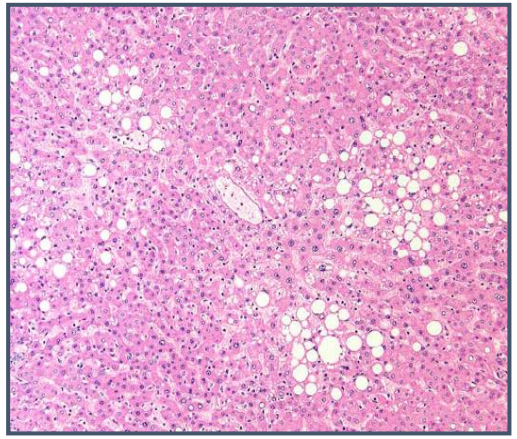
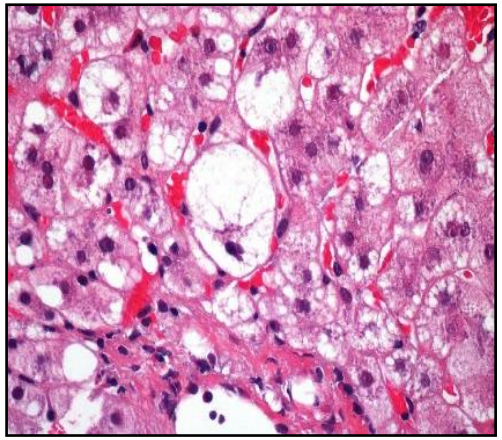
Using Digital Pathology to untangle assessment of fibrosis change in clinical trials of NASH

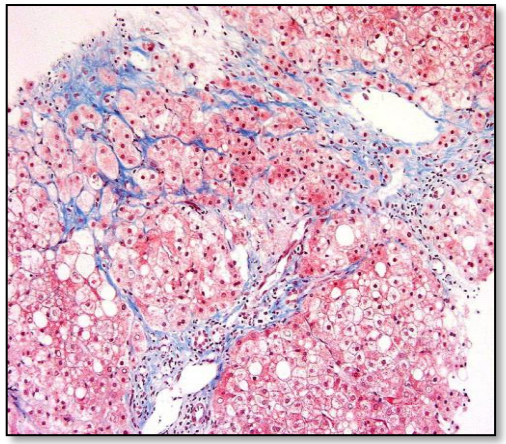
NAFL



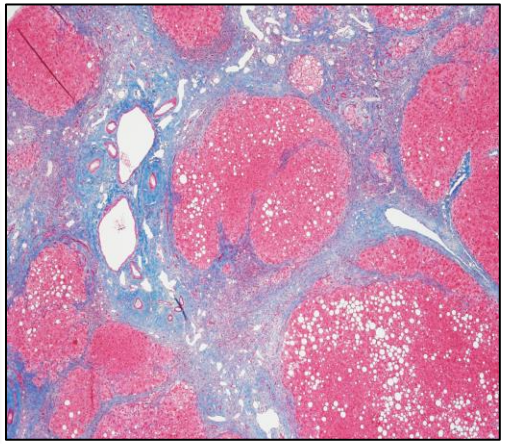
NASH



NASH with fibrosis



NASH Cirrhosis



Arun J. Sanyal MBBS, MD

Z Reno Vlahcevic Professor of Medicine

Virginia Commonwealth University School of Medicine

Richmond, VA

Disclosures

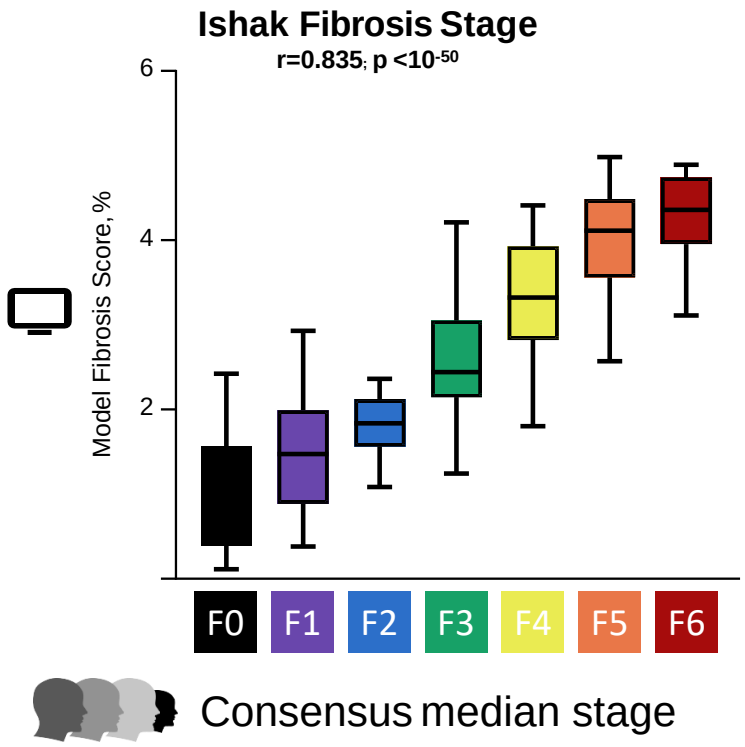
[Arun J. Sanyal]

I disclose the following financial relationship(s) with a commercial interest:

- Ownership interests: Sanyal Bio, Durect, Tiziana, Genfit, Exhalenz
- Consultant: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Merck, Pfizer, Boehringer Ingelhiem, Bristol Myers Squibb, Eli Lilly, Genentech, Amgen, Alnylam, Regeneron, Thera Technologies, Madrigal, Salix, Malinckrodt, Gatehouse, Rivus, Siemens, Lipocine
- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb

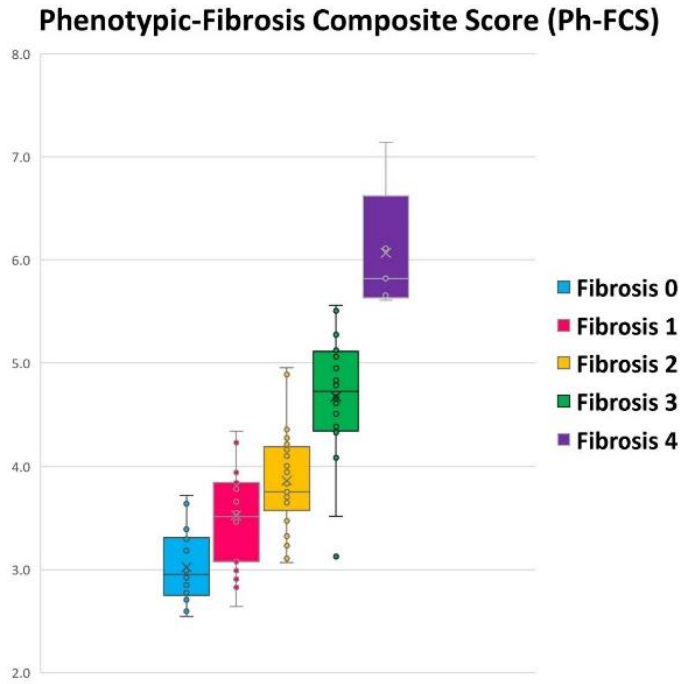
Machine learned tools can evaluate fibrosis with relative precision

PATH-AI



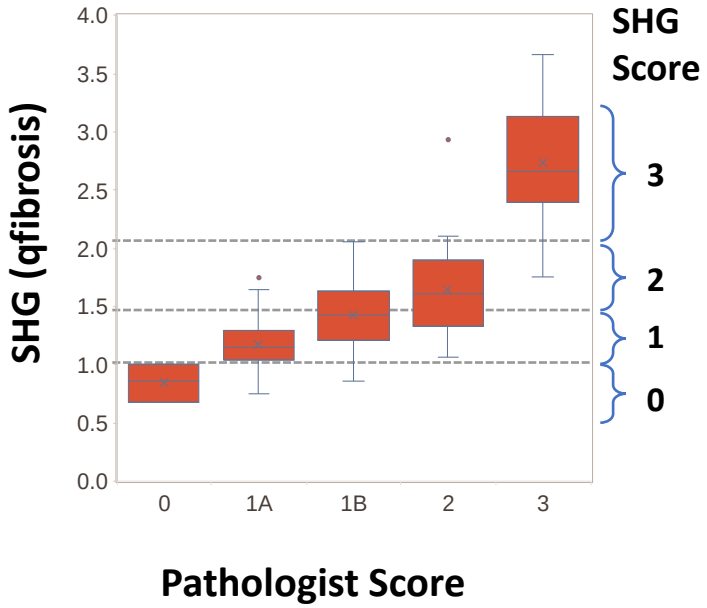
Younossi et al., AASLD 2019

PHARMANEST



Chen et al., AASLD 2019

HISTOINDEX



Harrison et al., AASLD 2018

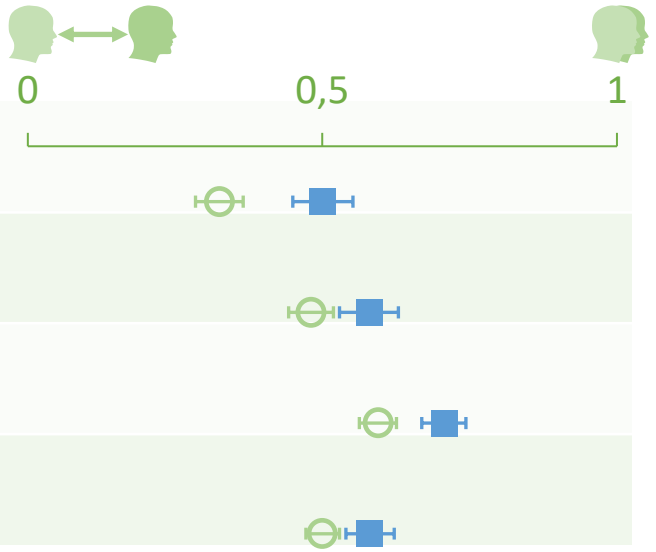
Application of digital pathology to assess changes in fibrosis in NASH trials

- Gaining certainty about the reproducibility of the histological analysis
- Phase 2B and 3- assessment of fibrosis trajectory within the time-frame of such trials

Machine learned algorithms may increase robustness of histological grading and staging

Kappa statistic (95% CI, bootstrap)*

Histologic feature	ML vs consensus	Mean pairwise pathologist
Lobular inflammation	0.50 (0.45, 0.55)	0.33 (0.29, 0.37)
Ballooning	0.58 (0.53, 0.63)	0.48 (0.44, 0.52)
Steatosis	0.71 (0.67, 0.74)	0.60 (0.56, 0.63)
Fibrosis	0.58 (0.54, 0.62)	0.50 (0.47, 0.53)



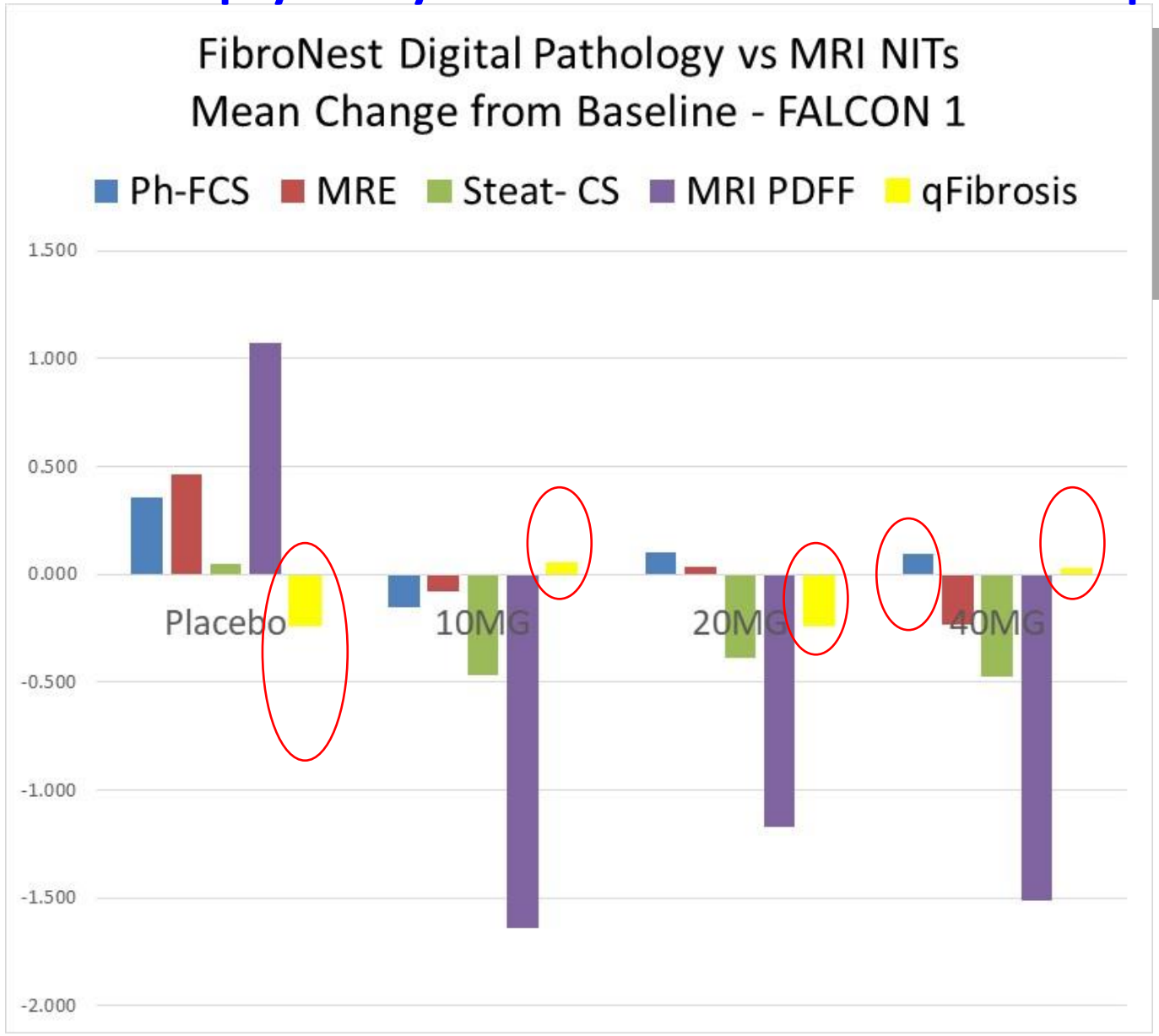
- Pilot analytic validation data using 631 biopsies from a phase 2 clinical trial, read by ML models and 3 expert hepatopathologists
- Agreement of ML with consensus reads was superior to agreement amongst pathologists
- *Linearly weighted kappa statistic. Unpublished data (kindly provided by Path-AI).

AI-assisted reads can improve intra and interobserver variability

	Liver Fibrosis Scoring	Unassisted Read	Assisted Read
Inter-Observer	Mean Percentage Agreement	89.37%	92.92%
	Mean Linearly Weighted Kappa	0.72	0.82
Intra-observer	Mean Percentage Agreement	92.08%	96.46%
	Mean Linearly Weighted Kappa	0.79	0.91

Soon et al, CGH, 2022

Paired Biopsy Study Results – MRI vs FibroNest vs qFibrosis



FibroNest Digital Pathology scores for fibrosis and steatosis correlated with MRI non invasive Tests and establish similar drug effect detection performance

Petitjean, Minnich et al, ILC 2022

Assessment of the multidimensional evolution of fibrosis

Closer Look at the Collagen Fibrosis

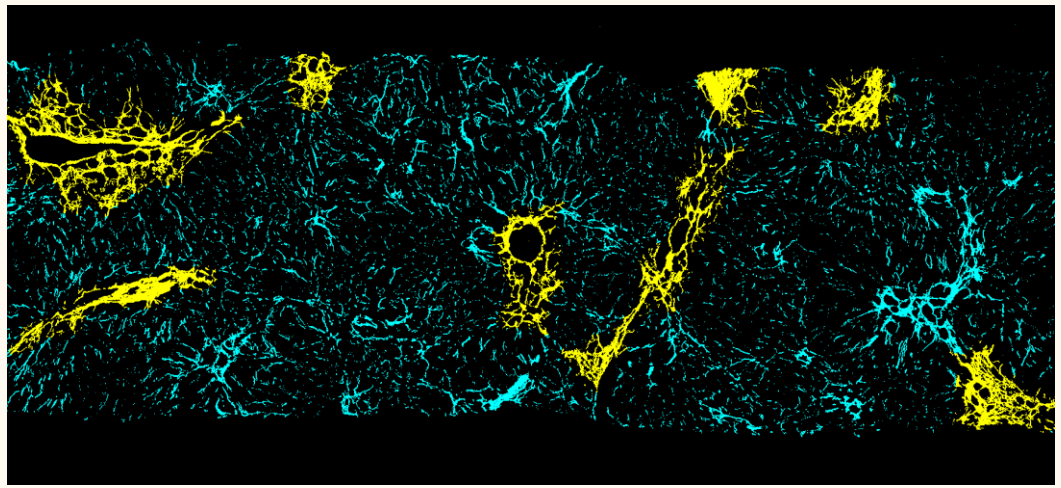
HISTOINDEX®
New Standard | New Life

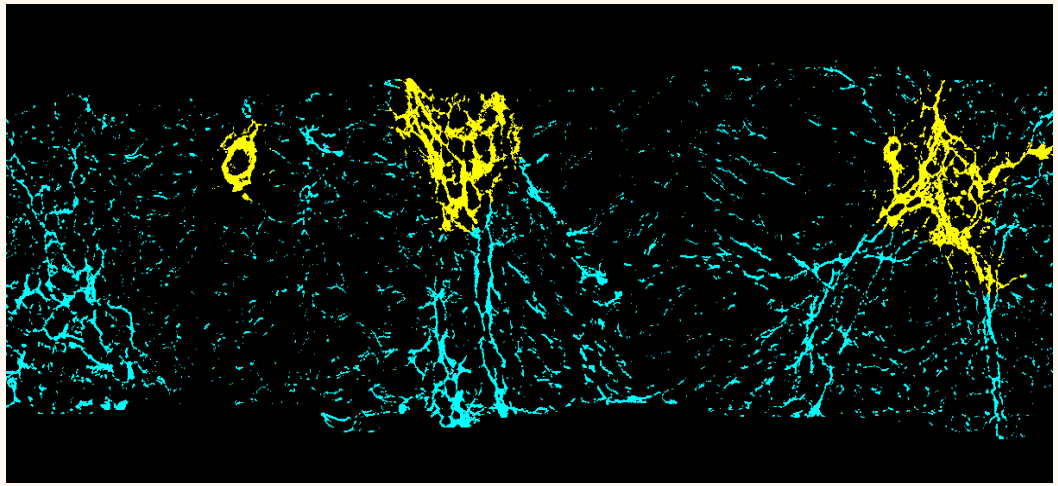
Baseline F2 → End of Treatment F2

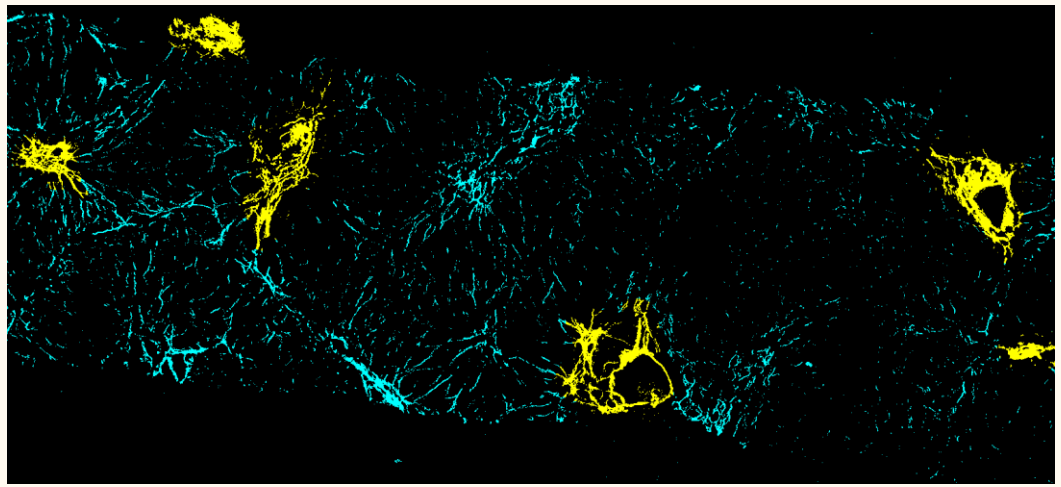
Baseline F3 → End of Treatment F3

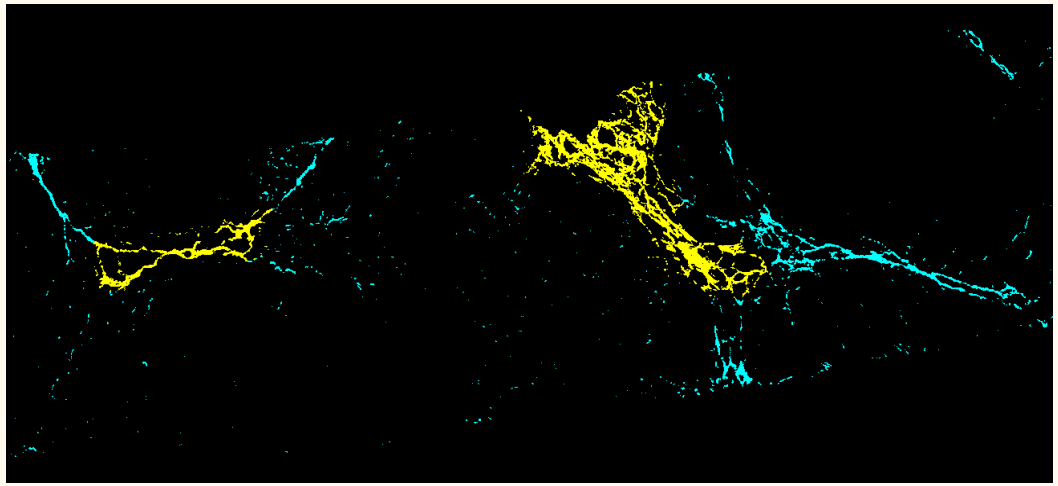
Before Treatment

End of Treatment





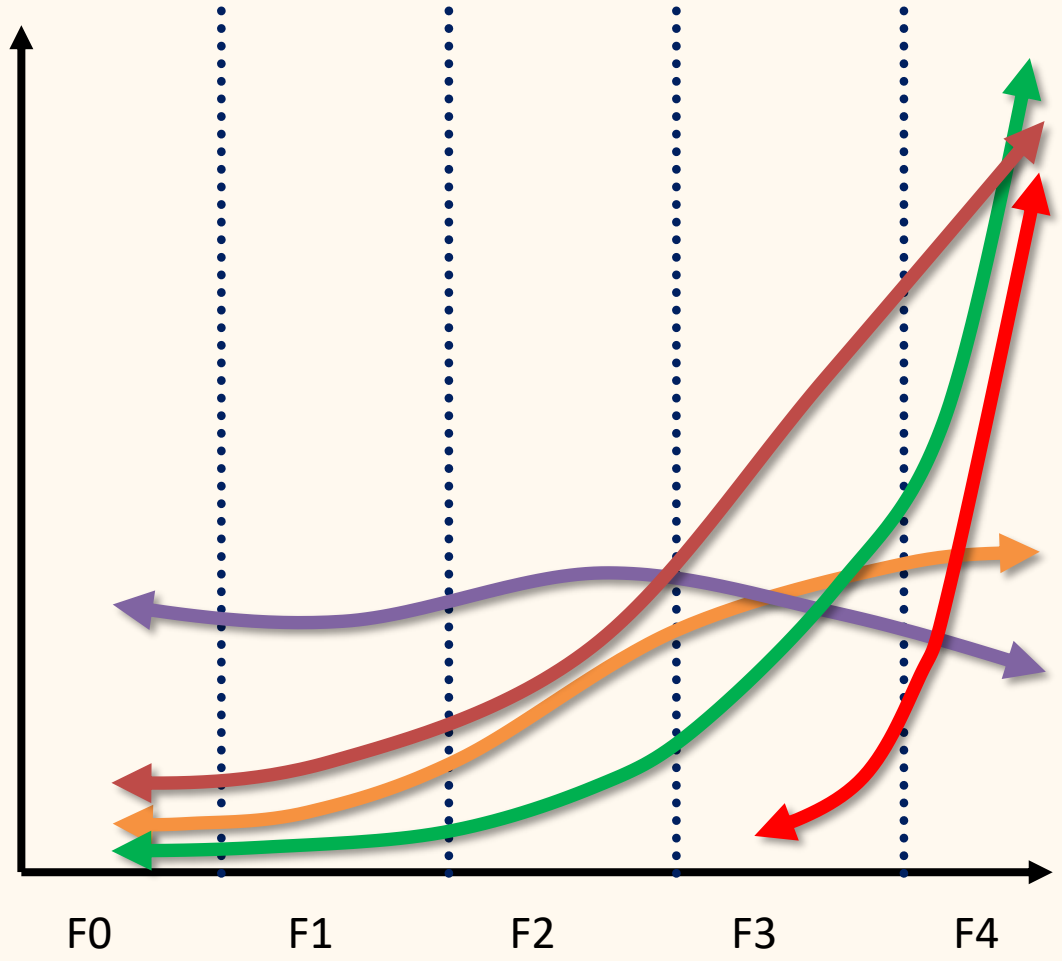




PT/CV collagen

PS collagen

Fibrosis is a Multi-dimensional Activity



Portal Fibrosis

Peri Portal Fibrosis

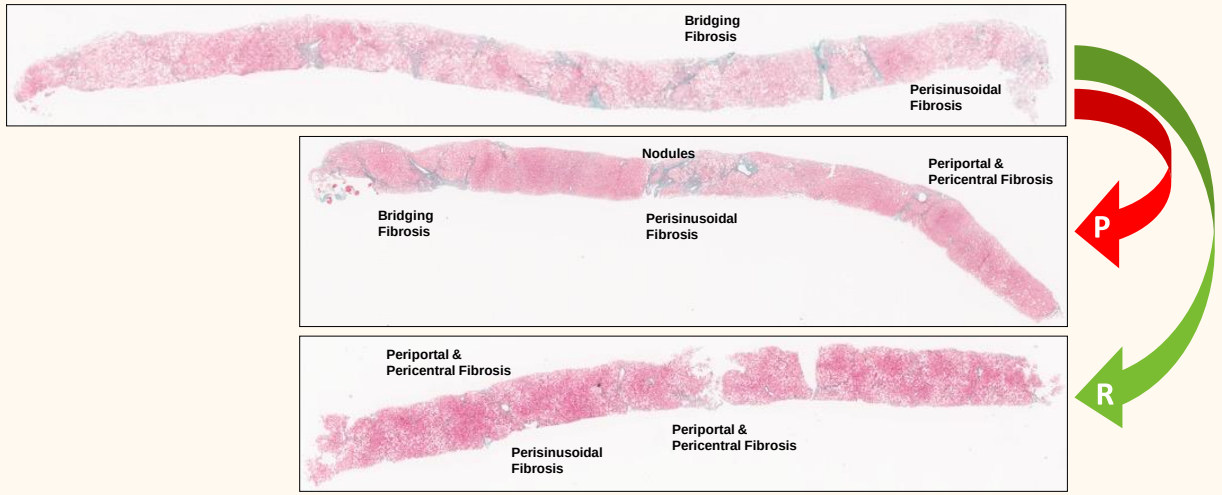
Bridging Fibrosis

Peri-sinusoidal Fibrosis

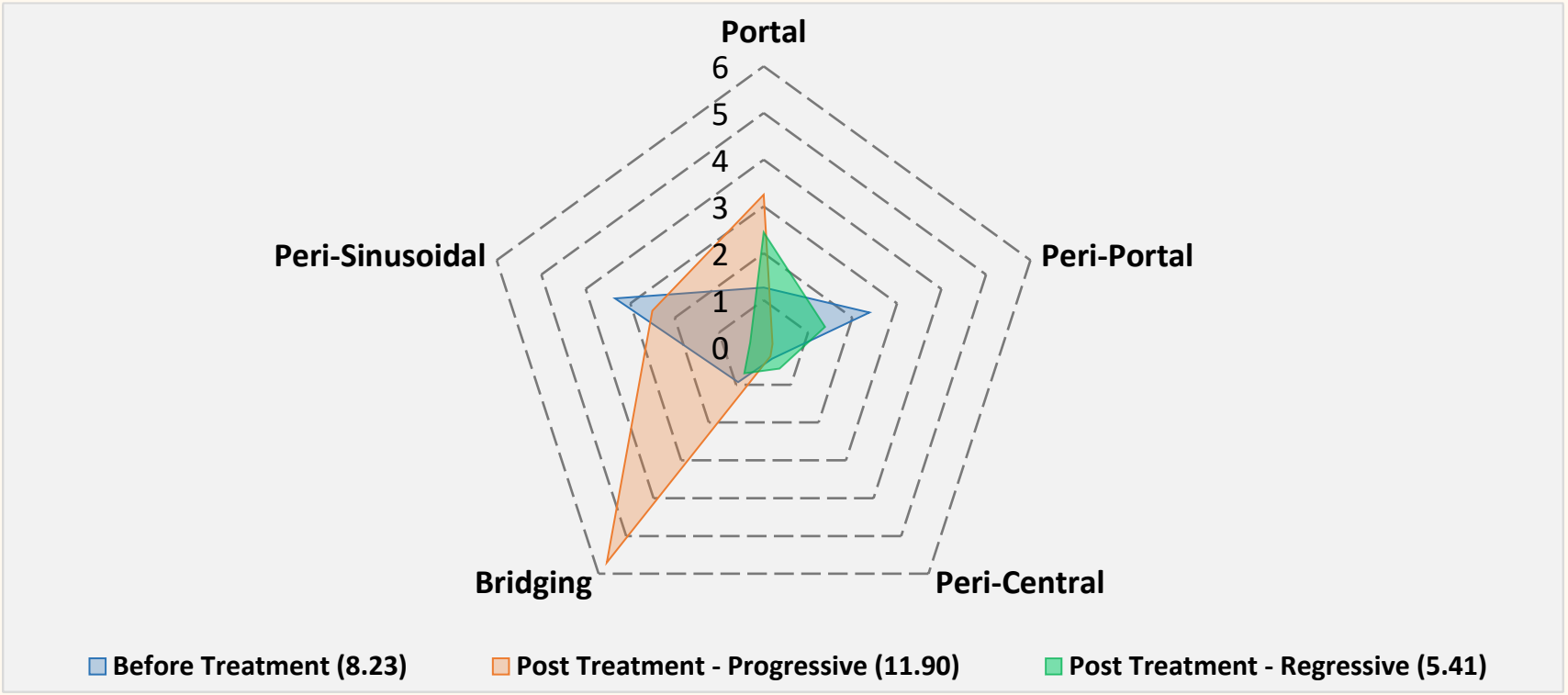
Nodule

Graph is plotted based on data obtained from clinical projects

Use of Radar Map for Comparison Between Paired Biopsies



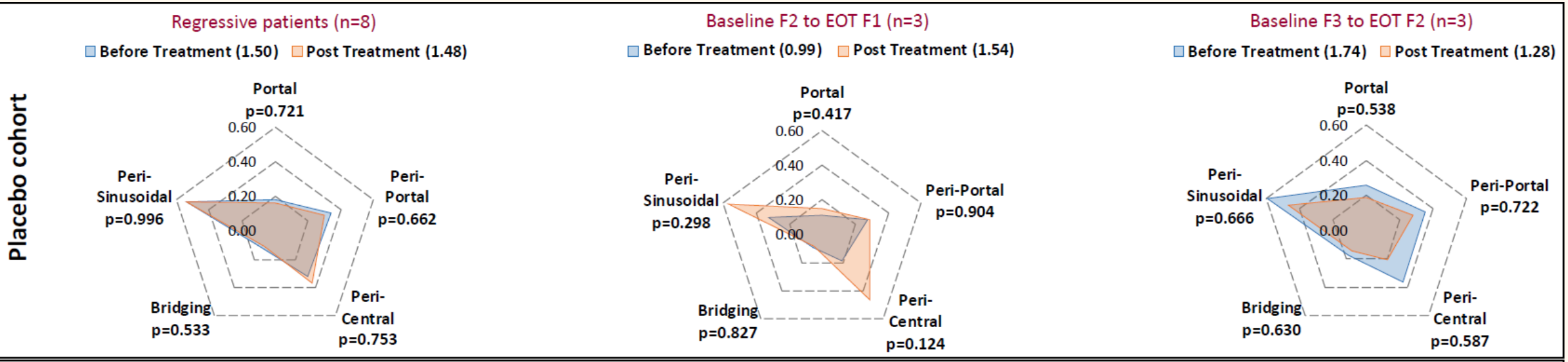
	Before Treatment	Post Treatment (Progressive)	Post Treatment (Regressive)
Portal Fibrosis	1.27	3.25	2.45
Peri-Portal Fibrosis	2.38	0.2	1.38
Peri-Central Fibrosis	0.31	0.25	0.58
Bridging Fibrosis	0.93	5.7	0.7
Peri-Sinusoidal Fibrosis	3.34	2.5	0.3
Total Weighted Score	**8.23**	**11.9**	**5.41**



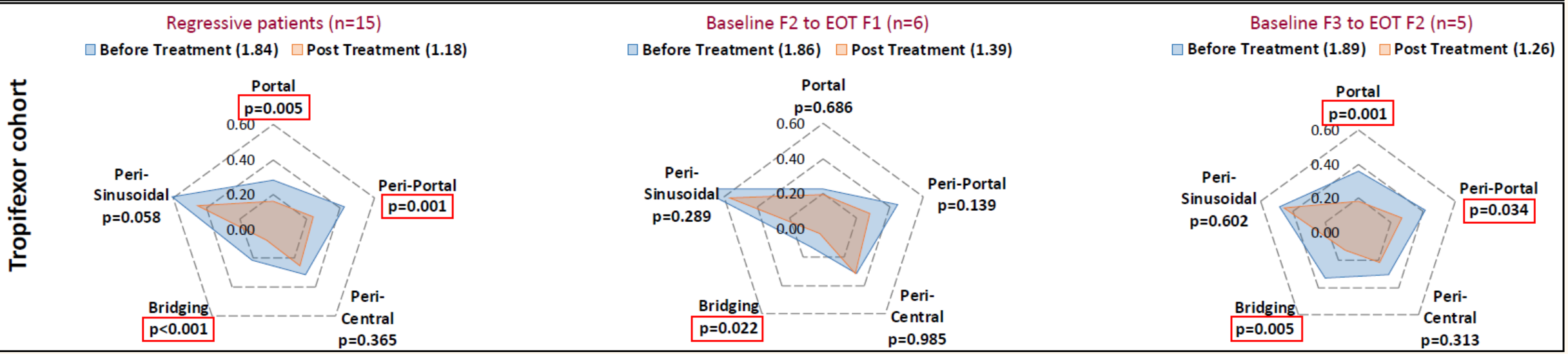
From Baseline to EOT: Decrease in Fibrosis Staging

HISTOINDEX®
New Standard | New Life

Placebo cohort



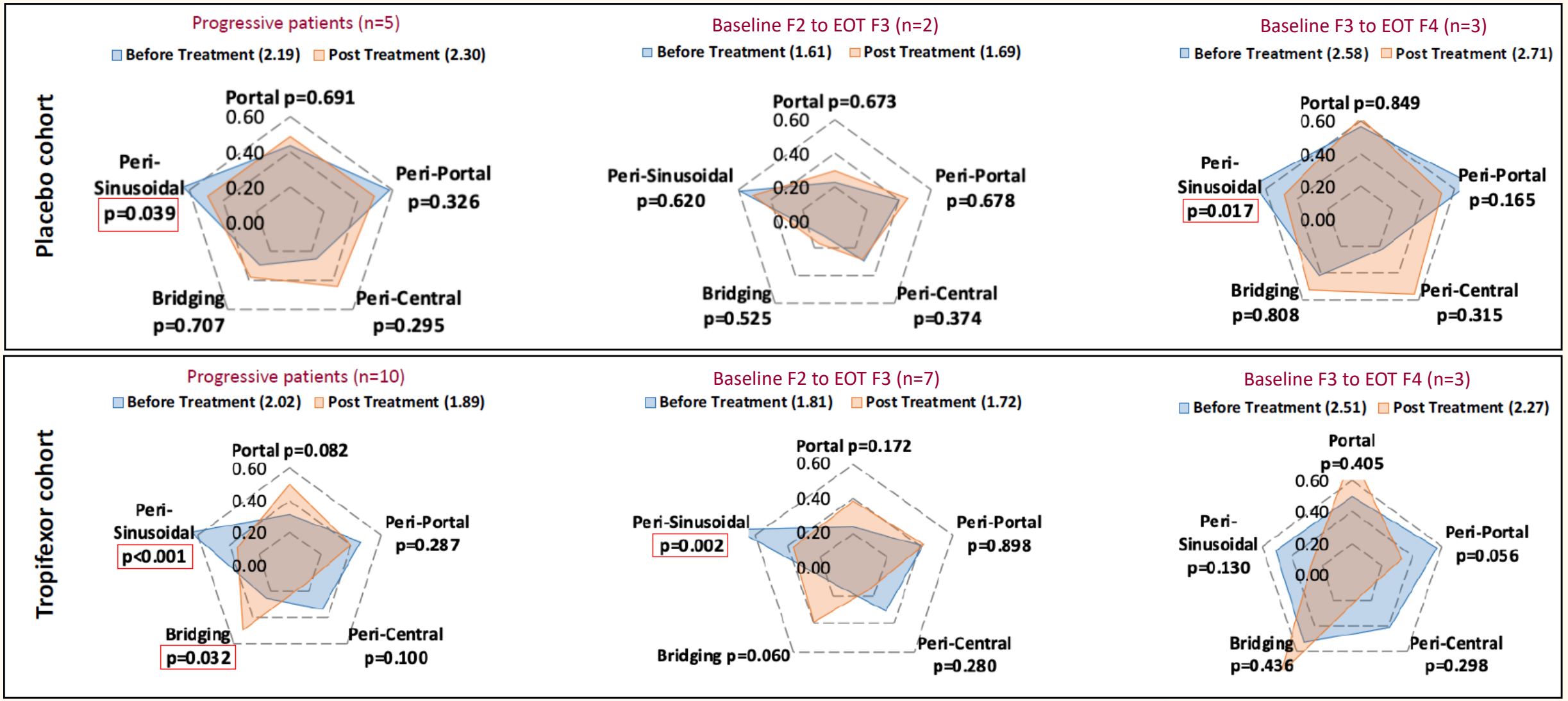
Tropifexor cohort



p values were calculated by the paired-sample t-test.
The radar maps indicate the mean value of %collagen in different regions for samples

From Baseline to EOT: Increase in Fibrosis Staging

HISTOINDEX®
New Standard | New Life



p values were calculated by the paired-sample t-test.
The radar maps indicate the mean value of %collagen in different regions for samples

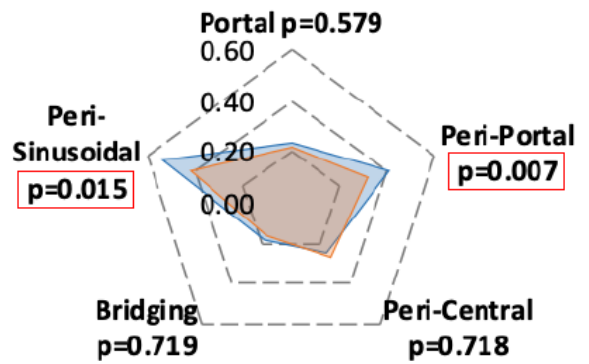
From Baseline to EOT: No-change in Fibrosis Staging

HISTOINDEX®
New Standard | New Life

Placebo cohort

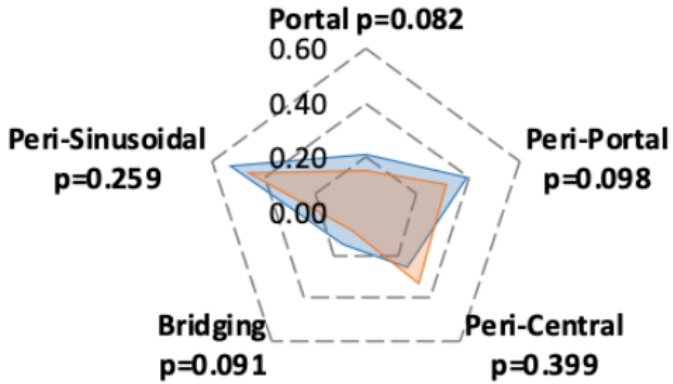
No-change patients (n=21)

Before Treatment (1.60) Post Treatment (1.39)



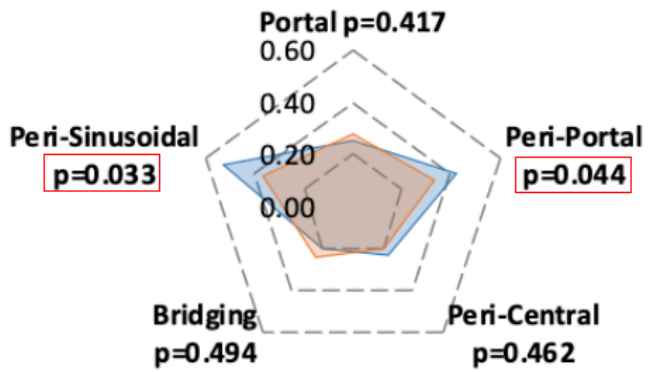
Baseline F2 to EOT F2 (n=10)

Before Treatment (1.55) Post Treatment (1.35)



Baseline F3 to EOT F3 (n=11)

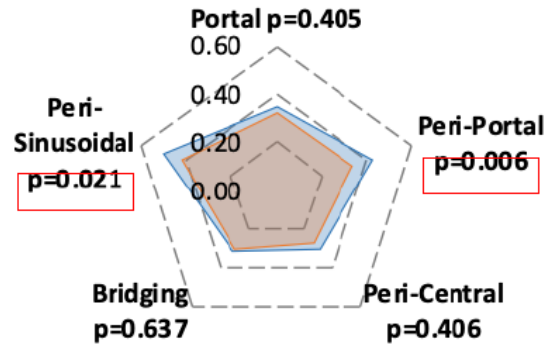
Before Treatment (1.64) Post Treatment (1.42)



Tropifexor cohort

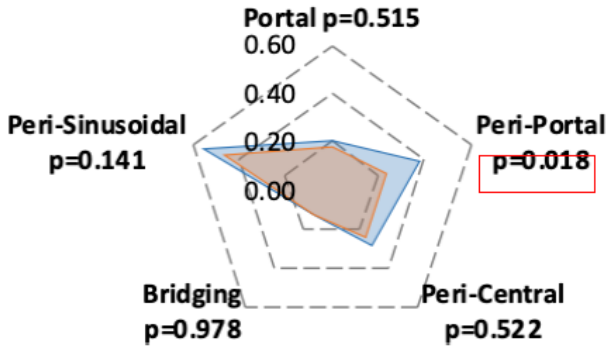
No-change patients (n=40)

Before Treatment (1.90) Post Treatment (1.66)



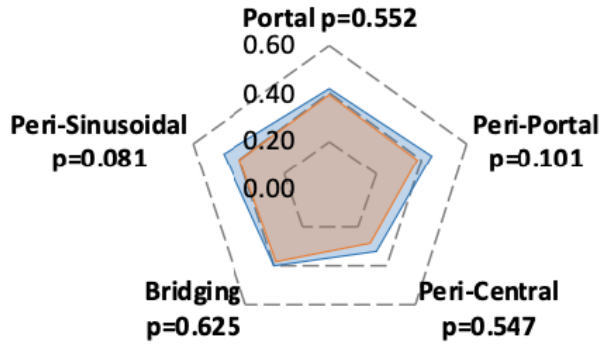
Baseline F2 to EOT F2 (n=12)

Before Treatment (1.54) Post Treatment (1.23)



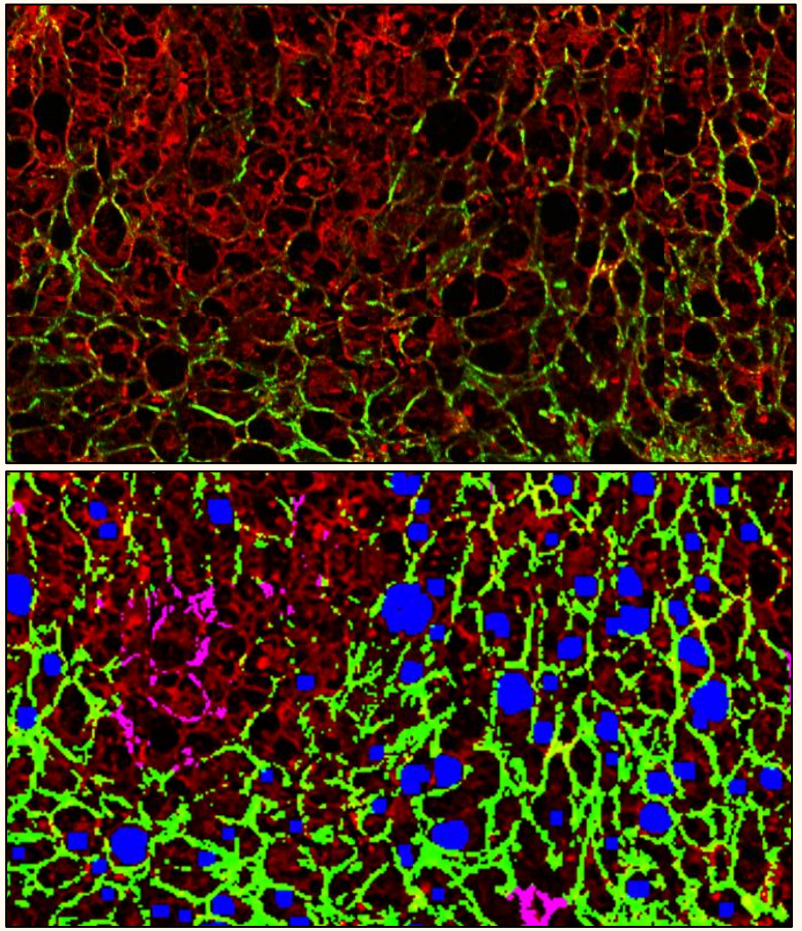
Baseline F3 to EOT F3 (n=28)

Before Treatment (2.05) Post Treatment (1.84)



p values were calculated by the paired-sample t-test.
The radar maps indicate the mean value of %collagen in different regions for samples

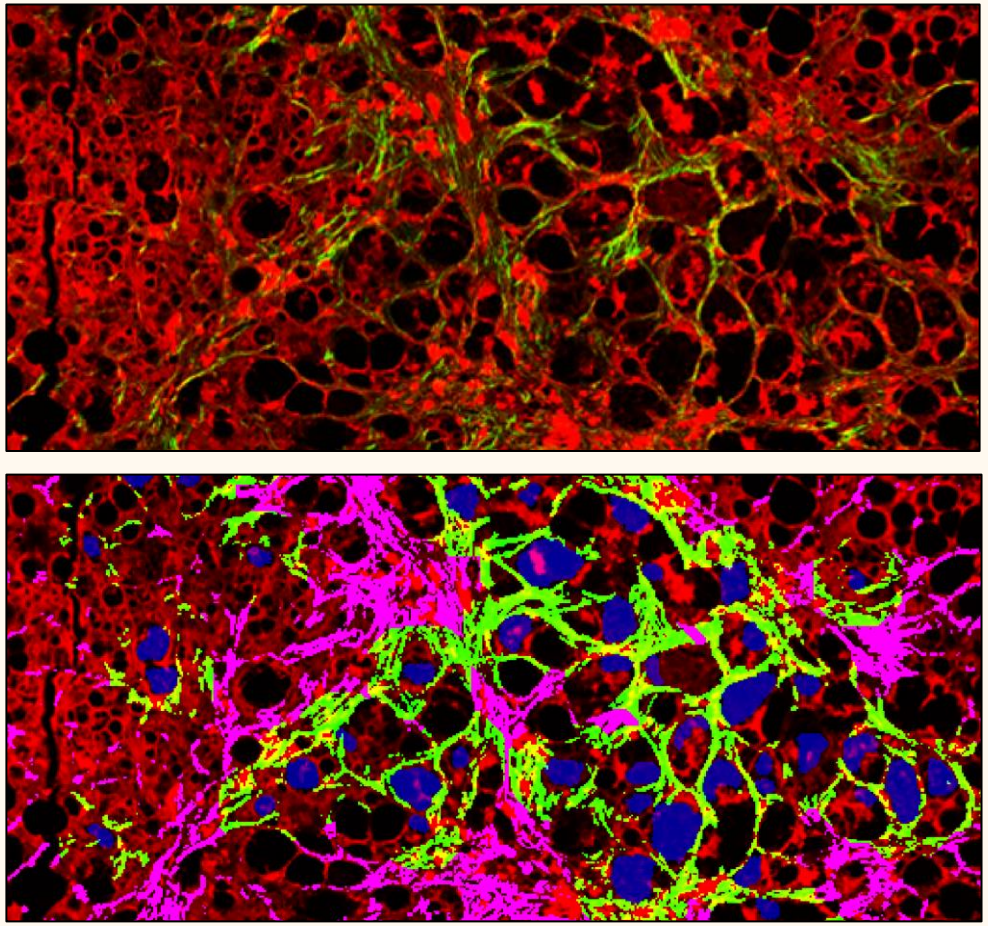
Additional Research Use Only Tools: qFibrosis/qSteatosis Co-localisation



qFibrosis/qSteatosis co-localization can reveal treatment-induced steatosis changes and fibrosis dynamics from simultaneous quantitation of qSteatosis and qFibrosis in selected areas.

	Steatosis
	Collagen around steatosis
	Other collagen

Additional Research Use Only Tools: qFibrosis/qBallooning Co-localisation

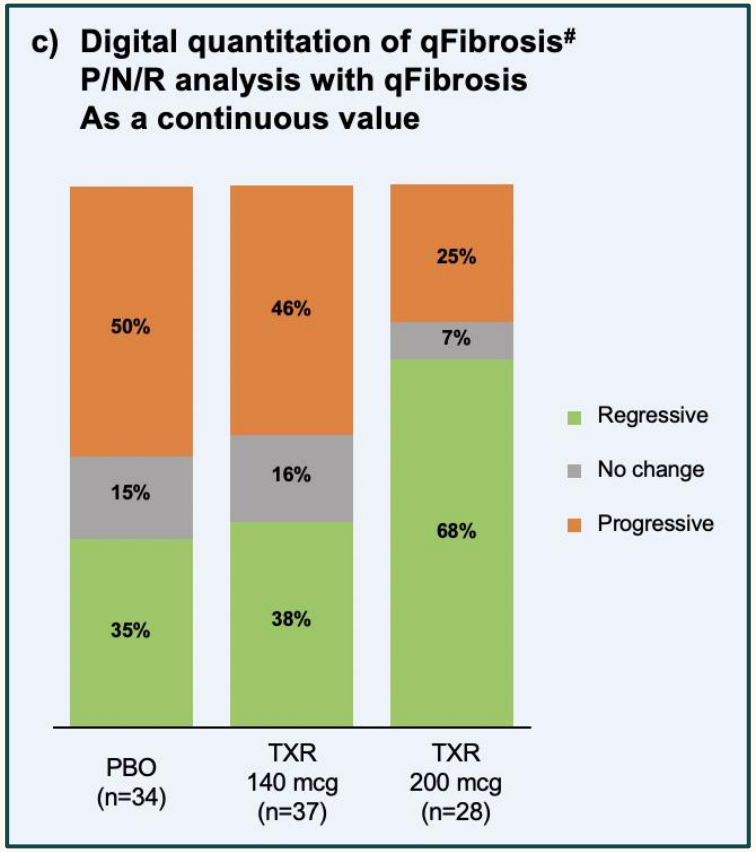


qFibrosis/qBallooning co-localization can reveal treatment-induced changes in ballooned hepatocytes and fibrosis dynamics in selected areas

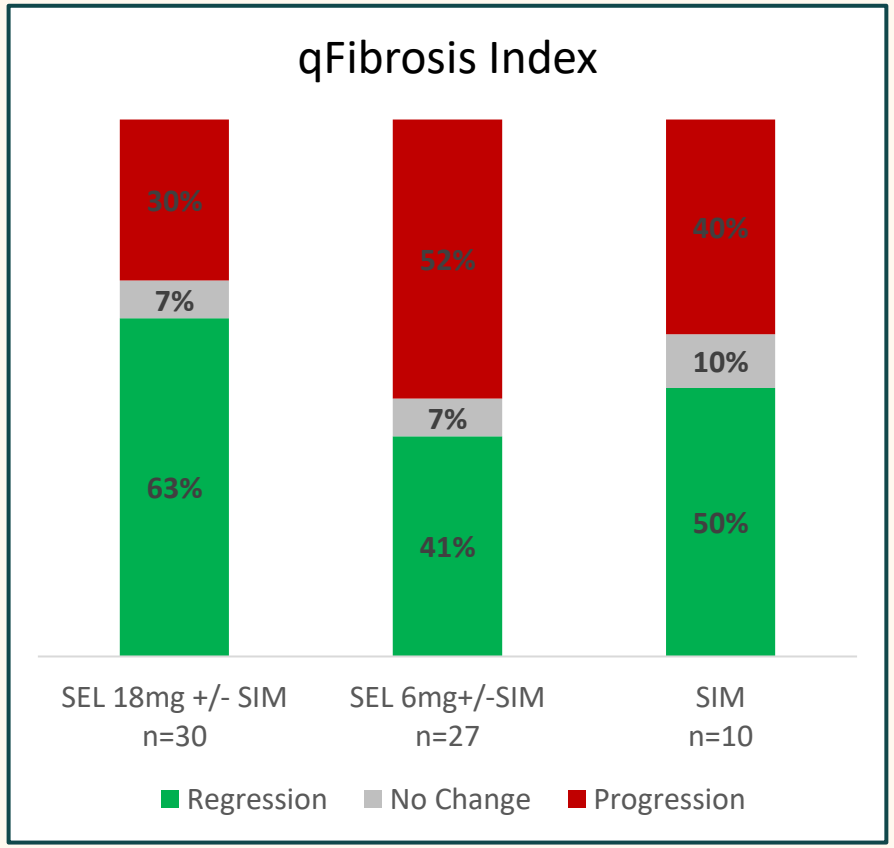
	Ballooned cell
	Collagen around ballooned cell
	Other collagen

Use of AI Digital Pathology for Quantitative Assessment

Phase 2 FLIGHT-FXR (NCT02855164)

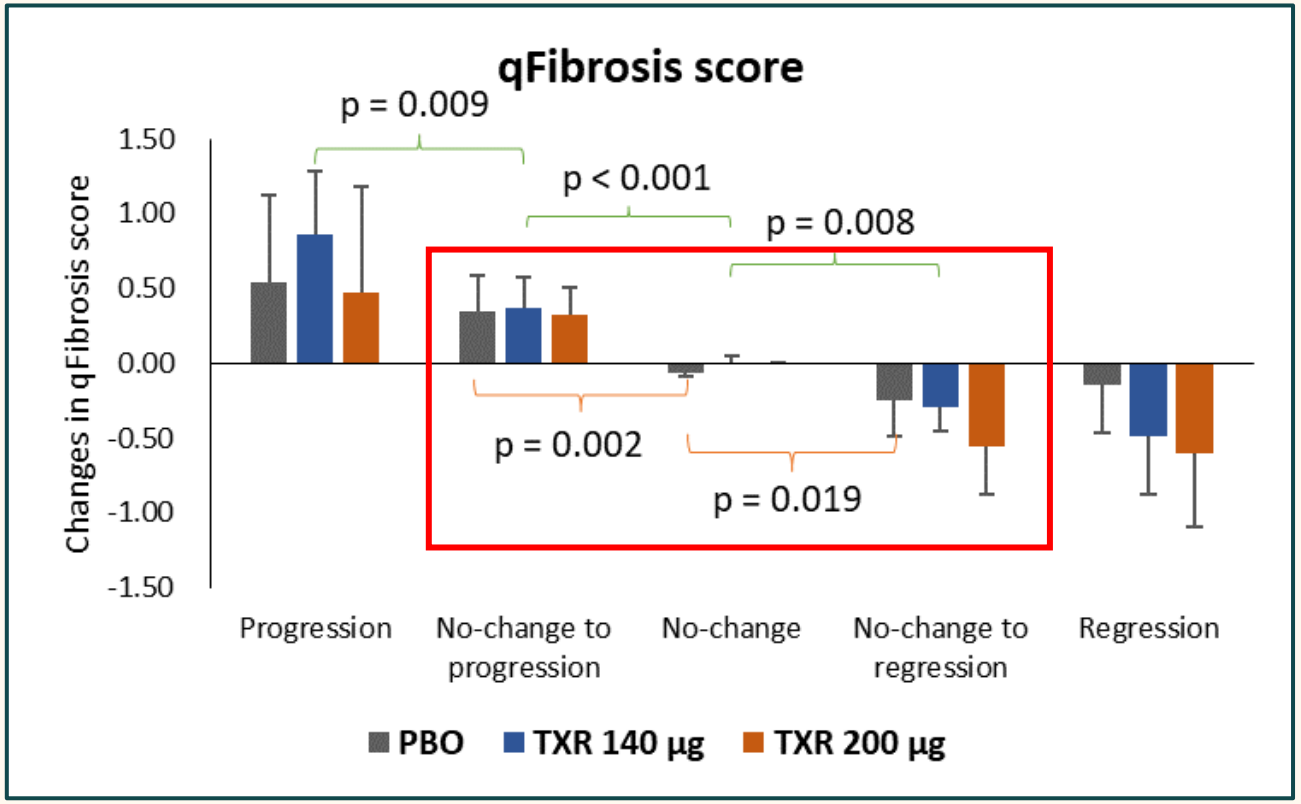


EASL 2021 PO-889

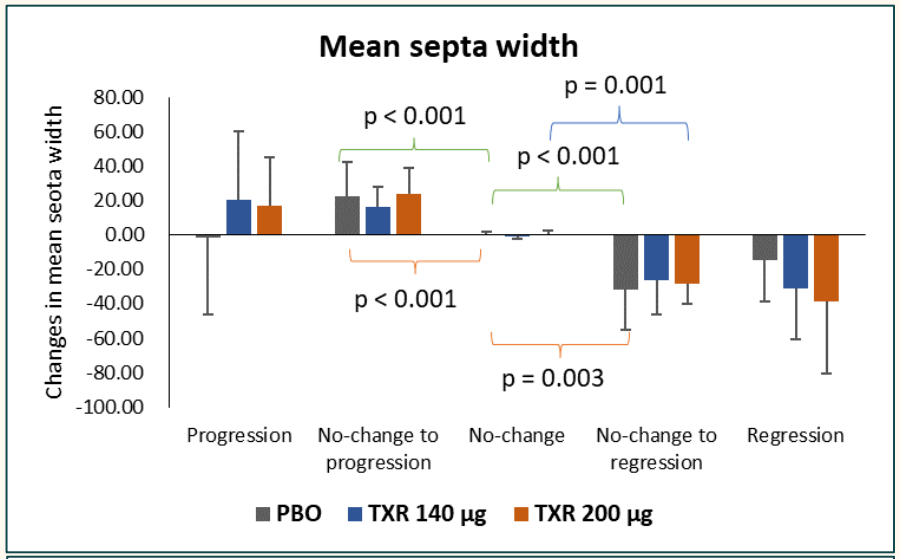


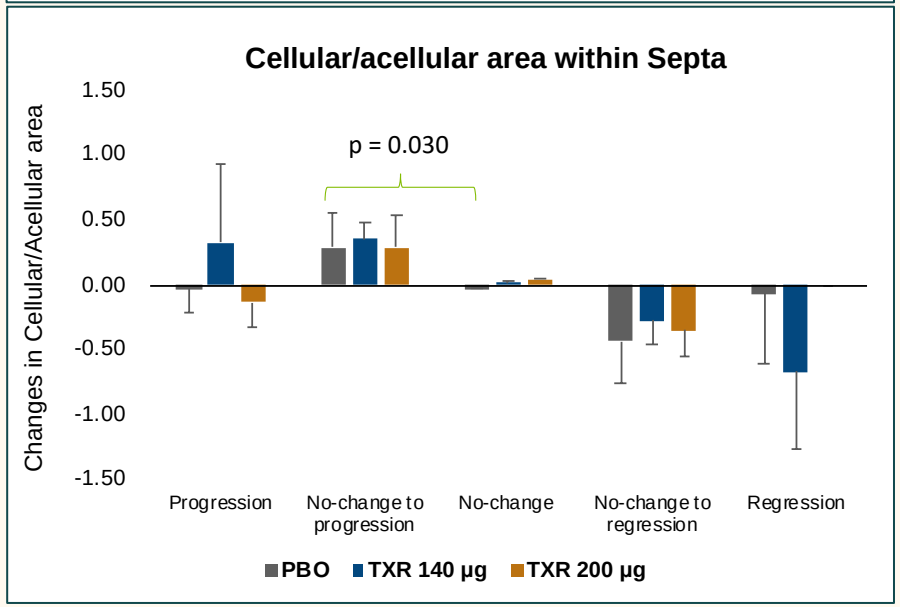
Data Source: Gilead Sciences

Changes Observed for Intra-stage Patients



Manuscript in preparation





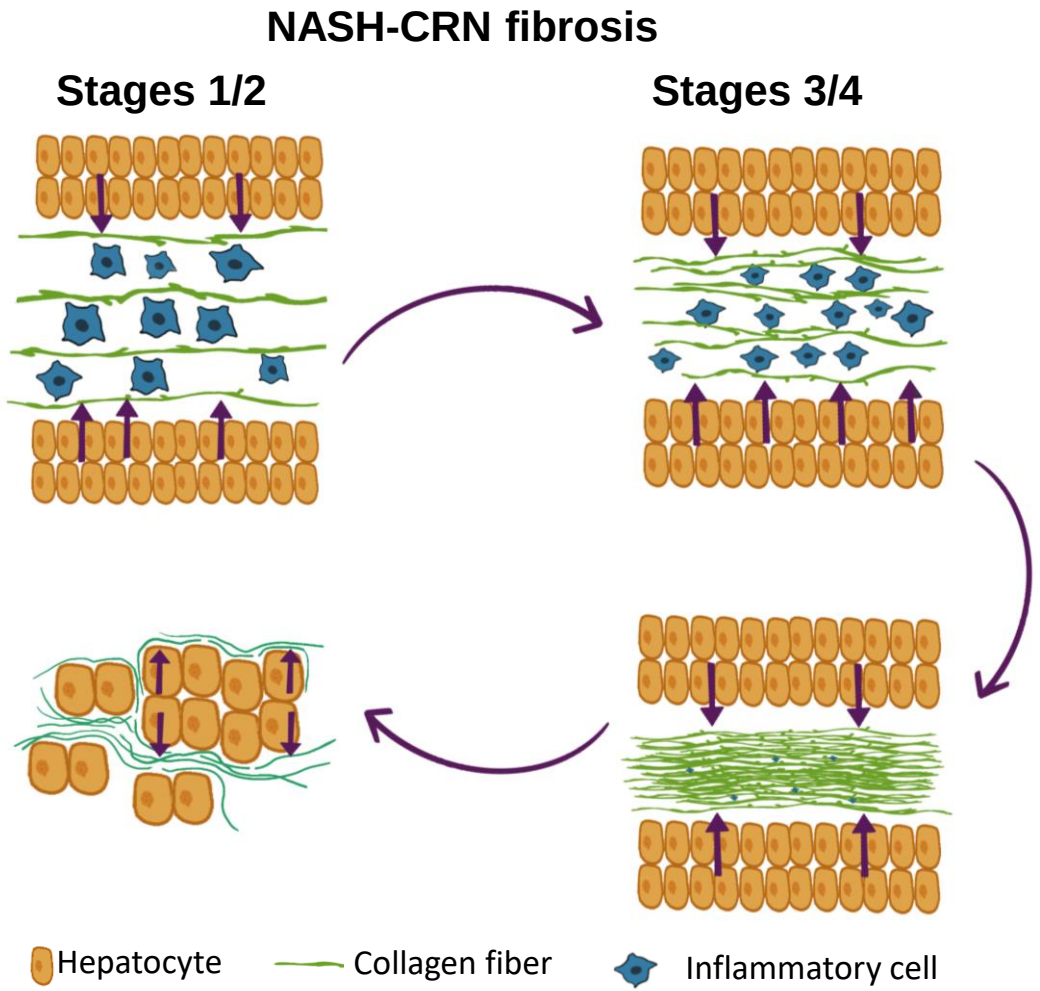
A dynamic model of fibrosis in NASH

Progressive septa

Fine collagen fiber runs between **inflammatory cells**, in parallel formation

Regressive Broken septa

Septa infiltrated by newly regenerated hepatocytes, and collagen fiber runs around hepatocytes in circular formation



Established septa

Fine collagen fiber collapsed into denser bundles with **fewer inflammatory cells** in between

Mature or regressive septa

Septa squeezed into thin and dense forming **relatively acellular** septa

Sanyal et al, AASLD 2020 and Naumov et al J Hepatol 2022

Summary and future directions

- Digital approaches allow more robust read out of fibrosis stage
- A combination of collagen burden and distribution and characteristics of collagen fibrillar properties in different regions of the liver section allow one to assess of fibrosis is progressing or regressing in the context of clinical trials
- These can also be used to develop a fibrosis scoring system along a continuous range that is sensitive to change
- Long term studies are needed with third biopsy to see if the changes seen in the short term translate in to altered rates of progression to cirrhosis.