Fecal Transplantation: Come e Quando

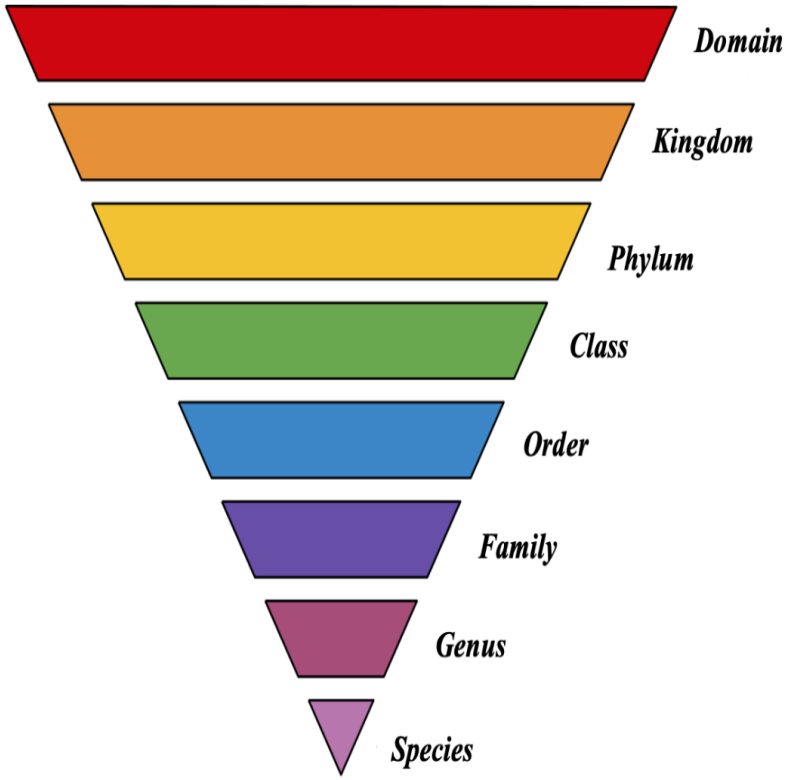
Edoardo V. Savarino MD, PhD
Professore Associato
Azienda Ospedaliera Universitaria di Padova
Università di Padova
Italy

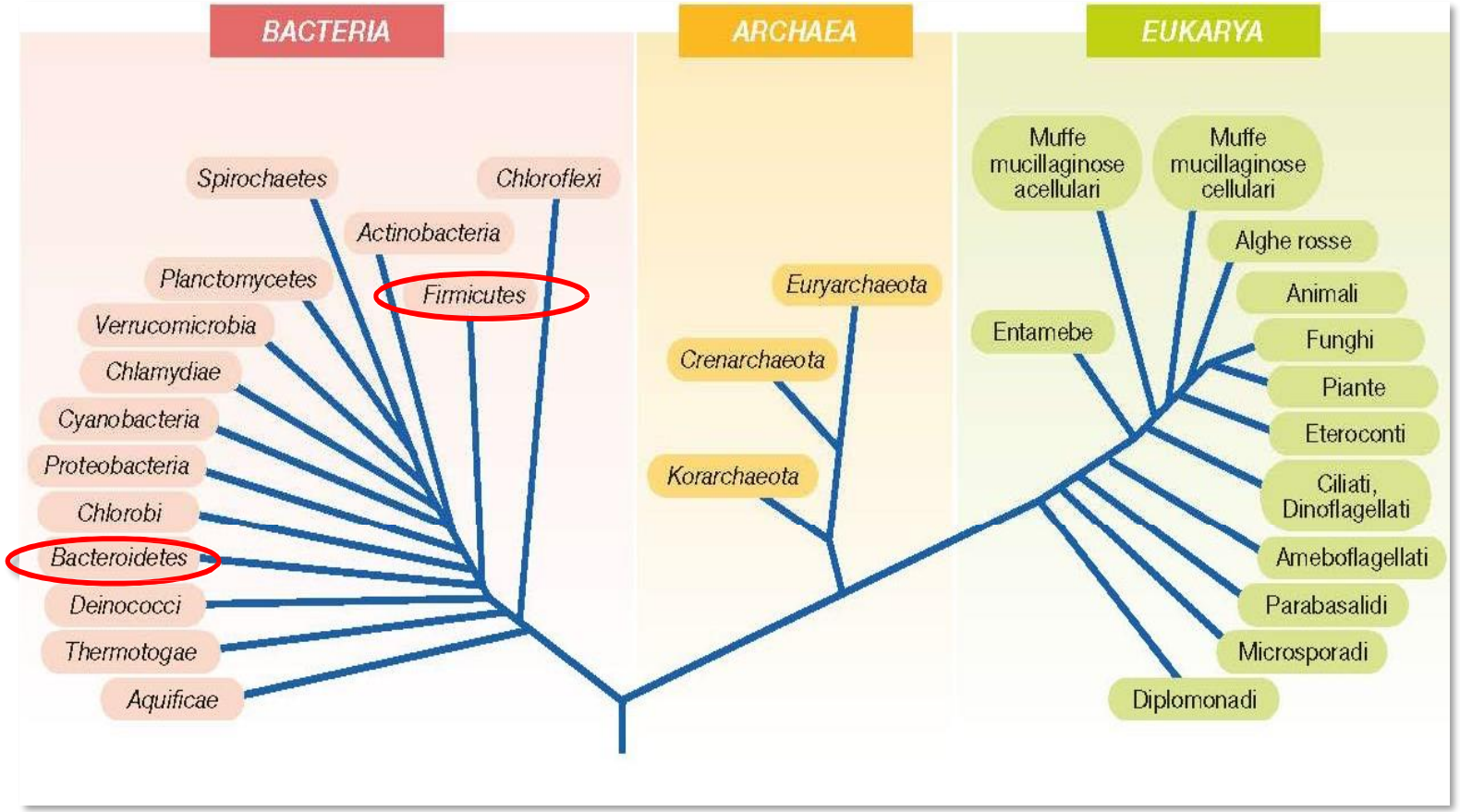
Disclosure of Conflict of Interests

- Edoardo Vincenzo Savarino has served as speaker for Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici

Gut Microbiota as a Superorganism

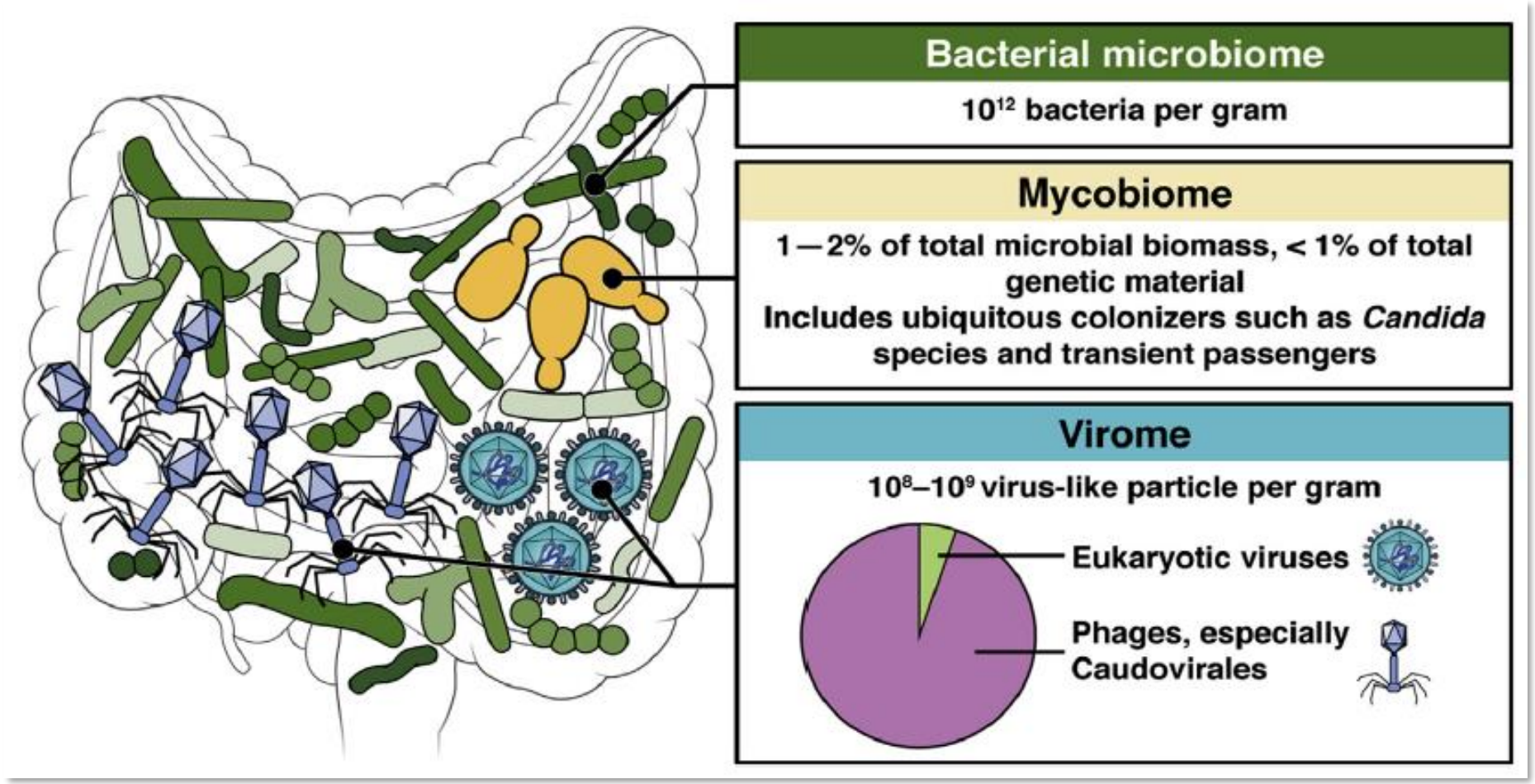
The **human microbiota** consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut; the human microbiome consists of the genes these cells harbor





Before the advent of molecular biology, only 4 phyla were known: Actinobacteria (Bifidobaterium) Proteobacteria (E.coli), Firmicutes (Ruminococcus, Clostridium, Lactobacillus, Eubacterium, Faecalibacterium, Roseburia) and Bacteroides (Bacteroides, Prevotella, Xylanibacter). Today we know that 30 different phyla coexist: Verrucomicrobia (Akkermansia muciniphila, specialized in the degradation of mucus)

Gut Microbiota as a Superorganism, but……



Iliev DI, et al. Gastroenterology 2021;160:1050–1066

What is EUBIOSIS?

Eubiosis is the healthy relationship among commensal microbes of the gut

COMPOSITION

- Richness
- Relative Abundance
- Diversity

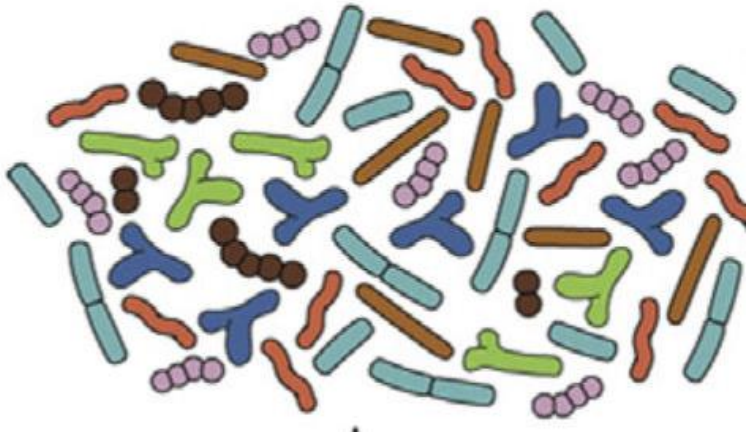
FUNCTION

- Microbiota's effect on host health

Never forget the clinic!

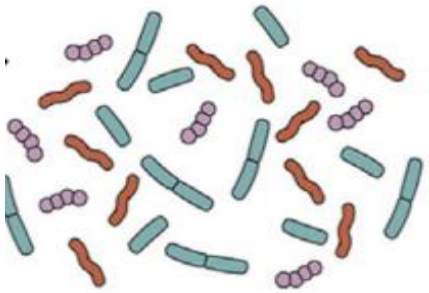
From EUBIOSIS to DYSBIOSIS

Healthy microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis
(Loss of eubiosis)

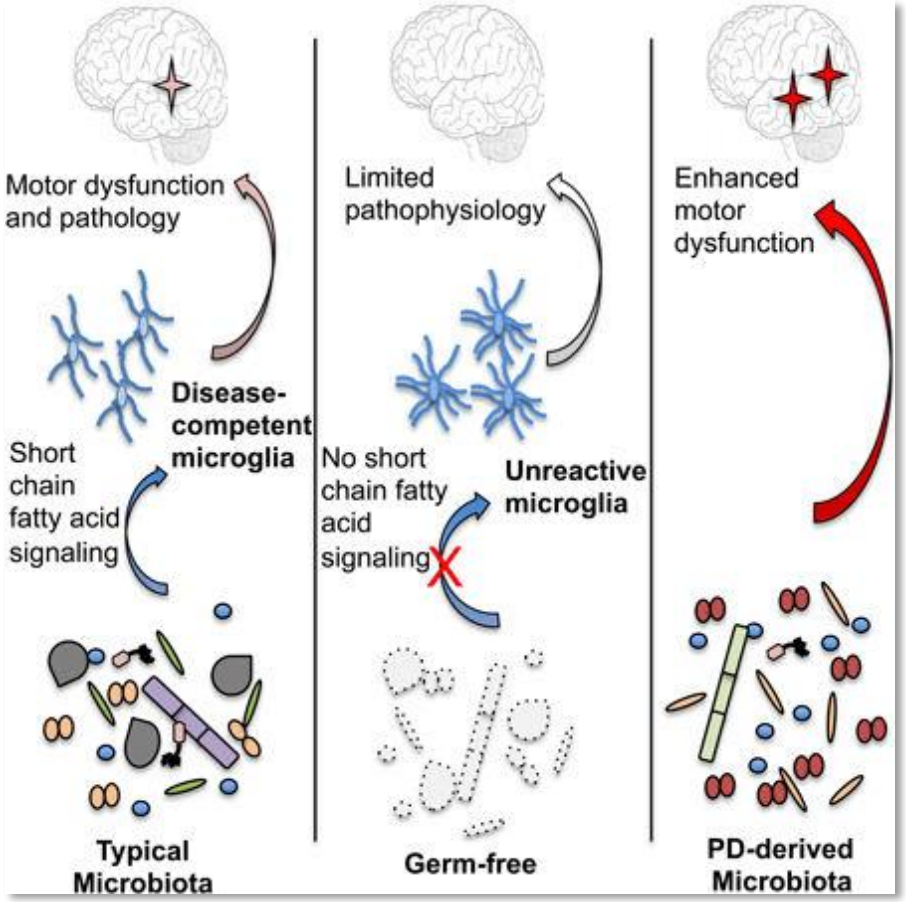


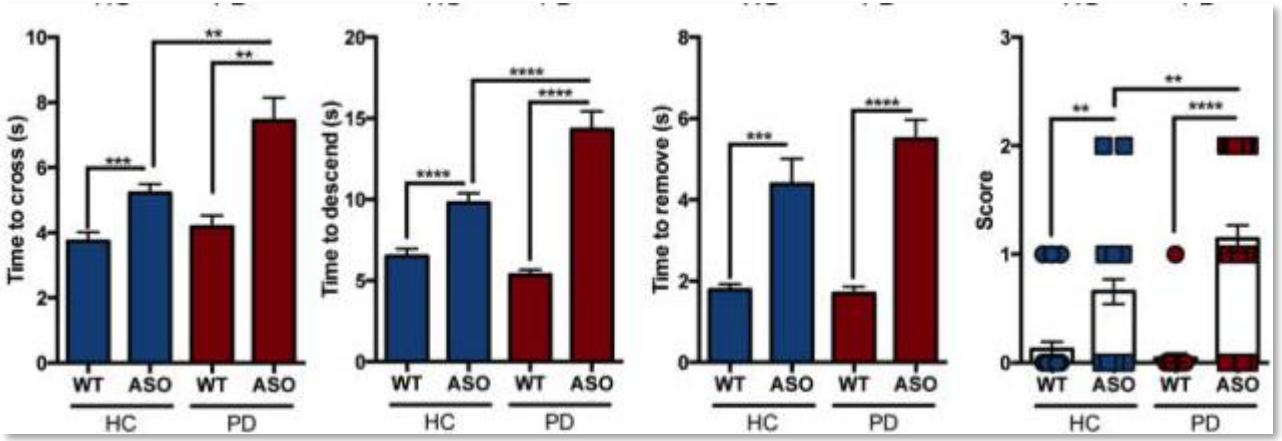
Quantity

Quality

Microbiota Composition and Parkinson's Disease

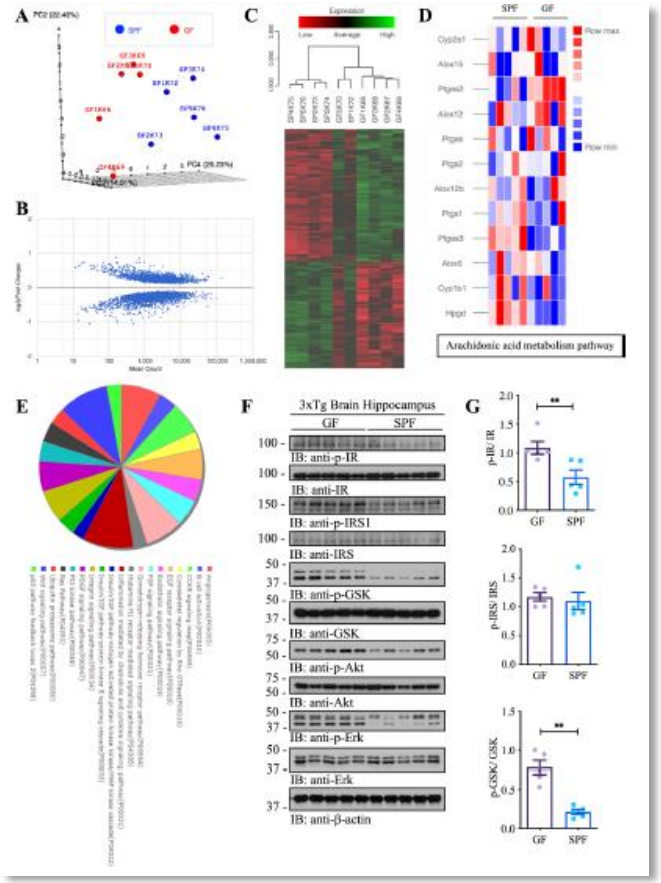
Microbiota from PD patients induce increased α-synuclein (αSyn)-mediated motor deficits, often resulting in motor dysfunction

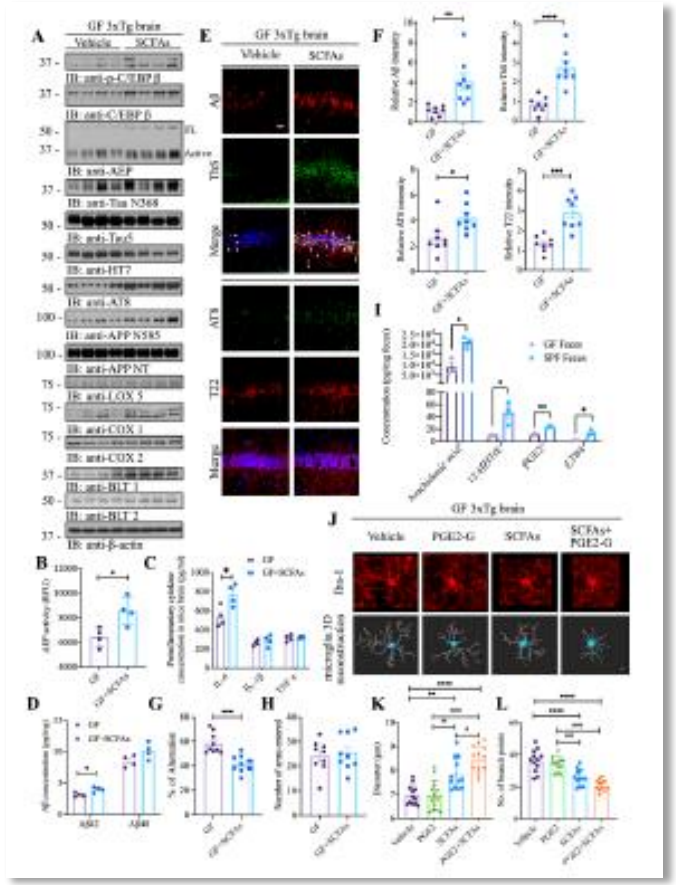


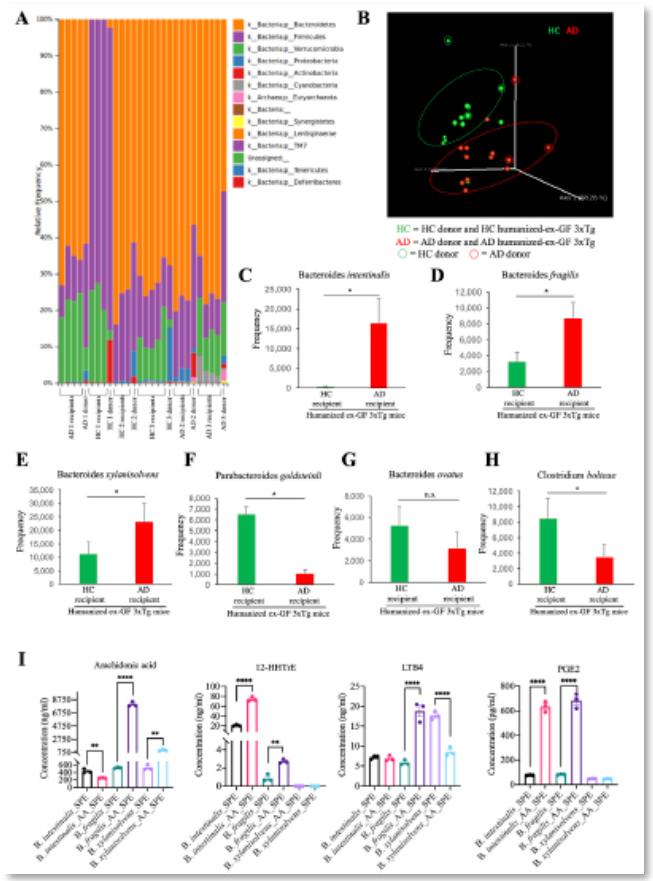


Sampson TR, et al. Cell. 2016 Dec 1;167(6):1469-1480.e12

Gut Microbiota Regulate Alzheimer's Disease Pathologies and Cognitive Disorders via Poly-Unsaturated Fatty Acid-associated Neuroinflammation





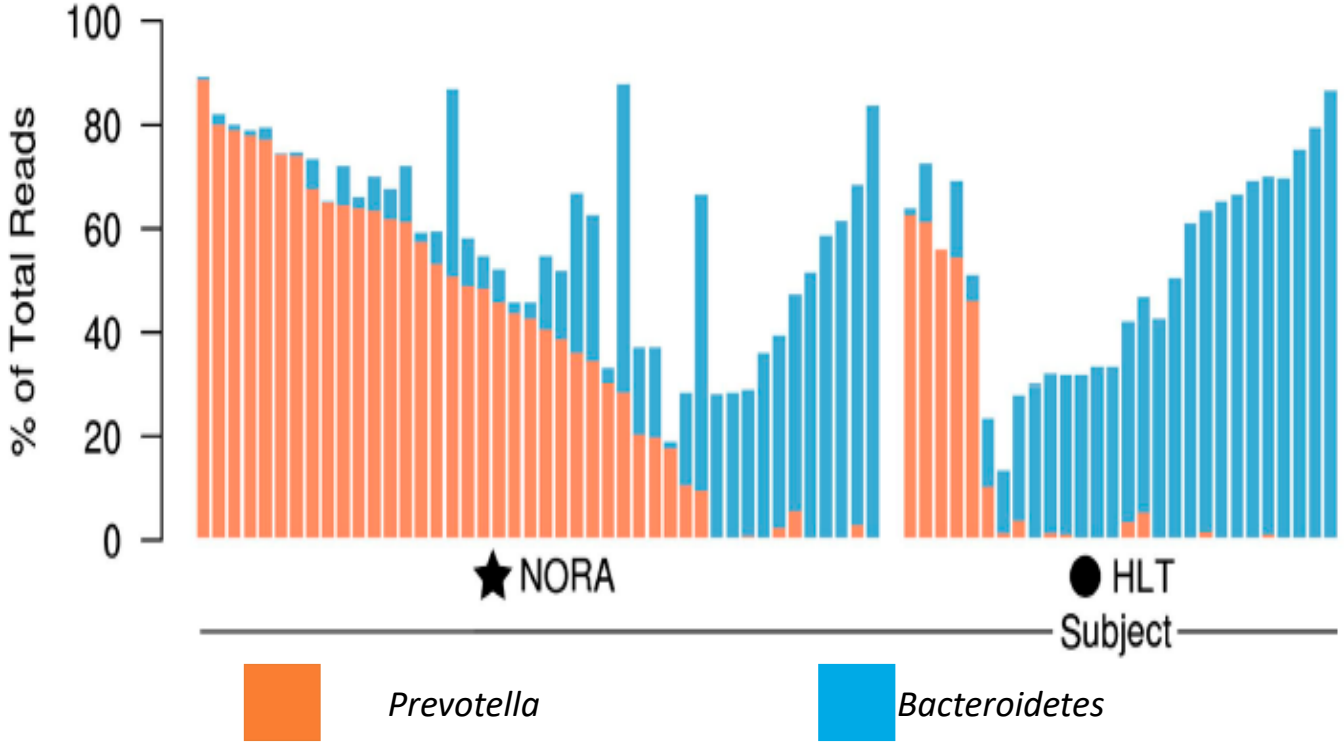


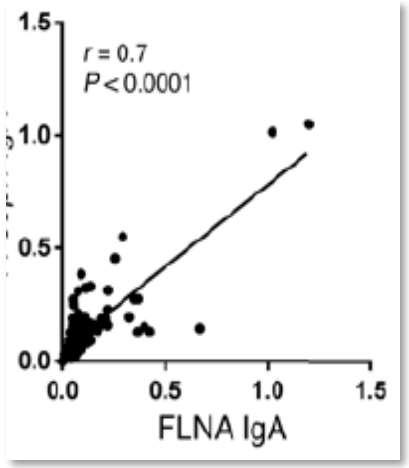
A complex gut microbiome is required for behavioural defects, microglia activation and AD pathologies, the gut microbiome contributes to pathologies in an AD mouse model and that dysbiosis of the human microbiome might be a risk factor for AD.

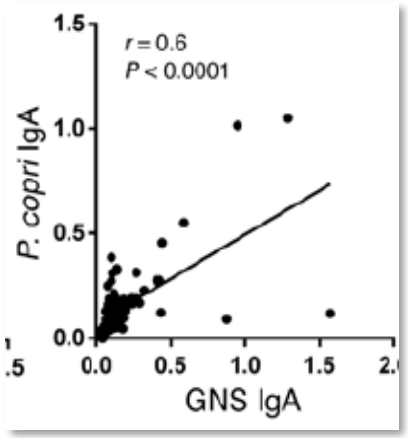
Chen C, et al. Gut. 2022 Nov;71(11):2233-2252

Microbiota Composition and Rheumatoid Arthritis

- 16S sequencing on 114 stool samples from RA patients and controls
- **Prevotella copri** strongly correlates with disease in new-onset untreated rheumatoid arthritis (NORA)
  - Anti-GNS/FLNA abs levels correlate with *Prevotella copri* Ab responses

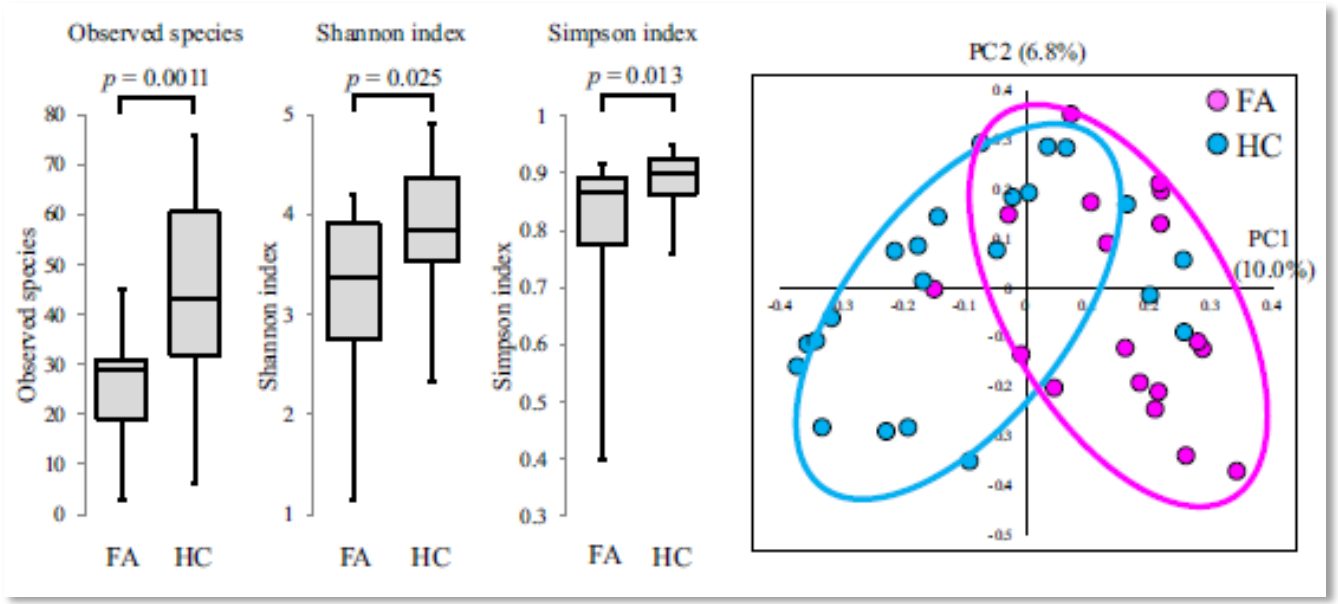






Scher JU, et al. Elife. 2013 Nov 5;2:e01202

Decreased Butyric acid-producing Bacteria in Gut Microbiota of Children with Egg Allergy



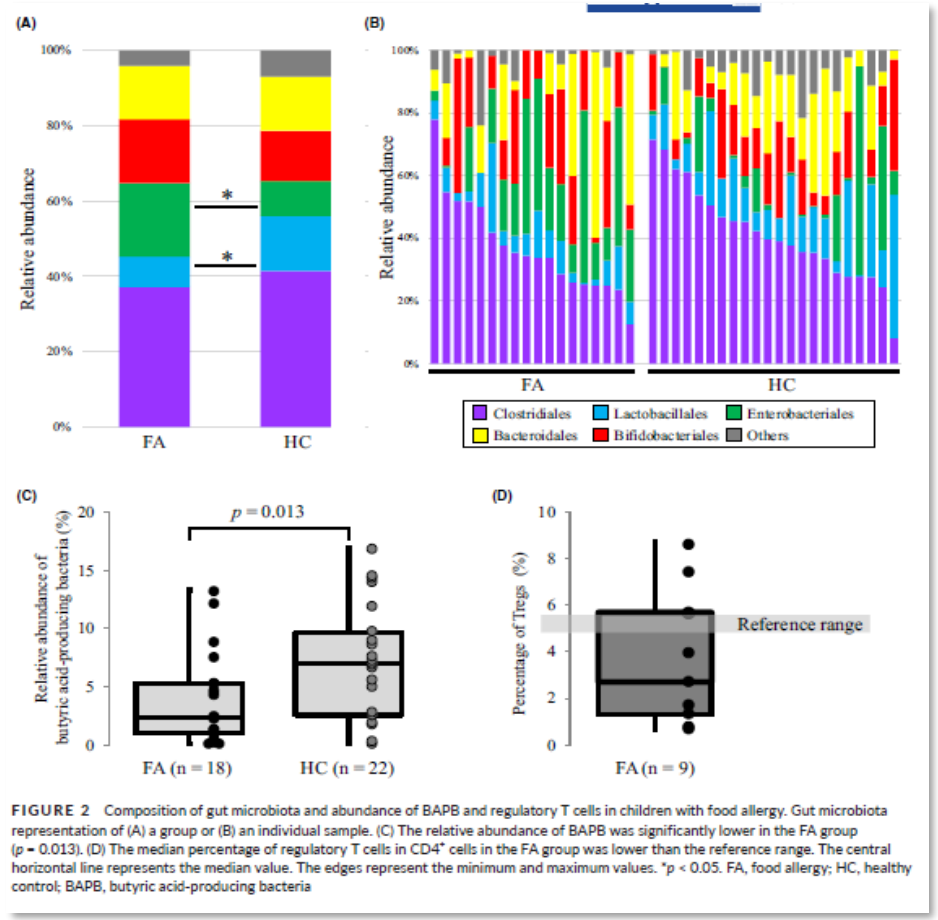
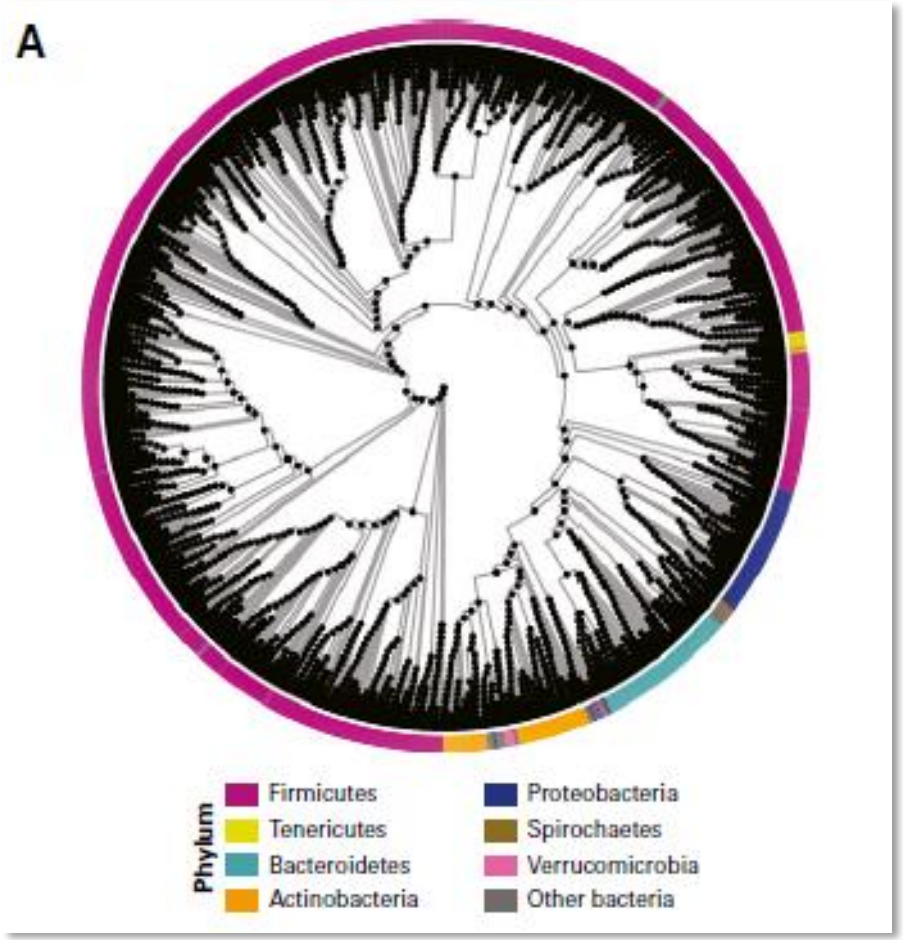


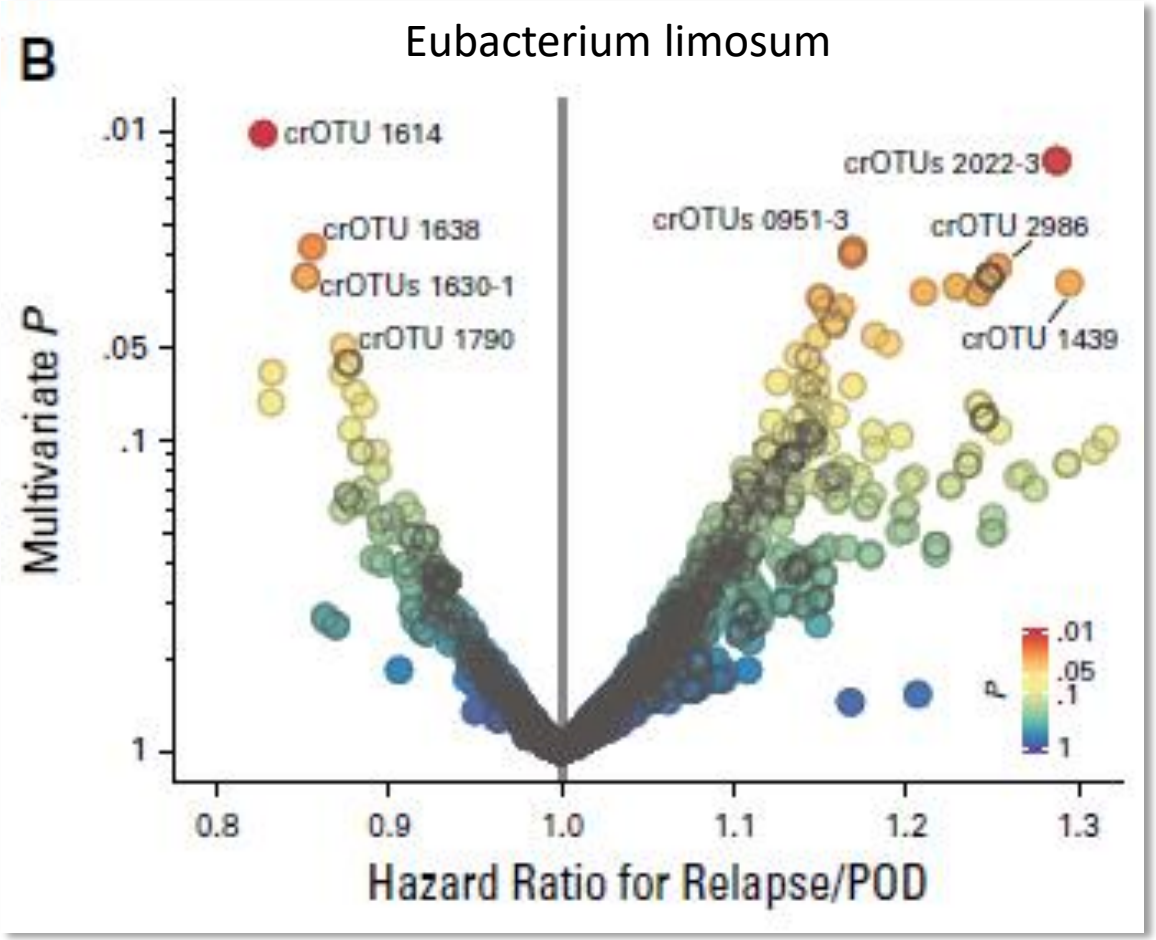
FIGURE 2 Composition of gut microbiota and abundance of BAPB and regulatory T cells in children with food allergy. Gut microbiota representation of (A) a group or (B) an individual sample. (C) The relative abundance of BAPB was significantly lower in the FA group ($p = 0.013$). (D) The median percentage of regulatory T cells in $CD4^+$ cells in the FA group was lower than the reference range. The central horizontal line represents the median value. The edges represent the minimum and maximum values. *$p < 0.05$. FA, food allergy; HC, healthy control; BAPB, butyric acid-producing bacteria

This study revealed that children with egg allergies have less butyric acid-producing bacteria and tendentially fewer circulating Treg cells

Yamagishi M, et al. Allergy. 2021 Jul;76(7):2279-2282

Intestinal Microbiota and Relapse After Hematopoietic-Cell Transplantation

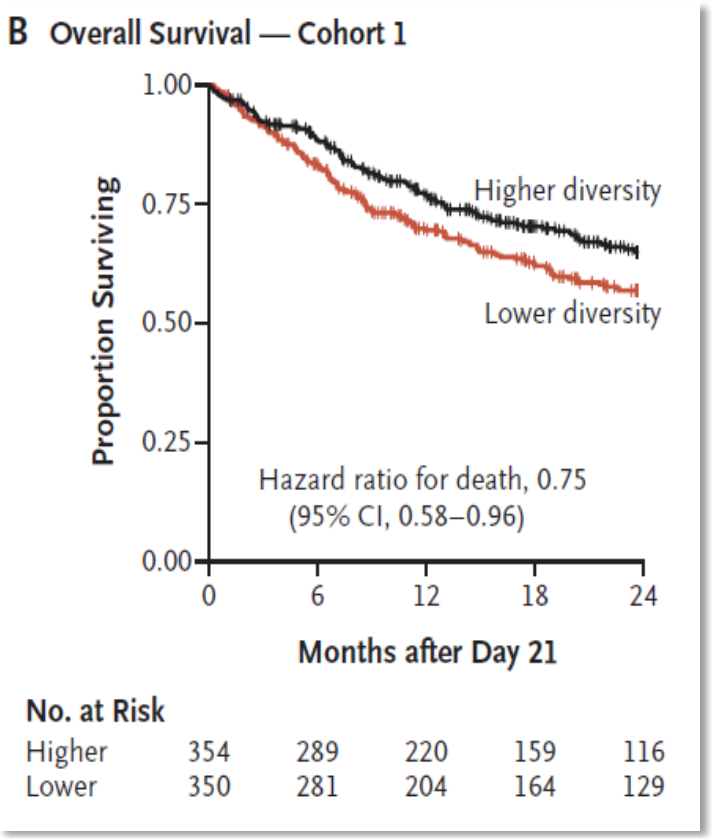


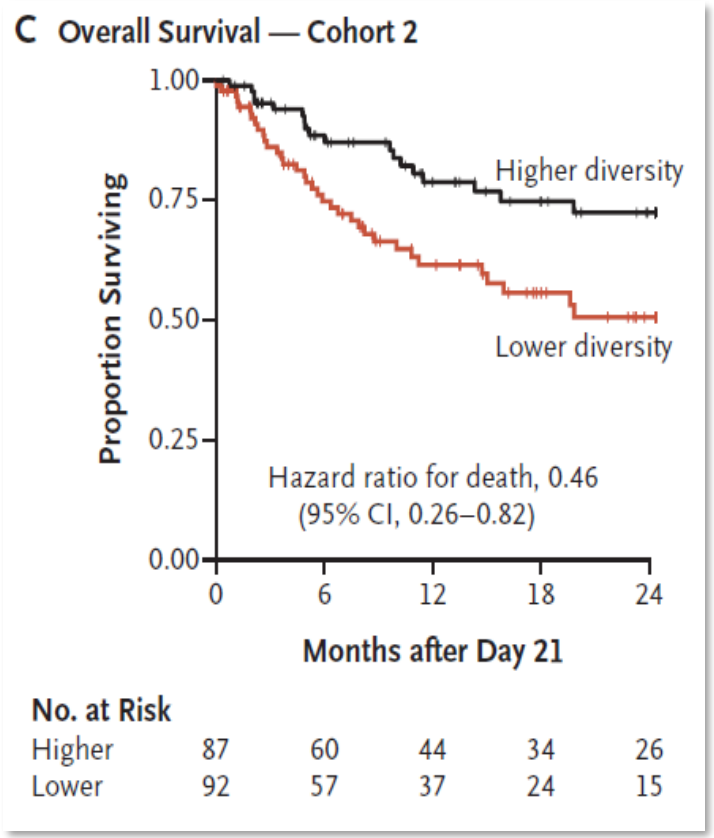


N=541 patients admitted for allo-HCT with a 2-year follow-up

Peled JU, et al. J Clin Oncol 2017 May 20;35(15):1650-1659

Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation

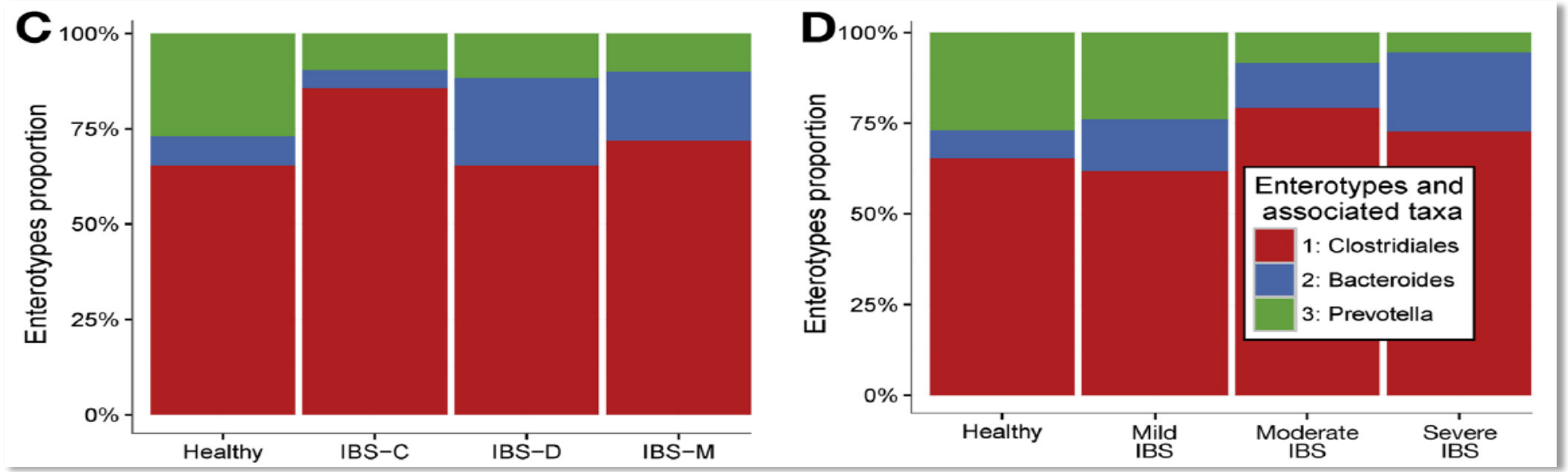


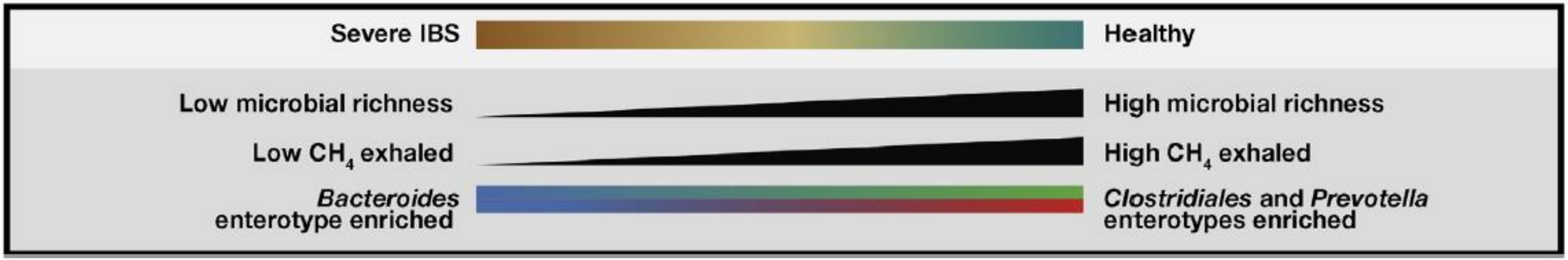


- Higher diversity of intestinal microbiota was associated with a lower risk of death in independent cohorts
- Subgroup analyses identified an association between lower intestinal diversity and higher risks of transplantation-related death and death attributable to graft-versus-host disease
- Baseline samples obtained before transplantation already showed evidence of microbiome disruption, and lower diversity before transplantation was associated with poor survival

Peled JU, et al. N Engl J Med . 2020 Feb 27;382(9):822-834

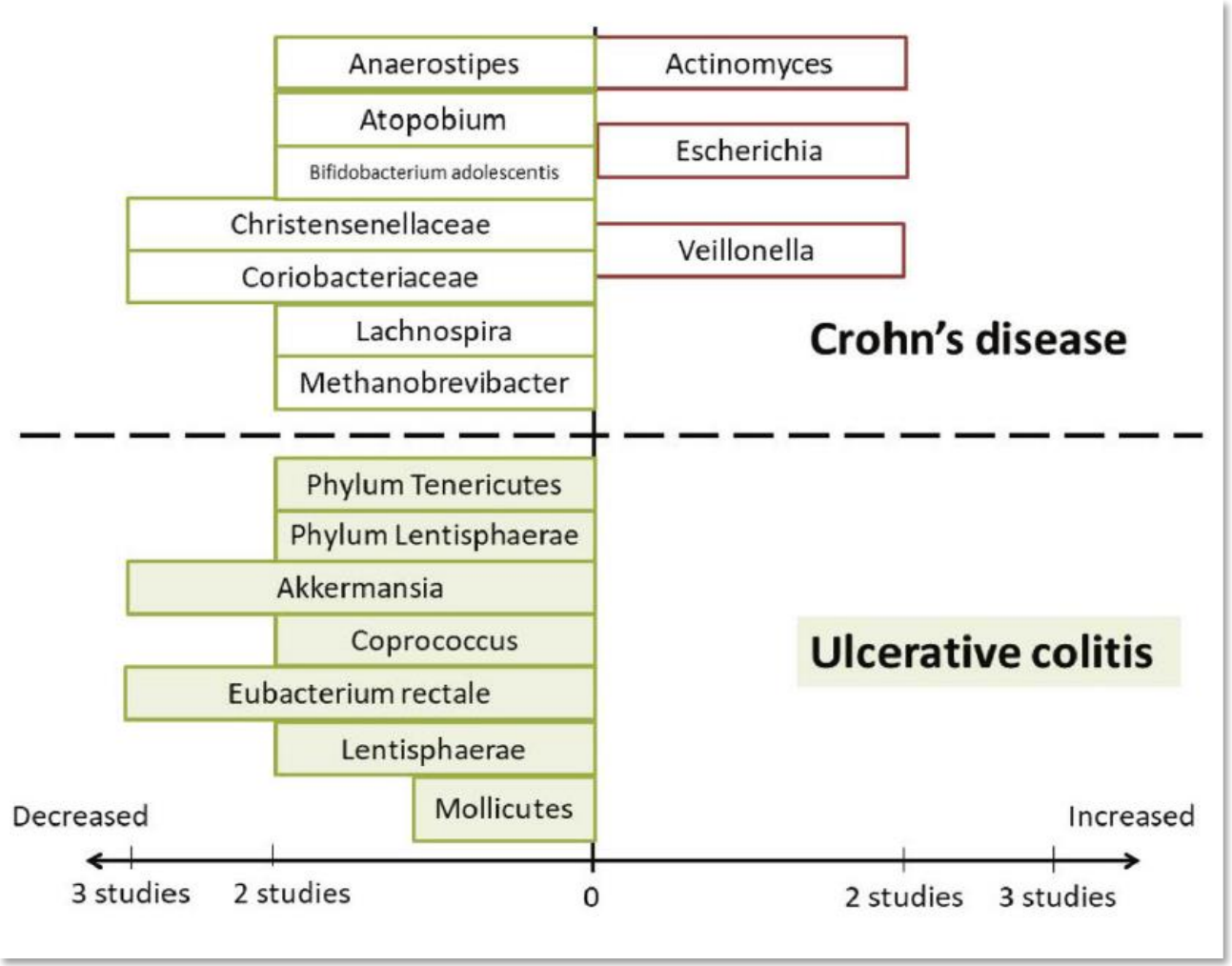
Identification of an Intestinal Microbiota Signature Associated With Severity of Irritable Bowel Syndrome





Tap J et al. Gastroenterology 2017;152:111–123

Differences in Gut Microbiota in Patients With vs Without Inflammatory Bowel Diseases: A Systematic Review



WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Altering the intestinal microbiota has been proposed as a treatment for inflammatory bowel diseases (IBD), but there are no established associations between specific microbes and IBD.

NEW FINDINGS

In a systematic review, we found the bacteria Christensenellaceae, Coriobacteriaceae, and *Faecalibacterium prausnitzii* to be decreased in patients with Crohn's disease compared to controls, whereas *eubacterium rectale* and Akkermansia were decreased in patients with ulcerative colitis.

LIMITATIONS

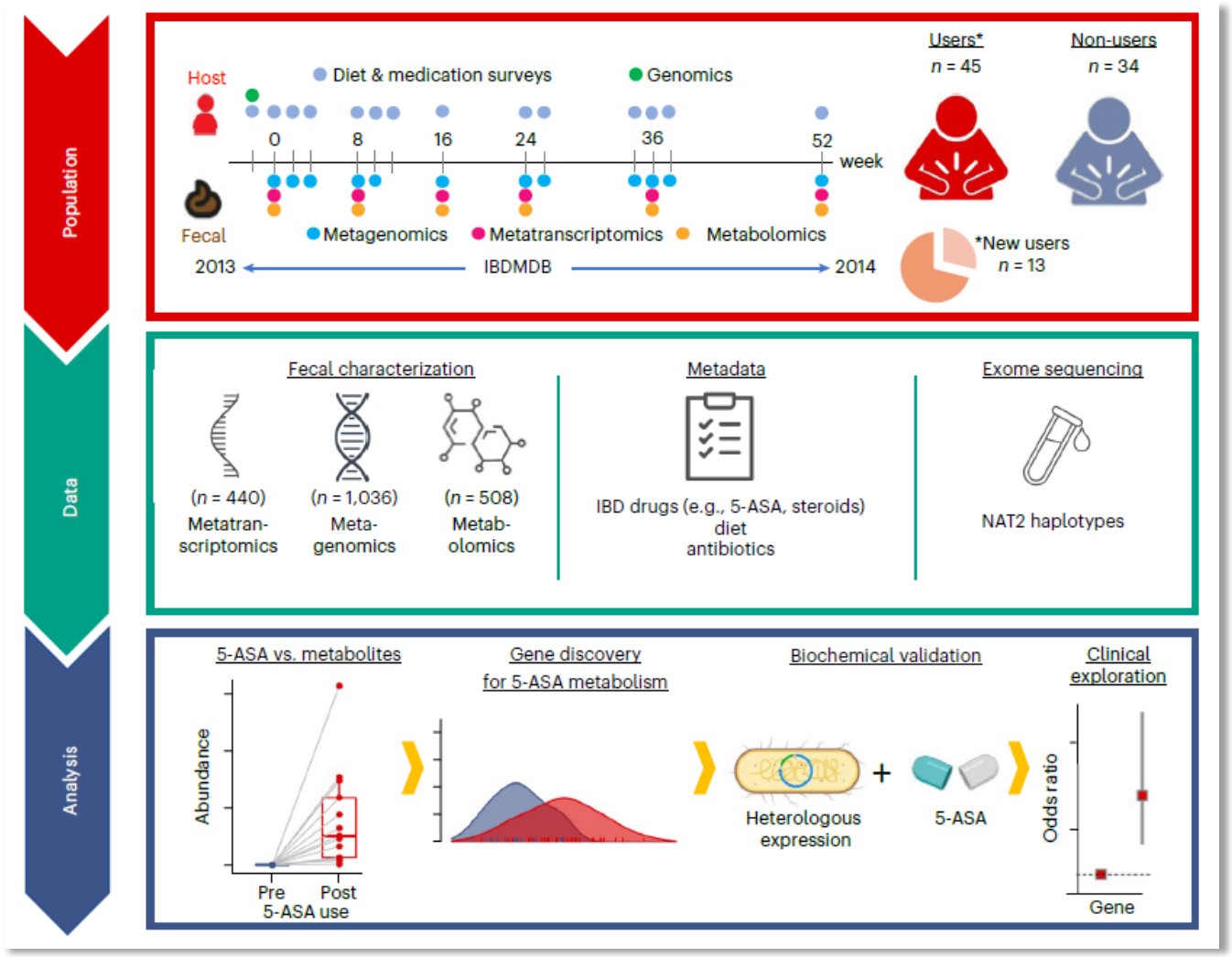
There was heterogeneity in methods of microbe assessment among the studies, as well as possible bias in either selection of controls or comparability of demographic data. No study fulfilled the quality criteria for all relevant domains

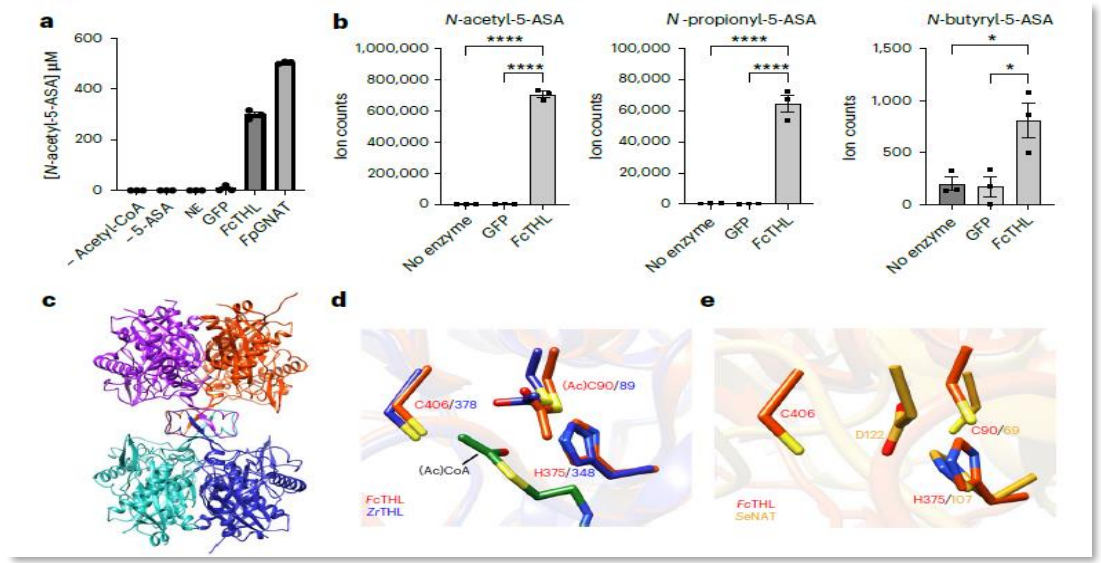
IMPACT

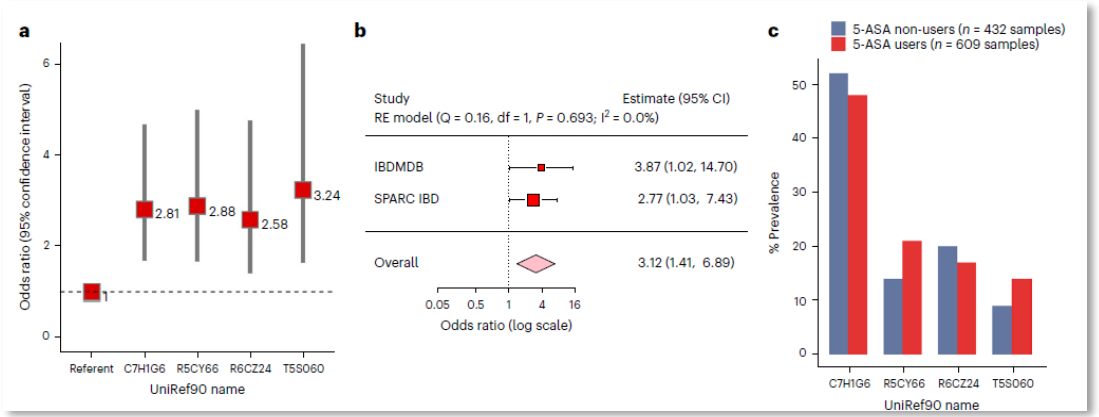
These findings provide guidance for design of future studies of individual bacterial species or genera associated with IBD and microbe-based treatments.

Pittayanon R, et al. Gastroenterology. 2020 Mar;158(4):930-946.e1

Gut Microbial Metabolism of 5-ASA Diminishes its Clinical Efficacy in Inflammatory Bowel Disease



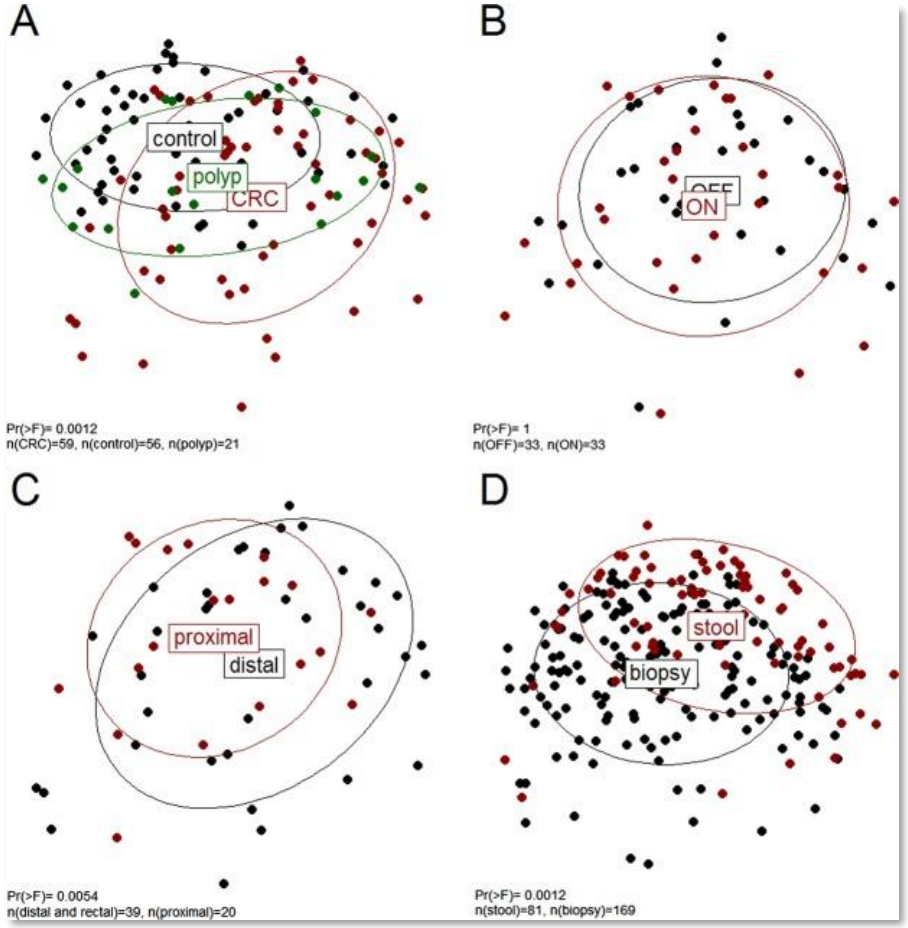


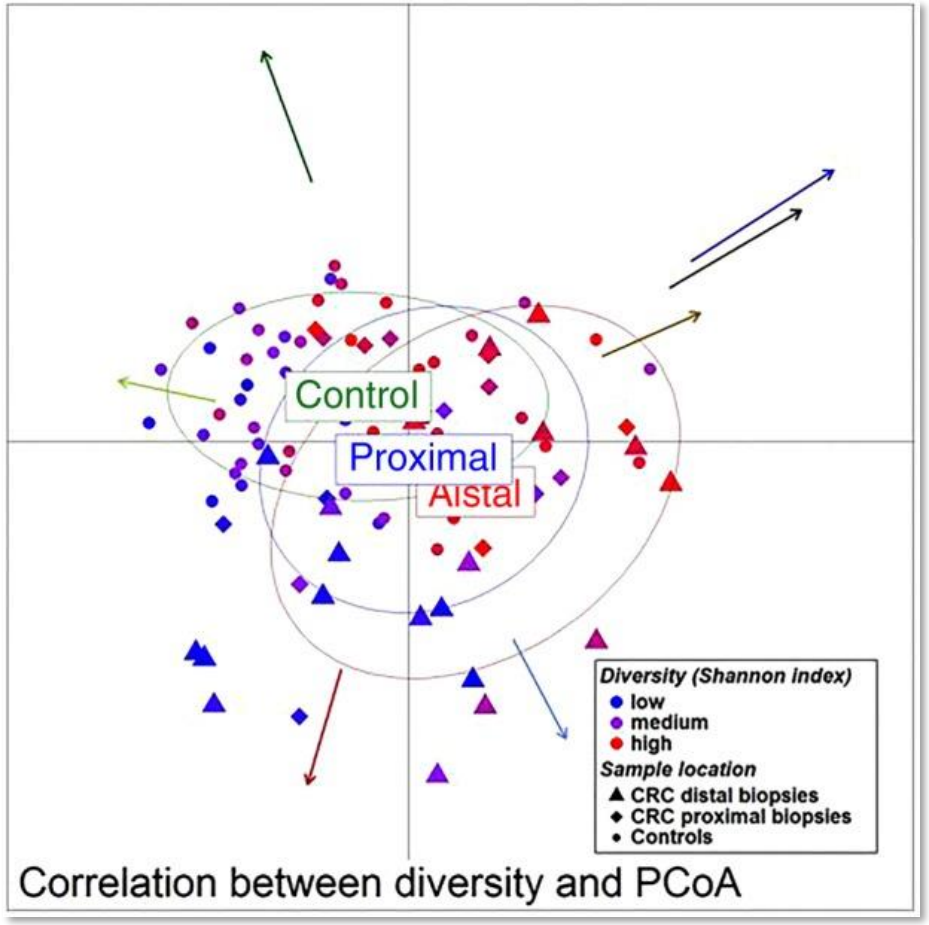


Meetha RS, et al. Nat Med. 2023 Mar;29(3):700-709

Microbiota Composition and Colo-Rectal Cancer

CRC-associated microbiota profiles differ from those in healthy subjects and are linked with distinct mucosal gene-expression profiles. Compositional alterations in the microbiota are not restricted to cancerous tissue and differ between distal and proximal cancers

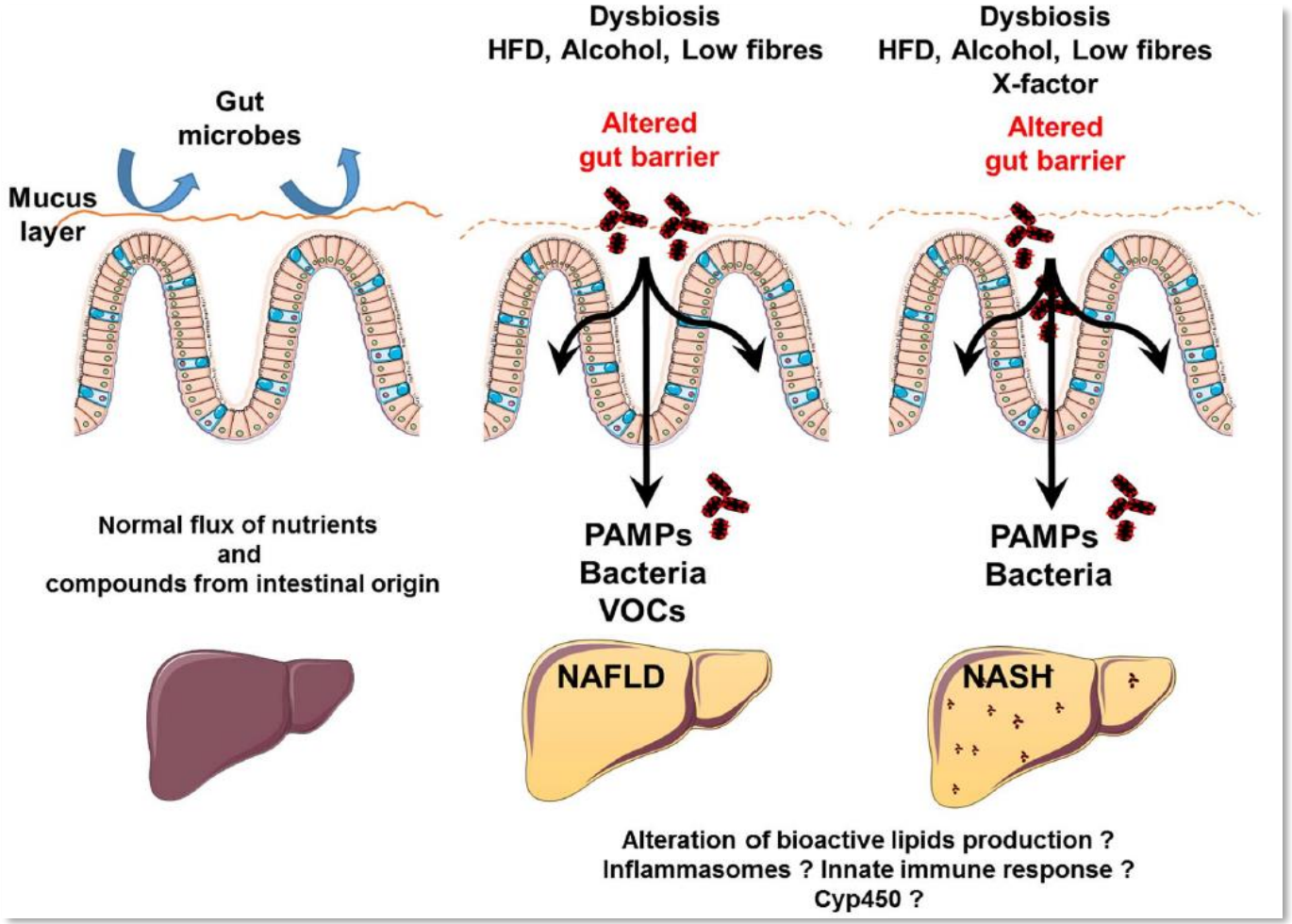


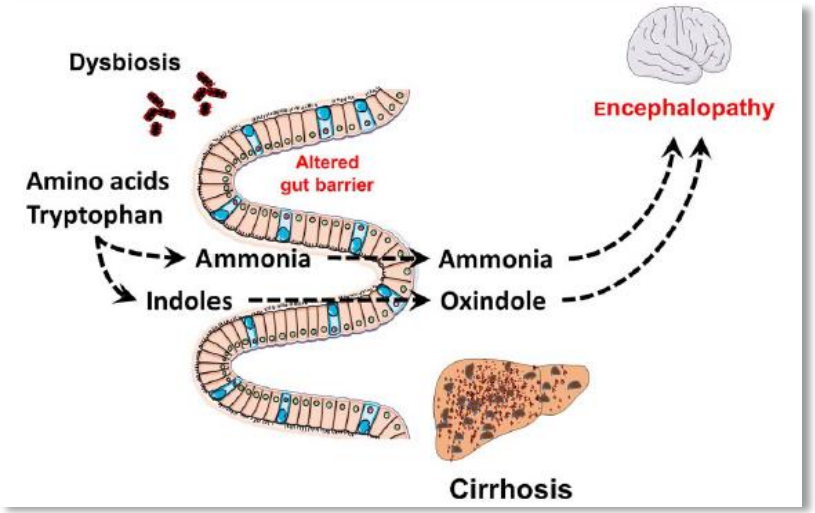


Flemer B, et al. Gut. 2017 Apr;66(4):633-643

Microbiota Composition and Liver Diseases

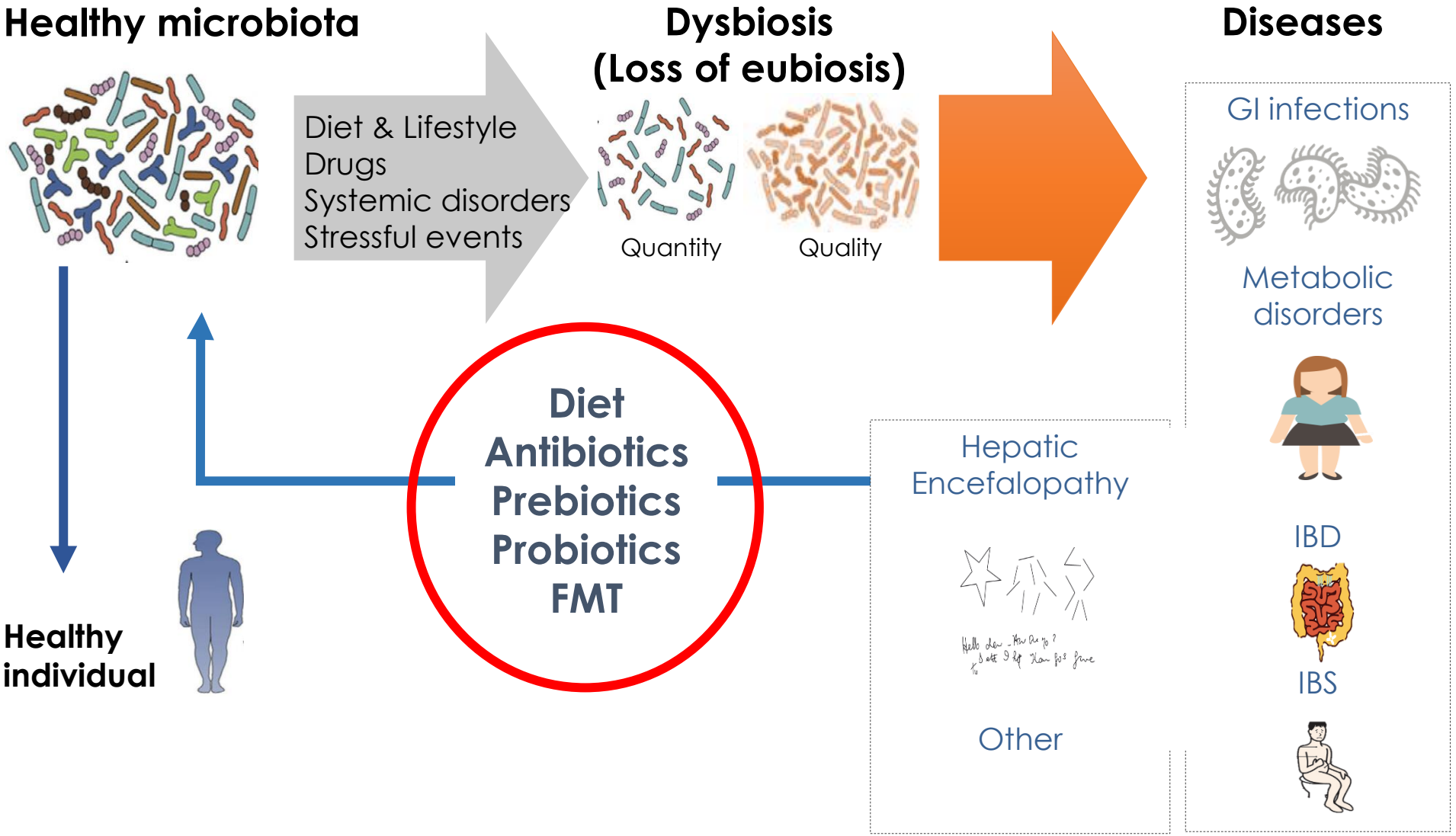
Various liver disorders such as alcoholic liver disease, non-alcoholic liver disease and primary sclerosing cholangitis have been associated with an altered microbiome.





Tilg H, et al. Gut. 2016 Dec;65(12):2035-2044

Rationale of Microbiota Modulation



FMT As Treatment of Many Intestinal and Extraintestinal Diseases

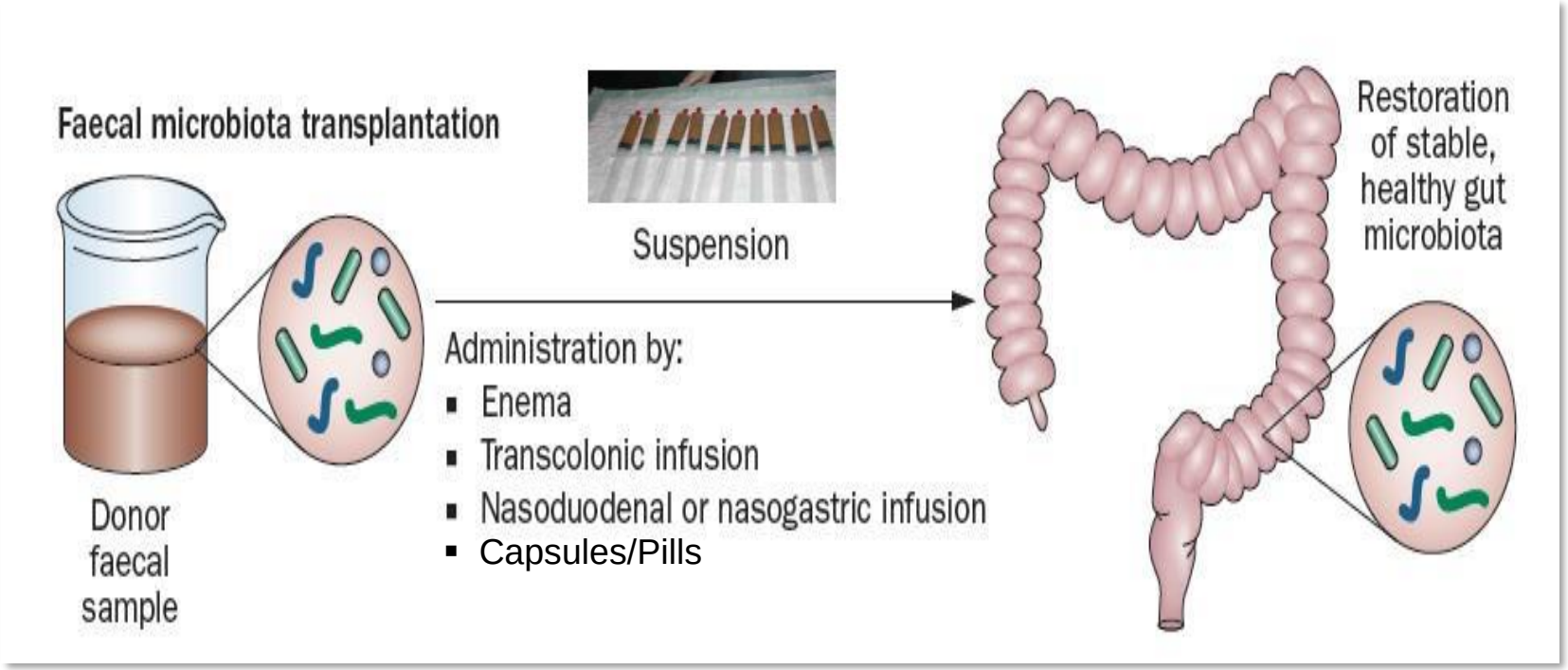
Faecal microbiota transplantation (FMT) involves the engraftment of the gut microbiota of healthy individuals into diseased recipients to reconstitute a normal intestinal microbial composition

Type od Supension

- Fresh Faeces
- Frozen Faeces
  - -20°
  - -80°

Donor's Selection

- Healthy
- Healthy and Specific

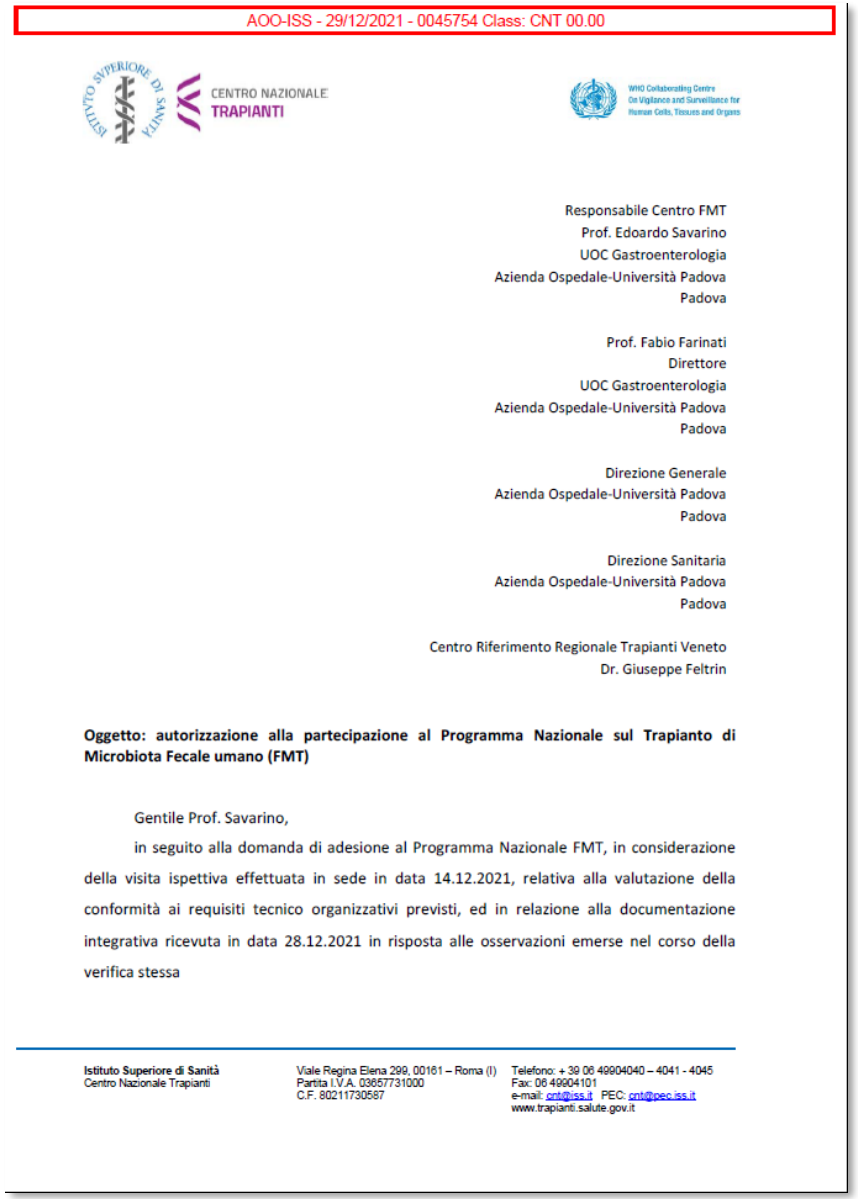


Konturek PC et al. J Physiol Pharmacol. 2015 Aug;66(4):483-91
Lai C Y et al, Aliment Pharmacol Ther. 2019 Feb;49(4):354-363

FMT in Real-Word at Azienda Ospedale Università PD

Dott. Giuseppe Dal Ben
Dott. Michele Tessarin
Prof. Fabio Farinati

Dott.ssa Valeria Besutti
Dott.ssa Sonia Facchin
Dott.ssa Manuela Sciro
Dott. Michele Cognolato
Dott.ssa Romilda Cardin
Dott. Brigida Barberio
Dott.ssa Fabiana Zingone
Prof. Andrea Crisanti
Prof.ssa Annamaria Cattelan
Dott. Marco Trevenzoli
Prof. Ignazio Castagliulolo
Prof. Edoardo V. Savarino



AOO-ISS - 29/12/2021 - 0045754 Class: CNT 00.00

ISTITUTO SUPERIORE DI SANITÀ
CENTRO NAZIONALE TRAPIANTI

WHO Collaborating Centre On Vigilance and Surveillance for Human Cells, Tissues and Organs

Responsabile Centro FMT
Prof. Edoardo Savarino
UOC Gastroenterologia
Azienda Ospedale-Università Padova
Padova

Prof. Fabio Farinati
Direttore
UOC Gastroenterologia
Azienda Ospedale-Università Padova
Padova

Direzione Generale
Azienda Ospedale-Università Padova
Padova

Direzione Sanitaria
Azienda Ospedale-Università Padova
Padova

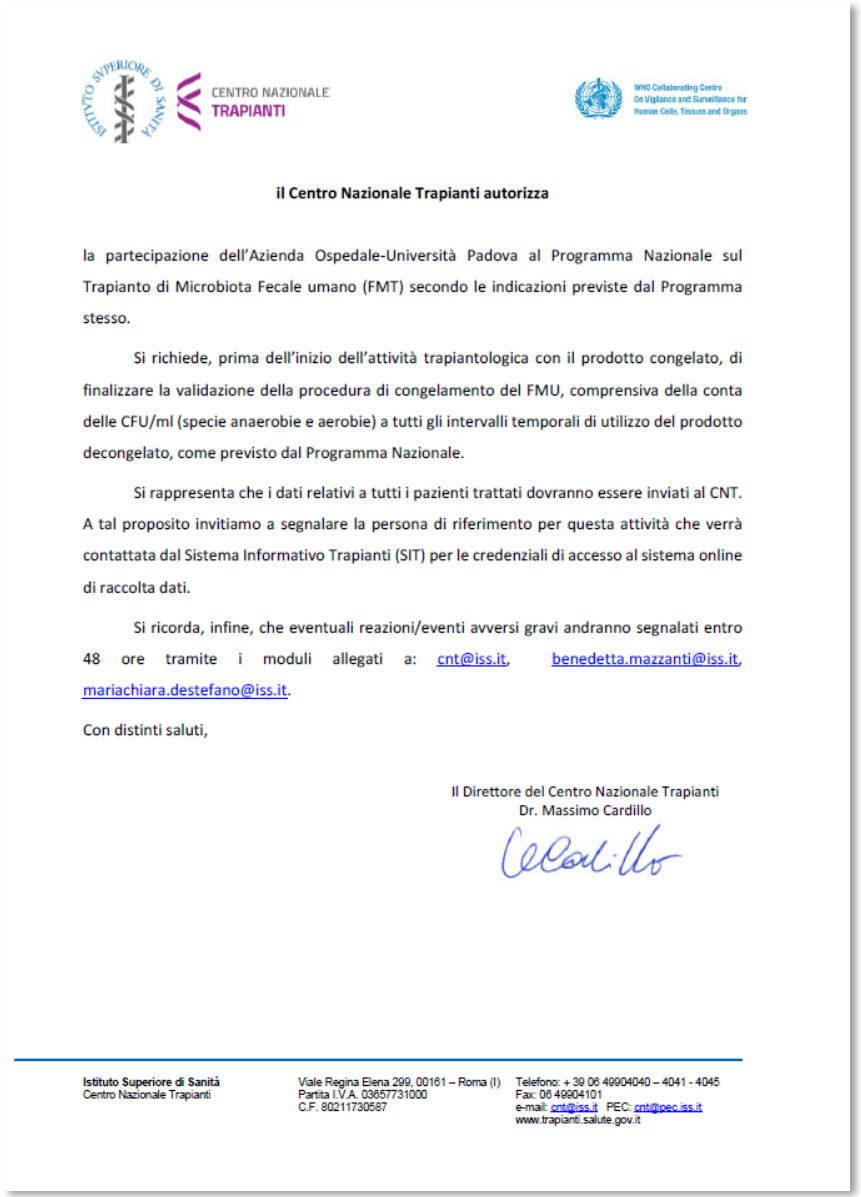
Centro Riferimento Regionale Trapianti Veneto
Dr. Giuseppe Feltrin

Oggetto: autorizzazione alla partecipazione al Programma Nazionale sul Trapianto di Microbiota Fecale umano (FMT)

Gentile Prof. Savarino,

in seguito alla domanda di adesione al Programma Nazionale FMT, in considerazione della visita ispettiva effettuata in sede in data 14.12.2021, relativa alla valutazione della conformità ai requisiti tecnico organizzativi previsti, ed in relazione alla documentazione integrativa ricevuta in data 28.12.2021 in risposta alle osservazioni emerse nel corso della verifica stessa

Istituto Superiore di Sanità
Centro Nazionale Trapianti
Viale Regina Elena 299, 00161 – Roma (I)
Partita I.V.A. 03657731000
C.F. 80211730587
Telefono: + 39 06 49904040 – 4041 - 4045
Fax: 06 49904101
e-mail: cnt@iss.it PEC: cnt@pec.iss.it
www.trapianti.salute.gov.it



ISTITUTO SUPERIORE DI SANITÀ
CENTRO NAZIONALE TRAPIANTI

WHO Collaborating Centre On Vigilance and Surveillance for Human Cells, Tissues and Organs

Il Centro Nazionale Trapianti autorizza

la partecipazione dell'Azienda Ospedale-Università Padova al Programma Nazionale sul Trapianto di Microbiota Fecale umano (FMT) secondo le indicazioni previste dal Programma stesso.

Si richiede, prima dell'inizio dell'attività trapiantologica con il prodotto congelato, di finalizzare la validazione della procedura di congelamento del FMU, comprensiva della conta delle CFU/ml (specie anaerobie e aerobie) a tutti gli intervalli temporali di utilizzo del prodotto decongelato, come previsto dal Programma Nazionale.

Si rappresenta che i dati relativi a tutti i pazienti trattati dovranno essere inviati al CNT. A tal proposito invitiamo a segnalare la persona di riferimento per questa attività che verrà contattata dal Sistema Informativo Trapianti (SIT) per le credenziali di accesso al sistema online di raccolta dati.

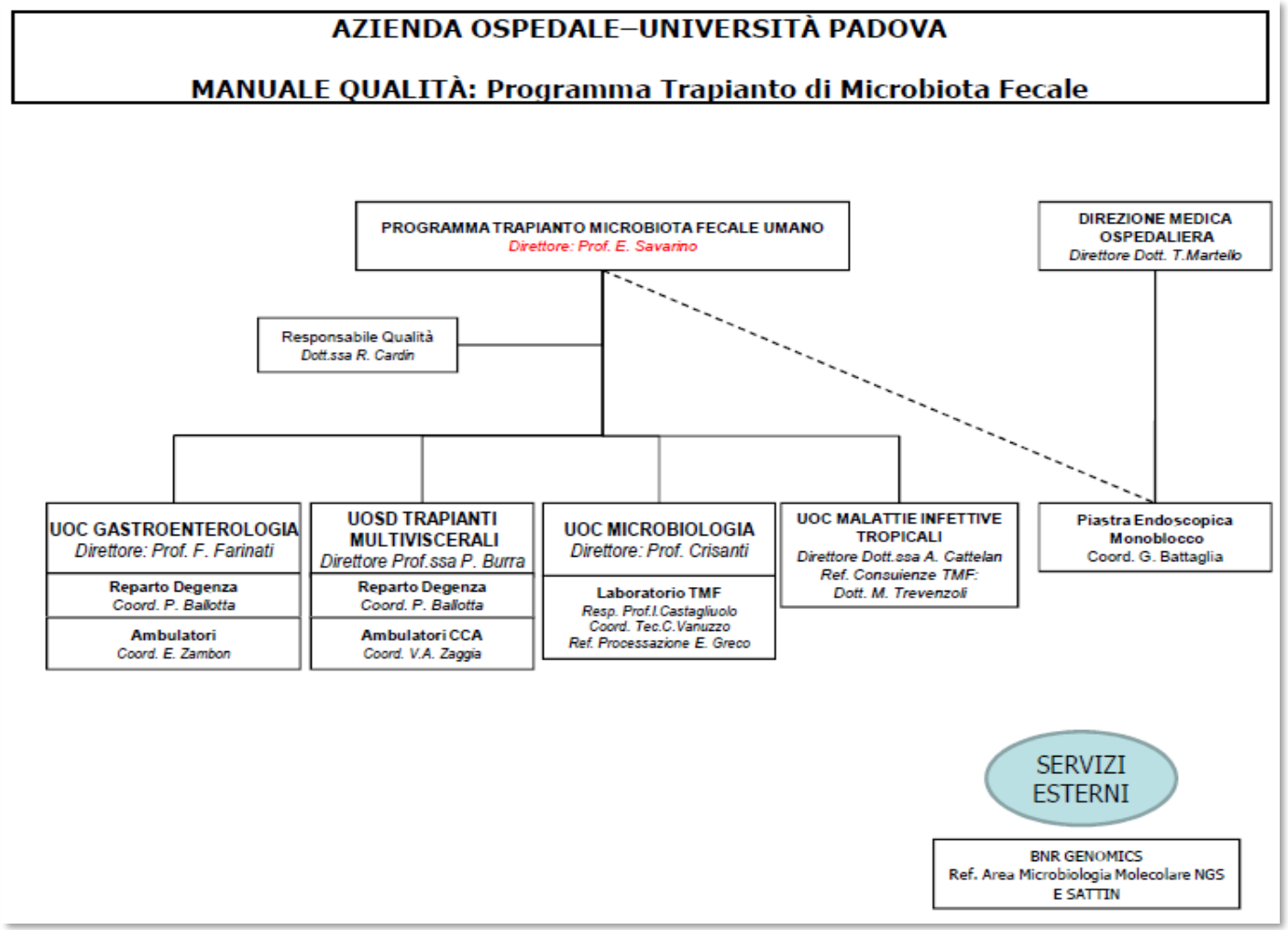
Si ricorda, infine, che eventuali reazioni/eventi avversi gravi andranno segnalati entro 48 ore tramite i moduli allegati a: cnt@iss.it, benedetta.mazzanti@iss.it, mariachiara.destefano@iss.it.

Con distinti saluti,

Il Direttore del Centro Nazionale Trapianti
Dr. Massimo Cardillo

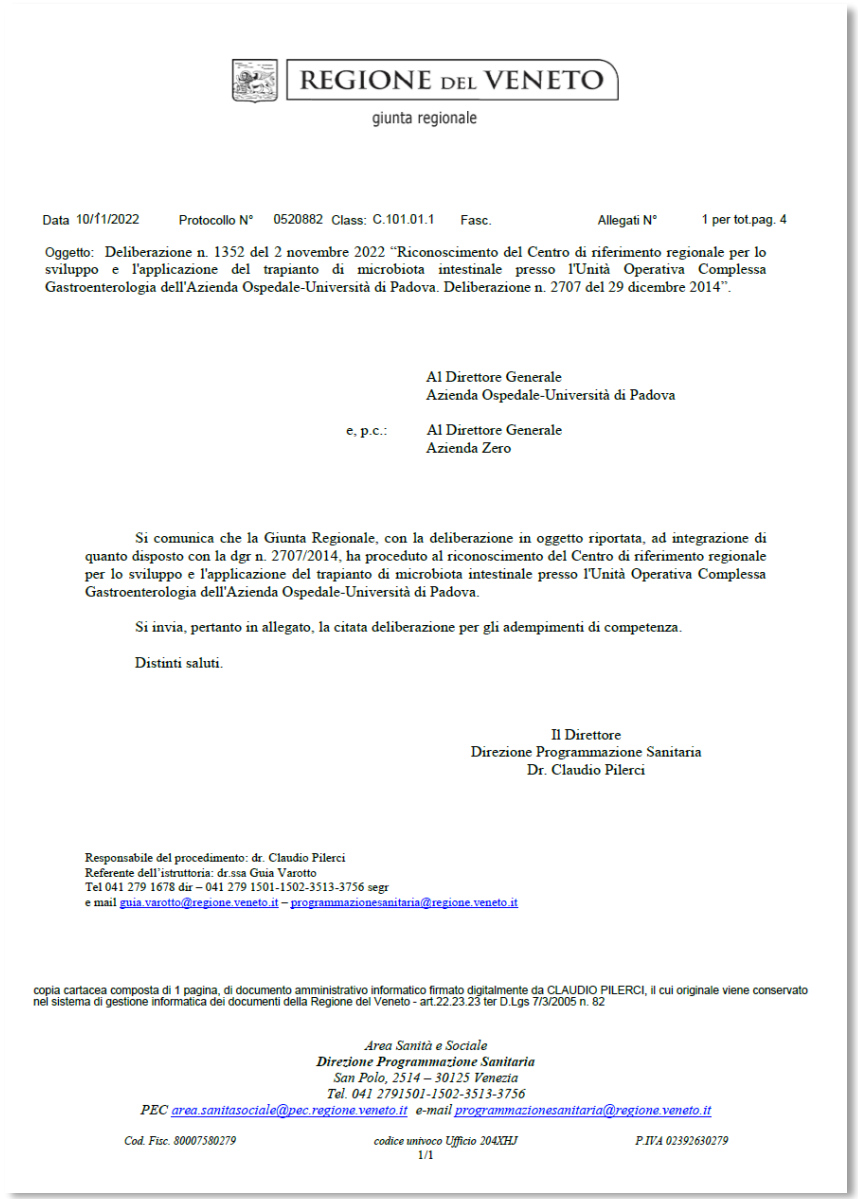
Istituto Superiore di Sanità
Centro Nazionale Trapianti
Viale Regina Elena 299, 00161 – Roma (I)
Partita I.V.A. 03657731000
C.F. 80211730587
Telefono: + 39 06 49904040 – 4041 - 4045
Fax: 06 49904101
e-mail: cnt@iss.it PEC: cnt@pec.iss.it
www.trapianti.salute.gov.it

FMT in Real-Word at Azienda Ospedale Università PD



FMT in Real-Word at Azienda Ospedale Università PD

RICONOSCIMENTO DEL CENTRO DI RIFERIMENTO REGIONALE PER LO SVILUPPO E L'APPLICAZIONE DEL TRAPIANTO DI MICROBIOTA INTESTINALE



REGIONE DEL VENETO
giunta regionale

Data 10/11/2022 Protocollo N° 0520882 Class: C.101.01.1 Fasc. Allegati N° 1 per tot.pag. 4

Oggetto: Deliberazione n. 1352 del 2 novembre 2022 "Riconoscimento del Centro di riferimento regionale per lo sviluppo e l'applicazione del trapianto di microbiota intestinale presso l'Unità Operativa Complessa Gastroenterologia dell'Azienda Ospedale-Università di Padova. Deliberazione n. 2707 del 29 dicembre 2014".

Al Direttore Generale
Azienda Ospedale-Università di Padova

e, p.c.: Al Direttore Generale
Azienda Zero

Si comunica che la Giunta Regionale, con la deliberazione in oggetto riportata, ad integrazione di quanto disposto con la dgr n. 2707/2014, ha proceduto al riconoscimento del Centro di riferimento regionale per lo sviluppo e l'applicazione del trapianto di microbiota intestinale presso l'Unità Operativa Complessa Gastroenterologia dell'Azienda Ospedale-Università di Padova.

Si invia, pertanto in allegato, la citata deliberazione per gli adempimenti di competenza.

Distinti saluti.

Il Direttore
Direzione Programmazione Sanitaria
Dr. Claudio Pilerci

Responsabile del procedimento: dr. Claudio Pilerci
Referente dell'istruttoria: dr.ssa Guia Varotto
Tel 041 279 1678 dir – 041 279 1501-1502-3513-3756 segr
e mail guia.varotto@regione.veneto.it – programmazionesanitaria@regione.veneto.it

copia cartacea composta di 1 pagina, di documento amministrativo informatico firmato digitalmente da CLAUDIO PILERCI, il cui originale viene conservato nel sistema di gestione informatica dei documenti della Regione del Veneto - art.22.23.23 ter D.Lgs 7/3/2005 n. 82

Area Sanità e Sociale
Direzione Programmazione Sanitaria
San Polo, 2514 – 30125 Venezia
Tel. 041 2791501-1502-3513-3756
PEC area.sanitasociale@pec.regione.veneto.it e-mail programmazionesanitaria@regione.veneto.it

Cod. Fisc. 80007580279 *codice univoco Ufficio 204XHJ* *P.IVA 02392630279*
1/1

REGIONE DEL VENETO
giunta regionale
XI legislatura

Proposta n. 1817 / 2022

PUNTO 16 DELL'ODG DELLA SEDUTA DEL 02/11/2022

ESTRATTO DEL VERBALE

DELIBERAZIONE DELLA GIUNTA REGIONALE n. 1352 / DGR del 02/11/2022

OGGETTO:
Riconoscimento del Centro di riferimento regionale per lo sviluppo e l'applicazione del trapianto di microbiota intestinale presso l'Unità Operativa Complessa Gastroenterologia dell'Azienda Ospedale-Università di Padova. Deliberazione n. 2707 del 29 dicembre 2014.

Pagina 1 di 4

bb754e66

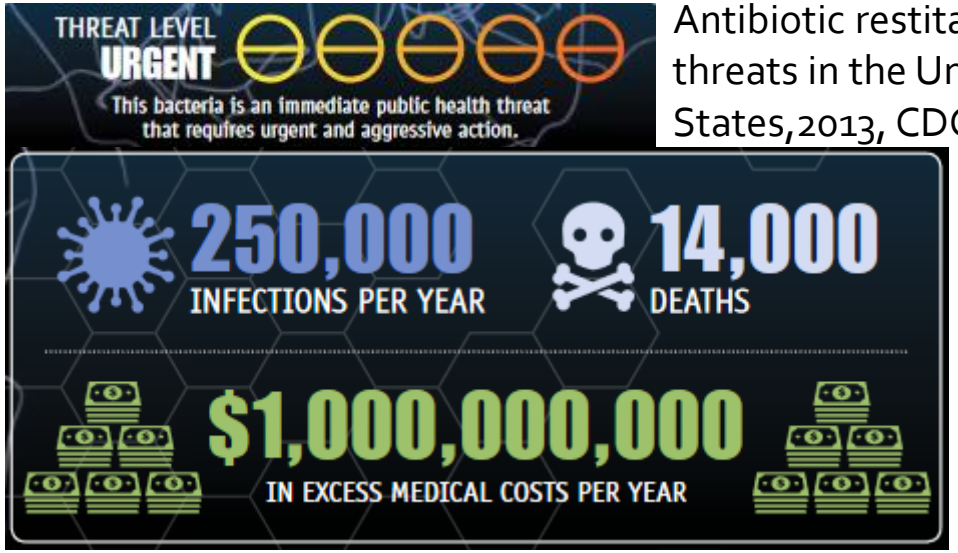
FMT in Real-Word at Azienda Ospedale Università PD

Evidence for Different Indications of FMT in 2022

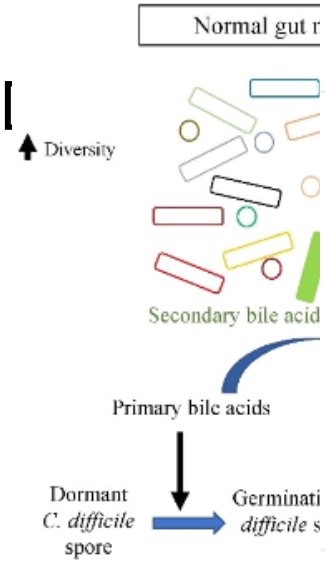
	Metanalyses	RCTs	Open label trials	Case series/reports	Efficacy data	Used in clinical practice
C. difficile infection	+++	+++++	++++	++++	Outstanding	YES
Ulcerative colitis	+	+++	+++	+++	Promising	NO
Hepatic encefalopathy		+		+	Quite promising	NO
Metabolic syndrome	+	+++		+	Quite promising	NO
Crohn's disease		+	++	+	Poor	NO
IBS	+	++++	++	+	Quite promising	NO
Multi-resistant infections		+	++	++	Quite promising	NO
Autism			+	+	Poor	NO
GVHD				+	Poor	NO
Chemotherapy-dependent diarrhea		+	+	+	Quite promising	NO
Boost of ICI response			+		Quite promising	No

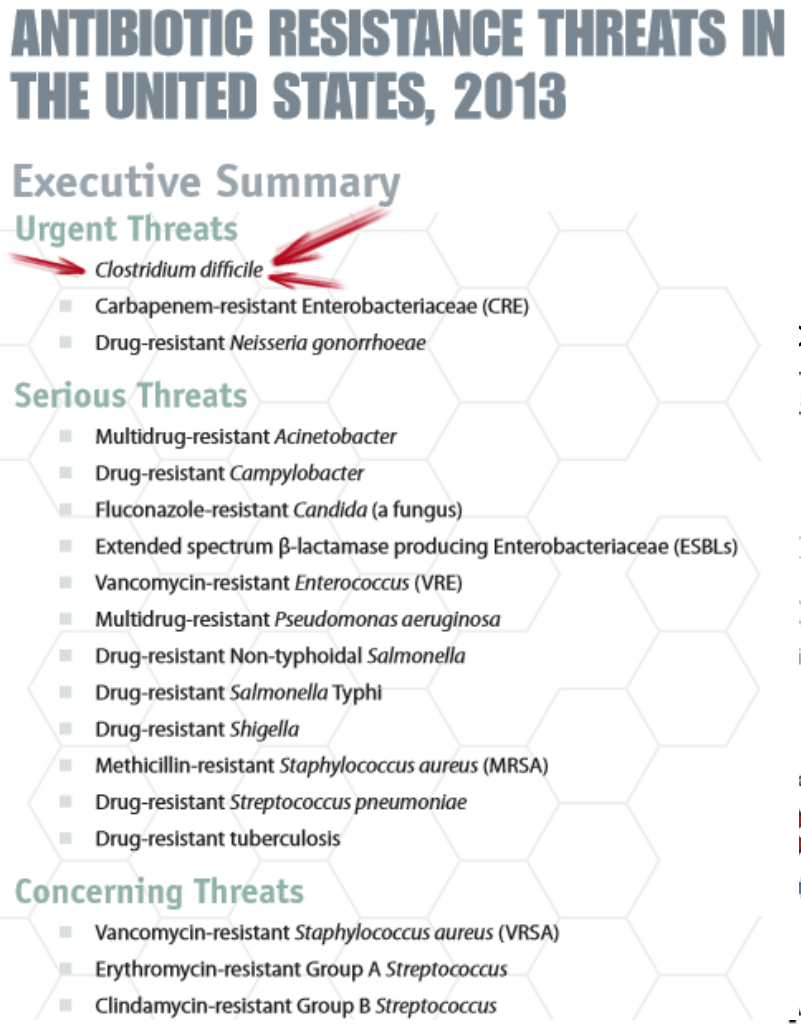
FMT in Clostridioides difficile Infection

- ✓ Gram + bacterium
- ✓ spore-forming
- ✓ Resistant to common sterilization techniqu
- ✓ Cause 1 \ 5 of diarrhea associated with antib
- ✓ It can produce toxins
- ✓ 60% of the isolated strains are MI



Antibiotic restitance threats in the United States,2013, CDC





biol, 2018

gut microbiota

icrobes

ary bile acids

C. difficile
(vegetative growth)

Toxin production

Inflammation of gut epithelium

Cammarota G, et al. Gut. 2017 Apr;66(4):569-580

FMT in Clostridioides difficile Infection

- **FMT recommended as a highly effective and safe treatment option for both mild and severe recurrent CDI. Its implementation in clinical practice is recommended**

- **FMT can be considered as a treatment orption for refractory CDI**

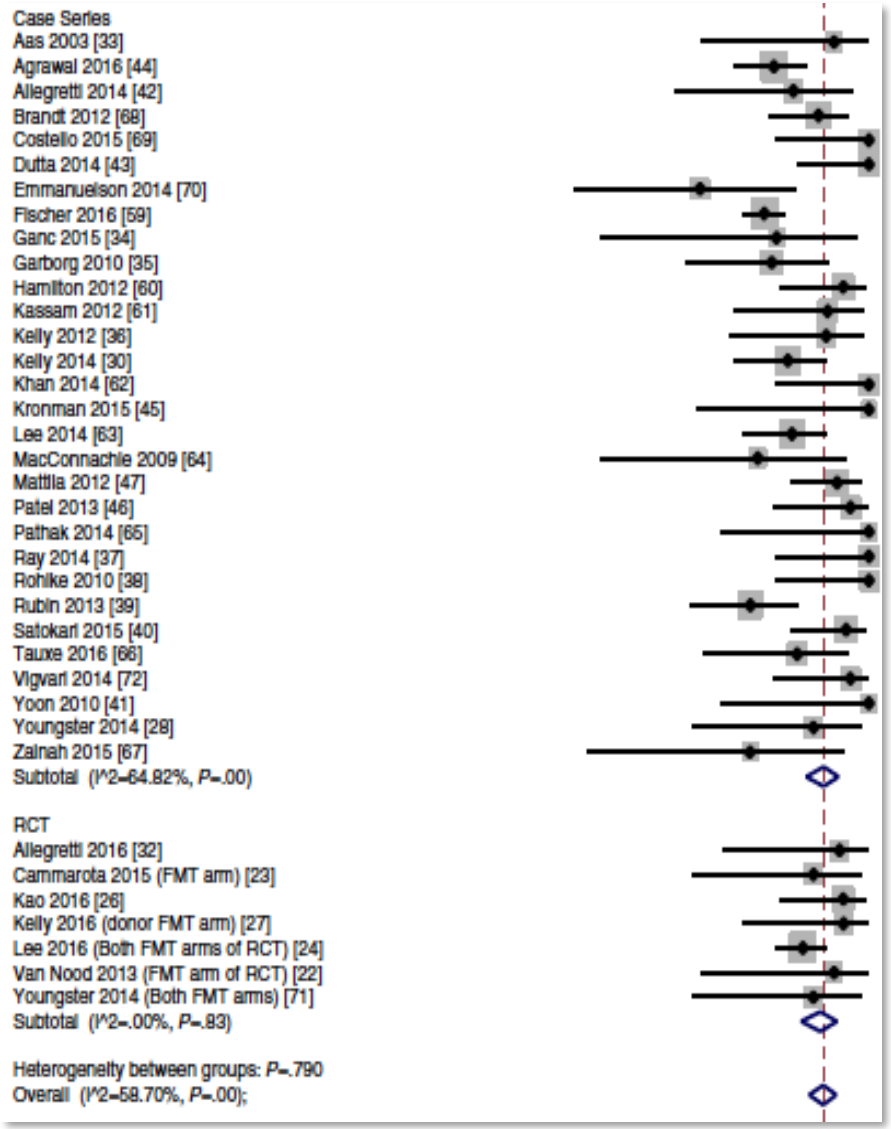
Quality of evidence: high

Strenght of recommandation : strong

Cammarota G, et al. Gut. 2017 Apr;66(4):569-580

Outstanding Efficacy of FMT in rCDI

Year	1st auth	Design	CDI Cure
2013	Van nood	RCT (FMT vs vancomycin)	94%
2013	Kassam	Metanalysis	89.7%
2014	Cammarota	Systematic Review	87%
2015	Cammarota	RCT (FMT vs vancomycin)	90%
2015	Drekonja	Systematic Review	85%
2016	Lee	RCT (fresh vs frozen)	85% vs 83%
2016	Kelly	RCT (donor vs autologous)	91% vs 62%
2017	Quraishi	Metanalysis	92%
2018	Ianiro	RCT (single vs mult. FMT)	75% vs 100%
2018	Ianiro	Metanalysis	93% overall



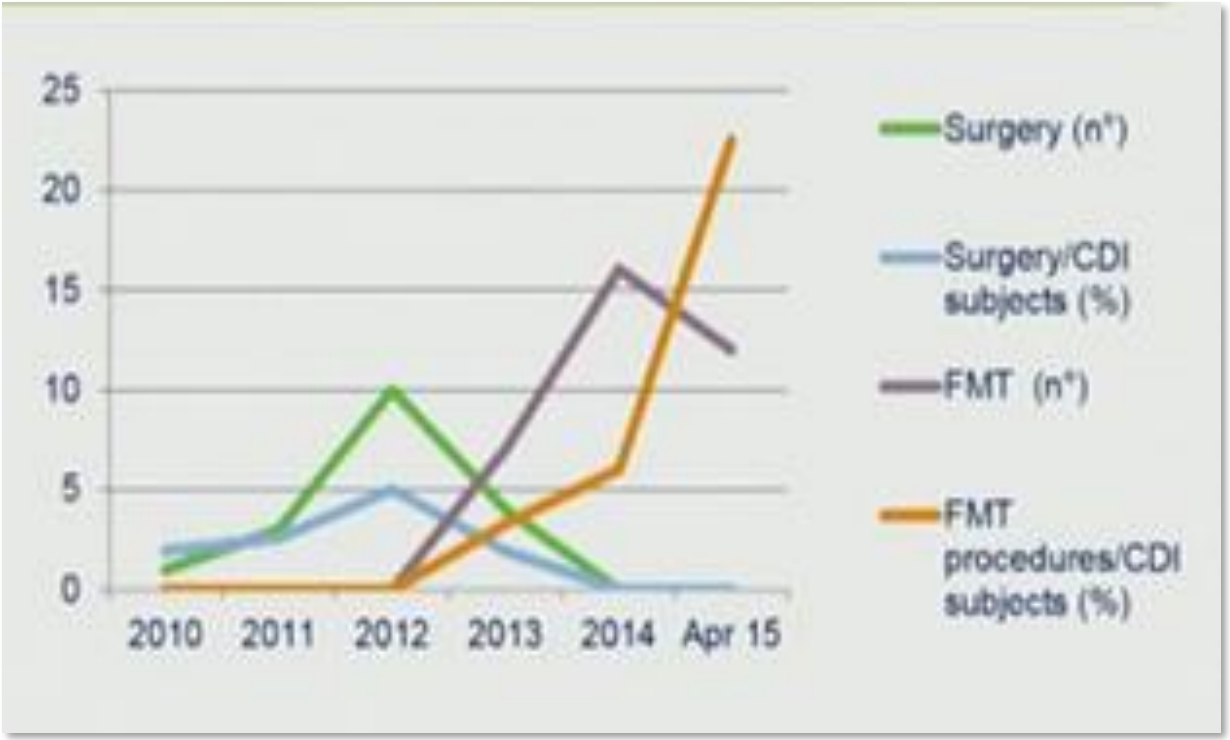
FMT Cuts the Need for C. difficile-related Surgery

Retrospective review of 901 patients with CDI

- The number of patients with this infection increased gradually over time: 54 patients were diagnosed in 2010, 116 in 2011, 200 in 2012, 212 in 2013, 268 in 2014, and 71 between January and April 2015

- No more surgery after the establishment of a FMT service

- Relevant decrease in CDI-related mortality (surgical patients:83%; FMT patients 6%)



Cammarota G, et al. Ann Intern Med. 2015 Sep 15;163(6):487-8

FMT in Clostridioides difficile Infection in Padua

Patient code	Age	Gender	Total number of relapse	Risk factor for relapse	Previous antibiotics	Fresh or frozen stools	Full colonoscopy	Efficacy	Relapse post-FMT
1[c]	70	F	4	4	V, M	Fresh	YES	YES	YES[d]
2	46	M	4	0	V, M	Fresh	YES	YES	NO
3	87	F	3	3	V, F	Fresh	YES	YES	NO
4	69	F	3	2	V, M	Fresh	YES	YES	NO
5	52	M	2	2	V, F	Fresh	YES	YES	NO
6	77	F	5	2	V, F	Fresh	YES	YES	NO
7[c]	70	F	5	0	V, M	Fresh	YES[a]	NO	
8	74	F	4	3	V, F	Fresh	YES	YES	YES[d]
9	51	F	4	2	V, M	Fresh	YES	YES	NO
10	81	F	3	3	V, M, F	Fresh	YES	YES	NO
11	22	F	3	1	V	Fresh	YES	YES	NO
12	86	F	3	3	V	Frozen	YES	YES	YES[d]
13	73	F	3	3	V	Frozen	YES	YES	NO
14	77	F	2	2	V	Frozen	YES	YES	NO
15	86	F	2	3	V, F	Frozen	YES	YES	NO
16	71	F	3	2	V, M	Frozen	YES[a]	NO	NO
17	63	F	2	2	V	Frozen	YES	YES	NO
18	79	F	3	2	V, M, F	Frozen	YES	YES	NO
19	78	F	3	2	V, M	Frozen	NO	NO	–[a]
20	52	F	2	2	V	Frozen	YES	YES	NO

F, Fidaxomicin; FMT, faecal microbiota transplantation; M, Metronidazole; V, Vancomycin.
[a]Patients expelled the infused faecal material in the first hours following the procedure.
[b]Patient without subsequent follow up, due to inefficacy of FMT.
[c]1 and 7 were the same patient, treated with FMT twice.
[d]Different relative abundance of g_*Bacteroides* in donor faeces: donor of P(1):51.51%; donor of P(8): 56.61%; donor of P(12):50.82% *versus* a mean value of 39.43%.

C. diff. Toxin Negativazation

85%

Mean Days of Hospitalization

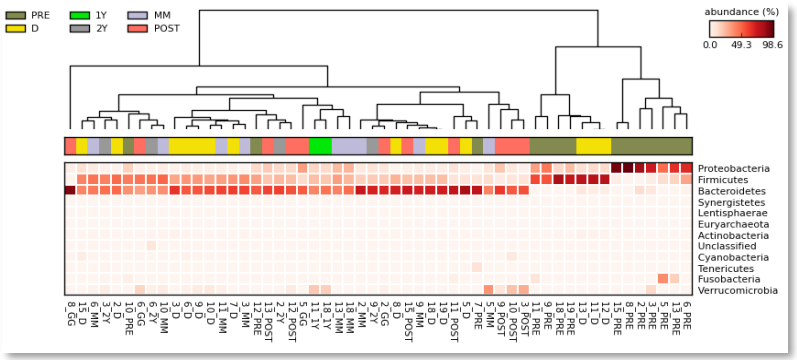
7,40 σ 5,79

84%

Reported Effectiveness

14,6 σ 13,14

Days of hopitalization with Traditional Antibiotics



EFFECTIVENESS ON METAGENOMIC

Barberio B, et al. Therap Adv Gastroenterol. 2020 Jul 29;13:1756284820934315

FMT in Clostridioides difficile Infection in Padua

During Hospitalization

PZ	Rialzo Temp.	Dolore Addome	Addome Disteso	Stipsi	Diarrea	Sintomi Urinari
1	+					
2		+				
3				+		
4				+		
5						
6		+	+			+
7	N	N	N	N	N	N
8						
9		+	+			
10			+		+	
11						
12						
13					+	
14		+				
15			+			
16	N	N	N	N	N	N
17						
18						
19						
20		+			+	
Totale	1	5	4	2	3	1
%	5%	25%	20%	10%	15%	5%
% Let	0.57%	4.79 %	9,3%	3.84 %	14.23 %	ND

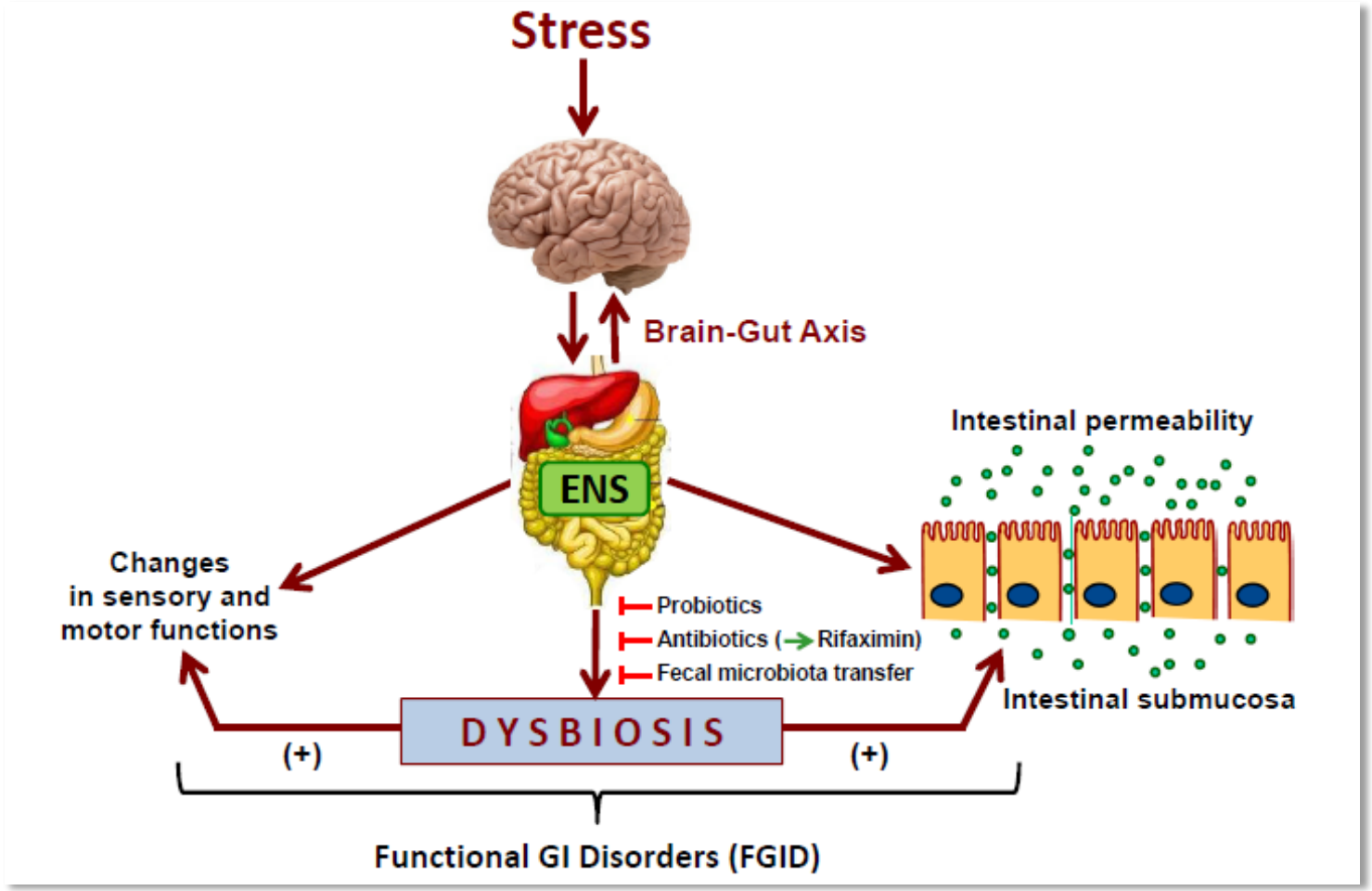
During Follow-up

Sintomatologia	Numero Casi
Abdominal Pain	4
IVU	3
Diarrhea	2
Requiring Hospitalization	1
Recurrence C. Difficilis Infection	3

Other studies have described histologic findings consistent with MC on colonoscopic biopsies taken at the time of FMT, suggesting its pathogenesis may be associated with *C. difficile* rather than FMT.[11]

Rationale of FMT for the Treatment of IBS

THE PROPOSED MECHANISM OF STRESS ACTING *VIA* BRAIN-GUT AXIS AFFECTING THE ENTERIC NERVOUS SYSTEM (ENS) AND GUT MICROBIOTA THAT MAY LEAD TO DYSBIOSIS, INCREASED INTESTINAL PERMEABILITY AND FUNCTIONAL GASTROINTESTINAL DISORDERS (FGID).

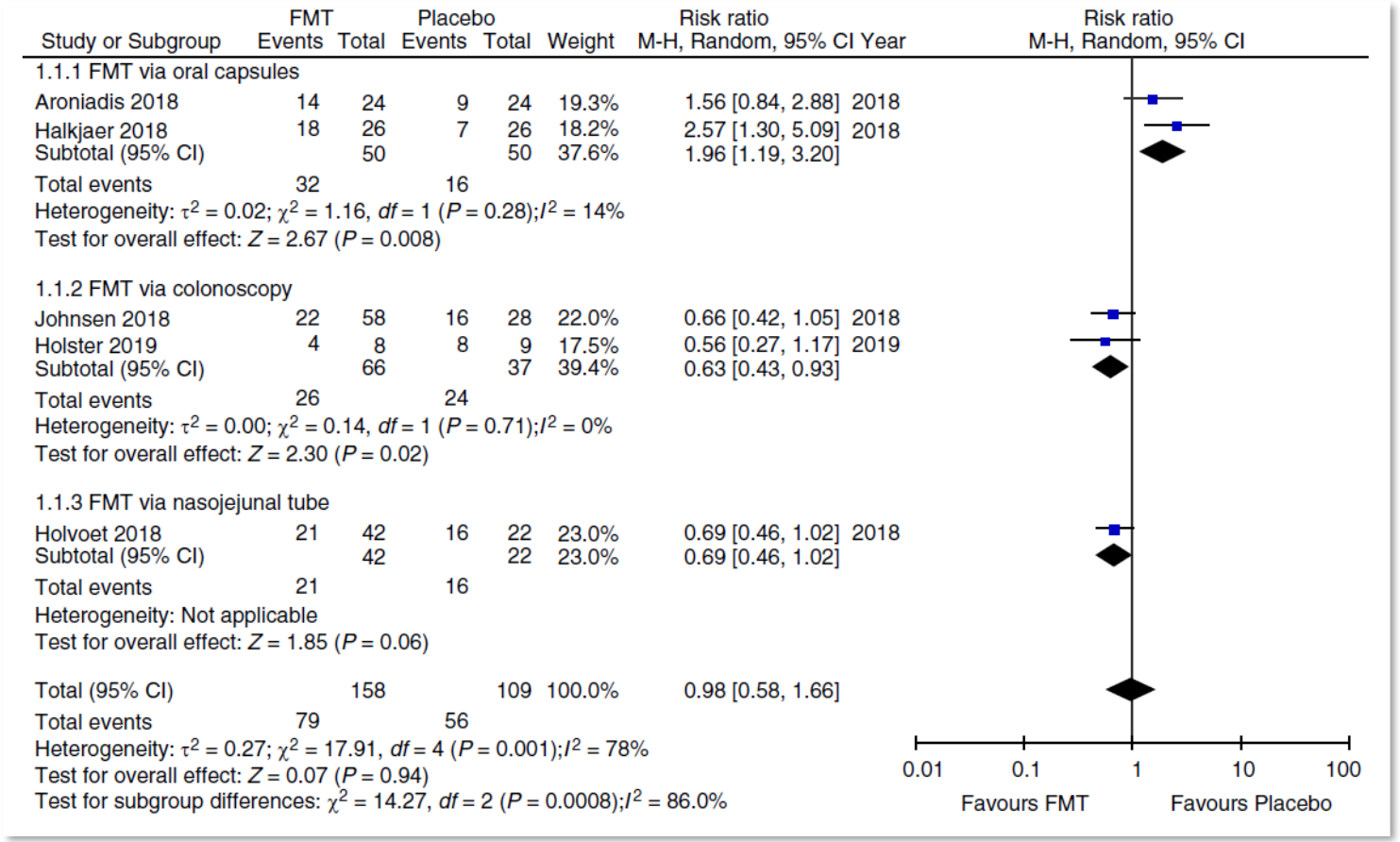


Konturek PC et al. J Physiol Pharmacol. 2015 Aug;66(4):483-91

Efficacy of FMT for the Treatment of IBS

- **RR of IBS symptoms not improving was 0.98 (95% CI 0.58-1.66**).
- **Placebo capsules superior to capsules** containing donor stool (RR = 1.96; 95% CI 1.19-3.20).
- **FMT from donor stool delivered via colonoscopy was superior to autologous stool** (RR = 0.63; 95% CI 0.43-0.93).

FOREST PLOT OF RANDOMISED CONTROLLED TRIALS OF FAECAL MICROBIOTA TRANSPLANTATION VS PLACEBO IN IRRITABLE BOWEL SYNDROME



Ianiro G et al, Aliment Pharmacol Ther. 2019 Aug;50(3):240-248

Efficacy of FMT for the Treatment of UC

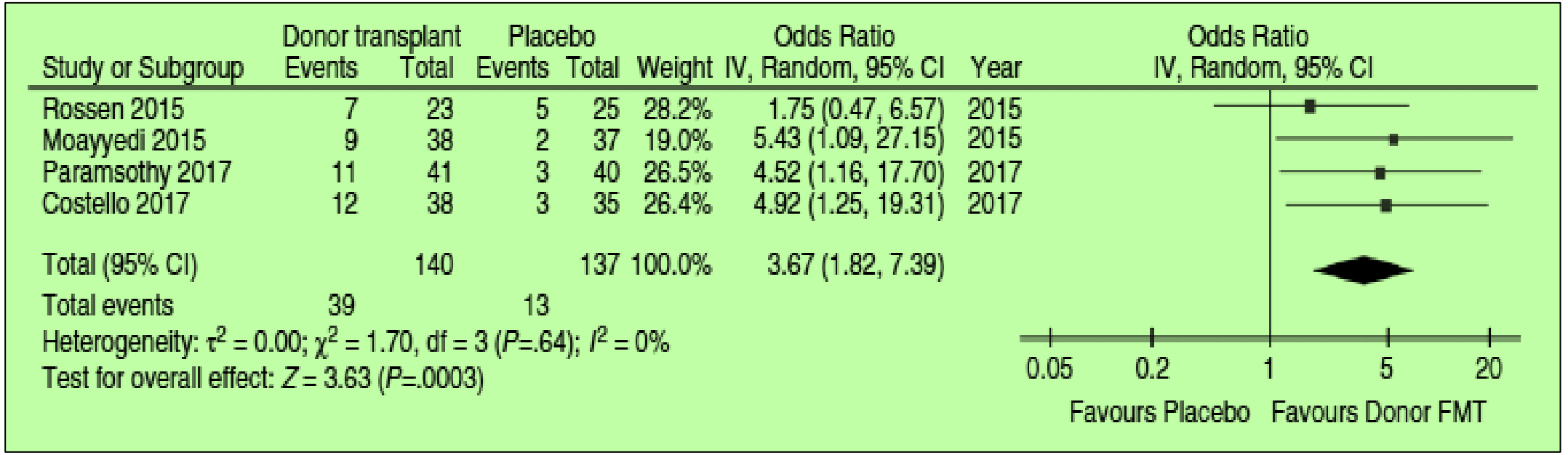
4 RCTs

- **Clinical remission 28%** vs 9% placebo (OR 3.67- 95%CI 1.82-7.39, P<0.01)
- **Endoscopic remission 14%** vs 5% placebo (OR 2.89 – 95%CI 1.07-6.74, P=0.04)

14 cohort studies

- **Clinical remission 24%**

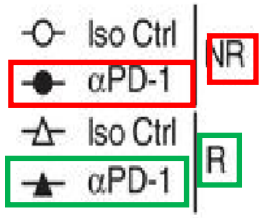
Marked differences between FMT working protocols



Costello SP et al, Aliment Pharmacol Ther. 2017 Aug;46(3):213-224

Microbiota Transplantation Influences Immunotherapy against Epithelial Tumors

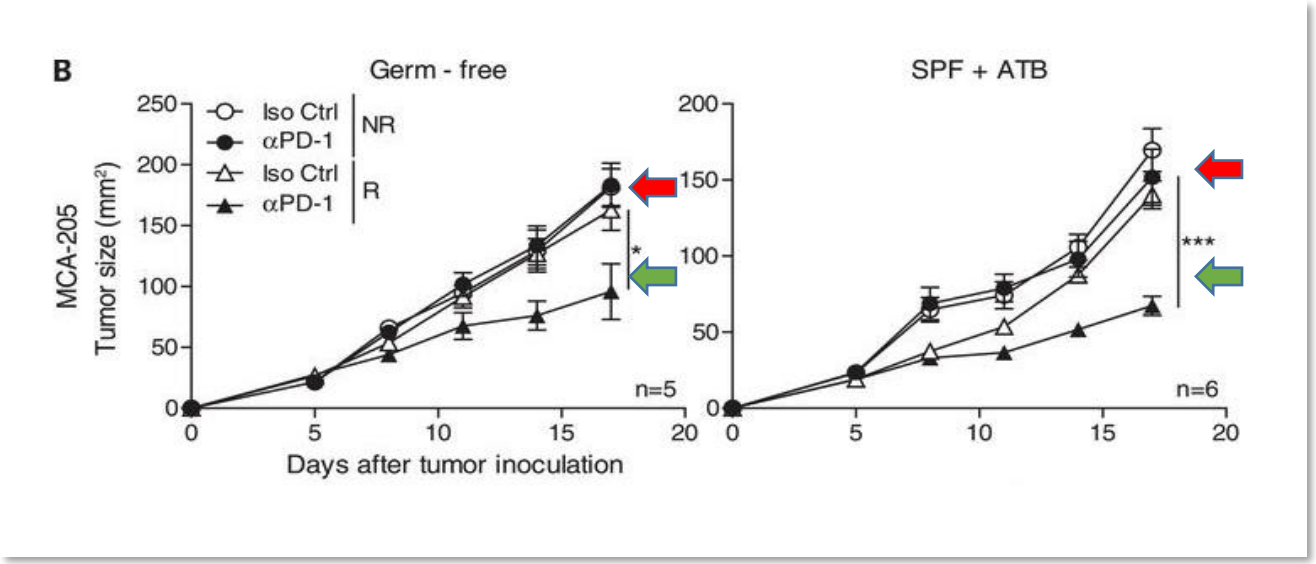
FMT of feces from NON-RESPONDER or RESPONDER patients in germ free mice

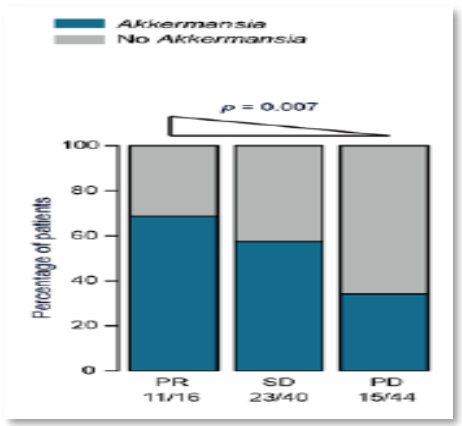


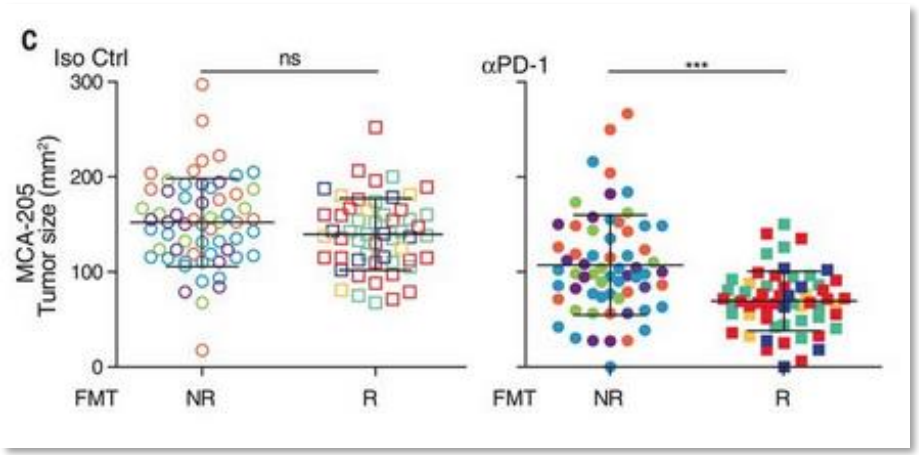
PD-1 treatment is more effective in mice receving feces from RESPONDER patients

PD-1 therapy response is influenced by microbial donor characteristics

Frequency of patients with detectable A. muciniphila in their feces according to:
PR: partial response
SD: stable disease
PD: progressed or died







Routy B, et al. Science. 2018 Jan 5;359(6371):91-97

Fecal Microbiota Transplantation As a Treatment of Severe Steroid-Resistant Acute and Chronic Graft Versus Host Disease

INTRODUCTION

50% of the patients with gut predominant acute graft-versus-host disease (aGvHD) and chronic (c) GvHD, respond to corticosteroids.

MATERIAL AND METHODS

12 patients (26-67 years) underwent a total of 15 FMTs to decolonize the gastrointestinal tract (GI) from antibiotic-resistant bacteria (ARB). In all of them steroid resistant GvHD (2 patients with cGvHD and 10 with aGvHD) coexisted. All patients with aGvHD had GI tract involvement (median grade: 3), 7 had skin (median grade: 3) and 5 had liver (median grade: 1) GvHD symptoms. FMT was performed as two infusions by nasoduodenal tube of a 100g/200 ml solution of feces, on following days.

OUTCOMES

10/12 patients (83%) ARB decolonization was observed.

Overall response rate (ORR) in the case of aGvHD reached 58% (7/12 performed FMTs), including CR in 4/12 (33%) cases.

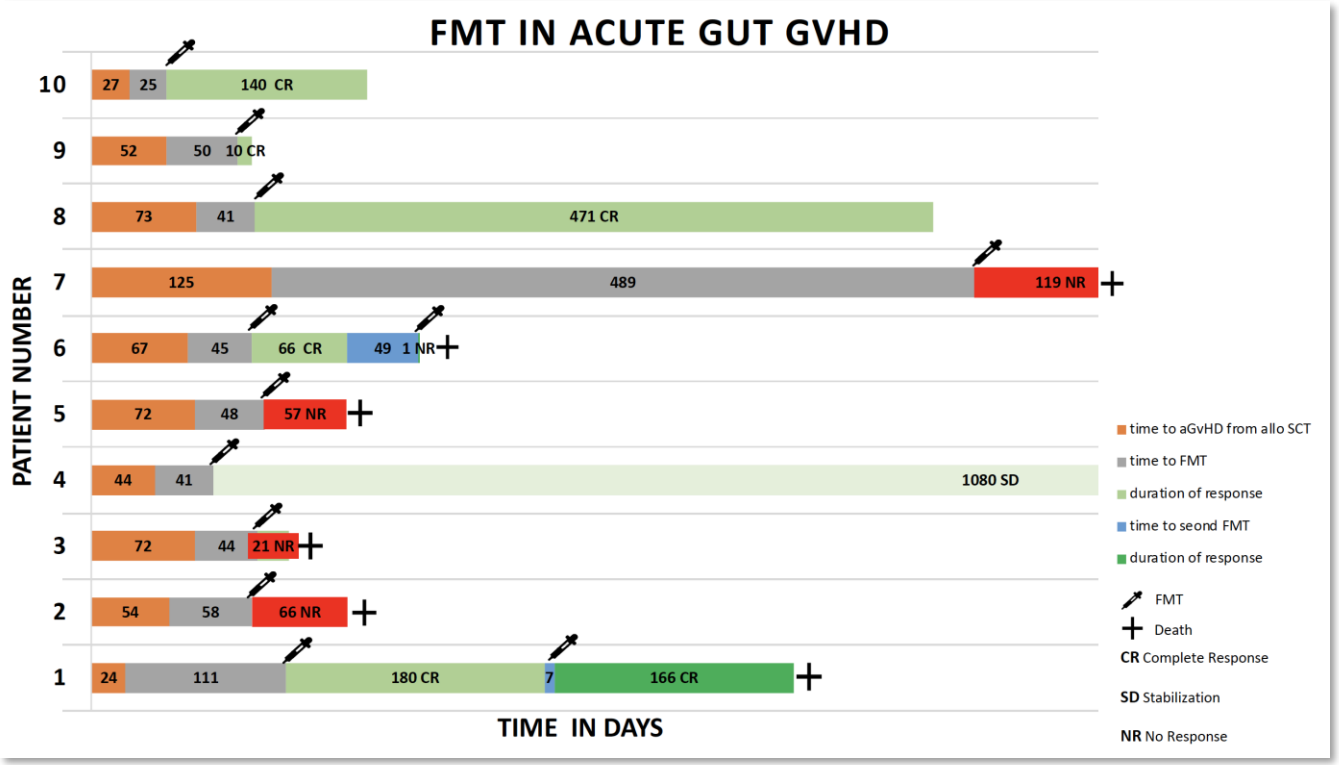
Median duration of response to relapse or death was 168 days (10-1080 days).

COMPLICATIONS

1 death in close relation with FMT (respiratory failure in the course of pneumonia), 3 septic episodes, 2 subileus episodes and one case of diarrhea.

CONCLUSIONS

The described results indicate that FMT may be an effective treatment option for severe GvH disease.



Bilinski J, et al. Blood (2019) 134 (Supplement_1): 5667

Is FMT Safe?

FDA In Brief: FDA warns about potential risk of serious infections caused by multi-drug resistant organisms related to the investigational use of Fecal Microbiota for Transplantation

- **On June 13, 2019, the FDA issued a safety alert concerning the risk of serious adverse reactions due to transmission of MDRO by FMT**
- This was in response to transmission of an ESBL producing *Escherichia coli* strain from a feces donor to two immunocompromised recipients, with one death. For reasons not specified, the donor had not been screened for MDRO
- **The FDA now requires inclusion of MDRO screening into all active and future FMT-based study protocols**

- **All major stool banks have implemented screening protocols to detect MDRO, without SAEs** (>45000 FMTs by OpenBiome since 2012)
- **Adherence to standard screening protocols** used by major stool banks worldwide **could have prevented these incidences**
- Specific donor screening for **immunocompromised patients**?
- **Different quality control measures**, mostly adapted from laws regulating blood transfusions and/or drugs can be applied.

Kuijper EJ, et al Lancet Infect Dis. 2019 Nov;19(11):1161-1162

Disseminations Of FMT: Barriers

Despite methodological improvements of working protocols (frozen feces, capsules, etc.), **FMT has not yet experienced a comparable widespread dissemination** because of **several obstacles**, including:

- Lack of dedicated centres
- Complexity of bureaucratic steps
- Donor recruitment
- Safety monitoring

As **FMT** represents a necessary treatment option to manage recurrent CDI and save human lives, therefore **its provision should be widely and rapidly available to most centres**

Stool banks may guarantee a **reliable, timely and equitable access** to FMT for recurrent CDI, disseminate FMT, drive further research

Stool Banks: the Time Is Now

Rome II consensus meeting:

International working group:

Cammarota G, Ianiro G, Kelly CR, Mullish B, Allegretti JR, Kassam Z, Putignani L, Fischer M, Keller JJ, Costello SP, Sokol H, Kump P, Satokari R, Khan S, Kao D, Arkkila P, Kuijper EJ, Vehreschild MJGT, Pintus C, Lopetuso LR, Masucci L, Scaldaferri F, Nieuwdorp M, Kupcinskas J, Lopez Sanroman A, Khorutz A, Terveer EM, Hart A, Tilg H, Gasbarrini A

Development of statements on **key issues**:

- Organization of the stool bank;
- Selection and recruitment of donors
- Preparation and storage of faeces
- Quality control
- Registries & monitoring of outcomes
- Evolving role of FMT in clinical practice

- **28 experts**
- **GRADE System** to address quality of evidence and strength of recommendation
- **Delphi process** to achieve consensus

Cammarota G, et al Gut. 2019 Dec;68(12):2111-2121

UNIVERSITÀ
DEGLI STUDI
DI PADOVA