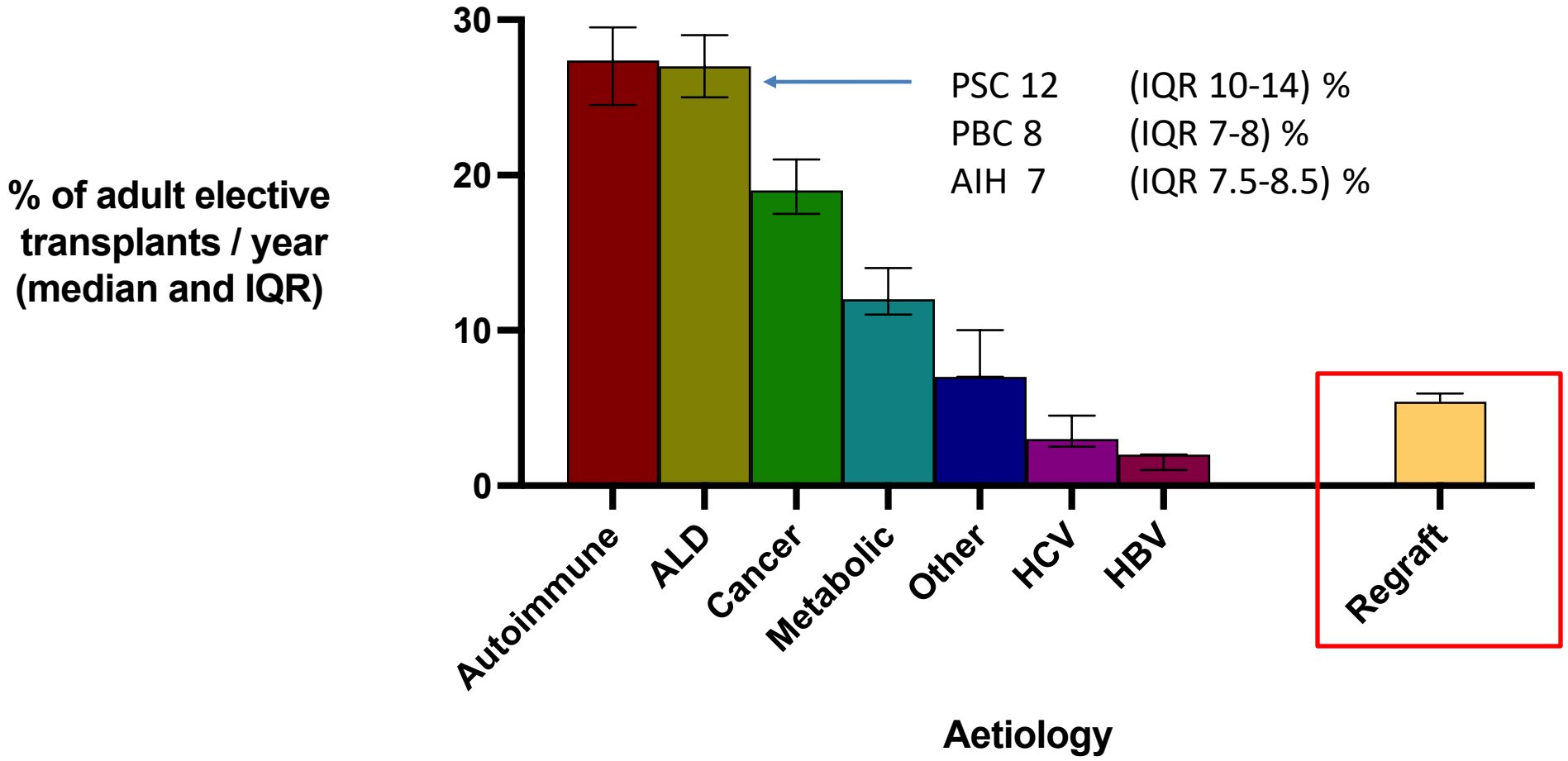
Gut Microbiome Therapeutics in Primary Sclerosing Cholangitis (PSC)

Palak J. Trivedi; @CholestasisDoc

NIHR Birmingham BRC,

Centre for Liver and Gastrointestinal Research

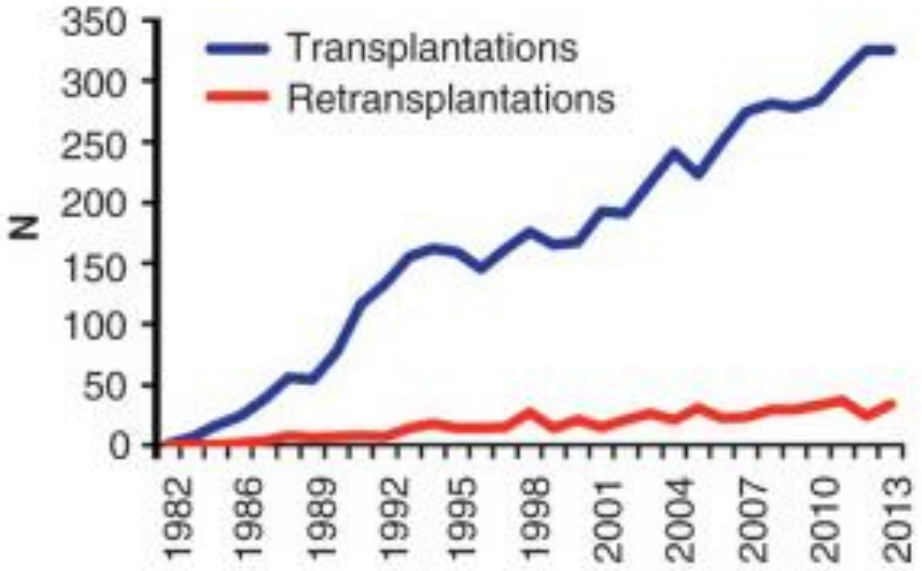
Autoimmune liver disease: the lead indication for adult liver transplantation in the UK



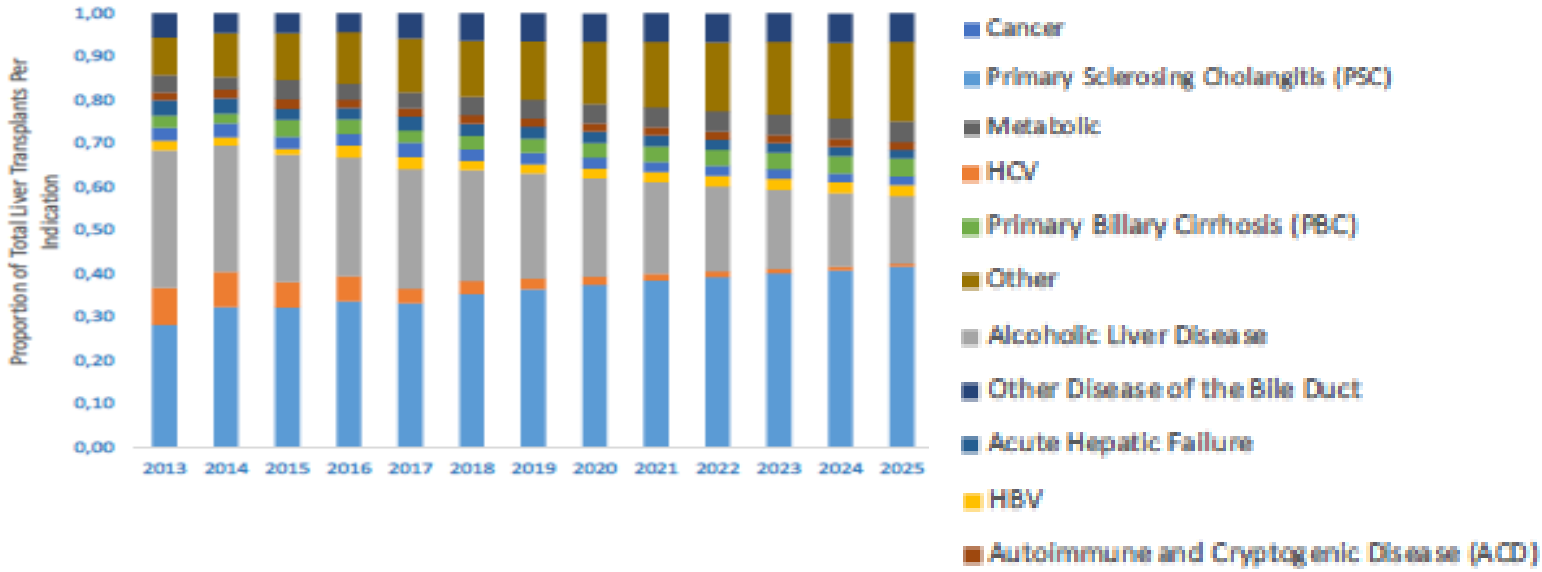
NHSBT summary data 2017-2022

PSC is one of the most common indications for liver transplantation

Nordic liver transplant programme
- 15.3% are performed for PSC

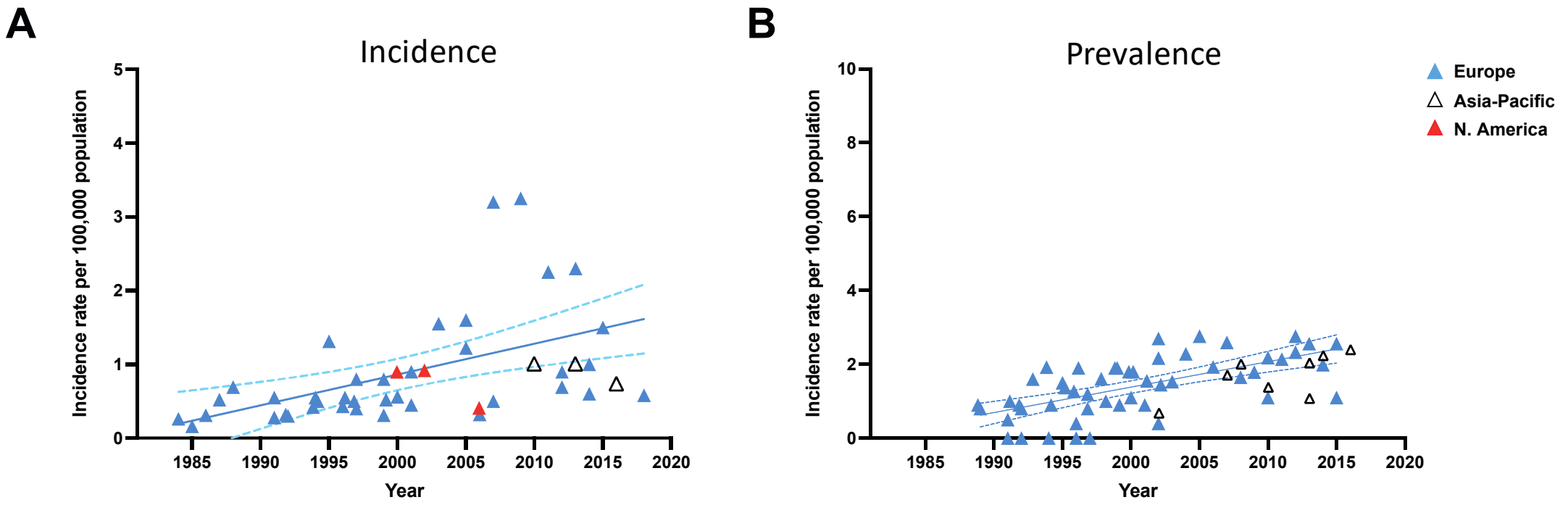


French liver transplant programme
- PSC will be the lead indication by 2025



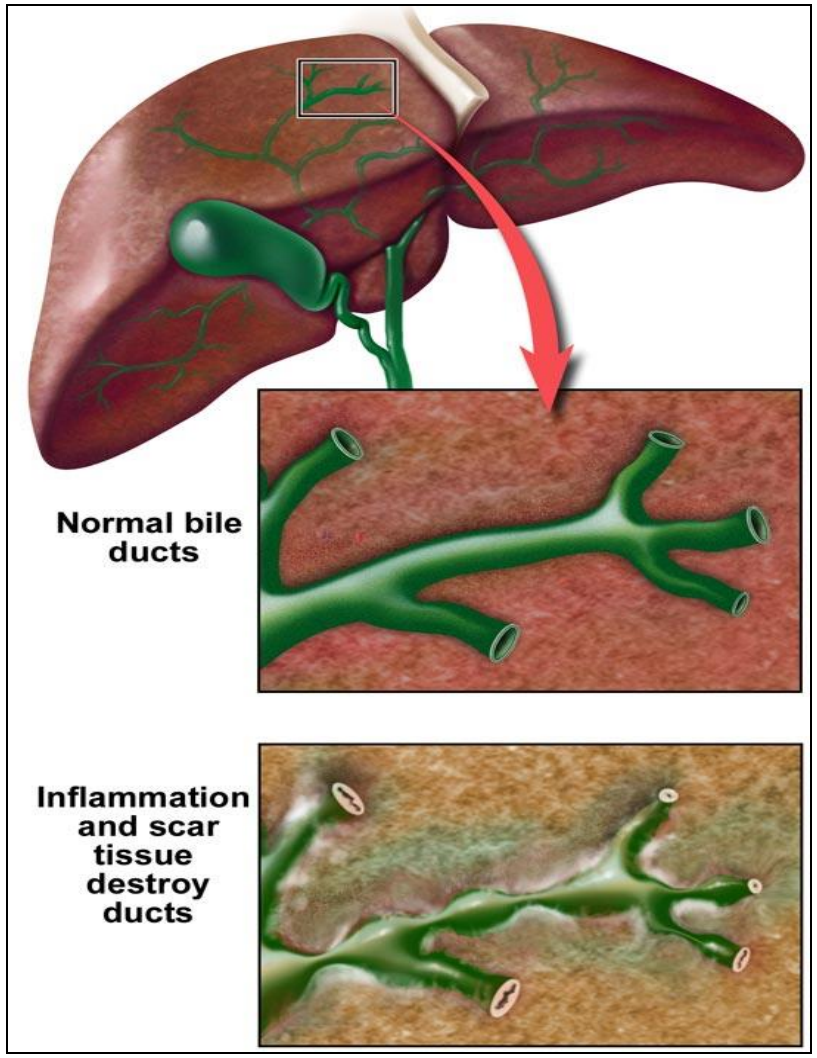
1) Fosby *et al. Scand. J. Gastro 2015*
2) Conolly *et al. J. Hepatol. 2020A*

PSC is rare but the incidence and prevalence are rising

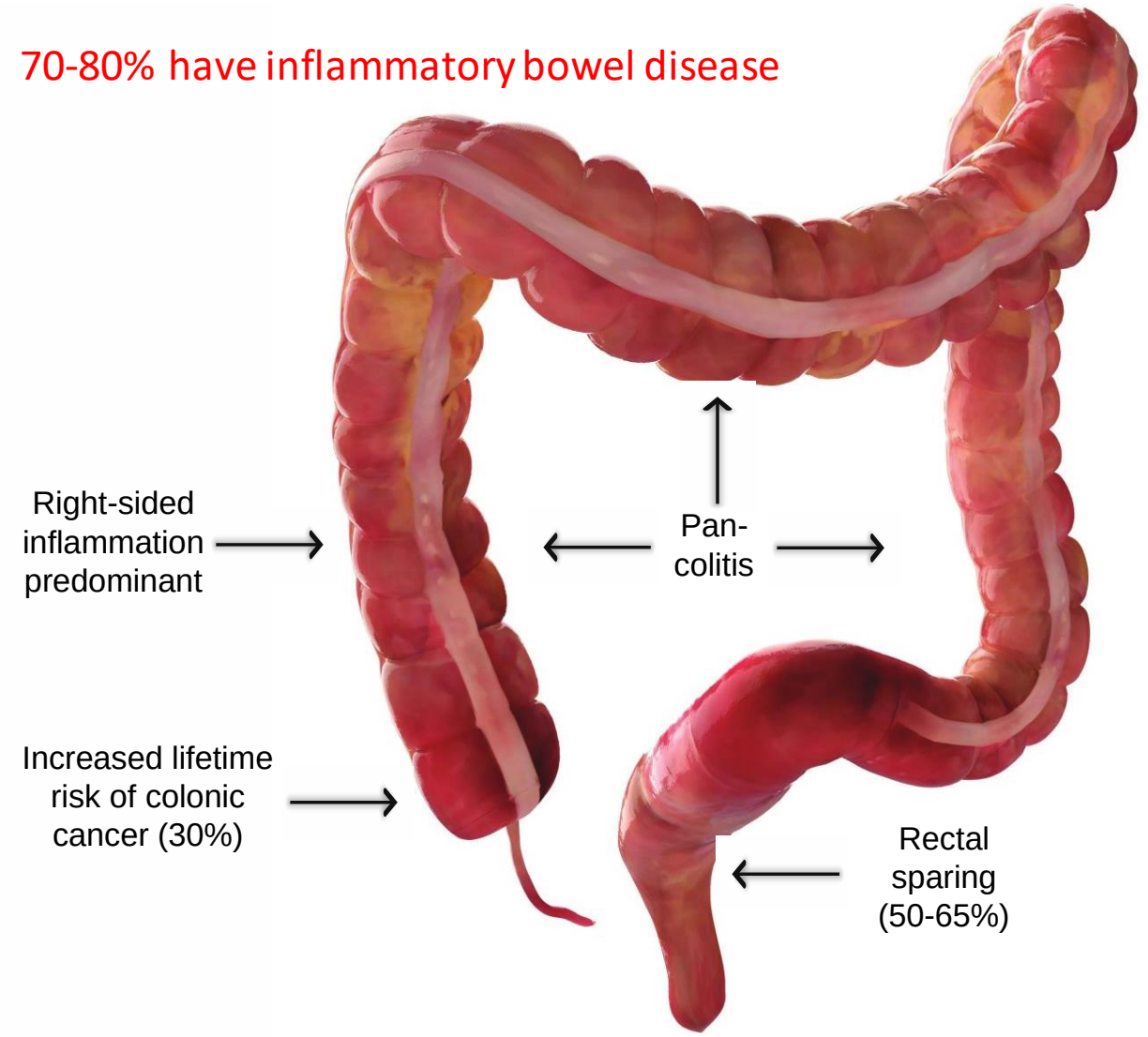


Trivedi et al. Gut 2021
Trivedi et al. Clin. Gastroenterol. Hepatol. 2022

PSC is not just a condition of the liver

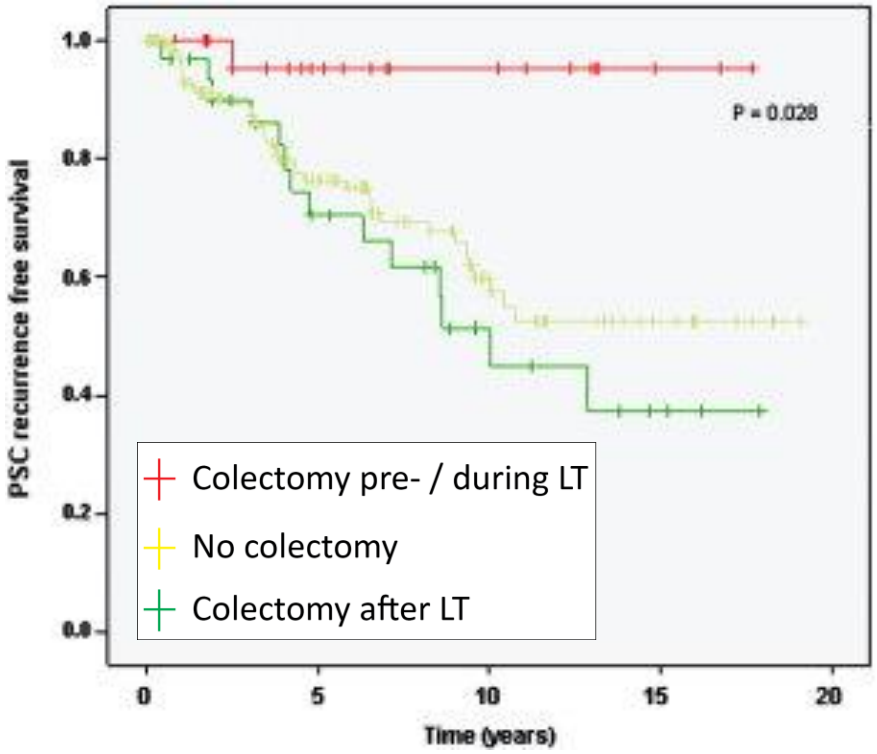


70-80% have inflammatory bowel disease



The presence /activity of colitis and recurrent PSC post-transplant

- Birmingham (UK) [1]



Hazard ratios (vs. pre-LT colectomy)
- Post-LT colectomy: 11.8
- No colectomy: 8.85

Validation:

- UK (multiple centres)
  - –Presence of UC post-LT
    H.R.: 2.4
- Germany (multicentre) [3]
  - –Presence of UC post-LT
    H.R.: 2.07
  - –Active colitis post-LT
    H.R.: 2.31
- Nordic transplant registry
  - –Colectomy pre-LT
    H.R.: 0.49

1. Alabraba E. *et al. Liver Transplantation* 2009
2. Ravikumar *et al. J. Hepatol.* 2015
3. Hildebrand *et al. Liver Transplantation* 2015
4. Lindstrøm et al. Scand. J. Gastro. 2018

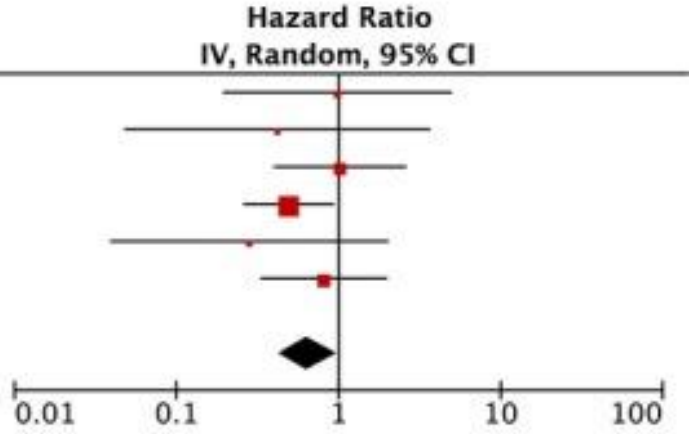
Colectomy prior to transplantation lowers the risk of recurrent PSC

(A) Colectomy before liver transplantation

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Alexander et al. 2008	-0.02	0.83	6.8%	0.98 [0.19, 4.99]
Gelley et al. 2014	-0.87	1.11	3.8%	0.42 [0.05, 3.69]
Gordon et al. 2016	0.02	0.48	20.2%	1.02 [0.40, 2.61]
Lindstrom et al. 2018	-0.71	0.33	42.7%	0.49 [0.26, 0.94]
Moncrief et al. 2010	-1.27	1.01	4.6%	0.28 [0.04, 2.03]
Ravikumar et al. 2015	-0.21	0.46	22.0%	0.81 [0.33, 2.00]
Total (95% CI)			**100.0%**	**0.65 [0.42, 0.99]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.92$, $df = 5$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 2.03$ ($P = 0.04$)

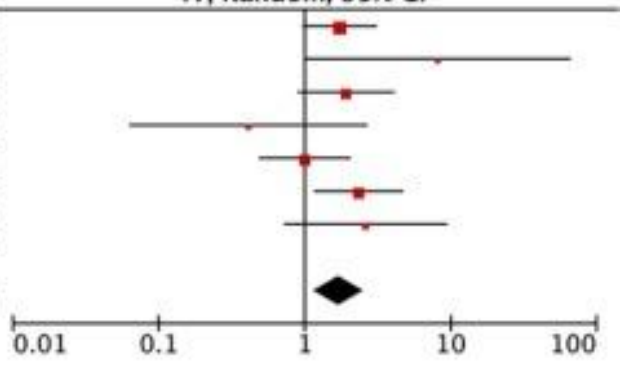


(B) IBD presence

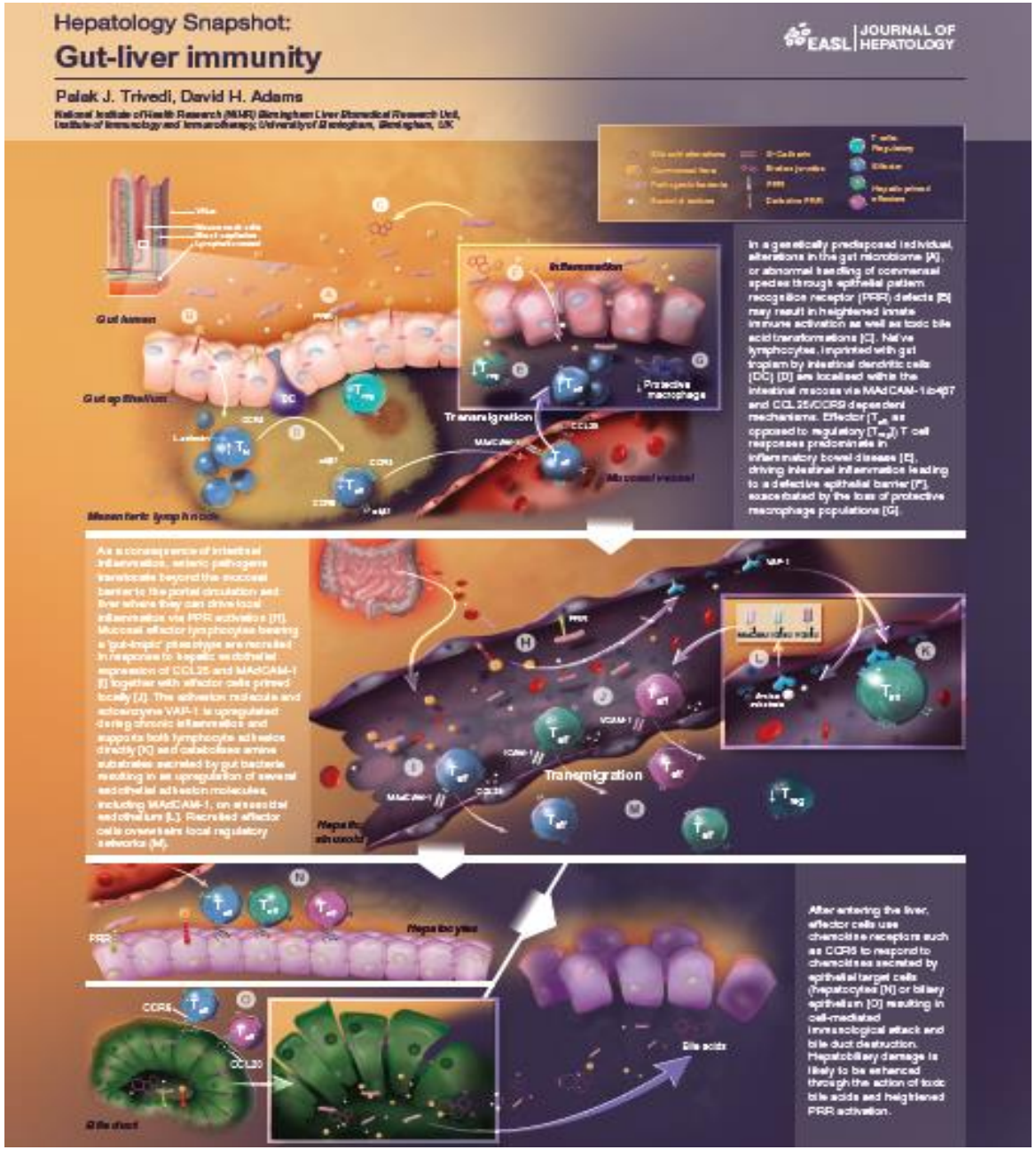
Study or Subgroup	log[Hazard Ratio]	SE	IBD Total	No IBD Total	Weight	Hazard Ratio IV, Random, 95% CI
Alabraba et al. 2009	0.55	0.3	162	68	26.1%	1.73 [0.96, 3.12]
Alexander et al. 2008	2.1	1.07	59	10	3.2%	8.17 [1.00, 66.50]
Egawa et al. 2011	0.65	0.39	44	49	18.4%	1.92 [0.89, 4.11]
Gelley et al. 2014	-0.89	0.96	21	4	4.0%	0.41 [0.06, 2.70]
Gordon et al. 2016	0	0.37	217	90	19.8%	1.00 [0.48, 2.07]
Hildebrand et al. 2016	0.85	0.36	220	76	20.6%	2.34 [1.16, 4.74]
Moncrief et al. 2010	0.96	0.66	48	11	7.8%	2.61 [0.72, 9.52]
Total (95% CI)			**771**	**308**	**100.0%**	**1.73 [1.17, 2.54]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.70$, $df = 6$ ($P = 0.26$); $I^2 = 22\%$

Test for overall effect: $Z = 2.78$ ($P = 0.006$)



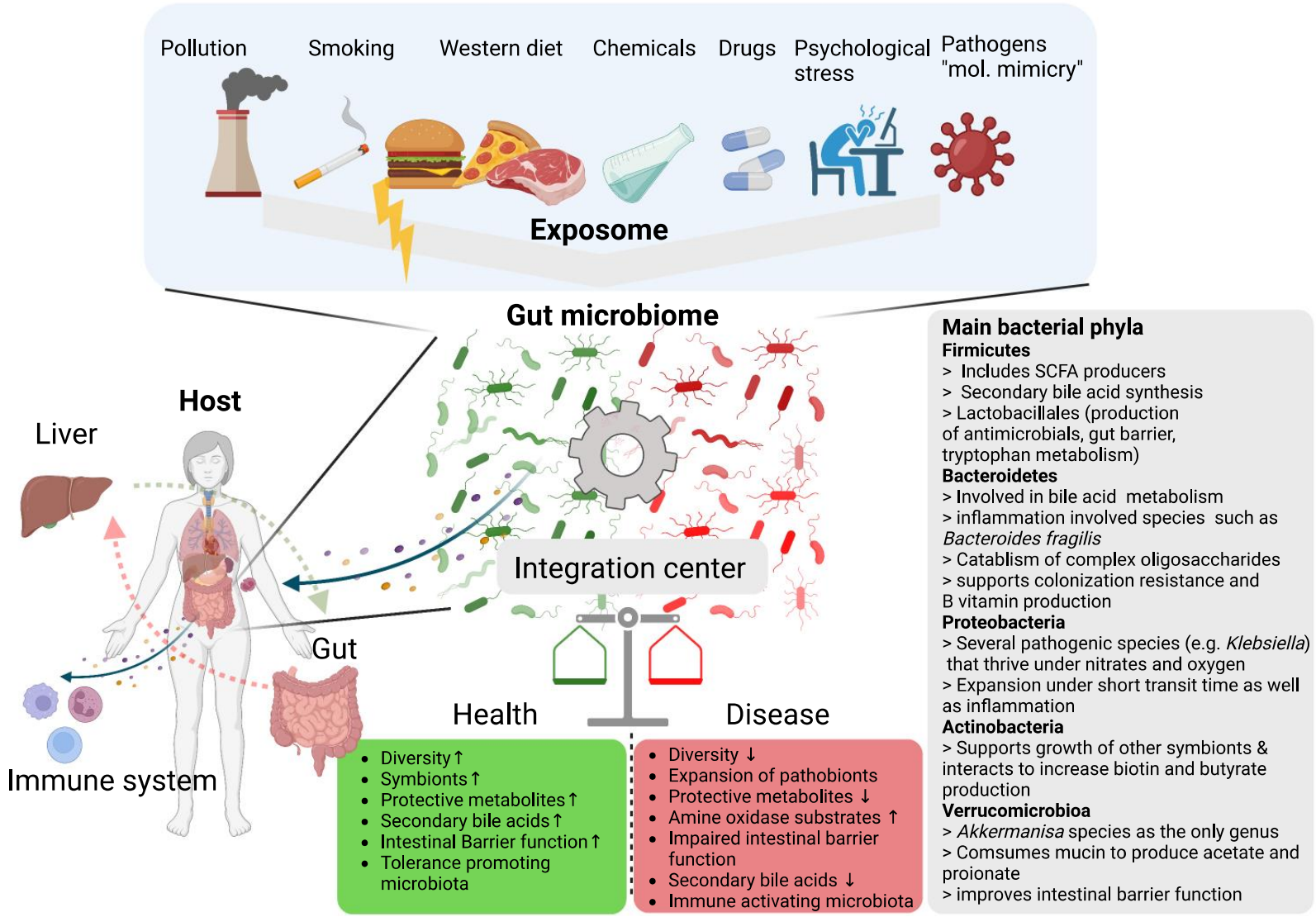
Steenstraten, Trivedi *et al. Aliment. Pharmacol.* 2019



- Enteric microbiome changes
  - Reduced microbial diversity
  - Enrichment of amine-producing species
  - Increased carcinogenic potential
- Disrupted intestinal barrier
  - Lower expression of tight-junction proteins
  - Reduced short-chain fatty acids
- Dysregulated mucosal immunity
  - Heightened T_h17 responses to pathogen stimulation
  - Pertubed regulatory T-cell function
  - Aberrant mucosal lymphocyte homing
- Pathological enterohepatic bile acid shifts
  - Reduced TGR5 expression
  - Increased gut FXR expression

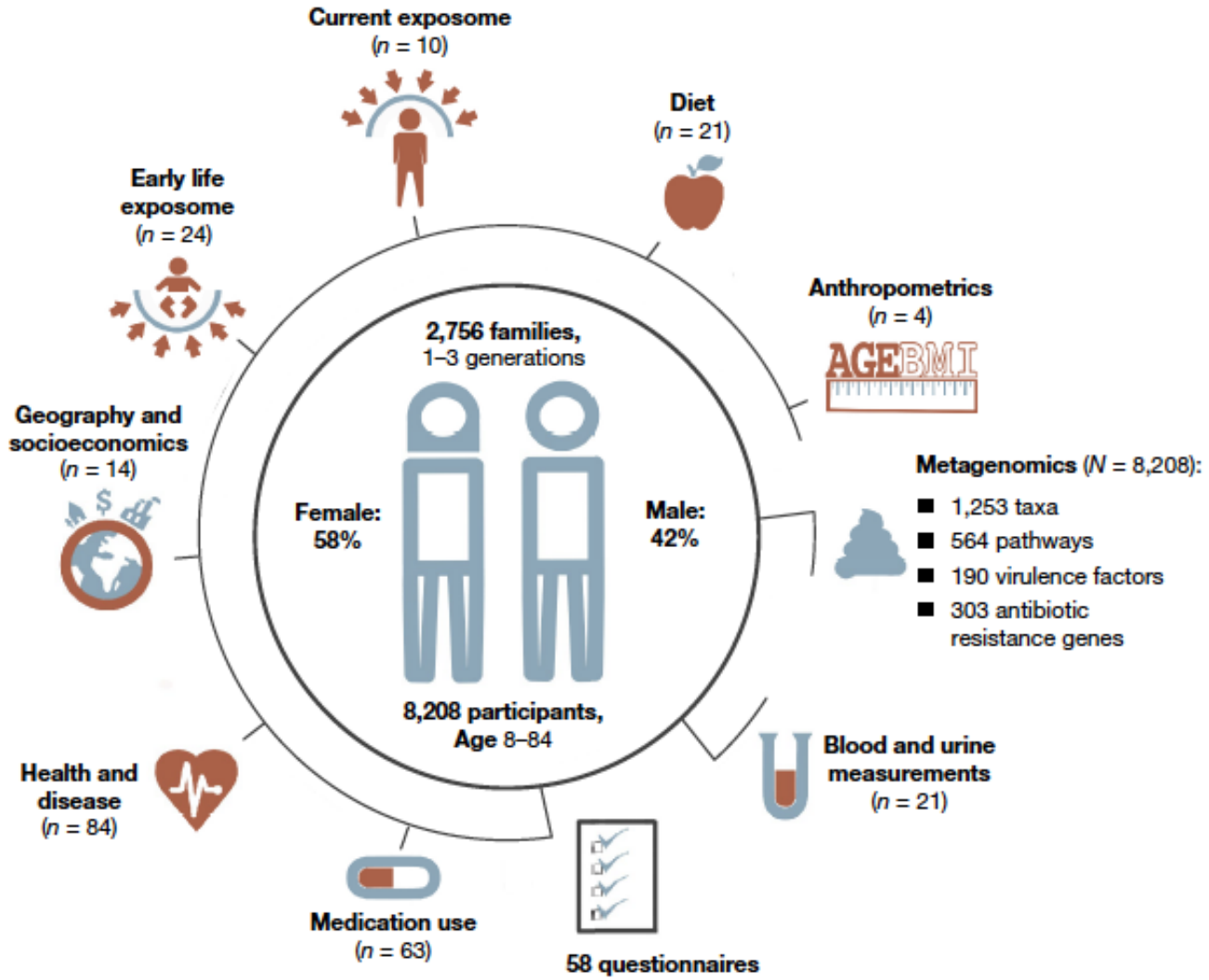
Trivedi and Adams *J. Hepatol.* 2016

Gut microbiome integrates environmental influences into host physiology



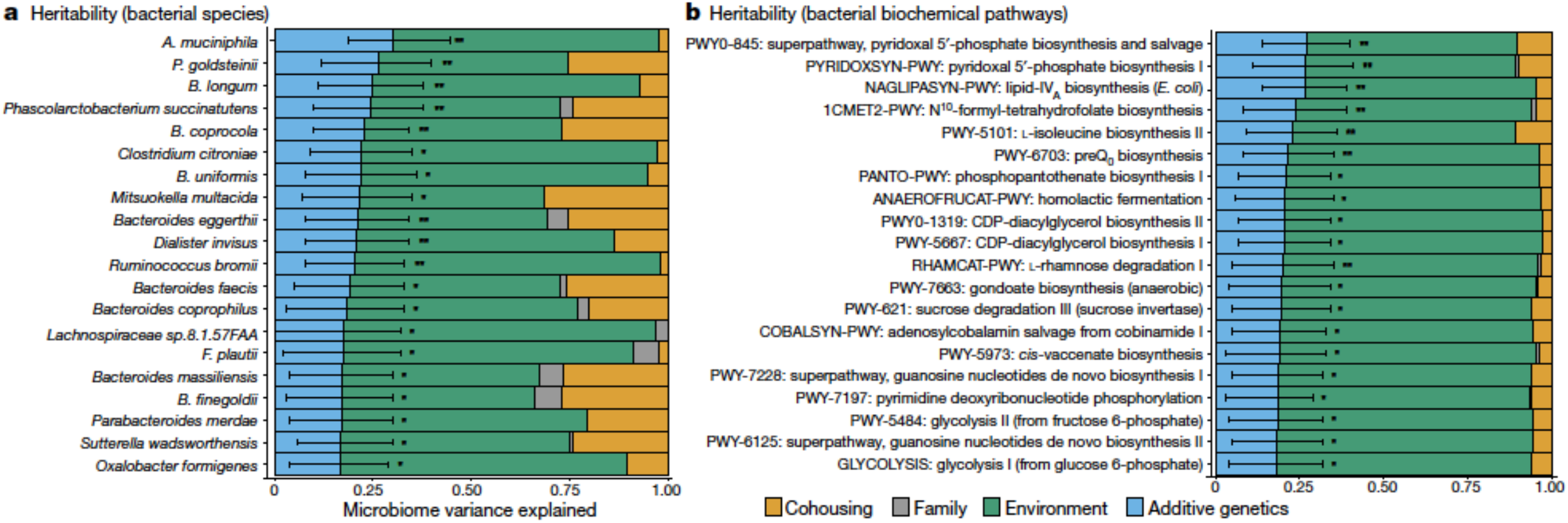
Schneider, Kummen, Trivedi, Hov; Hepatology 2023

Dutch microbiome project



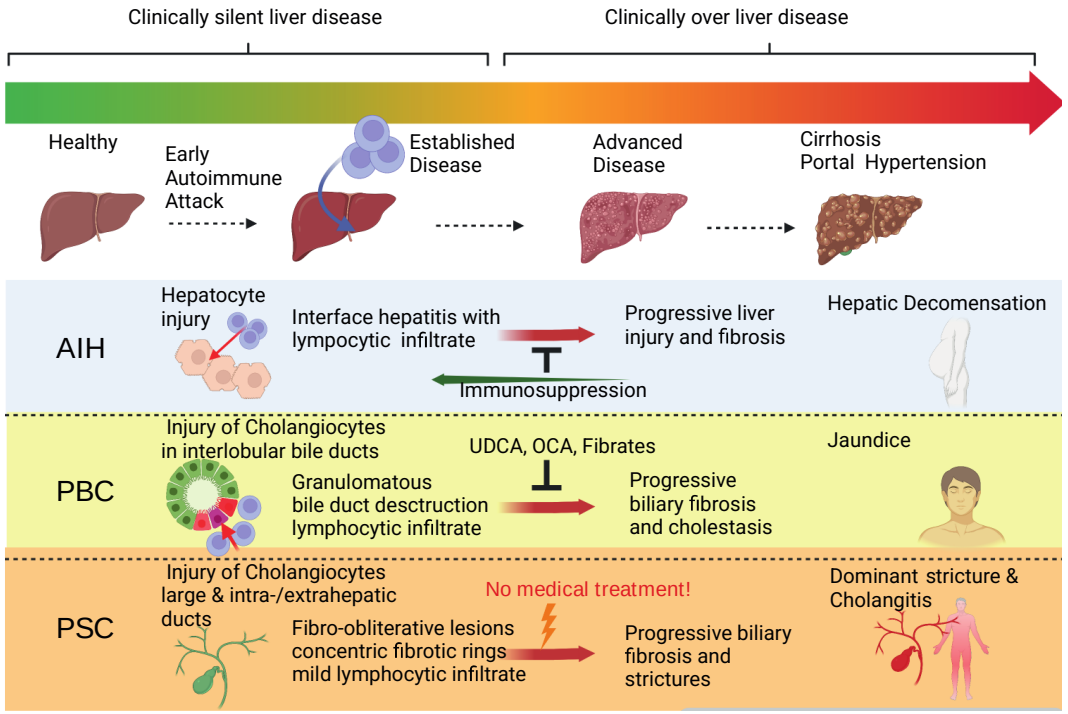
Gacesa et al. Nature 2022

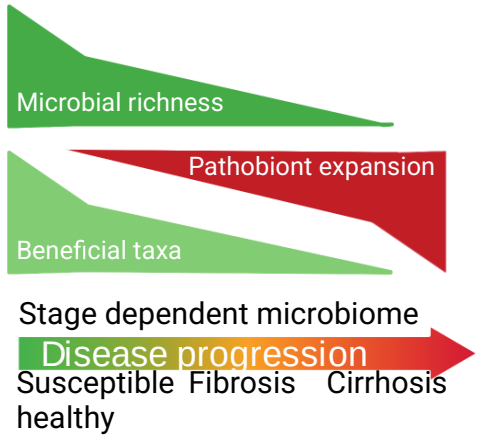
Heritability and effect of cohabitation on the gut microbiome

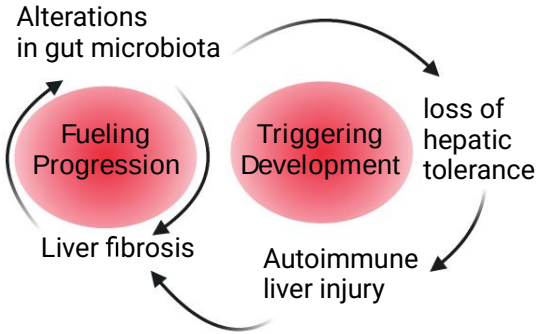


Gacesa et al. Nature 2022

Microbiome changes in autoimmune liver disease: aetiology or severity?

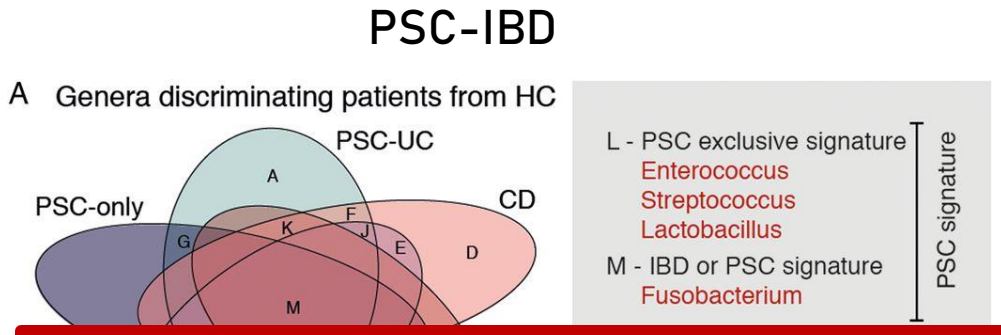


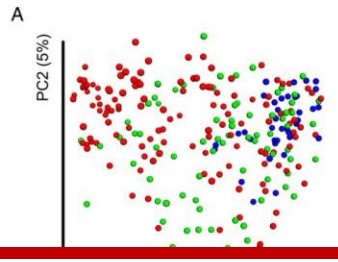


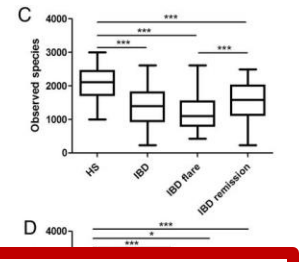


Schneider, Kummen, Trivedi, Hov; Hepatology 2023

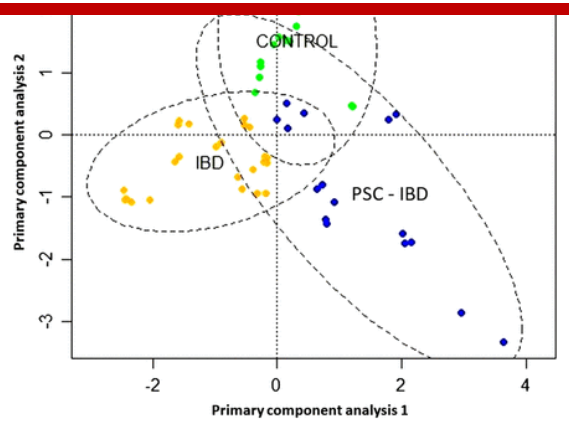
Dysbiosis in PSC and PSC-IBD

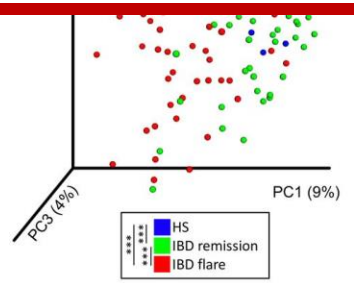


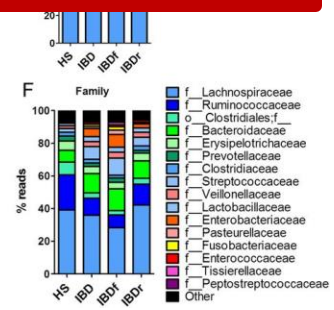




Does this mean something or is it just a correlation due to changes in outflow of bile acid from liver?



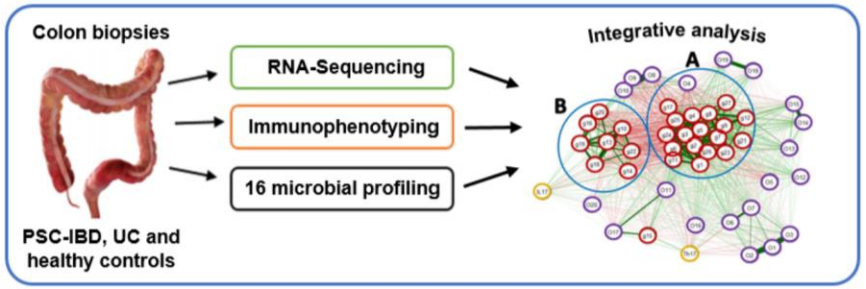


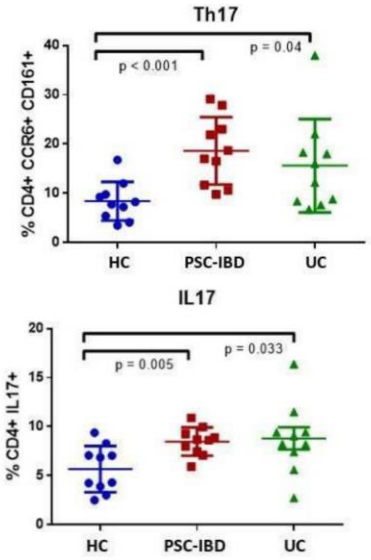


Quraishi MN et al. Gut. 2017

Sokol et al. Gut. 2015

PSC-IBD disease mechanisms appear to be different to IBD alone at a mucosal level

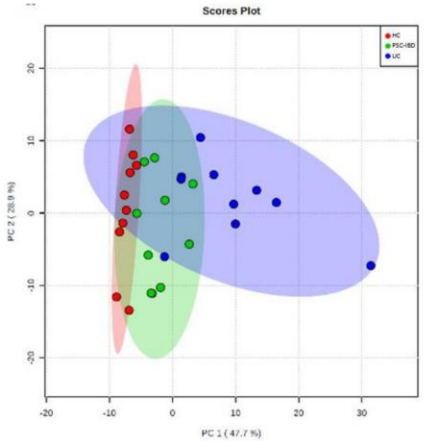


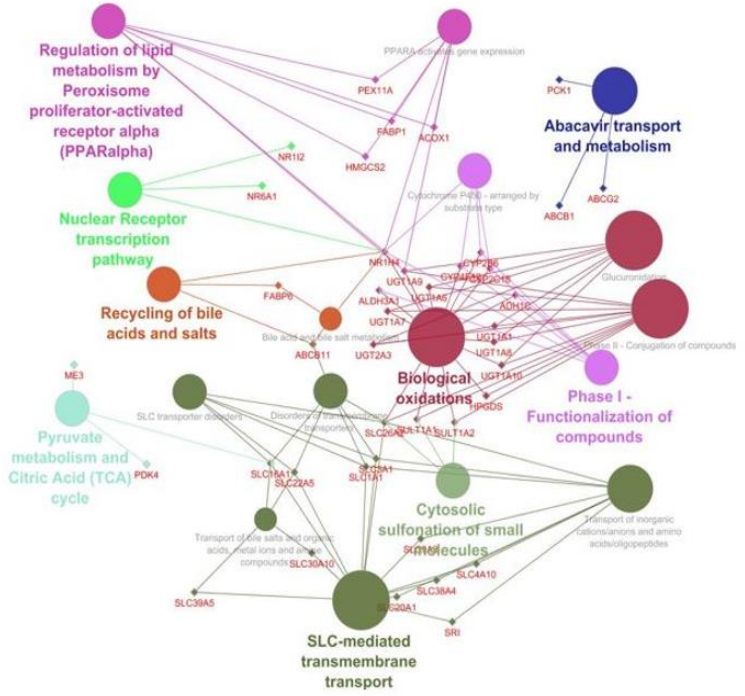


PSC-IBD and IBD have similar immune mediated pro-inflammatory signals

Different triggers for this immune response

Large differences in colonic mucosal gene expression versus IBD



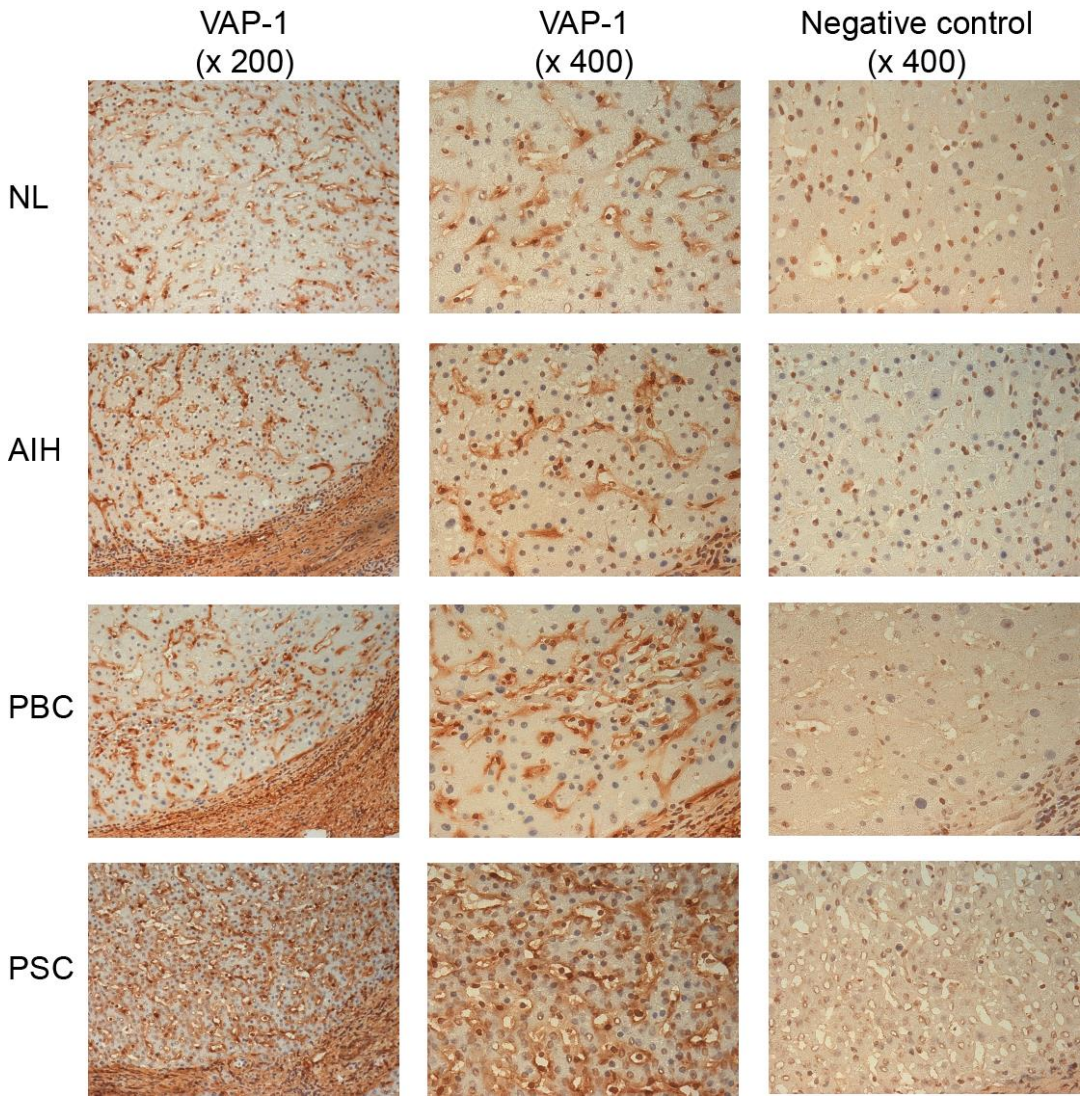


Bile acid homeostatic pathways significantly aberrant in PSC-IBD compared to UC

? Bile acid mediated inflammation

Quraishi, Hirschfield, Iqbal, et al. J Crohns Colitis. 2020

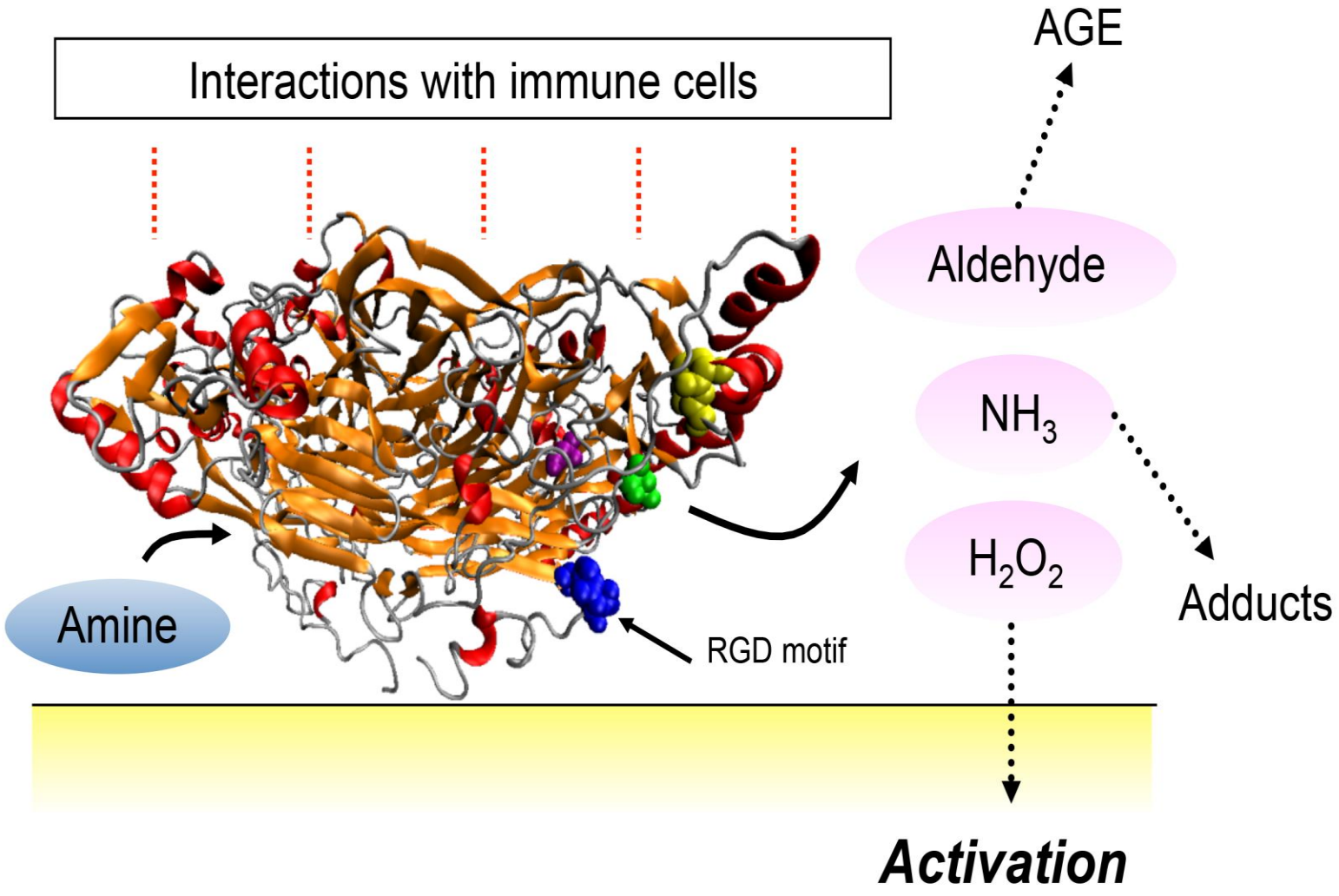
Hepatic vascular adhesion protein (VAP)-1 expression in autoimmune liver disease



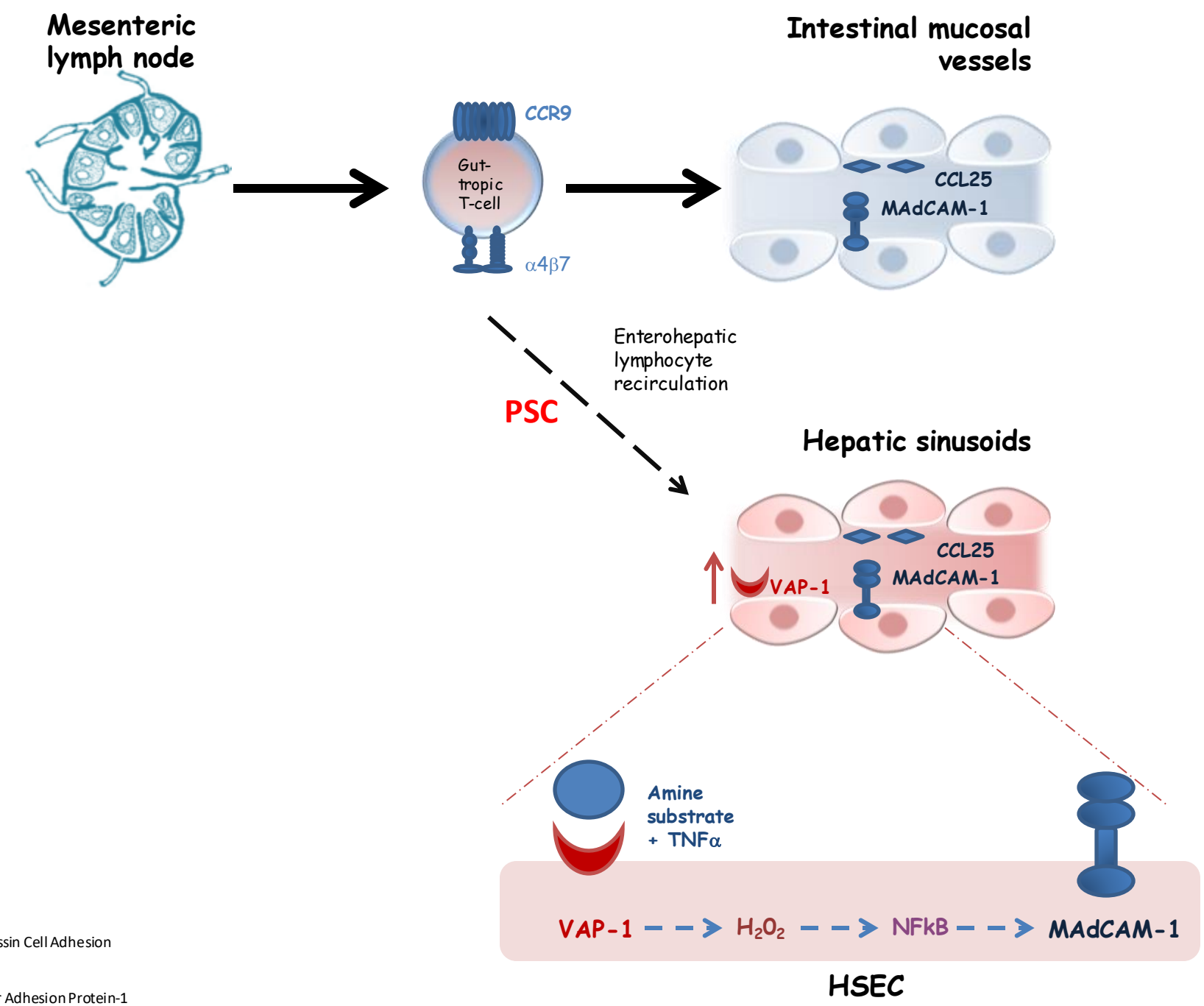
Trivedi, Liaskou, Adams, Weston *et al.* *Gut* 2018

Consequences of hepatic VAP-1 activation

What are the sources of amine substrates?



Weston and Adams *J. Neur. Trans.*. 2011



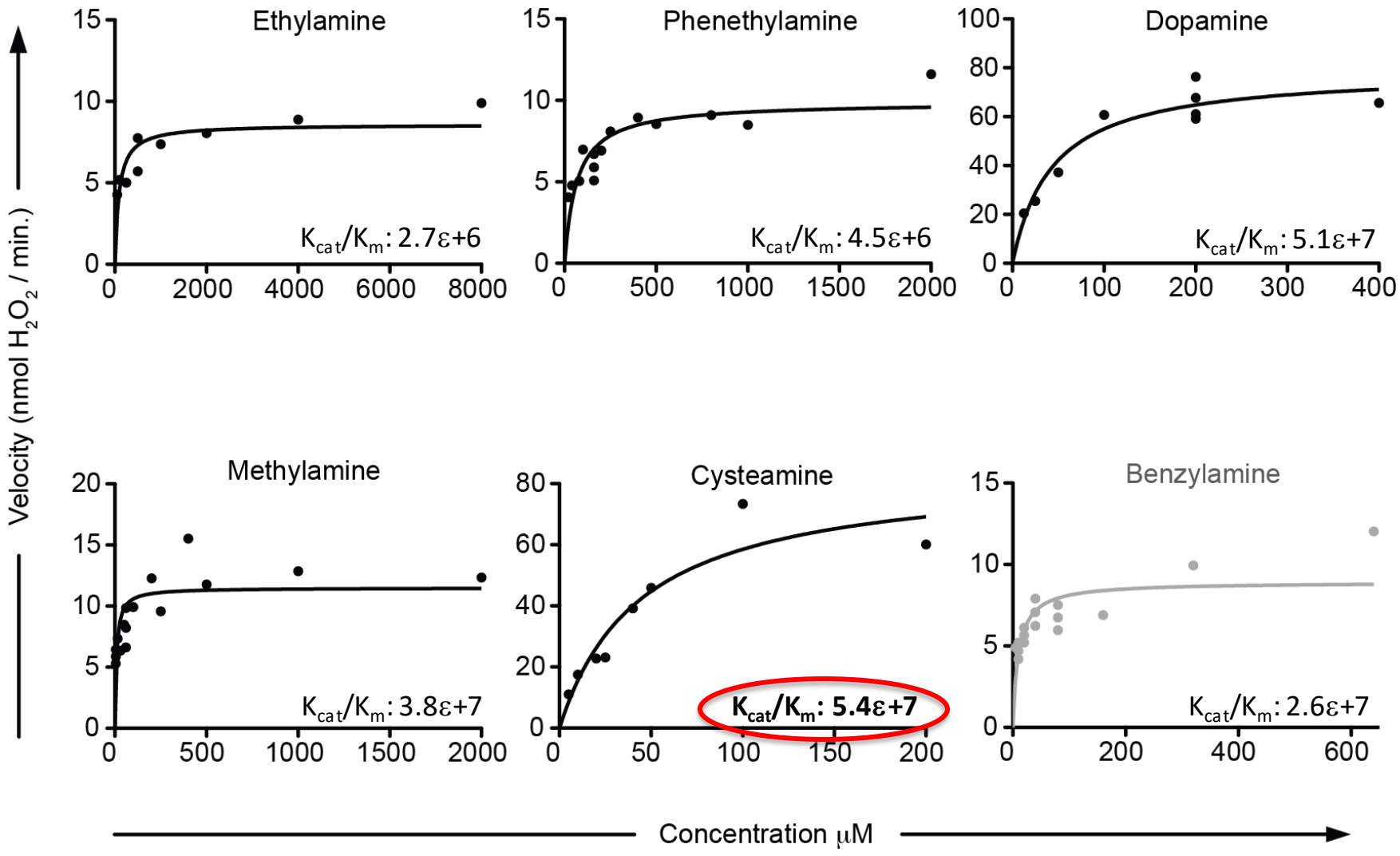
KEY:

MAdCAM-1:
Mucosal Addressin Cell Adhesion Molecule-1

VAP-1: Vascular Adhesion Protein-1

Trivedi and Adams. J. Autoimmun. 2013

VAP-1 activity is substrate dependent



Trivedi, Liaskou, Adams, Weston *et al.* *Gut* 2018

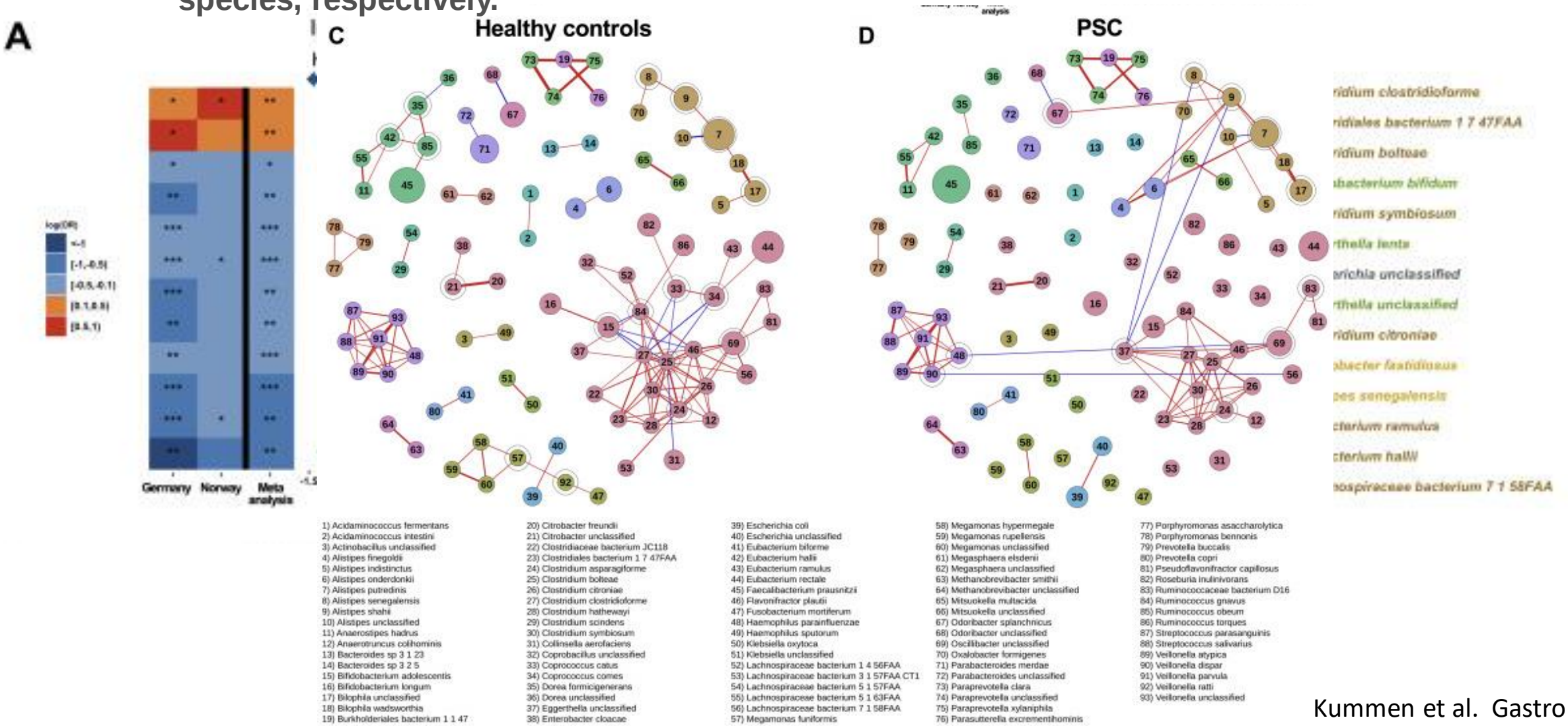
Cysteamine exposure can lead to colitis in mice

- Cysteamine induces colitis in mice
  - Klicek et al. 2013; *J. Physiol Pharmacol*.

- Inflamed colonic epithelium and *Escherichia* and *Enterobacter* spp. – main provider of cysteamine
  - Overexposure to cysteamine, colitis and cancer
    - Martin et al. 2004 *J. Clin. Inv.*
    - Gensollen et al. 2013 *Inflamm. Bowel Dis*
  - Inhibit cysteamine generation: attenuates colitis / prevents colorectal cancer
    - Berruyer et al. 2006 *J. Exp. Med*

Bacterial abundance co-correlation network

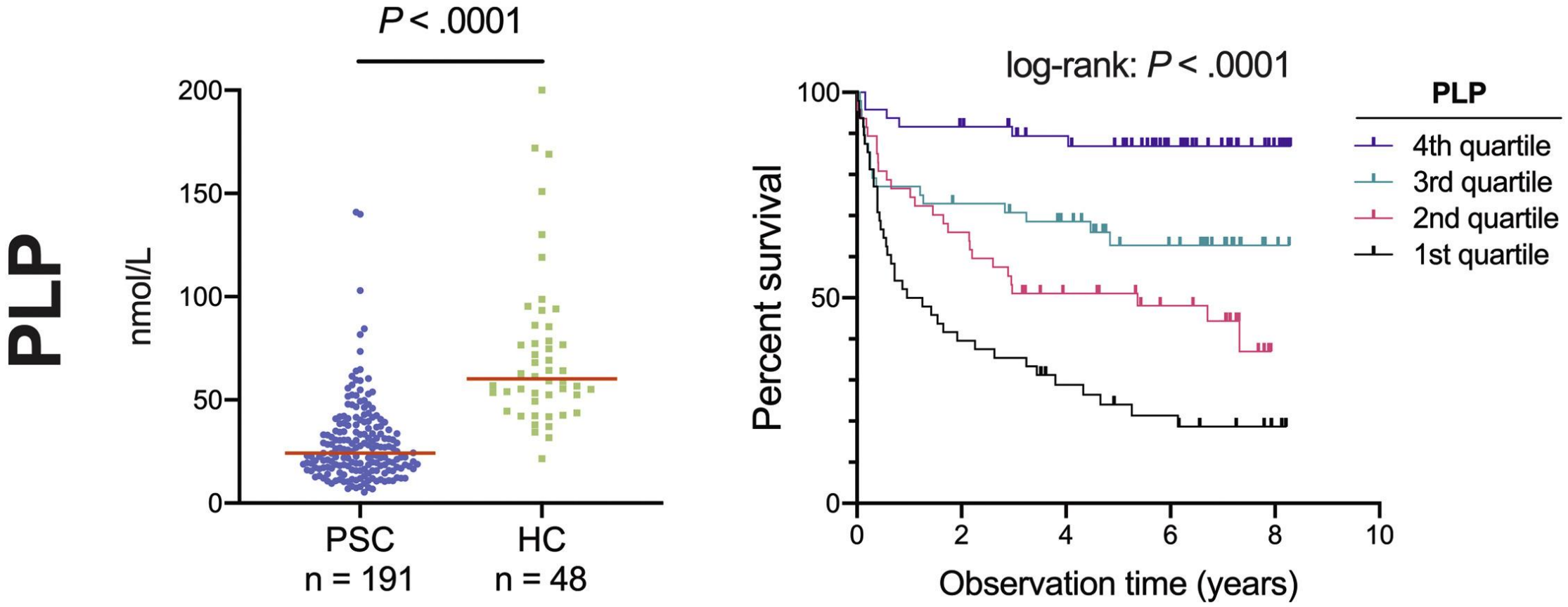
***Red* and *blue lines* in (*C*) and (*D*) indicate positive and negative correlations between species, respectively.**



1) Acidaminococcus fermentans
2) Acidaminococcus intestini
3) Actinobacillus unclassified
4) Alistipes finegoldii
5) Alistipes indistinctus
6) Alistipes onderdonkii
7) Alistipes putredinis
8) Alistipes senegalensis
9) Alistipes shahii
10) Alistipes unclassified
11) Anaerostipes hadrus
12) Anaerotruncus colihominis
13) Bacteroides sp 3 1 23
14) Bacteroides sp 3 2 5
15) Bifidobacterium adolescentis
16) Bifidobacterium longum
17) Bilophila unclassified
18) Bilophila wadsworthia
19) Burkholderiales bacterium 1 1 47
20) Citrobacter freundii
21) Citrobacter unclassified
22) Clostridiaceae bacterium JC118
23) Clostridiales bacterium 1 7 47FAA
24) Clostridium asparagiforme
25) Clostridium bolteae
26) Clostridium citroniae
27) Clostridium clostridioforme
28) Clostridium hathewayi
29) Clostridium scindens
30) Clostridium symbiosum
31) Collinsella aerofaciens
32) Coprobacillus unclassified
33) Coprococcus catus
34) Coprococcus comes
35) Dorea formicigenerans
36) Dorea unclassified
37) Eggerthella unclassified
38) Enterobacter cloacae
39) Escherichia coli
40) Escherichia unclassified
41) Eubacterium biforme
42) Eubacterium hallii
43) Eubacterium ramulus
44) Eubacterium rectale
45) Faecalibacterium prausnitzii
46) Flavonifractor plautii
47) Fusobacterium mortiferum
48) Haemophilus parainfluenzae
49) Haemophilus sputorum
50) Klebsiella oxytoca
51) Klebsiella unclassified
52) Lachnospiraceae bacterium 1 4 56FAA
53) Lachnospiraceae bacterium 3 1 57FAA CT1
54) Lachnospiraceae bacterium 5 1 57FAA
55) Lachnospiraceae bacterium 5 1 63FAA
56) Lachnospiraceae bacterium 7 1 58FAA
57) Megamonas funiformis
58) Megamonas hypermegale
59) Megamonas rupellensis
60) Megamonas unclassified
61) Megasphaera elsdenii
62) Megasphaera unclassified
63) Methanobrevibacter smithii
64) Methanobrevibacter unclassified
65) Mitsuokella multacida
66) Mitsuokella unclassified
67) Odoribacter splanchnicus
68) Odoribacter unclassified
69) Oscillibacter unclassified
70) Oxalobacter formigenes
71) Parabacteroides merdae
72) Parabacteroides unclassified
73) Paraprevotella clara
74) Paraprevotella unclassified
75) Paraprevotella xylaniphila
76) Parasutterella excrementihominis
77) Porphyromonas asaccharolytica
78) Porphyromonas bennonis
79) Prevotella buccalis
80) Prevotella copri
81) Pseudoflavonifractor capillosus
82) Roseburia inulinivorans
83) Ruminococcaceae bacterium D16
84) Ruminococcus gnavus
85) Ruminococcus obeum
86) Ruminococcus torques
87) Streptococcus parasanguinis
88) Streptococcus salivarius
89) Veillonella atypica
90) Veillonella dispar
91) Veillonella parvula
92) Veillonella ratti
93) Veillonella unclassified

Kummen et al. Gastro 2021

Down regulation of vit. B6 synthesis is associated with poorer clinical outcomes in PSC



PLP = pyridoxal 5′-phosphate
Active form of vitamin B6

Kummen et al. Gastro. 2021
Braadland et al. J. Hepatol. 2023

Vancomycin for colitis in PSC-IBD

- 17 children with PSC-IBD
- All 15/15 normalised to <200
- Mean faecal calprotectin improved from 1055 to 51

- PSC-IBD (n=8, OLT=5)
- Vancomycin 125mg QDS 6 to 8 weeks
- Mean reduction of Mayo Score (UC) – 7 points

Table 1 Comparison of indication, colonoscopy findings, mucosal biopsies, PUCAI scoring, FC and liver phenotype at baseline and during treatment with oral vancomycin (OV)

	Age OV	Indication		Colonoscopy	PUCAI	FC	Liver phenotype
1	15	Failed CMT: 5-ASA steroids	Pre-OV	Mayo 3 Pancolitis Rectal sparing	40	960	Cirrhosis negative PHT negative Fibrosis 3
		TP UDCA	On OV	Mayo 0 Histology normal	0	26	
2	17	Failed CMT: Steroids	Pre-OV	Mayo 3 Worse right side	30	500	Cirrhosis negative PHT negative Fibrosis 1
		TP MTX IFX	On OV	Mayo 0 Histology mild	0	150	
3	15	Failed CMT: EEN Steroids TP MTX IFX	Pre-OV	Mayo 2 Pancolitis	45	1531	Cirrhosis negative PHT negative
			On OV	Mayo 0 Histology normal	0	77	

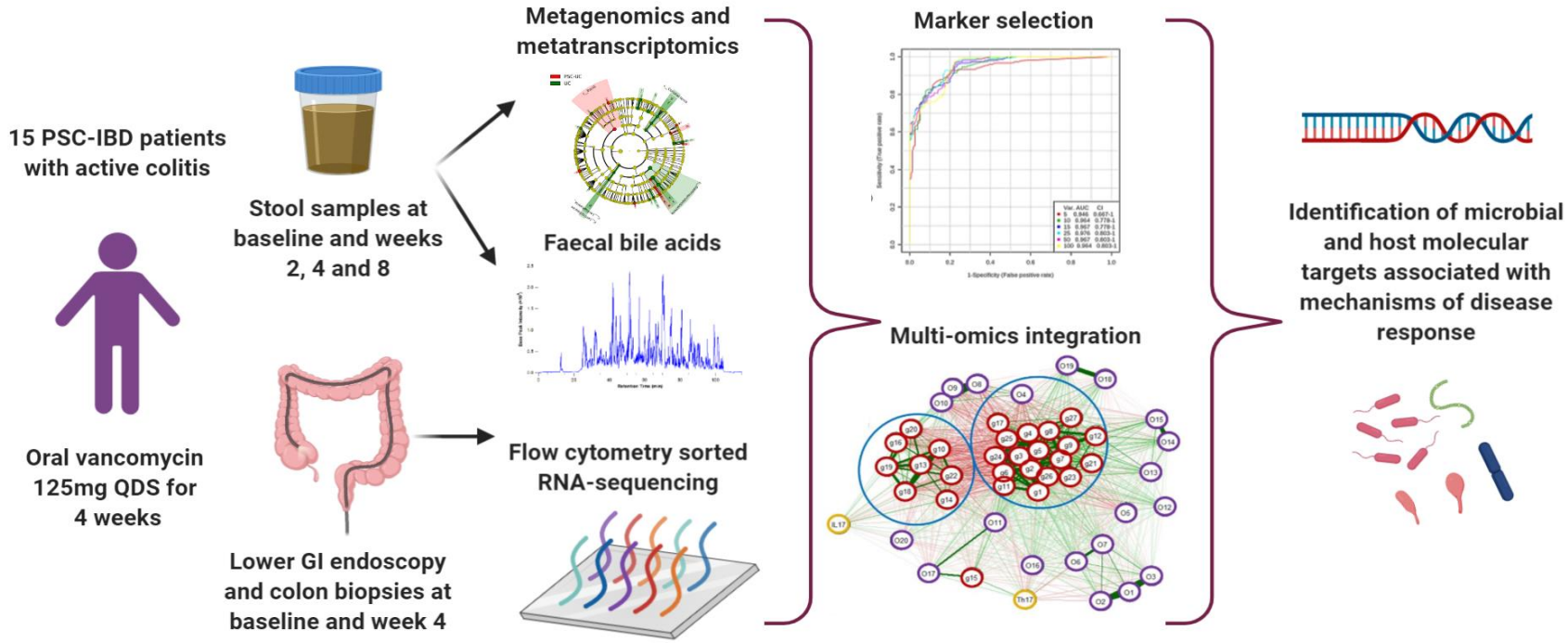
TABLE 1. Oral Vancomycin Effects on Clinical and Endoscopic UC Mayo Score

Patient	Liver Transplant for PSC	Prior Failed Treatment	Current OV, Total Dose/ Day, mg	Additional Immunosuppression While on OV	UC Mayo Score Pre-OV Initiation (Clinical/ Endoscopic/ Physician Assessment)	UC Mayo Score Post-OV Initiation (Clinical/ Endoscopic/ Physician Assessment)	UC Mayo Score Reduction After OV Initiation	Longest Remission Time/Current Status
Female 19 y	Liver transplant	5-ASA 6-MP Methotrexate Budesonide Infliximab Adalimumab	250	Low-dose prednisone Tacrolimus Sirolimus	9 (5/2/2)	0 (0/0/0)	–9	30 mo Clinical Mayo 0 Endoscopic Mayo at 24 mo: 0
Female 31 y	PSC without cirrhosis	5-ASA	375	None	8 (5/2/1)	0 (0/0/0)	–8	24 mo Clinical Mayo 0 Endoscopic Mayo at 24 mo: 0
Female 52 y	Liver transplant	5-ASA 6-MP Vedolizumab	375	Tacrolimus Mycophenolate	11 (6/2/3)	0 (0/0/0)	–11	19 mo Clinical Mayo 0 However, underwent total colectomy for flat high-grade dysplasia
Female 44 y	Liver transplant x2	5-ASA 6-MP	375	Budesonide Tacrolimus	7 (3/2/2)	0(0/0/0)	–7	36 mo Clinical Mayo 0 Endoscopic Mayo at 36 mo: 1
Male 39 y	Liver transplant	Infliximab Ustekinumab Vedolizumab	750	Low-dose prednisone	7 (3/2/2)	0(0/0/0)	–7	14 mo Clinical Mayo 0
Female 33 y	Liver transplant	5-ASA 6-MP Infliximab Adalimumab Vedolizumab q8 wk	375	Vedolizumab	8 (4/2/2)	2(2/NA/0) fecal calprotectin normalized	–6	9 mo Clinical Mayo 0
Male 42 y	PSC without cirrhosis	5-ASA Infliximab Vedolizumab	375	Azathioprine	6 (2/2/2)	1 (0/1/0)	–5	12 mo Clinical Mayo 0 Endoscopy Mayo at 12 mo 1

Tan Li-Za et al. Gut. 2019

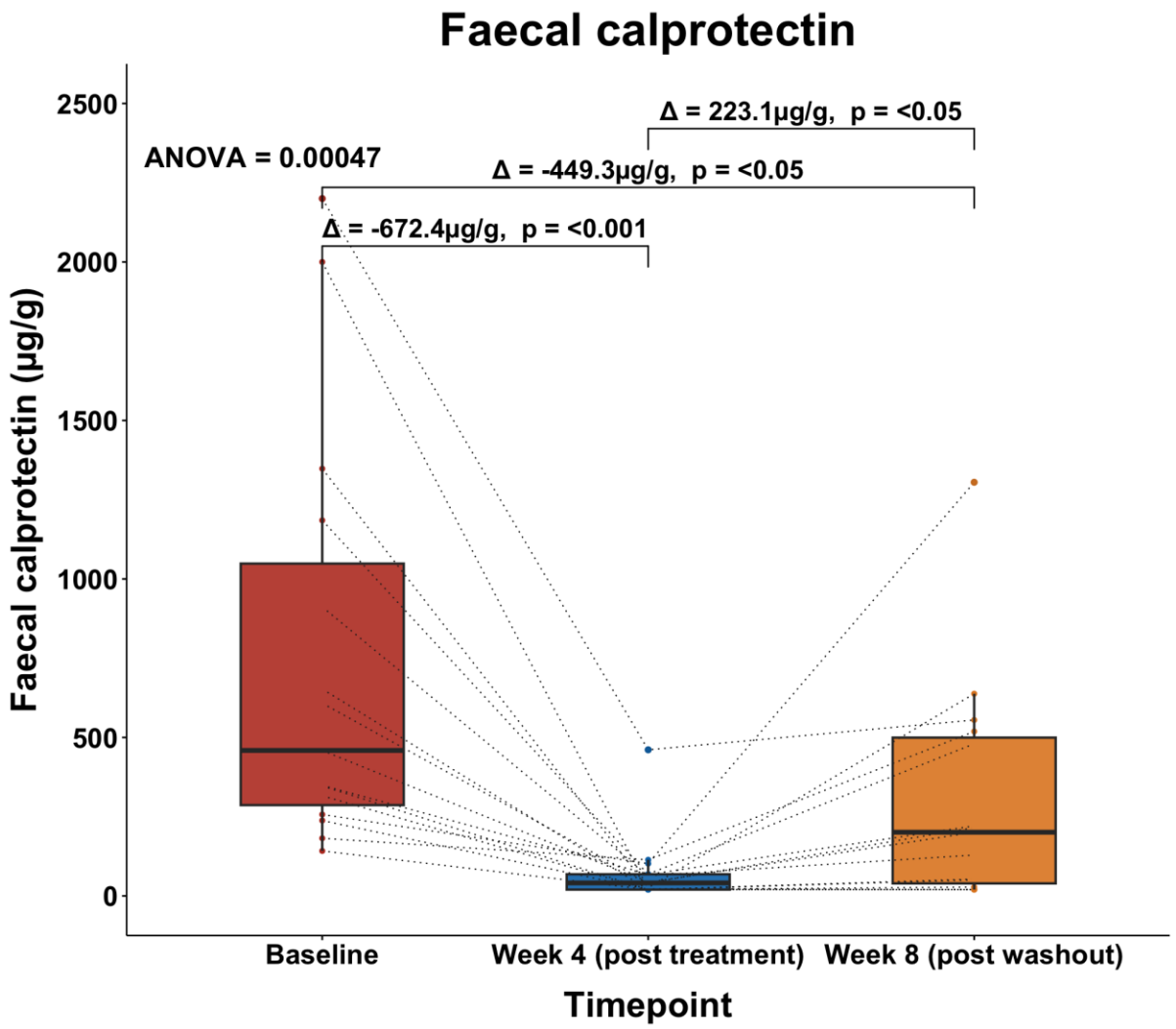
Dao A et al. IBD. 2019

PSC-Vancomycin study (NCT05376228)
ECCO Grant 2021

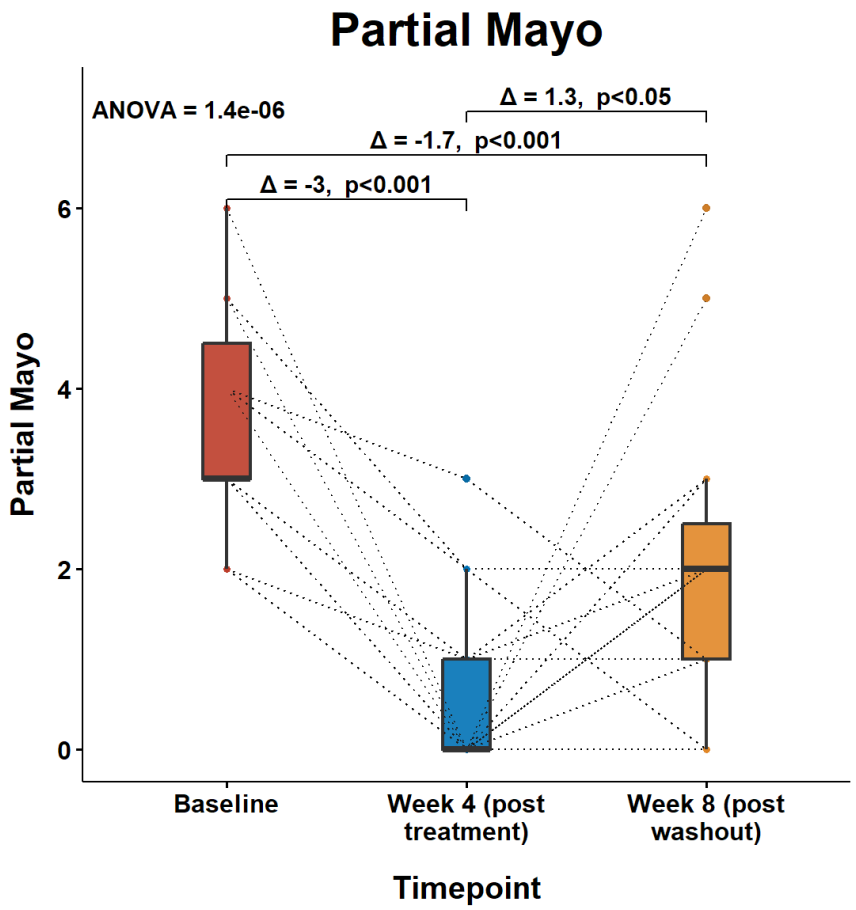


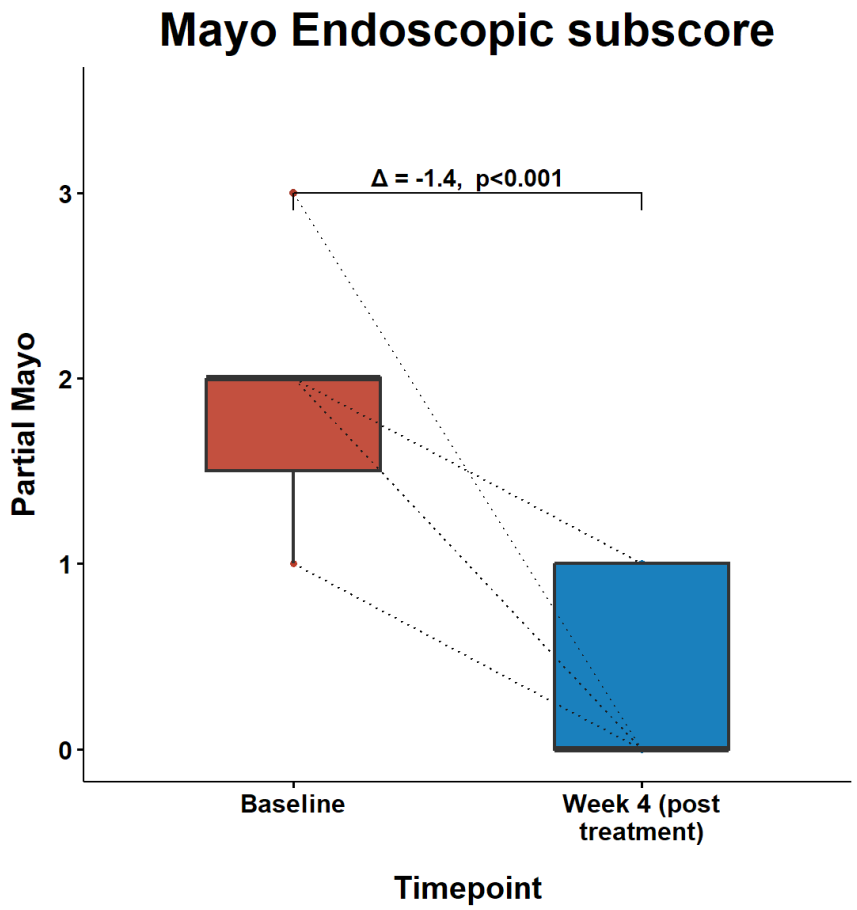
- Completed in Nov 2022
- Clinical and mucosal microbiota data so far
- Colonic RNA-seq, metagenomic, metatranscriptomics readouts by Jan 2024

IBD activity – faecal calprotectin

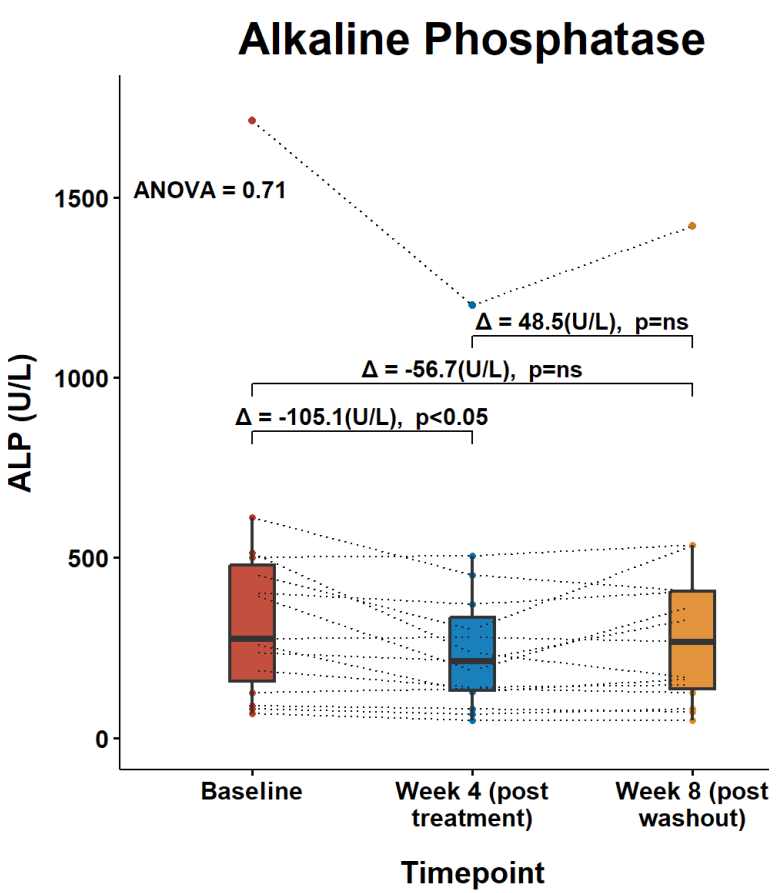


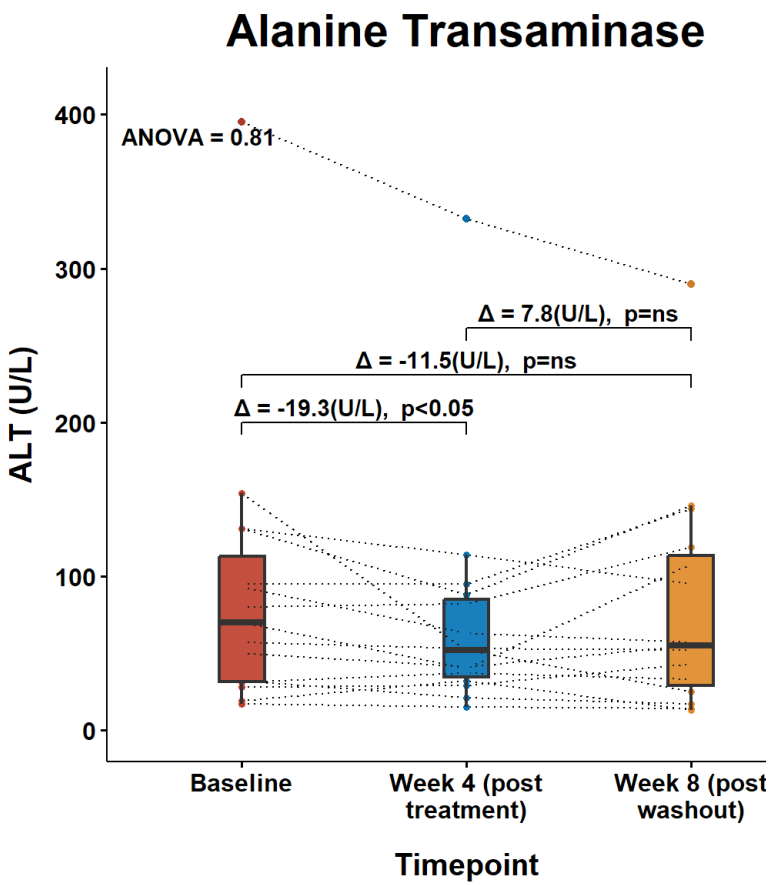
Clinical outcomes – Mayo scores

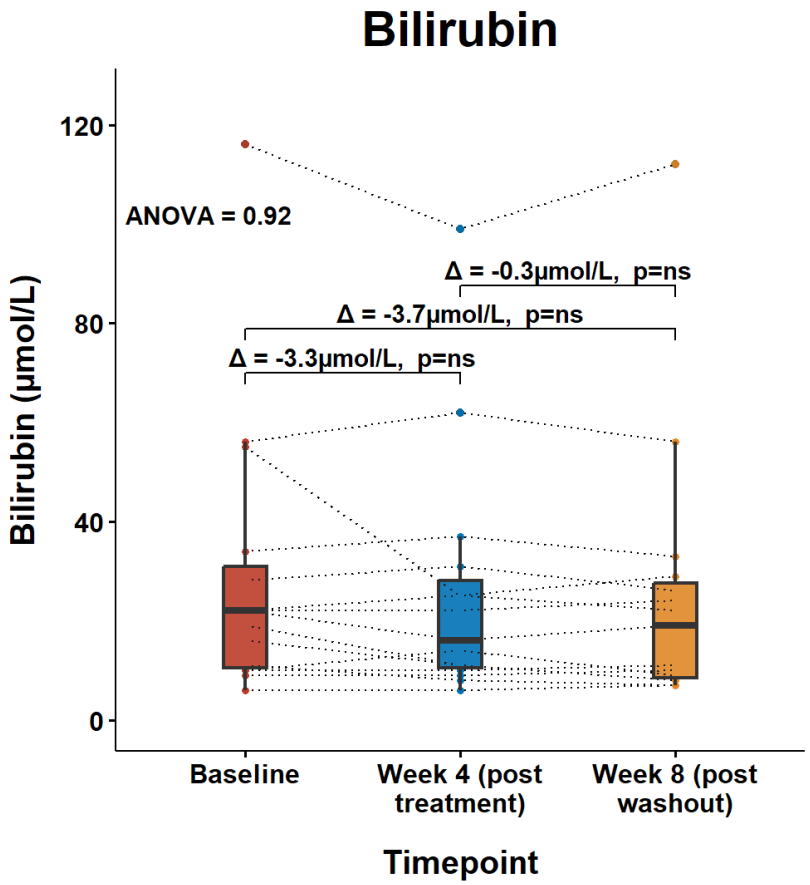




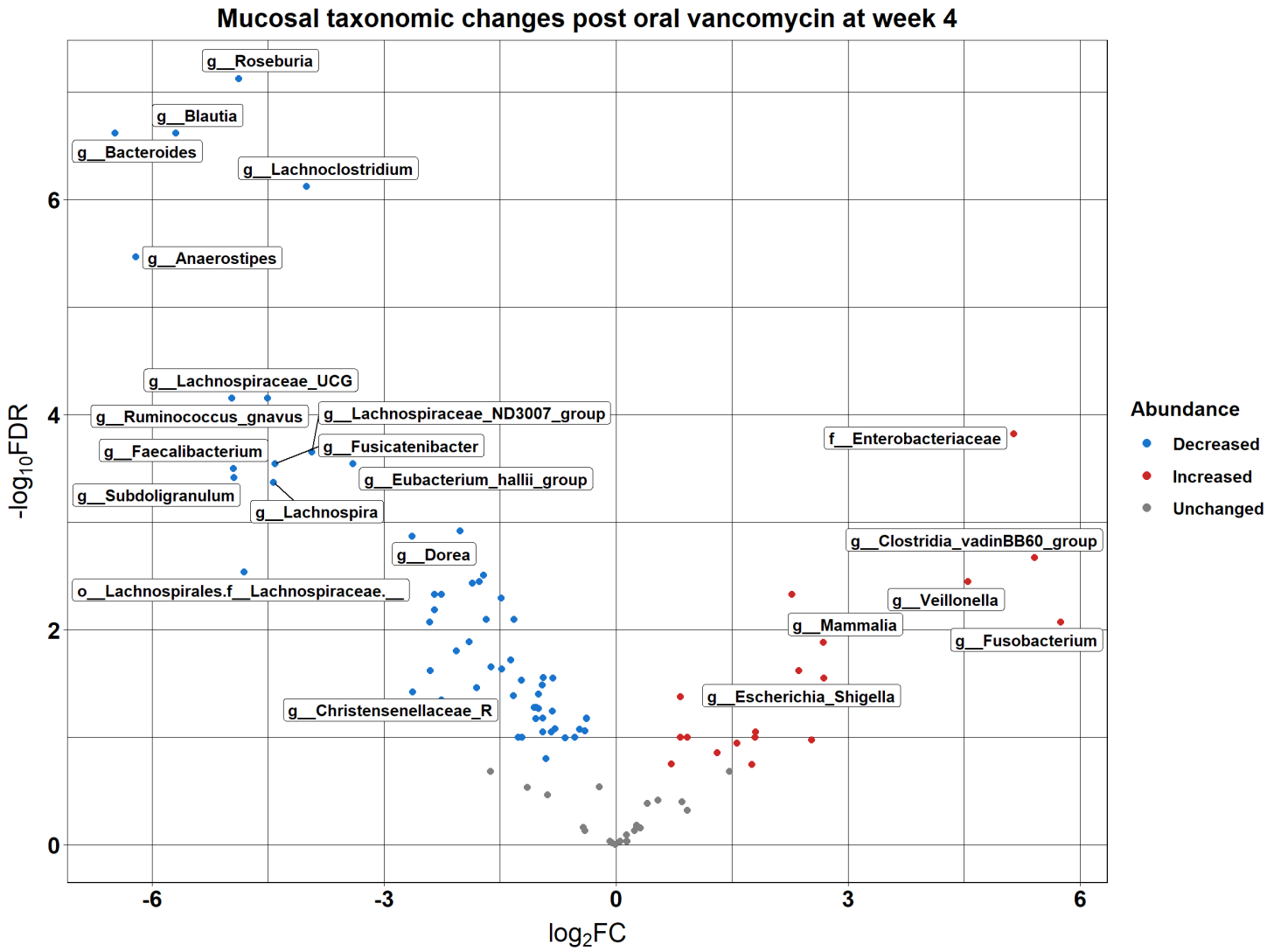
Clinical outcomes – liver biochemistry





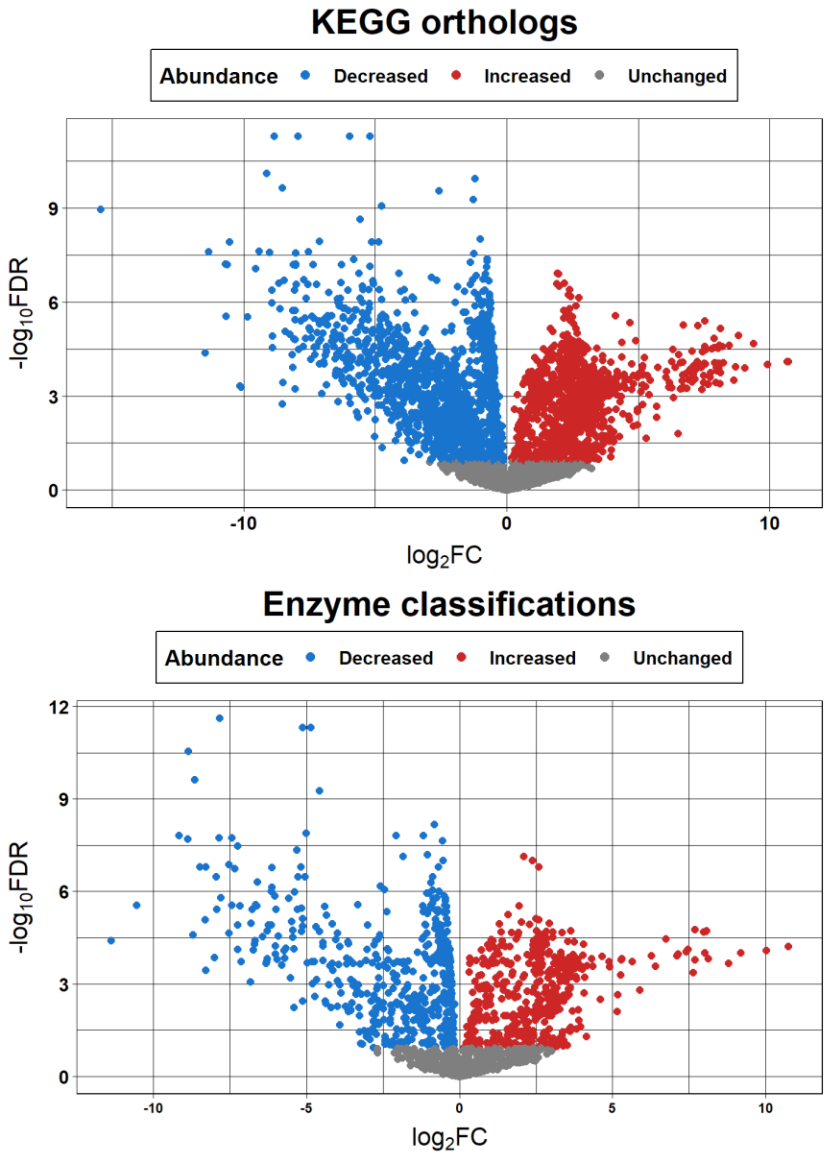


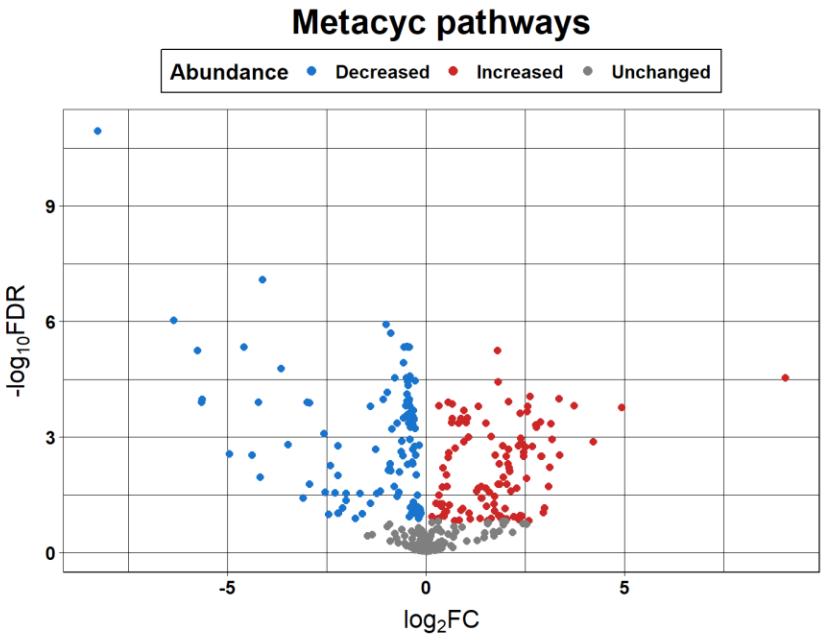
Taxonomic changes post oral vancomycin



Dr M Nabil Quraishi

Shifts in microbial metabolic pathways



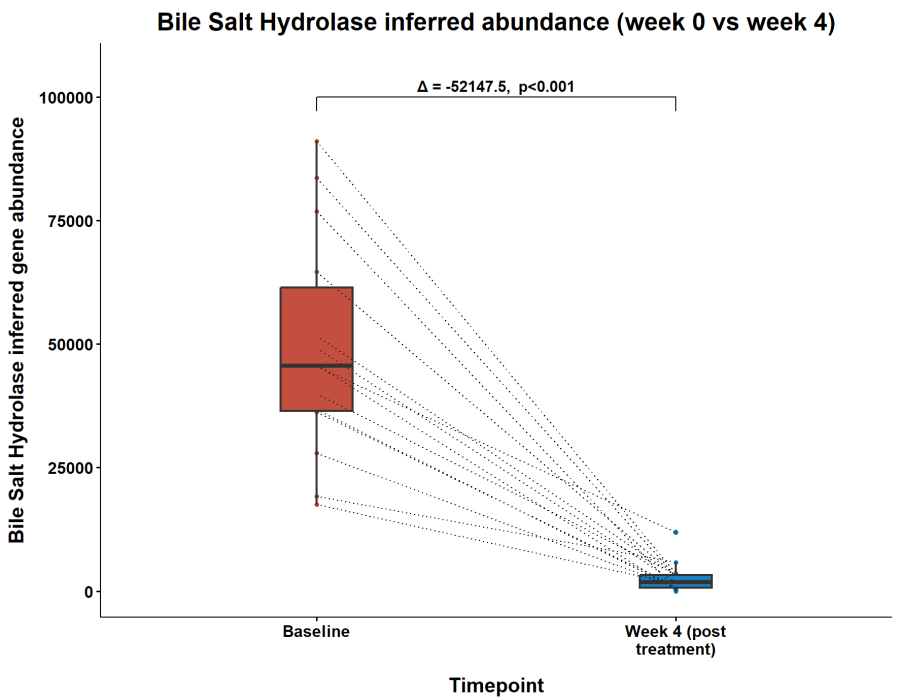


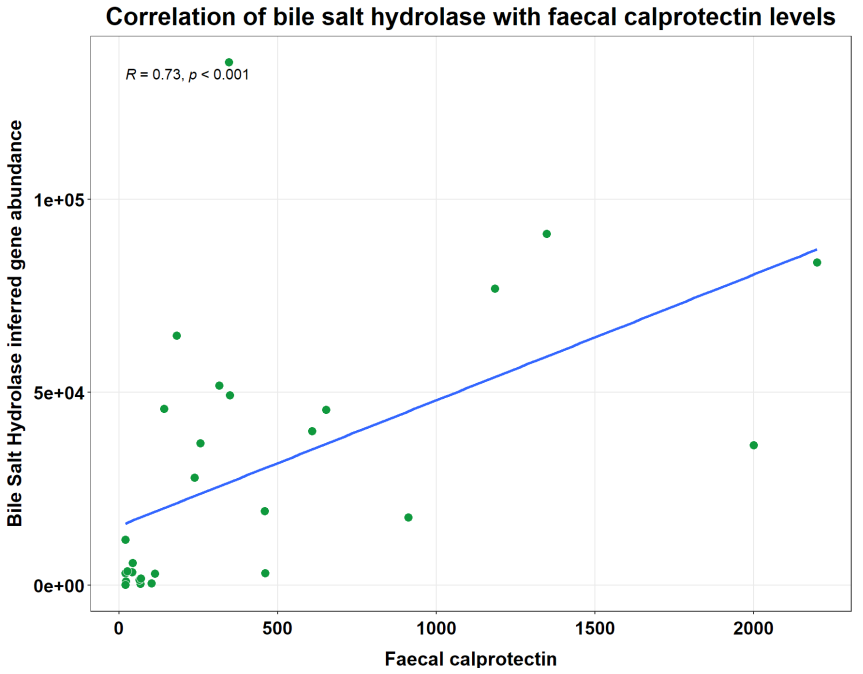
Summary of inferred functional changes*

Functional.classification	Upregulated	Downregulated	Unchanged
KEGG orthologs	2144	1677	1793
Enzyme classifications	590	585	609
MetaCyc pathways	124	122	102

**mucosal microbiota post oral vancomycin in patients with PSC-IBD*

The bile acid deconjugation pathway





- Bile salt hydrolase (BSH) producing bacteria are knocked out
- BSH levels correlate strongly with faecal calprotectin
- BSH producers depletion cause of remission or just an effect of vancomycin?

Oral vancomycin for PSC in adults

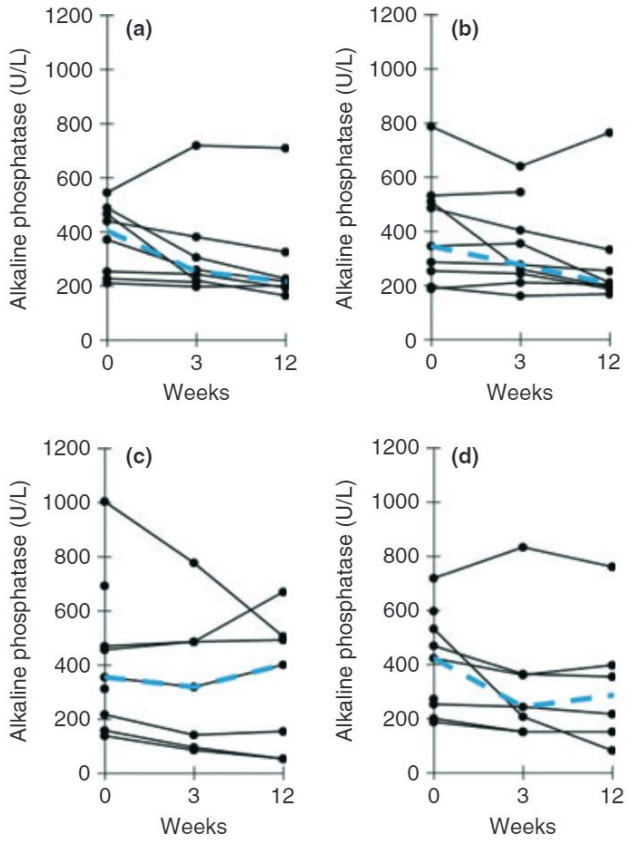


Figure 1 | Change in alkaline phosphatase in low- and high-dose vancomycin and metronidazole groups: (a) low-dose vancomycin, (b) high-dose vancomycin, (c) low-dose metronidazole, (d) high-dose metronidazole. Decrease in alkaline phosphatase was significant in the low- and high-dose vancomycin groups ($P = 0.03$ and $P = 0.02$ respectively). Note: Bold, dashed lines represent the group medians. Outlier present (top curve) in low-dose vancomycin group.

Tabibian J et al. AP&T. 2013

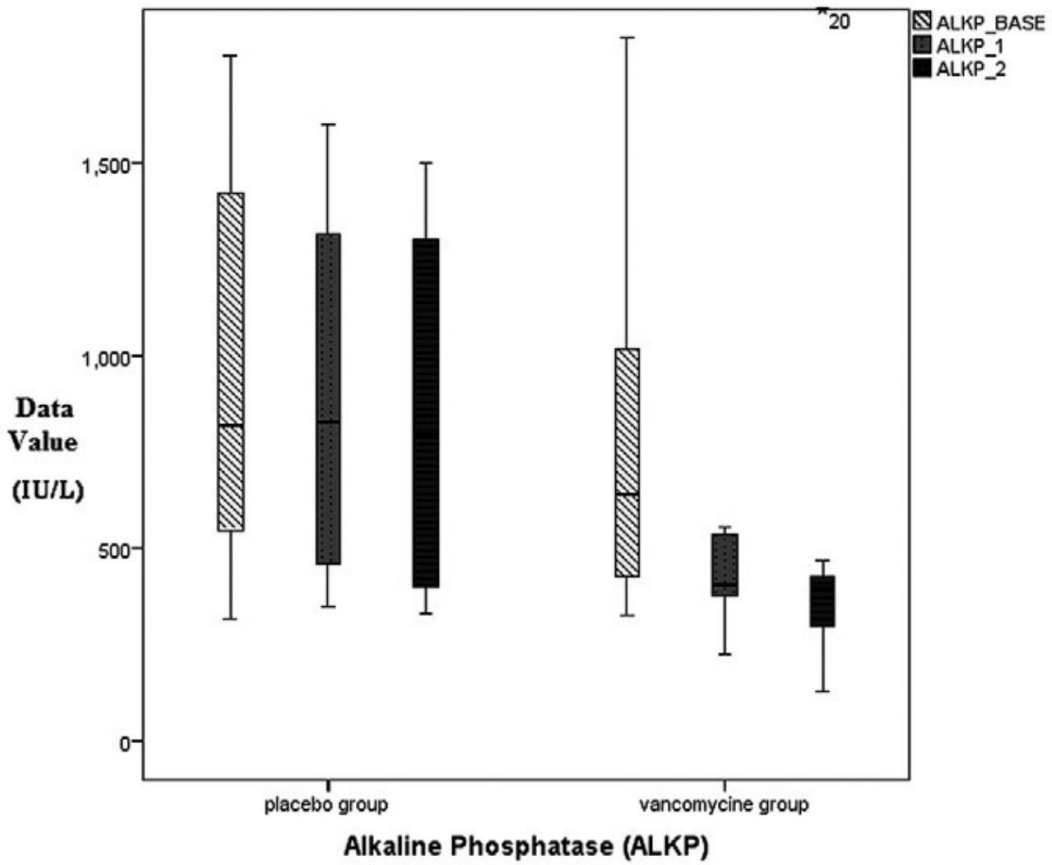
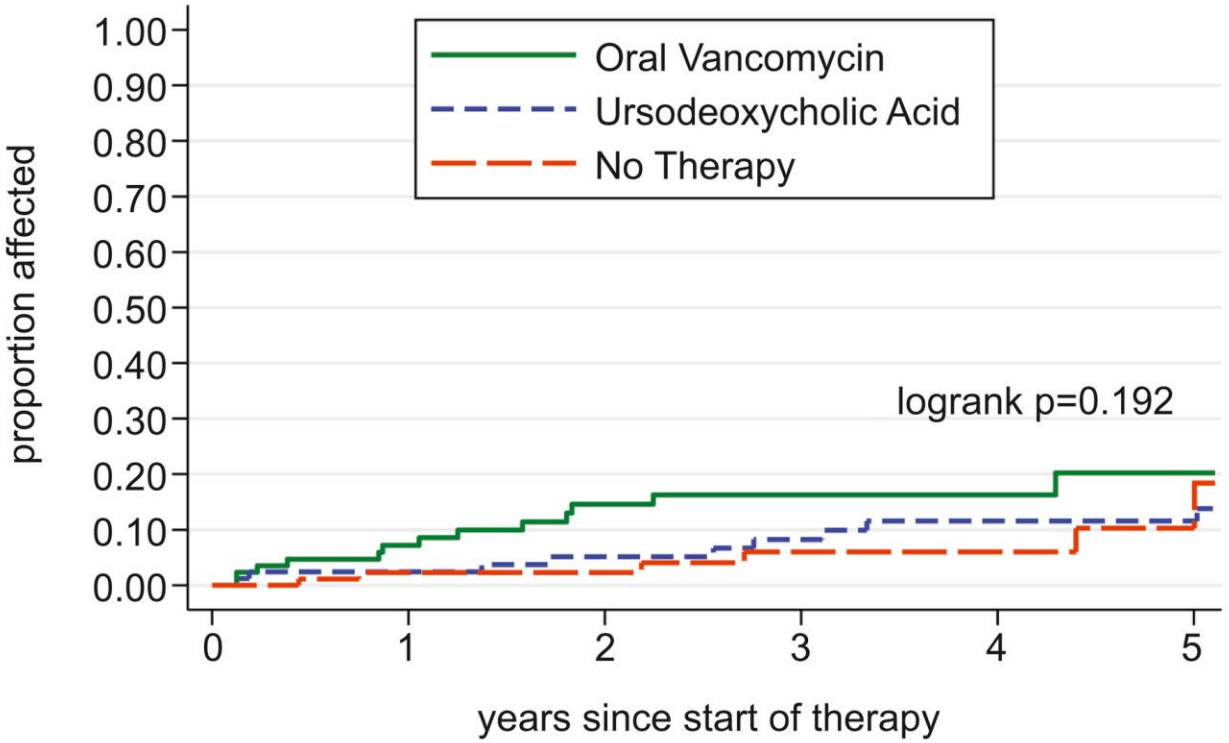


Fig. 4. Serum alkaline phosphatase (ALP) level box plot for the vancomycin and placebo groups during 3 moments of the study (baseline, first month, and third month)

Rahimpour S et al. J Gastro Liver Disease. 2016

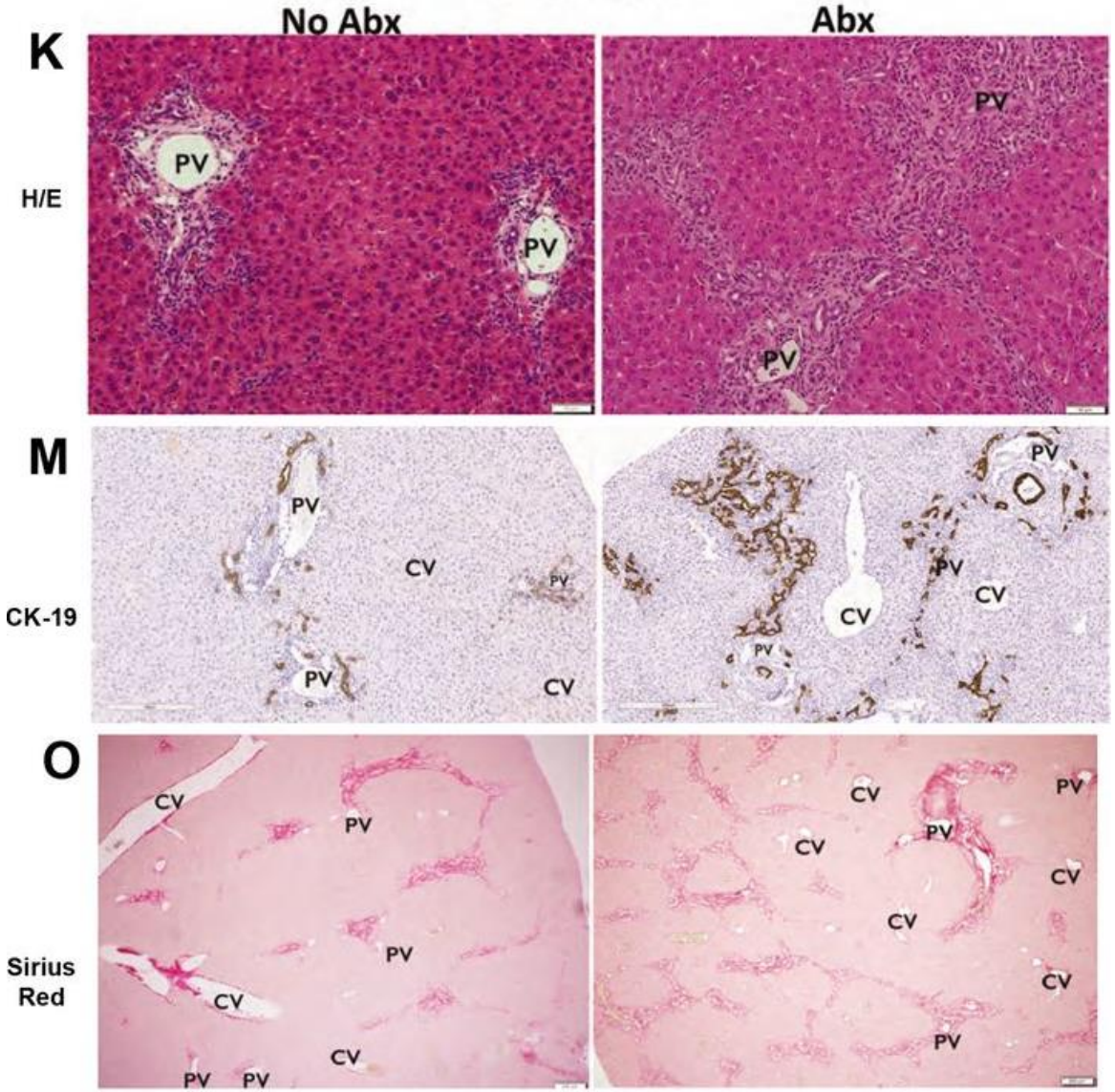
Is oral vancomycin beneficial for liver disease in PSC?



Number at risk						
Oral Vancomycin	88	70	51	32	22	14
Ursodeoxycholic Acid	88	77	66	56	50	37
No Therapy	88	85	60	44	27	21

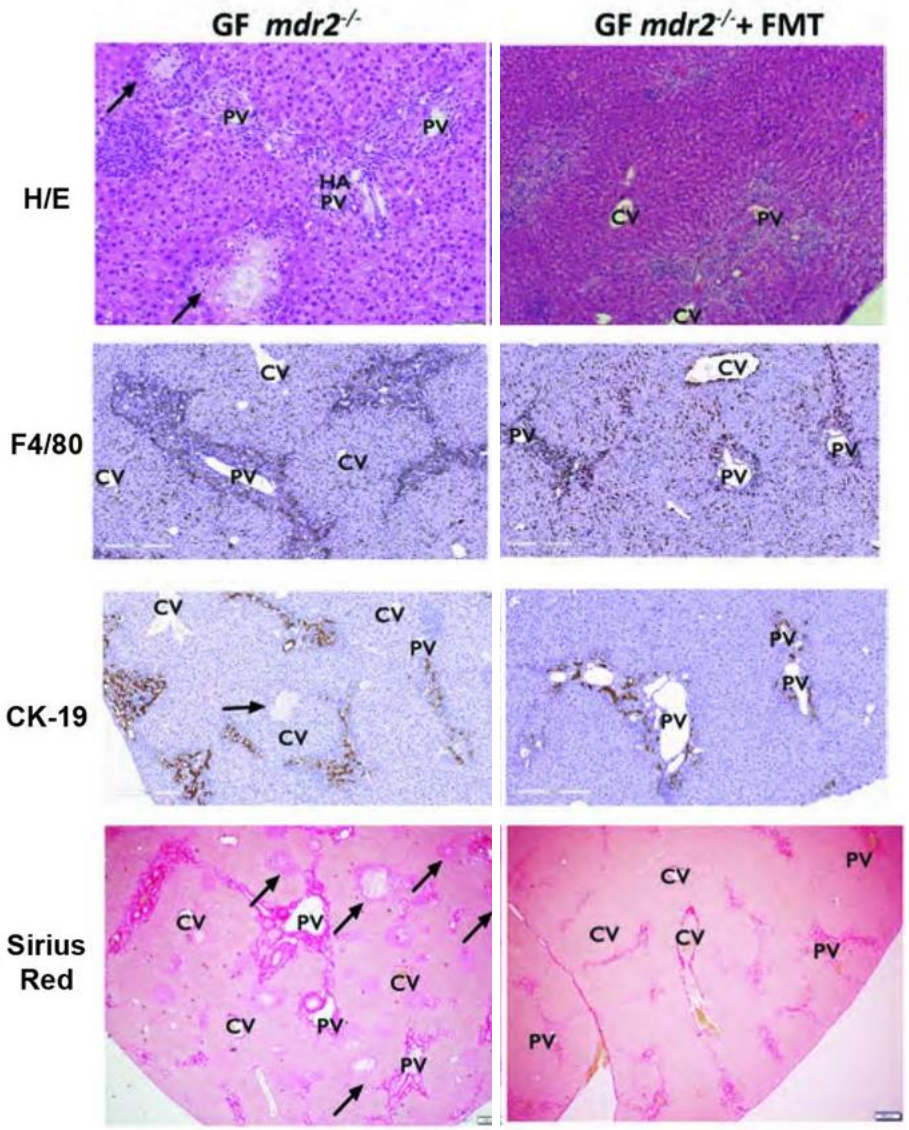
Data from the International Paediatric PSC Consortium; Deneau et al. Hepatology. 2020

Oral vancomycin exacerbates biliary fibrosis in mice

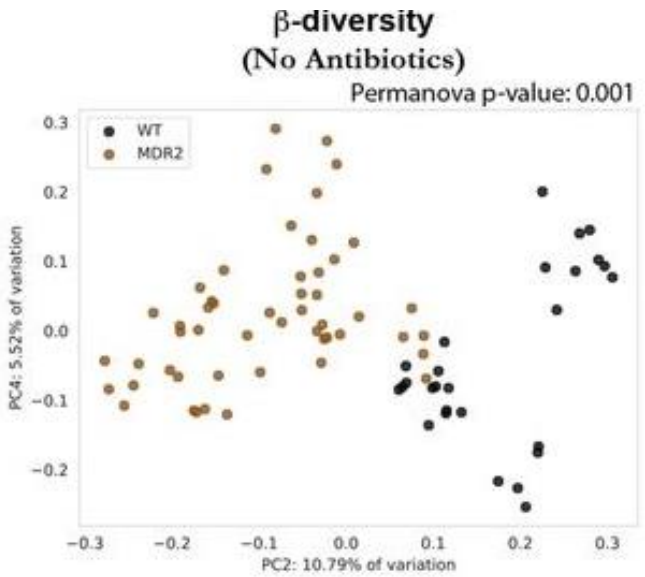


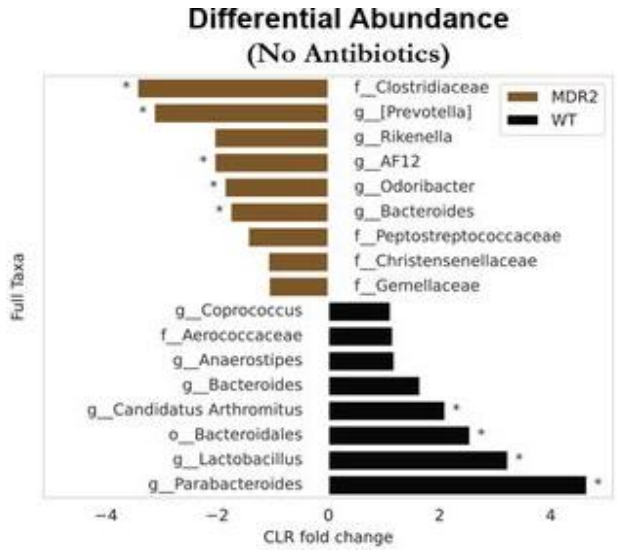
Awoniyi et al. Gut 2022

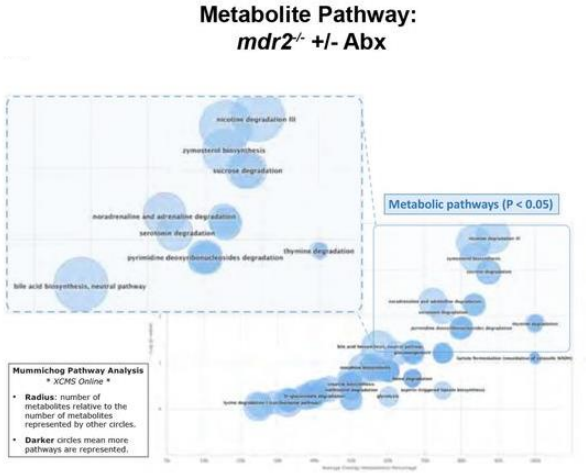
Faecal microbiota transplantation attenuates biliary injury in an experimental model of sclerosing cholangitis



”Lachnospiraceae-enriched”





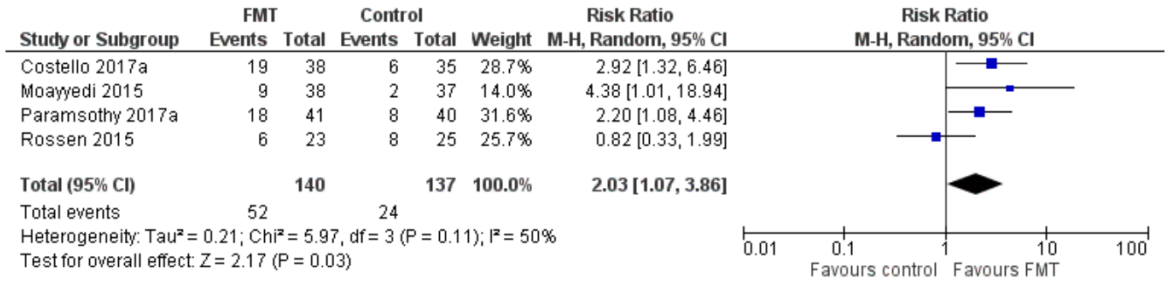


Awoniyi et al. Gut 2022

Faecal microbiota transplantation (FMT) in u. colitis

- Meta-analysis: Remission in 28% patients in the donor FMT groups compared with 9% patients in the placebo groups

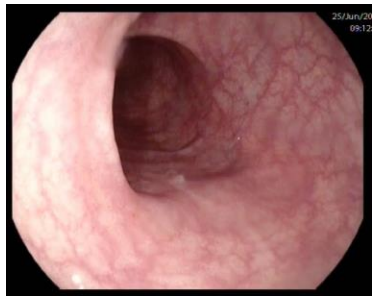
Figure 3. Forest plot of comparison: 1 Fecal microbiota transplantation versus control for participants with ulcerative colitis, outcome: 1.1 Clinical remission at 8 weeks.



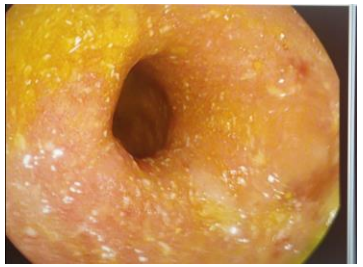
Imdad A et al. Cochrane Review. 2018

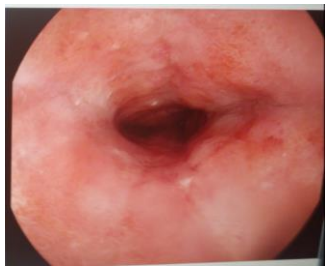
STOP-Colitis pilot (FMT for UC – Birmingham, St Marks, Glasgow)

Patient A – < 1 year, on azathioprine



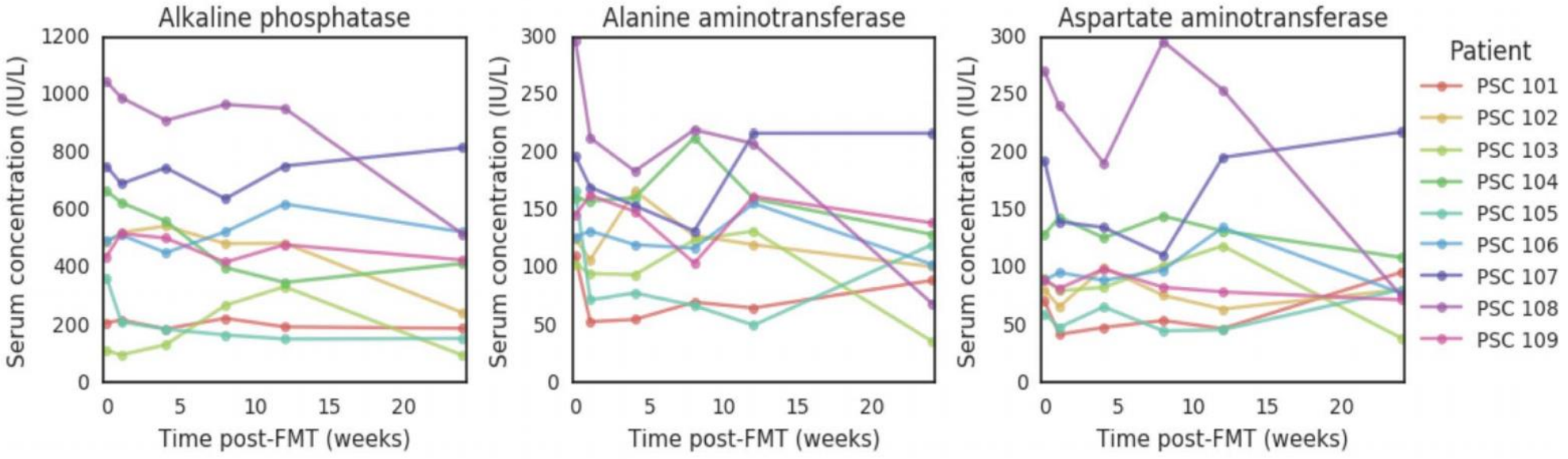
Patient B – > 5 years, failed 3 biologics





FMT for PSC - Pilot

- 10 patients with PSC; primary outcome was safety
- 9 with IBD and 9 with large duct PSC
- Single dose of colonoscopically administered FMT



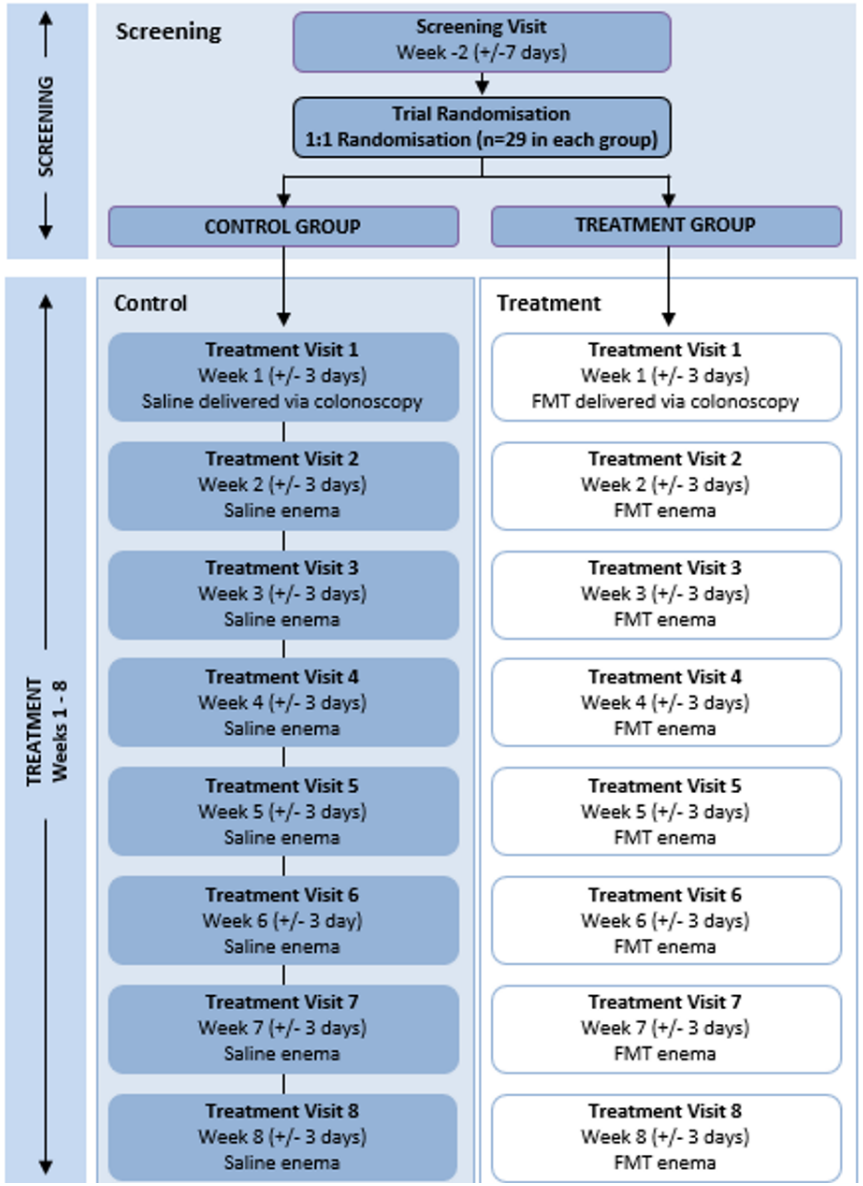
Allegretti, Mullish et al. AJG. 2019

FMT in PSC – FARGO RCT

FARGO: A randomised, phase IIa, multi-centre, (double blind) placebo-controlled trial of **FA**ecal microbiota transplantation in prima**R**y sclerosin**G** ch**o**langitis

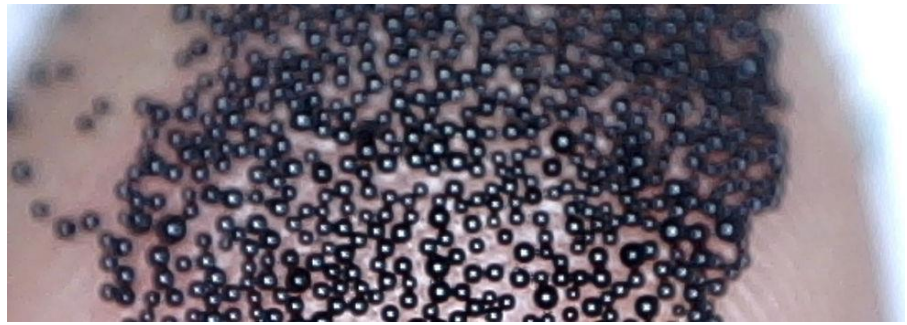
Grant awarded 2022
Due to open in Q4 2023

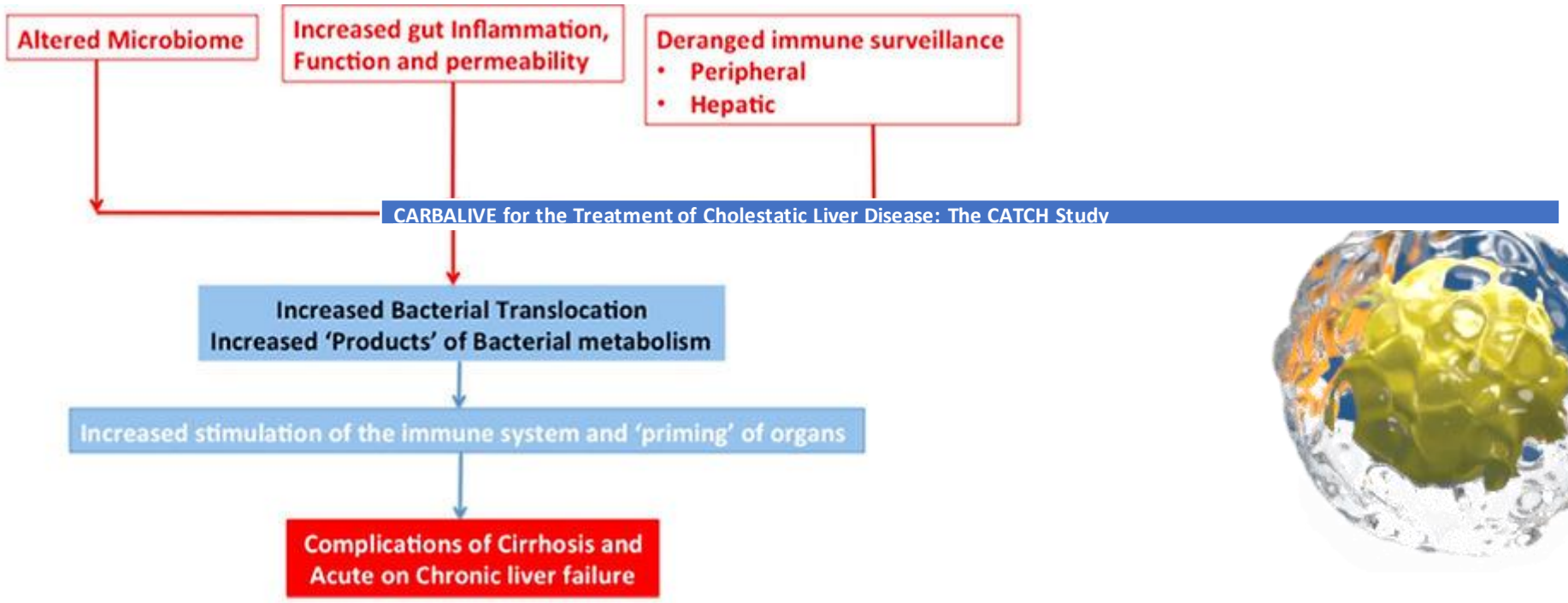
Multicentre, nationwide RCT



CARBALIVE for the Treatment of Advanced Cholestatic Disease: The CATCH Study

Funded March 2023



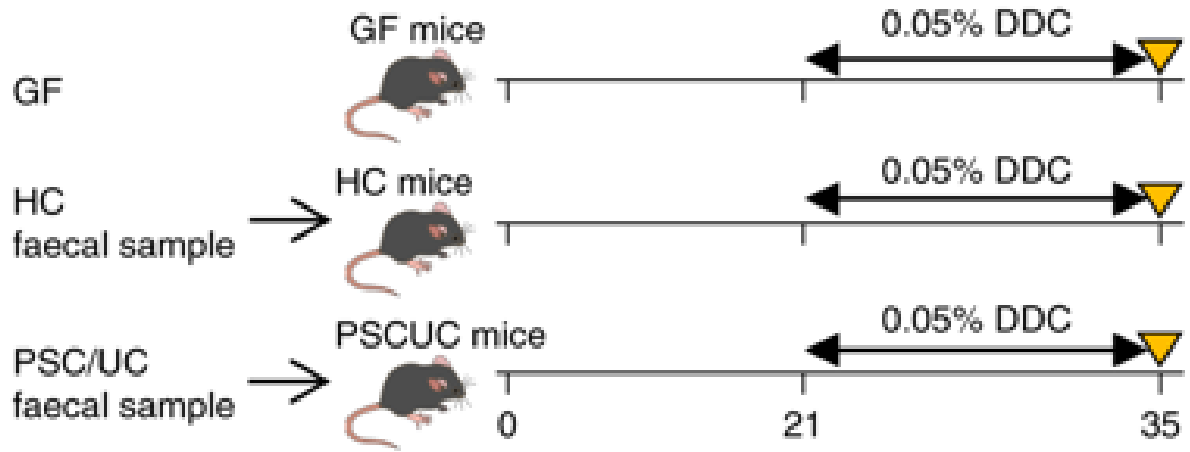


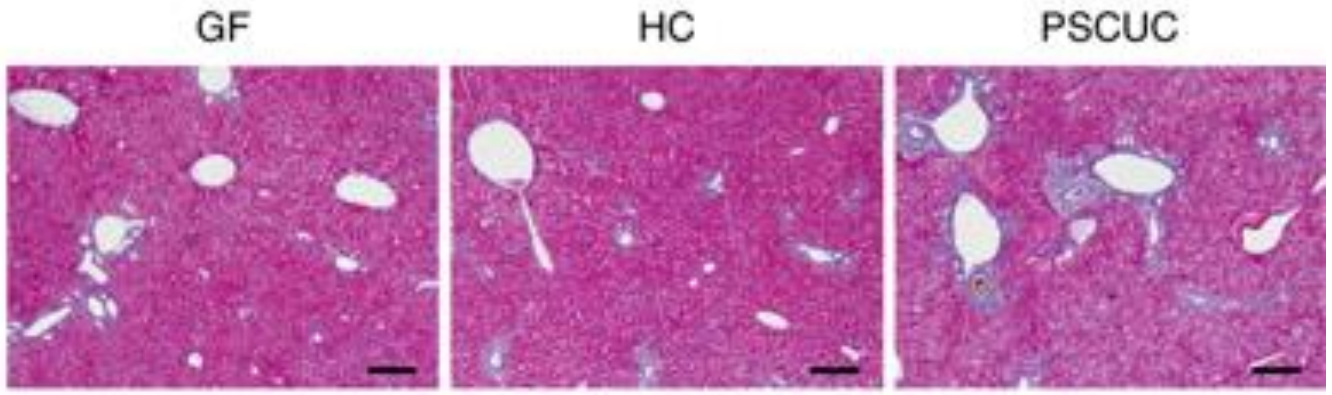
Images courtesy of Yaqrit Discovery Ltd.

UK PSC microbial therapeutics' programme

Gut microbial 'depletion'	Gut microbial 'replacement'	Reduced gut 'toxin adsorption'
Vancomycin; n=15 (NCT05376228) Phase 2A; open-label 125 mg QID for 4w, with 4w washout **1° outcome:** IBD remission at 4w **2° outcomes:** IBD remission at 8w; liver biochemistry at 4w, safety (AMR) **Translational outcomes:** colonic microbial, transcriptomic and metabolic profiles	**Faecal microbiota transplantation; n=58** Phase 2A; RCT (blinded) Colonic delivery, once weekly for 8w **1° outcome:** ALP reduction at 48w **2° outcomes:** liver biochemistry, ELF PROs, ProC3/C5, C4M, elastography **Translational outcomes:** colonic microbial, transcriptomic, mucosal immune cell phenotyping, metabolic profiles	**CARBALIVE; n=12** Phase 2A; open-label Seq. dose finding: 8g and 12g OD **1° outcome:** safety; 12w **2° outcomes:** liver biochemistry, ELF PROs, ProC3/C5, C4M **Translational outcomes:** colonic microbial, transcriptomic, metabolic profiles
PSC with active colitis	PSC-IBD without advanced fibrosis	PSC-IBD with mod-advanced fibrosis

Faecal matter transfer from patients induces colitis and biliary fibrosis in mice





Specific bacterial species associated with PSC/UC:

- *K. pneumoniae*
- *P. mirabilis*
- *E. gallinarum*

RESEARCH

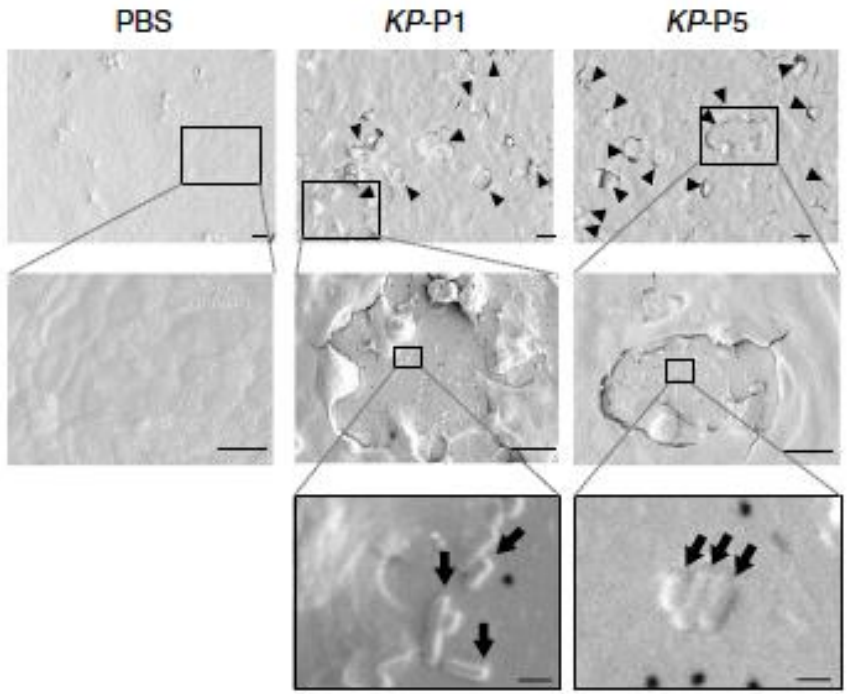
MICROBIOTA

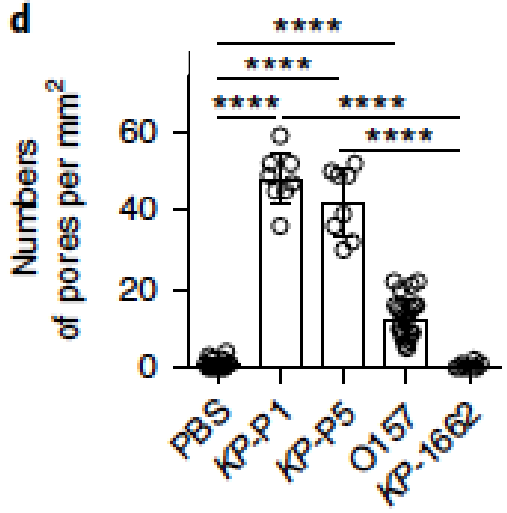
Translocation of a gut pathobiont drives autoimmunity in mice and humans

S. Manfredo Vieira,[1] M. Hiltensperger,[1] V. Kumar,[2] D. Zegarra-Ruiz,[1] C. Dehner,[1] N. Khan,[1] F. R. C. Costa,[1*] E. Tiniakou,[1†] T. Greiling,[1‡] W. Ruff,[1] A. Barbieri,[3] C. Kriegel,[1] S. S. Mehta,[4] J. R. Knight,[4] D. Jain,[3] A. L. Goodman,[5] M. A. Kriegel[1,2§]

Nakamoto et al. *Nature Microb.* 2019

- ***Klebsiella pneumoniae (Kp)*** in stool of patients with PSC-IBD
- Transplanted *Kp* to germ-free mice
- *Kp* directly ruptured the intestinal epithelia with translocation, endotoxemia, and liver damage
- *Kp* was associated with susceptibility to Th17-mediated hepatobiliary injury
- Antibiotic therapy ameliorated Kp induced immune responses.





Is Kp relevant to human PSC?
Therapeutic approach?

Assis DN et al. Yale

Nakamoto et al Nat Microbiol. 2019;4:492-503

Primary sclerosing cholangitis industry drug development pipeline

Preclinical		Phase I	Phase II	Phase III
			Volixibat potassium **Mirum Pharmaceuticals** *IBAT inhibitor*	
Vedolizumab **Takeda Evotec** *a4b7 integrin agonist*			Berberine ursodeoxycholate **HighTide Therapeutics** *Unspecified*	
GRI-0124 **GRI Bio** *NKT cell stimulant*	HM-15211 **Hanmi Pharmaceutical** *GLP-1/GIP/GCG agonist*	SCO-240 **Scohia Pharma** *SSTR5 antagonist*	CM-101 **Chemomab/Abzena** *CCL24 antagonist*	
H-01 **Halo Biosciences** *Hyaluronan synthase inhibitor*	Metabolic and infectious disease therapy **CD3 Centre for Drug Design** *IBAT inhibitor*	A-3907 **Albireo Pharma** *IBAT inhibitor*	HK-660S **Curome Biosciences** *NAD+ modulator*	
Rock2 Inhibitor **Angion Biomedica** *ROCK2 inhibitor*	odevixibat **Albireo Pharma/Jadeite Medicines** *IBAT inhibitor*	CS-0159 **Cascade Pharmaceuticals** *FXR agonist*	Orbcell-C **Orbsen Therapeutics** *IV MSC therapy*	
ST-003 **SteroTherapeutics** *GAL antagonist*	PSC therapy **Engitix Therapeutics** *Unspecified*	HPG-1860 **Hepagene Therapeutics** *FXR agonist*	PLN-74809 **Pilant Therapeutics** *a1b6 integrin antagonist*	
BX-002 **BiomX** *Microbiome modulator*	PV-201 **Parvus Therapeutics** *Unspecified*	INVA-8001 **Invea Therapeutics** *Immunosuppressant*	Seladelpar **CymaBay Therapeutics** *PPAR-d agonists*	Norursodeoxycholic acid **Dr. Falk Pharma/Eisai** *Cholesterol inhibitor*
Elafibranor **Genfit Ipsen** *PPAR-a/PPAR-d agonist*	setanaxib **Calliditas Therapeutics** *NADPH oxidase 1/4 inhibitor*	STP-707 **Sirnaomics** *TGF-ß1/Cox-2 gene inhibition*	Vidofludimus calcium **Immunic 4SC** *DHODH inhibitor*	Cilofexor **Gilead/Phenex** *FXR agonist*

Trivedi (unpublished)