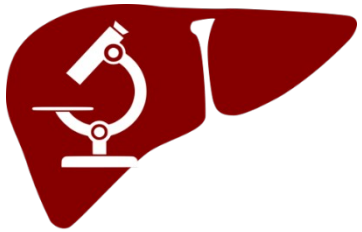


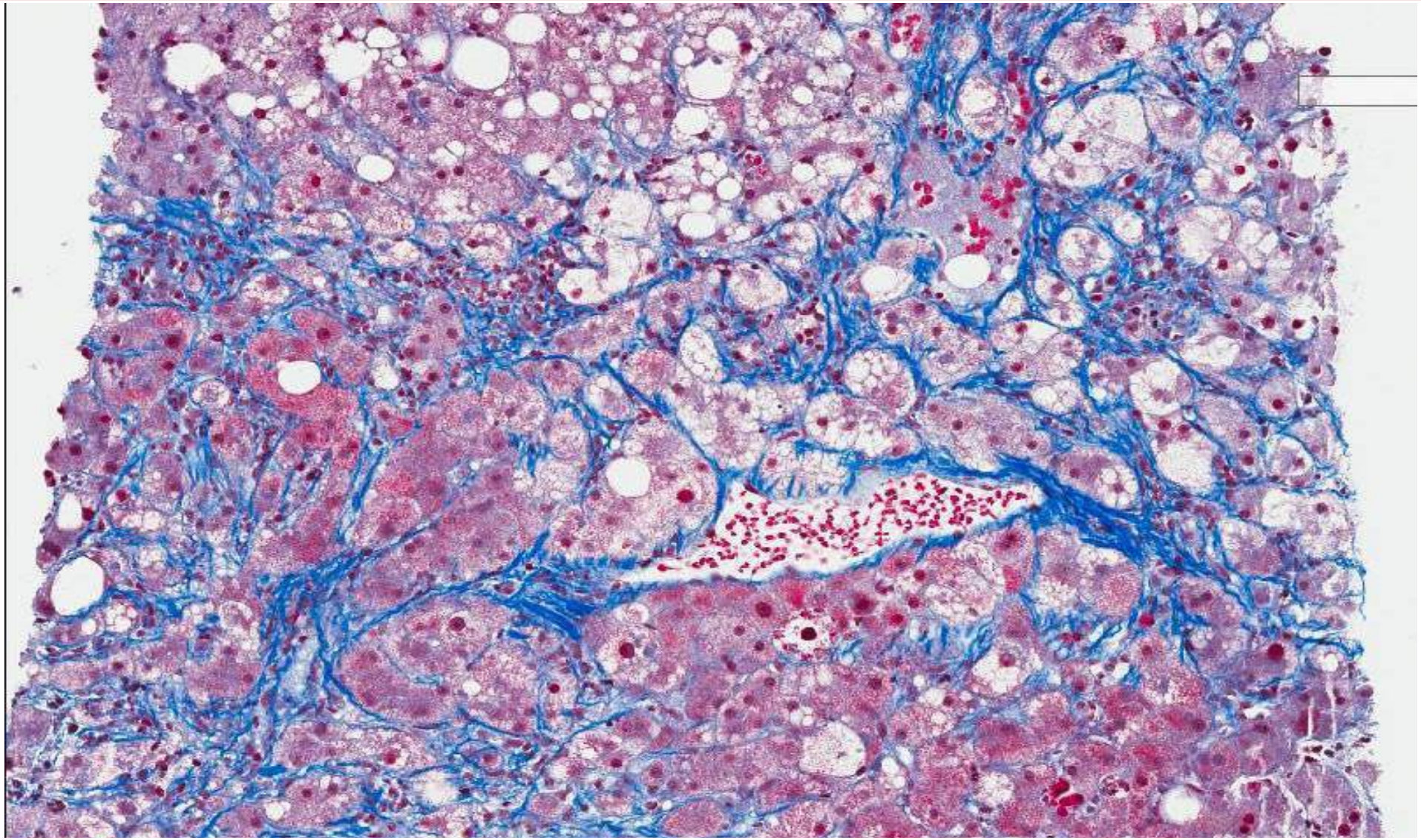
Characterization of NASH
Histology

Pierre BEDOSSA

LIVERPAT, Paris, France

Institute of cellular Medicine, Newcastle UK

NASH : AN ENTITY DEFINED BY AN ASSOCIATION OF HISTOLOGICAL PATTERNS



The only chronic liver disease whose definition is based solely on histology

Characterization of NASH: Histology

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. *Draft Guidance from Food and Drug Administration, December 2018*

« Nonalcoholic fatty liver disease (NAFLD) includes **a spectrum of histological changes** that begin with simple fatty infiltration of the liver (NAFL), which may gradually progress to the development of chronic inflammation (steatohepatitis or NASH), fibrosis, and ultimately cirrhosis. ……. Currently, there are **no clear criteria to identify this group of patients**."

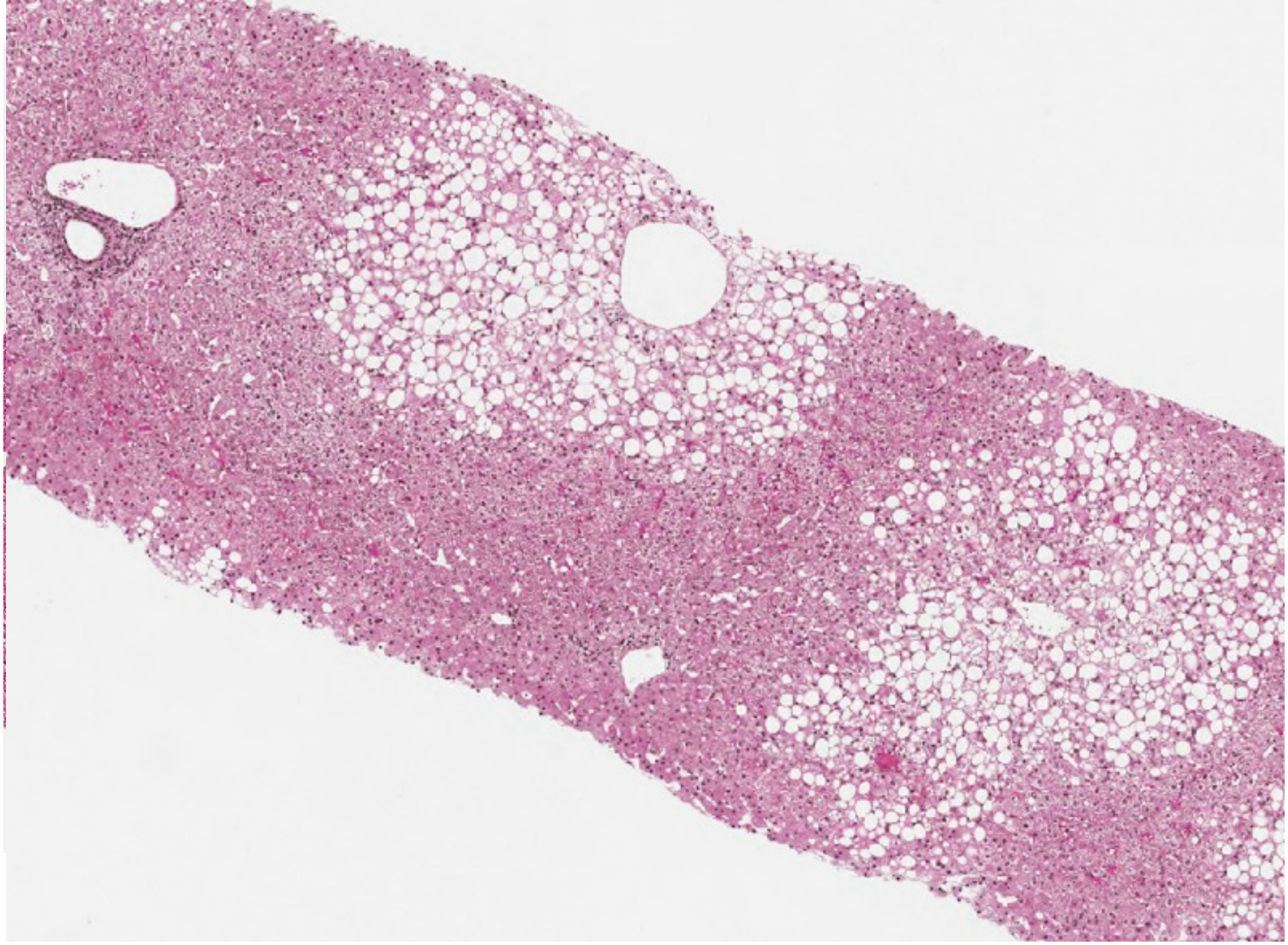
→ **If a diagnosis of NASH is required, then liver biopsy is mandatory**

Liver biopsy is a reliable procedure

Liver biopsy is a reliable procedure

- **Sampling issue:** A 20mm biopsy done with a 16 Gauge needle provides enough material for robust diagnosis of NASH

- **Observer variation:** not an issue between experienced liver pathologists using clearly-defined histological criteria



Liver biopsy: a reliable procedure

- **Sampling issue:** A 20mm biopsy done with a 16 Gauge needle provides enough material for robust diagnosis of NASH

- **Observer variation:** not an issue between experienced liver pathologists using clearly-defined histological criteria *(NASH CRN 2005, FLIP, 2014)*

→ Training and experience are essential for:

- the hepatologist/radiologist who will perform the biopsy
- the pathology lab that will prepare the sections
- the liver pathologist who will review the section

Histological characterization of NASH

- Acute Alcoholic Hepatitis-like : Steatosis + Mallory hyaline + Polymorphonuclear

  (Ludwig J, et al. Mayo Clin Proc. 1980 Jul;55(7):434-8.)

- Steatosis + ballooning + mixed acute and chronic lobular inflammation + zone 3 perisinusoidal fibrosis

  (Brunt E. Am J Gastroenterol 1999;94:2467–2474)

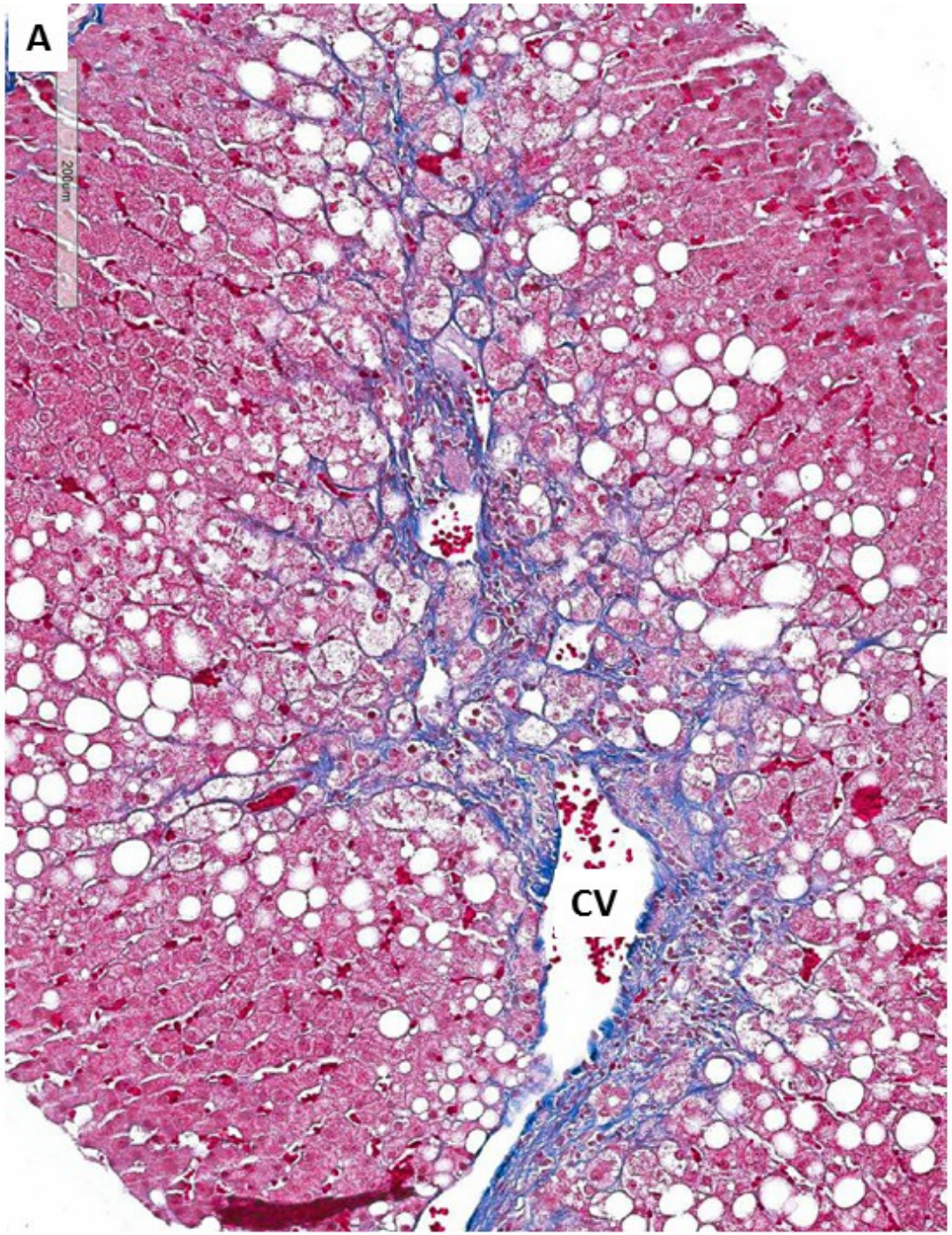
- Steatosis + inflammation + hepatocellular ballooning

  (Brunt E et al. Hepatology 2011;53:810-820)

  - NAS ≥ 4 and 1 point in each category (clinical trials)

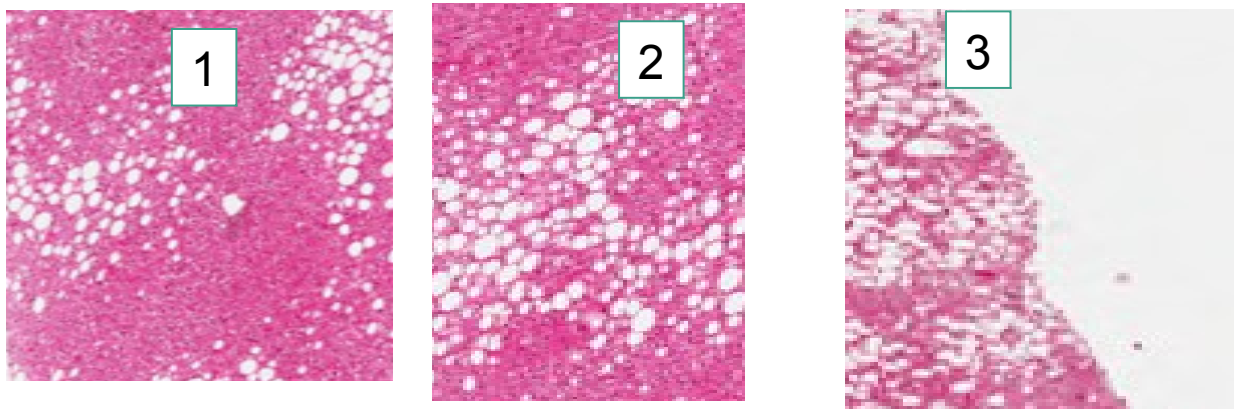
    (*Draft Guidance from Food and Drug Administration, December 2018)*

→ **A shift from a rare and severe disease to a wide histological spectrum including mainly minor histological diseases**

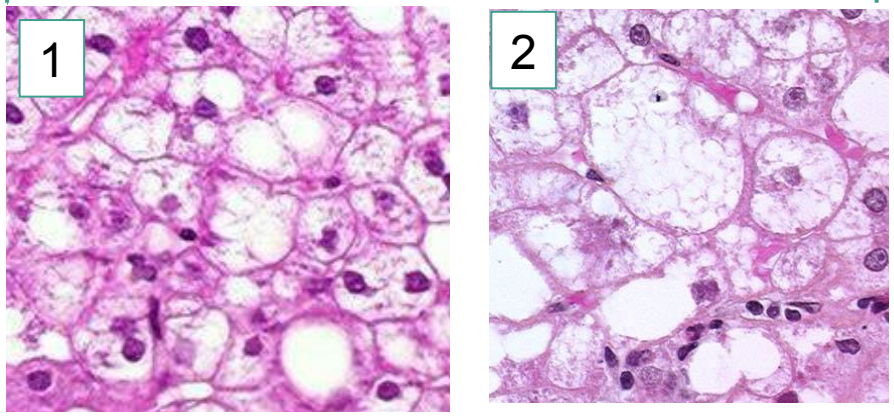

A
200µm
CV

NAFLD Activity Score (NAS, 0-8)

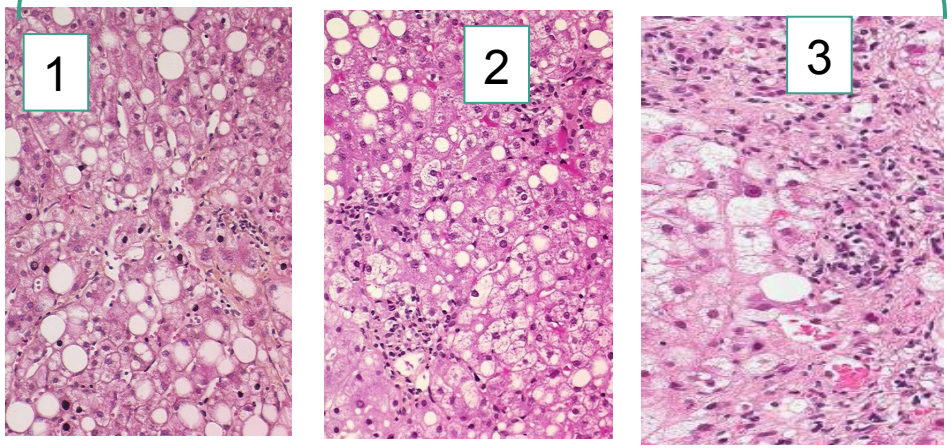
STEATOSIS



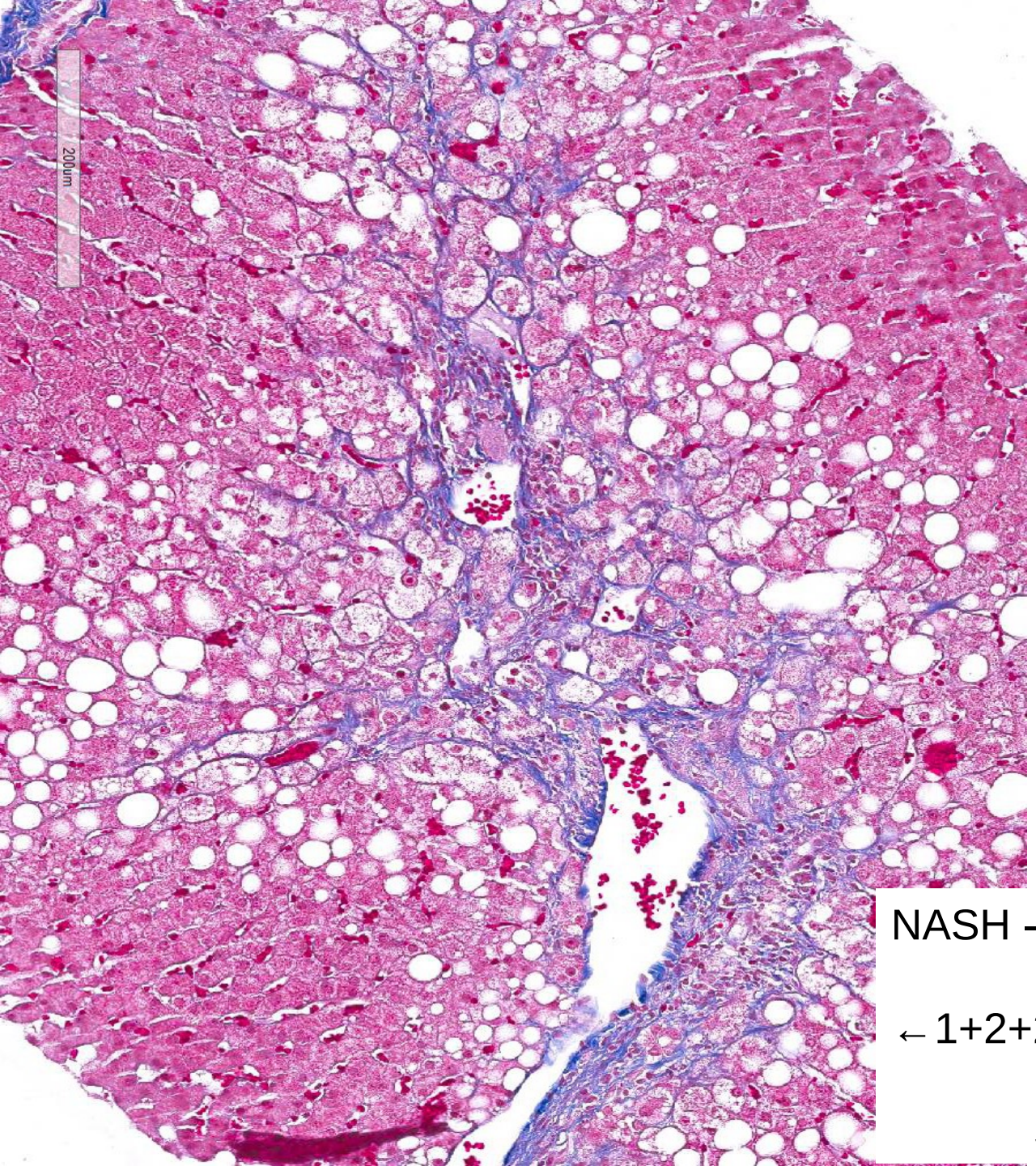
+ BALLONING

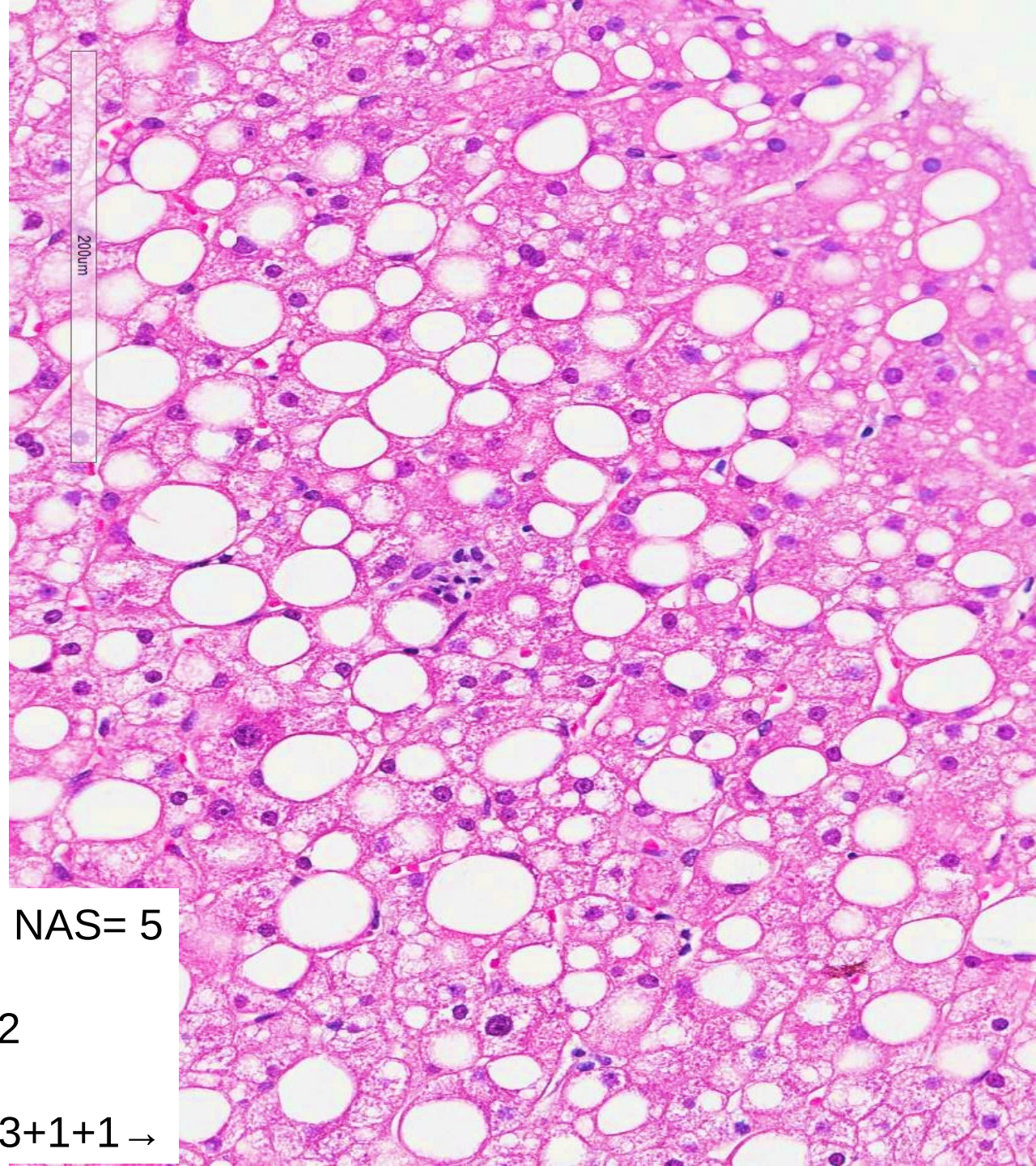


+ INFLAMMATION



NASH CRN, Hepatology 2005



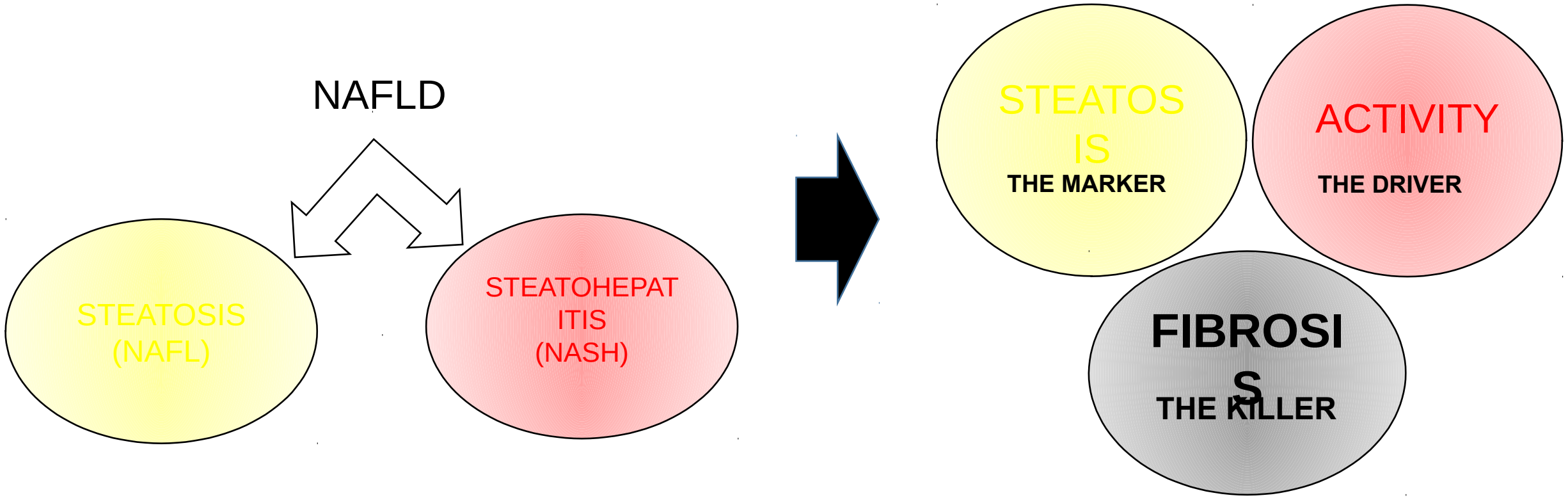


NASH - NAS= 5

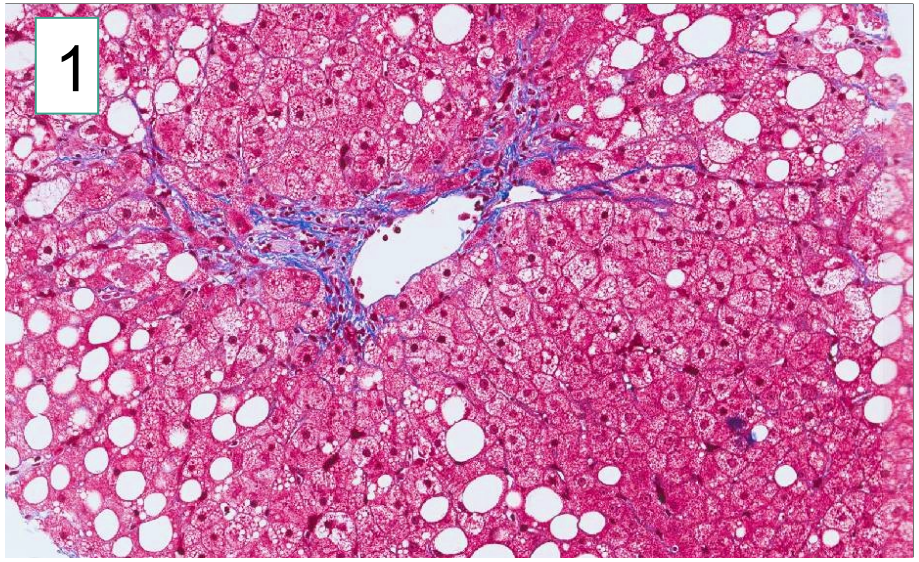
←1+2+2

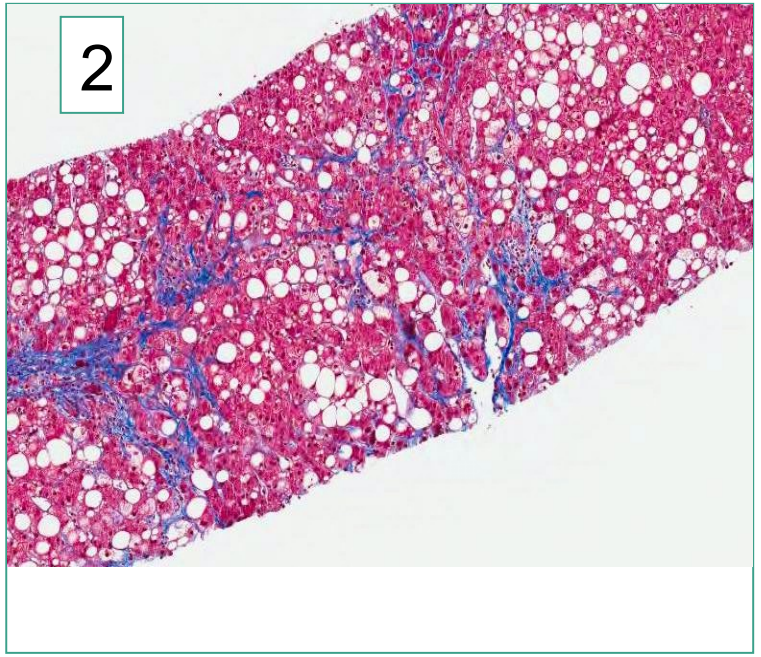
3+1+1→

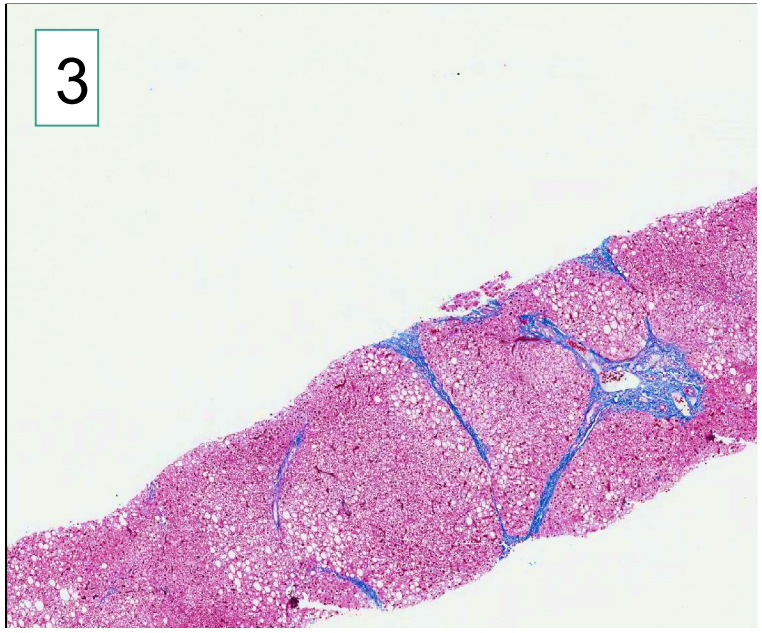
Shifting from a dichotomized to an analytical classification

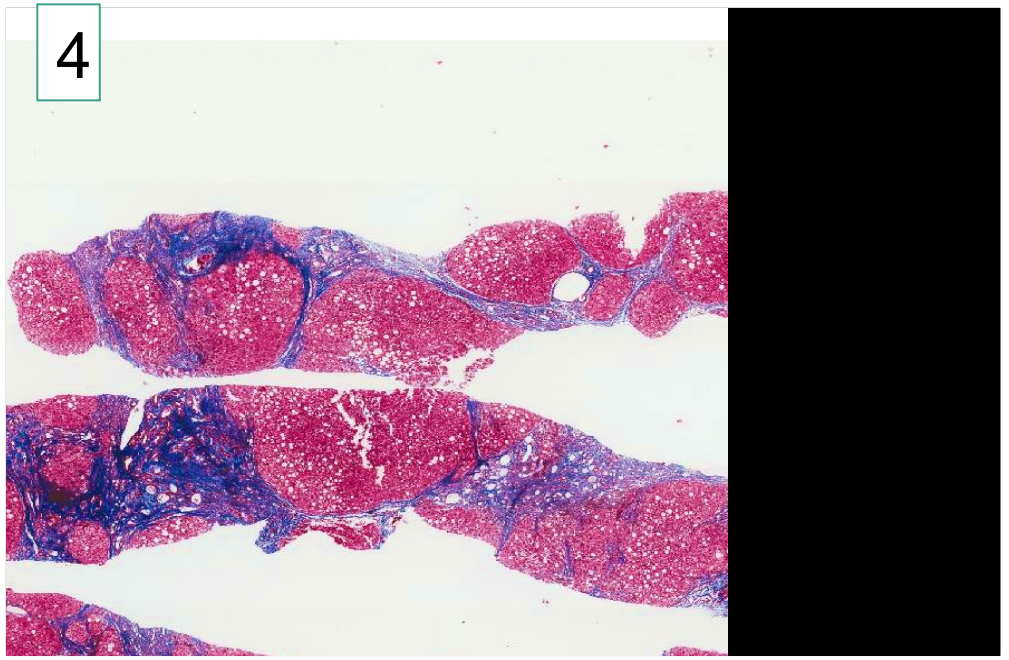


Stage of Fibrosis (Kleiner et al, Hepatology 2005)



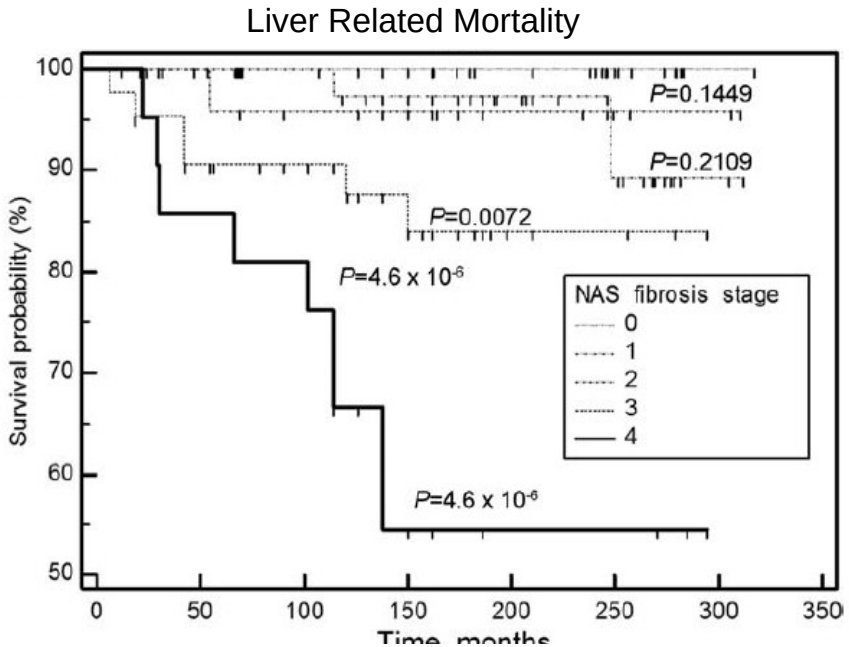






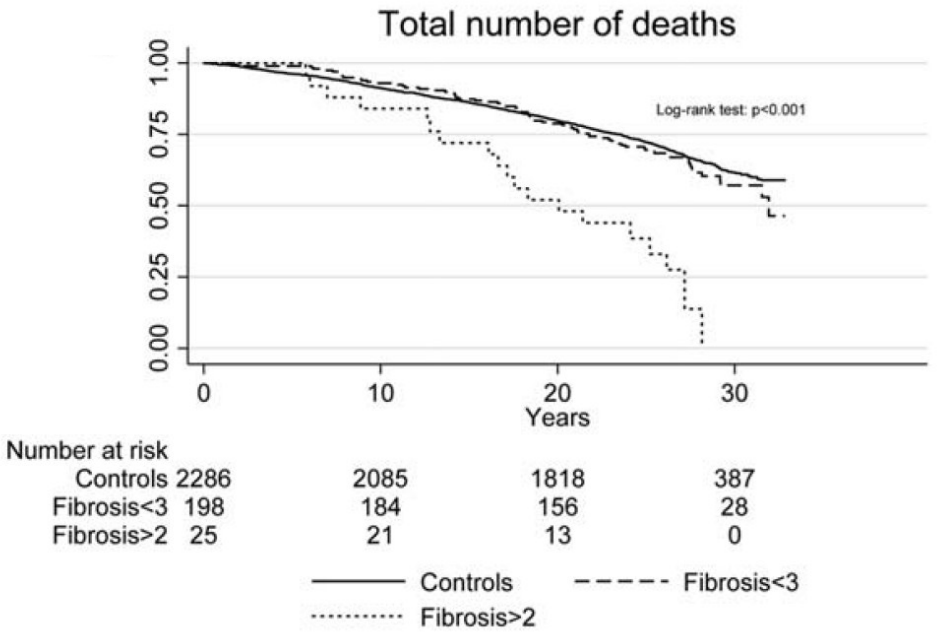
LIVER FIBROSIS : MAJOR PROGNOSTIC FACTOR

Liver-related mortality according to stage of fibrosis in index biopsy



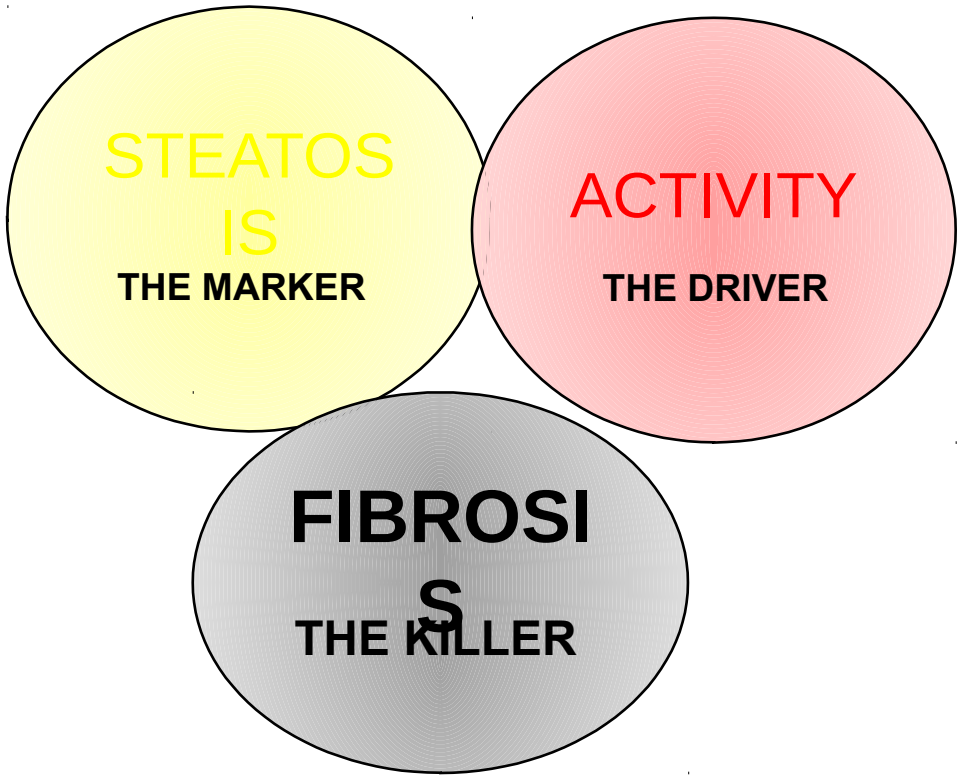
Younossi ZM, Stepanova M, Rafiq N, et al.. Hepatology 2011

Overal survival according to fibrosis stage and compared to control population



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

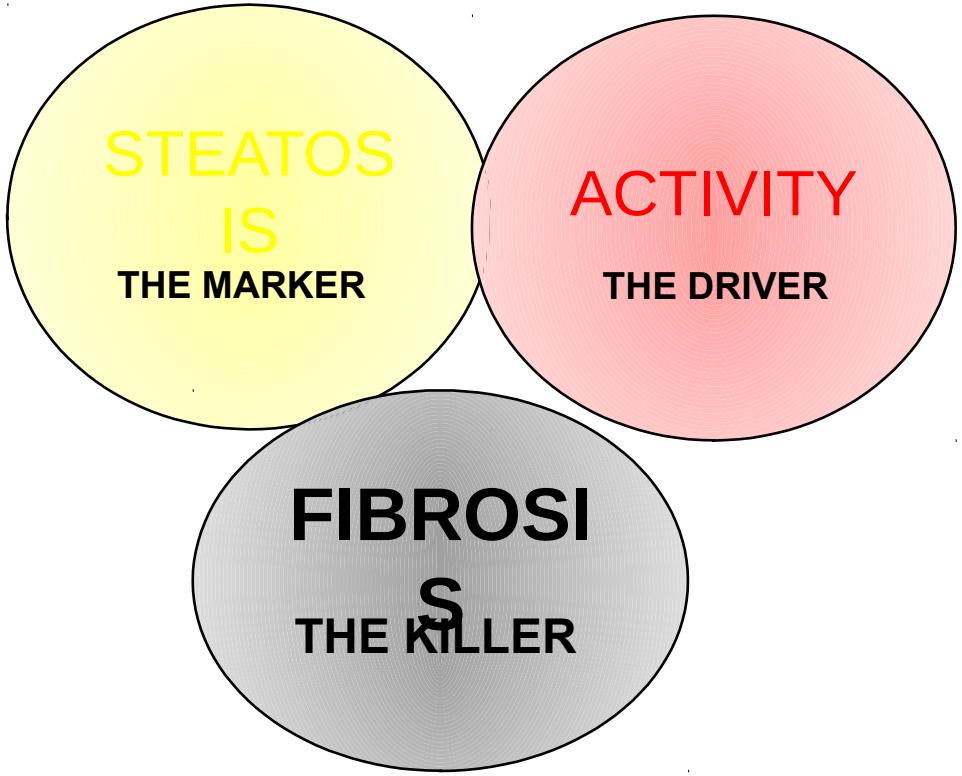
Liver biopy interpretation
Integrative classification (FLIP consortium, SAF)

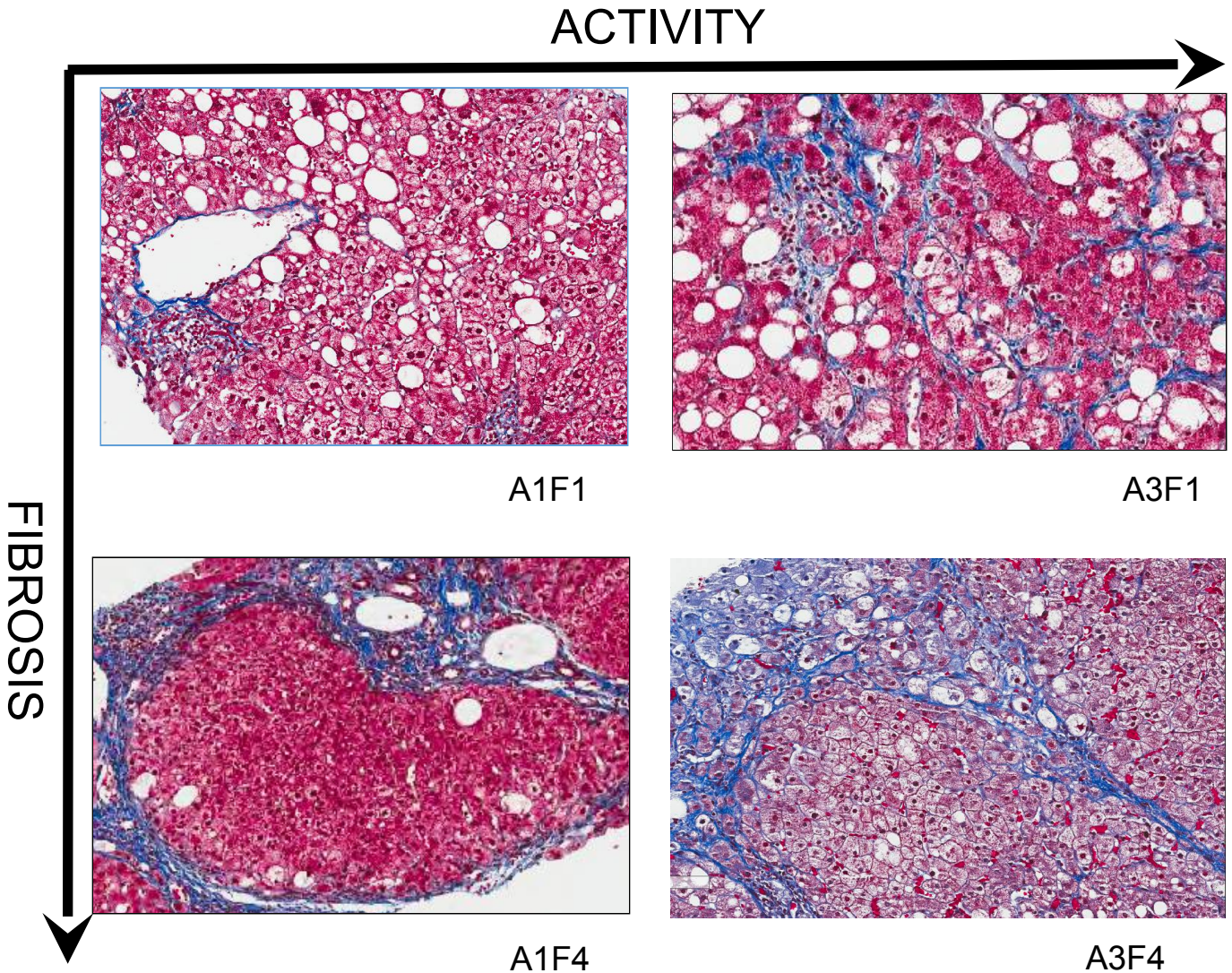


STEATOSIS	A0	A1	A2	A3	A4
F0	A0F0	A1F0	A2F0	A3F0	A4F0
F1	A0F1	A1F1	A2F1	A3F1	A4F1
F2	A0F2	A1F2	A2F2	A3F2	A4F2
F3	A0F3	A1F3	A2F3	A3F3	A4F3
F4	A0F4	A1F4	A2F4	A3F4	A4F4

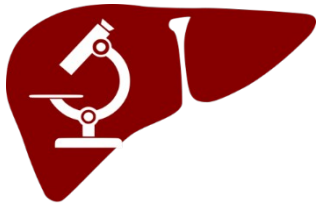
Hepatology 2012, Hepatology 2014, Gut 2016

Liver biopy interpretation
Integrative classification (FLIP consortium, SAF)





Hepatology 2012, Hepatology 2014, Gut 2016



Take-home messages

- NASH is defined by histology. If a diagnosis is needed (clinical trials…) then liver biopsy is mandatory.
- Liver biopsy is a robust procedure that can assess all components of NAFLD if performed by trained physicians (hepatologists and pathologists)
- An analytical description that reports Activity and Fibrosis in a semi-linear fashion is more appropriate than a dichotomous classification (NASH vs No NASH)
- LB is obviously not a screening tool and biomarkers are strongly needed to select patients at high risk of severe disease and who will need a biopsy.
- BUT

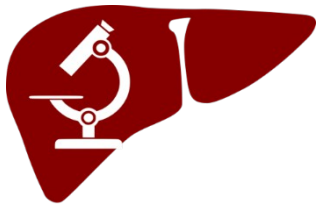
THE WHOLE LIVER
The perfect standard
Sharp image

LIVER BIOPSY
Estimator of the perfect standard
Fuzzy picture

NON INVASIVE BIOMARKER
Estimator of the Estimator
Misty picture

ACCURACY

Predicting histology with a biomarker



THANK YOU FOR YOUR ATTENTION !

pierre.bedossa@liverpat.com