# AI-powered computational pathology for liver diseases

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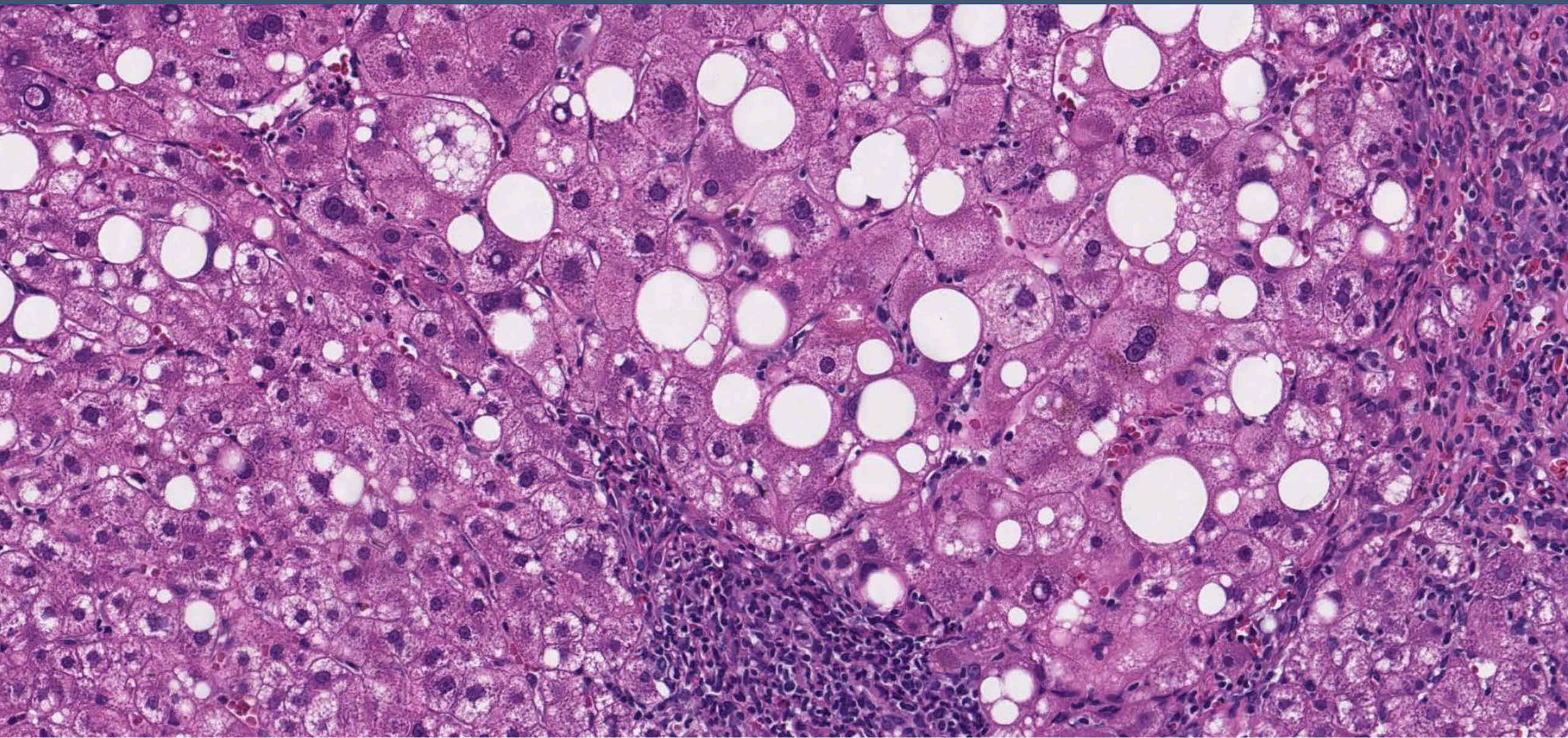
PathAI

# Interpretation of liver histology is prone to error and current scoring systems do not fully capture disease heterogeneity



# Interpretation of liver histology is prone to error and current scoring systems do not fully capture disease heterogeneity

## Ishak scoring system

| Ishak Grade | Score |
|---|---|
| *Periportal or periseptal interface hepatitis* (*piecemeal necrosis*) | |
| None | 0 |
| Mild (focal, few portal areas) | 1 |
| Mild/moderate (focal, most portal areas | 2 |
| Moderate (continuous around < 50% of tracts or septa) | 3 |
| Severe (continuous around > 50% of tracts or septa) | 4 |
| *Portal inflammation* | |
| None | 0 |
| Mild, some or all portal areas | 1 |
| Moderate, some or all portal areas | 2 |
| Moderate/marked, all portal areas | 3 |
| Marked, all portal areas | 4 |

## CRN NAFLD activity scoring system

| Grade | Steatosis (%) | Lobular inflammation | Ballooning |
|---|---|---|---|
| 0 | <5 | No foci | None |
| 1 | 5–33 | <2 foci per 200× field | Few ballooning cells |
| 2 | >33–66 | 2–4 foci per 200× field | Many cells/prominent ballooning |
| 3 | >66 | >4 foci per 200× field | N/A |

*N/A* not applicable

1 David E. Kleiner et al. “Design and validation of histological scoring system for nonalcoholic fatty liver disease.” *Hepatology 2005*
2 Zach Goodman, et al. “Grading and staging systems for inflammation and fibrosis in chronic liver diseases.” *Journal of Hepatology* 2007

# Histologic scoring systems have limited reproducibility

- Published literature has shown only moderate levels of inter- and intra-reader concordance for grading key features of chronic hepatitis and NASH
  - Inter-reader kappas were 0.61, 0.48, 0.33, and 0.52 for steatosis, fibrosis, lobular inflammation, and ballooning, respectively[1]
  - Inter-reader kappas were 0.4-0.6 for portal inflammation, interface hepatitis and parenchymal injury and inflammation[2]

**Intra-observer discordance for grading key NASH features grading is high[3] (Particularly for lobular inflammation and ballooning, 22–47% of cases)**

| Number of Biopsies | Steatosis | | Lobular Inflammation | | Ballooning | |
|---|---|---|---|---|---|---|
| | Kappa | Cases with Discordance | Kappa | Cases with Discordance | Kappa | Cases with Discordance |
| 166 | 0.69 | 22% | 0.38 | 42% | 0.66 | 22% |
| 162 | 0.50 | 29% | 0.29 | 43% | 0.43 | 36% |
| 149 | 0.59 | 26% | 0.42 | 39% | 0.29 | 47% |

1 Beth A. Davison, et al. “Liver biopsies in nonalcoholic steatohepatitis (NASH) clinical trials.” *Hepatology 2020*
2 Zach Goodman, et al. “Grading and staging systems for inflammation and fibrosis in chronic liver diseases.” *Journal of Hepatology* 2007
3 PathAI Analysis: AASLD 2019, median interval between biopsy re-reads, 16 weeks (range 9, 20).

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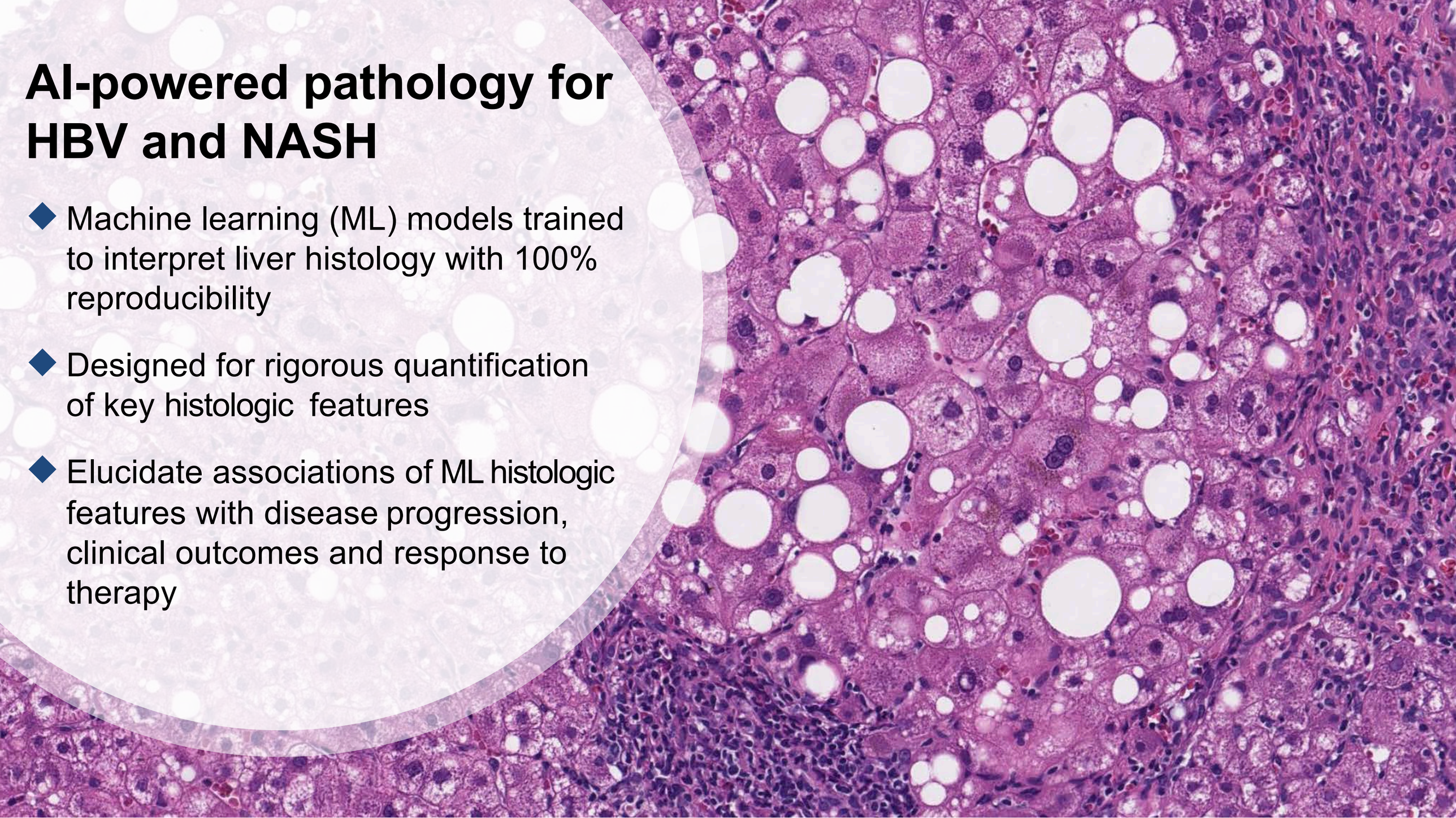
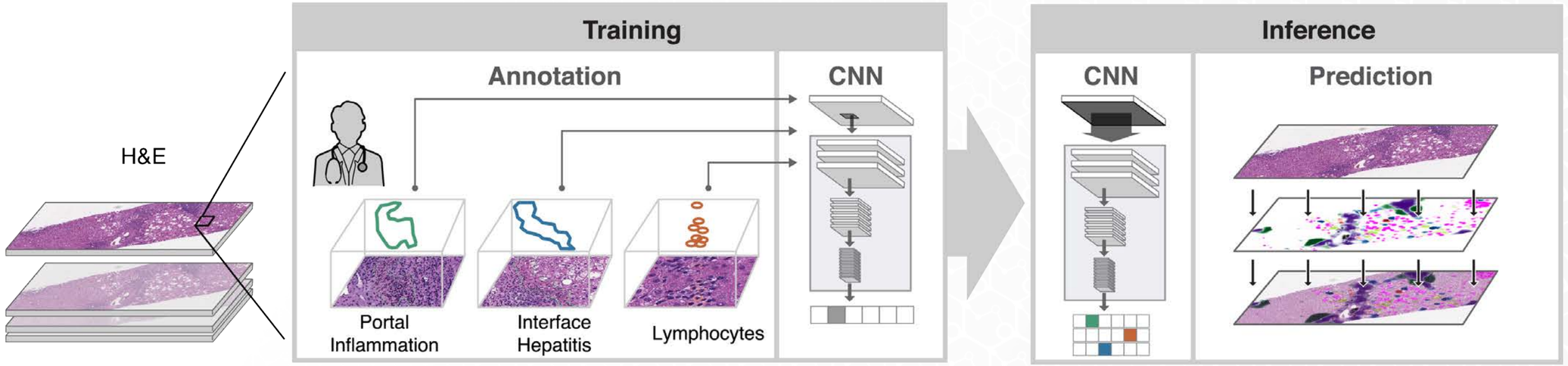
# AI-powered pathology for HBV and NASH

- Machine learning (ML) models trained to interpret liver histology with 100% reproducibility
- Designed for rigorous quantification of key histologic features
- Elucidate associations of ML histologic features with disease progression, clinical outcomes and response to therapy



# ML model development for automated assessment and quantitation of liver histopathology




Pokkalla H, et al., Oral presentation #187, AASLD 2019
Juyal D, et al., Poster presentation LBP31, EASL ILC 2020 (Late-breaker abstract submission)

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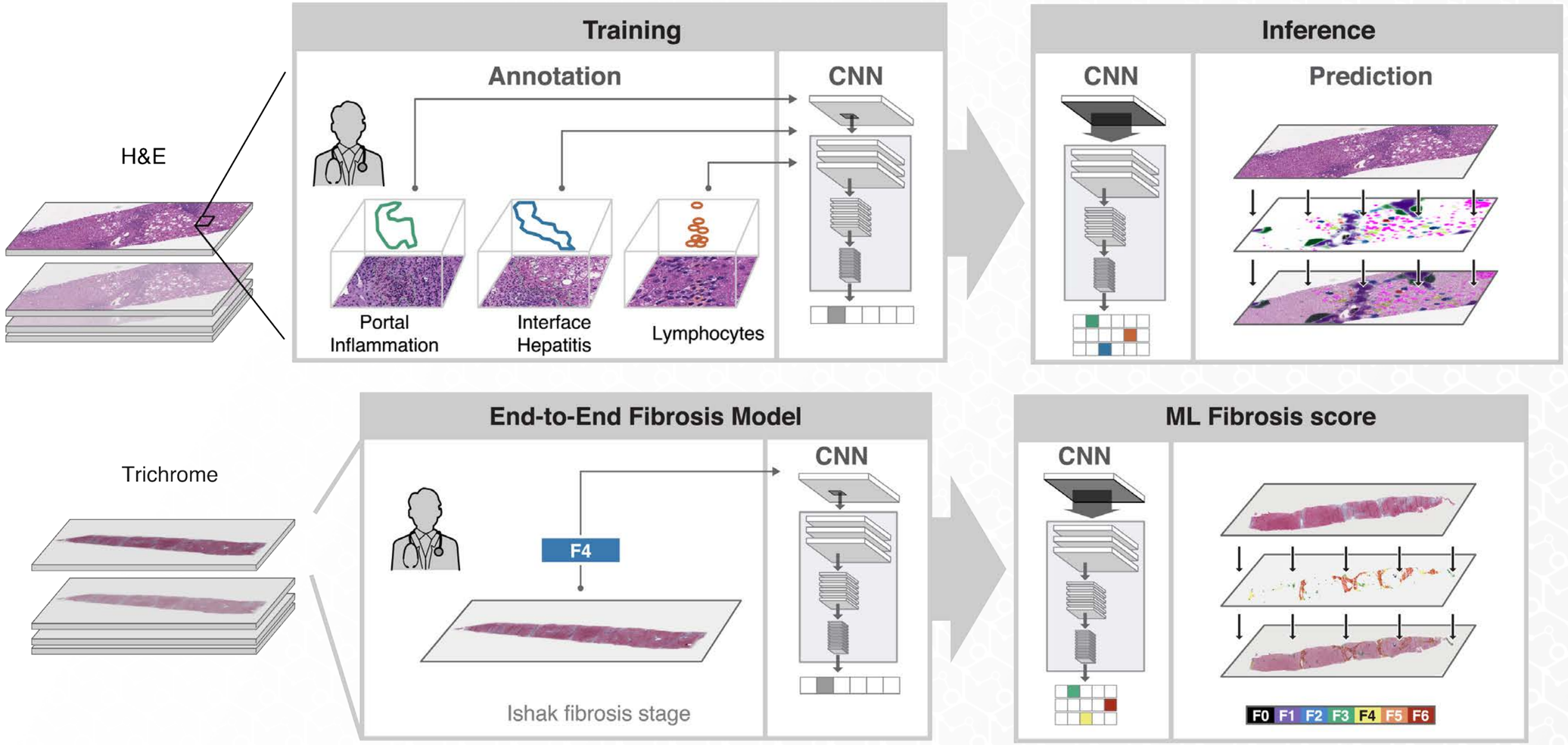
# ML model development for automated assessment and quantitation of liver histopathology

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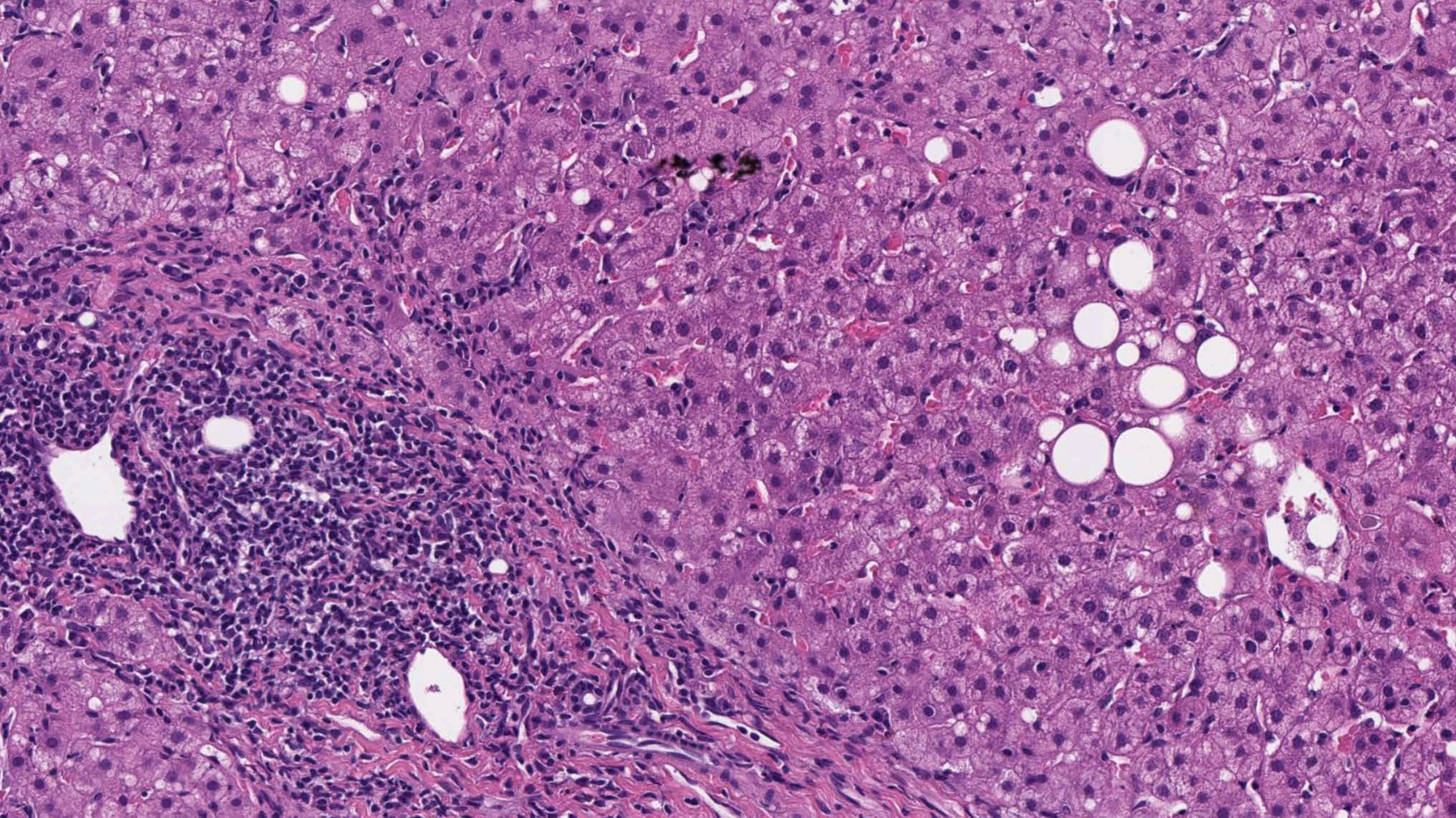
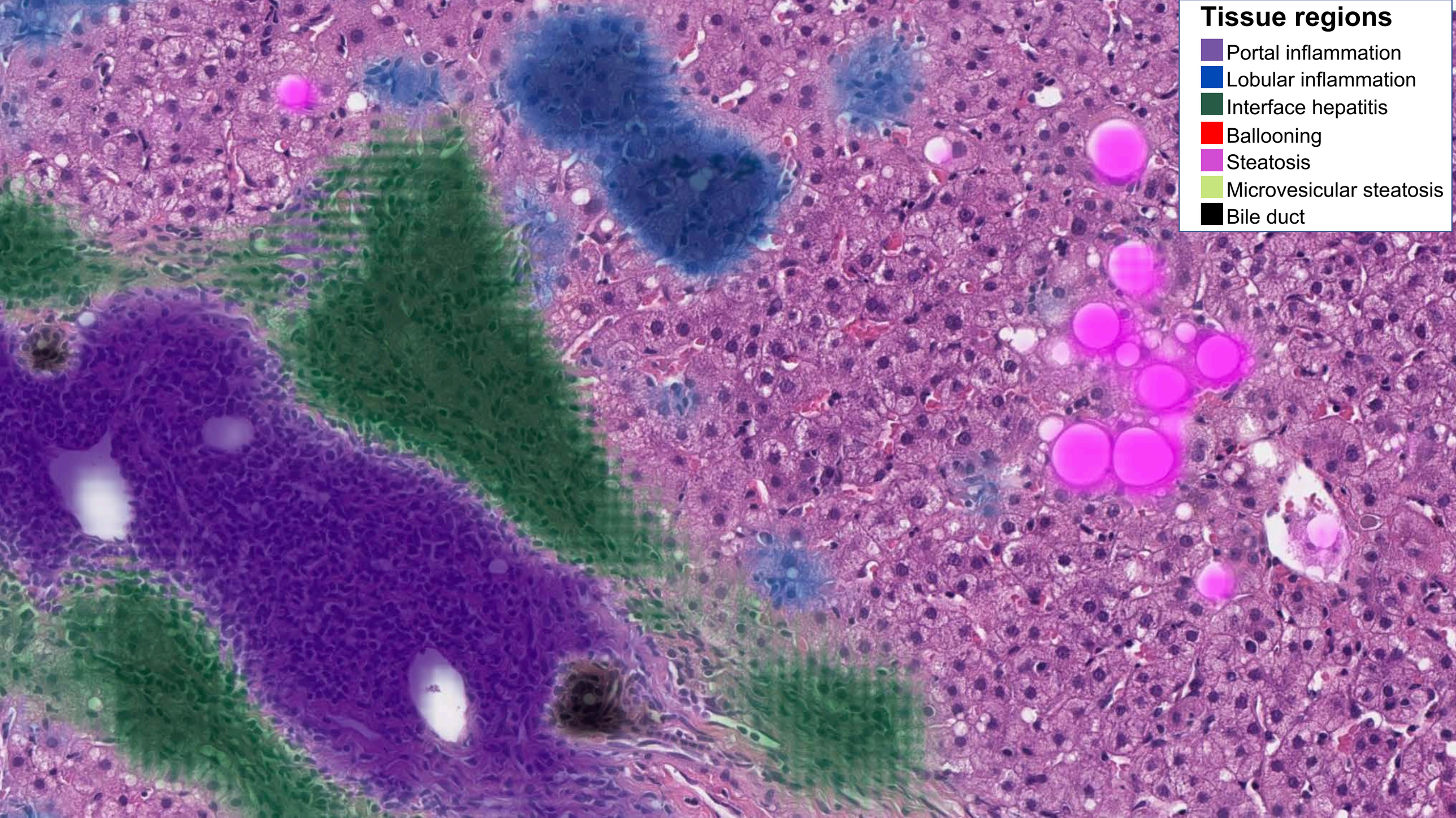
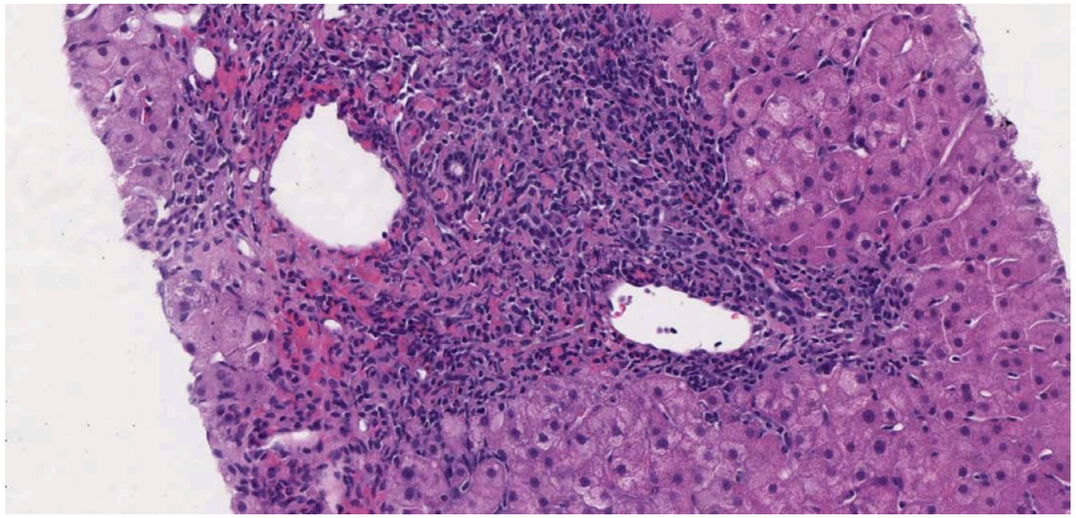
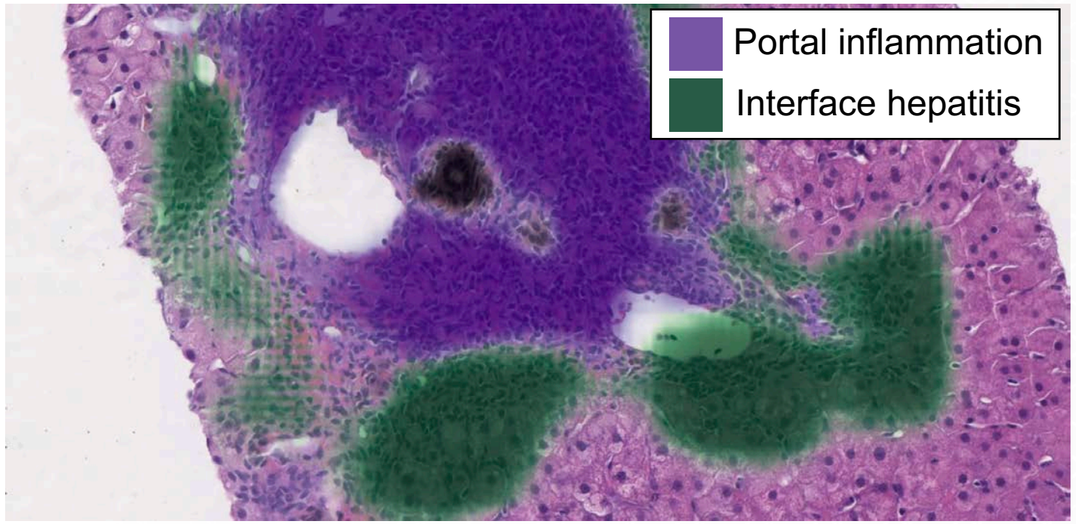
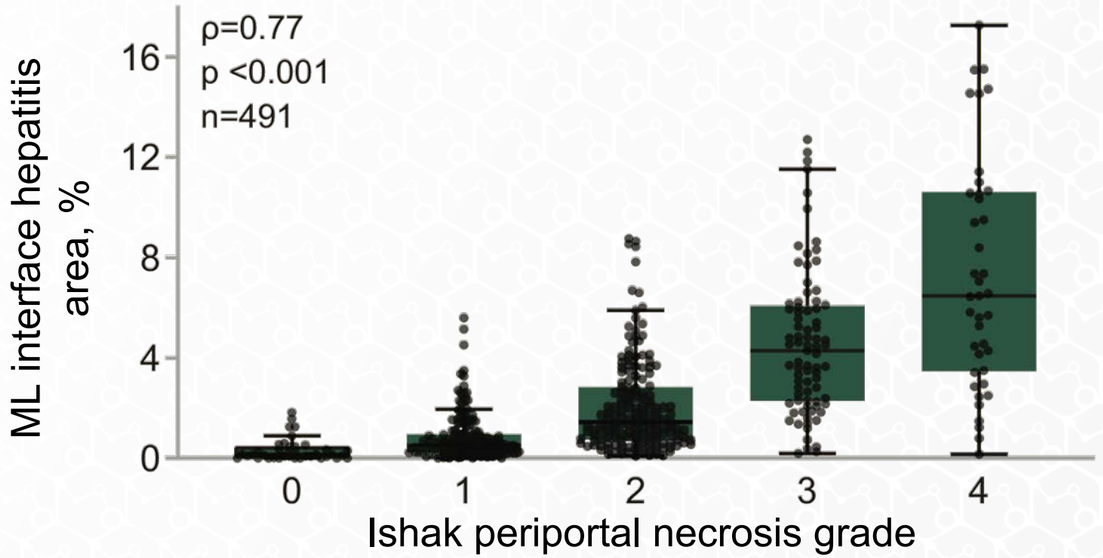


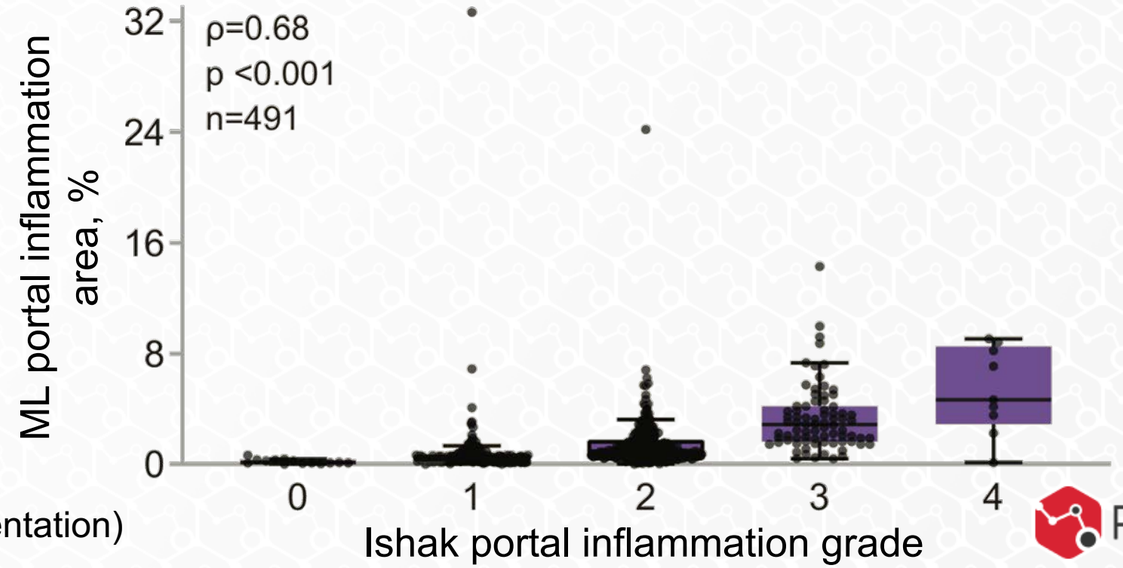

Tissue regions
Portal inflammation
Lobular inflammation
Interface hepatitis
Ballooning
Steatosis
Microvesicular steatosis
Bile duct

# ML-based quantification of histologic features of chronic inflammation correlate with expert pathologist assessment[1]






Juyal D, et al., Poster presentation LBP31, EASL ILC 2020 (Late-breaker presentation)

1: Pathologist reads followed clinical trial protocol

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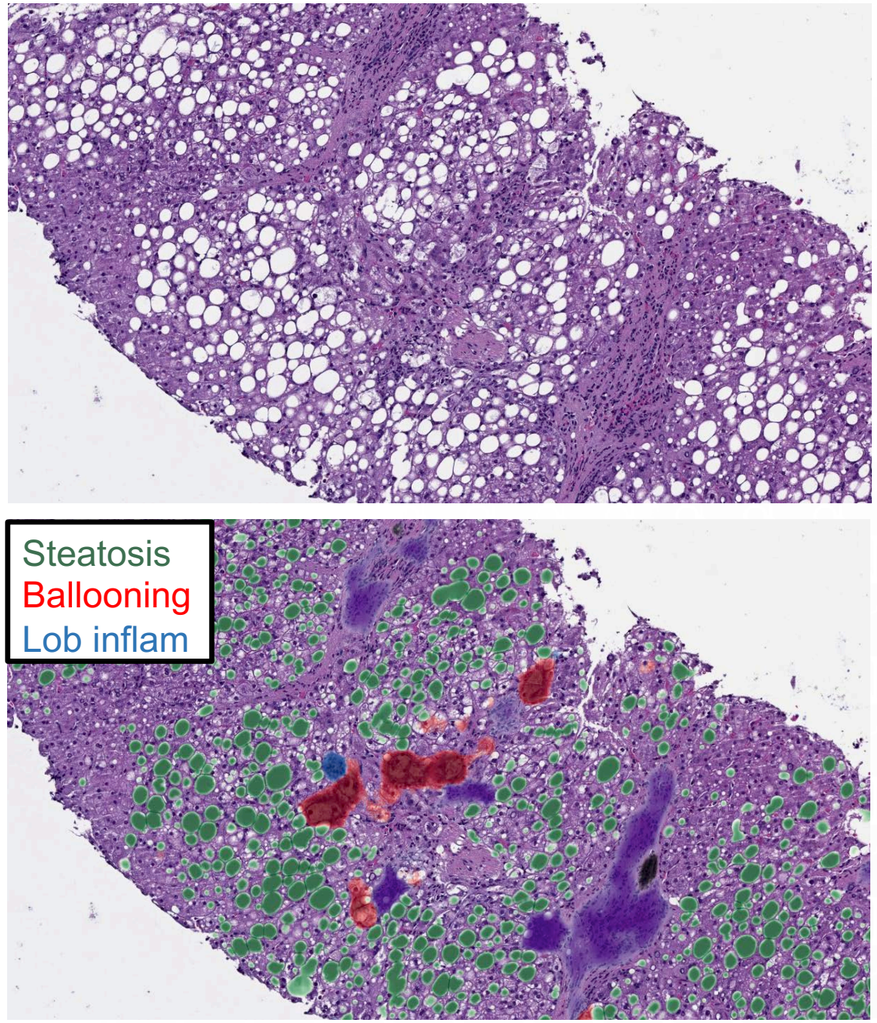
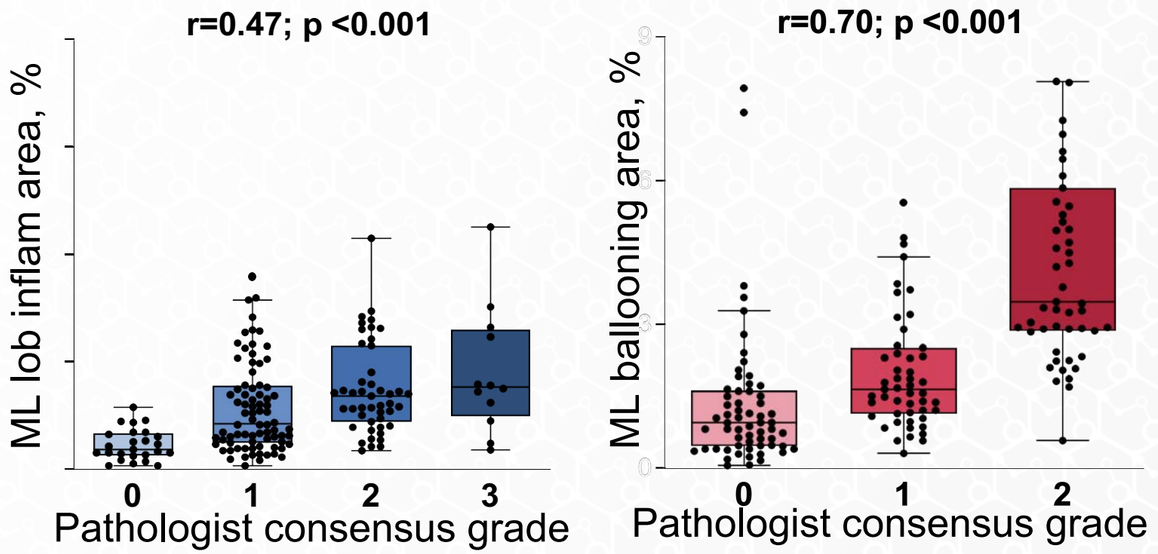
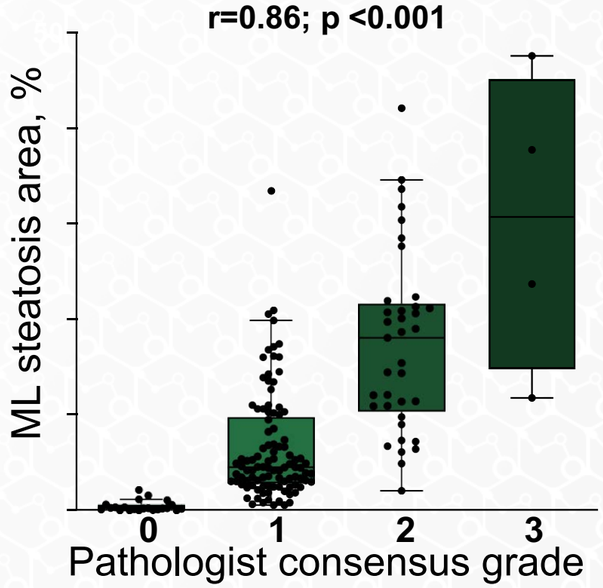
# ML-based quantification of histologic features of NASH correlates with consensus pathologist assessment[1]




Pokkalla H, et al., Oral presentation #187, AASLD 2019

1: Consensus pathologist reads obtained for research purposes

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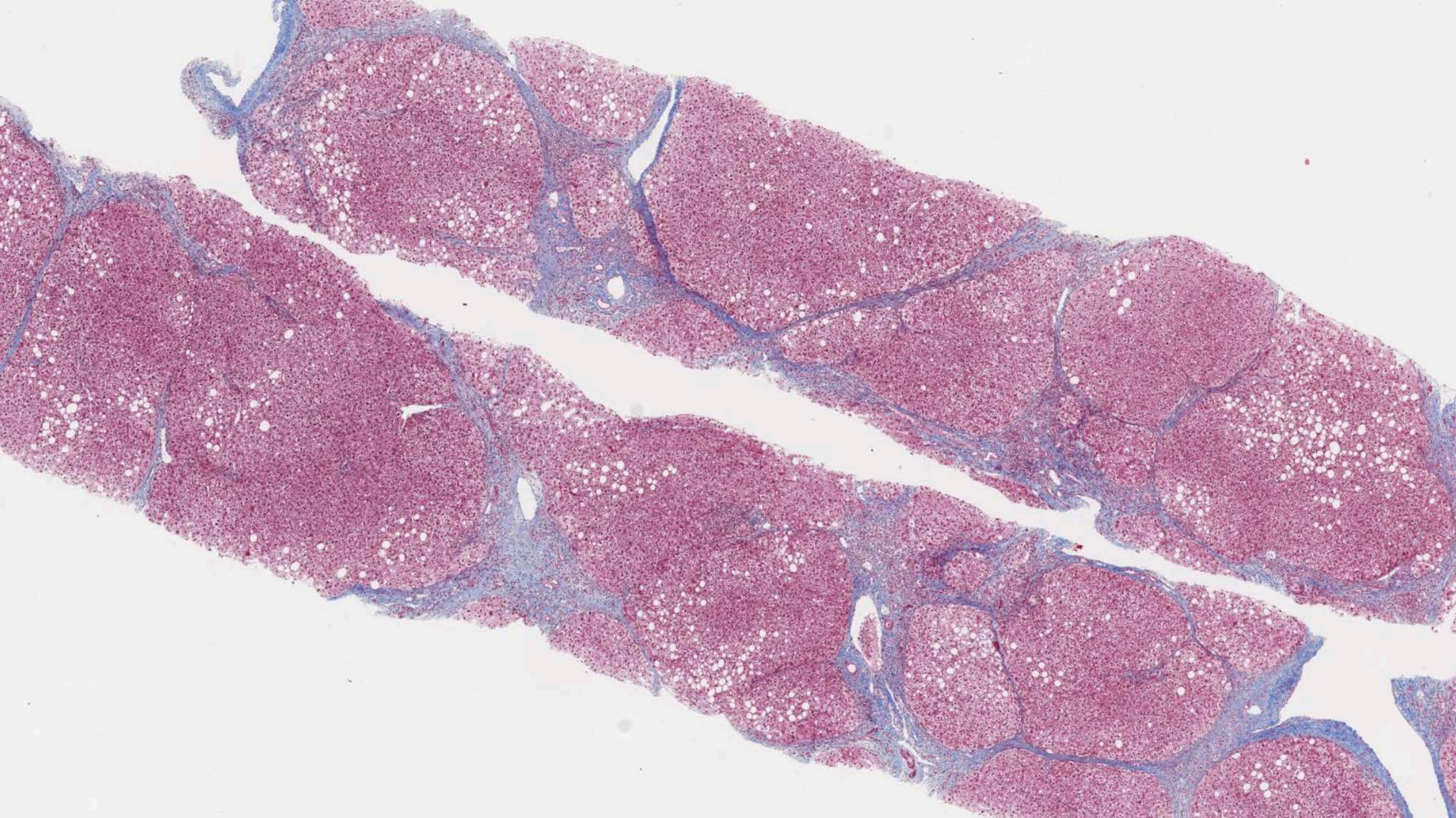
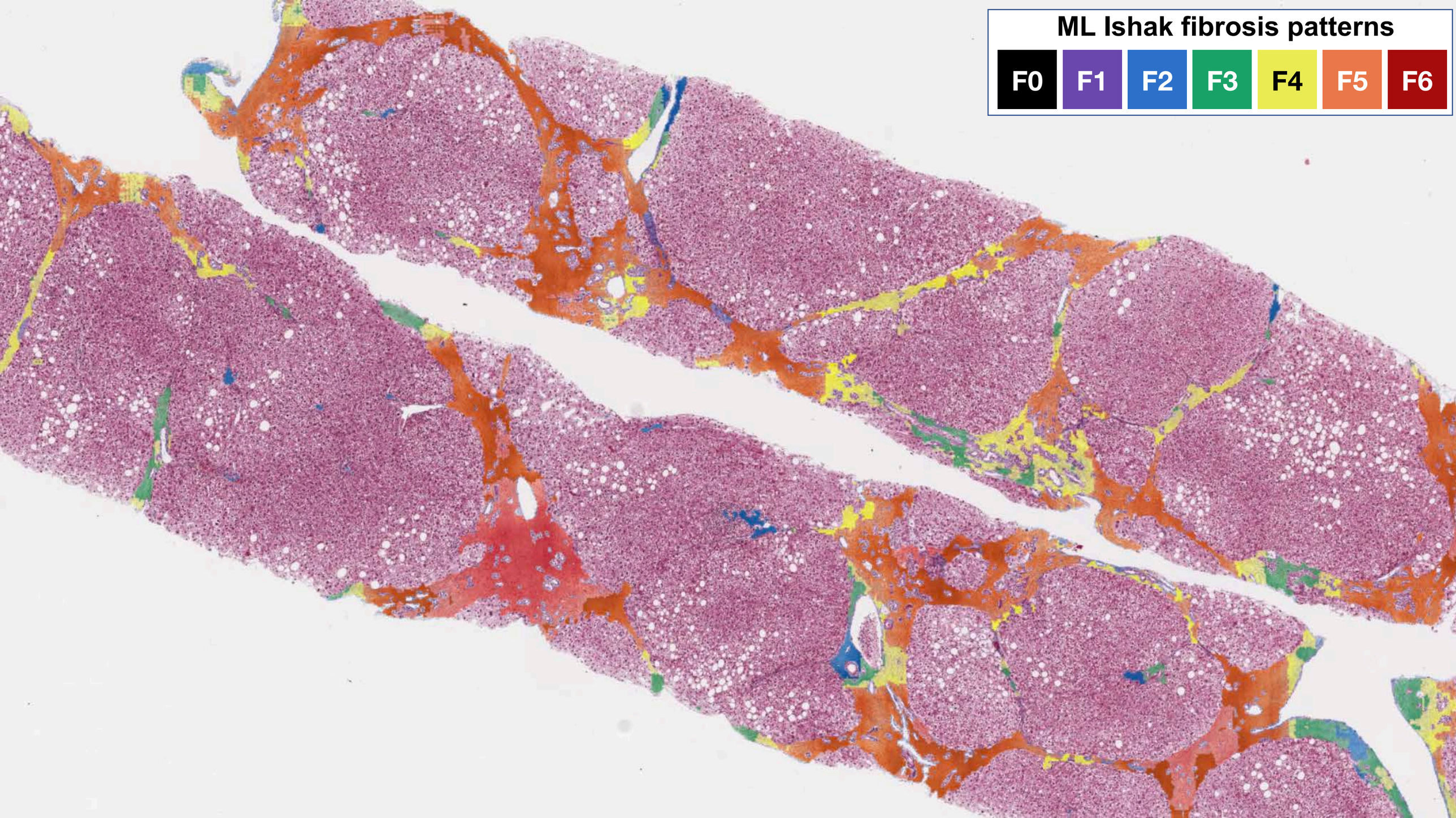
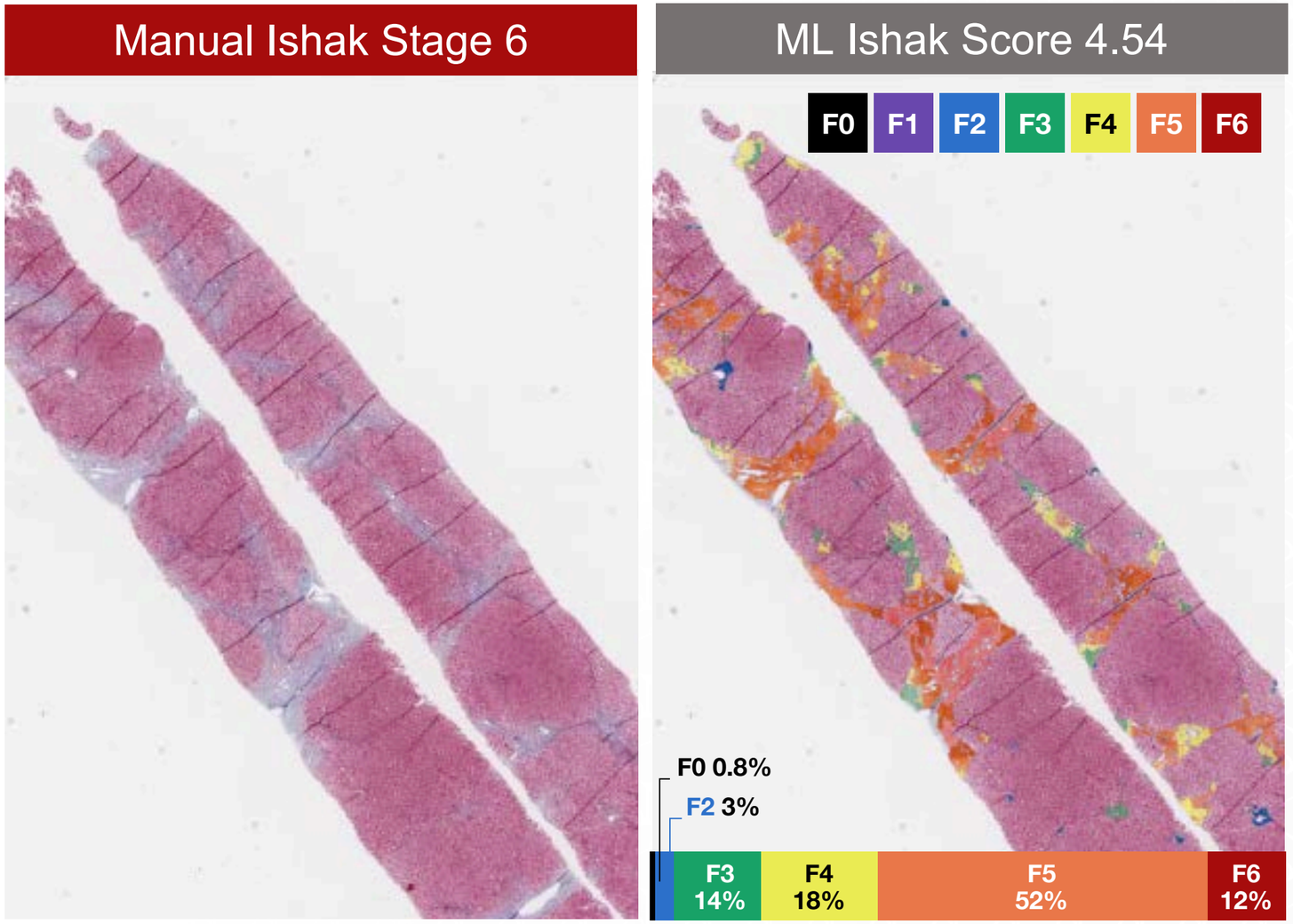
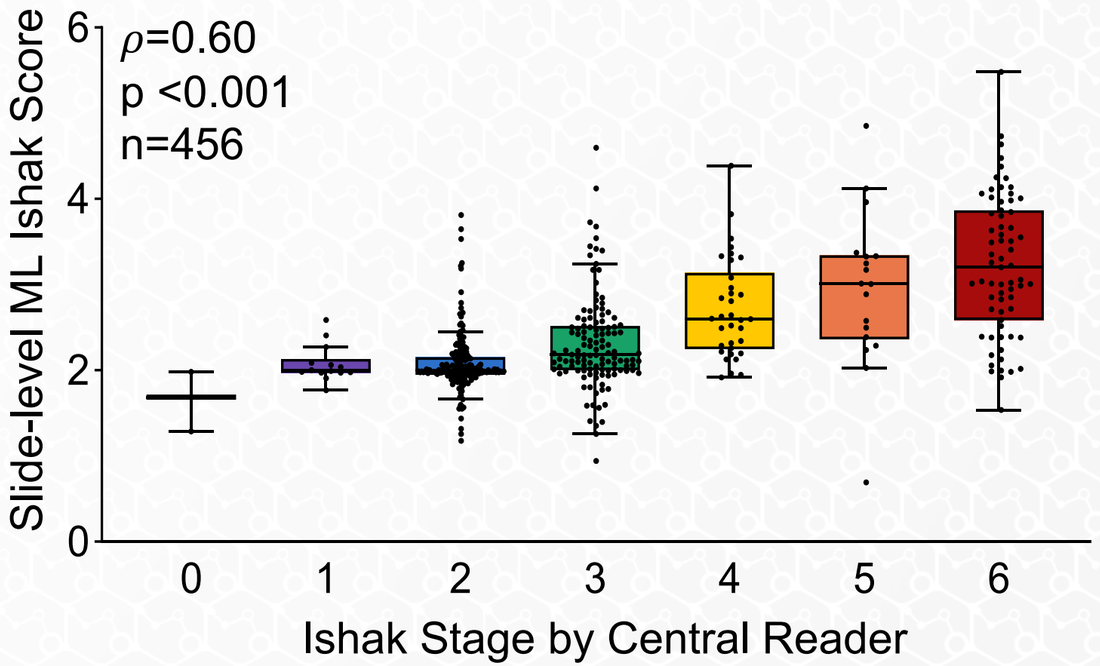



ML Ishak fibrosis patterns
F0
F1
F2
F3
F4
F5
F6

# ML fibrosis score quantifies heterogeneity and correlates with expert pathologist assessment[1]




Juyal D, et al., Poster presentation LBP31, EASL ILC 2020 (Late-breaker presentation)

1: Pathologist reads followed clinical trial protocol

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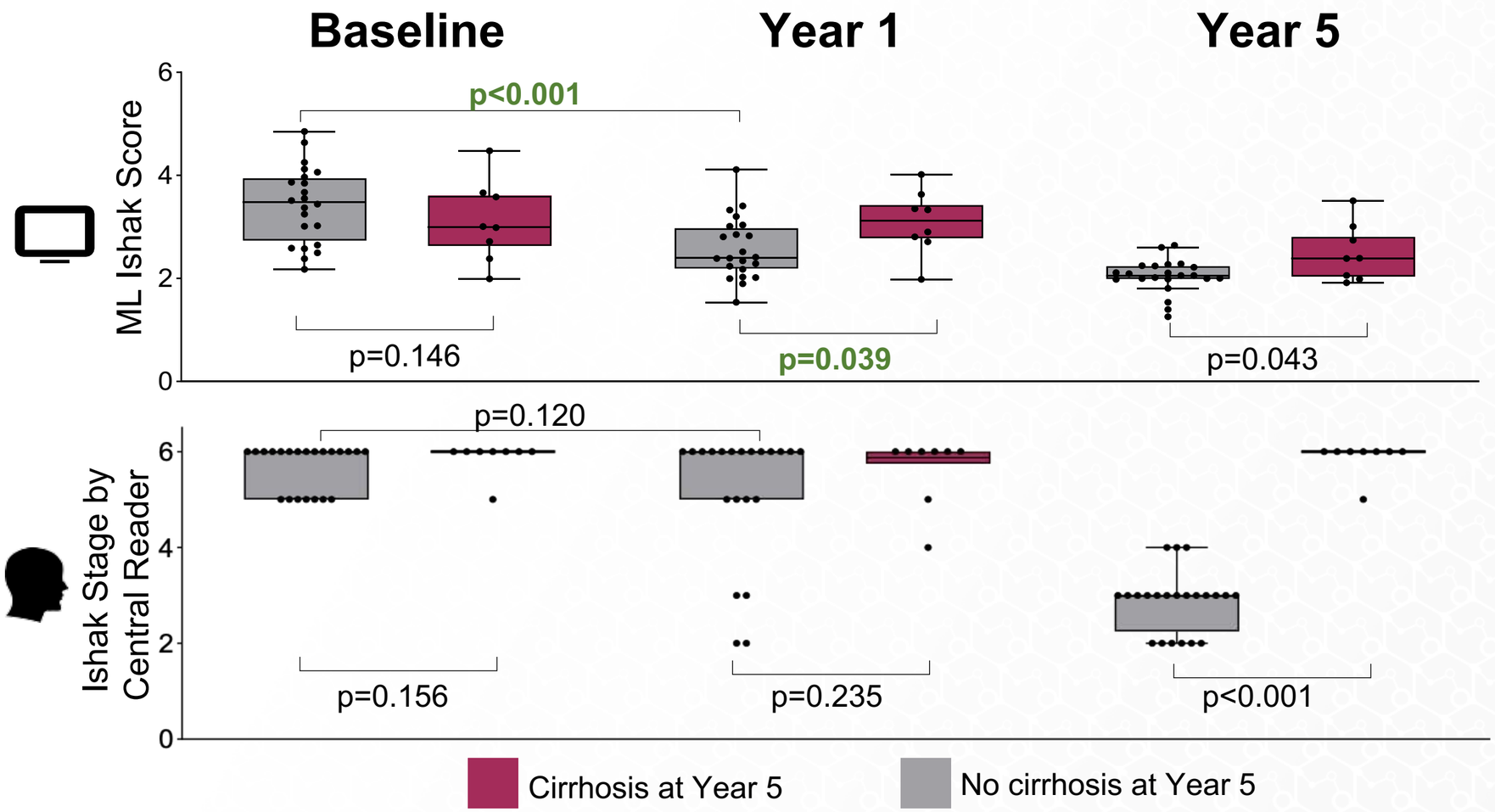
# In subjects whose cirrhosis regressed at year 5, fibrosis improvement by year 1 is evident only on ML Ishak score




- 22/30 HBV subjects achieved cirrhosis regression after 5 years of therapy
- Subjects who achieved cirrhosis regression at year 5 had significant reduction in ML Ishak score from baseline to year 1
- Fibrosis improvement was not evident on manual histology by year 1

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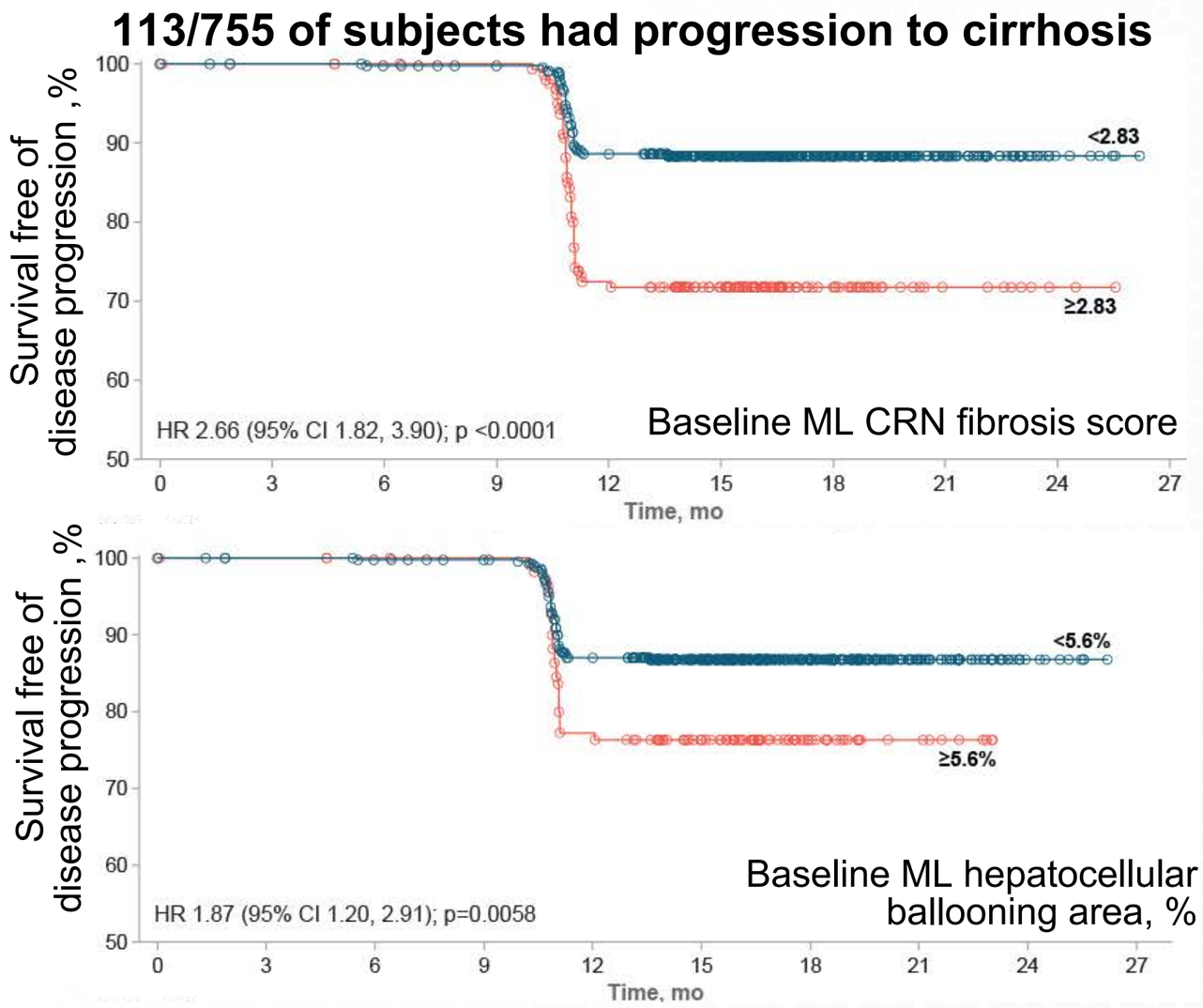
Juyal D, et al., Poster presentation LBP31, EASL ILC 2020 (Late-breaker presentation)

# ML-based histologic features are predictive of progression to cirrhosis in subjects with bridging fibrosis due to NASH




- Progression to cirrhosis was associated with higher ML CRN fibrosis score at baseline (HR 2.66 [95% CI: 1.82, 3.90])
- Progression to cirrhosis was associated with higher ML ballooning proportionate area at baseline (HR 1.87 [95% CI: 1.20, 2.91])

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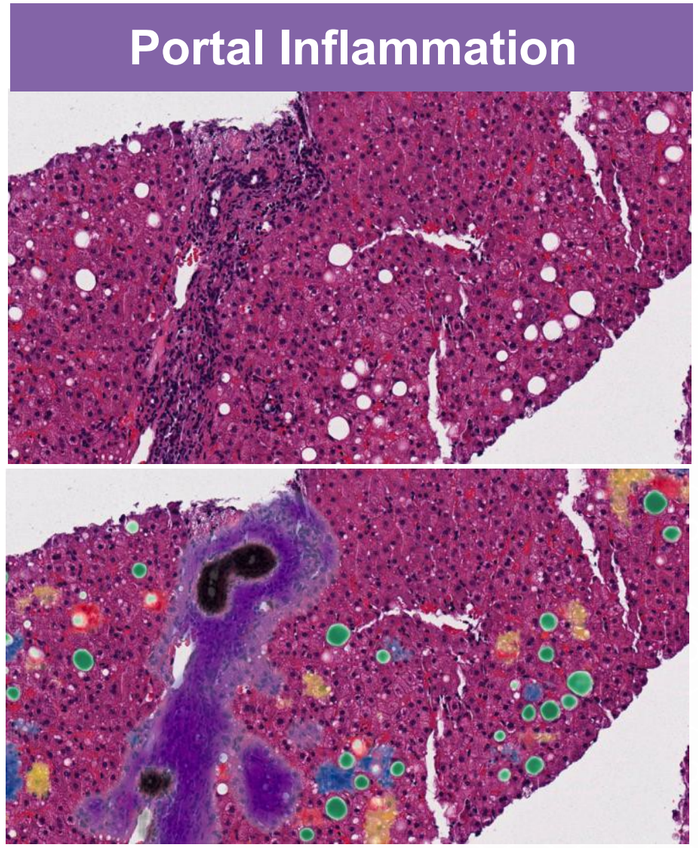
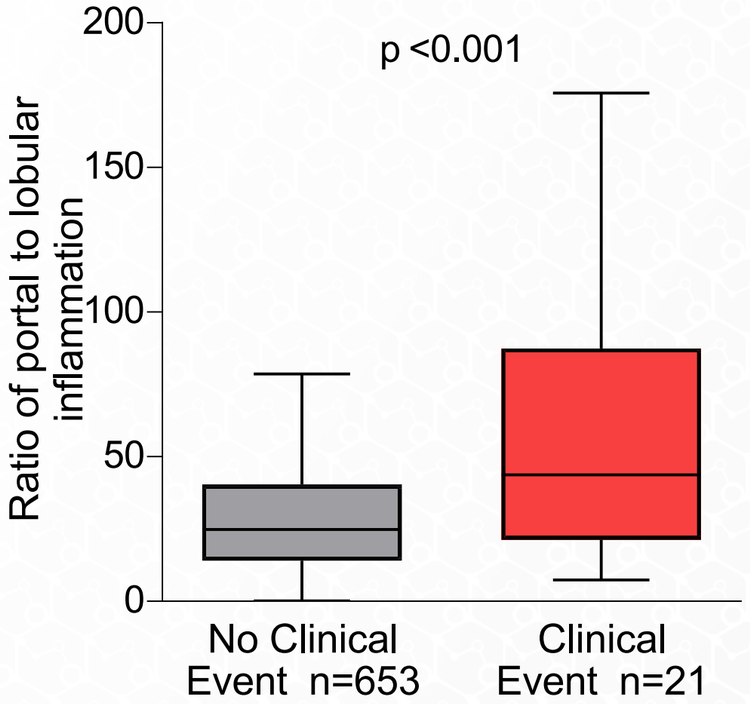
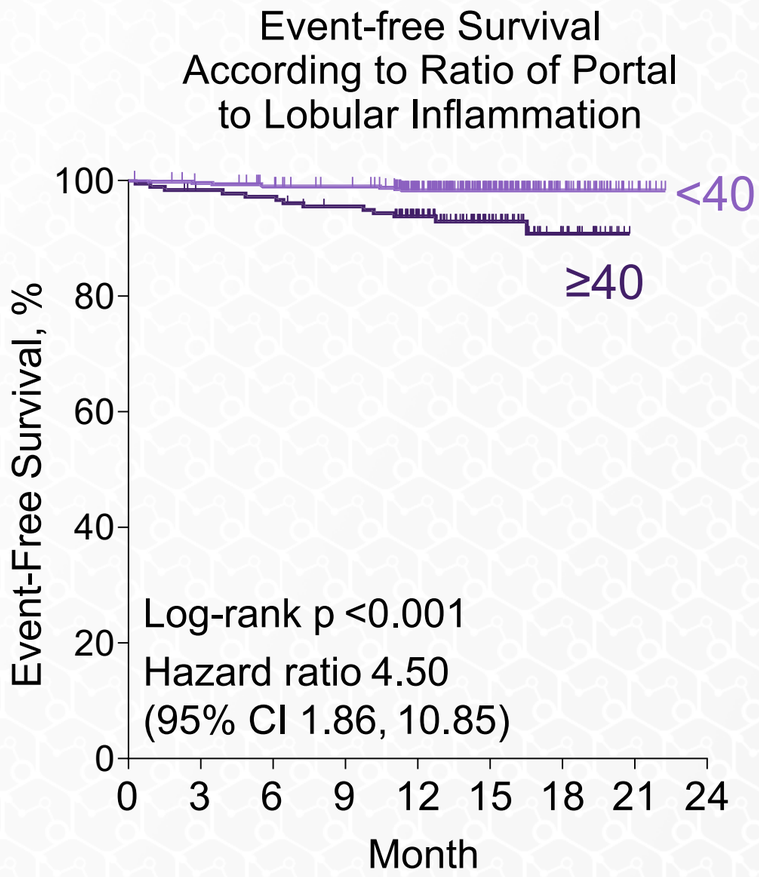
Pokkalla H, et al., Poster presentation #2497, EASL ILC 2020 (Selected for “Best of ILC Summary”)

# Ratio of portal/lobular inflammation is associated with increased risk of clinical disease progression in NASH




Boxes depict median (IQR); whiskers based on Tukey method.
Richardson MM, et al. Gastroenterology 2007;133:80-90; Gadd VI, et al. Hepatology 2014;59:1393-1405; Brunt EM, et al. Hepatology 2019;70:522-31.

Pokkalla H, et al., Oral presentation #187, AASLD 2019

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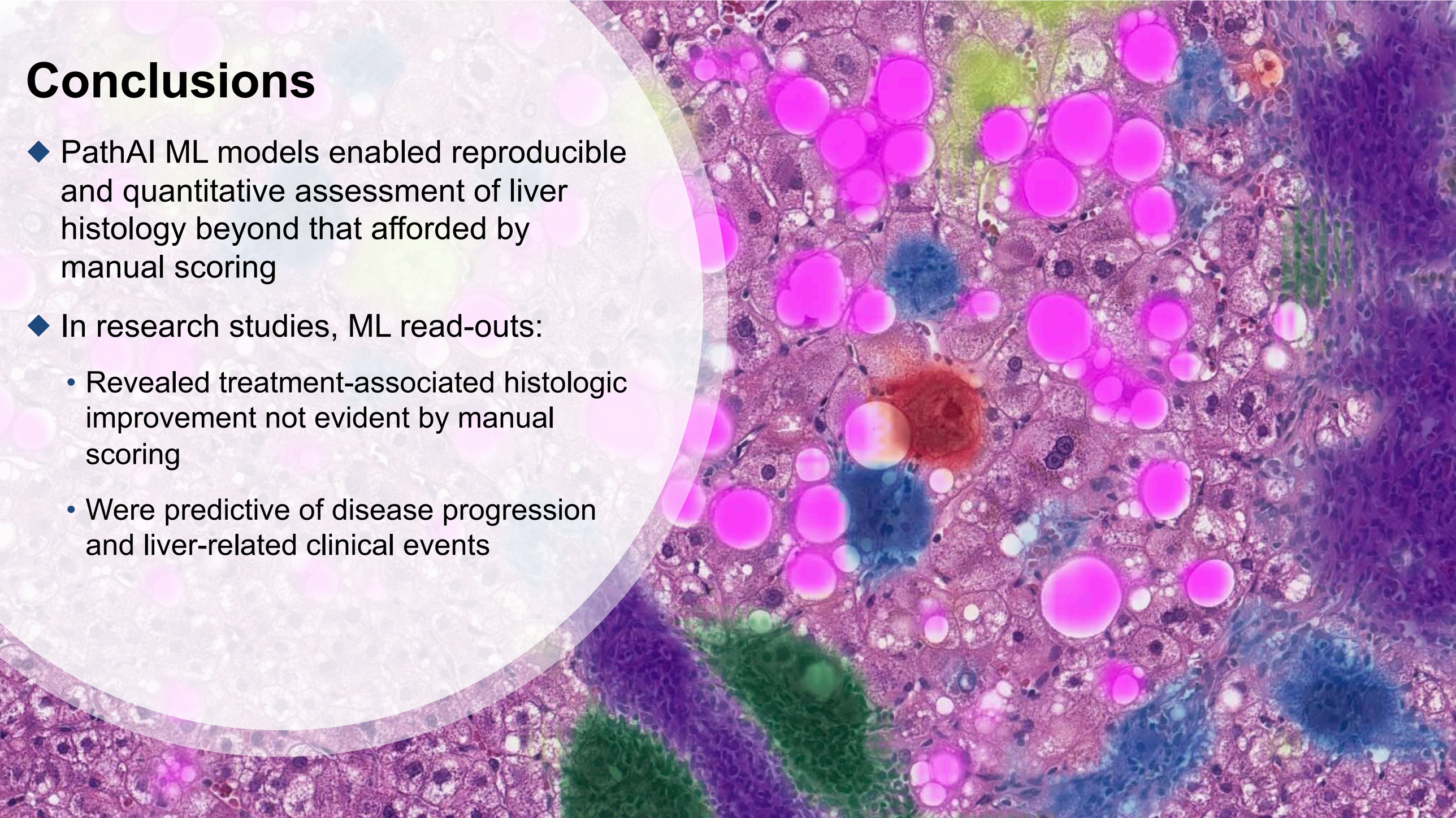
# Conclusions

- PathAI ML models enabled reproducible and quantitative assessment of liver histology beyond that afforded by manual scoring
- In research studies, ML read-outs:
  - Revealed treatment-associated histologic improvement not evident by manual scoring
  - Were predictive of disease progression and liver-related clinical events



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# Thank You

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