Compensated Cirrhosis & Clinically Meaningful Benefit

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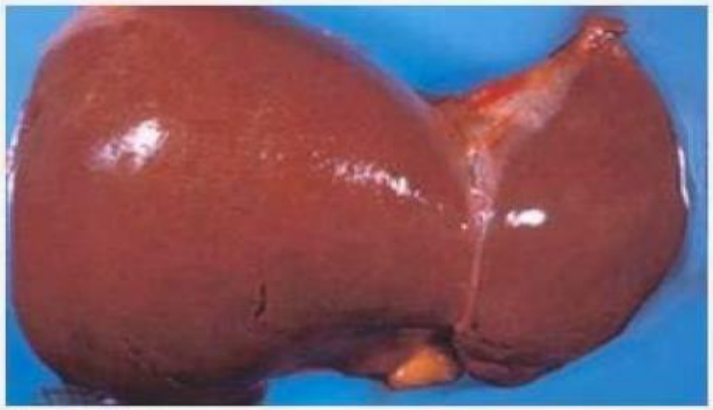
Outline

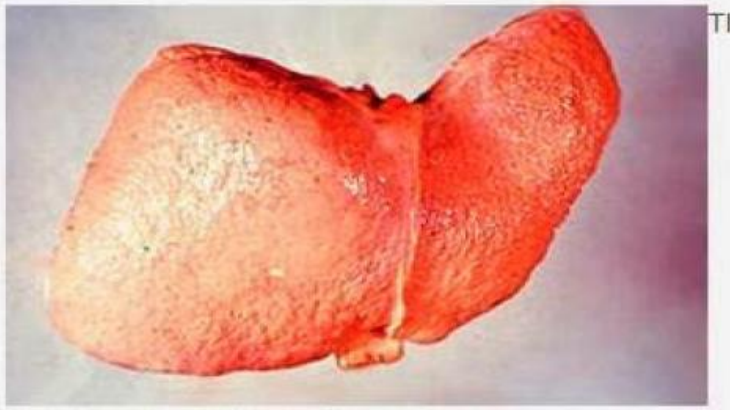
- Can **Compensated Cirrhosis regardless of the underlying etiology** be a standalone indication for marketing approval?
- If so, what should be the endpoints?
  - Are hard end points (death, transplant, decompensation events, etc) are impractical?
  - What surrogate are worthy of consideration?

Cirrhosis of the liver

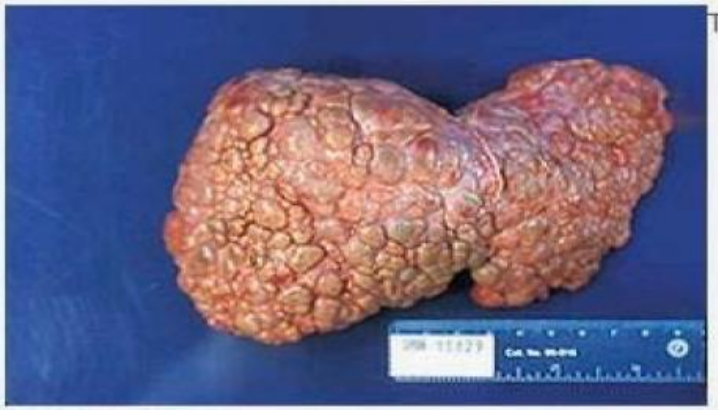


Normal liver

Hepatitis liver



The initial stage of liver cirrhosis



The final stage of liver cirrhosis

Retrieved from Google Images – October 14, 2017

Categories & Common Causes

Parenchymal

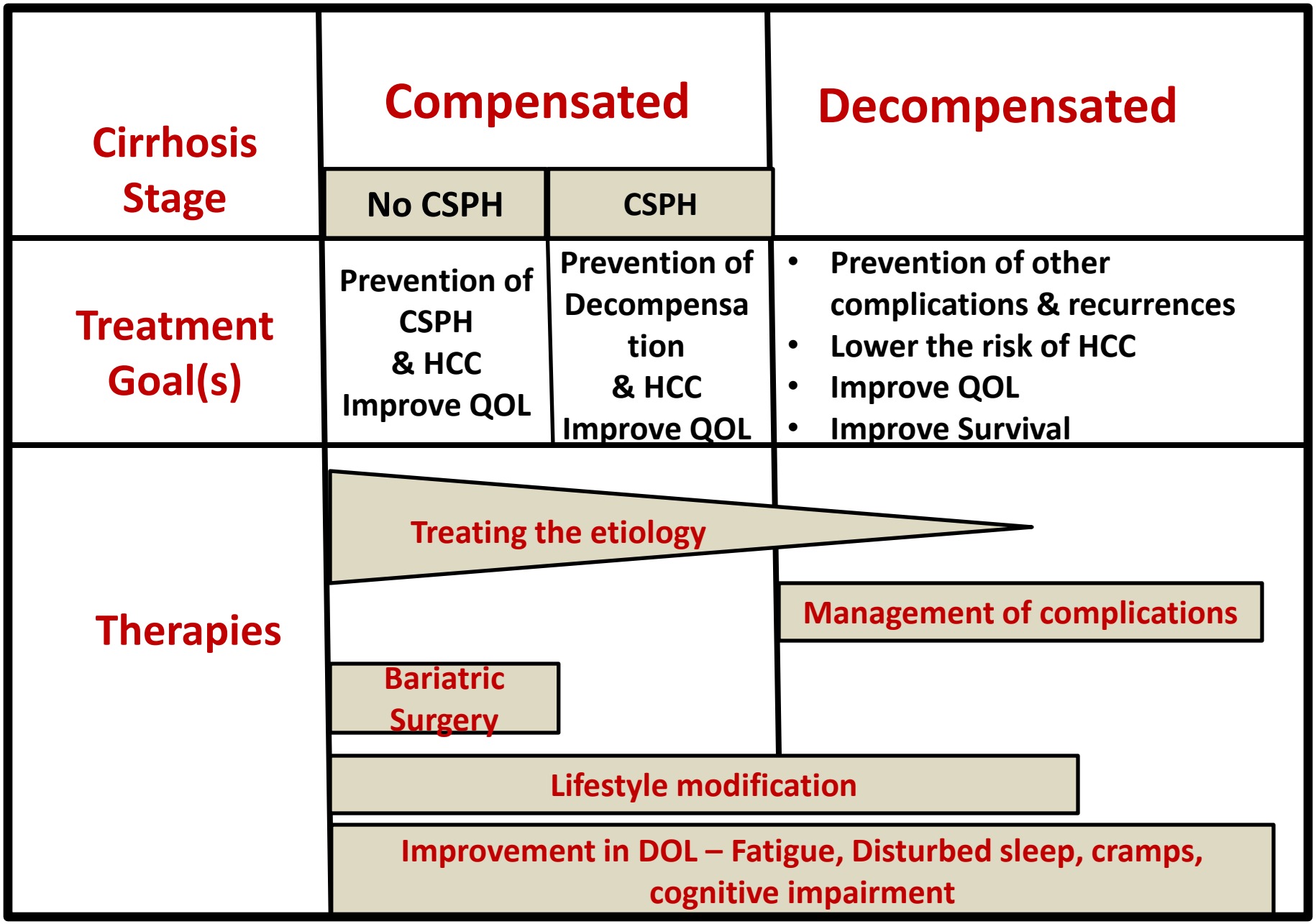
- Alcoholic Liver Disease
- NAFLD
- Hepatitis C
- Hepatitis B
- Wilson disease
- Autoimmune liver disease
- A1 antitrypsin deficiency

Biliary

- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Secondary biliary cirrhosis

Vascular

- Budd-Chiari Syndrome
- Cardiac cirrhosis
- ? Nodular regenerative hyperplasia



Adopted from presentation by Prof. Savino Bruno. Courtesy of Prof. Banares & Prof. de Franchis

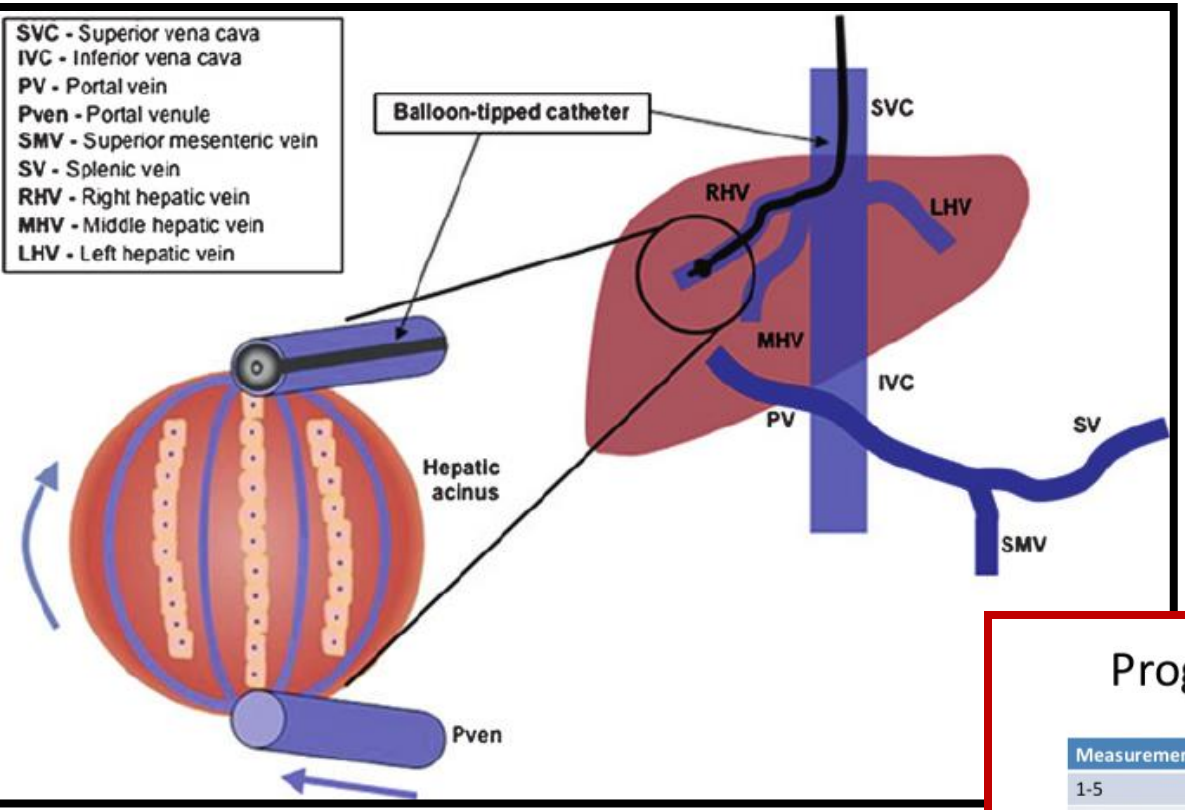
Challenges for considering any-cause cirrhosis as a single approvable indication

- Natural history is somewhat distinct based on underlying liver disease
- Treatment for underlying liver disease modifies the natural history
- Alcohol consumption
- Development of HCC (although rare) is a complicating issue
- Trials will likely enroll patients with common etiologies (HCV, NASH, ALD) – would the results be generalizable to cirrhosis due to rarer causes?

Surrogates endpoints: Compensated Cirrhosis

- Hepatic venous pressure gradient
- Worsening in liver function
  - MELD based
  - Hepaquant
  - ^{13}C MethacetIn breath test
- Patient Reported Outcomes?
  - Improved muscle cramps
  - Better sleep
  - QOL

Hepatic Venous Pressure Gradient



Prognostic value of HPVG in CLD

Measurement(mmhg)	Significance
1-5	normal
6-10	Preclinical sinusoidal portal htn
≥10	**Clinically significant phtn**
≥12	Increase risk of rupture of varices
≥16	Increase risk of mortality
≥20	Treatment failure and mortality in acute variceal bleeding

An HPVG of ≥10 mmHg defines clinically significant portal hypertension

Ref: Iris W. Liou, MD. Screening for Varices and Prevention of Bleeding http://hepatitisc.uw.edu/

Portal hypertension is defined as elevation of hepatic venous pressure gradient to >5mmHg.

Attributes of HVPG as a surrogate

Attribute	HVPG
Biological Plausibility	YES
Quantifiable	YES
Reproducible	Not known
Repeatability	Yes (painfully)
Performance characteristics	Well known
Can it be deployed easily?	Challenging
Supportive evidence	Extensive
Risks & Costs	Not insignificant
Risks due to misclassification	Not insignificant

Comment: Invasive, uncomfortable, high level expertise, and expensive

Attributes of MELD as a surrogate

Attribute	MELD
Biological Plausibility	YES
Quantifiable	YES
Reproducible	Yes
Repeatability	Yes
Performance characteristics	Not well studied
Can it be deployed easily?	Yes
Supportive evidence	Change in MELD as a surrogate for outcomes in compensated cirrhosis is not well studied
Risks & Costs	Negligible
Risks due to misclassification	Negligible (easily reconfirmed)

Comment: Relatively static in compensated cirrhosis, cut-off not well studied, and influence of co-morbidities and warfarin

J Hepatology 2015:63: 1345-1351

Use of the methacetin breath test to classify the risk of cirrhotic complications and mortality in patients evaluated/listed for liver transplantation

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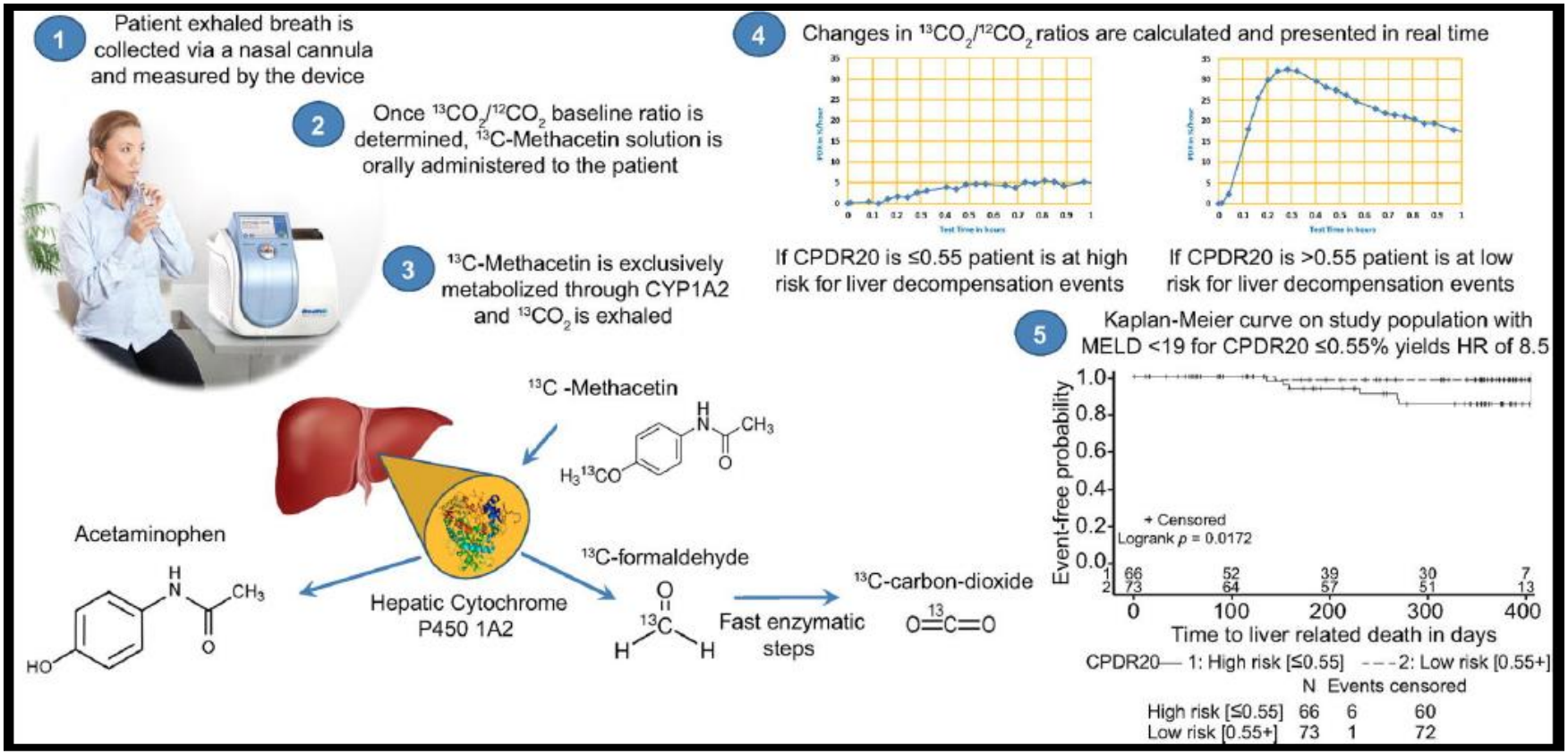


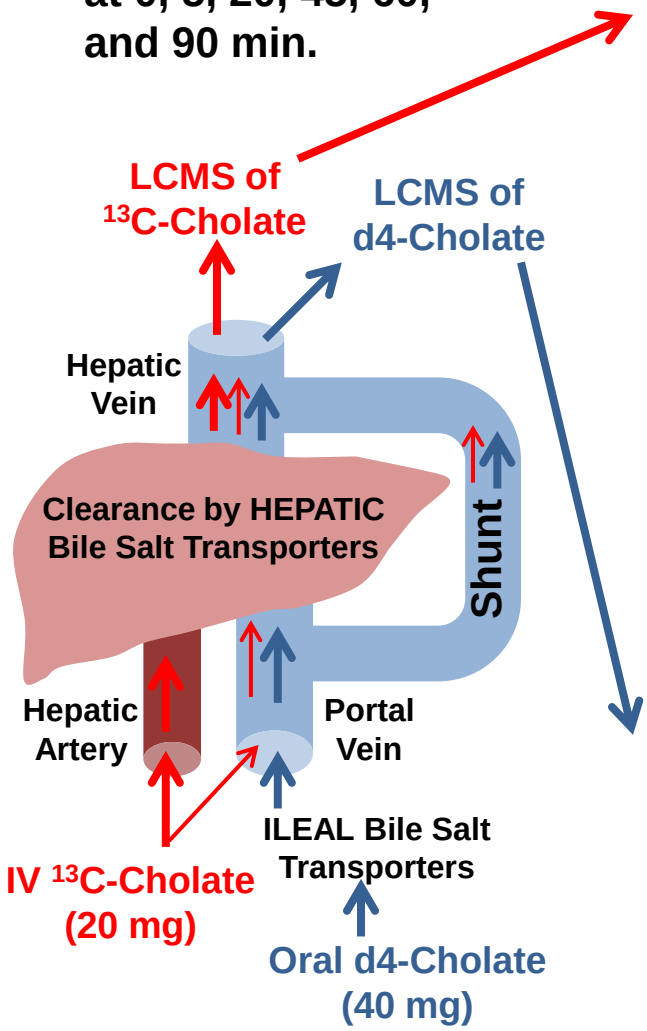
Attributes of MBT as a surrogate

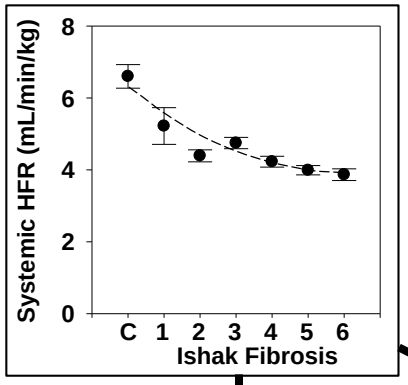
Attribute	HVPG
Biological Plausibility	YES
Quantifiable	YES
Reproducible	Not known
Repeatability	Yes
Performance characteristics	Not well studied
Can it be deployed easily?	Probably
Supportive evidence	Modest
Risks & Costs	Risks are negligible Cost unknown
Risks due to misclassification	Unknown

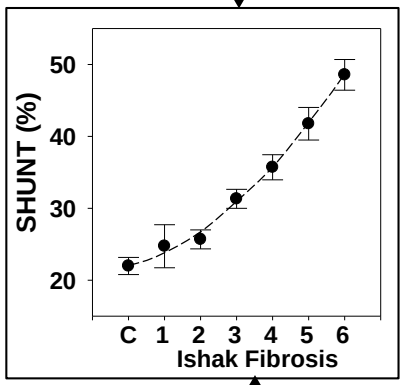
Comment: Limited scientific evidence to date and depends on a single CYP. Due to proprietary nature, external independent validation may not be possible

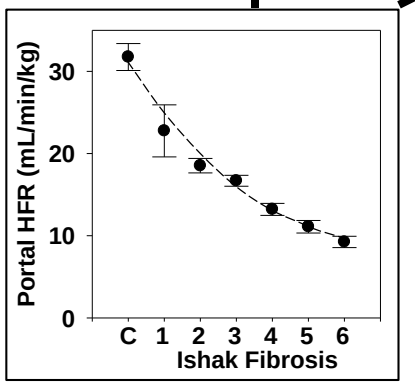
HepQuant: Disease Severity Index (DSI)

1. Administer test compounds.
2. Serum samples at 0, 5, 20, 45, 60, and 90 min.

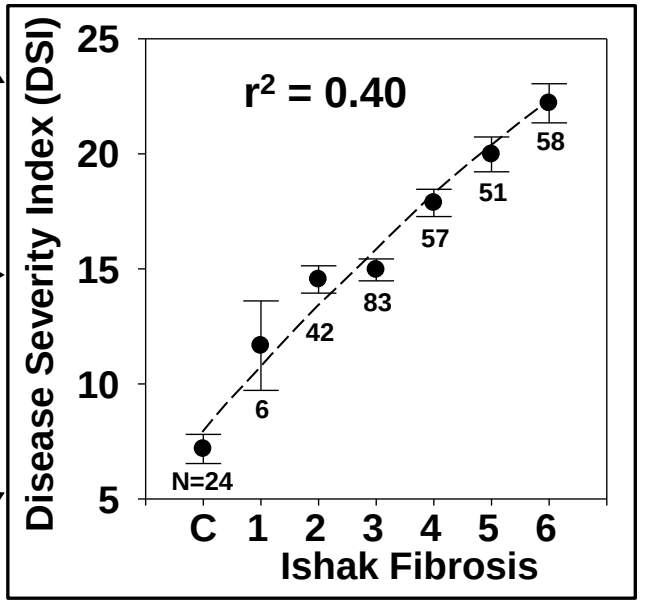








3. LCMS of ^{13}C and d4-cholates.
4. Calculate systemic and portal hepatic filtration rates, shunt, and DSI.



DSI = A (SHUNT)
– B (Log Portal HFR)
– C (Log Systemic HFR)
+ D

Courtesy – Dr. Greg Everson

Attributes of DSI as a surrogate

Attribute	HVPG
Biological Plausibility	YES
Quantifiable	YES
Reproducible	Probably
Repeatability	Yes
Performance characteristics	Studied but limited peer reviewed publications
Can it be deployed easily?	Not as easy
Supportive evidence	Limited peer reviewed publications. Lot of abstracts
Risks & Costs	Risks are negligible Cost unknown
Risks due to misclassification	Unknown

Major pitfall: Limited scientific evidence to date and depends on cholate extraction/shunting. Due to proprietary nature, external independent validation may not be possible

Patient Reported Outcomes

- HR-QOL instruments
  - CLDQ (25 Likert items)
  - LD-QOL (75 Likert items + SF-36 items)
  - SF-LDQOL (36 Likert items + SF-36 items)
  - LDSI (18 Likert items)
- Itching
- Cramps
- Disturbed sleep
- Minimal hepatic encephalopathy

Orr JG, et al. J Hepatology 2014:61: 1158-1165

Summary

- It is likely premature to consider “Any-cause Cirrhosis” as an approval indication
- Cirrhosis due to specific etiologies such as NASH and alcoholic liver disease are attractive for further consideration
- A number of important knowledge gaps remain, including lack of externally validated liver function tests
- Close attention to hepatic safety is critical