



International Workshop on **NASH Biomarkers 2017**

**A pathologist, a radiologist and a
hepatologist walked into a bar...**

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COI

- Consultant/Advisor:
 - Allergan
 - Boehringer-Ingelheim
 - Bristol Myers Squibb
 - Conatus
 - ConSynance
 - Enanta
 - Galmed
 - Janssen
 - Karos
 - MedImmune
 - Nimbus Therapeutics (Gilead)
 - Novartis
 - Pfizer
 - Receptos
 - Tobira (Allergan)
 - Zafgen

NASH: a typical case

- 57 year old white female with elevated LFTs
 - Clinic visit in 2008
 - No symptoms
 - History of obesity, type 2 diabetes, hypertension, hyperlipidemia, depression/anxiety
 - Meds: metformin, olmesartan/HCTZ, thyroxine, alprazolam, metoprolol, sertraline, clonidine, vitamins
 - SH: Occasional alcohol; nonsmoker
 - PE: BMI 41 kg/m²
 - Lab: ALT 77, AST 81, AP 179, T bili 0.3, gluc 199, plts 168, INR 1.1

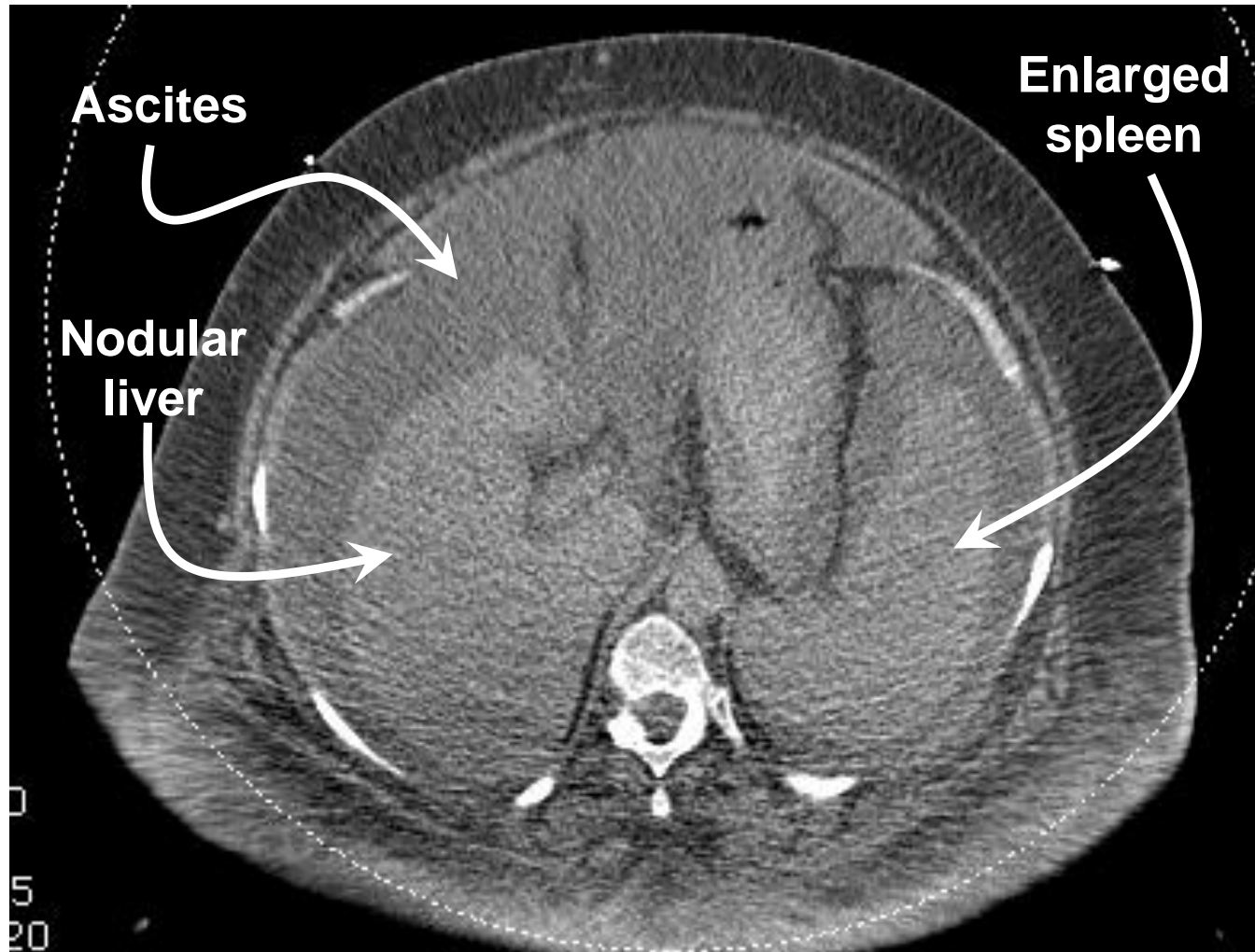
NASH: a typical case

- Liver biopsy: NASH, NAS 4, stage 2 with extensive periportal fibrosis
 - Plan: weight loss, exercise
 - Follow up at 6 months: no symptoms; "working on weight loss"
 - PE: weight down 3 lbs/6 months
 - ALT 79, AST 64

NASH: a typical case

- Admitted 8/19/11 (no follow up x 2 years)
 - Increased abdominal girth, dyspnea, leg edema
 - Interim diagnosis: obstructive sleep apnea
 - Wt up 60 lbs in 6 weeks
 - Recent minor MVA with confusion
 - PE: Ascites, 3+ leg edema, alert/oriented
 - Lab: ALT 55, AST 102, Alb 2.6, INR 1.7, MELD 15, plts 149
 - Abdominal CT...

NASH: a typical case



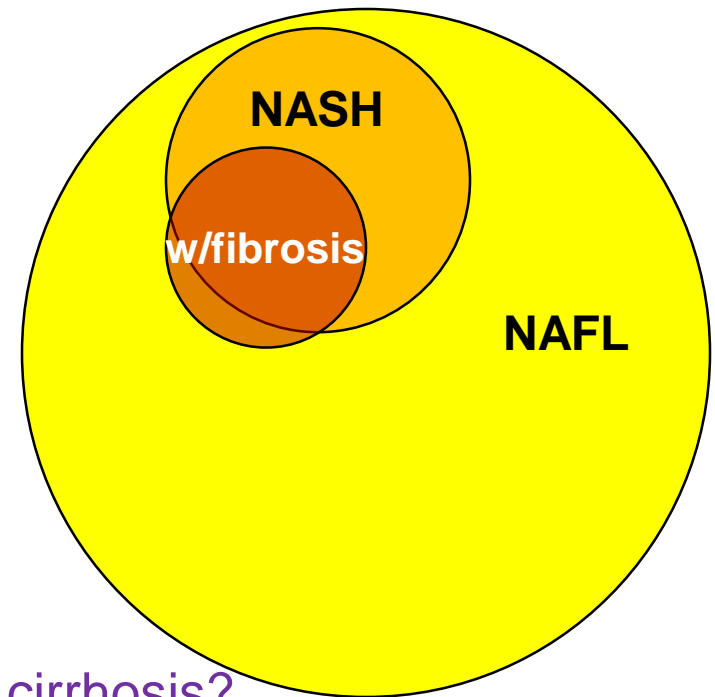


Knowledge Gaps

- Tests that a primary care provider could use to identify this person as somebody
 - At risk for NASH before onset
 - Having NASH
 - At risk for liver fibrosis in response to steatohepatitis
 - Having fibrosis or cirrhosis
- Tests that a specialist can use to assess response to therapy
 - Resolution of steatohepatitis
 - Improvement (resolution) of fibrosis
- Tests that can be used in clinical trials to:
 - Identify steatohepatitis and fibrosis for screening
 - Measure changes in steatohepatitis
 - Measure changes in fibrosis

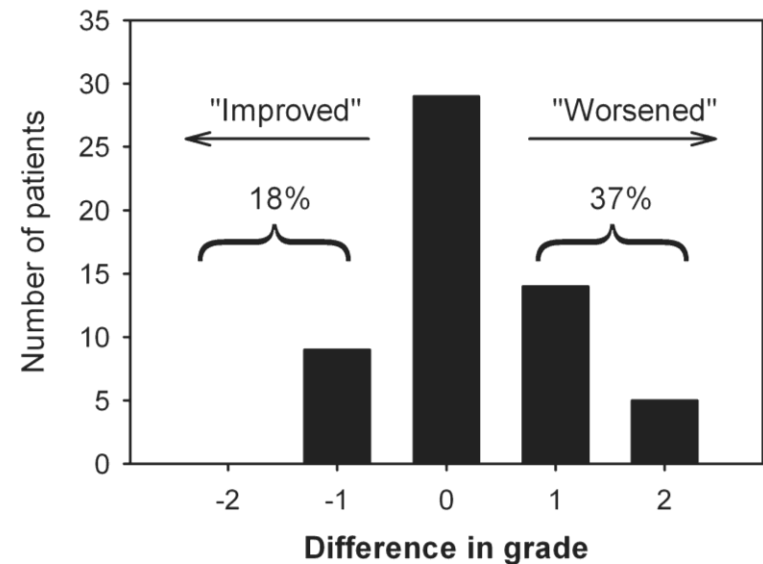
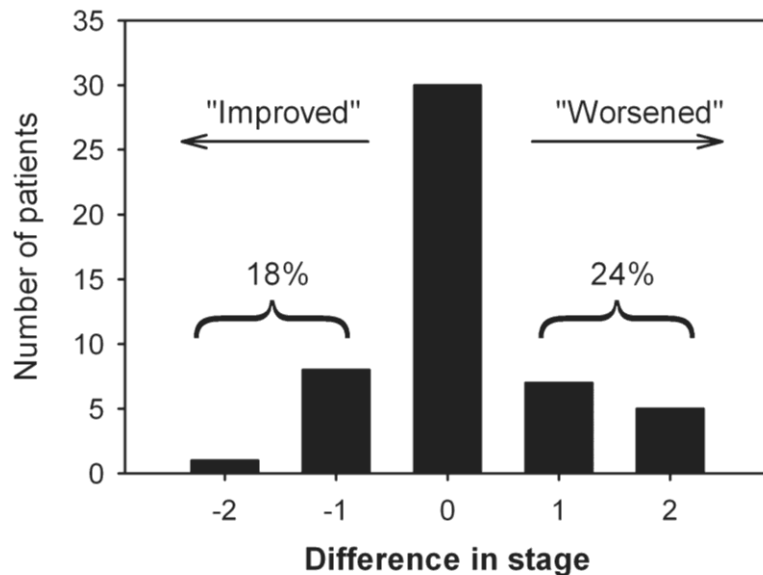
Issue: the mushy linguistics of NASH

- NAFL = non-NASH NAFLD (3 non's)
- NAFLD
- NAFLD severity
- NASH
- Progression
- Normal to NAFL?
 - NAFL to NASH?
 - Increasing fibrosis?
 - Cumulative disease to the point of cirrhosis?
 - Death, liver transplant, liver cancer?
- Resolution
 - “Complete resolution”
- Disease activity



Issue: liver biopsy as a comparator for biomarkers

- Sampling variability
 - Ratziu study:
 - 51 patients with suspected NAFLD
 - Two simultaneous biopsies
 - Independent grading and staging (Brunt)



Biopsy as a comparator for biomarker development

- What would be the AUROC for a perfect biomarker if biopsy is imperfect?
 - 0.8? 0.9?

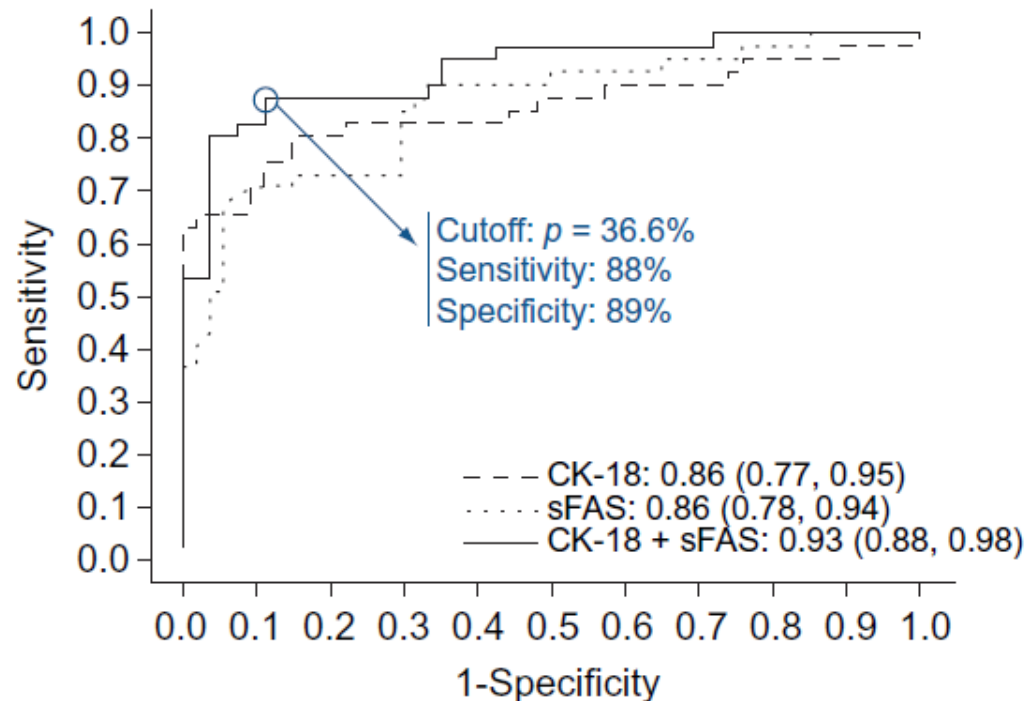
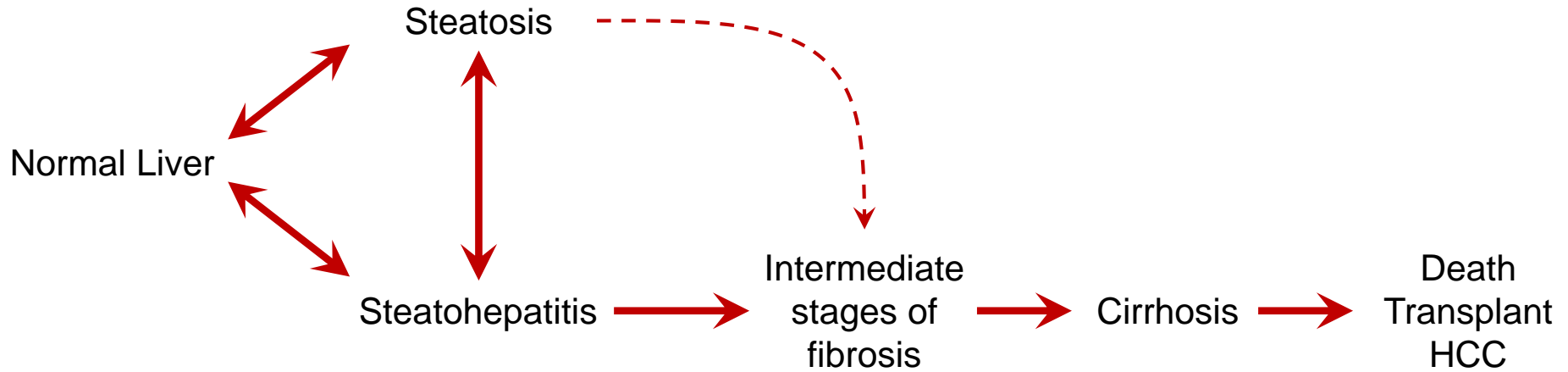
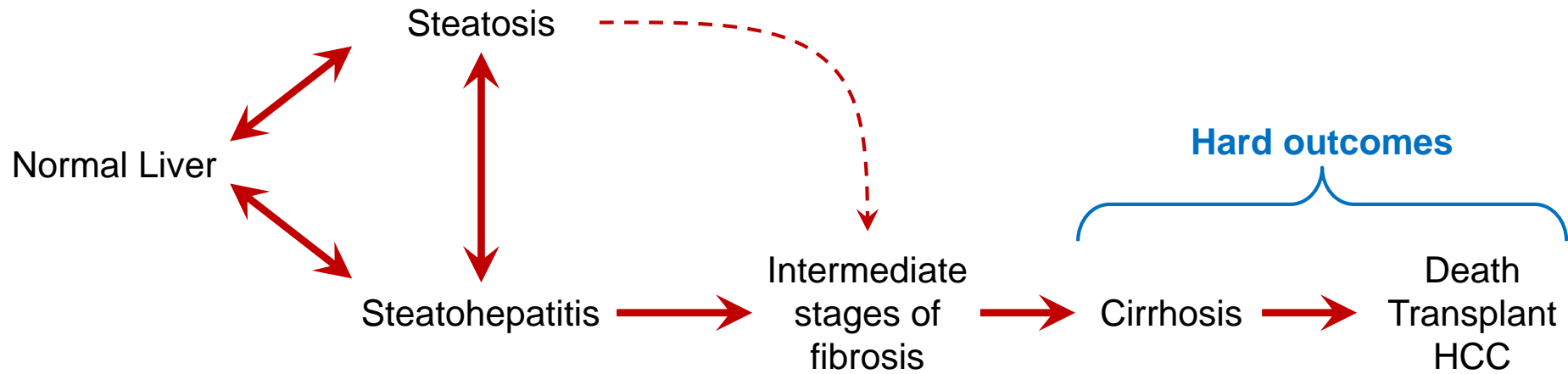


Fig. 1. An apoptosis panel consisting of plasma CK-18 fragments and sFas levels accurately diagnoses NASH in patients with suspected NAFLD (initial cohort). The area under the ROC curve is shown for the performance of this panel

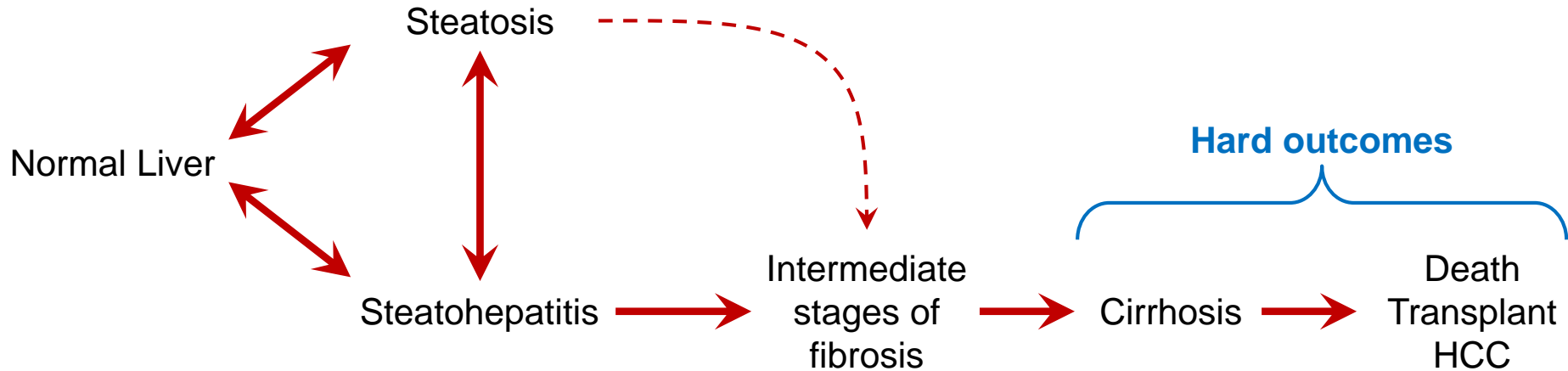
Progression of NAFLD—Need for Biomarkers



Progression of NAFLD—Need for Biomarkers



Progression of NAFLD—Need for Biomarkers



Biomarkers:

- ALT
- Clinical algorithms
- Lipidomics
- Proteomics
- Circulating miRNAs, exosomes, etc
- MR
- Genomic risks
- Clinical algorithms
- Elastography
 - VCTE
 - ARFI
 - MRE
- Proteomics
- Other serum markers
- Genomic risks
- Biopsy
- HVPG
- Imaging contour
- Elastography
- Breath tests
- Quant fxn testing
- Clinical:
 - Ascites
 - Varices
 - Encephalopathy

Determinants of progression *to cirrhosis and death*

- Hypothesis: the net outcome is the result of

$$\textit{Steatohepatitis activity} \times \textit{Fibrosis tendency} = \textit{Risk of cirrhosis}$$

- Both low: low risk of cirrhosis
 - One high, one low: moderate risk of cirrhosis
 - Both high: high risk of cirrhosis
- Conclusion:
 - We need to assess both to assess likelihood of hard outcomes
 - Caveat: with current tests, we assess presence of fibrosis, not proclivity to develop fibrosis

Current reality

- Grade disease activity
- Stage fibrosis

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Nonalcoholic Steatohepatitis: A Proposal for Grading and Staging the Histological Lesions

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Hypothetical concepts in changes in NASH severity and fibrosis stage

< 5%
steatosis

Steatosis
only

Steatosis w/
inflammation,
indeterminate
NASH

Steatohepatitis

NAFLD severity

NAFL-NAFLD-NASH Musical Scale

A musical scale diagram consisting of four horizontal lines. The notes are placed on the lines as follows: NAFL on the first line, NAFLD with a flat symbol on the second line, NAFLD with a sharp symbol on the third line, and NASH on the fourth line. The word 'Normal' is written to the left of the first line. A thick vertical bar is on the right side of the diagram.

Hypothetical concepts in changes in NASH severity and fibrosis stage

< 5%
steatosis

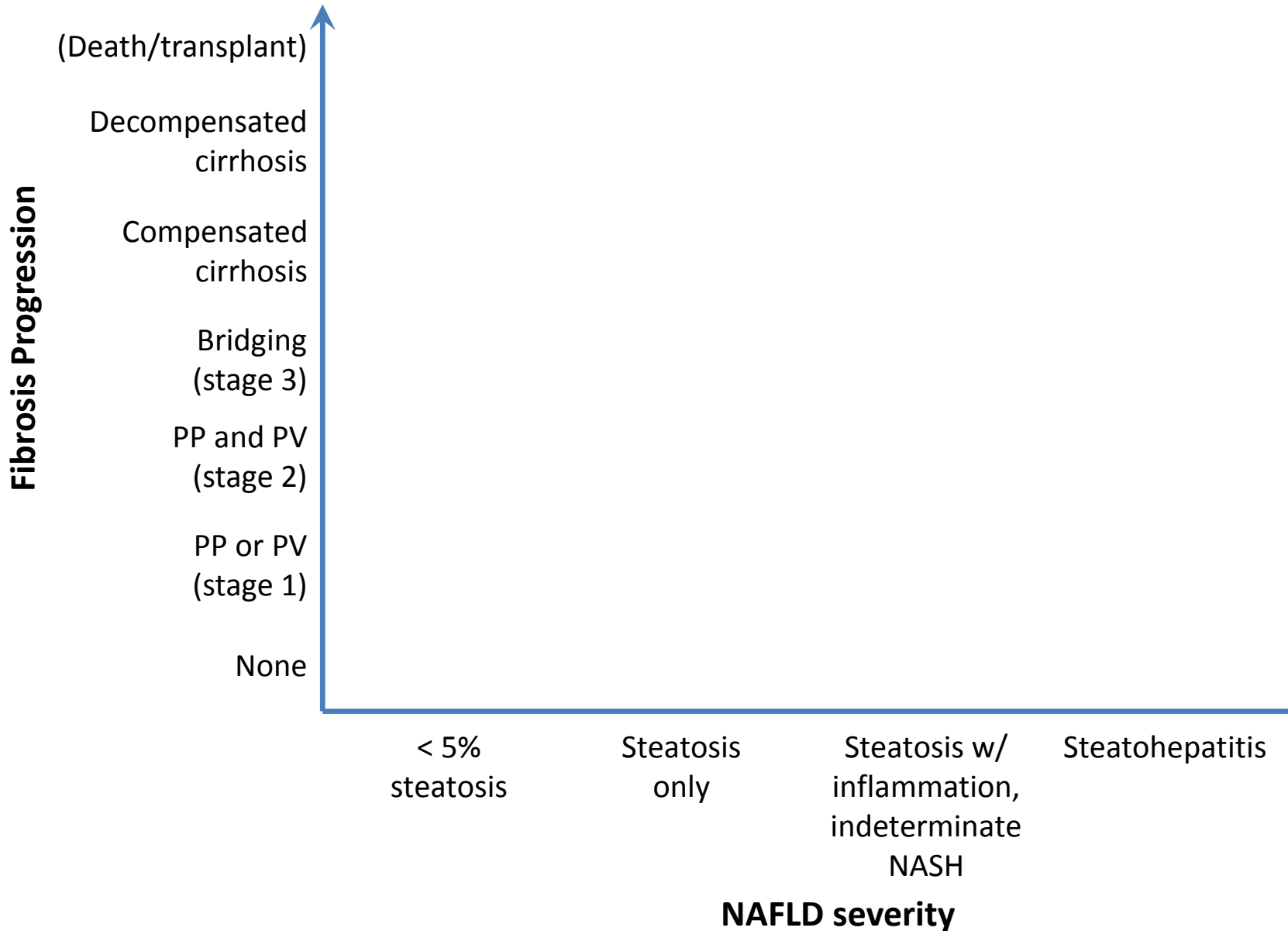
Steatosis
only

Steatosis w/
inflammation,
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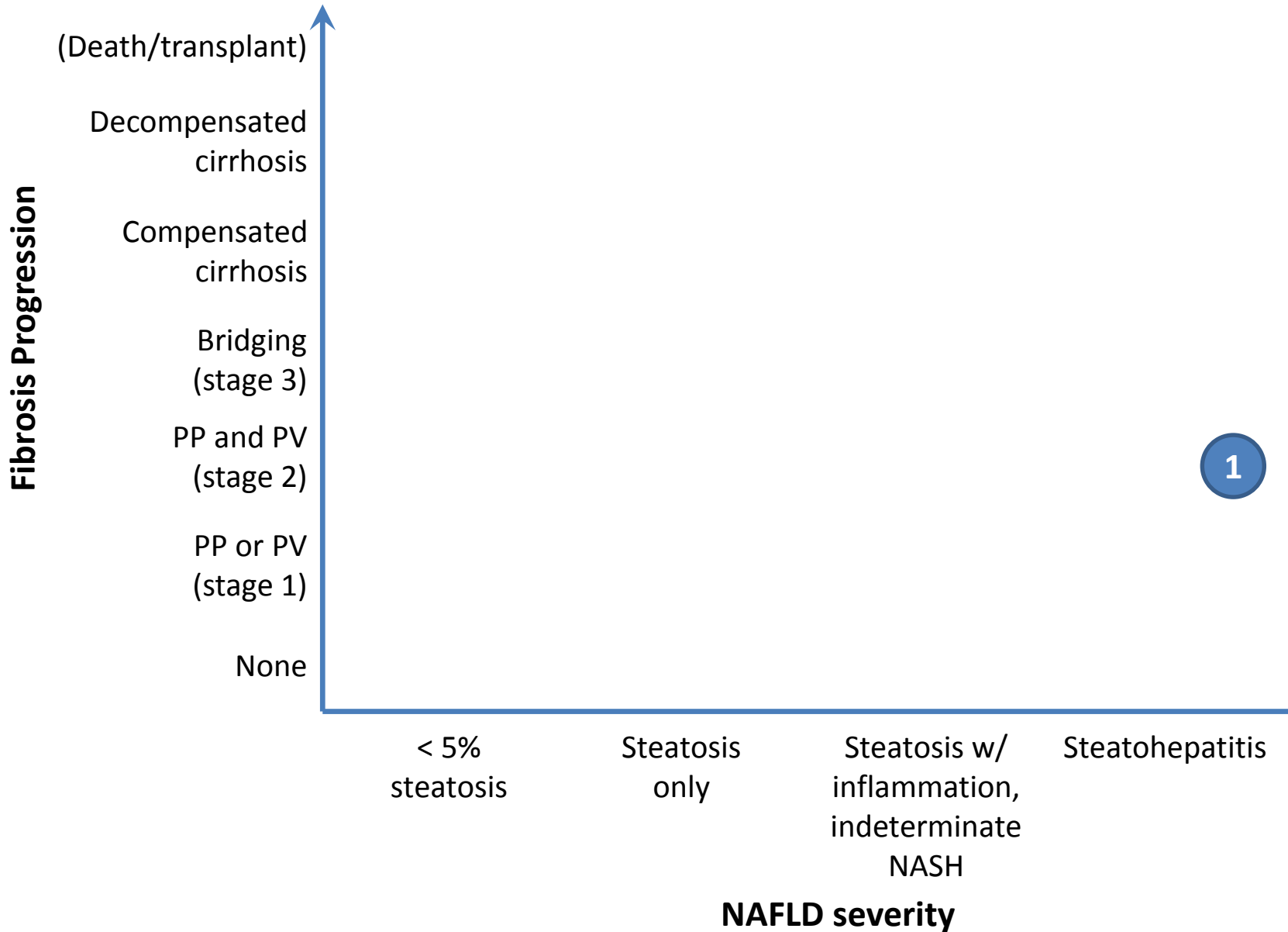
Steatohepatitis

NAFLD severity

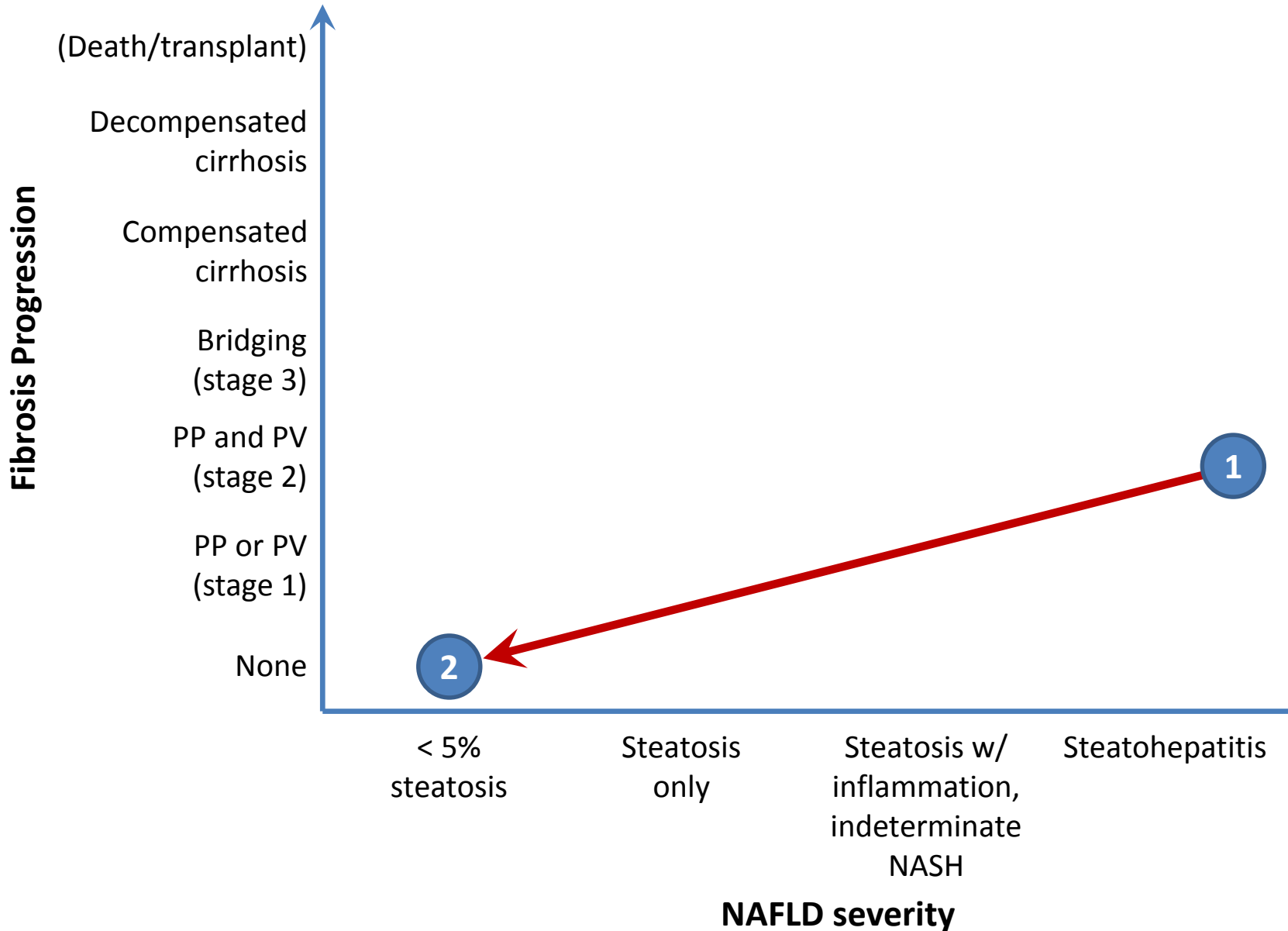
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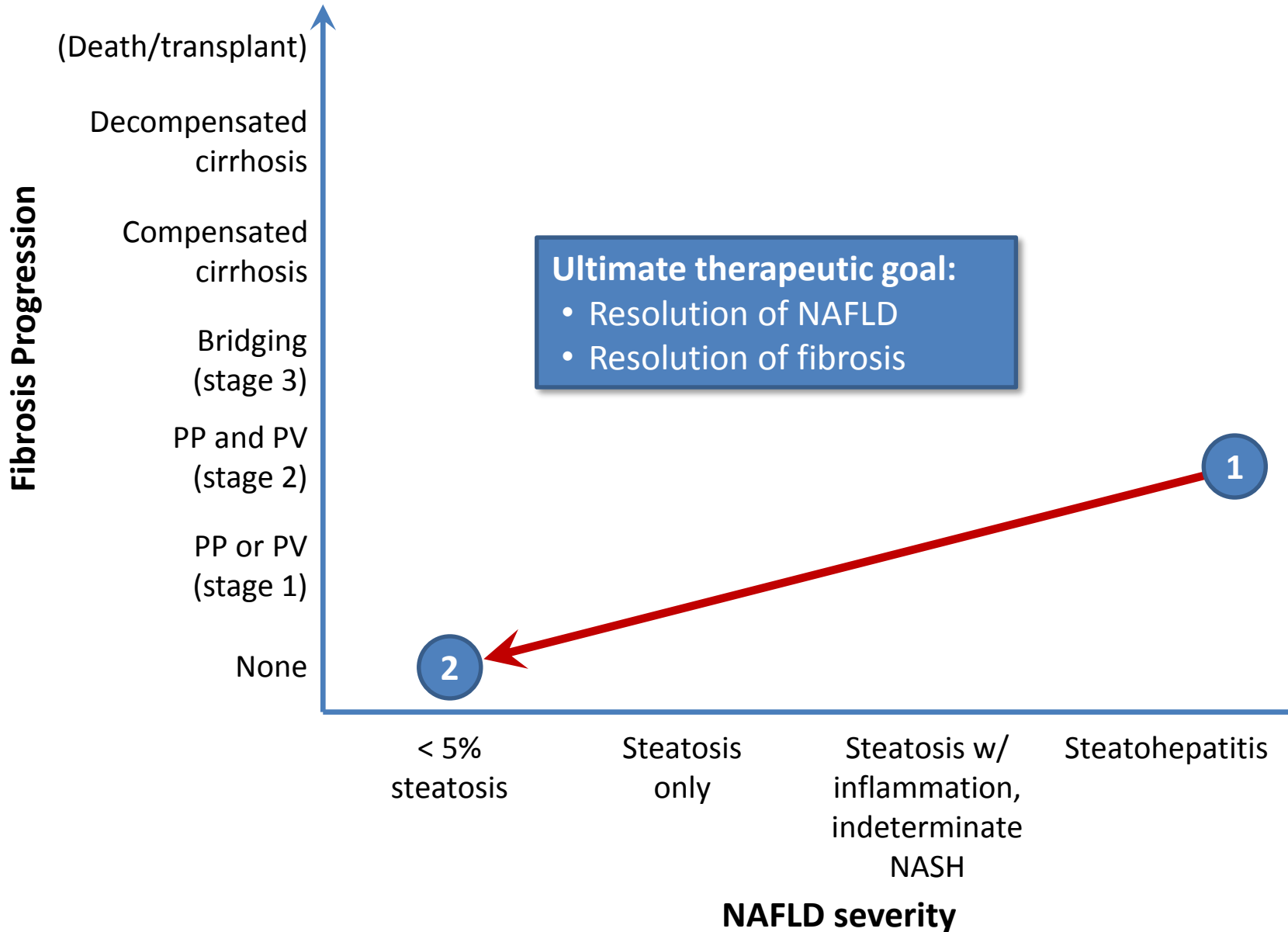
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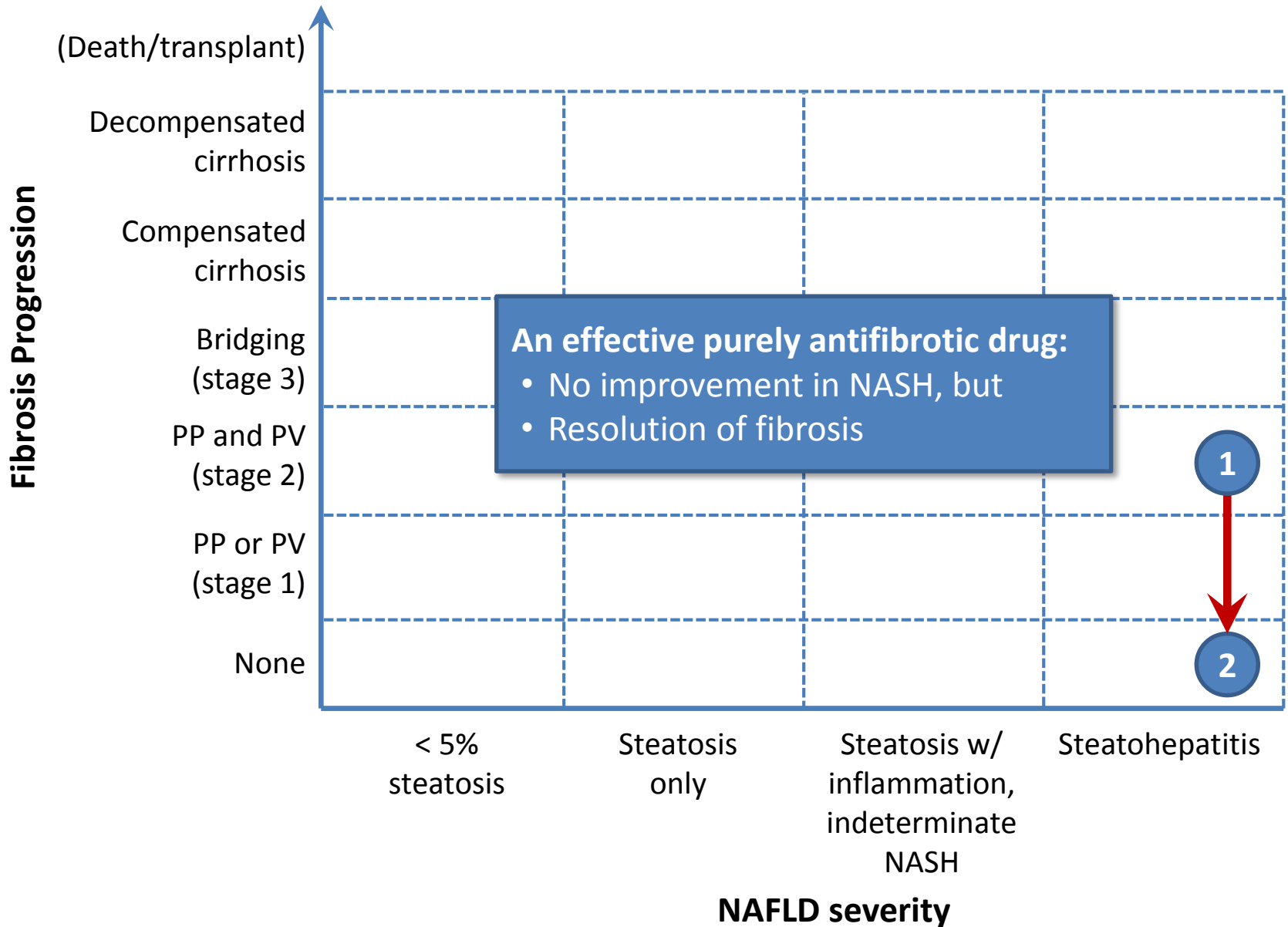
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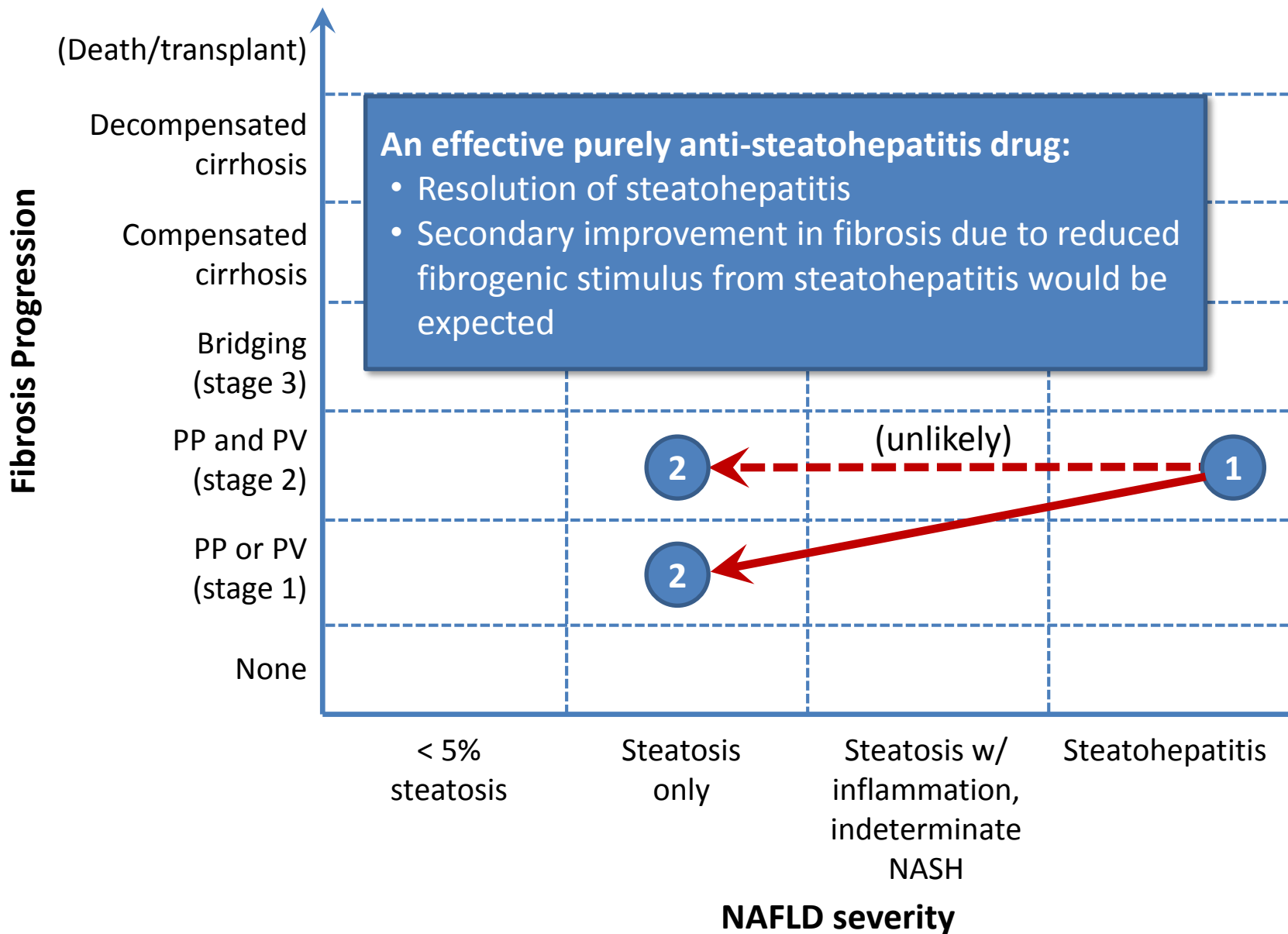
Hypothetical concepts in changes in NASH severity and fibrosis stage



Hypothetical concepts in changes in NASH severity and fibrosis stage



Hypothetical concepts in changes in NASH severity and fibrosis stage



Summary



- We need biomarkers for steatohepatitis
- We need biomarkers for fibrosis presence and tendency
- Net outcome is the result of

$$\textit{Steatohepatitis activity} \times \textit{Fibrosis tendency} = \textit{Risk of cirrhosis}$$

- Ideal world:
 - Genetic markers identify risks of steatohepatitis and fibrosis
 - Biomarkers identify the presence of steatohepatitis and fibrosis
- To get there:
 - Lots of good science
 - Acknowledge linguistic limitations, modify as we go

Summary: Perspectives on NASH

- Pathologist
 - When should I call it NASH?
 - How do I convey information regarding borderline measures, e.g. borderline NASH, stage 2.5 fibrosis?
 - What should features should biomarkers predict?
- Radiologist
 - I see fat—so what?
 - Can I detect NASH?
 - Can I measure fibrosis?
- Hepatologist
 - Who is at risk for NASH?
 - Who should I biopsy?
 - When will I have reliable non-invasive markers?
 - How will I use biomarkers for NASH and fibrosis?

Summary



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Summary



- A pathologist, a radiologist and a hepatologist walked into a bar...

We need a drink!