

Imagine

Imagine

- Diagnosing Crohn's disease only when strictures are present

That's what we do with PSC

Imagine

- Four horsemen of liver disease
 - Trigger/Cause
 - Inflammation
 - Fibrosis
 - Cirrhosis/Portal Hypertension

Hopeless?

No!

- Hypertension
- Diabetes

Every single piece of the puzzle matters

We just need to have clarity

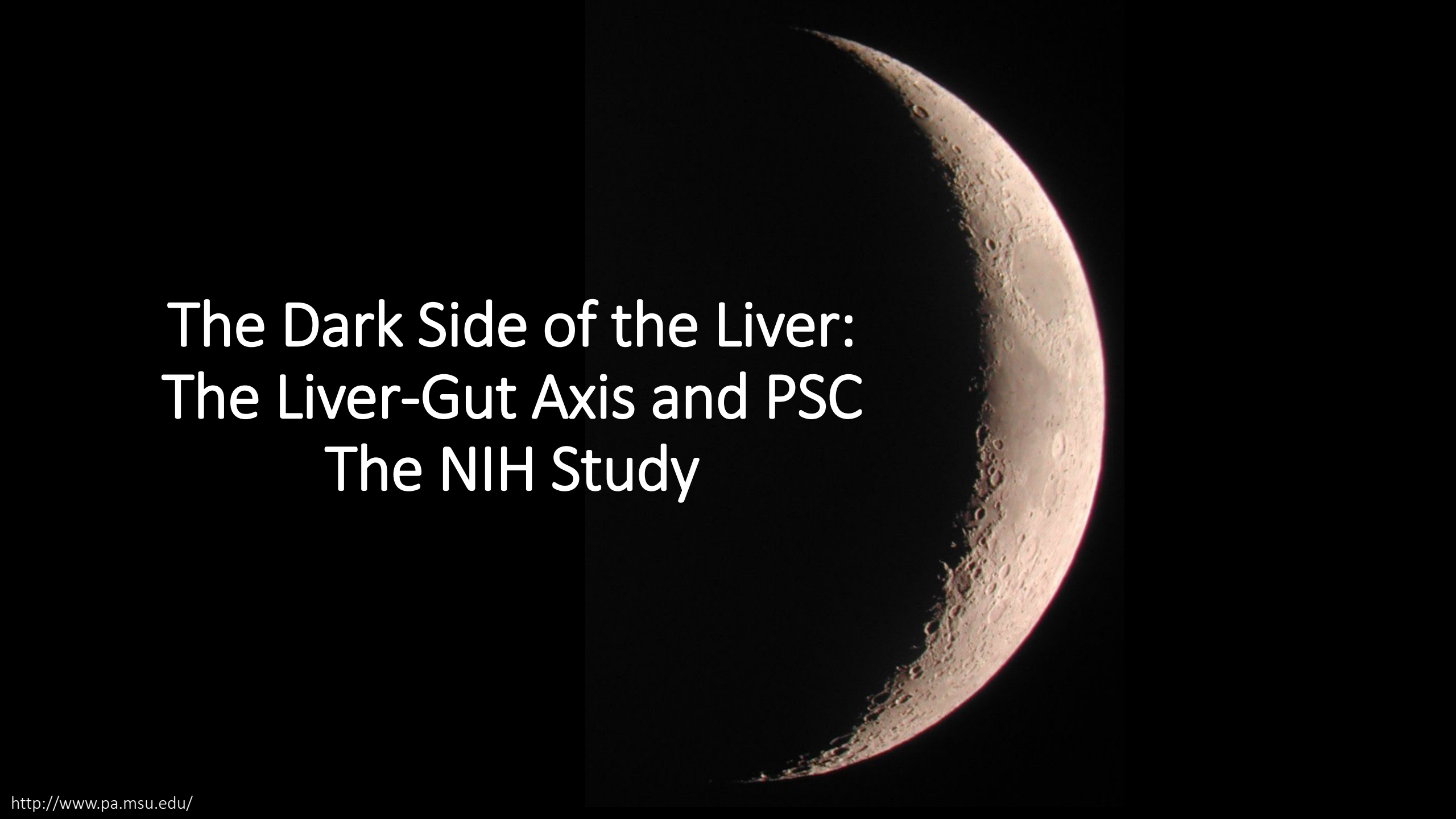
Theo Heller



Disclosures

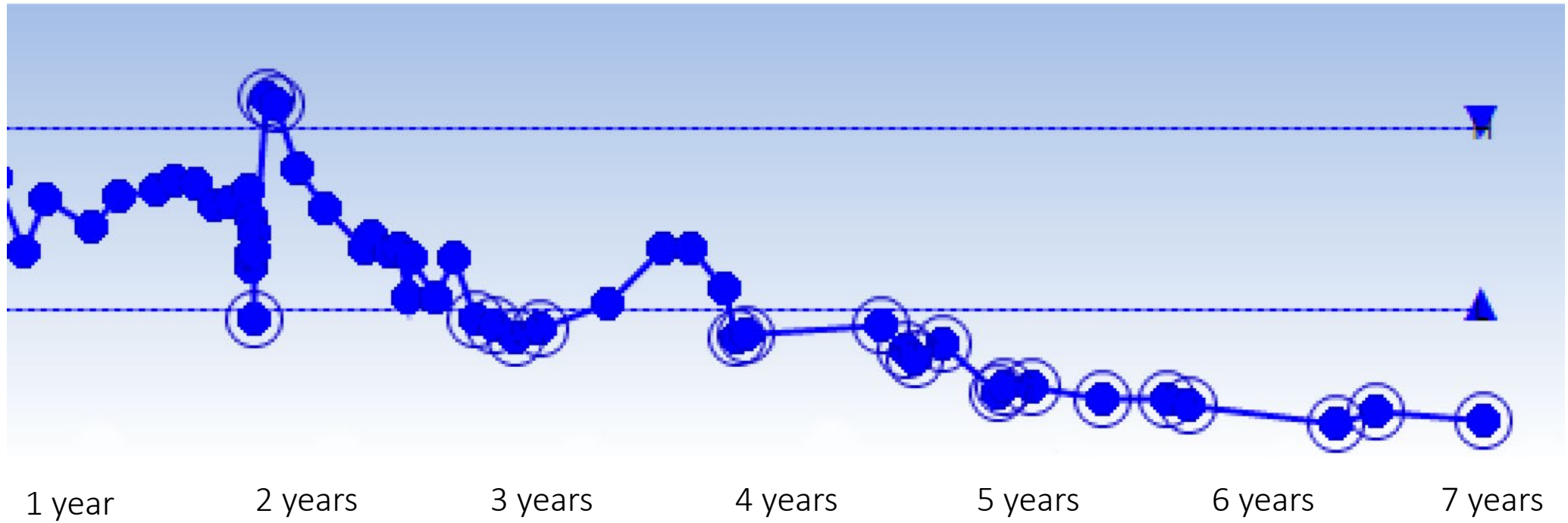
- I love hepatology
- I love my job
- I love coffee!
- I am not a PSC guy

- I have no financial disclosures but do wish I had some



The Dark Side of the Liver: The Liver-Gut Axis and PSC The NIH Study

Platelet Count



PSC Study Background Concepts

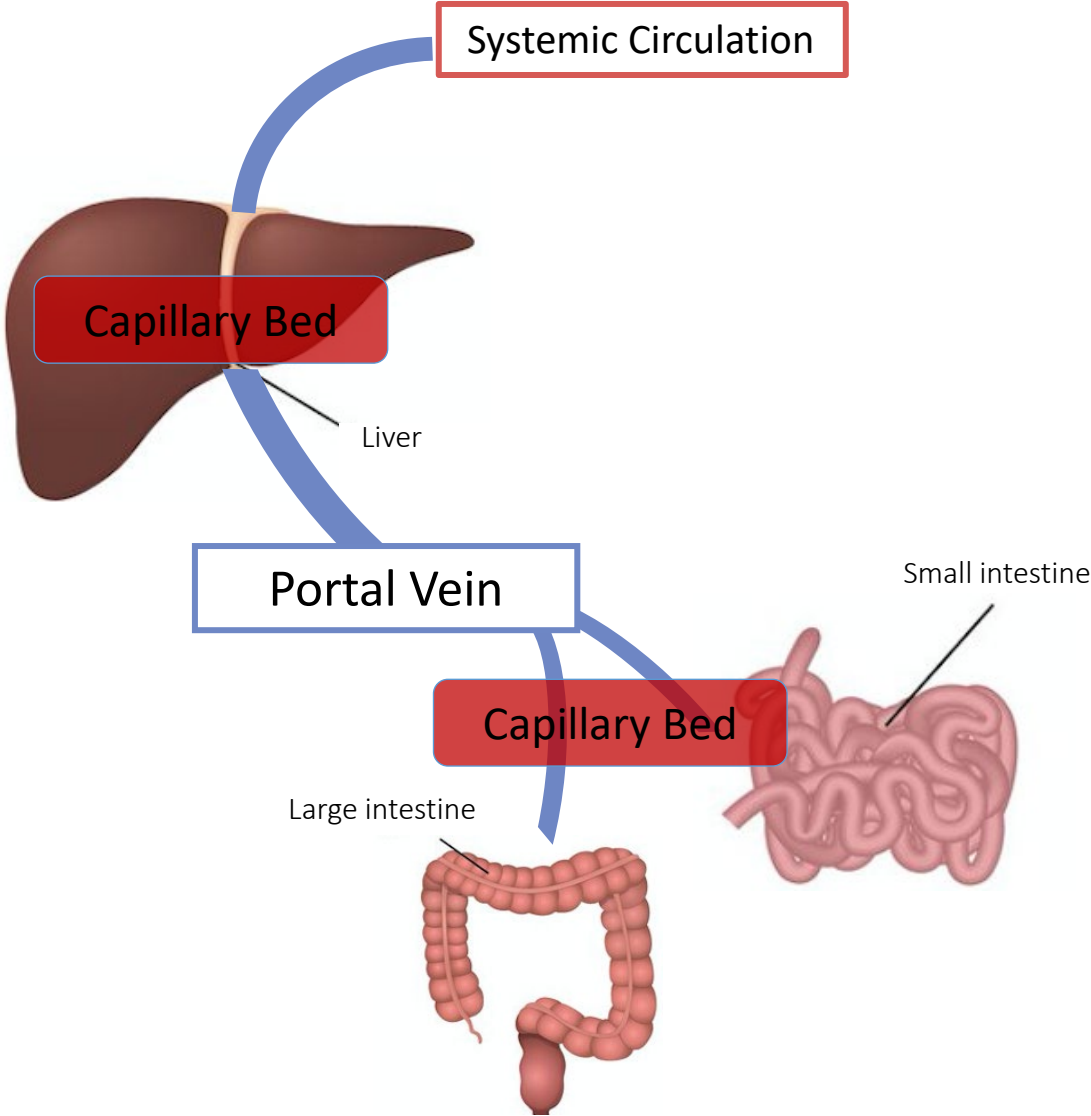
- Ann takes me to PSC
- Gut liver axis in PSC
 - Liver in isolation?
 - We behave differently in different situations
 - Context counts
 - Integrated data

Liver – Gut Axis

Portal Vein



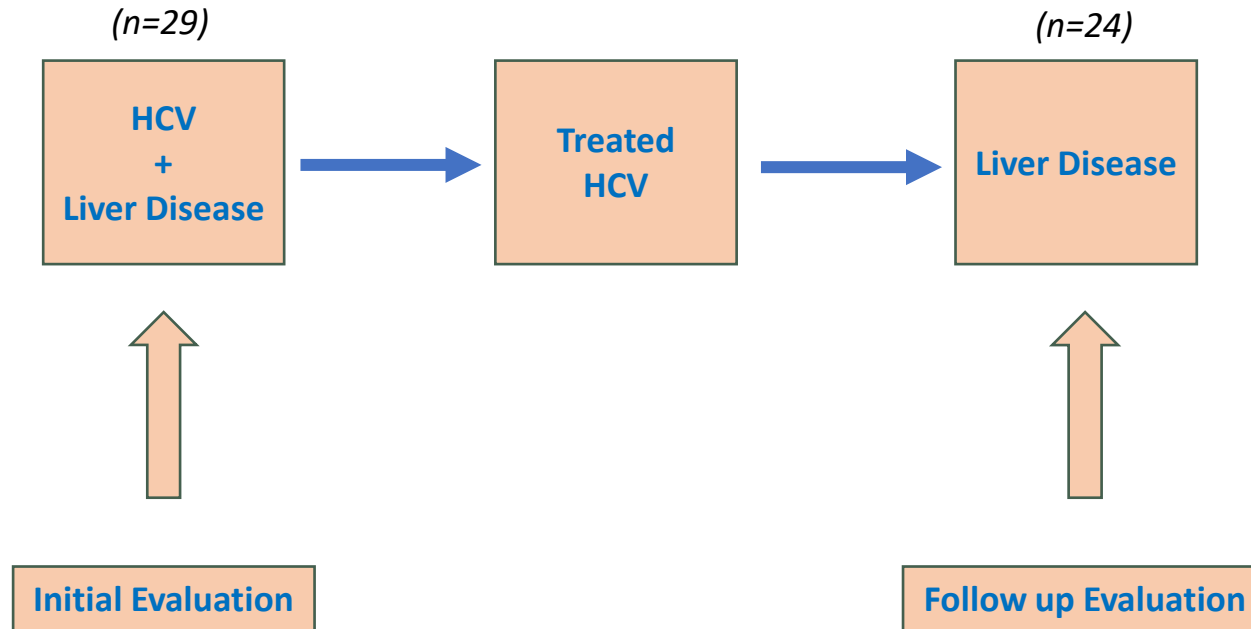
The Dark Side of the Liver – Portal Vein



So?

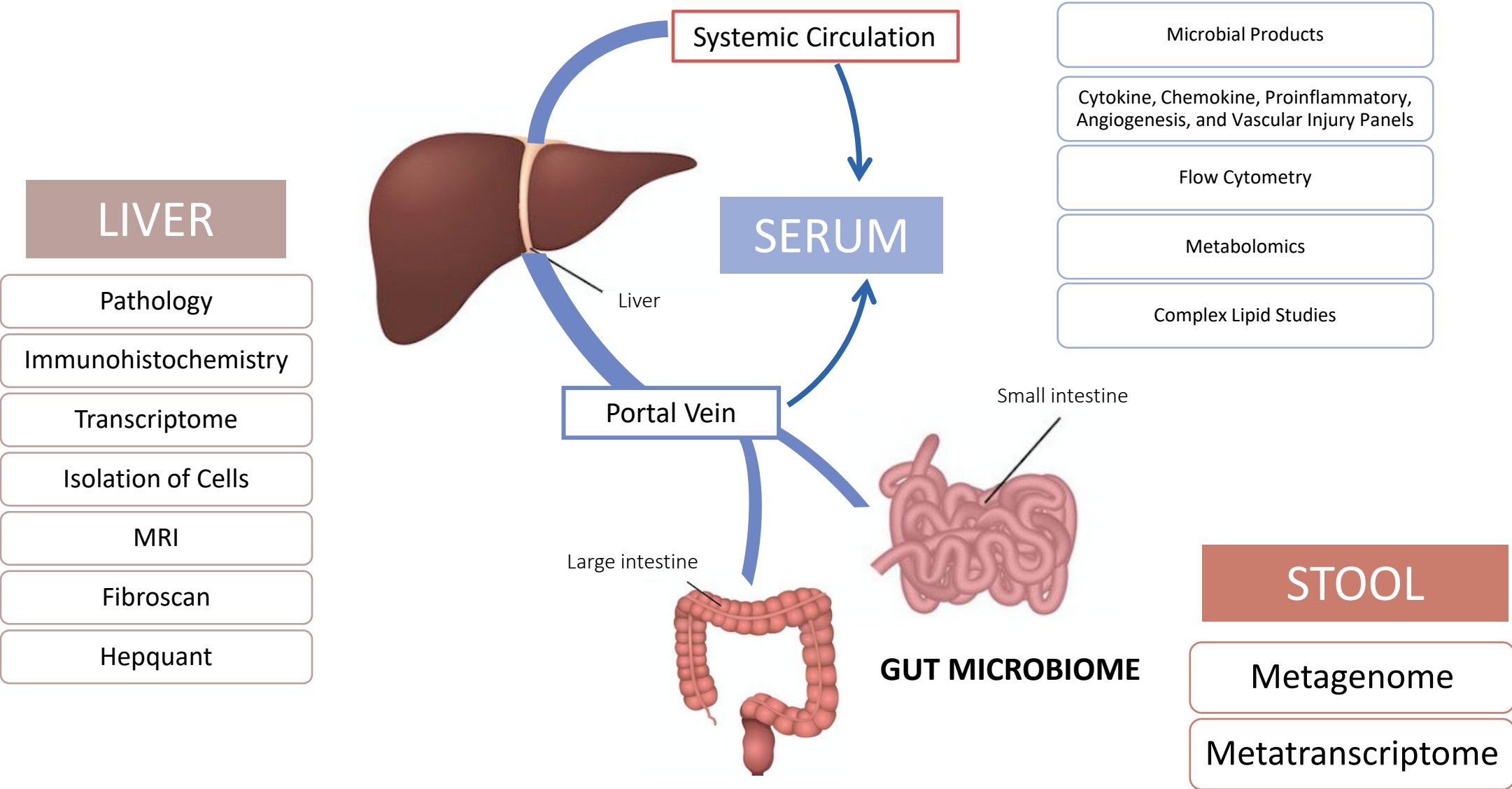
- Portal vein links gut liver axis
- Conversation/symphony
 - Many means of communication, word/note equivalents
 - small molecules, bile acids, big molecules, nucleic acids, microorganisms, extracellular vesicles
 - all come to the liver via portal flow
 - (lymphatics – systemic)
- Identify and integrate to understand or decode that conversation

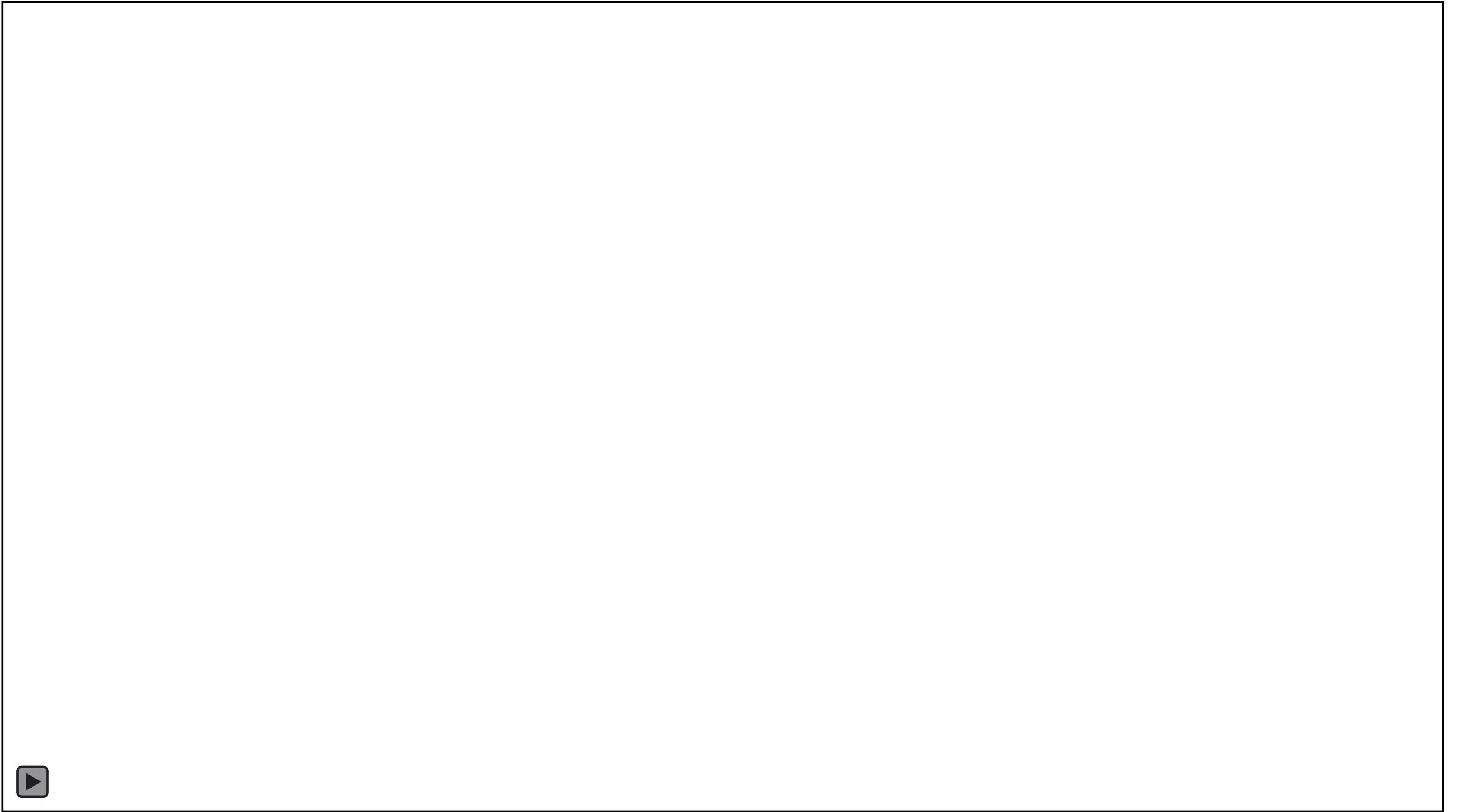
HCV as a Trial Run 15 DK-0100



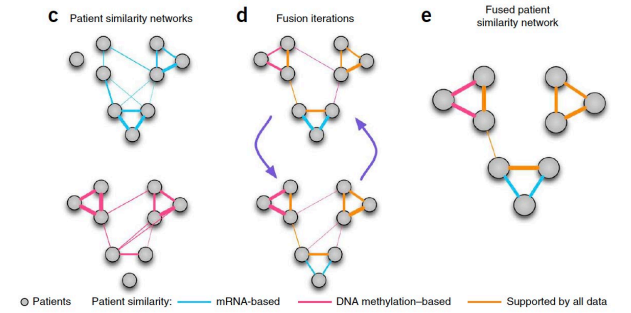
Ali RO et al Nature Microbiology 2023
Quinn G et al Liver International 2023
Hill K et al Submitted
Ali RO et al Submitted
Others in draft form

Assessment of the Gut-Liver Axis



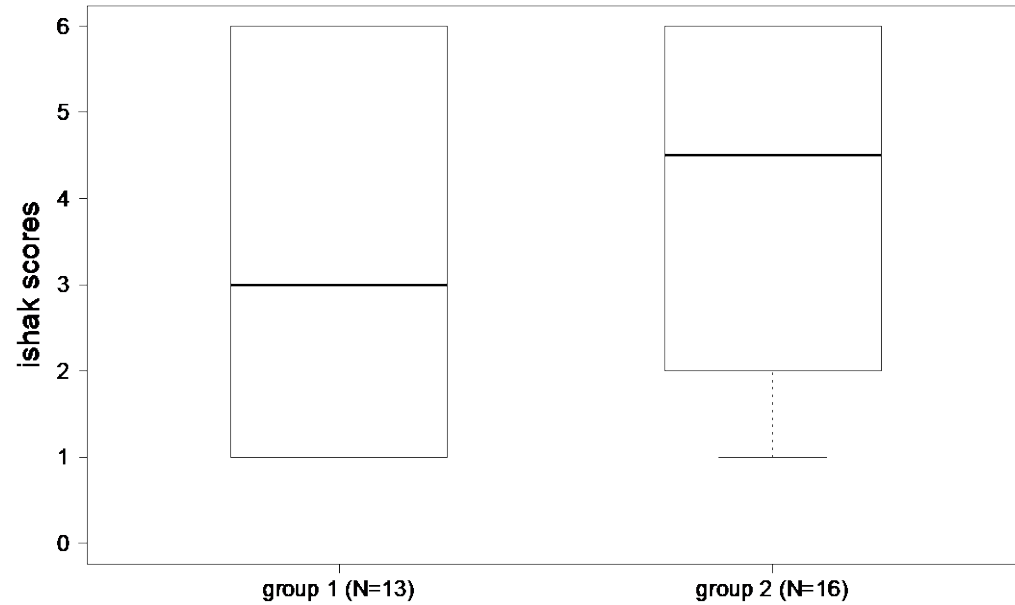


Cytokines and Immune Markers (65 analytes)



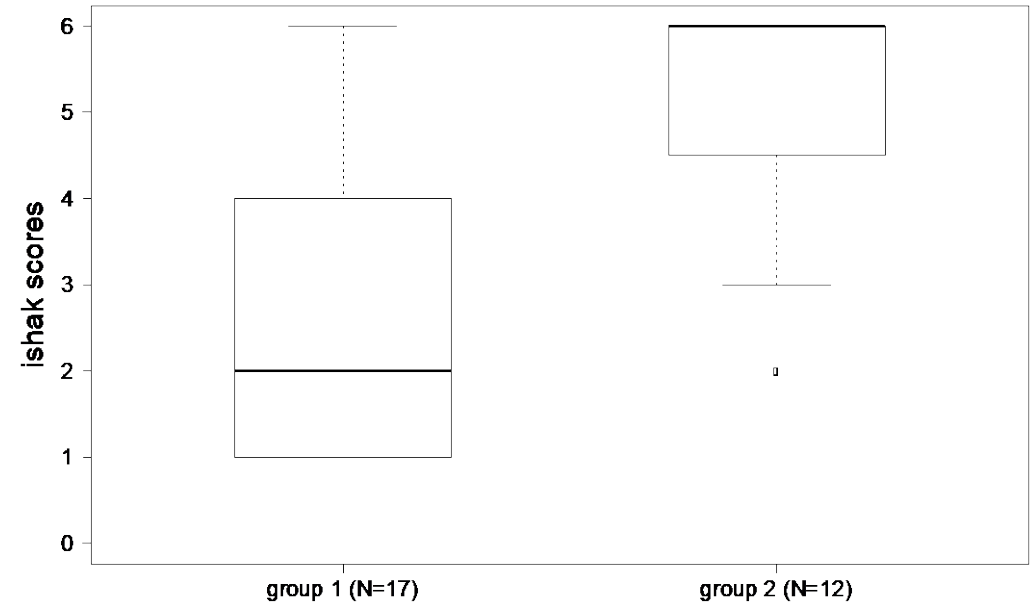
Peripheral Cytokines

$p = 0.564$

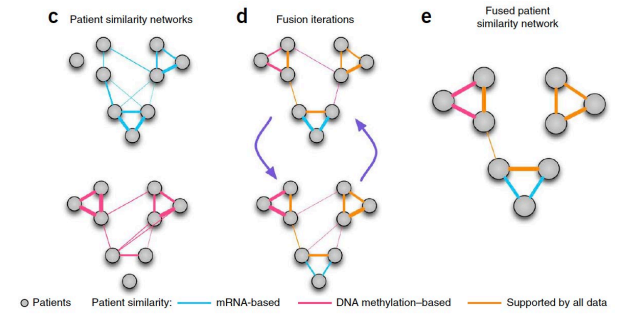


Portal Cytokines

$p = 0.0007$

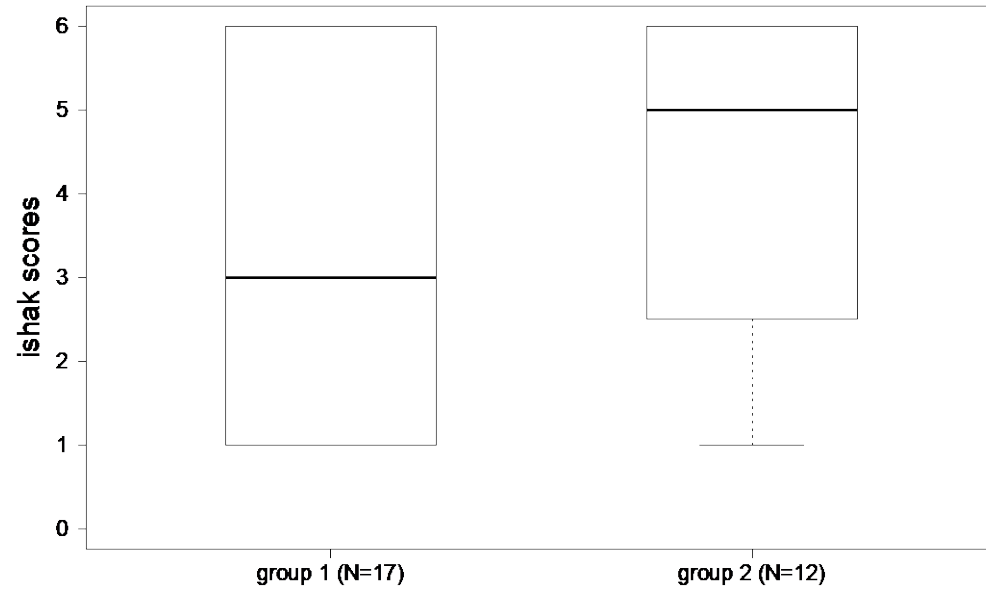


Metabolomics (1541 analytes)



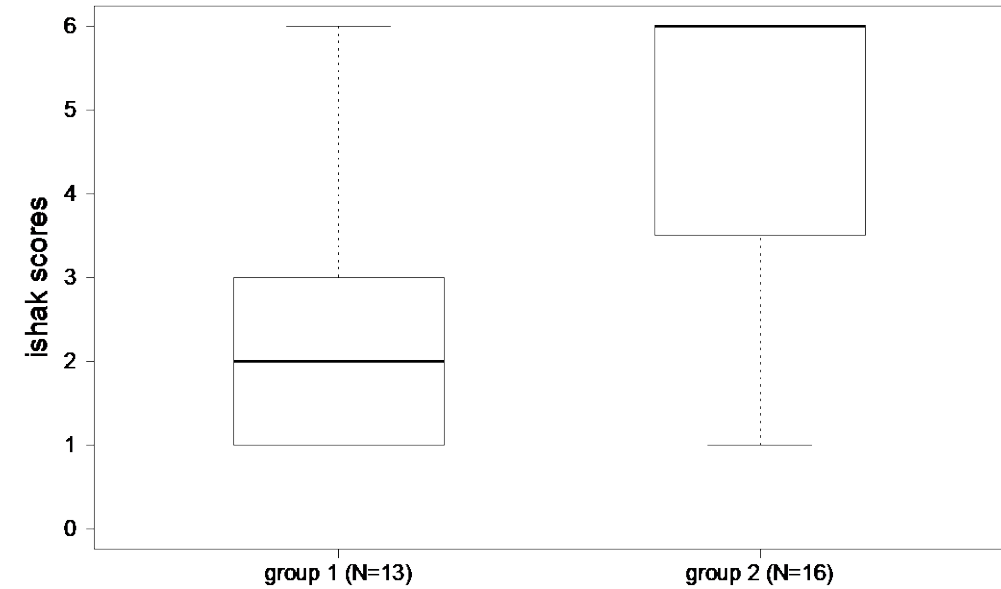
Peripheral Metabolites

$p = 0.231$



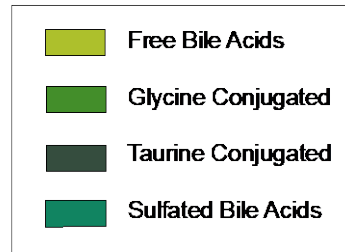
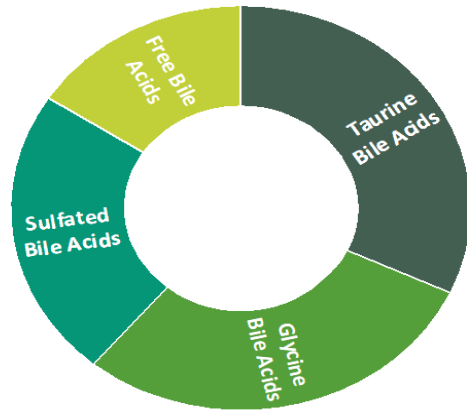
Portal Metabolites

$p = 0.007$

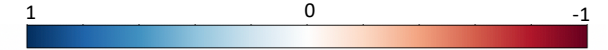
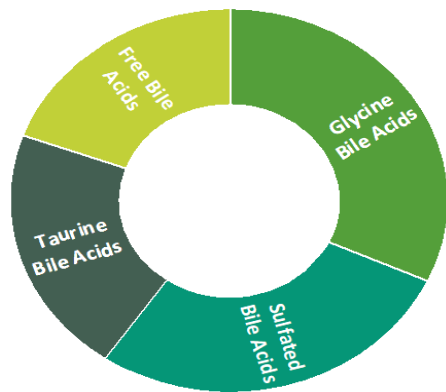


Bile Acid Profile is Different in Portal Vein

Portal Bile Acids

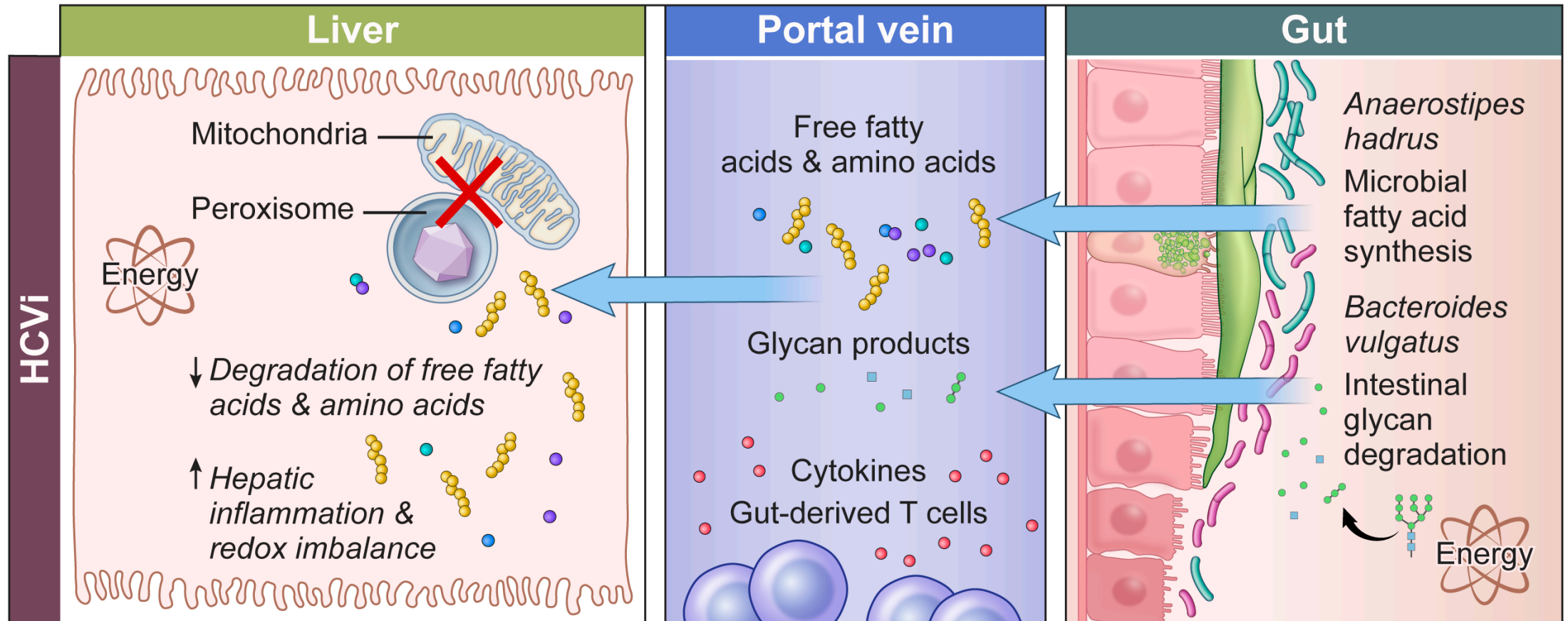


Peripheral Bile Acids



Bile Acids	Portal FGF19	Peripheral FGF19
Chenodeoxycholate (CDCA)		
Cholate (CA)		
Deoxycholate (DCA)		
Ursodeoxycholate (UDCA)		
Hyocholate (HCA)		
Glycochenodeoxycholate (GCDCA)		
Glycocholate (GCA)		
Glycodeoxycholate (GDCA)		
Glycoursodeoxycholate (GUDCA)		
Glycolithocholate (GLCA)		
Taurochenodeoxycholate (TCDCA)	1	
Taurocholate (TCA)	1	
Taurodeoxycholate (TDCA)	1	
Tauroursodeoxycholate (TUDCA)	1	
Taurolithocholatesulfate (TLCAS)	1	1
Taurochenatesulfate (TCNS)	1	1
Glycochenatesulfate (GCNS)		
Glycochenodeoxycholatesulfate (GCDCAS)		
Glycodeoxycholatesulfate (GDCAS)		
Glycolithocholatesulfate (GLCAS)		
Taurobetamuricholate (TBMCA)	1	1
Glycohyocholate (GHC)	1	1

Integration



PSC 000130

- HCV in some ways was a trial run
- If the portal blood had so much to say in HCV,
 - Which is not at all an intestinal disease,
 - What will we find in PSC?
- Across the disease spectrum
 - Allow for inferences about disease progression?
- Déjà vu all over again

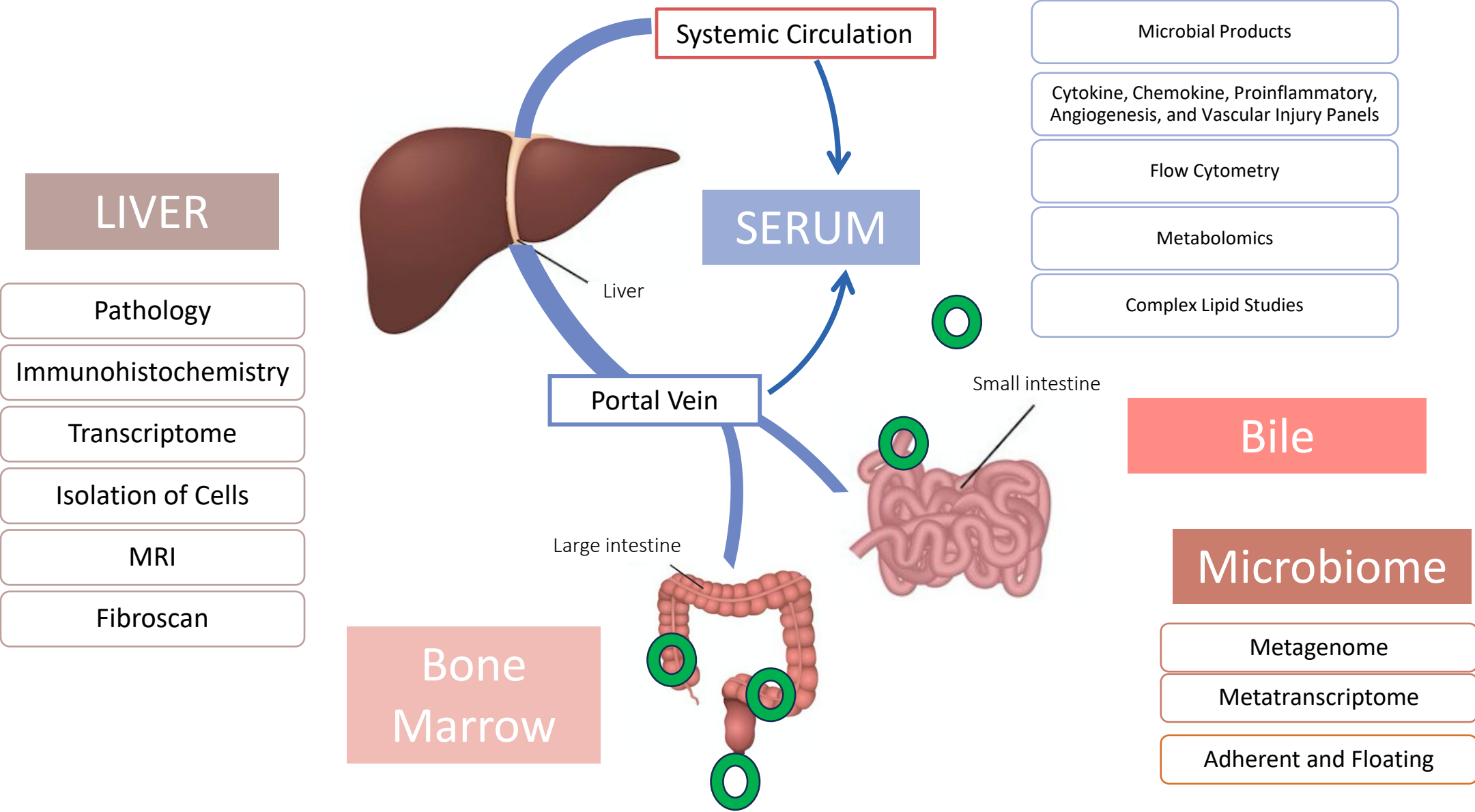
People

- 40
 - Up to 30 with IBD
 - Focus on large duct
 - Exclude decompensated disease
- One time
- Controls
 - 2 family or household
 - No procedures!

Power is in:

- Hidden compartment
- Disease spectrum
- Integration

Assessment of the Gut-Liver Axis



The background of the image is a monochromatic blue. It features a large, dark silhouette of a tree with many bare, intricate branches that spread across the frame. The lighting is soft, creating a slightly grainy texture in the blue background.

First Three People are Enrolled

Hope

- We want to understand that conversation
 - What upset the liver?
 - Biomarkers
 - Cause and cure are aspirational
 - If not, pathways to progression

Lead us to therapies that work!



Thank YOU

- So many who really understand PSC
- Patients
- Alaina Magnani
- Gian Rodriguez Franco
- Rownock Afruza
- Moumita Chakraborty
- Jenna Oringher
- Matt Menkart
- NIDDK/NIH

- Naga Chalasani
- Raj Vuppalanchi
- Ohad Etzion
- Julian Hercun

- PSC Partners
- Ricky Safer

