Paris, 14th January 2020

Improving histological score for NASH

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Paris

Conflict of Interests

- Funding from Genfit, Intercept, Allergan, Inventiva, OWL, BMS, MSD, Histoindex, Echosens and Cirius Therapeutics

- Director of LIVERPAT

Histology and NAFLD

« 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 (NASH), fibrosis, and ultimately cirrhosis. …….. Currently, there are no clear criteria to identify this group of patients." *Draft Guidance from FDA, Dec 2018*

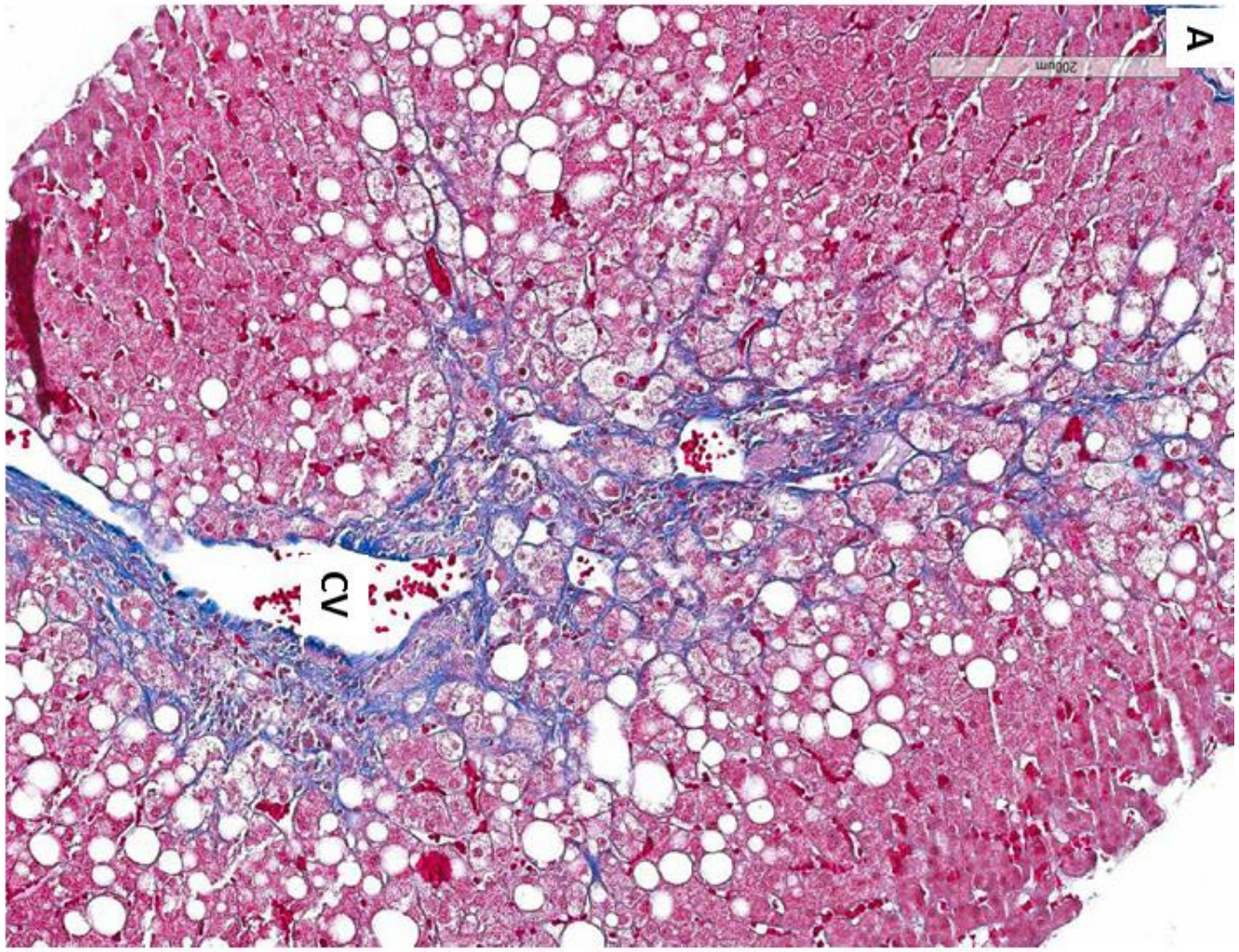
→ If a diagnosis of NASH is required, then liver biopsy is necessary

- NAFLD clinical trials (eligibility and end-points)
- Comorbidities
- Suspicion of advanced liver disease

HISTORICAL LANDMARK

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.

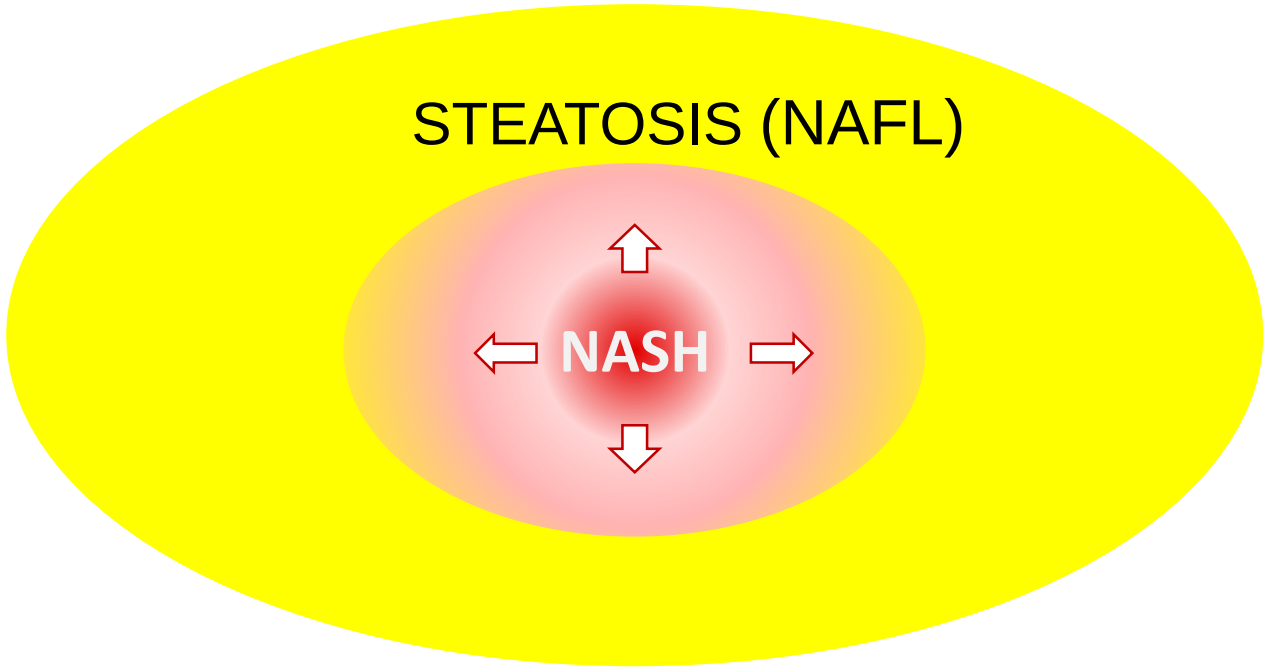
Ludwig J, et al. Mayo Clin Proc. 1980



- acute alcoholic hepatitis-like pattern
- small subset of NAFLD
- Typical histologic feature
- Easily recognizable
- Severe disease
- High risk of progression

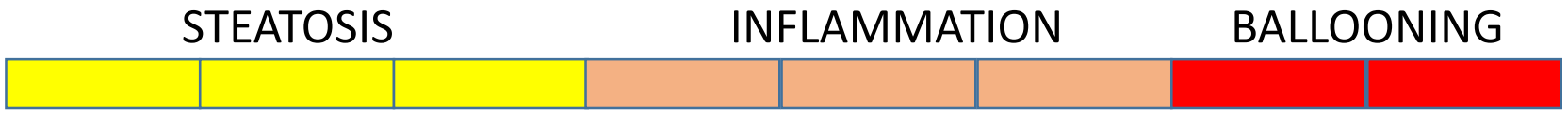
Brunt (1999), NASH CRN (2005)

- Expanding histological spectrum : From typical severe (1980) to mild disease
- but still using dichotomous classification: NAFL vs NASH



- Characterization of mild diseases uneasy
- Loose correlation with prognosis
- No validated non invasive biomarker available

The NAFLD Activity Score (NAS) (Kleiner 2005)



TROUBLES WITH NAS

- Conceptual mistakes:
  - Steatosis not a marker of activity (steatosis not a driver of fibrosis)
  - Ballooning underweighted in NAS (2 points vs 3 for inflammation and steatosis), max 2 out of 8 points

- Scoring not accurate enough:
  - Inflammation and ballooning grading moderatly reproducible

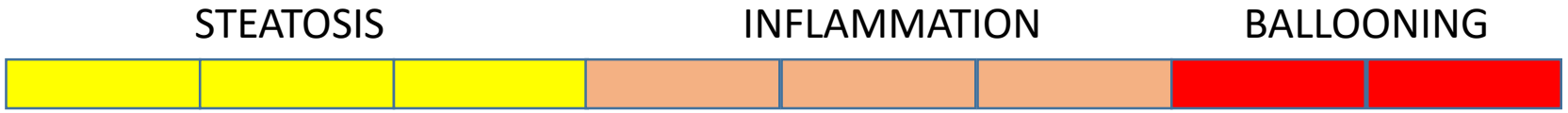
- Consequences
  - NAS has never been demonstrated a prognosis value
  - Significant interobserver variability in scoring, a challenge in clinical trials

Reference		NASH Diagnosis	Steatosis	Inflammation	Ballooning
Inter-observer variability (Kappa)					
Younossi 1998		0.5	0.64	0.33	0.50
Kleiner 2005		0.61	0.79	0.45	0.56
Bedossa 2014		0.54	0.61	0.41	0.52
Kleiner 2019		0.66	0.77	0.46	0.54

- High inter-observer variability in grading of ballooning and inflammation
- Explained by vague or inaccurate definition criteria

Ballooning: 0=none, 1=few, 2=many

The NAFLD Activity Score (NAS)



ISSUES OF NAS

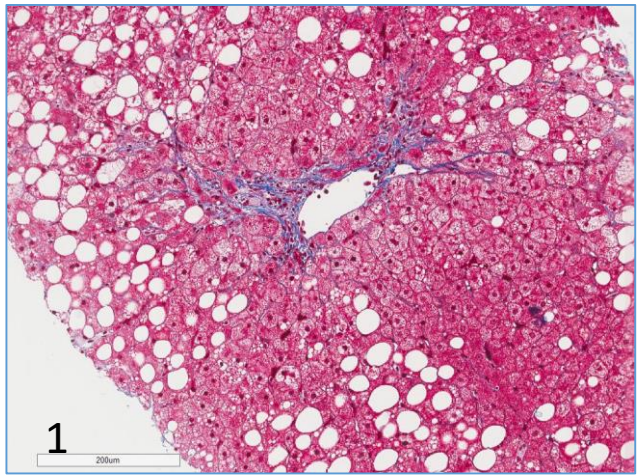
- Conceptual mistakes:
  - Steatosis not a marker of activity (steatosis not a driver of fibrosis)
  - Ballooning underweighted in NAS (2 points vs 3 for inflammation and steatosis), max 2 out of 8 points
- Definition and scoring not accurate enough
  - Inflamation and ballooning poorly reproducible

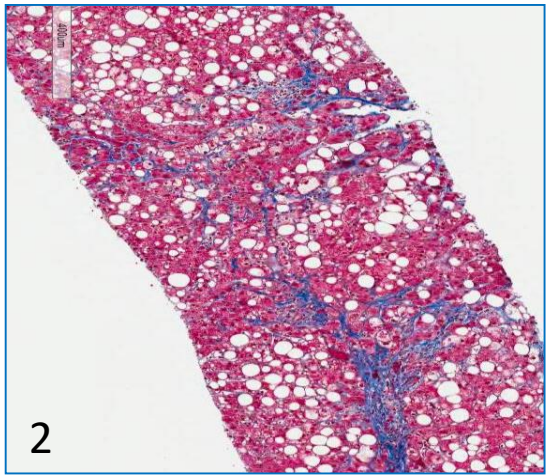
- Consequences
  - NAS has never demonstrated a prognosis value
  - Significant interobserver variability in scoring

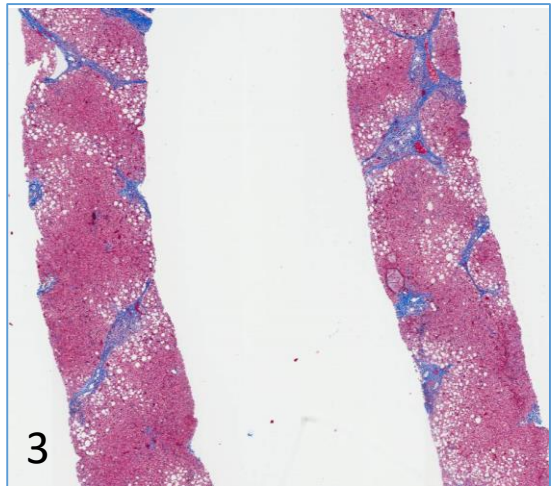
➢ a major challenge in clinical trials (Phase 3) where NAS belong to eligibility criteria

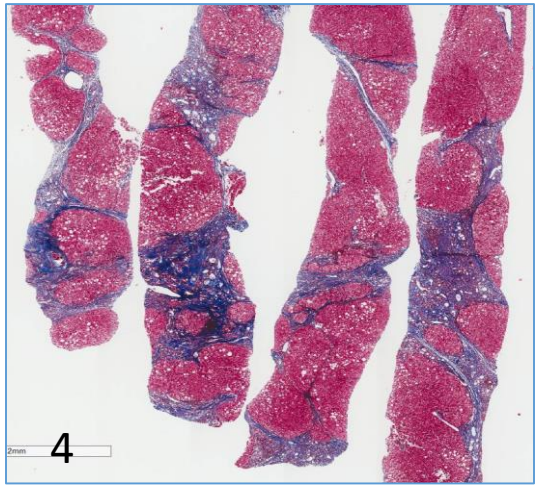
NASH-CRN Fibrosis score (Kleiner 2005)

Stage	Histological findings
1a	Mild pericellular fibrosis (only seen on connective tissue stain)
1b	Moderate pericellular fibrosis (readily seen on H&E)
1c	Portal/periportal fibrosis without pericellular fibrosis
2	Pericellular and portal/periportal fibrosis
3	Bridging fibrosis
4	Cirrhosis



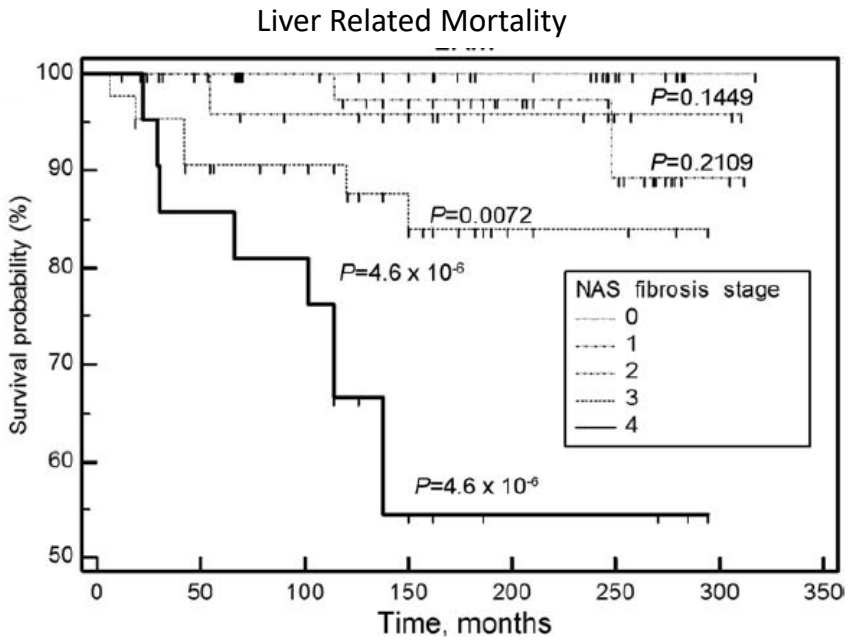






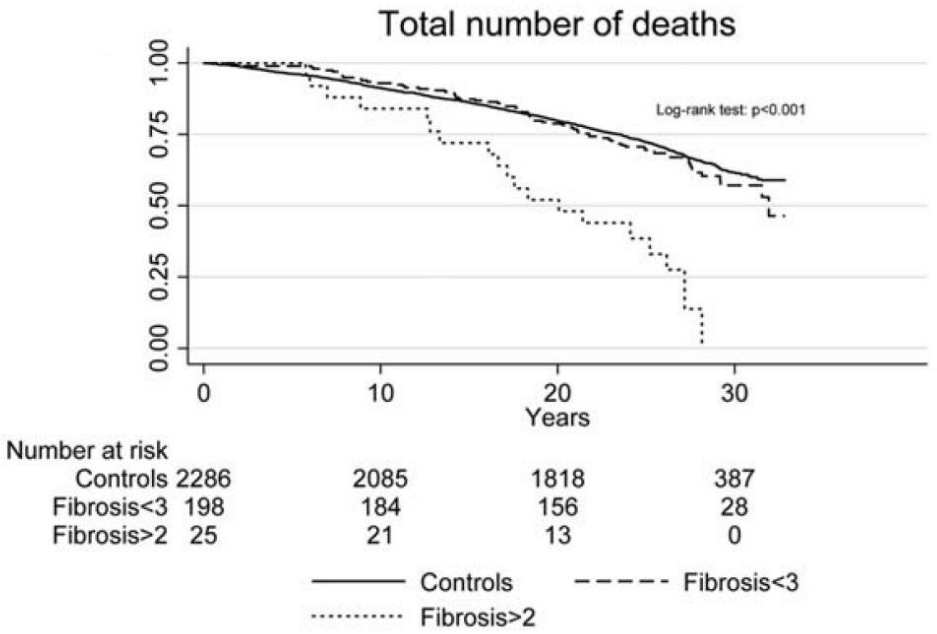
LIVER FIBROSIS : MAJOR PROGNOSTIC FACTOR

Liver related mortality according to stage of fibrosis in index biopsy



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

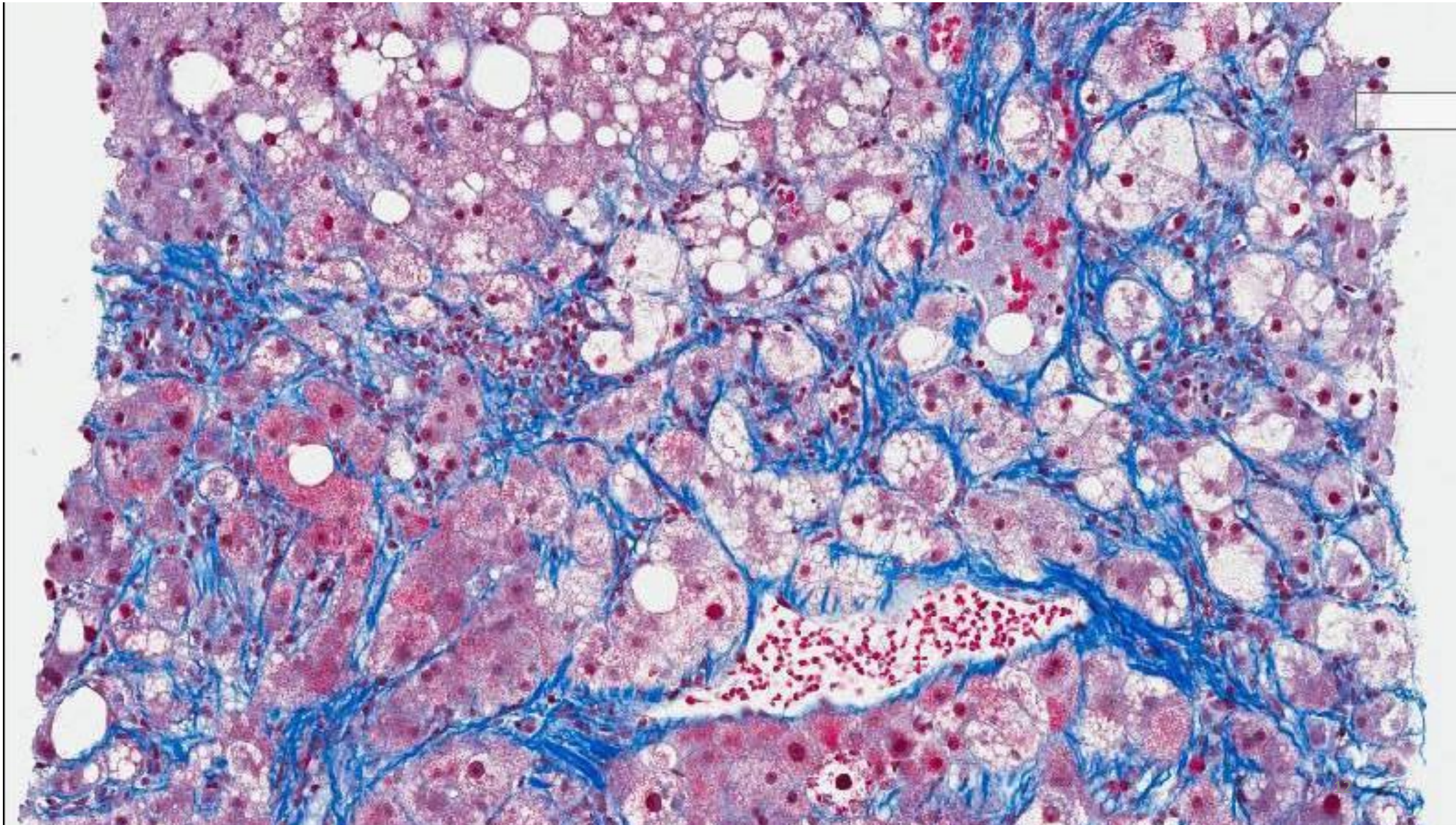
Overal survival according to fibrosis stage and compared to control population



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

Weakness of staging fibrosis with NASH CRN

- Do not capture perisinusoidal fibrosis, a hallmark of NASH
- Poorly descriptive in advanced fibrosis
- Not enough granularity to capture fibrosis changes in short-term clinical trials for F2-F3
- Highly accurate for early/very early stages (1a, 1b, 1c) but high interobserver variability, sampling variability and no clinical significance



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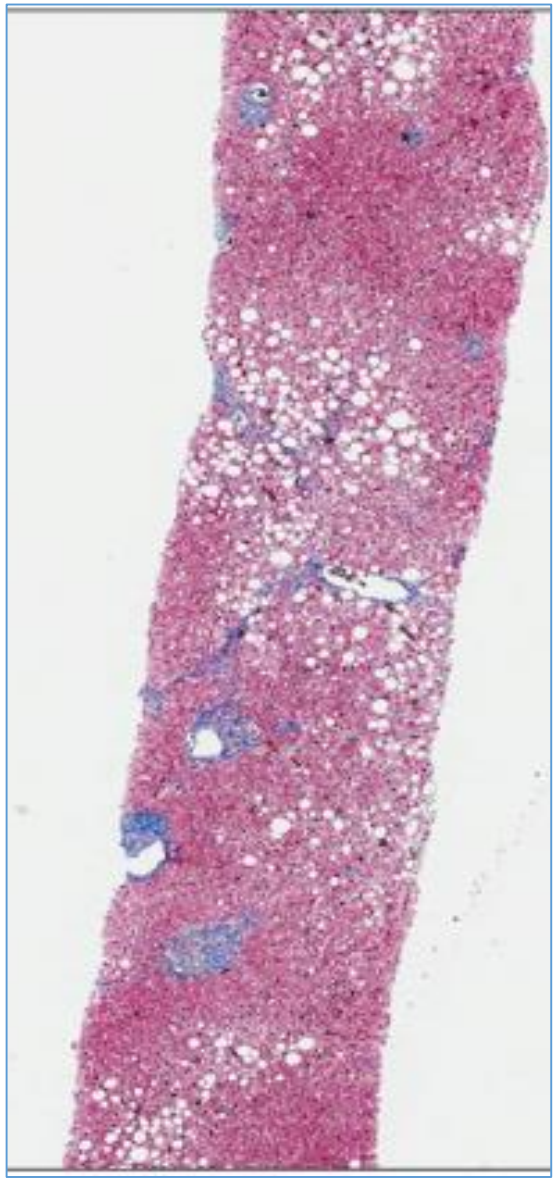
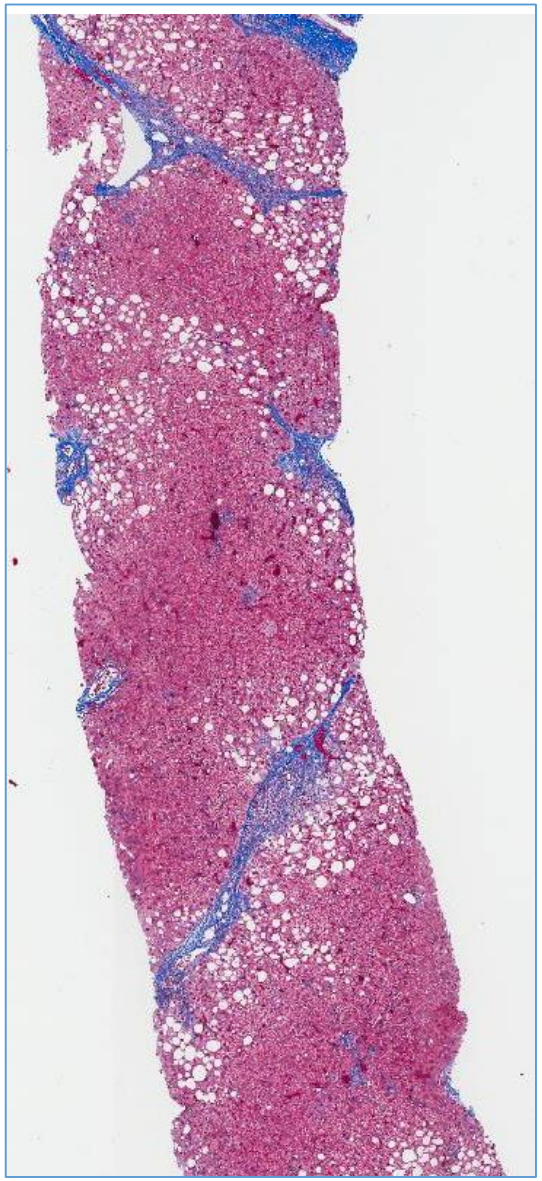
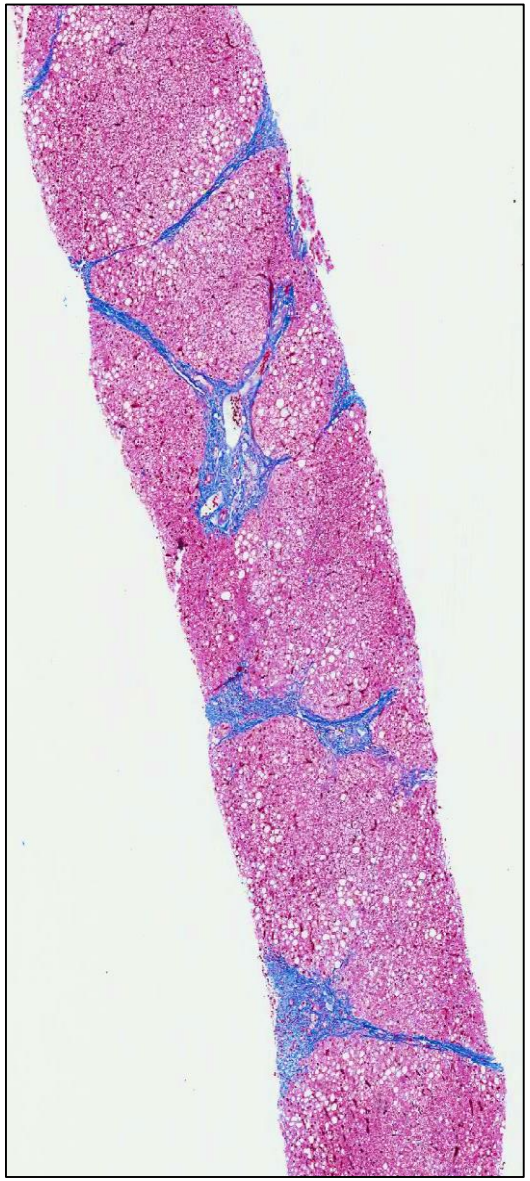
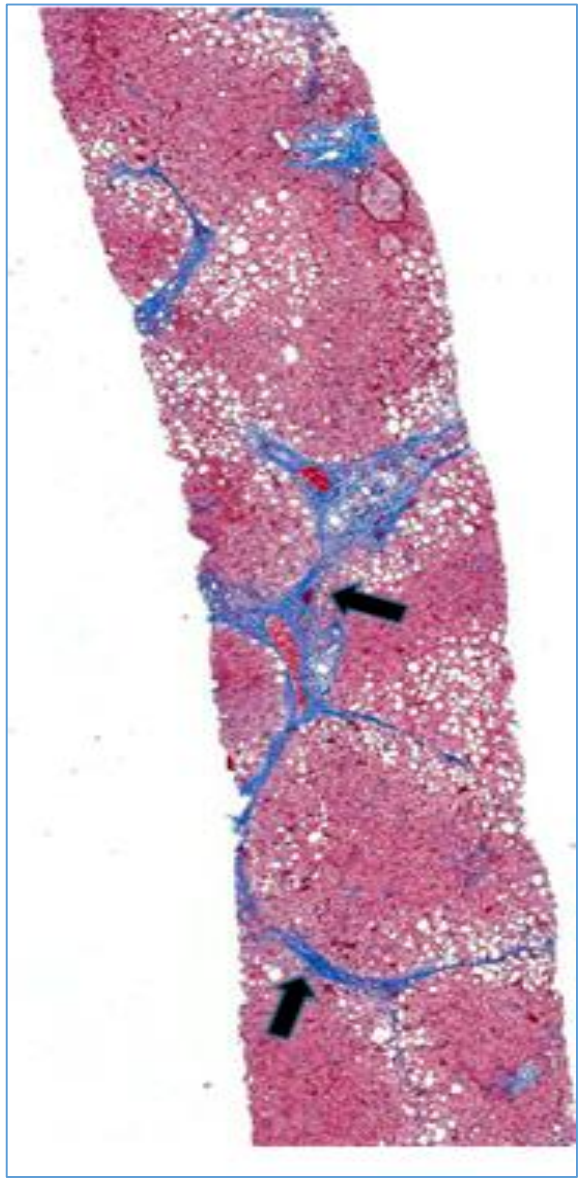
NASH CRN Stage 3

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Reference		Fibrosis NASH CRN 1, 2, 3, 4	Fibrosis NASH CRN 1a, 1b, 1c, 2, 3, 4
Inter-observer variability (Kappa)			
Younossi 1998		0.60	
Kleiner 2005		0,84	
Merriman 2006			0,53
Bedossa 2014		0,77	0,51
Kleiner 2019		0,75	

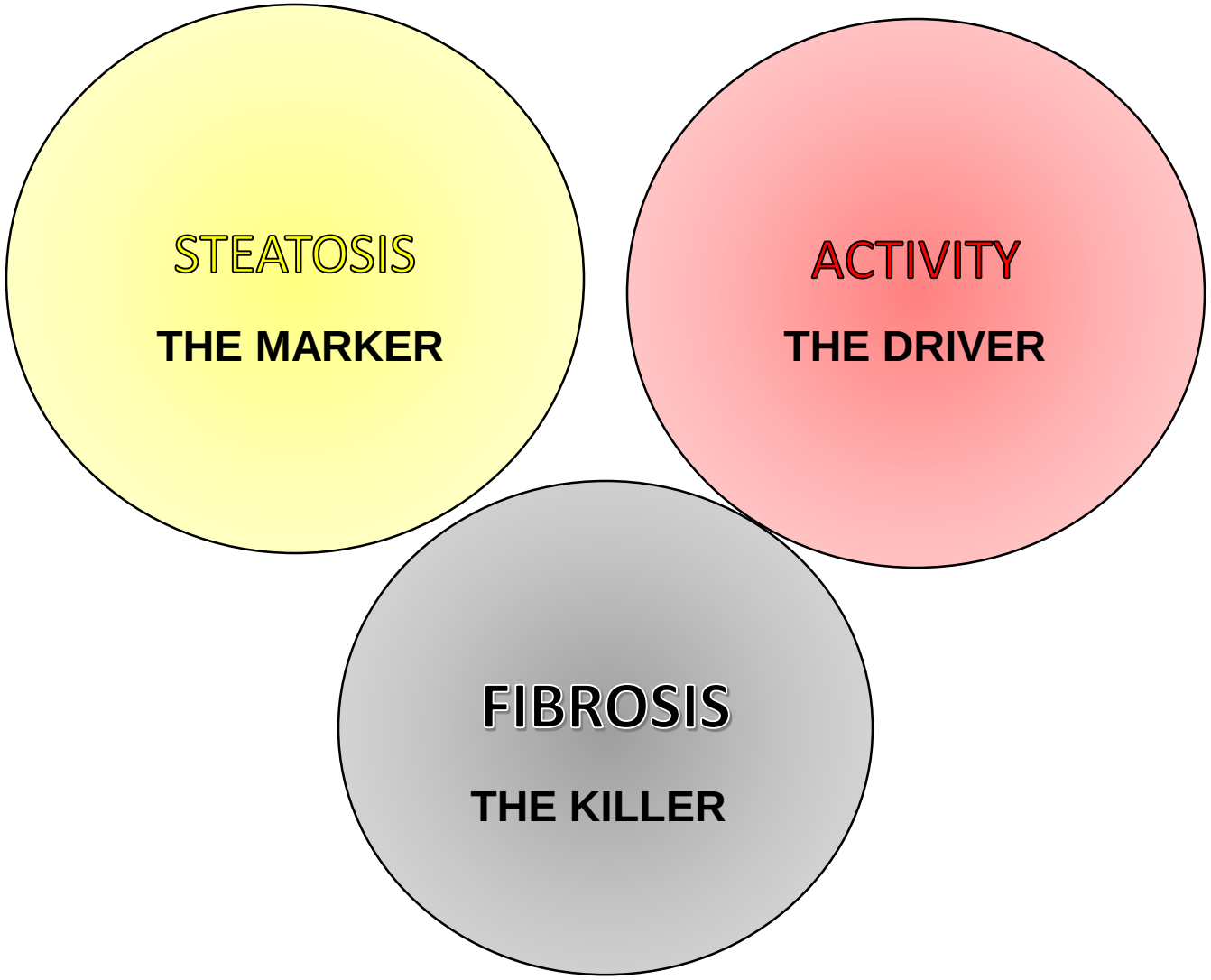
Improving histological scores in NAFLD
Moving forward

- The dichtomous approach (NASH / no NASH) is an oversimplification of the reality, a need for a more flexible approach
- The NAS has conceptual and practical important limitation (observer variability)
- The staging of fibrosis, also clinically relevant, needs in depth review to capture more linearity and granularity

Standardising the interpretation of liver biopsies in non-alcoholic fatty liver disease clinical trials. Pai RK, Kleiner DE, et al. Aliment Pharmacol Ther. 2019 Nov;50(10):1100-1111

UNDER THE LENS : THE 3 HISTOLOGICAL COMPONENTS OF NAFLD

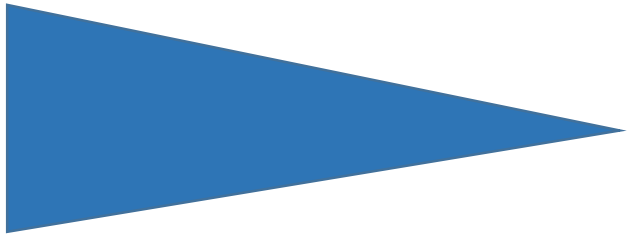
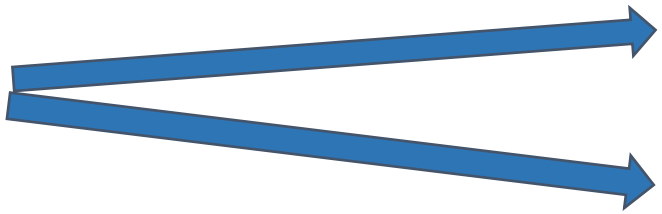
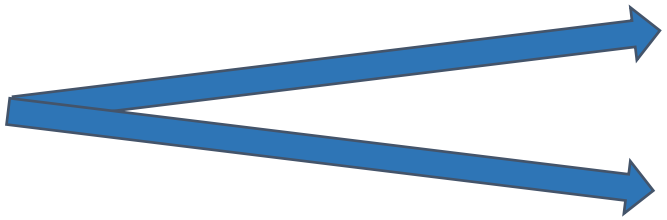
FLIP consortium, Hepatology 2012, Hepatology 2014



CHANGING THE PARADIGM

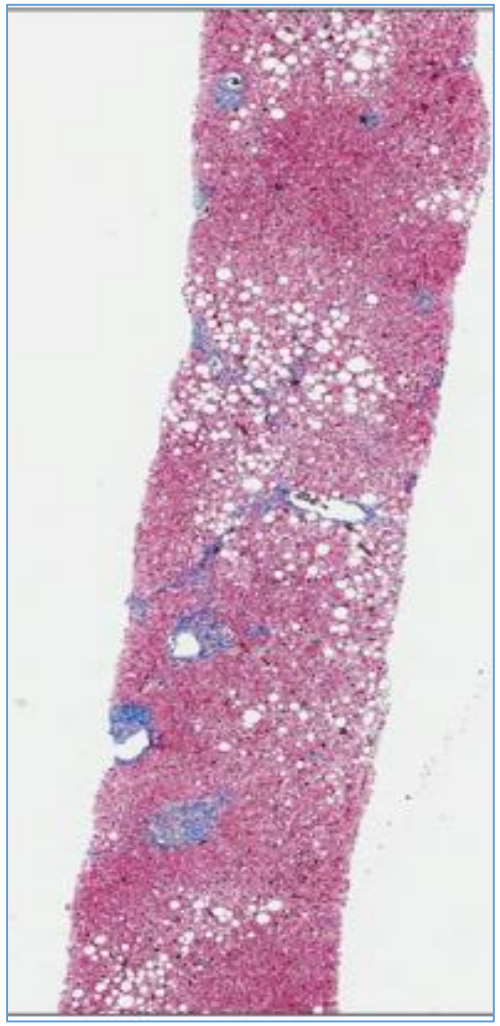
FROM DICHOTOMOUS CLASSIFICATION TO A TWO-DIMENSIONAL CONTINUOUS SCALING SYSTEM

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

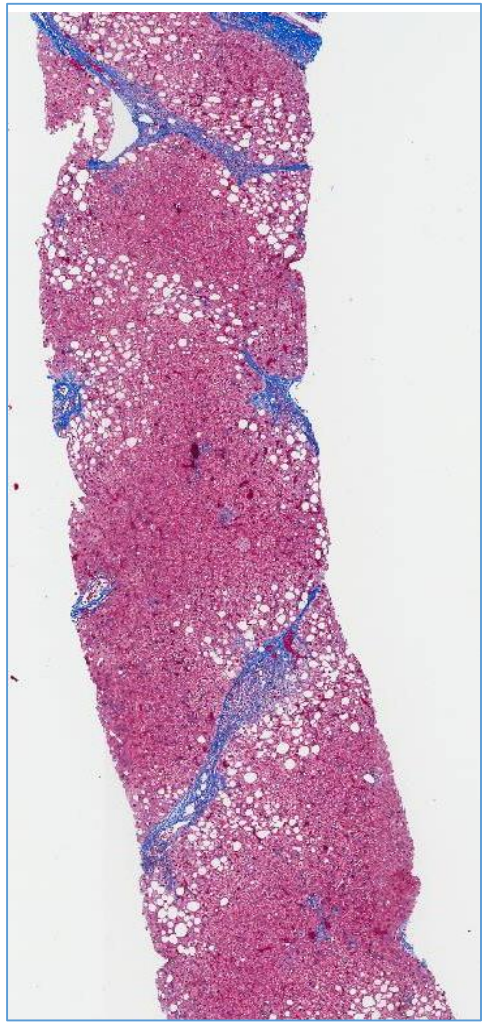
NASHCRN →	EPOS	Comments
1a 1b 1c 	1	**Aggregate** because: - Poor reproducibility, Sampling error - No clinical relevance
2	2	**Changing definition** : - Introducing perisinusoidal fibrosis central or portal fibrosis + lobular fibrosis or portal + central fibrosis
	3 4	**Increase granularity**: - Few septa (no more than 2 /10mm length of biopsy) - Many septa (> 2….) without nodule
4 	5 6	**Increase granularity**: - Many septa with few nodules - Annular fibrosis with complete nodulation

EASL 2018

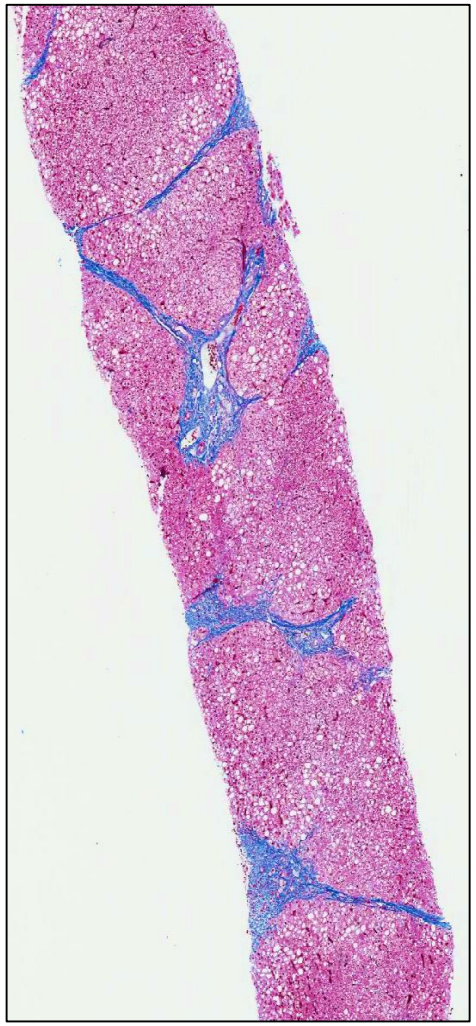
NASH CRN Stage 3



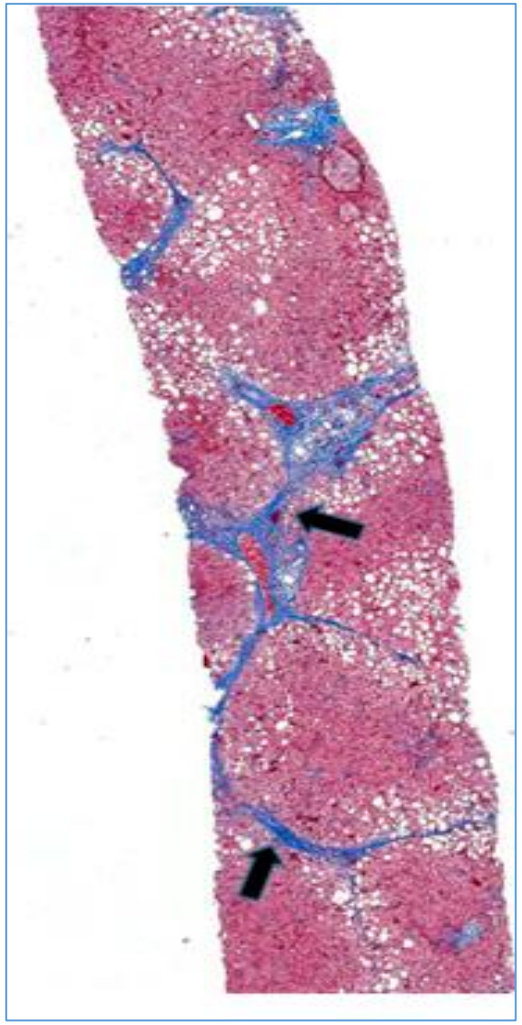
Stage 2



Stage 3



Stage 4



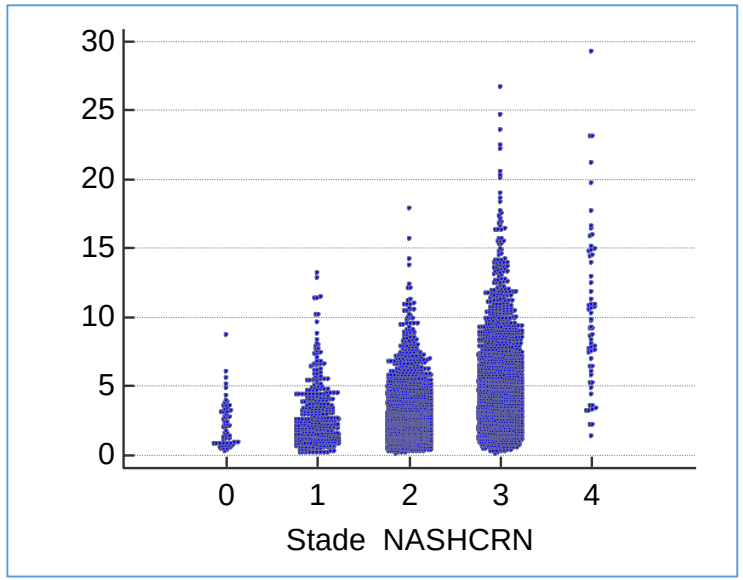
Stage 5

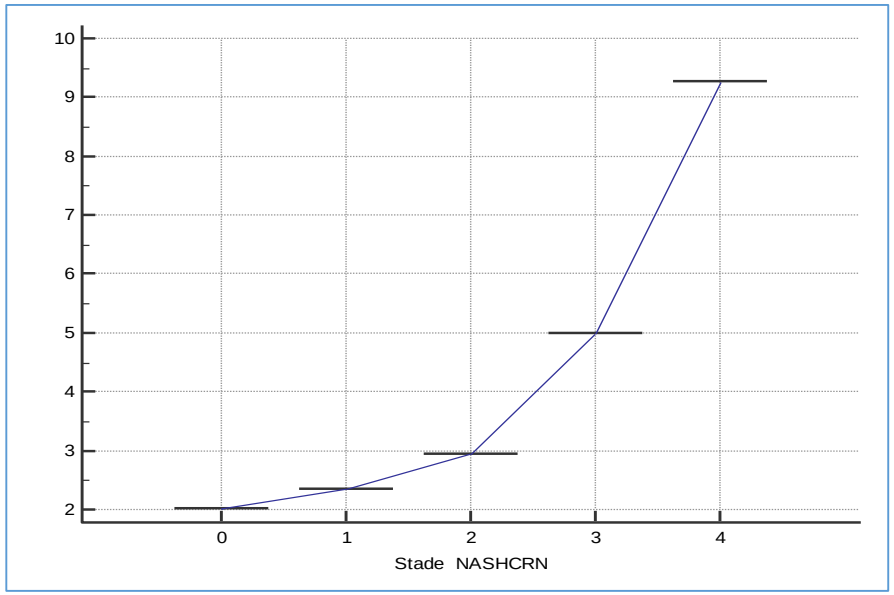
Kappa score 0.86

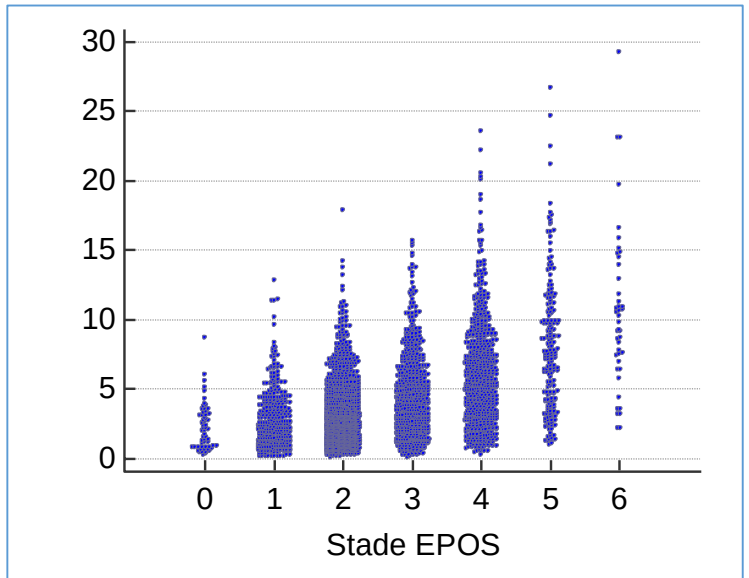
FLIP consortium, J Hepatol 2018

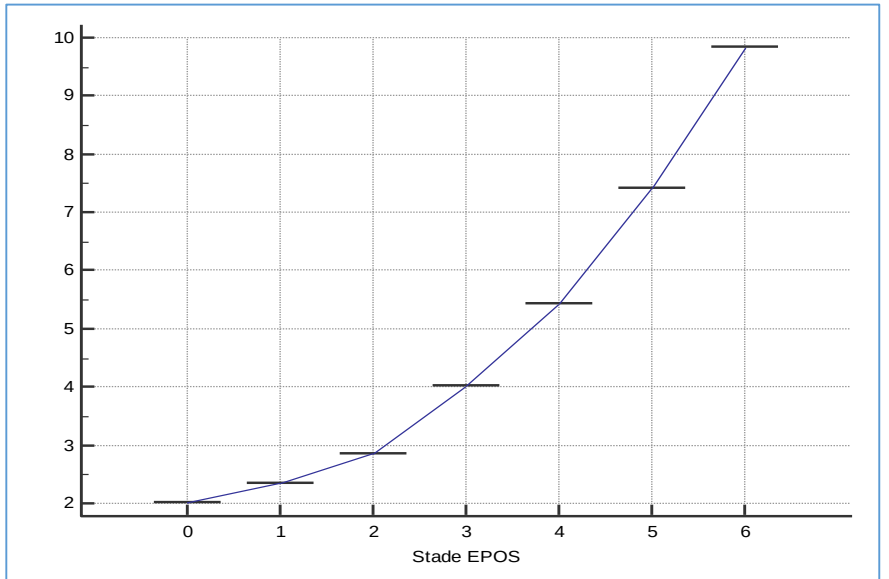
Collagen Proportional area / Fibrosis stages

(2900 liver biopsies, Phase 3 clinical trial with permission)









How to define and mitigate a NAFLD activity score

- No steatosis
- Equal weight for Inflammation (lobular) and ballooning
- Strong observer reproducibility for any feature (Kappa $\geq$ 0.7)
- Relevance to clinical outcome

SAF score: interobserver variation

	κ score	
Steatosis (0 1 2 3)	κ = 0.61	Substantial
Activity (0, 1, 2, 3, 4) Ballooning (0, 1, 2) Lob. Infl (0, 1, 2)	κ = 0.75 κ = 0.8 κ = 0.72	Substantial
Fibrosis (1-2-3-4)	κ = 0.83	Perfect

SAF score : highly reproducible semiquantitative features

https://www.esp-pathology.org/

European Society of Pathology

LITMUS

Non-alcoholic fatty liver disease (NAFLD)
Atlas of histological images
Guidelines for diagnosis and scoring

HORIZON 2020

imi innovative medicines initiative

efpia European Federation of Pharmaceutical Industries and Associations

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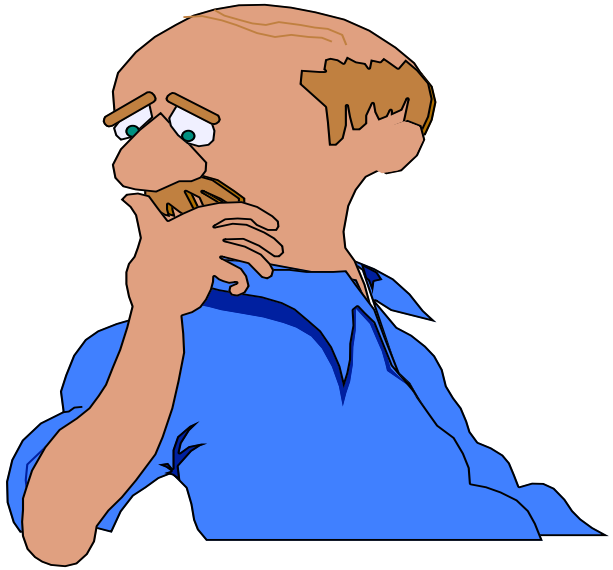
Take-home message



It is time to move forward: lesson from the past

Yrs

LESSONS FROM THE PAST

Chronic viral hepatitis	
Chronic persistent hepatitis / Chronic active hepatitis (1960)	
+ Chronic lobular hepatitis (1970)	
CLINICAL TRIALS → HISTOLOGICAL SCORES	
Knodell Histological Activity Index (HAI=Activity + Fibrosis) (1980)	
…… **+ 15 YRS** ……	
METAVIR (1994) ISHAK score (1995) A and F	

LESSONS FROM THE PAST

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Yrs

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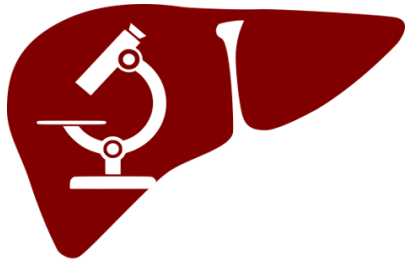
METAVIR (1994) ISHAK score (1995) A and F	**2020** **Time to move forward !!**



THANK YOU FOR YOUR ATTENTION !

Pierre.bedossa@liverpat.com