Liver Forum Histology Series – 5 Webinars

- **Session 1**: Increasing the Reliability of Histology in NASH Clinical Trials 9/1/20
- **Session 2**:Innovations: Utilizing Digital Methods and New Technology 10/27/20
- **Session 3**:The Role of Liver Biopsy as Part of Causality Assessment for Suspected DILI in NASH Clinical Trials
  - **Part 1**: 1/22/21 Lessons Learned from seladelpar
  - **Part 2**: 7/20/21 Improving The Reliability of NASH Clinical Trial Outcomes: What Is the Optimal Number of Hepatopathologists? Digital Slides, Pros and Cons?
  - **Part 3**: 1/28/22 Causality Assessment and the Role of Liver Biopsy as Part of the Evaluation of Suspected DILI in NASH Clinical Trials

Histology Working Group Members

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- **Melissa Palmer Chair**
- **Raj Vuppalanchi Co-Chair**

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- **Stephen Harrison**
- **Massimo Siciliano**
- **Jim Lewis**

Industry

- **Charles McWherter**
- **Arie Regev**

Forum

- **Veronica Miller**

3 -4 Manuscripts
Manuscript Number 1 to be submitted in a few weeks

Manuscript 1: Liver Biopsy as Part of DILI Assessment in NASH Clinical Trials

- No guidelines exist
- Benefits and risks of liver biopsy
  - Histology changed causality adjudication in 68% of cases -increased likelihood of DILI in 48%; a decrease in 20% [1]
  - Prognosis – eosinophils or ductular reactions
  - No pathognomonic feature of DILI
- Differentiating DILI from natural history of NASH
- When there is a new onset of elevated liver biochemical tests during a clinical trial is and when a liver biopsy helpful?
- Phase of trial and liver biopsy?
- Autoimmunity and histology
- COVID-19 / covid vaccine and histology

1. DILI 2022 JHEP

Manuscript 2:
Best Practices to Implement When Abnormal Histologic Findings are Discovered on Liver Biopsy

- Cymabay/Seladelpar – lessons learned
  - Seladelpar and the histologic findings of liver biopsy in a larger context.
- Best practices when finding atypical histologic lesions on EOT liver biopsy?
- There is a dearth of literature available on atypical histologic findings such as interface hepatitis in
- NASH this paper will address that gap and encourage more publications regarding these types of findings.
- The paper could be improved by including data from abnormal findings in other clinical trials – Vierling study[1]

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DHINGRA …..VIERLINGe al Prevalence and clinical significance of portal inflammation, portal plasma cells, interface hepatitis and biliary injury in liver biopsies from patients with NASH anatomic pathology2021

Manuscript #3: Best Practices for Increasing the Reliability of Histologic Outcomes

- The field is moving towards digital slides but there are currently no best practices and importantly, digital slides need to be validated - - There is a diferenent regulatory division of the FDA that does this
- There are two separate issues with digital slides.
  - The first issue is digital vs glass slides.
  - The second issue is digital slides and artificial intelligence learning. A manuscript focused on digital slides may also need to address machine learning and computer algorithm-based readouts.
  - Pathologists need to review the algorithms to verify that they are able to appropriately identify the data on the slides. This type of discussion would need to include a place such as PathAI.
- For some issues, such as the required number of hepatopathologists needed for successful assessment of NASH, there may not be enough evidence to make a determination at this time.
- What is the optimal number of specimen slices need to be reviewed?
- Best Practices for writing a standardized liver pathology manual