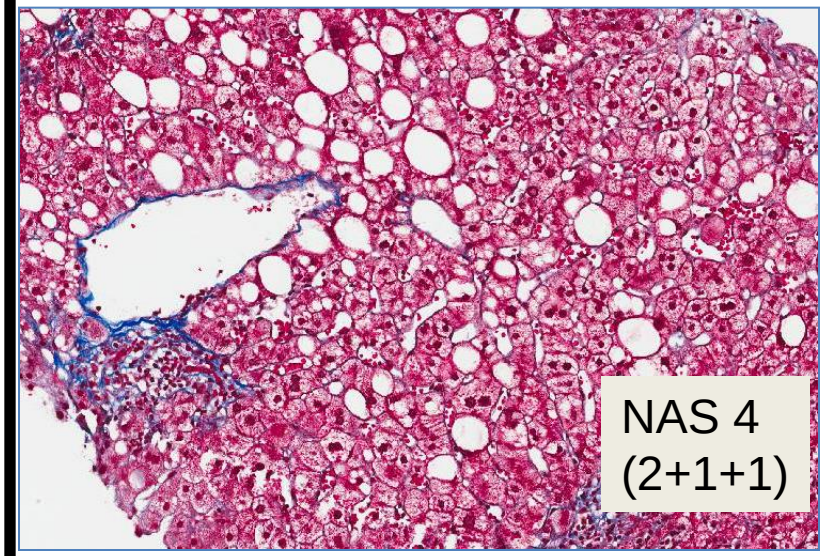
Fibrosis	(0–4)

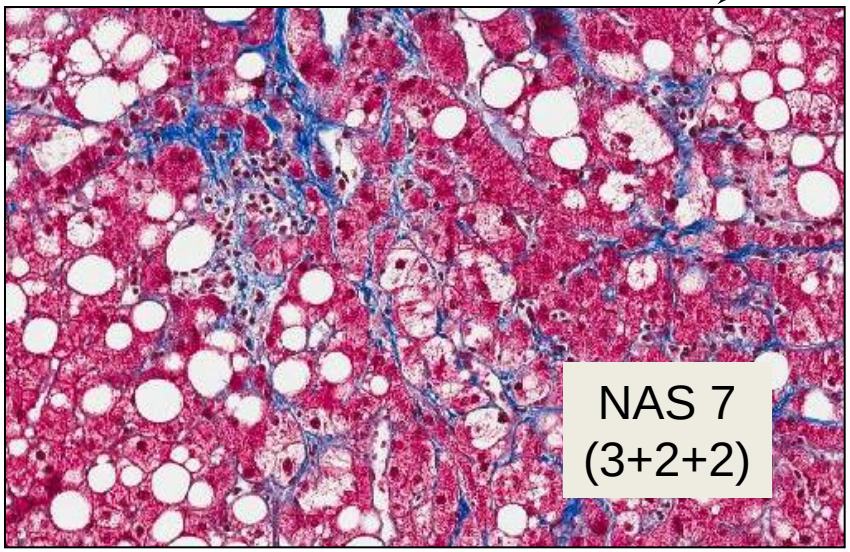
$S_{0-3}\,A_{0-4}\,F_{0-4}$

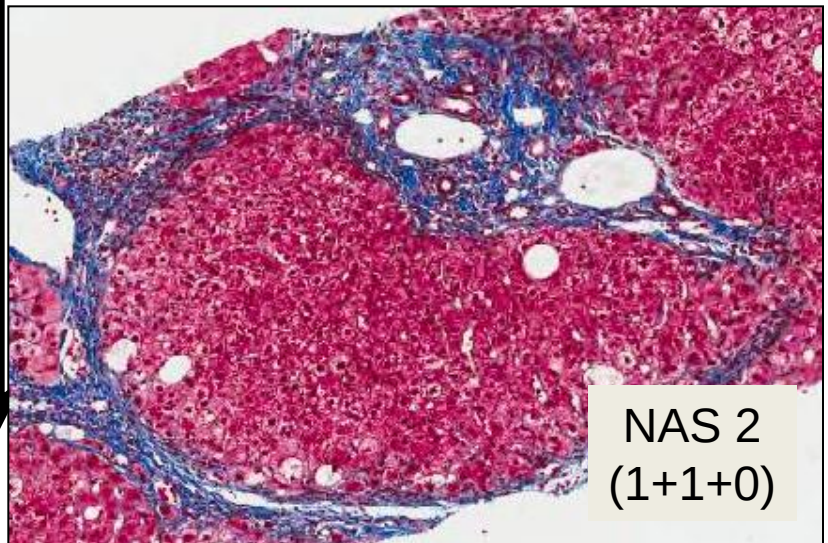
MANY SHADES OF NASH

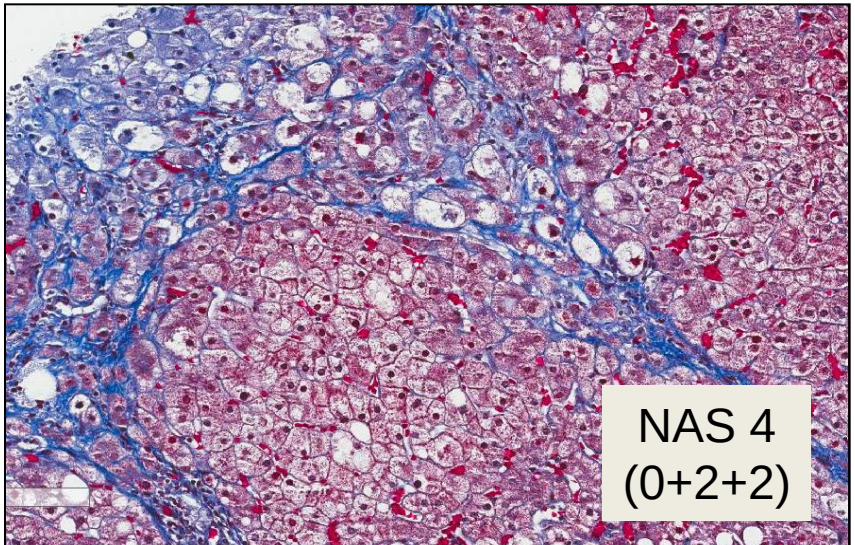
ACTIVITY

FIBROSIS





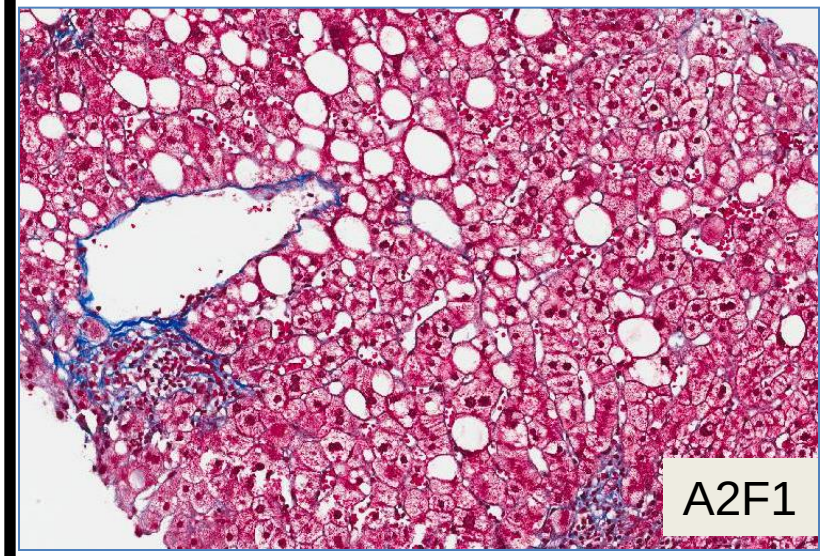


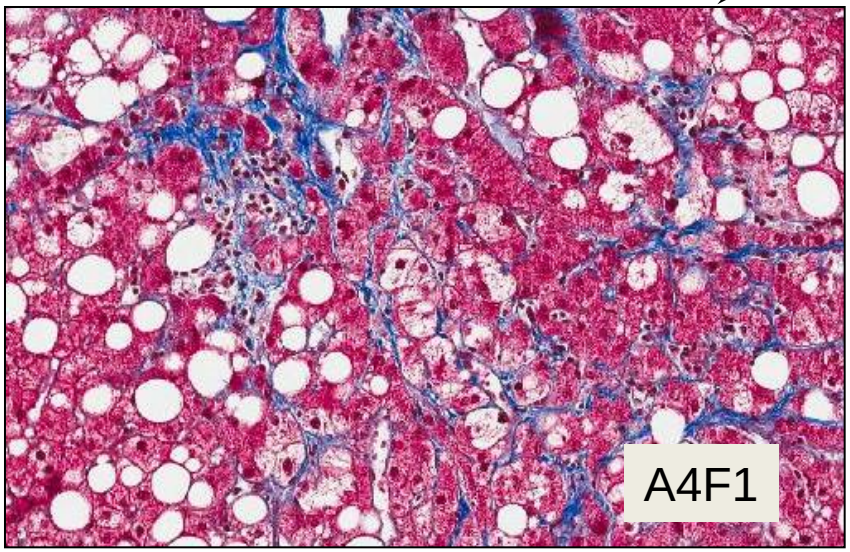


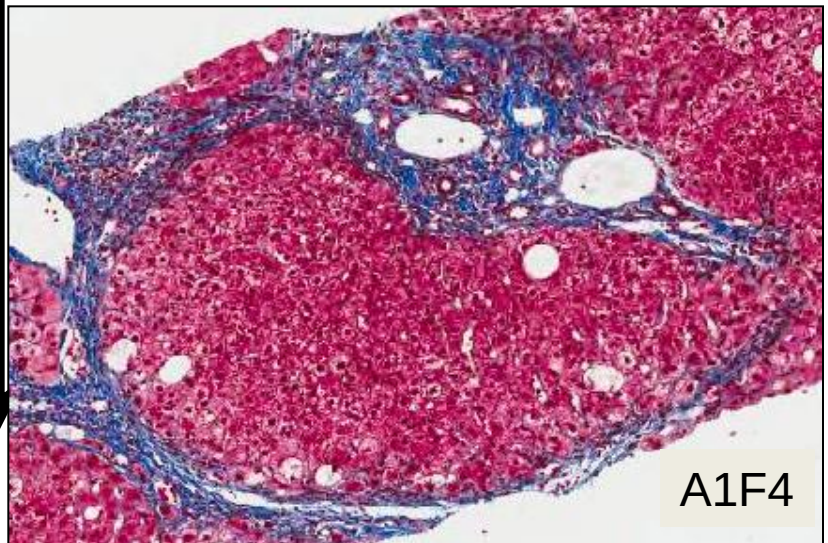
MANY SHADES OF NASH

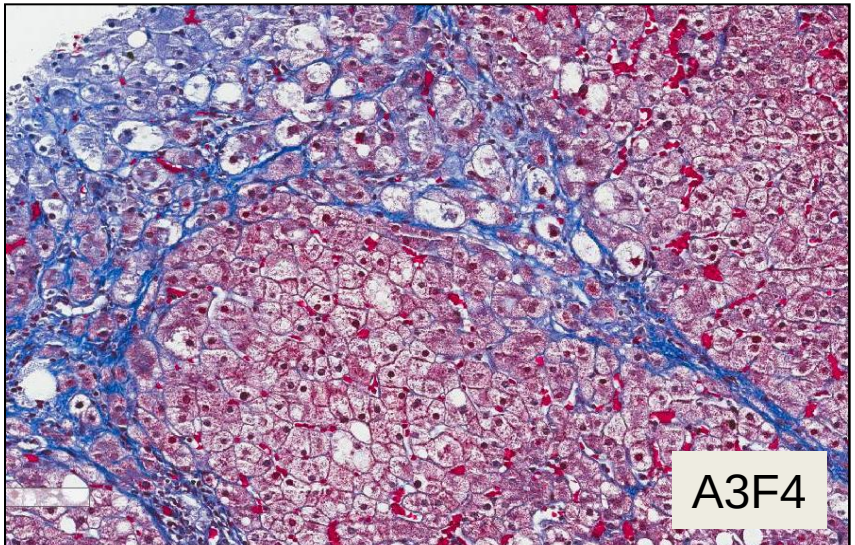
ACTIVITY

FIBROSIS

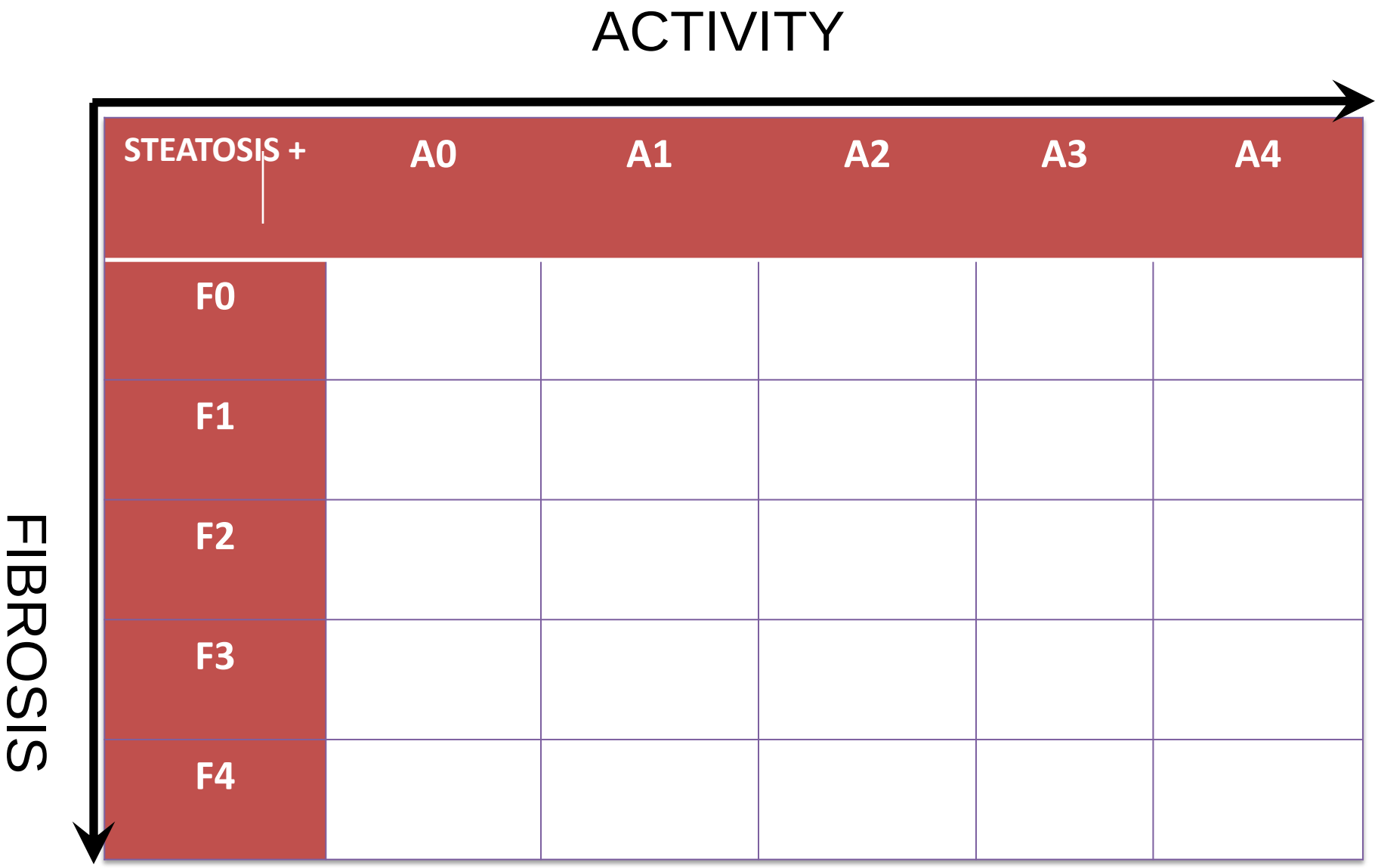








HOW TO HANDLE THE SAF SCORE IN CT



HOW TO HANDLE THE SAF SCORE IN CT

ACTIVITY

FIBROSIS

STEATOSIS +	A0	A1	A2	A3	A4
F0	Mild	Mild		Severe	Severe
F1	Mild	Mild		Severe	Severe
F2				Severe	Severe
F3	Severe	Severe	Severe	Severe	Severe
F4	Severe	Severe	Severe	Severe	Severe

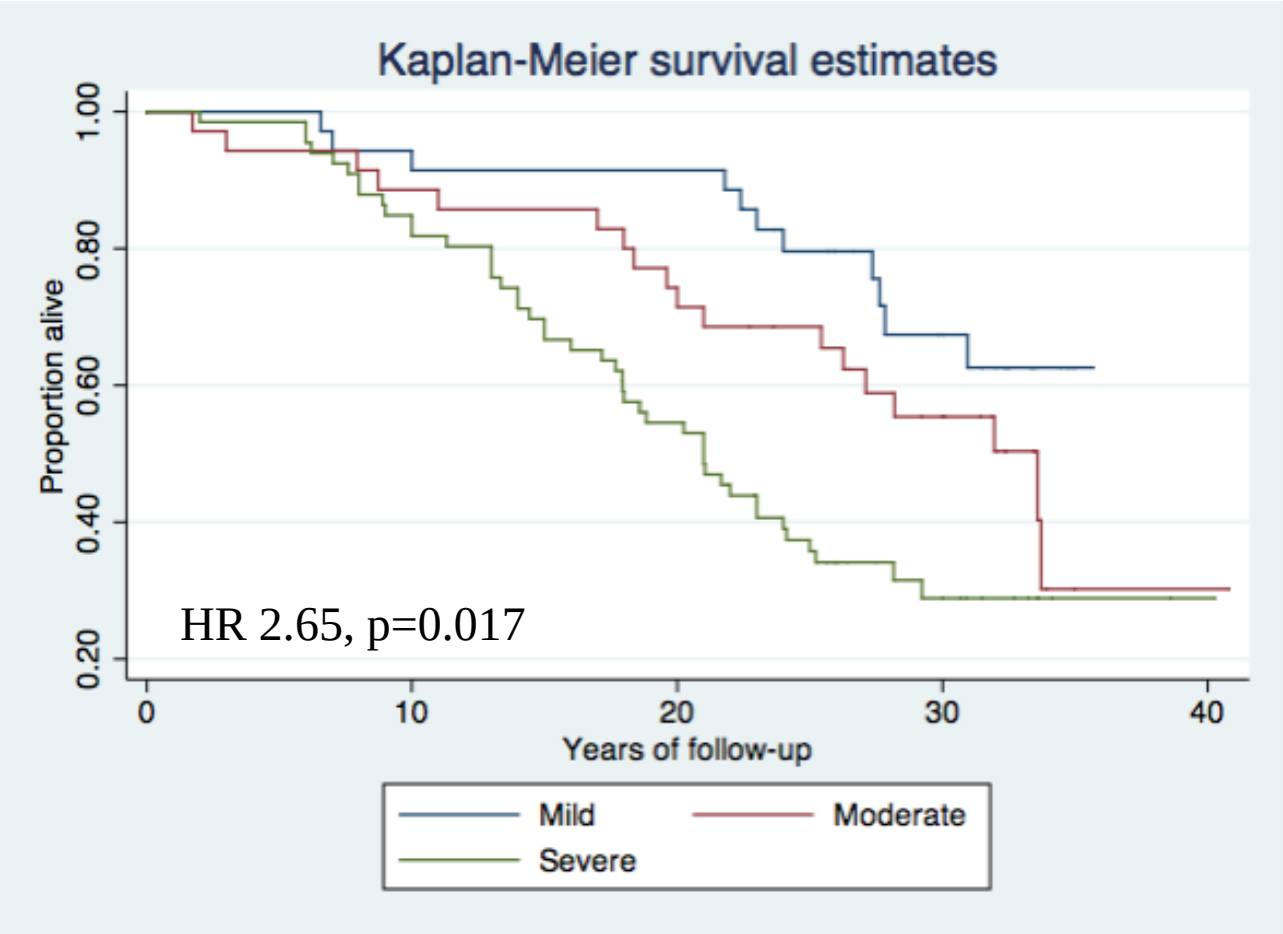
HOW TO HANDLE THE SAF SCORE IN CT

ACTIVITY

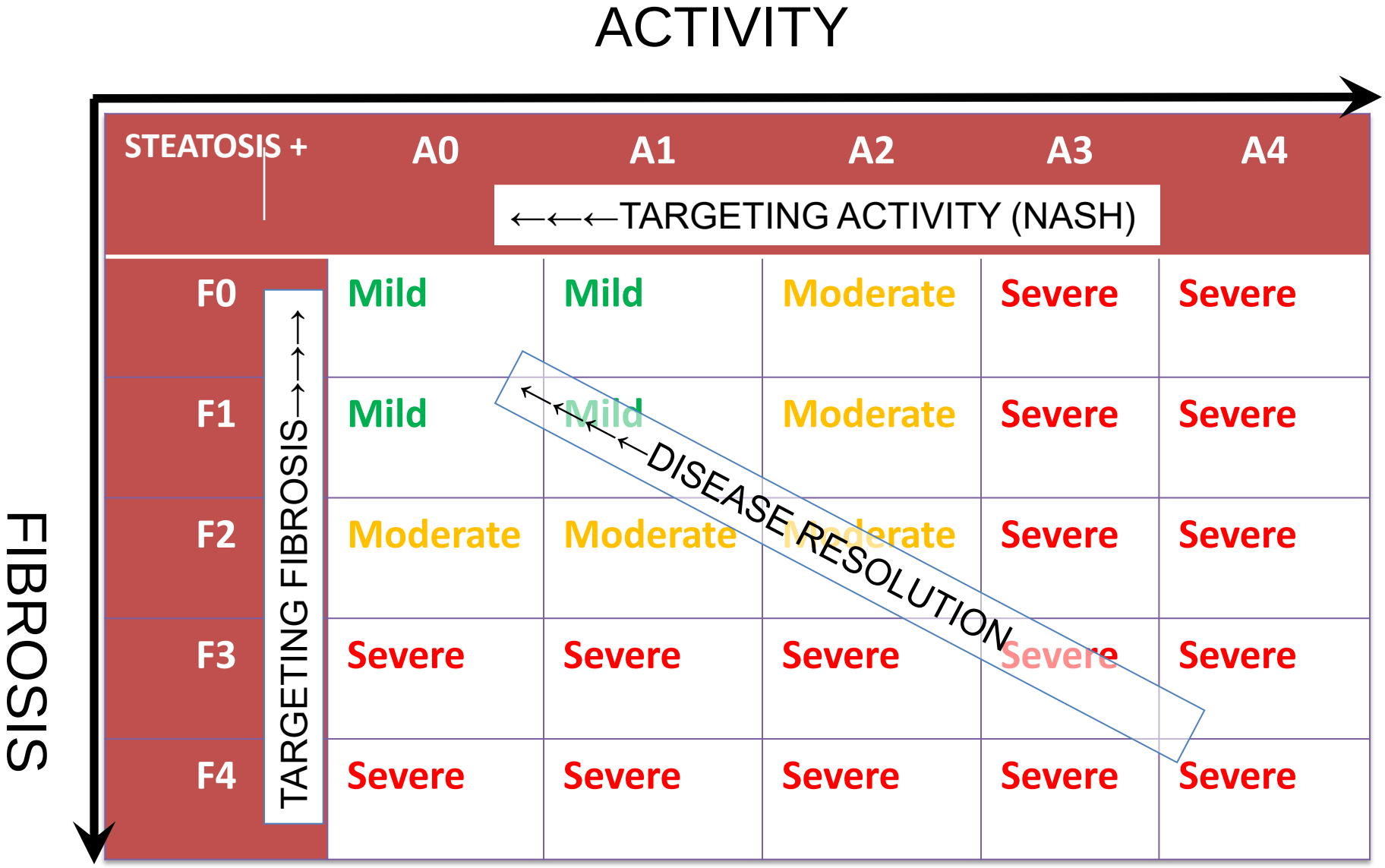
FIBROSIS

STEATOSIS +	A0	A1	A2	A3	A4
F0	Mild	Mild	Moderate	Severe	Severe
F1	Mild	Mild	Moderate	Severe	Severe
F2	Moderate	Moderate	Moderate	Severe	Severe
F3	Severe	Severe	Severe	Severe	Severe
F4	Severe	Severe	Severe	Severe	Severe

Overall mortality



Hannes Hagström, EASL, 2016


ACTIVITY
FIBROSIS
STEATOSIS +
A0
A1
A2
A3
A4
←←←TARGETING ACTIVITY (NASH)
F0
F1
F2
F3
F4
TARGETING FIBROSIS→→→
Mild
Mild
Moderate
Severe
Severe
Mild
Mild
Moderate
Severe
Severe
Moderate
Moderate
Moderate
Severe
Severe
Severe
Severe
Severe
Severe
Severe
Severe
Severe
Severe
Severe
←←←DISEASE RESOLUTION

LESSONS FROM THE PAST
Progress in classification of CHC

Yrs

Chronic viral hepatitis	
Chronic persistent hepatitis / Chronic active hepatitis (1960)	
Chronic lobular hepatitis (1970)	
Histological Activity Index (HAI=Activity + Fibrosis) (1980)	
METAVIR (1994) Ishak score (1995) **A and F**	

CLINICAL TRIALS → HISTOLOGICAL SCORES

LESSONS FROM THE PAST
Progress in classification of CHC

Yrs

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(2015) **End of the story**	

CLINICAL TRIALS → HISTOLOGICAL SCORES

Yrs

We are running 20 years behind….

Chronic viral hepatitis	NAFLD
Chronic persistent hepatitis / Chronic active hepatitis (1960)	NAFL / NASH (1980)
Chronic lobular hepatitis (1970)	Borderline NASH (2000)
CLINICAL TRIALS → HISTOLOGICAL SCORES	
Histological Activity Index (HAI=Activity + Fibrosis) (1980)	NAFLD Activity Score (NAS) (NAS = Activity + Steatosis) (2005)
METAVIR (1994) Ishak score (1995) **A and F**	SAF (FLIP 2012) ……. **S and A and F**
(2015) End of the story	

Yrs

We are running 20 years behind….

Chronic viral hepatitis	NAFLD
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CLINICAL TRIALS → HISTOLOGICAL SCORES	
Histological Activity Index (HAI=Activity + Fibrosis) (1980)	NAFLD Activity Score (NAS) (NAS = Activity + Steatosis) (2005)
METAVIR (1994) Ishak score (1995) **A and F**	SAF (FLIP 2012) …… **S and A and F**
(2015) End of the story	**Still 20 years to go**

Thank you for your attention !