Le microbiote intestinal comme nouveau terrain de jeu en médecine

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MCU-PH thérapeutique
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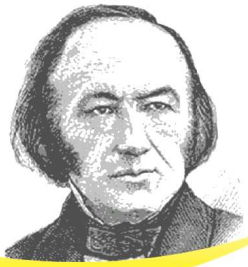
JEUDI 28 NOVEMBRE 2019
UFR Médecine Paris 7 Diderot,
site Xavier-Bichat - Paris 18ème



62ème journée
Claude-Bernard

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

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The MiHAR Lab
Microbiotas, Hosts, Antibiotics and bacterial Resistances

MiBioGate
MICROBIOTA BIOLOGICAL GATE

UNIVERSITY OF MINNESOTA

Je n’ai aucun lien d’intérêt à déclarer

Microbiote: biomarqueur

nature medicine

ARTICLES

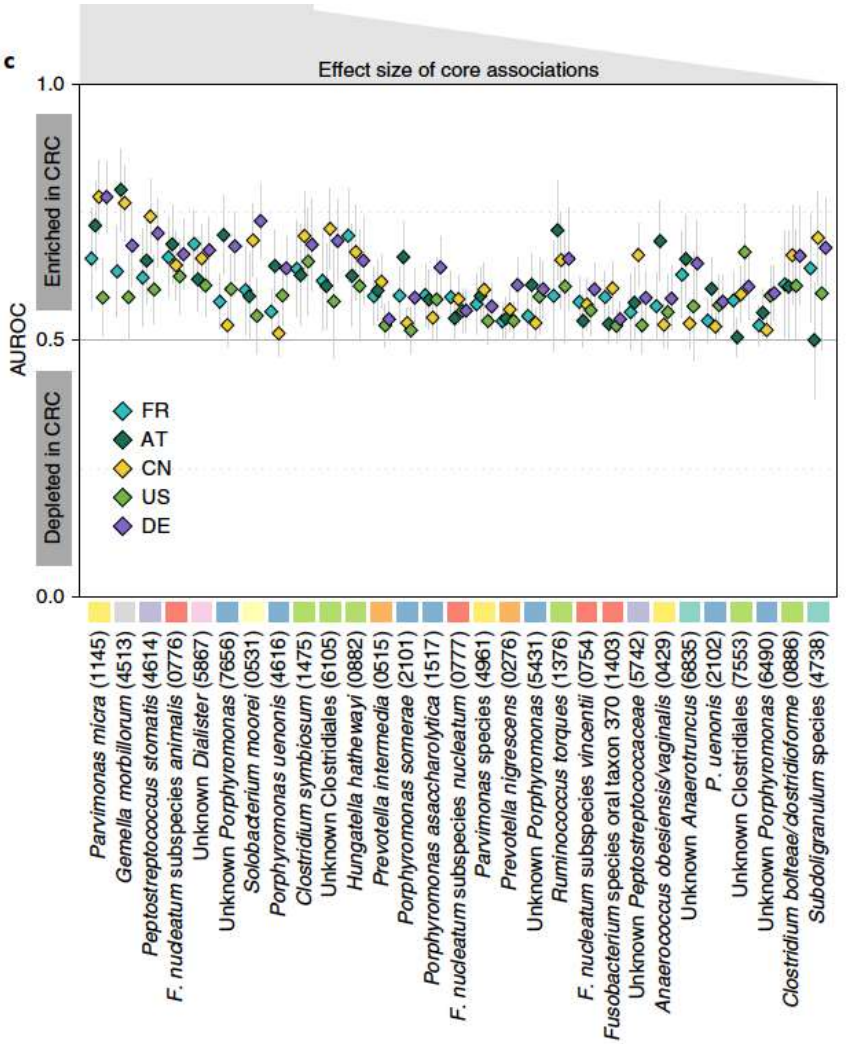
https://doi.org/10.1038/s41591-019-0406-6

Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer

Jakob Wirbel[1,31], Paul Theodor Pyl[2,3,31], Ece Kartal[1,4], Konrad Zych[1], Alireza Kashani[2], Alessio Milanese[1], Jonas S. Fleck[1], Anita Y. Voigt[1,5], Albert Palleja[2], Ruby Ponnudurai[1], Shinichi Sunagawa[1,6], Luis Pedro Coelho[1,30], Petra Schrotz-King[7], Emily Vogtmann[8], Nina Habermann[9], Emma Niméus[3,10], Andrew M. Thomas[11,12], Paolo Manghi[11], Sara Gandini[13], Davide Serrano[13], Sayaka Mizutani[14,15], Hirotsugu Shiroma[14], Satoshi Shiba[16], Tatsuhiro Shibata[16,17], Shinichi Yachida[16,18], Takuji Yamada[14,19], Levi Waldron[20,21], Alessio Naccarati[22,23], Nicola Segata[11], Rashmi Sinha[8], Cornelia M. Ulrich[24], Hermann Brenner[7,25,26], Manimozhiyan Arumugam[2,27,32*], Peer Bork[1,4,28,29,32*] and Georg Zeller[1,32*]

Table 1 | Fecal metagenomic studies of CRC included in this meta-analysis

Country code	Reference	No. of cases	No. of controls
France	Zeller et al.[8]	53	61
Austria	Feng et al.[9]	46	63
China	Yu et al.[11]	74	54
United States	Vogtmann et al.[10]	52	52
Germany	The current study	60	60
External validation cohorts			
Italy 1	Thomas et al.[27]	29	24
Italy 2	Thomas et al.[27]	32	28
Japan	Courtesy of T. Yamada et al.	40	40



Microbiote: biomarqueur

- 29 species significantly enriched in CRC metagenomes (FDR < 1.10−5)
- Functional analysis of CRC metagenomes: enriched protein and mucin catabolism genes and depleted carbohydrate degradation genes

Meta-analysis firmly establishes globally generalizable, predictive taxonomic and functional microbiome CRC signatures as a basis for future diagnostics

Microbiote: biomarqueur

CANCER IMMUNOTHERAPY

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2†]

- Patients responding to anti-PD1 therapy: high incidence of *Faecalibacterium*
- Patients who did not respond to treatment: high incidence of *Bacteroidales*
- People with metastatic melanoma AND better response to treatment: high prevalence of *Bifidobacterium longum*.

The presence of these species in the tumor-bearing rat intestine showed improved treatment for anti-PD-L1

Science

REPORTS

Cite as: V. Gopalakrishnan *et al.*, *Science* 10.1126/science.aan4236 (2017).

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6‡] T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9§] E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1||] L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3¶] P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3#] J. A. Wargo.[1,3#**]

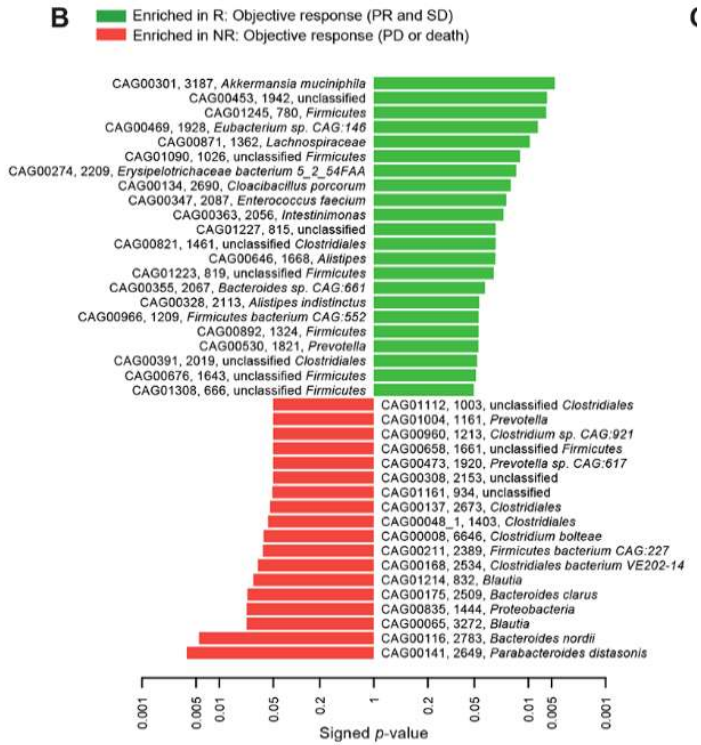
Science

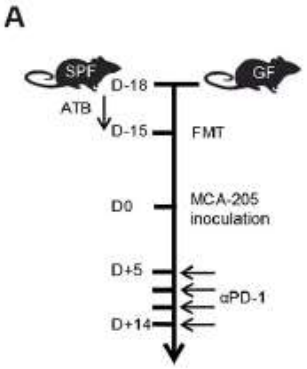
REPORTS

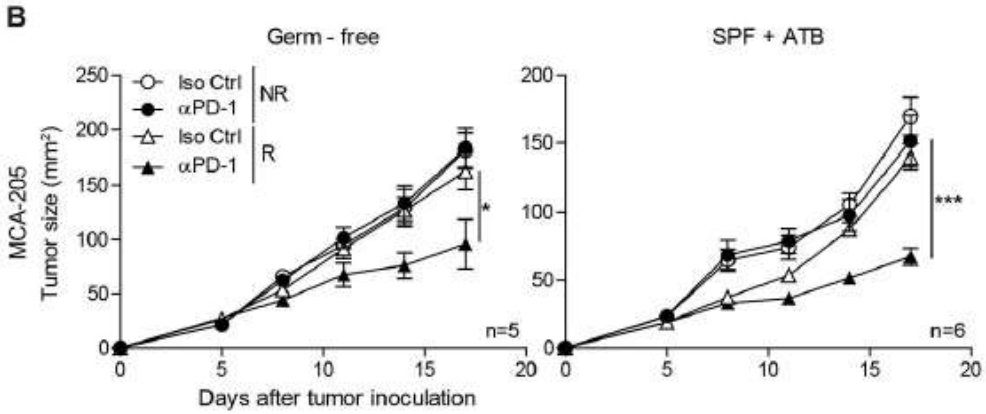
Cite as: B. Routy *et al.*, *Science* 10.1126/science.aan3706 (2017).

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou Poirier-Colame,[1,2,5] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[9,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28*] Laurence Zitvogel[1,2,3,5*]







- In patients: correlation between clinical response and relative abundance of *Akkermansia muciniphila*
- In mice: FMT from cancer patients who responded ameliorated antitumor effects
- Oral supplementation with *A. Muciniphila* post-FMT with non-responder feces restored the efficacy of PD-1 blockade

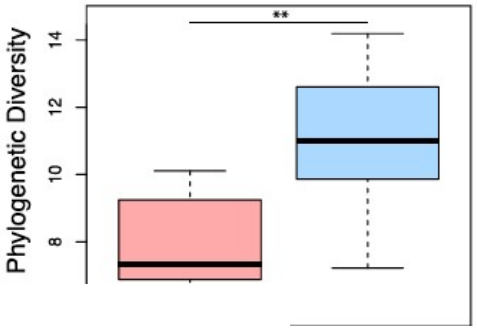
Montassier et al. Genome Medicine (2016) 8:49
DOI 10.1186/s13073-016-0301-4

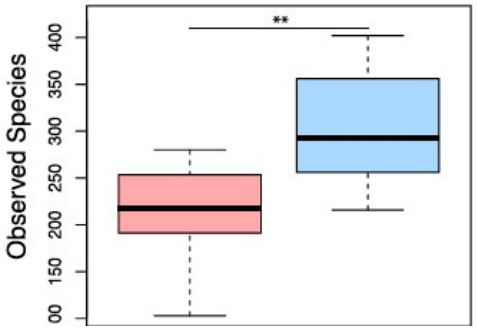
Genome Medicine

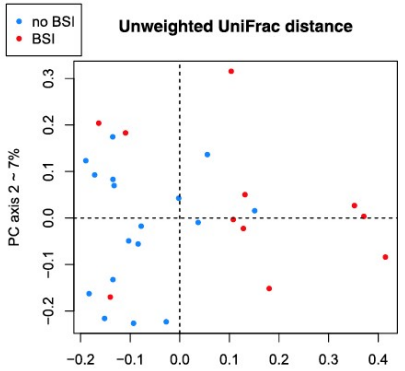
RESEARCH Open Access

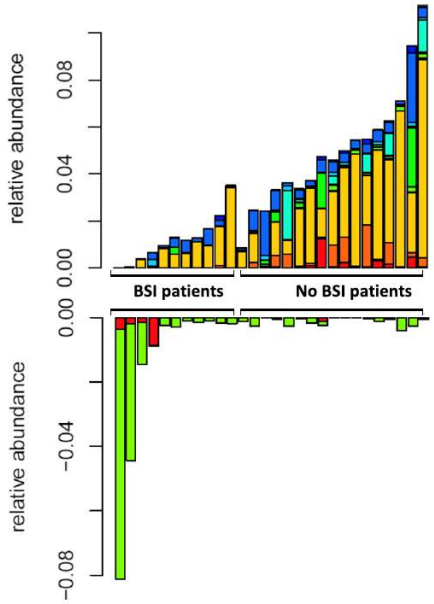
Pretreatment gut microbiome predicts chemotherapy-related bloodstream infection

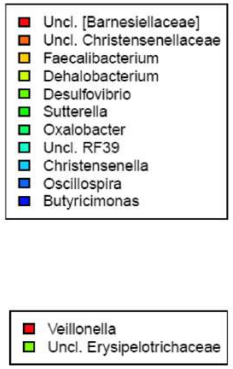
Emmanuel Montassier[1,2], Gabriel A. Al-Ghalith[2,3], Tonya Ward[4], Stephane Corvec[1,5], Thomas Gastinne[6], Gilles Potel[1], Philippe Moreau[6], Marie France de la Cochetiere[1], Eric Batard[1] and Dan Knights[2,4*]

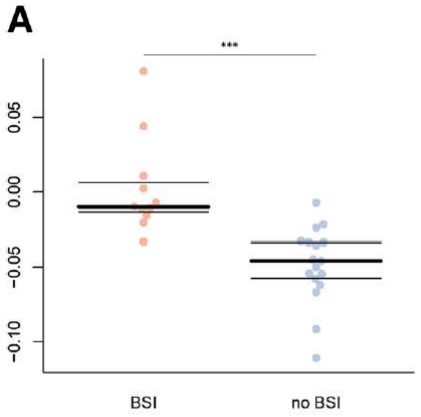


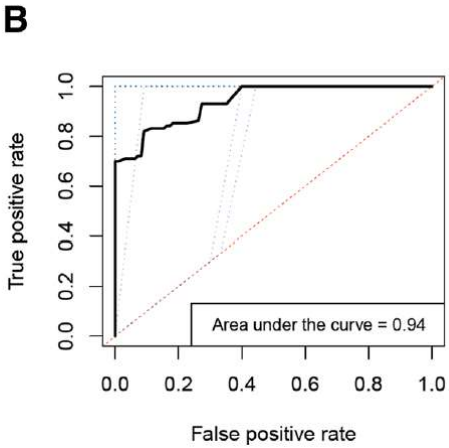












Leukemia
https://doi.org/10.1038/s41375-019-0547-0

LETTER

Infectious medicine, virology

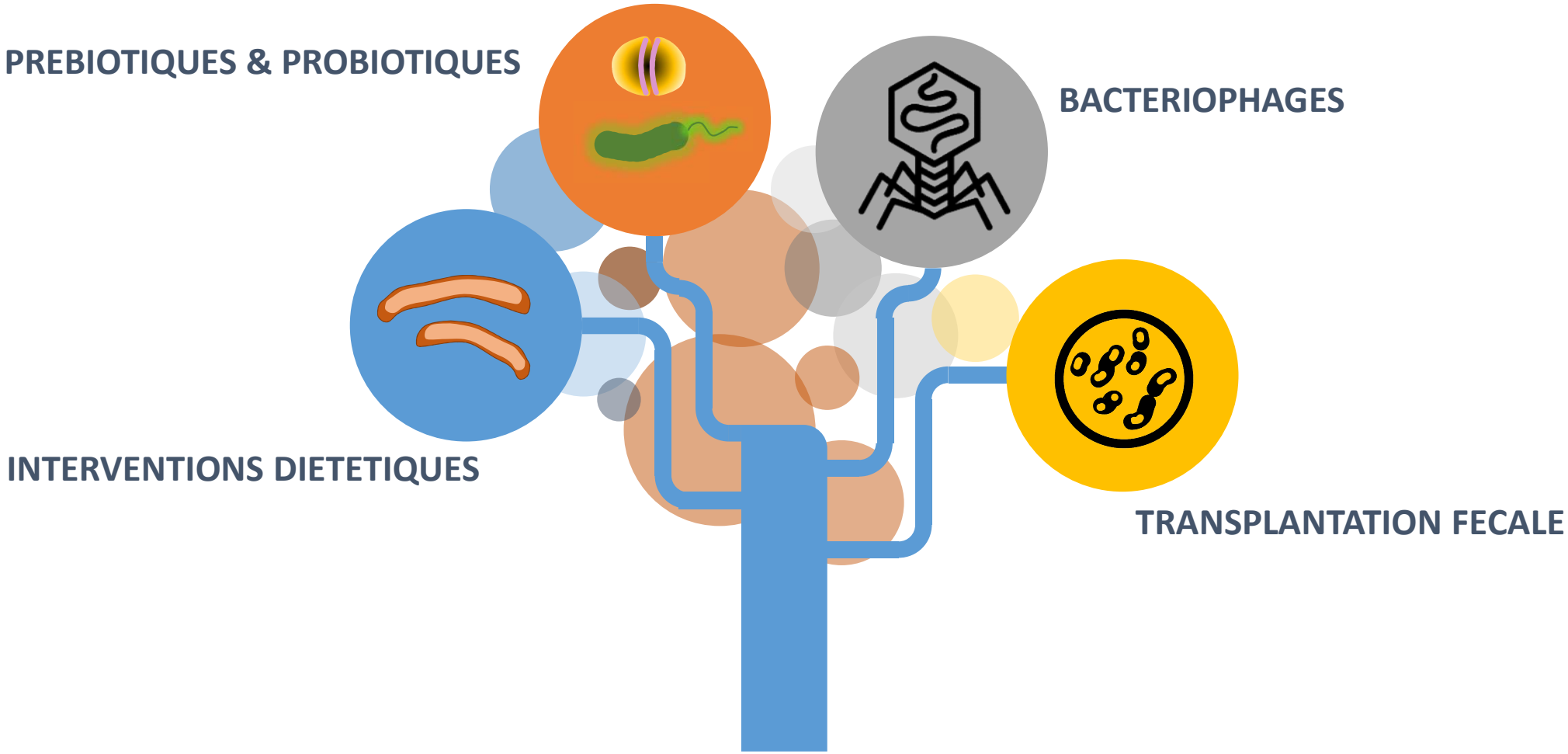
Specific gut microbiota changes heralding bloodstream infection and neutropenic fever during intensive chemotherapy

Armin Rashidi[1] · Thomas Kaiser[2,3] · Carolyn Graiziger[4] · Shernan G. Holtan[1] · Tauseef Ur Rehman[4] · Daniel J. Weisdorf[1] · Alexander Khoruts[3,4] · Christopher Staley[2,3]

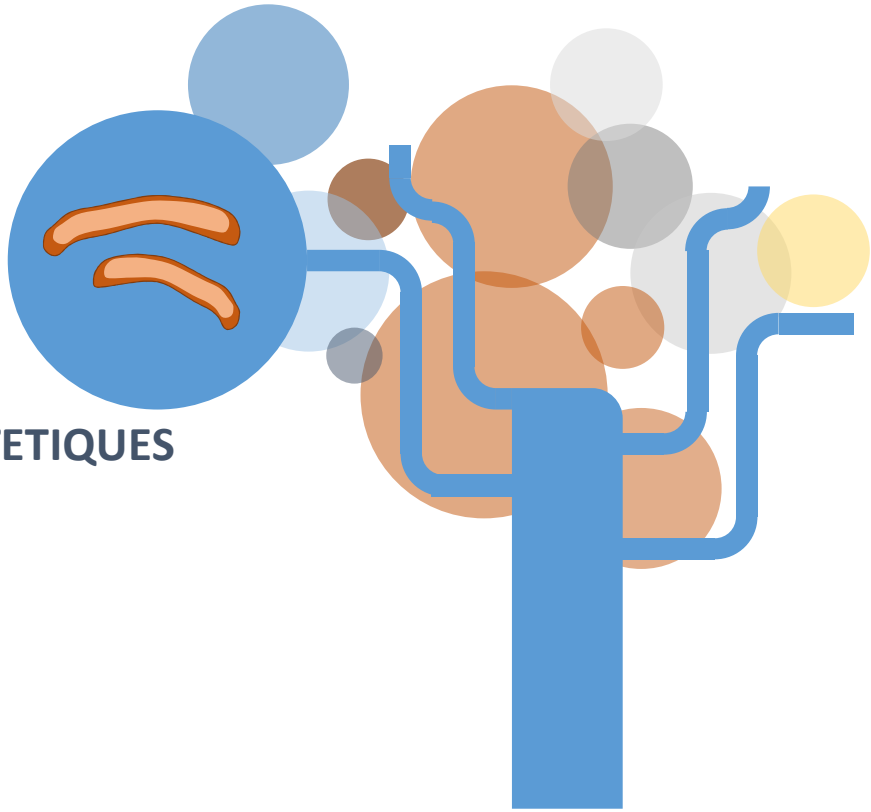
Received: 27 February 2019 / Revised: 10 June 2019 / Accepted: 26 June 2019

Model	Variables included	Variables retained	Repeatability	Regressior
7-day interval		*Lactobacillus*	100%	5.02
		Akkermansia	96%	1.78
		Week 1	99%	−1.21
		Week 3	78%	0.28
		Disease (ALL vs. AML)	97%	−0.82
5-day interval	All models:	*Lactobacillus*	100%	4.18
		Akkermansia	93%	1.64
	Predictors:	*Blautia*	93%	−1.17
	Week of chemotherapy	*Roseburia*	88%	−0.83
	Treatment phase	Week 1	100%	−1.27
	Disease	Week 3	88%	0.42
	Genera ($n = 15$)	Disease (ALL vs. AML)	98%	−0.87
	Outcome:			
	Serum flagellin			
2-day interval		*Lactobacillus*	100%	2.74
		Blautia	85%	−0.54
		Faecalibacterium	74%	−0.41
		Clostridium cluster XIVa	85%	−1.21
		Roseburia	74%	−0.31
		Week 1	100%	−1.11
		Week 3	85%	0.23
		Disease (ALL vs. AML)	74%	−0.16

Modulation du microbiote intestinal



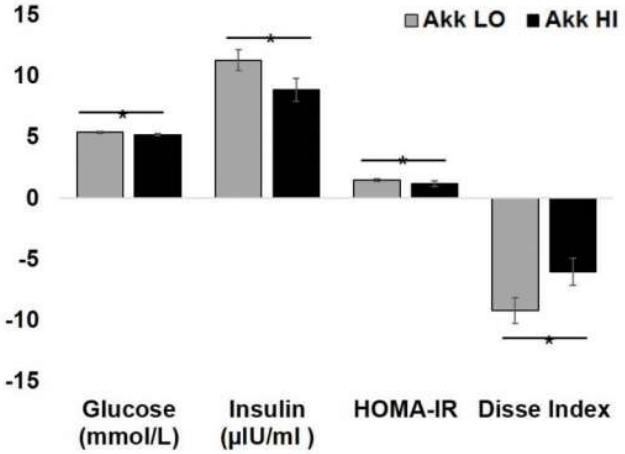
Modulation du microbiote intestinal

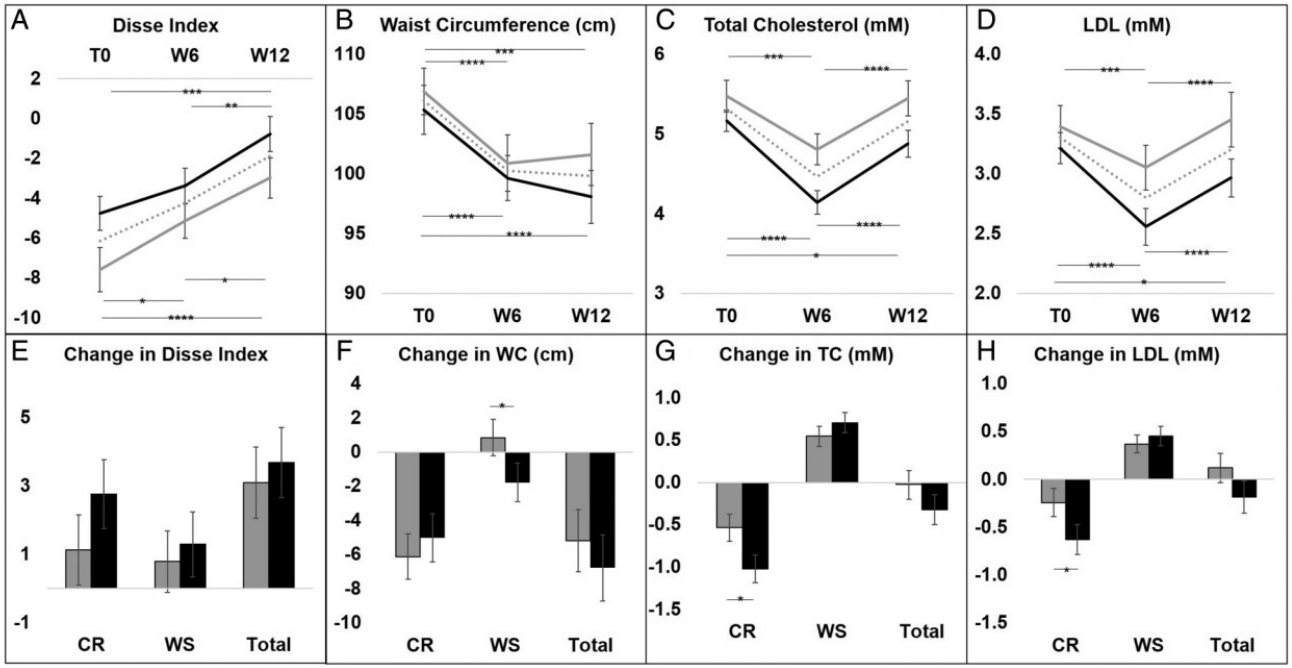


INTERVENTIONS DIETETIQUES

A. muciniphila

Gut



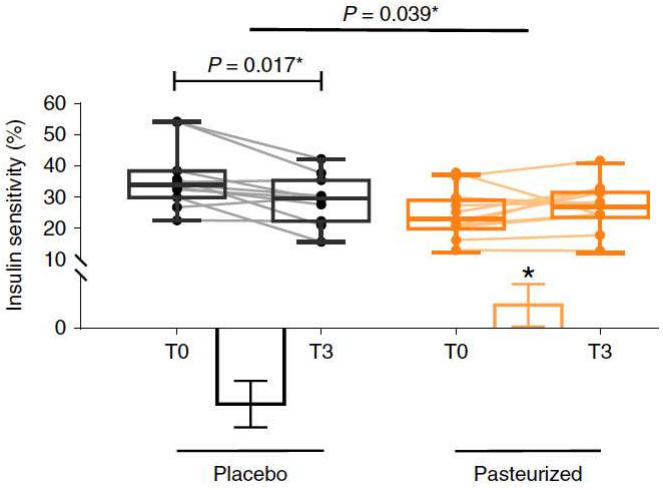


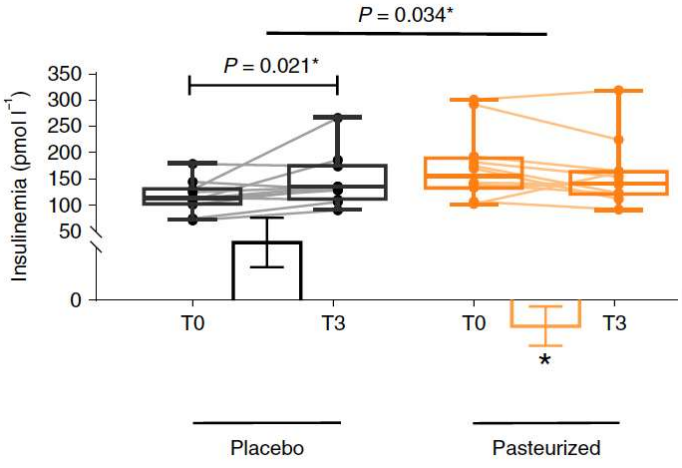
Dao et al, 2016

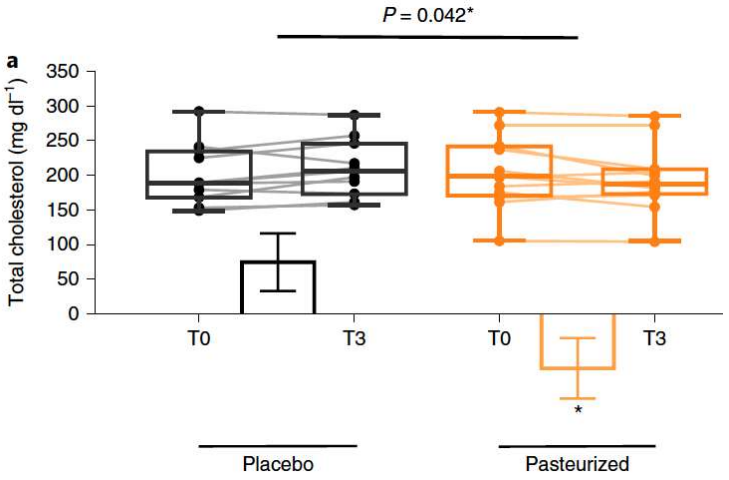
LETTERS
https://doi.org/10.1038/s41591-019-0495-2
nature medicine

Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study

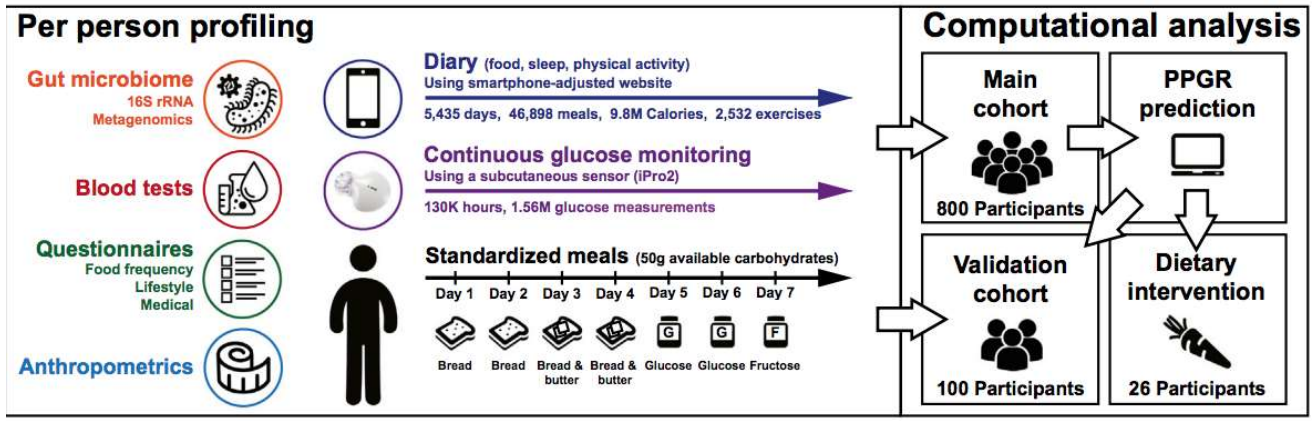
Clara Depommier[1,9], Amandine Everard[1,9], Céline Druart[1], Hubert Plovier[1], Matthias Van Hul[1], Sara Vieira-Silva[2,3], Gwen Falony[2,3], Jeroen Raes[2,3], Dominique Maiter[4,5], Nathalie M. Delzenne[6], Marie de Barsy[4,5,10], Audrey Loumaye[4,5,10], Michel P. Hermans[4,5,10], Jean-Paul Thissen[4,5,10], Willem M. de Vos[7,8,10] and Patrice D. Cani[1*]



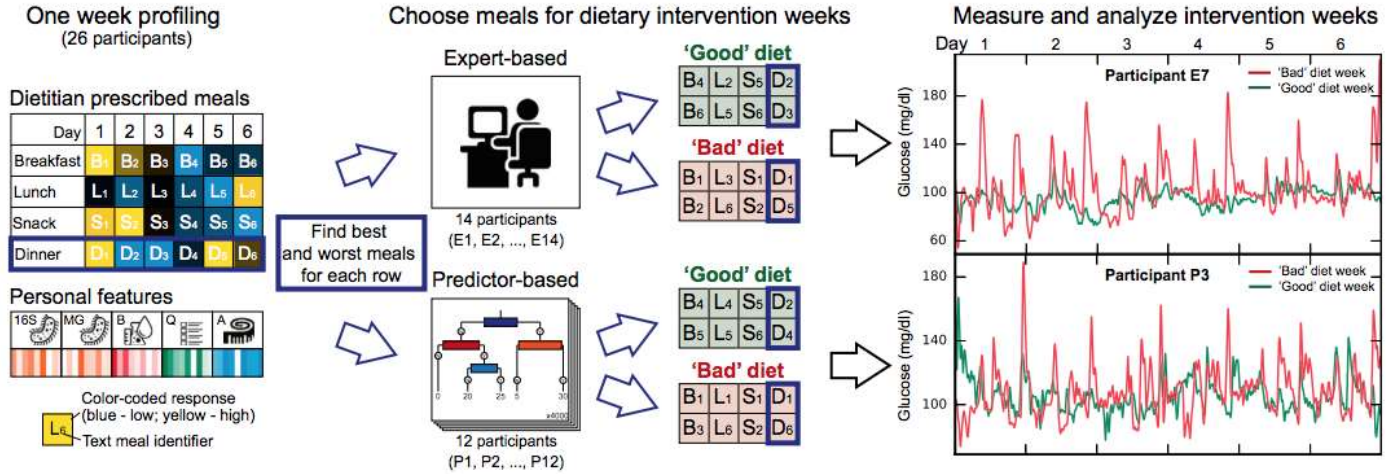




Intervention diététique personnalisée: prédire la réponse du microbiome à une intervention

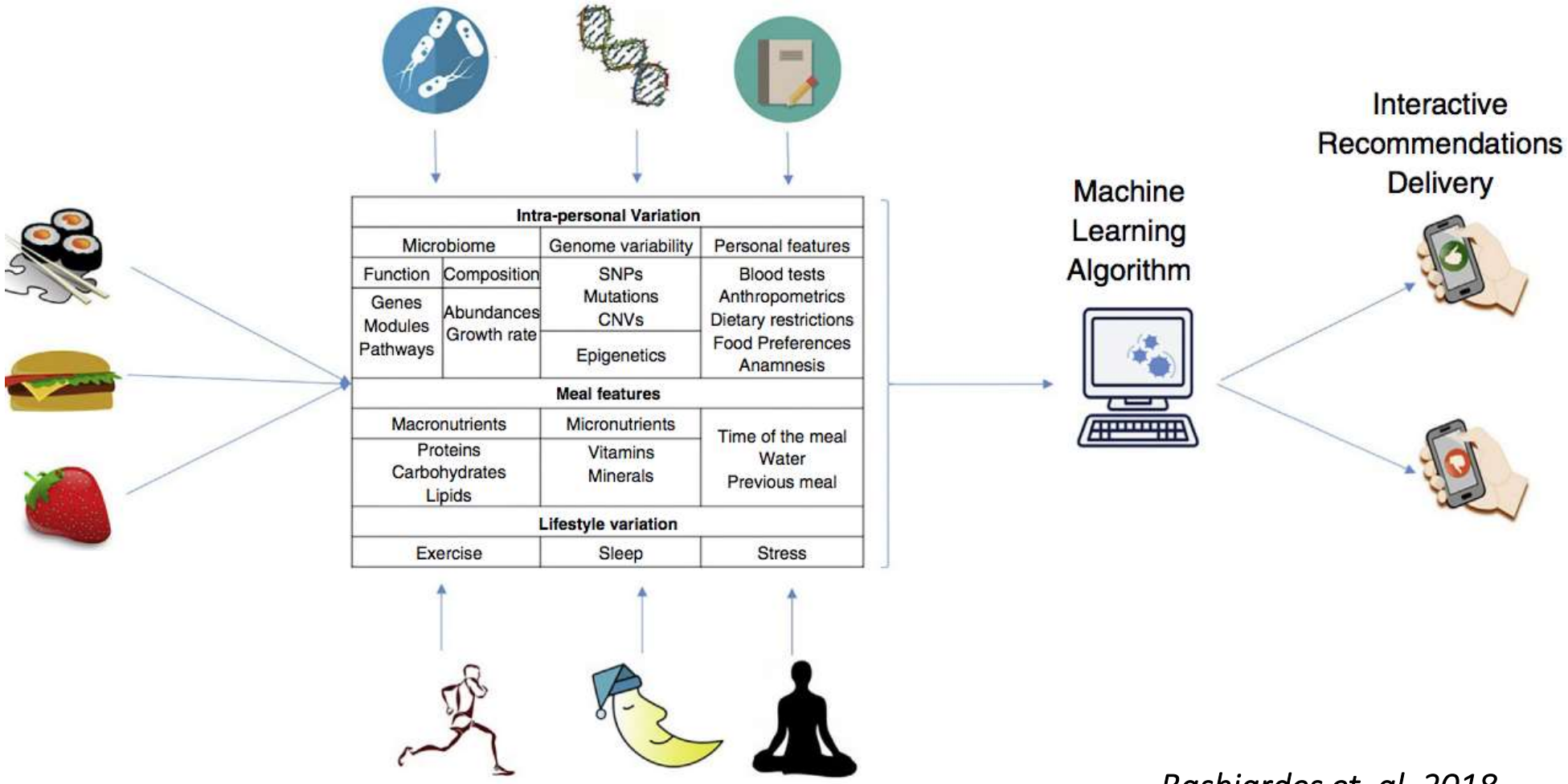


Cell



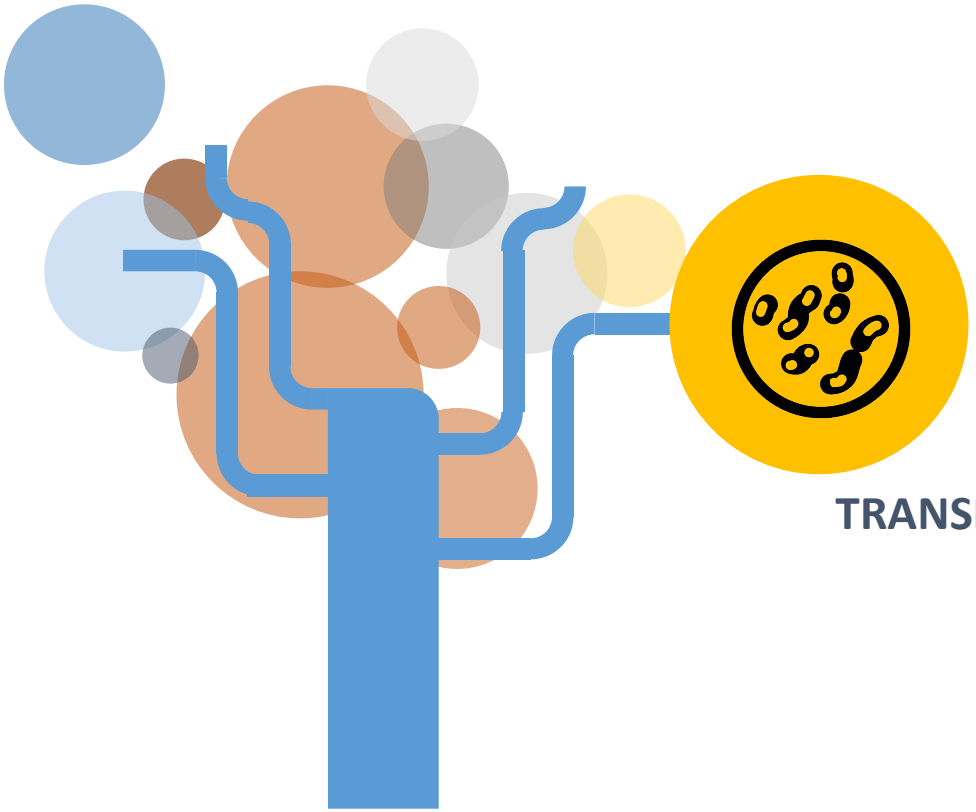
Zeevi et al, 2015

Le futur ?



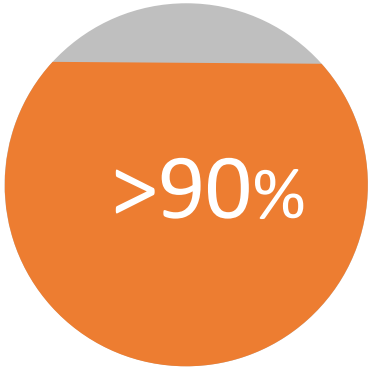
Bashiardes et al, 2018

Modulation du microbiote intestinal

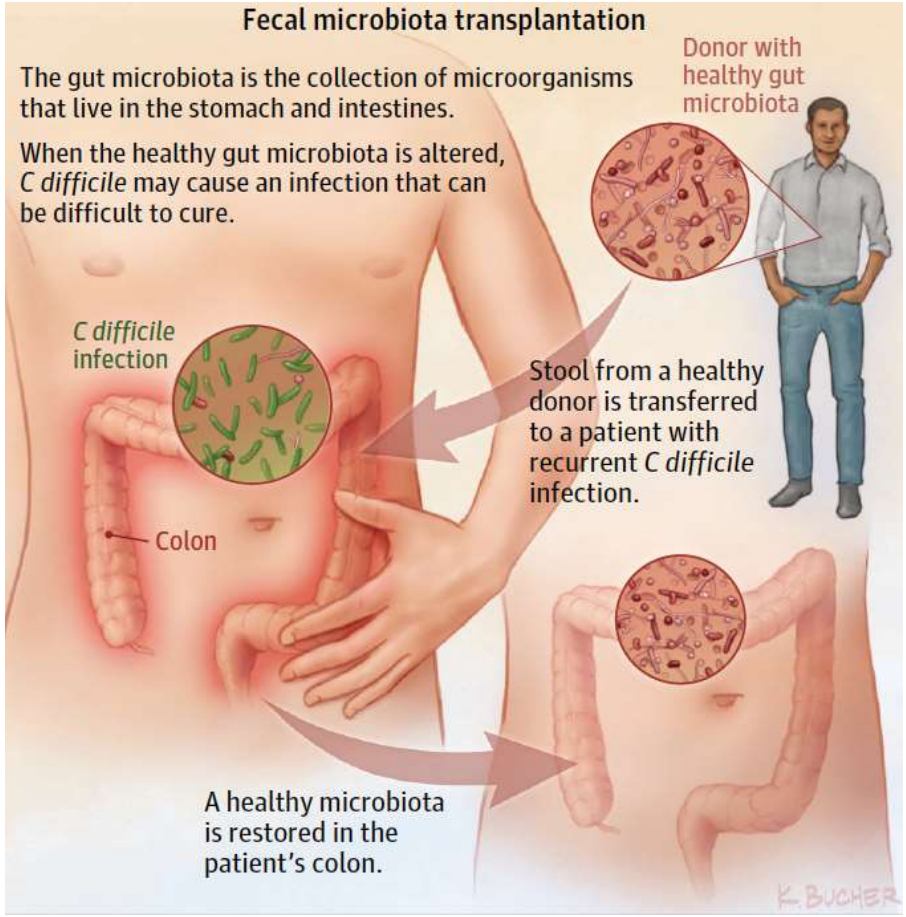


TRANSPLANTATION FECALE

Transplantation fécale



Colite à *C. difficile* réfractaire



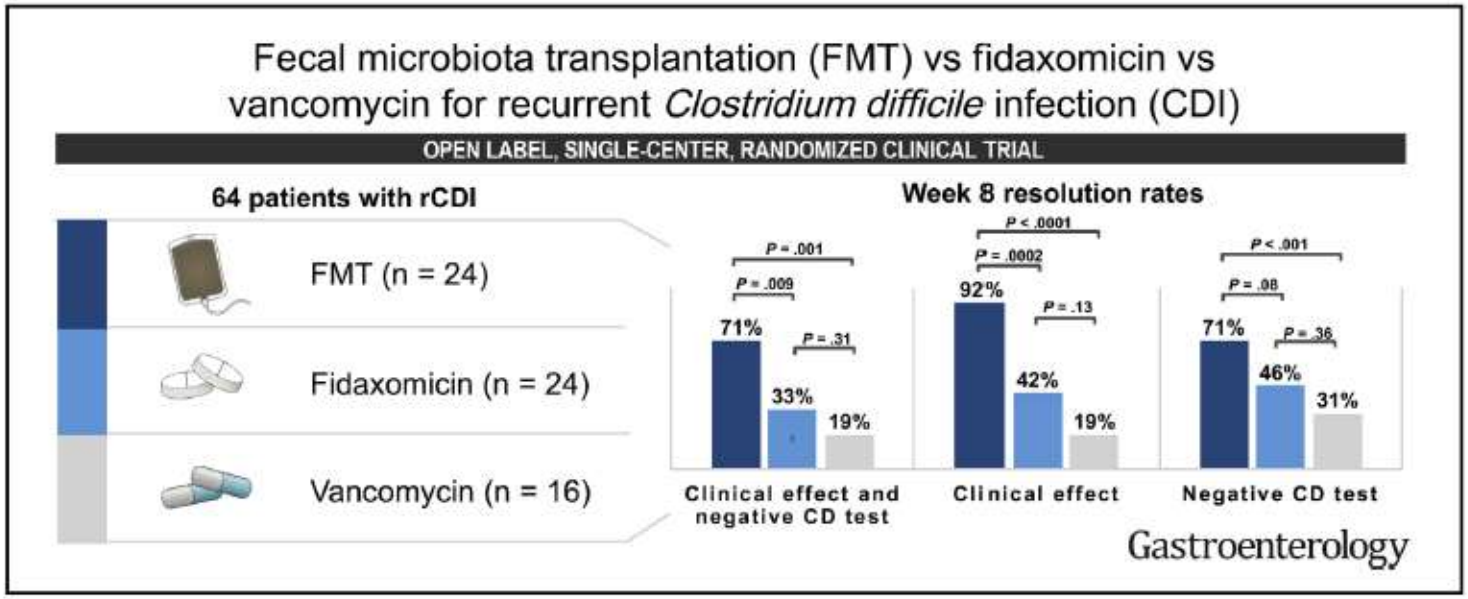
van Nood et al, 2013

Gastroenterology 2019;156:1324–1332

Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection

Christian Lodberg Hvas,[1] Simon Mark Dahl Jørgensen,[1] Søren Peter Jørgensen,[1] Merete Storgaard,[2] Lars Lemming,[3] Mette Mejlby Hansen,[1] Christian Erikstrup,[4] and Jens Frederik Dahlerup[1]

[1]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark; and [4]Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark



Gut

European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,[1] Gianluca Ianiro,[1] Herbert Tilg,[2] Mirjana Rajilić-Stojanović,[3] Patrizia Kump,[4] Reetta Satokari,[5] Harry Sokol,[6] Perttu Arkkila,[7] Cristina Pintus,[8] Ailsa Hart,[9] Jonathan Segal,[9] Marina Aloi,[10] Luca Masucci,[11] Antonio Molinaro,[12] Franco Scaldaferri,[1] Giovanni Gasbarrini,[1] Antonio Lopez-Sanroman,[13] Alexander Link,[14] Pieter de Groot,[15] Willem M de Vos,[5,16] Christoph Högenauer,[4] Peter Malfertheiner,[14] Eero Mattila,[17] Tomica Milosavljević,[18] Max Nieuwdorp,[12,15,19] Maurizio Sanguinetti,[11] Magnus Simren,[20] Antonio Gasbarrini,[1] The European FMT Working Group

FMT for refractory CDI

Statement: FMT can be considered as a treatment option for refractory CDI.

FMT for the first episode of CDI

Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI.

Other indications

The experts panel took into account other clinical indications for a possible use of FMT in the clinical practice, such as IBD, IBS, metabolic disorders, paediatrics, but for none of them emerged an evidence-based recommendation to use FMT except that in a context of research (see online supplementary 1).

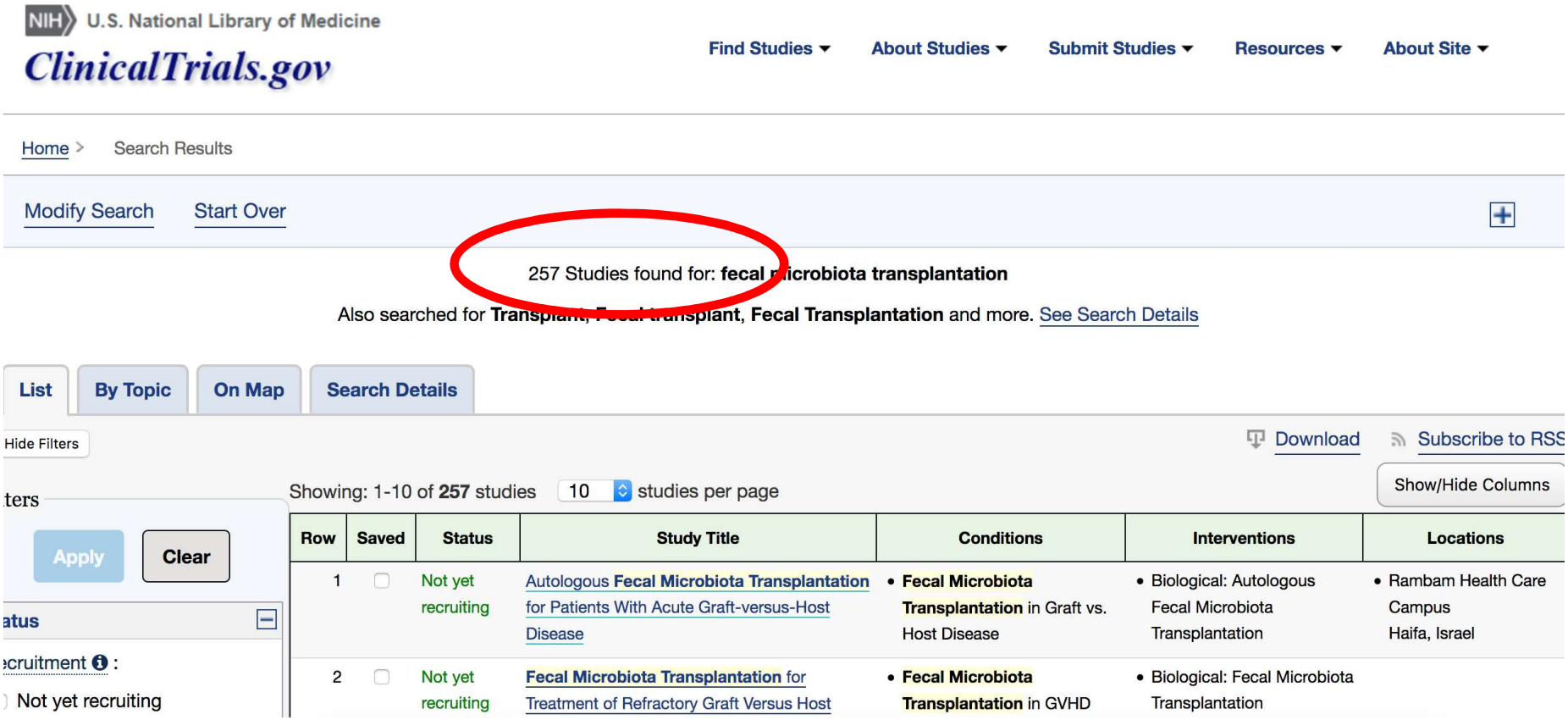
Autres indications

Table 3 Overview of the outcome of FMT studies performed in patients with various conditions

Disorder	Type of study (references)	Outcome	Comments and important unresolved questions
Recurrent CDI	RCT (30–32) Meta-analysis (3)	Highly effective, cure rate single infusion >80%	Advised in guidelines for recurrent rCDI (1, 2)
Severe CDI	Case series (34)	Effective, probably safe	May be lifesaving
UC	RCT (47–50) Meta-analysis (51, 52)	Pooled response rate of 29% for achieving endoscopic remission	Optimization of protocol required: Is rational selection of donors required? Is it possible to select patients that are more likely to respond? Should FMT be offerd as induction or maintenance treatment?
CD	Cohort studies Meta-analysis (52)	Pooled clinical response rate of 53%. No endoscopic remission achieved	RCT needed Rational donor selection
IBS	RCT (59)	Improvement of symptoms in 65% of patients after FMT versus 43% in controls. No sustained effect after 1 year	Larger RCTs needed Which patients may benefit? Is repeated FMT required? How should patients be pre-treated before FMT?
HE	RCT (65)	Safe, no SAEs related to FMT, no new episodes of HE 150 days post-FMT	Confirmative study needed Rational donor selection
MDRO	Cohort studies (72–75)	Suggestive of some effectivity eradicating *VRE* and ESBL bacteria	Rational donor selection needed RCT needed
Metabolic syndrome/hepatic steatosis	RCT (78, 79)	No effect on clinical endpoints Transient increased insulin sensitivity	Strictly experimental
Autism	Open-label trial (84)	Effect noted on psychiatric and GI symptoms	Further studies are needed
GVHD	Case series (68, 69)	Steroid refractory GVHD: decreased symptoms	Further studies are needed

Keller et al, 2018

Investigations en cours



Investigations en cours

Show/Hide Columns

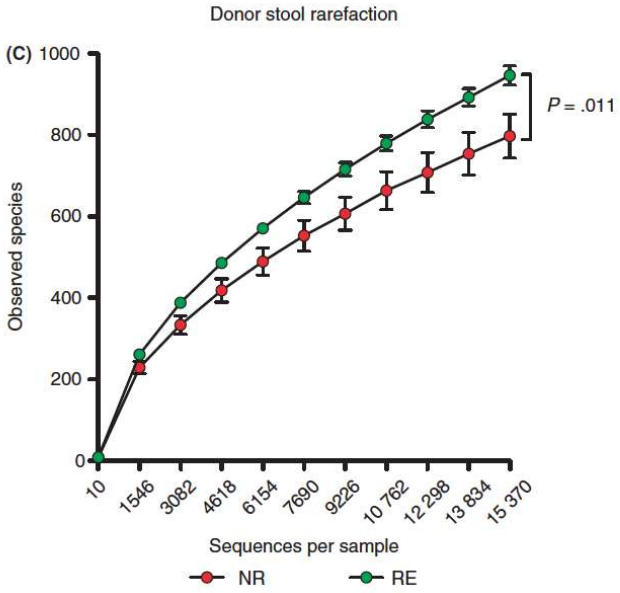
Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Evaluating the Safety and Efficacy of Oral Encapsulated **Fecal Microbiota Transplant** in Peanut Allergic Patients	• Peanut **Allergy**	• Biological: Fecal Microbiota Capsule	• Boston Children's Hospital Boston, Massachusetts, United States

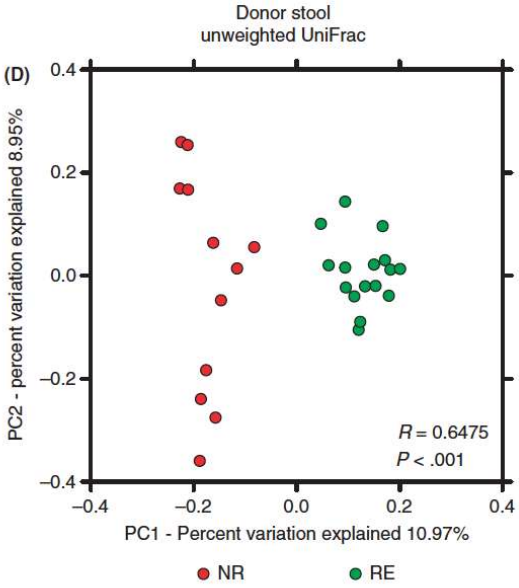
Quelle est la différence entre un bon donneur et un mauvais donneur?

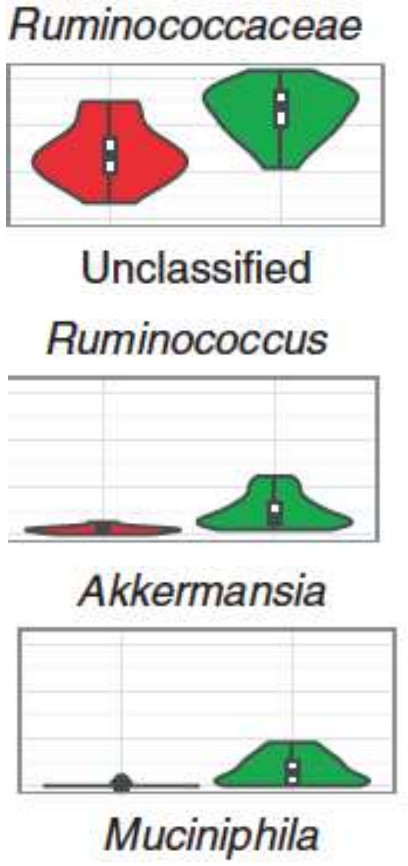
WILEY AP&T Alimentary Pharmacology & Therapeutics

The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis

P. Kump[1,2] | P. Wurm[2,3] | H. P. Gröchenig[4] | H. Wenzl[1] | W. Petritsch[1] | B. Halwachs[2,3,5] | M. Wagner[1] | V. Stadlbauer[1] | A. Eherer[1] | K. M. Hoffmann[6] | A. Deutschmann[6] | G. Reicht[7] | L. Reiter[7] | P. Slawitsch[7] | G. Gorkiewicz[2,3,5] | C. Högenauer[1,2,5]







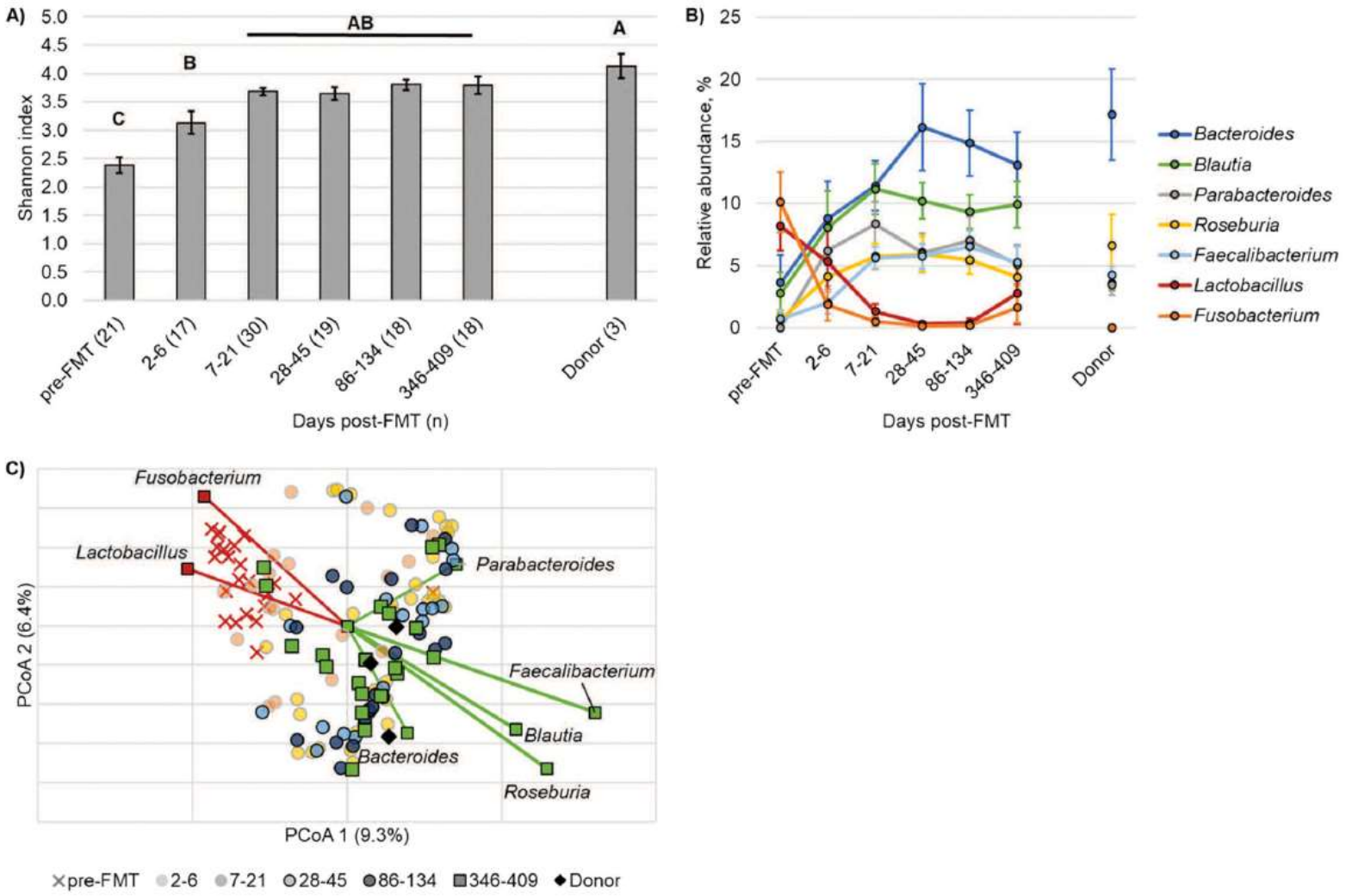
Quelle est la différence entre un bon receveur et un mauvais receveur?

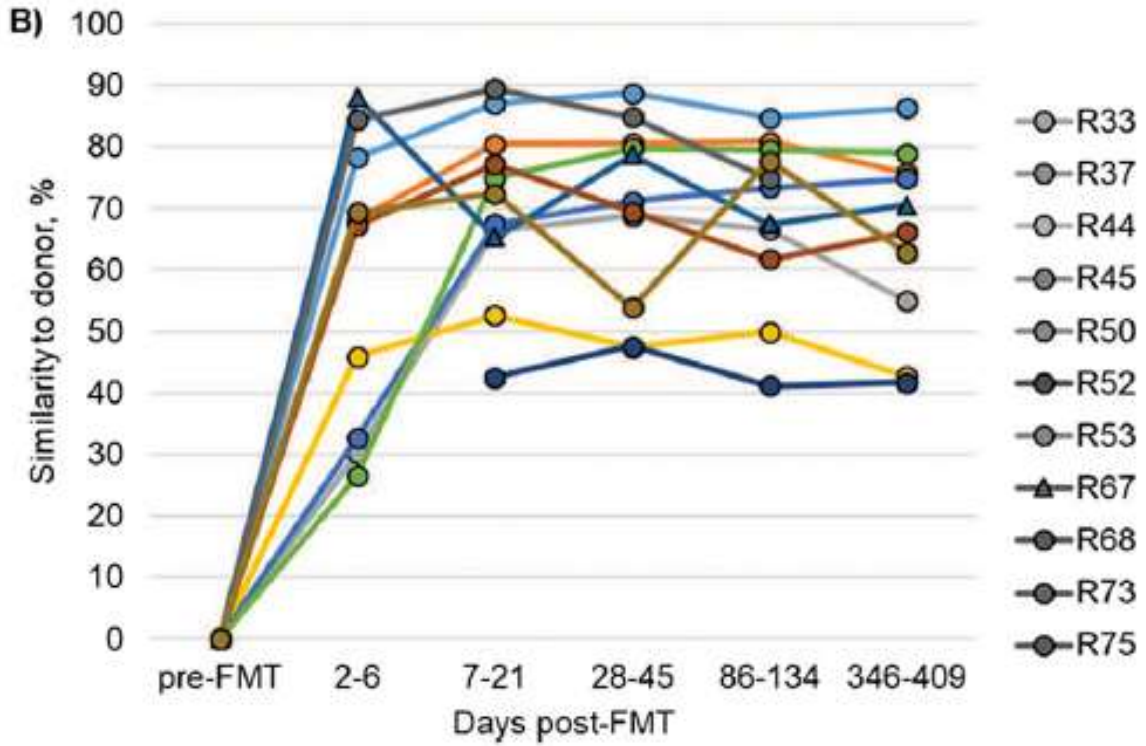
AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

RESEARCH ARTICLE
Therapeutics and Prevention

Durable Long-Term Bacterial Engraftment following Encapsulated Fecal Microbiota Transplantation To Treat *Clostridium difficile* Infection

Christopher Staley,[a,b] Thomas Kaiser,[a,b] Byron P. Vaughn,[c] Carolyn Graiziger,[c] Matthew J. Hamilton,[b] Amanda J. Kabage,[c] Alexander Khoruts,[b,c] Michael J. Sadowsky[b,d,e]


A)
Shannon index
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
AB
A
B
C
pre-FMT (21)
2-6 (17)
7-21 (30)
28-45 (19)
86-134 (18)
346-409 (18)
Donor (3)
Days post-FMT (n)
B)
Relative abundance, %
25
20
15
10
5
0
pre-FMT
2-6
7-21
28-45
86-134
346-409
Donor
Days post-FMT
Bacteroides
Blautia
Parabacteroides
Roseburia
Faecalibacterium
Lactobacillus
Fusobacterium
C)
Fusobacterium
Lactobacillus
Parabacteroides
Faecalibacterium
Blautia
Bacteroides
Roseburia
PCoA 2 (6.4%)
PCoA 1 (9.3%)
pre-FMT
2-6
7-21
28-45
86-134
346-409
Donor



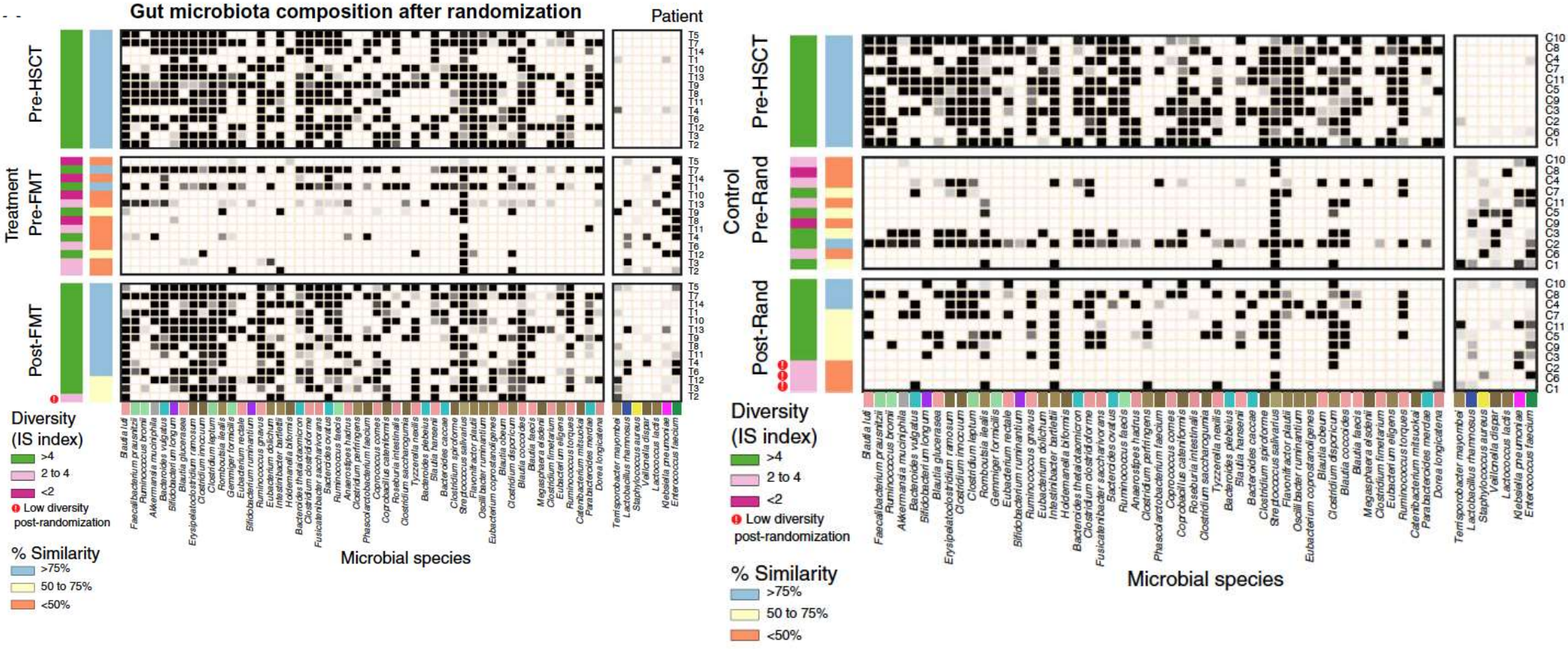
- *Bacteroides*, *Parabacteroides*, and *Faecalibacterium* were significantly and positively correlated with donor similarity
- All patients recovered clinically but showed differing patterns in long-term microbial community similarity to the donor that were associated with members of the bacterial group *Bacteroidetes*, previously shown to be prominent contributors to rCDI resistance

SCIENCE TRANSLATIONAL MEDICINE | REPORT

GUT MICROBIOTA

Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant

Ying Taur[1], Katharine Coyte[1,2,3], Jonas Schluter[1], Elizabeth Robilotti[1], Cesar Figueroa[1], Mergim Gjonbalaj[1], Eric R. Littmann[1], Lilan Ling[1], Liza Miller[1,4], Yangtsho Gyaltshen[1,5], Emily Fontana[1], Sejal Morjaria[1], Boglarka Gyurkocza[1], Miguel-Angel Perales[1], Hugo Castro-Malaspina[1], Roni Tamari[1], Doris Ponce[1], Guenther Koehne[1], Juliet Barker[1], Ann Jakubowski[1], Esperanza Papadopoulos[1], Parastoo Dahi[1], Craig Sauter[1], Brian Shaffer[1], James W. Young[1,6,7], Jonathan Peled[1], Richard C. Meagher[1], Robert R. Jenq[8], Marcel R. M. van den Brink[1,6], Sergio A. Giralt[1], Eric G. Pamer[1]*, Joao B. Xavier[1]*


Gut microbiota composition after randomization
Patient
Pre-HSCT
Treatment
Pre-FMT
Post-FMT
Control
Pre-Rand
Post-Rand
Diversity
(IS index)
>4
2 to 4
<2
Low diversity
post-randomization
% Similarity
>75%
50 to 75%
<50%
Microbial species

Quels risques de la FMT?

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

November 21, 2019
N Engl J Med 2019; 381:2043-2050
DOI: 10.1056/NEJMoa1910437

Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

Quels risques de la FMT?

Effect	Number of patients	Overall % (*N*=1190)
Abdominal distension/bloating/cramping	28	2.35%
Flatulence	25	2.1%
Diarrhoea	23	1.93%
'Irregularity of bowel movements'	14	1.18%
IBS symptoms	13	1.09%
Constipation	13	1.09%
Abdominal pain/tenderness	11	0.92%
Fever	11	0.92%
Nausea	7	0.59%
IBD flare/deterioration	5	0.42%
Gram-negative bacteraemia	4	0.34%
Perforation/tear	3	0.25%
Belching	3	0.25%
Attributable death[a]	3	0.25%
Blood in stools	2	0.17%

Minor	
	Abdominal discomfort
	Bloating
	Flatulence
	Diarrhea/Constipation
	Borborygmus
	Nausea/Vomiting (particularly with oral FMT route)
	Transient fever
Serious	
	Complications of endoscopy (perforation, bleeding)
	Adverse effects related to sedation (aspiration)
	Transmission of enteric pathogens
	Peritonitis in a patient undergoing peritoneal dialysis
	Pneumonia
	IBD flares
	Infection and/or sepsis (infection may be a long-term sequelae)
	Post-infectious irritable bowel syndrome
Potential	
	Transmission of unrecognized infectious agents that cause illness years later (e.g., hepatitis C, HIV)
	Induction of chronic diseases based on alterations in the gut microbiota (e.g., obesity, diabetes, atherosclerosis, IBD, colon cancer, nonalcoholic fatty liver disease, IBS, asthma, autism)

Abbreviations: FMT: fecal material transplantation, HIV: human immunodeficiency virus, IBD: Inflammatory bowel disease.

- American Gastroenterological Association (NIH funded)
  - Fecal Microbiota Transplantation National Registry
  - Pool and track 4,000 fecal transplant patients over 10 years
  - Risks and long-term benefits of fecal transplants.

Wang et al, 2018

LETTER

https://doi.org/10.1038/s41586-019-1560-1

Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

Yan Shao[1], Samuel C. Forster[1,2,3], Evdokia Tsaliki[4], Kevin Vervier[1], Angela Strang[4], Nandi Simpson[4], Nitin Kumar[1], Mark D. Stares[1], Alison Rodger[4], Peter Brocklehurst[5], Nigel Field[4]* & Trevor D. Lawley[1]*

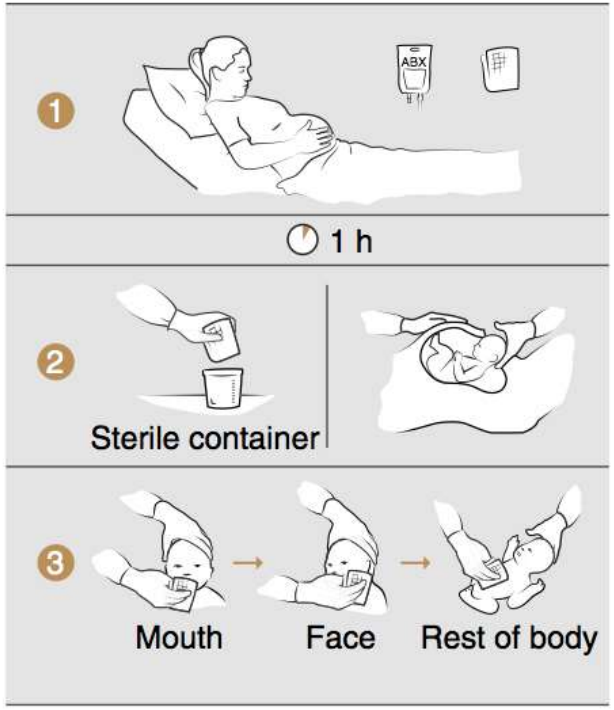
During neonatal period and infancy:

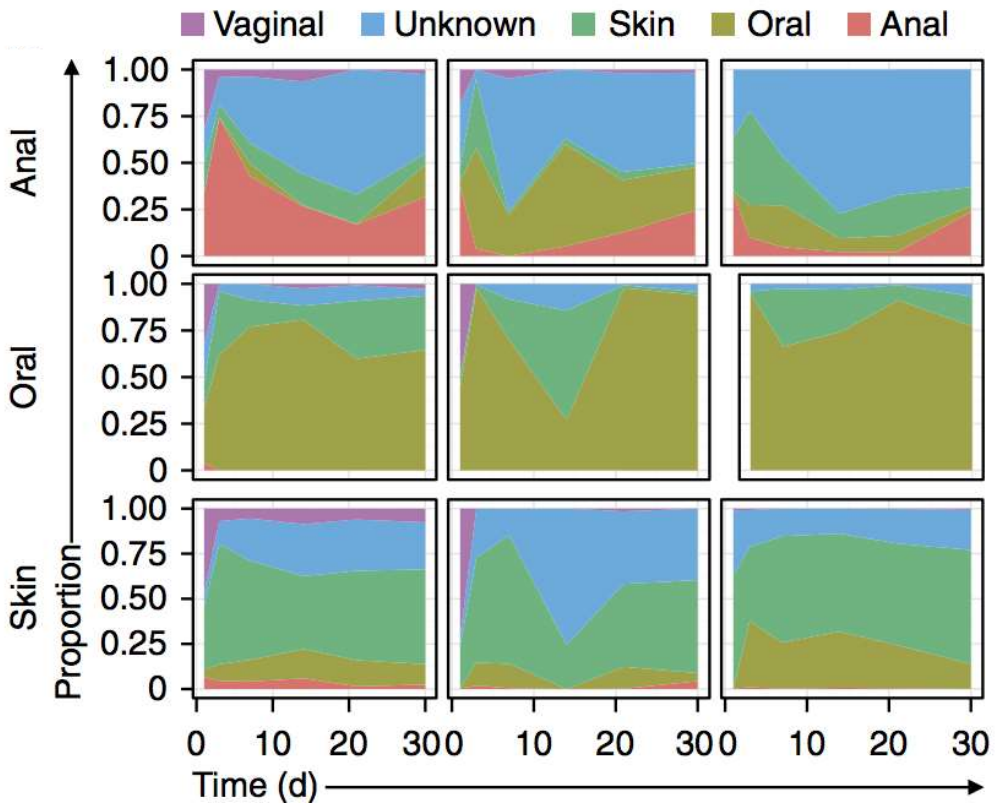
- disrupted transmission of maternal *Bacteroides* strains
- high-level colonization by opportunistic pathogens associated with the hospital environment (including *Enterococcus*, *Enterobacter* and *Klebsiella* species)

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G Dominguez-Bello[1,2], Kassandra M De Jesus-Laboy[2], Nan Shen[3], Laura M Cox[1], Amnon Amir[4], Antonio Gonzalez[4], Nicholas A Bokulich[1], Se Jin Song[4,5], Marina Hoashi[1,6], Juana I Rivera-Vinas[7], Keimari Mendez[7], Rob Knight[4,8] & Jose C Clemente[3,9]

nature medicine





NEWS · 16 AUGUST 2019

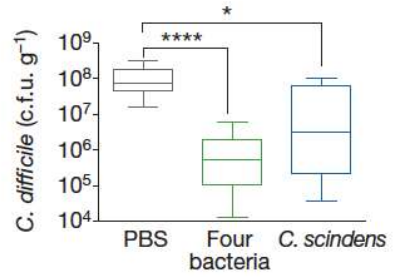
Do C-section babies need mum's microbes? Trials tackle controversial idea

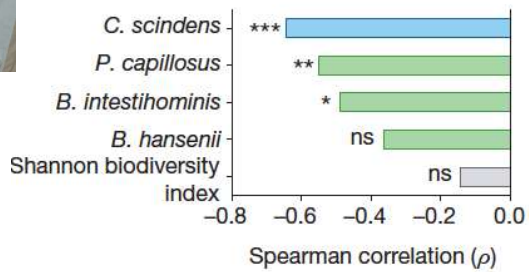
Swabbing infants with mothers' vaginal bacteria could affect the children's health, but critics warn of sparse data and high risk.

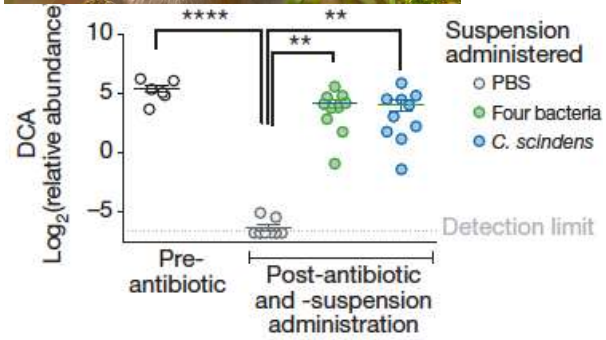
- Each team plans to monitor its study participants over several years in the hope of learning more about how the collection of microbes in their bodies might influence weight, allergy risk and other factors.
- Adam Ratner, a microbiologist at New York University: *« In the worst-case scenario, you've taken a kid with low risk of infection and you've rubbed herpes all over their face »*

Le futur de la FMT

Replacement of rather undefined donor stool samples with formulated, recipient-tailored mixes of defined microbial strains



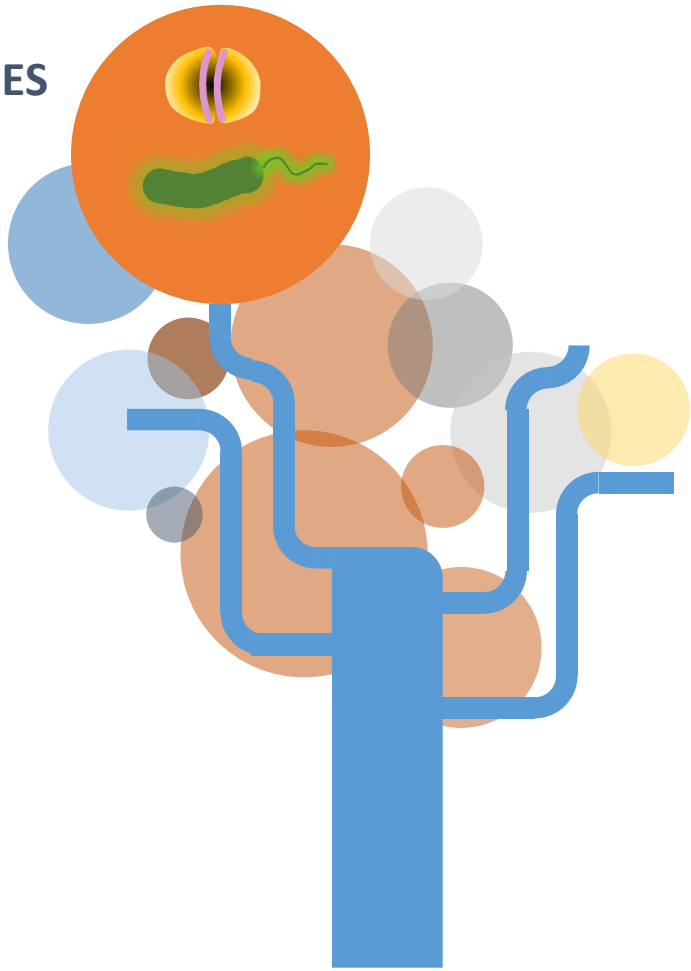




Keith et al, 2018

Modulation du microbiote intestinal

PREBIOTIQUES & PROBIOTIQUES



Définitions

- Probiotiques: microorganismes vivants qui, administrés en quantité adéquate, confère un effet bénéfique sur la santé de l'hôte
- Prébiotiques: substrats utilisés de façon sélective par les microorganismes de l'hôte pour conférer un effet bénéfique sur la santé

Hill et al, 2014; Wang et al, 2018

Kristensen *et al. Genome Medicine* (2016) 8:52
DOI 10.1186/s13073-016-0300-5

Genome Medicine

RESEARCH Open Access

Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials

Nadja B. Kristensen*, Thomas Bryrup, Kristine H. Allin, Trine Nielsen, Tue H. Hansen and Oluf Pedersen

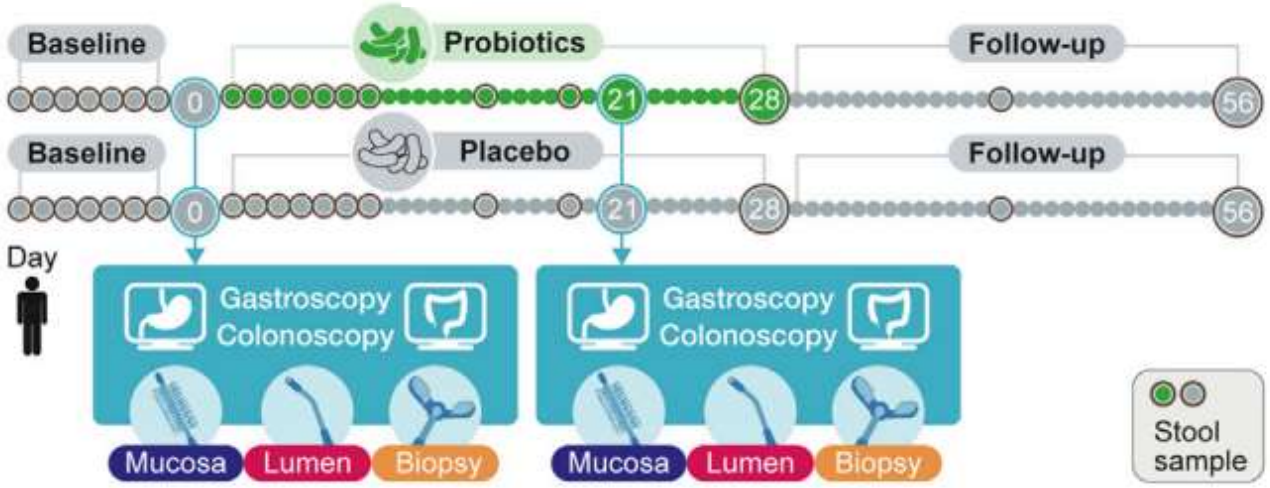
- Des données pré-cliniques prometteuses mais en clinique:
  - Pas d'effet sur la composition du microbiote
  - Pas d'implantation persistante: résistance à la colonisation par pathogènes … et probiotiques

Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

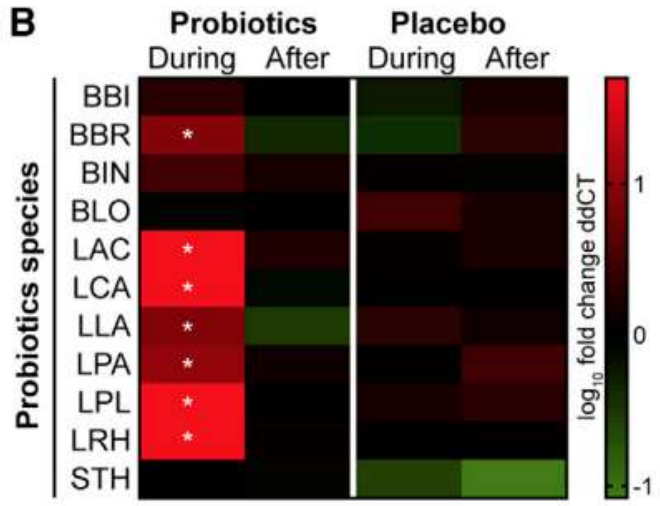
Cell

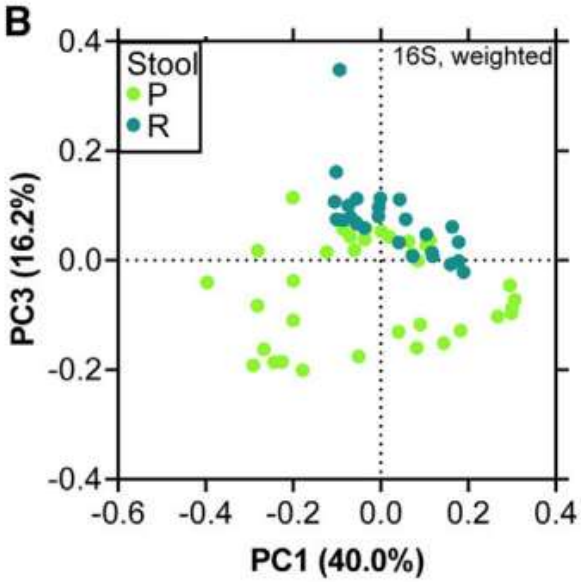
Niv Zmora,[1,2,11] Gili Zilberman-Schapira,[1,11] Jotham Suez,[1,11] Uria Mor,[1,11] Mally Dori-Bachash,[1] Stavros Bashiardes,[1] Eran Kotler,[3,4] Maya Zur,[1] Dana Regev-Lehavi,[1] Rotem Ben-Zeev Brik,[1] Sara Federici,[1] Yotam Cohen,[1] Raquel Linevsky,[1] Daphna Rothschild,[3,4] Andreas E. Moor,[3] Shani Ben-Moshe,[3] Alon Harmelin,[5] Shalev Itzkovitz,[3] Nitsan Maharshak,[6,7,8] Oren Shibolet,[6,7,8] Hagit Shapiro,[1] Meirav Pevsner-Fischer,[1] Itai Sharon,[9,10] Zamir Halpern,[6,7,8,12,*] Eran Segal,[3,4,12,*] and Eran Elinav[1,12,13,*]

- 15 healthy volunteers received either an identical 11-strain probiotics preparation or a cellulose placebo bi-daily for a 4-week period



- The fed probiotic bacteria were detected in stool samples of all participants as long as they were consuming the product, but were found in the colonic mucosa in only some participants.
- This transient engraftment was dependent on the microbiome composition of the participants, and transfer of human microbiota into germ-free mice replicated the permissive versus resistant phenotypes in the recipient animals.

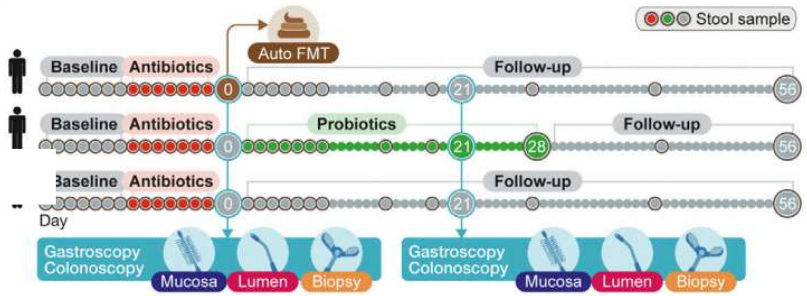


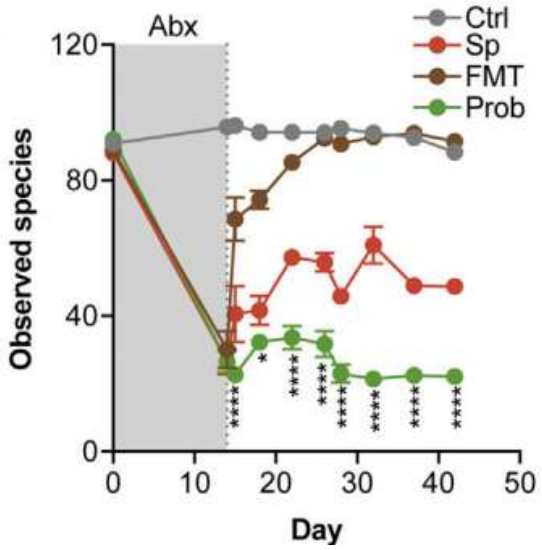


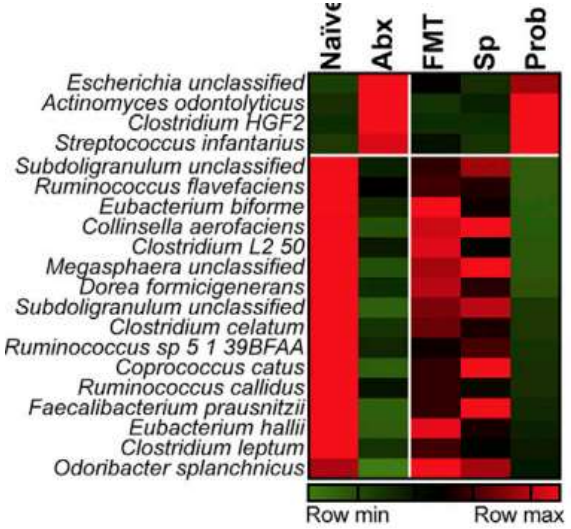
Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Cell

Jotham Suez,[1,11] Niv Zmora,[1,2,11] Gili Zilberman-Schapira,[1,11] Uria Mor,[1,11] Mally Dori-Bachash,[1] Stavros Bashiardes,[1] Maya Zur,[1] Dana Regev-Lehavi,[1] Rotem Ben-Zeev Brik,[1] Sara Federici,[1] Max Horn,[1] Yotam Cohen,[1] Andreas E. Moor,[3] David Zeevi,[3,4] Tal Korem,[3,4] Eran Kotler,[3,4] Alon Harmelin,[5] Shalev Itzkovitz,[3] Nitsan Maharshak,[6,7,8] Oren Shibolet,[6,7,8] Meirav Pevsner-Fischer,[1] Hagit Shapiro,[1] Itai Sharon,[9,10] Zamir Halpern,[6,7,8,12,*] Eran Segal,[3,4,13,*] and Eran Elinav[1,12,13,*]



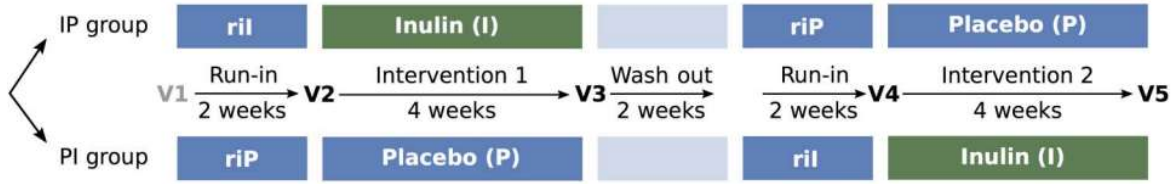


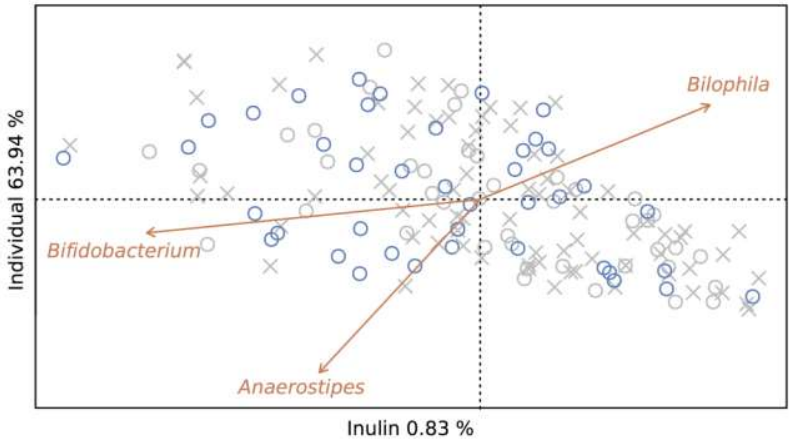


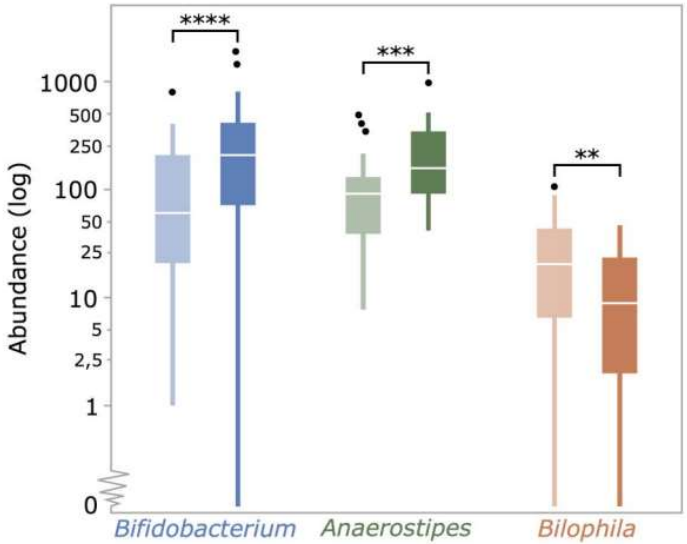
Gut

Prebiotic inulin-type fructans induce specific changes in the human gut microbiota

Doris Vandeputte,[1,2,3] Gwen Falony,[1,2] Sara Vieira-Silva,[1,2] Jun Wang,[1,2] Manuela Sailer,[4] Stephan Theis,[4] Kristin Verbeke,[5] Jeroen Raes[1,2,3]

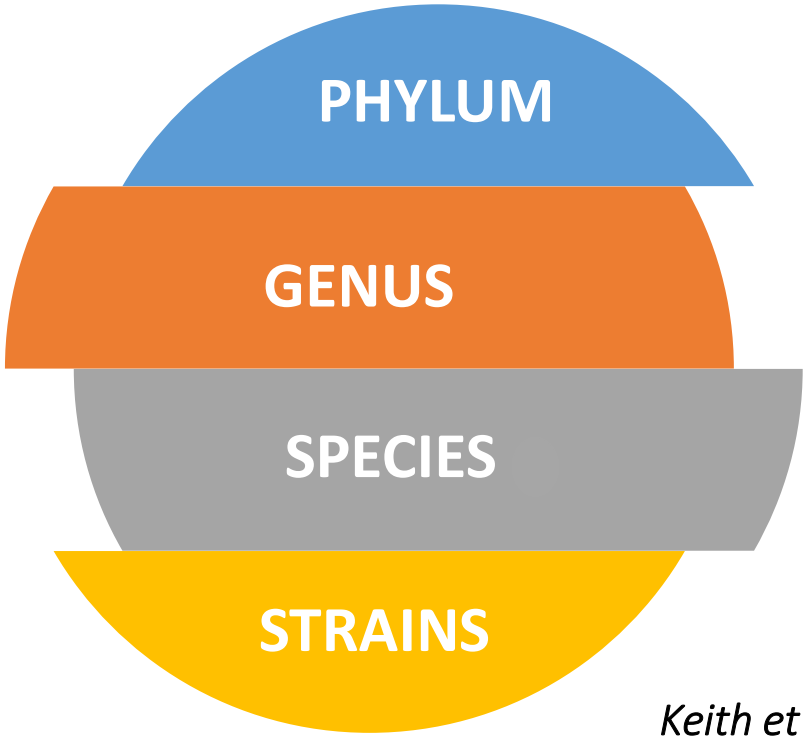




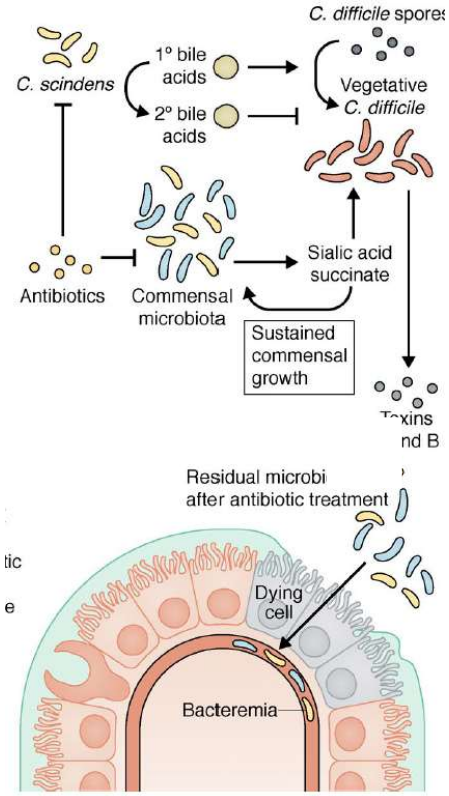


Next-generation probiotics

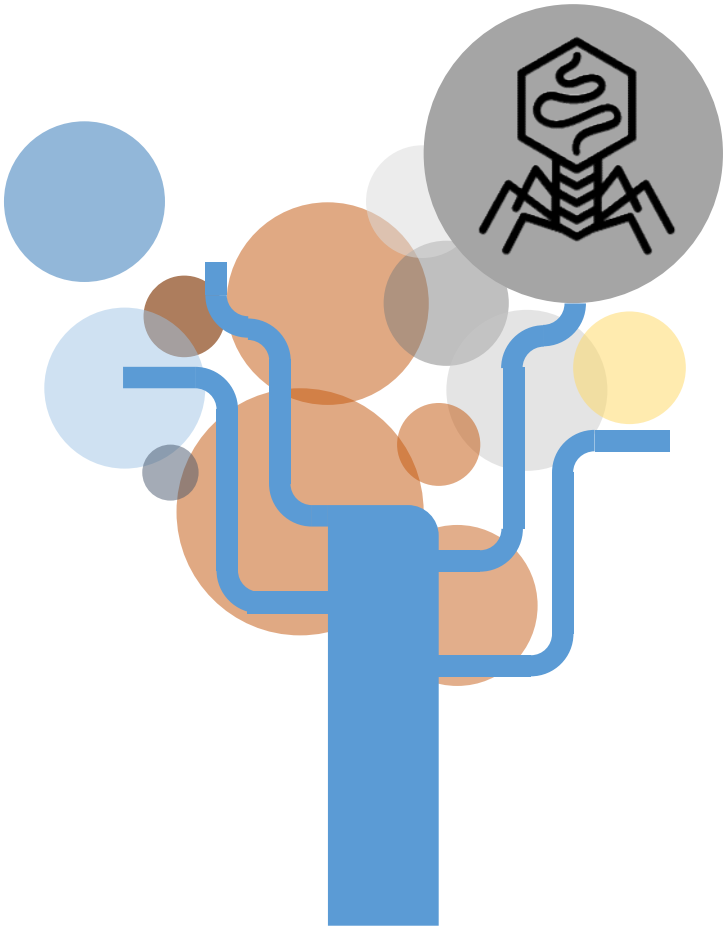
- Supplémentation avec des fonctions bénéfiques pour l'hôte + fournir un contexte écologique permettant leur implantation
- Améliorer la résolution taxonomiques



Keith et al, 2018



Modulation du microbiote intestinal

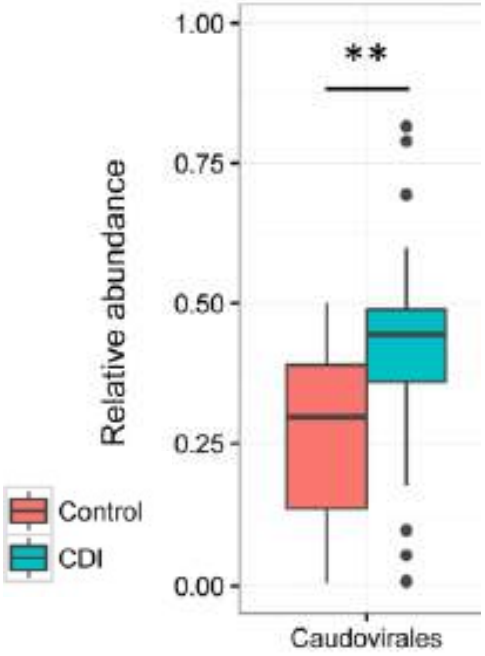


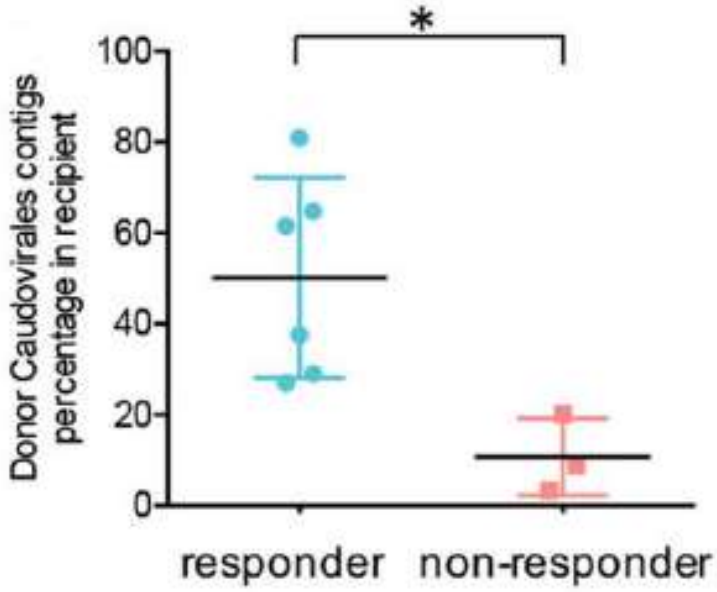
BACTERIOPHAGES

Gut

Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome

Tao Zuo,[1,2] Sunny H Wong,[1,2] Kelvin Lam,[1] Rashid Lui,[1] Kitty Cheung,[1] Whitney Tang,[1] Jessica Y L Ching,[1] Paul K S Chan,[3] Martin C W Chan,[3] Justin C Y Wu,[1,2] Francis K L Chan,[1,2] Jun Yu,[1,2] Joseph J Y Sung,[1,2] Siew C Ng[1,2]



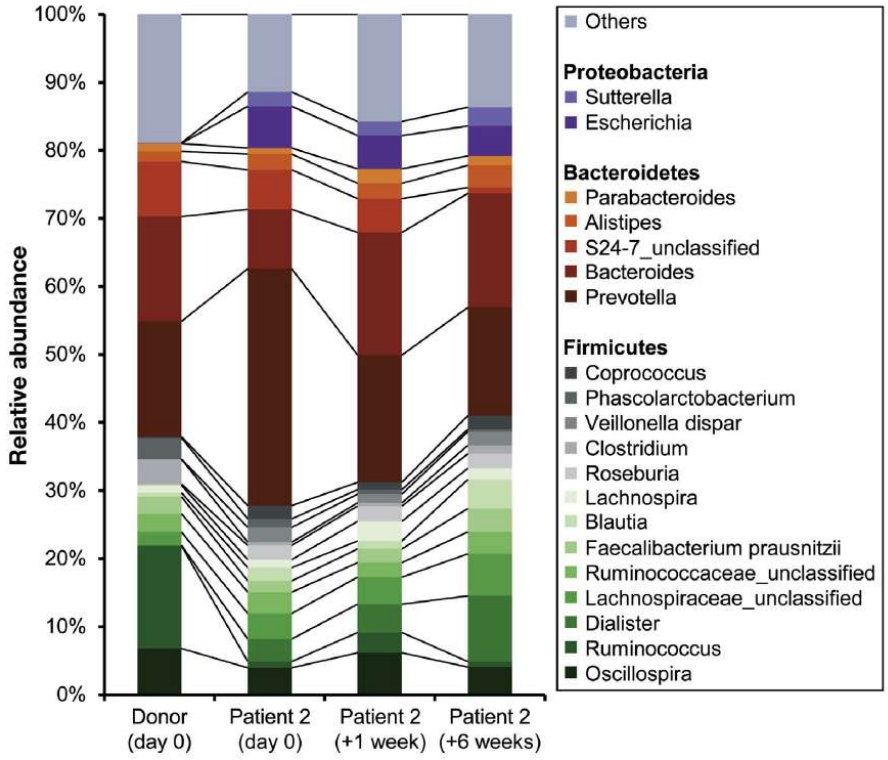


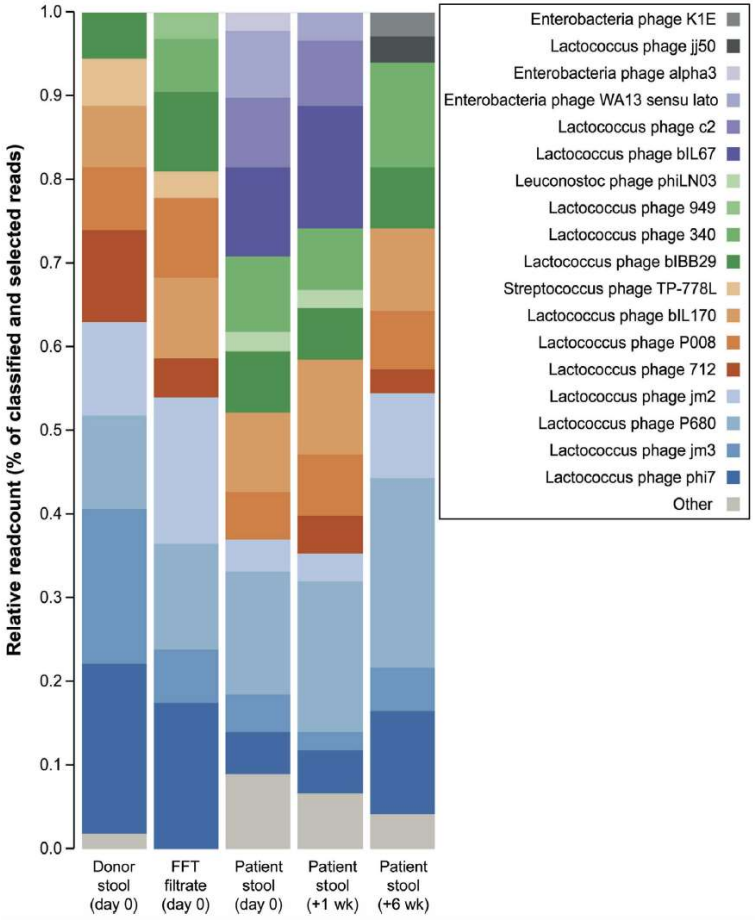
Gastroenterology

OFFICIAL JOURNAL OF THE AGA INSTITUTE

Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With *Clostridium difficile* Infection

Stephan J. Ott,[1,*] Georg H. Waetzig,[2,*] Ateequr Rehman,[3,*] Jacqueline Moltzau-Anderson,[3,4] Richa Bharti,[3] Juris A. Grasis,[5] Liam Cassidy,[6] Andreas Tholey,[6] Helmut Fickenscher,[7] Dirk Seegert,[2] Philip Rosenstiel,[3,§] and Stefan Schreiber[1,3,§]





Eradication of a multi-drug resistant, carbapenemase-producing *Klebsiella pneumoniae* isolate following oral and intra-rectal therapy with a custom-made, lytic bacteriophage preparation.

Authors: Mario Corbellino[1], Nicolas Kieffer[2], Mzia Kutateladze[3], Nana Balarjishvili[3], Lika Leshkasheli[3], Lia Askilashvili[3], George Tsertsvadze[3], Sara Giordana Rimoldi[4], Deia Nizharadze[5], Naomi Hoyle[5], Lia Nadareishvili[5], Spinello Antinori[1, 6], Cristina Pagani[4], Daniele Giuseppe Scorza[7], Ai Ling Loredana Romanò[8], Sandro Ardizzone[9, 6], Piergiorgio Danelli[10, 6], Maria Rita Gismondo[4, 6], Massimo Galli[1, 6], Patrice Nordmann[2] and Laurent Poirel[2].

Quelques problématiques

Collection et stockage

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OBSERVATION
Clinical Science and Epidemiology

Rectal Swabs from Critically Ill Patients Provide Discordant Representations of the Gut Microbiome Compared to Stool Samples

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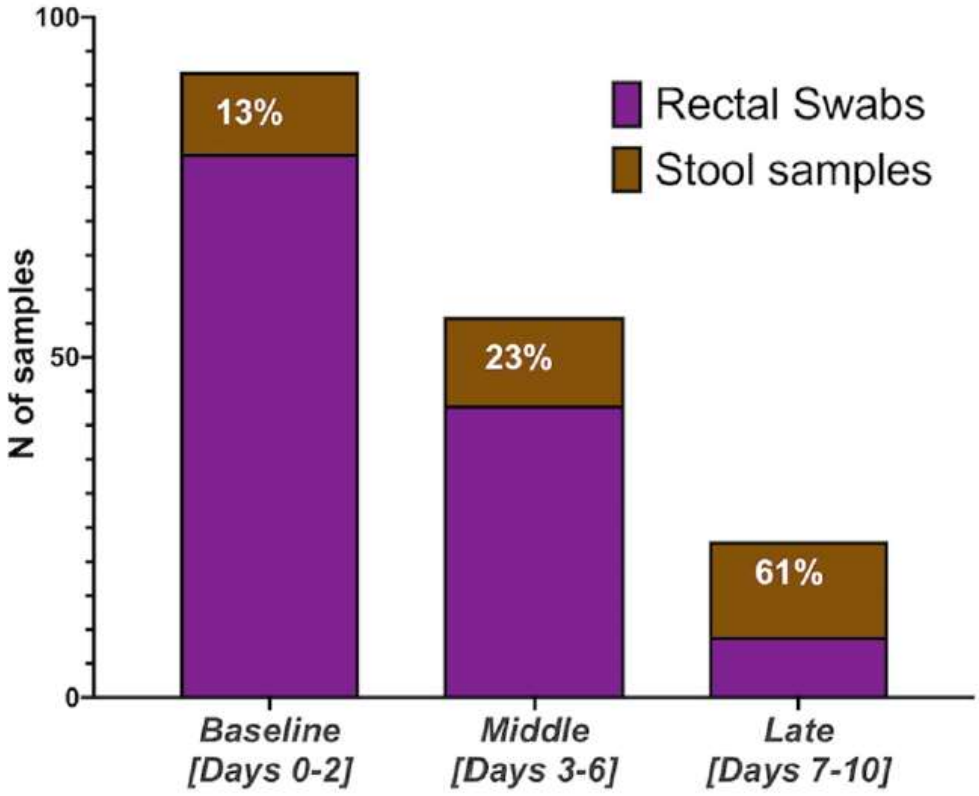
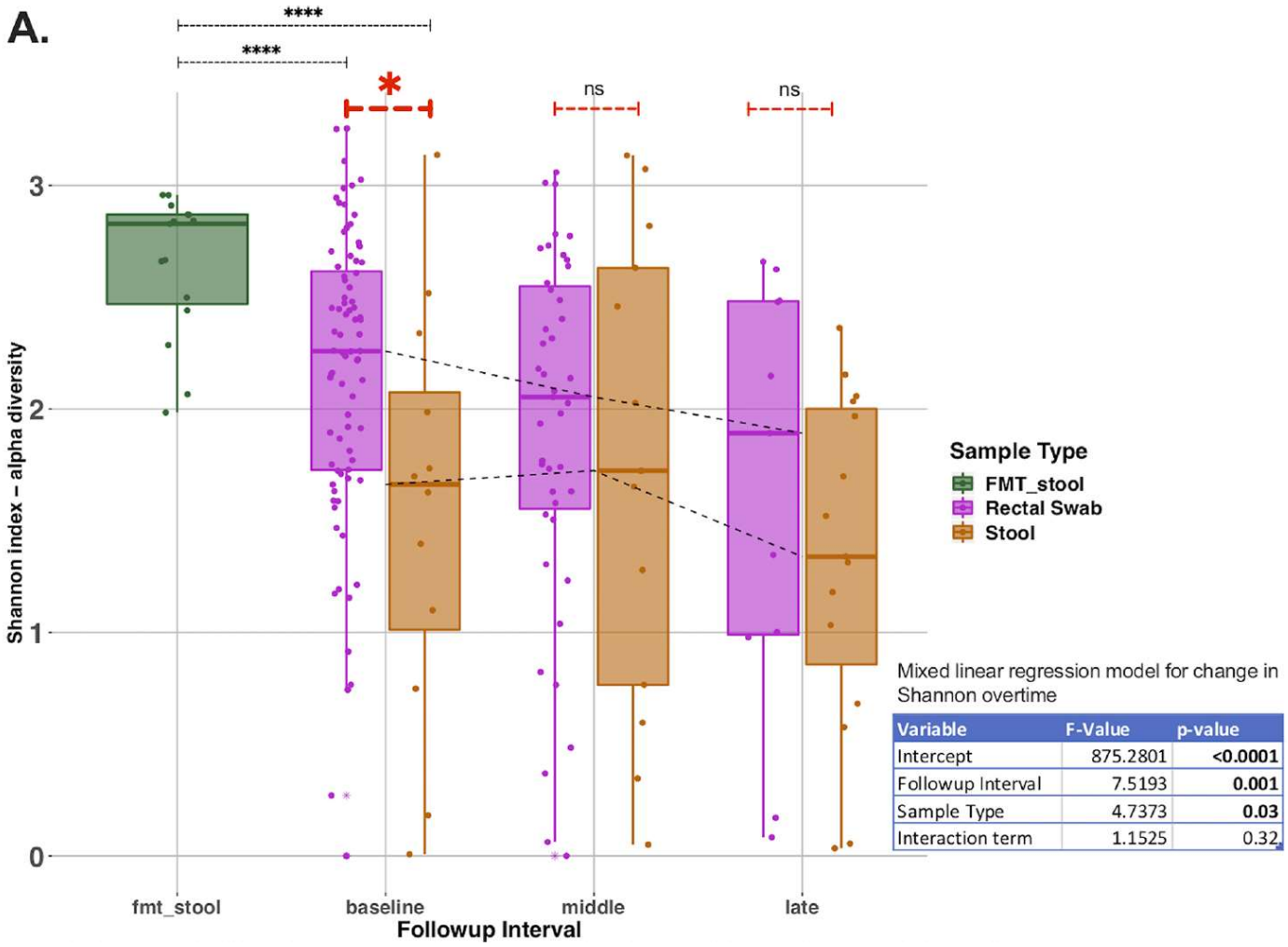
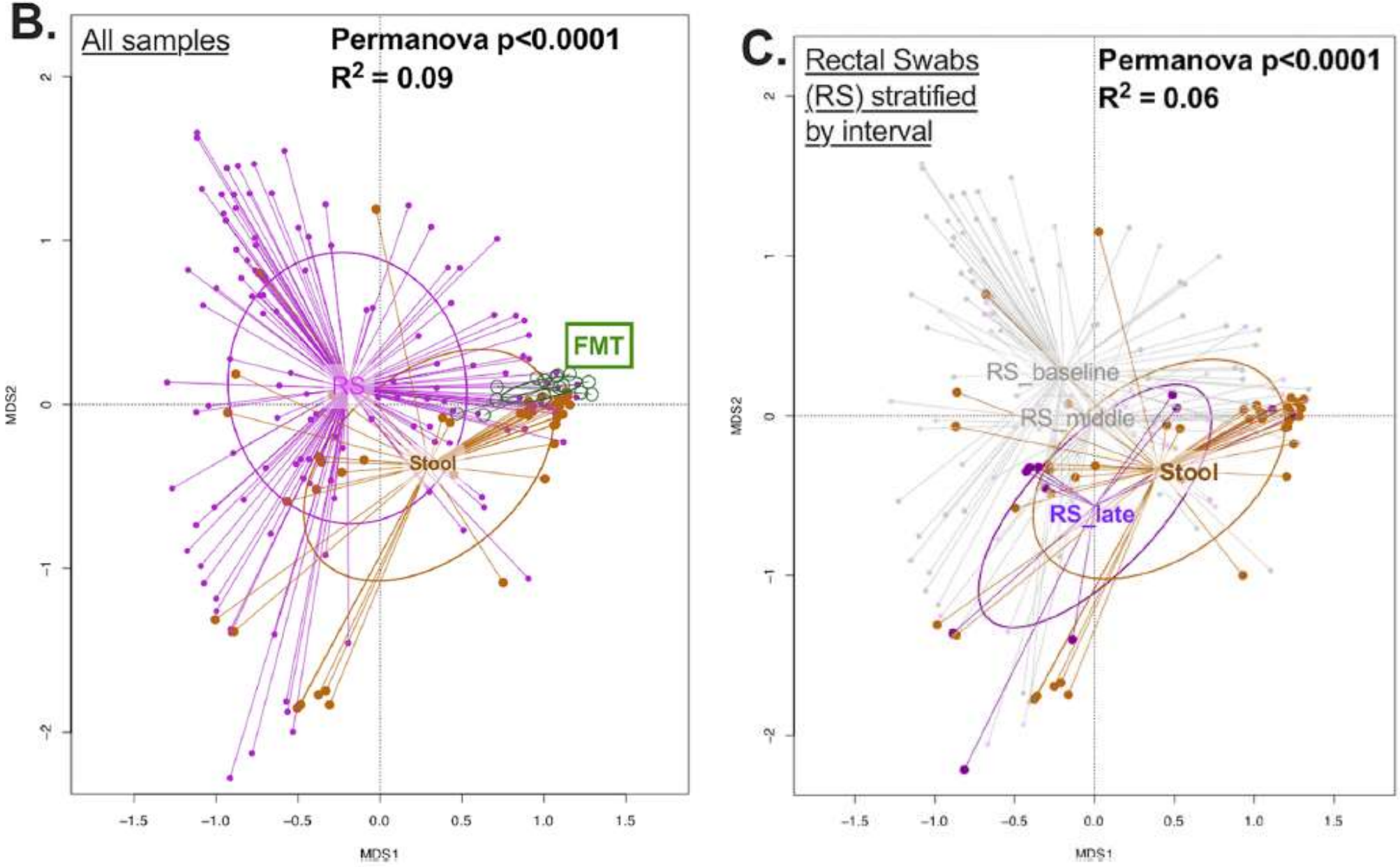

100
50
0
N of samples
13%
23%
61%
Rectal Swabs
Stool samples
Baseline
[Days 0-2]
Middle
[Days 3-6]
Late
[Days 7-10]



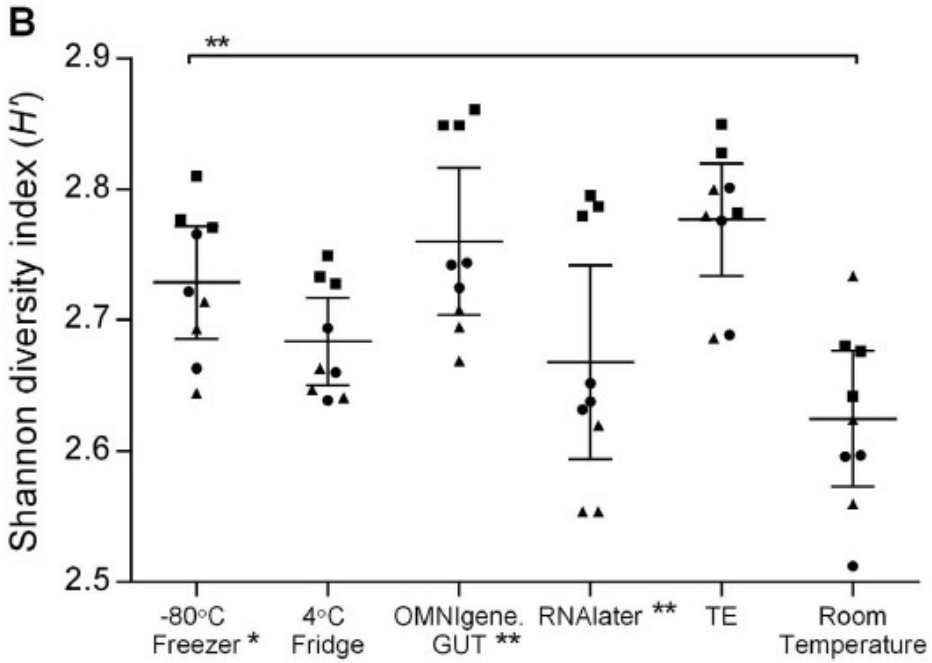
Mixed linear regression model for change in Shannon overtime

Variable	F-Value	p-value
Intercept	875.2801	**<0.0001**
Followup Interval	7.5193	**0.001**
Sample Type	4.7373	**0.03**
Interaction term	1.1525	0.32

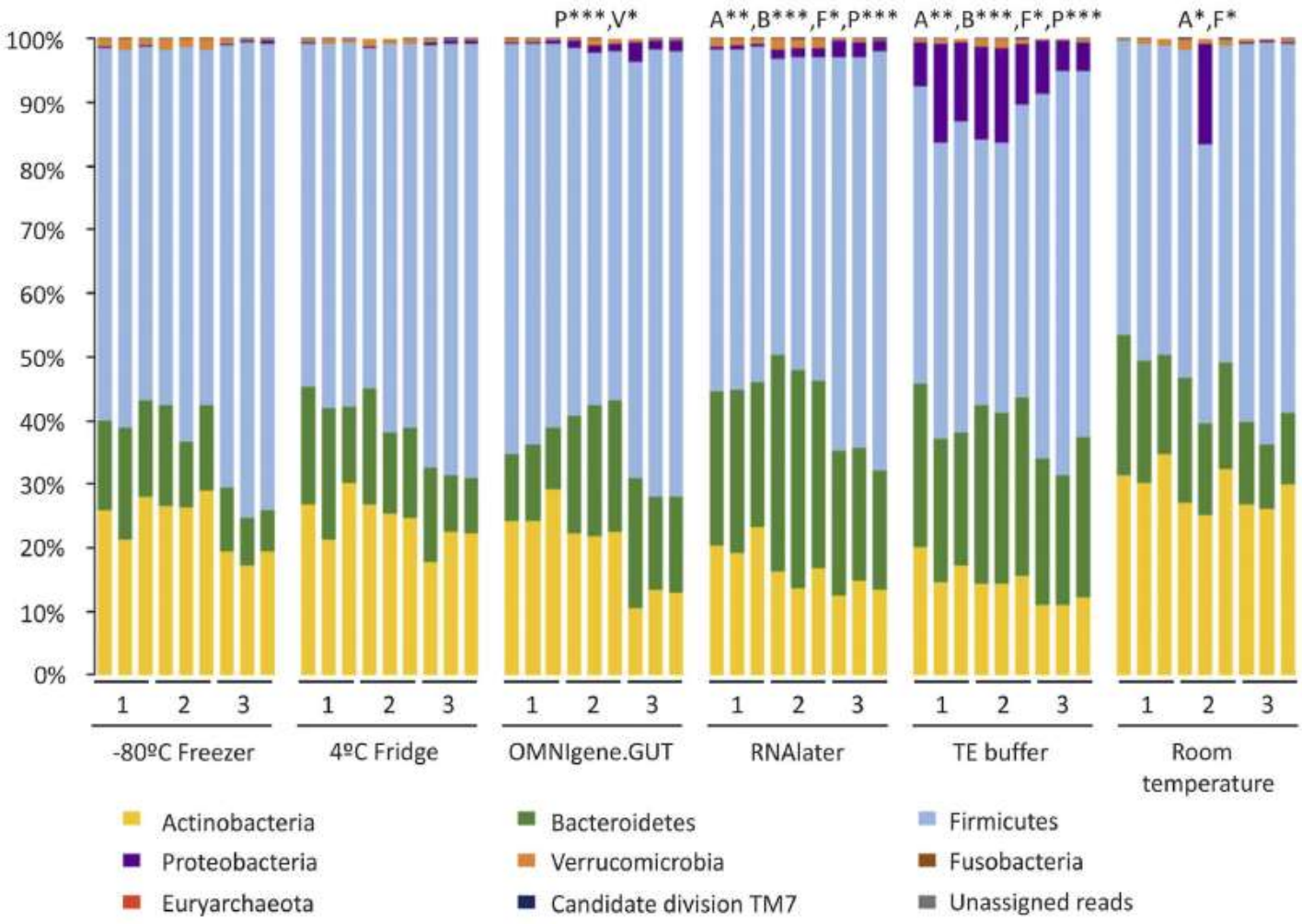

B.
All samples
Permanova p<0.0001
R^2 = 0.09
FMT
RS
Stool
MDS1
MDS2
C.
Rectal Swabs (RS) stratified by interval
Permanova p<0.0001
R^2 = 0.06
RS_baseline
RS_middle
Stool
RS_late
MDS1
MDS2

- At the phylum level: rectal swabs higher relative abundances of Actinobacteria
- Actinobacteria abundance declined significantly over time only in rectal swabs and not in stool samples
- At the genus level: stool samples higher relative abundances of members of the *Akkermansia*, *Bacteroides*, *Enterococcus*, and *Parabacteroides* taxa

Collection et stockage



Choo et al., 2017



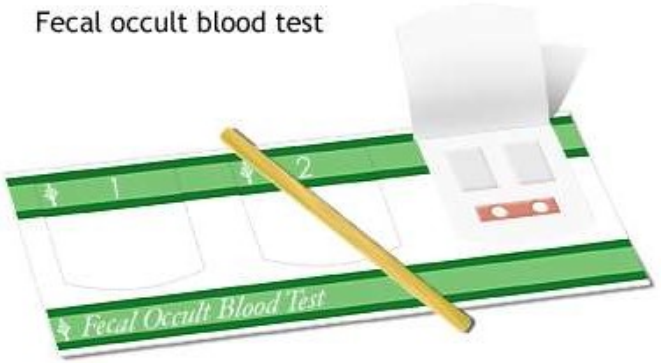
Choo et al., 2017

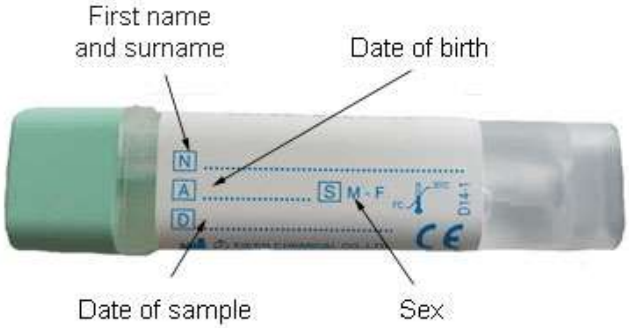
Reproducibility, stability, and accuracy of microbial profiles by fecal sample collection method in three distinct populations

Doratha A. Byrd[1☯*], Jun Chen[2,3☯], Emily Vogtmann[1], Autumn Hullings[1], Se Jin Song[4], Amnon Amir[4], Muhammad G. Kibriya[5], Habibul Ahsan[5], Yu Chen[6], Heidi Nelson[2,7], Rob Knight[4,8], Jianxin Shi[9], Nicholas Chia[2,3,7,10], Rashmi Sinha[1]

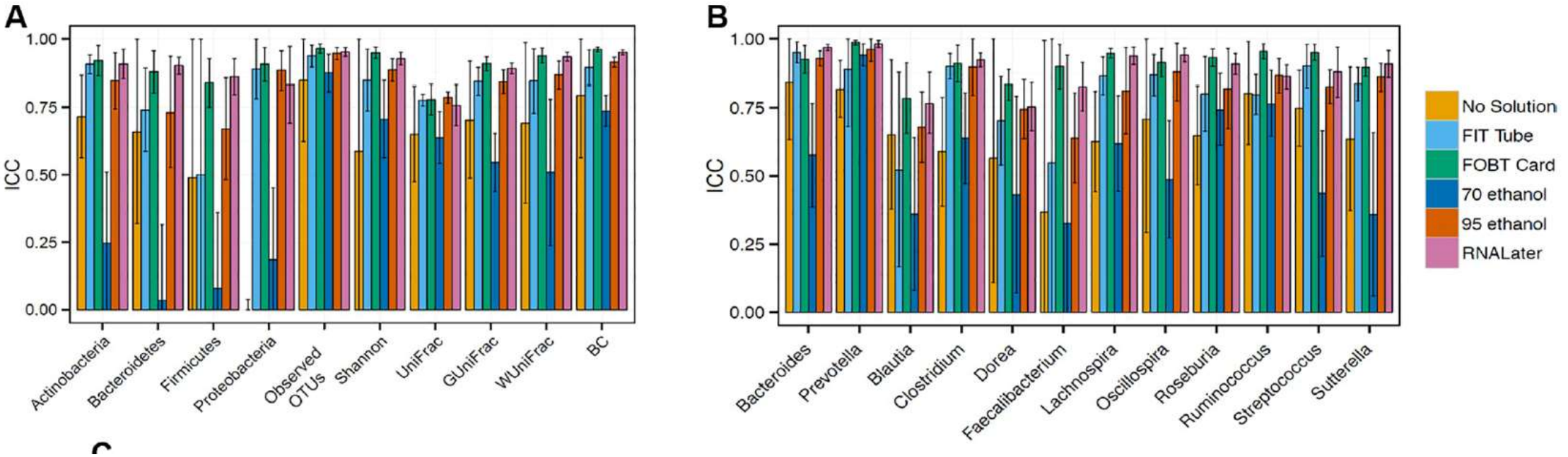
PLOS ONE

FOBT card, FTA card, FIT tubes

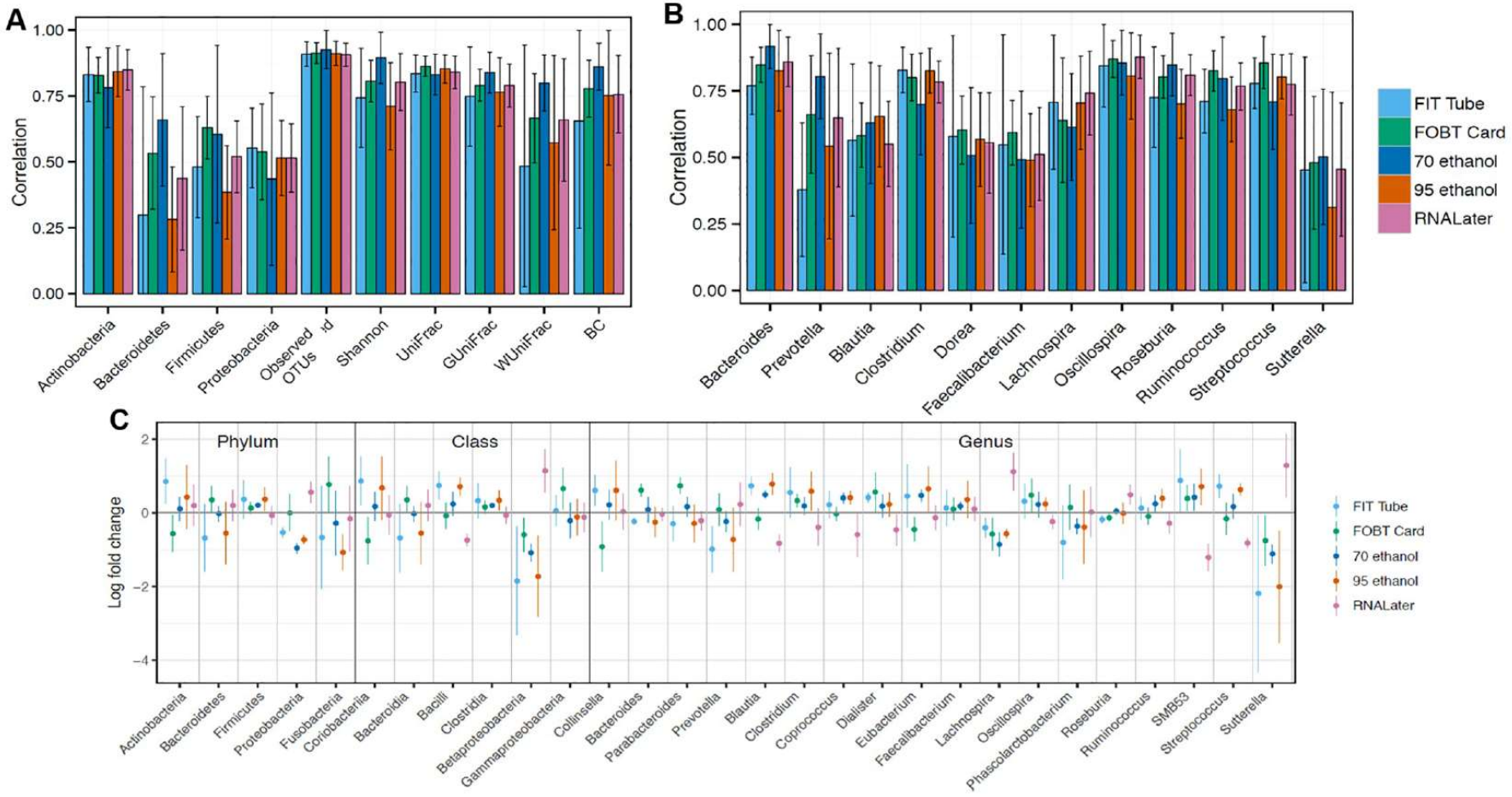




frozen on day-4/7 to those frozen at day-0



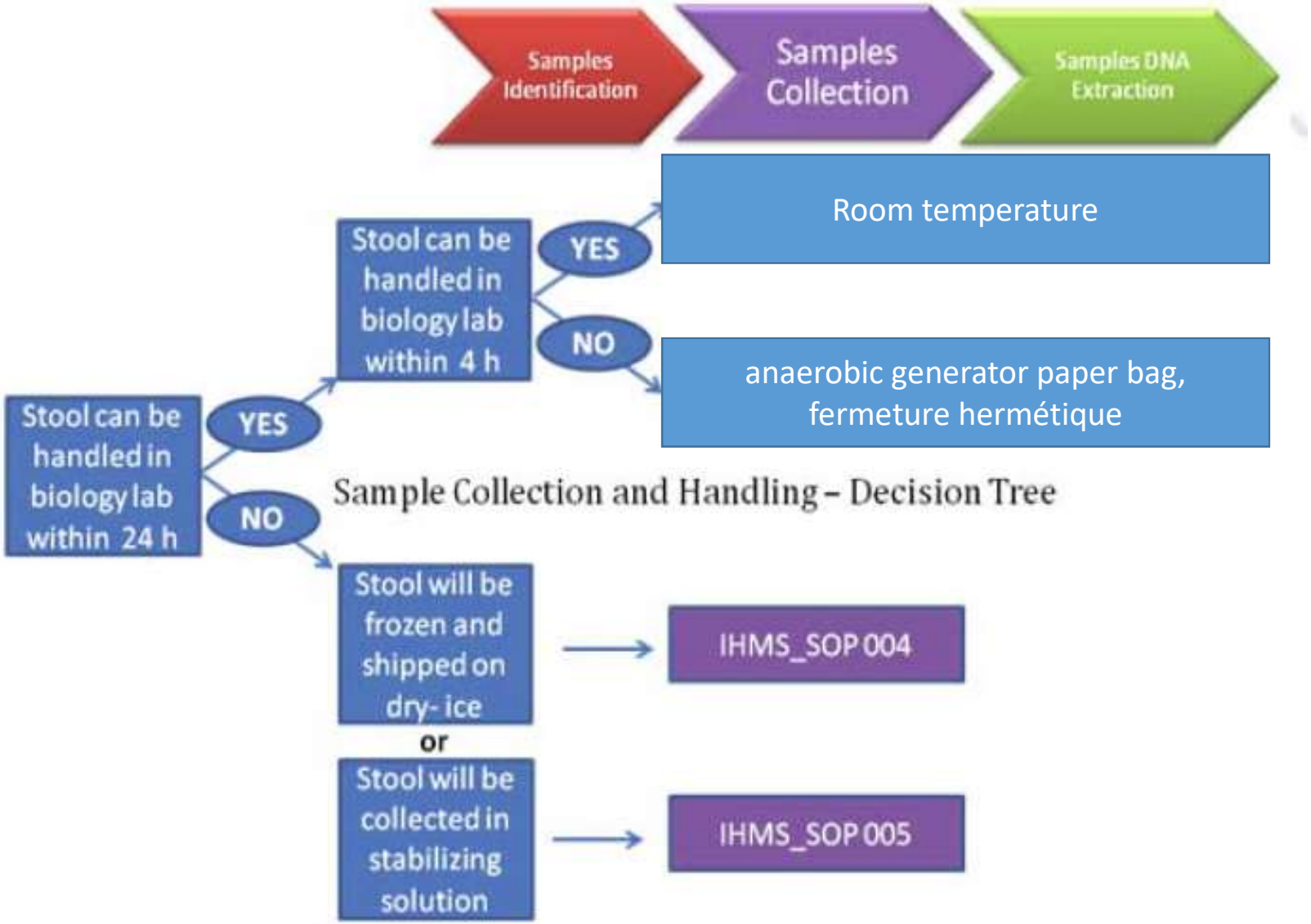
each collection method compared to no-solution samples frozen on day-0 (the gold standard)



- FOBT/FTA cards, FIT tubes, RNAlater , and 95% ethanol samples may be an appropriate choice to collect fecal samples for the measurement of microbiome data in future studies, as these options are reproducible, stable, and relatively accurate.
- move toward standardization of fecal sample collection across study populations.
- Future studies should further investigate the long-term stability (over the course of years) of these collection methods, and reproducibility of each fecal collection method for other -omics, such as shotgun metagenomics.

IHMS Consortium	IHMS - QUALITY PROTOCOL SOP FOR FECAL SAMPLES DNA EXTRACTION Protocol Q	Code : IHMS_SOP 06 V2 Version : 2 Date : 2015-04-12 Number of pages : 8 Page n° : 8	Last Contributor : Sebastian BURZ Approved by: IHMS CONSORTIUM Date : 2015-01-31

- http://www.microbiome-standards.org/

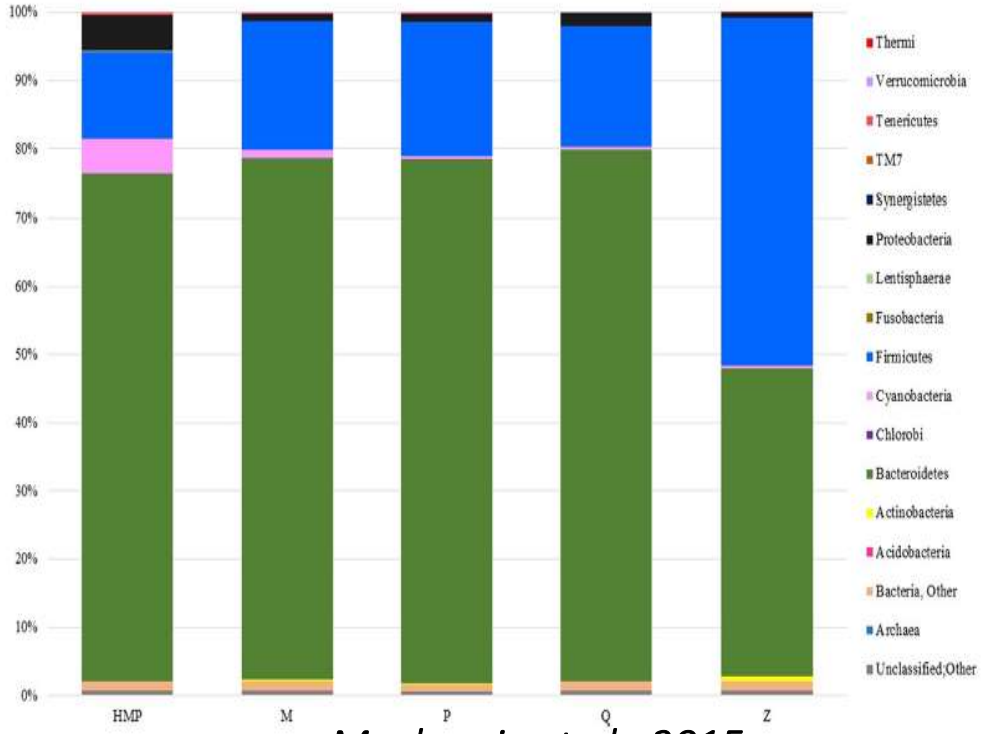

Samples Identification
Samples Collection
Samples DNA Extraction
Stool can be handled in biology lab within 24 h
YES
NO
Stool can be handled in biology lab within 4 h
YES
NO
Room temperature
anaerobic generator paper bag, fermeture hermétique
Sample Collection and Handling – Decision Tree
Stool will be frozen and shipped on dry- ice
IHMS_SOP 004
or
Stool will be collected in stabilizing solution
IHMS_SOP 005


6)

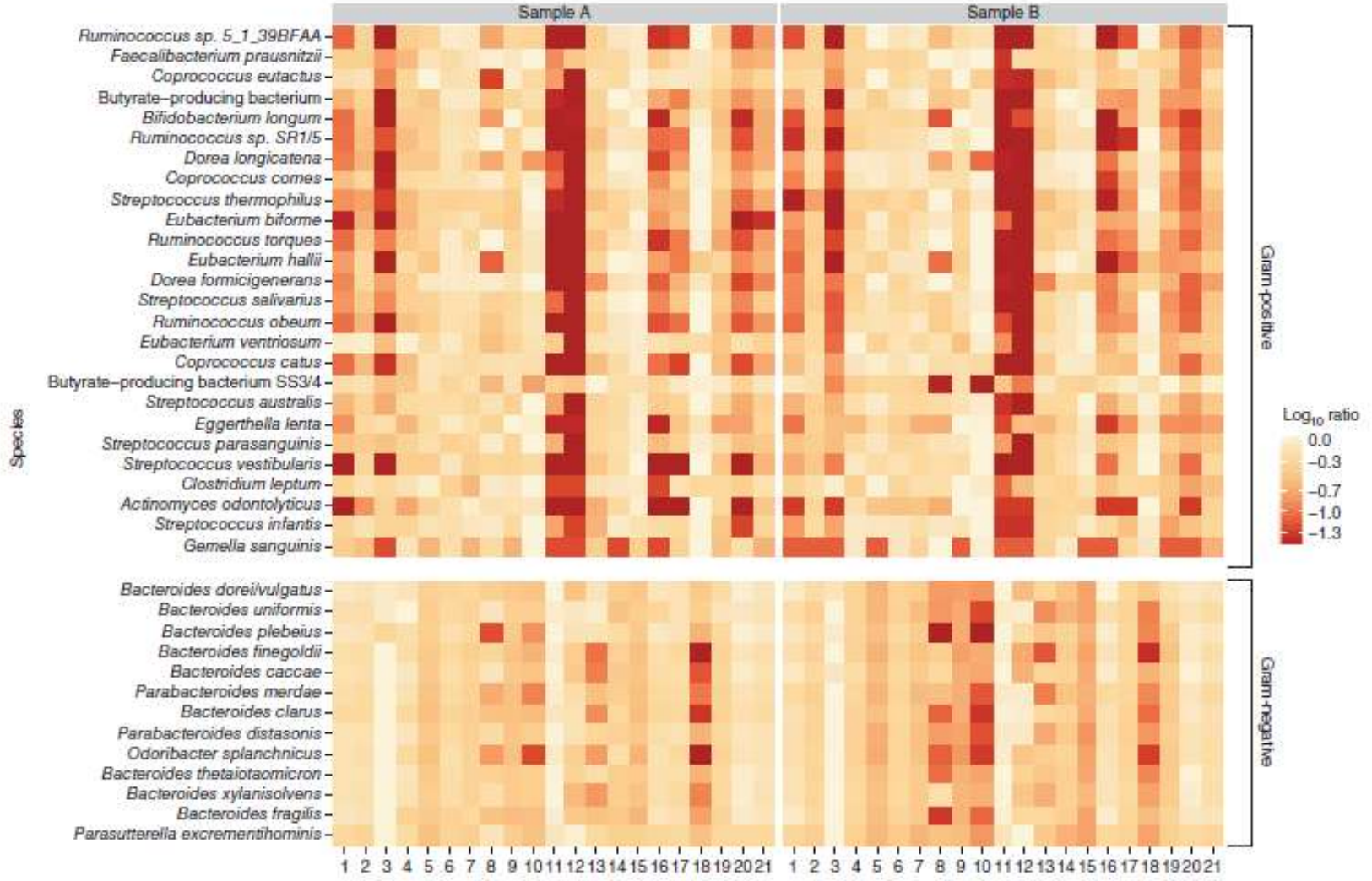
Processing

Extraction method	Kit abbreviation	Recommended fecal starting amount (mg)	Lysis Type
Human Microbiome Project Extraction Method	HMP	1 mL supernatant	Heat, Mechanical
MoBio PowerSoil® DNA Isolation Kit	M	250	Mechanical
Qiagen QIAamp® DNA Stool Mini Kit	Q	180–220	Heat, Chemical, Enzymatic
Zymo ZR Fecal DNA MiniPrep™	Z	150	Mechanical
Phenol: chloroform-based DNA isolation	P	200	Mechanical

A total of 135 samples were analyzed from 5 extraction methods, comprising 3 sub-samples from each of 3 entire stool samp



Mackenzie et al., 2015

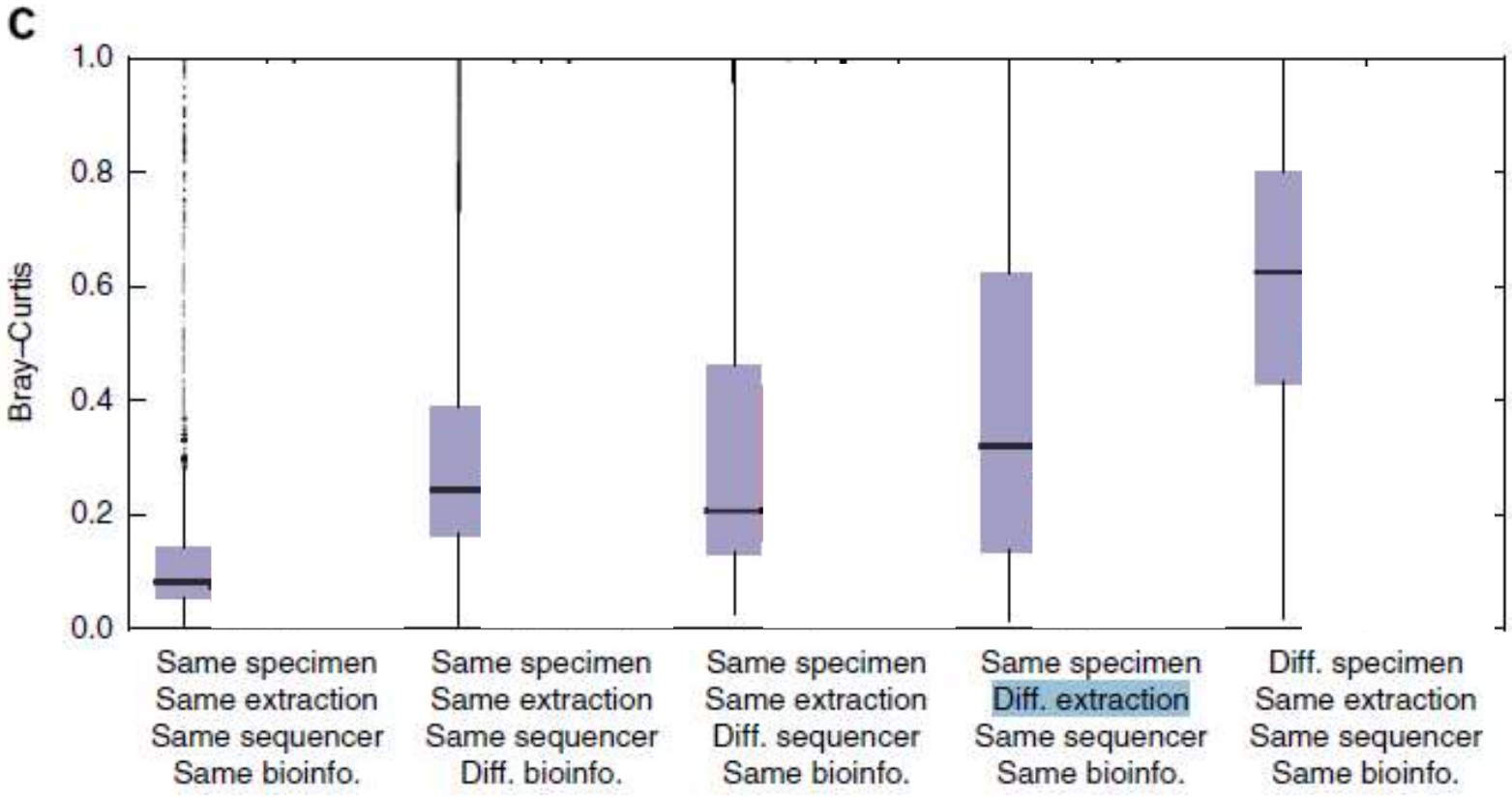


Costea et al., 2017

Handling	
DNA extraction kit manufacturer[a]	
Chemagen	1
GeneRite	1
MO-BIO	7
Omega BioTek	1
Promega	1
Qiagen	2
Zymo Research	1
Not reported/custom	2
Homogenizer used?	
Yes	12
No	3

Sinha et al., 2017

Microbiome Quality Control



Sinha et al., 2017

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6. Step by step procedure:

Fecal DNA extraction with the use of Qiagen QIAamp DNA stool kit

6. Step by step procedure:

Fecal DNA extraction IHMS Protocol H
(see annex for preparation of solutions and suggested suppliers)

Take home notes

- Le microbiote => **biomarqueur** en devenir:
  - Nécessité de méta-analyses (variabilité des études +++)
  - Définir des signatures du microbiote par indications pour intervention préventives/thérapeutiques

- Le microbiote => Des applications cliniques encore limitées:
  - A l'heure actuelle, la transplantation fécale semble être le traitement le plus efficace pour restaurer un microbiote décimé
  - Développer les traitements personnalisées
  - De nombreux essais cliniques randomisés en cours

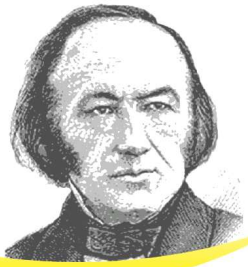
- On intervient sur un **écosystème**: Evaluer les risques court/moyen/long terme

- **STANDARDISATION DES PROCEDURES**

Le microbiote intestinal comme nouveau terrain de jeu en médecine

Emmanuel Montassier
MCU-PH thérapeutique
MiHAR lab

JEUDI 28 NOVEMBRE 2019
UFR Médecine Paris 7 Diderot,
site Xavier-Bichat - Paris 18ème



62ème journée
Claude-Bernard

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

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The MiHAR Lab
Microbiotas, Hosts, Antibiotics and bacterial Resistances

MiBioGate
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