

# Case Definitions Working Group MS #3: Defining Improvement in NASH

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## WG accomplishments: MS #1 (Case Definitions)

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- Siddiqui MS, et al. Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science. *Hepatology*, in press, 2017.
  - Establish uniform definitions of disease states that meet regulatory standards
  - Allow comparison of trial results
  - Allow pooled analysis of studies in the future
  - Facilitate development of biomarkers of disease and response to therapy
  - (Not intended to guide clinical management)

# WG accomplishments: MS #1 (Case Definitions)

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- Goals of phenotype definitions
  - Objective
  - Quantifiable
  - Analyzable using quantitative approaches
  - Sensitive to change
  - Logistically feasible to operationalize in the context of multi-center clinical trials

# WG accomplishments: MS #1 (Case Definitions)

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- NAFLD phenotypes

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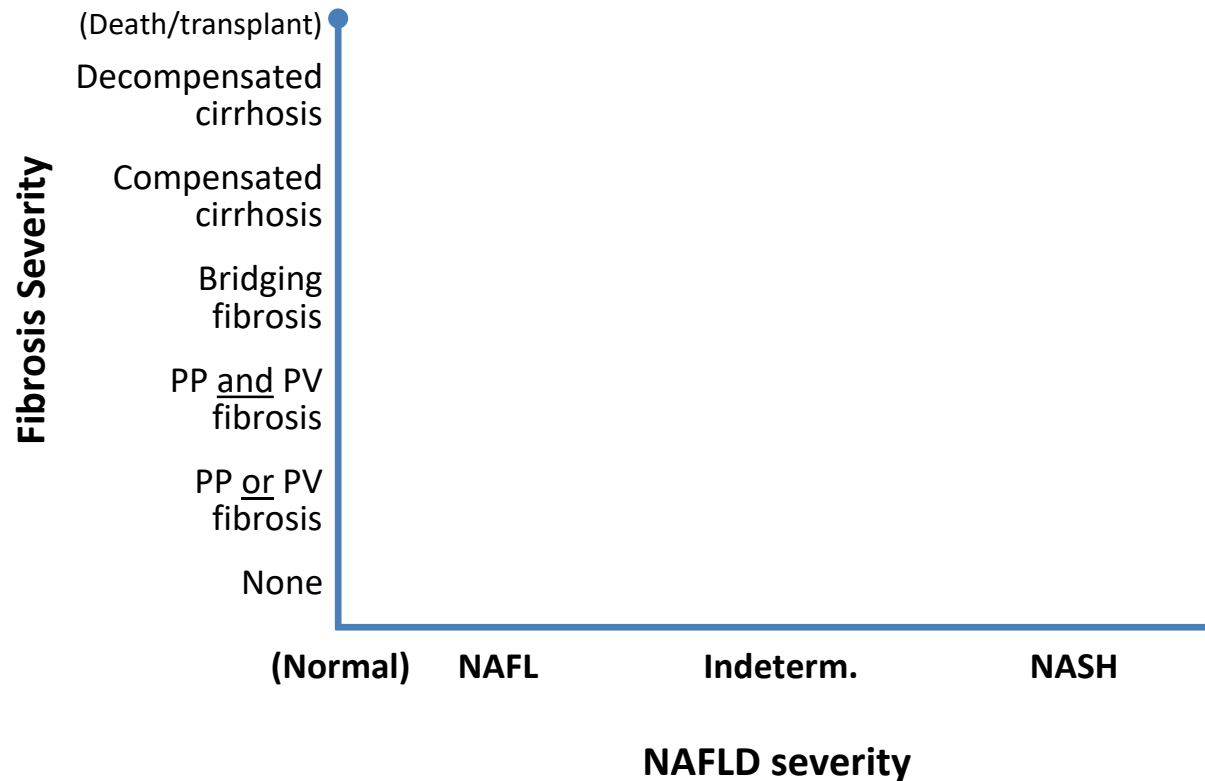
(Normal)    NAFL                    Indeterm.                    NASH

NAFLD severity

# WG accomplishments: MS #1 (Case Definitions)

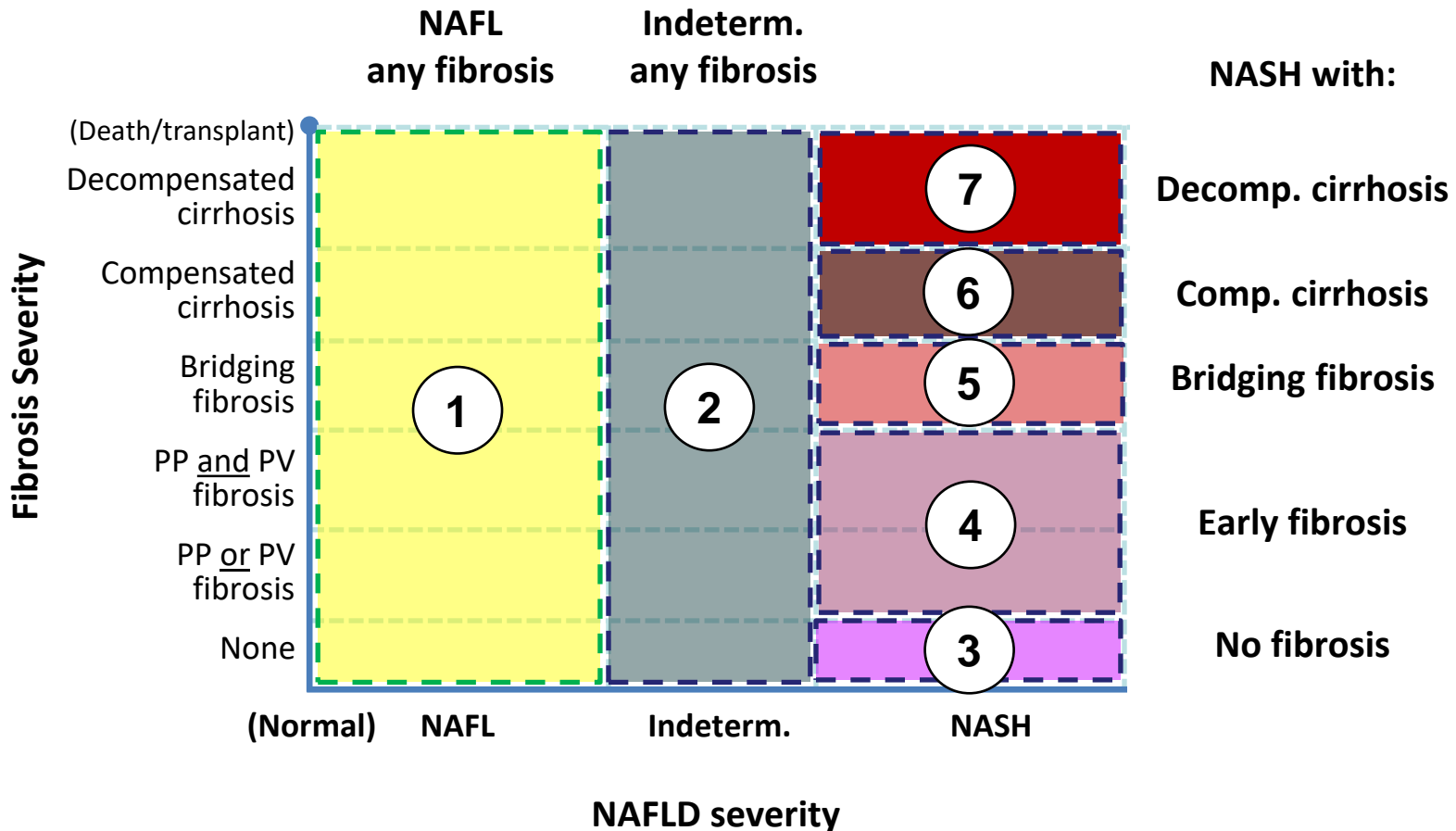
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- NAFLD phenotypes



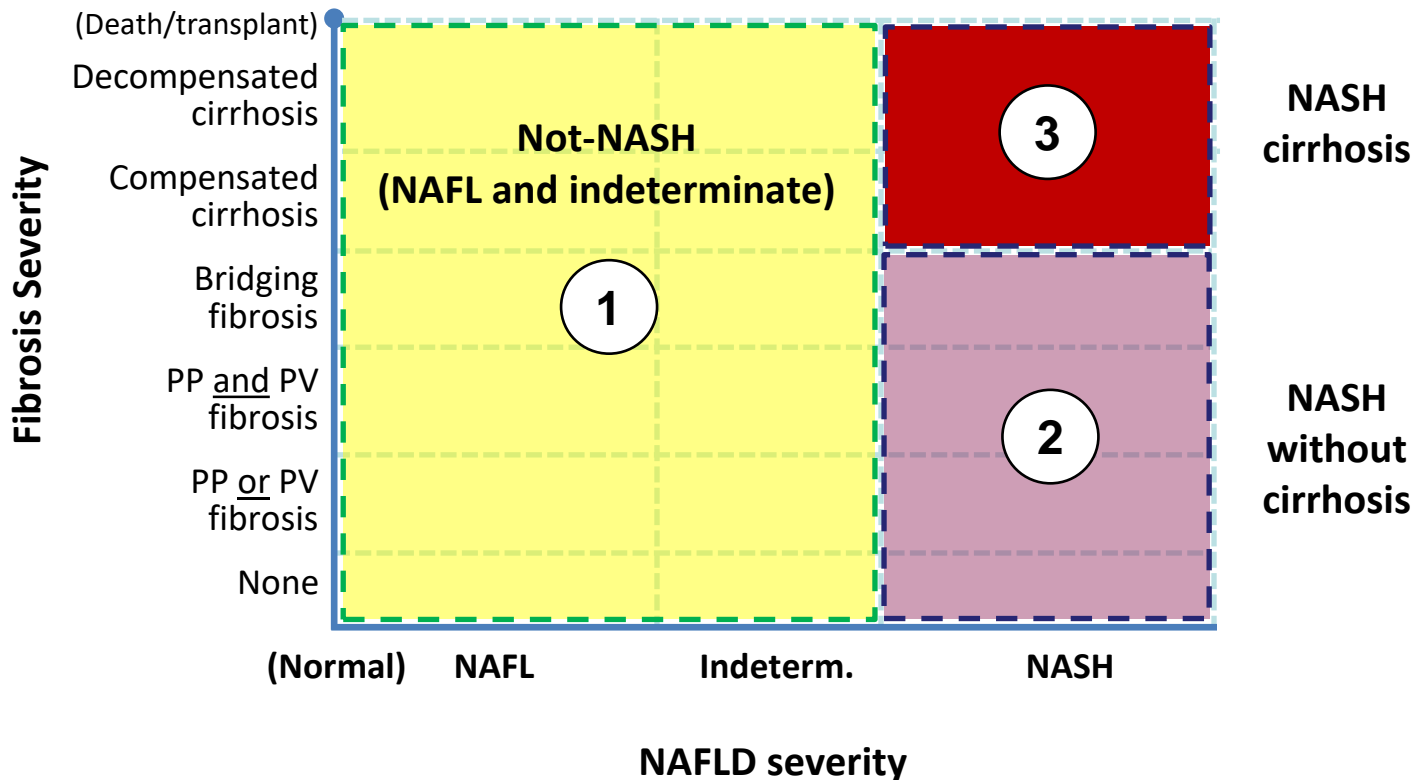
# WG accomplishments: MS #1 (Case Definitions)

- Seven NAFLD phenotypes considered



# WG accomplishments: MS #1 (Case Definitions)

- Three NAFLD phenotypes for clinical trials



# WG accomplishments: MS #2 (Baseline Parameters)

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- Patel YA, et al. Baseline parameters in clinical trials for nonalcoholic steatohepatitis: Recommendations from the Liver Forum. *Gastroenterology* (2017) 153: 621-625.
  - Metabolic Measures and Lab Data
  - Demographics and Genetics
  - Diet and Lifestyle
  - Concomitant meds
  - Histology
  - Comorbidities and Surgeries
  - Anthropometrics
  - Imaging and Non-invasive Measures
  - Health-Related Quality of Life



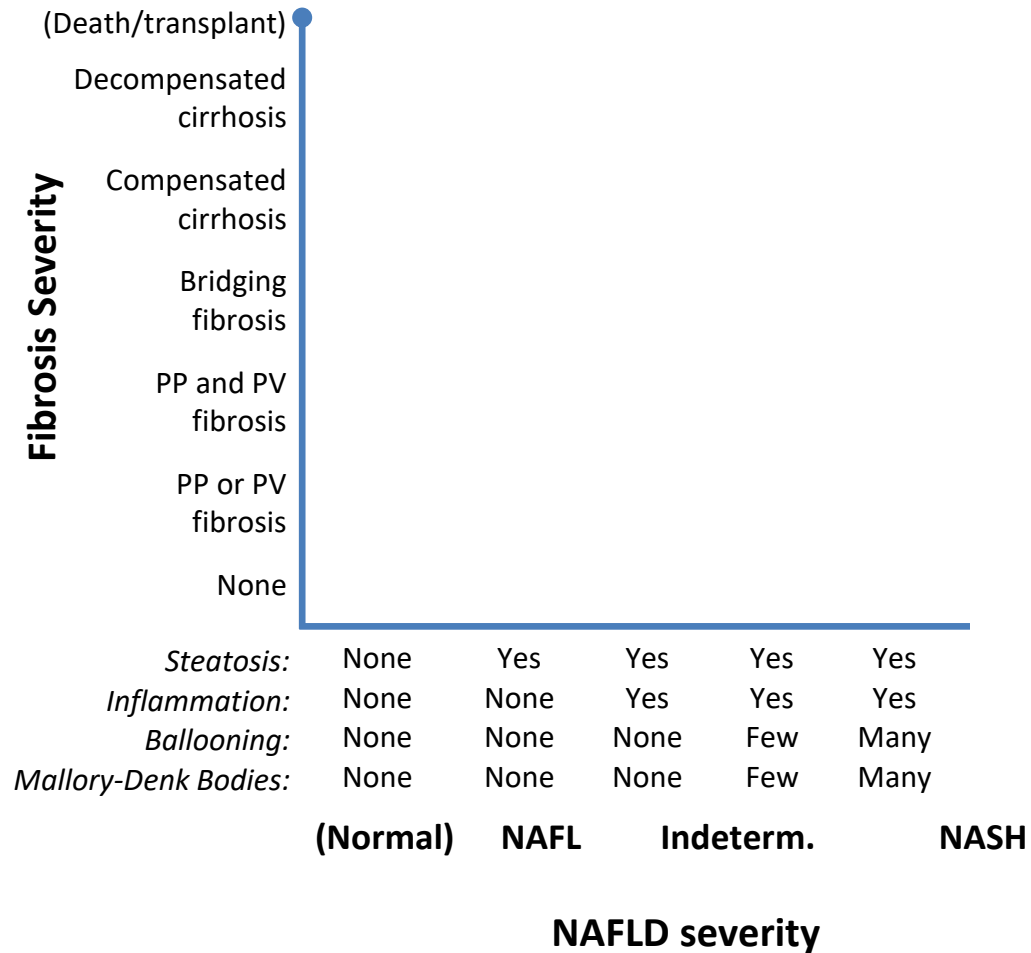
# MS #3: Measuring changes in clinical trials

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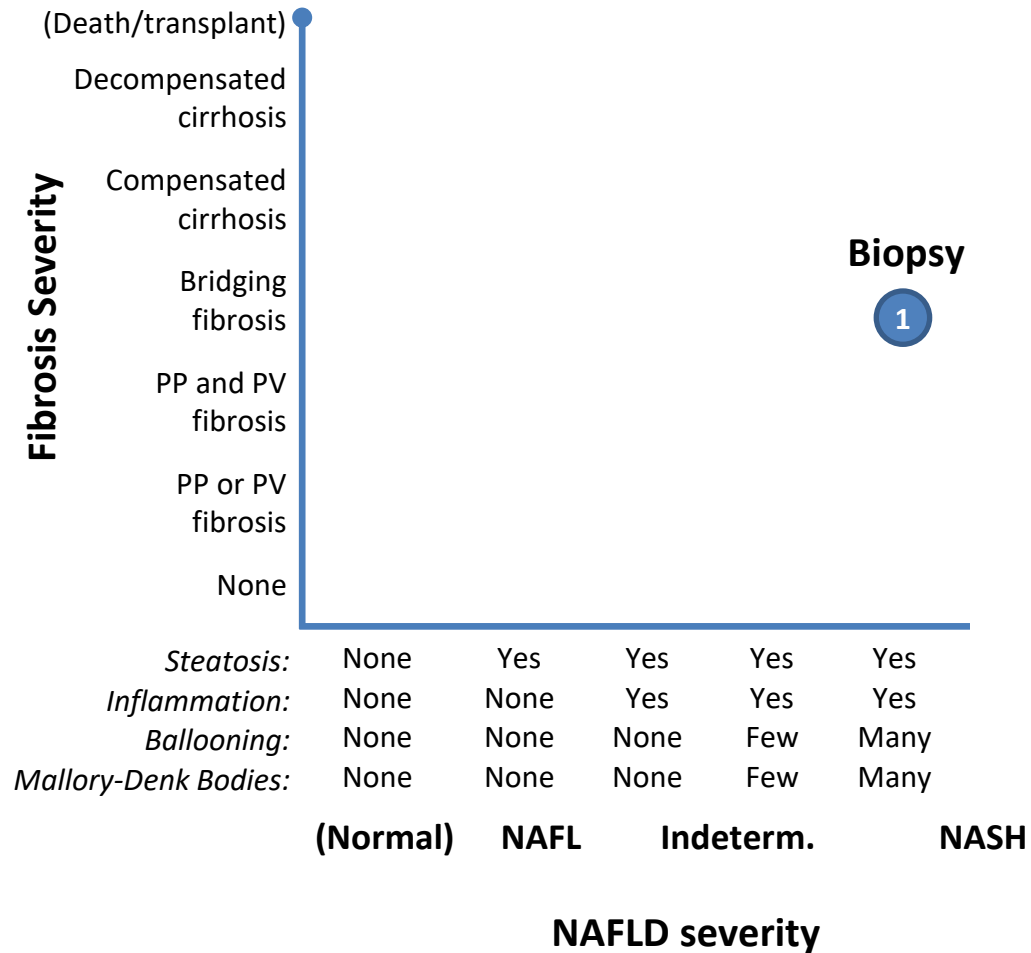
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- Brent A. Neuschwander-Tetri, MD
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- David Kleiner, MD, PhD
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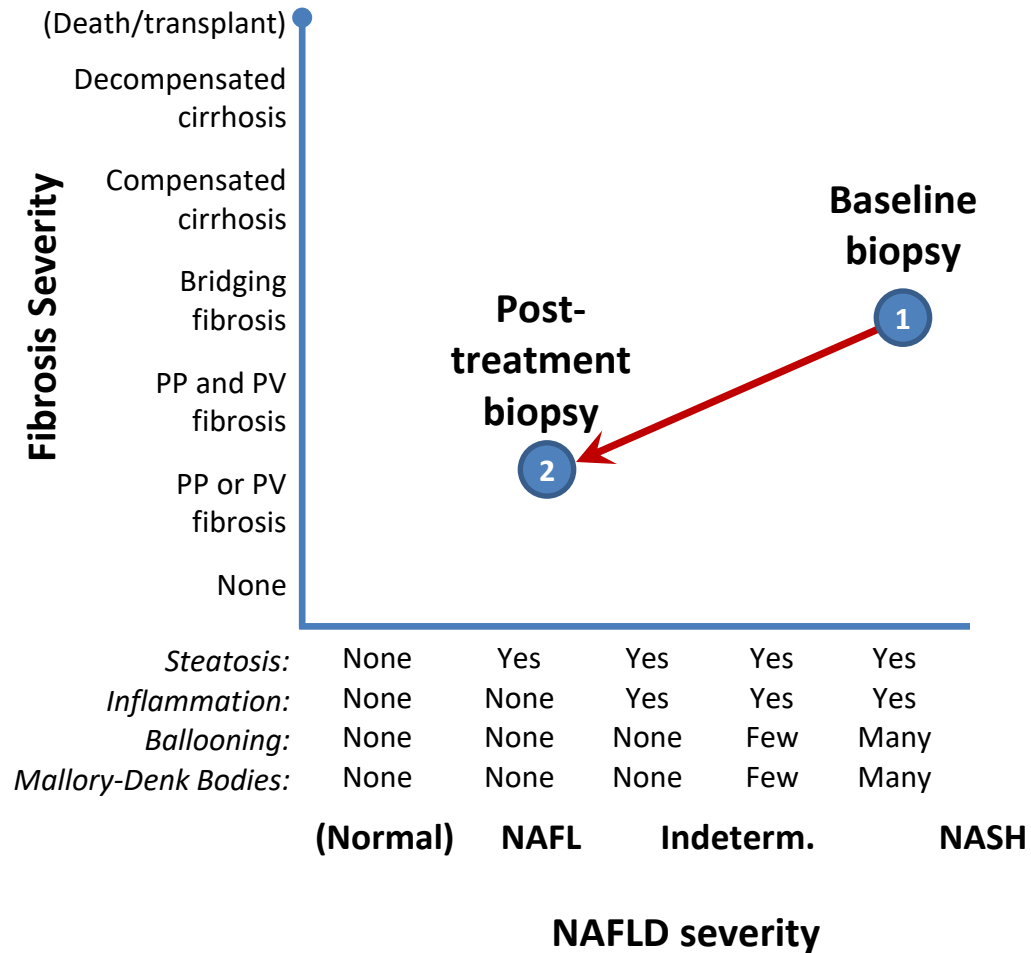
# MS #3: Measuring changes in clinical trials



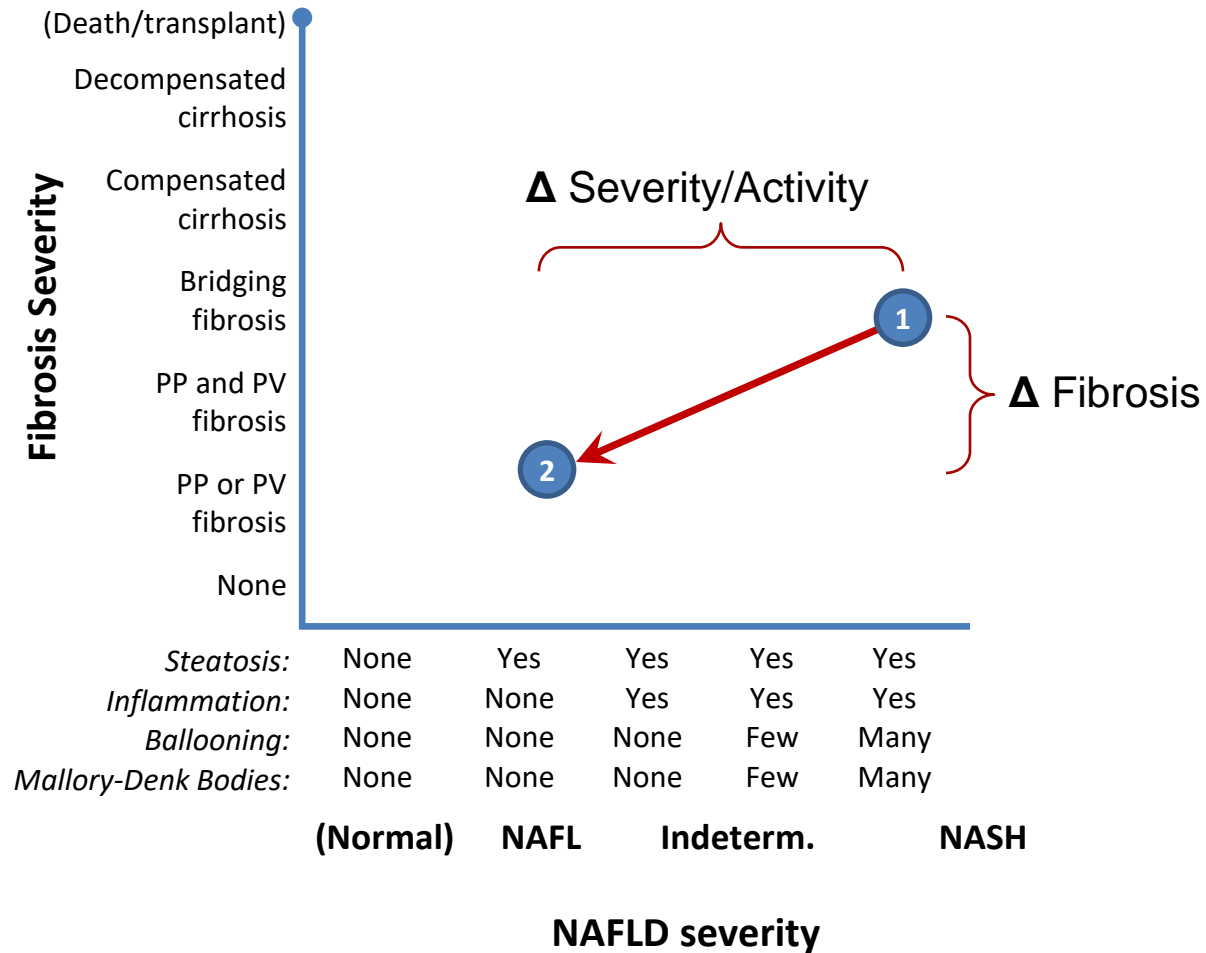
# MS #3: Measuring changes in clinical trials



# MS #3: Measuring changes in clinical trials



# MS #3: Measuring changes in clinical trials



**Healthy**



Metabolic stress  
(increased lipogenesis,  
increased deliver of fatty acids  
to the liver, decreased  
oxidative disposal of fatty  
acids, oxidative stress  
mitochondrial dysfunction, ER  
stress)



Hepatocellular  
injury  
Ballooning  
changes  
Inflammation  
Apoptosis  
("steatohepatitis")



Accumulation of  
excess  
extracellular  
matrix  
(Fibrosis)



Hard outcomes:  
Cirrhosis  
Death/Transplant  
Hepatocellular  
carcinoma

## Assessments:

### Blood tests:

- Lipidomic signature?
- Proteomic signature?
- Metabolomic signature?
- miRNA signature?
- Genetic signature?

### Blood tests:

- ALT, AST
- K18 fragments
- Panels/algorithms

### Liver biopsy

- Ballooning
- Inflammation
- Steatosis
- Other features

### Imaging

- Multiparametric MRI

### Blood tests:

- APRI, FIB4, other algorithms

### Biopsy:

- Fibrosis staging
- Collagen proportional area

### Imaging:

- MRE
- VCTE
- ARFI, SSI

### Clinical outcomes

**Patient reported outcomes (PRO's)**



**Healthy**



Metabolic stress  
(increased lipogenesis,  
increased deliver of fatty acids  
to the liver, decreased  
oxidative disposal of fatty  
acids, oxidative stress  
mitochondrial dysfunction, ER  
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### Blood tests:

- APRI, FIB4, other algorithms

### Biopsy:

- Fibrosis staging
- Collagen proportional area

### Imaging:

- MRE
- VCTE
- ARFI, SSI



**Clinical outcomes**  
**Patient reported outcomes (PRO's)**



**Healthy** →

Metabolic stress  
(increased lipogenesis, increased deliver of fatty acids to the liver, decreased oxidative disposal of fatty acids, oxidative stress, mitochondrial dysfunction, ER stress)



Hepatocellular injury  
Ballooning changes  
Inflammation  
Apoptosis  
("steatohepatitis")



Accumulation of excess extracellular matrix  
(Fibrosis)



Hard outcomes:  
Cirrhosis  
Death/Transplant  
Hepatocellular carcinoma

## Treatments:



### Weight loss

**Healthy eating habits**

**Regular exercise**

### Drugs

- Improve satiety
- Augment metabolic energy disposal
- Inhibit de novo lipogenesis
- Improve adipose insulin signaling



### Drugs

- Antioxidants
- Wound repair
- Anti-inflammatories
- Anti-apoptotics



### Drugs

- Antifibrotics



**Liver transplantation**