



**Microbiome
Center**

The gut microbiome is an ecology



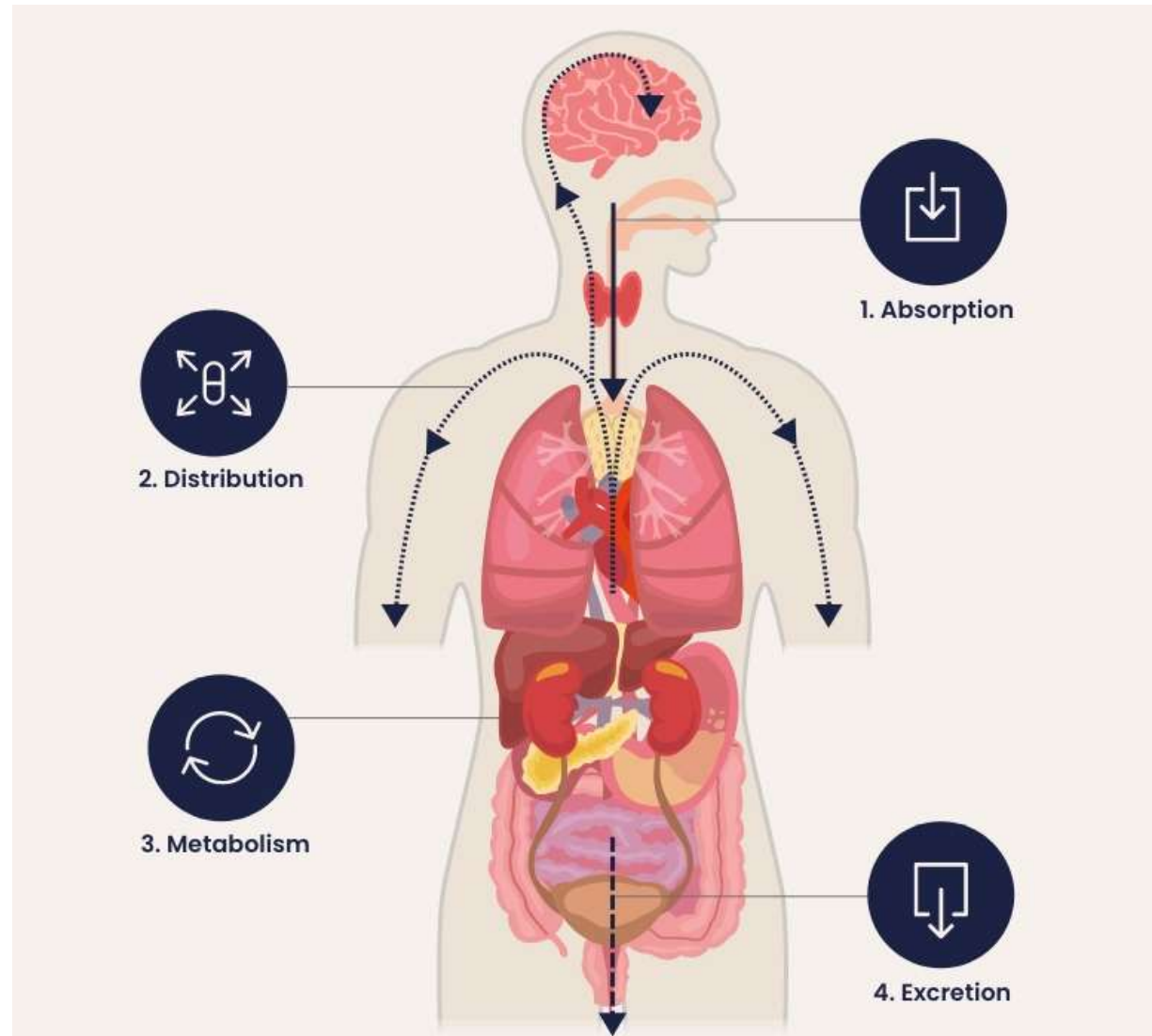
Dennis Zeilstra, Jes Schalkwijk, Barbera Eijgel

14.04.2025

Classical view vs. ecological perspective

Classical pharmacokinetics

Starts from one
organism: human



1. <https://www.pharmaceuticalpress.com/resources/article/what-is-pharmacokinetics/>

The microbiome: an ecology

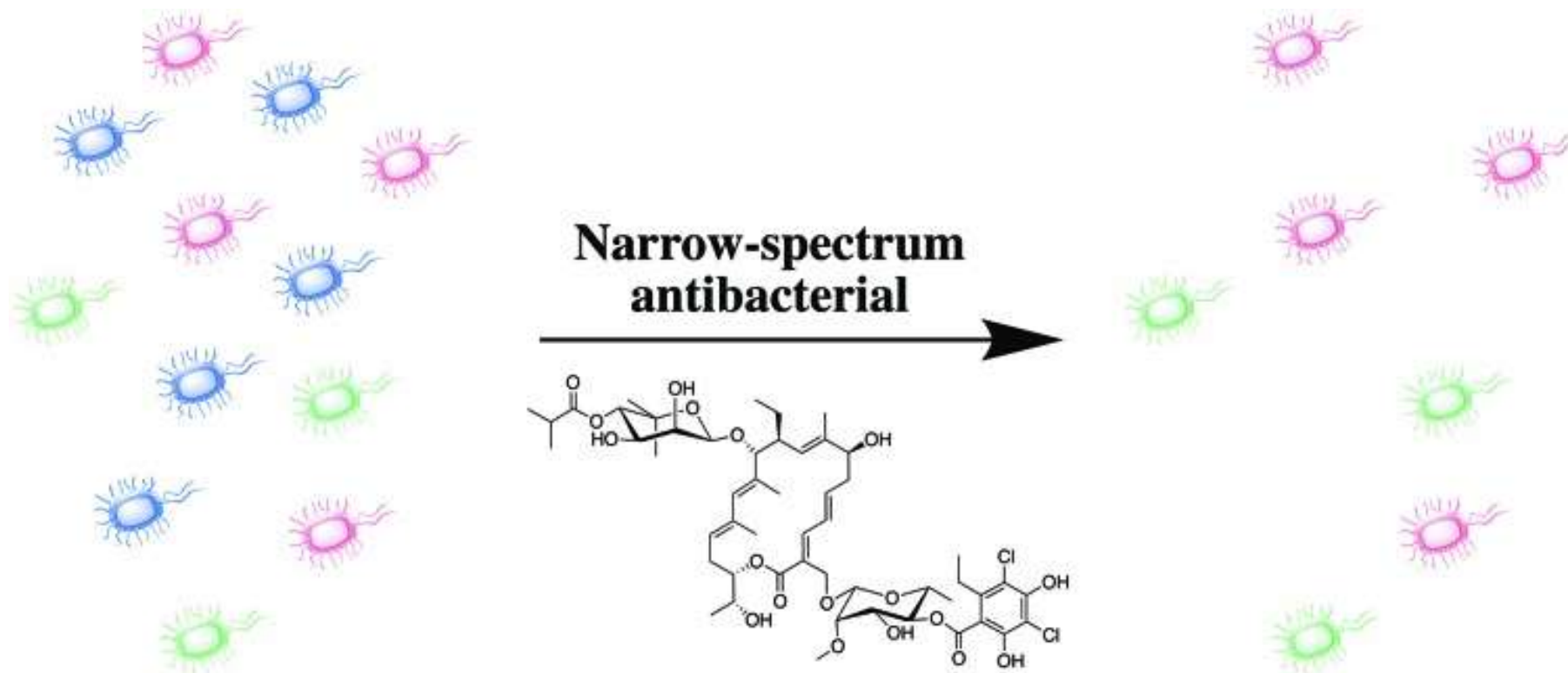


Different
organisms that
interact with a high
degree

What does this mean for treatments?

Example: narrow-spectrum antibiotics

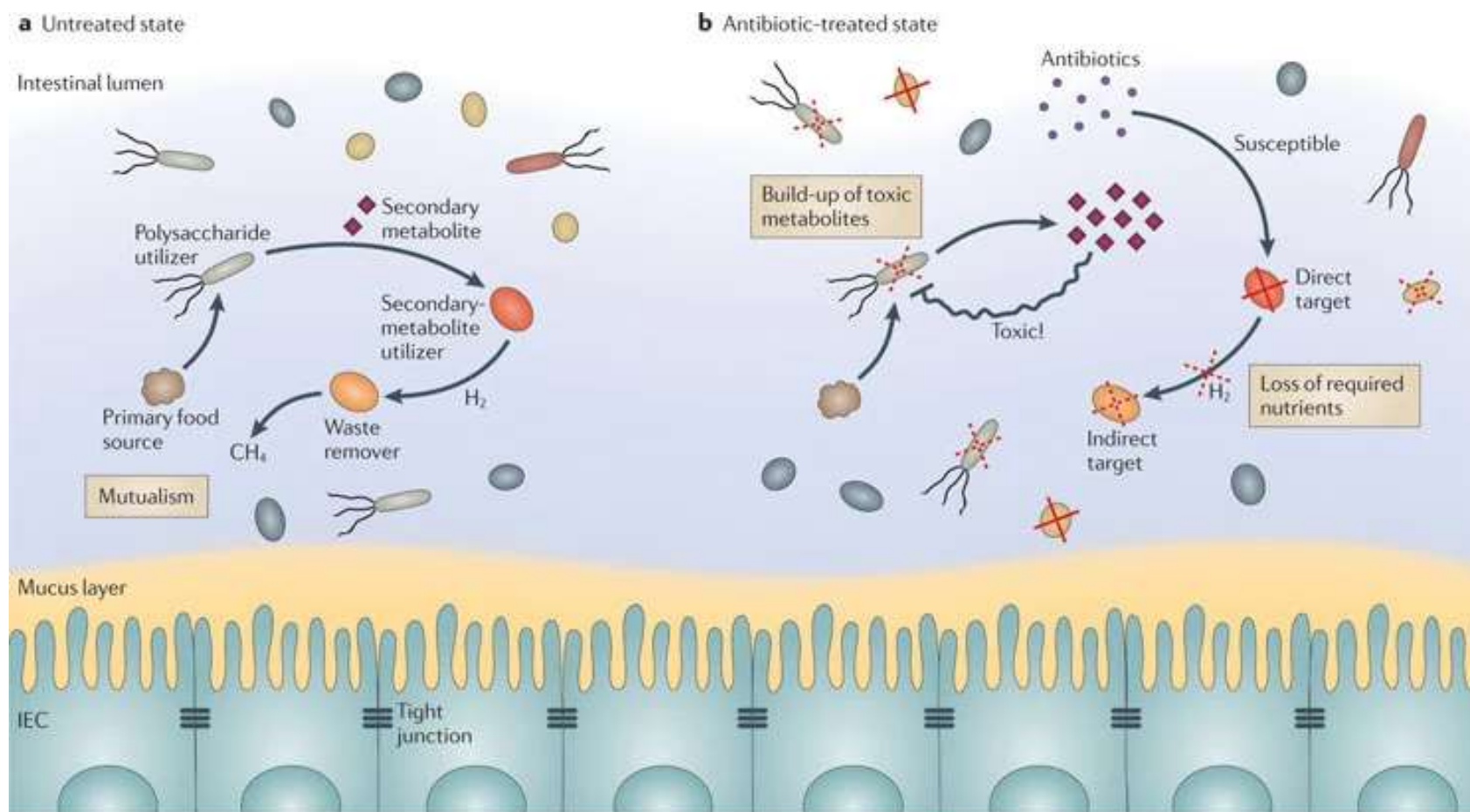
From a classical
perspective:



What does this mean for treatments?

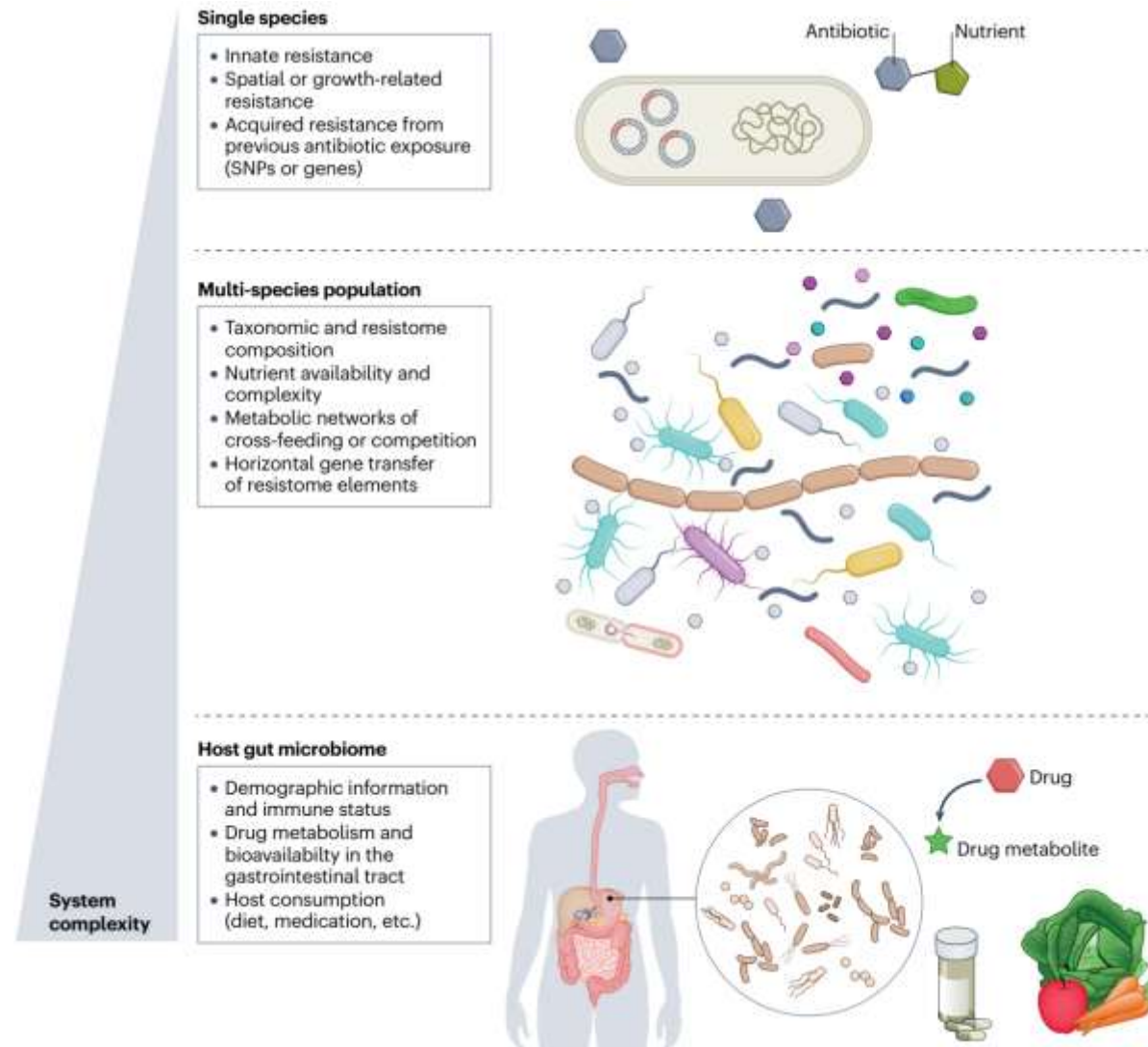
Example: narrow-spectrum antibiotics

The ecological reality:



What does this mean for treatments?

Example: narrow-spectrum antibiotics¹



1. Fishbein, S. R. S. et al. Nat Rev Microbiol. 21, 772–788. (2023)

What does this mean for treatments?

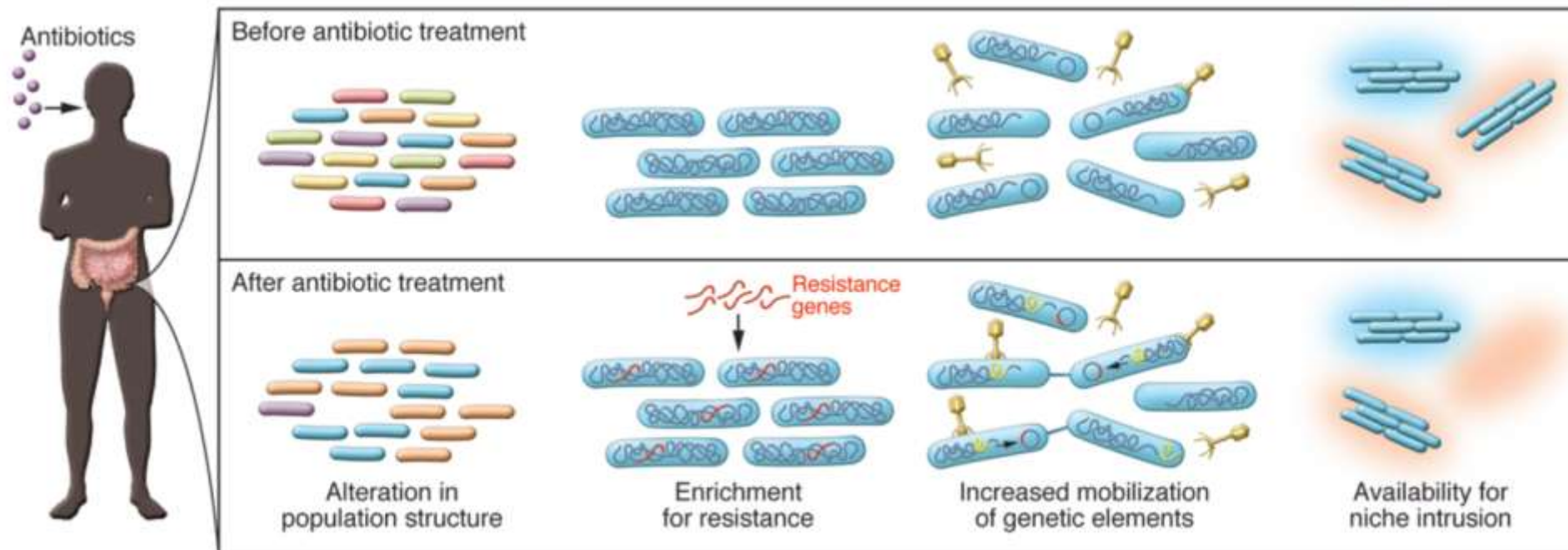
Example: narrow-spectrum antibiotics

Antibiotics cause^{1,2}:

- Decrease in alpha diversity
- Decrease in Firmicutes, Bacteroidetes and Actinobacteria
- Less metabolic activity (conversion of bile acids, SCFAs)

- Increase in resistance and its transmission
- More simple carbohydrates and amino acids opens niches for opportunistic pathogens

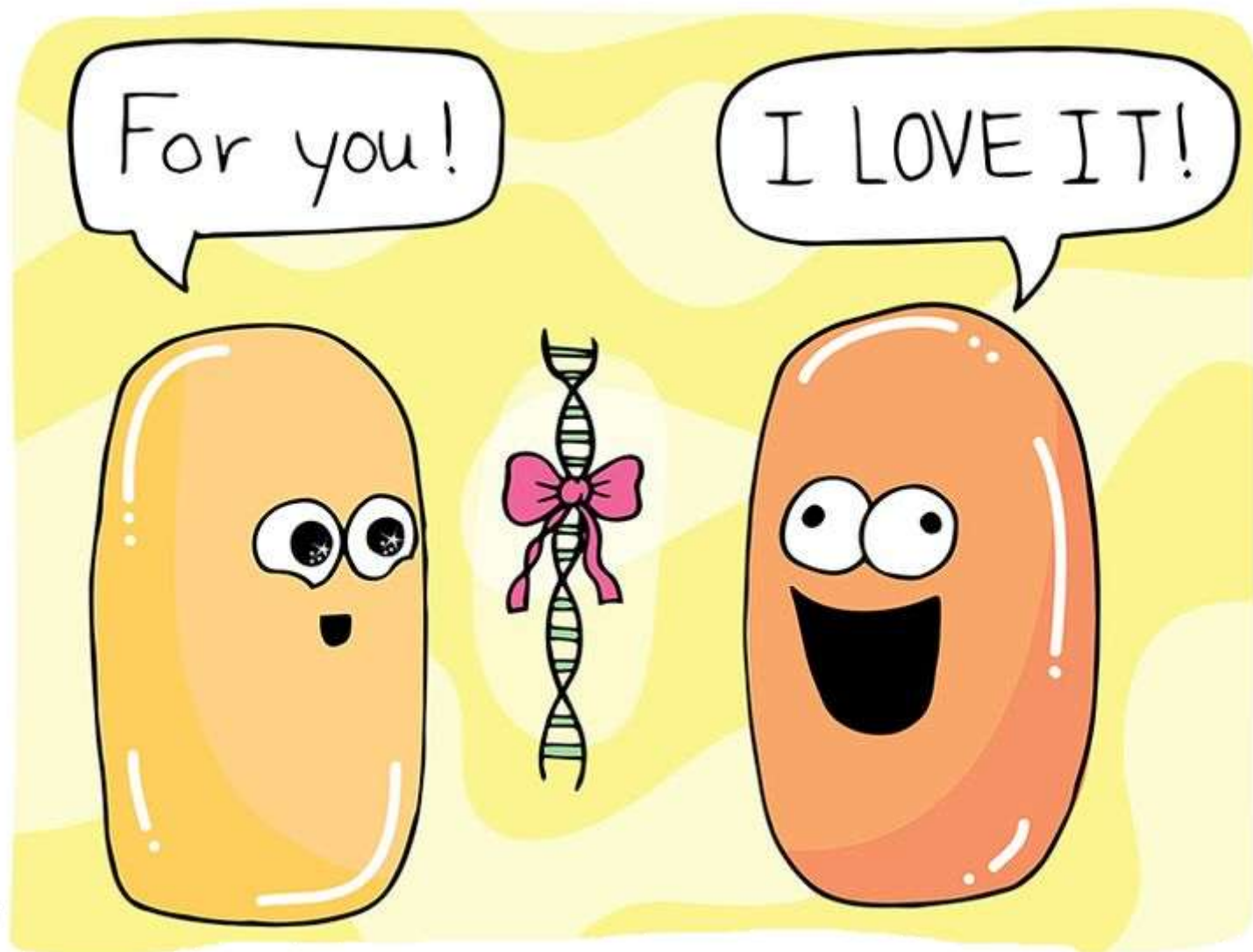
NB: narrow-spectrum (and reserve) antibiotic vancomycin has much more negative effects than broad-spectrum amoxicillin¹.



1. Fishbein, S. R. S. et al. *Nat Rev Microbiol.* 21, 772–788. (2023)

2. Modi, S. et al. *The Journal of clinical investigation.* 124, 4212–4218. (2014)

Antibiotic-resistant 'gene transfer'



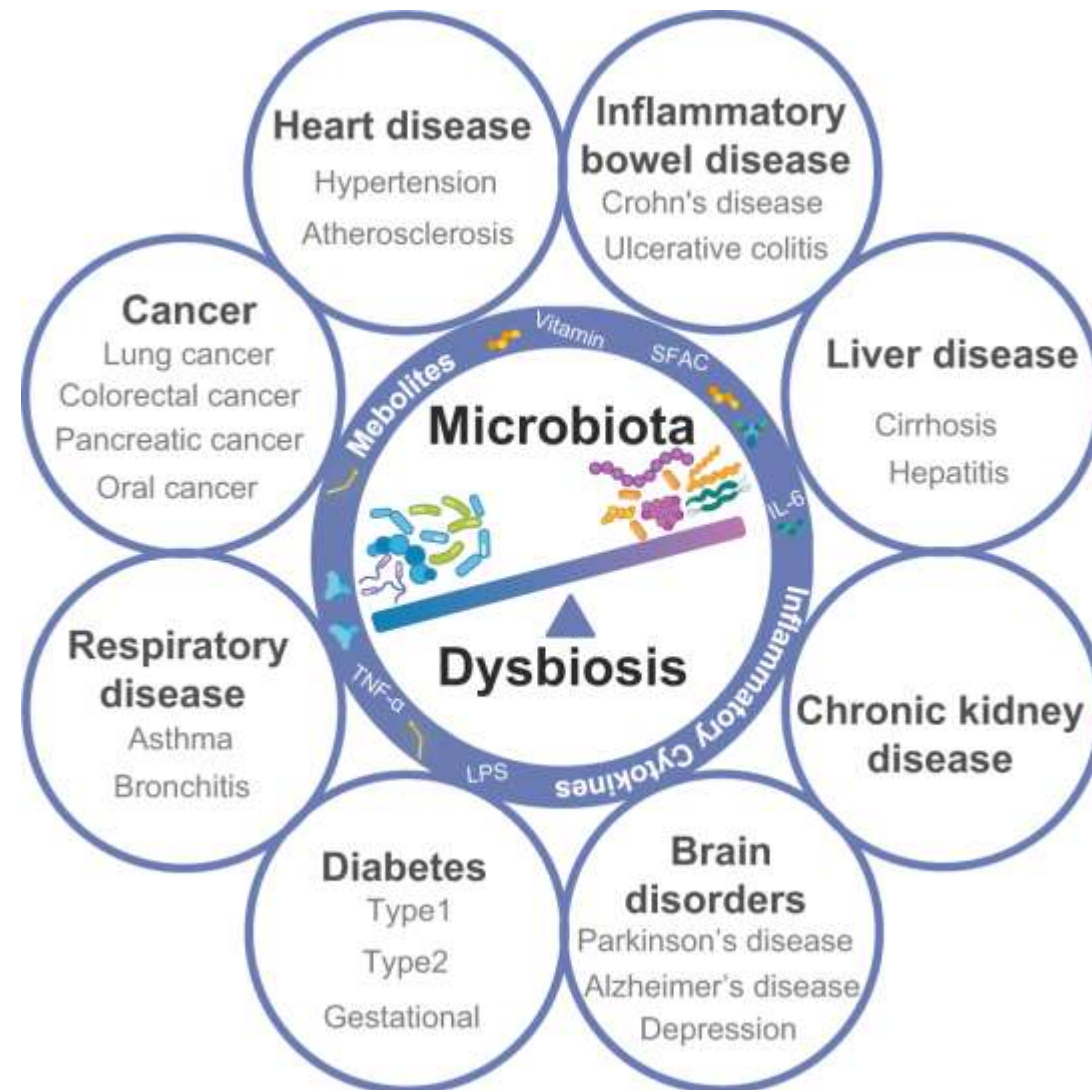
The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

The gut (microbiome) is at the root of our health

The gut is at the center of many, if not all, diseases

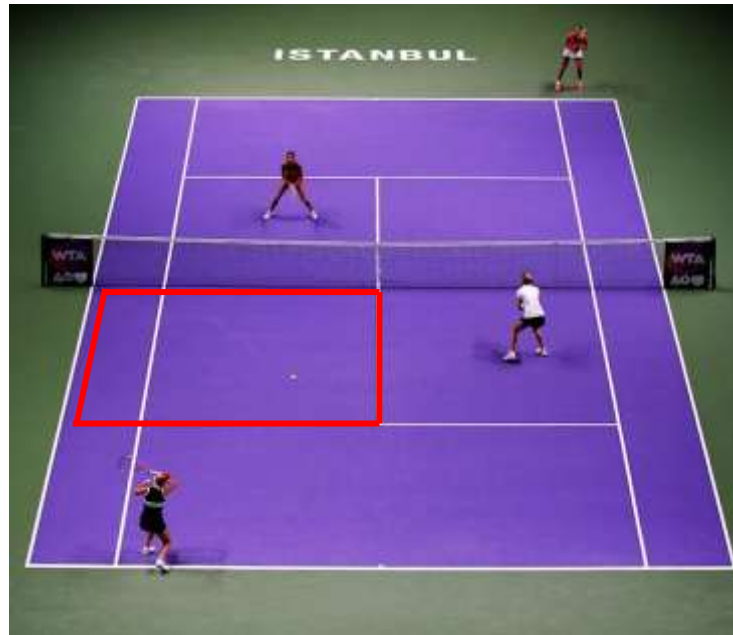
“We could consider microbiome therapy for patients with GI problems”

- The gut is often seen as just another organ that needs treatment when problems
- Reality: **the gut microbiome is involved in (almost) all diseases¹**



The large role of the microbiota makes sense...

- The **intestines** are the largest area of contact with the outside world: approximately 32 m².¹
- The **microbial density in the gut** is very high: we harbor approximately **10¹⁴** bacterial cells in our gut.²
 - This is 1.3x more bacterial cells than human cells².



Number of human genes⁴:

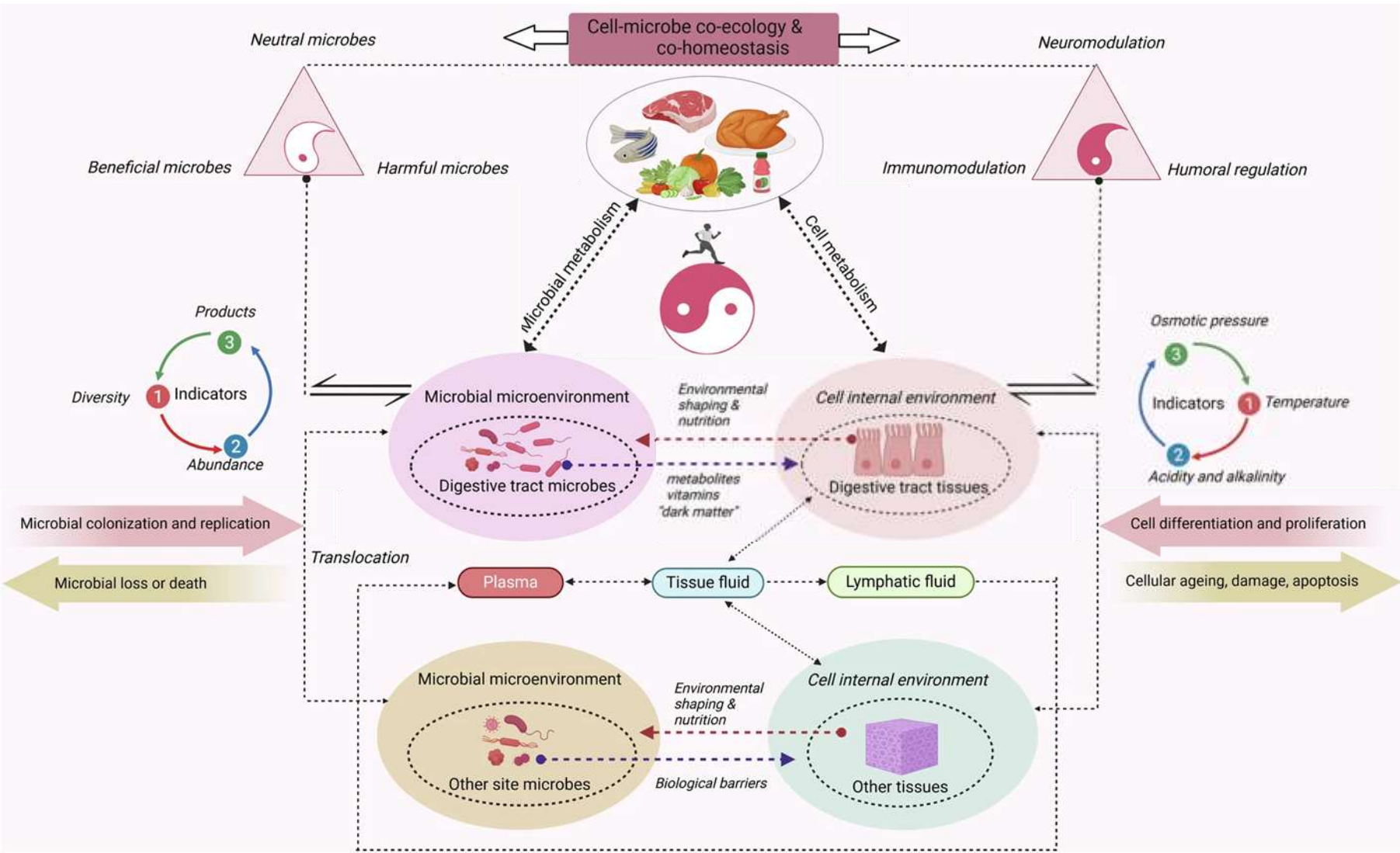
STATISTICS	T2T-CHM13
Summary	
Assembled bases (Gbp)	3.05
Gene annotation	
Number of genes	63,494
Protein coding	19,969

Number of bacterial genes³:



1. Helander, H. F. et al. Scandinavian Journal of Gastroenterology 49, 681–689 (2014)
2. Sender, R. et al. PLoS Biol 14, (2016)
3. Tierney, B. T. et al. Cell Host & Microbe 26, 283–295.e8 (2019)
4. Nurk, S. et al. Science.376,44–53.(2022)

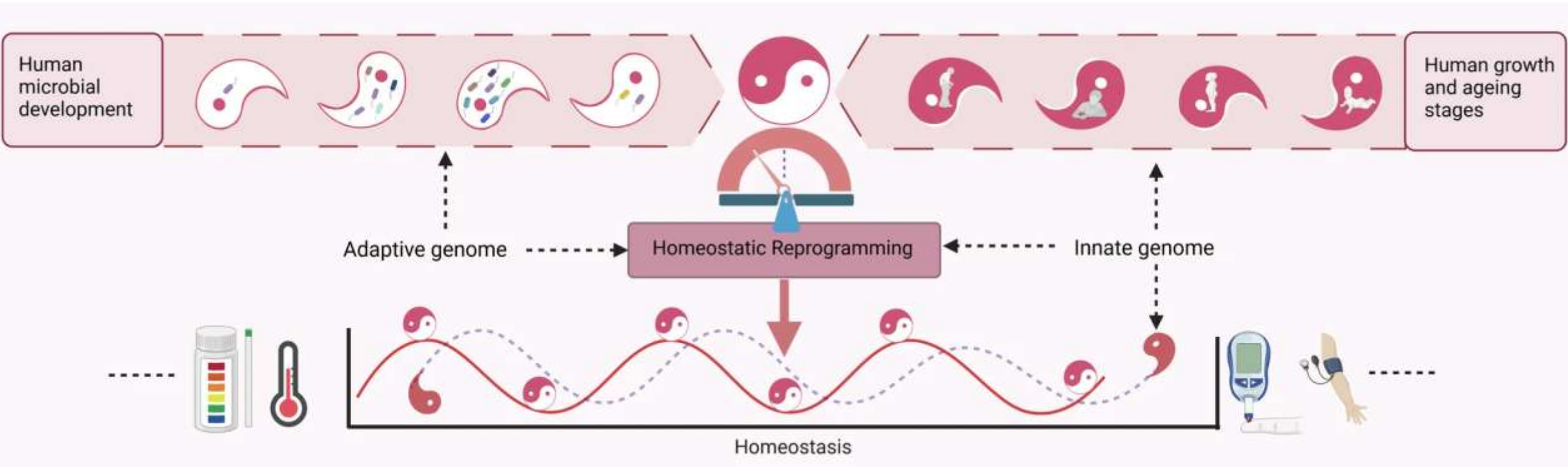
We are holobionts: human and microbial cells together determine homeostasis¹



The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

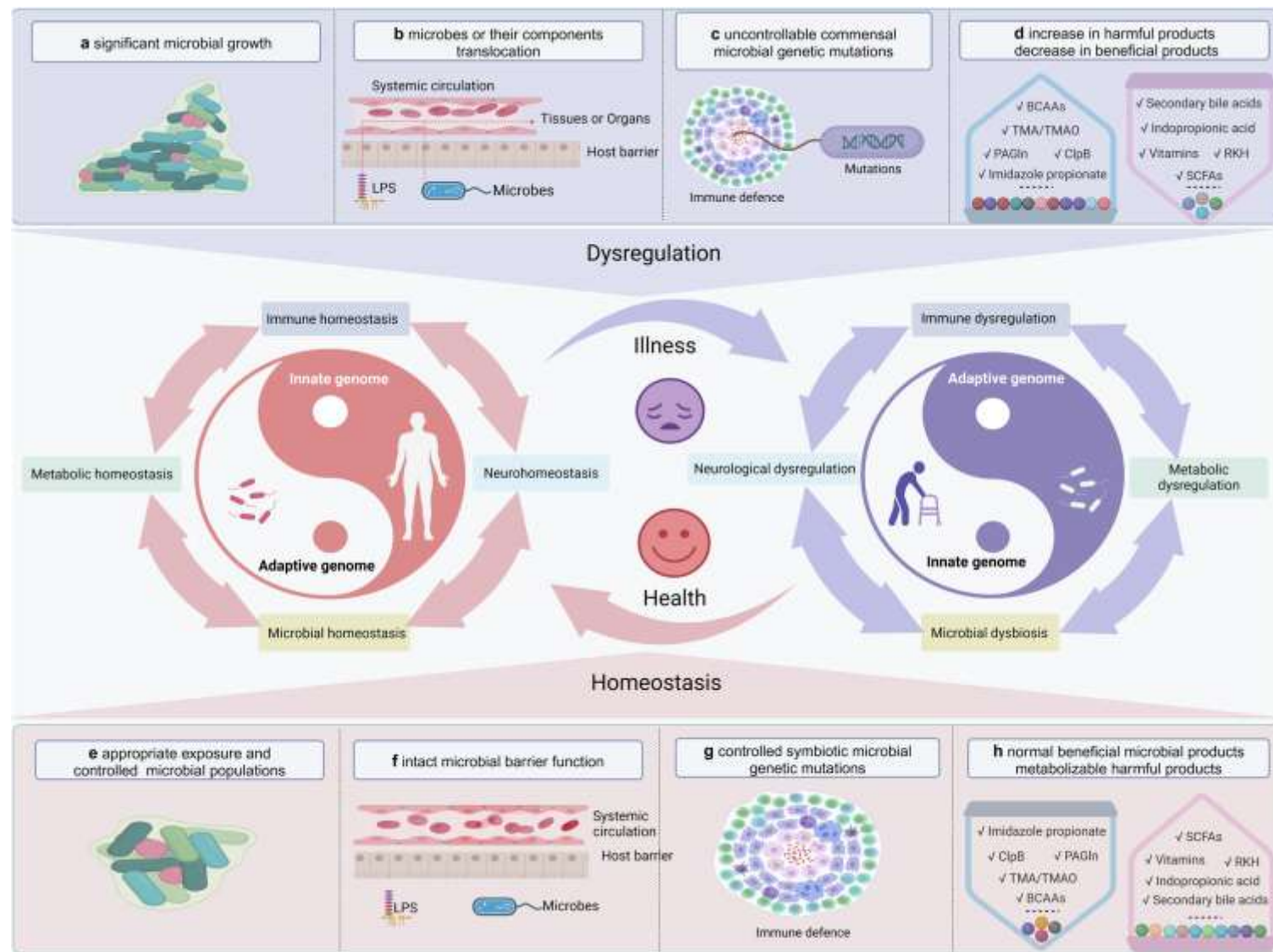
1. Ma, Z. et al. *Sig Transduct Target Ther.* 9, 1–36. (2024)

The commensal microbiota form the *adaptive genome*¹

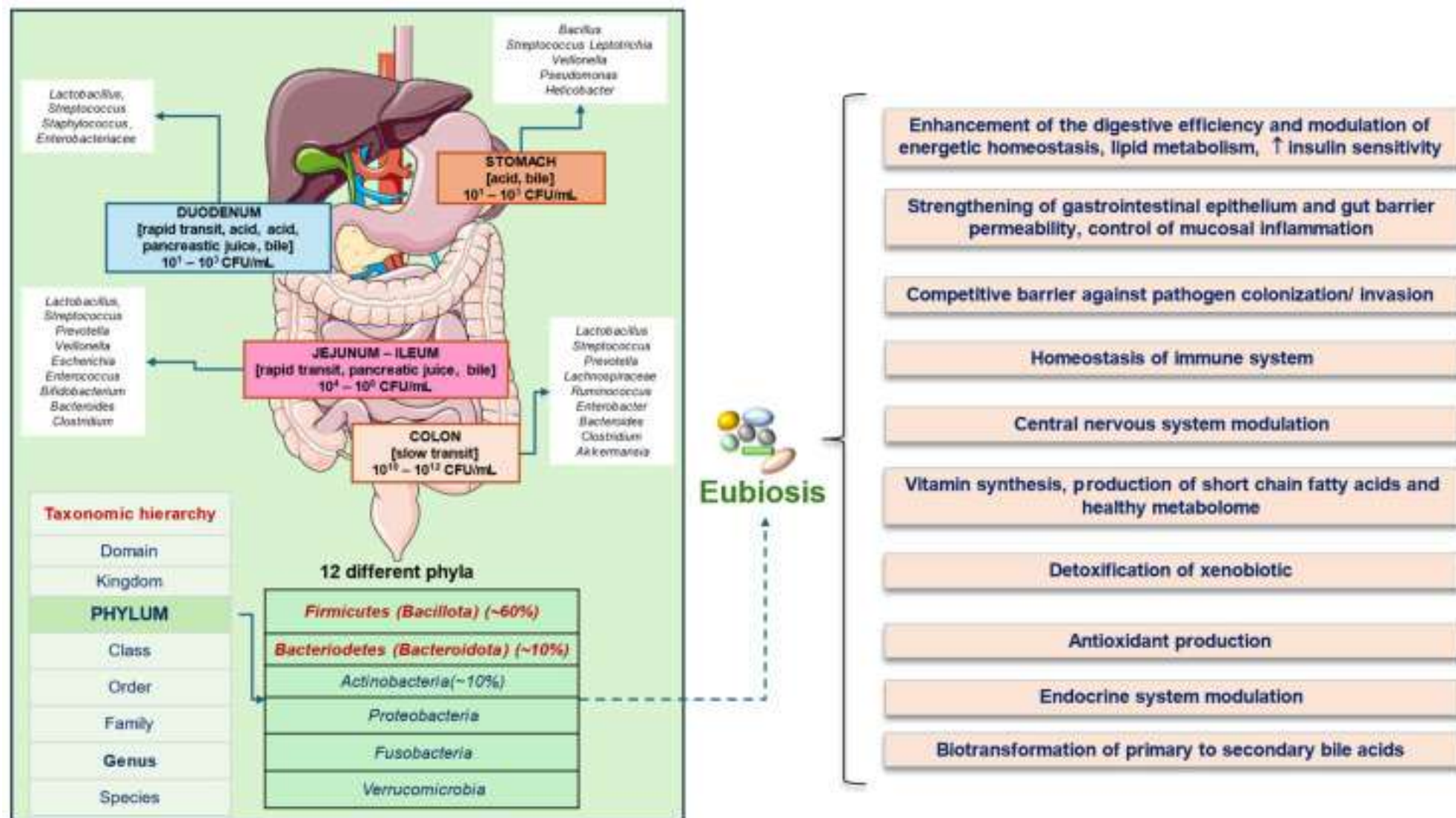


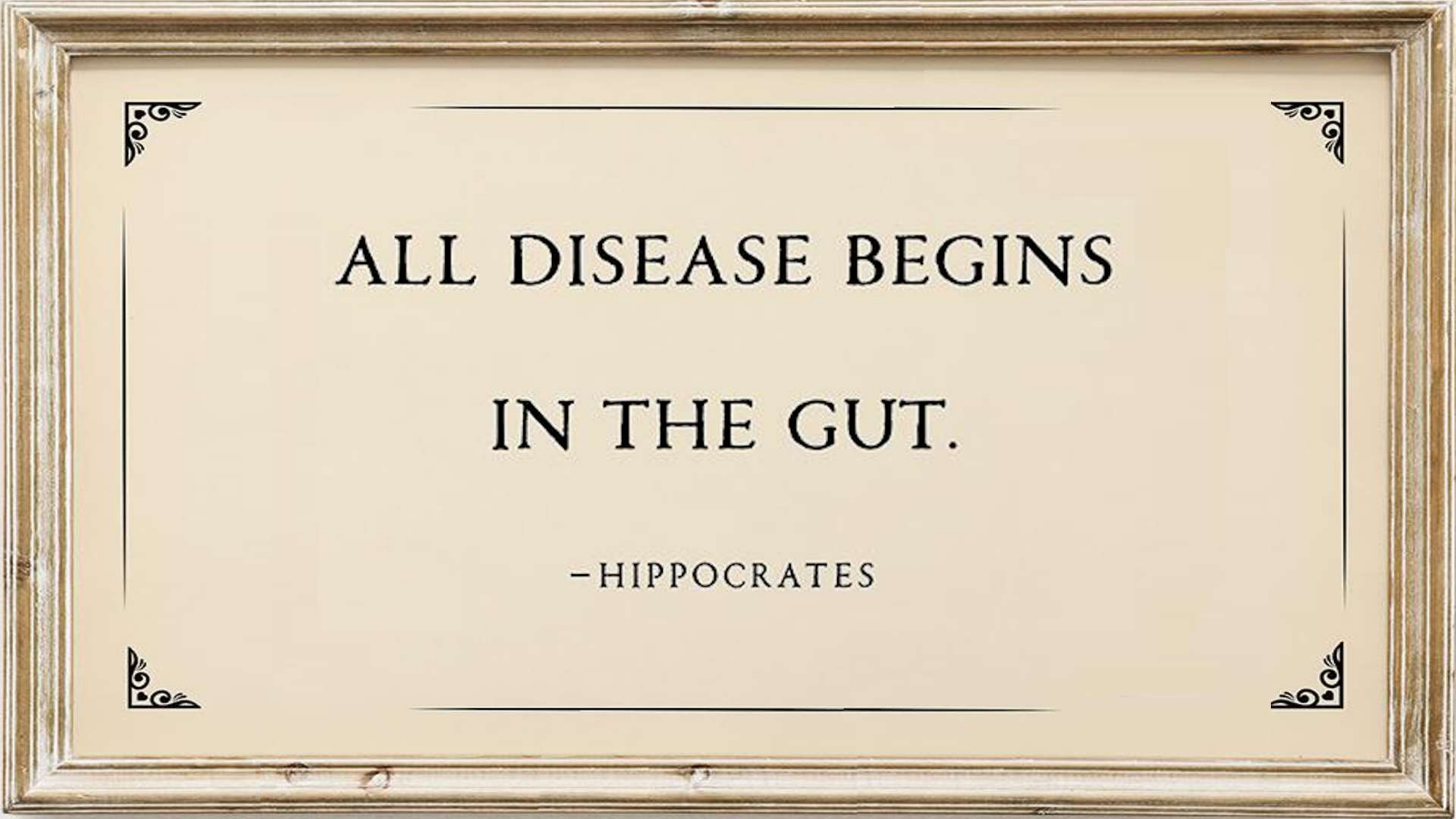
1. Ma, Z. et al. *Sig Transduct Target Ther.* 9, 1–36. (2024)

Holobiont and the main regulations of our physiology¹



Every aspect of our physiology starts in the gut¹



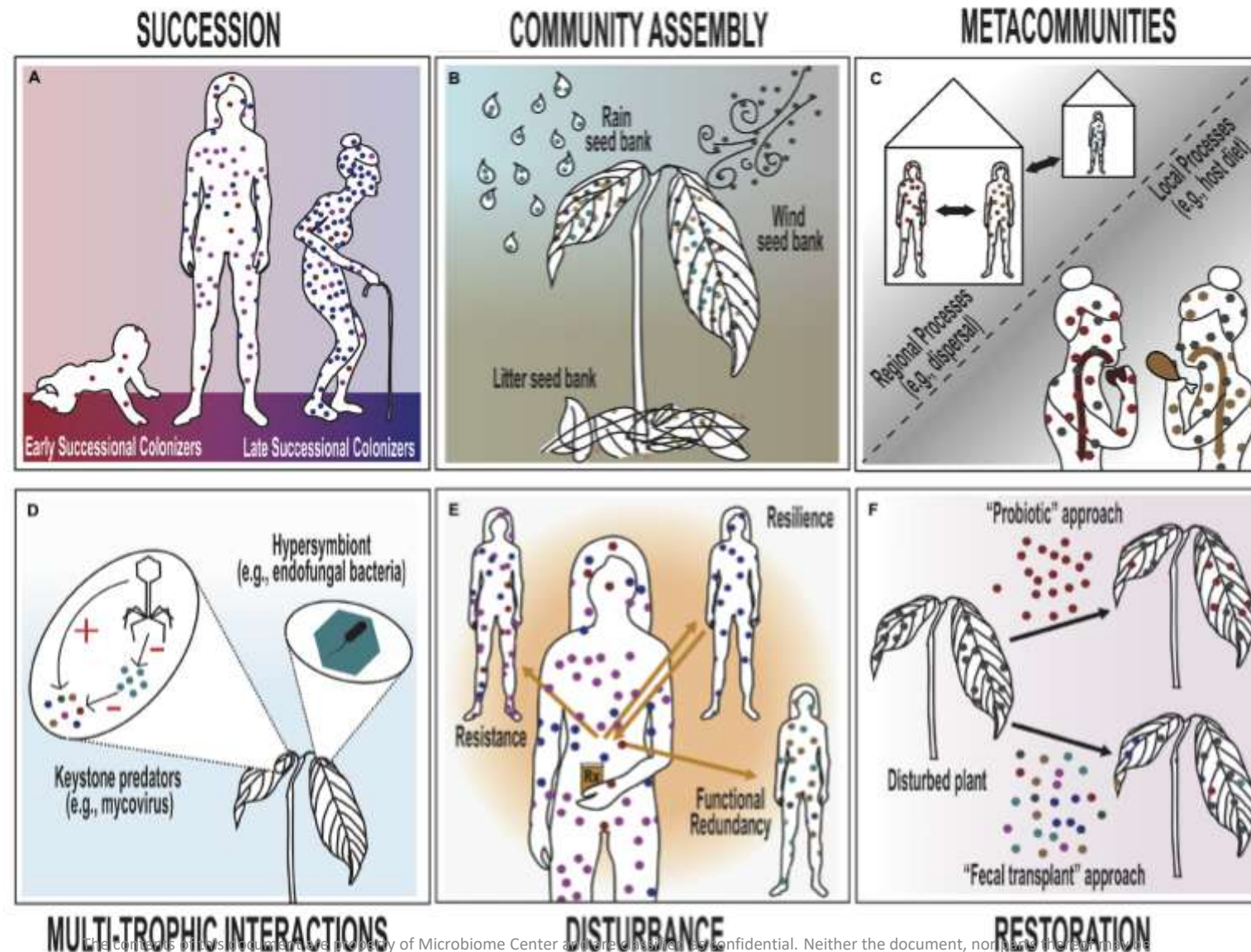


ALL DISEASE BEGINS
IN THE GUT.

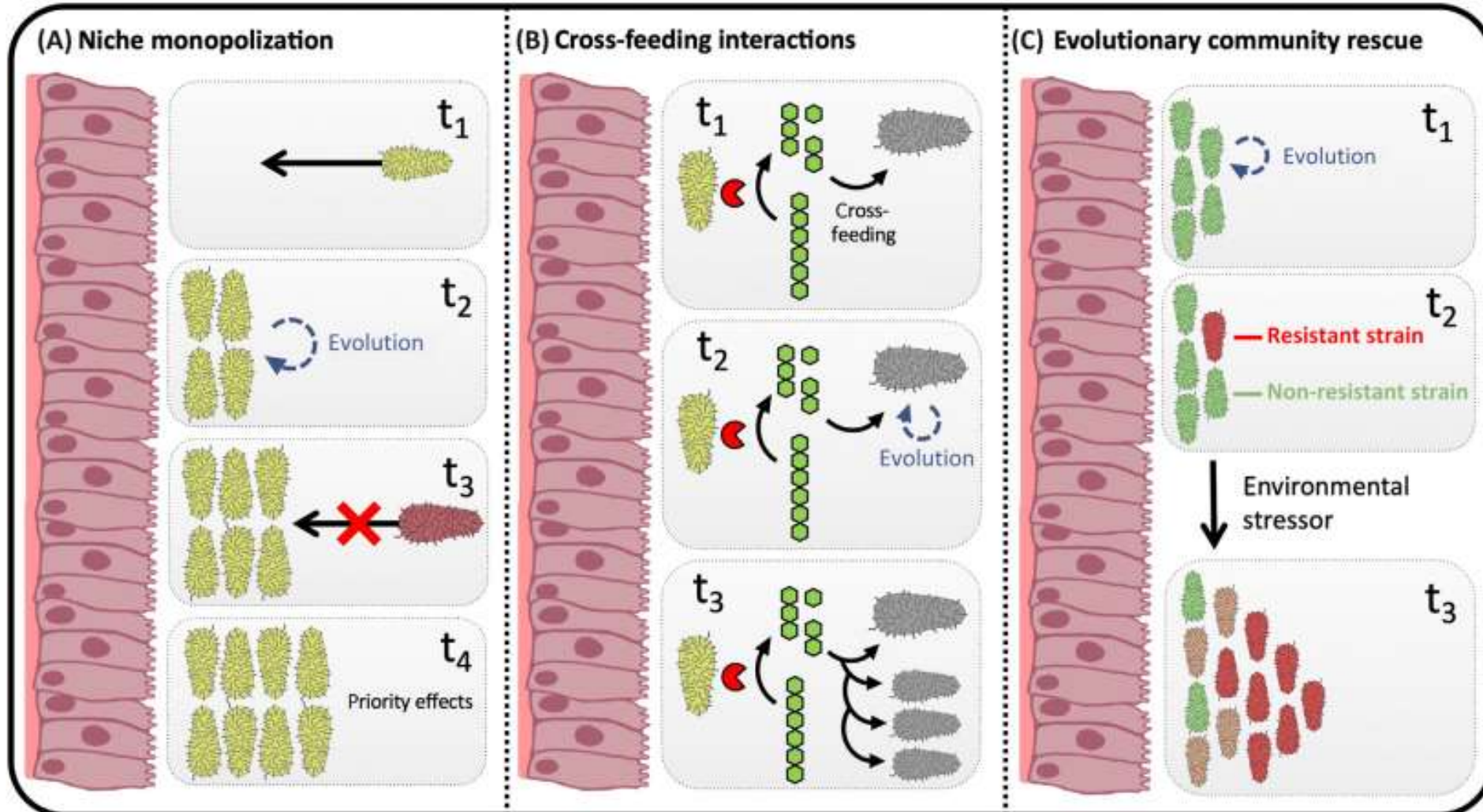
-HIPPOCRATES

Characteristics of ecologies

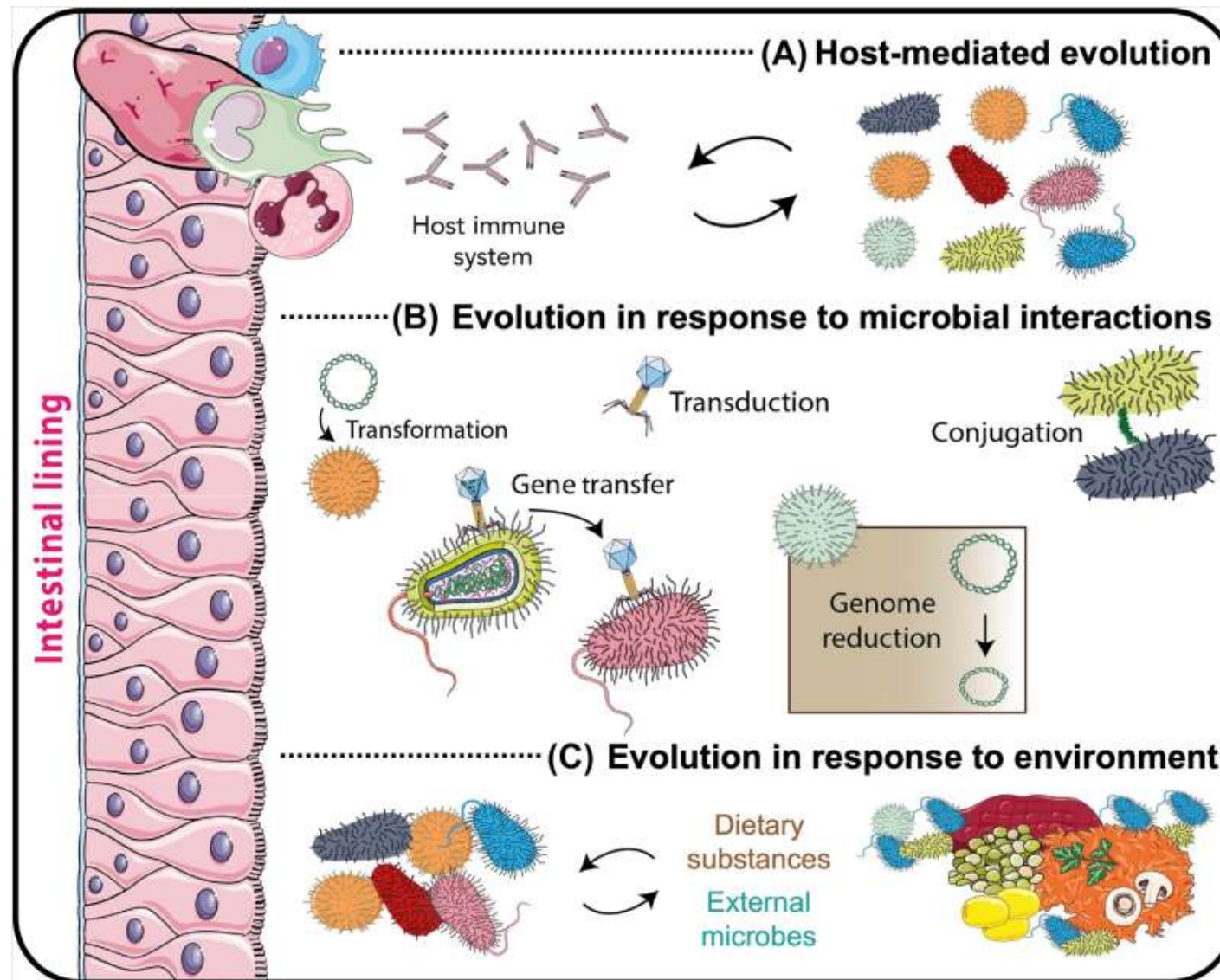
Characteristics of the microbiome as an ecology¹



Characteristics of the microbiome as an ecology¹

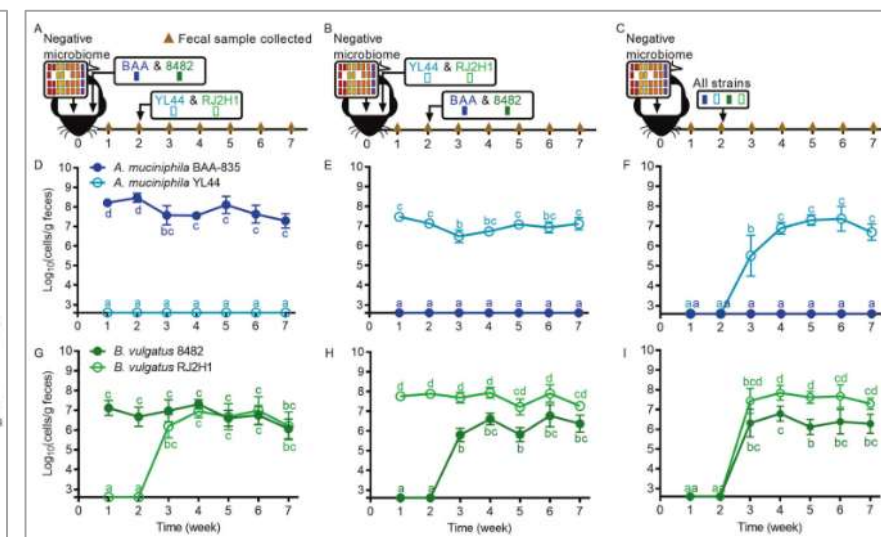
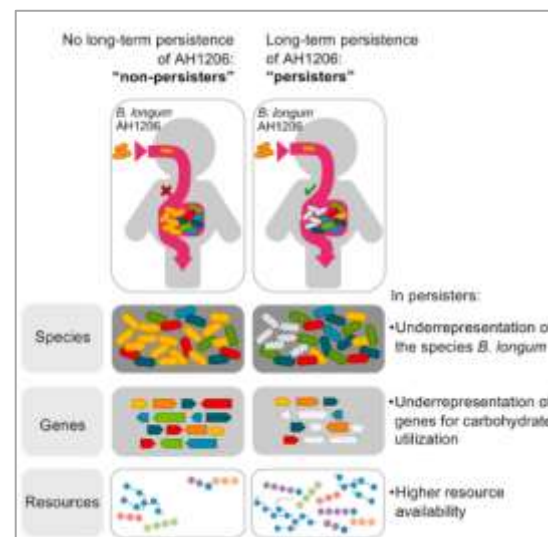
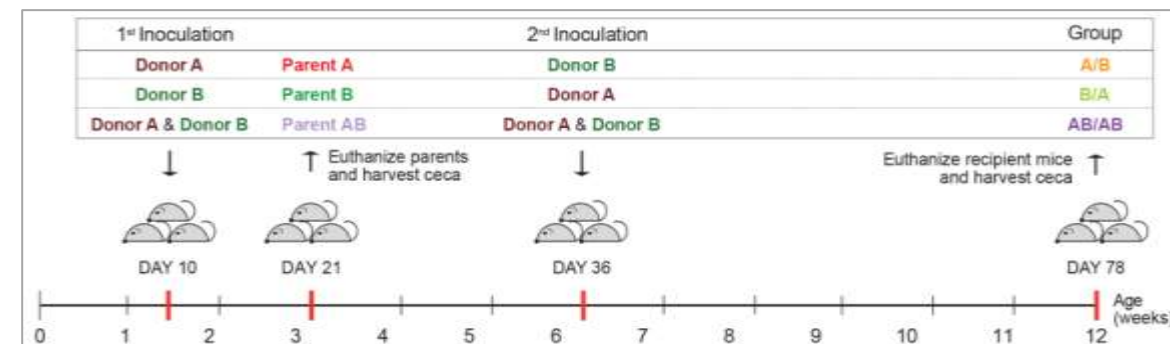


Characteristics of the microbiome as an ecology¹



Characteristics of the microbiome as an ecology

- Useful ecological principles:
 - Order of colonization¹
 - Open niches enable colonization^{2,3}
 - Species adapt to the host/niche⁴
- Host actively selects/supports bacteria:
 - Bacterial entero-breast transfer⁵⁻⁷
 - Prevents commensals from starving, manages the composition of the microbiome⁸



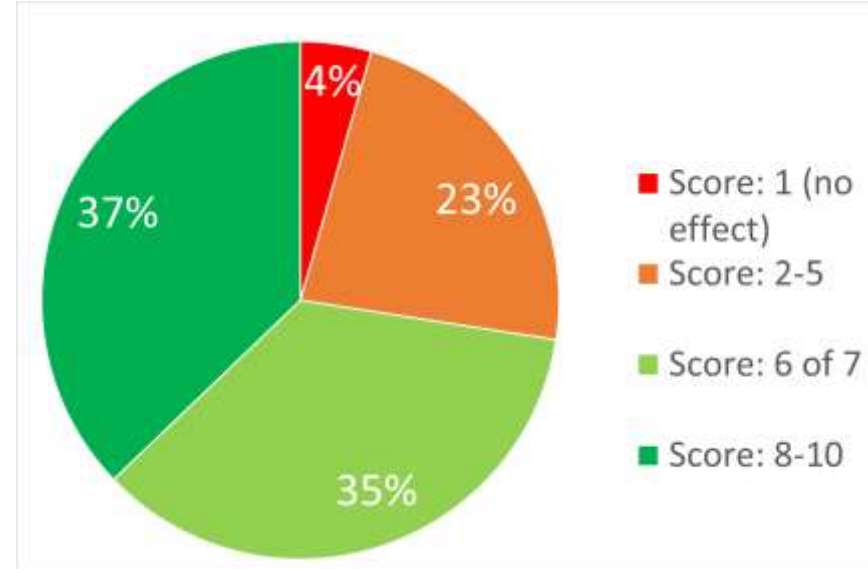
- Martínez, I. et al. *Elife* 7, e36521 (2018)
- Segura Munoz, R. R. et al. *ISME J* 16, 1594–1604 (2022)
- Maldonado-Gómez, M. X. et al. *Cell Host Microbe* 20, 515–526 (2016)
- Zhao, S. et al. *Cell Host Microbe* 25, 656–667.e8 (2019)
- Rodríguez, J. M. *Adv Nutr* 5, 779–784 (2014)
- Jiménez, E. et al. *Appl Environ Microbiol* 74, 4650–4655 (2008)
- Arroyo, R. et al. *CLIN INFECT DIS* 50, 1551–1558 (2010)
- Tuganbaev, T. et al. *European Journal of Immunology* 51, 2120–2136 (2021)

What can we do with ecological principles?

1. 'Gut enricher' Building block

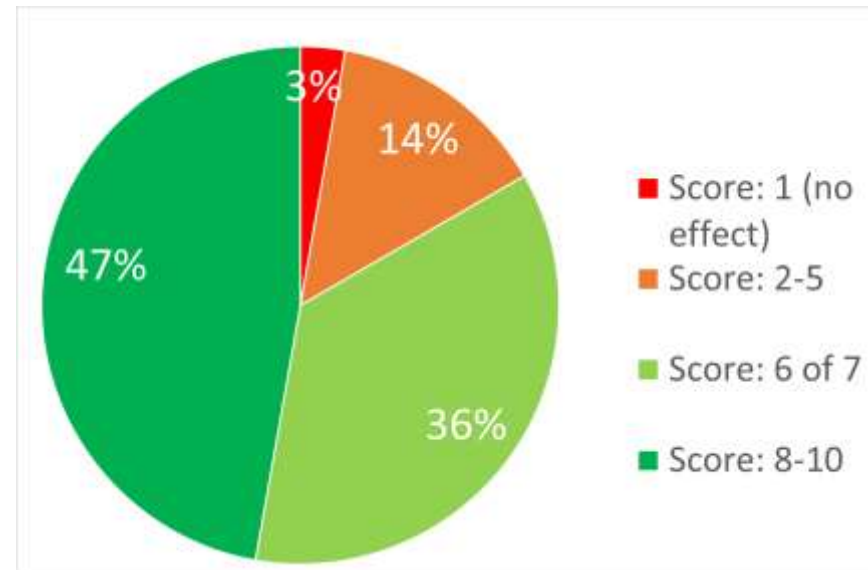
Unique building block:

- For use at low diversity:
 - Low diversity and richness of the microbiome is associated with many diseases^{1,2}.
- Consists of large number of strains (~40) in low dosage (~10⁶ cfu/g).
- Supports strain selection based on **individual ecology and host factors** in patients with low diversity (≤4).



**Low diversity
(n=113)**

73% good or excellent



**Low diversity+ gut
enricher
(n=36)**

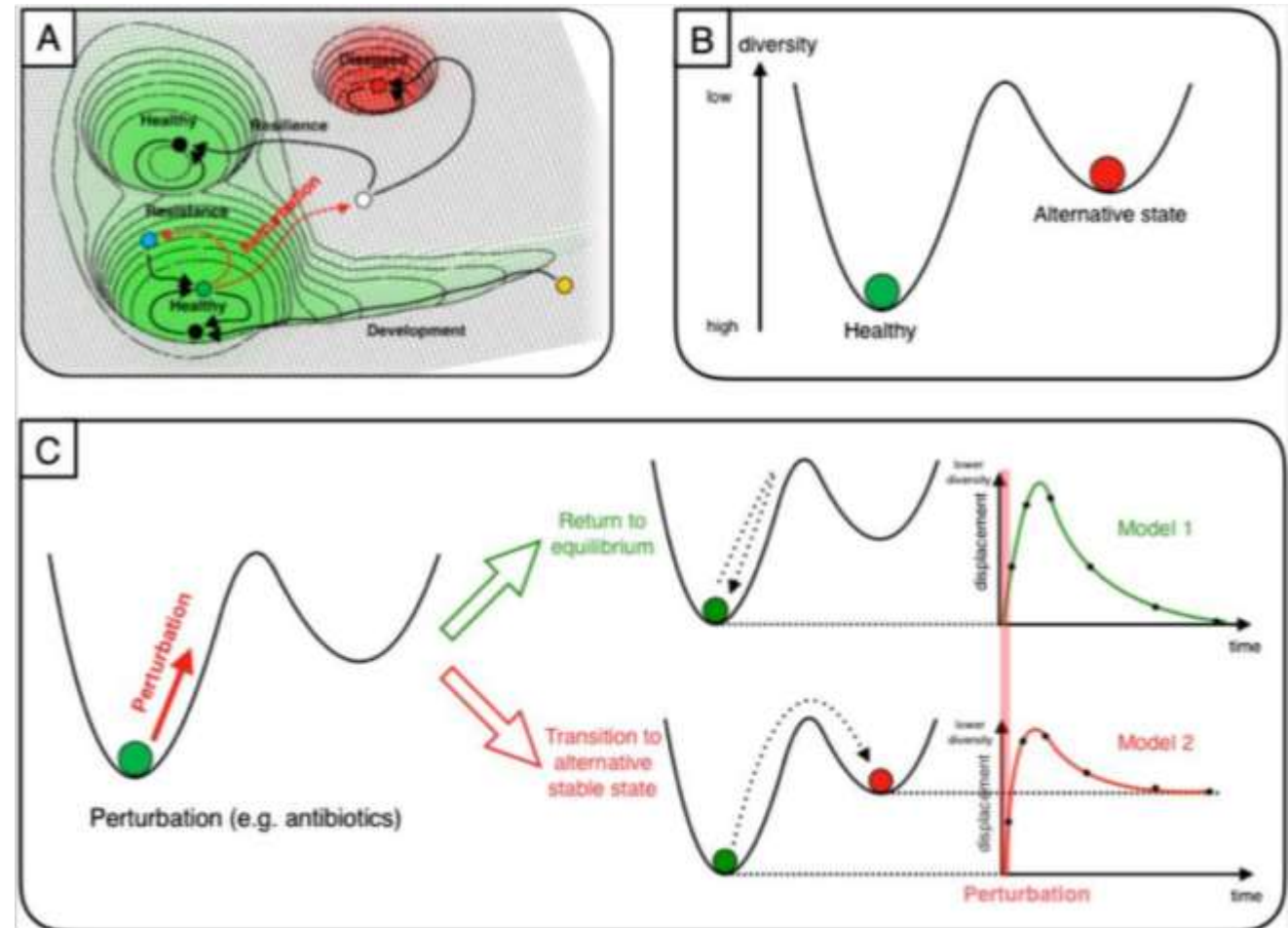
83% good or excellent

1. Tuddenham, S. et al. Curr Opin Infect Dis 28, 464–470 (2015)
2. Álvarez, J. et al. Gastroenterol Hepatol 44, 519–535 (2021)

What can we do with ecological principles?¹

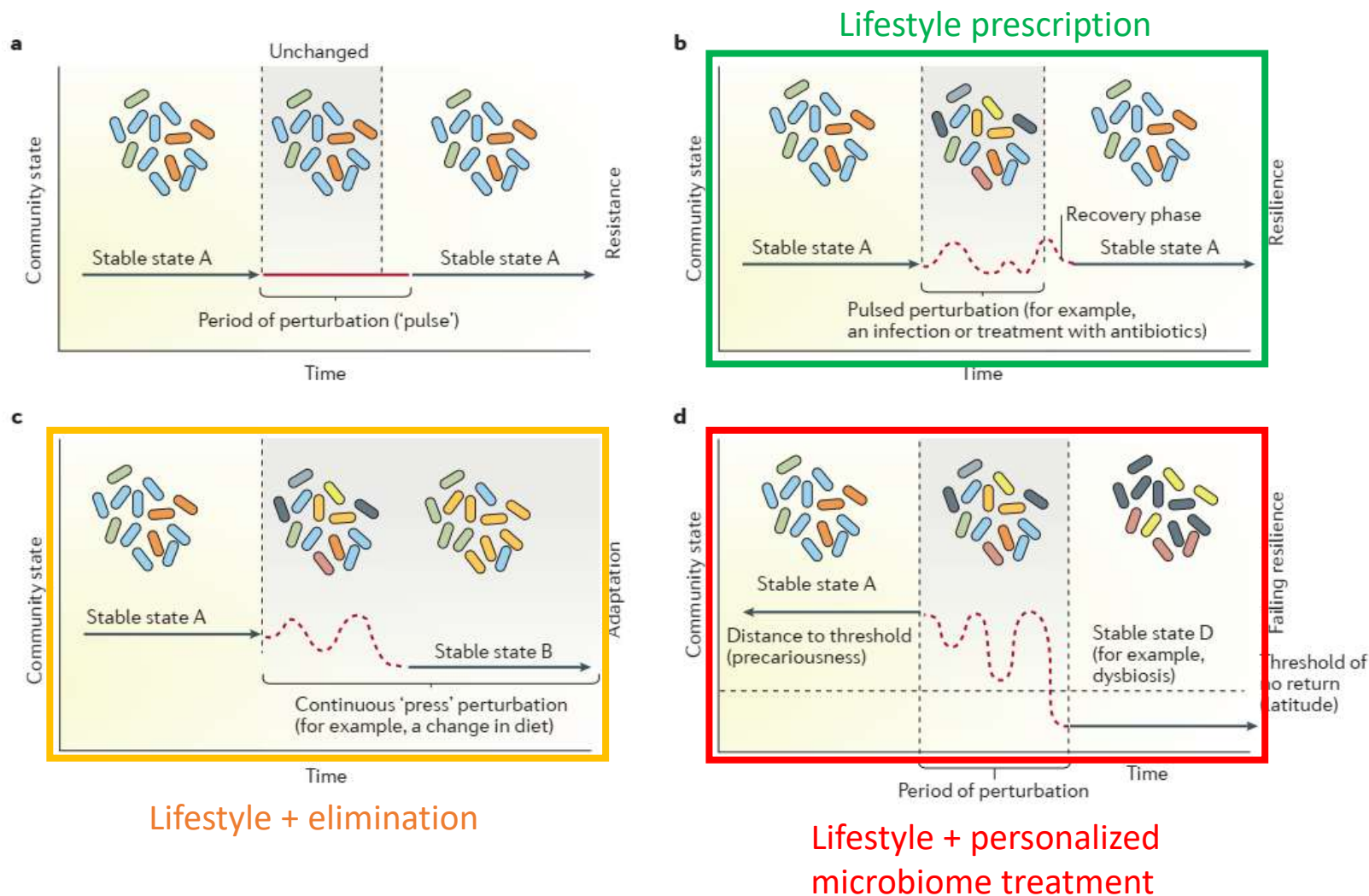
2. Understanding the purpose of treatments

- In a healthy ecosystem, there is 'resilience': resistance to change.
- Goal of microbiome treatment: to move the 'ball' to a stable and desired equilibrium point.
- Personalization helps to 'steer' the direction of change as accurately as possible for the individual patient.



What can we do with ecological principles?^{1,2}

2. Understanding the purpose of treatment



1. Fassarella, M., et al., 2020. Gut *gutjnl-2020-321747*.
2. Sommer, F., et al., 2017. *Nature Reviews Microbiology* 15, 630–638.

The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

What can we do with ecological principles?

3. Revising the logic behind phased treatment



5Rs Approach

The functional medicine approach to supporting and healing your digestive tract

But....



In an ecology, everything happens at the same time



Remove

Remove anything irritating the gut



Replace

Replace any missing digestive elements



Reinoculate

Reinoculate the gut microbiome with good bacteria



Repair

Repair intestinal cells



Rebalance

Rebalance lifestyle elements

What can we do with ecological principles?

3. Revising the logic behind phased treatment



Duration of replication

Intervention equivalent

Bacteria

Minutes to hours¹

First eradicate pathogens,
month later
probiotics for build-up

Forest

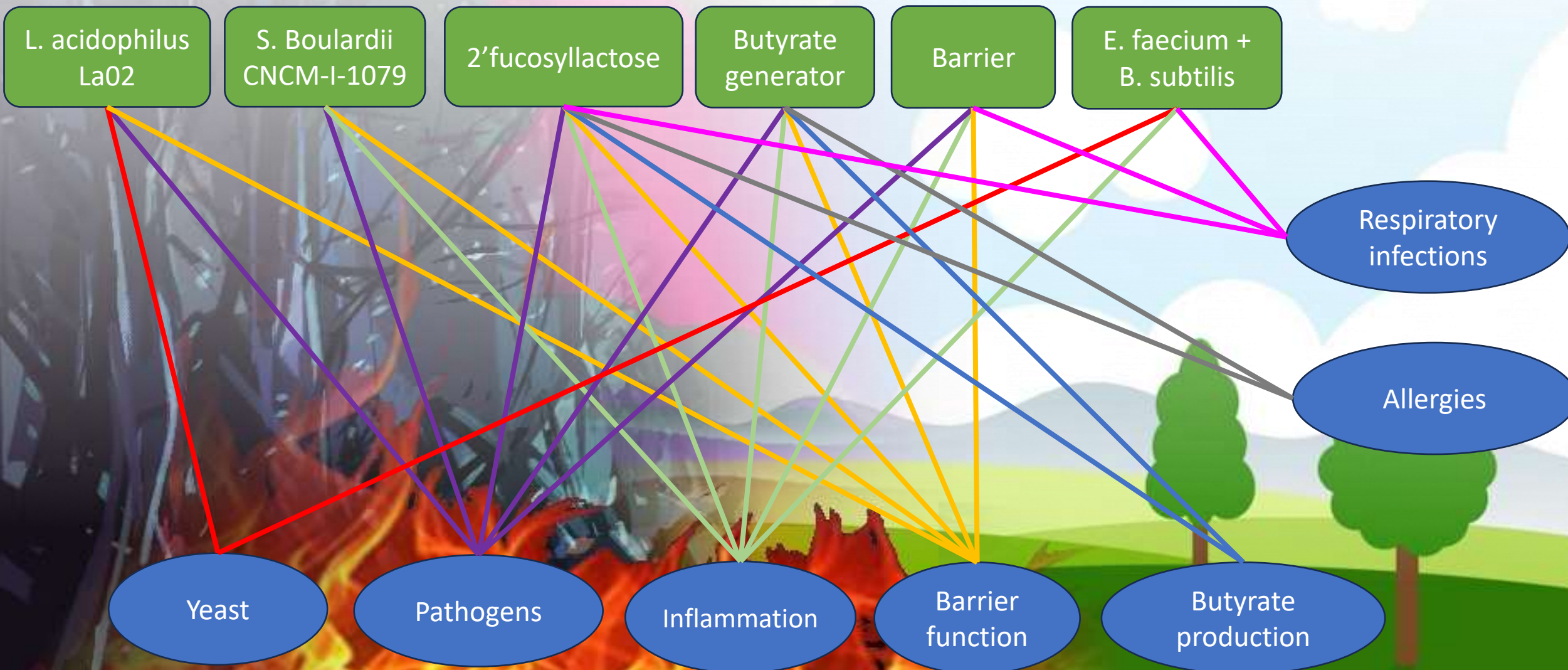
Decades²

First burn down the forest,
plant new trees
decades later

1. Lim, J. J. et al. Nat Commun 14, 5682 (2023)
2. Defense, F. W. Frontline (2019)

What can we do with ecological principles?

4. In microbiome treatment, everything happens at the same time



What can we do with ecological principles?

4. In microbiome treatment, everything happens at the same time

Example probiotic: *Saccharomyces cerevisiae* var *boulardii* CNCM-I-1079

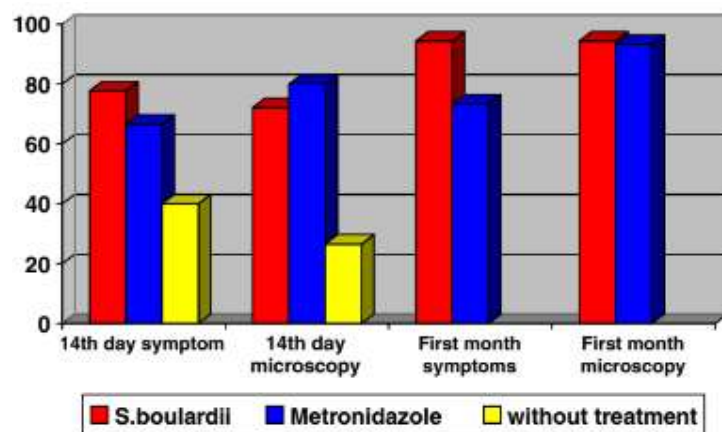


Fig. 1 Cure rate for clinical findings and parasitological examinations between study groups on the 14th day and first month

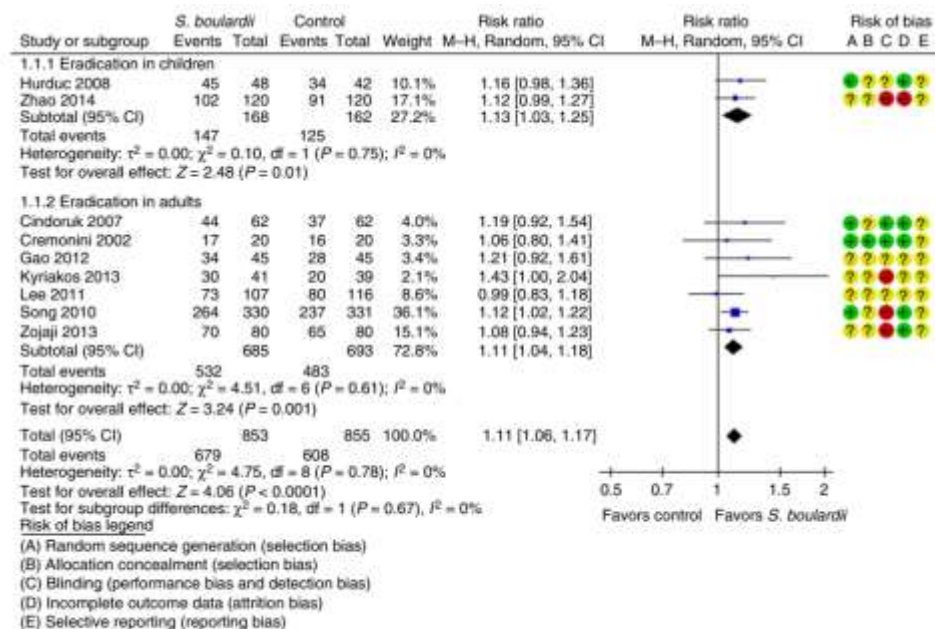
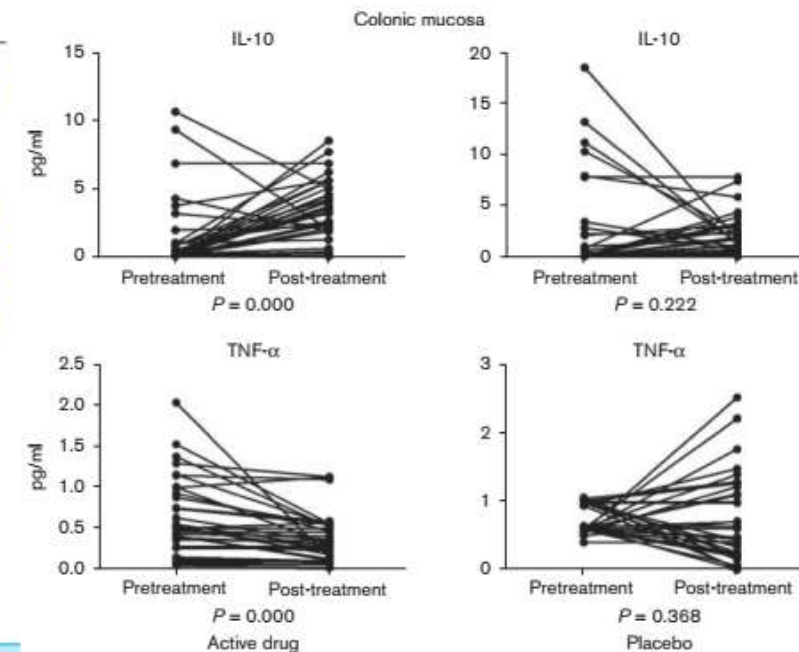


Figure 1 | Primary outcome: Effect of *Saccharomyces boulardii* (58) on *Helicobacter pylori* eradication rates.



Inhibits parasites (*Entameba histolytica*, *Blastocystis hominis*, *Giardia lamblia*)¹⁻³

Inhibits *Helicobacter pylori*⁴

Anti-inflammatory and intestinal barrier function-enhancing effects^{5,6}

1. Dinleyici, E. C. et al. Am. J. Trop. Med. Hyg. 80, 953–955 (2009)
2. Dinleyici, E. C. et al. Parasitol. Res. 108, 541–545 (2011)
3. Besirbellioglu, B. A. et al. Scandinavian Journal of Infectious Diseases 38, 479–481 (2006)
4. Szajewska, H. et al. Alimentary Pharmacology & Therapeutics 41, 1237–1245 (2015)
5. Abbas, Z. et al. European Journal of Gastroenterology & Hepatology 1 (2014)

6. Garcia Vilela, E. et al. Scandinavian Journal of Gastroenterology 43, 842–848 (2008)

The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

What can we do with ecological principles?

4. In microbiome treatment, everything happens at the same time

Example prebiotic: 2'fucosyllactose

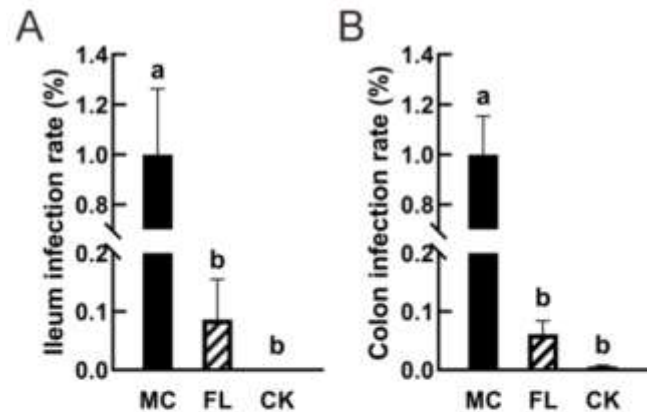


Figure 1. *Escherichia coli* O157 colonization and pathological section of ileum. (A) The colonization in ileum; (B) colonization in colon;

Inhibits pathogens^{1,2}

Stimulates 'healthy' commensals such as *Akkermansia* and *A. soehngenii*^{4,4}

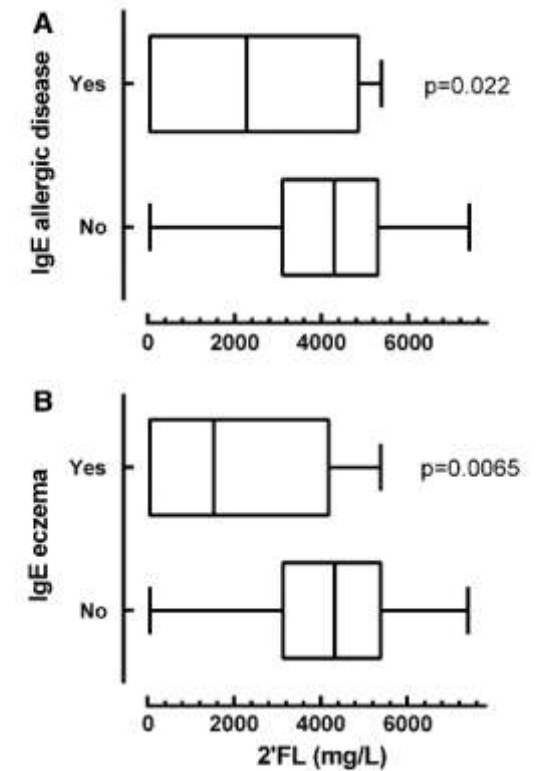
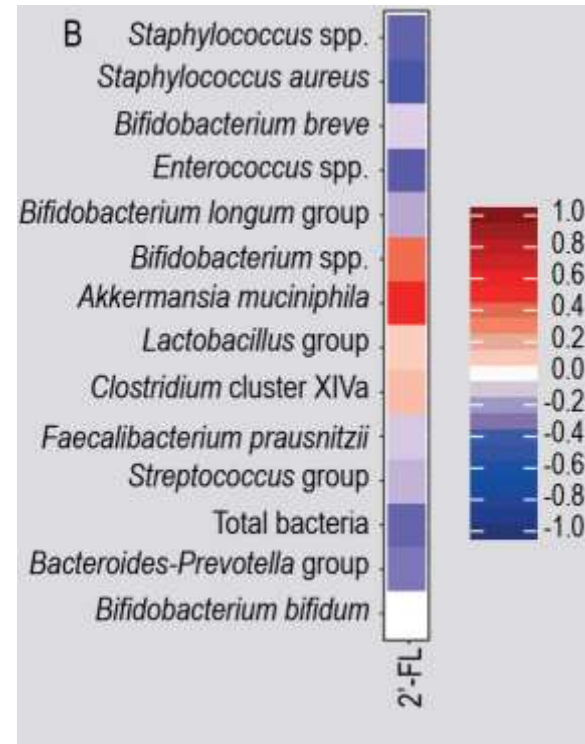


Fig. 2 Breast milk consumed by C-section-born infants who did not show IgE-associated allergic disease and IgE-associated eczema contained higher levels of 2'-fucosyllactose a proxy for FUT2-dependent oligosaccharides. 2'-Fucosyllactose (2'FL) levels in early breast milk (2.6 ± 1.1 days postpartum) that was consumed by C-section-born infants who showed IgE-associated allergic disease (a) or IgE-associated eczema (b) at 2 years or not. Box and whisker plots are shown with median and minimal and maximal values. Two-tailed *p* values from unpaired *t* test are indicated

Beneficial effect on allergies^{5,6}

- Wang, Y. et al. Nutrients 12, (2020)
- Facinelli, B. et al. The Journal of Maternal-Fetal & Neonatal Medicine 32, 2950–2952 (2019)
- Aakko, J. et al. Beneficial Microbes 8, 563–567 (2017)
- Kostopoulos, I. et al. Scientific Reports 10, 14330 (2020)

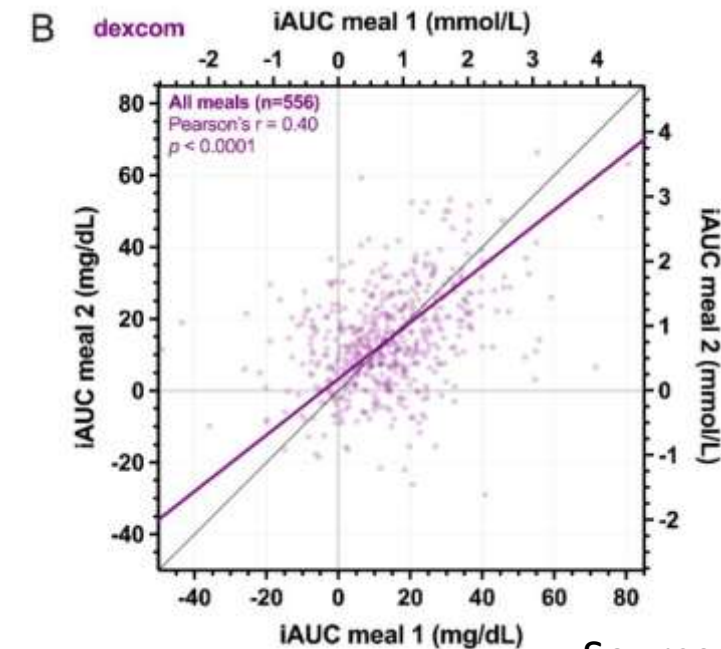
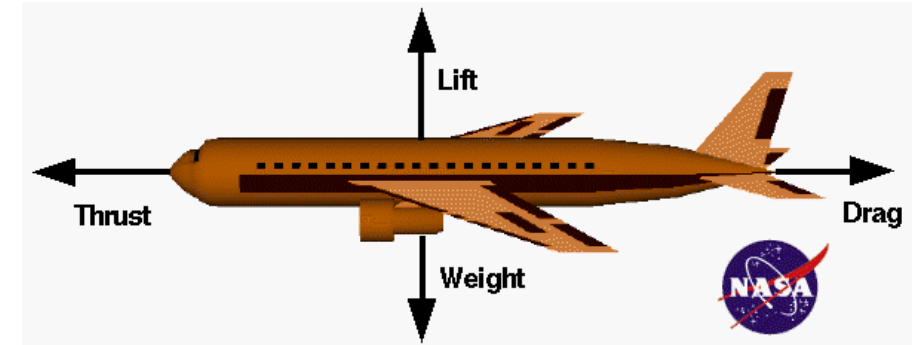
- Sprenger, N. et al. Eur J Nutr 56, 1293–1301 (2017)
- Castillo-Courtade, L. et al. Allergy 70, 1091–1102 (2015)

The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

Our biology is 'complex'

Reductionism doesn't work in complex systems

- Many life science studies have a pitfall:
 - Reductionism: study separate factors to understand the whole.
 - Borrowed from physics. There, it works because the superposition principle applies¹.
- Superposition does not apply if a system is either:
 - non-linear
 - Regulated
 - Interactive
- In physiology all three apply!

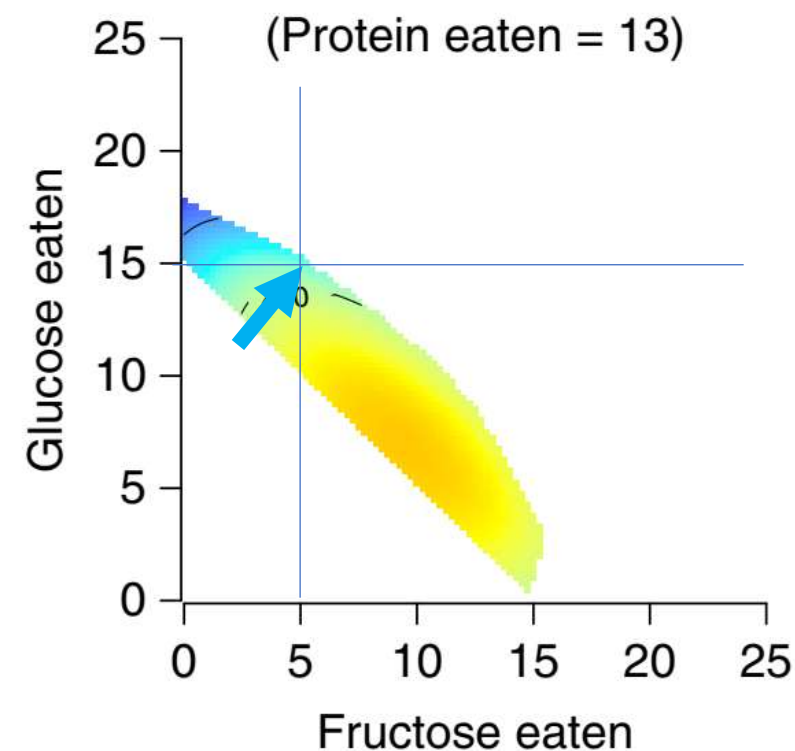
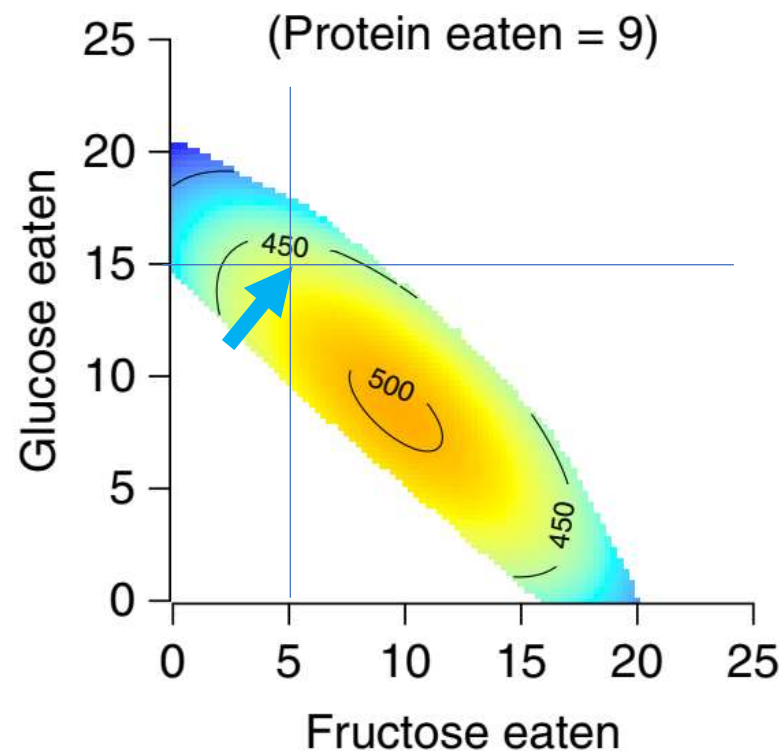
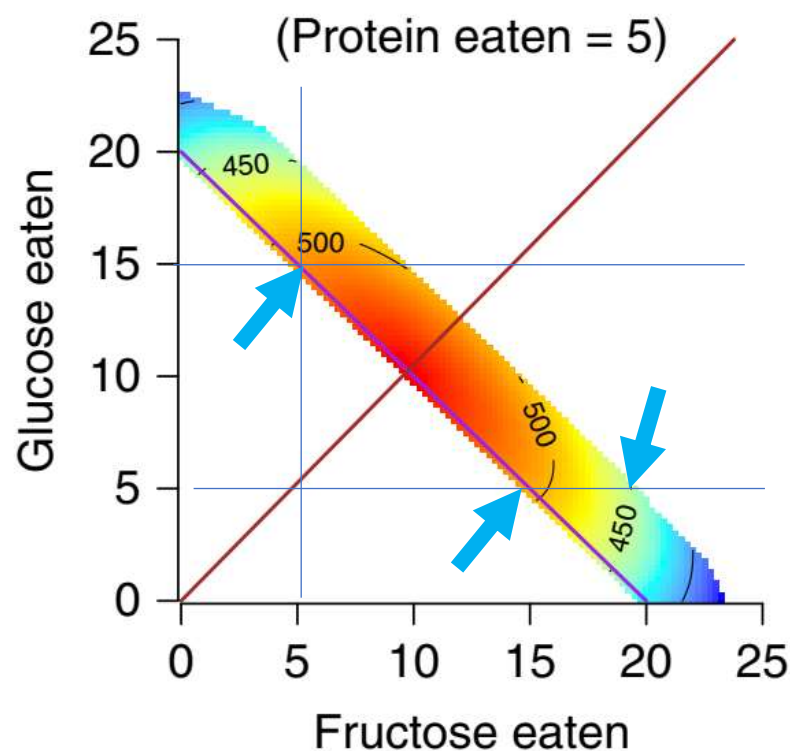


Source: ²

In a complex system context is key!

But if I prescribe everything at once, I don't know what effect has what effect....

...True, but in a complex biological system you can't know that anyway.



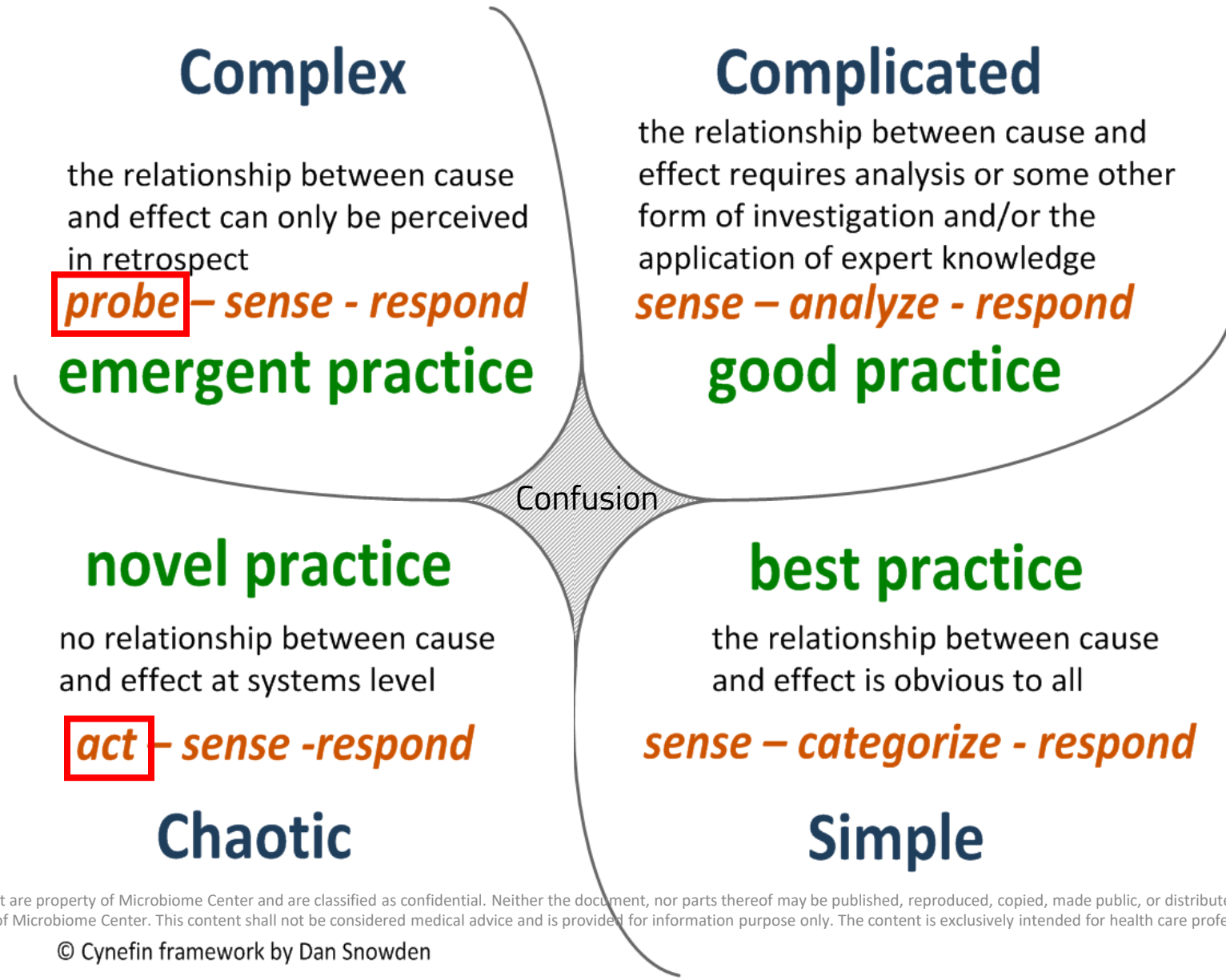
Insulin tolerance test (ITT)

1. Wali, J. A. et al. Nat Metab.3.,810–828.(2021)

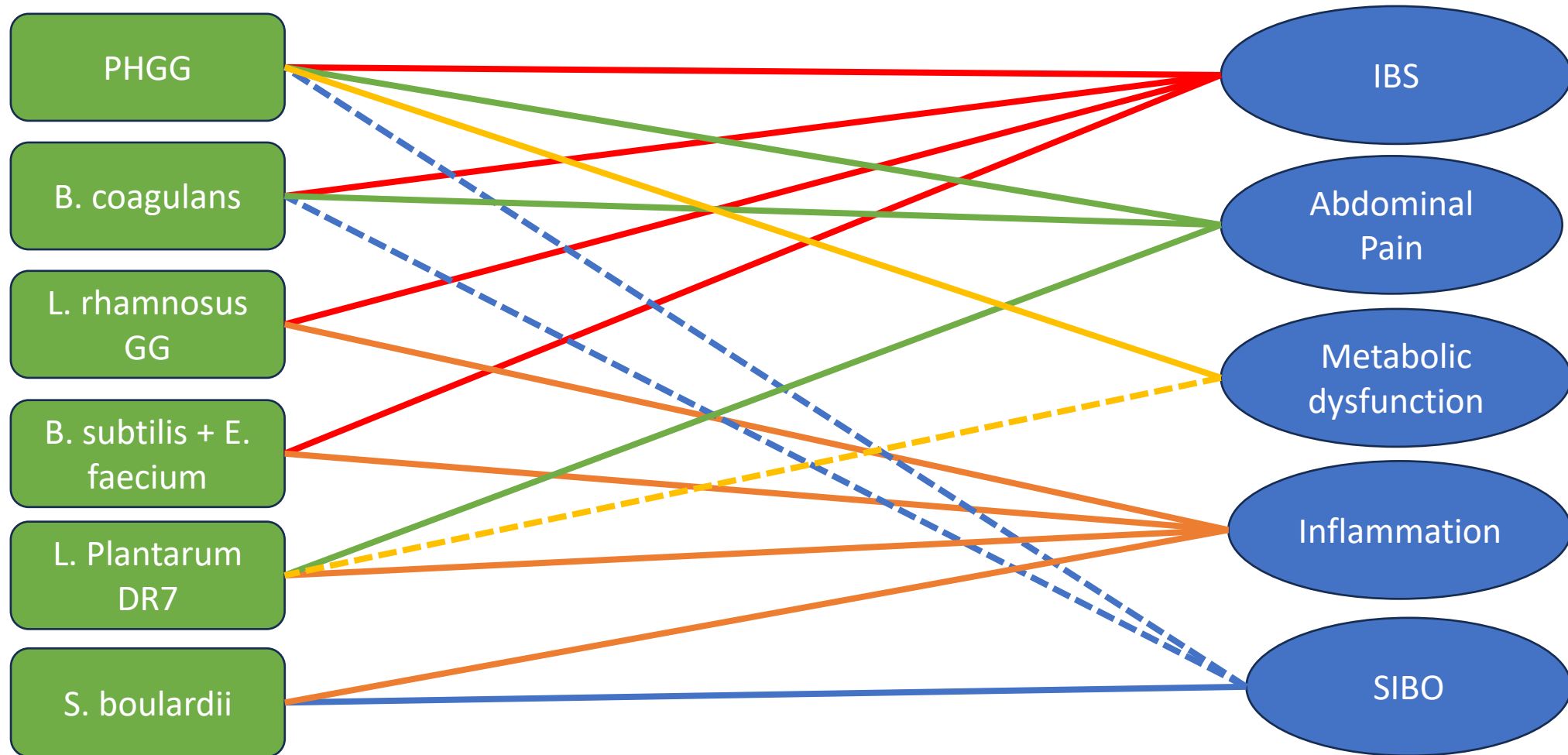
The contents of this document are property of Microbiome Center and are classified as confidential. Neither the document, nor parts thereof may be published, reproduced, copied, made public, or distributed without explicit written permission of Microbiome Center. This content shall not be considered medical advice and is provided for information purpose only. The content is exclusively intended for health care professionals.

How to work with a complex/chaotic system?

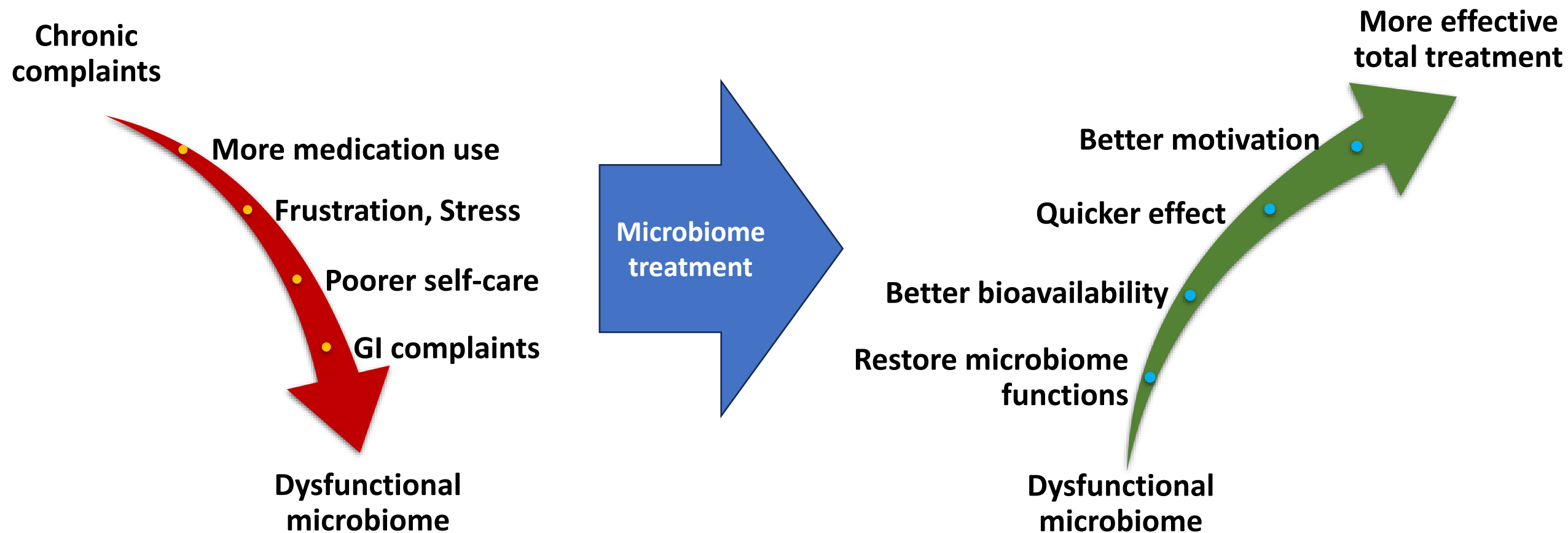
→ Cynefin framework



Start with acting: using the best conceivable intervention



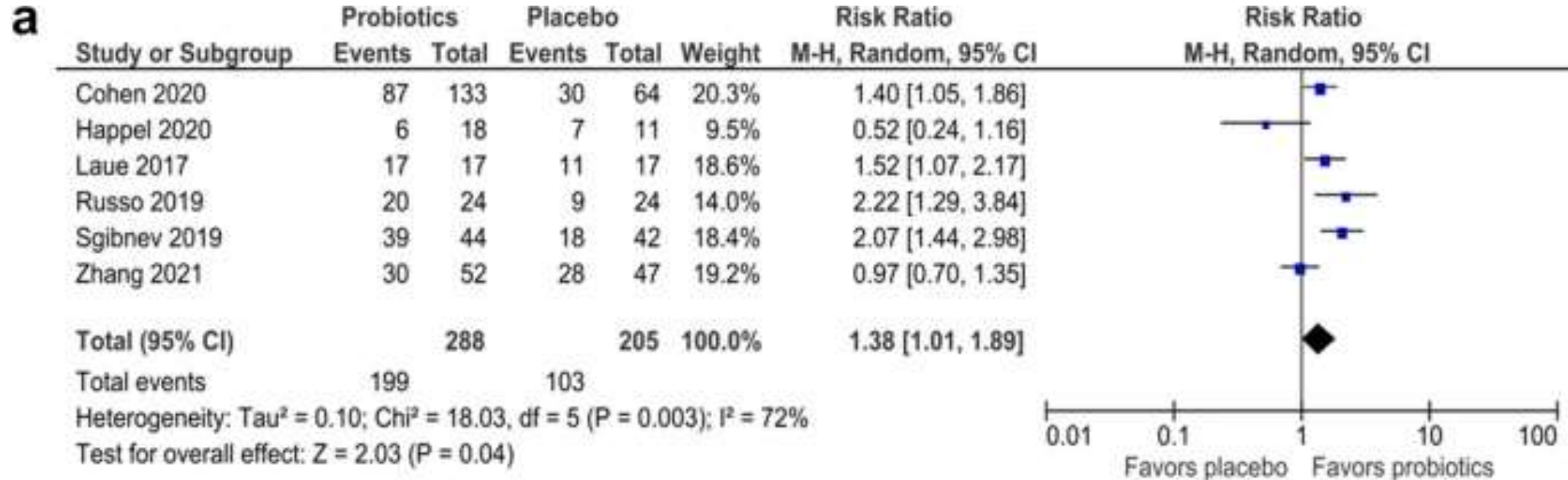
Why start with gut treatment?



Example 1: more effective treatment of urinary tract infections

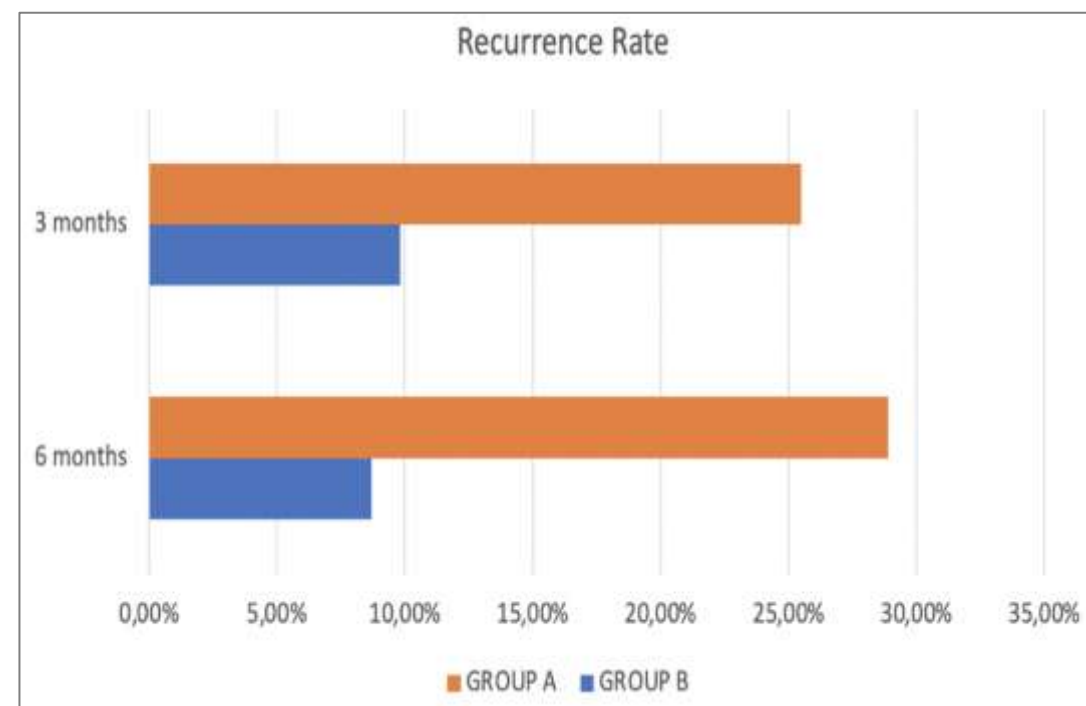
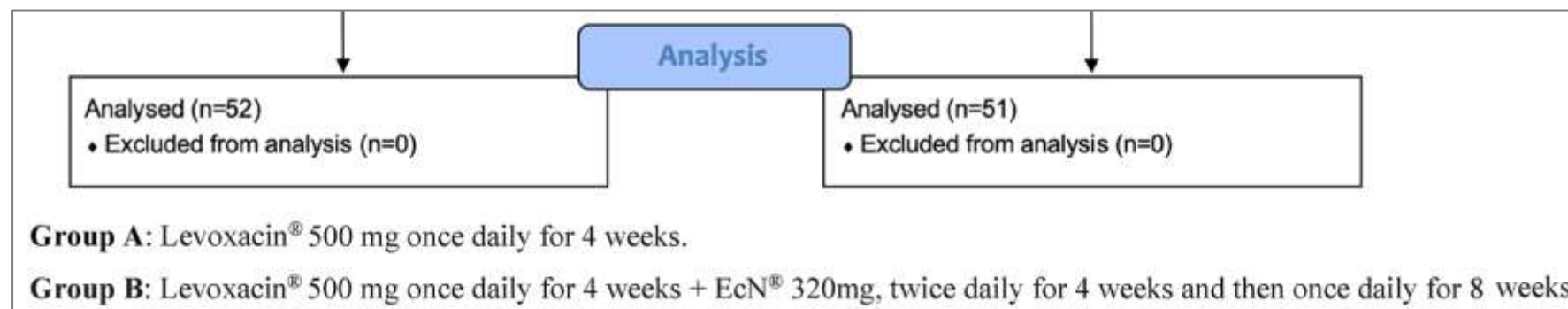
Meta-analyses of RCTs of antibiotic treatment of UTIs¹:

→ more effective with probiotics



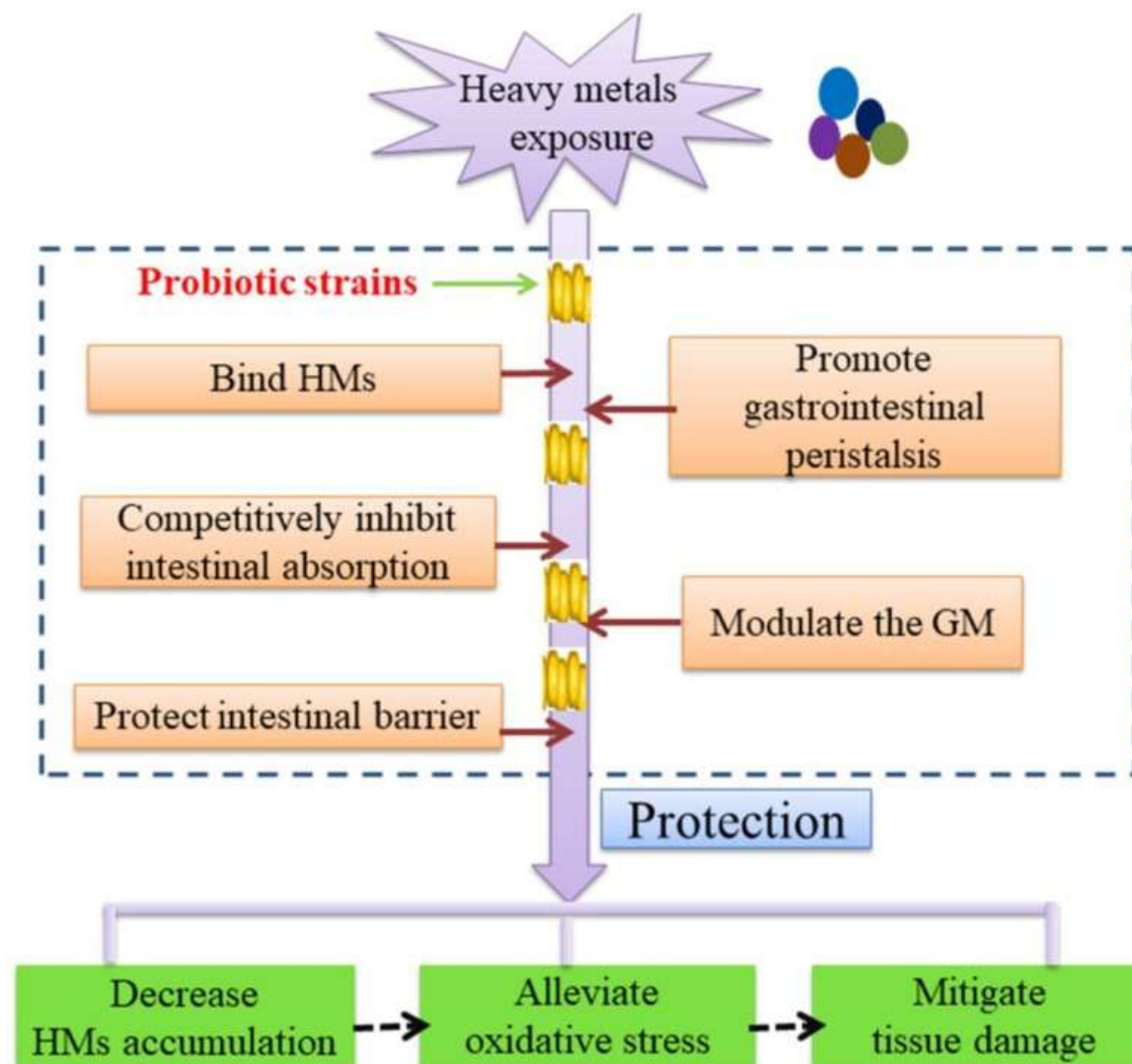
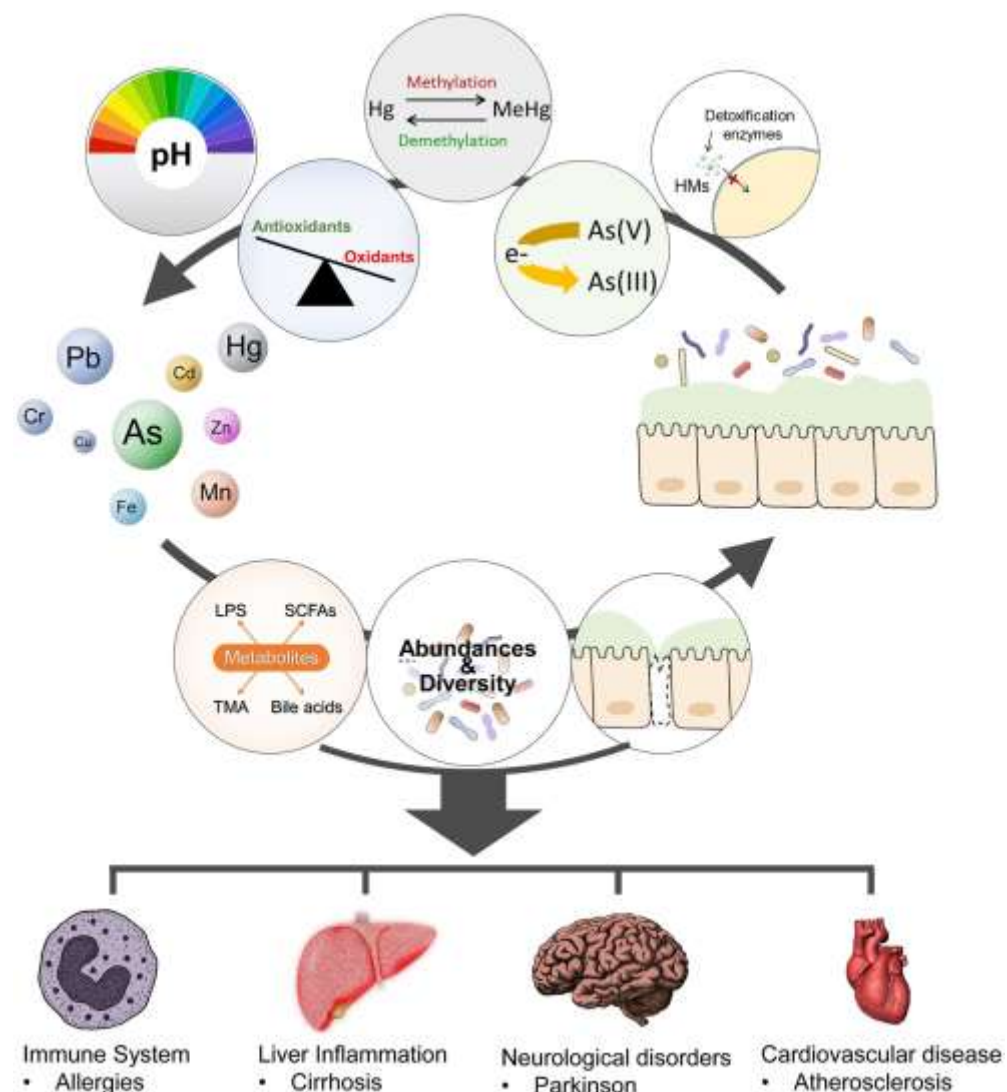
1. Nelwan, E. J. et al. BMC Infectious Diseases. 24, 505. (2024)

Example 2: more effective treatment of chronic bacterial prostatitis¹: *E. coli* MC231



1. Manfredi, C. et al. World J Urol.39,.4373–4379.(2021)

Example 3: detoxification: the microbiome helps^{1,2}



1. Zhu, Q. et al. *Front. Nutr.* 11, (2024)
2. Feng, P. et al. *Nutrients* 11, 22, (2018)



ALL Treatment BEGINS

IN THE GUT.

—HIPPOCRATES

Casus thema microbioom als ecosysteem

Jes Schalkwijk
Praktijk voor Integrale Geneeskunde



Weten het niet-weten, dat is hoog.
Niet weten het weten, dat is een ziekte.
Wie ziek is van die ziekte is niet ziek.
De wijze is niet ziek,
omdat hij ziek is van die ziekte.
Daarom is hij niet ziek

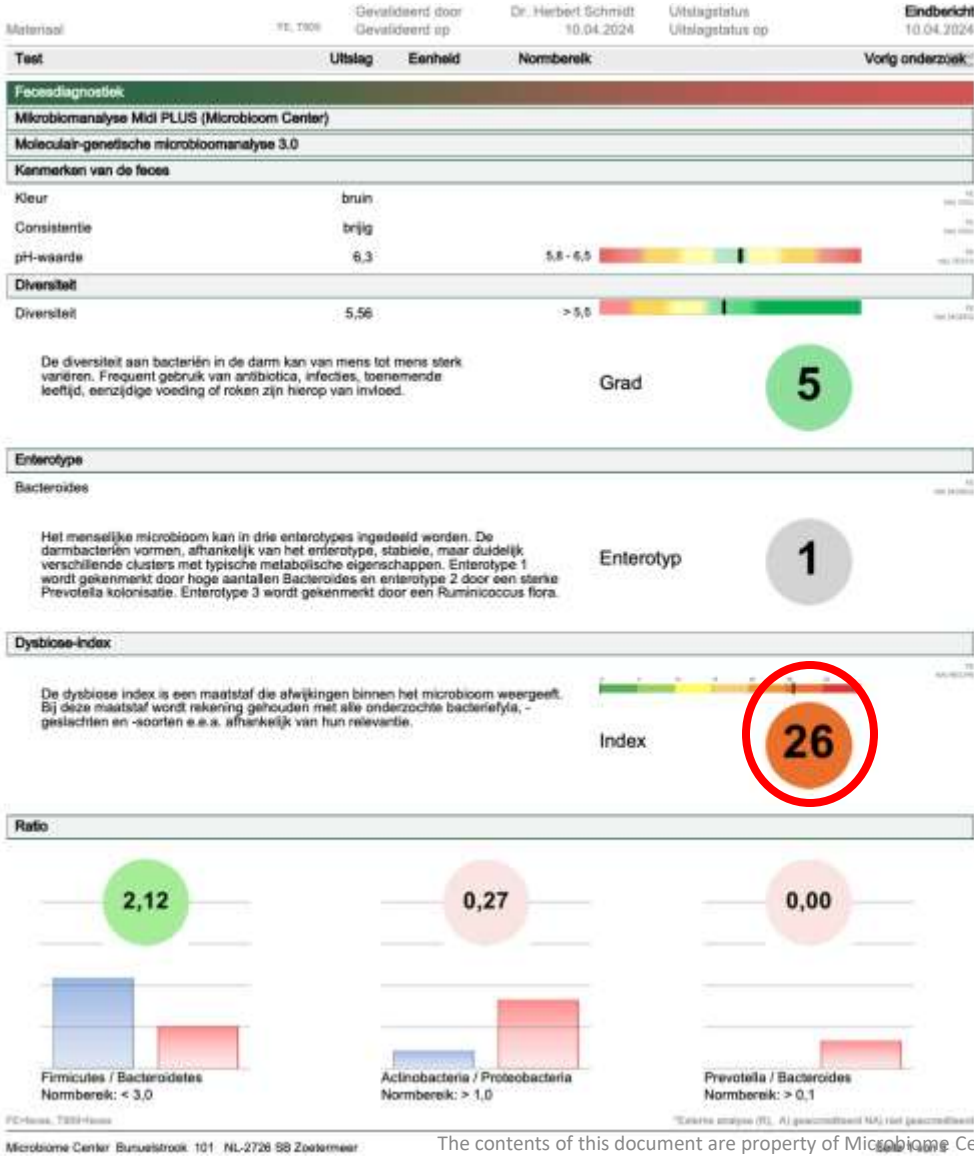
Lao Tseu

Algemene klachten voorgeschiedenis

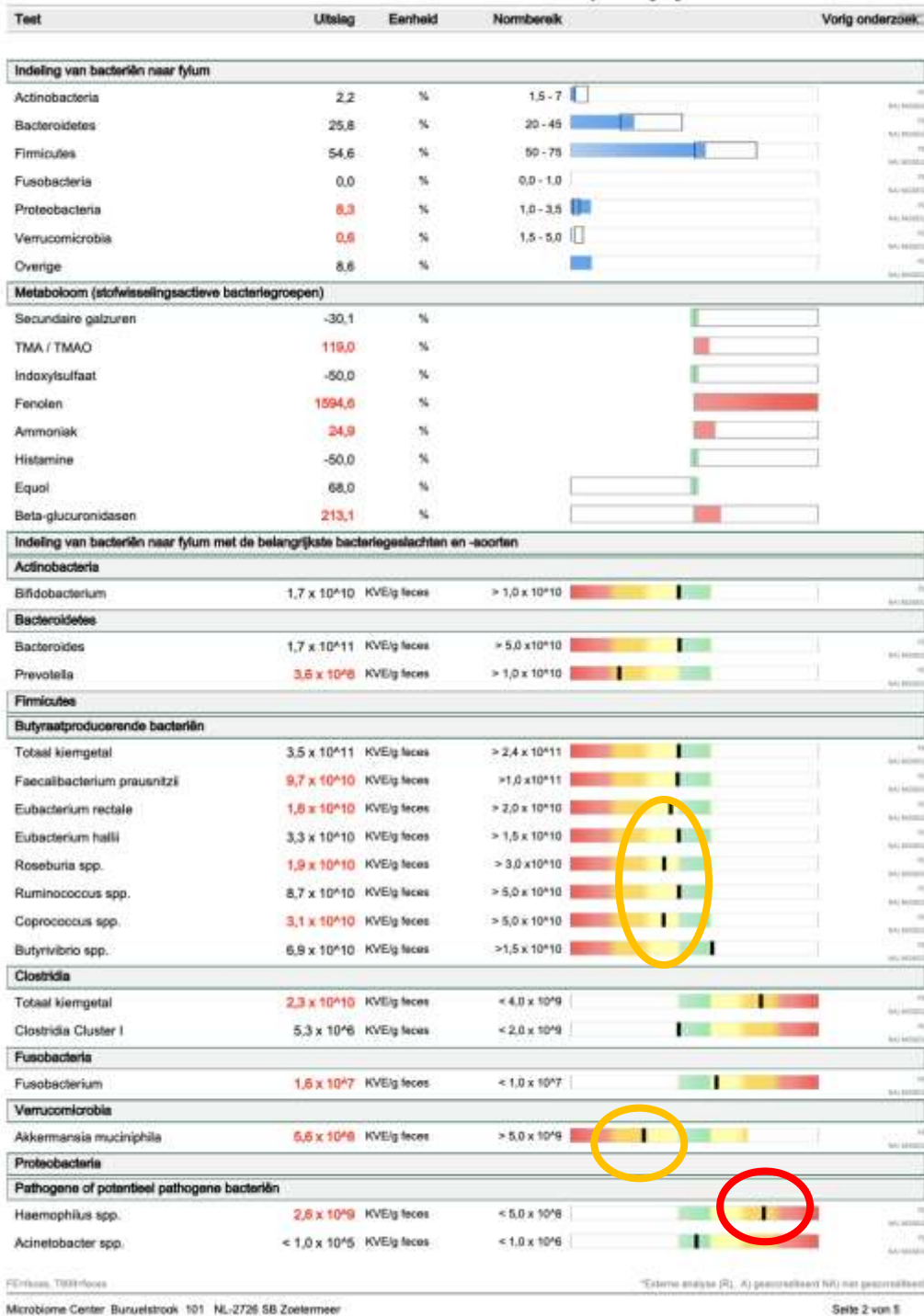


- Sinds maart 2024 onder behandeling
- 3 maal per ochtend dunne, gele, brijige, ontlasting
- Opgeblazen maag en buik, ruikende winderigheid
- Probiotica maakte ontlasting iets steviger
- Daarnaast: extreme moeheid, misselijkheid (lijkt samen te hangen)
- Veel krampen in het lichaam, pijnklachten verspreid door het lichaam
- Branderig gevoel in de mond, diagnose *Lichen Planus* via tandarts

Microbioom analyse



The contents of this document are property of Microbioom Center and are classified as confidential, reproduced, copied, made public, or distributed without explicit written permission is prohibited. The content is considered medical advice and is provided for information purpose only. The content is



Test	Uitslag	Eenheid	Normbereik	Vorig onderzoek
Proteus spp.	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁶	FE
Klebsiella spp.	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁷	FE
Enterobacter spp.	5,1 x 10 ¹⁰	KVE/g feces	< 1,0 x 10 ⁶	FE
Serratia spp.	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁷	FE
Haflnia spp.	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁶	FE
Morganella spp.	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁶	FE
Citrobacter spp.	1,1 x 10 ⁹	KVE/g feces	< 5,0 x 10 ⁸	FE
Pseudomonas spp.	< 1,0 x 10 ⁵	KVE/g feces	< 5,0 x 10 ⁷	FE
Providencia spp.	< 1,0 x 10 ⁵	KVE/g feces	< 5,0 x 10 ⁷	FE
H2S-vorming				
Sulfaatreducerende bacteriën (SRB)	4,2 x 10 ⁹	KVE/g feces	< 2,5 x 10 ⁹	FE
Desulfovibrio piger	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁹	FE
Desulfomonas pigra	< 1,0 x 10 ⁵	KVE/g feces	< 1,0 x 10 ⁹	FE
Bilophila wadsworthii	< 1,0 x 10 ⁵	KVE/g feces	< 2,0 x 10 ⁹	FE
Immunogeniteit / mucine vorming				
Immunogeen werkende bacteriën				
Escherichia coli	2,2 x 10 ⁶	KVE/g feces	10 ⁶ - 10 ⁷	FE
Enterococcus spp.	1,63 x 10 ⁹	KVE/g feces	10 ⁶ - 10 ⁷	FE
Lactobacillus spp.	6,9 x 10 ⁵	KVE/g feces	10 ⁵ - 10 ⁷	FE
Mucine vorming / slijmvliesbarrière				
Akkermansia muciniphila	5,6 x 10 ⁸	KVE/g feces	> 5,0 x 10 ⁹	FE
Faecalibacterium prausnitzii	9,7 x 10 ¹⁰	KVE/g feces	> 1,0 x 10 ¹¹	FE
Archaea				
Methanogenen				
Methanobrevibacter spp.	3,9 x 10 ⁹	KVE/g feces	< 5,0 x 10 ⁸	FE
Opmerking: Het nieuwe Omicsnap-buik en de darm samenstelling metris maken een nog effectievere monitoring mogelijk, vooral bij grampositieve bacteriën. Dit resulteert in lichte verschuivingen in de normbereiken. We vragen u hier rekening mee te houden.				
Mycobiom: relevante gisten				
Candida albicans (CA)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida krusei (CK)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida glabrata (CG)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida dubliniensis (CD)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida parapsilosis (CP)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida tropicalis (CTp)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Candida lusitanae (CL)	< 1,0 x 10 ³	KVE/g feces	< 1,0 x 10 ³	FE
Parasieten				
Pathobiënten				
Blastocystis hominis	positief	negatief		FE
Dientamoeba fragilis	positief	negatief		FE
Pathogene darmprotozoa				
Giardia lamblia	negatief	negatief		FE
Entamoeba histolytica	negatief	negatief		FE
Cryptosporidium spp.	negatief	negatief		FE

Test	Uitslag	Eenheid	Normbereik	Vorig onderzoek
Cyclospora cayetanensis	negatief		negatief	FE A) MOLEK
Vertering				
Vetgehalte	5,61	g/100g	< 3,5	FE NA) PHOT
Stikstofgehalte	0,53	g/100g	< 1,0	FE NA) PHOT
Suikergehalte	2,39	g/100g	< 2,5	FE NA) PHOT
Watergehalte	77,27	g/100g	75 - 85	FE NA) PHOT
Extra parameter(s)				
Calprotectine	< 17,90	mg/l	< 50	FE A) ELISA
Alfa-1-antitripsine	< 1,8	mg/dl	< 27,5	FE A) ELISA
Secretair Immunoglobuline A	311,0	µg/ml	510 - 2040	FE A) ELISA
Zonuline	64,89	ng/ml	< 55	FE A) ELISA
Histamine in feces	467,9	ng/ml	< 959	FE A) ELISA
Maldigestie				
Pancreas elastase in feces	243,24	µg/g	> 200	FE A) ELISA
Galzuren in feces	18,70	µmol/l	< 70	FE NA) PHOT

Treatment starten April 2024

- MyOwnBlend direct ingezet, zonder eerst af te doden

BB058	S. Boulardii	2
BB061	Bifidobacterium lactis HN019	3
BB056	L. rhamnosus GG	2
BB011	Butyrate generator	1
BB020	Bacillus clausii UBB C-07	1
BB027	L. rhamnosus SP1	1
BB054	Akkermansia mucinip hila, pasteurized	1
BB004	DJ repair	4

Aanvullend werden de volgende supplementen ingezet:

- Chrysil, curcumine, ADP(biotisch)
- Pro-Praebioma (Tisso)

Resultaten



- Ontlasting werd beter: steviger
- Stinkende winden verdwenen
- Algehele gesteldheid verbeterde

- Bij stoppen met suppletie: klachten kwamen terug

Vervolg

- Herstart MyOwnBlend
- Behandeling *Helicobacter Pylori* via huisarts:
 - Eerst antroposofisch: geen effect
 - Daarna trippeltherapie
- Klachten keerden hierdoor terug
- Nogmaals MyOwnBlend herhaald
- December 2024: mondklachten trokken volledig weg
- Moeheid en misselijkheid zijn beide verdwenen of aanzienlijk verbeterd en goede ontlasting

Overige observaties

- Altijd veel kloven in vingers en voeten: sterk verminderd

P.m.

- Ter controle nog een ontlastingsonderzoek

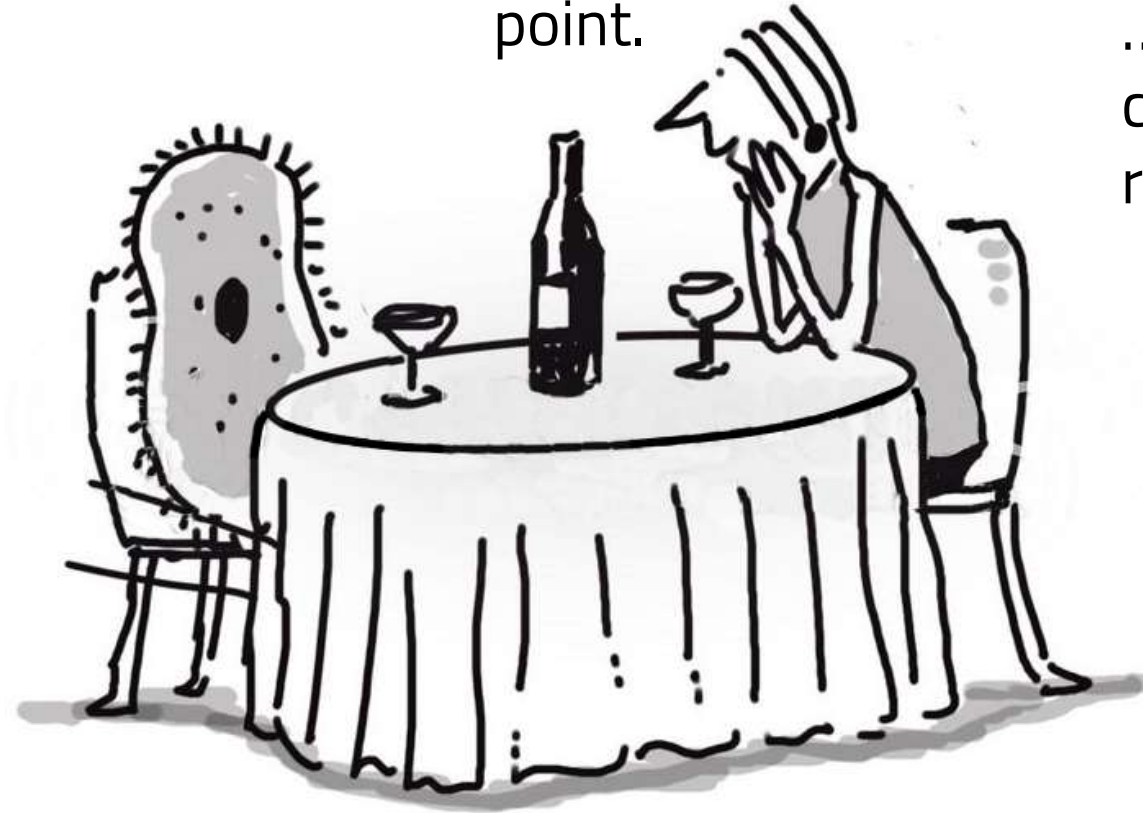
Take home messages

In an ecology,
everything happens
at the same time

...there is cross-feeding,
niche competition,
evolutionary adaptation,
exchange, etc.

...there are rarely
direct cause-and-
effect relationships:
complex/chaotic

Treatment is about
shifting the balance
point.



“You don’t strike me as being complicated”

... phased construction
contradicts biological
reality

... is the use of niche
selection useful in
case of low diversity

... pre- and
probiotics have a
multitude of effects

... all diseases /
treatments **start in
the gut**

A petri dish containing various microbial colonies, including a large white one at the bottom and several yellow and orange ones arranged in a pattern.

Thank you for your attention!