The Gut Microbiota in Health and Diseases: A New Therapeutic Target?

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Disclosure Statement

Speaker:

Dr. Ghizlane Bendriss

- Has no relevant financial relationships to disclose
- Will not be discussing unlabeled/unapproved use of drugs or products

Goal of this presentation

TO RAISE AWARENESS ON THE ROLE OF MICROBIOTA AMONG HEALTHCARE PROFESSIONALS, SCIENTISTS, STUDENTS, AND GENERAL PUBLIC.

Presentation Agenda

01

Introduction

What is Microbiota?

02

Modulation of Gut Microbiota

Nutrition, Antibiotics, Probiotics, transplants

03

Experimental & Clinical trials

Most impressive results: Diabetes, Obesity, Autoimmune, Inflammatory, etc…

04

Microbiota & Health

Development of Gut microbiota and mechanisms

05

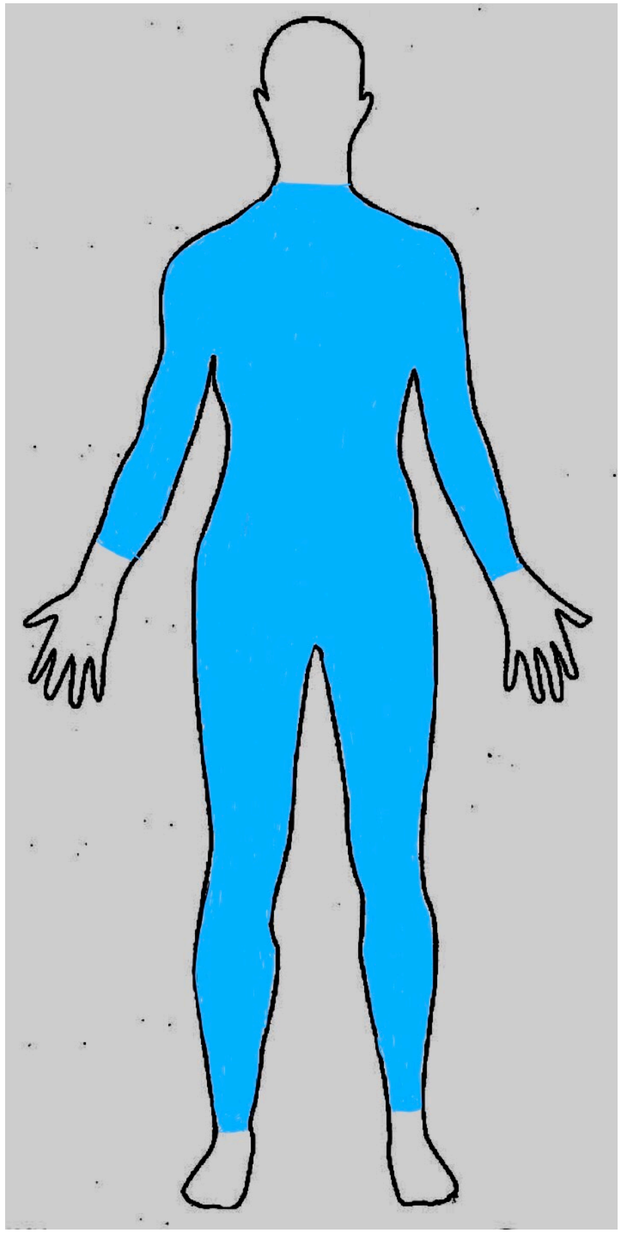
Microbiome studies in Qatar

06

Conclusion

1

What is Microbiota?



Microbiota

01

Composition

Bacteria, Fungi, Archae, Viruses. Composition vary with location.

02

Digestive Tube (mouth to anus), Skin, Vagina, uterus, urethra, bladder, conjunctiva, lung, biliary tract.

03

Number

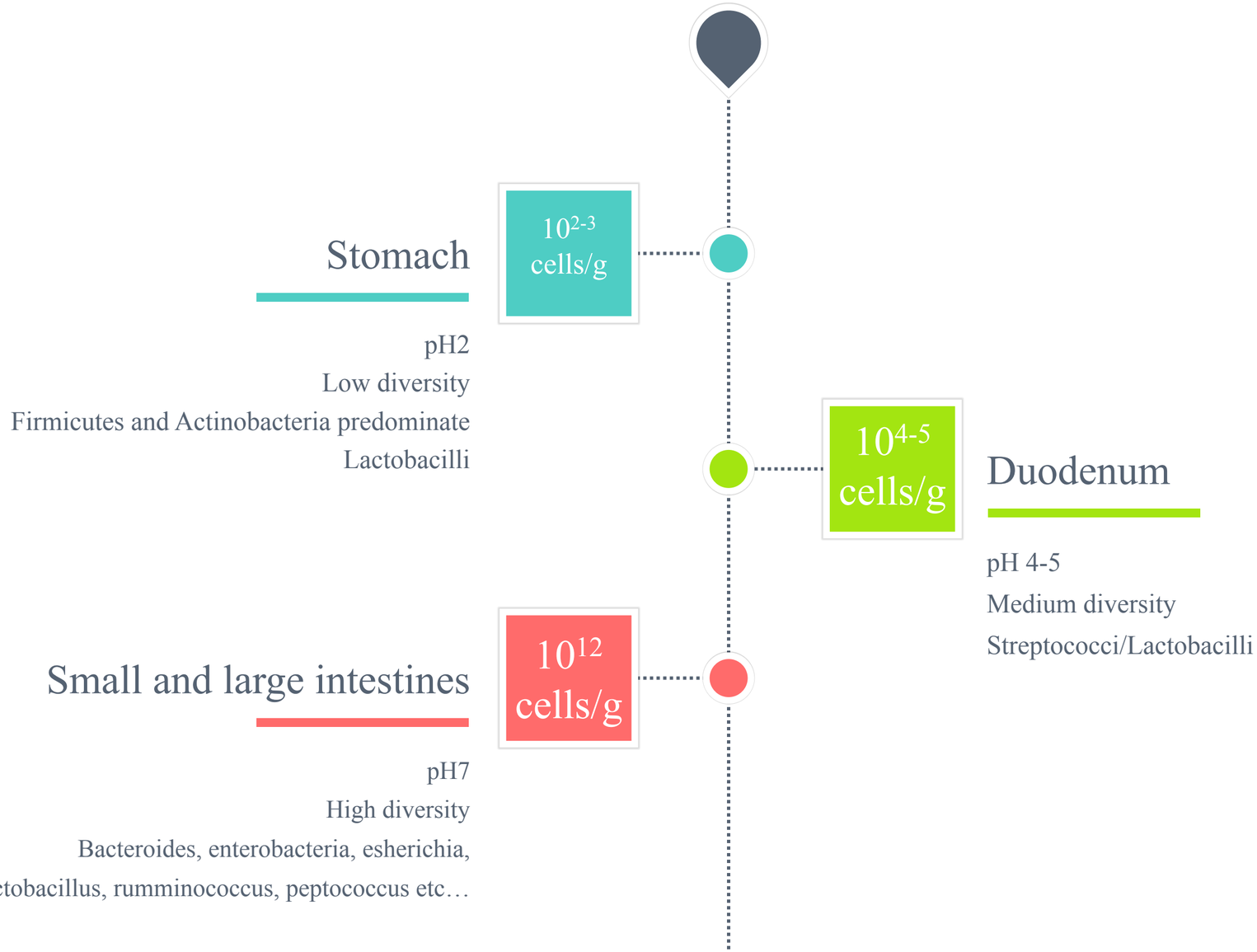
Over 100 trillion microbial cells; 10 times more than human eukaryotic cells.
Microbiome (collection of genomes) 100 times more than human genes.

04

Effects on human physiology

Influence physiology, metabolism, nutrition, immune function.

Microbiota composition differs with location



Stomach

10^{2-3} cells/g

pH2

Low diversity

Firmicutes and Actinobacteria predominate

Lactobacilli

Duodenum

10^{4-5} cells/g

pH 4-5

Medium diversity

Streptococci/Lactobacilli

Small and large intestines

10^{12} cells/g

pH7

High diversity

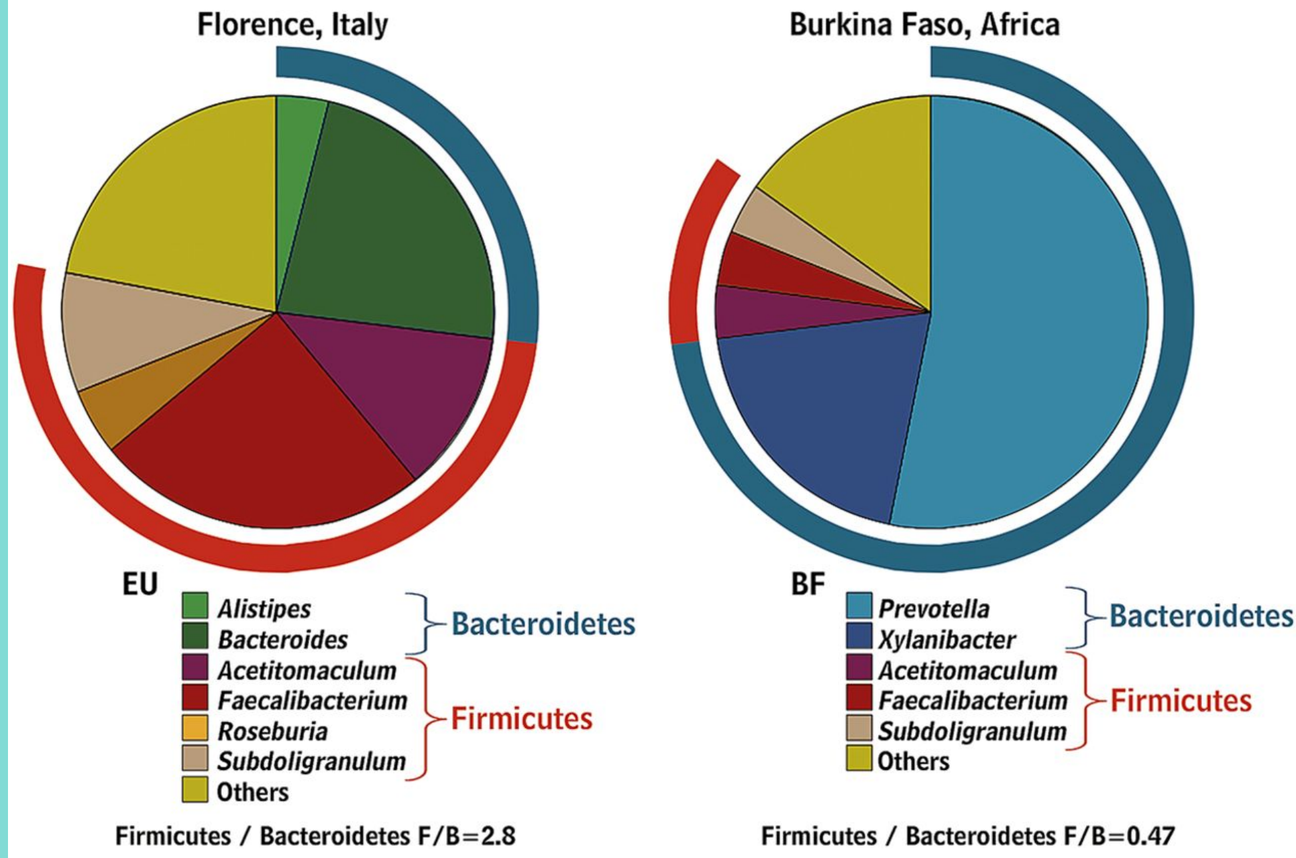
Bacteroides, enterobacteria, esherichia, lactobacillus, rumminococcus, peptococcus etc…

Microbiota differs

Individuals

Microbiota composition differs between healthy individuals.

Rank or level	Example
Species	*E. coli*
Genus	*Escherichia*
Family	Enterobacteriaceae
Order	Enterobacteriales
Class	γ-Proteobacteria
Phylum	Proteobacteria
Domain	Bacteria

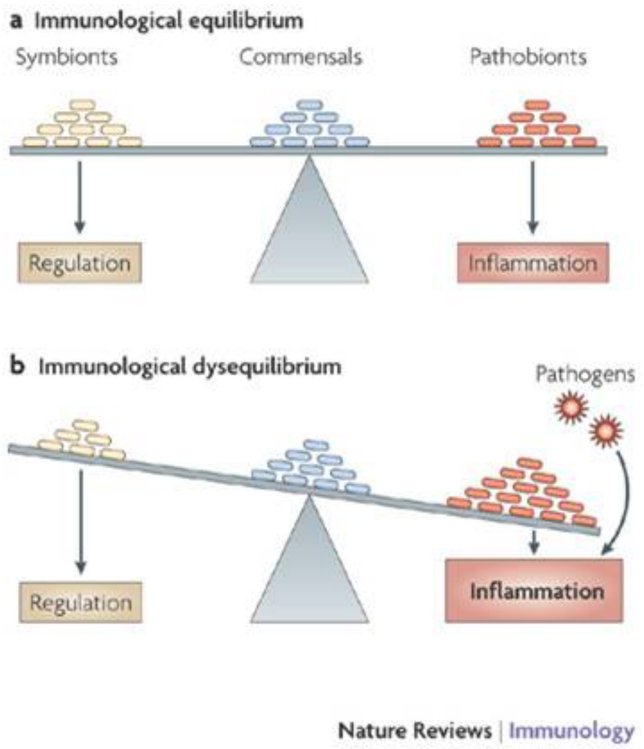


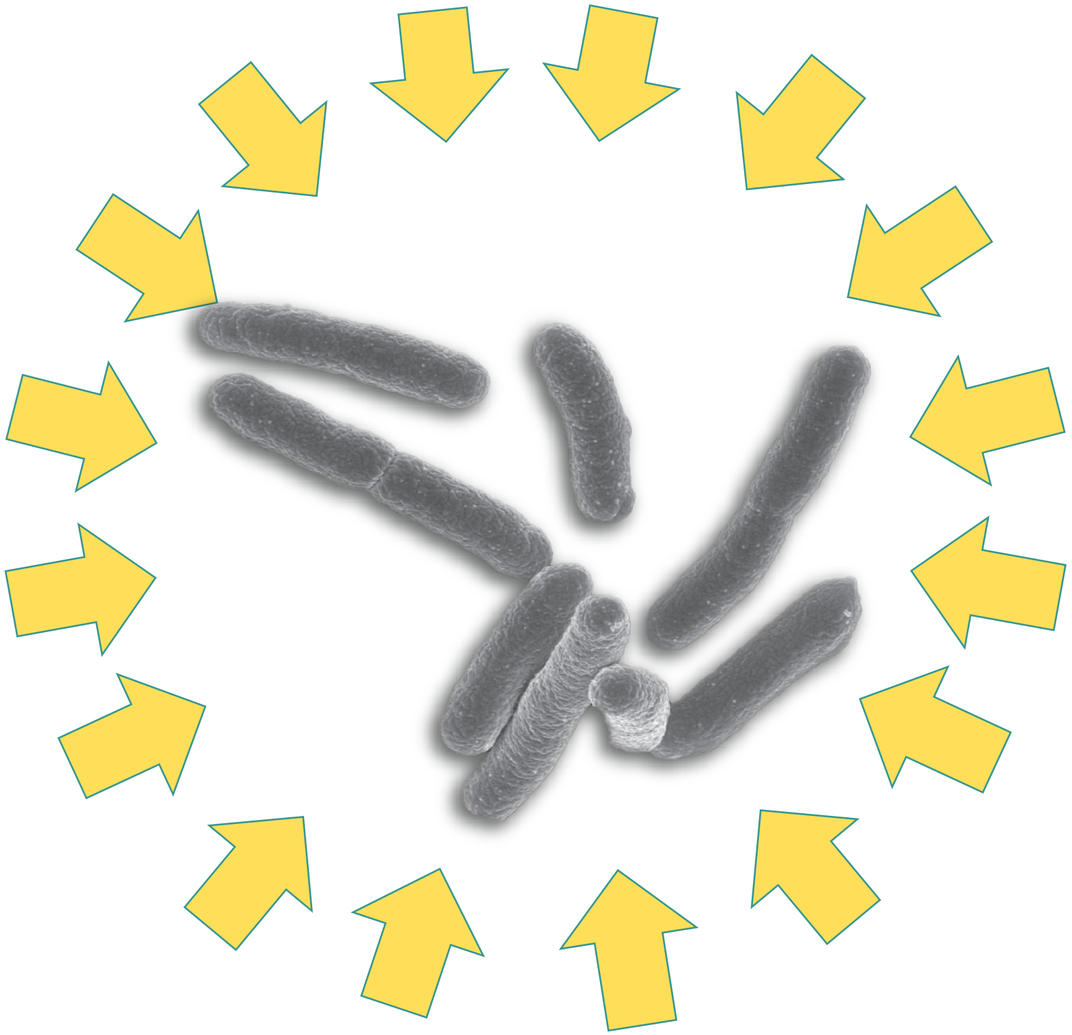
Gut microbiota composition in African children living in rural areas with a polysaccharide-rich diet when compared with Italian city children.35 (Reprinted with permission from Proc Natl Acad Sci USA).

Magnus Simrén et al. Gut 2013;62:159-176

Dysbiosis is observed in most diseases/disorders

- Three categories: beneficial / commensal / opportunistic
- Symbiosis: composition is in equilibrium
- Dysbiosis: unbalanced composition
- Challenge: can we treat diseases by reestablishing a balanced microbiota?





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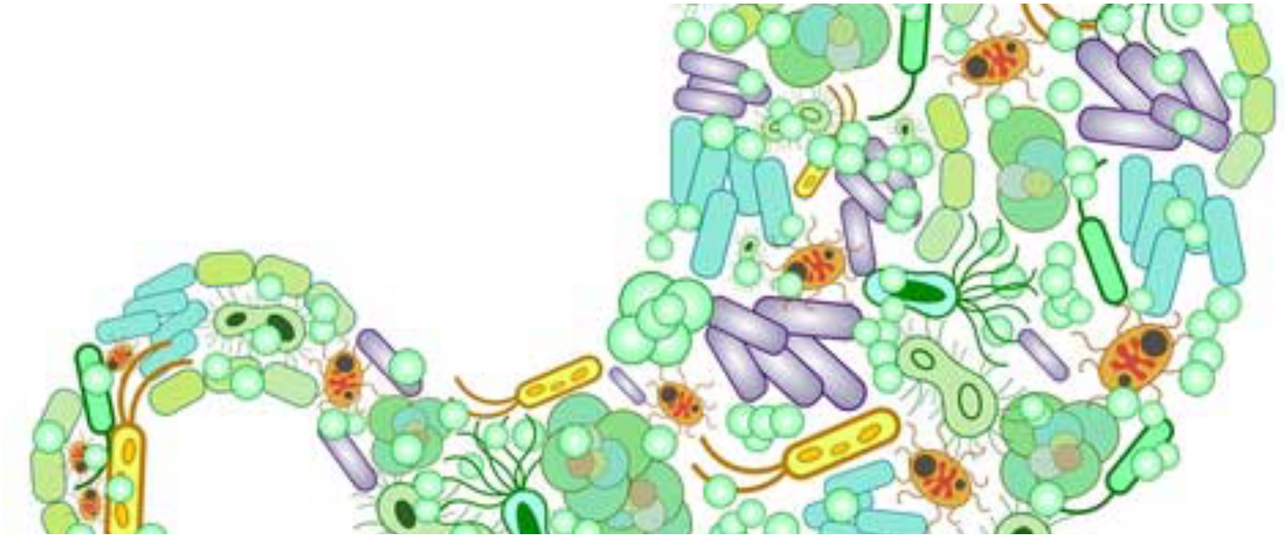
Modulation of the Gut Microbiota



Nutrition/ Lifestyle

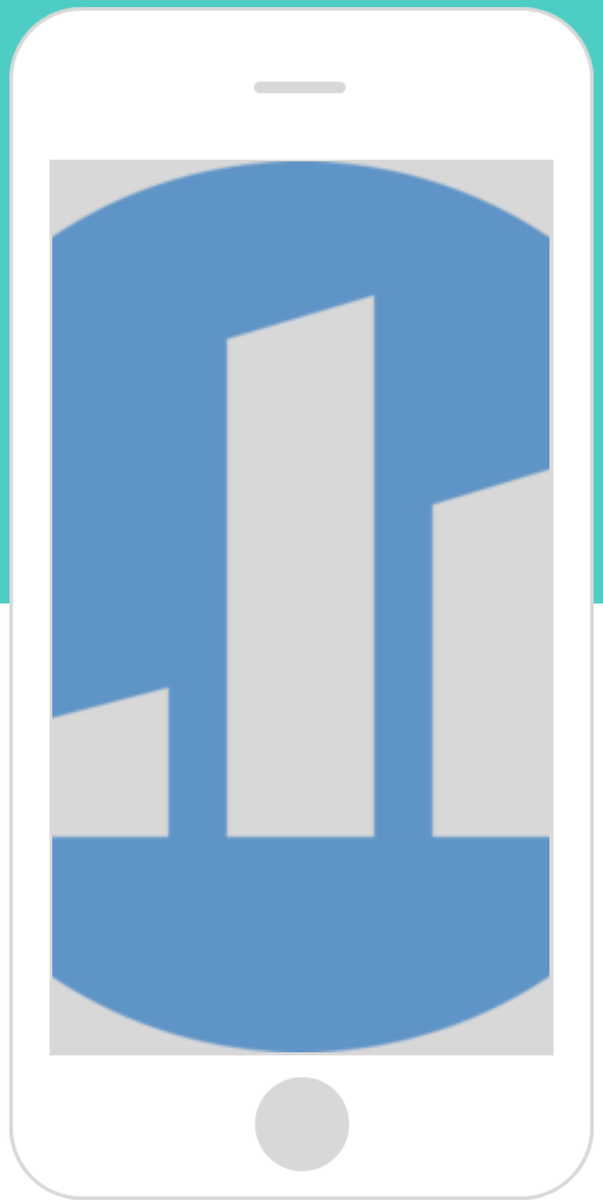
Bacteria and Fungi feed themselves from starch, complex sugars, lactose. They also use fibers for fermentation and production of short chain fatty acids which play a major role in health.
The type of diet high carb -low fiber is generally worsening any dysbiosis.

Antibiotics

Antibiotic misuse promote selection of resistant species and decrease biodiversity in the gut.
It promotes fungal overgrowth.
The use of antibiotics in the first three years of age is critical.

Biotics: pre-, pro-, transplants

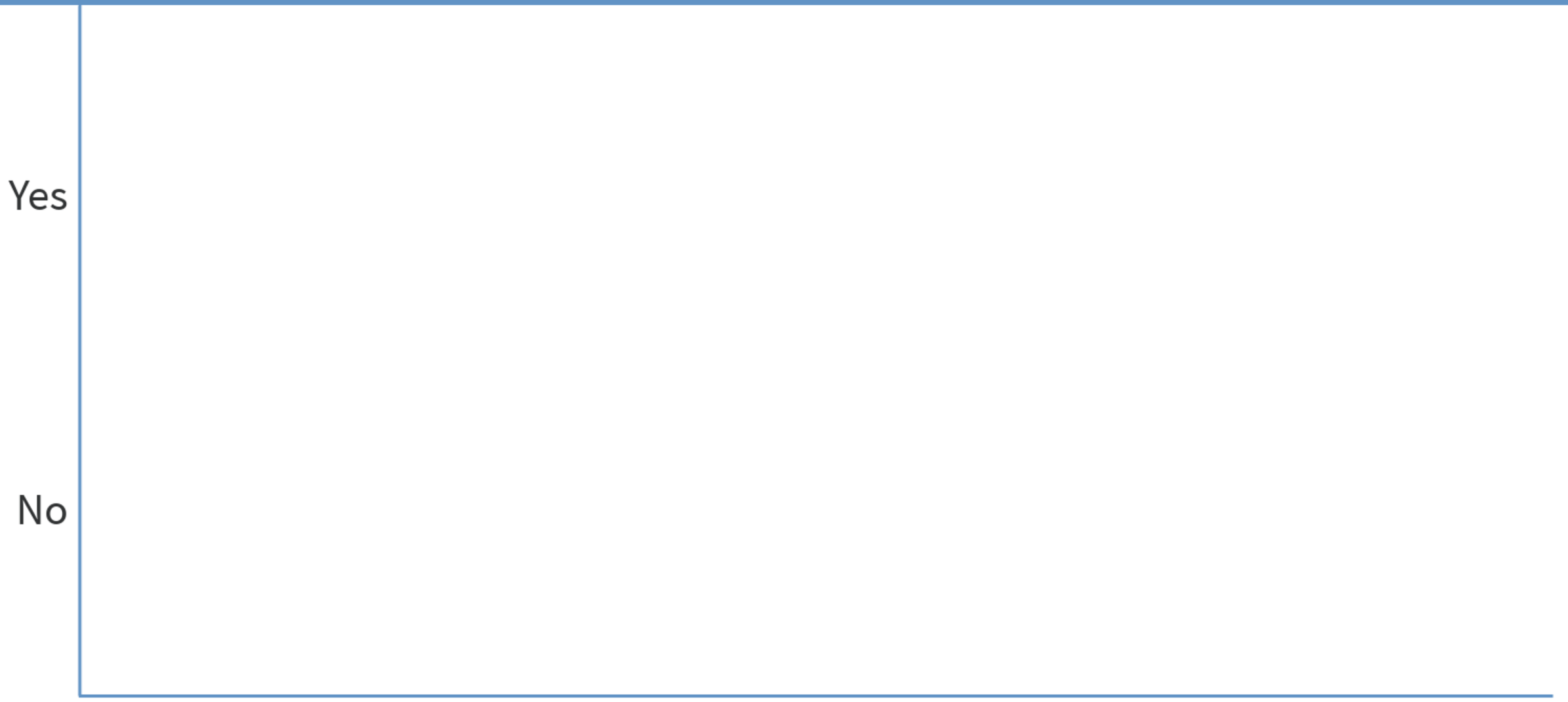
Prebiotics: fibers, non digestible parts of food, get fermented in colon, fermentation is feeding beneficial bacteria.
Probiotics: live beneficial bacteria like lactobacillus, bifidobacterium in yogurts, kefir, kimchi…



PollEverywhere

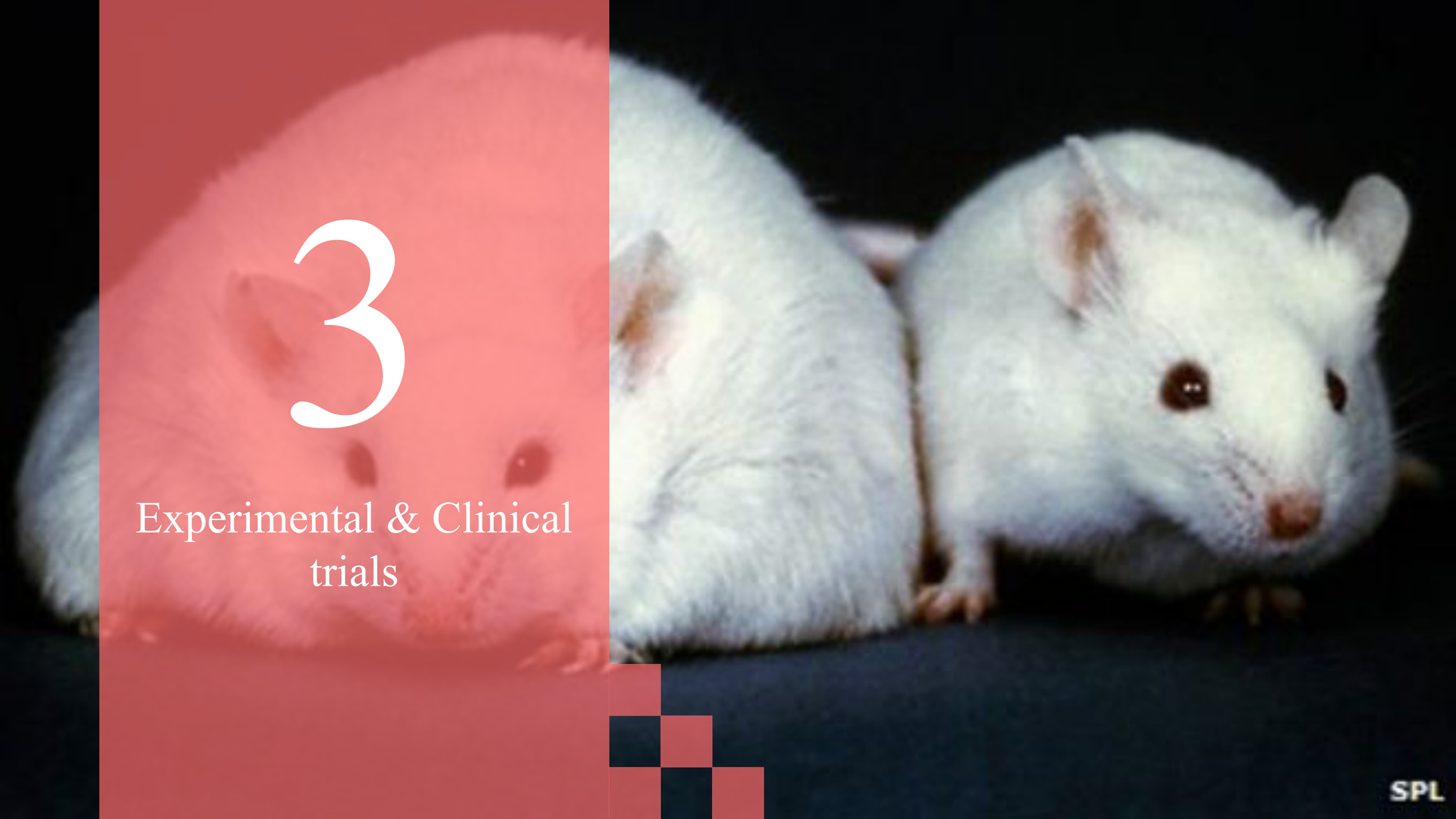
- Download Polleverywhere on your mobile device.
- PollEv.com/microbiota
- You are ready!

In your opinion, should the gut microbiota composition be taken into consideration while devising treatment plans for diseases?



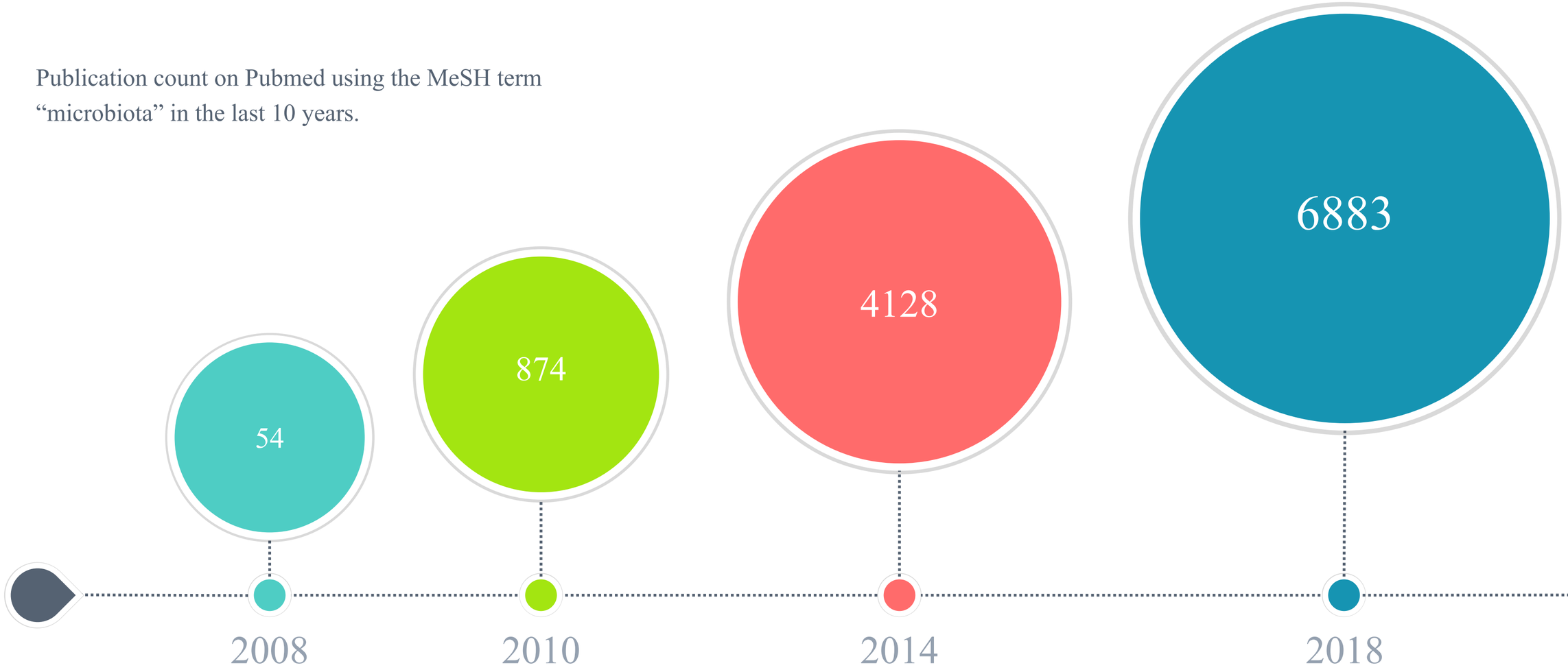
3

Experimental & Clinical trials



Worldwide publications on Microbiota

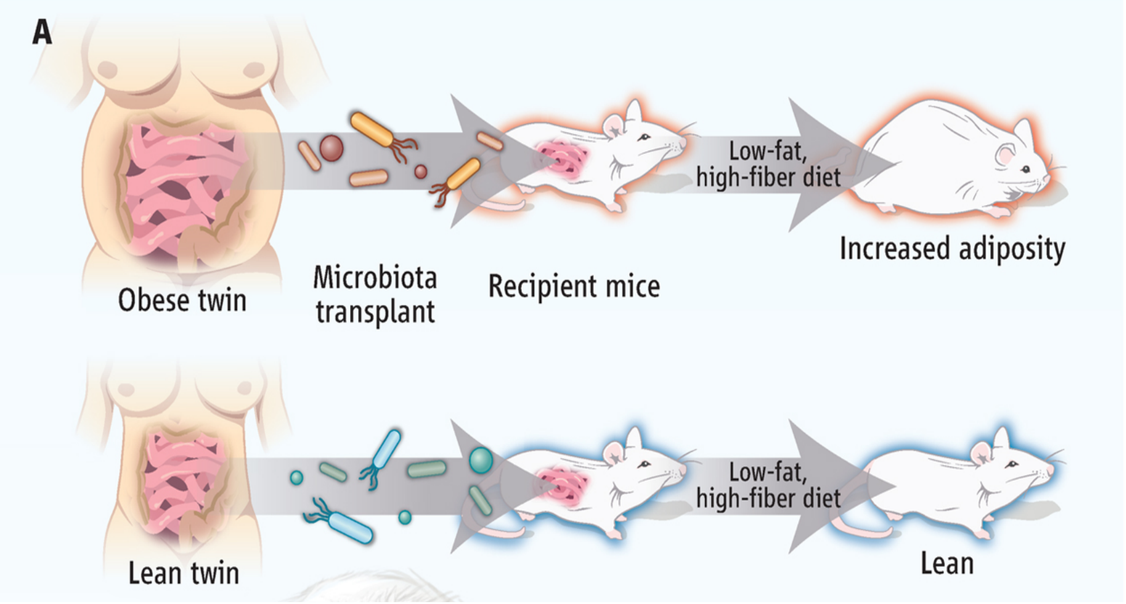
Publication count on Pubmed using the MeSH term “microbiota” in the last 10 years.



In 2018

463	532	1171	1304
Diabetes	Obesity	Inflammatory	Immune
427	603	289	685
Neurodegenerative/Brain	Neuropsychiatric/Mood	Cardiovascular	Cancer

Obesity



Alan W. Walker, and Julian Parkhill Science 2013;341:1069-1070

Fecal transplant

Germ-free mice inoculated with microbiota from obese or lean human twins take on the microbiota characteristics AND the phenotype of the donor.

Clostridium difficile

Fecal Transplant recognized by FDA as an Investigational New Drug with no permit required to treat Clostridium Difficile infections

The US Food and Drug Administration (FDA) has classified human stool as a biological agent and determined that its use in fecal microbiota transplantation (FMT) therapy and other research should be regulated to ensure patient safety.

To use FMT to treat recurrent *Clostridium difficile* infection (RCDI), an investigational new drug (IND) permit is not required, but is strongly encouraged and may ultimately be required.

To use FMT for research or to treat any condition other than RCDI, an IND permit is required.

I. INTRODUCTION

We, FDA or Agency, are informing members of the medical and scientific community and other interested persons that we intend to exercise enforcement discretion under limited conditions, regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C. difficile*) infection not responding to standard therapies. FDA intends to exercise this discretion, provided that: 1) the licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. The consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its reasonably foreseeable risks; 2) the FMT product is not obtained from a stool bank; and 3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product for treatment of the patient.[1]

Case report

EDITOR'S CHOICE

Weight Gain After Fecal Microbiota Transplantation

Neha Alang ✉, Colleen R. Kelly Author Notes

Open Forum Infectious Diseases, Volume 2, Issue 1, 1 January 2015, ofv004,
https://doi.org/10.1093/ofid/ofv004
Published: 01 February 2015 **Article history** ▾

Abstract

Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor. This case may stimulate further studies on the mechanisms of the nutritional–neural–microbiota axis and reports of outcomes in patients who have used nonideal donors for FMT.

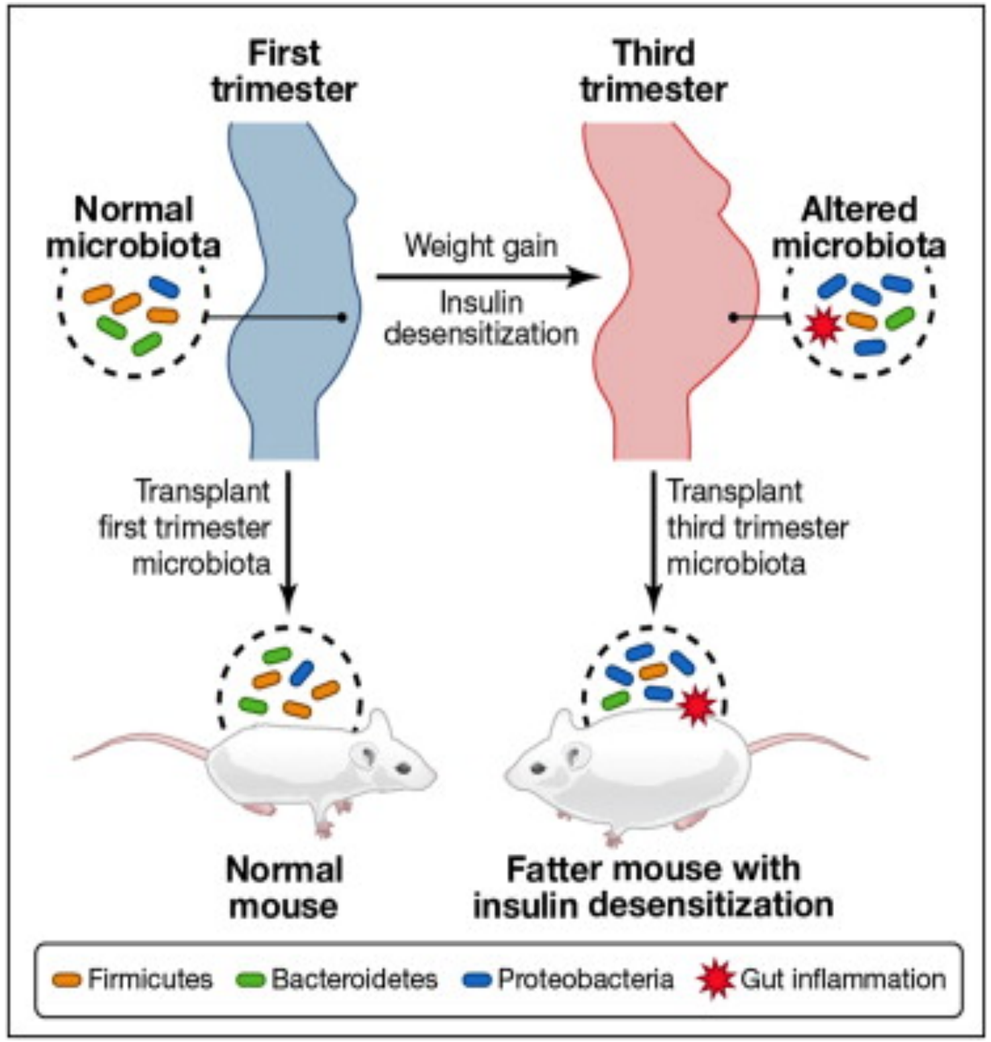
Keywords: *Clostridium difficile* infection, fecal microbiota transplantation, gut microbiota, obesity

Topic: obesity, clostridium difficile infections, feces, weight gain, transplantation, overweight, fecal transplantantation, microbiome, symptom onset, donors

Obesity developed by a woman who got a fecal transplant from an obese donor.

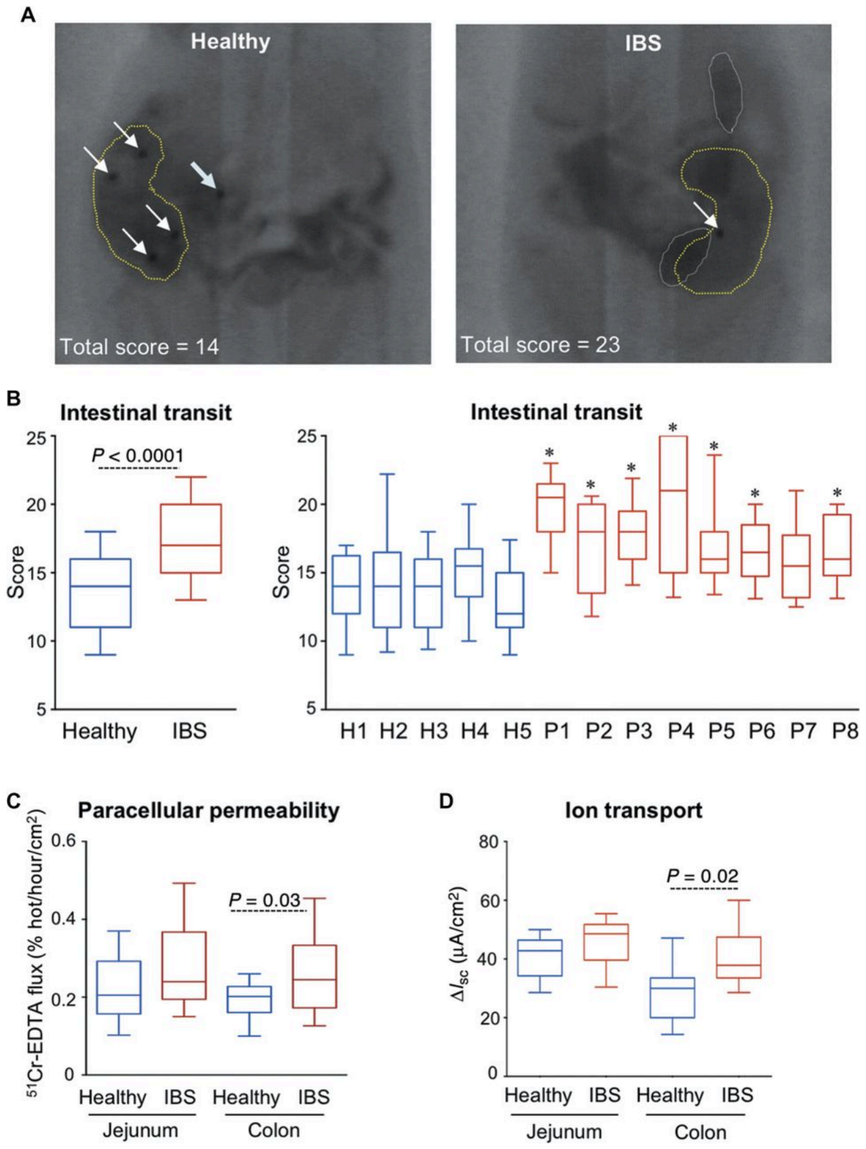
Volume 2, Issue 1
Winter 2015

Diabetes



Insulin desensitization is transferred with fecal transplant to mice.

Inflammatory bowel diseases

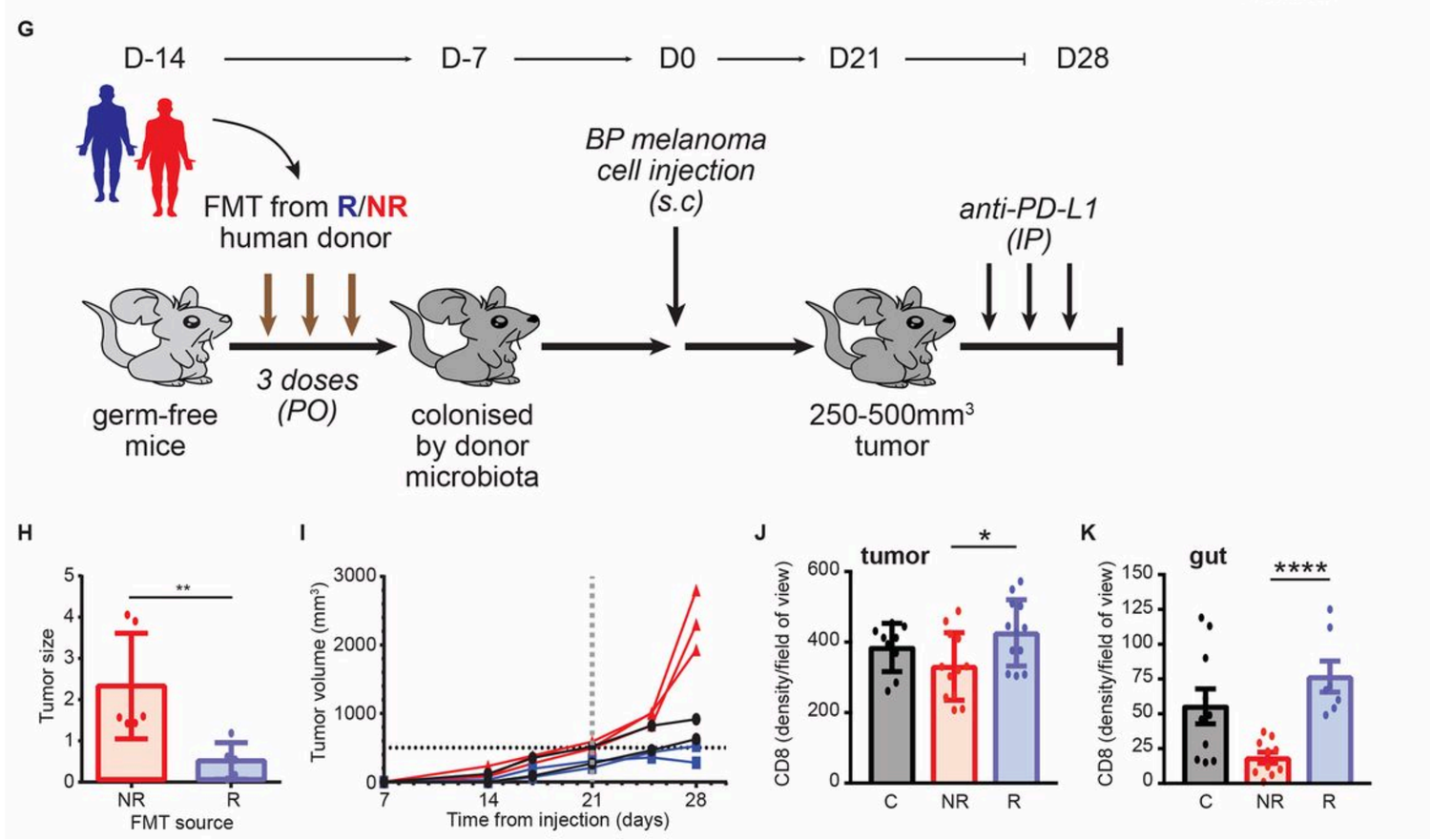


Gastrointestinal transit and intestinal barrier function are altered in mice colonized with IBS-D fecal microbiota from colon.

Science Translational Medicine
AAAS

Giada De Palma et al., Sci Transl Med 2017;9:eaaf6397

Cancer



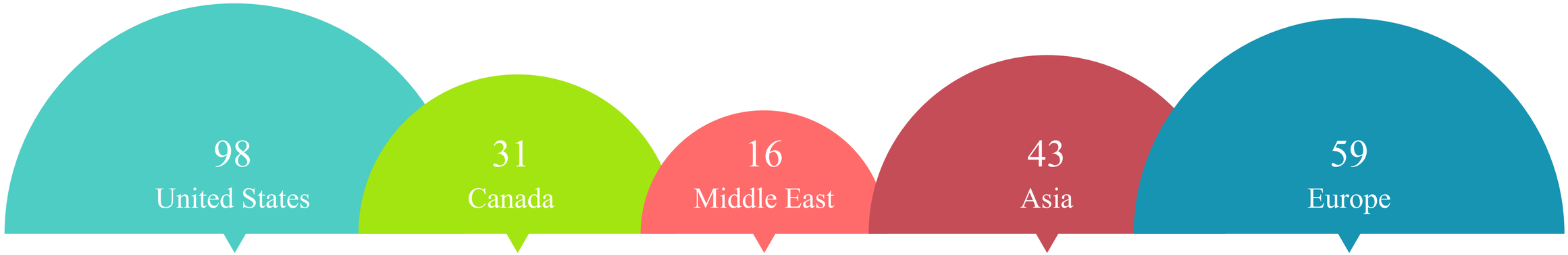
A favorable gut microbiome is associated with enhanced systemic and anti-tumor immunity.

Science
AAAS

V. Gopalakrishnan et al. Science 2017;science.aan4236

Clinical trials worldwide using Fecal Transplant

266 studies- 52 completed



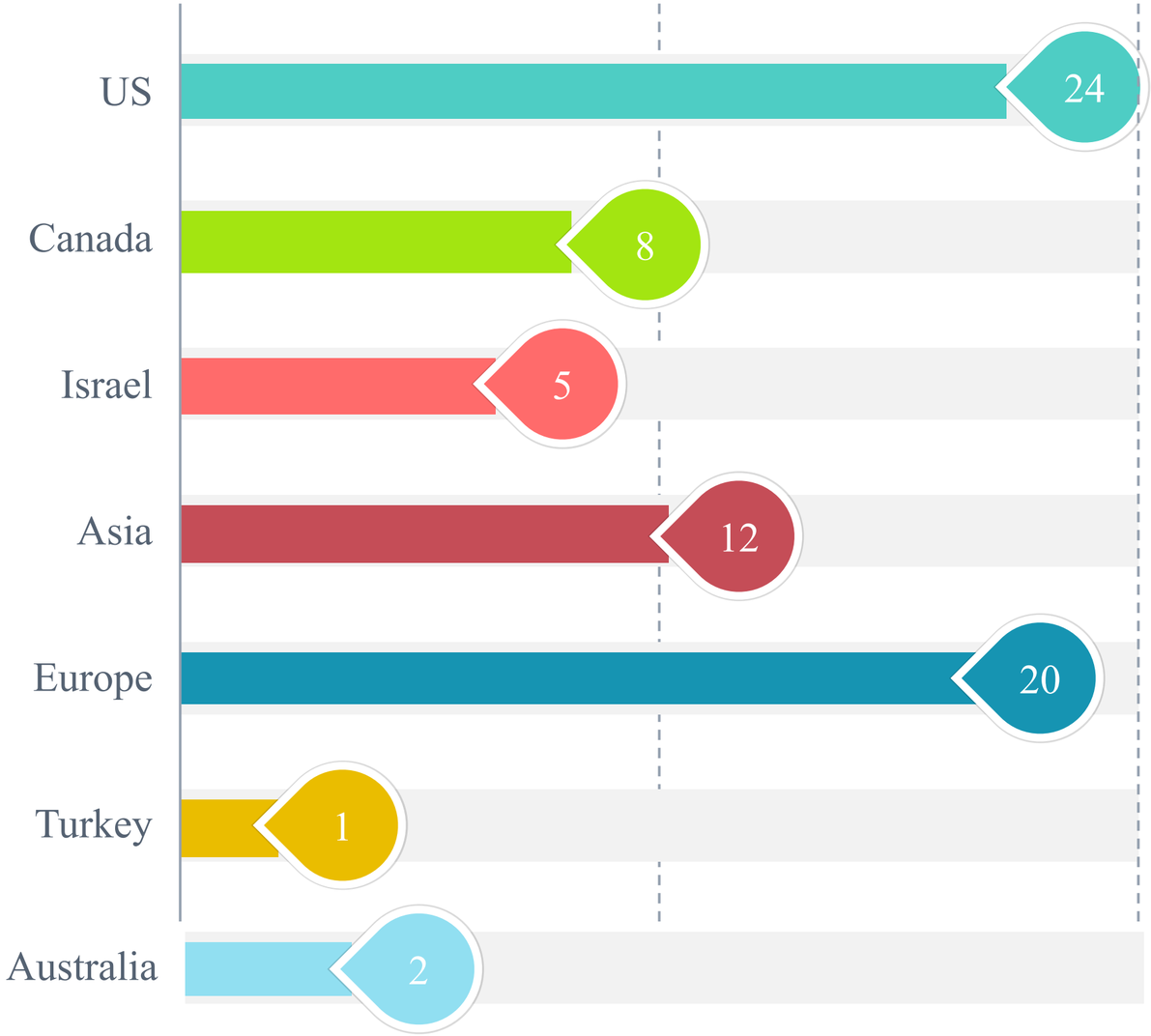
15 in Israel

1 in Turkey

* 2 in South America and 2 in Australia

Source: Clinicaltrial.gov

Inflammatory Bowel Diseases

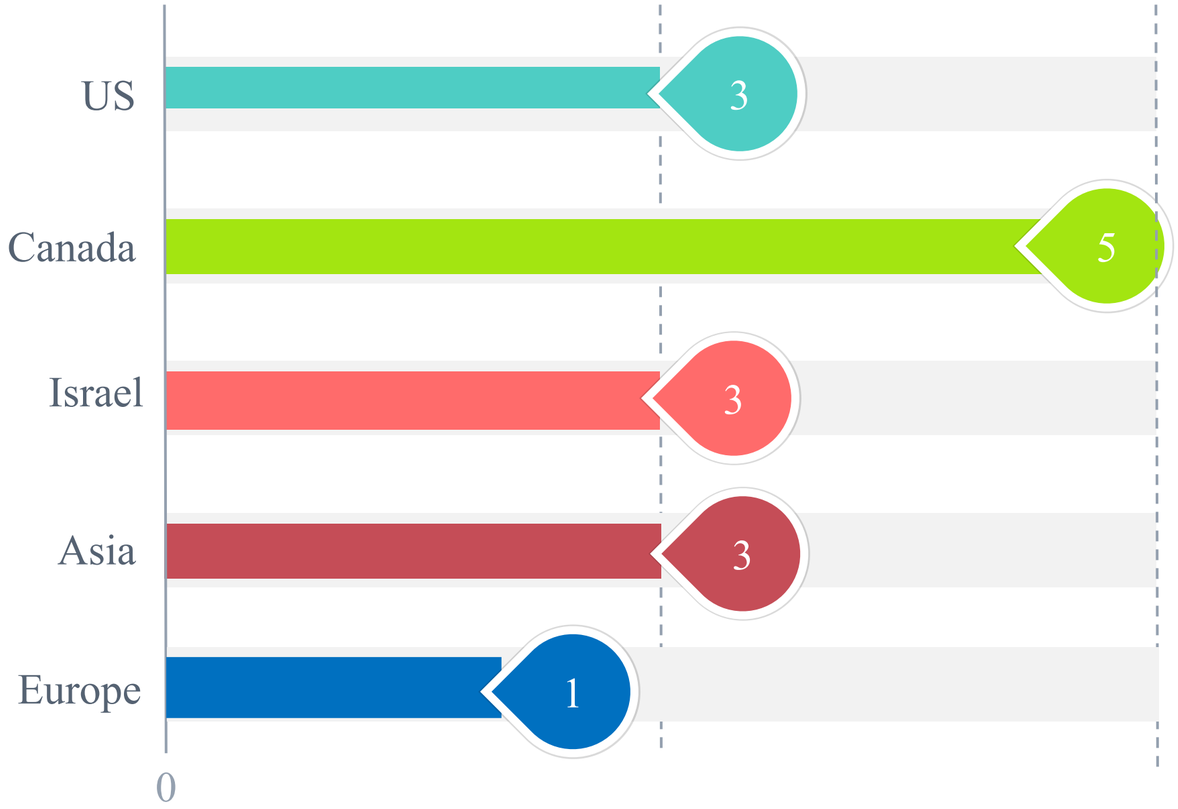


73 studies – 22 completed

2 results published

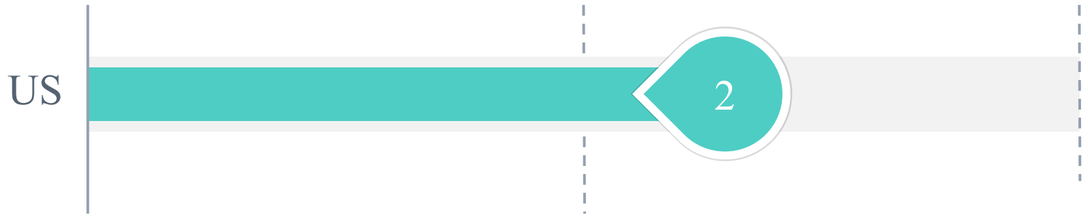
- Seattle Children's Hospital
  Seattle, Washington, United States
- Helen DeVos Children's Hospital of Spectrum Health Hospitals
  Grand Rapids, Michigan, United States

Diabetes/Obesity



15 studies on fecal transplant in Diabetes/Obesity

Autism



2 studies on fecal transplant in Autism

- Currently recruiting
- Children's Hospital Los Angeles, California, United States
- Arizona State University, Tempe, Arizona, United States

Results

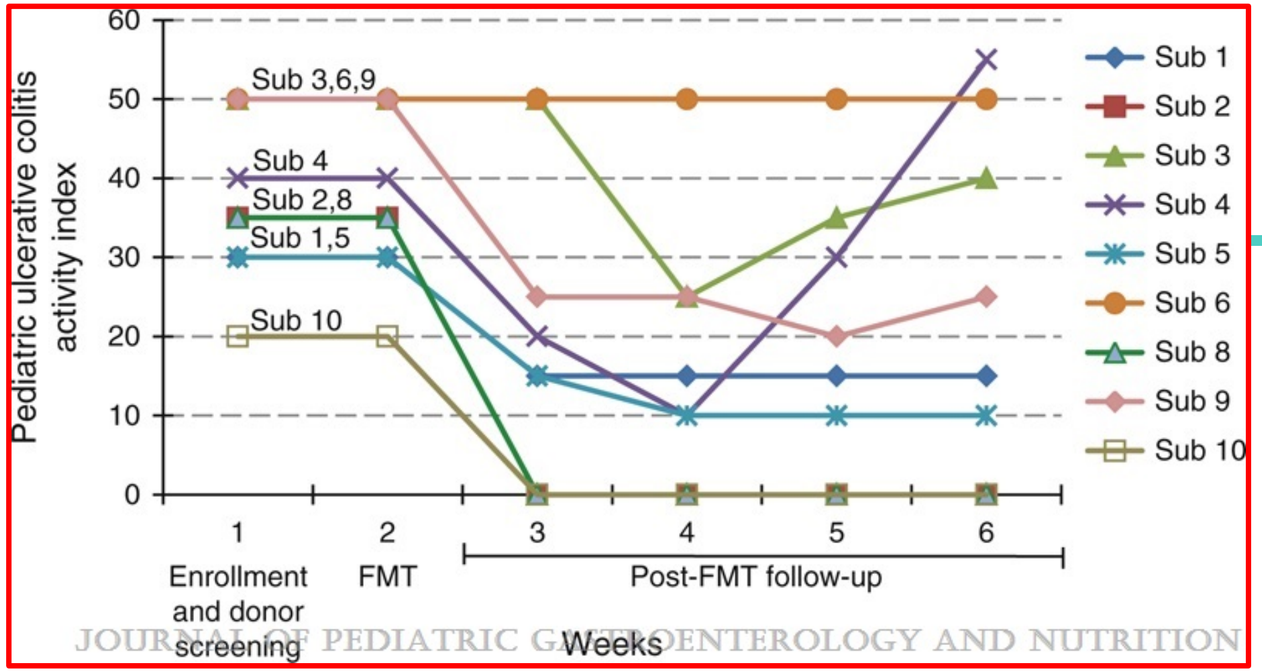
Ohio State University. "Autism symptoms improve after fecal transplant, small study finds: Parents report fewer behavioral and gastrointestinal problems; gut microbiome changes." ScienceDaily. ScienceDaily, 23 January 2017.

RESULTS

2	☐	Completed Has Results	Gut Microbial **Transplantation** in Pediatric Inflammatory Bowel Diseases	• Inflammatory Bowel Disease (IBD)	• Drug: Gut Microbial **Transplantation**	• Helen DeVos Children's Hospital of Spectrum Health Hospitals Grand Rapids, Michigan, United States

ClinicalTrials.gov Identifier: NCT01560819

Recruitment Status : Completed
First Posted : March 22, 2012
Results First Posted : December 4, 2013
Last Update Posted : December 30, 2013



Ulcerative Colitis in children and young adults

Clinical response to fecal microbial transplantation (FMT). Fecal enemas were provided in the second week of the study. Clinical disease activity was determined using pediatric ulcerative colitis activity index. Changes in disease activity can be seen after FMT (weeks 3–6). Subject no. 7 was not included in this analysis because of intolerance to fecal enemas.

Safety, Tolerability, and Clinical Response After Fecal Transplantation in Children and Young Adults With Ulcerative Colitis

Kunde, Sachin; Pham, Angela; Bonczyk, Sarah; Crumb, Teri; Duba, Meg; Conrad, Harold Jr; Cloney, Deborah; Kugathasan, Subra
Journal of Pediatric Gastroenterology and Nutrition56(6):597-601, June 2013.
doi: 10.1097/MPG.0b013e318292fa0d

Inflamm Bowel Dis. 2015 Mar;21(3):556-63. doi: 10.1097/MIB.0000000000000307.

Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease.

Suskind DL[1], Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, Singh N, Damman CJ, Hager KR, Nielson H, Miller SI.

Author information

Abstract

BACKGROUND: Crohn's disease (CD) is a chronic idiopathic inflammatory intestinal disorder associated with fecal dysbiosis. Fecal microbial transplant (FMT) is a potential therapeutic option for individuals with CD based on the hypothesis that changing the fecal dysbiosis could promote less intestinal inflammation.

METHODS: Nine patients, aged 12 to 19 years, with mild-to-moderate symptoms defined by Pediatric Crohn's Disease Activity Index (PCDAI of 10-29) were enrolled into a prospective open-label study of FMT in CD (FDA IND 14942). Patients received FMT by nasogastric tube with follow-up evaluations at 2, 6, and 12 weeks. PCDAI, C-reactive protein, and fecal calprotectin were evaluated at each study visit.

RESULTS: All reported adverse events were graded as mild except for 1 individual who reported moderate abdominal pain after FMT. All adverse events were self-limiting. Metagenomic evaluation of stool microbiome indicated evidence of FMT engraftment in 7 of 9 patients. The mean PCDAI score improved with patients having a baseline of 19.7 ± 7.2, with improvement at 2 weeks to 6.4 ± 6.6 and at 6 weeks to 8.6 ± 4.9. Based on PCDAI, 7 of 9 patients were in remission at 2 weeks and 5 of 9 patients who did not receive additional medical therapy were in remission at 6 and 12 weeks. No or modest improvement was seen in patients who did not engraft or whose microbiome was most similar to their donor.

CONCLUSIONS: This is the first study to demonstrate that FMT for CD may be a possible therapeutic option for CD. Further prospective studies are required to fully assess the safety and efficacy of the FMT in patients with CD.

Patients with active Crohn's disease:

- 7/9 in remission at 2 weeks
- 5/9 no medication and still in remission at 12 weeks
- Response correlated to similarity of donor vs receiver's microbiota compositions.

Dietary Interventions

Tell me what you eat and I will tell you what you are.

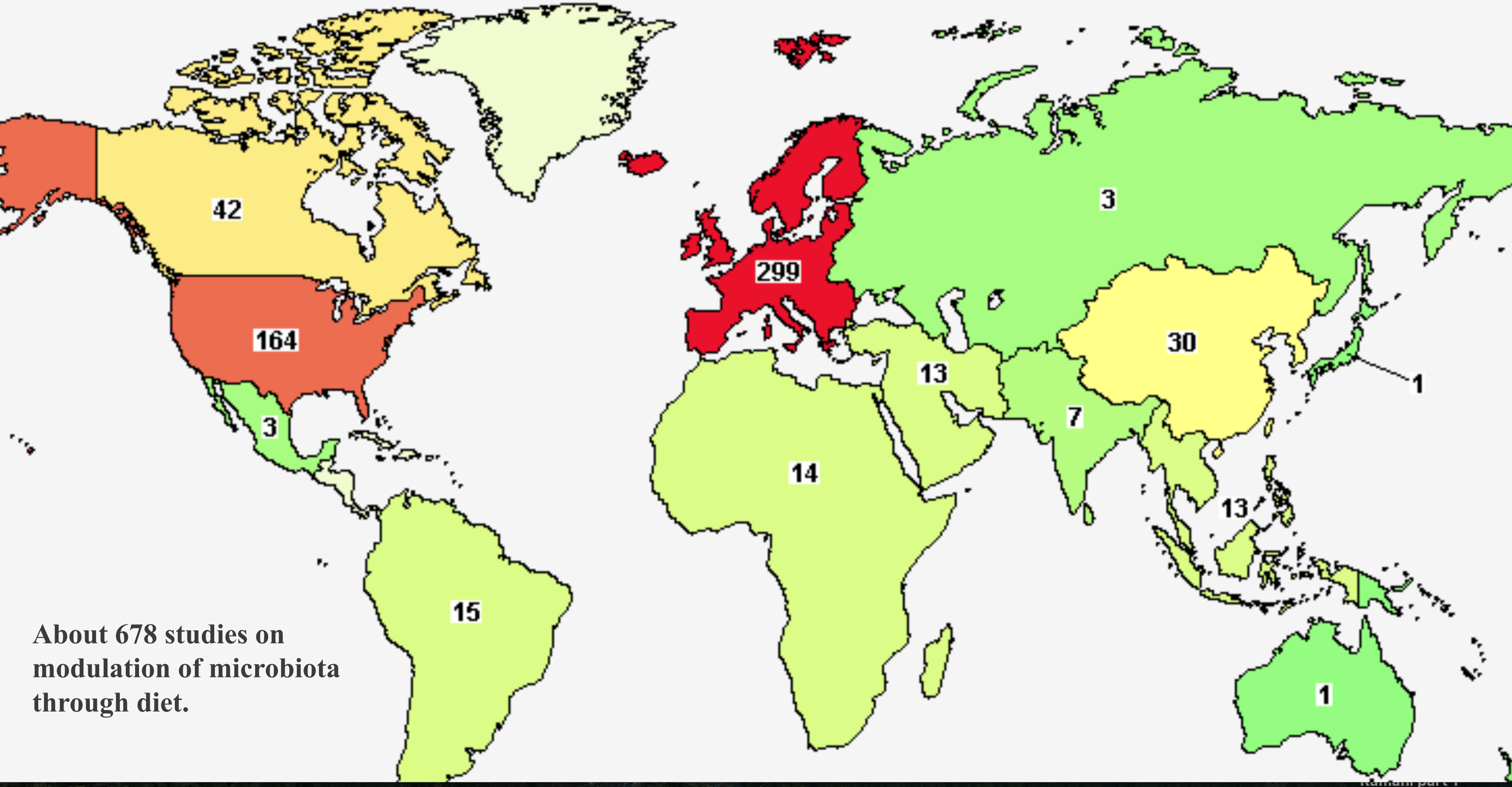
1826, Anthelme Brillat-Savarin

Anthelme Brillat-Savarin wrote, in *Physiologie du Gout, ou Meditations de Gastronomie Transcendante, 1826*:

Dis moi ce que tu manges, je te dirai ce que tu es.

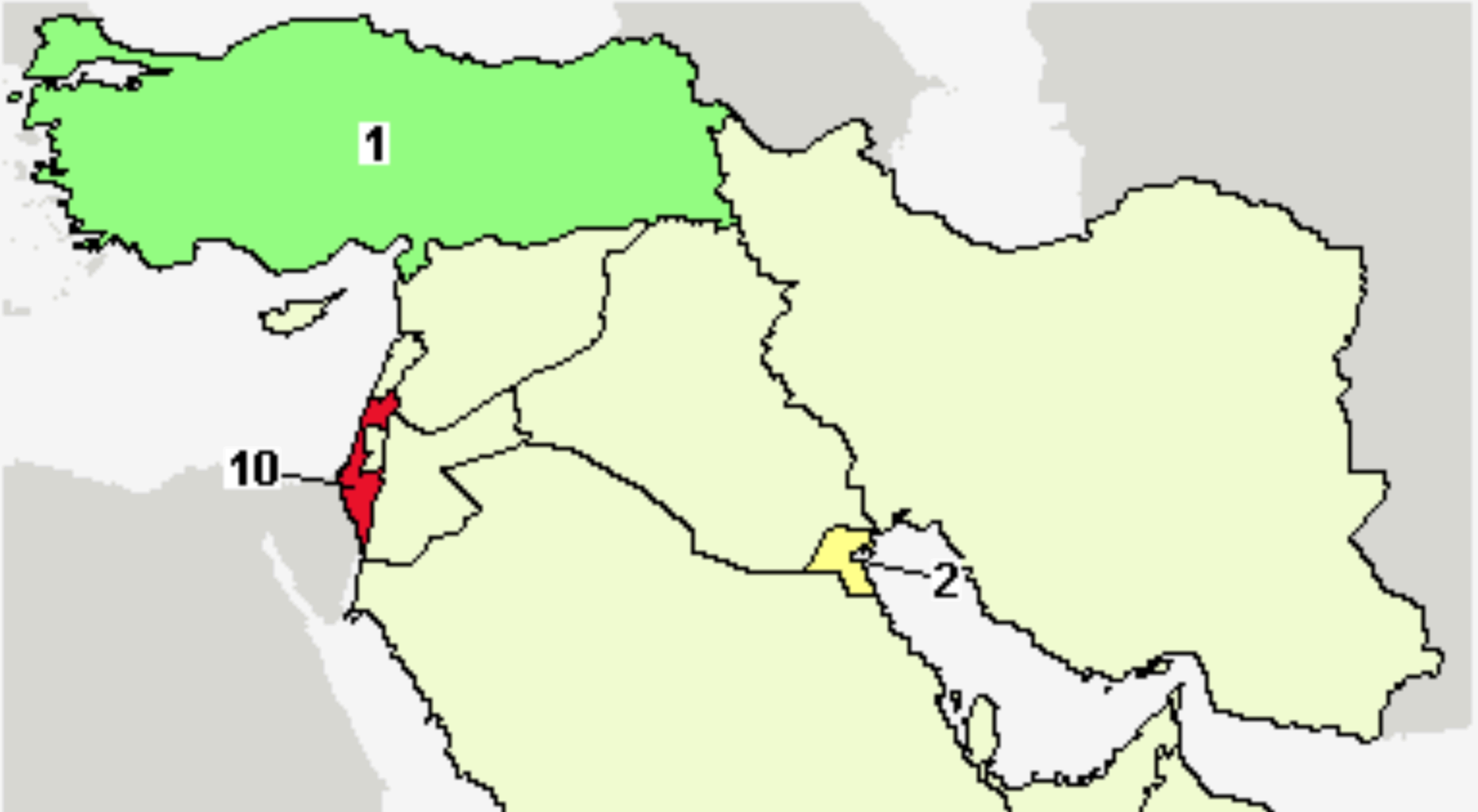
is available for all studies in ClinicalTrials.gov

map below to show a more detailed map (when available) or search for studies (when map not available).



About 678 studies on modulation of microbiota through diet.

below to show a more detailed map (when available) or search for studies (when map not available).

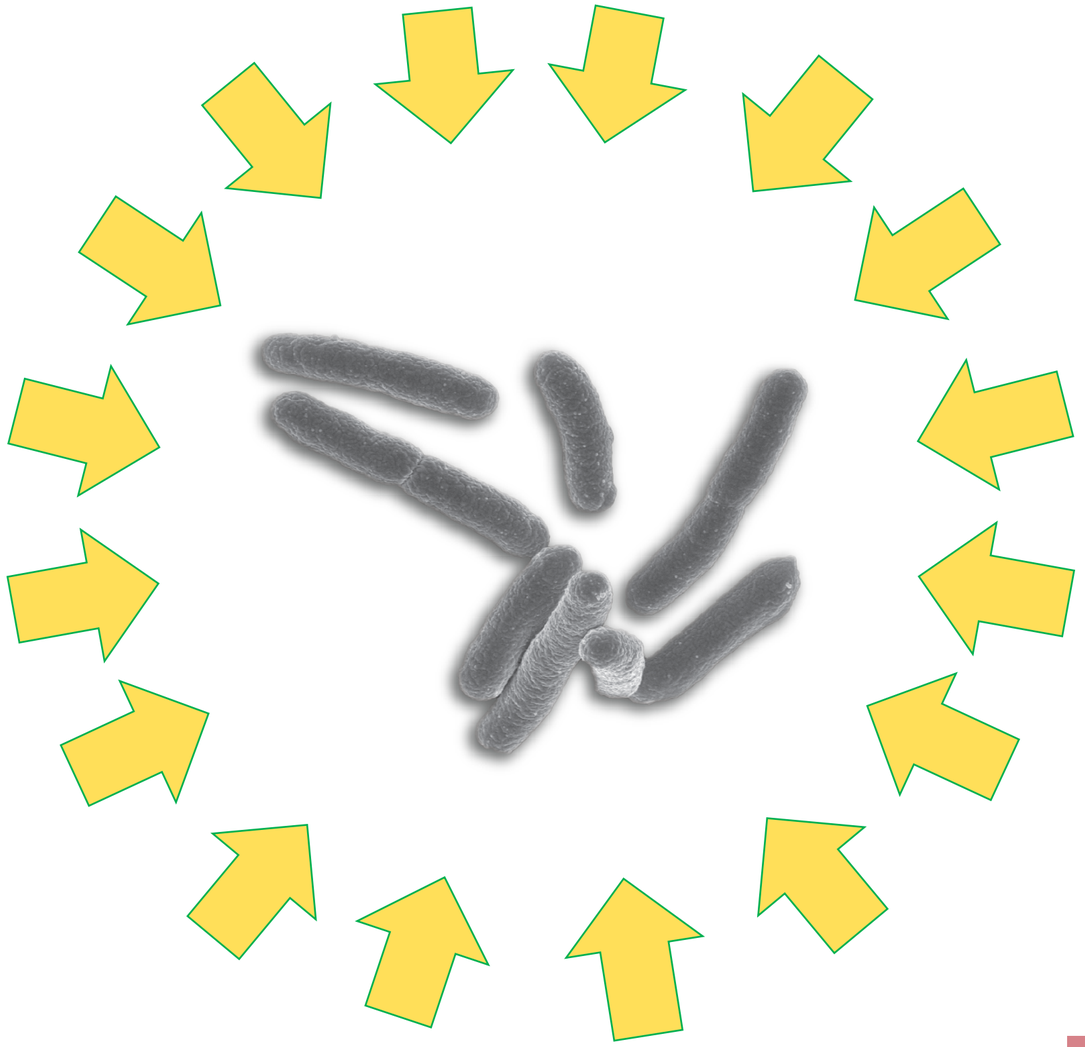


Dietary Interventions

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Completed Has Results	Effect of Xylitol on Oral **Microbiota** in Children	• Bacterial Infections	• **Dietary** Supplement: xylitol • **Dietary** Supplement: sorbitol	• Faculty of Dentistry, Kuwait University Kuwait, **Kuwait**
2		Completed Has Results	Effects of Probiotics on Oral Health	• Periodontal Health • Dental Plaque Accumulation	• **Dietary** Supplement: Probiotics • **Dietary** Supplement: Placebo	• Abdullah Alwaheeb intermediate School Kuwait, **Kuwait**

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Active, not recruiting	The Impact of Vitamin B12 Deficiency on Infant Gut **Microbiota**	• Vitamin B 12 Deficiency		• Marmara University School of Medicine Istanbul, **Turkey**

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Active, not recruiting	Personalized **Diet**-driven **Microbiota** Alterations as a Tool for Improving Mood Status in Elderly	• Depression	• Behavioral: Personalized **Diet**-driven **microbiota** • Behavioral: General information on nutrition and health	• Shamir Research Institute Katsrin, **Israel**
2		Unknown †	Fecal **Microbiota** Transplantation for Diabetes Mellitus Type II in Obese Patients	• Diabetes Mellitus, Type 2 • Obesity	• Procedure: gastroscopy • Drug: Fecal **Microbiota** Transplantation • Other: high fat low fiber **diet** • (and 2 more...)	• Department of Gastroentherology Tel Aviv, **Israel**
3		Recruiting	Insomnia in Older Adults: Impact of Personalized, **Diet**-Induced Alterations in the **Microbiota**	• Insomnia	• Behavioral: PDM nutritional intervention • Behavioral: General information on nutrition and health	• University of Haifa Haifa, Mount Carmel, **Israel**
4		Recruiting	Effects of Green-MED **Diet** Via the Gut-fat-brain Axis	• Abdominal Obesity Metabolic Syndrome	• Other: Physical activity • Other: Physical activity+ MED **diet** • Other: Physical activity+green MED **diet**	• Nuclear research center Negev Dimona, **Israel**
5		Recruiting	Use of a Novel **Diet** (UC **DIET**) for Treatment of Mild to Moderate Active Pediatric Ulcerative Colitis	• Ulcerative Colitis (UC)	• Other: Ulcerative Colitis **Diet** • Drug: Antibiotic cocktail	• The Children's Hospital of Philadelphia Philadelphia, Pennsylvania, United States • IWK Health Centre, Dalhousie University Halifax, Nova Scotia, Canada • The E. Wolfson.Medical Center Holon, **Israel**
6		Recruiting	Pilot Study of Fecal Transplantation Using a Unique **Diet** for Donor and Recipient in Mild to Moderate Treatment Refractory Colitis in Inflammatory Bowel Disease	• Ulcerative Colitis	• Other: Fecal transplantation • Other: Unique novel **Diet** for UC and Unique novel **Diet** for the donor + FMT • Other: Unique novel **Diet** for UC	• Saint-Antoine Hospital, Universite Pierre et Marie Curie Paris, France • Wolfson Medical Center Holon, **Israel** • Tel Aviv Sourasky Medical Center Tel Aviv, **Israel** • (and 2 more...)
7		Unknown †	Low FODMAP (Fermentable Oligo-,di-,Mono-saccharides and Polyols) Versus Gluten-free **Diet** in Pediatric IBS Patients; a Cross-over Randomized Trial.	• Effects of Low FODMAP **Diet** Versus Gluten-free **Diet** on IBS Symptoms in Children	• Other: low FODMAP **diet** vs Gluten free **diet**	• Hadassah Medical Organization Jerusalem, **Israel**
8		Terminated	Use of the Ulcerative Colitis **Diet** for Induction of Remission	• Ulcerative Colitis (UC)	• Other: Ulcerative Colitis **Diet** • Drug: Antibiotic cocktail	• The E.Wolfson Medical Center Holon, **Israel**
9		Active, not recruiting	Probiotics and **Microbiota** in Bariatric Surgery	• NAFLD	• **Dietary** Supplement: Bio-25 (Supherb) • **Dietary** Supplement: Placebo (for Bio-25, Supherb)	• Tel Aviv Sourasky Medical Center Tel Aviv, **Israel**
10		Completed	Testing the Effect of Whole-wheat Sourdough Bread Compared to White Bread on Healthy Individuals	• **Dietary** Modification • Bread • Gastrointestinal Microbiome • (and 2 more...)	• Other: Consumption of sourdough bread • Other: Consumption of white bread	• Weizmann Institute of Science Rehovot, **Israel** • Department of Gastroentherology Tel Aviv, **Israel**



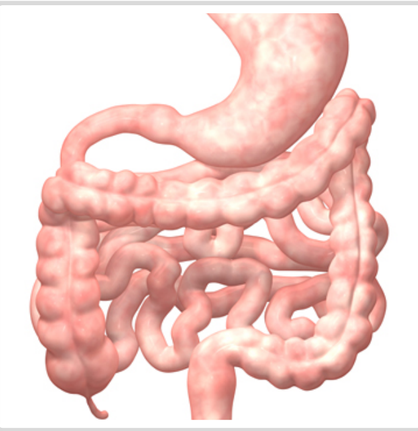
4

Microbiota and Health

Mechanisms involved

The Microbiota-Gut-Brain axis

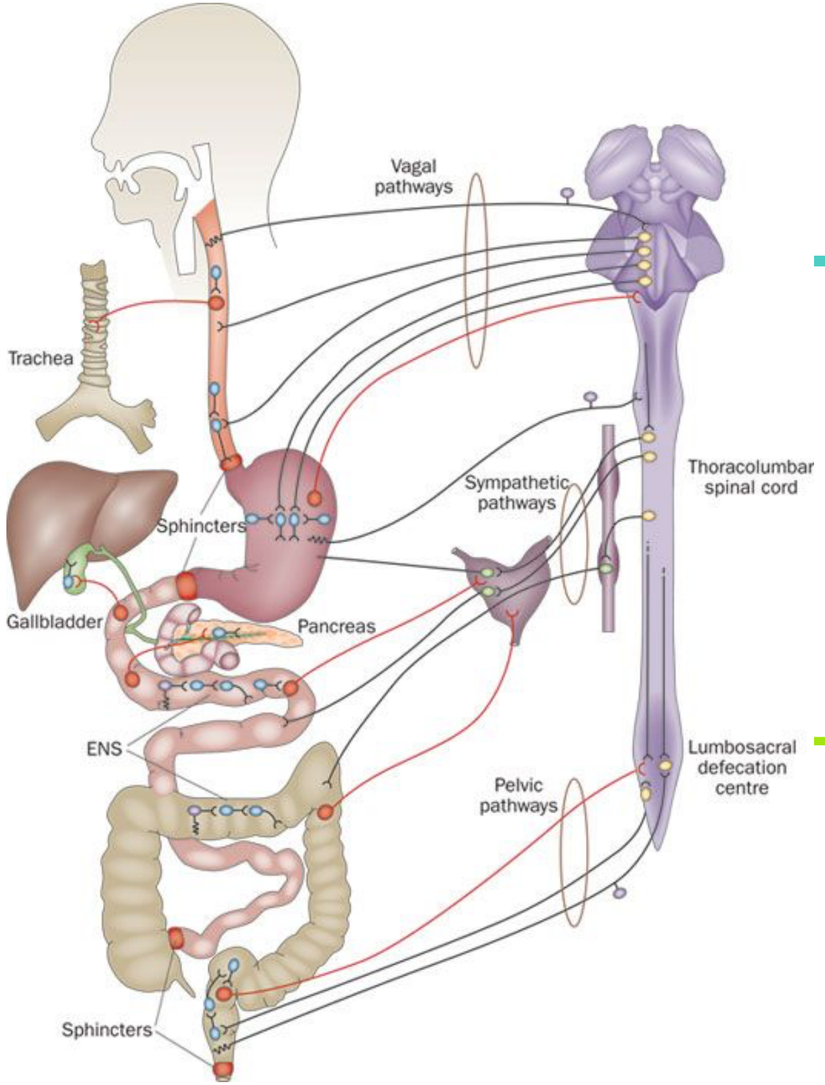
- Gut and Brain continue their development after birth
- First 3 years of life are critical window for both organs
- Several mechanisms for bidirectional communication



The Gut: the forgotten Endocrine organ

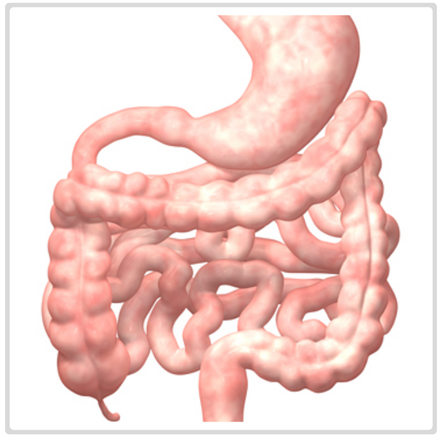
- The Gut microbiota processes food and produce metabolites
- Metabolites from bacteria trigger secretion of hormones by the Gut
- Hormones circulate in the blood and act on various organs

Microbiota-Gut-Brain axis



The Brain

- Size: birth = 25% of adult's brain size; 3 years= 80% adult size
- 100 billion cells
- Myelination
- Synapses formation



The Gut

- Microbiota builds up during first 3 years of age
- Low biodiversity at birth
- Permeability high decreases with biodiversity

Gut Microbiota Development

Week 1	1 year	2 years	3 years
01	02	03	04
■ From few species to over 300 species (Park et al., 2005). ■ Diversity + ■ Breastfeeding ■ Formula milk ■ Delivery mode ■ Antibiotics	■ Diversity ++ ■ Breastfeeding ■ Formula milk ■ Food ■ Antibiotics	■ Diversity ++ ■ Breastfeeding ■ Formula milk ■ Food ■ Antibiotics	■ 500-1000 species (Eckburg et al., 2005) ■ Diversity +++ ■ Immunity +++ ■ Vaccines response depends on microbiota?

Microbiota-Gut-Brain axis

Vagus Nerve

Neuromodulators / neurotransmitters: adrenergic (-), cholinergic (+), serotonergic (+), dopaminergic, GABAergic, neuropeptides may be released and affect smooth muscle **contractility** and hence affect **transit** (Kien, 1996).

Short Chain Fatty Acids

SCF fermentation strengthens tight junctions (Neu, 2007; Sanderson, 2004). Physical and chemical barrier.

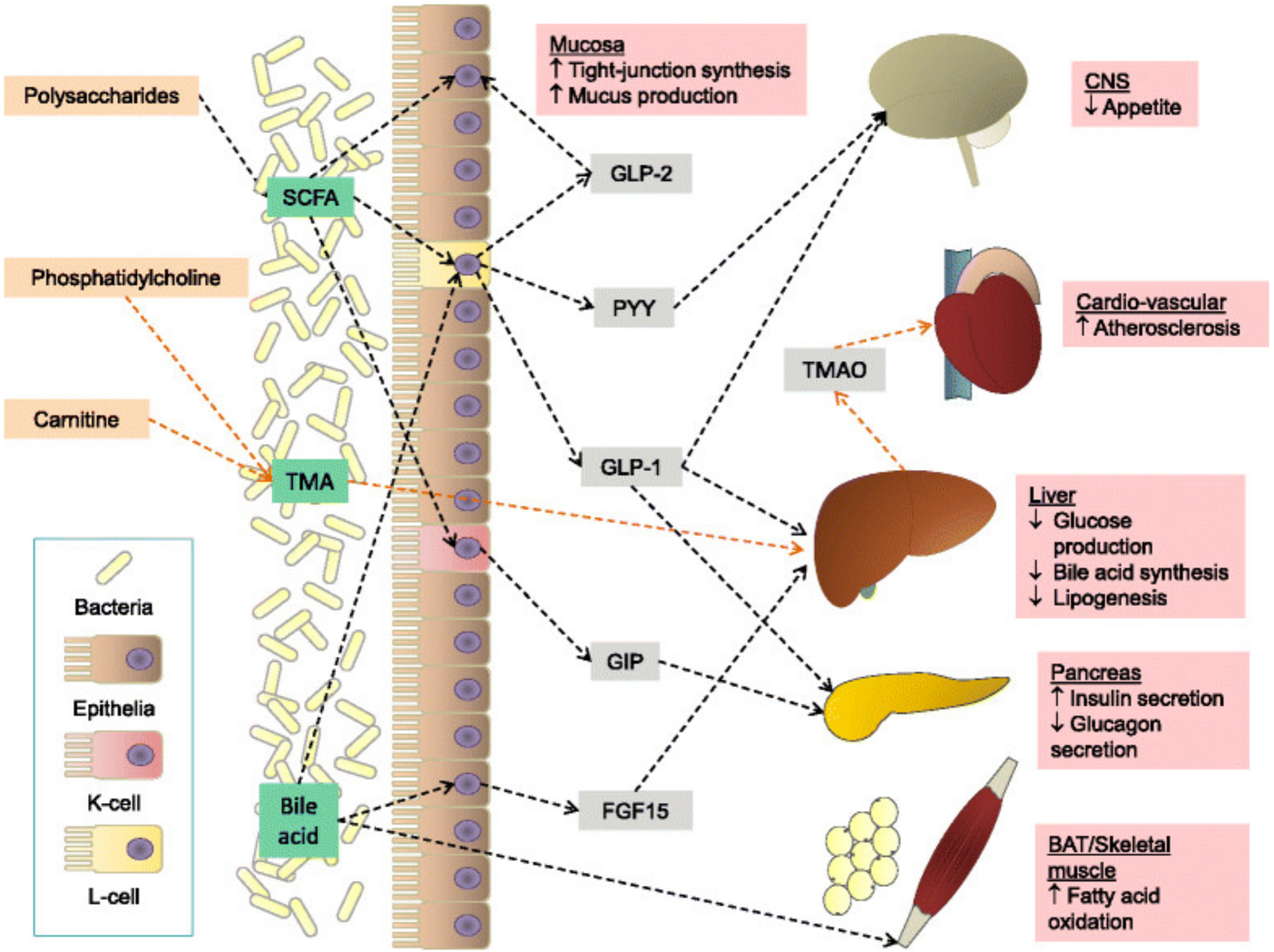
Immunity

The intestinal immune system must fulfill the dual tasks of tolerance to dietary antigens and immune defense (Rautava & Walker, 2008).

Hormones

The gut is an endocrine organ. It releases hormones: serotonin, dopamine, norepinephrine, progesterone, corticosterone.

The neglected endocrine organ



Microbiota processes food

Metabolites derived from food processing are key to understand hormone secretion by the Gut.

SCFA: short chain fatty acids (acetate, butyrate, propionate)

TMA: trimethylamine

Hansen, Tue & Gøbel, Rikke & Hansen, Torben & Pedersen, Oluf. (2015). The gut microbiome in cardio-metabolic health. Genome medicine. 7. 33. 10.1186/s13073-015-0157-z.

5

Microbiota studies in Qatar

Projects

WCMQ	SIDRA	HBKU	Qatar University

Microbiome sequencing, Clinical correlations, epidemiological studies.

At WCM-Q

The Role of Human Gut microbiota in Autism Spectrum Disorders and Inflammatory bowel diseases.

Principal Investigator: Ghizlane Bendriss, PhD Neuroscience

Mentors: Dalia Zacharia, PhD Microbiology-Immunology; Noha Yousri, PhD, Genetic Medicine

Med Students:

Dana Al Ali, Nada Mhaimeed, Ameena Shafeeq, Mohamed Salameh, Zain Burney, Krishnadev Pillai

Sponsored by QNRF.

1

State-of-the-art

Writing literature reviews with most updated results found. Raise awareness: seminars, workshops, conferences etc

2

Evaluate readiness & awareness

Questionnaires for:
Healthcare professionals
Scientists
General public

3

Microbial signatures ASD vs IBD

16sRNA sequencing from stool samples.

4

Correlation study

Correlating questionnaires data with microbial profiles

4 main actors

Patients

Patient needs to be aware of the importance of microbiota and how his lifestyle and nutrition can maintain dysbiosis.

Researchers

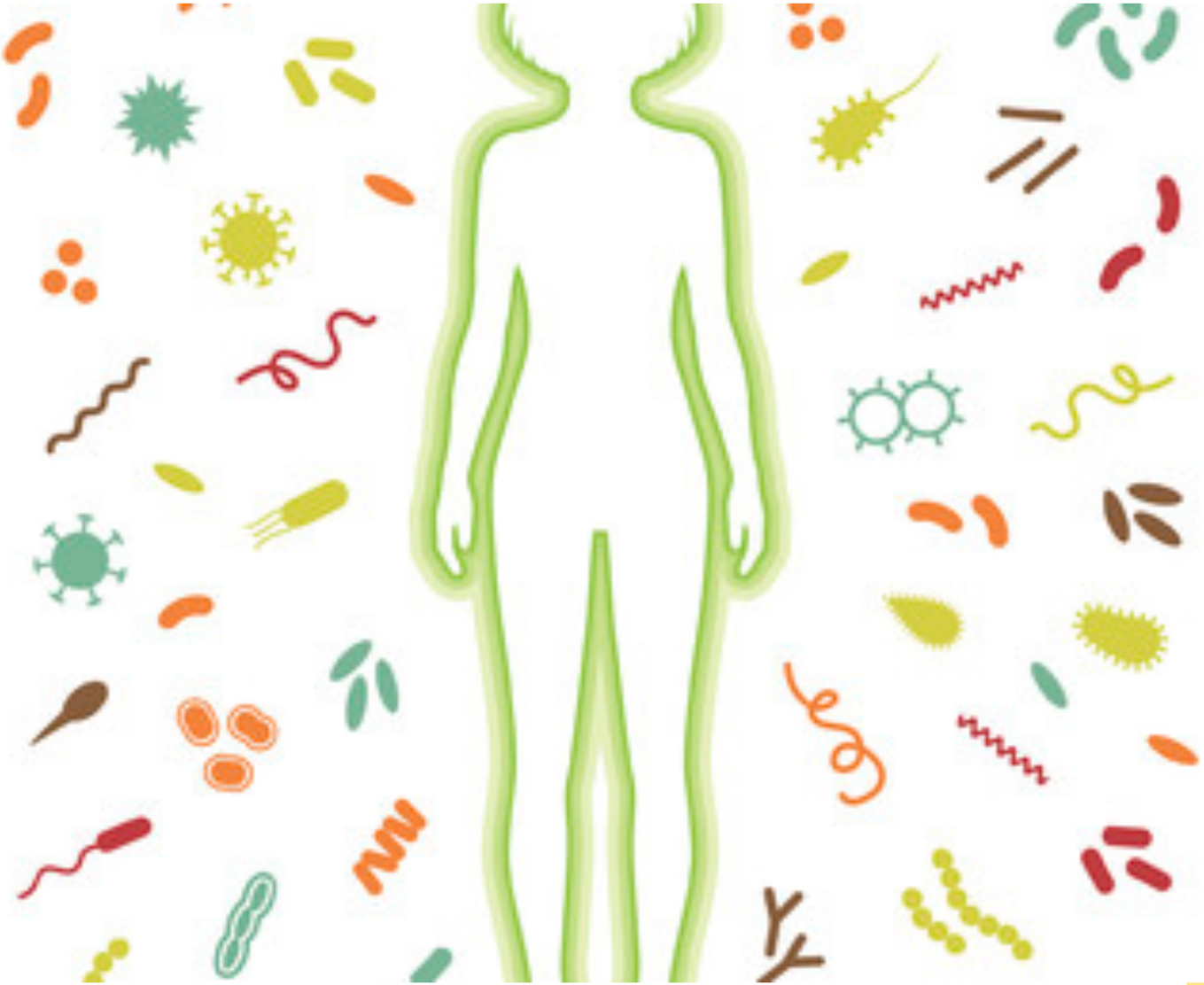
Microbiologists, Immunologists, Neurophysiologists, Biochemists, Endocrinologists, Biologists.

Public health actors

Regulations, Recommendations, Awareness campaigns, Approvals

Physicians and other healthcare professionals

Physicians from all specialties, nutritionists and dieticians, holistic health coaches, nurses, pharmacists etc



6

Conclusion

Imagine …

Each disease having a microbial signature

Microbial signatures would become:

- powerful diagnostic tools: distinguishing between closely related disorders such as Crohn's, Celiac, ulcerative colitis; ASD and ADHD.
- prognostic tools: predict response to a treatment

Key Takeaways

Microbiota

Bacteria, Fungi, Archae, Viruses
10 times more cells than human eukaryotic cells, 100 times more genes than human genes.

Paradigm shift

New area of research, rapidly expanding knowledge.

Experimental and Clinical Trials

Diseases

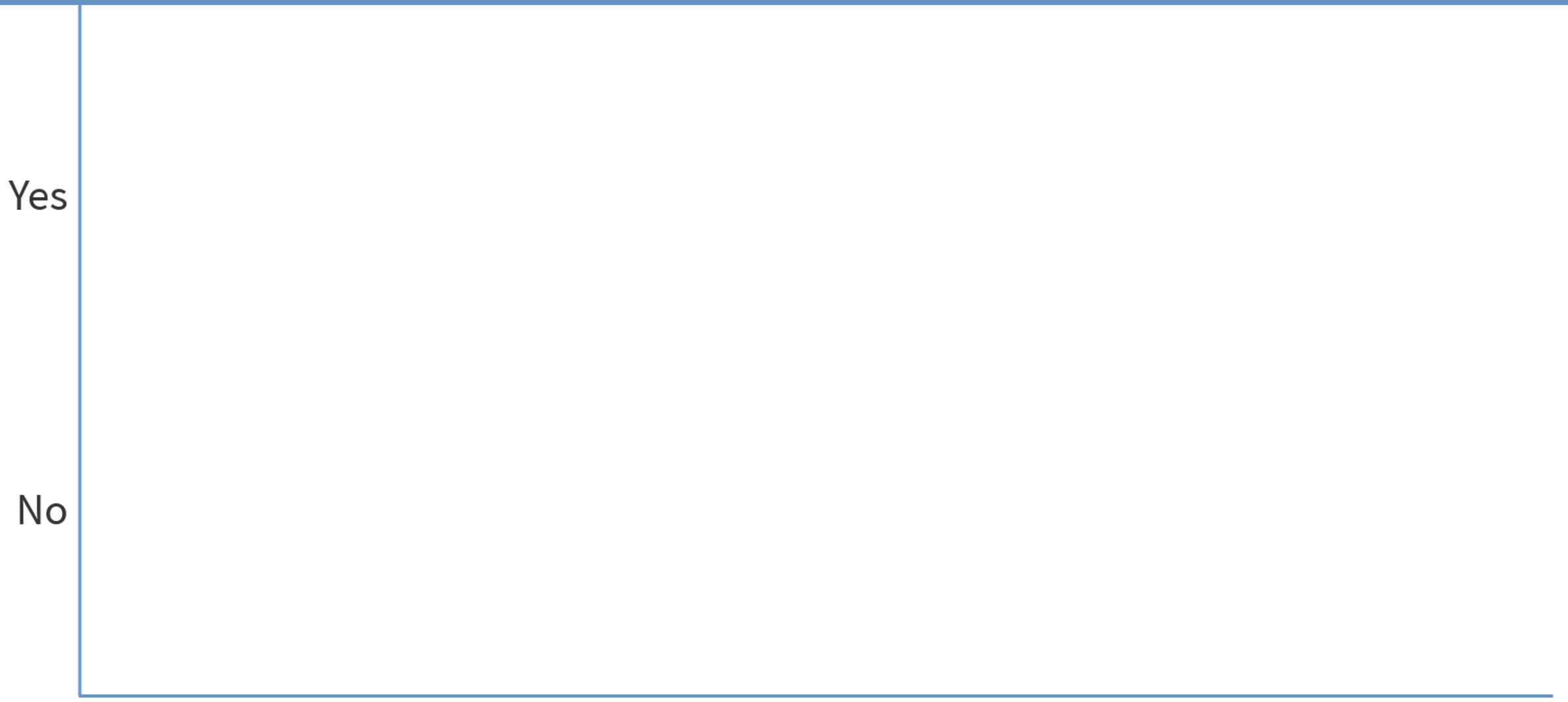
Nearly all diseases have been linked to Dysbiosis.

Multidisciplinary

Necessity of close collaboration between various professions

Fecal Transplant, Nutrition, Probiotics

Post- POLL: In your opinion, should the gut microbiota composition be taken into consideration while devising treatment plans for diseases?



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Thank you!

Any questions?