PROMISE TRIAL

A **PRO**spective double-blind placebo-controlled multicentre trial of faecal **MI**crobiota tran**S**plantation to improve outcom**E**s in patients with cirrhosis

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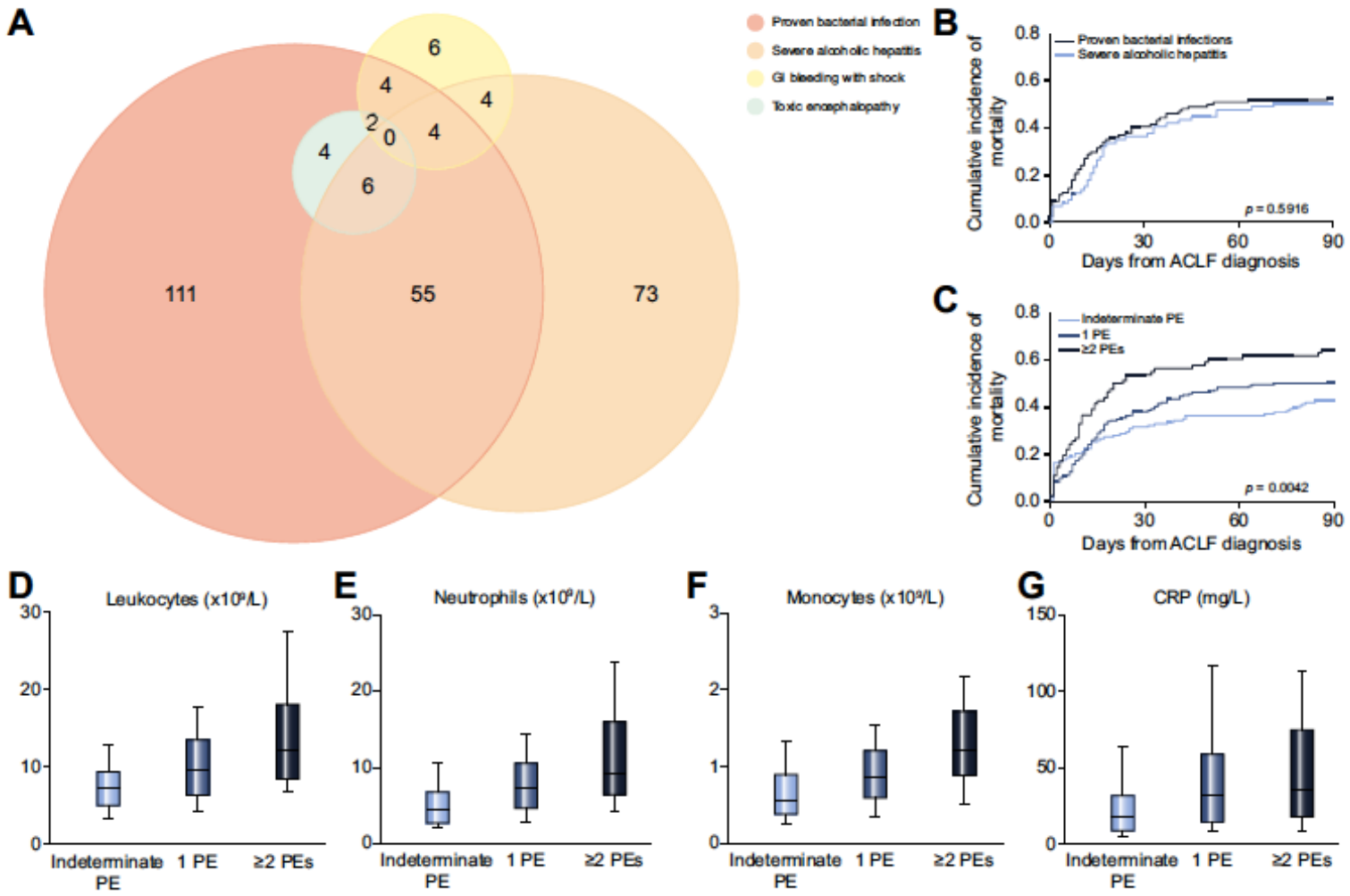
UKRI Medical Research Council
NIHR | National Institute for Health Research
King's College London

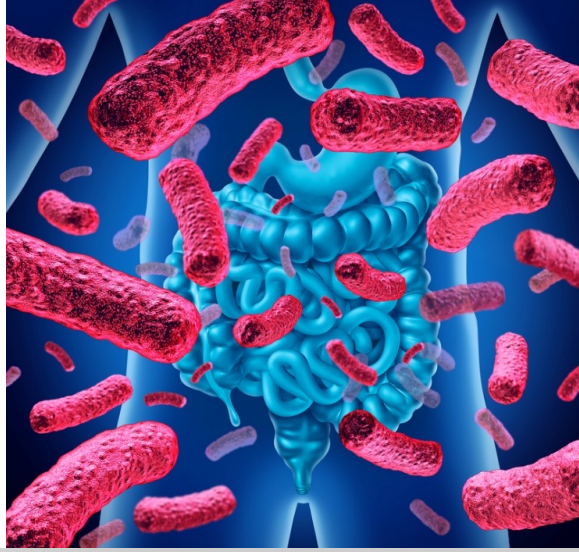
Infection as a precipitant of acute decompensation /ACLF

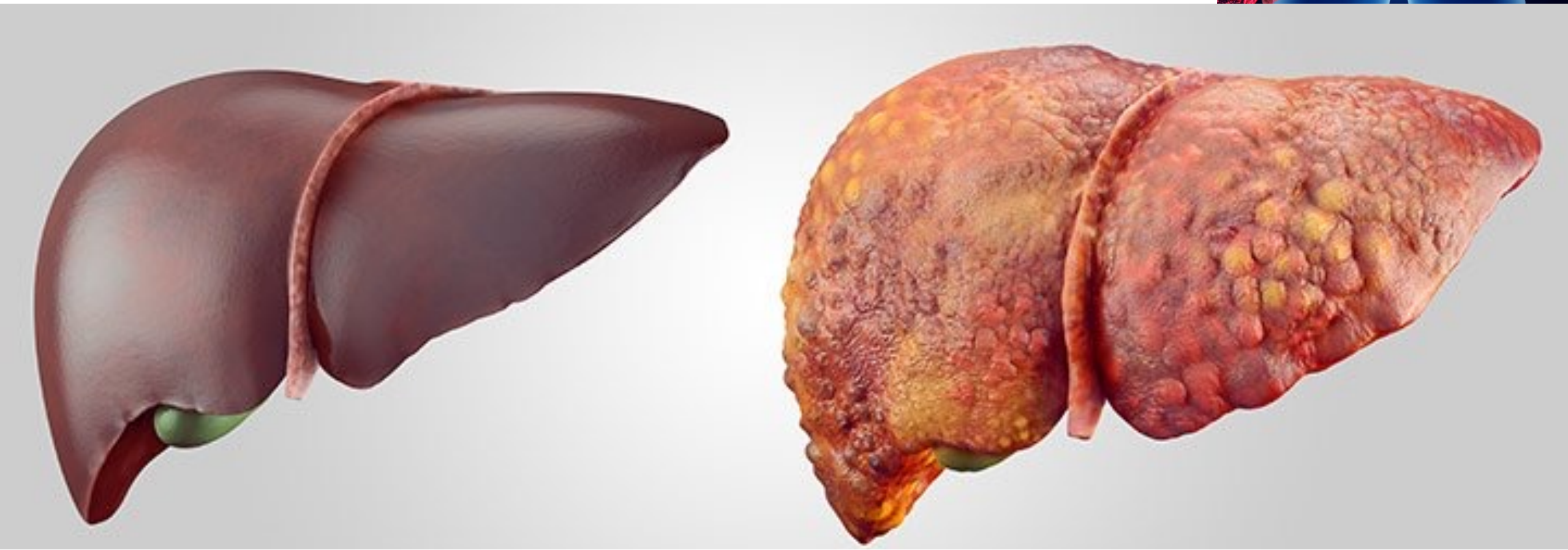


PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis

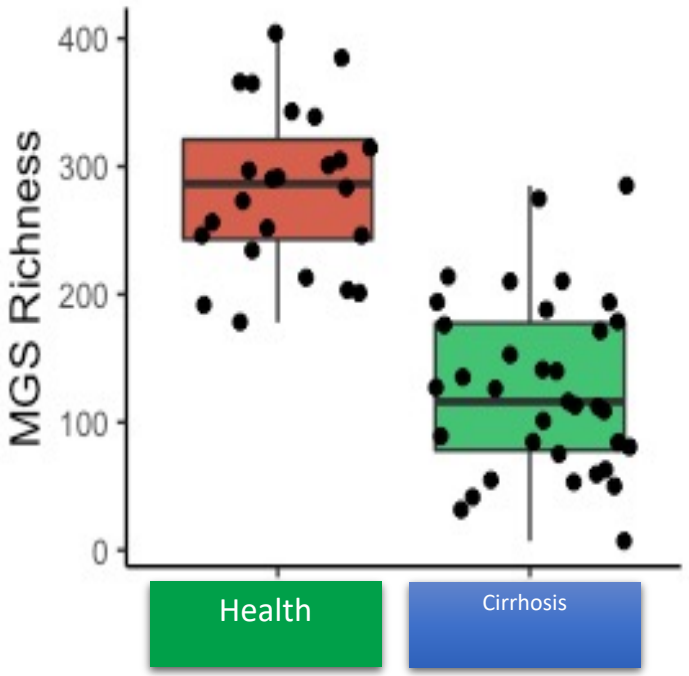
Trebicka J et al. Journal of Hepatology 2021

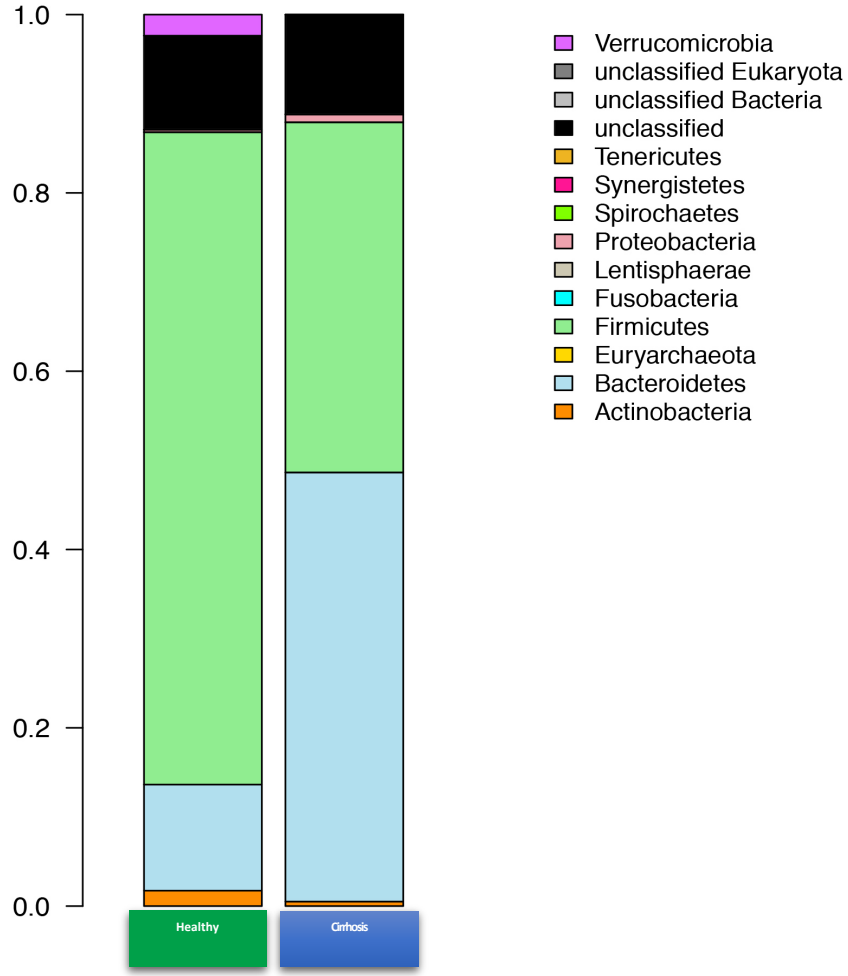
Gut microbiome in cirrhosis





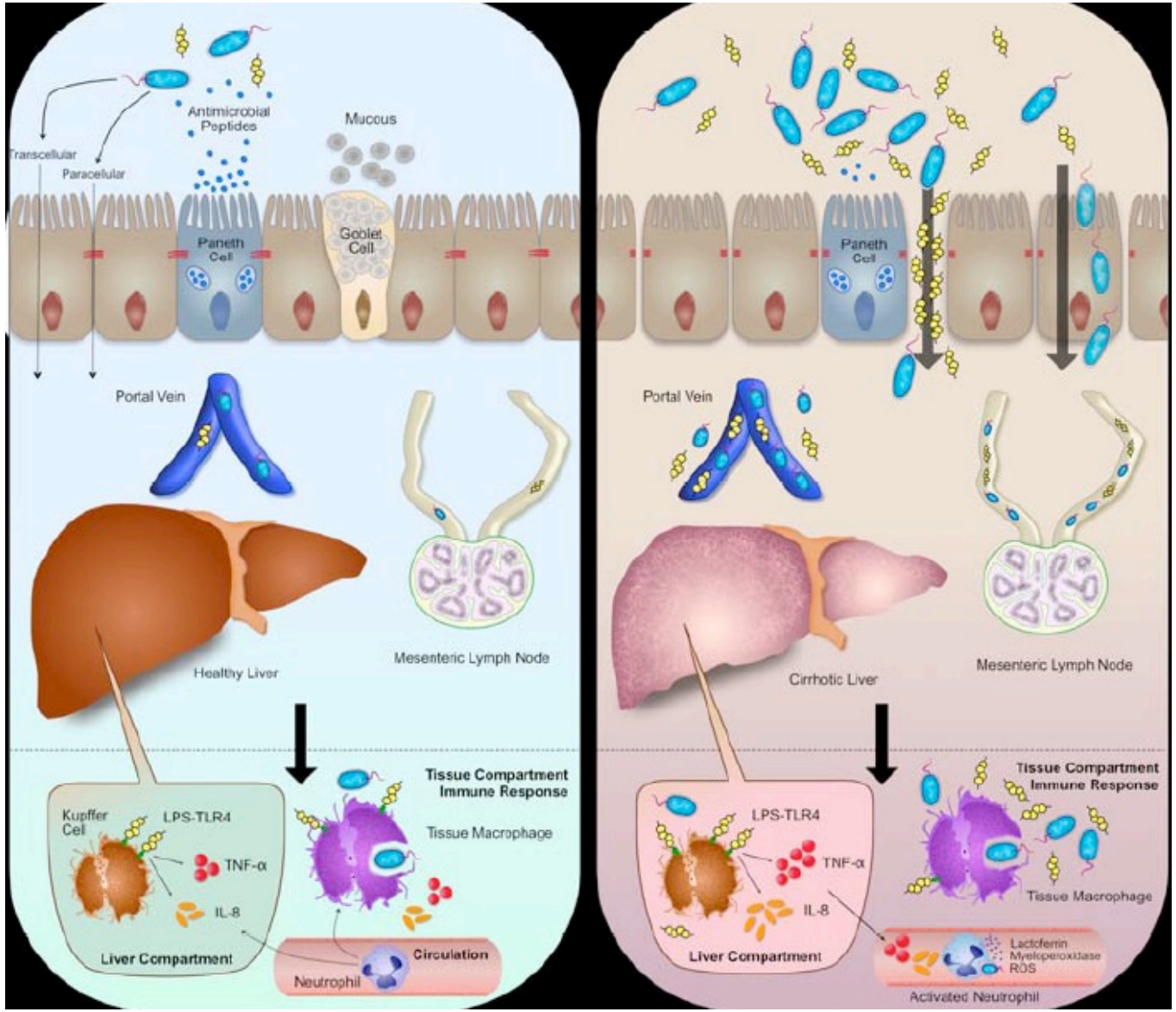
Stool microbial diversity is reduced in cirrhosis





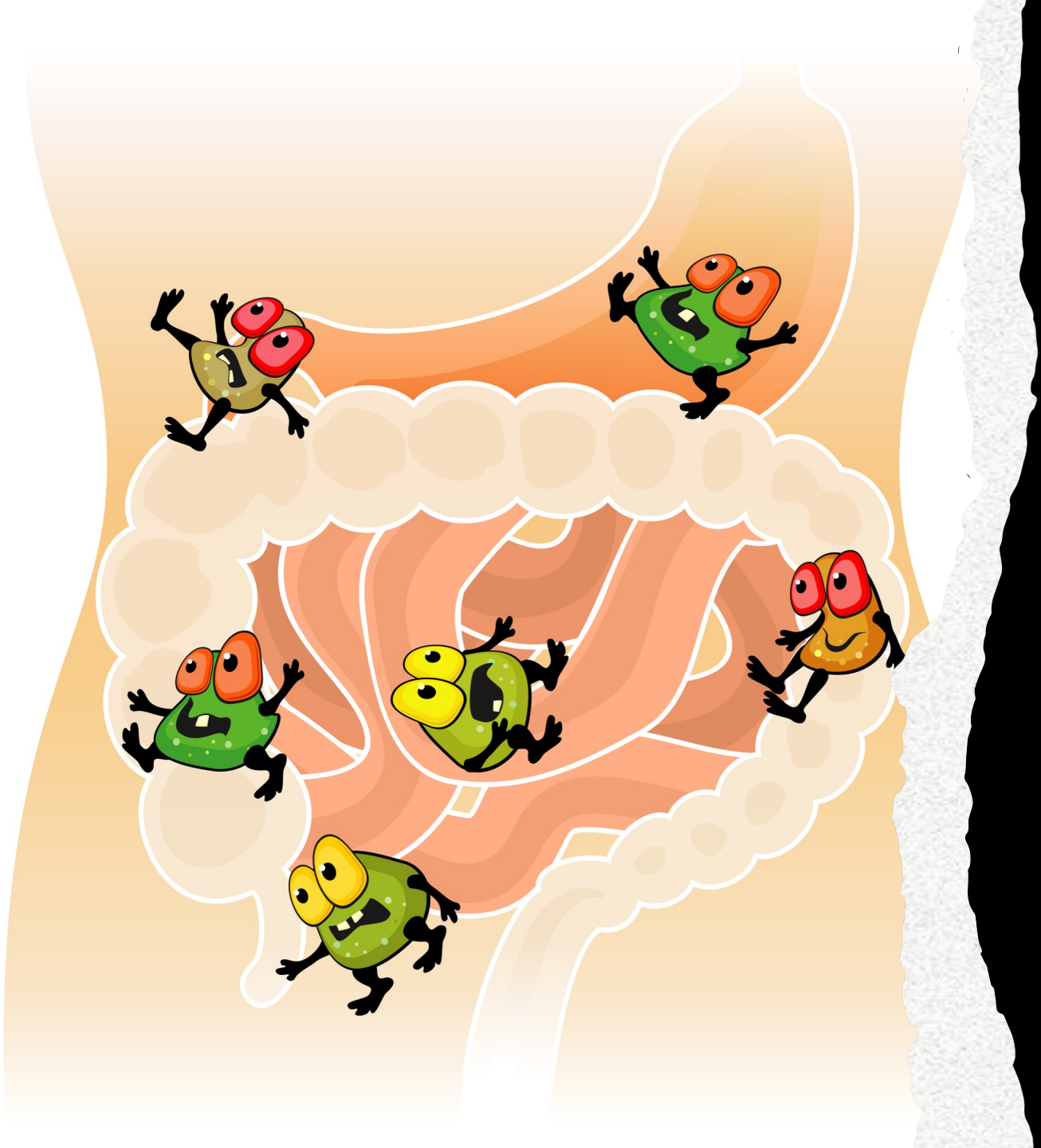
- Higher abundance of bacteroidetes
- Reduction in actinobacteria and firmicutes in cirrhosis

Patel VC et al. Results of a placebo-controlled double blind randomised trial to investigate the efficacy of rifaximin-α versus placebo in improving systemic inflammation in patients with cirrhosis and chronic hepatic encephalopathy (RIFSYS Trial). Journal of Hepatology 2018; 68: S105-364. LBA 005.



Movement of bacteria from the gut lumen to the liver in health and in cirrhosis generates inflammation

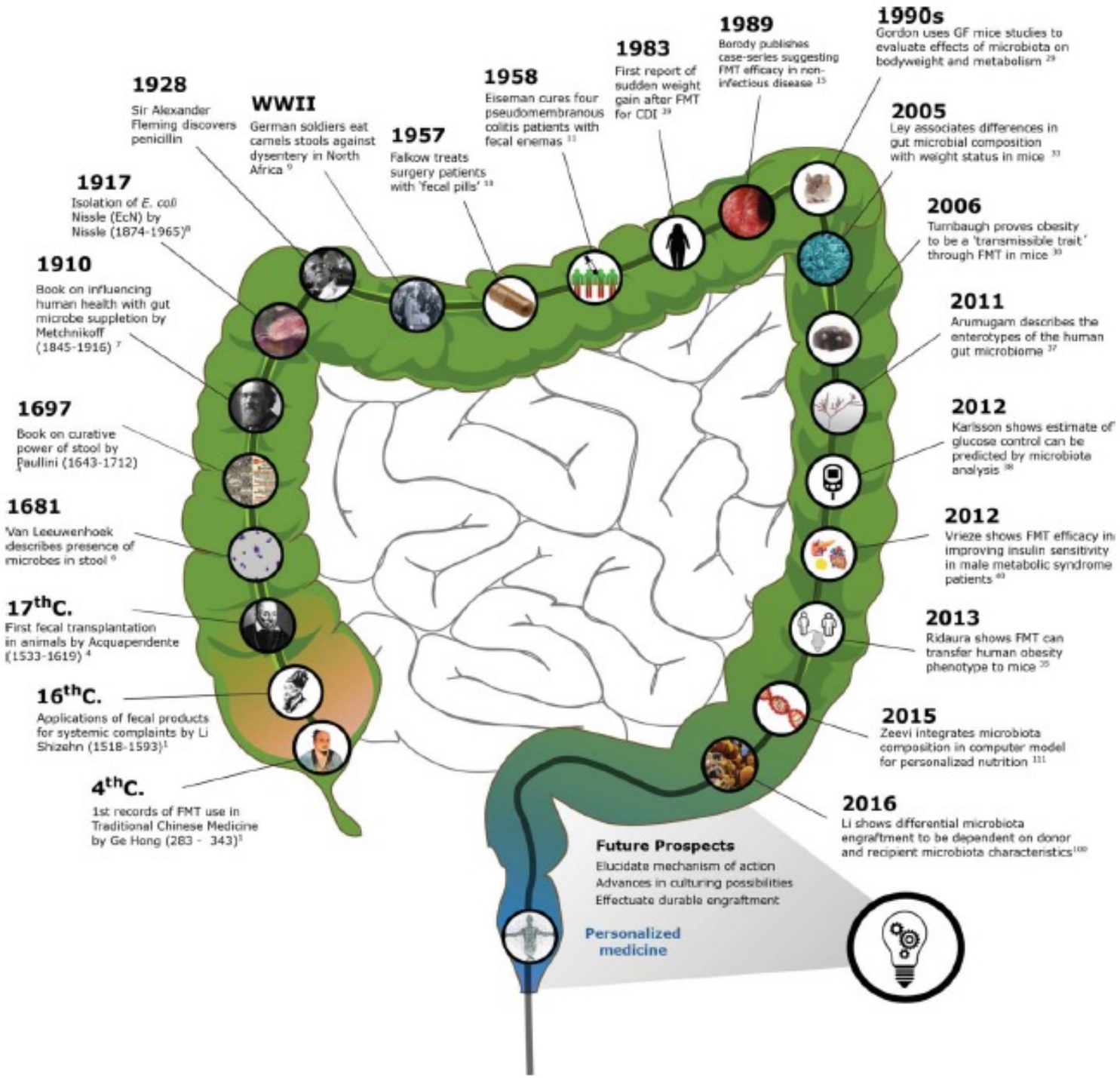
Woodhouse C et al. APT 2018;47(2):192-202.



Manipulating the gut microbiota in cirrhosis

- Diet
- Antibiotics (rifaximin)
- Probiotics
- **Faecal Microbiota Transplantation**
- Bacteriophages

Faecal microbiota transplantation (FMT) to treat cirrhosis



Key contributions to FMT development and research

de Groot et al. Gut Microbes 2017; 8(3): 253-67.

PROFIT: PROspective, randomised placebo-controlled feasibility trial of Faecal mIcrobiota Transplantation in cirrhosis

FUNDED BY NIHR | National Institute for Health Research

PROFIT

- 32 patients [24 FMT and 8 placebo]
- 50g stool in 200mL 0.9% saline with 12.5% glycerol (frozen)
- Manufactured in MHRA licensed facility
- Rigorous donor screening
- Bowel preparation with 2 sachets of Moviprep
- Nasojejunal instillation at gastroscopy
- No antibiotics for 14 days pre-FMT
- 90-day follow-up

Woodhouse CA et al. BMJ Open 2019;9(2):e023518.

FMT: Healthy Donors

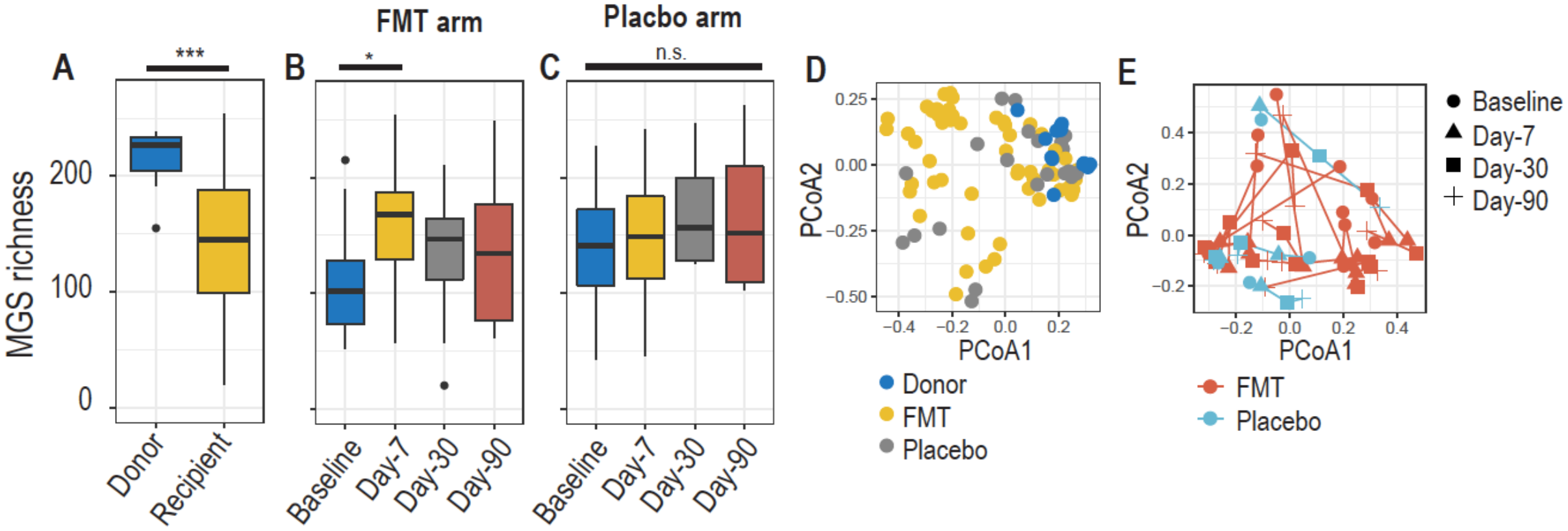
- Age 18 - 60
- BMI 18 - 30
- No regular meds or antibiotics for 3-months prior to donation
- Screened for risk factors and a range of infectious agents incl.
  - ESBL
  - Covid

Box 2 Blood and stool testing of donor faecal microbiota transplantation samples

Blood (serology)
- HIV 1+2 serology.
- (human T-lymphotrophic virus) HTLV I/II Ab.
- Hepatitis A IgG (and if positive IgM).
- Hepatitis B surface antigen and core antibody.
- Hepatitis C virus antibody.
- Hepatitis E.
- Syphilis.
- cytomegalovirus (CMV)/Epstein Barr Virus (EBV) IgG/M.
- *Strongyloides stercoralis* (ELISA).

Stool
- PCR for gastroenteritis agents (*Campylobacter, Salmonella, Shigella* and *Escherichia coli* 0:157).
- Ova, cysts and parasites x3.
- *Clostridium difficile* test.
- Norovirus PCR.
- Screen for gentamicin and carbapenem-resistant Gram-negative organisms.
- Screen for methicillin resistant staphylococcus aureus (MRSA).
- Helicobacter pylori antigen.
- Entamoeba histolytica PCR.

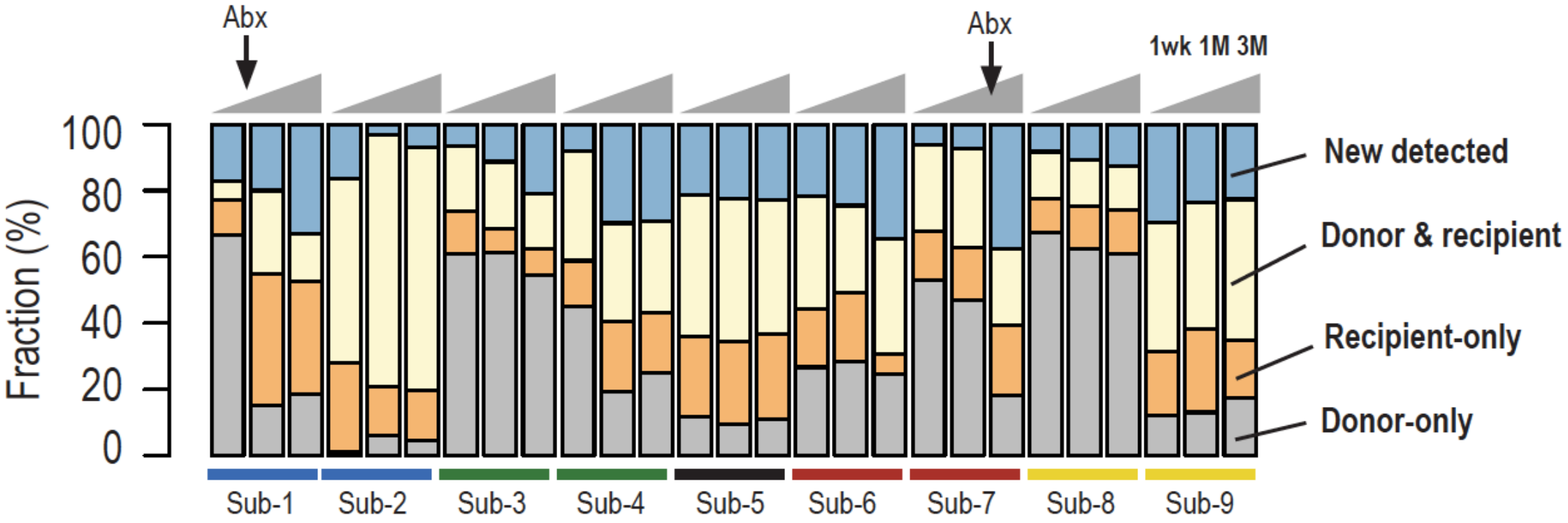
Change in bacterial diversity (species richness) before and after FMT



*Woodhouse CA, Lindsay LAE, **Lee S**, Portlock T, Shoaie S, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)*

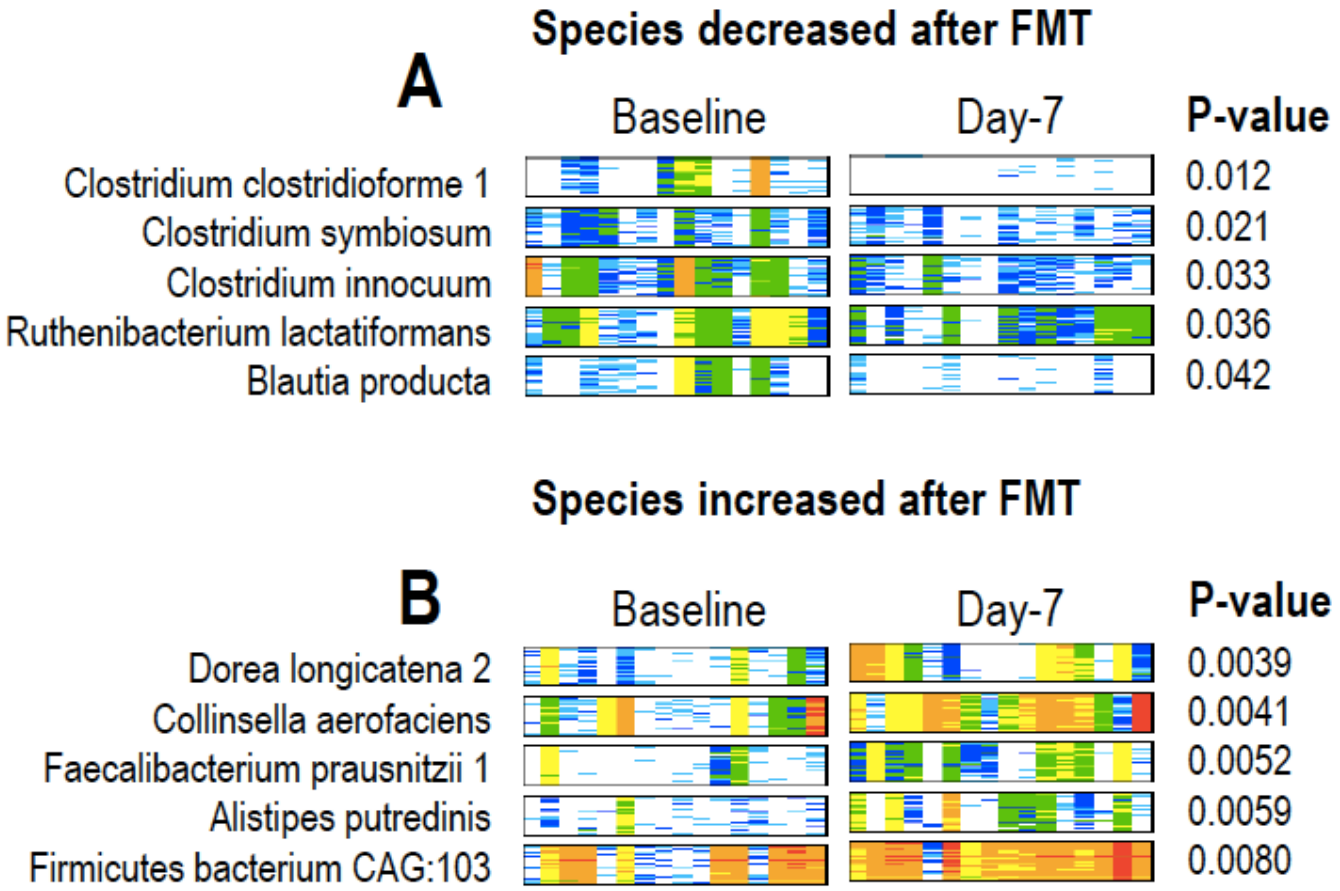
FMT donor engraftment

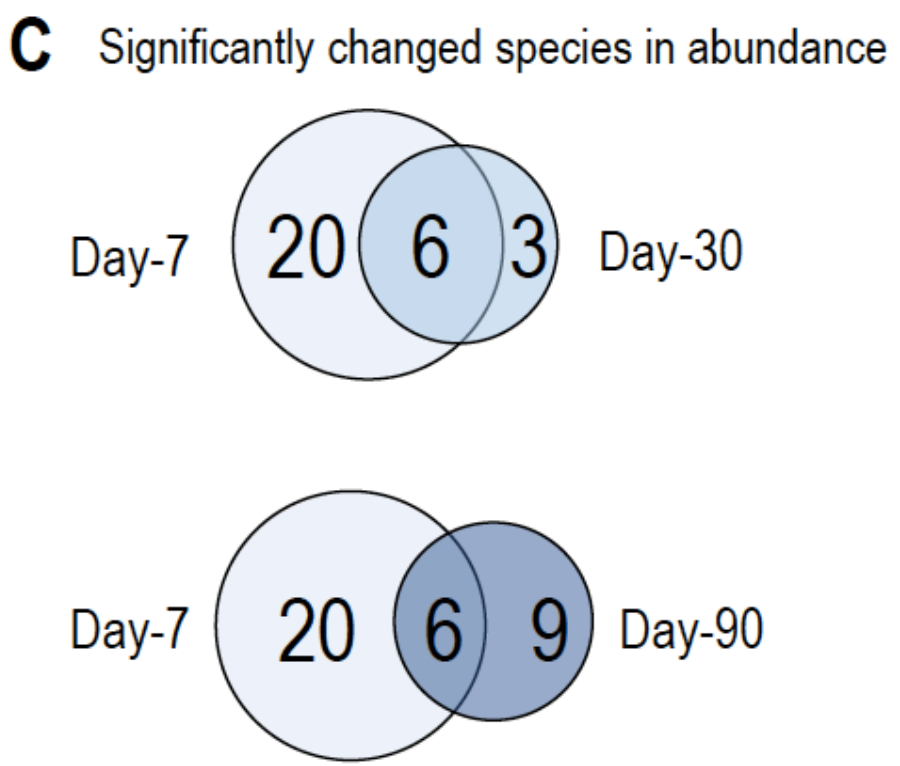
A high proportion of donor species are detected in the recipients after 7-days which in several patients remain engrafted for the 90-day trial duration.



*Woodhouse CA, Lindsay LAE, **Lee S**, Portlock T, Shoaie S, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)*

Change in faecal metagenomic species over 90-days post FMT

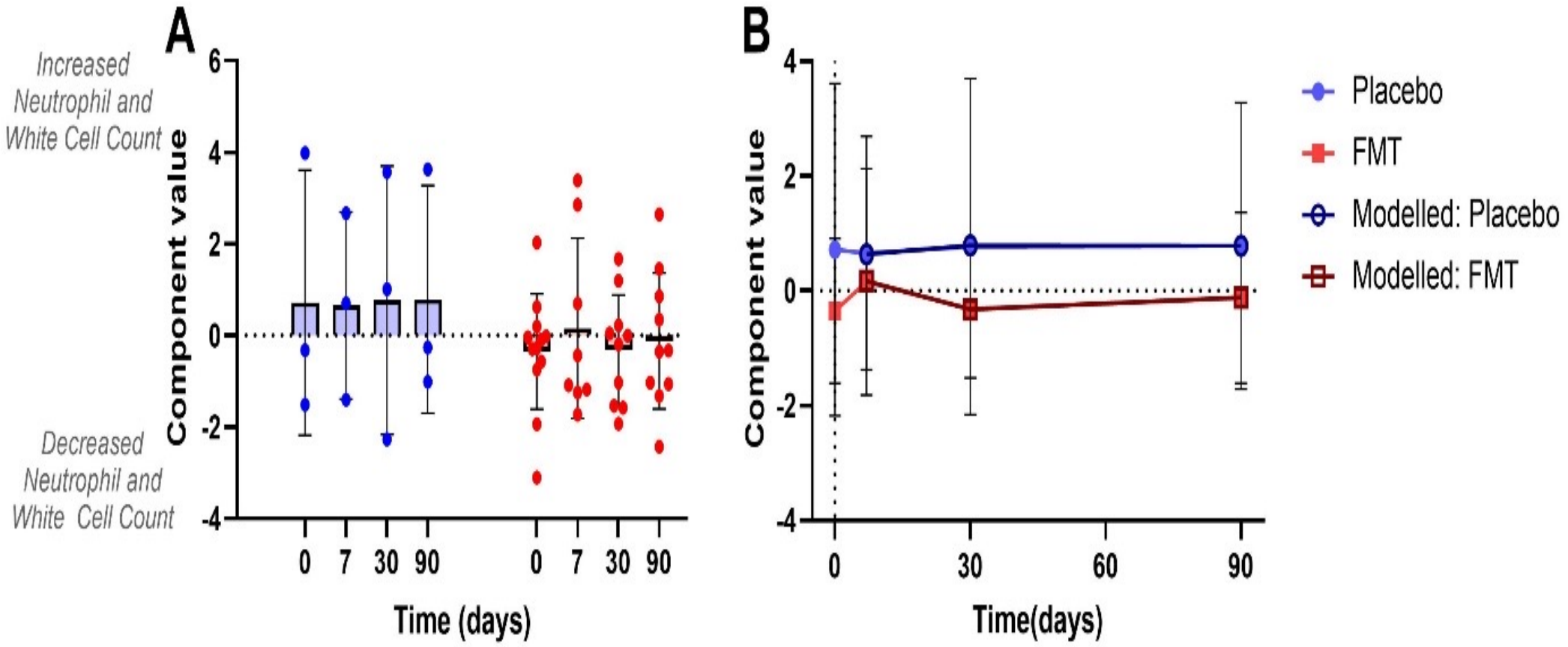




*Woodhouse CA, Lindsay LAE, **Lee S**, Portlock T, Shoaie S, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)*

FMT reduced blood neutrophils

Principal Component Analysis was analysed in Linear Mixed Models

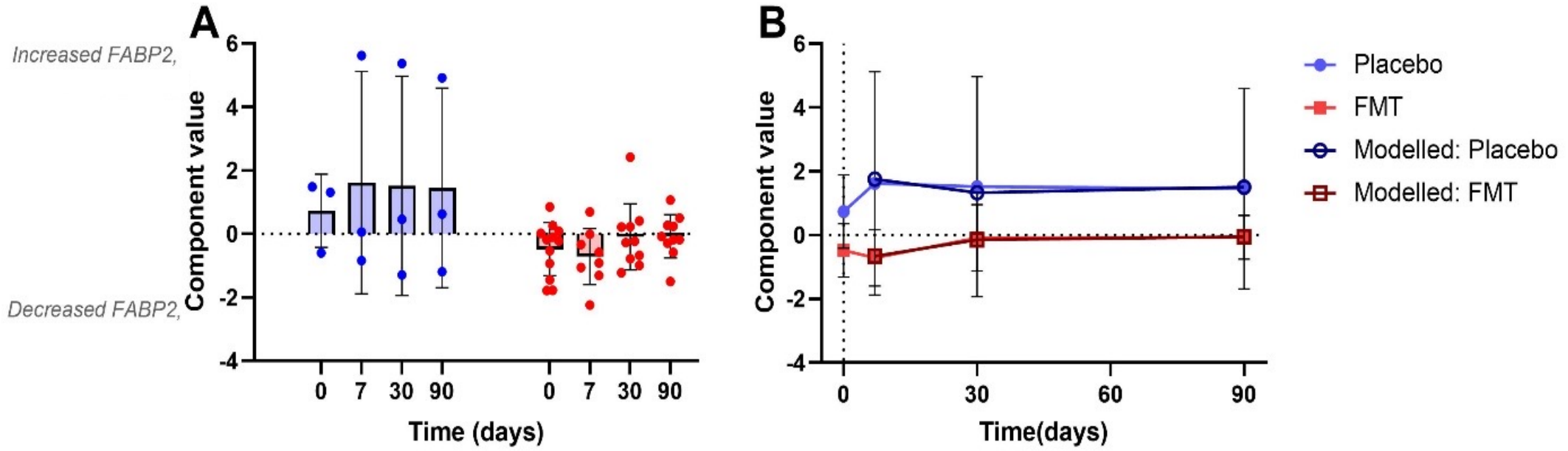


FMT administration significantly decreased neutrophils over the 90-day observation period (β=-2.38 (-4.40, -0.37), p=0.021)

Woodhouse CA, Lindsay LAE, Annastazia Learoyd, Abdel Douiri, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)

FMT reduced stool Intestinal Fatty Acid Binding Protein 2 (FABP2)

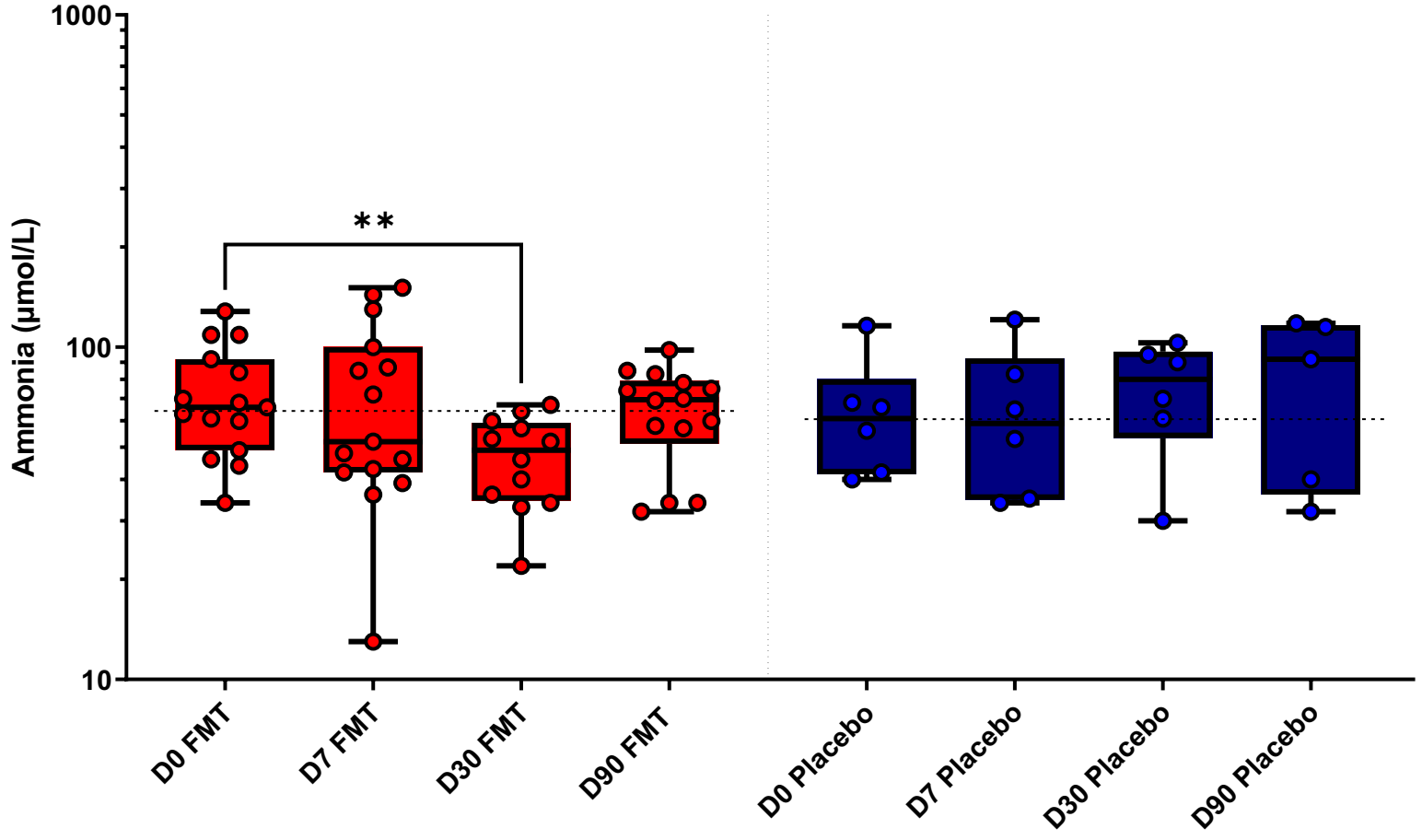
- **Expressed in the epithelial cells of the mucosal layer of the small intestine.**
- **May represent reduced intestinal epithelial cell shedding from the epithelial monolayer into the lumen reducing transient gaps or micro-erosions in the gut barrier, resulting in reduced intestinal permeability.**



FMT administration significantly decreases the FABP2 over the 90-day observation period (β=-1.89 (-3.09, -0.68), p=0.002)

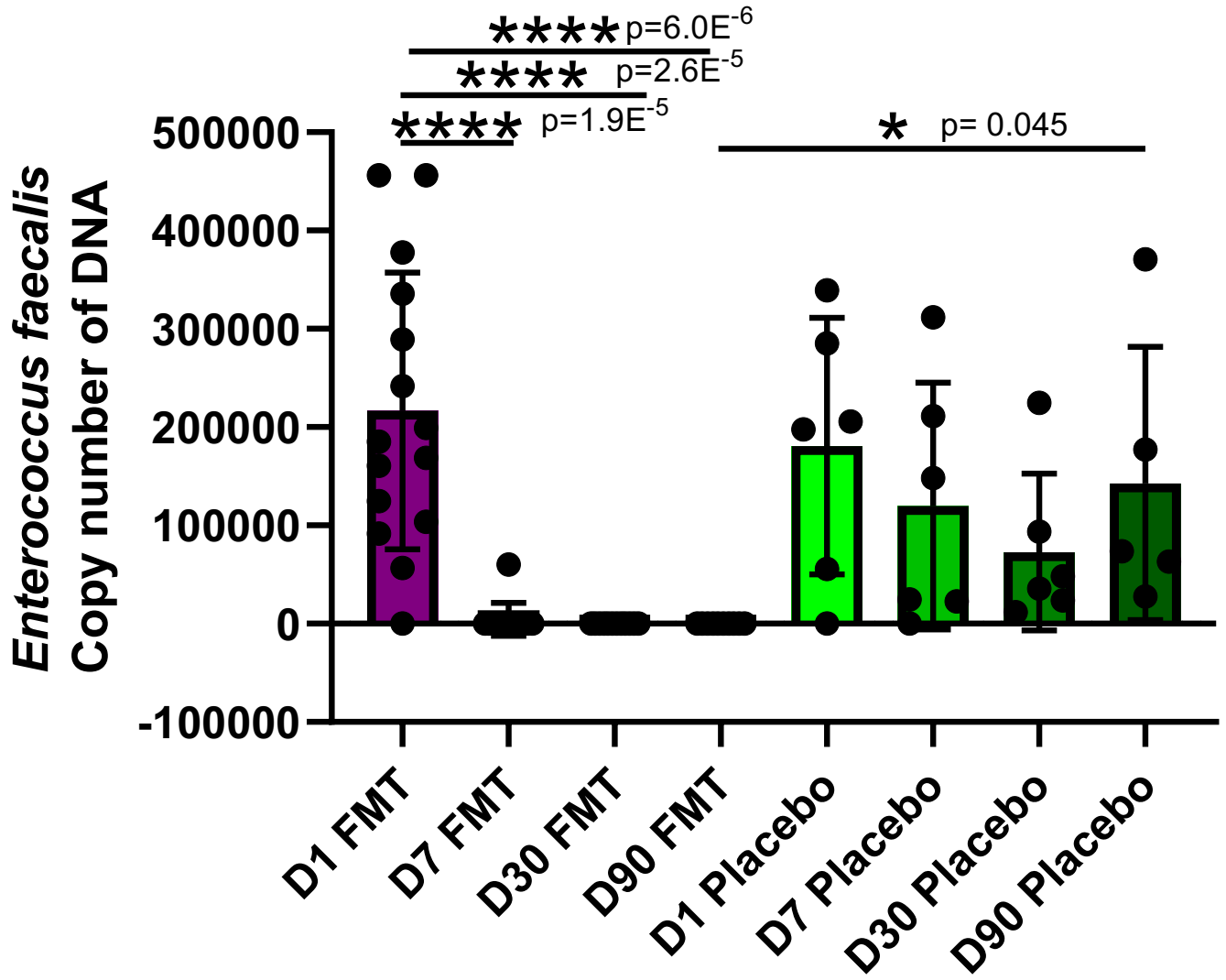
Woodhouse CA, Lindsay LAE, Annastazia Learoyd, Abdel Douiri, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)

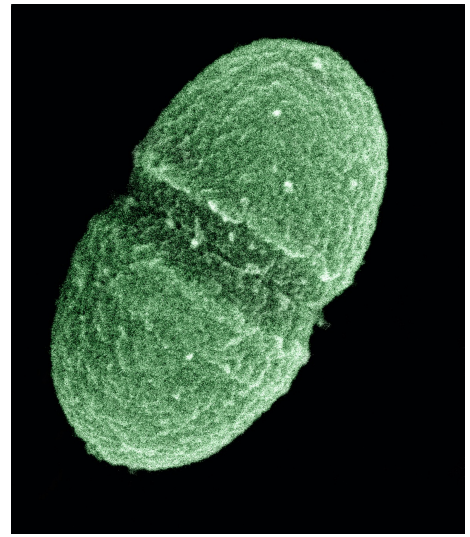
FMT Lowers Blood Ammonia



Woodhouse CA, Lindsay LAE, Annastazia Learoyd, Abdel Douiri, Goldenberg S and Shawcross DL. PROFIT Trial 2021 (unpublished data)

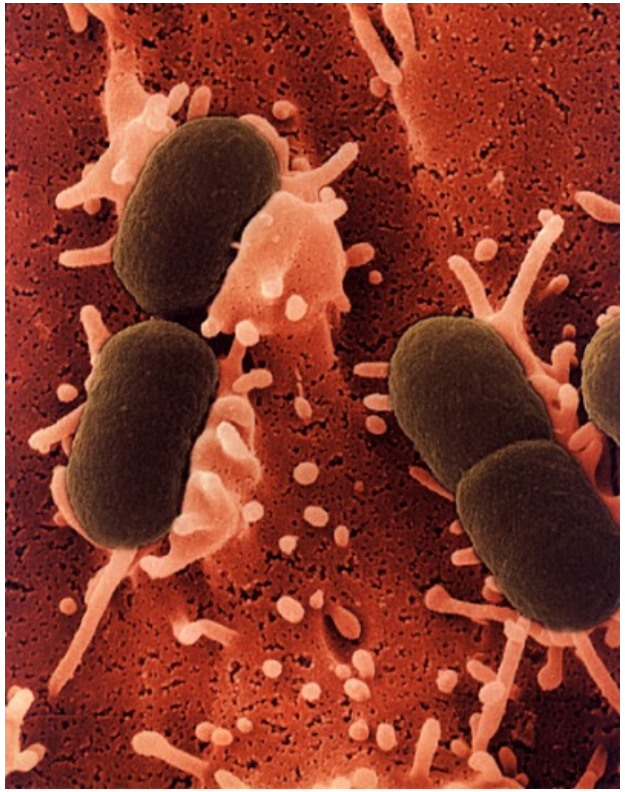
FMT reduces *Enterococcus Faecalis*

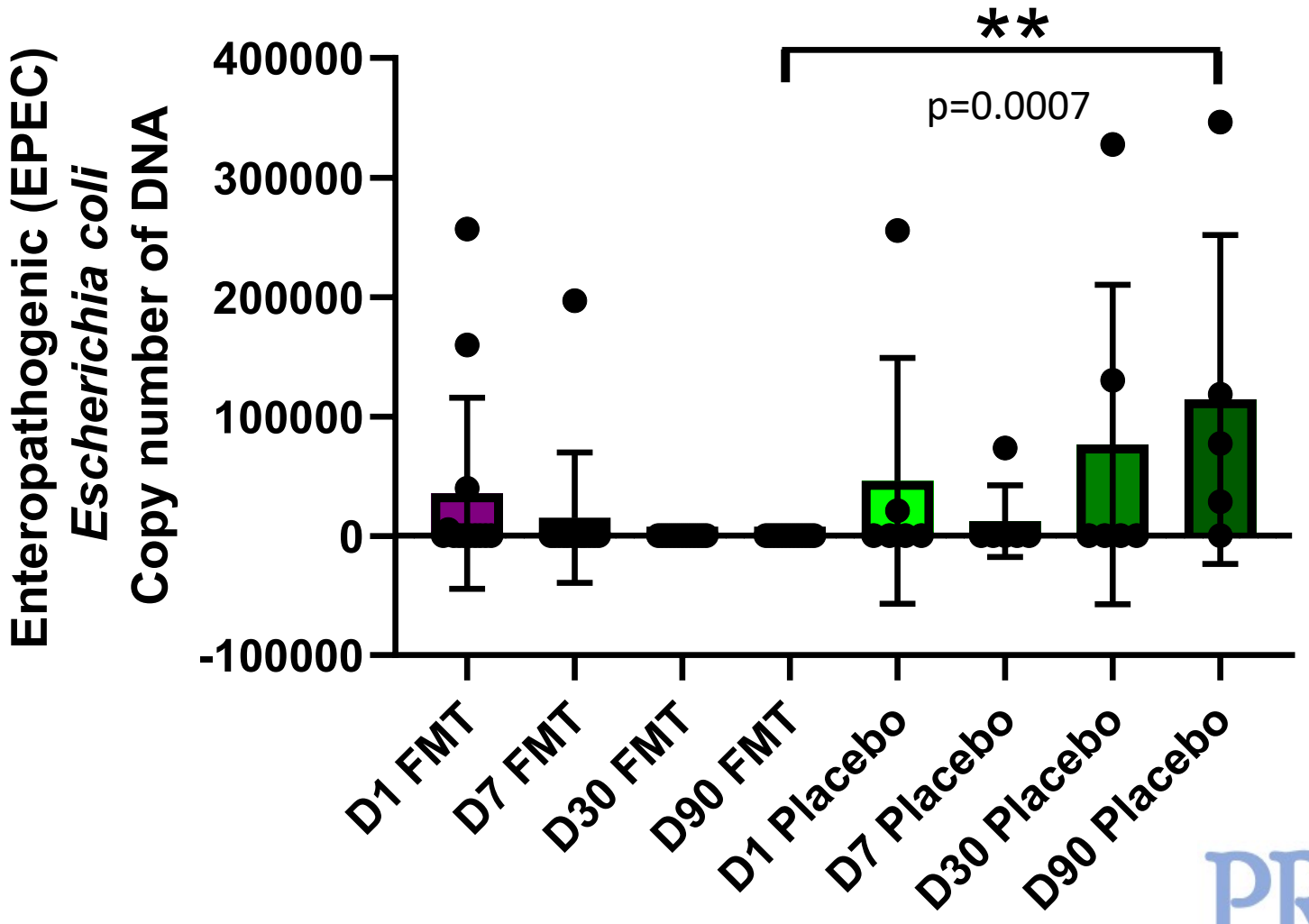




***Edwards L** and Woodhouse C et al. PROFIT Trial 2021 (unpublished data)*

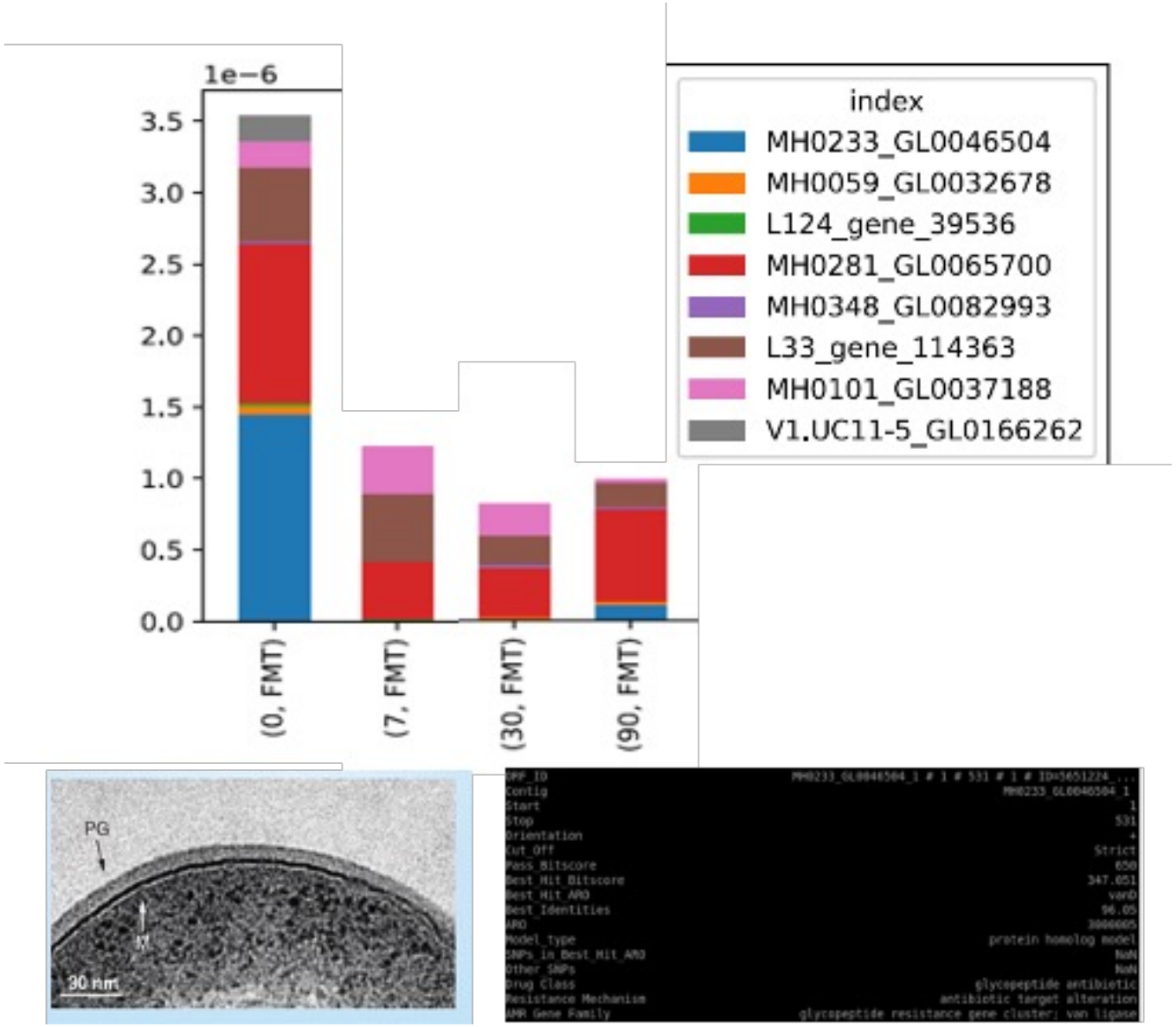
FMT reduces *Enteropathogenic E. coli*





Edwards L and Woodhouse C et al. PROFIT Trial 2019 (unpublished data)

FMT reduces AMR gene carriage



Edwards LAE et al. PROFIT Trial 2021 (unpublished data)

FMT reduces AMR gene carriage particularly the gene MH0233 van ligase. This gives rise to vancomycin resistance by preventing vancomycin binding to *E. faecalis* peptidoglycan.

Open **Faecal microbiota transplant to ERadicate gastrointestinal carriage Antibiotic Resistant Organisms (FERARO): a prospective, randomis placebo-controlled feasibility trial**

Blair Merrick ,[1,2] Emily Robinson ,[3] Catey Bunce ,[4] Liz Allen,[5,6] Karen Bisnauthsing,[1] Chi Chi Izundu,[7] Jordana Bell,[8] Gregory Amos,[9] Manu Shankar-Hari,[2,10] Anna Goodman,[1,2] Debbie L Shawcross,[11] Simon D Goldenberg [1,2]

‘Poo capsules’

PROMISE TRIAL

A **PRO**spective double-blind placebo-controlled multicentre trial of faecal **MI**crobiota tran**S**plantation to improve outcom**E**s in patients with cirrhosis

- 5-year trial
- n=300 patients
- 14 UK centres – London, Midlands, Wales, North-West, North-East and Scotland
- Patients given 5 capsules (containing 80g freeze dried donor stool, lypholised) every 3-months or identical placebo capsules for 2 years.
- Donors will be robustly screened including for ESBL and covid (PCR)

MRC Medical Research Council

NHS National Institute for Health Research

Efficacy and Mechanism Evaluation Programme

- **Primary endpoint: time to first infection resulting in hospitalisation**

Inclusion Criteria

Age over 18

Confirmed alcohol-related cirrhosis or metabolic-associated fatty liver (MAFLD) cirrhosis based on clinical, radiological and/or histological criteria.

MELD score 8-16

Patients with alcohol-related cirrhosis must have been abstinent for a minimum of 4-weeks prior to randomisation.

Exclusion Criteria

Patients treated for acute variceal bleeding, infection, overt hepatic encephalopathy, bacterial peritonitis or ACLF within 14 days prior to randomisation.
Active alcohol consumption of >20 grams/day [1 unit of alcohol contains 10mLs or 8g of alcohol].
Previous liver transplantation.
Patients with inflammatory bowel disease.
Patients with coeliac disease.
Patients with a history of prior gastrointestinal resection such as gastric bypass.
Patients with an expected life expectancy <6 months or listed for liver transplantation.
Patients who have received antibiotics or probiotics within 7 days prior to randomisation.

PROMISE TRIAL

BRITISH LIVER TRUST

PROMISE TRIAL

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UKRI Medical Research Council

NIHR | National Institute for Health Research

PROMISE TRIAL

Scan this QR code to find out more about the PROMISE trial, or visit fmt-trials.org

NIHR | Guy's and St Thomas' Biomedical Research Centre

https://www.nihr.ac.uk/

Fecal Microbiota Transplant (FMT) Trials

Investigating the application of FMT therapy to combat antimicrobial resistance and improve patient outcomes

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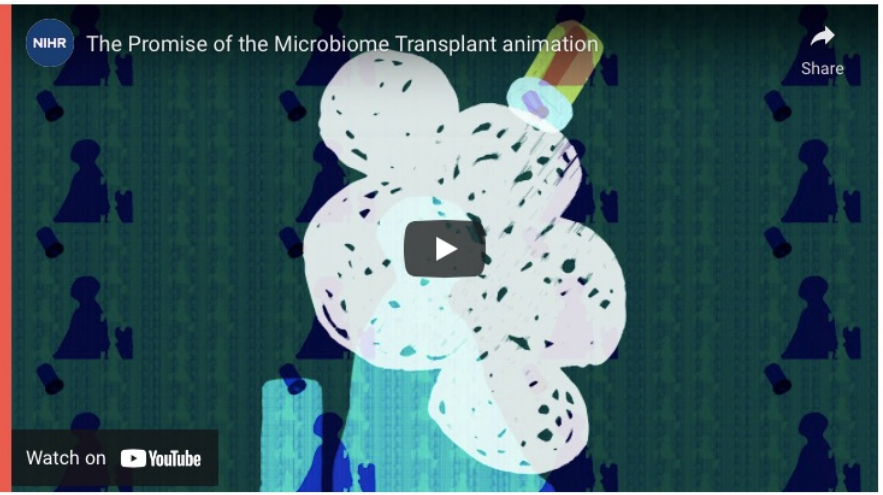
PROMISE

A PROspective double-blind placebo-controlled multicentre trial of faecal MIcrobiota tranSplantation to improve outcomEs in patients with cirrhosis - PROMISE trial



BRITISH LIVER TRUST

Evolving crisis of chronic liver disease (CLD) in the UK

There is an evolving crisis of chronic liver disease (CLD) in the UK and it is the only major chronic disease which is on the rise. The advanced stages of CLD, known as cirrhosis (a hardening and scarring of the liver), is the third biggest cause of death and loss of working life years behind heart disease and self-harm.

THANK YOU

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