Case Definitions For Use As Reference Standards

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NASH Biomarkers Workshop
Disclosure

• None
**Background**

- **Nonalcoholic Fatty Liver (NAFL)**
  - Low Risk of Fibrosis Progression
  - Increase risk of metabolic conditions
  - May progress to NASH, fibrosis

- **NAFLD**
  - High Prevalence
  - Diagnostic challenges

- **NASH**
  - Fibrosis progression
  - Cirrhosis
  - Increase mortality
  - ?HCC

- **NASH CIRRHOSIS**
  - Fastest growing indication for LT
  - HCC
  - Risk of Decompensation
  - High liver related mortality

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**No Approved Therapy for NAFLD and its Subtypes**
Regulatory Limitations to NAFLD Research

- Case definitions
- Methods for identification of subjects
- Assessment of outcomes
BACKGROUND – LIVER FORUM

Regulatory Agencies
- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)

LIVER FORUM

- AASLD
- EASL
- Academic Investigators

Academia

Industry
- Diagnostics
- Therapeutics
Case definitions that meet regulatory standards
Process of Developing Case Definitions

1. NAFL with any fibrosis
2. Indeterminate NASH with any fibrosis
3. Definite NASH without fibrosis
4. NASH with early fibrosis
5. NASH with bridging fibrosis
6. NASH cirrhosis - compensated
7. NASH cirrhosis - decompensated
Characterization of Each Disease State

Clinical Phenotype

- Objective
- Quantifiable
- Sensitive to change
- Logistically feasible to operationalize
- Link to clinical outcomes

Histology

Non-invasive assessment
Minimal Diagnostic Criteria for NAFLD

• Documentation of fatty liver

• Not related to harmful amounts of alcohol
  – More than 20g/day in female
  – More than 30g/day for males
Case Definitions Working Group
Recommendations

1. NAFL with any fibrosis
2. Indeterminate NASH with any fibrosis
3. Definite NASH without fibrosis
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Case Definitions Working Group Recommendations

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1. CLINICAL PHENOTYPE
   • Co-morbidities

2. HISTOLOGY
   • NASH-CRN
   • SAF Schema
   • Goodman

3. NON-INVASIVE
   • Radiological
   • Serum based
   • Models
# Histological Phenotypes of Non-NASH

<table>
<thead>
<tr>
<th></th>
<th>Steatosis</th>
<th>Lobular Inflammation</th>
<th>Cytological ballooning</th>
<th>Fibrosis</th>
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<tbody>
<tr>
<td>Fatty Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Indeterminate NASH</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Steatofibrosis</td>
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Comparison of Histological Schema for Grading Steatosis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NASH-CRN</th>
<th>SAF</th>
<th>GOODMAN</th>
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<tbody>
<tr>
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<tr>
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<tr>
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<td>Yes</td>
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<tr>
<td>Used in Clinical Trials</td>
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# Accuracy of Non-Invasive Biomarkers in Detecting and Quantifying Steatosis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Models</th>
<th>CK-18</th>
<th>US</th>
<th>CAP</th>
<th>MRI/MRS</th>
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<tbody>
<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Subjective</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Inter-Observer Reliability</td>
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<td>N/A</td>
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<tr>
<td>Used in Clinical Trials</td>
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Summary Recommendations for Non-NASH

• Histology is the gold standard
• Distinguished from NASH – none to minimal activity
• Routine clinical laboratory tests are insufficient for diagnosis of non-NASH
• MRI-PDFF is accurate & sensitive for detection and quantification of hepatic steatosis
• Natural history of non-NASH subtypes not well defined
Histological Phenotypes of NASH

• Definite NASH with no fibrosis
• NASH with early fibrosis
  – Fibrosis stage 1 and 2
• NASH with bridging fibrosis
Comparison of the Histological Schema for Diagnosing NASH

<table>
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<td>Both</td>
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<tr>
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Accuracy of Non-Invasive Biomarkers in Detecting NASH

• No non-invasive tools to diagnose definite NASH – Biopsy is required for diagnosis & disease staging
• Non-invasive models (i.e. FIB-4) can detect advance fibrosis but less accurate for separating individual stages
• Cross sectional imaging may provide evidence of cirrhosis but a negative study does not exclude it
• MRE and VCTE can detect cirrhosis with high accuracy but studies limited by sample size
Summary Recommendations for NASH

• For phase 2b and 3 trials, histology required for diagnosis
  – NASH and fibrosis stage should be defined using the NASH CRN criteria

• For phase 1 and 2A proof of concept trials, following criteria can be used:
  – 2 more more features of metabolic syndrome
  – Evidence of steatosis by MR-PDFF or CAP
  – Evidence of >F0 fibrosis via MRE or VCTE
NASH Cirrhosis - Diagnosis

• Histology is the gold standard
• Can be suspected based on clinical data
• Limited data with non-invasive serum models
• Cross-sectional imaging can not rule out cirrhosis
• MRE and VCTE may be used to identify cirrhosis
• Evidence of portal hypertension (EGD, imaging, high SAAG)
• HVPG>10 is diagnostic of clinically significant portal hypertension
Identification of NASH as Etiology of Cirrhosis

<table>
<thead>
<tr>
<th>Modalities</th>
<th>Diagnostic Criteria</th>
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<tr>
<td><strong>Histological</strong></td>
<td>• NASH along with cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Steatosis with cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Indeterminate NASH with cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Historical biopsy with NAFLD and current biopsy with cirrhosis</td>
</tr>
<tr>
<td><strong>Clinical Criteria</strong></td>
<td>• Clinically apparent cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Prior history of NAFLD</td>
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<tr>
<td></td>
<td>• History of features of metabolic syndrome plus cirrhosis</td>
</tr>
<tr>
<td><strong>Biomarker Criteria</strong></td>
<td>• HVGP &gt; 6 mmHg</td>
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<td>• Any imaging modality showing a nodular liver contour</td>
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<td></td>
<td>• MRE with cirrhosis</td>
</tr>
<tr>
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<td>• VCTE with cirrhosis</td>
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<td></td>
<td>• EGD showing varices in the absence of splenic vein thrombosis</td>
</tr>
</tbody>
</table>
Summary Points

• Three broad subtypes:
  – Non-NASH, NASH, NASH cirrhosis
• Histology remains the gold standard
• Non-invasive tests may be reliable for quantification of steatosis and fibrosis
• Key limitations include natural history of NAFLD subtypes and non-invasive assessment
Acknowledgement

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