Modulazione del Microbiota nelle Malattie Digestive

Giovanni Barbara

Department of Medical and Surgical Sciences

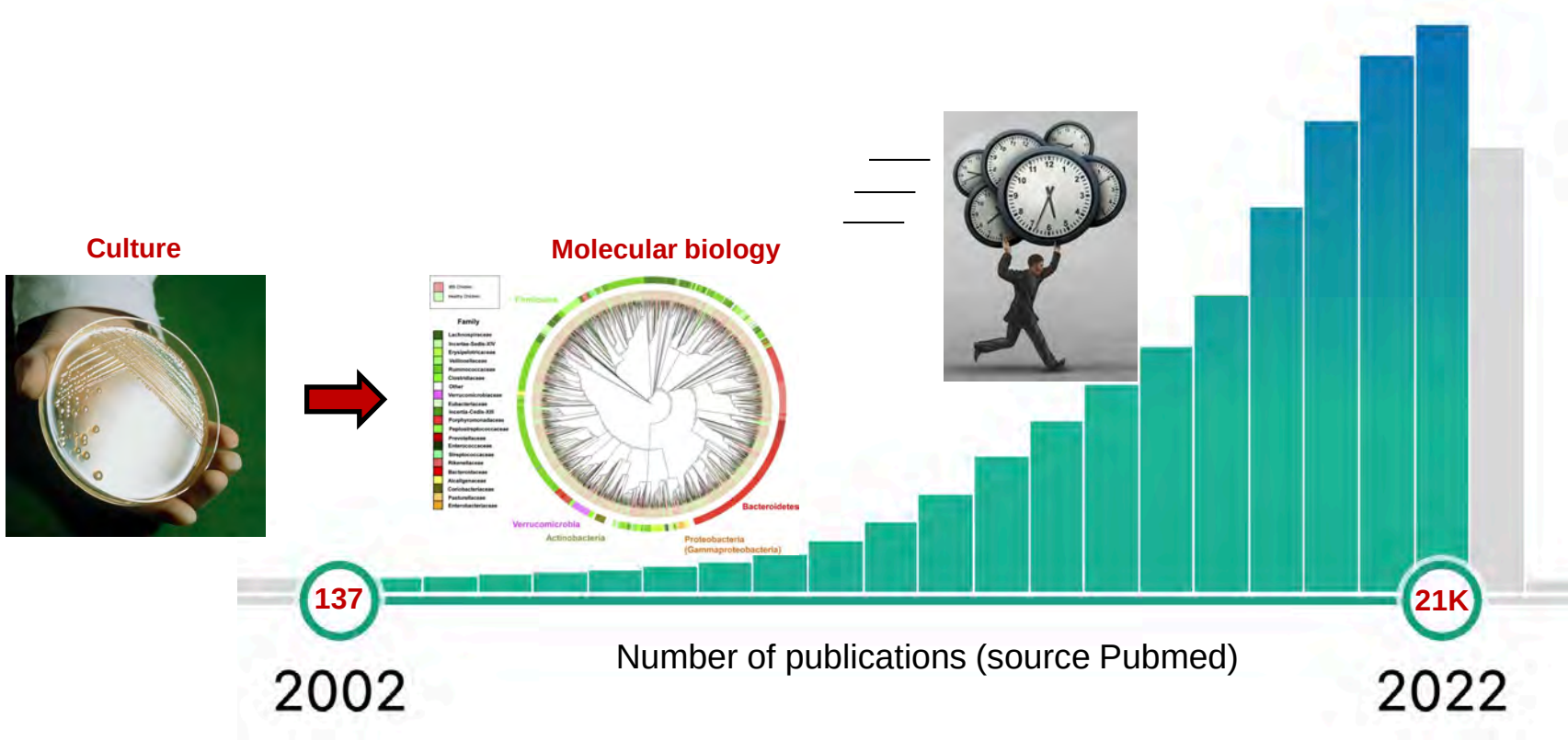
Alma Mater Studiorum, University of Bologna

Italy

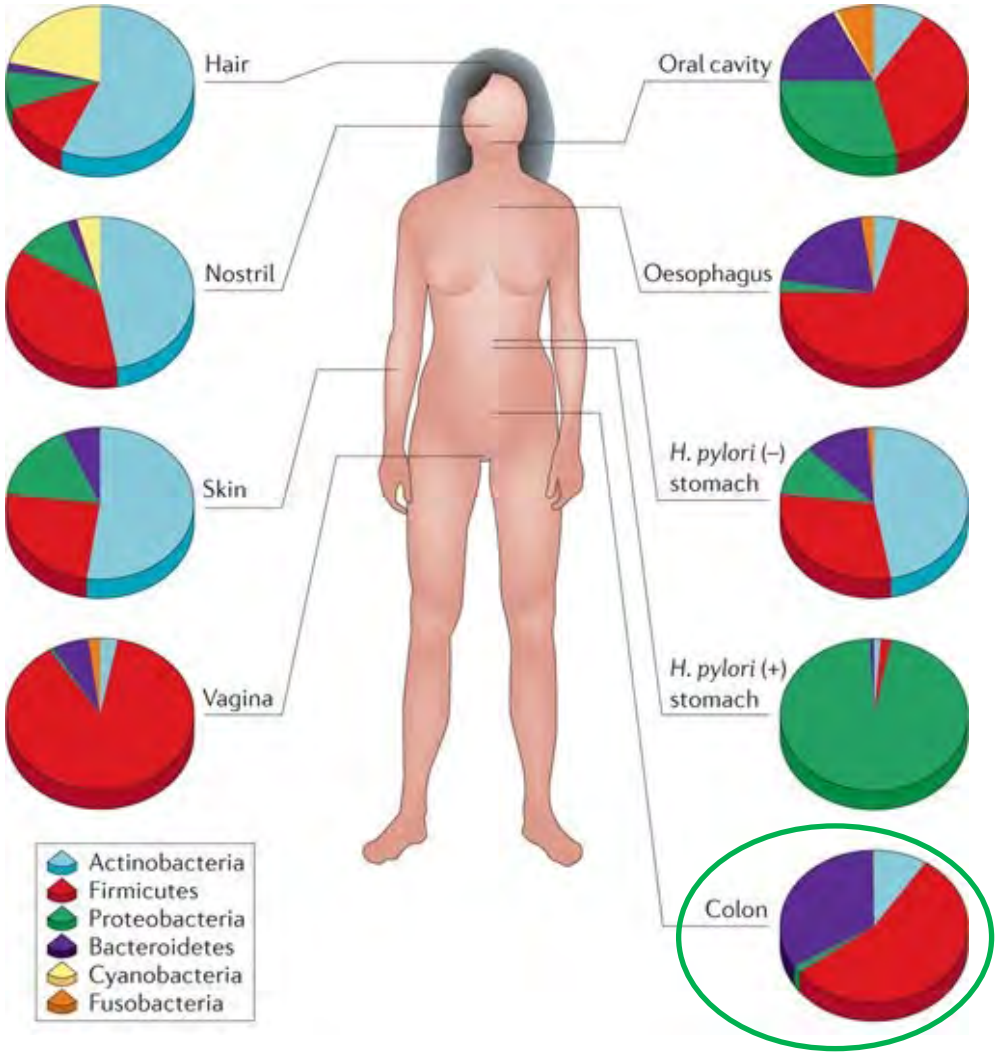
(1088 – 2023)
Anno 935

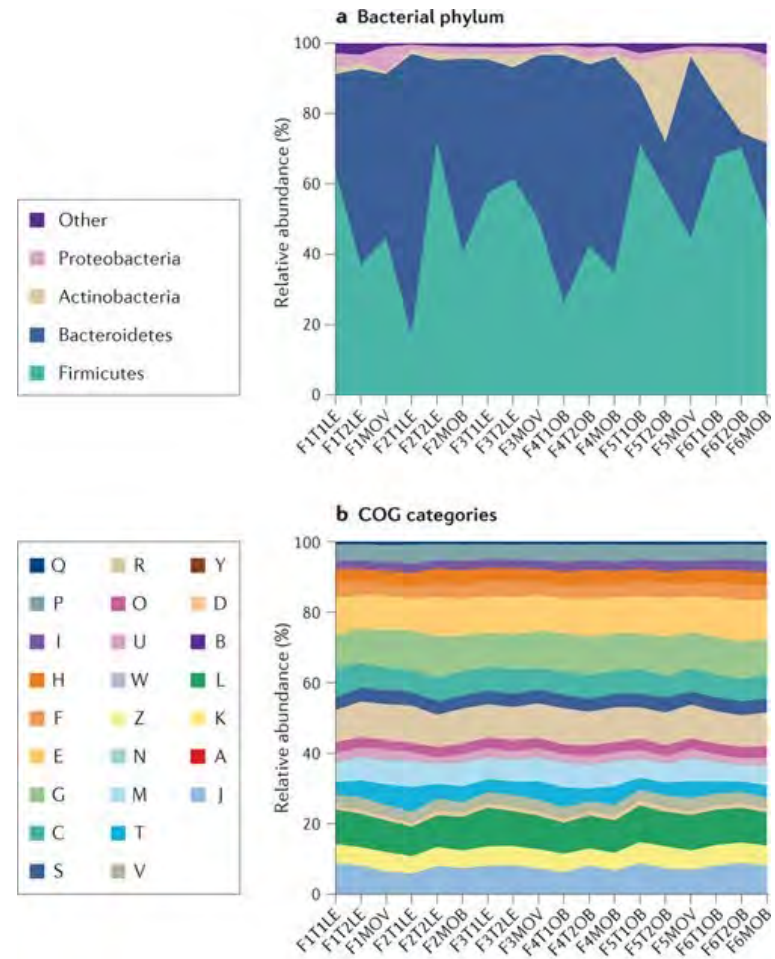
I ritmi della Scienza: lunghe attese e impreviste accelerazioni

The Microbiota Revolution

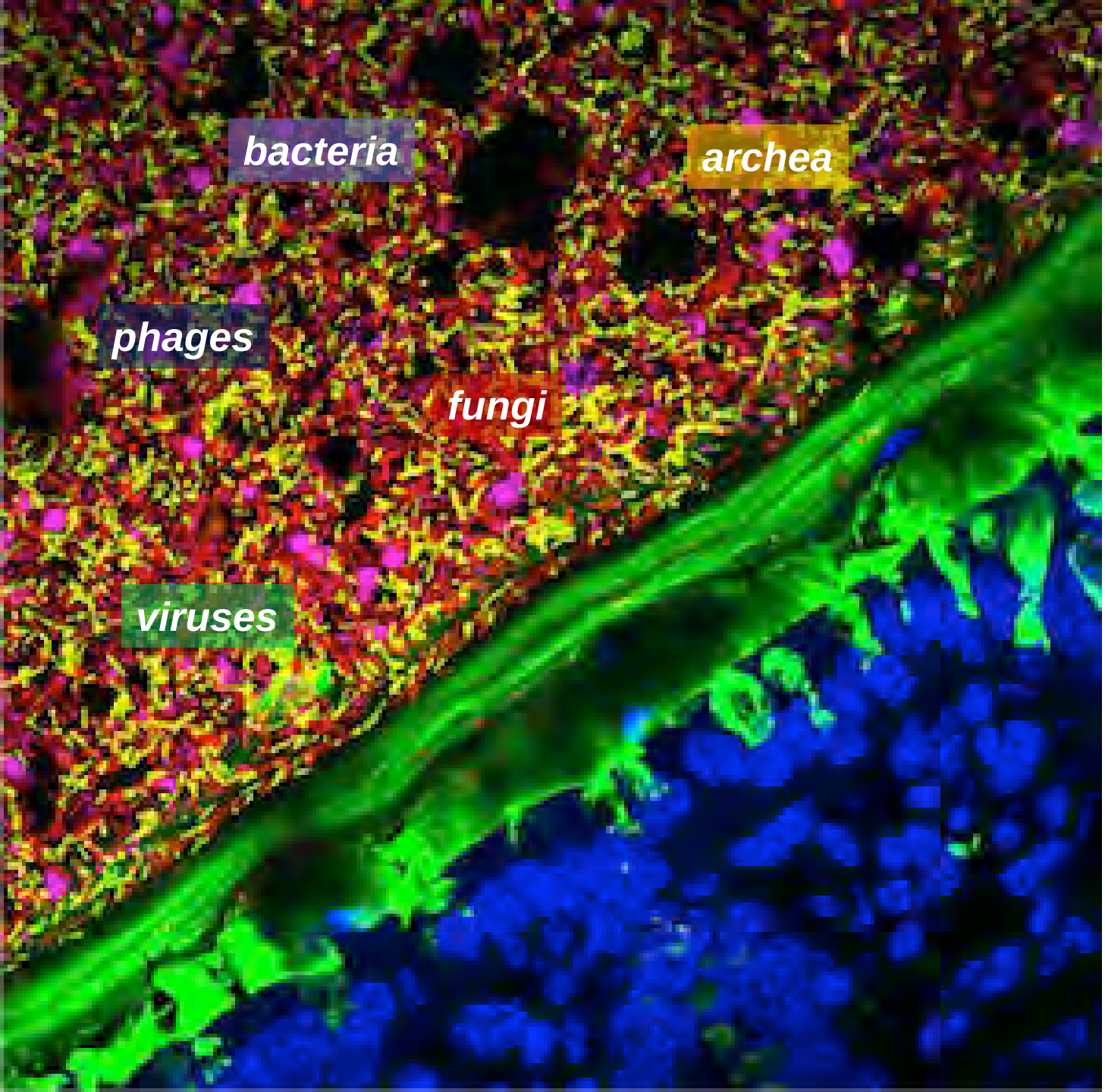


The Human Microbiome





Cho I and Blaser MJ. Nat Rev Genet 2012;13:260-70



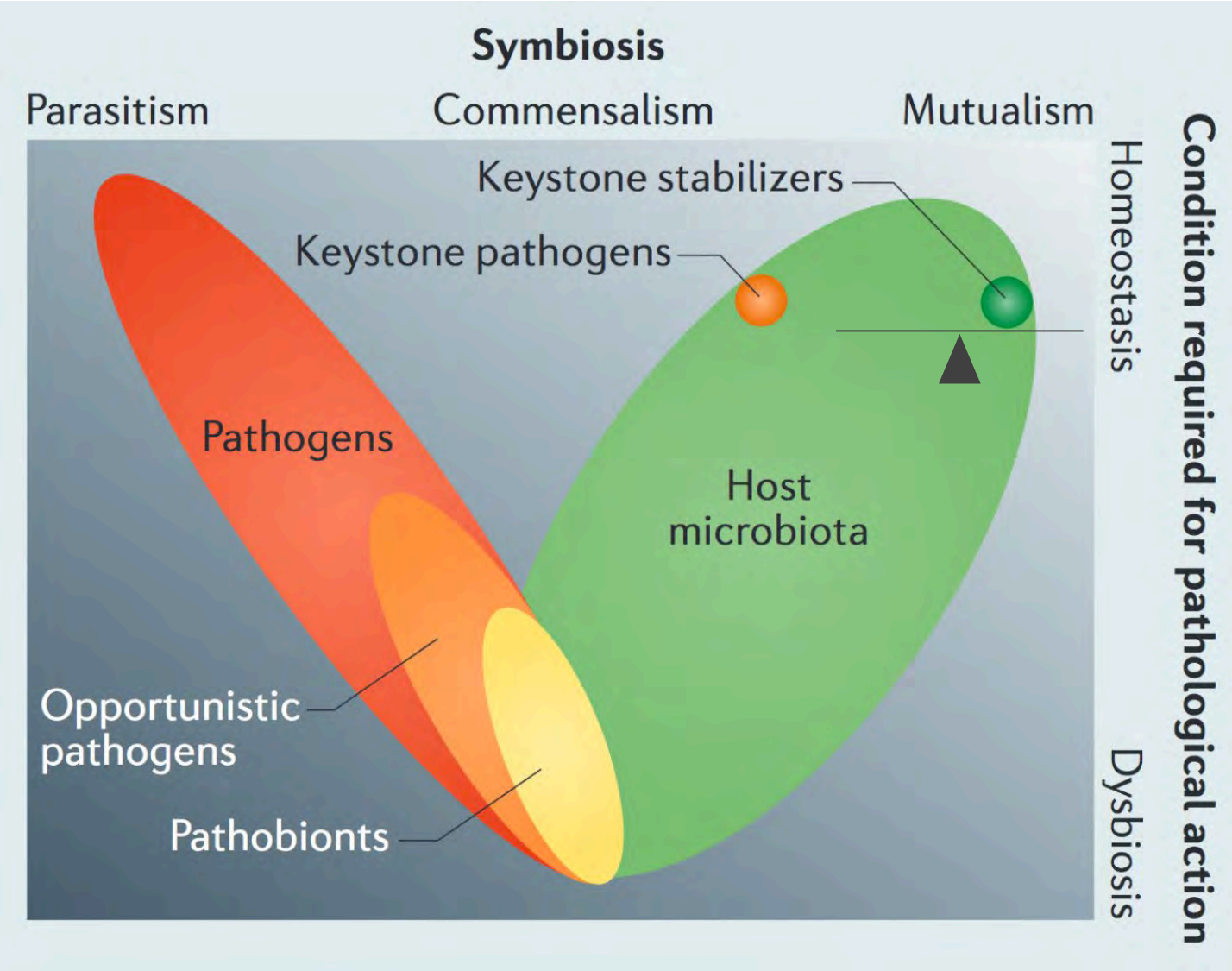
← **Lumen**

← **Mucus**

← **Mucosa**

Earle KA et al.,
Cell Host Microbe2015;18:478-88

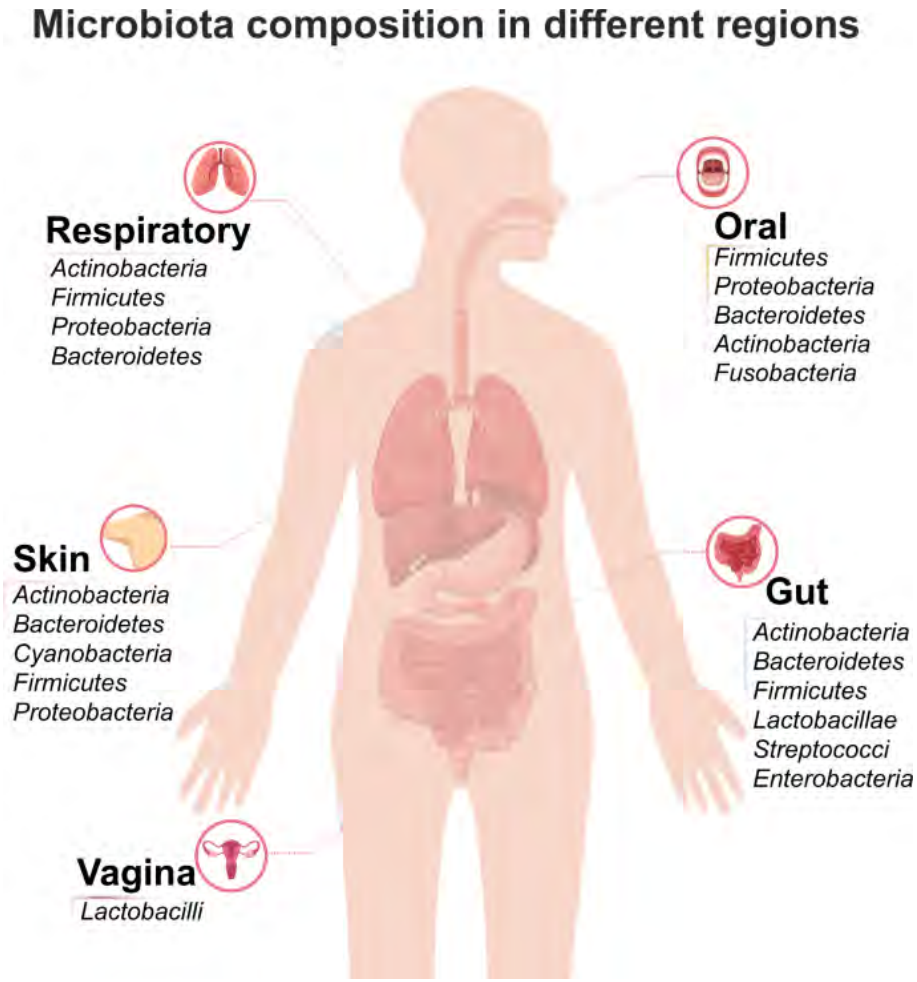
Loss of Equilibrium: The Dysbiosis Concept

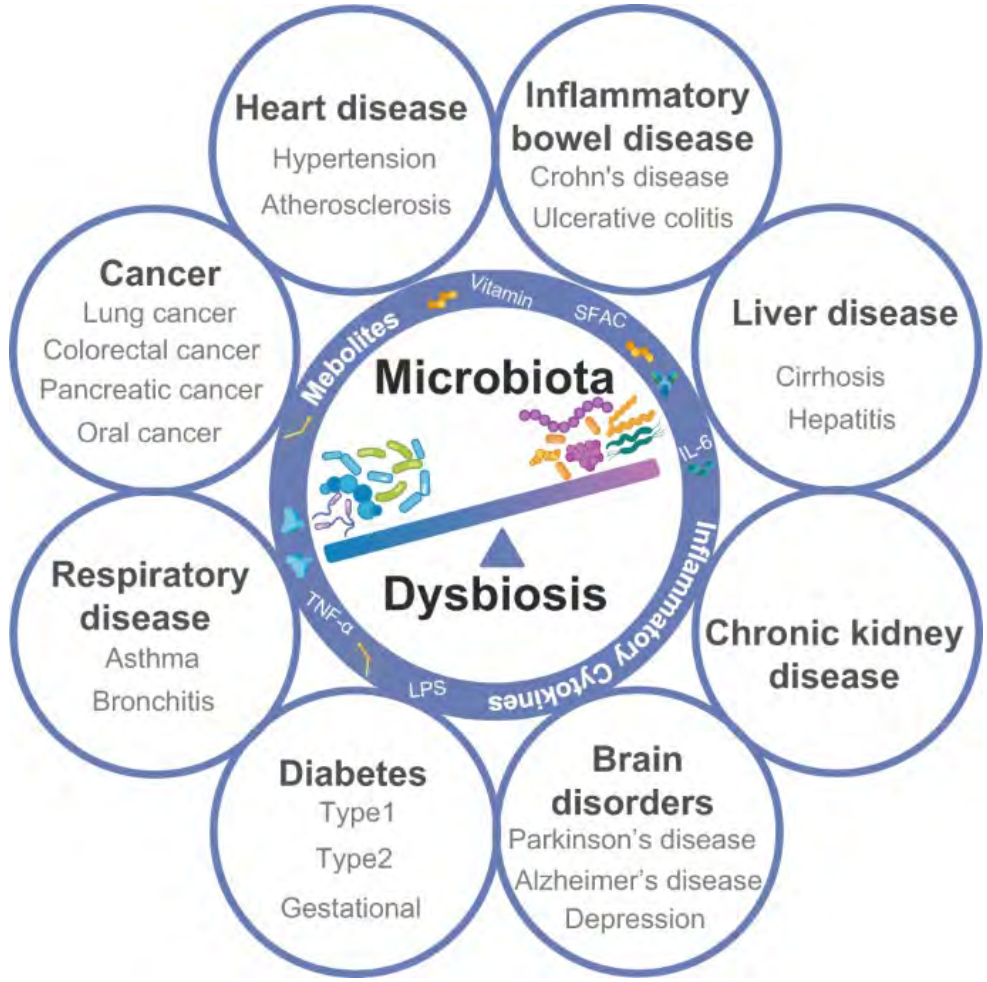


- Cesarean delivery
- Formula feeding
- Diet
  - Low fiber
  - Processed foods
  - Emulsifiers
- Drugs (eg, ATB, NSAIDS, PPI)
- Infections
- Age
- Chronic disease
- …

Stecher B et al. Nat Rev Microbiol 2013;11:277-84

Diseases Associated with Dysbiosis

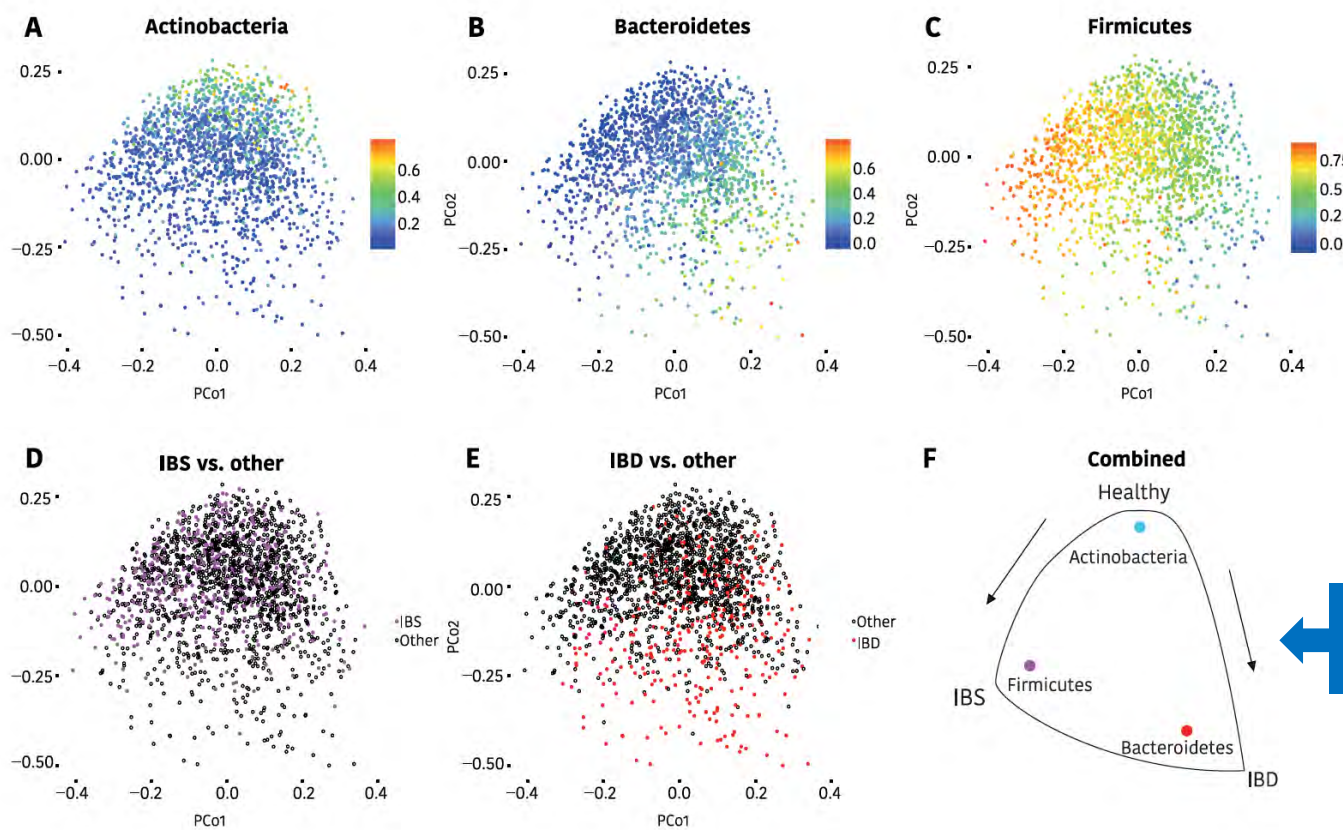




Hou K et al., Signal Transduct Target Ther 2022;7:135

Metagenomic / Metabolomic features are Biomarkers of IBD and IBS

- 1792 Subjects
- Shotgun metagenomics
- Metabolomics
- Virulence factor analyses



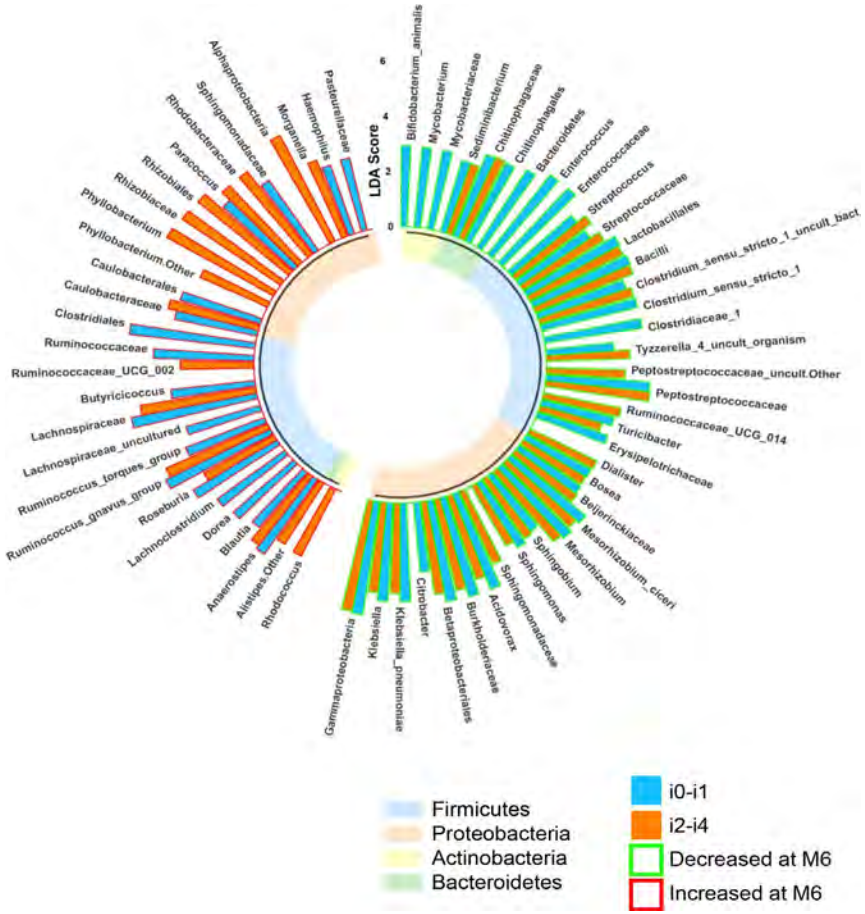
Key signatures of IBD and IBS

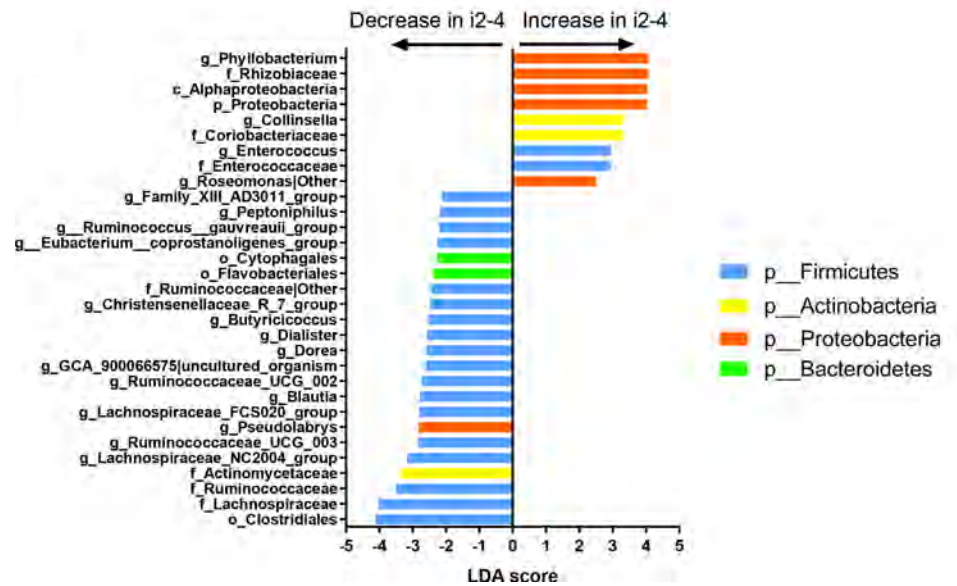
Vich Vila A et al., Sci Transl Med 2018;10;13

Gut Microbiome can Predict Disease Course

Post-Surgical Crohn's Disease Recurrence

Endoscopic recurrence is associated with strong changes in ileal mucosa-associated microbiota



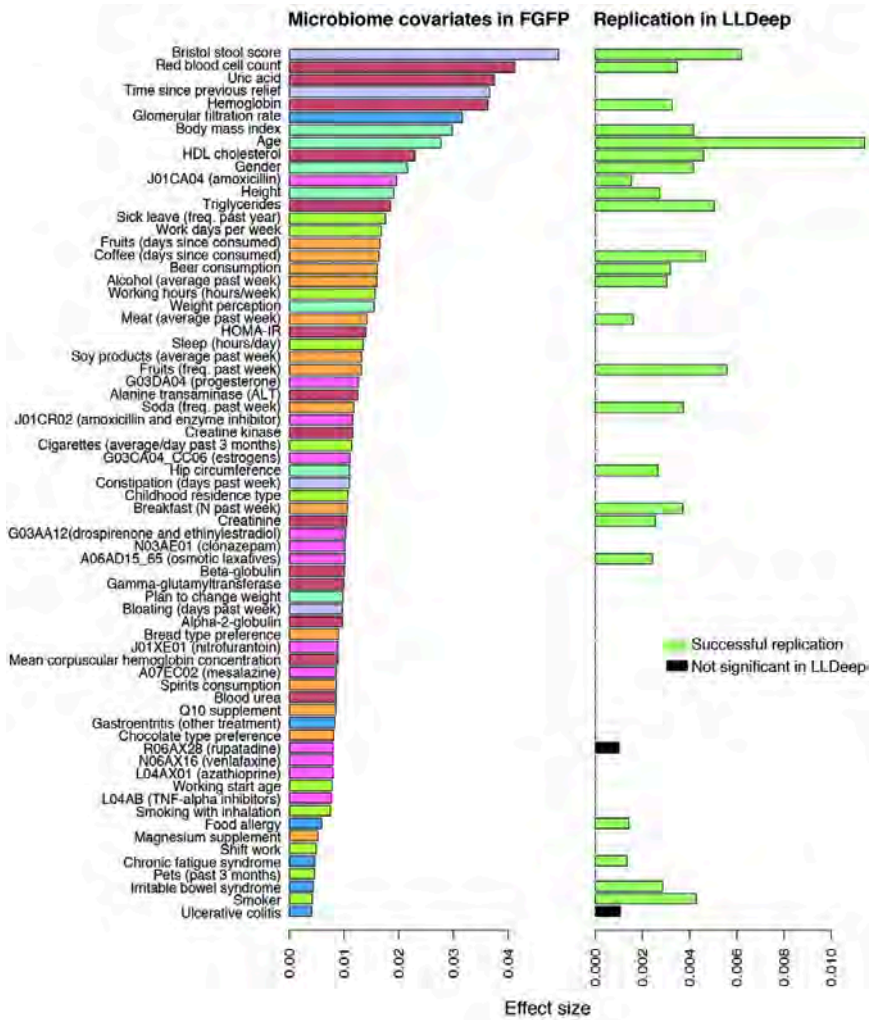


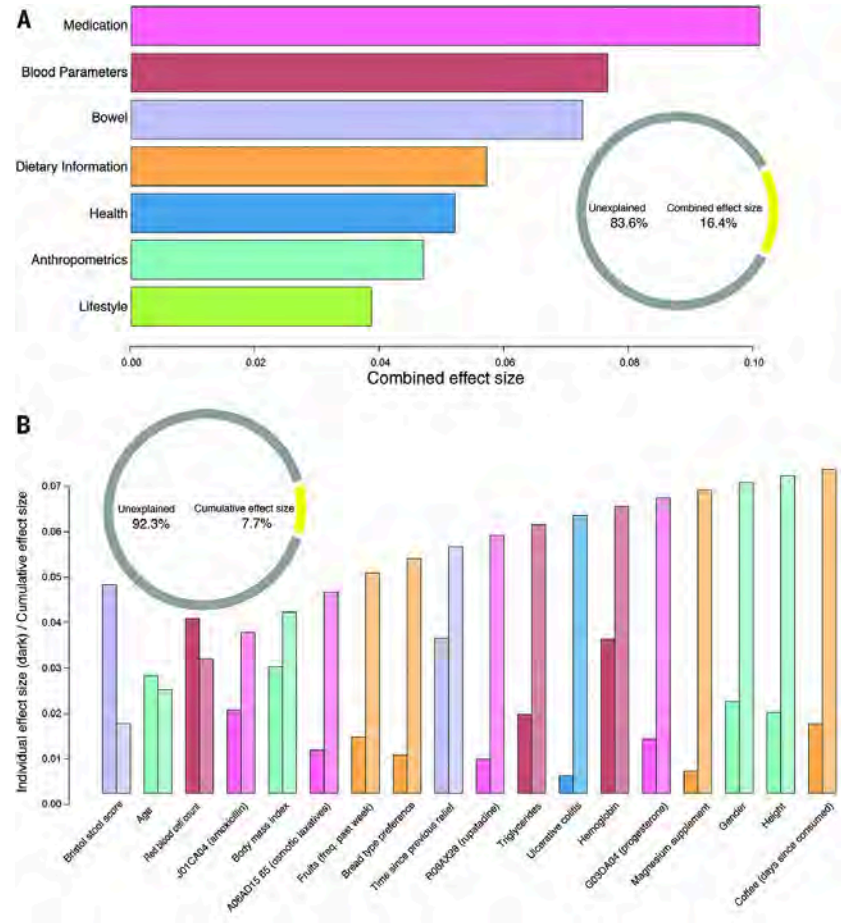
Gut microbiota at the time of surgery can predict endoscopic recurrence

Sokol H et al., Gut 2020;69:462-472

69 Factors Associated with Microbiota Variation

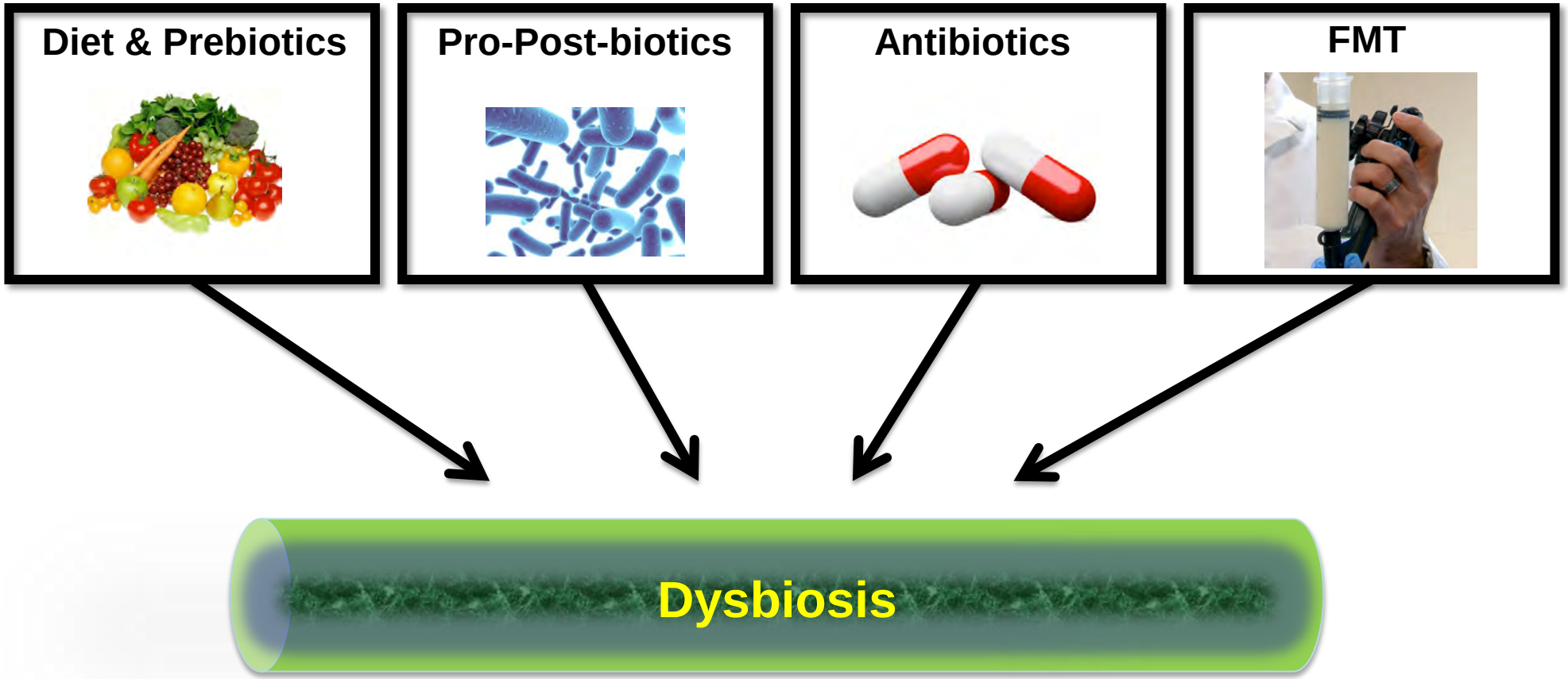
Belgian Flemish Gut Flora Project (N = 1106)
Dutch LifeLines-DEEP study (N = 1135)



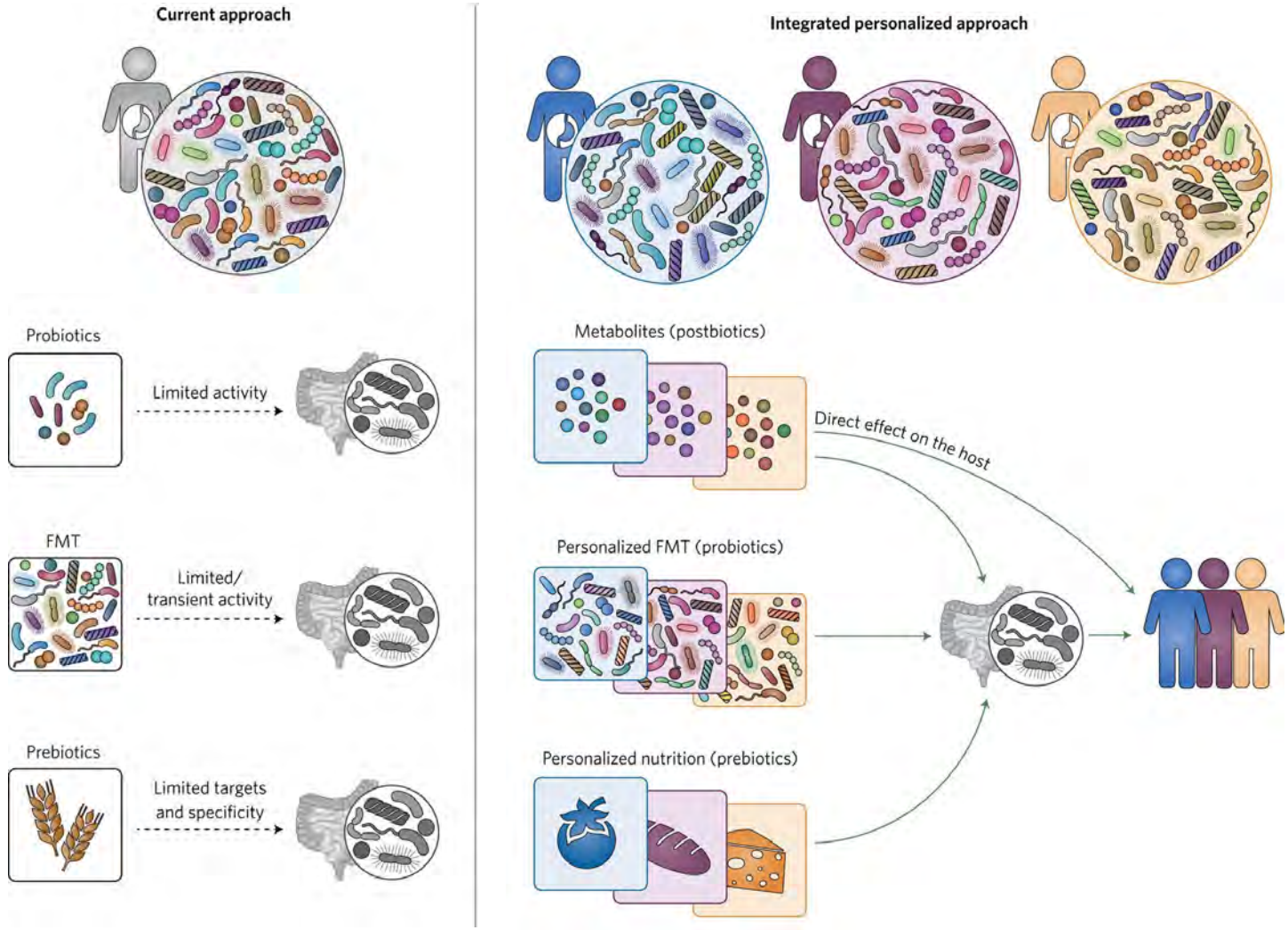


Falony G et al., *Science* 2016;352:560-564

Therapeutic Approaches for Dysbiosis

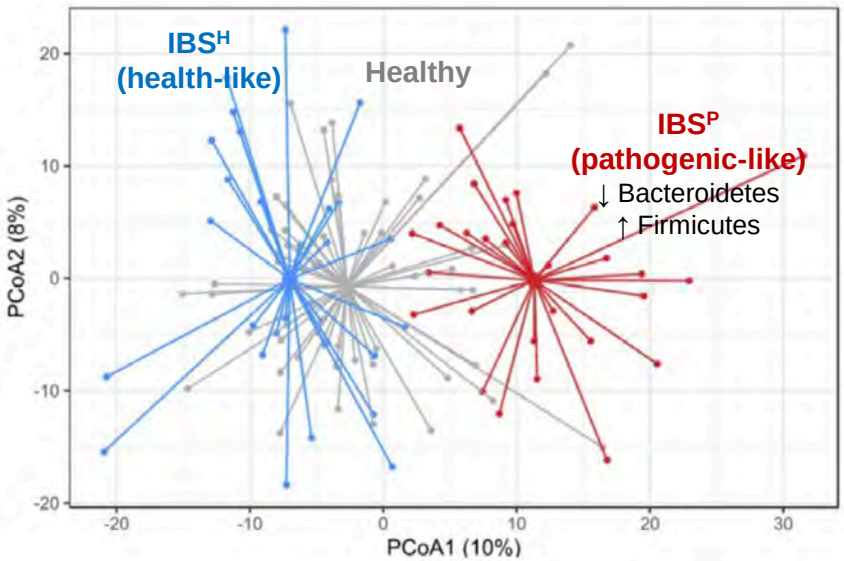


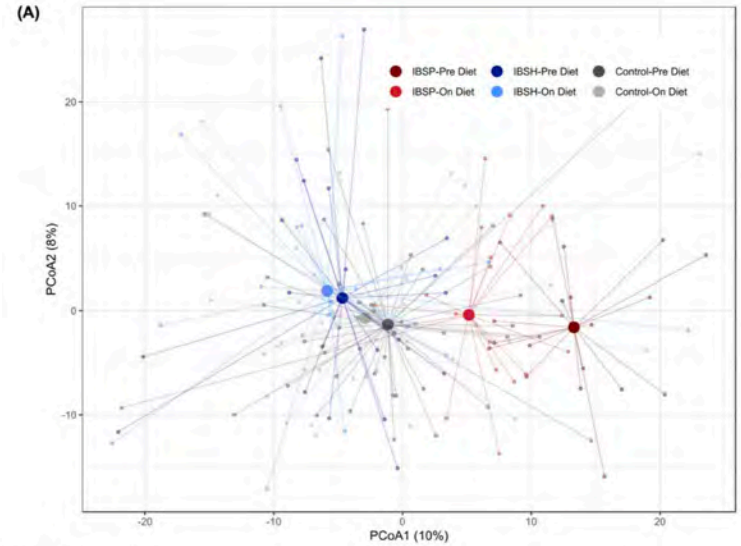
Paradigme Shift in Microbiota Modulation

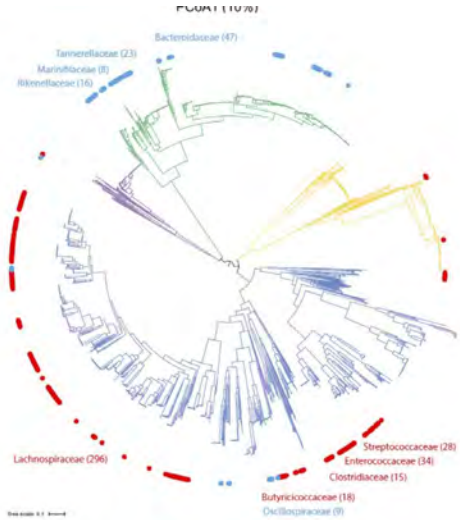


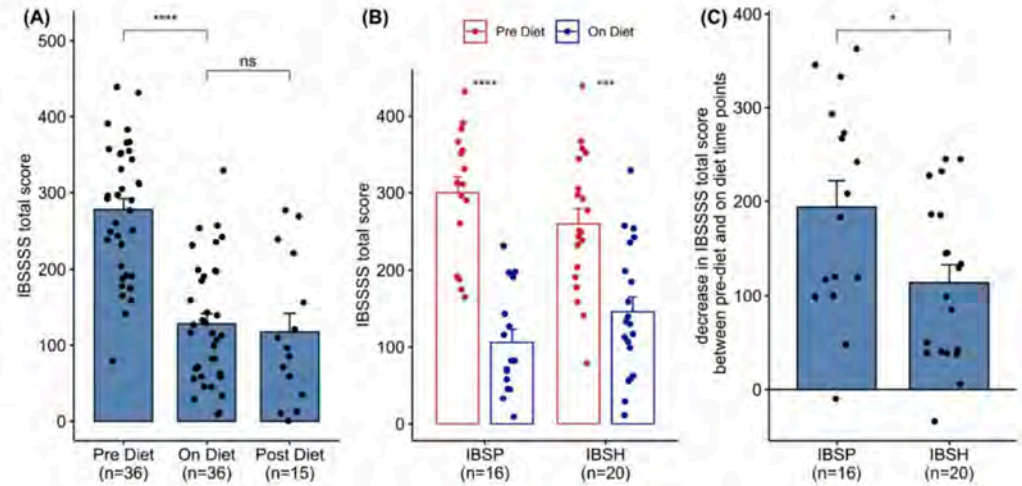
Suez J et al. Nat Microbiol 2017;2:17075

Two Microbiota Subtypes in IBS with Distinct Responses to Low FODMAP Diet







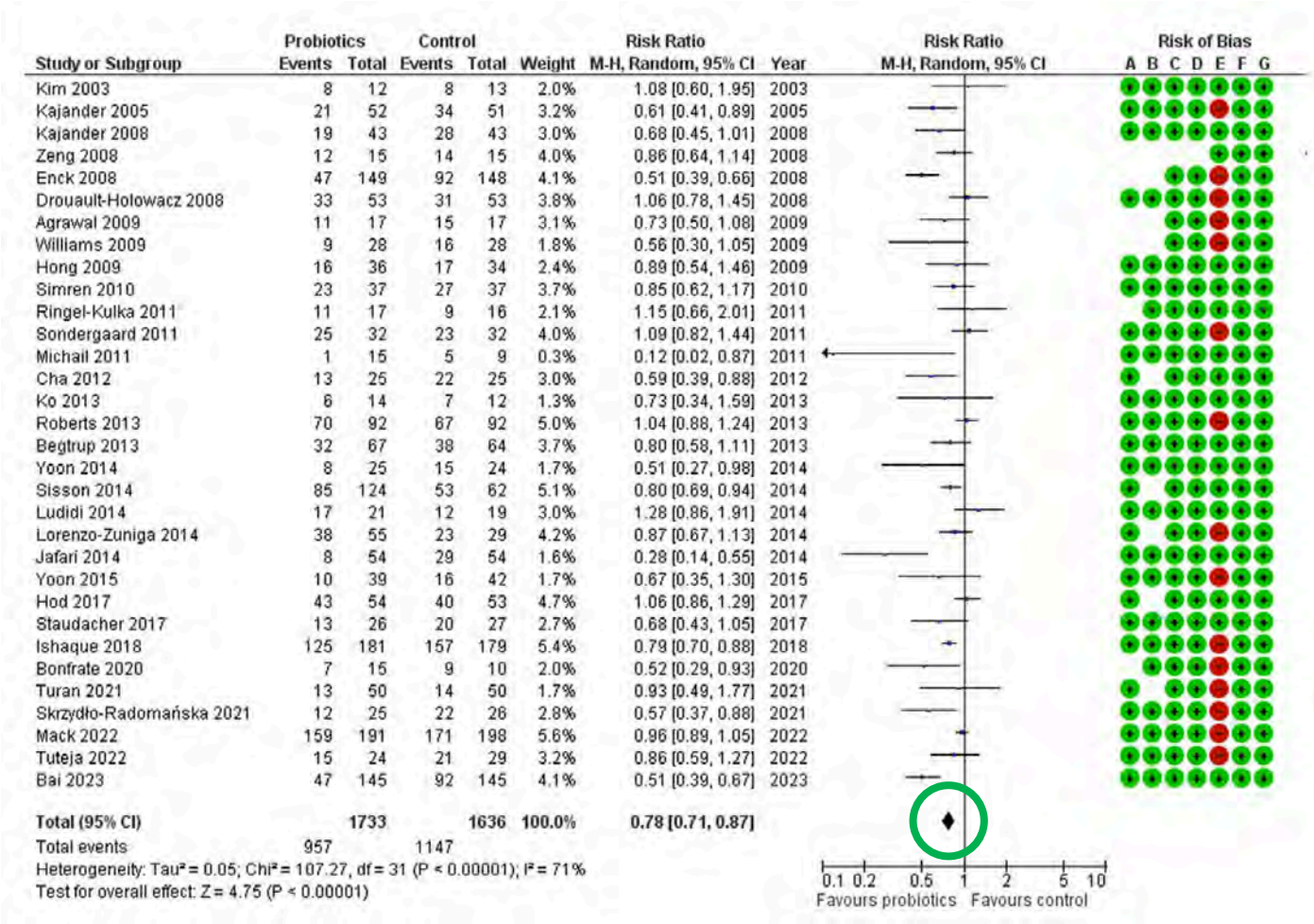


Vervier K, etv al., Gut 2022;71:1821–1830

Efficacy of Probiotics in IBS: Meta-analysis

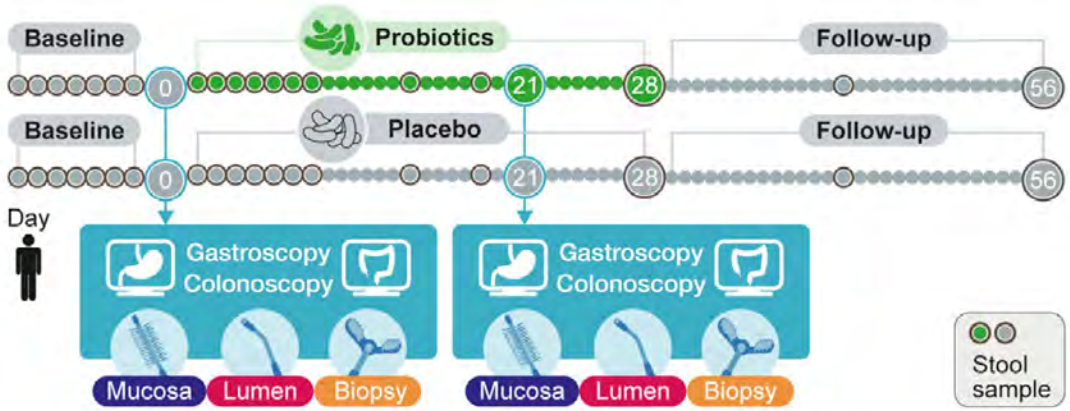
RESULTS

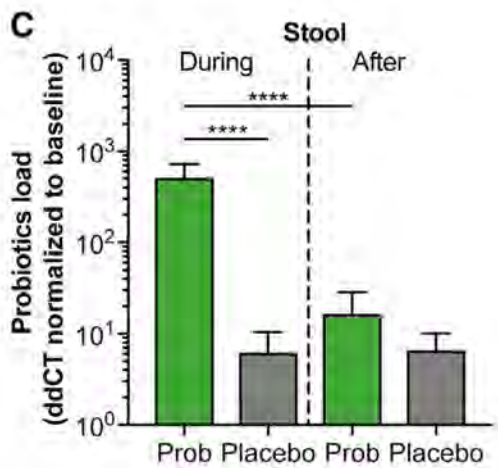
- 82 eligible trials, 10’332 patients
- 24 RCTs were at low risk of bias
- **Some combinations of probiotics or strains may be beneficial in IBS**
- **Evidence for efficacy by GRADE criteria was low to very low**

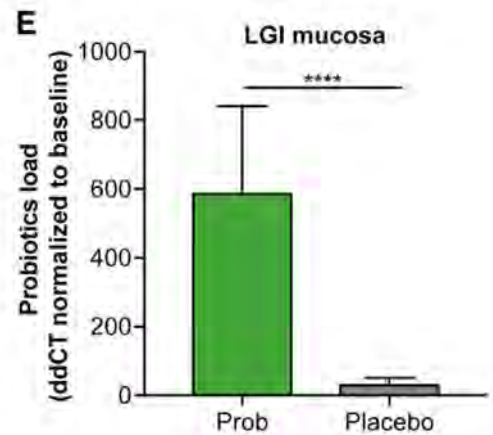


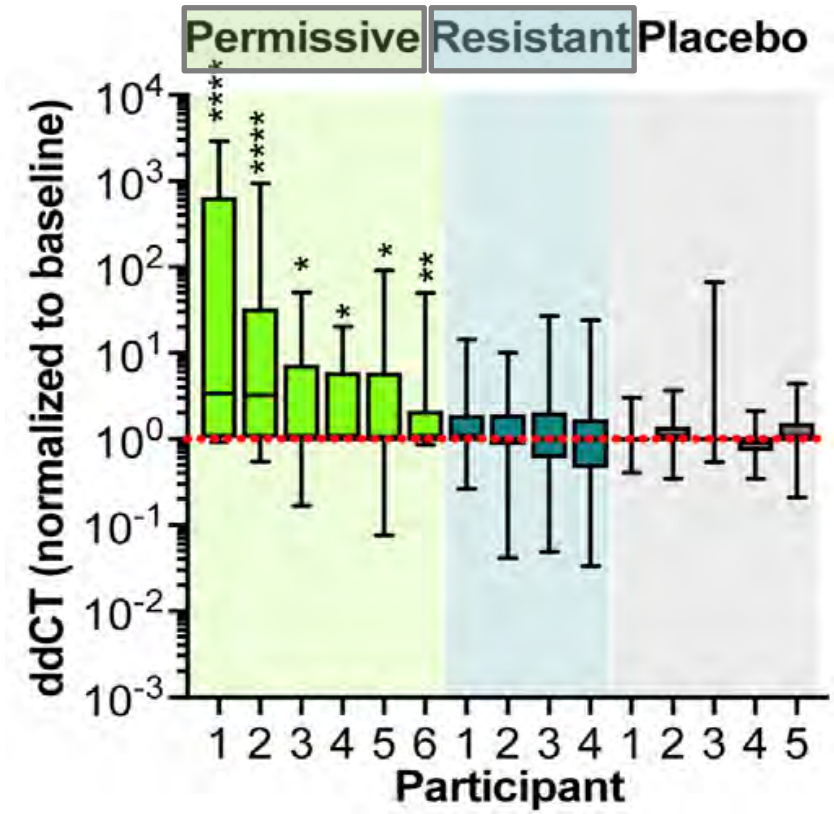
Goodoory VC, et al., Gastroenterology 2023;165:1206-1218

What Happens with the Empiric Use of Probiotics





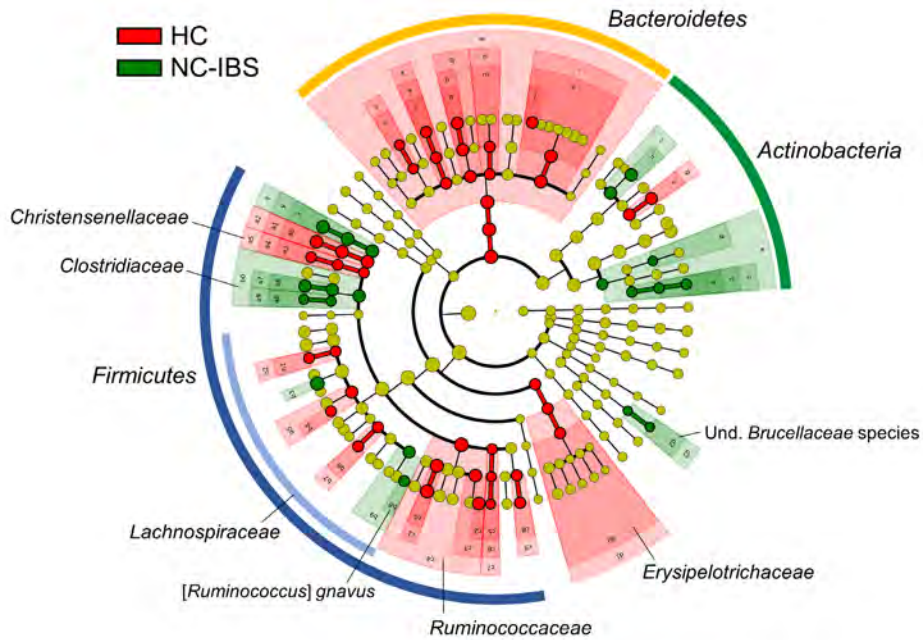


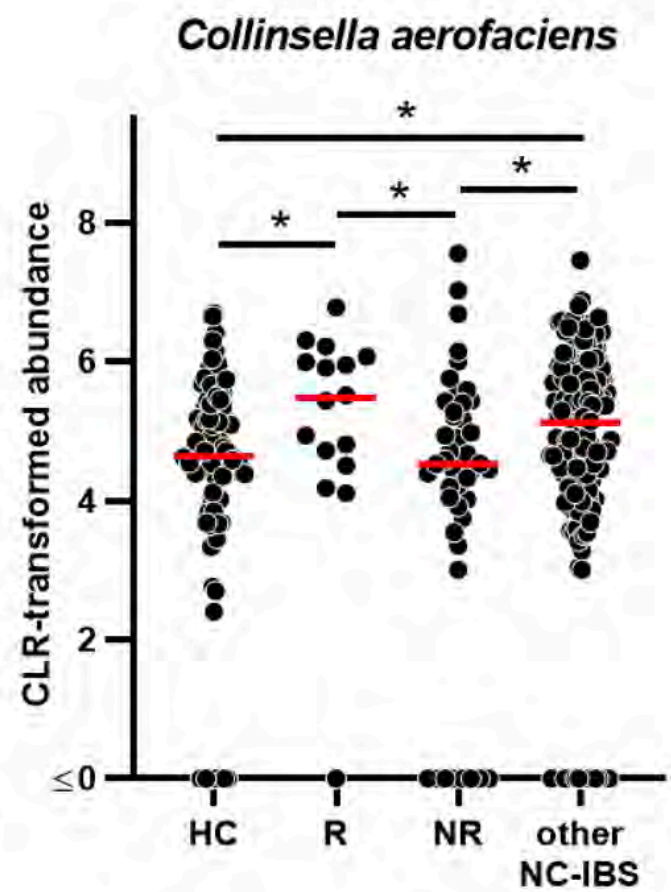


Zmora N et al., Cell 2018;174:1388-1405

Microbiota Predictors of Probiotic Response in IBS

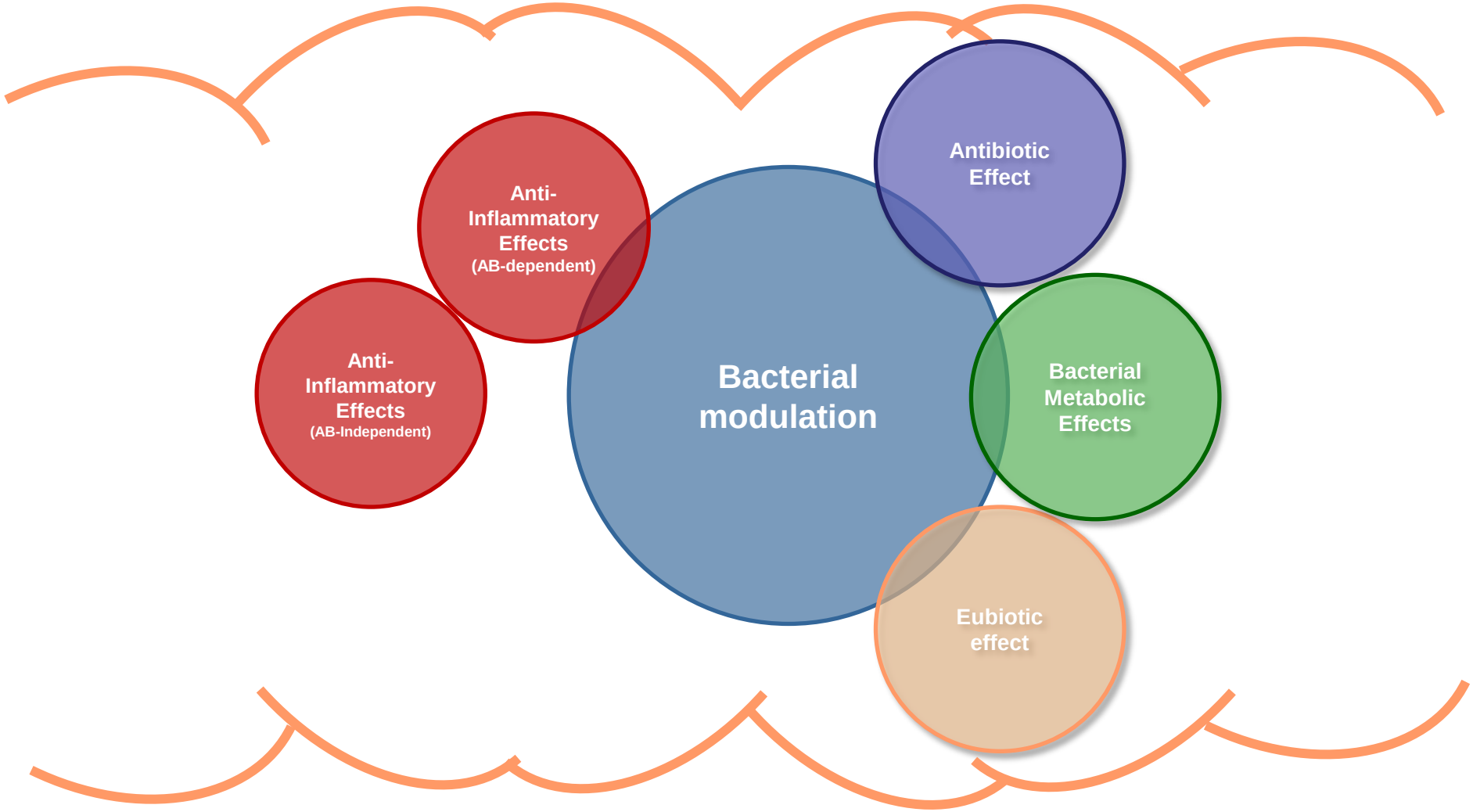
Collinsella aerofaciens as a predictive marker of response to
L. paracasei DG in non-constipated IBS





Gargari G et al., Gut Microbes. 2023;15:2274128

Multiple Mechanisms of Action of Rifaximin



Cuomo R, Barbara G, Annibale B Dig Liv Dis 2017;49:595-603

The Eubiotic Effect of Rifaximin

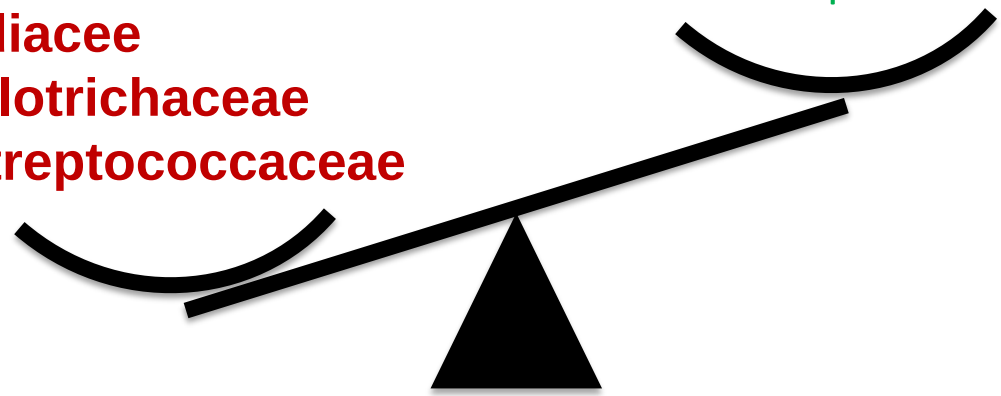
Dysbiosis
eg, proinflammatory

→ Rifaximin

Eubiosis
eg, anti-inflammatory

↑ Biodiversity
↑ Lactobacillaceae
↑ Lactobacilli
↑ Bifidobacteria
↑ Fecalibacterium

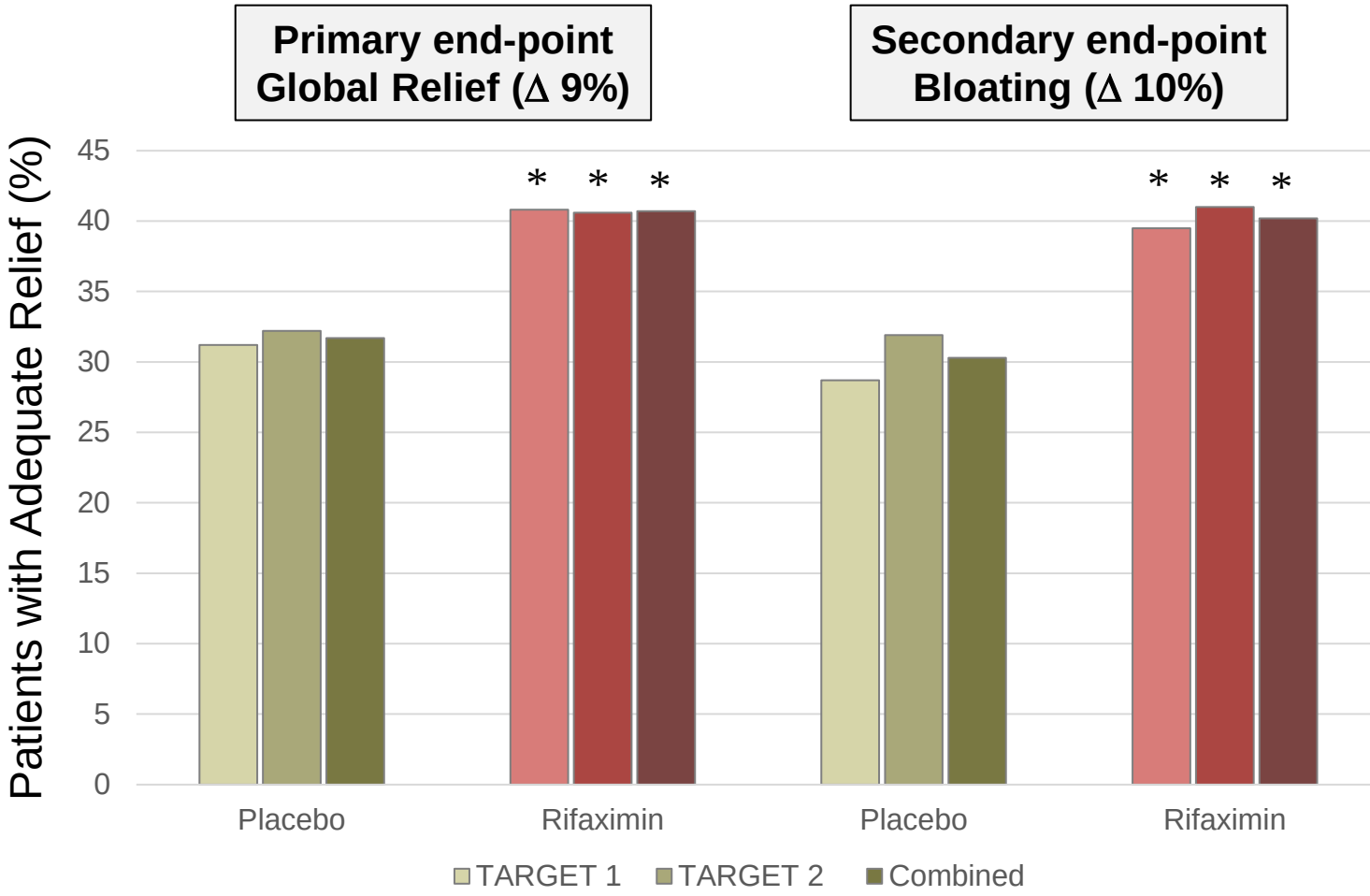
↓ Clostridiacee
↓ Erysipelotrichaceae
↓ Peptostreptococcaceae



Xu D et al., Gastroenterology 2014;146:484-96
Ponziali FR et al., Dig Dis 2016;34:269-78
Soldi S et al., Clin Exp Gastroenterol 2015;8:309-25
Ivaskin v, Barbara G et al. BMC Gastroenterology 2023;23:82

Effect of Rifaximin in IBS Patients without Constipation

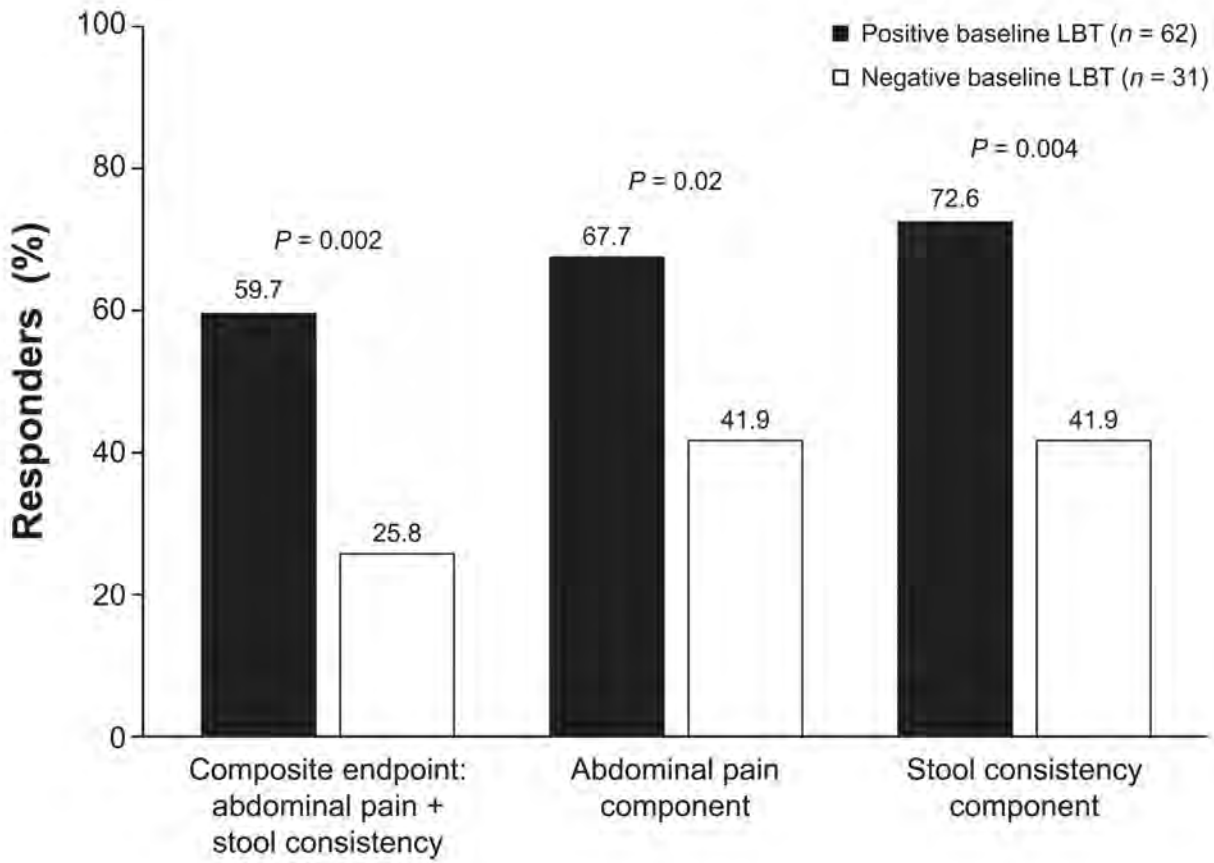
Results from TARGET 1 & TARGET 2 Studies (n=1217)



NNT = 9

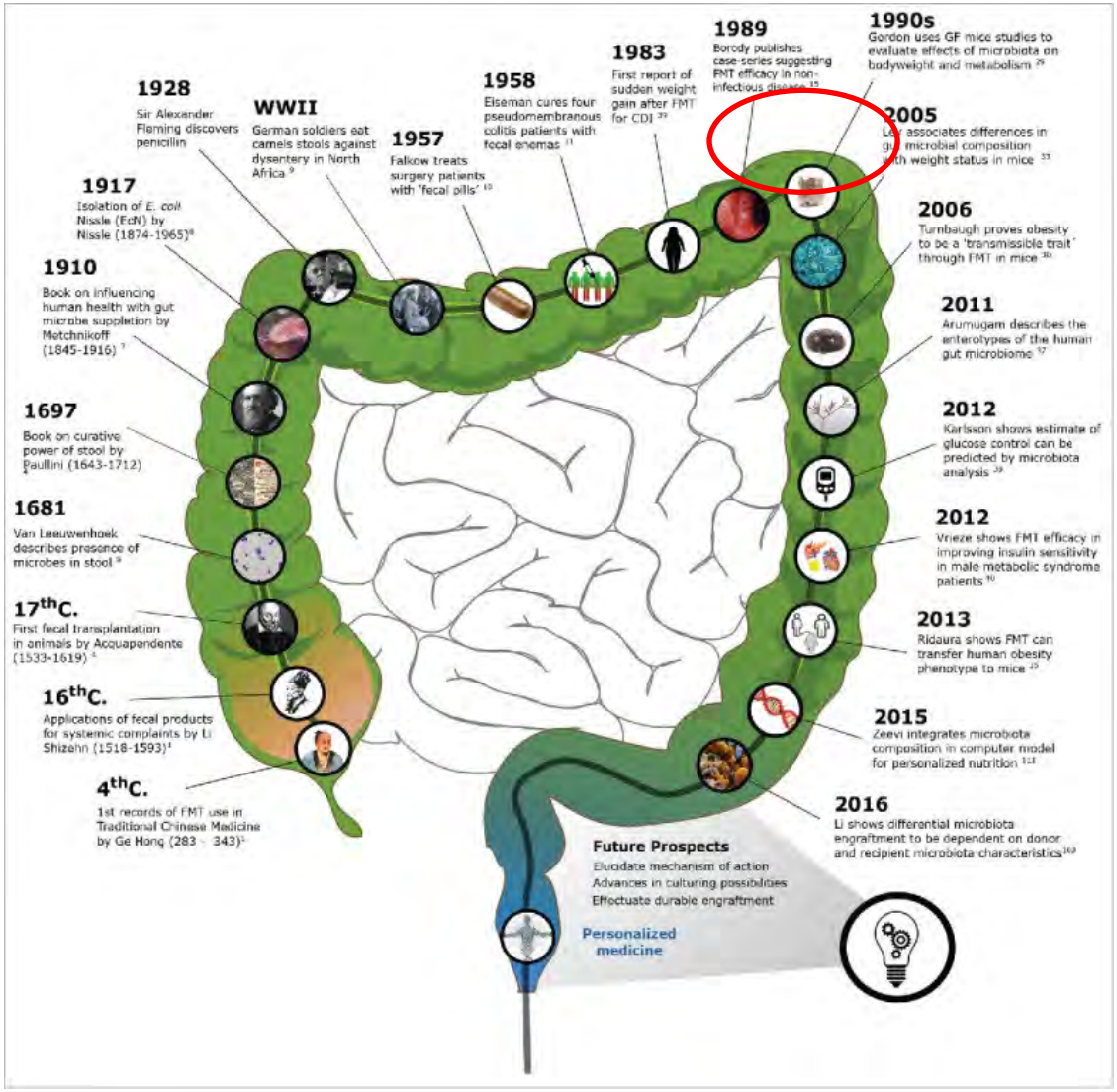
Pimentel et al., NEJM 2011;364;22-32

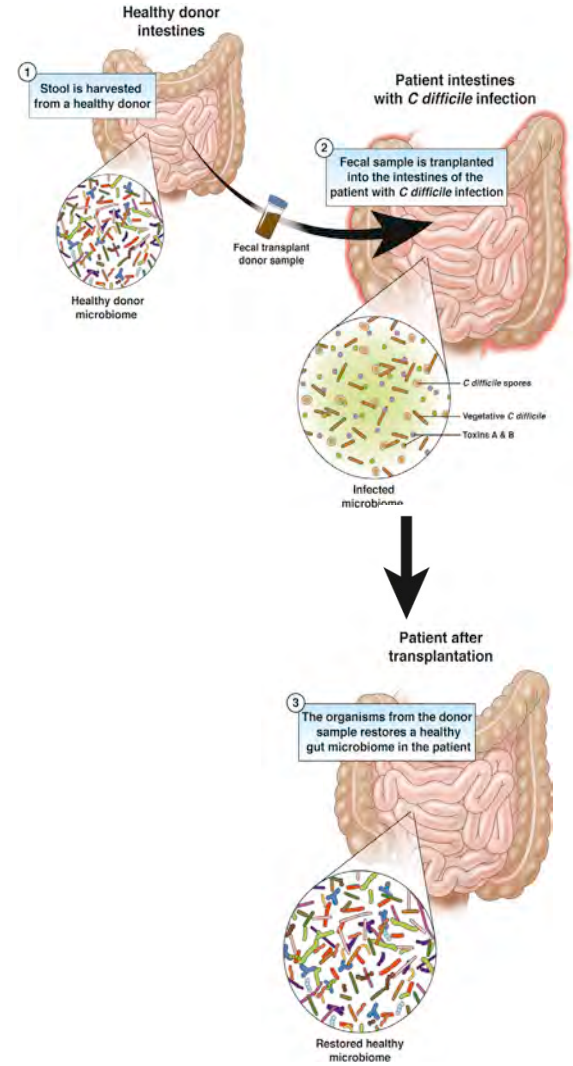
H_2BT Predicting Response to Rifaximin?



Rezaie A, Am J Gastroenterol. 2019;114:1886-1893

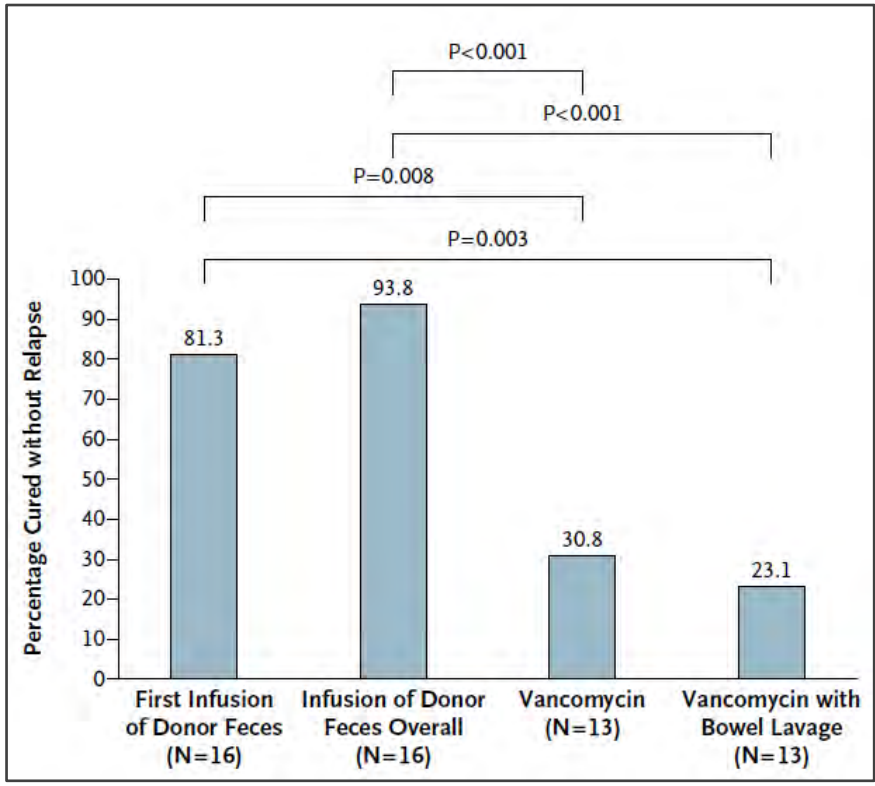
Evolution of Gut Microbiota Modulation





de Groot PF et al., Gut Microbes 2017;8:253-267

FMT is Highly Effective for *C.difficile* Infection



Year	1st auth	Design	CDI Cure
2013	Van nood	RCT (FMT vs vanco)	94%
2013	Kassam	Metanalysis	89.7%
2014	Cammarota	Syst rev	87%
2015	Cammarota	RCT (FMT vs vanco)	90%
2015	Drekonja	Syst rev	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
2019	Hvas	RCT (FMT vs fidaxo)	92% vs 42%

van Nood E, et al. N Engl J Med 2013;368:407–15

Potential Therapeutic Targets for FMT

C. Difficile infection (I)

Eradication of gastrointestinal MDROs (III-2)

Ulcerative colitis (I)

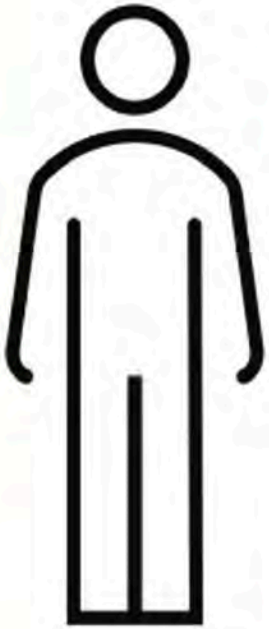
Crohn's disesase (III-2)

Pouchitis; microscopic colitis (IV)

Checkpoint inhibitor colitis (IV)

Functional constipation (I)

Irritable bowel syndrome (II)



Autism (II)

Parkinson's disease (IV)

Schizophrenia, Alzheimer's, multiple sclerosis, anxiety and depression (IV)

Weight loss (IV)

Augmenting immunotherapy cancer responses (IV)

Level of evidence: I: Meta-analyses of RCTs; II: Randomised controlled trials (RCTs); III: Case-controls studies, cohort studies, pseudo-randomized trials; IV: Case series

Waller KMJ, et al., J Gastroenterol Hepatol 2022;37:246-255

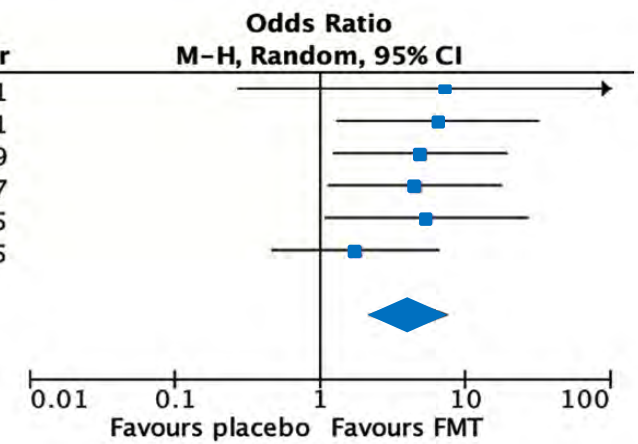
MDROs, multi-drug resistant organisms

FMT in IBD

Study or Subgroup	FMT Events	FMT Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Crothers et al. 2021	2	6	0	6	3.7%	7.22 [0.28, 189.19]	2021
Haifer et al. 2021	8	15	3	20	15.7%	6.48 [1.32, 31.83]	2021
Costello et al. 2019	12	38	3	35	21.3%	4.92 [1.25, 19.31]	2019
Paramsothy et al. 2017	11	41	3	40	21.3%	4.52 [1.16, 17.70]	2017
Moayyedi et al. 2015	9	38	2	37	15.3%	5.43 [1.09, 27.15]	2015
Rossen et al. 2015	7	23	5	25	22.7%	1.75 [0.47, 6.57]	2015
Total (95% CI)		**161**		**163**	**100.0%**	**4.11 [2.19, 7.72]**	
Total events	49		16				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.23$, df = 5 (P = 0.82); $I^2 = 0\%$

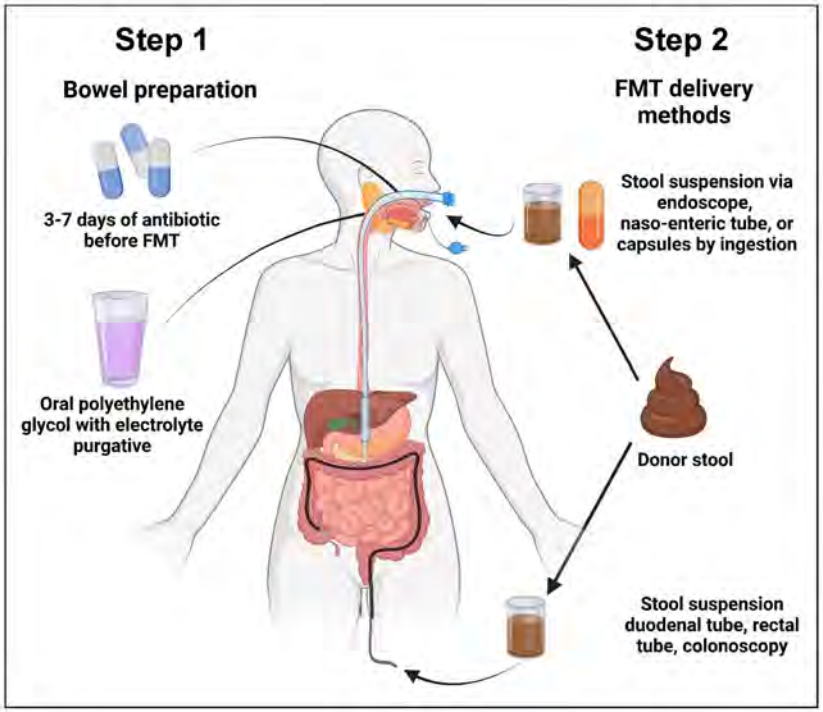
Test for overall effect: Z = 4.40 (P < 0.0001)



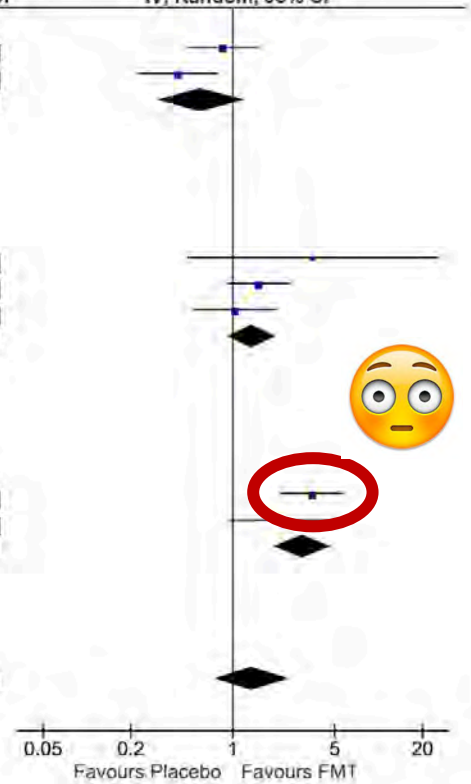
- Evidence predominantly in UC, only 1 small RCT in Crohn's
- Clinical and endoscopic benefit in the short-term
- Comparable safety profile to placebo
- Remission in FMT *vs* placebo, comparable to conventional agents
- Maintenance of remission is at an earlier stage
- Risk of flare lower than suggested from original retrospective case series

El Hage Chehade N et al., Inflamm Bowel Dis 2023;29:808-817

FMT in IBS



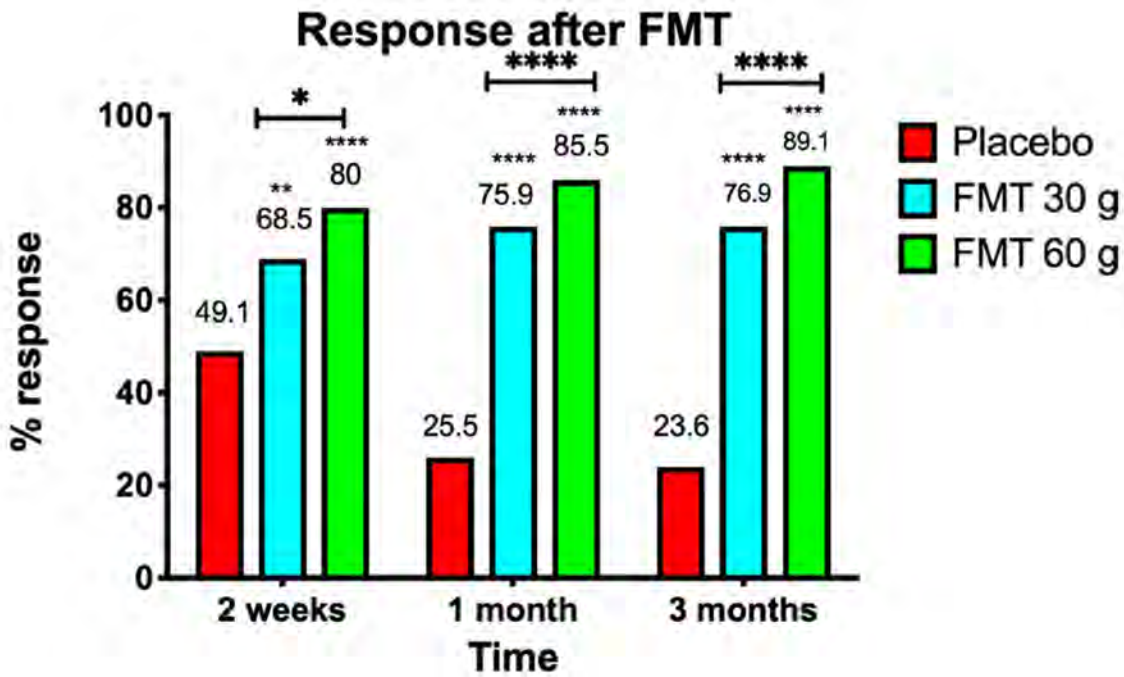
Study or Subgroup	FMT Events	FMT Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Capsules						
Aroniadis et al., 2019	11	23	14	25	16.1%	0.85 [0.49, 1.48]
Halkjær et al., 2018	8	26	19	26	15.5%	0.42 [0.23, 0.78]
Subtotal (95% CI)		**49**		**51**	**31.6%**	**0.61 [0.30, 1.22]**
Total events	19		33			
Heterogeneity: Tau² = 0.16; Chi² = 2.79, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 1.40 (P = 0.16)						
2.3.2 Colonoscopy						
Holster et al., 2019	4	9	1	8	6.0%	3.56 [0.49, 25.59]
Johnsen et al., 2017	36	60	12	30	16.6%	1.50 [0.92, 2.44]
Lahtinen et al., 2020	11	27	11	28	15.3%	1.04 [0.54, 1.98]
Subtotal (95% CI)		**96**		**66**	**37.9%**	**1.36 [0.93, 1.99]**
Total events	51		24			
Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
2.3.3 Gastroscopy/ Nasojejunal tube						
El-Salhy et al., 2020	91	110	13	55	16.6%	3.50 [2.16, 5.67]
Holvoet et al., 2020	24	43	5	19	13.9%	2.12 [0.95, 4.71]
Subtotal (95% CI)		**153**		**74**	**30.5%**	**3.03 [1.94, 4.73]**
Total events	115		18			
Heterogeneity: Tau² = 0.01; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 4.87 (P < 0.00001)						
Total (95% CI)		**298**		**191**	**100.0%**	**1.35 [0.75, 2.43]**
Total events	185		75			
Heterogeneity: Tau² = 0.48; Chi² = 34.06, df = 6 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 16.01, df = 2 (P = 0.0003), I² = 87.5%						



Rodrigues T et al., J Clin Med. 2023;12:1725

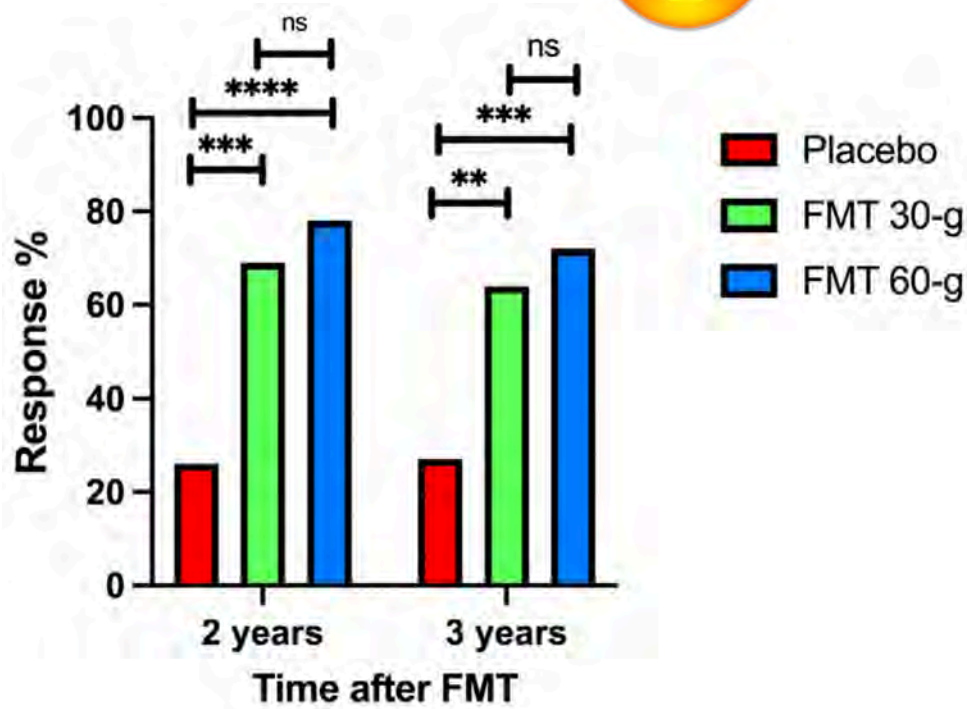
Short and Long Term Efficacy of FMT in IBS

Short Term



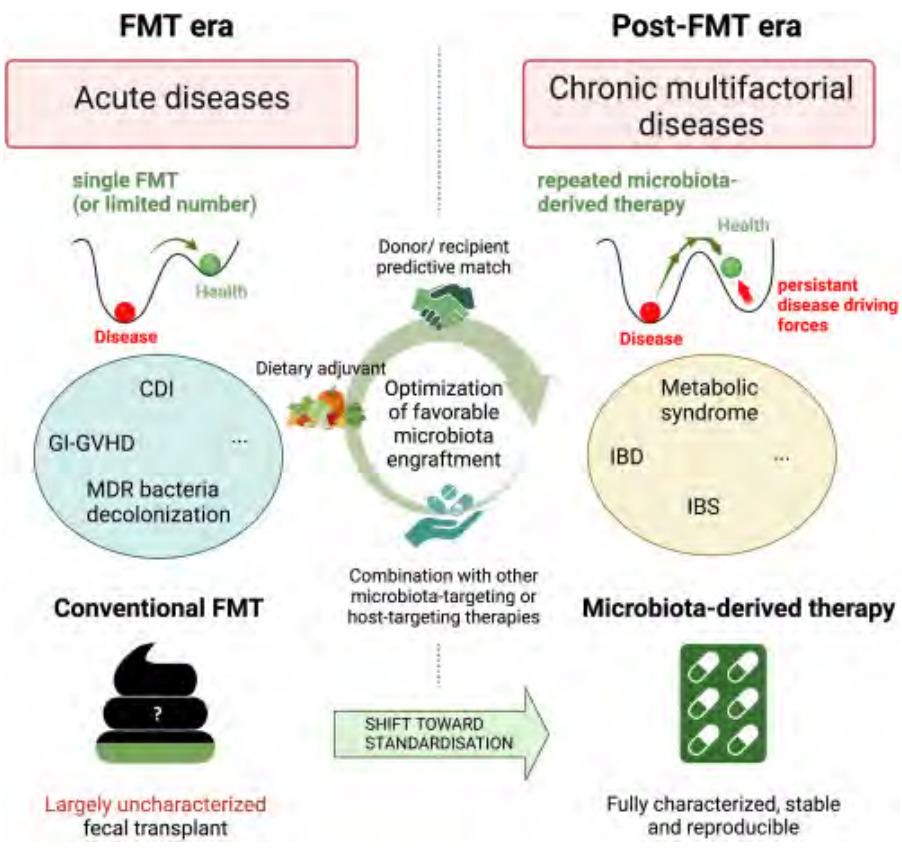
El-Salhy M et al., Gut. 2020;69:859-867

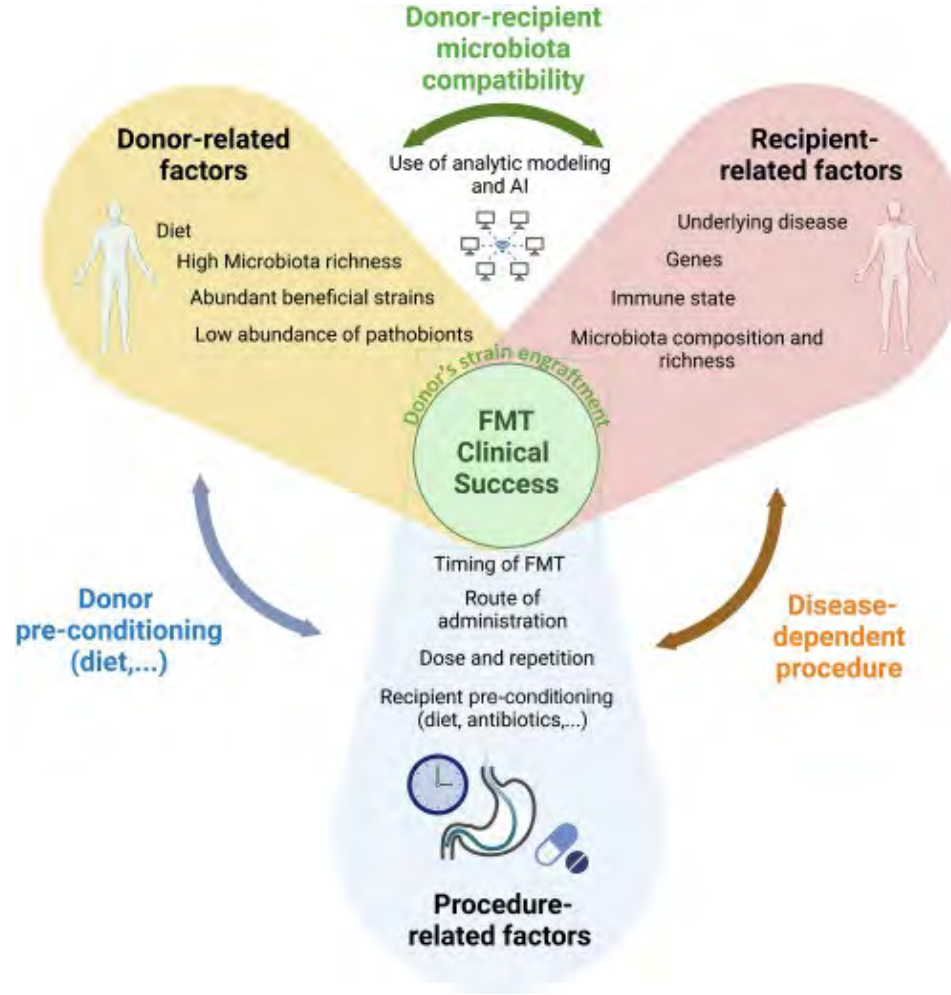
Long Term



El-Salhy M et al., Gastroenterology 2022;163:982–994

Factors Influencing FMT Outcome

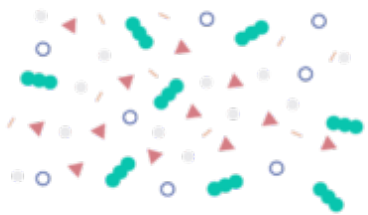




Porcari S et al., Cell Host Microbe 2023;31:712-733

Future Microbiome Therapeutics

Microbial consortia



Postbiotics

Phages

Engineered bacteria

È semplice, è sicuro e
ti garantisce
un approfondito screening
del tuo stato di salute

Compila il form sul
sito del Policlinico di
Sant'Orsola e candidati a
diventare donatore

PER INFORMAZIONI

051 3256589

Ufficio Comunicazione e stampa

DIVENTA SUPER DONATORE DI MICROBIOTA

Hai dai 18 ai 45 anni?
Sei di Bologna?
Godi di buona salute e hai sane abitudini di vita??

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

POLICLINICO DI SANT'ORSOLA

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA