AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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European Association for the Study of the Liver

Forum for Collaborative HIV Research

DISEASE DEFINITIONS WORKING GROUP PROGRESS REPORT

NOVEMBER 12, 2015

Working Group

facilitating collaborative research
drug development & health policy

- Sophie Megnien, Stephen Harrison
- Subgroup Leads:
  - Manal Abdelmalek, Stephen Harrison, Quentin Anstee, Vlad Ratziu,Laurent Castera, Scott Friedman, Brent Tetri
- WG members:
  - Bill Baldyga, Rajarshi Banerjee, Sander Banga, Melanie Baxter, Mark Berner-Hansen, Helena Brett-Smith, Gary Burgess, Brian Burkey, Manu Chakravarthy, Michael Cooreman, Marcello Costa, Greg Everson, Goran Gannedahl, Michael Hambleton, Dean Hum, Joanne Iperial, Stuart Kentrick, Ruby Mehta, Melissa Palmer, Markus Peck, Dan Peres, Arie Regev, Arun Sanyal, David Shapiro, Chinwe Ukomadu, Teresa Wright
- Staff/interns: Myrna Cozen, Lauren Smith

Joint Leadership

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EASL European Association for the Study of the Liver
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Overall Goals & Objectives

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- Facilitate drug and diagnostic development for NASH
  - Derive consensus on disease definitions that are better able to distinguish patient populations for the purpose of clinical trials for regulatory approval

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Mechanisms to Achieve Goals

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- Develop clarity on disease definition
  - Move from "what it is not" to "what it is"
  - Apply histological, clinical and laboratory criteria
  - Provide a platform to plug-in new diagnostics
- Develop benchmark criteria for
  - Natural history studies
  - Assessing the efficacy of trial drugs under review for regulatory approval.

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Mandate to Working Group

- Evidence based review of definitions
- Deconstruct and Reconstruct!
- Don’t be shy about it

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PROCESS

- Seven disease stages proposed as a starting point for discussion:

1. Isolated Steatosis
2. Indeterminate NASH
3. Definite NASH without Fibrosis
4. NASH with early fibrosis
5. NASH with advanced fibrosis
6. NASH with compensated cirrhosis
7. NASH with decompensated cirrhosis

Process, cont'd

- Each stage to be defined (described) by:
  - Histologic Phenotype
  - Disease Activity
  - Fibrosis Stage
  - Clinical Phenotype
  - Non-invasive Diagnostics
    - To the extent that data is available

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Subgroups

- Working Group members assigned to one of seven sub-groups
  - Work towards a consensus definition
    - Histology, disease activity, fibrosis stage, clinical phenotype, non-invasive dx
  - Identify research gaps
  - Recommend key references

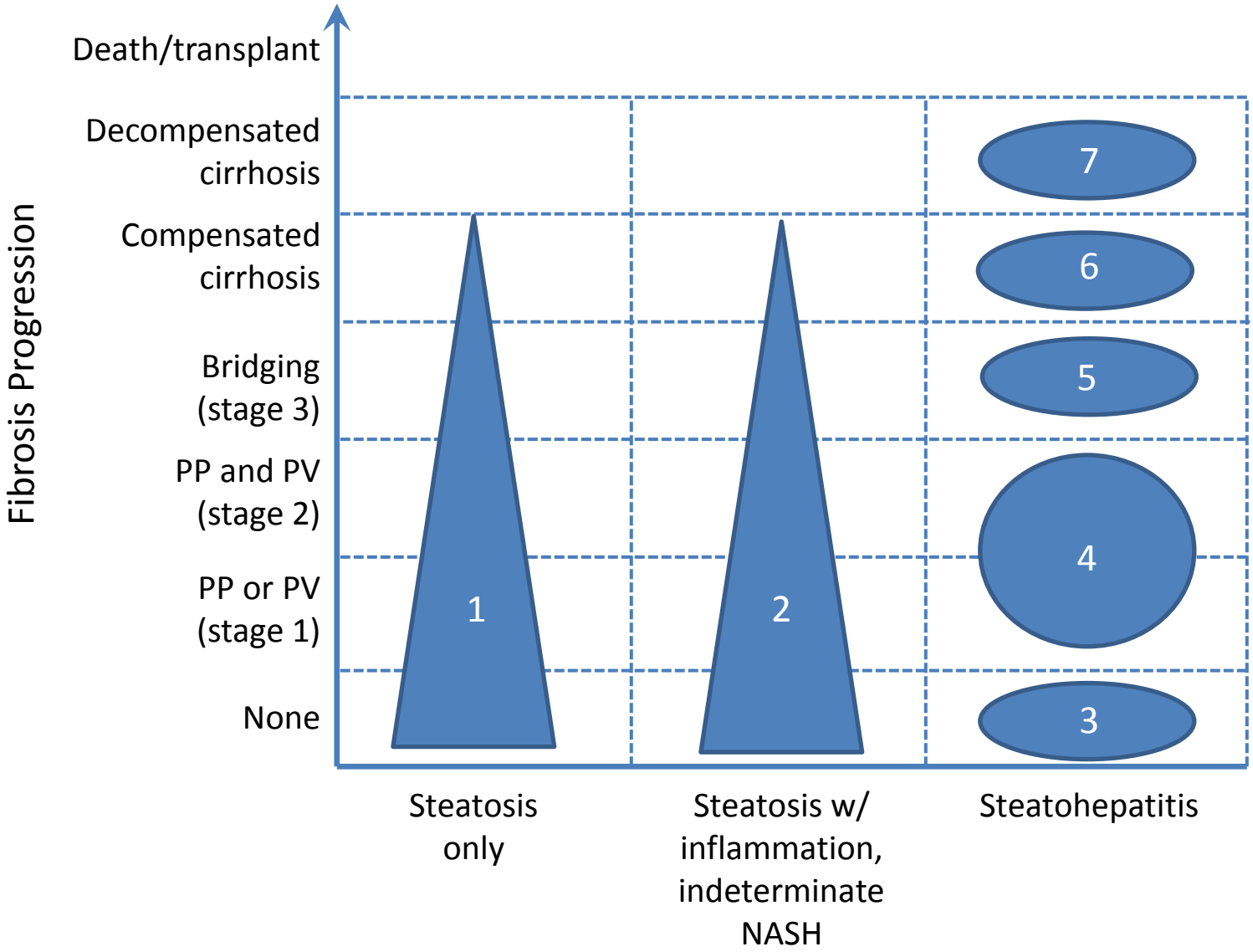
Defining characteristics of each disease category (Task 1)

- Subgroup members submitted their recommendations in writing and during conference calls
- Exhaustive process allowed for overlap of categorical definitions and captured the areas that require further clarification
- Preliminary results have been collated, edited and assembled into the composite table that has been distributed

Was this the right approach?

We needed to start somewhere

“Stages” of NASH



Structured chaos worked!

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- We found
  - Adjacent stage characteristics that are not mutually exclusive
    - Some categorical definitions overlap
  - Fuzzy definitions
    - e.g., are minimum amounts of inflammation in the setting of steatosis considered simple steatosis or indeterminate NASH?
- We completed first round of iterative process
  - As more input is obtained, consensus will continue to evolve

Ongoing Input: Pathology and Pediatrics

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- Pathologists invited to provide input on composite document
  - Pierre Bedossa and David Kleiner
- Pediatric experts will provide expert input on pediatric specific disease definition issues
  - Miriam Vos, Joel Lavine, Saul Karpen, Rohit Kohli

Research Gaps (Task 2)

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- Large scale, long-term natural history studies needed
- Questions remain about etiology of NASH
  - Studies needed to clarify risk factors for metabolic disease associated NASH versus non-metabolic disease – associated NASH
  - What are acceptable levels of alcohol consumption to still be considered NASH?
- Studies needed to elucidate risk factors for disease progression:
  - Simple or isolated steatosis → NASH
  - Indeterminate NASH → Definite NASH with and without fibrosis
  - Bridging fibrosis → cirrhosis
  - Compensated cirrhosis → decompensated cirrhosis

More research gaps

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- Studies needed to determine whether biopsy still required for definitive diagnosis of both early and late stage NASH
  - Are imaging technologies sufficiently reliable that they can be used to replace biopsy?
  - Are specific biomarkers far enough along in development that they can be used in combination with imaging for definitive diagnosis?
  - Is there a staging system (e.g., NAS or SAF) that can be used with confidence in clinical diagnosis, natural history studies and as outcome measure for clinical trials?

Reference list (Task 3)

- Reference List has been compiled and distributed
- Will be expanded and used as basis for annotated bibliography

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Where do we go from here?

- How do we address the identified gaps?
- What are the LF network opportunities?
- How do we best integrate new data, new diagnostics, as it becomes available?

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