

Berkeley

 School of  
Public Health

 **EASL**  
European Association  
for the Study of the Liver



**Forum for  
Collaborative HIV Research**

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# **Session III: Disease Definition WG Update**

# **Disease Definitions Working Group**

**Presentation of WG Output: Manuscript**

**Current Focus: NASH Resolution and Progression**



# WG Output #1: Manuscript

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Facilitating collaborative research in drug  
development and health policy

## **An evaluation of case definitions for inclusion and analysis of endpoints in clinical trials for non-alcoholic steatohepatitis through the lens of regulatory science**

- Siddiqui, Harrison, Abdelmalek, Anstee, Bedossa, Castera, Dimick-Santos, Friedman, Kleiner, Megnien, Neuschander-Tetri, Schabel, Miller, Sanyal *on behalf of WG members*
- *WG members: Abdelmalek, Anstee, Baldyga, Banerjee, Bangma, Bashir, Baxter, Bedossa, Berner Hansen, Boulos, Brett-Smith, Burgess, Burkey, Castera, Chakravarthy, Coombs, Cooreman, Costa, Dimick-Santos, Everson, Francque, Friedman, Gannedahl, Hambleton, **Harrison**, Hughes, Hum, Imperial, Jenkins, Kelly, Kendrick, Klein, Lavine, Lumsden, **Megnien**, Mehta, Miller, Naumov, Palmer, Pan, Peck, Peres, Ratziu, Regev, Sanyal, Schabel, Schelch, Schuppan, Shapiro, Siddiqui, St. Pierre, Neuschander-Tetri, Ukumadu, Voros, Vos, Williams, Wright.*



# WG Phase 2: In progress

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## Outcomes:

- Definition of NASH Resolution
- Definition of “no worsening” and “worsening” of NASH
- Fellow: Amanda Cheung, MD
  - University of St. Louis



## Phase 2 Working Group Members

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Manal Abdelmalek, Quentin Anstee, Bill Baldyga, Rajarshi Banerjee, Sander Bangma, Mustafa Bashir, Melanie Baster, Pierre Bedossa, Mark Berner Hansen, Sherif Boulos, Gary Burgess, Bryan Burkey, Laurent Castera, Manu Chakravarthy, Edgar Charles, Amanda Cheung, Rose Christian, Anthony Coombs, Lara Dimick-Santos, Judith Ertle, Gregory Everson, Sven Francque, Scott Friedman, Goran Gannedahl, Michael Hambleton, **Stephen Harrison**, Dean Hum, Joanne Imperial, Catherine Kelly, Stuart Kendrick, David Klein, Joel Lavine, Robert Lumsden, **Sophie Megnien**, Ruby Mehta, Veronica Miller, Nikolai Naoumov, Melissa Palmer, Wenjie Pang, Markus Peck, Dan Peres, Meg Powell, Vlad Ratziu, Arie Regev, Glenn Rosen, Arun Sanyal, Elmer Schabel, Corinna Schoelch, Detlef Schuppan, Jeffrey Schwimmer, David Shapiro, Reshma Shringarpure, Shadab Siddiqui, Tim St. Pierre, Brent Tetri, Chinweike Ukomadu, Viktor Voros, Miriam Vos, Liangsu Wang, Jessica Williams, Vincent Wong, Terry Wright



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# NASH Resolution, Worsening and No-Worsening

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- Fit-for-Purpose: Need definitions that are precise, quantifiable, and reproducible for clinical trials and acceptable by regulatory agencies



# NASH Resolution

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**WG Consensus:** *Resolution of NASH is defined as an expert liver pathologist assessing the overall pattern of injury, reporting the disappearance of hepatocyte ballooning (grade 0) and the disappearance of persistence of minimal lobular inflammation (grade 0 or 1)*

Distinct from resolution of NAFLD, which requires disappearance of steatosis



# Resolution: Gaps, Needs, Questions

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- Standardize how ballooning is assessed
  - Increase inter-pathologist reproducibility
  - Important for cross-trial comparison
- Include portal inflammation?
  - Not ready for “prime time” in adults
  - More important in pediatrics
  - Recommend: all trials collect data on portal inflammation to inform the field moving forward
- Define Resolution in pediatrics (based on different drivers of disease severity)
- Continue efforts to correlate liver biopsies with other biomarkers/surrogate markers
- WG needs to continue to develop a definition of NASH resolution that correlates with new biomarkers/surrogate endpoints as data becomes available





# Worsening and No-Worsening of NASH

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- “Worsening” and “No-Worsening” are two separate definitions with different metrics
- No-Worsening of NASH in the context of endpoint of “Improvement of fibrosis without worsening of NASH”



# No-Worsening of NASH

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Starting definition: *No worsening of either ballooning or inflammation by 1 point*

Discussion points:

- Relative contribution of ballooning and inflammation to progression of disease
  - Does a 1-point increase in inflammation carry the same weight as a 1-point increase in ballooning?
  - Different relative scales
- Need a data driven approach to tease out relative contribution
- How do we document “no worsening” (and “worsening”) in patients already at the top of gradient?