Abstract # 2698

Characterizing the histologic implications of resmetirom-induced liver volume reduction using artificial intelligence-powered digital pathology

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STUDY BACKGROUND

In nonalcoholic steatohepatitis (NASH) clinical trials, liver biopsies are evaluated for histologic evidence of 1) NASH and fibrosis at screening, and 2) drug effect at study completion. Liver volume is typically increased in patients with NASH, and an emerging hypothesis suggests that drug-induced fat and potentially related liver volume (LV) reduction may complicate histologic interpretation of liver biopsies by altering the apparent abundance of cardinal histologic biomarkers of disease progression and regression.[1,2,3]

It is unclear how this potential effect may impact NASH clinical trial outcomes; in particular, accurate measurement of histologic endpoints could be difficult without an improved understanding of drug-induced global changes in the liver.

Here, we used artificial intelligence (AI) models, trained to characterize and quantify cell types and tissues present in NASH biopsies, to investigate whether histological changes resulting from LV reduction could be detected in biopsies from the Phase 2 trial of resmetirom (MGL-3196) for treatment of NASH in patients with NASH CRN Fibrosis Stage 1-3 and NAFLD Activity Score ≥4 with at least a grade of 1 for each component feature. The impact of drug-induced fat loss on cell and tissues, as well as on fibrosis staging, was evaluated.

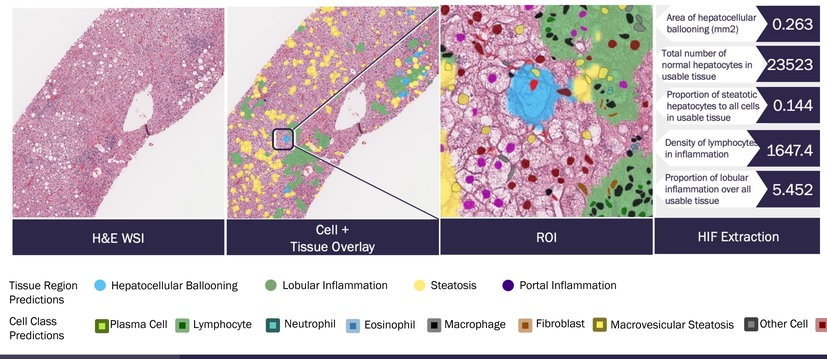


Figure 2. Human Interpretable Feature (HIF) Extraction from Model Predictions

Human Interpretable Features (HIFs) describing proportions and densities of cells and tissues are computed from cell and tissue model predictions (shown as colored heatmap overlays). Individual cells and tissue types can be seen in the magnified region of interest (ROI). Example HIFs and corresponding slide-level quantities are shown.

METHODS

Cell Model Training and Development

- Convolutional neural network (CNN) models were developed to identify and quantify 11 classes of liver cell types from whole slide images (WSIs) of hematoxylin and eosin (H&E)-stained tissue (Figure 1).
- These cell models were trained using over 2100 WSIs of liver biopsy tissue from NASH clinical trials in addition to diagnostic samples from PathAI Diagnostics (Memphis, TN). Expert liver pathologists provided over 275,000 annotations of distinct types of liver cells (Figure 2).
- Model performance accuracy was confirmed by comparison with cell-type labels provided by five pathologists for each cell type (data not shown).

Model Deployment

- AI models were deployed on an independent set of WSIs of liver biopsies from 101 patients (H&E: N=190 evaluable WSIs; Masson's Trichrome [MT]: N=182 evaluable WSIs) that participated in the randomized, placebo-controlled Phase 2 trial of resmetirom for treatment of NASH (NCT02912260).[4]
- The cell model was deployed to quantify the presence of different cell types within WSIs.
- Previously-trained segmentation models that predict tissue regions (e.g. steatosis, lobular inflammation, portal inflammation, and fibrosis) and distinguish between pathologic fibrosis and structural collagen were also deployed on the same dataset (Figure 1).[5]

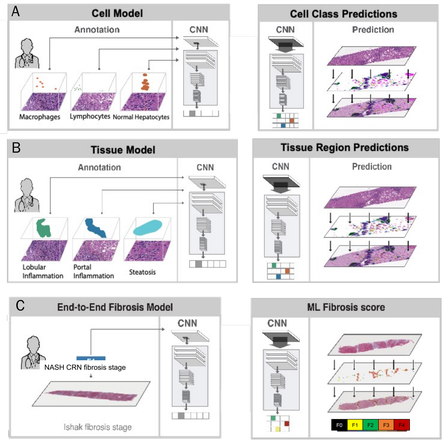
Quantitative Human Interpretable Feature (HIF) Extraction

- HIFs that quantitatively describe the composition of cells in relation to tissue region (specifically, count proportions and densities of individual and combinations of cell classes) and proportionate areas of fibrosis in each WSI were extracted from cell and tissue model predictions (Figure 2).

Liver volume

- Liver volume (LV) was previously calculated during the clinical trial period using magnetic resonance imaging.[4]
- Treatment response was defined as at least 15% reduction in liver volume.[6]

Figure 1. Training and deployment of cell, tissue, and fibrosis predictive models



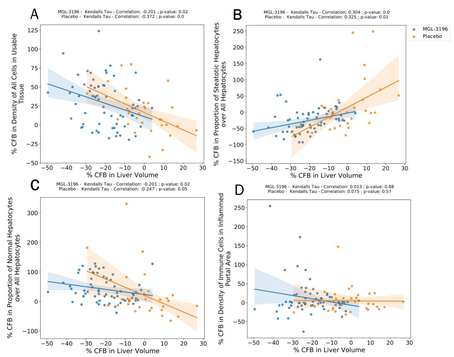
Models were deployed on WSIs of paired H&E- and MT-stained tissue samples. Cell (A) and Tissue (B) models exhaustively identified and quantified individual cells and tissue regions, respectively. Example annotations used in model training per model type are shown. A Fibrosis Model (C) predicted and scored regions of fibrosis (NASH CRN), characterizing the within-biopsy variability in patterns of fibrosis throughout the tissue.

Statistical Analysis

- Kendall's Tau was used to compute correlations between changes in AI-derived cellular features and liver volume.
- Mean percent change from baseline (%CFB) was computed to compare changes in proportionate area of steatosis-adjusted and –unadjusted fibrosis occurring in treated vs. placebo subjects.

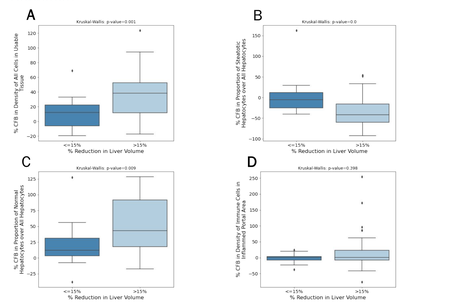
RESULTS

Figure 3. Correlation of change in cellular HIFs with change in liver volume



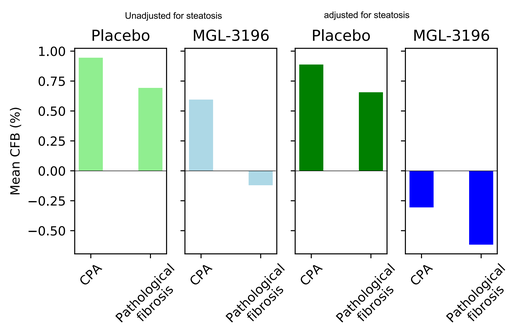
Correlation between mean percent change from baseline (%CFB) in AI-derived HIFs and %CFB in LV in resmetirom (MGL-3196, N=64) vs. placebo treated subjects (N=31).

Figure 4. Change in cellular HIFs by percentage of volume reduction



Comparison between %CFB in cellular HIFs between responders (> 15% LV reduction) and non-responders (<15% LV reduction).

Figure 5. Change from baseline in pathological fibrosis and collagen proportionate area (CPA)



Mean %CFB in CPA and pathological fibrosis in resmetirom (MGL-3196)-treated vs placebo treated subjects. CPA and fibrosis area measurements were adjusted by subtracting steatosis area at each timepoint.

- AI quantification revealed a statistically significant increase in overall cell density in resmetirom- versus placebo-treated participants (p = 0.037; data not shown).
- AI quantification of the density of all cells showed that a decrease in liver volume correlated with increased cell density in both treated and placebo participants (Figure 3A).
- The proportion of AI-quantified steatotic hepatocytes was positively correlated with LV, where there were fewer steatotic cells with reduced liver volume (Figure 3B). The proportion of normal hepatocytes over all hepatocytes (Figure 3C) increased with decreasing LV.
- The density of immune cells in areas of portal inflammation showed no correlation with LV change (Figure 3D).
- Cellular HIFs of hepatocytes, but not immune cells, differentiated between LV responders and non-responders (Figure 4).
- Adjusting fibrosis proportionate area quantification for reduction in steatosis resulted in greater measured reductions in fibrosis in the treatment but not the placebo arm, likely due to greater reduction in pathological fibrosis (Figure 5).

CONCLUSIONS

Here, we show that liver volume change is reflected in the abundance and densities of steatotic and normal hepatocytes, consistent with a model in which disintegration of large triglyceride-filled vesicles results in macroscopic liver volume reduction. These findings motivate further investigation into the morphologic biomarkers of liver volume change in NASH clinical trials and how these changes should be adjusted for when evaluating drug effect, particularly in fibrosis.

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PathAI