PATHOLOGY OF NAFLD

Pierre Bedossa

Departement of Pathology

Hôpital Beaujon

University Paris-Diderot
Paris - FRANCE

PATHOLOGY OF NAFLD

- NAFLD: a chronic liver disease with a wide range of tissue lesions
- Liver biopsy allows an integrated evaluation of tissue damages related to various pathophysiological mechanisms
- Histology is central for disease definitions and prognosis in NAFLD
- Non invasive biomarkers are still unmet need

OUTLINES

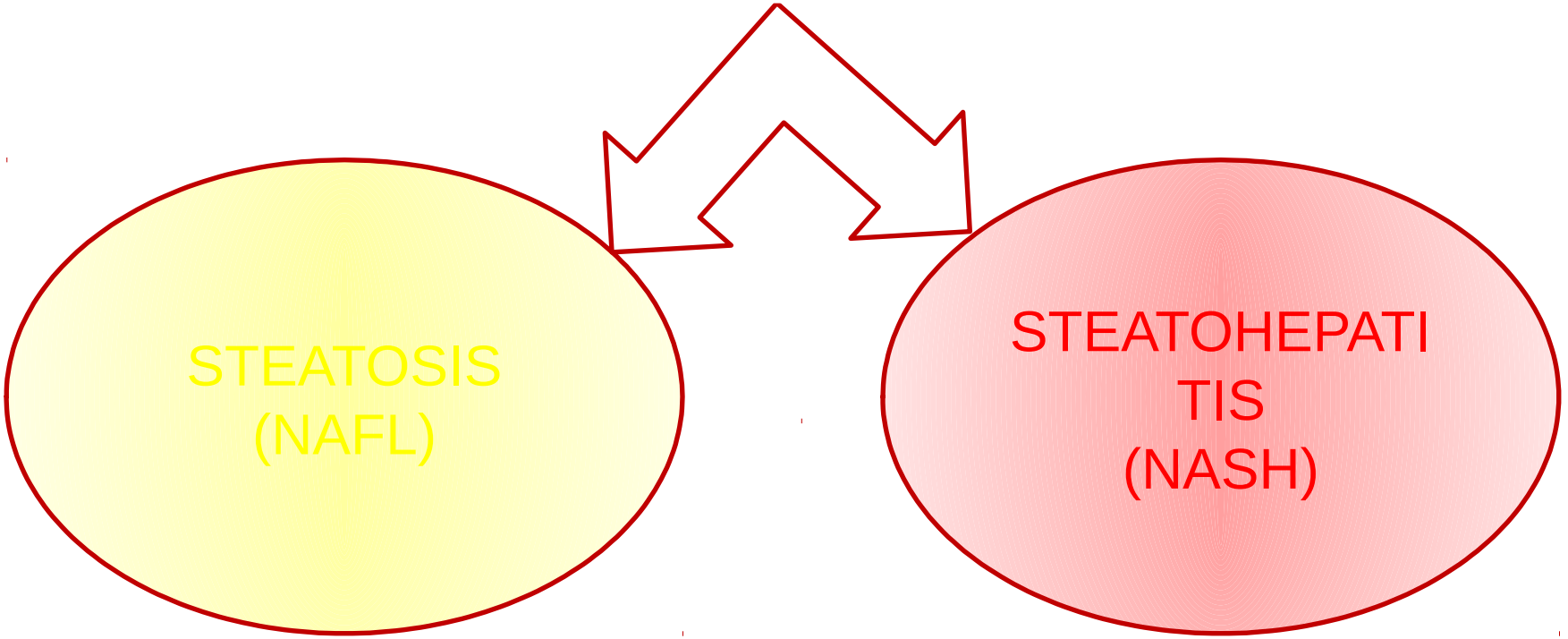
- **CLASSIFICATIONS OF NAFLD :**
  - INTEGRATED APPROACH (NASH CRN)
  - ANALYTICAL APPROACH (SAF)
- **HISTOLOGY IN CLINICAL TRIALS**

THE CLASSICAL VIEW : A DICHOTOMOUS CLASSIFICATION

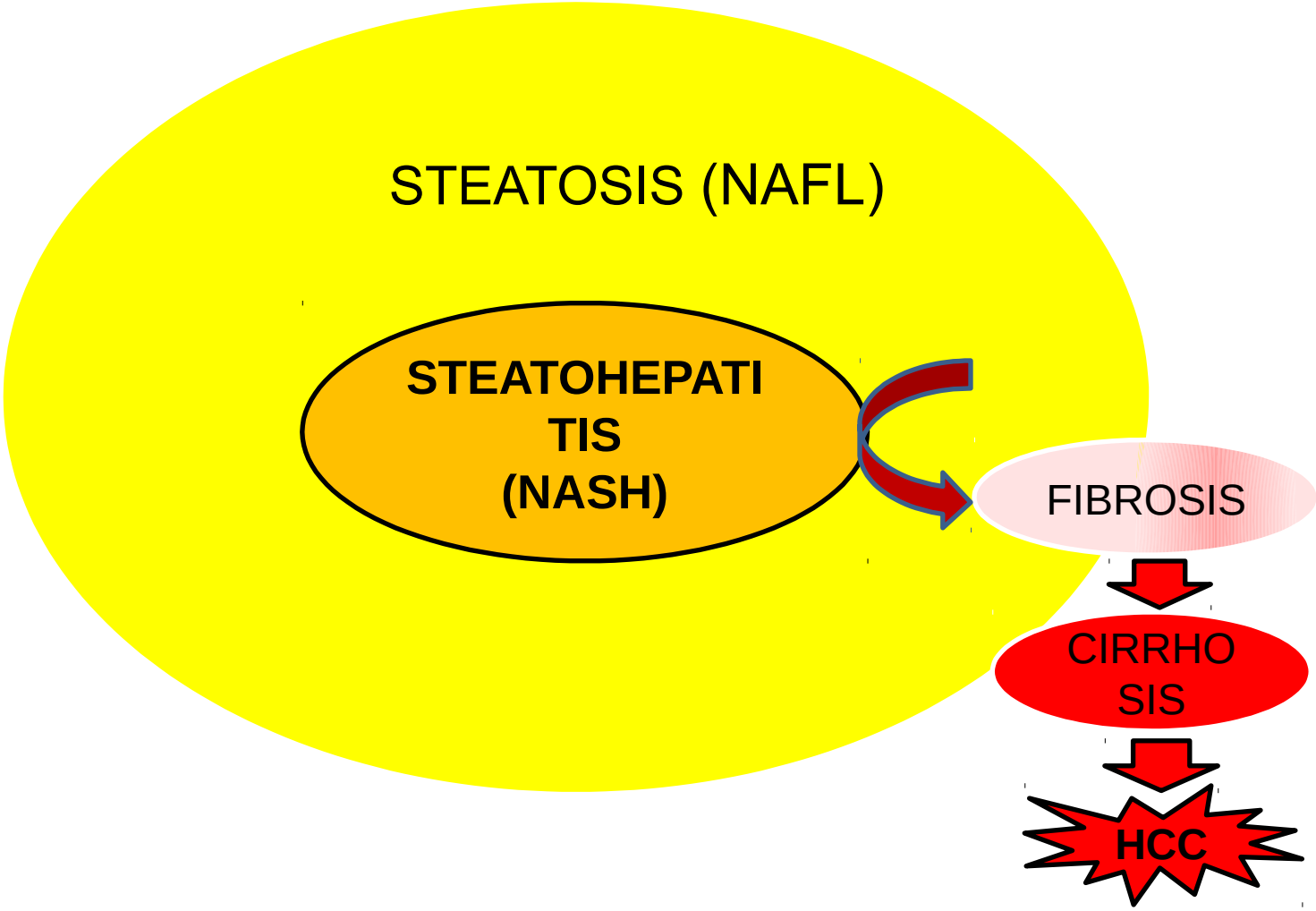
HISTORICAL LANDMARK

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Ludwig J, et al. Mayo Clin Proc. 1980

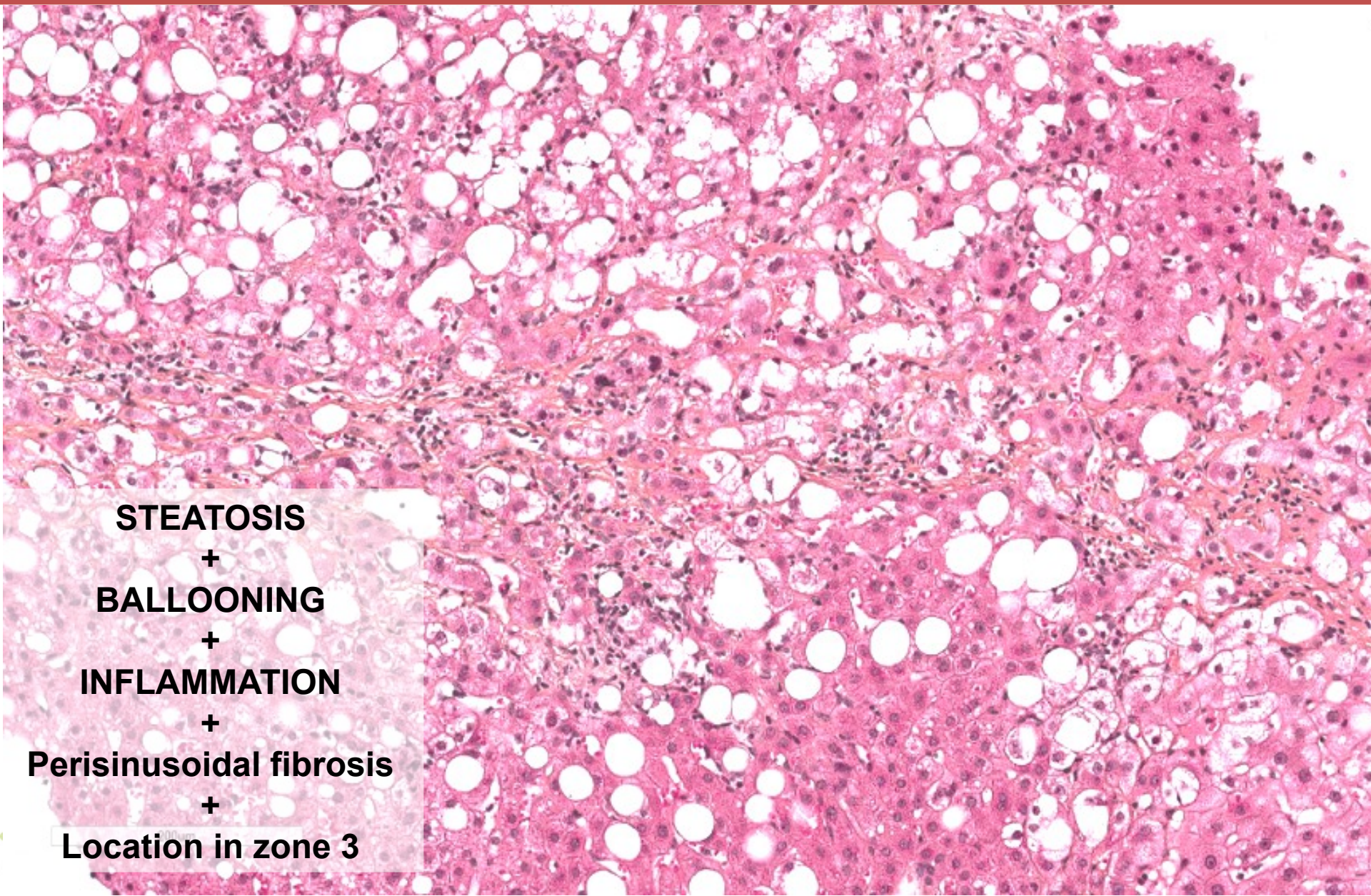
Non Alcoholic Fatty Liver Diseases (NAFLD)



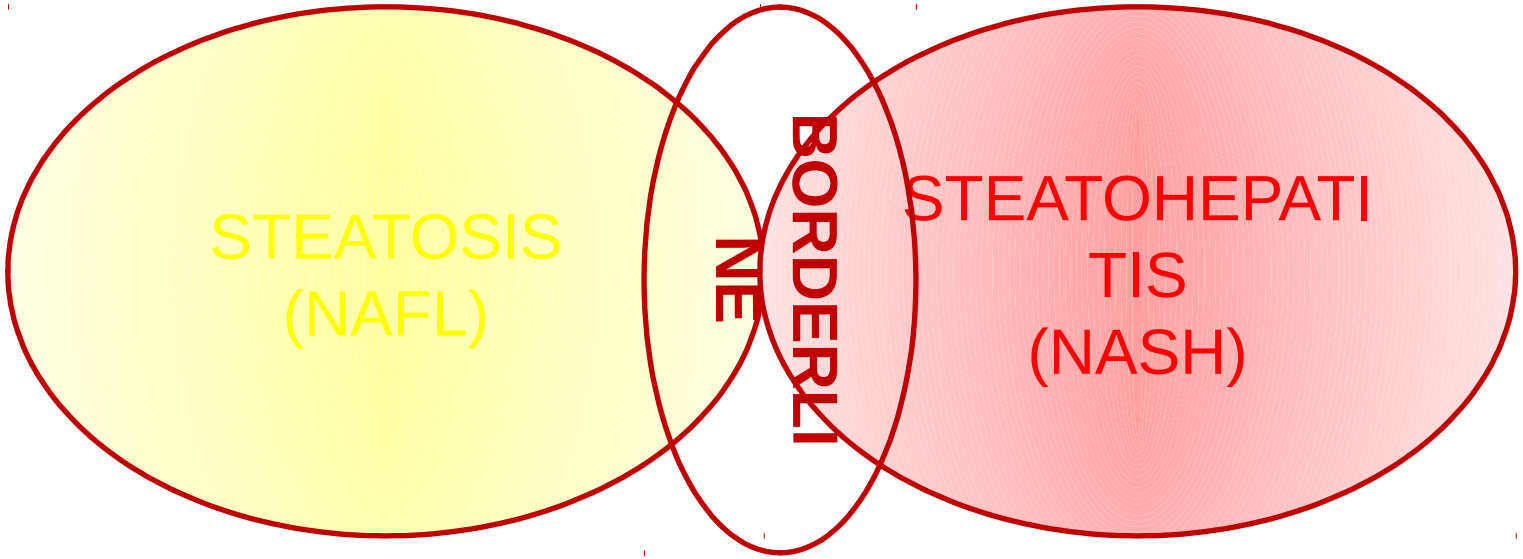
THE NATURAL HISTORY OF NAFLD



NASH : ASSOCIATION OF HISTOLOGICAL PATTERNS



THE LIMIT OF A DICHOTOMOUS CLASSIFICATION



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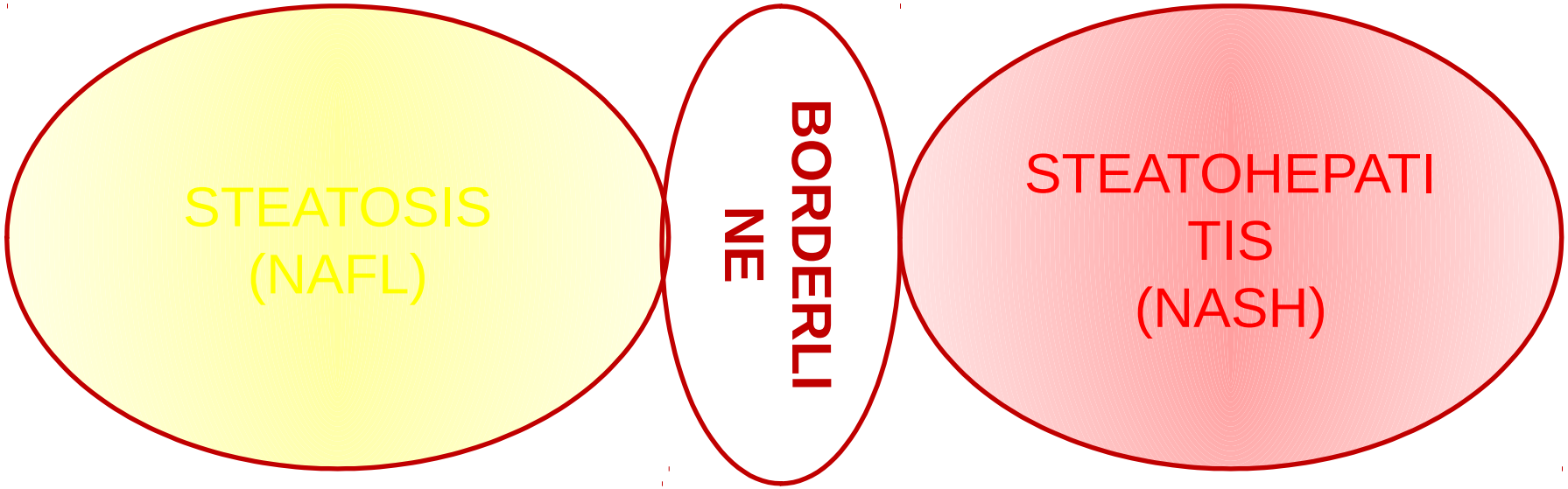
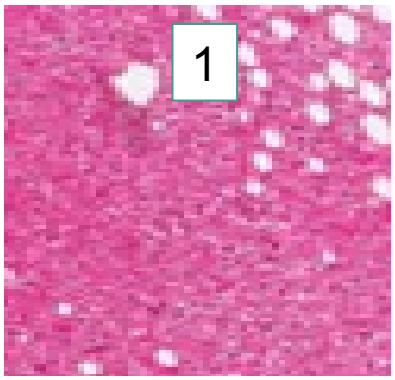
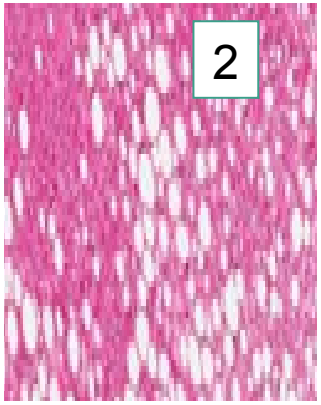


NAFLD Activity Score (NAS, 0-8)

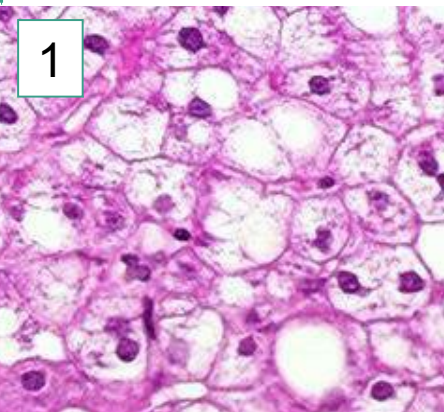
STEATOSIS

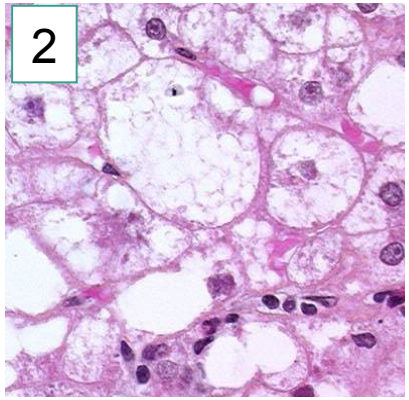




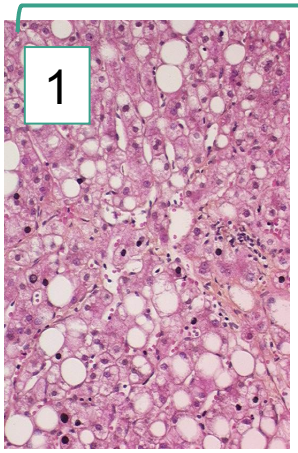
3

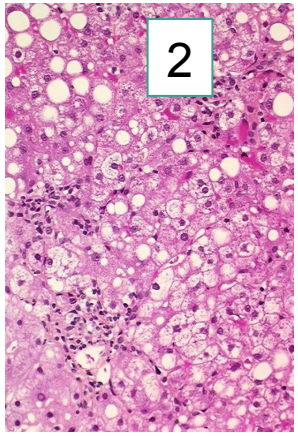
+ BALLONING

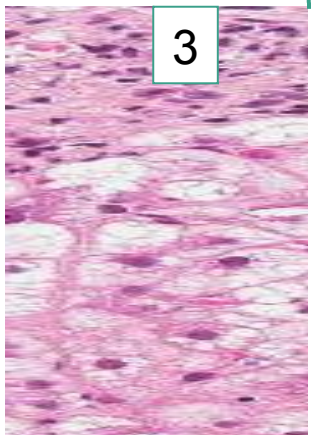




+ INFLAMMATION







NASH CRN, Hepatology 2005

NAFLD Activity Score (NAS, 0-8)

- Correlation between NAS and histologic diagnosis of NASH

  < 3: no NASH

  3-4 : GREY ZONE

  >5 : definitively NASH

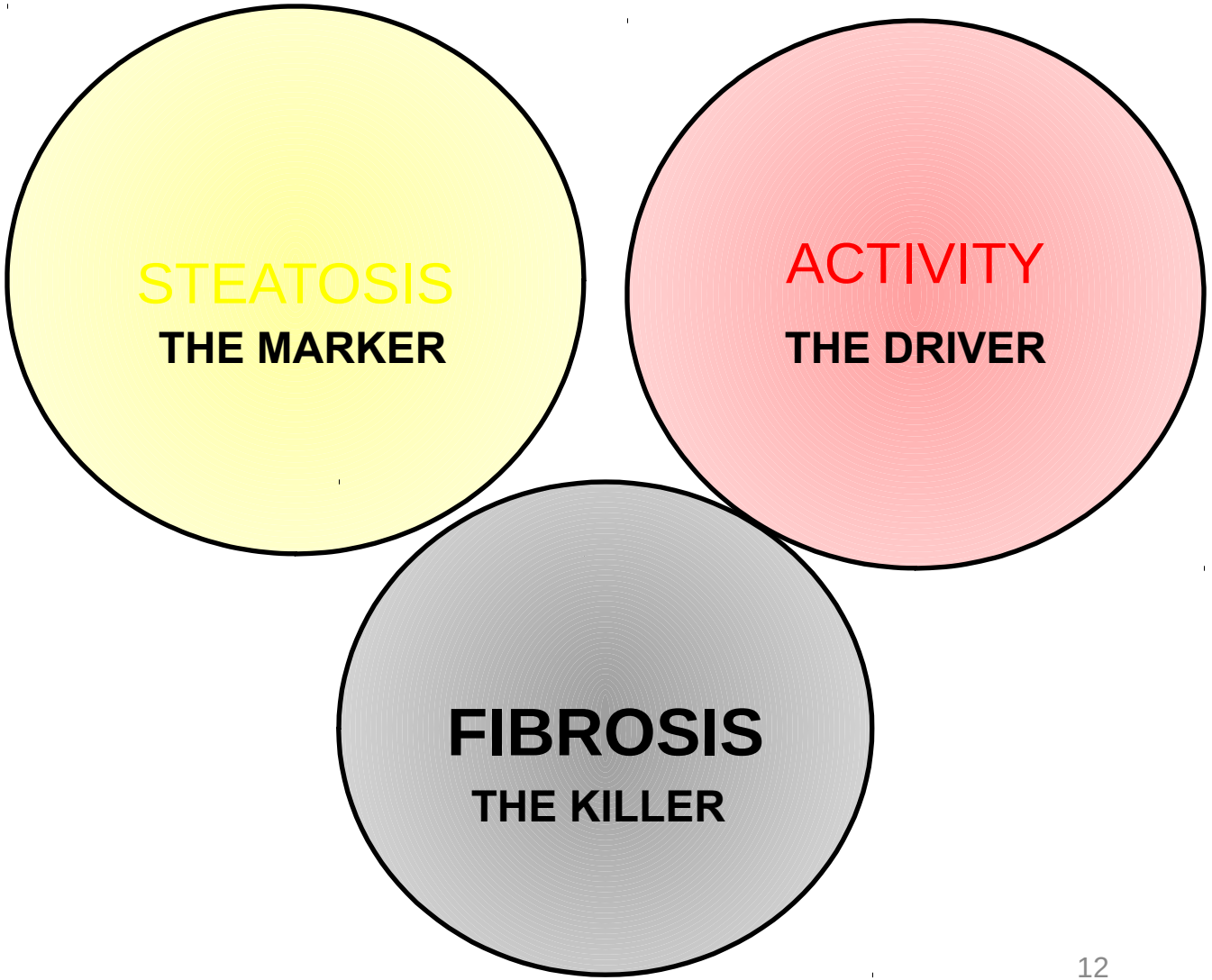
- NAS = Sum of lesions related to different mechanisms and with different clinical relevance (steatosis vs hepatocellular injury)
- Ballooning (0-2) underweighted vs steatosis (0-3) or inflammation (0-3)
- NAS has not been shown as a prognostic factor

OUTLINES

- CLASSIFICATIONS OF NAFLD :
  - INTEGRATED APPROACH (NASH CRN)
  - **ANALYTICAL APPROACH (SAF)**
- HISTOLOGY IN CLINICAL TRIALS

UNDER THE LENS : THE 3 HISTOLOGICAL COMPONENTS OF NAFLD

FLIP consortium, Hepatology 2012, Hepatology 2014

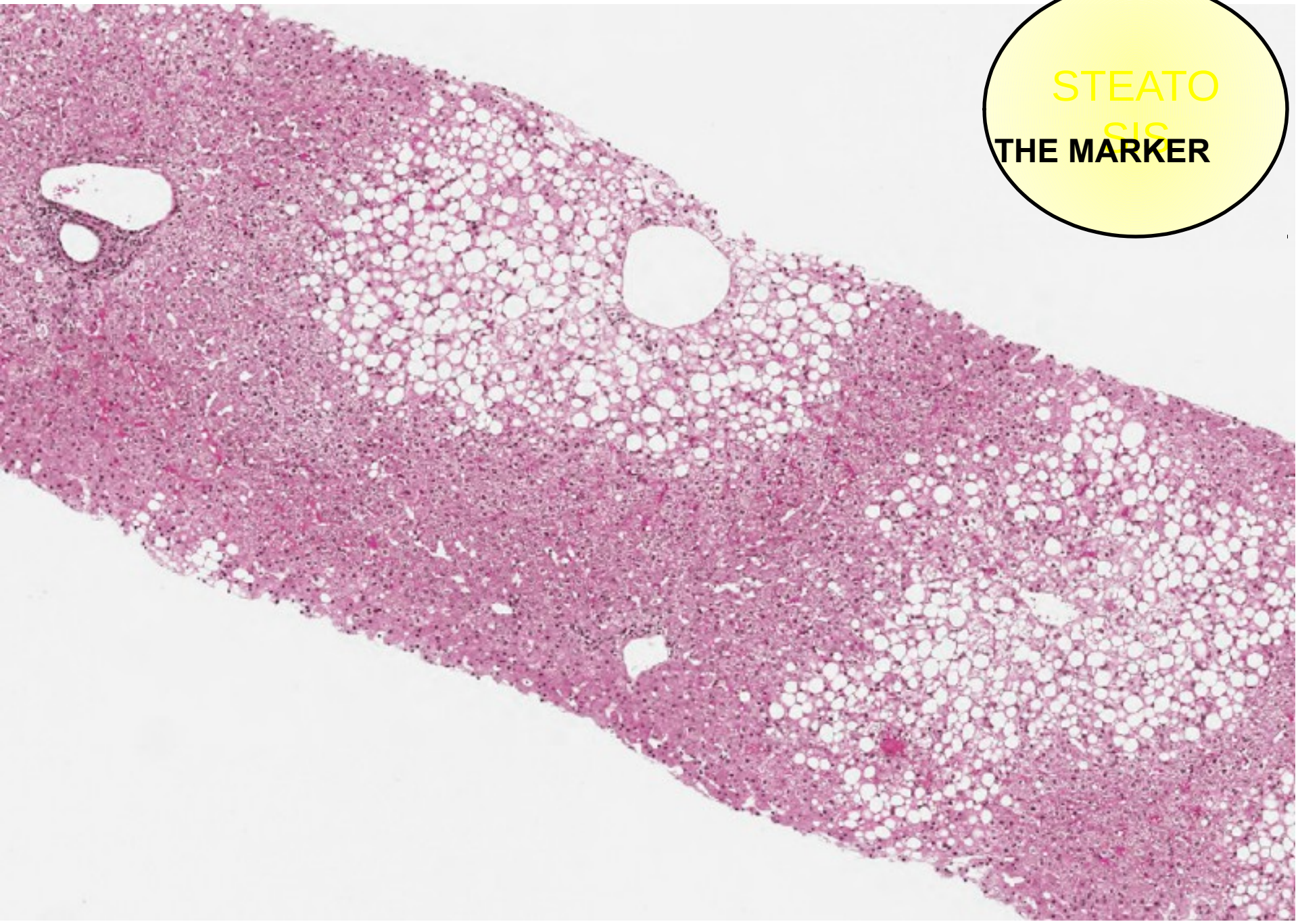


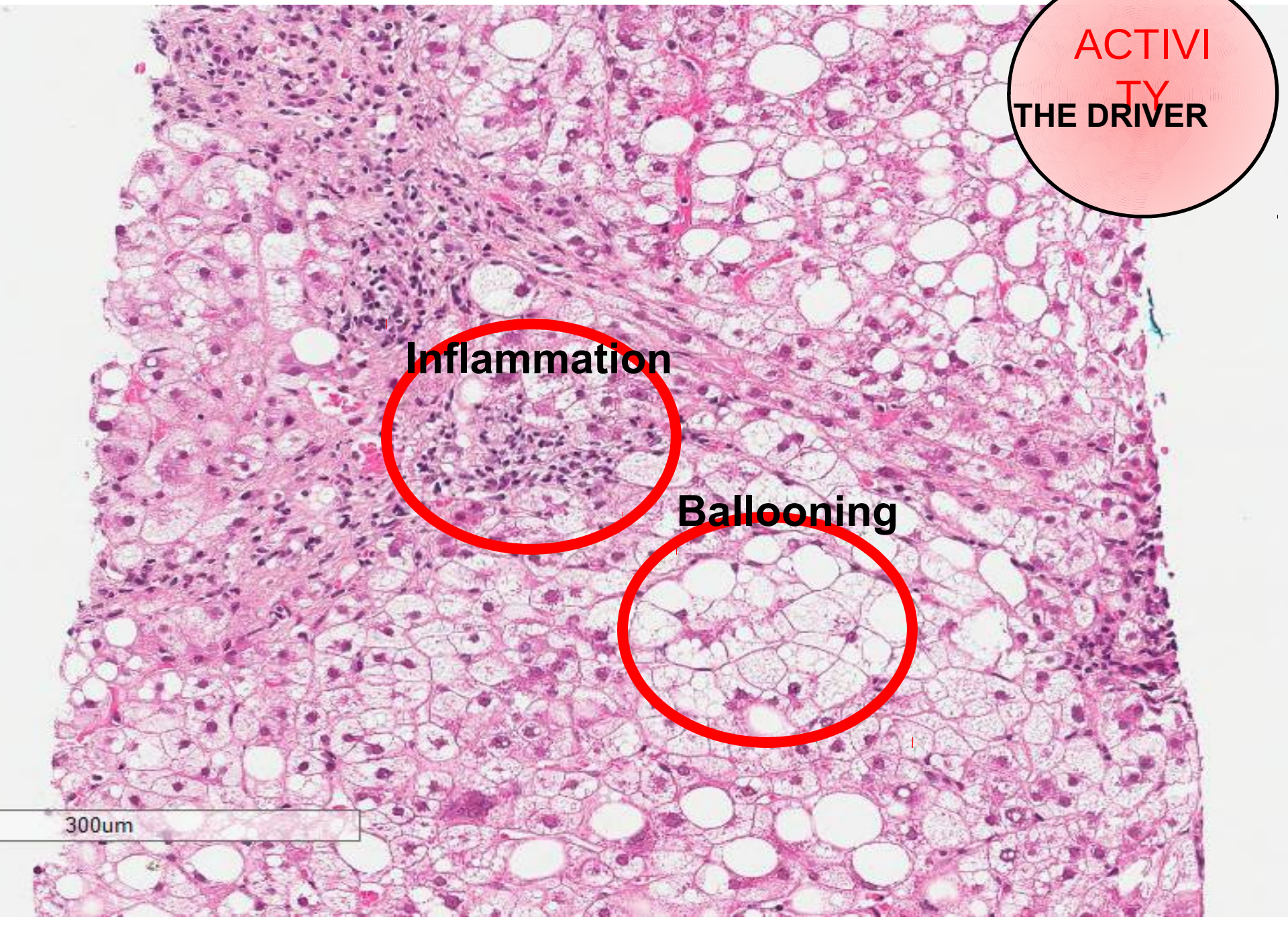
The S.A.F. score
(Steatosis-Activity-Fibrosis)

- **S**teatosis (0-3) as for NASH CRN
- **A**CTIVITY (0-4) = BALLOONING (0-2) + LOBULAR INFLAMMATION (0-2)
- **F**ibrosis (0 – 4) as for NASH CRN

S0-3A0-4F0-4

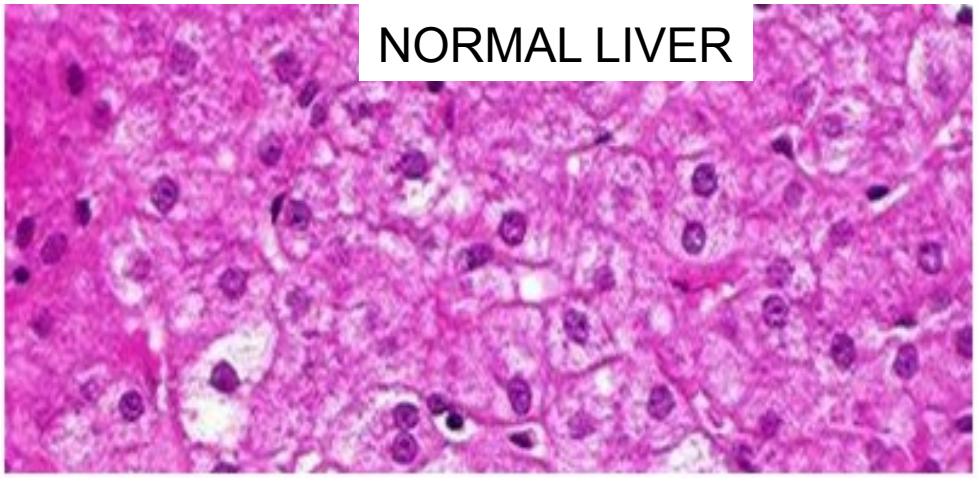
Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Hepatology. 2012 Nov;56(5):1751-9

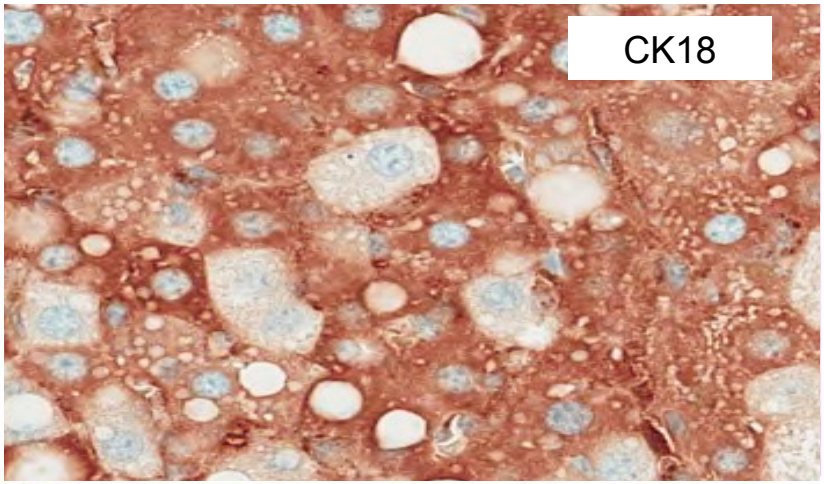

STEATOSIS
THE MARKER

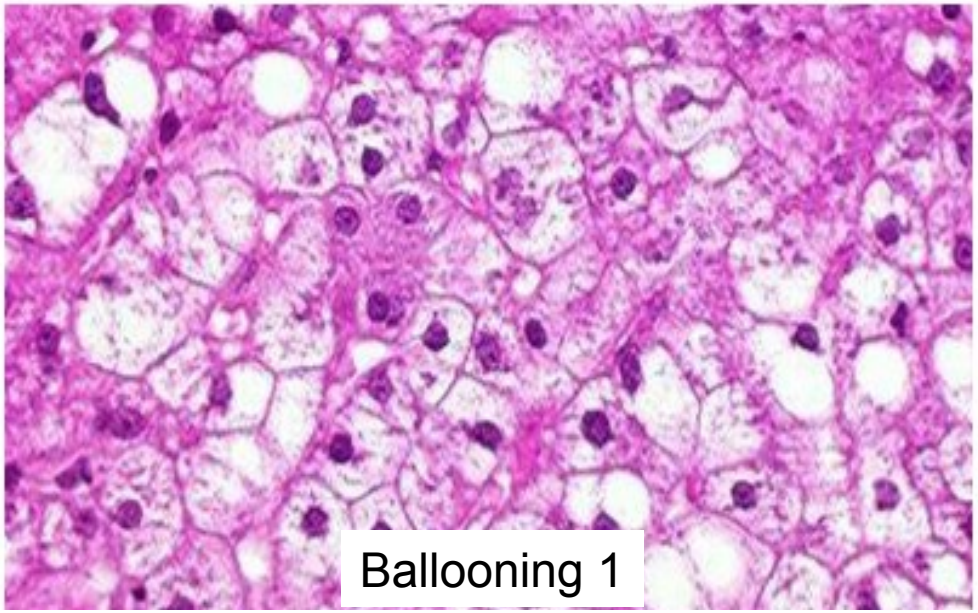

ACTIVITY
THE DRIVER
Inflammation
Ballooning
300um

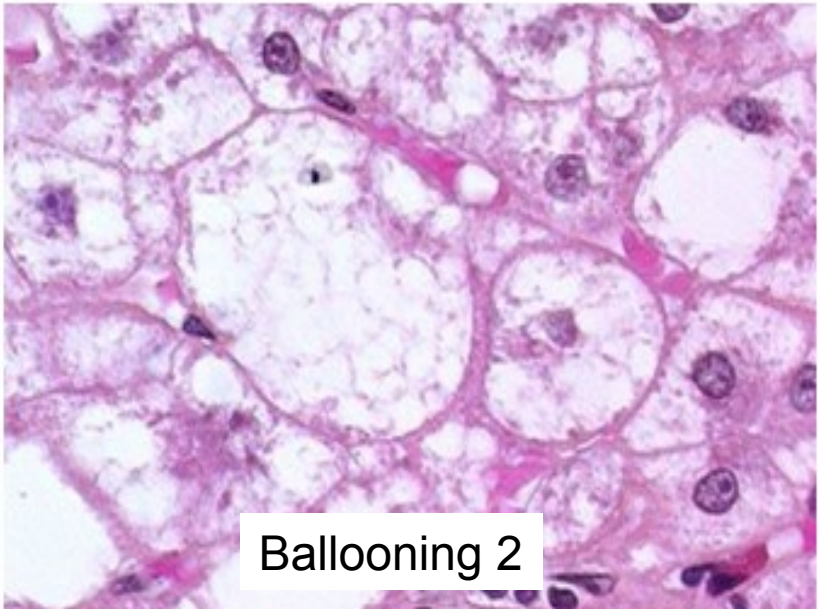
HEPATOCELLULAR BALLOONING: THE HALLMARK OF NASH

SHAPE + COLOR + SIZE

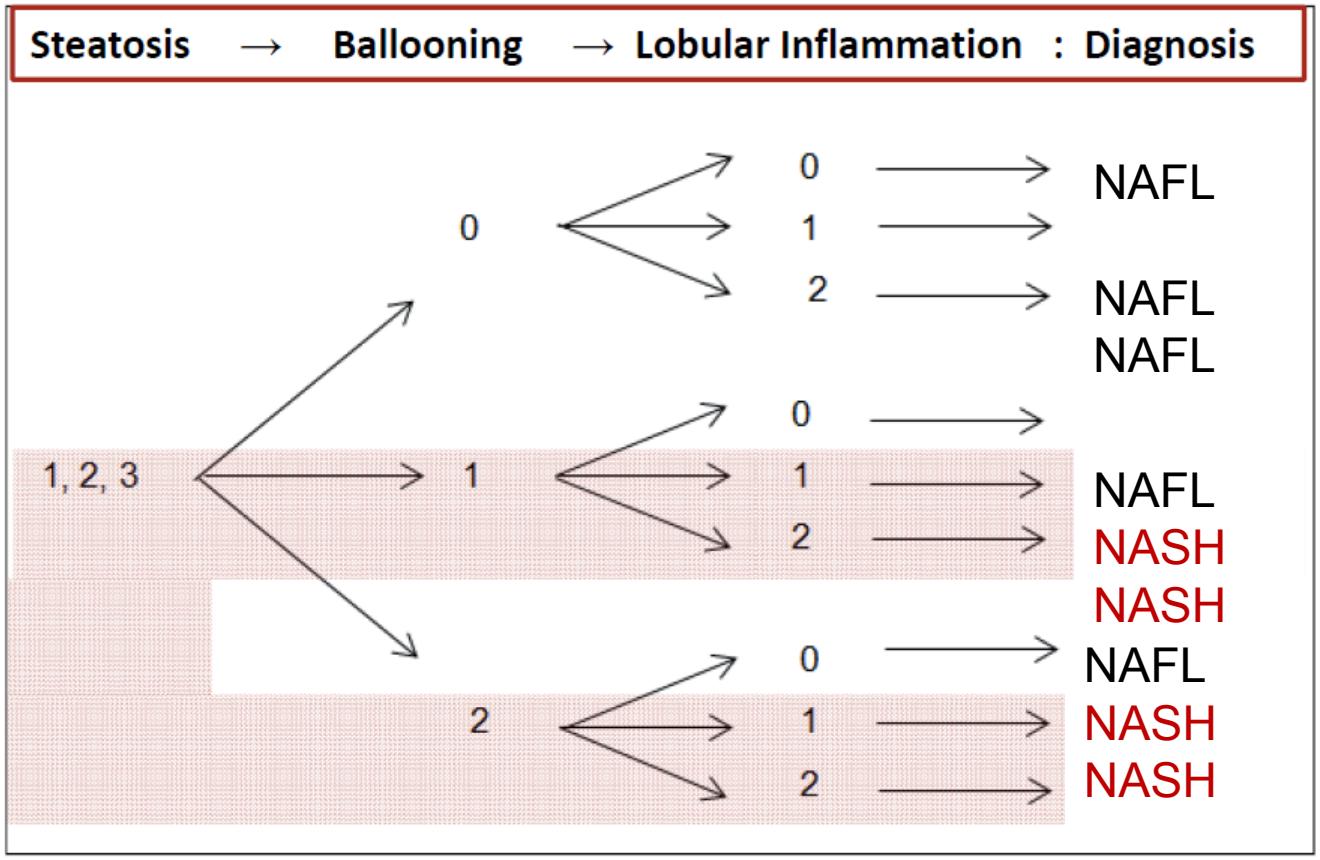








The FLIP algorithm



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REPRODUCIBILITY OF DIAGNOSIS OF NASH WITH FLIP ALGORITHM

Liver Pathologists (n=6)

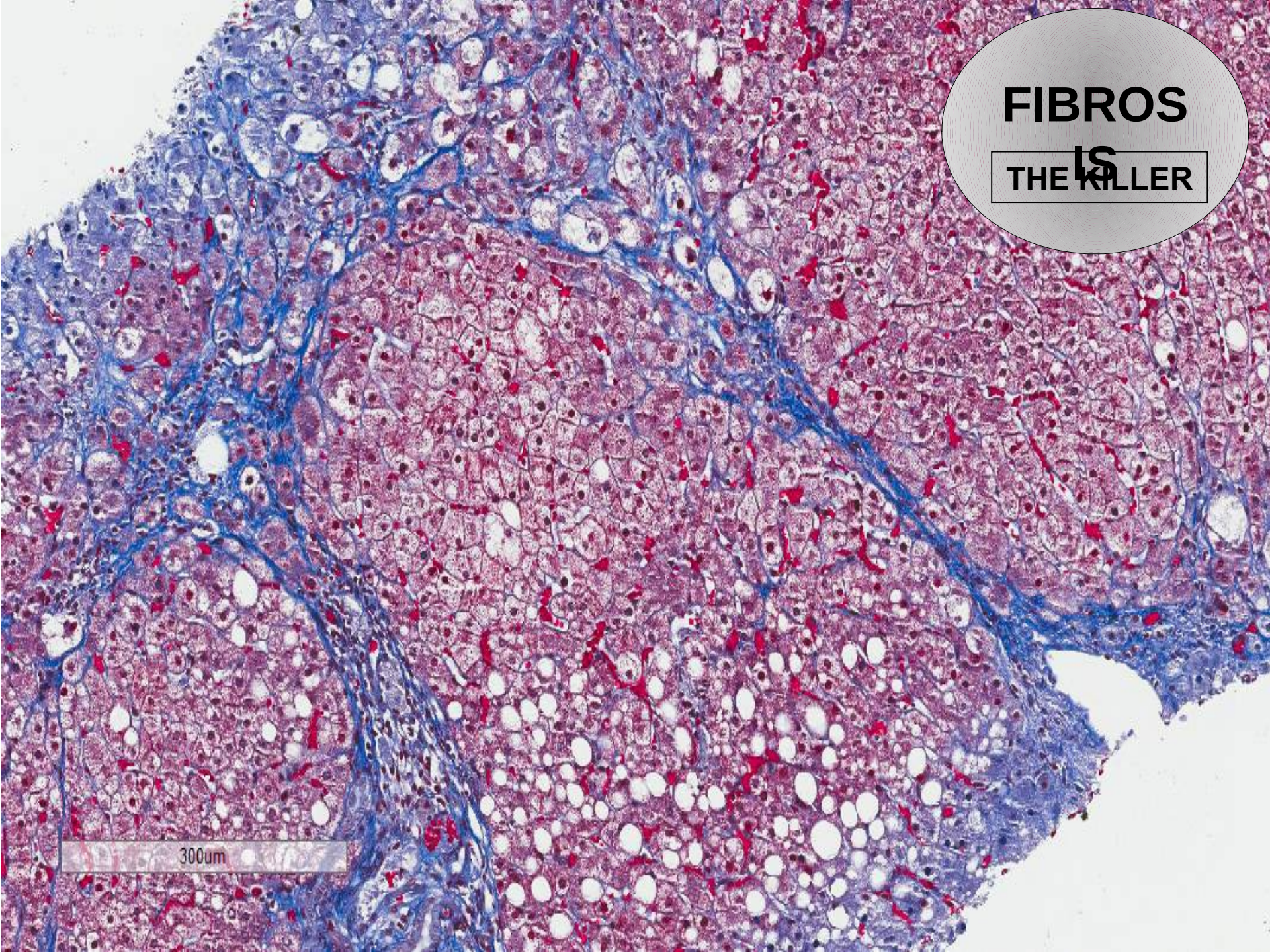
• **κ score**	**0.54 (moderate)**	➡	**0.66 (substantial)**
• Nbr of biopsies with agreement between all pathologists	26/40 (65 %)	➡	34/40 (85 %)

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 %)

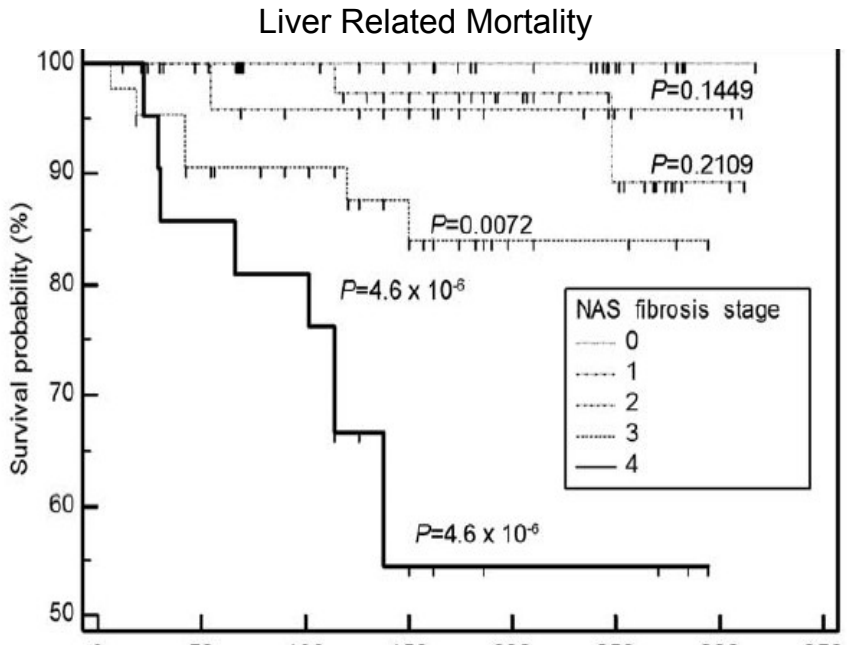
The FLIP Pathology consortium, Hepatology 2014

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


FIBROSIS
THE KILLER
300um

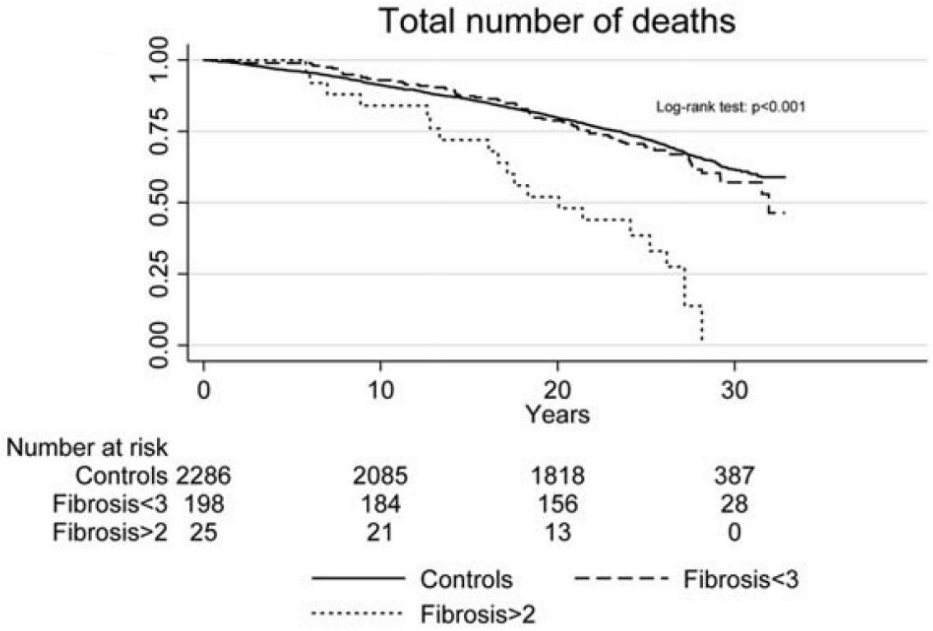
LIVER FIBROSIS : MAJOR PROGNOSTIC FACTOR

Overal survival according to stage of fibrosis in index biopsy



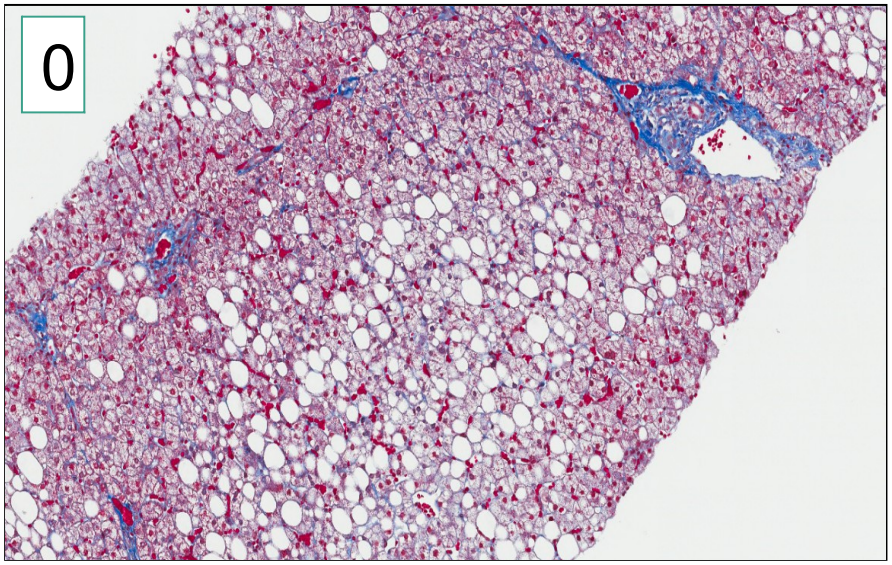
Younossi ZM, Stepanova M, Rafiq N, et al.. Hepatology 2011

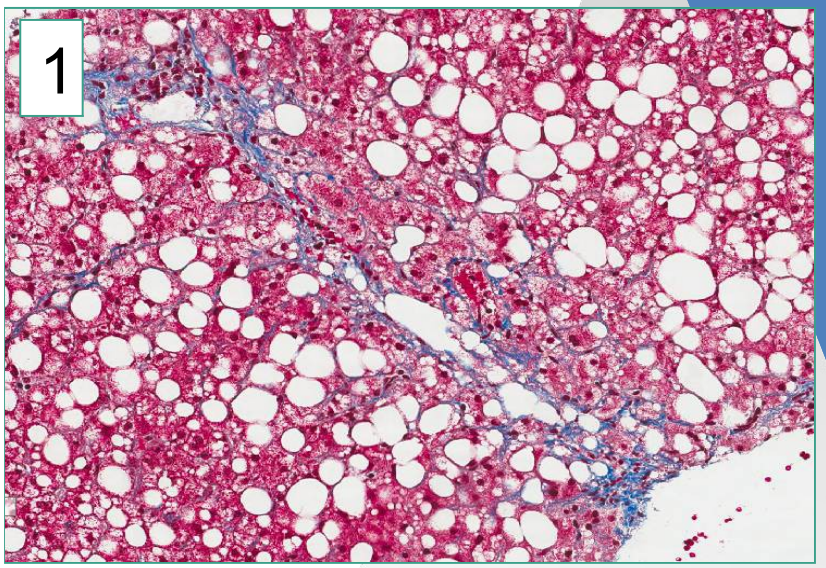
Overal survival according to fibrosis stage and compared to control population

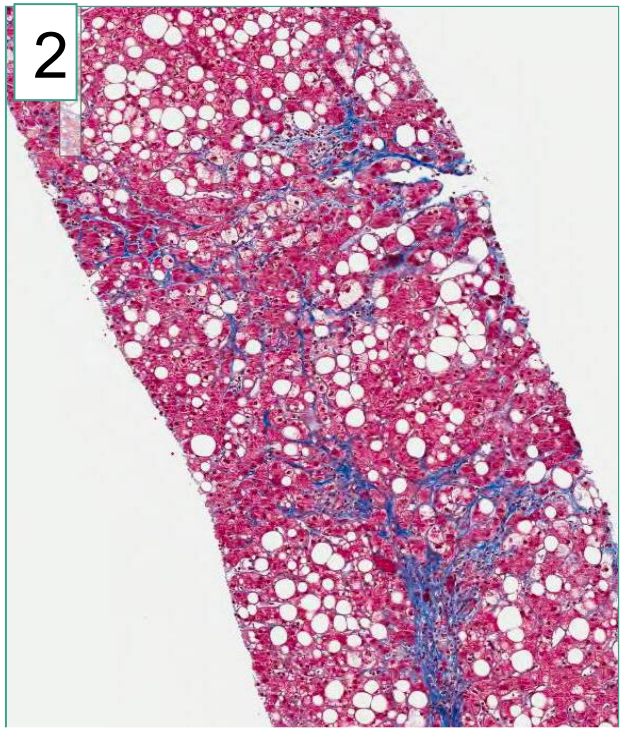


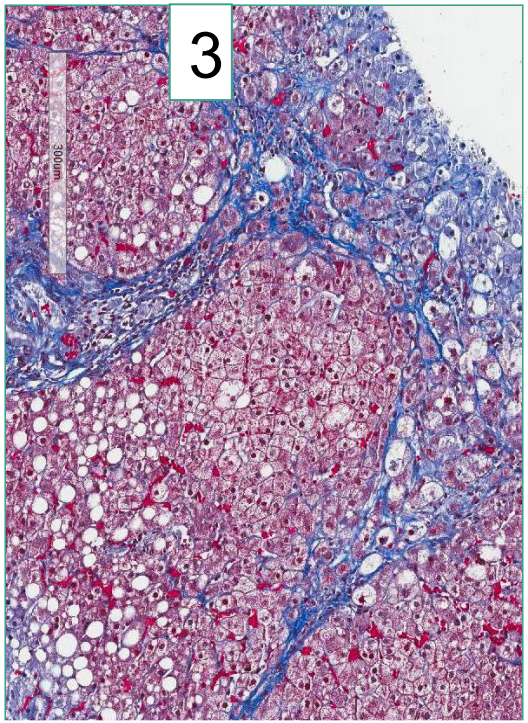
Ekstedt M, Hagström H, Nasr P et al, Hepatology 2015

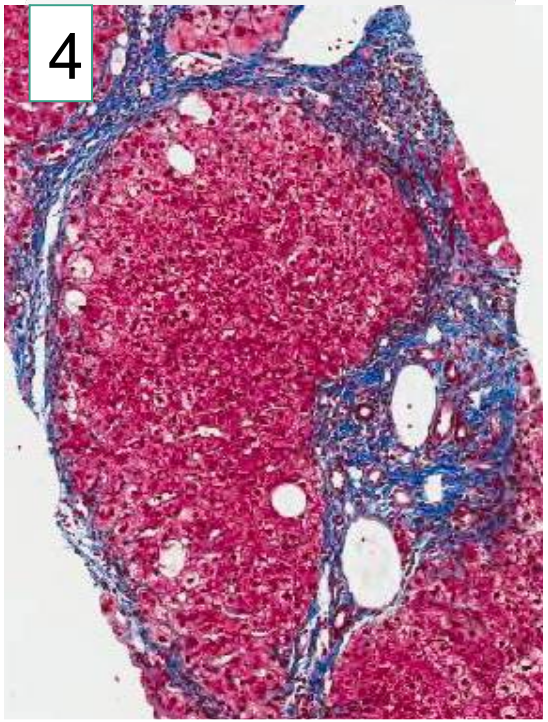
Stage of Fibrosis (Kleiner et al, Hepatology 2005)



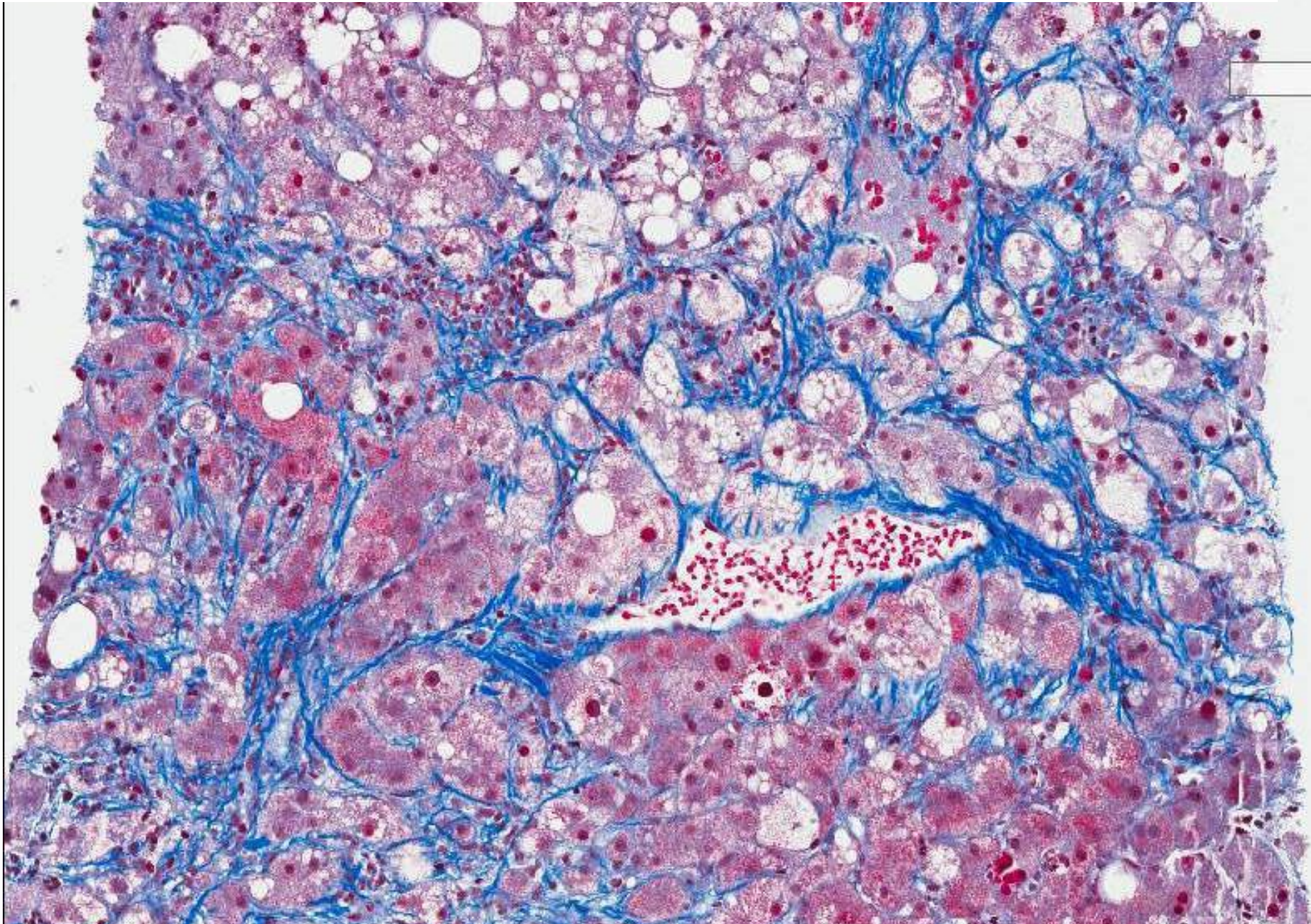




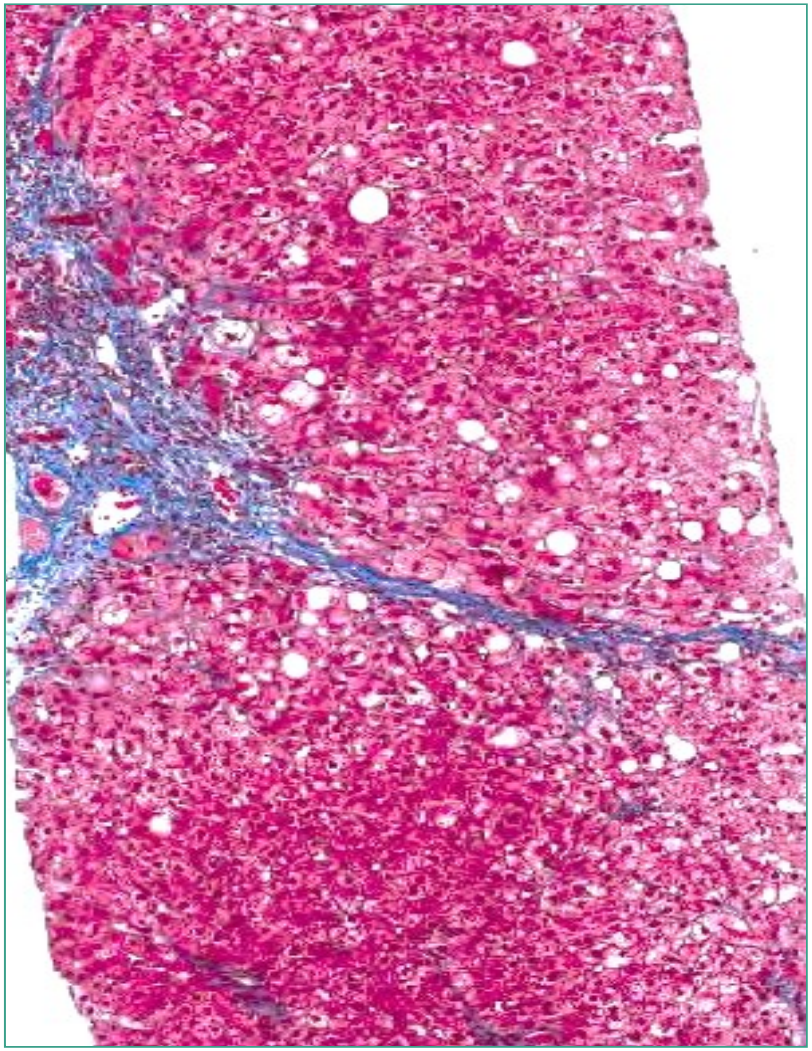


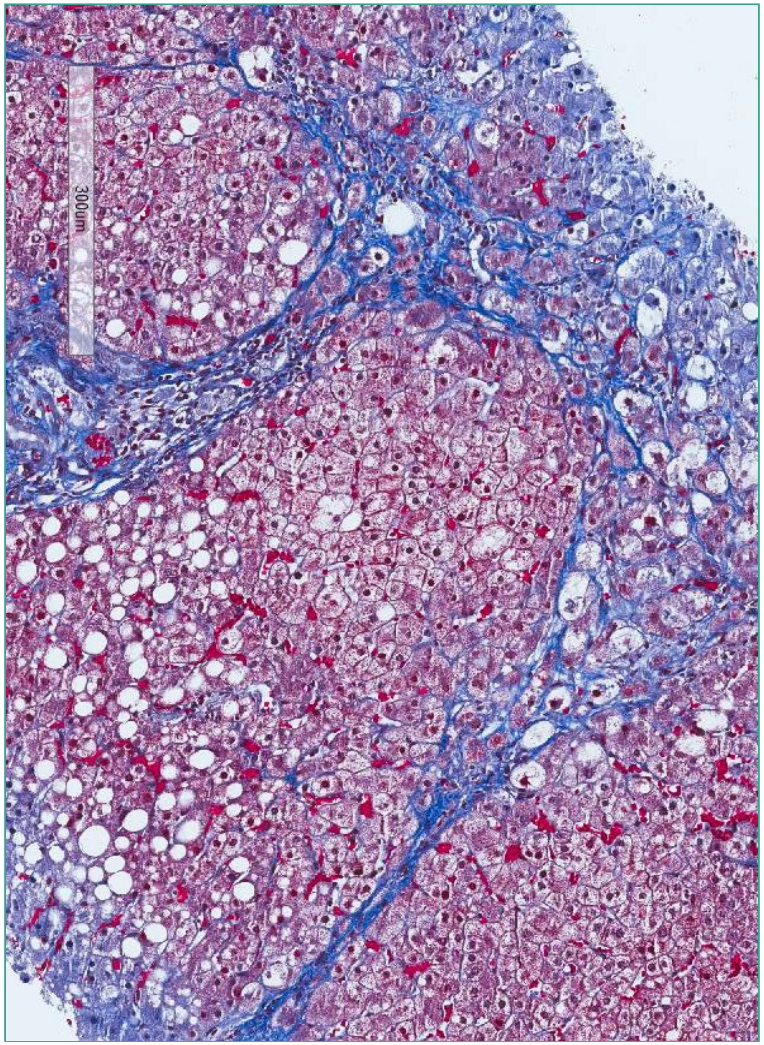


STAGE OF FIBROSIS: ROOM FOR IMPROVEMENT



STAGE OF FIBROSIS: ROOM FOR IMPROVEMENT





STAGE 3 / SEPTAL FIBROSIS

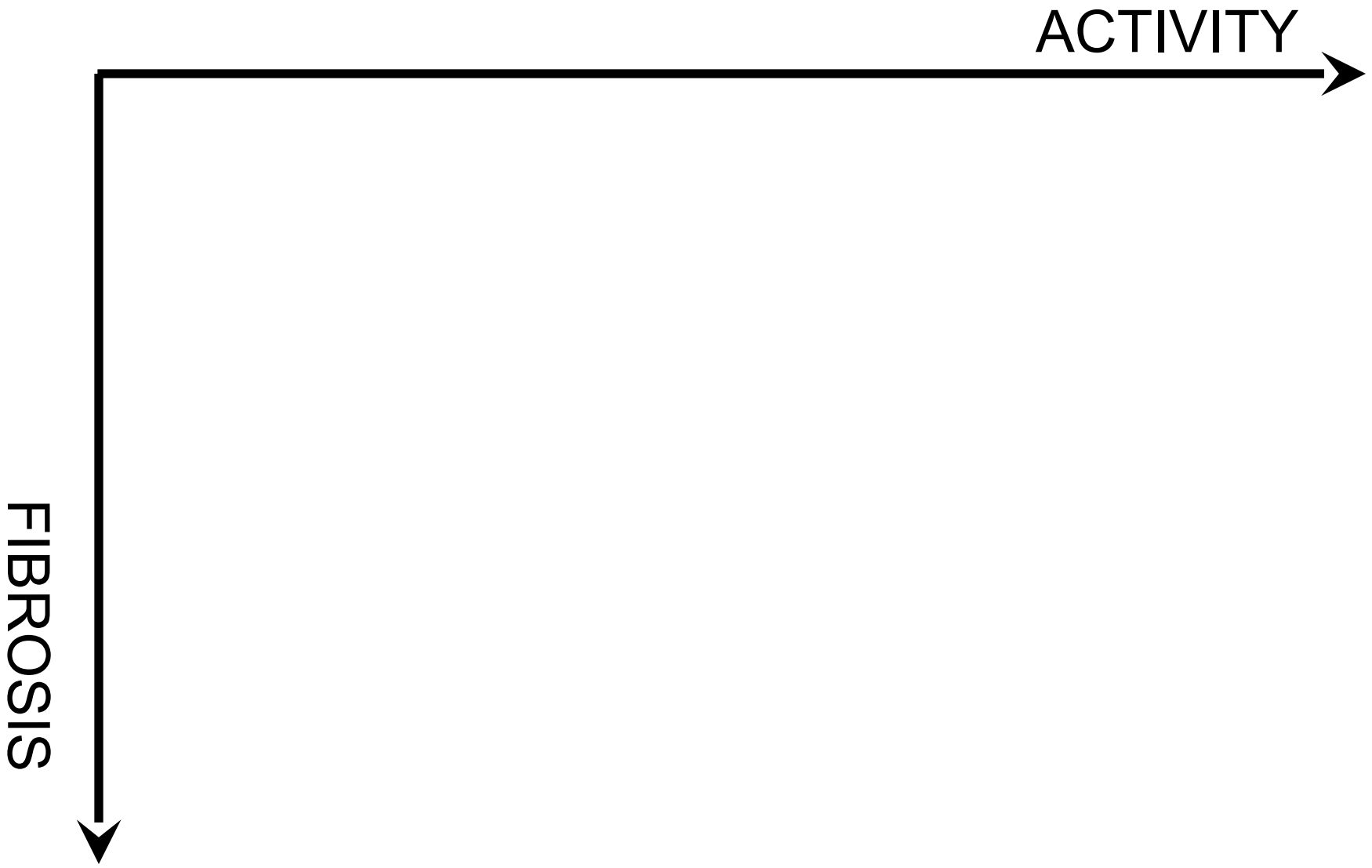
OUTLINES

- CLASSIFICATION OF NAFLD :
  - INTEGRATED APPROACH
  - ANALYTICAL APPROACH

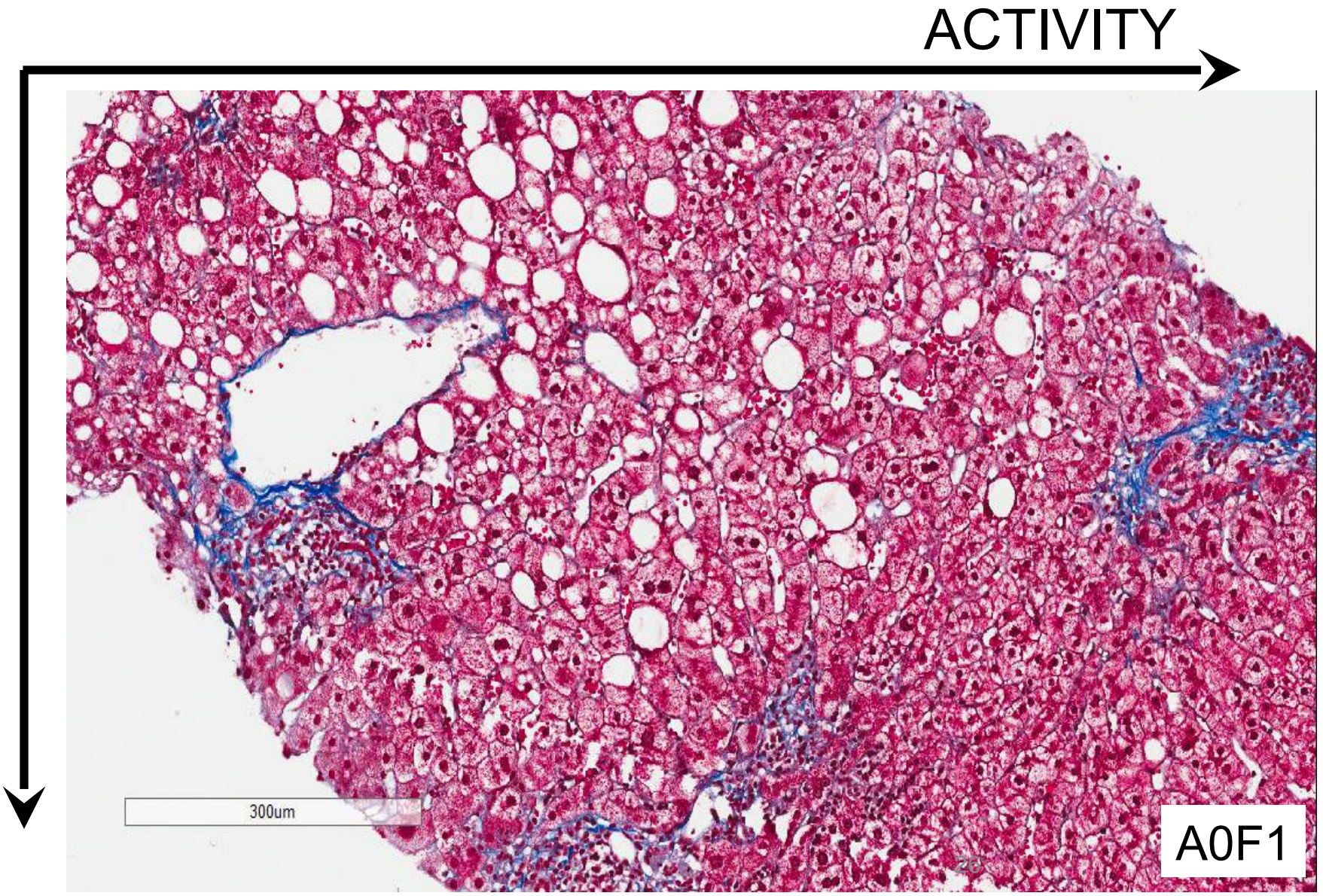
➢ **HISTOLOGY IN CLINICAL TRIALS**

  - Histology is a validated surrogate endpoint

MANY SHADES OF NAFLD



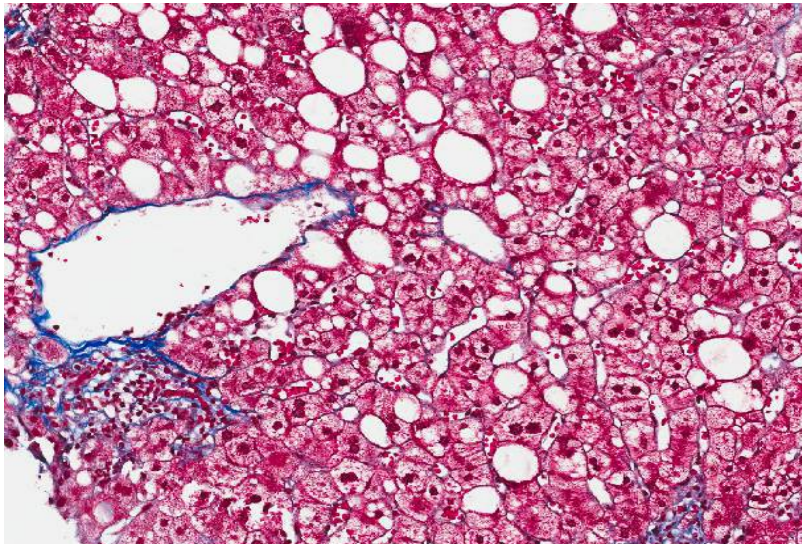
MANY SHADES OF NAFLD



MANY SHADES OF NAFLD

ACTIVITY

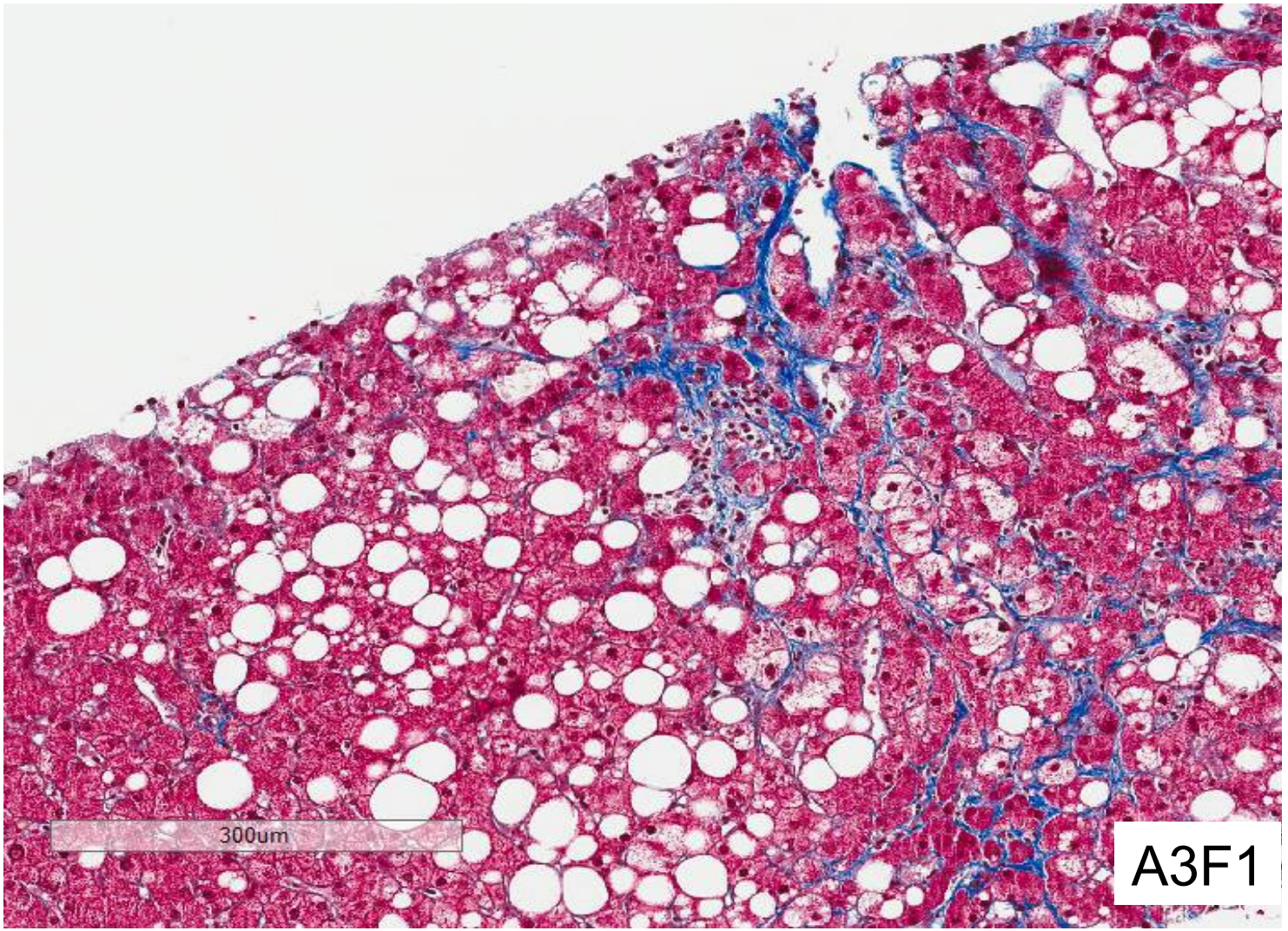
FIBROSIS



MANY SHADES OF NAFLD

ACTIVITY

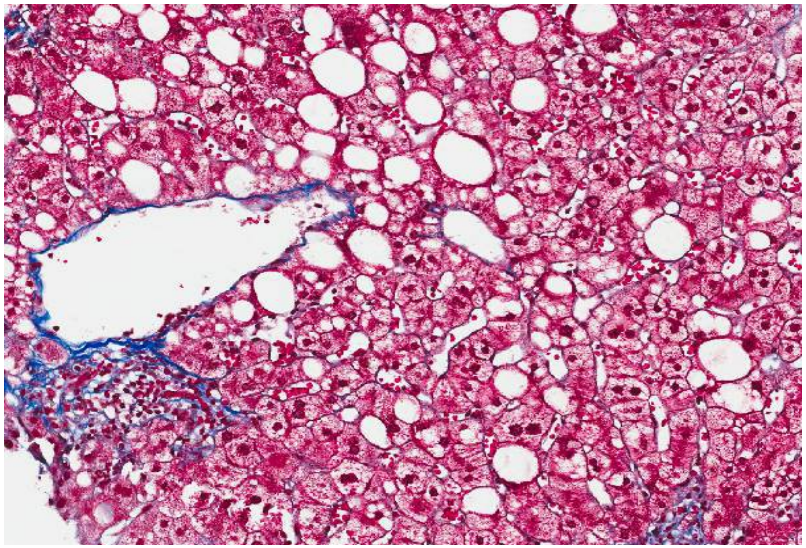
FIBROSIS

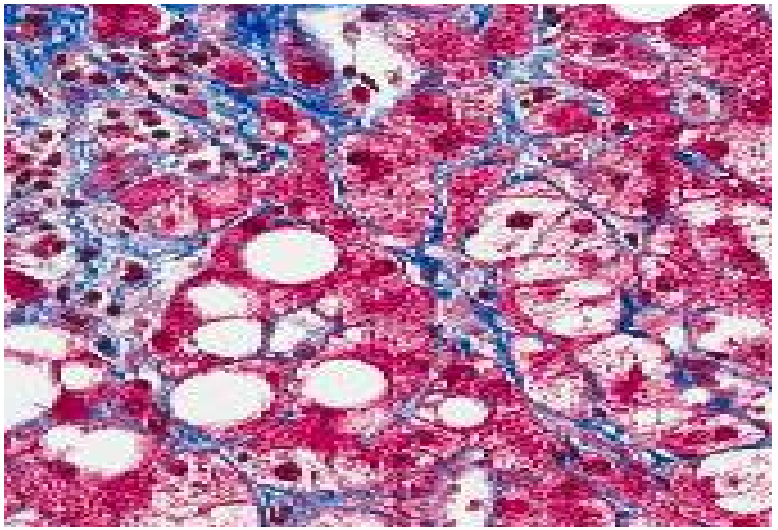


MANY SHADES OF NAFLD

ACTIVITY

FIBROSIS





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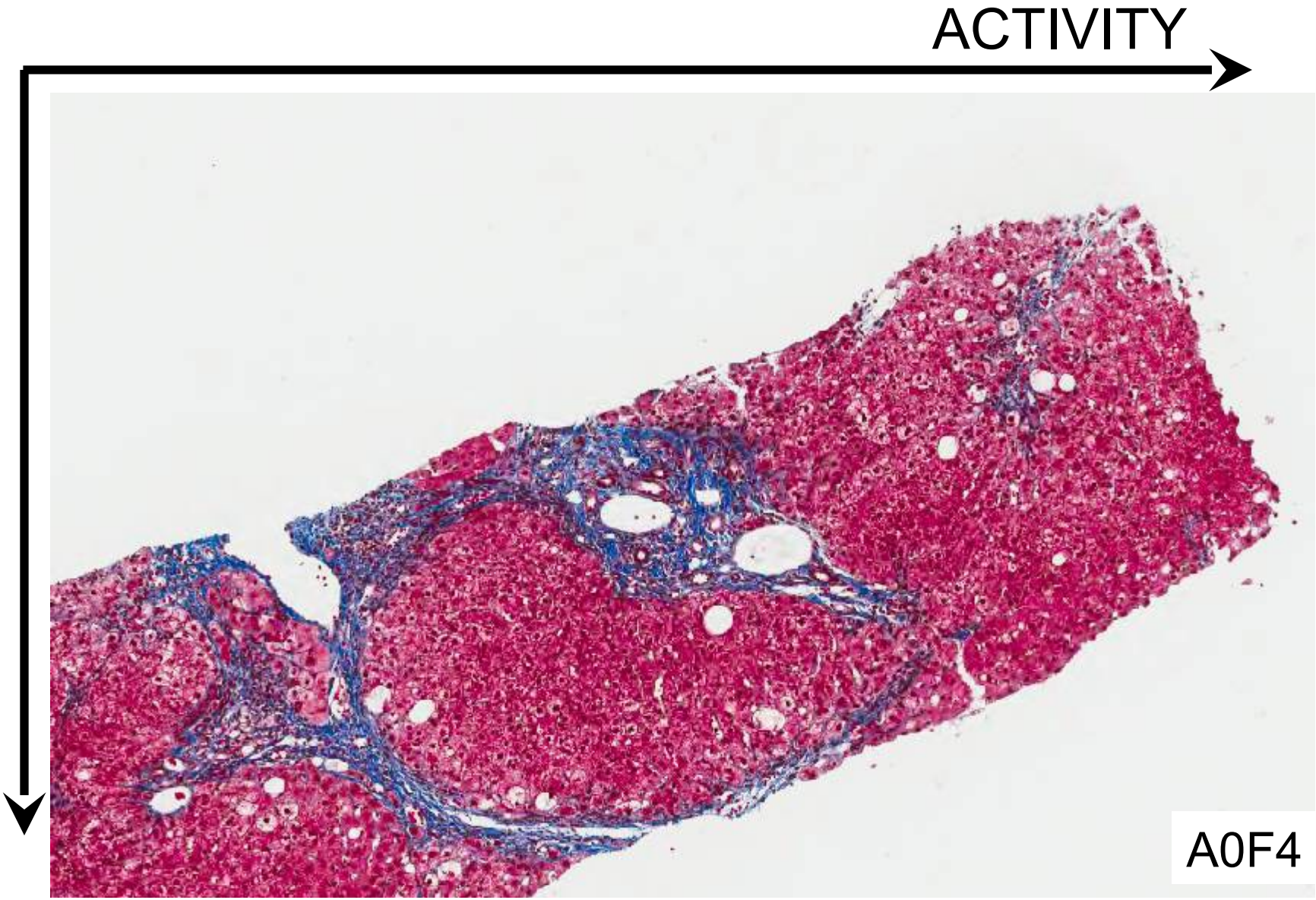
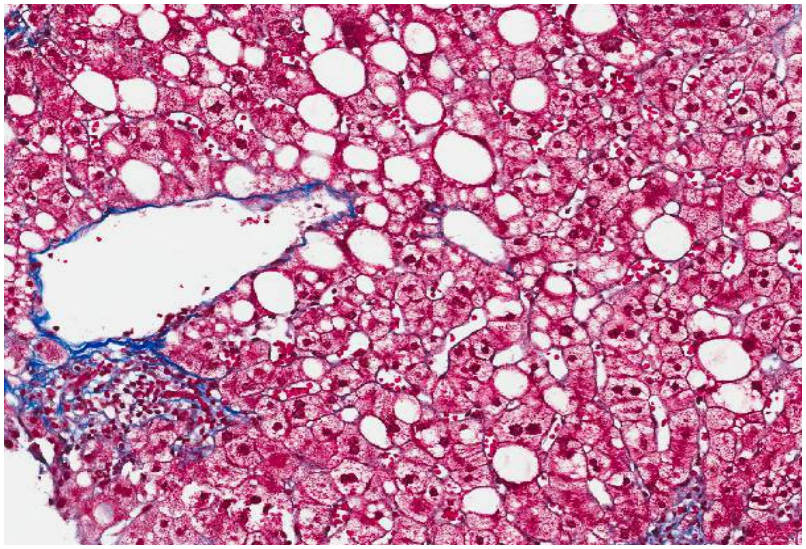
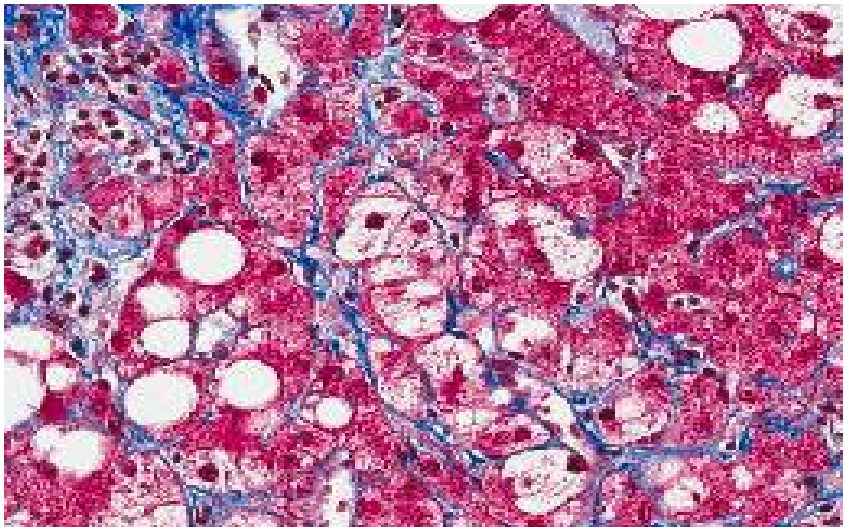


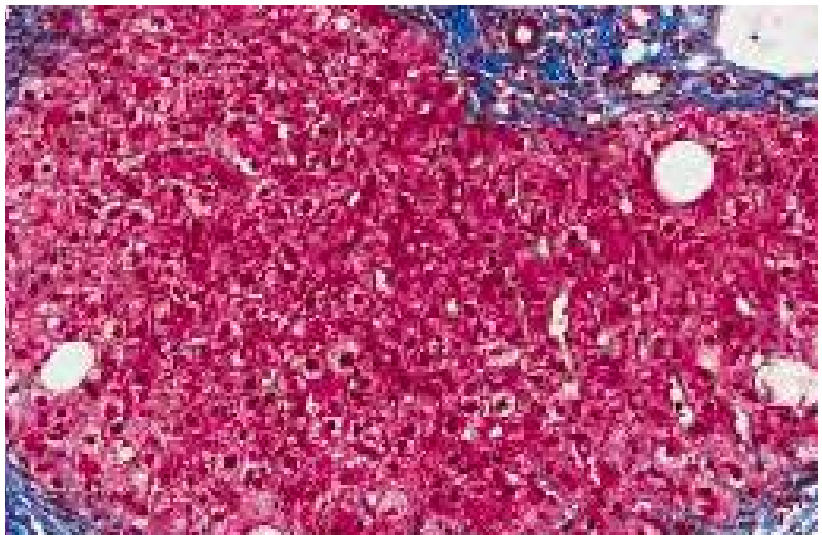
MANY SHADES OF NAFLD

ACTIVITY

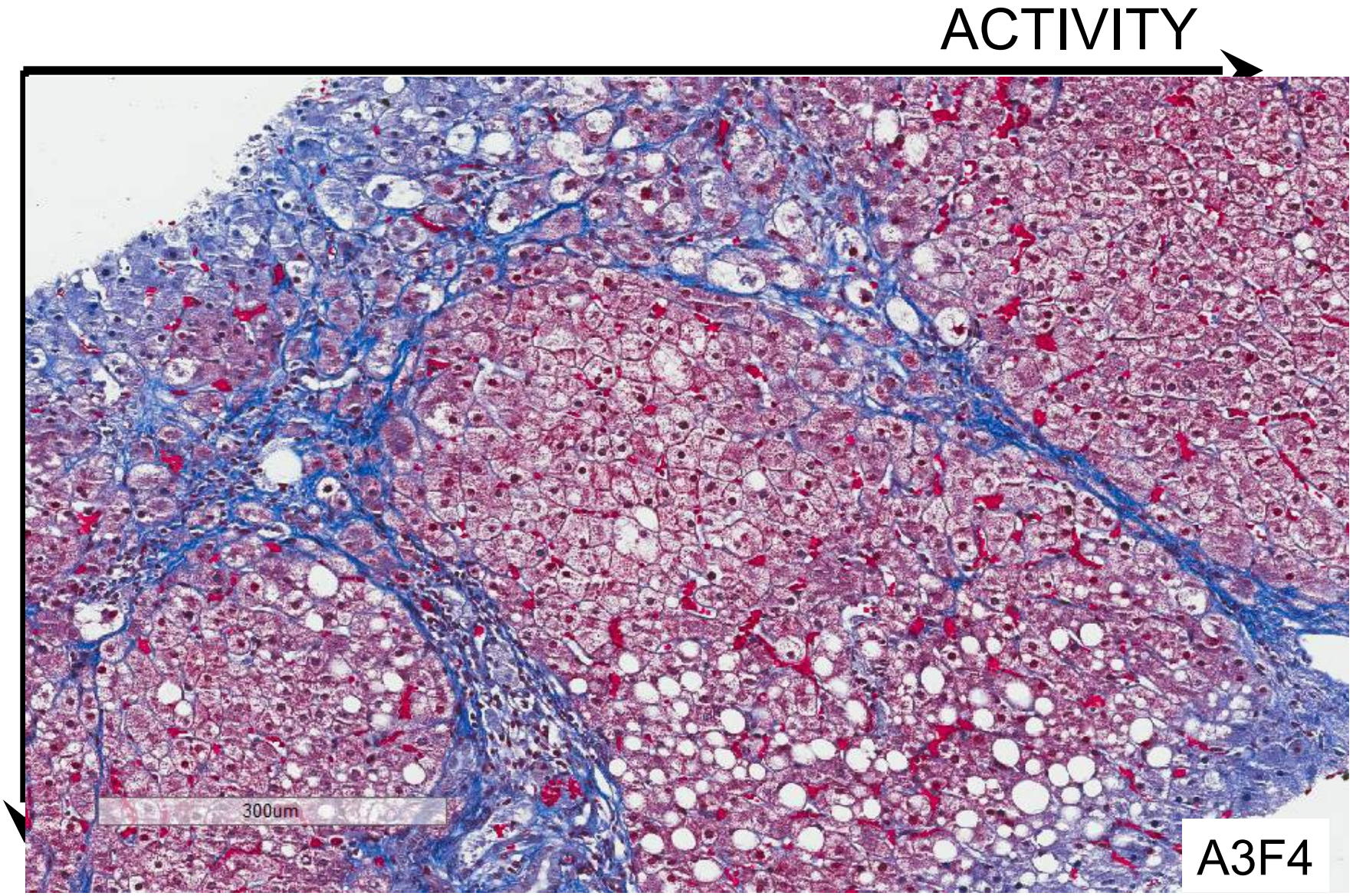
FIBROSIS







MANY SHADES OF NAFLD



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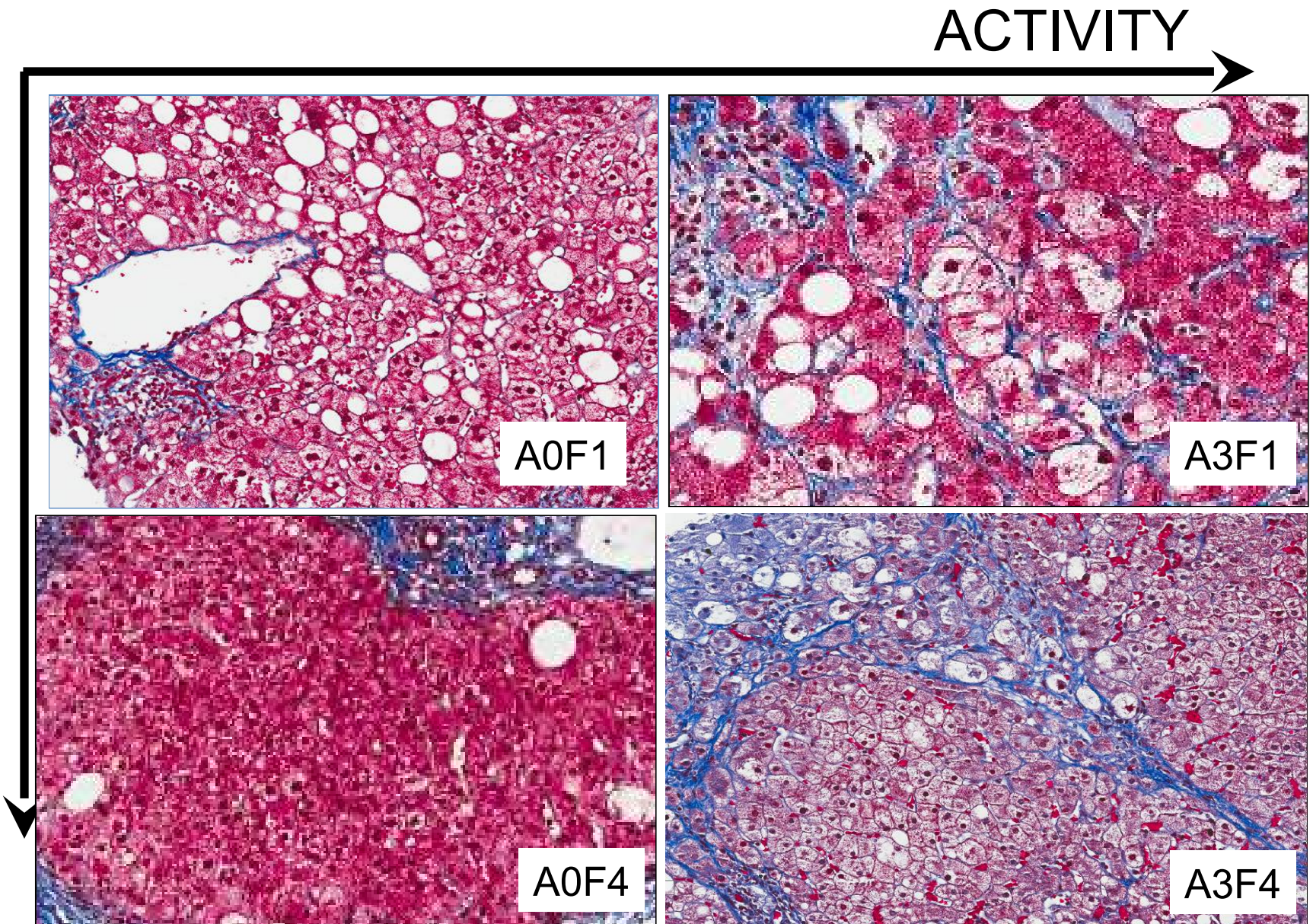


HISTOLOGY IN NAFLD CLINICAL TRIALS

STEATOSIS +	A0	A1	A2	A3	A4
F0	A0F0	A1F0	A2F0	A3F0	A4F0
F1	A0F1	A1F1	A2F1	A3F1	A4F1
F2	A0F2	A1F2	A2F2	A3F2	A4F2
F3	A0F3	A1F3	A2F3	A3F3	A4F3
F4	A0F4	A1F4	A2F4	A3F4	A4F4

HISTOLOGY IN NAFLD CLINICAL TRIALS

STEATOSIS +	A0	A1	A2	A3	A4
F0	A0F0	A1F0	A2F0	A3F0	A4F0
F1	A0F1	A1F1	A2F1	A3F1	A4F1
F2	A0F2	A1F2	A2F2	A3F2	A4F2
F3	A0F3	A1F3	A2F3	A3F3	A4F3
F4	A0F4	A1F4	A2F4	A3F4	A4F4

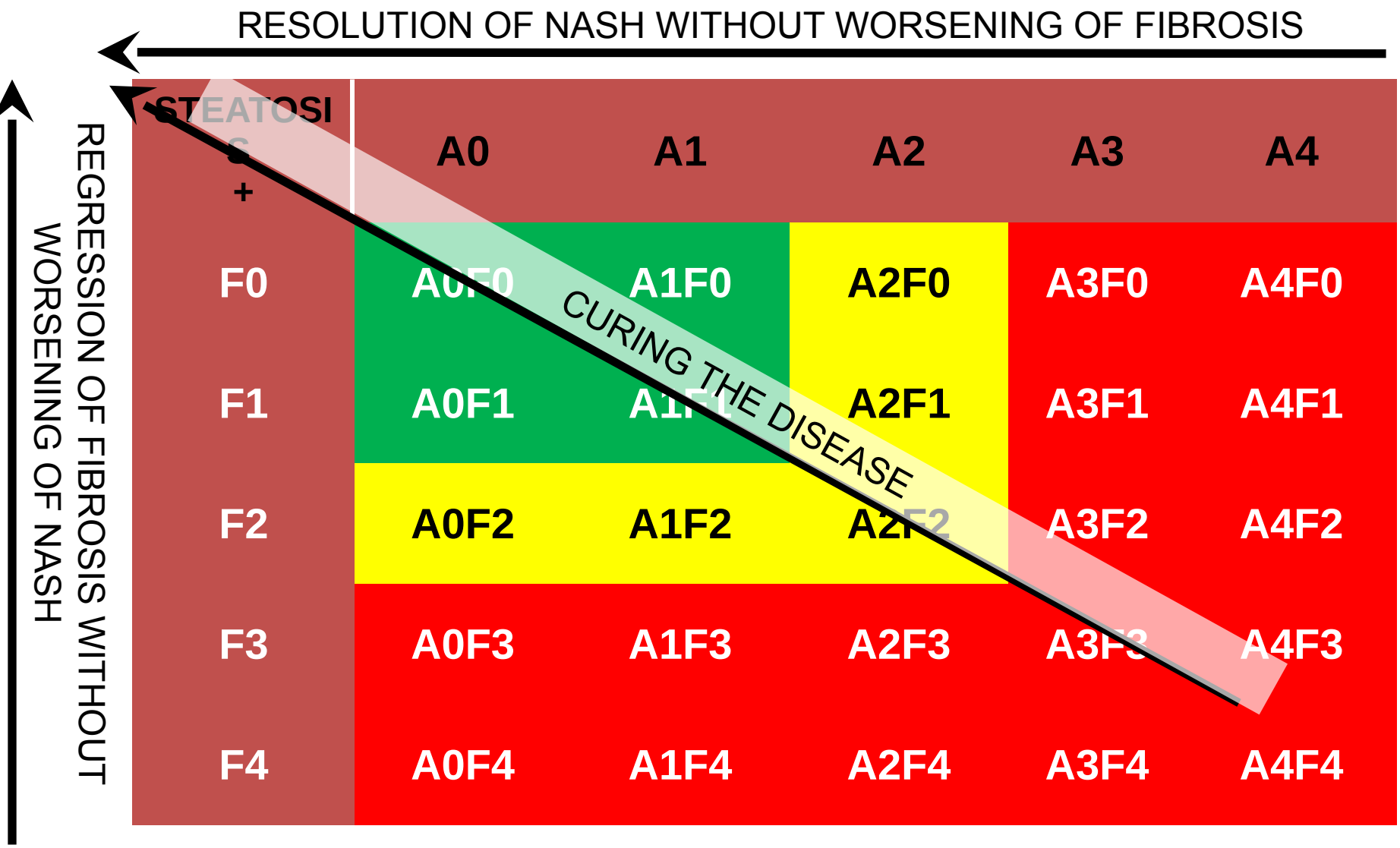
HISTOLOGY IN NAFLD CLINICAL TRIALS

STEATOSIS +	A0	A1	A2	A3	A4
F0	A0F0	A1F0	A2F0	A3F0	A4F0
F1	A0F1	A1F1	A2F1	A3F1	A4F1
F2	A0F2	A1F2	A2F2	A3F2	A4F2
F3	A0F3	A1F3	A2F3	A3F3	A4F3
F4	A0F4	A1F4	A2F4	A3F4	A4F4

HISTOLOGY IN NAFLD CLINICAL TRIALS

STEATOSIS +	A0	A1	A2	A3	A4
F0	A0F0	A1F0	A2F0	A3F0	A4F0
F1	A0F1	A1F1	A2F1	A3F1	A4F1
F2	A0F2	A1F2	A2F2	A3F2	A4F2
F3	A0F3	A1F3	A2F3	A3F3	A4F3
F4	A0F4	A1F4	A2F4	A3F4	A4F4

ENDPOINT IN CLINICAL TRIALS



PATHOLOGY OF NAFLD
Take-home messages

- NAFLD is the combination of several features of variable intensity and of different prognostic values.
- The dichotomous classification NAFL vs NASH is an oversimplification which is no more relevant in clinical practice. New proposals have been formulated.
- NASH is defined by histological criteria. Therefore, biopsy is needed if diagnosis and evaluation of severity are required.
- Histology is the only accepted surrogate marker in clinical trials
- Non invasive markers are urgently needed

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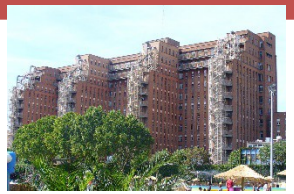

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PARIS
DIDEROT
PARIS 7

THANK YOU FOR YOUR ATTENTION !