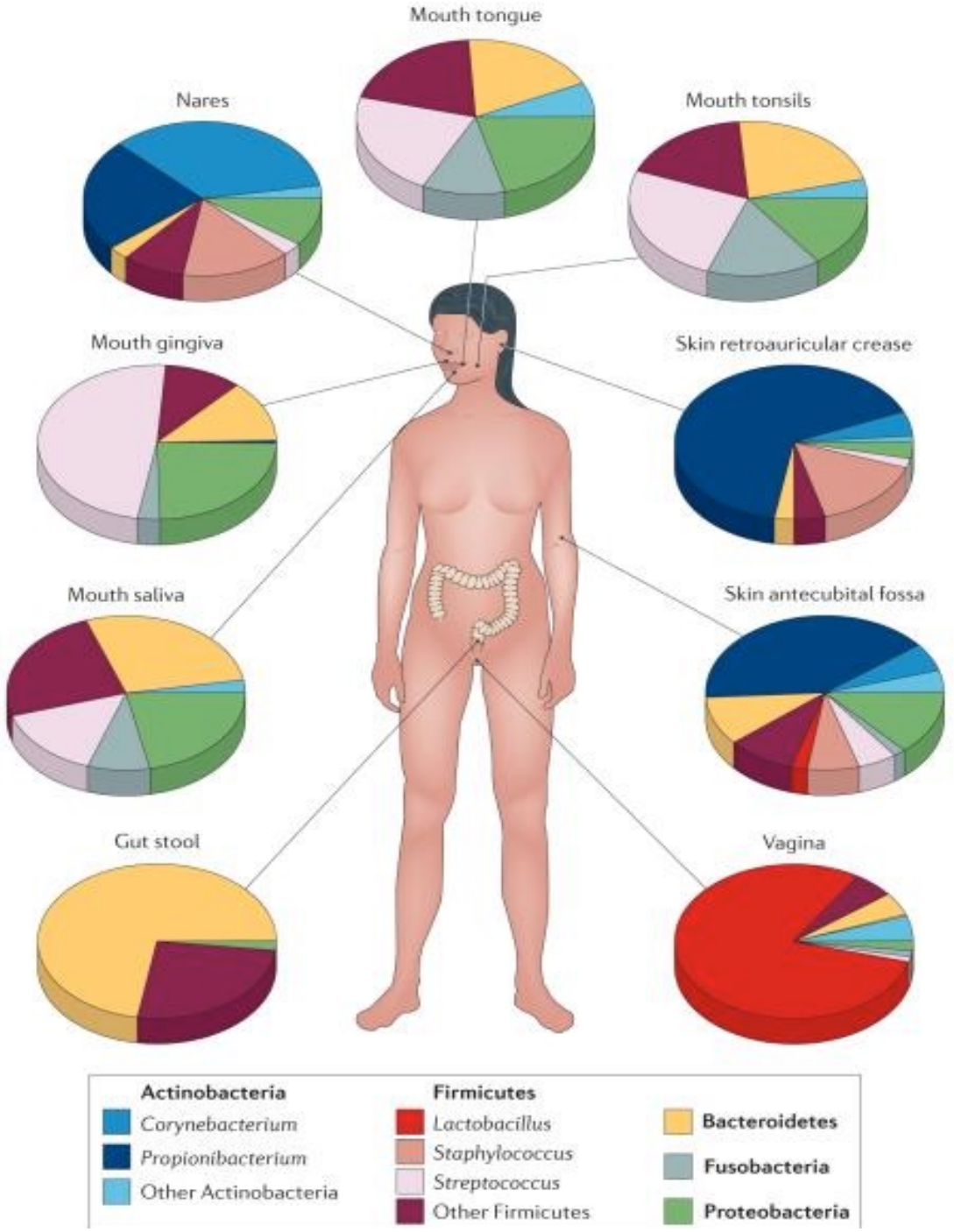
Webinar 3

Gut Microbiome

WHAT IS THE HUMAN MICROBIOME?

- The Human Microbiome is the collection of all the microorganisms living in association with the human body along with their genetic material.
- These communities consist of bacteria ,viruses , yeast, helminths.

Where Does The Microbiome Reside?

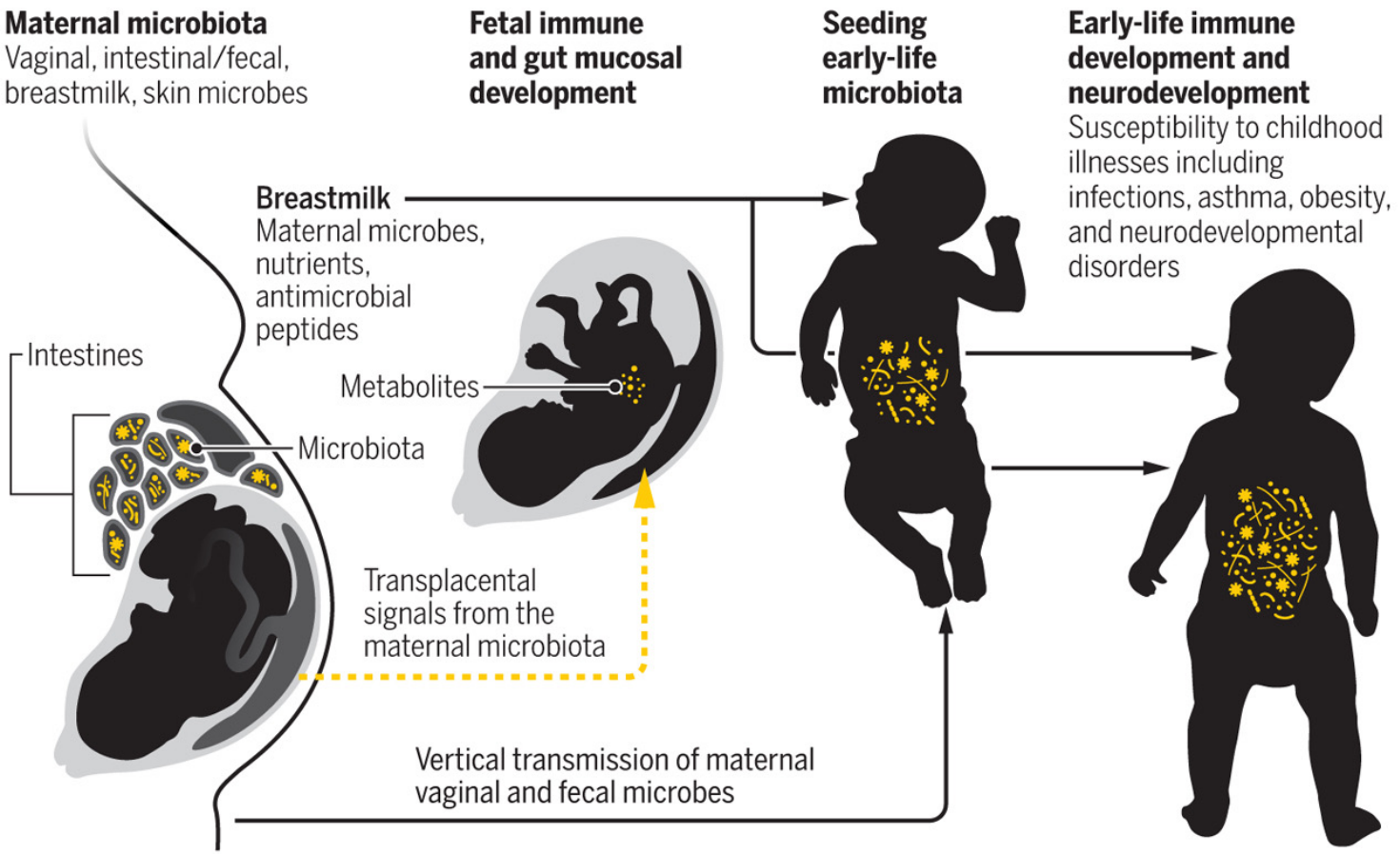


Lasken, Roger S., and Jeffrey S. McLean. "Recent advances in genomic DNA sequencing of microbial species from single cells." *Nature Reviews Genetics* 15.9 (2014): 577-584.

Origin Of
The Human Gut Microbiome

Effects of the maternal microbiota in pregnancy and early life

Through effects on early-life colonization, immune development, and neurodevelopment, the maternal microbiota regulates susceptibility to a number of childhood illnesses and can vertically transmit dysbiosis-mediated pathologies.



McDonald, Braedon, and Kathy D. McCoy. "Maternal microbiota in pregnancy and early life." *Science* 365.6457 (2019): 984-985.

FACTORS THAT INFLUENCE THE GUT MICROBIOME

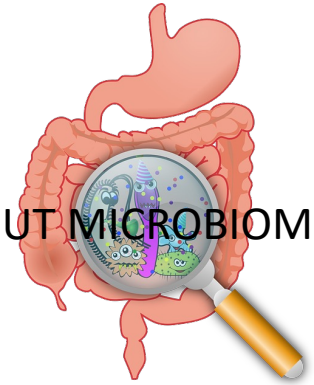

Birth Mode


Geography


Genes


Age


Sex



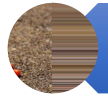

Breast Feeding


Food


Medications


Exercise


Sleep/Circadian Rhythm

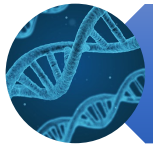

Stress


Disease

FACTORS THAT YOU CANNOT CONTROL

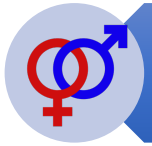
Birth Mode

Geography



Genes

Age



Sex

FACTORS THAT YOU CAN CONTROL


Breast Feeding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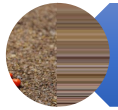
Exercise

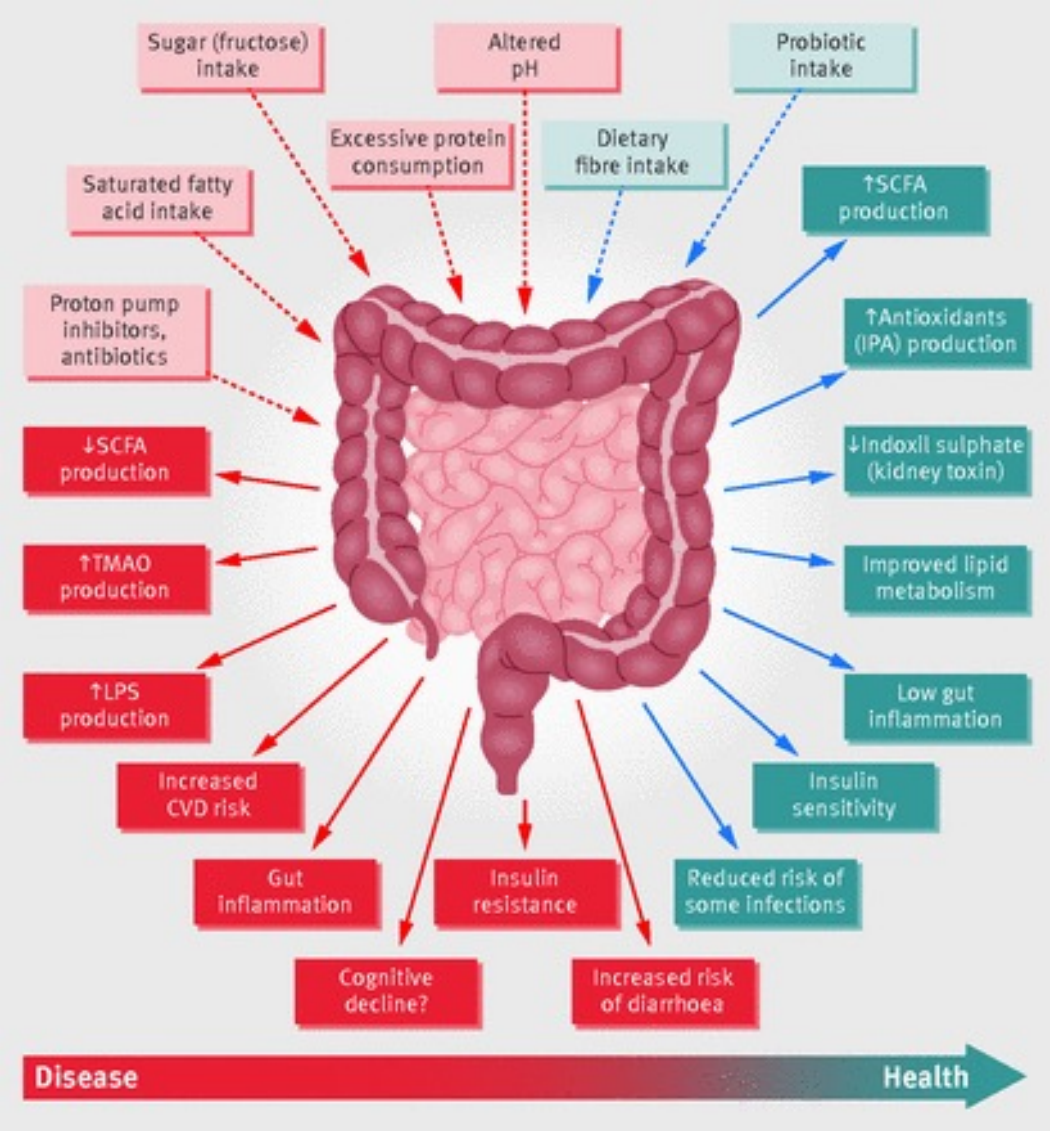

Sleep/Circadian Rhythm


Stress Resilience


Disease

There are no “good” and “bad” gut bacteria

- Who
- How many
- Who are their friends
- What are they doing together?



Valdes, Ana M., et al. "Role of the gut microbiota in nutrition and health." *Bmj* 361 (2018).

What does the gut microbiome do

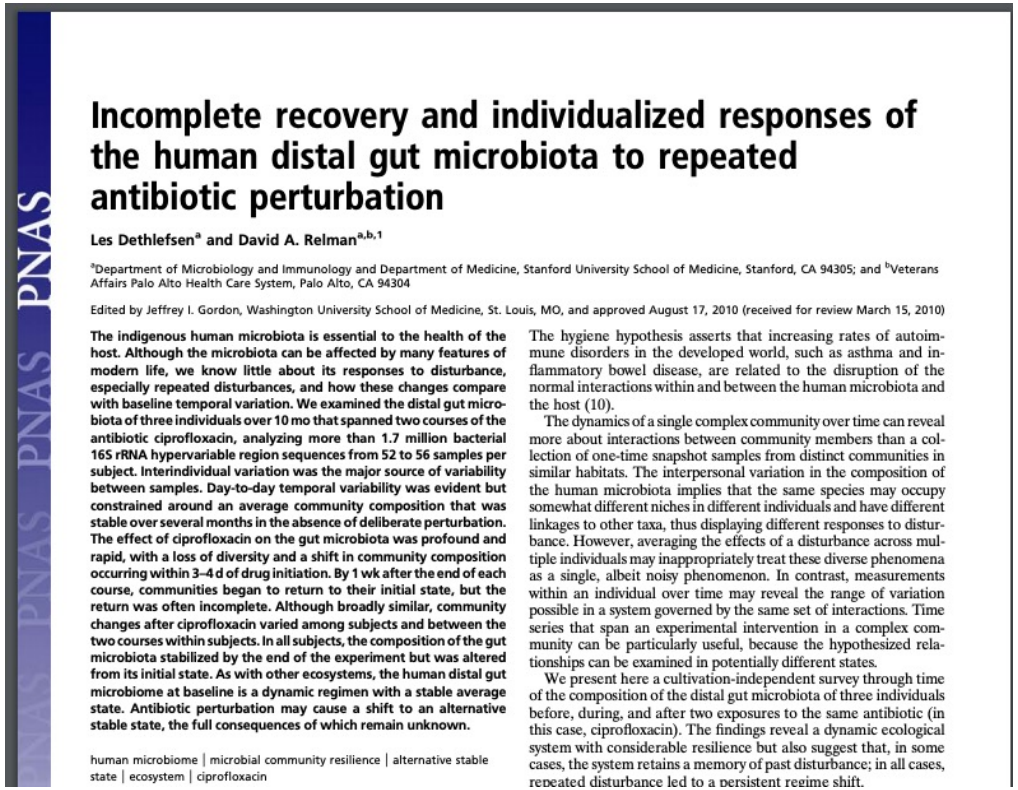
- Development and maintenance of the immune system
- Absorption and assimilation of nutrients
- Storage and elimination of waste
- Vitamin synthesis. K, B
- Metabolism of xenobiotics, medications, melamine, dioxin
- Metabolism of hormones (E2) Estrobolome
- Providing additional enzymes for carbohydrate digestion.
- Produce neurotransmitters like GABA, dopamine, noradrenaline, acetylcholine, histamine.
- SCFA production
- Gasotransmitters
- Bile acid metabolism
- Prevention of colonization by pathogenic microorganisms
- Intestinal barrier function.

SCFA production

- Butyrate is the main energy source for human colonocytes, can induce apoptosis of colon cancer cells.
- Butyrate can activate intestinal gluconeogenesis, having beneficial effects on glucose and energy homeostasis.
- Butyrate prevents gut dysbiosis.
- Propionate is transferred to the liver, where it regulates gluconeogenesis and satiety signalling through interaction with the gut fatty acid receptors.
- Acetate is an essential metabolite for the growth of other bacteria. May play a role in central appetite regulation.

Valdes, Ana M., et al. "Role of the gut microbiota in nutrition and health." *Bmj* 361 (2018).

ANTIBIOTICS AND DISRUPTION OF GUT BACTERIA



PNAS PNAS PNAS PNAS

Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation

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Edited by Jeffrey I. Gordon, Washington University School of Medicine, St. Louis, MO, and approved August 17, 2010 (received for review March 15, 2010)

The indigenous human microbiota is essential to the health of the host. Although the microbiota can be affected by many features of modern life, we know little about its responses to disturbance, especially repeated disturbances, and how these changes compare with baseline temporal variation. We examined the distal gut microbiota of three individuals over 10 mo that spanned two courses of the antibiotic ciprofloxacin, analyzing more than 1.7 million bacterial 16S rRNA hypervariable region sequences from 52 to 56 samples per subject. Interindividual variation was the major source of variability between samples. Day-to-day temporal variability was evident but constrained around an average community composition that was stable over several months in the absence of deliberate perturbation. The effect of ciprofloxacin on the gut microbiota was profound and rapid, with a loss of diversity and a shift in community composition occurring within 3–4 d of drug initiation. By 1 wk after the end of each course, communities began to return to their initial state, but the return was often incomplete. Although broadly similar, community changes after ciprofloxacin varied among subjects and between the two courses within subjects. In all subjects, the composition of the gut microbiota stabilized by the end of the experiment but was altered from its initial state. As with other ecosystems, the human distal gut microbiome at baseline is a dynamic regimen with a stable average state. Antibiotic perturbation may cause a shift to an alternative stable state, the full consequences of which remain unknown.

human microbiome | microbial community resilience | alternative stable state | ecosystem | ciprofloxacin

The hygiene hypothesis asserts that increasing rates of autoimmune disorders in the developed world, such as asthma and inflammatory bowel disease, are related to the disruption of the normal interactions within and between the human microbiota and the host (10).

The dynamics of a single complex community over time can reveal more about interactions between community members than a collection of one-time snapshot samples from distinct communities in similar habitats. The interpersonal variation in the composition of the human microbiota implies that the same species may occupy somewhat different niches in different individuals and have different linkages to other taxa, thus displaying different responses to disturbance. However, averaging the effects of a disturbance across multiple individuals may inappropriately treat these diverse phenomena as a single, albeit noisy phenomenon. In contrast, measurements within an individual over time may reveal the range of variation possible in a system governed by the same set of interactions. Time series that span an experimental intervention in a complex community can be particularly useful, because the hypothesized relationships can be examined in potentially different states.

We present here a cultivation-independent survey through time of the composition of the distal gut microbiota of three individuals before, during, and after two exposures to the same antibiotic (in this case, ciprofloxacin). The findings reveal a dynamic ecological system with considerable resilience but also suggest that, in some cases, the system retains a memory of past disturbance; in all cases, repeated disturbance led to a persistent regime shift.

- Examined the distal gut microbiota of three individuals over 10 months given two courses of the antibiotic ciprofloxacin.
- Ciprofloxacin 500 mg orally two times daily for 5 days (x2)
- Within 3-4 days of ciprofloxacin, there was a loss of diversity.
- Some of the changes persisted.

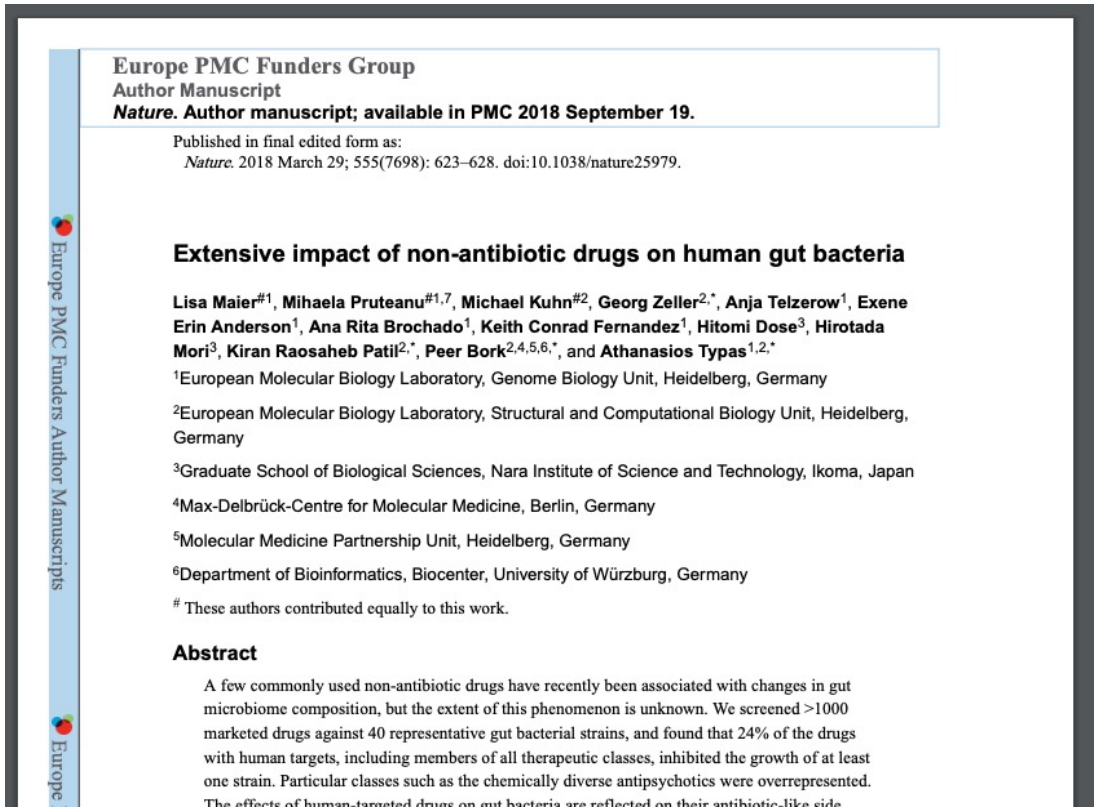
Dethlefsen, L., & Relman, D. A. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences*, *108*(Supplement 1), 4554-4561.

ANTIBIOTICS IN FEEDLOTS

Out of 70 samples tested 40% were found to contain residues of one or more antibiotics.

Sahu, Ramakant & Saxena, Poornima. (2014). Antibiotics in Chicken Meat.

NON-ANTIBIOTIC DRUGS



Published in final edited form as:
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Extensive impact of non-antibiotic drugs on human gut bacteria

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[3]Graduate School of Biological Sciences, Nara Institute of Science and Technology, Ikoma, Japan

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[5]Molecular Medicine Partnership Unit, Heidelberg, Germany

[6]Department of Bioinformatics, Biocenter, University of Würzburg, Germany

[#] These authors contributed equally to this work.

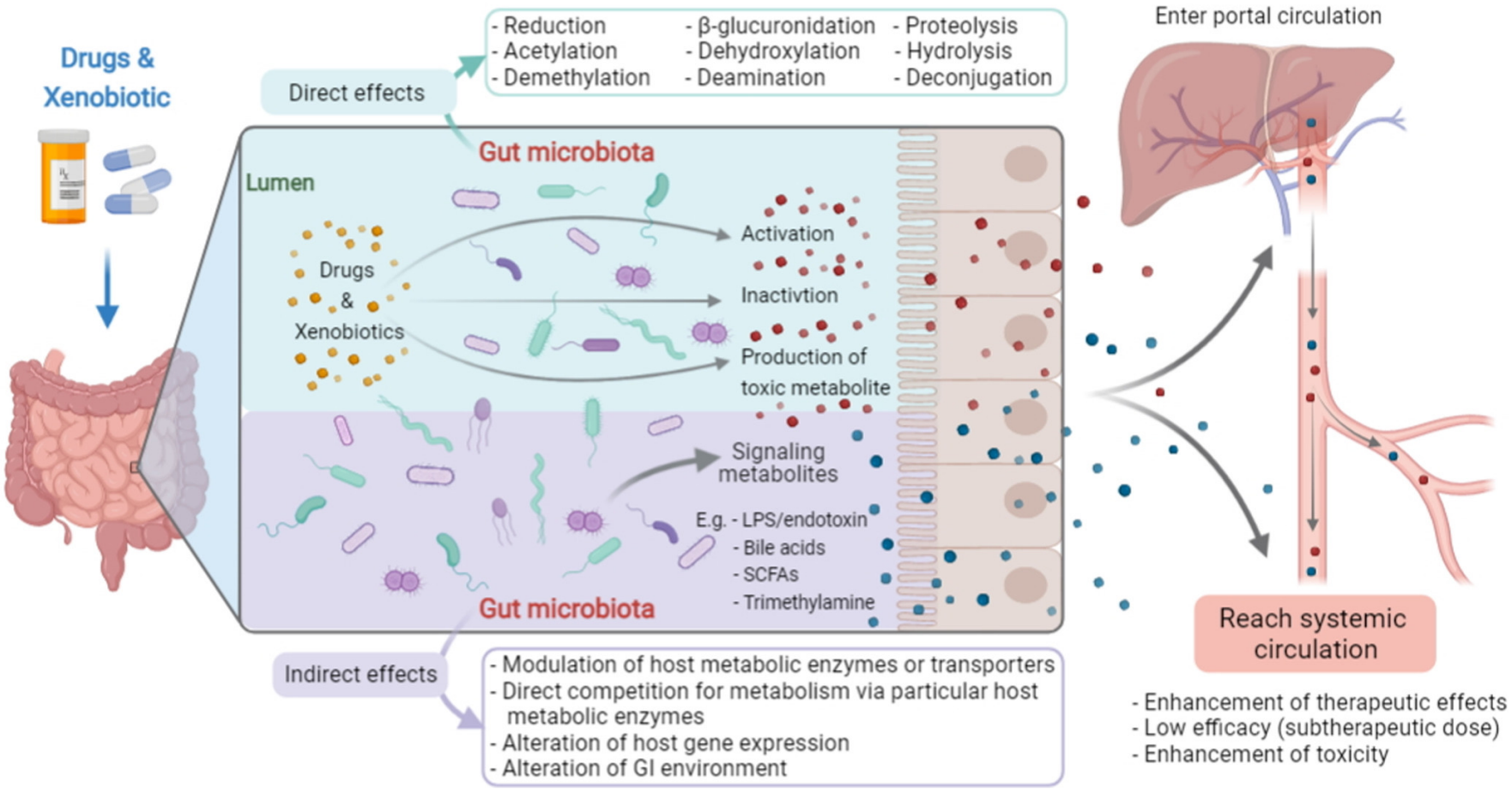
Abstract

A few commonly used non-antibiotic drugs have recently been associated with changes in gut microbiome composition, but the extent of this phenomenon is unknown. We screened >1000 marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain. Particular classes such as the chemically diverse antipsychotics were overrepresented. The effects of human-targeted drugs on gut bacteria are reflected on their antibiotic-like side

Metformin
Proton pump inhibitors (PPIS). Lansoprazole, omeprazole
Nonsteroidal anti-inflammatory drugs
Atypical antipsychotics (AAPS) Clonazipine, Aripiprazole
Clomiphene Citrate
Azathioprine
Antidepressant venlafaxin
Mesalazine
BP medications
Estradiol Valerate
Statins

Maier, Lisa, et al. "Extensive impact of non-antibiotic drugs on human gut bacteria." *Nature* 555.7698 (2018): 623-628.

Gut Microbiome And Biotransformation Of Pharmaceuticals

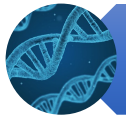


Dikeocha, Ifeoma Julieth, et al. "Pharmacomicrobiomics: Influence of gut microbiota on drug and xenobiotic metabolism." *The FASEB Journal* 36.6 (2022): e22350.

FACTORS THAT INFLUENCE THE GUT MICROBIOME

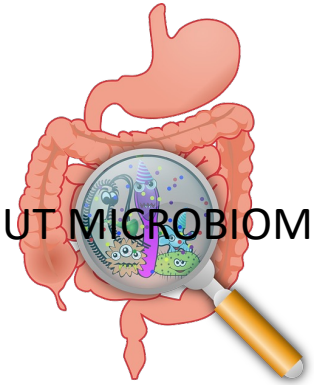

Birth Mode


Geography


Genes


Age


Sex



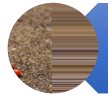

Breast Feeding


Food


Medications


Exercise


Sleep/Circadian Rhythm


Stress


Disease

Ways to manipulate the gut microbiome

- Lifestyle: Food, sleep, movement, stress resilience
- Vaginal seeding (Vaginal Microbiome Transfer)
- Fecal Microbiota Transplant (FMT). Poop caps, Rebyota
- Probiotics

Food

- Food can rapidly change the gut microbiome.1-3 days.
- Habitual diets have a greater influence on the gut microbiota than short-term diets.
- Baseline diet impacts change in gut microbes after an intervention.
- A higher initial microbiome diversity favours the stability of the gut microbiota in response to dietary changes.

Korpela, Katri, et al 2014
Bourdeau-Julien, Isabelle, et al.2023
Griffin, Nicholas W., et al 2017

Vaginal Seeding

- Vaginal seeding is inoculating a cotton gauze with vaginal fluids to transfer the vaginal flora to the mouth, nose, or skin of a new-born infant.
- Infant neurodevelopment, as measured by the Ages and Stages Questionnaire (ASQ-3) score at 6 months, was significantly higher with VMT than saline.

Zhou, Lepeng, et al. "Effects of vaginal microbiota transfer on the neurodevelopment and microbiome of cesarean-born infants: A blinded randomized controlled trial." *Cell Host & Microbe* (2023).

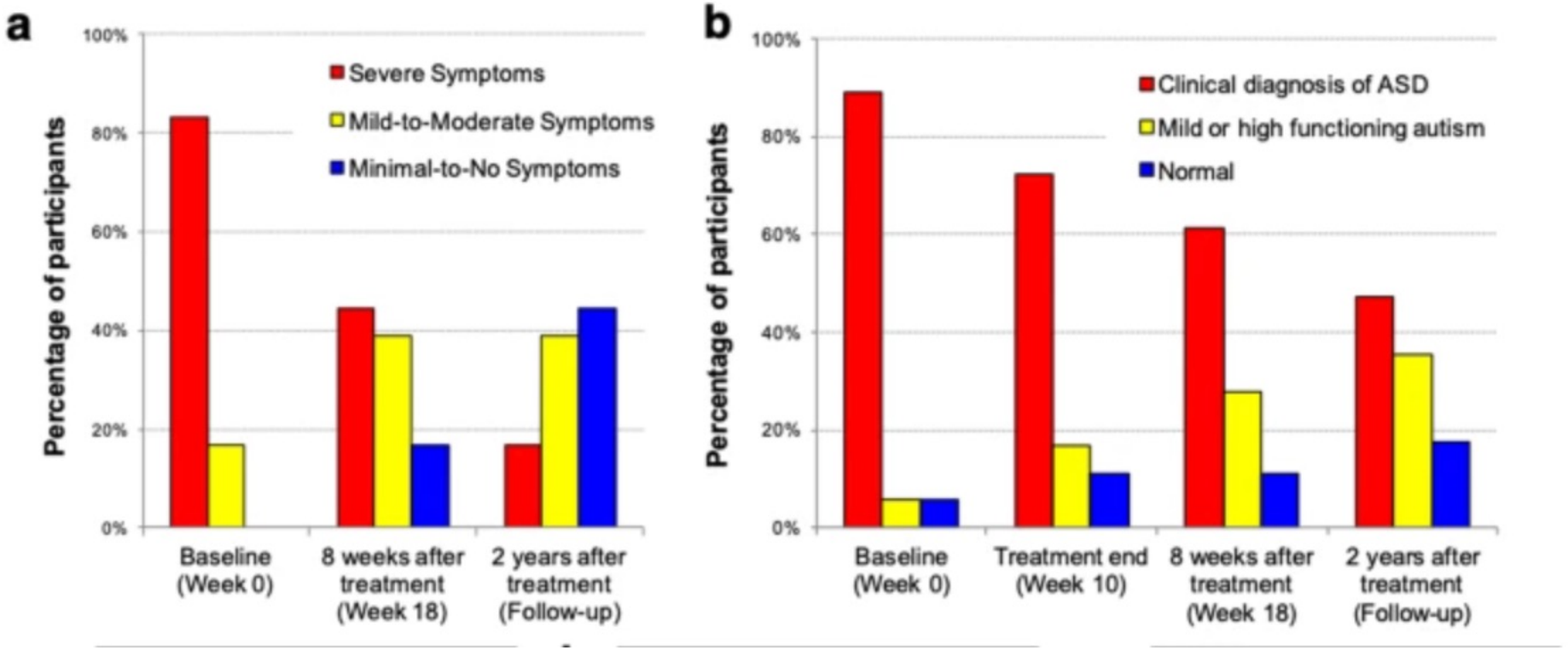
FMT for Recurrent C Diff. Infection

- RBX2660 (Rebyota) consists of a broad consortium of live microbes prepared from human stool collected from rigorously screened healthy donors.
- Single dose, given rectally.
- The FDA has approved Rebyota® for the prevention of recurrence of CDI in patients 18 years of age and older who have completed antibiotic treatment for recurrent *Clostridium Difficile* Infection.

Khanna, Sahil, et al. "Efficacy and safety of RBX2660 in PUNCH CD3, a phase III, randomized, double-blind, placebo-controlled trial with a Bayesian primary analysis for the prevention of recurrent Clostridioides difficile infection." *Drugs* 82.15 (2022): 1527-1538.

Microbiota Transfer Therapy In Autism

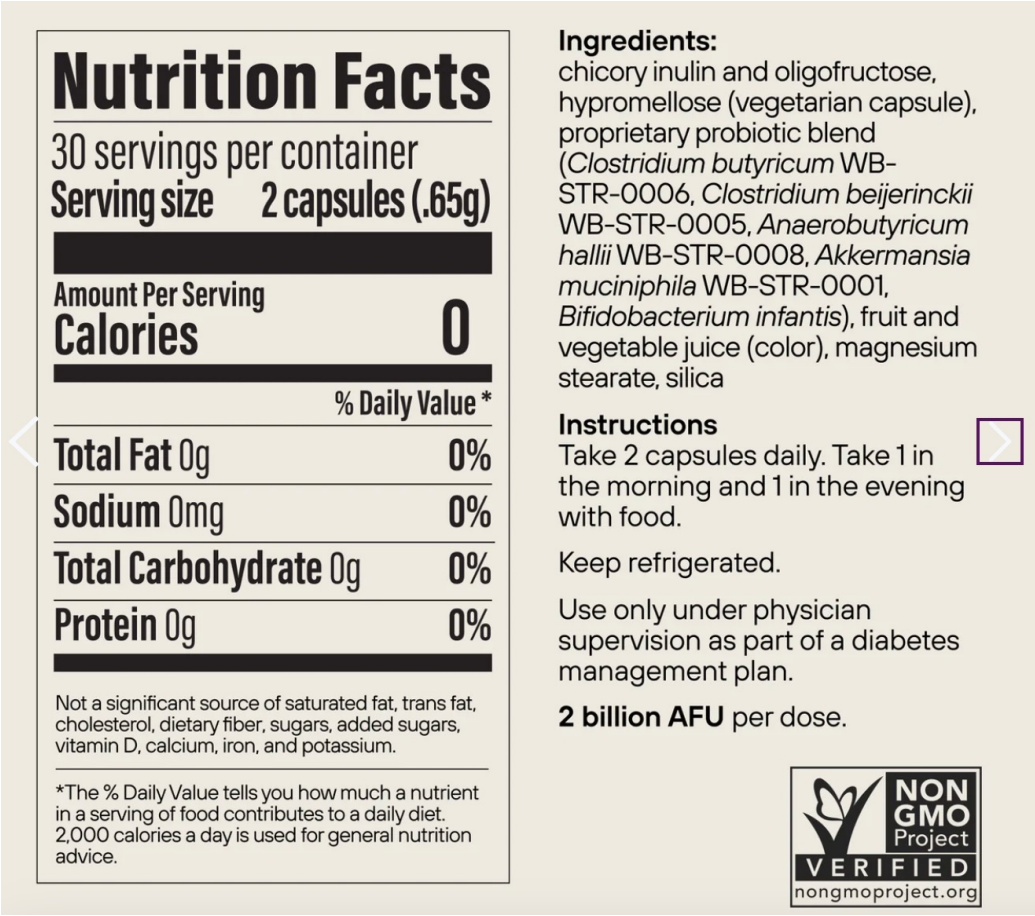
Figure 2



Kang, Dae-Wook, et al. "Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota." *Scientific reports* 9.1 (2019): 5821.

Probiotics in T2DM (Pendulum Glucose Control)

https://pendulumlife.com/products/pendulum-glucose-control-2-og



Nutrition Facts

30 servings per container

Serving size 2 capsules (.65g)

Amount Per Serving

Calories 0

	% Daily Value *
Total Fat 0g	0%
Sodium 0mg	0%
Total Carbohydrate 0g	0%
Protein 0g	0%

Not a significant source of saturated fat, trans fat, cholesterol, dietary fiber, sugars, added sugars, vitamin D, calcium, iron, and potassium.

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Ingredients:
chicory inulin and oligofructose, hypromellose (vegetarian capsule), proprietary probiotic blend (*Clostridium butyricum* WB-STR-0006, *Clostridium beijerinckii* WB-STR-0005, *Anaerobutyricum hallii* WB-STR-0008, *Akkermansia muciniphila* WB-STR-0001, *Bifidobacterium infantis*), fruit and vegetable juice (color), magnesium stearate, silica

Instructions
Take 2 capsules daily. Take 1 in the morning and 1 in the evening with food.

Keep refrigerated.

Use only under physician supervision as part of a diabetes management plan.

2 billion AFU per dose.

NON GMO Project VERIFIED nongmoproject.org

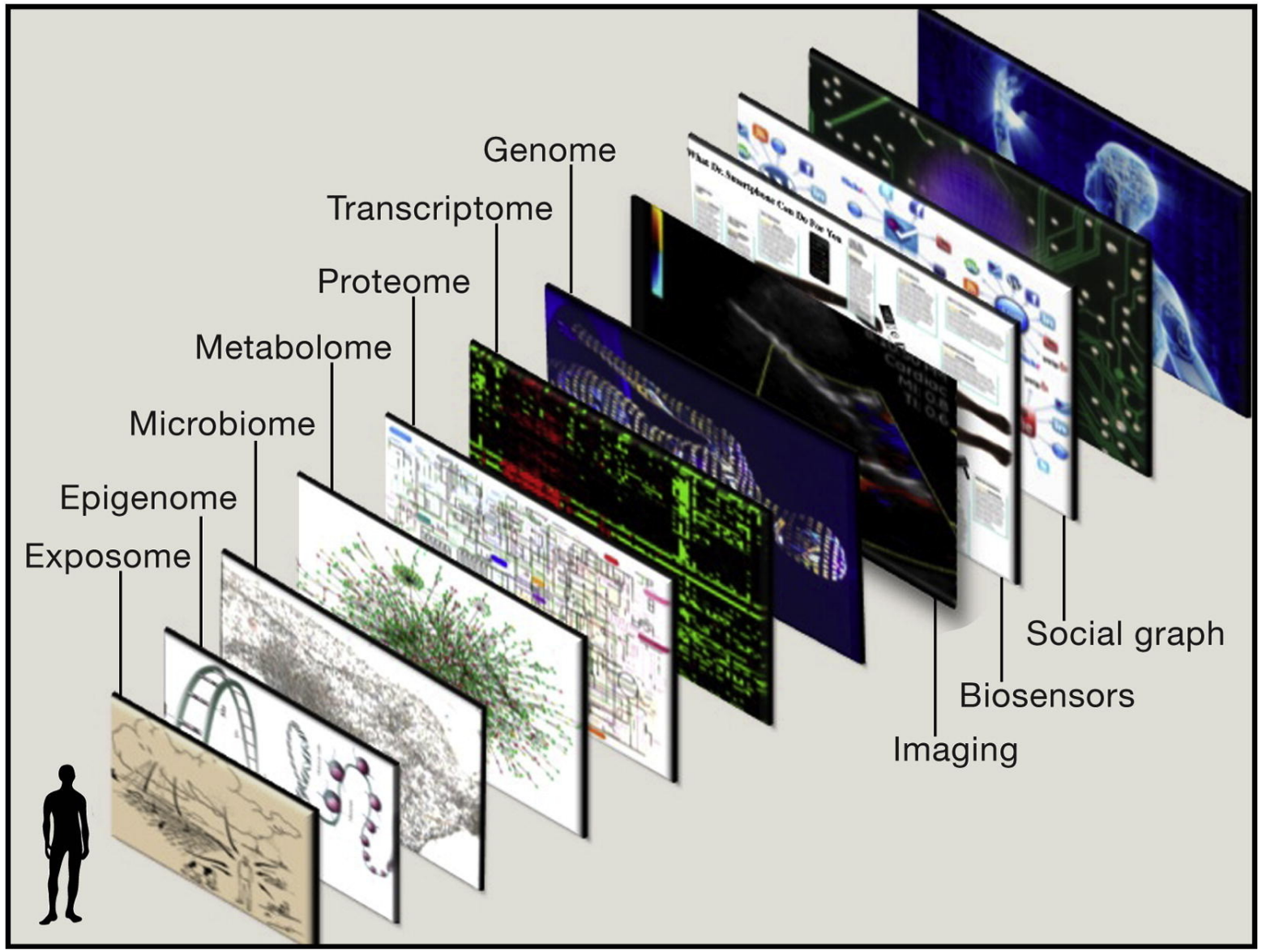
76 people with T2DM on metformin given probiotic formulation containing butyrate producing bacteria and *Akkermansia muciniphila* for 12 weeks.

HbA1C reduced by 0.6%

Active Fraction Units (AFU) not CFU

Perraudeau, Fanny, et al. "Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation." *BMJ Open Diabetes Research and Care* 8.1 (2020): e001319.

The gut microbiome is only one piece of the puzzle……



Topol, Eric J. "Individualized medicine from prewomb to tomb." *Cell* 157.1 (2014): 241-253.

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