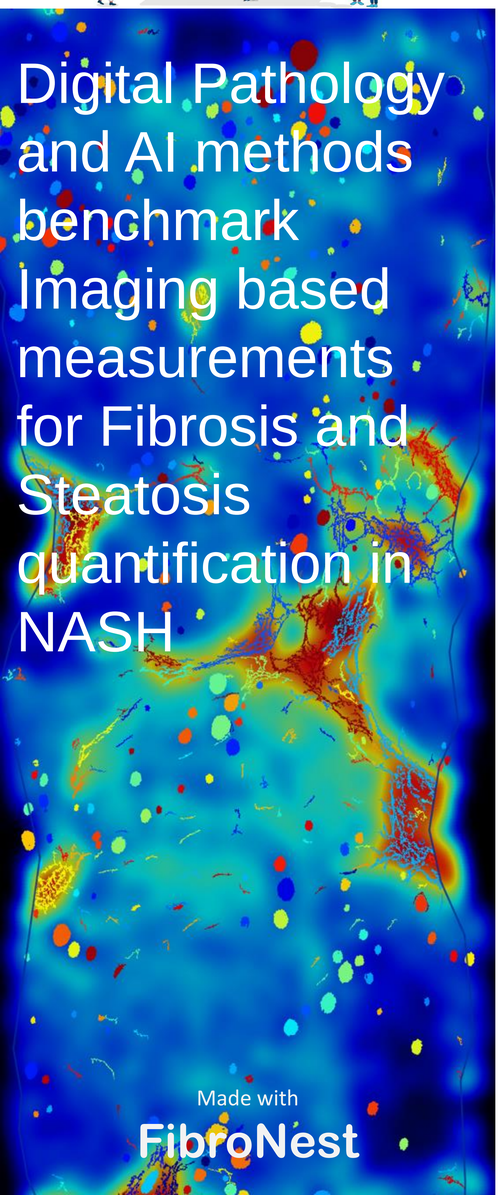


Novel Digital Pathology quantitative image analysis and AI method detects the treatment effect of NASH drug candidates with a performance that benchmarks Imaging based measurements.

Li CHEN[1], Elizabeth BROWN[2], Anne MINNICH[2], Vipul BAXI[2], Dimple PANDYA[2], Edgar CHARLES[2], Shuyan DU[2], Mathieu PETITJEAN[1], Zach GOODMAN[3] , Arun J. SANYAL[4]

1 PharmaNest, Princeton, NJ, USA 2 Bristol Myers Squibb, Princeton, NJ, USA 3 Inova Health Systems, Falls Church, VA 4 Virginia Commonwealth University, Richmond, VA, USA

1 Introduction

Manual histological evaluation of liver biopsy is the gold standard for fibrosis and steatosis staging in Non-Alcoholic Steatohepatitis (NASH), but it is limited by its inter and intra-reader variability. Quantitative Digital Pathology image analysis and AI (**FibroNest™**) as well as quantitative MRI signal analysis methods have the potential to overcome the limitation of these standards

2 Aim

This exploratory post-hoc analysis compared FibroNest digital pathology scoring methods (Fibrosis and Steatosis) with NASH-CRN categorical stages and imaging-based scores (MRI Mean Liver Stiffness and MRI Mean Proton Density Fat Fraction (MRI-PDFF) in patients with NASH from the **Phase 2b FALCON1** study (NCT348699).

3 Method

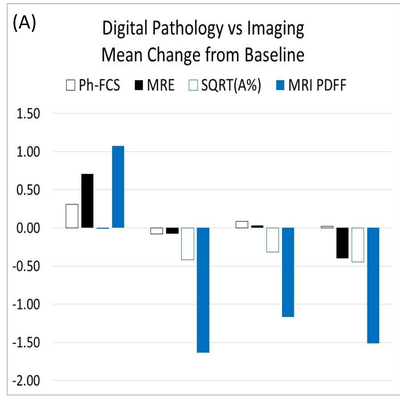
- N=197 adults were 18-75 years of age with NASH and stage 3 fibrosis (NASH-CRN)
- 48-week double-blind treatment period, 10mg, 20mg, or 40mg PGBF subcutaneous or placebo once weekly.
- Liver biopsies (N=394) six months before or during screening and at week 24
- **NASH-CRN categorical stages** (F0 to F4)are adjudicated for each biopsy
- MRI imaging resulting in **Mean Liver Stiffness (MRE)** and **MRI-PDFF** for most patients

Pathology, Digital Pathology and AI:

- **40X** digital images of **Masson Trichrome** stained of FFPE sections of liver biopsies at Baseline and week 24 (same as adjudicated by Pathologists)
- **Digital Biopsy Adequacy Score** (**DBA**): each digital image was evaluated for quality along 20 dimensions (tissue processing, staining, and scanning) (FibroNest-Check™)
- **Fibrosis severity continuous score** (**Ph-FCS**, 1 to 10). Quantitative image analysis extracts single-fiber quantitative traits (qFTs, N=315) from the fibrosis histological phenotype. A previously validated selection of principal qFTs [1] is normalized and combined to form the severity continuous score (FibroNest™ method).
- Additional **sub-Phenotypic scores** (fine and assemble fiber sub-classes, morphometry, architecture, fibrosis scar) are used to further describe the fibrosis phenotypes and its remodeling as fibrosis progress or regresses
- **Steatosis Severity Continuous Score:** the non-fibrotic parenchymal tissue area fat ratio (A%) is measured. Its square root **SQRT(A%)** is used as an exploratory marker

4 Results

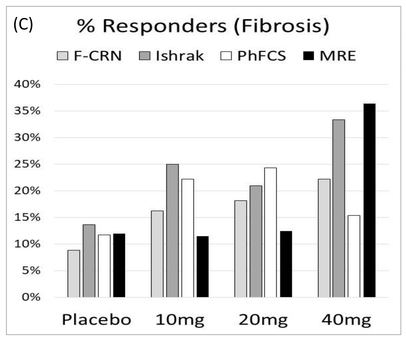
- Patients with biopsies with a DBA lower than 5 (non-adequate, ~10% of the cohort) were not included.
- Groups sizes ranged from 27 to 40 patients per group.



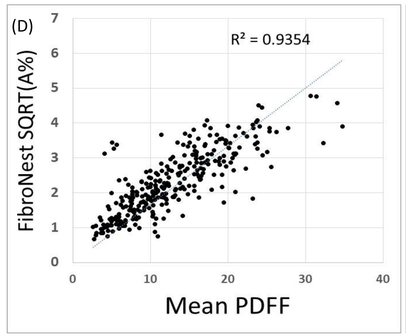
- The quantification of the antifibrotic effect of the treatments is similar using the mean change from baseline of the Ph-FCS and MRE (Fig. A).
- SQRT(A%) highly correlates to PDFF (N=334) and quantifies the anti-steatotic effects for each group with the same performance as PDFF (Fig. A, Table B)

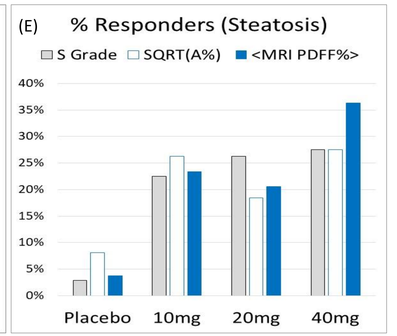
(B)

		Mean Change From Baseline						
		Placebo	10MG	*pValue*	20MG	*pValue*	40MG	pValue
FibroNest Fibrosis Scores	**N =**	**34**	**36**		**37**		**39**	
	Ph-FCS	0.312	-0.082	*0.1534*	0.089	*0.4188*	0.020	*0.2735*
	Scar - FCS	0.117	-0.148	*0.4268*	0.086	*0.9292*	0.056	*0.8721*
	Morpho FS	0.296	-0.034	*0.2430*	0.089	*0.4493*	0.014	*0.2928*
	Morpho FS -FINE	0.348	-0.069	*0.1911*	0.190	*0.6207*	-0.011	*0.2380*
	Morpho FS -ASBL	0.265	-0.008	*0.2271*	0.085	*0.4331*	0.050	*0.3474*
	Architecture FCS	0.401	-0.264	*0.0688*	0.207	*0.6248*	0.024	*0.2881*
MRE - MRI Mean Liver Stiffness	**N=**	**25**	**26**		**32**		**33**	
	MRE	0.707	-0.078	*0.0749*	0.035	*0.1261*	-0.399	*0.0250*
FibroNest Steatosis Scores	**N=**	**37**	**38**		**38**		**40**	
	SQRT(A%)	-0.005	-0.421	*0.0159*	-0.316	*0.0732*	-0.449	*0.0068*
	Steat-CS	-0.003	-0.306	*0.0740*	-0.255	*0.1418*	-0.268	*0.0987*
MRI - Mean PDFF	**N=**	**27**	**30**		**34**		**33**	
	MRI PDFF	1.070	-1.637	*0.0174*	-1.171	*0.0554*	-1.512	*0.0304*



- Responders were identified with a relative reduction from baseline as summarized in Table F.
- The experimental error of the FibroNest method (related to staining and tissue processing variability) was estimated between 5% and 7% [1]. A 25% relative reduction from baseline is chosen for fibrosis, and 30% for steatosis to fully align to MRI-PDFF.





(F) **Responder Criteria**

	Relative Reduction from Baseline
MRE	>=15%
Ph-FCS	>=25%
MRI-PDFF	>=30%
SQRT(A%)	>=30%
NASH CRN F Stage	Reduction in 1 stage or more

5 Conclusions

Combined to AI algorithms, quantitative digital pathology image analysis provides continuous read-outs of the histological parameters for severity and steatosis. This read outs are sensitive to subtle changes providing a more granular and accurate way to assess drug effects in clinical trials.

6 Contact information

Anne.Minnich@bms.com and Mathieu.Petitjean@pharmanest.com

[1] EASL2020: **Evaluation of a novel histology-based fibrosis phenotypic composite score and its correlation with NASH-CRN Fibrosis scores in patients with NASH.** Li Chen (1), Michael Lung (2), Cynthia Behling (2), Arun Sanyal (3), Mathieu Petitjean (1). 1 - PharmaNest, Princeton, NJ, USA; 2- University of California, San Diego, NAFLD Research Center, Division of Gastroenterology. 3-Virginia Commonwealth University, Richmond, VA, USA.