AI-powered computational pathology for liver diseases

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

<table>
<thead>
<tr>
<th>Ishak Grade</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild (focal, few portal areas)</td>
<td>1</td>
</tr>
<tr>
<td>Mild/moderate (focal, most portal areas)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate (continuous around &lt; 50% of tracts or septa)</td>
<td>3</td>
</tr>
<tr>
<td>Severe (continuous around &gt; 50% of tracts or septa)</td>
<td>4</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Steatosis (%)</th>
<th>Lobular inflammation</th>
<th>Ballooning</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5</td>
<td>No foci</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>5–33</td>
<td>&lt;2 foci per 200× field</td>
<td>Few ballooning cells</td>
</tr>
<tr>
<td>2</td>
<td>&gt;33–66</td>
<td>2–4 foci per 200× field</td>
<td>Many cells/prominent ballooning</td>
</tr>
<tr>
<td>3</td>
<td>&gt;66</td>
<td>&gt;4 foci per 200× field</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A not applicable

1 David E. Kleiner et al. “Design and validation of histological scoring system for nonalcoholic fatty liver disease.” *Hepatology* 2005
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)

<table>
<thead>
<tr>
<th>Number of Biopsies</th>
<th>Steatosis</th>
<th>Lobular Inflammation</th>
<th>Ballooning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kappa</td>
<td>Cases with Discordance</td>
<td>Kappa</td>
</tr>
<tr>
<td>166</td>
<td>0.69</td>
<td>22%</td>
<td>0.38</td>
</tr>
<tr>
<td>162</td>
<td>0.50</td>
<td>29%</td>
<td>0.29</td>
</tr>
<tr>
<td>149</td>
<td>0.59</td>
<td>26%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

\(^1\) Beth A. Davison, et al. “Liver biopsies in nonalcoholic steatohepatitis (NASH) clinical trials.” *Hepatology* 2020
\(^3\) PathAI Analysis: AASLD 2019, median interval between biopsy re-reads, 16 weeks (range 9, 20).
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)
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)
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.

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

1: Pathologist reads followed clinical trial protocol
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
ML fibrosis score quantifies heterogeneity and correlates with expert pathologist assessment\(^1\)

<table>
<thead>
<tr>
<th>Manual Ishak Stage 6</th>
<th>ML Ishak Score 4.54</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 0.8%</td>
<td></td>
</tr>
<tr>
<td>F2 3%</td>
<td></td>
</tr>
<tr>
<td>F3 14%</td>
<td></td>
</tr>
<tr>
<td>F4 18%</td>
<td></td>
</tr>
<tr>
<td>F5 52%</td>
<td></td>
</tr>
<tr>
<td>F6 12%</td>
<td></td>
</tr>
</tbody>
</table>

Slide-level ML Ishak Score

- \(\rho = 0.60\)
- \(p < 0.001\)
- \(n = 456\)

Pathologist reads followed clinical trial protocol

Juyal D, et al., Poster presentation LBP31, EASL ILC 2020 (Late-breaker presentation)
In subjects whose cirrhosis regressed at year 5, fibrosis improvement by year 1 is evident only on ML Ishak score.

- Baseline to Year 1: $p=0.146$; Year 1 to Year 5: $p=0.039$; Baseline to Year 5: $p=0.120$

- Ishak Stage by Central Reader:
  - Baseline to Year 1: $p=0.156$; Year 1 to Year 5: $p=0.235$; Baseline to Year 5: $p<0.001$

- 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.

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])

113/755 of subjects had progression to cirrhosis

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

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

Event-free Survival According to Ratio of Portal to Lobular Inflammation

- <40
- ≥40

(event-free survival graph with log-rank p <0.001, hazard ratio 4.50 (95% CI 1.86, 10.85))

Boxes depict median (IQR); whiskers based on Tukey method.

Pokkalla H, et al., Oral presentation #187, AASLD 2019
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
We extend our thanks to the patients, their families, and all participating investigators.

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Thank You

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