Overview of MorphoQuant Technology and Brainstorming on Qualification Process

Cindy Serdjebi, PharmD, PhD

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Disclosures

Biocellvia: patent owner, employee and shareholder
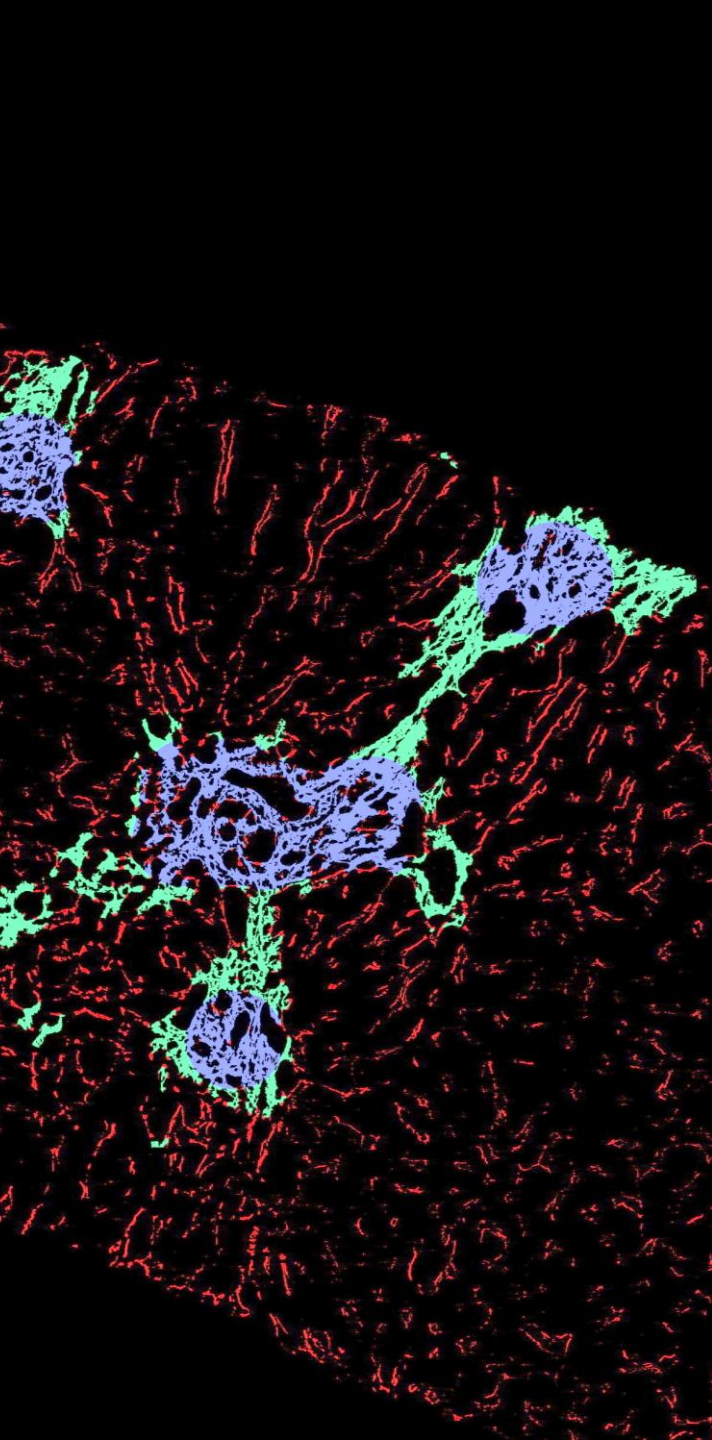
What is MorphoQuant™?

Fully automated software performing morphometry image analysis: size, shape, forms and colors, and textures to recognize specific patterns

- Uses elements from the images, based on development of original combinations of stains and/or IHC

- **Objectivity**: no room for subjective interpretation

- Accuracy and precision

Artificial intelligence expert system (if-then statements):

- **No need for annotations, no training set**

- **Fully automated :** no human intervention from receiving the scan to producing mapped images and raw data

- A favorable regulatory context : **100% traceable algorithm**, easier to maintain and evolve
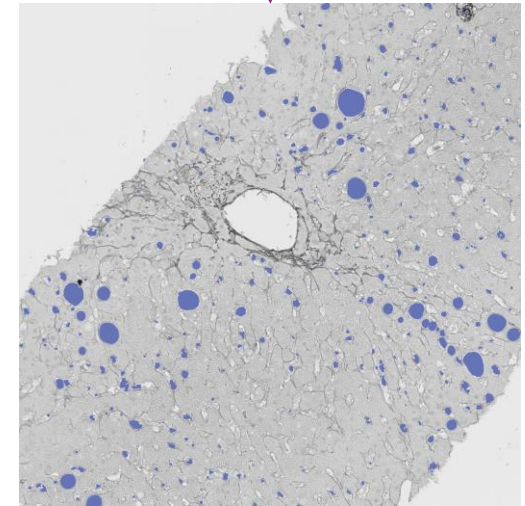
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Morphometric Image Analysis

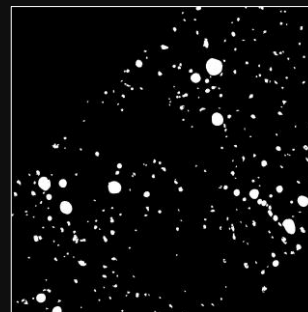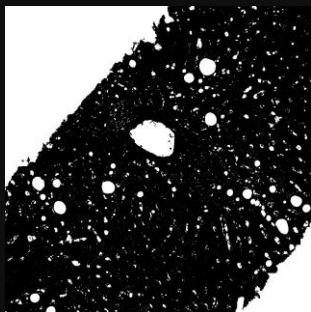
MorphoQuant™
Black Box?
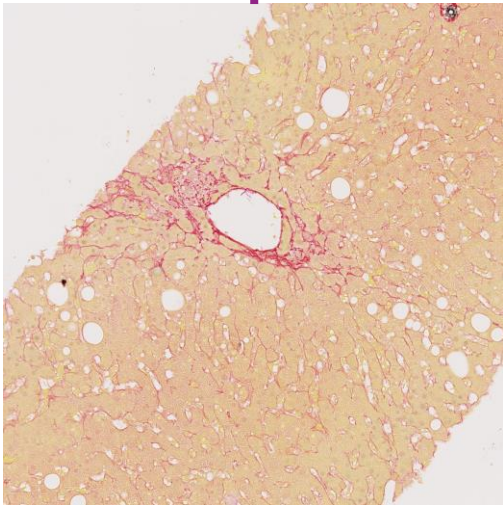
Criteria List:

- Uncolored spots
- Round (not oval)
- Regular outlines
- Dome-shaped
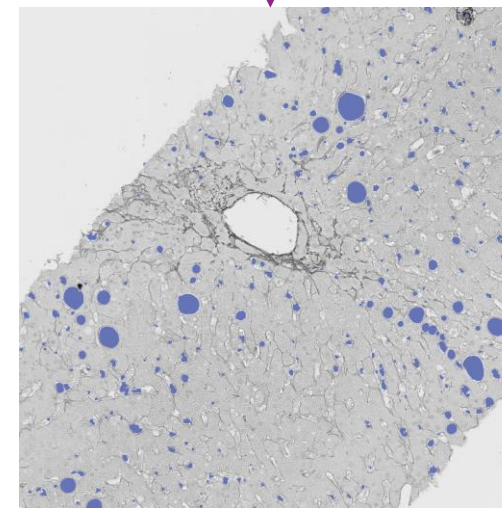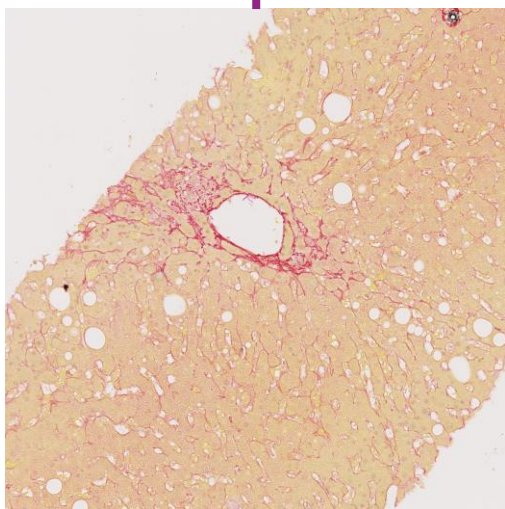- Area within a certain range

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Morphometric Image Analysis

Morphometric Analysis: 100% Explainable

Criteria List:

- Uncolored spots
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Key Benefits

Technology compatible with the current workflow:

- Standard histology allowing pathologists and Biocellvia to work from the same materials
    - Reduces the discrepancy due to consecutive slide reading
- Provides illustrative images for the pathologists to rely on
    - Strengthens the interpretation

Provides conventional readouts (S, I, B, F) + exploratory features

Objective data pathologist-independent

Full automation

Assessment of Steatosis Features in Mouse

Assessment of steatosis in an adipose tissue specific-Angiopoietin-2 KO mouse model.

Original Article

MOLECULAR
METABOLISM

**Selective adipocyte loss of Angiopoietin-2
prompts female-specific obesity and metabolic
syndrome**

Bin Ni [1,2], Shanshan Chen [1,3], Kathleen A. Ryan [4], Michael L. Maitland [5,6], Jared S. Farrar [7],
Martin Witzenrath [8,9], Birgitt Gubier [8], Cindy Serdjebi [10], Karine Bertotti [10], Rui Wang [11], Fadi N. Salloum [11],
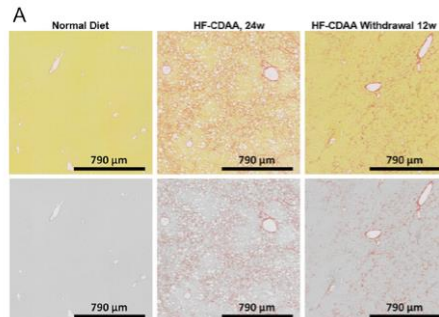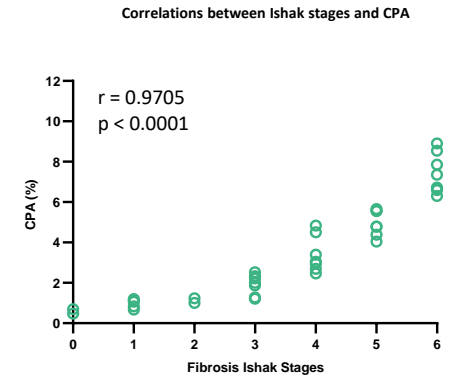Luigi Marino [1], Braxton D. Mitchell [4,12], Francesco S. Celi [1,*]

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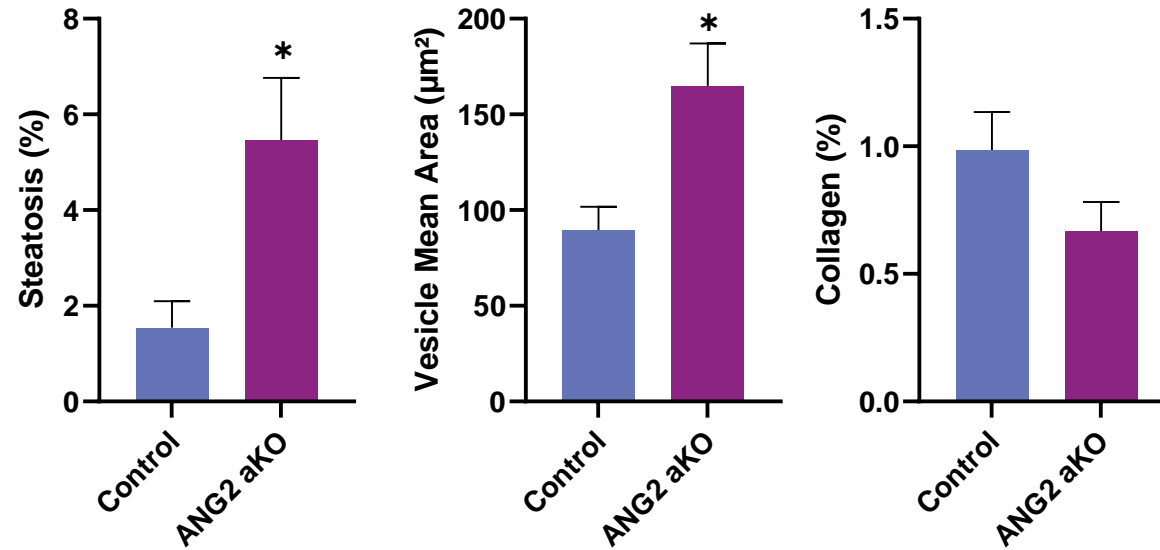
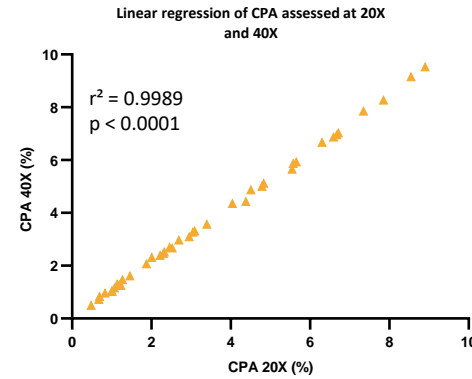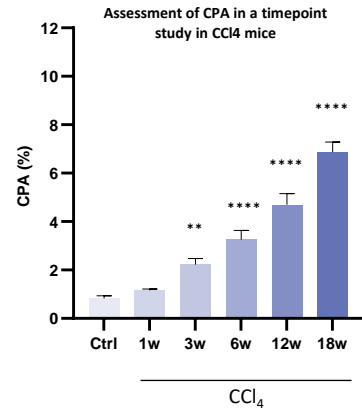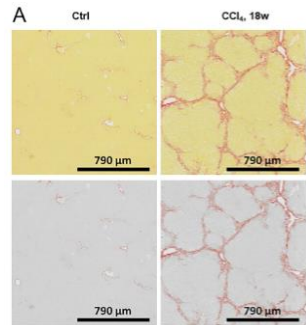# Assessment of Fibrosis in Mouse

Assessment of fibrosis in a timepoint study in two commonly used mouse models: CCl4 and HF-CDAA.

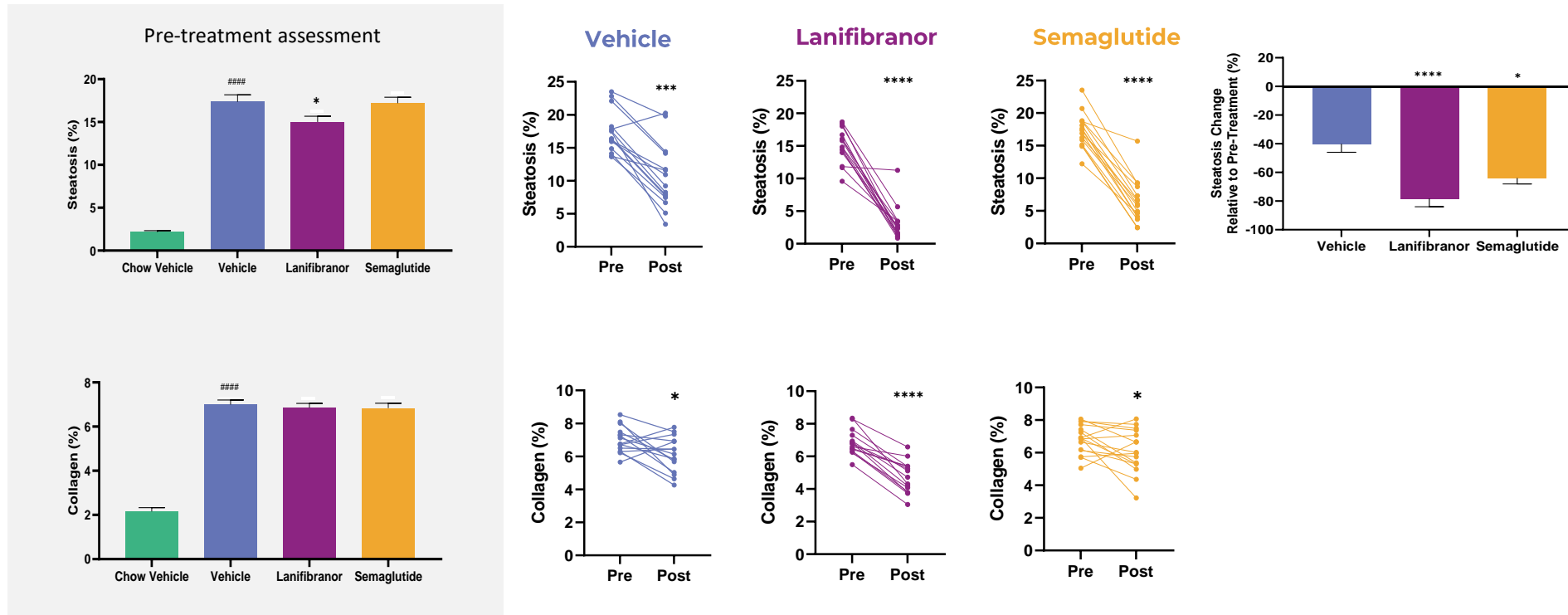# Further in Fibrosis Assessment

DIO GAN-MASH mouse model, treated with either lanifibranor or semaglutide, was assessed for steatosis and fibrosis on PSR-stained slides.
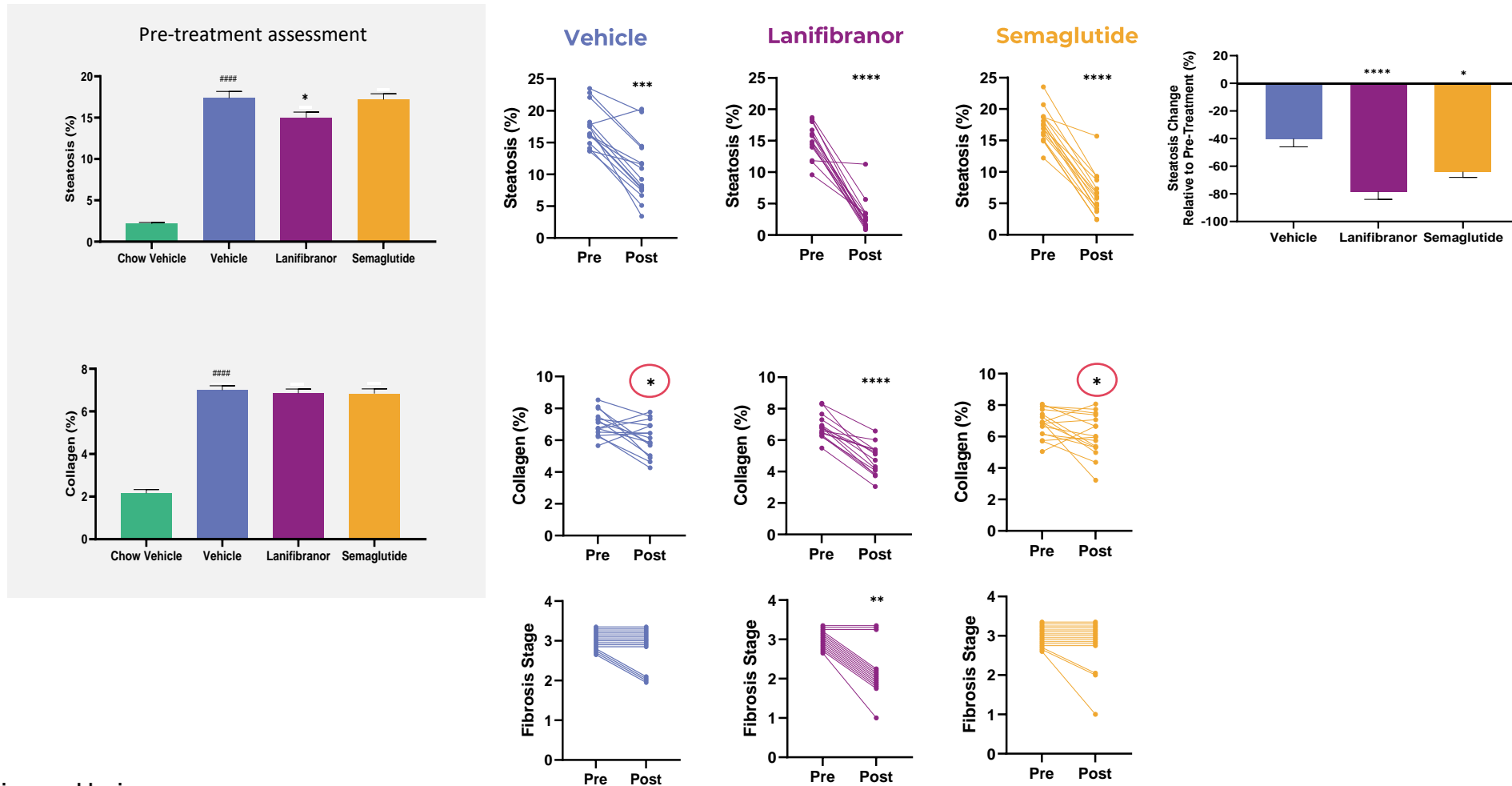
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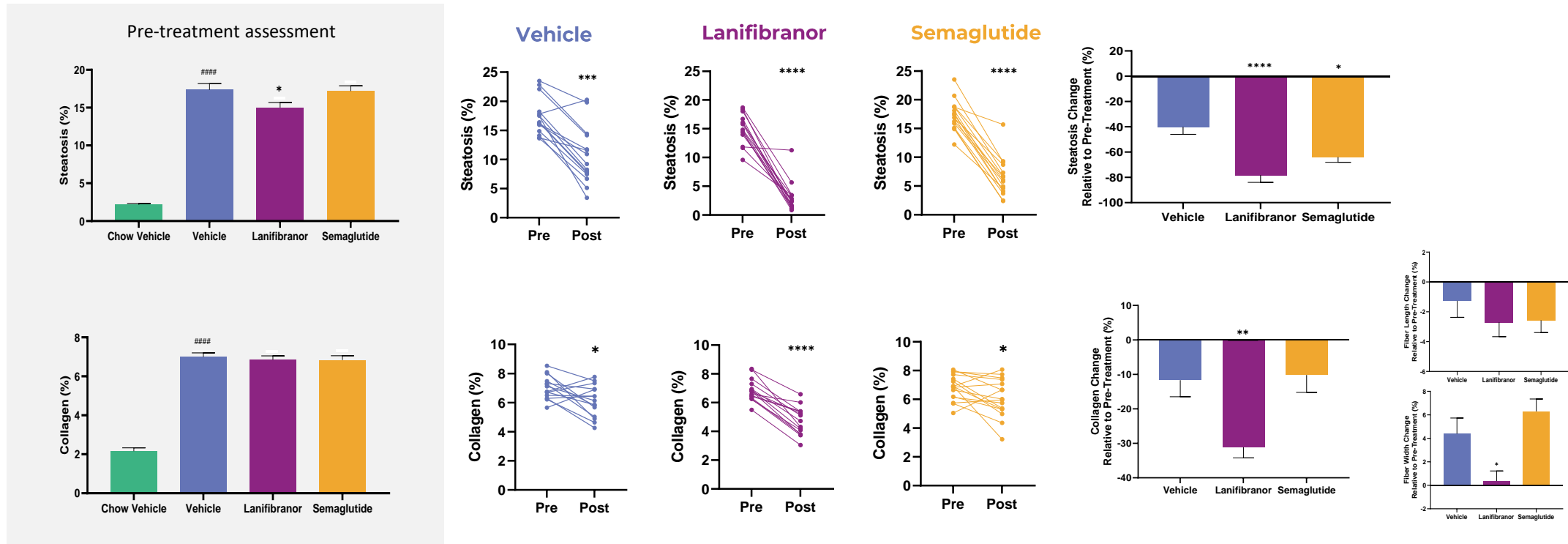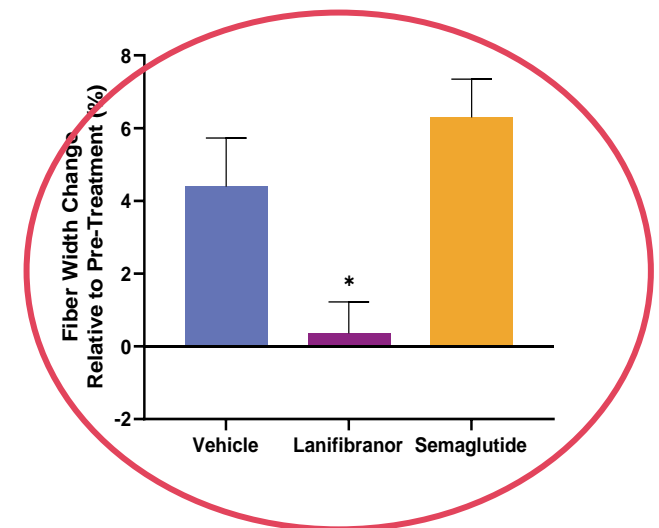
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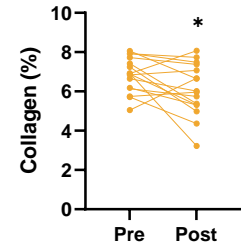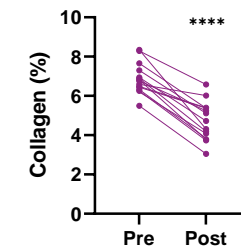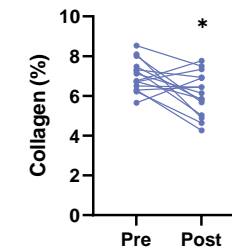
Assessment of Inflammation in Mouse

Assessment of macrophage inflammation (F4/80)in a timepoint study in foz/foz HF mouse
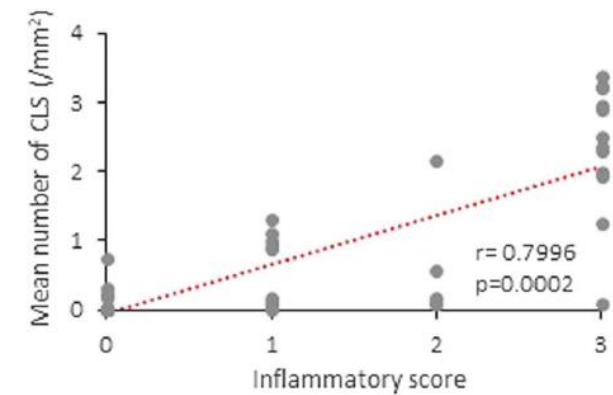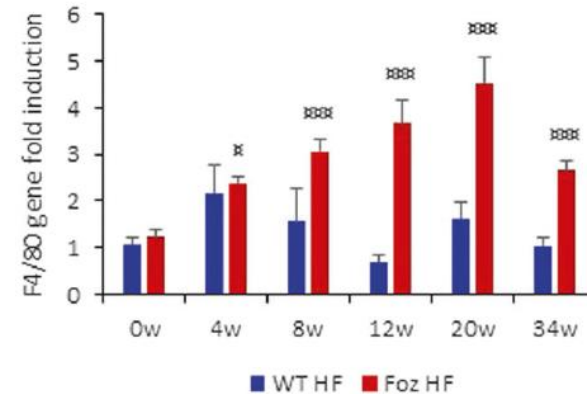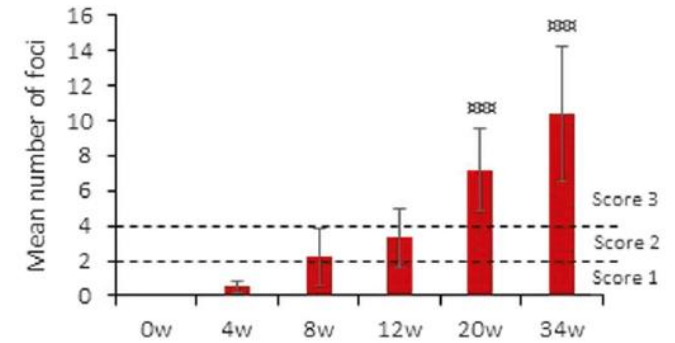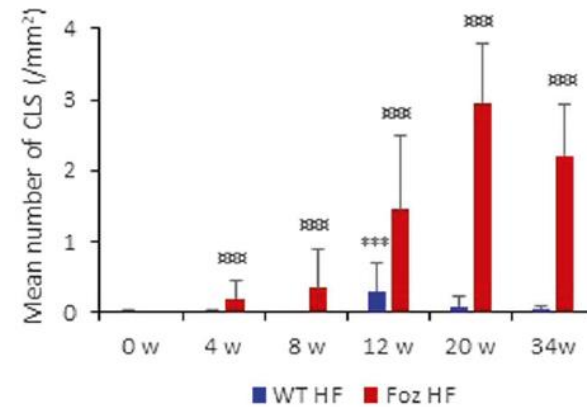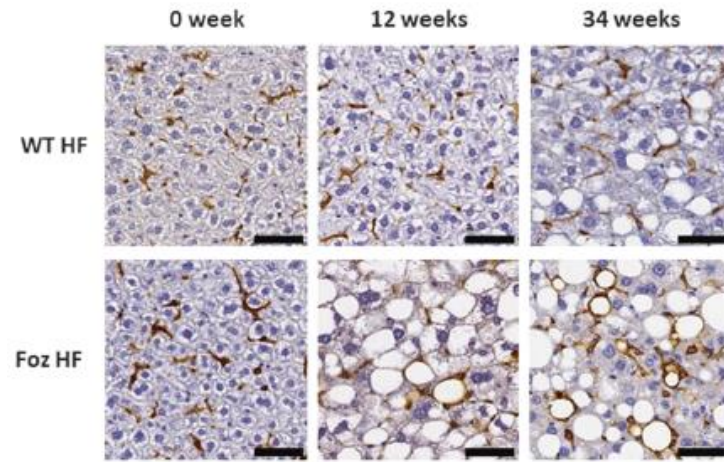
- Correlation between the number of hCLS and the inflammatory score

- The increase of hCLS is concordant with the induction of *ADGRE1* (gene encoding F4/80).

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MorphoQuant™ on Human Samples
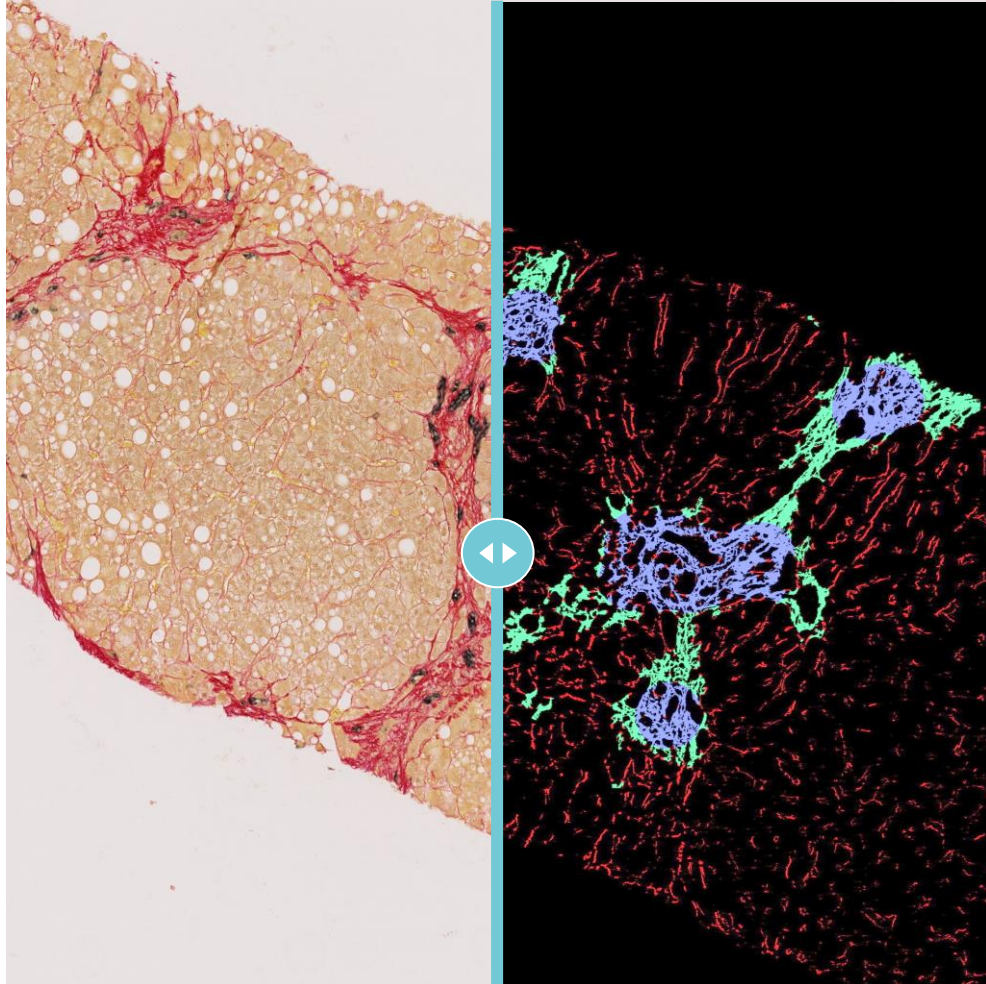
Conventional and Exploratory Readouts

PSR or PSR-CK19
- Biopsy area (mm²)
- Number of fragments
- Tissue density (%)
- Steatosis S and T (%)
- Mean vesicle area (μm²)
- Collagen S and T (%)
- Periductular collagen (%)
- Perisinusoidal / Perivascular/ Septal collagen (%)
- CK19 S and T (%)

H&E
- Inflammation area (%)
- Inflammatory foci (n/mm²)

CD68
- CD68 (%)
- Hepatic crown-like structures (n/mm²)

Shh
- Shh (‰)
- Active injury area (‰)

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MorphoQuant™ on Human Samples

271 liver biopsies collected and analyzed (multicenter, central histology and reading by one pathologist). Correlations with pathologist and comparison MASLD vs MASH:

Correlation with Staging/Grading	Spearman r
Fibrosis vs	
Collagen S	0.1436 *
Collagen T	0.1498 *
Periductular collagen	0.5904 ****
Perisinusoidal collagen	-0.3292 ****
Perivascular collagen	0.2753 ****
Septal collagen	0.5416 ****
Shh	0.4330 ****
Active injury area	0.5140 ****
Steatosis vs	
Steatosis S	0.7225 ****
Steatosis T	0.7212 ****
Lobular inflammation vs	
Inflammatory area	0.2671 ****
Inflammatory foci	0.2334 ***
CD68	0.2026 *
hCLS	0.3604 ***
Ballooning vs	
Shh	0.4257 ****
Active injury area	0.5329 ****
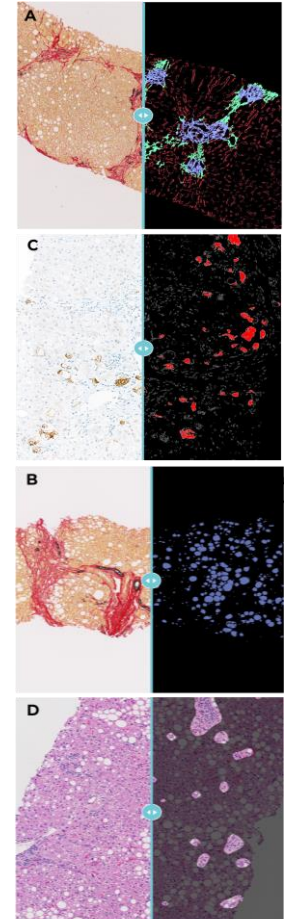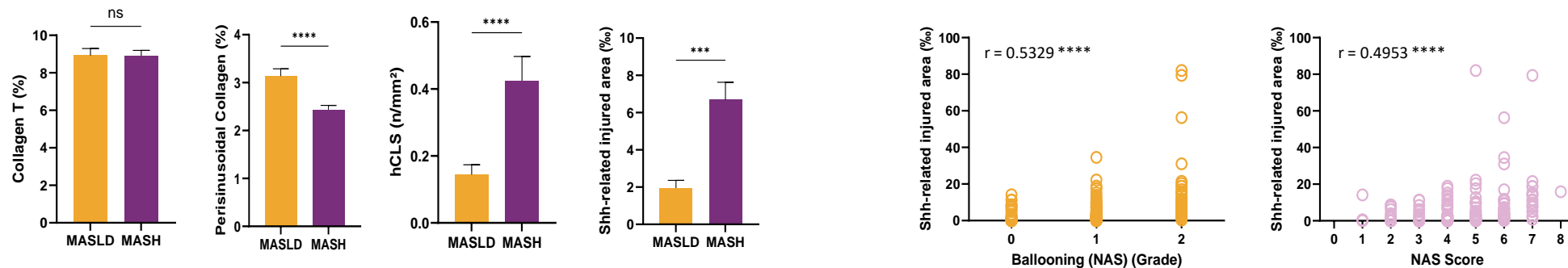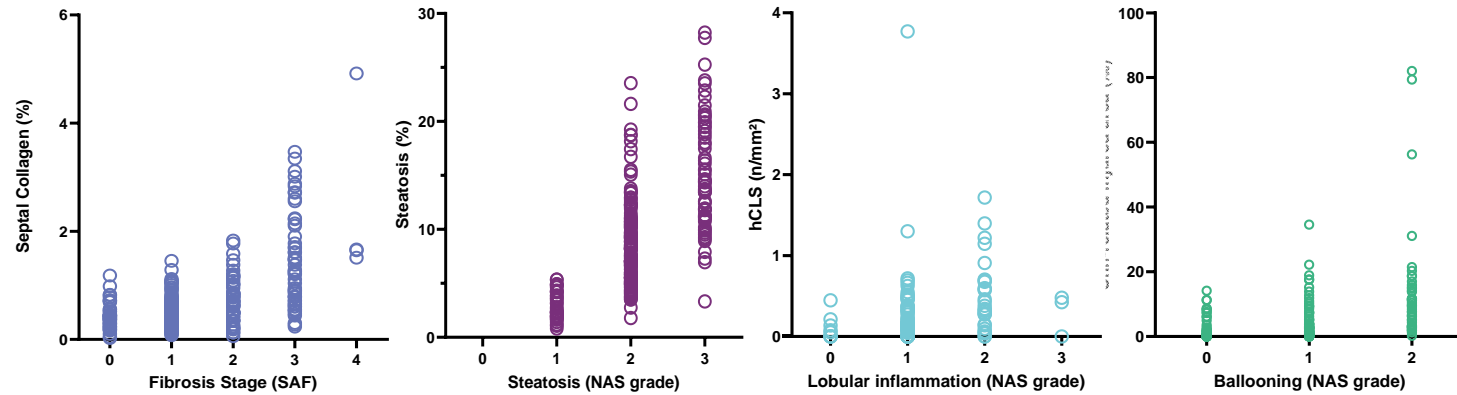
MorphoQuant™ on Human Samples

Post-hoc analysis on T2DM MASH patients for further assessment of fibrosis

	All Patients (n = 107)	
	n (%)	
Type 2 Diabetis Mellitus	No	Yes
(T2DM)	63	44
Steatosis grade		
S1	1	3
S2	42	27
S3	20	14
Lobular inflammation grade		
I1	24	22
I2	36	18
I3	3	4
Ballooning grade		
B1	44	28
B2	19	16
Fibrosis stage		
F0	0	0
F1	28	11
F2	19	17
F3	16	16
F4	0	0
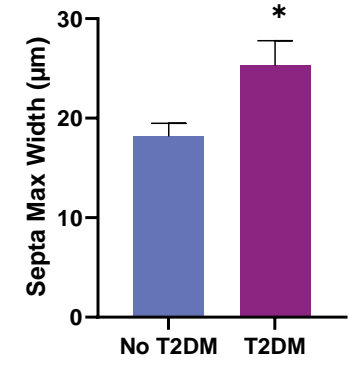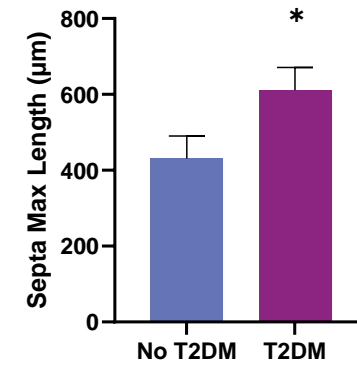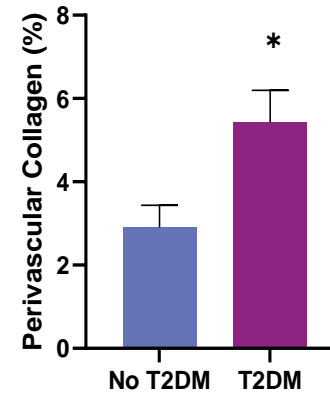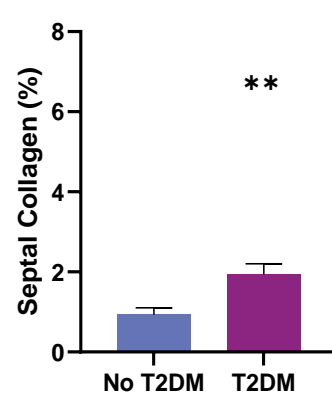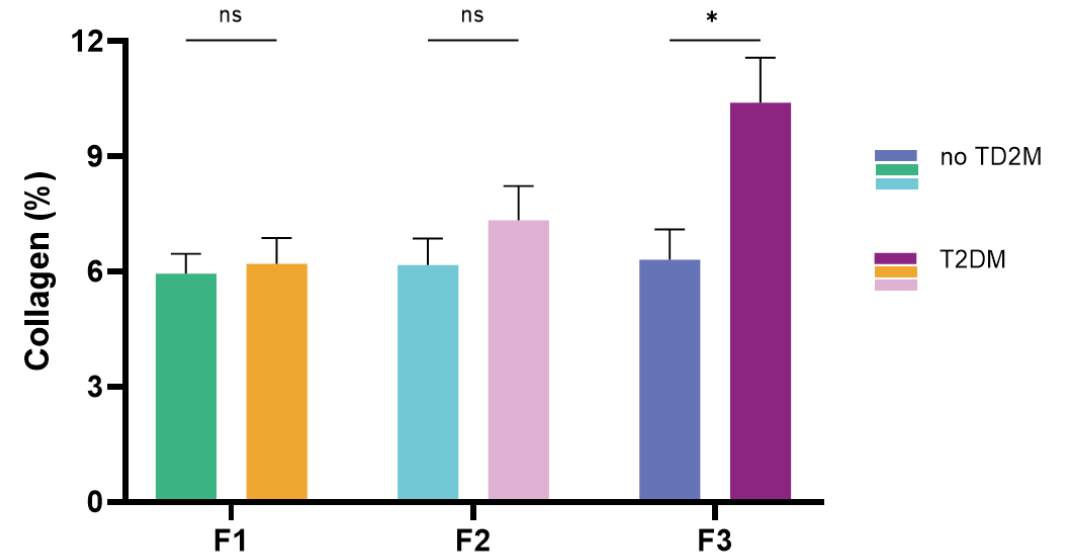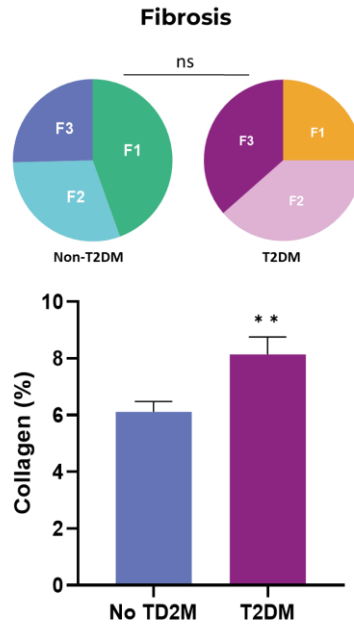
Qualification Process for Diagnosis

Glass vs digitized slide reading:
- good concordance expected as scanner brands already validated their technology according to the same process.
- Discussion around magnification impact on results?

Improvement of pathologist agreement
- important as demonstrates the added value of digital pathology to optimize patient's diagnosis and recruitment and should be done for each <u>readout</u> provided.
- ongoing at Biocellvia.

Considerations in Clinical Trials

The context of use is important to consider:
- NAS was built up in the context of diagnosis:
  - staging NASH and grading fibrosis during progression

Large number of failures in NASH clinical trials:
- pathology was pointed out as the main culprit: variability, subjectivity, etc..
- creation of the International NASH Pathology Group (INPG) gathering world expert pathologists to refine definitions for use in clinical trials.

The CONTEXT of USE matters!

Considerations in Clinical Trials

Conventional readouts (steatosis, inflammation, ballooning) are required to diagnose patients

Other exploratory features made available by AI-DP may provide better understanding of the underlying biology/pathology occurring during treatment

→ early detection of response?
- Stratify at-risk patients (severe NAS, advanced fibrosis, rapid progressers?...)
- Provide prognostic or predictive information
- Potential imaging biomarkers
- Should be challenged versus clinical outcome data

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