EVALUATION OF THE PERFORMANCE OF A NOVEL SINGLE-NUCLEI DIGITAL PATHOLOGY METHOD FOR THE CONTINUOUS QUANTIFICATION OF STEATOSIS AND INFLAMMATION IN LIVER BIOPSIES AND ITS CORRELATION WITH NASH-CRN SCORES IN PATIENTS WITH NASH

LOUIS PETITJEAN[1], LI CHEN[1], DIMITRI FEDOROV[2], ARAN MATTIS[3], MOJGAN HOSSEINI[4], MATHIEU PETITJEAN[1], ARIUN J. SANYAL[5], CYNTHIA BEHLING[6]

[1] PharmaNest, Princeton, NJ, USA, [2] ViQi Inc, Santa Barbara, CA, USA, [3] Department of Pathology, University of California San Francisco, San Francisco, CA, [4] Department of Pediatrics University of California, San Diego, CA, USA, [5] Virginia Commonwealth University, Richmond, VA, USA, [6] Department of Pathology, University of California, San Diego, California, USA

INTRODUCTION

The quantification of H&E liver biopsy with Digital Pathology methods based on annotation provided by pathologists (steatosis, inflammation) result in continuous scores of moderate performances.

AIM

Here, we report results of a new AI-assisted single-nuclei quantification approach that benefits from (a) training received from pathologists on highly consensual features (cell types) and (b) generates mathematically defined outcomes. This approach address limitations of current histological current nomenclatures and methods (doi:10.1002/hep.32475)

METHOD

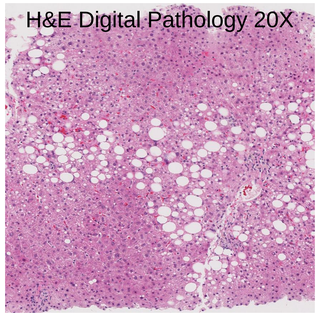
- This retrospective cohort included 87 patients with NASH diagnosed by histologic assessment of liver biopsy with lobular inflammation grades of 0 (N=7), 1 (68), and 2 (12), and steatosis grades of 0 (N=2), 1 (40), 2 (30) and 3 (14).
- Quantitative image analysis of 20X Digital pathology images of H&E stained sections was performed to identify cell nuclei (~ 20k per biopsy) and quantify their morphometric and local surroundings in 86 parameters.
- A subset of 13 images (~260K nuclei) was used to develop a machine learning (ML) model using 3.0K annotations (respectively 3.0K, 3.3K, 3.7K, 1.7K, 3.0K) for steatotic hepatocytes, normal hepatocytes, inflammatory cells (all kinds), liver specialized cells (all kinds), and “debris” (cells in apoptosis or distorted).
- Once classified, a cell tissue panel was calculated to account for cell densities (count /mm2) and relative cell count %.
- Macro-steatosis Area Ratio was calculated as well as % steatotic Hepatocytes. The later, which corresponds to the
- Clusters of inflammatory cells were identified using “closest neighbor” method and the morphometric features of these clusters was used to classify them into small (<5,000mm2), medium and large clusters which are then quantified by several continuous and normalized parameters (biopsy area ratio, count per mm2 or 200XFOV).

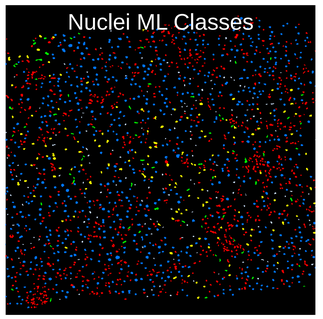
CONCLUSION

- Quantitative digital pathology can automatically generate tissues panels from H&E stained sections.
- While the scores extracted from these tissues panels moderately correspond to NASH-CRN histological stages, they present the benefit of being quantitative and translational, and not sensitive to liver tissue variation due to swelling, fat invasion, or various artifacts.

CONTACT: Mathieu.Petitjean@pharmanest.com

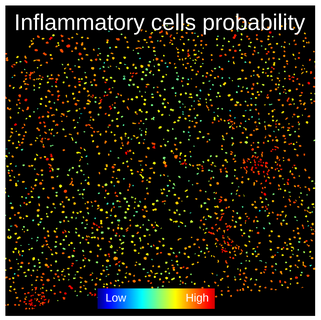
RESULTS

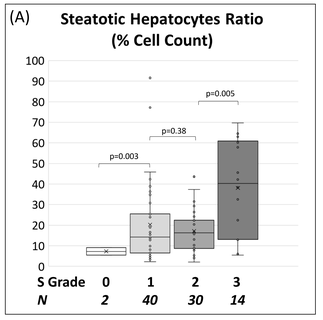


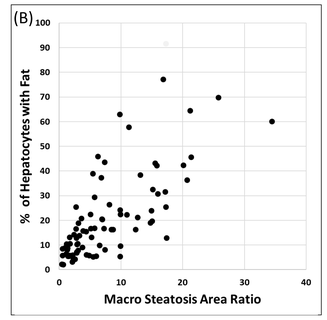


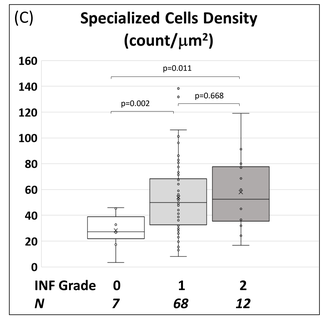
ML Model performance (5 classes)

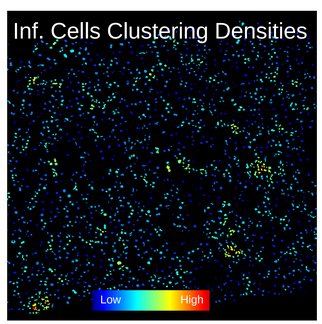
Class	Samples (n)	Accuracy %	Error %	F1 %	Validated (n)
Inflammatory cells	3743	86.2%	15.2%	73%	2019
Hep Nuclei w/o Fat	3189	78.2%	12.5%	68.5%	1994
Hep Nuclei w Fat	2931	74.4%	30.1%	52.0%	893
Debris	1623	76.6%	17.0%	63.6%	1224
Specialized cells	1599	34.9%	33.6%	23.2	370

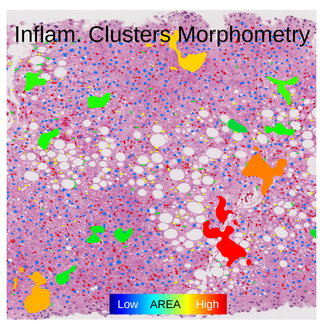


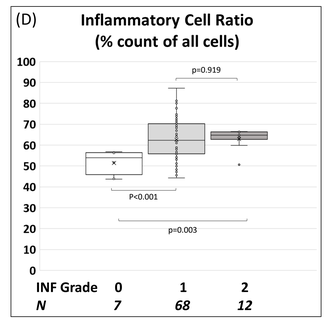


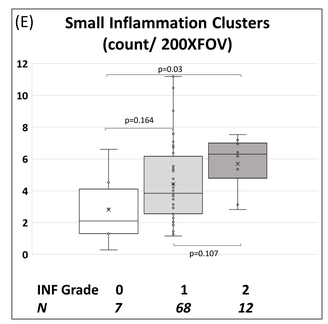












- The cell classification accuracy (error) of the ML model ranged from 14.6%(24.3%) for specialized cells to 77.7%(26.9%) for inflammatory cells.
- The steatotic hepatocytes count ratio (NASH-CRN definition, Fig. A, 0.008<p-values<0.38) exhibited similar trends reported previously using ML from pathologists’ annotations. The correlation with macro steatosis Area Ratio (Fig. B, R2=0.5226) is moderate as NASH-CRN definition (percentage of hepatocytes containing a lipid droplet, irrespective of their size) can overestimate the grade of steatosis if all hepatocytes contain lipid droplets, small medium or large.
- Quantitative Tissue Panels (used to derive Fig C-D) offer novel ways to quantify features of tissue injury: the inflammatory cell density detects the presence of inflammation with good performance (Fig. D).
- The count of small inflammation clusters (Fig. E, 0.107<p-values<0.034) moderately corresponds to the histological grades, which is attributed to the histological definition of inflammatory clusters and their assessment by pathologists, as reported elsewhere (doi: 10.1002/hep.32475).

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