



associazione
microbiologi
clinici italiani

**XLVIII
CONGRESSO
NAZIONALE
AMCLI**

2019



**9-12 NOVEMBRE 2019
PALACONGRESSI RIMINI**

**Il ruolo del
“Microbiota
Clinical Expert**

**IL MICROBIOTA: NON
SOLO INTESTINO**

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EUBIOSIS



Failure of HOST-MICROBIOTA equilibrium



***Quali-quantitative alterations of oral,
esophageal, gastric, small bowel and/or
colonic microbiota***



DYSBIOSIS



ENTEROPATHOGENETIC SYNDROMES

Almost any Digestive and extra-Digestive Diseases have been associated to a **DYSBIOTIC MICROBIOTA**

- ***Gastrointestinal infections***
- ***IBS and IBD***
- ***Small Intestine Bacterial Overgrowth***
- ***Colonic Diverticulosis***
- ***Gastro-intestinal and Liver Cancers***
- ***Food Intolerance/Allergy***
- ***Celiac disease/Non celiac gluten sensitivty***
- ***Liver and Pancreatic diseases***
- ***Obesity, Diabetes and Metabolic Syndrome***
- ***Gyneco-urological, Rheumatological, Oncological, Cardiovascular, Neurological, Neuropsychiatric disorders, Dermatologicalm Pneumological...***

To date, there is a **gap between microbiome basic scientists and clinicians** involved in dysbiosis-related disorders

Time for a translational figure: the MICROBIOME CLINICIAN
Time for a breakthrough in clinical practice: the MICROBIOME CLINIC

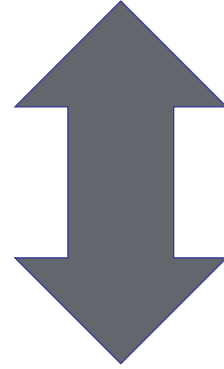
MICROBIOME CLINICIAN

- **Continuous up-to-date on microbiota research**
- **Knowledge of different dysbiotic profiles of GI and extra-GI Disorders**
- **Interpretation of gut microbiota profiling**
- **Application of microbiome research data in clinical practice**
- **Expertise in microbiota modulation (anti-pre-probiotics, FMT)**

MICROBIOME CLINIC

- **Multidisciplinary team**
(microbiome clinicians, microbiologists, immunologists, nutritionists, etc.)
- **Availability of microbiota sequencing tools**
- **Availability of stool bank/FMT Centre**
- **Hotspot for microbiota research**
- **Networking and teaching centre**

The microbiome clinic



Gut microbiome precision medicine

The microbiome clinic is the key to move microbiome precision medicine from basic science research to clinical practice

Microbiome clinic

Microbiota modulation

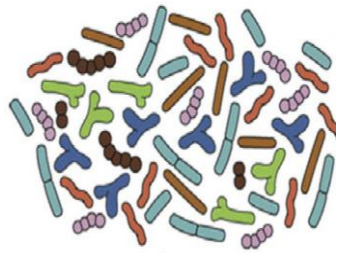
**Nutrition, novel food, probiotics,
prebiotics, antibiotics..**

Microbiota resetting

Fecal Microbiota Transplantation

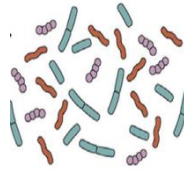
Rationale of microbiota modulation

Healthy microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis (Loss of eubiosis)



Quantity



Quality



Diseases

GI infections



Metabolic disorders



IBD



IBS



Diet
Antibiotics
Prebiotics
Probiotics
FMT

Hepatic
Encefalopathy



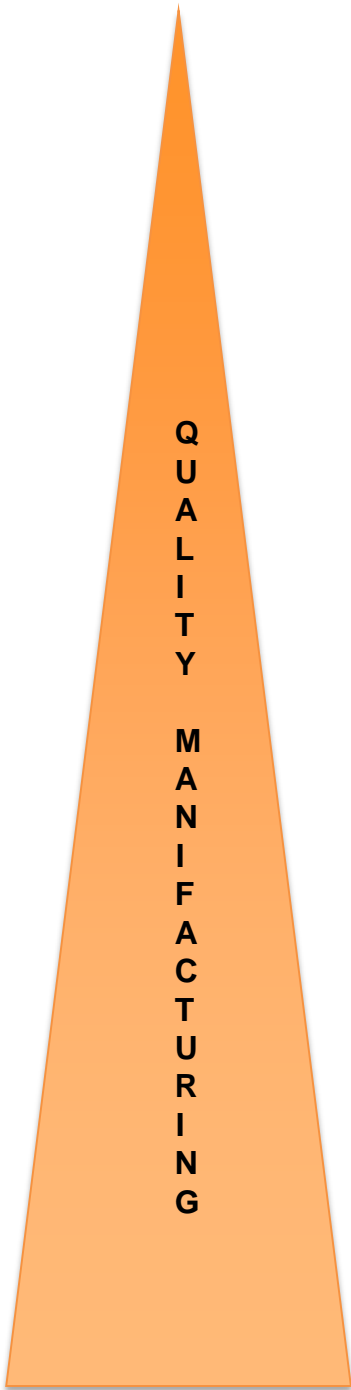
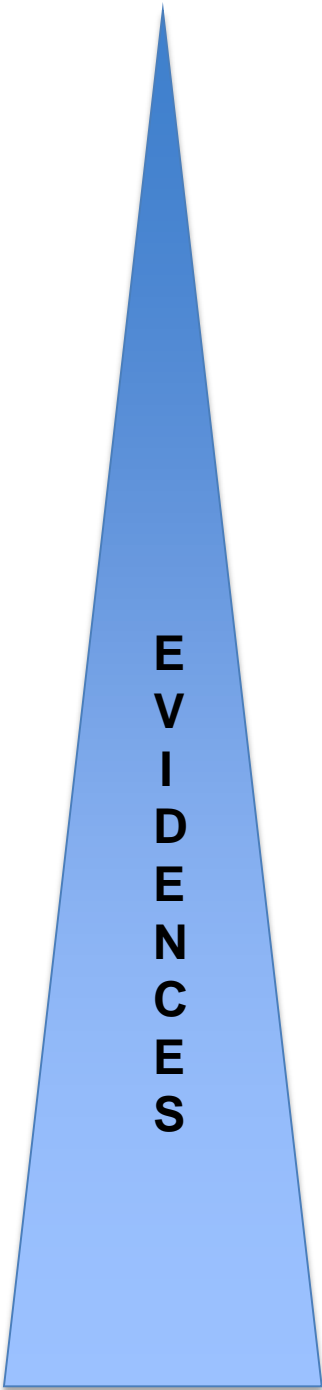
He'll do... You do?
I ate 3 kg of food

Other

Healthy
individual



| <i>Probiotic</i> | |
|--|---|
| Probiotic in food or supplement without health claim | "Contains probiotics" |
| Probiotic in food or supplement with a specific health claim | Specific health claim, such as "helps to reinforce the body's natural defences in children" or "helps reduce the risk of antibiotic-associated diarrhoea" |
| Probiotic drug | Specific indication for treatment or prevention of disease, such as "useful for the prevention of relapse of ulcerative colitis" |



FOOD CONSUMERS



DRUG



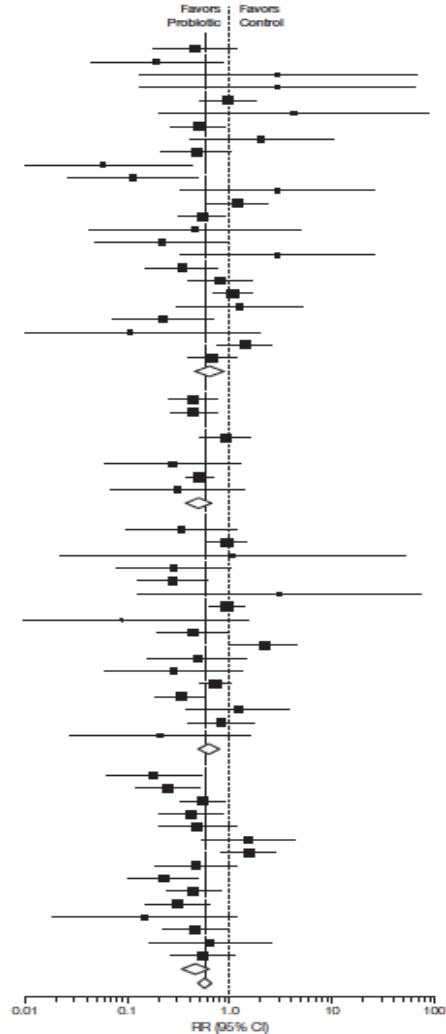
DOCTORS

Overall effect of probiotics in the prevention or treatment of AAD

82 RCTs

Probiotics vs no treatment, placebo, or a different probiotic or probiotic dose

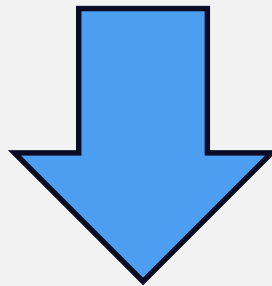
Statistically **significant reduction in AAD by probiotics** (RR 0.58; 95%CI, 0.50 to 0.68; $P < 0.001$)



**Pooling data on different probiotics is not appropriate
to assess the efficacy of probiotics**

Different action for each Probiotic

Knowledge of micro-organism functions and host genetic modulation by different Species/Strain is crucial



Need for a Specie (Strain)-specific Microbial Therapy

BACILLUS CLAUSII FOR THE TREATMENT OF ACUTE DIARRHEA IN CHILDREN

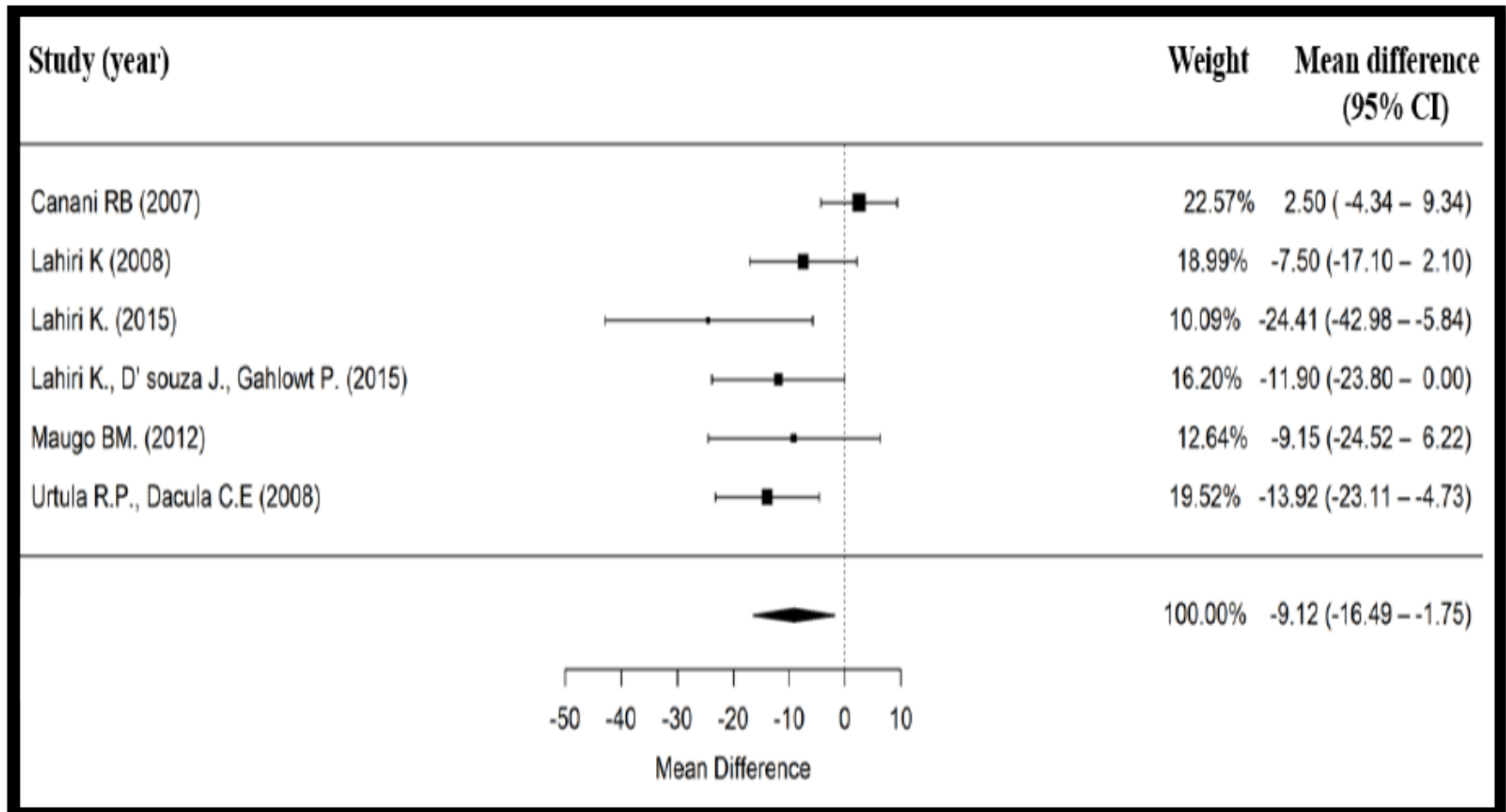
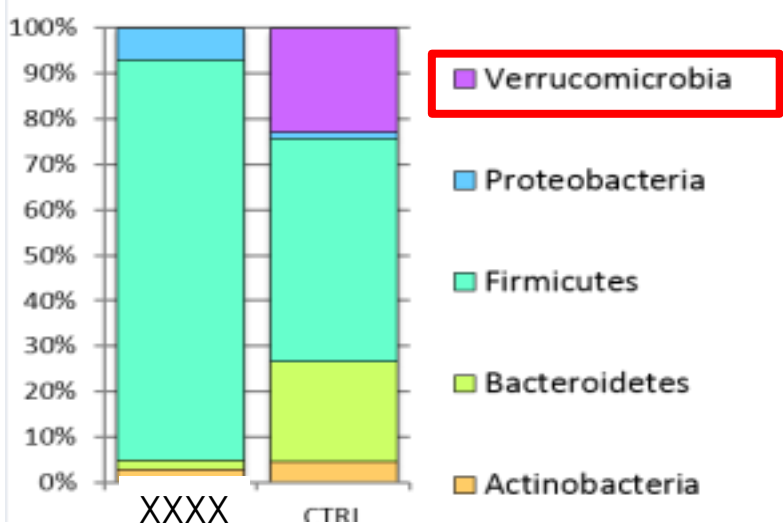
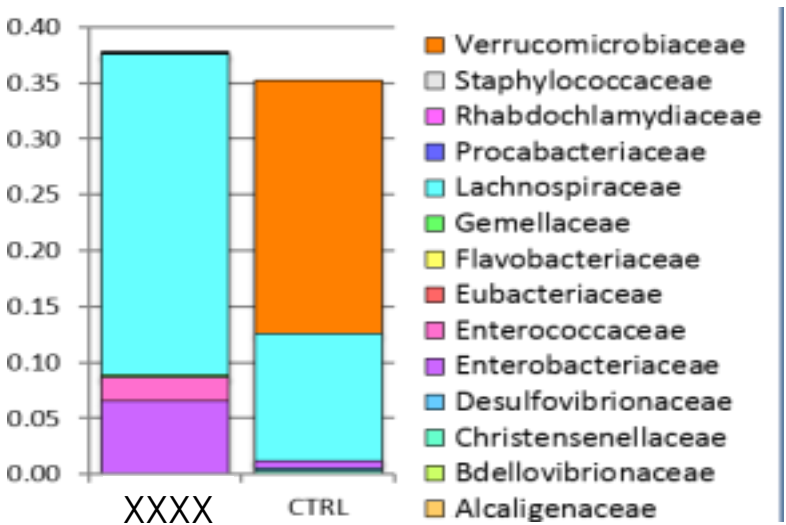


Figure 2. Forest plot showing effect of *Bacillus clausii* on mean duration of diarrhea. CI, confidence interval, RE, random effects.

Fecal microbiota of a patient undergoing therapy with nivolumab for non-small cell lung cancer



PHYLA



FAMILIES

| | | | | |
|-----------------|--------------------------------|---------|---------|---|
| Proteobacteria | <i>Acinetobacter</i> | 0.00007 | 0.00001 | + |
| Proteobacteria | <i>Bdellovibrio</i> | 0.00033 | 0.00000 | + |
| Proteobacteria | <i>Citrobacter</i> | 0.01191 | 0.00082 | + |
| Proteobacteria | <i>Klebsiella</i> | 0.00572 | 0.00050 | + |
| Proteobacteria | <i>Neisseria</i> | 0.00296 | 0.00000 | + |
| Proteobacteria | <i>Neisseria subflava</i> | 0.00004 | 0.00000 | + |
| Proteobacteria | <i>Pseudomonas</i> | 0.00003 | 0.00000 | + |
| Proteobacteria | <i>Serratia</i> | 0.01848 | 0.00003 | + |
| Proteobacteria | <i>Sutterella</i> | 0.00003 | 0.00083 | - |
| Verrucomicrobia | <i>Akkermansia muciniphila</i> | 0.00012 | 0.22570 | - |

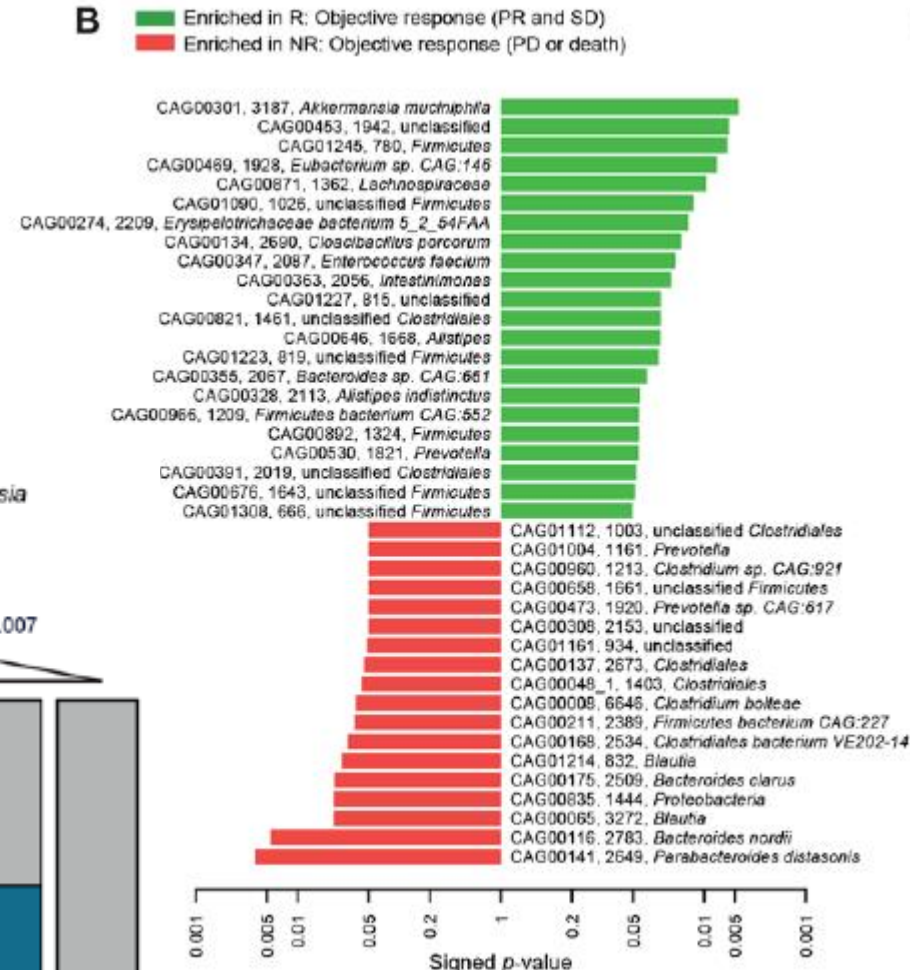
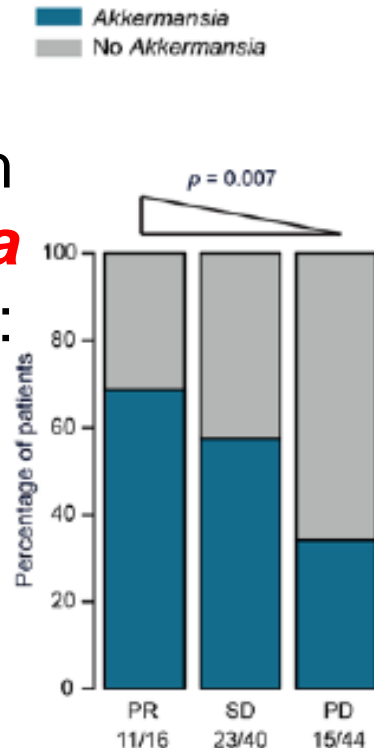
METAGENOMIC ANALYSES PREDICTS PD-1 RESPONSE AT 3 MONTHS

Shotgun sequencing of fecal samples at diagnosis in PD-1 therapy:

- **RESPONDER**
- **NON RESPONDER**

Frequency of patients with detectable *A. muciniphila* in their feces according to:

- **PR**: partial response
- **SD**: stable disease
- **PD**: progressed or died



FMT: a success story

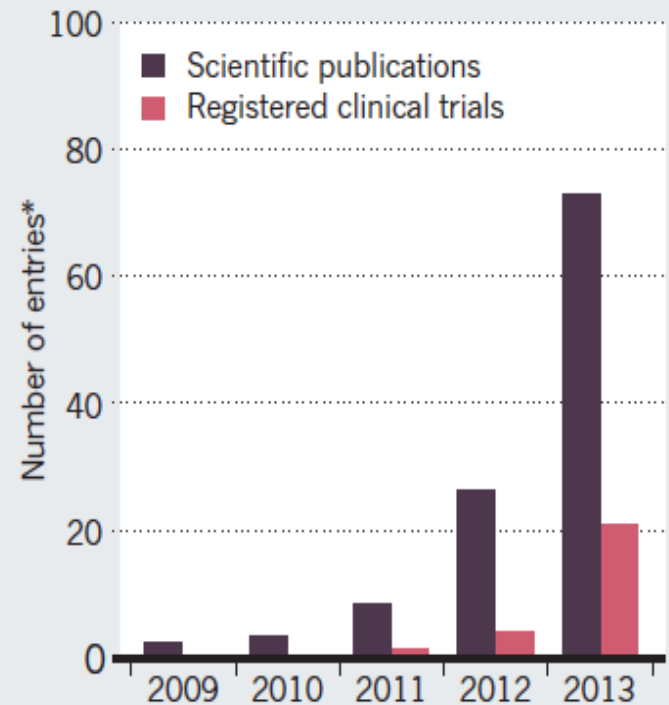
First reported application of FMT for pseudomembranous colitis



- | | |
|---|-------------|
| • First RCT on FMT for MetS | 2012 |
| • First RCT on FMT for CDI | 2013 |
| • FMT in American CDI guidelines | 2013 |
| • First capsule FMT study | 2014 |
| • First RCT on FMT for UC | 2015 |
| • First synthetic microbiota consortium | 2016 |
| • First Consensus Conference on FMT | 2016 |

STOOL TREATMENT

Interest in faecal transplants has surged in the past five years.



*For search term "fecal microbiota transplantation".

Eiseman B, et al. Surgery 1958; Surawicz C, et al. Am J Gastroenterol 2013; van Nood E, et al. N Engl J Med 2013
Youngster I, et al. JAMA 2014; Orenstein et al – Clin Infect Dis 2016; Cammarota G, et al. Gut 2017

FMT for recurrent CDI: guidelines on CDI

- **American College of Gastroenterology (ACG)**

- FMT at 3^o **recurrence** after vancomycin

Treatment of ≥ 3 CDI recurrences

Recommendation

20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)

- **European Society of Clinical Microbiology & Infectious Disease (ESCMID)**

- FMT + antibiotics for **multiply recurrent disease**

Non-antibiotic treatment in combination with oral antibiotic treatment

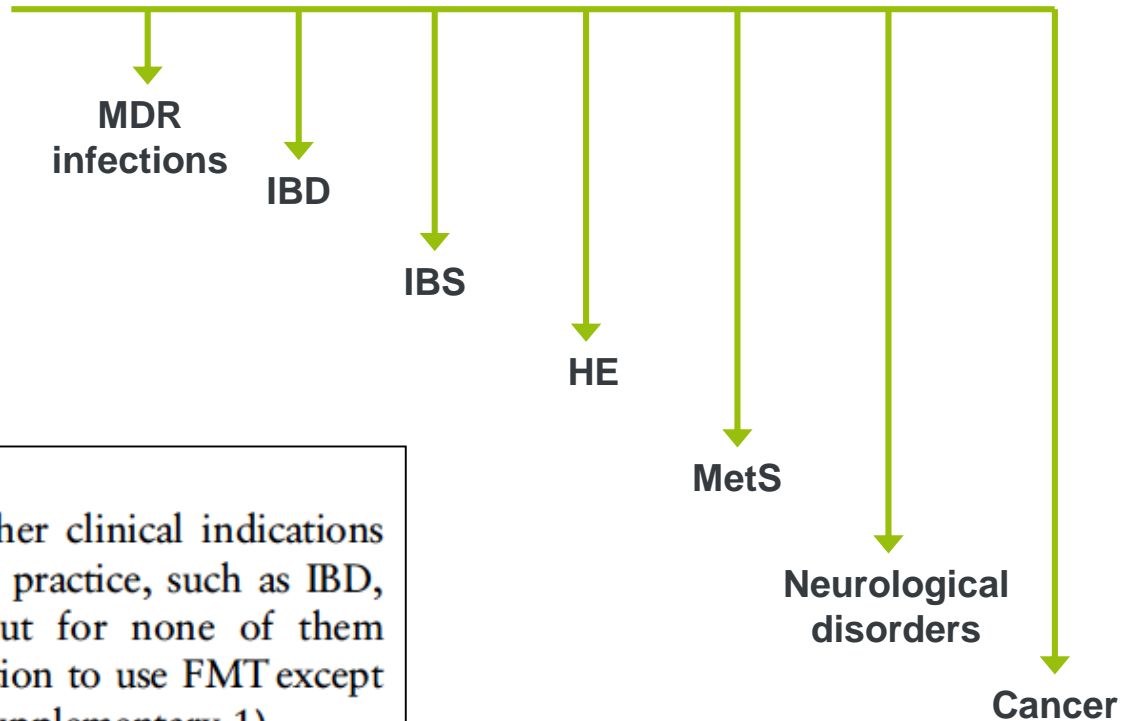
For multiple recurrent CDI unresponsive to repeated antibiotic treatment, faecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I).

What's new in FMT

- **Indications**

- **Methods**

Other indications beyond *C. difficile* infection?



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).

European Consensus Conference on FMT in clinical practice

Cammarota et al – Gut 2017

Evidence for different indications of FMT in 2019

| | Metanalyses | RCTs | Open label trials | Case series/reports | Efficacy data |
|-------------------------------|-------------|------|-------------------|---------------------|-----------------|
| <i>C. difficile</i> infection | +++ | +++ | ++++ | ++++ | Outstanding |
| Ulcerative colitis | + | + | ++ | +++ | Promising |
| Hepatic encefalopathy | | + | | + | Quite promising |
| Metabolic syndrome | | + | | + | Quite promising |
| Crohn's disease | | | + | + | Poor |
| IBS | | + | + | + | Poor |
| Multi-resistant infections | | | + | + | Poor |
| Autism | | | + | + | Poor |
| GVHD | | | | + | Poor |

Ulcerative colitis: not there yet

4 RCTs

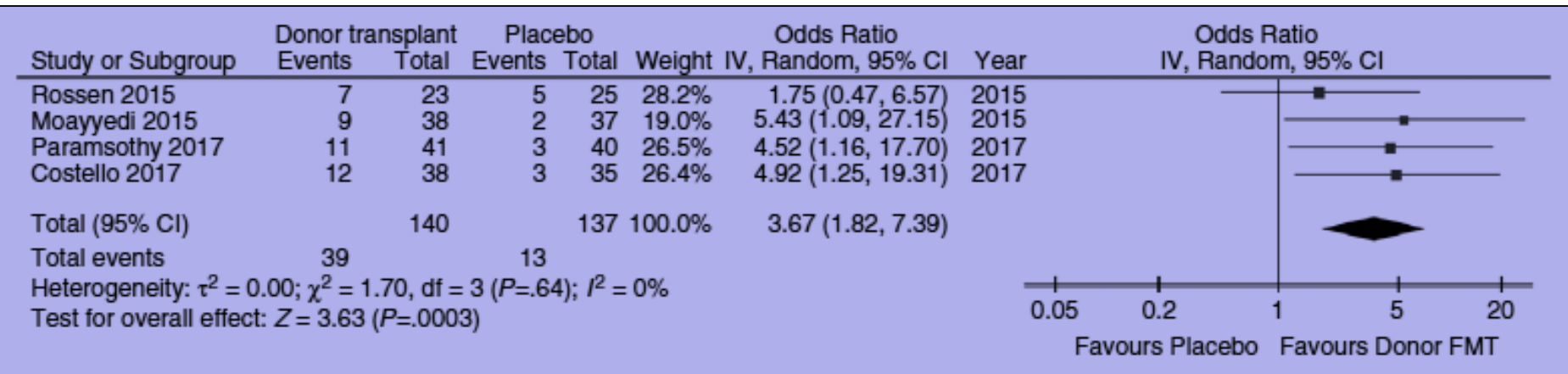
- **Clinical remission 28%** vs 9% placebo (OR 3.67- 95%CI 1.82-7.39, $P < 0.01$)
- **Endoscopic remission 14%** vs 5% placebo (OR 2.89 – 95%CI 1.07-6.74, $P = 0.04$)

14 cohort studies

- **Clinical remission 24%**

Marked differences between FMT working protocols

Costello et al – AP&T 2017



We are still far from finding a magic bullet

Metabolic syndrome

One-hit wonder or rising star?

| | Vrieze et al – 2012 | Kootte et al - 2017 |
|---|--|--|
| Design | RCT (donor vs autologous feces) | RCT (donor vs autologous feces) |
| Population | 18 treatment-naïve males w/ MetS | 44 treatment-naïve males w/ MetS |
| Donors | Lean male donors | Lean male donors |
| Route | Nasoduodenal tube | Nasoduodenal tube |
| Infusions | Single infusion | 2 infusions in some donor-FMT pts |
| Follow-up | 6 weeks | 6 weeks and 18 weeks |
| Main results (donor vs autol. FMT) | <ul style="list-style-type: none"> Improvement of periph insulin sensitivity Increase in microbiota diversity Increase of R. intestinalis abund. | <p><i>6-wk follow-up</i></p> <ul style="list-style-type: none"> Improvement of periph. insulin sensitivity and HbcA1 No increase in microbiota diversity Increase in A. muciniphila abund. <p><i>18-wk follow-up</i></p> <p>No differences between groups</p> |

Irritable Bowel Syndrome: still constipated?

| Year | 1° author | Design | N°of pts | Route | Symptoms Improv. | Microbial changes |
|------|-----------------------|------------------|----------------------|-----------|---|---|
| 1989 | Borody | Case series | 55 (IBS/IBD) | Colonosc. | 16% (short term) | - |
| 1995 | Andrews | Case series | 45 (CC) | Colonosc. | 89% (short term) 60% (long term) | - |
| 2014 | Pinn | Case series | 13 (IBS-D/C/M) | Duodenal | 70% (short term) 46% (long term) | - |
| 2017 | Hoelvet | Open label trial | 12 (IBS-D, bloating) | Colonosc. | 75% (short term) | <ul style="list-style-type: none"> Higher <i>Streptococci</i> abundance in successful donors Trend of higher enrichment potential in responders |
| 2017 | Mizuno | Open label trial | 10 (IBS-D/C/M) | Colonosc. | 60% (short term) | <ul style="list-style-type: none"> Higher <i>Bifidobacteria</i> abundance in successful donors Higher microbial diversity in responders |
| 2017 | Konig (UEGW abstract) | RCT vs placebo | 16 (IBS) | Colonosc. | Significant improv. of IBS-SSS scores and IBS-QoL tot. score in the treatment group | |
| 2017 | Johnsen | RCT vs placebo | 60 (Non-C IBS) | Colonosc. | Improvement of IBS-SSS in 65% of FMT group vs 43% of placebo (p=0.049) | - |
| 2018 | Halkjaer | RCT vs placebo | 52 | Capsules | Worse IBS-SSS and IBS-QoL in the FMT group | Diversity increase in the FMT group |

Multi-drug resistant pathogens

Successful case series/case reports on:

- Methicillin-resistant *Staphylococcus aureus* (MRSA) Enterocolitis
- Vancomycin-resistant *Enterococcus* (VRE)
- *K. pneumoniae* MBL(+)
- *Escherichia coli* ESBL(+)

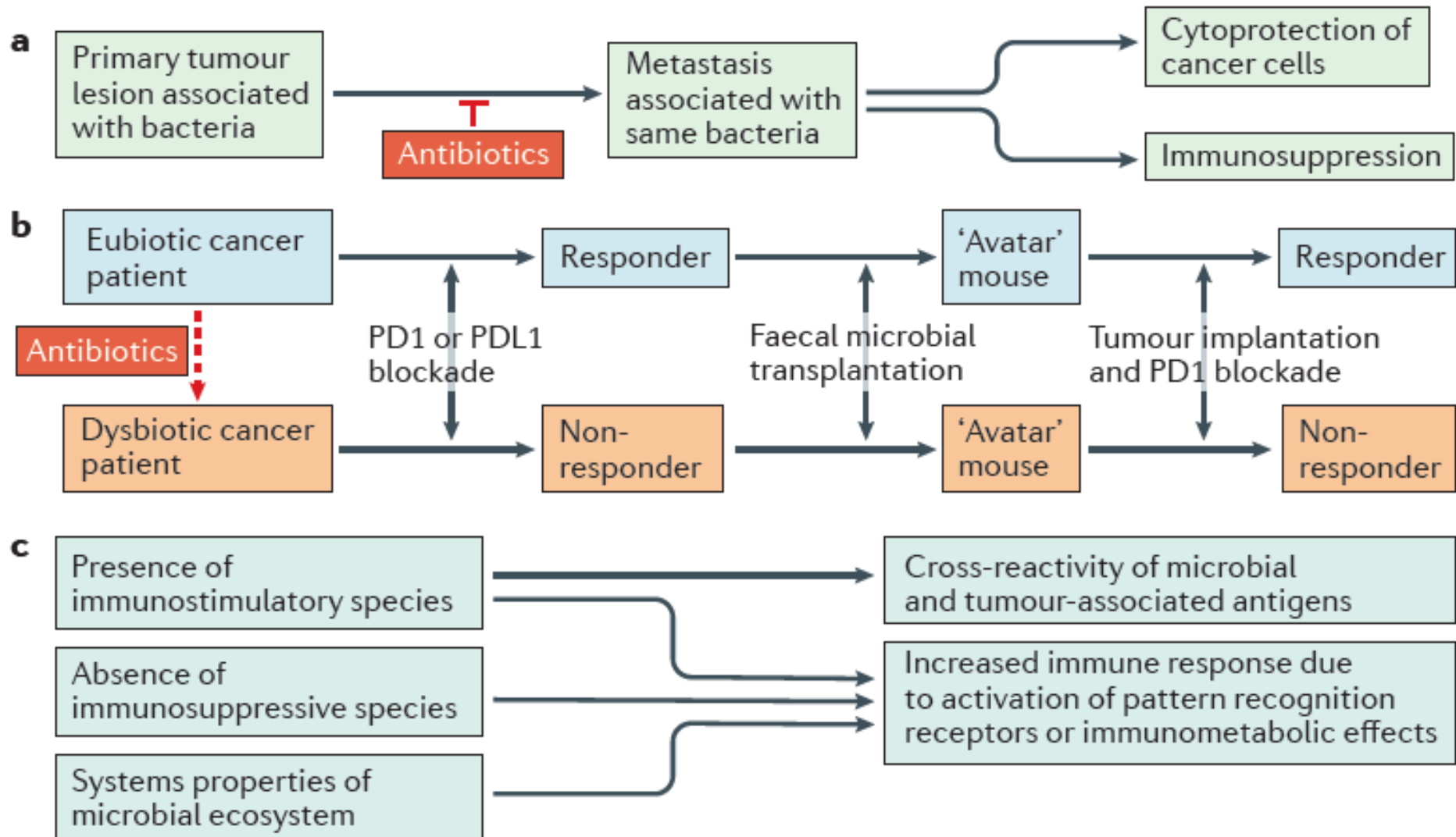
Wei et al – BMC Infect Dis 2015
Stripling et al – Open Forum Infect Dis 2015
Bilinsky et al- Arch Immunol Ther Exp 2016

One open-label trial:

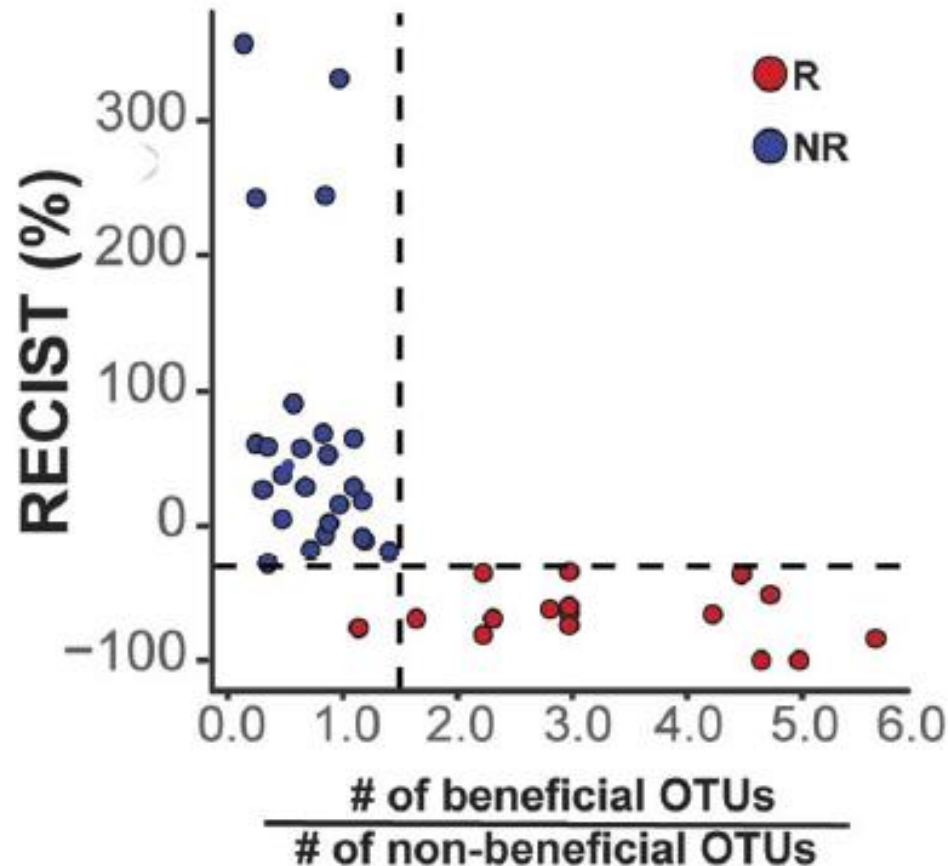
- 20 participants, median of 2 strains of ARB
- FMT by nasoduodenal tube
- Complete ARB decolonization in 15 of 20 patients (75%)
- No severe adverse events

Bilinsky et al – Clin Infect Dis 2017

THE BREAKTHROUGH OF THE MICROBIOTA IN CANCER



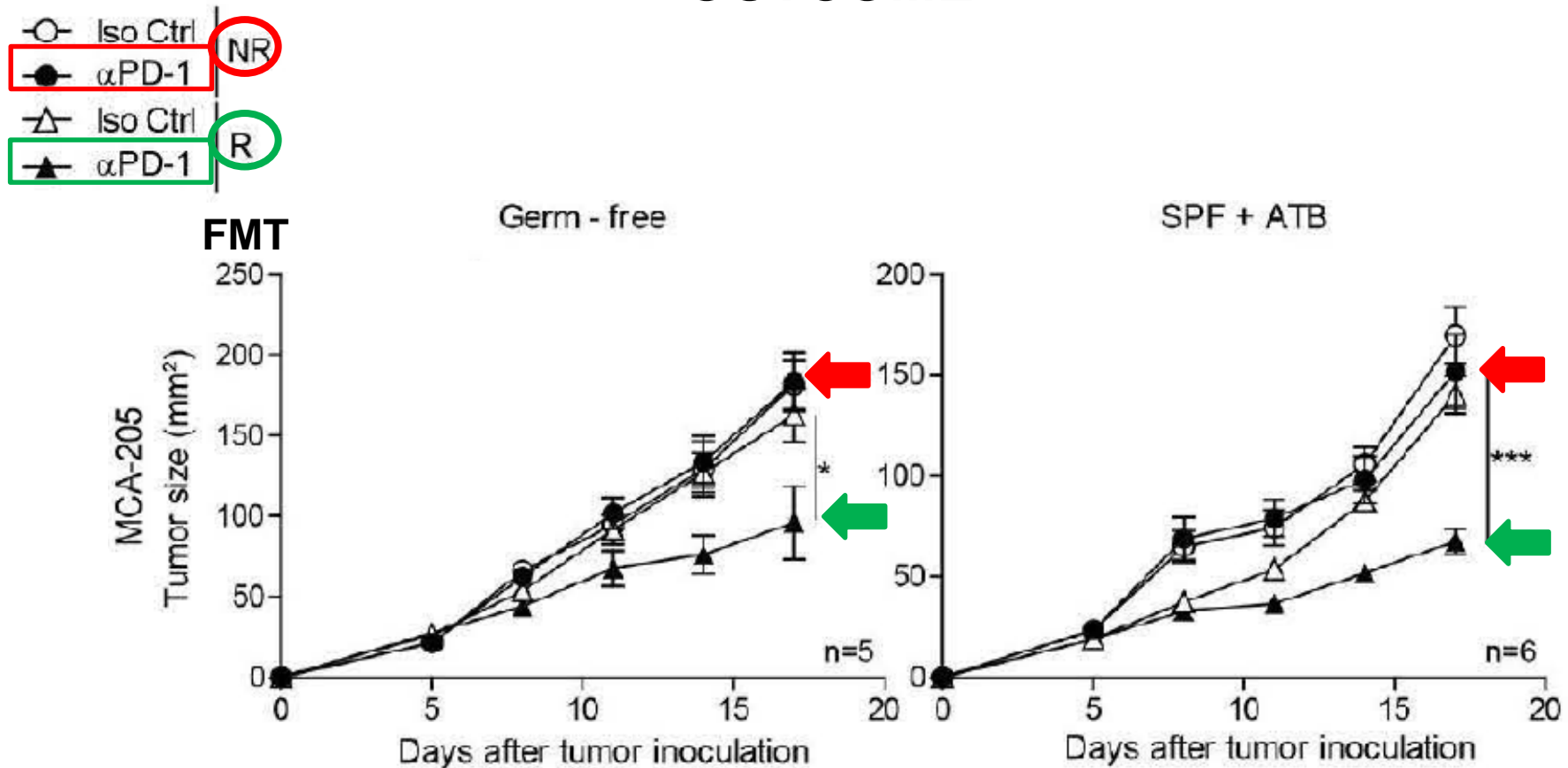
THE COMMENSAL MICROBIOME IS ASSOCIATED WITH ANTI-PD-1 EFFICACY IN METASTATIC MELANOMA PATIENTS



Ratio of beneficial over non-beneficial OTU numbers for each patient vs patient's RECIST aggregate tumor measurement change

ALL PATIENTS WITH A RATIO OVER 1.5 SHOWED CLINICAL RESPONSE

FECAL MICROBIOTA TRANSPLANTATION OF STOOL FROM PATIENTS INTO MICE DICTATES PD-1 BLOCKADE OUTCOME



FMT of feces from **NON-RESPONDER** or **RESPONDER** patients in GERM FREE mice. **PD-1 treatment more effective in mice receiving feces from RESPONDER patients**

What's new in FMT

- Indications

- **Methods**

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graph LR; A[Methods] --> B[Optimisation of working protocols]; A --> C[FMT 2.0 (Microbiota suspensions/microbial consortia)];
```

Optimisation of working protocols

- Routes of delivery
- Predictors of response

FMT 2.0 (Microbiota suspensions/microbial consortia)

Time for fine-tuning microbiota modulation?

FMT: as easy as swallowing a pill?

Capsule FMT has been being used since 2014 to treat CDI, with success

| Year | 1° author | Design | Sample | Feces/capsule | Single course | CDI Cure rate |
|------|-----------|---------------------|----------------------|------------------------|--------------------|---|
| 2014 | Youngster | Prospective | 20 | 1.6 g (mean) | 30 capsules | 70% (single course); 90% (multiple courses) |
| 2015 | Hirsch | Retrospective | 19 | 2.3 g (mean) | 8-12 capsules | 68% (single course); 89% (multiple courses) |
| 2016 | Hagel | Retrospective | 12 | NR | NR | 83% (single course); 92% (multiple courses) |
| 2016 | Youngster | Prospective | 180 | 1.6 g (mean) | 30 capsules | 82% (single course); 94% (multiple courses) |
| 2017 | Staley | Prospective | 49 | NR | Different n° | 88% (single course) |
| 2017 | Kao | Non-inferiority RCT | 57 caps. 59 colon | 80-100 g per treatment | 40 capsules | 96% (single course): not inferior to colonoscopy |

- Capsule FMT restored bacterial diversity and resolved dysbiosis
- Shifts in the fecal microbiome were incremental rather than immediate

Staley et al – Gut microbes 2017

Capsule FMT may boost **dissemination of FMT** and ease sustained **cure of chronic disorders** (e.g. UC) through repeated treatment sessions

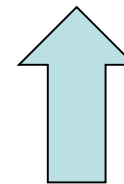
Need for optimised capsule protocols

FMT 2.0 – Culturomics-based synthetic microbiota consortium

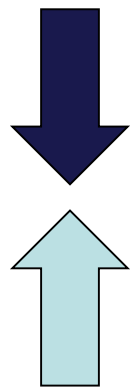
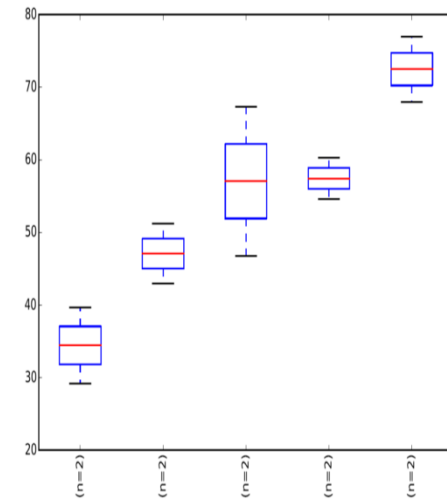
Synthetic microbiota consortium composed of **15 bacterial species** from a **successful FMT donor**, selected from those engrafting the recipients' gut

10 rCDI pts

100% cure of rCDI



Microbiota richness



Proteobacteria

**Verrucomicrobia/
*A. muciniphila***

