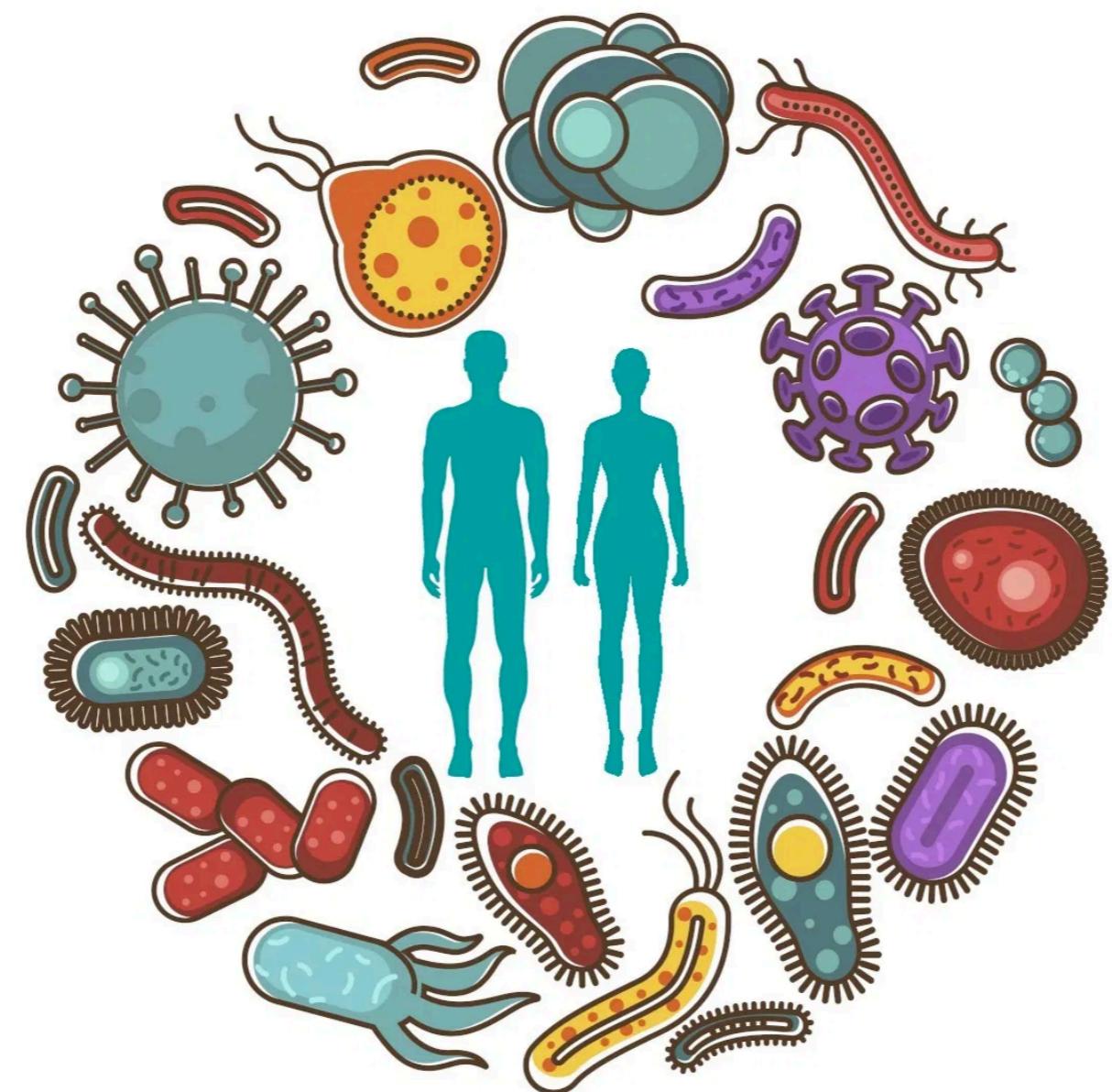


Exploring the Human Microbiome

Ece Kartal

Postdoctoral Fellow

 @psecekartal



Saez-Rodriguez Group

www.saezlab.org

 @saezlab





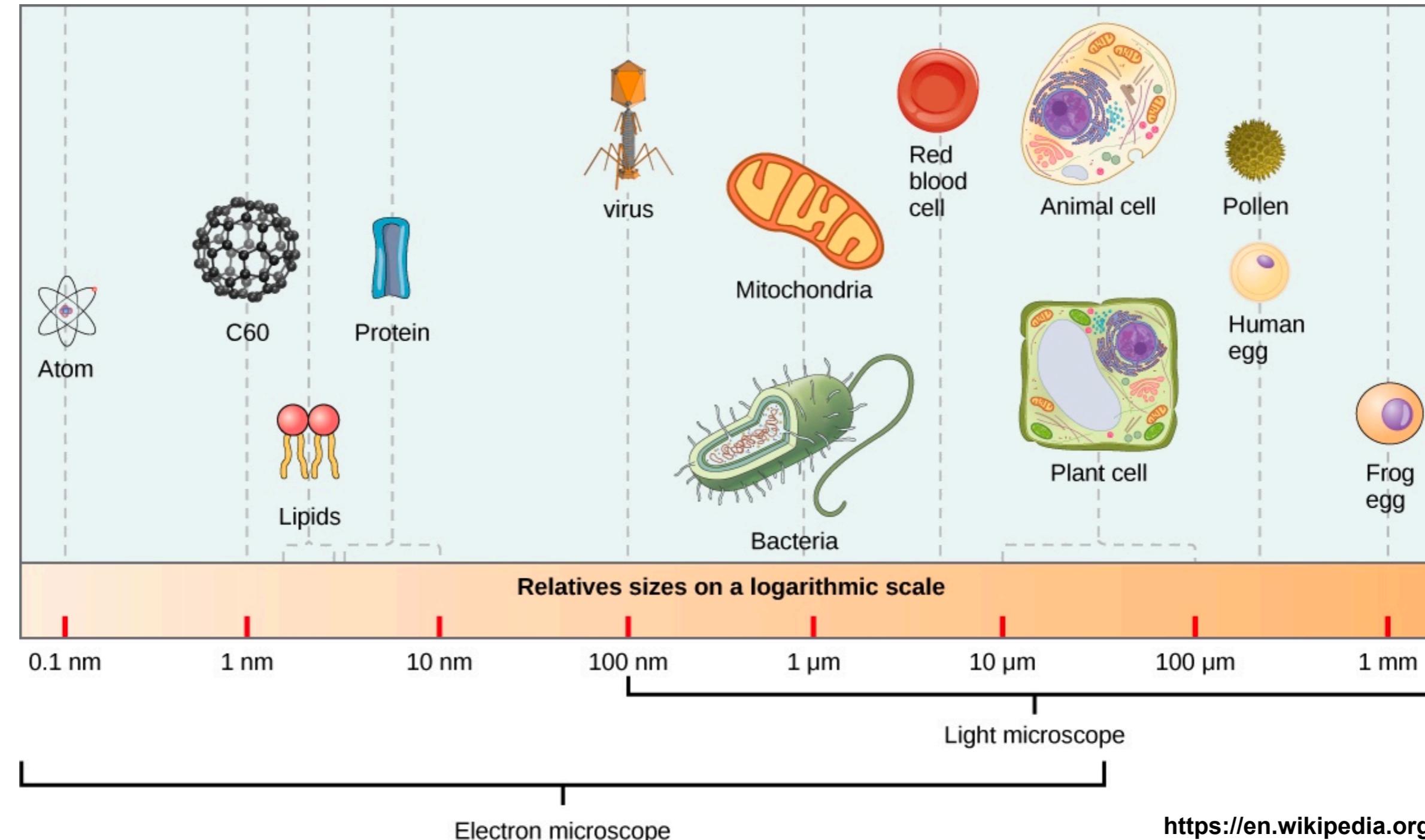
What will we talk about:

- The characteristics of microbiome
- Microbiome types; soil, marine and animal
- The role of human microbiome (in early age)
- Microbiome based applications: FMT-pro/prebiotics/phage therapy
- How do we study microbiome
- Can microbiome effect our health
- A case study



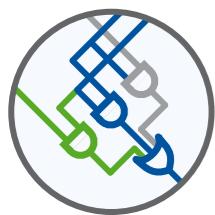
The composition of human microbiota

A complex ecosystem of many microscopic life forms, including virus, bacteria, archaea, fungi & protista



Electron microscope

https://en.wikipedia.org/wiki/Marine_microorganisms



A

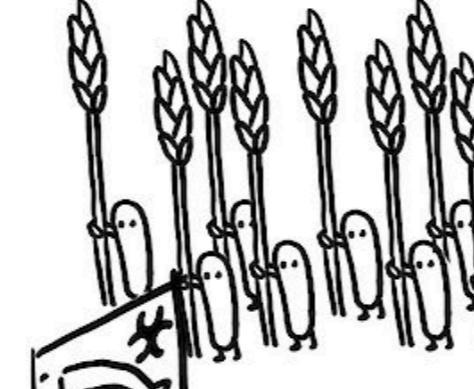
6 MICROORGANISMS
PURIFY WATER
Clean Water & Sanitation

2 IMPROVED LAND
FERTILITY
Zero Hunger

3 REDUCE DISEASE,
INCREASE HEALTH
Good Health & Wellbeing



YIELD

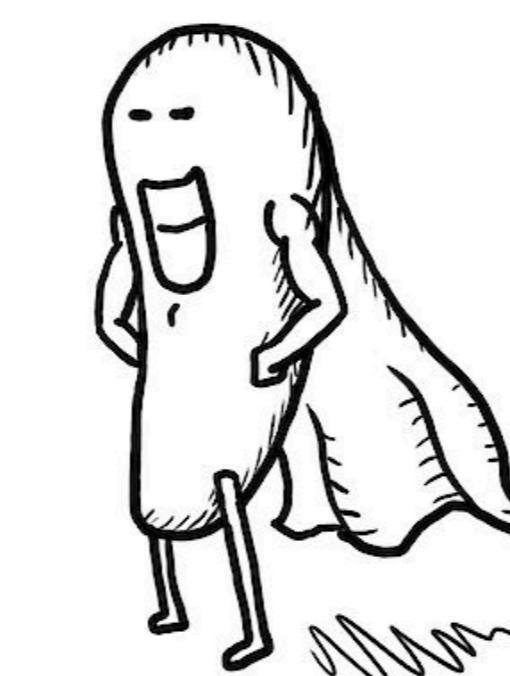
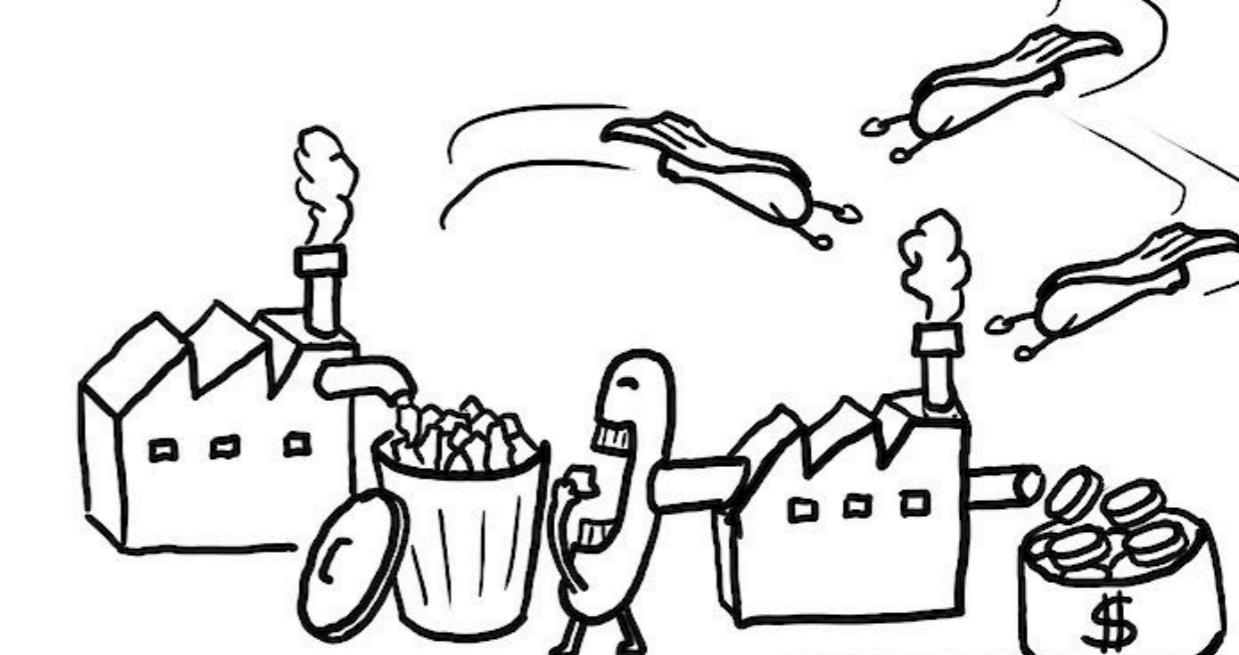
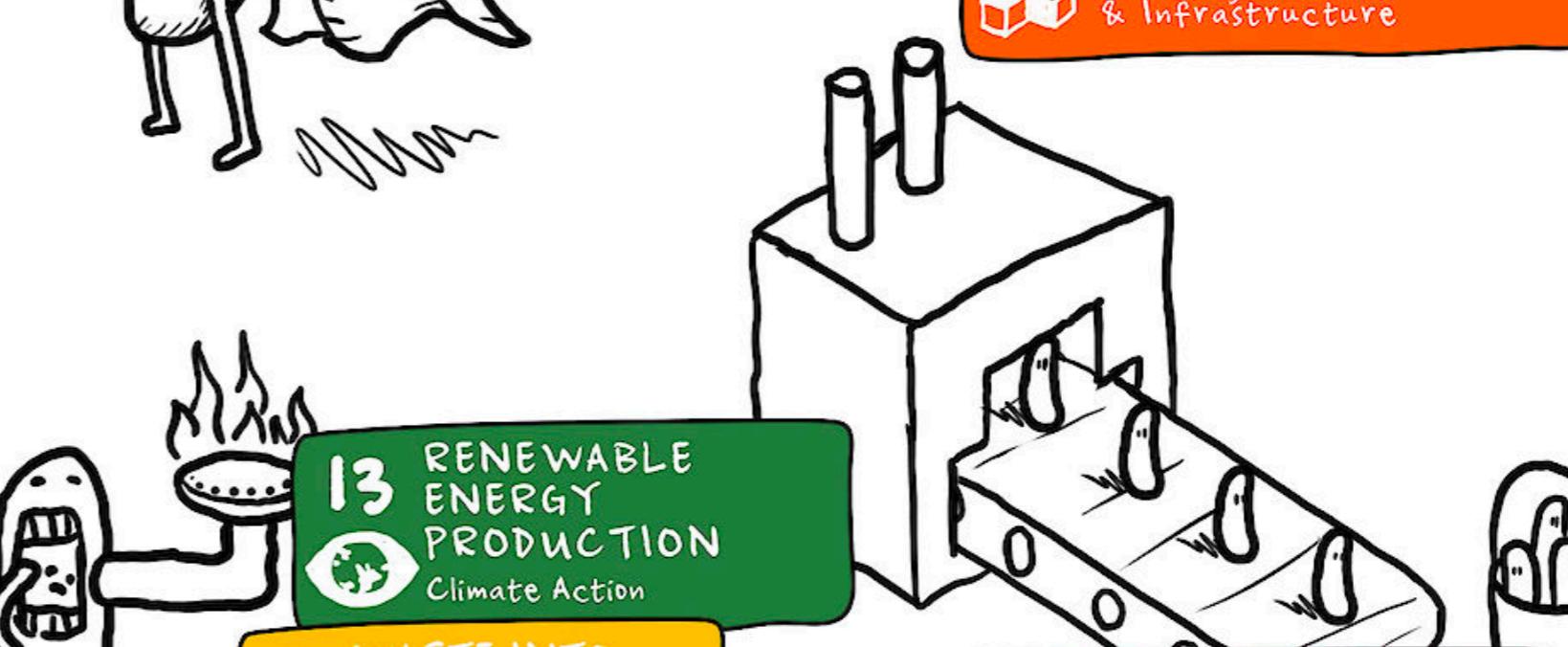


12 EFFICIENT/CLEANER
AGRICULTURE
Responsible Consumption
and Production

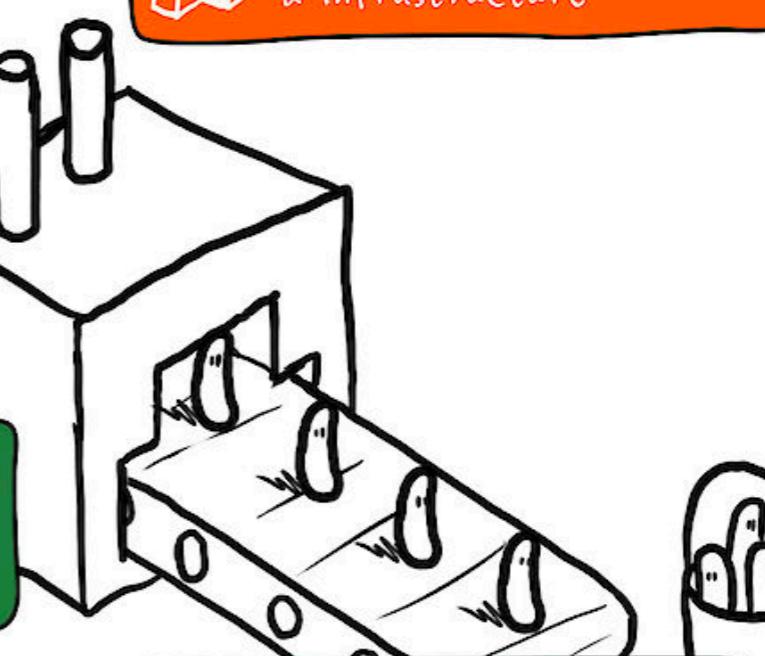
7 WASTE INTO
ENERGY
Affordable &
Clean Energy

13 RENEWABLE
ENERGY
PRODUCTION
Climate Action

8 NEW INDUSTRIES
Decent work & economic growth



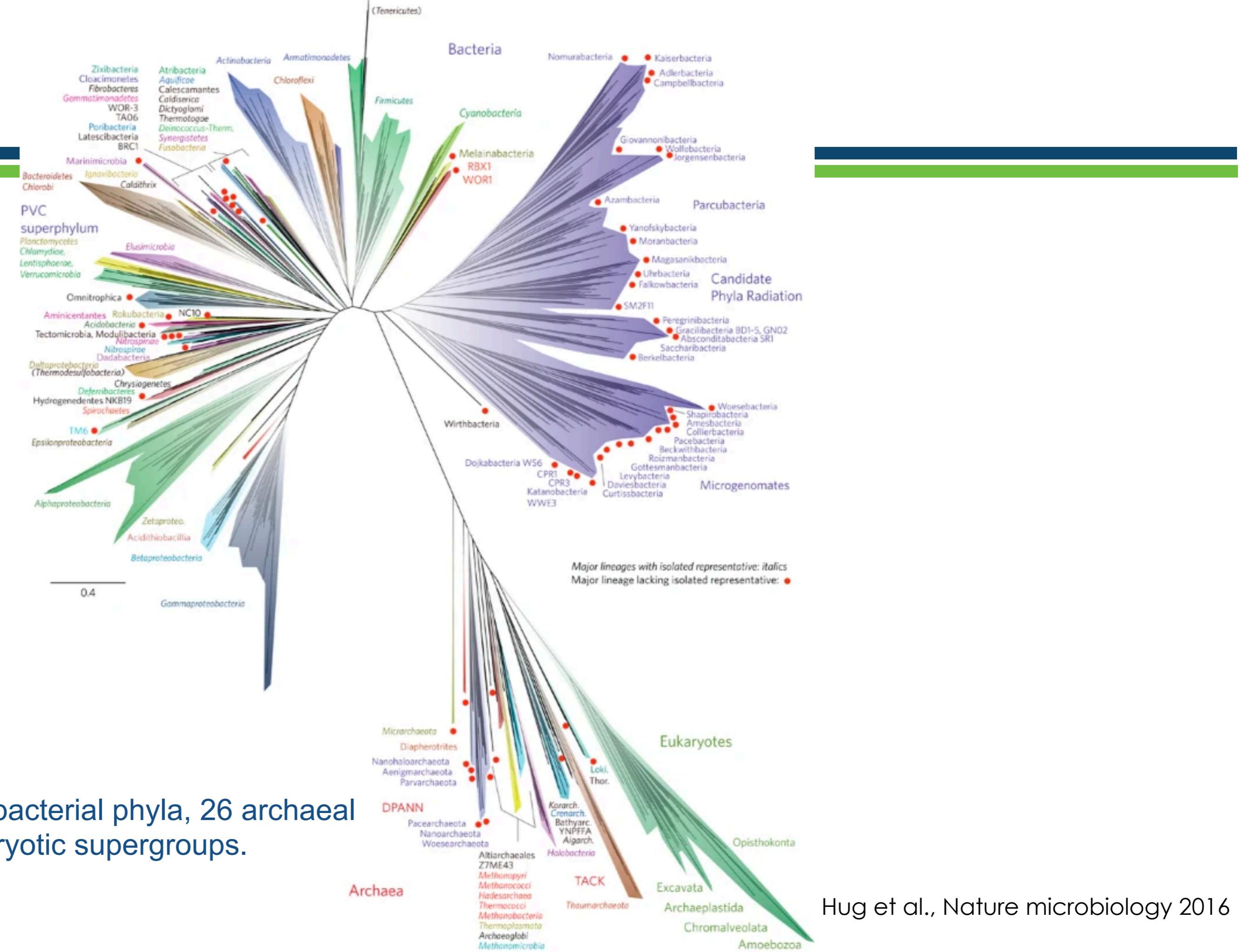
9 WASTE INTO
FEEDSTOCK
Industry, Innovation
& Infrastructure



11 HEALTHIER CITIES
Sustainable Cities
& Communities



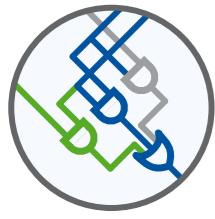
Tree of life





What we know about microbiome





Microbiome is an unforgettable



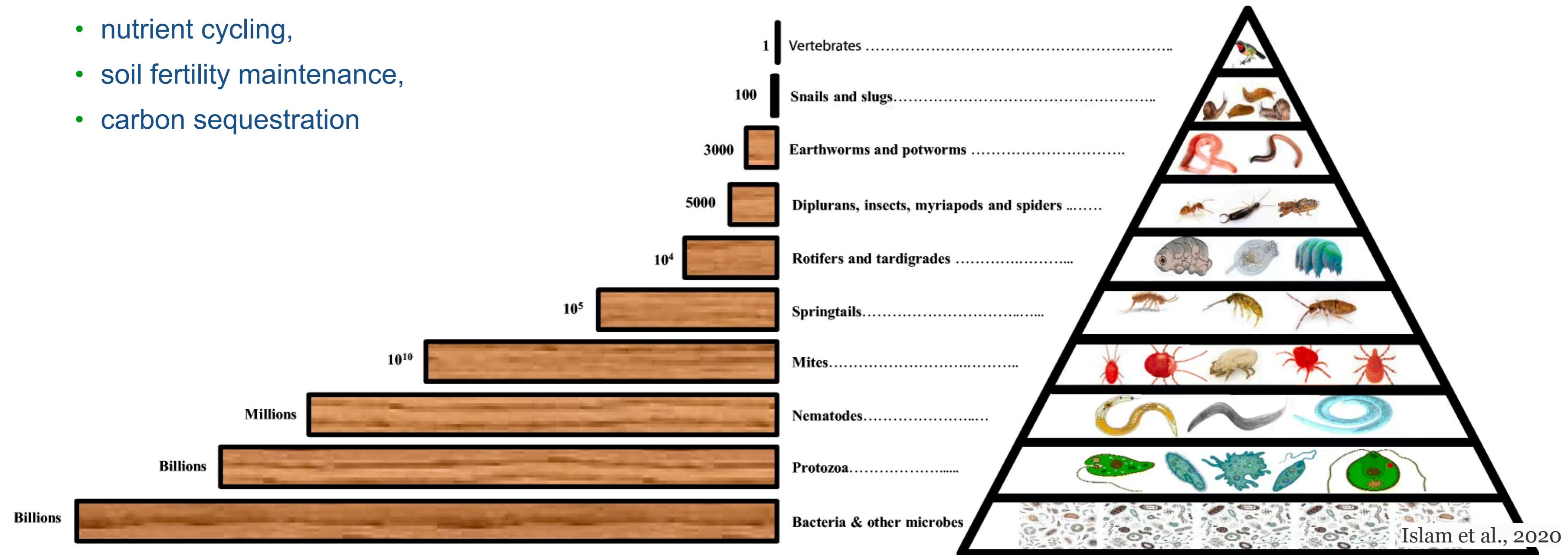


Soil microbiome is one of the most important & complex ecosystem

The soil microbiome comprises one of the most important and complex components of all terrestrial ecosystems

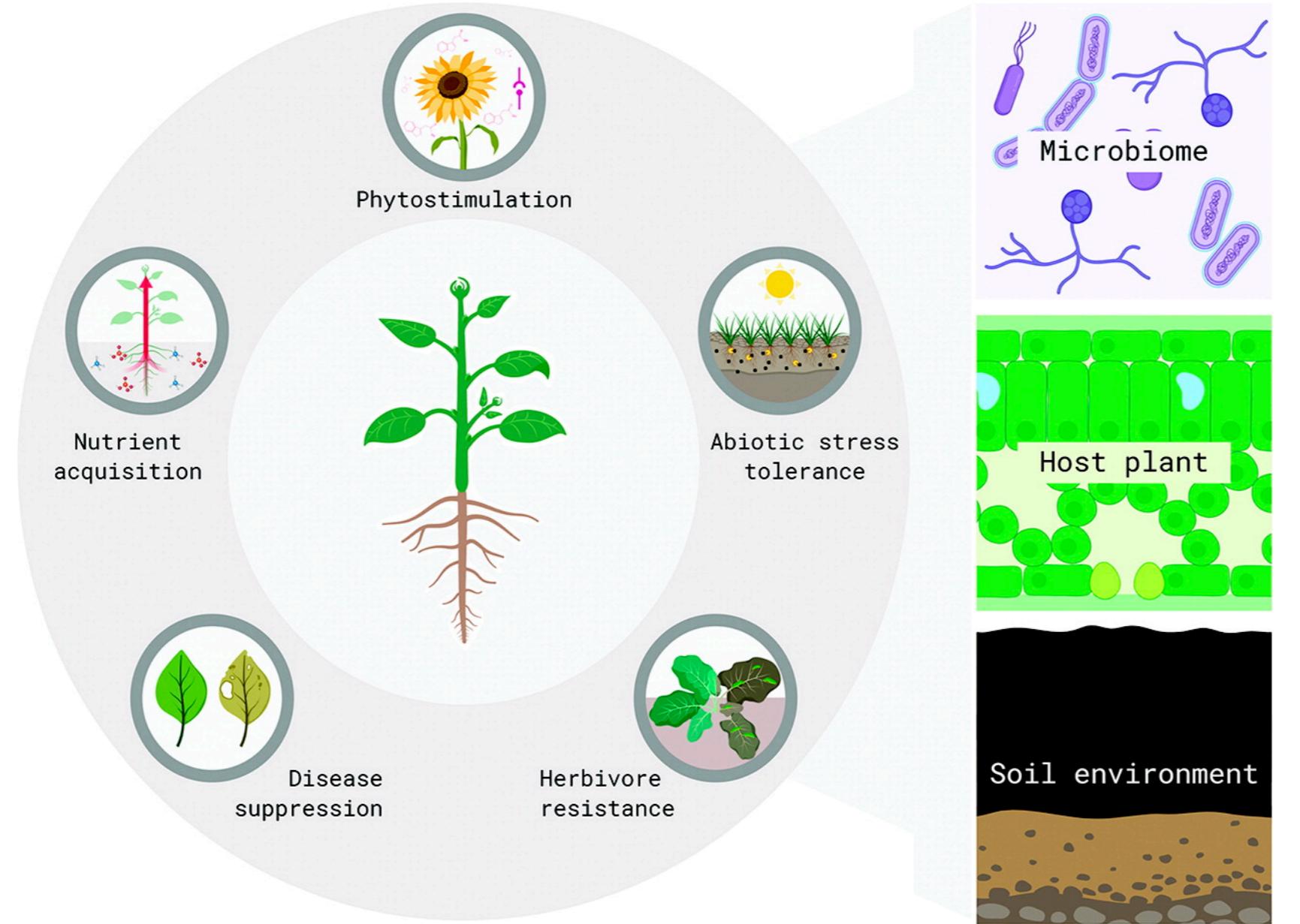
Soil microbiome provides critical contributions to

- nutrient cycling,
- soil fertility maintenance,
- carbon sequestration





The role of soil microbiome

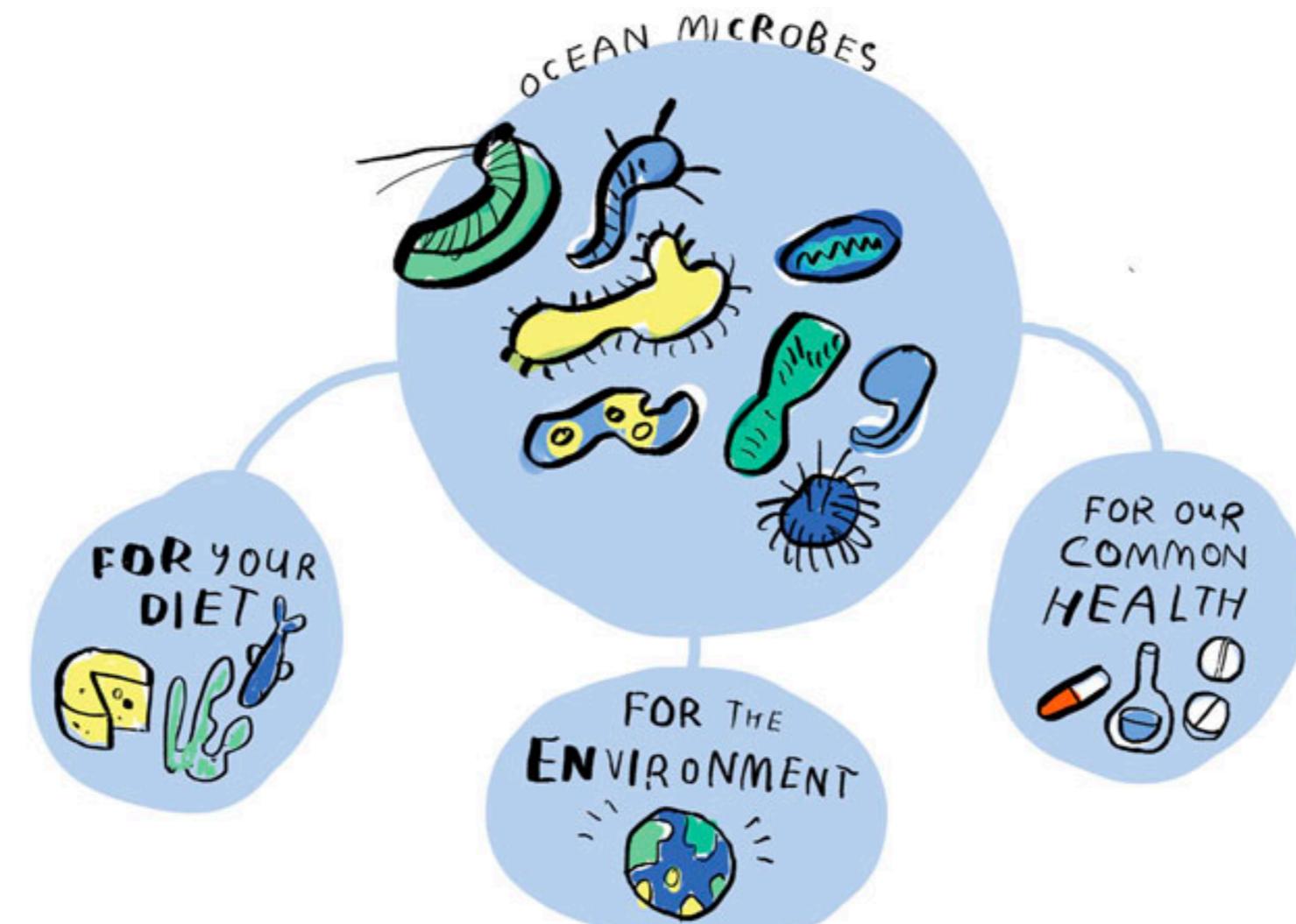




Marine microbiome

Microbes are responsible for virtually

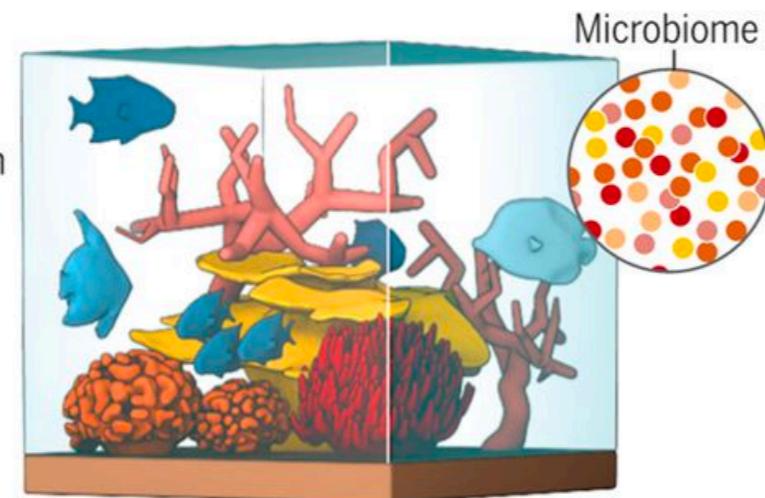
- all the **photosynthesis** that occurs in the ocean,
- the cycling of **carbon, nitrogen, phosphorus** and other **nutrients** and trace elements.



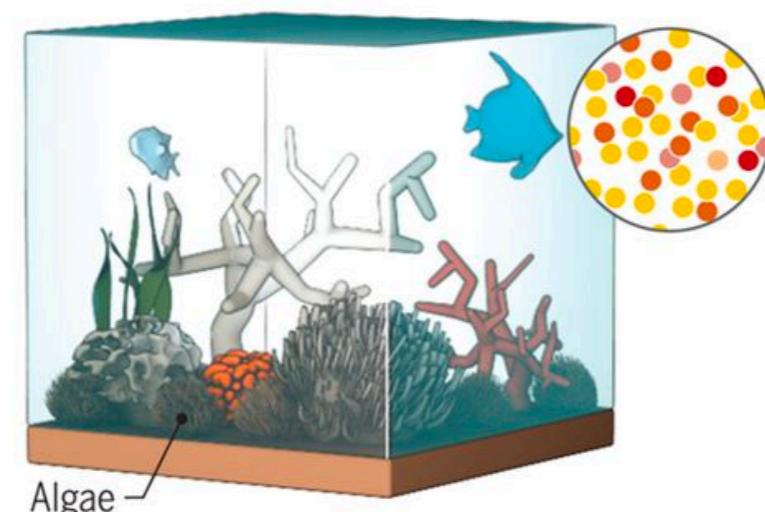


Why do we care for marine microbiome

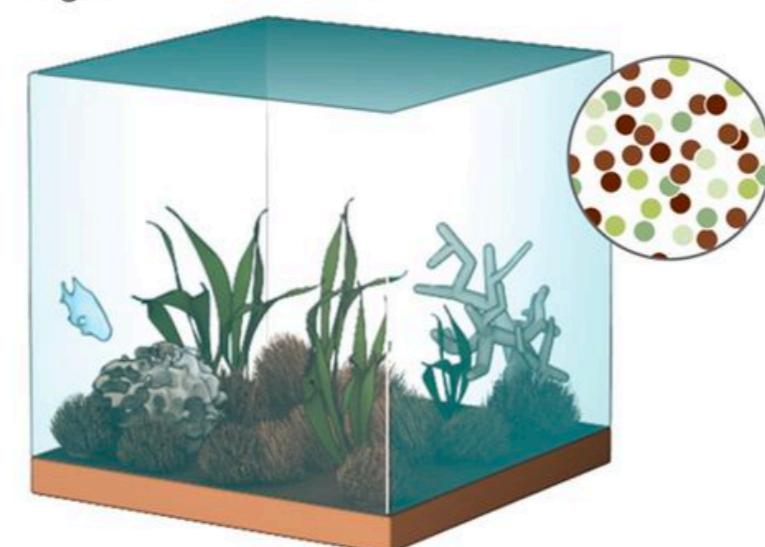
Historic coral state
The health of a highly diverse reef ecosystem is supported by a complex microbiome.



Degraded state
After disturbance, diversity of corals, fish, and microbiome is reduced, lowering resilience.



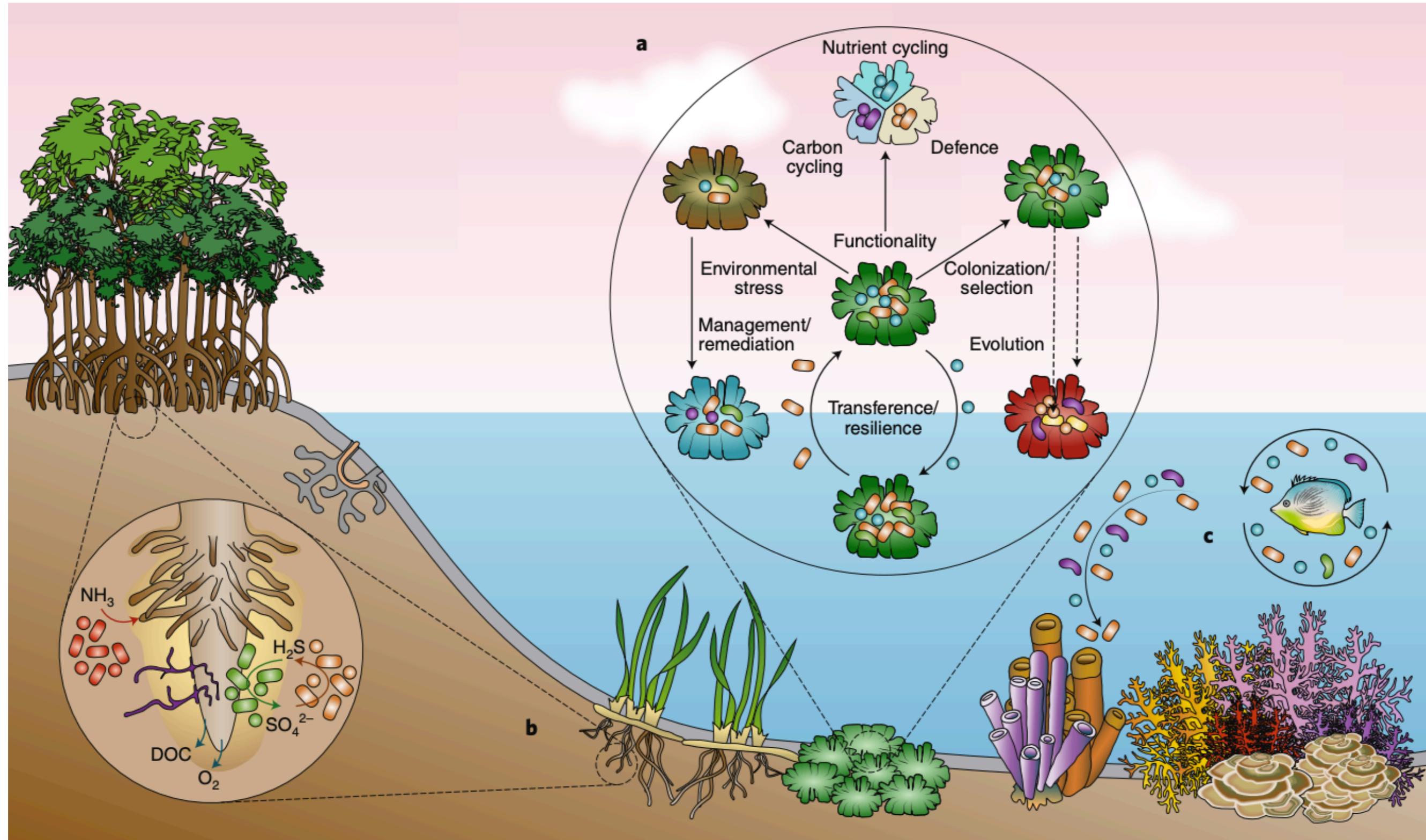
Alternate algal state
An algal-dominated ecosystem without living corals has a different microbiome.



- Microorganisms make up about 70% of the marine biomass
- Marine microorganisms recycle the major chemical elements

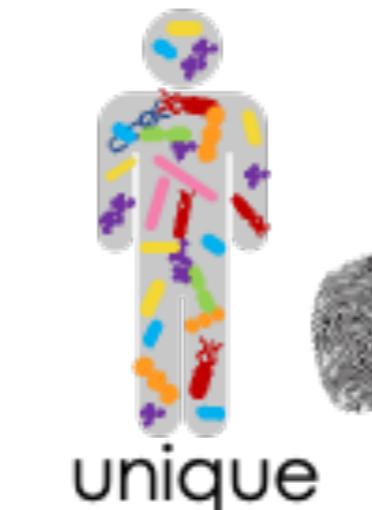
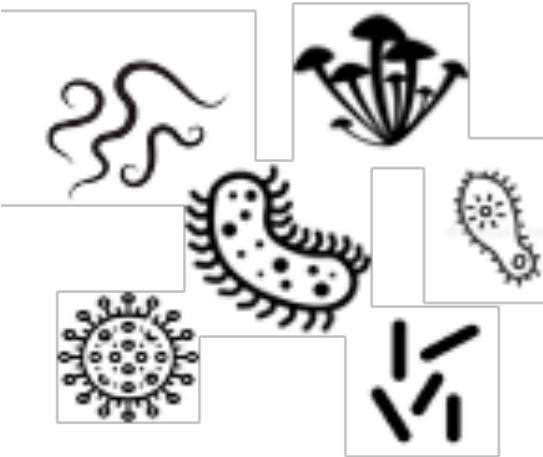
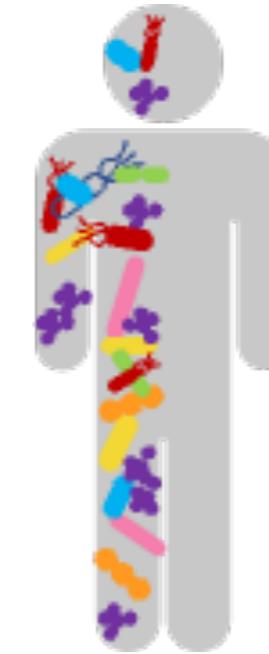


Interactions btw different biomes





What is human microbiome?

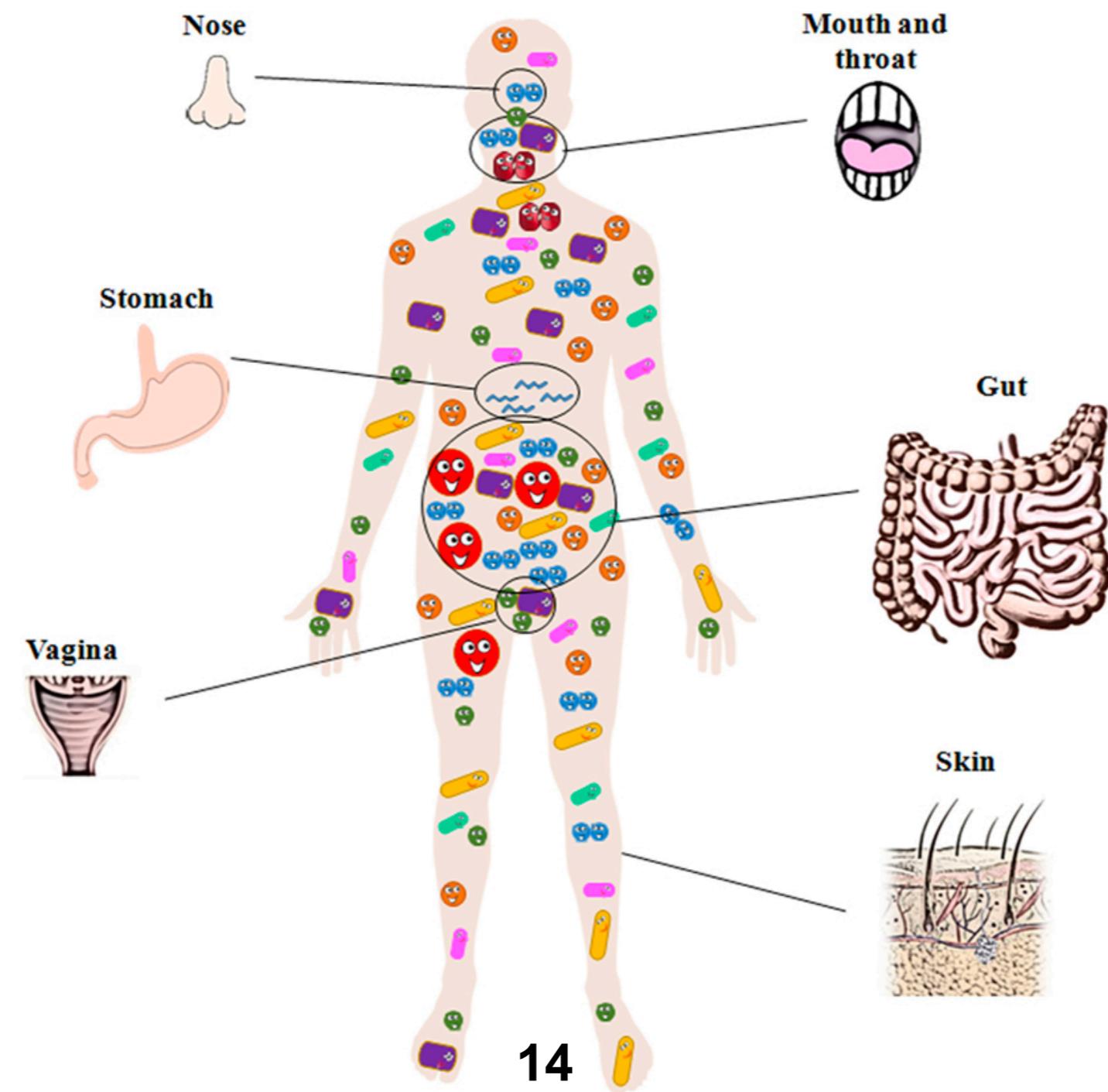


non-redundant genes



Human microbiome

Some microorganisms that colonize humans are commensal, meaning they co-exist without harming humans





The microbiome influencers

Relationship status

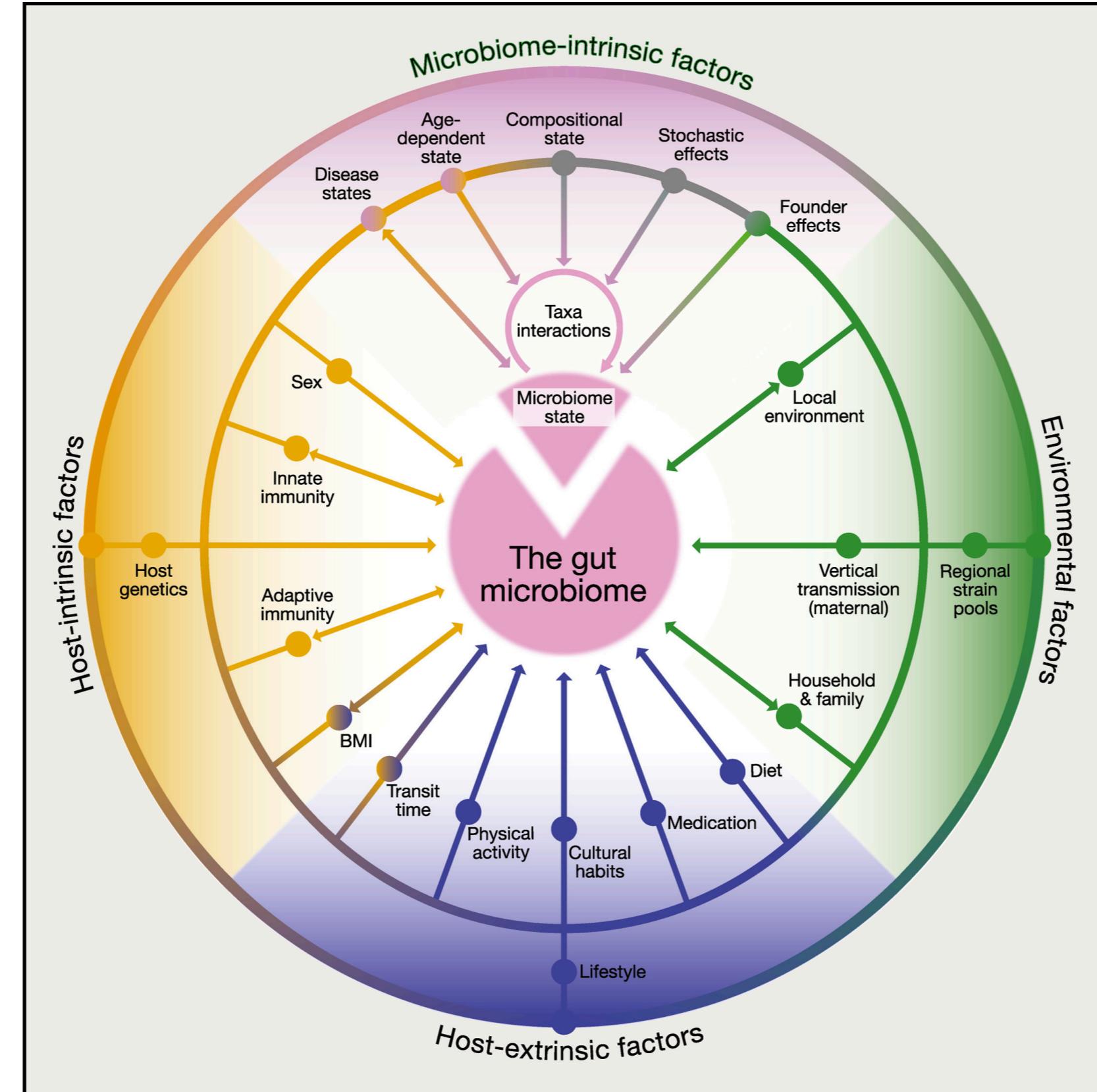
In a relationship

Engaged

Married

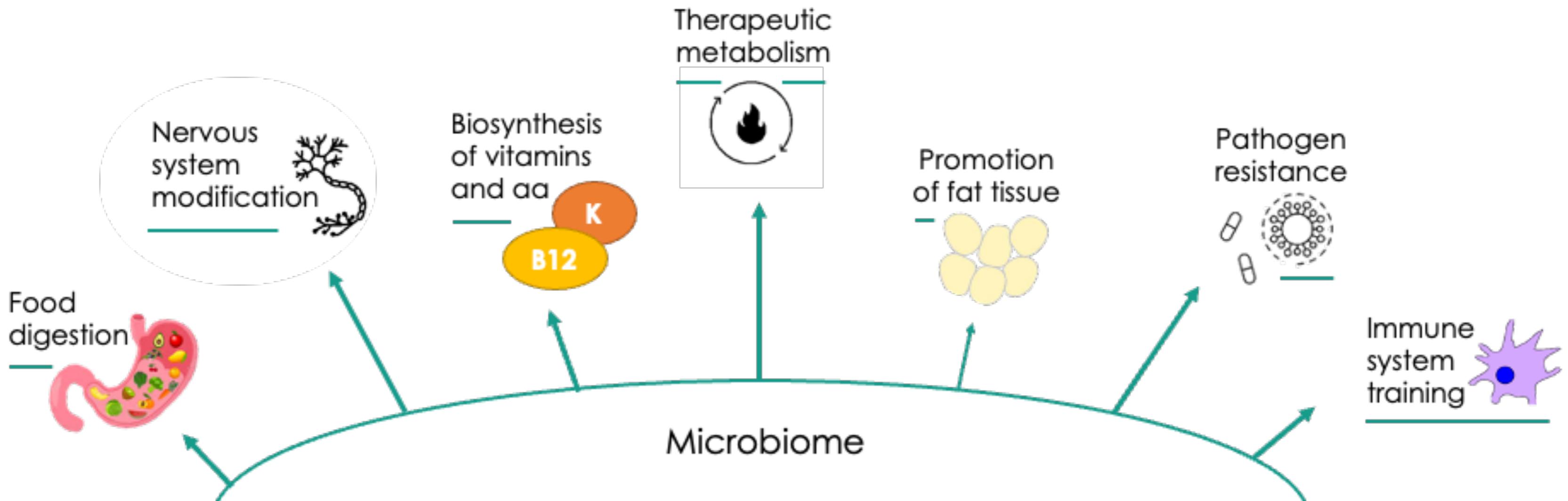
It is complicated

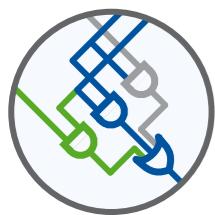
Divorced



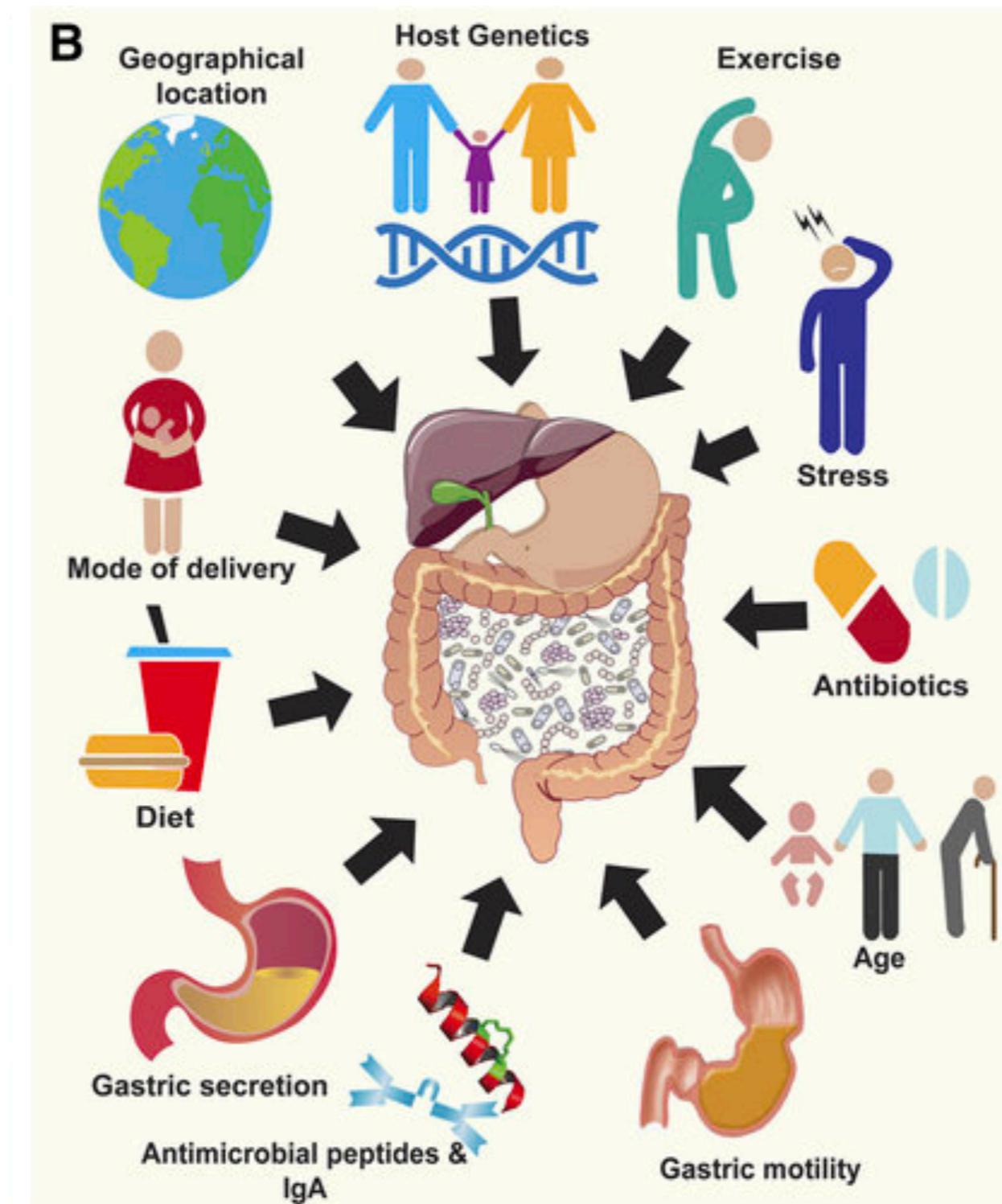


The functions of the human microbiota





Which forces shape the composition of the human microbiome

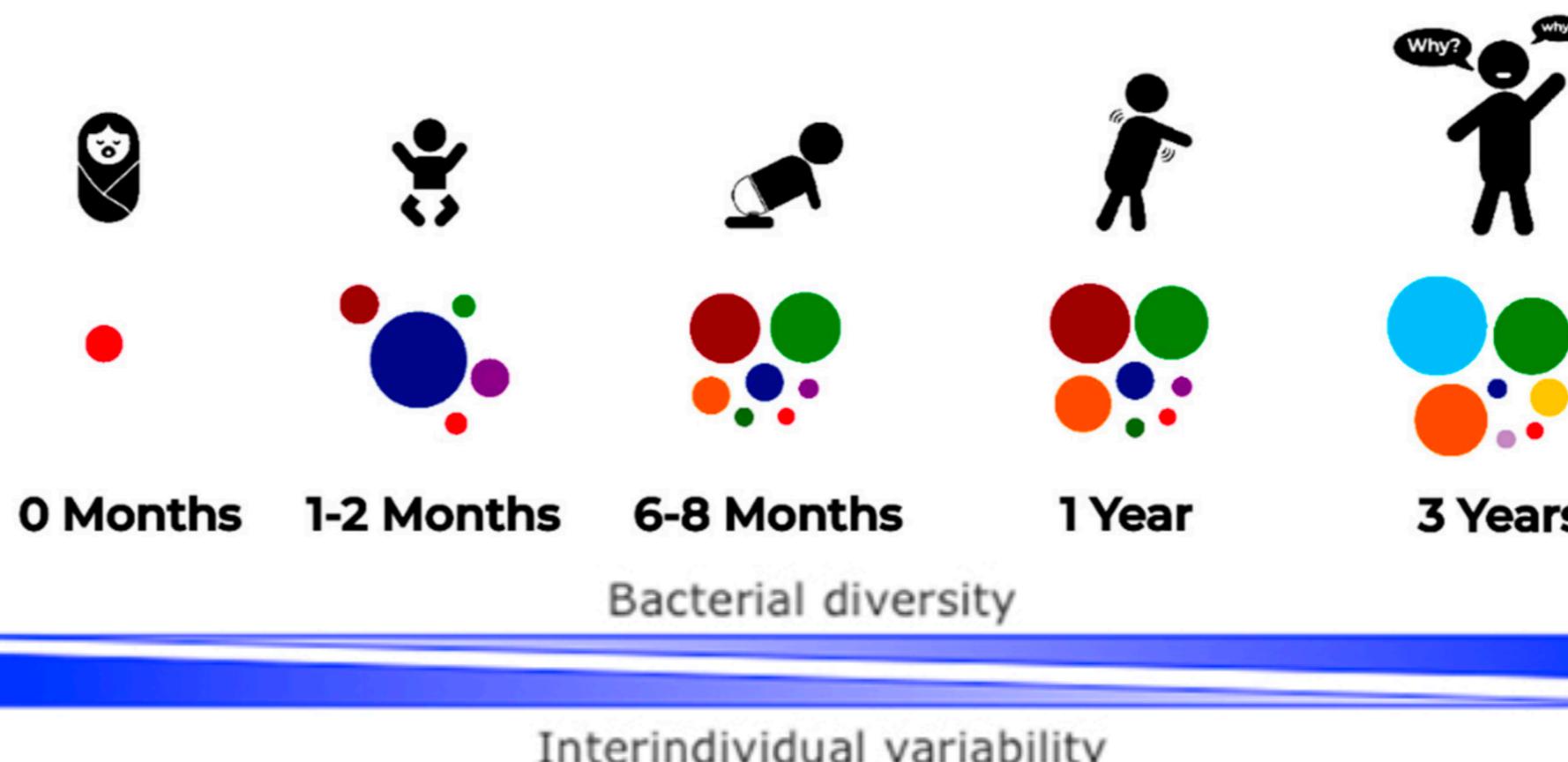
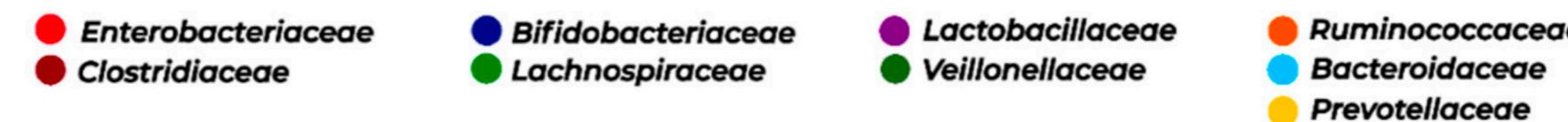




Where do we get our microbiome starter kit

- The mouth, skin, and intestines of newborns delivered vaginally are rich in *Lactobacillus* which is the core of the maternal vaginal microbiota.
- The gut microbiota are responsible for the activation and development of the immune system, the development of the central nervous system (CNS), and the digestion and metabolism of food
- In 2–3 years after birth, the infant gut microbiota gradually develops towards the adult gut microbiota

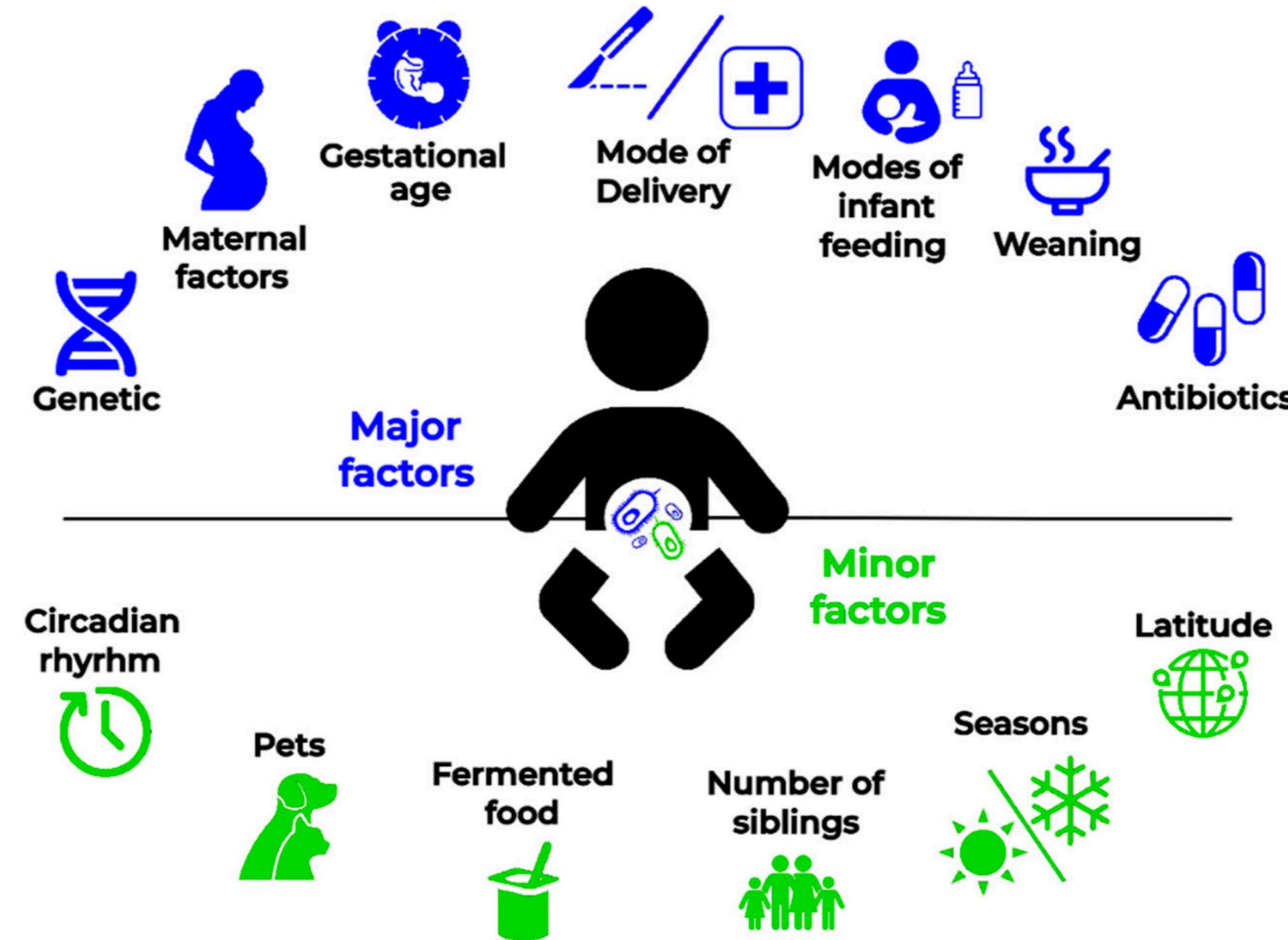
a) Gut microbiota composition during the first years of life





Which factors shape infant microbiome

b) Prenatal, perinatal and postnatal factors affecting microbiome composition

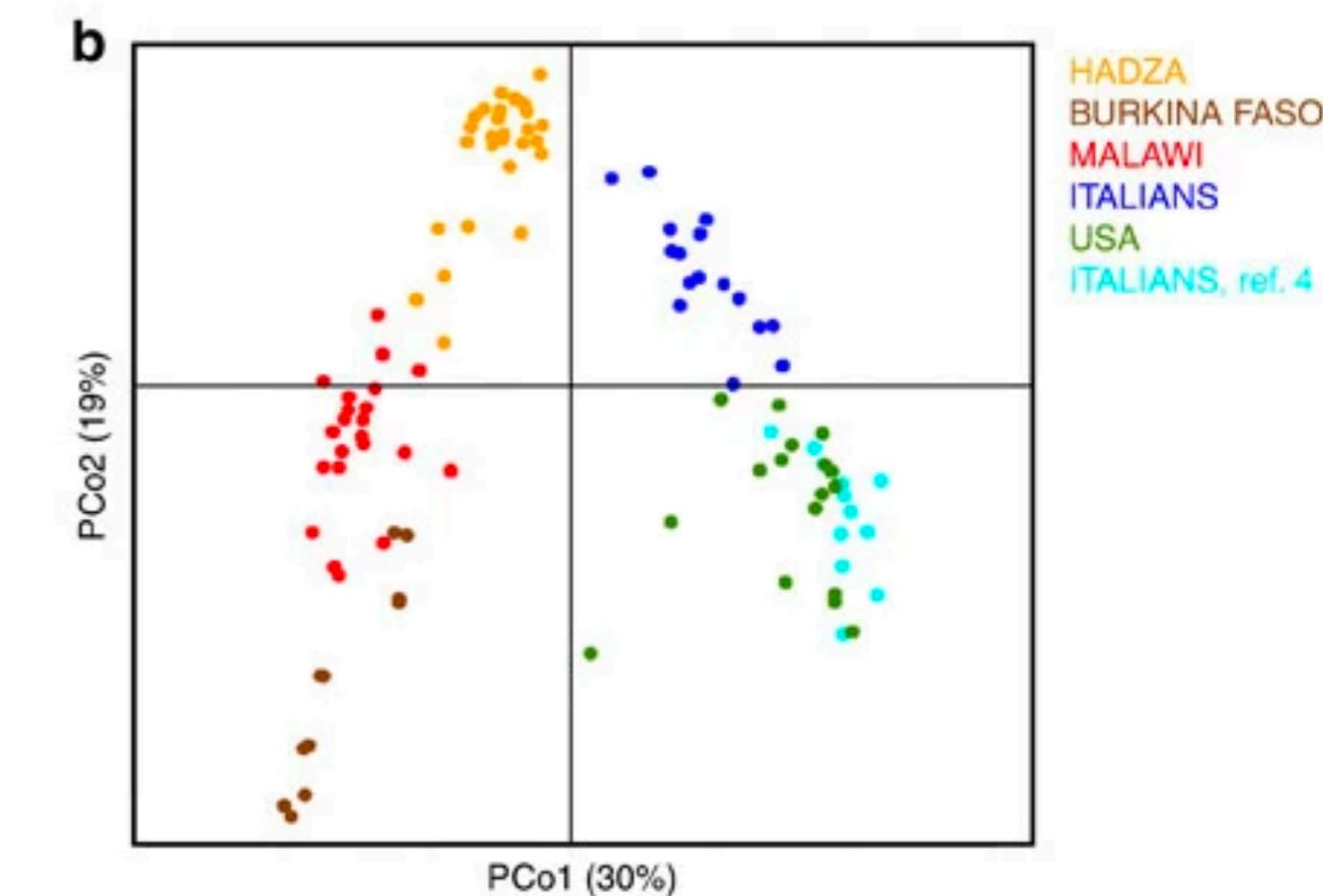
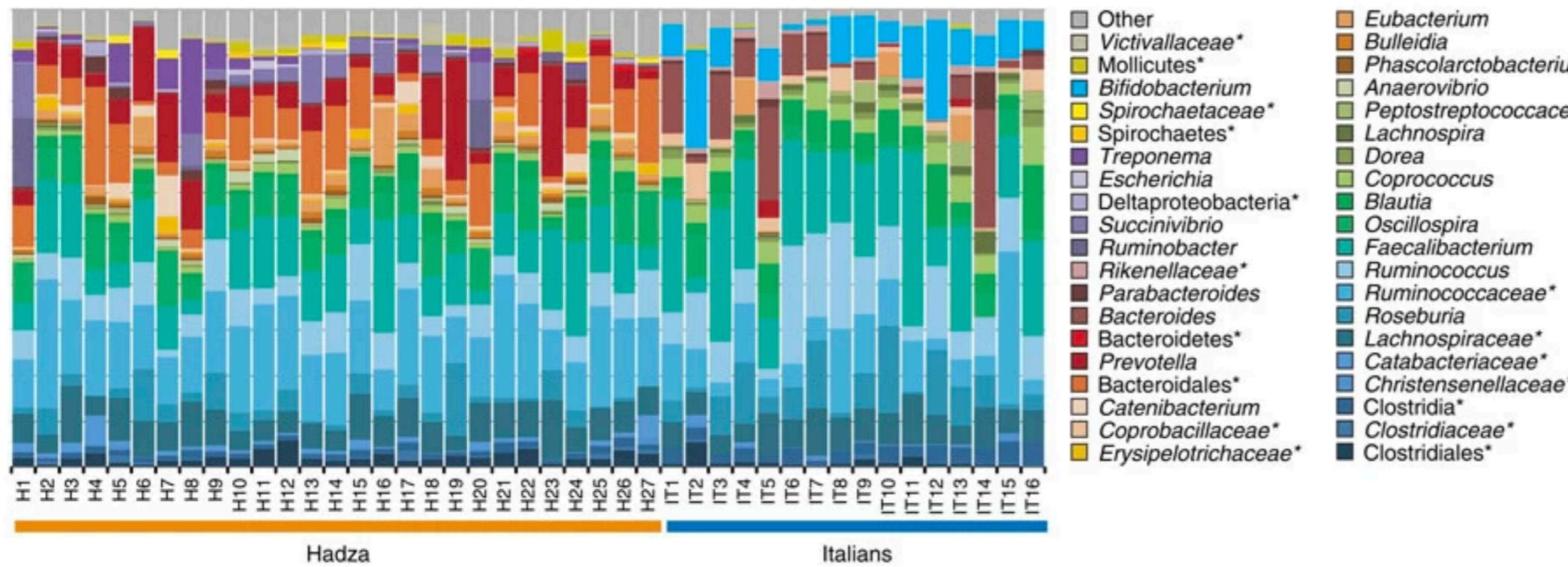




What is healthy microbiome?

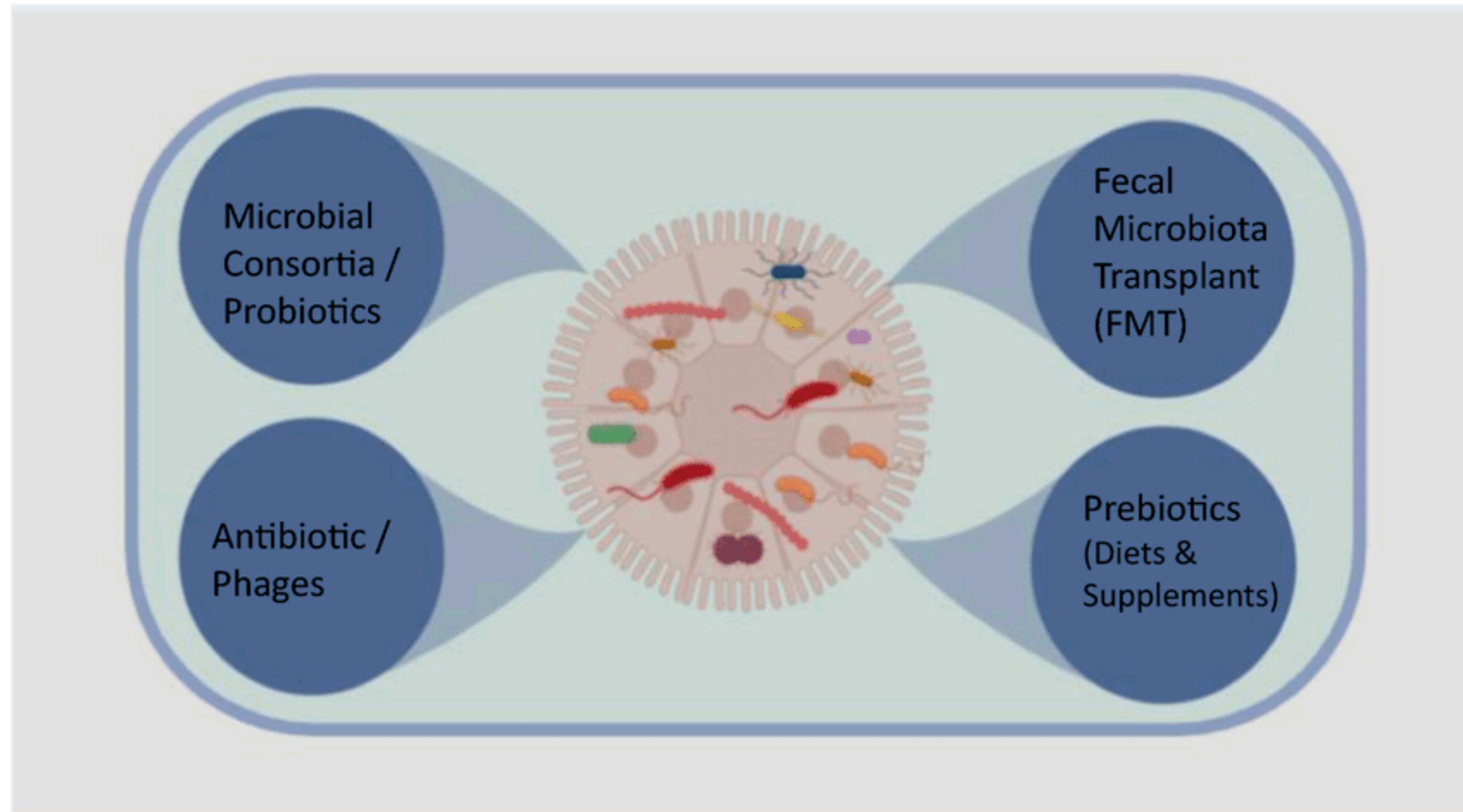
The Hadza, a population of hunter-gatherers living in Tanzania,

- eat 100–150 grams of dietary fibre per day (ten times as much as a typical person in the USA).
- eat only seasonal food depending on wet/dry seasons



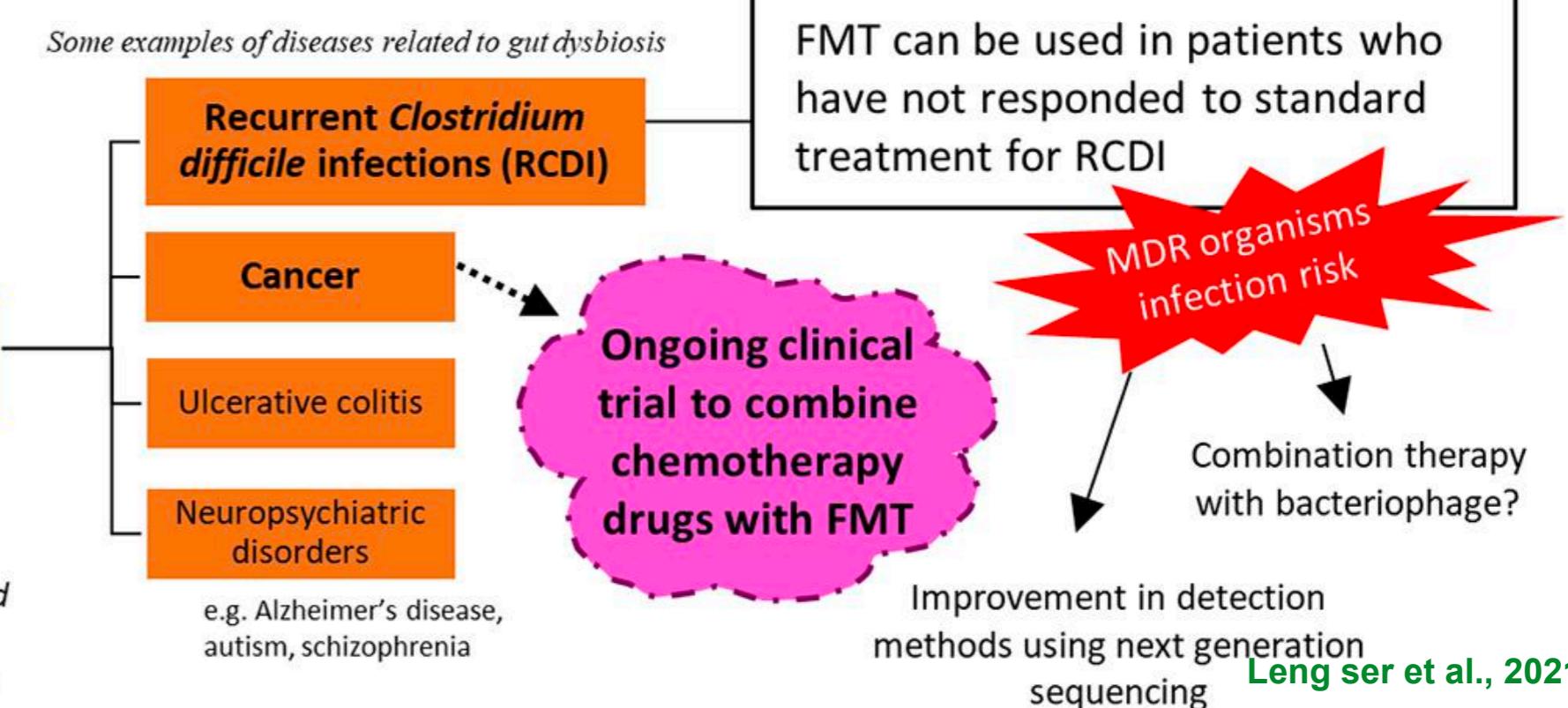
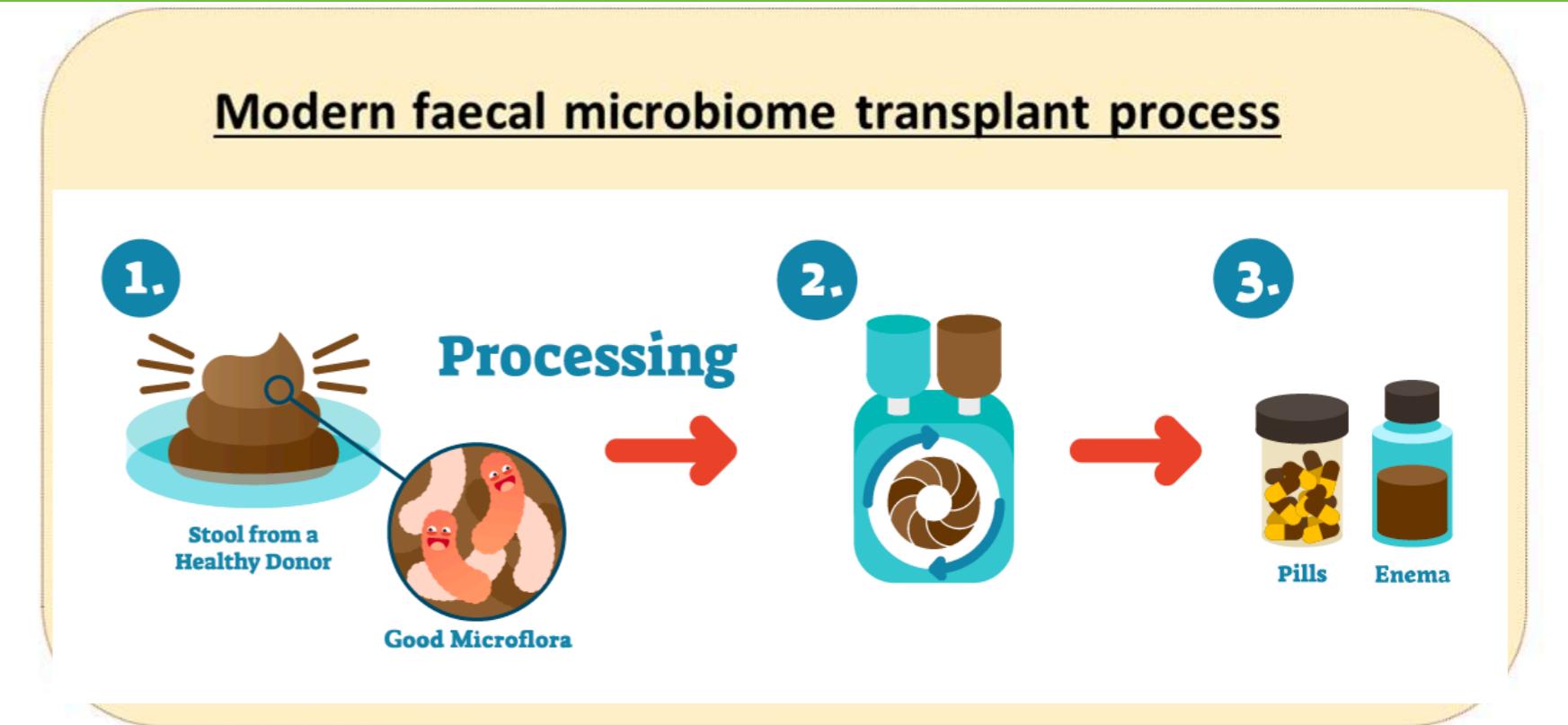
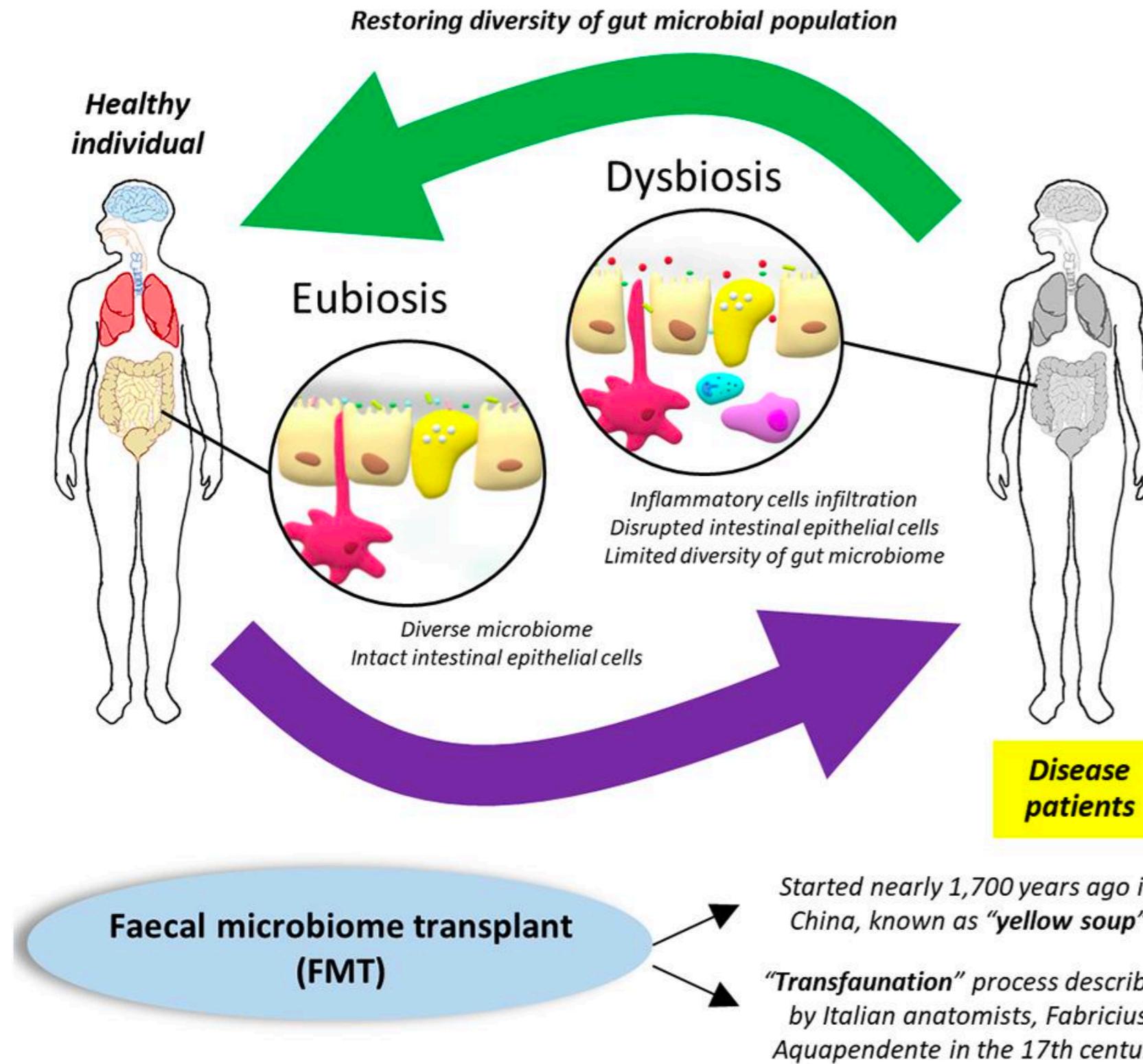


Applications based in microbiota





Fecal Microbiome Transplantation (FMT)

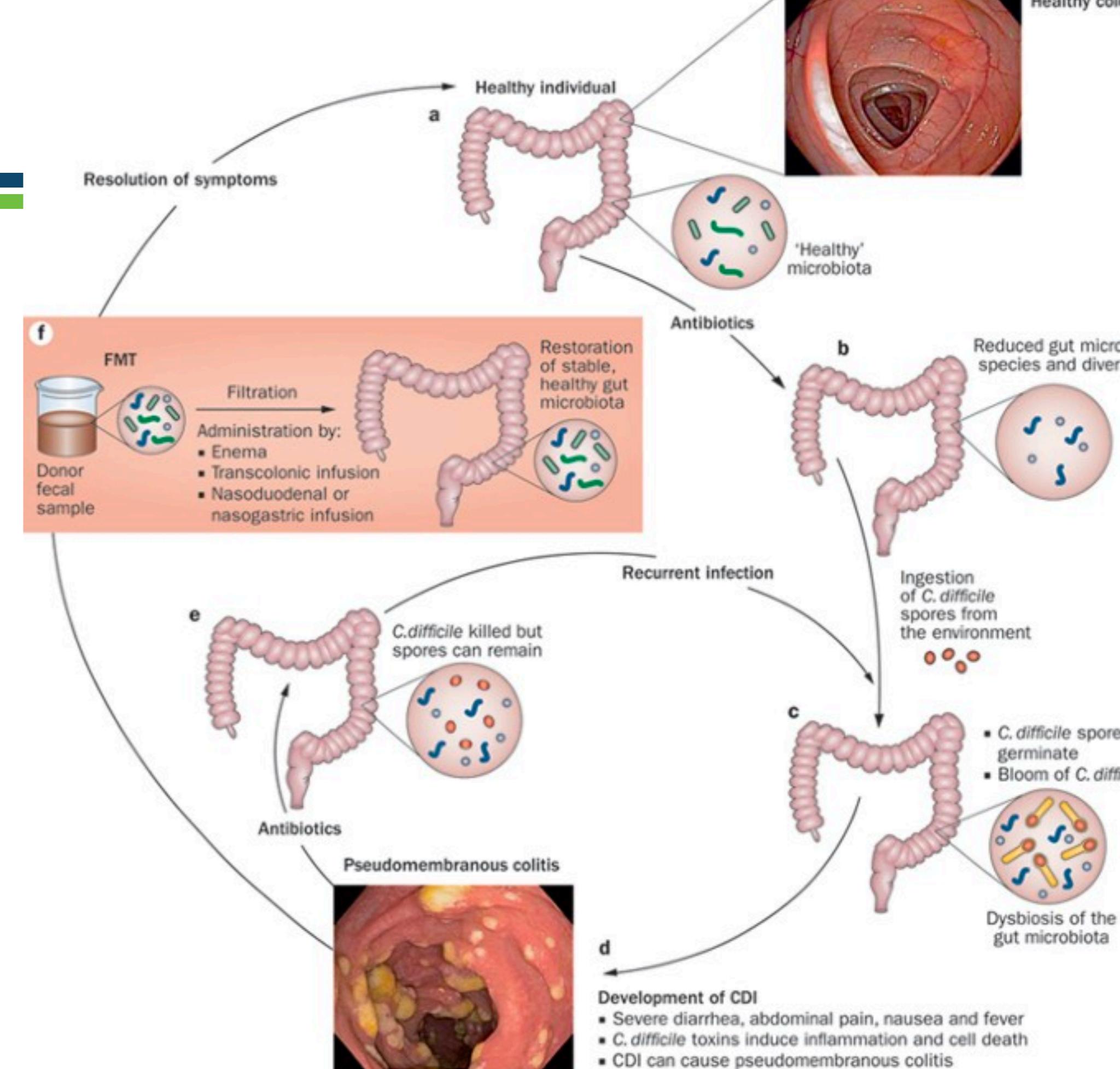


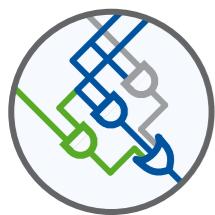


Poop for the Cure

C. difficile infection

- Fecal microbiota transplantation (FMT) is arguably the most effective method in treating recalcitrant *Clostridium difficile* infection (CDI), even more effective than vancomycin
- As multiple major diseases might be linked to dysfunction of gut microbiota, FMT could have potential applications beyond CDI





Cross-species FMT??

- **What would you do?**

- Time: World War II
- German troops were sick
- Solution: German soldiers

Colorectal Cancer
Bacteroides fragilis-toxin
Fusobacterium nucleatum ↑
(32)
(31)

IBD
Dorea spp. ↑
(29)

Multiple Sclerosis
Bacteroides spp.
Prevotella spp.
Parabacteroides spp. ↑
(30)



Parkinson's Disease
Lachnospiraceae
Ruminococcaceae ↓
(28)

FMT

Rheumatoid Arthritis
Prevotella copri ↑
(33)

- Problems:

- Contaminated pc
- Infections after F

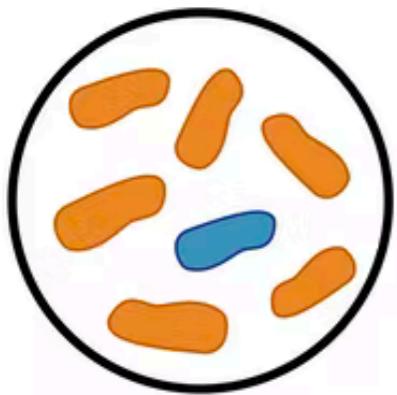
Atherosclerosis
Streptococcus spp.
Klebsiella spp.
Proteus vulgaris
Collinsella aerofaciens
(27) ↑

Coronary artery disease
Aggregatibacter actinomycetemcomitans ↑
(26)

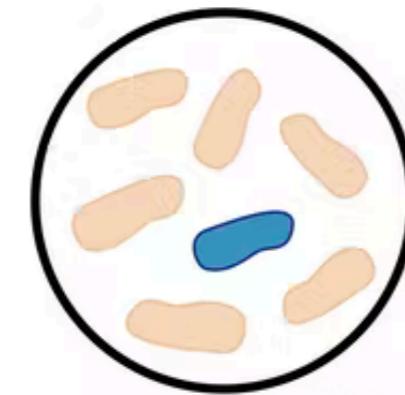


Superbugs: no antibiotics can fight against them

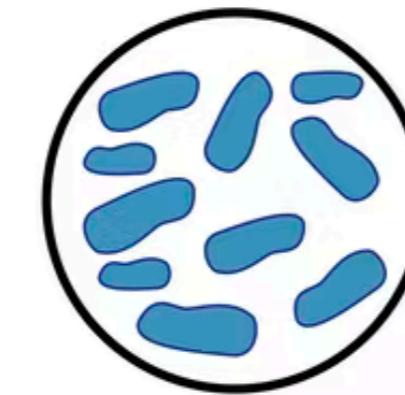
- > 2.8 million cases of drug-resistant bacterial infections only in USA every year



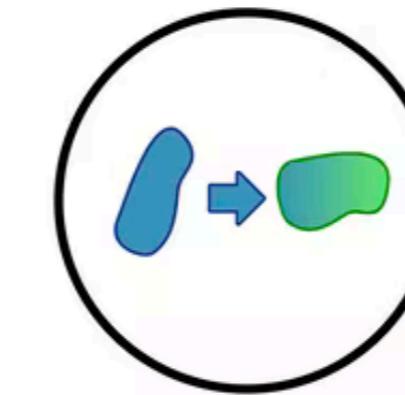
Lots of germs
and some are
drug resistant



Antibiotics kill the bacteria
causing the illness as well as
the good bacteria protecting
the body from infection



The drug resistant
bacteria is now able
to grow and take over



Some bacteria give
their drug resistance to
other bacteria



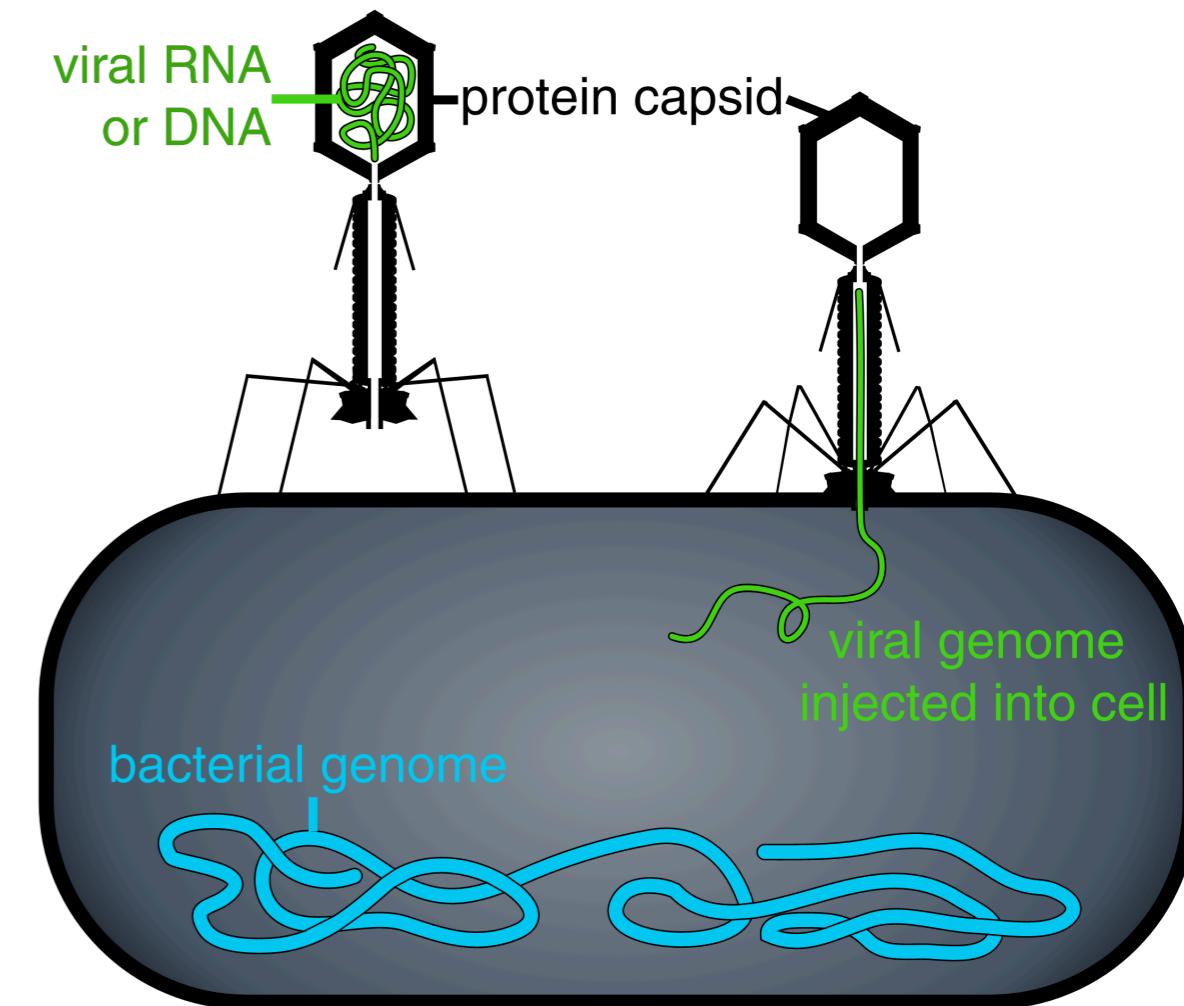
- Normal bacterium



- Resistant bacterium



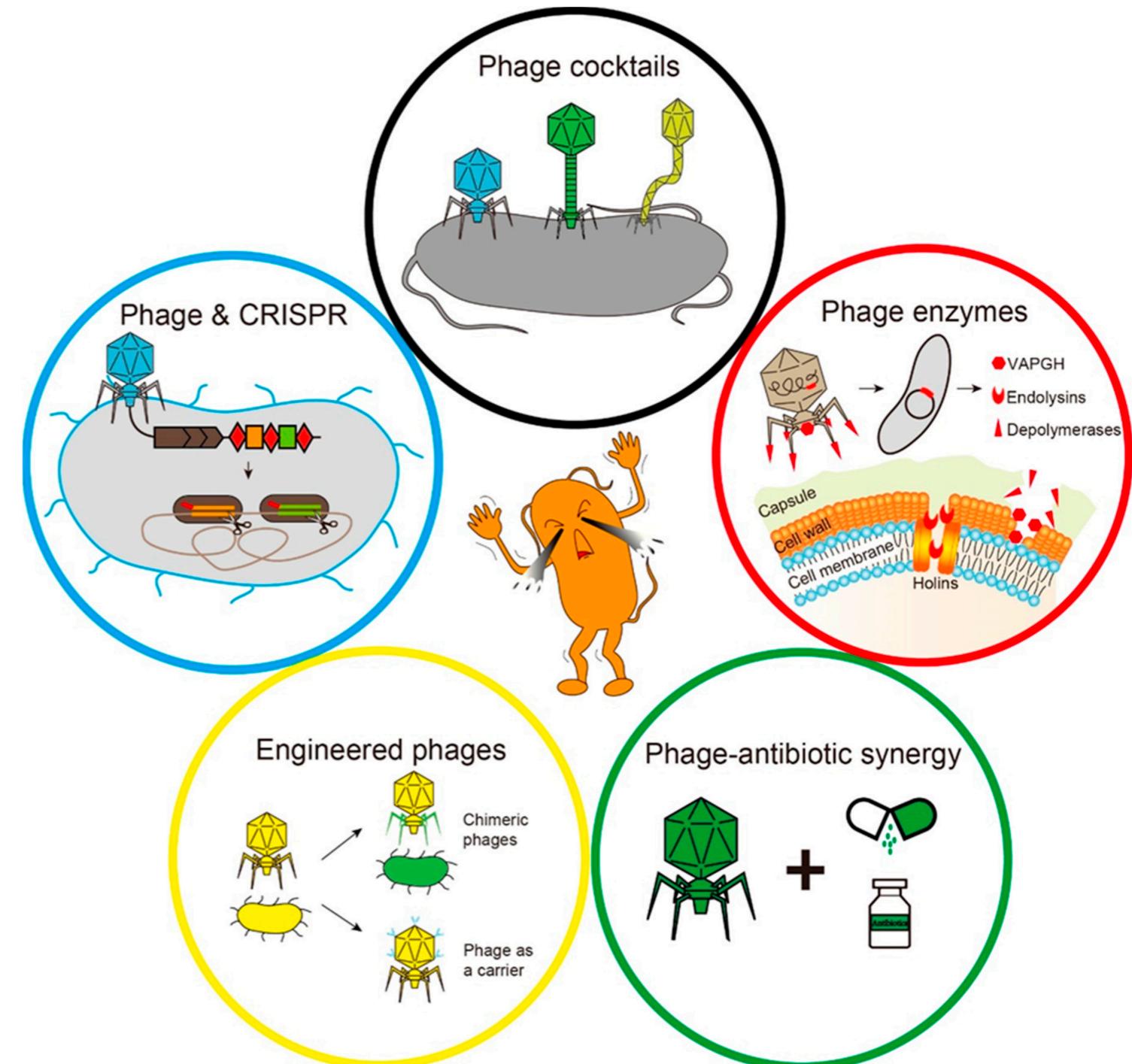
- Dead bacterium





Phage therapy

- Phages can effectively target Gram-positive and Gram-negative bacteria
- Phages only specifically target their corresponding host,
- The mutation rate of phage is faster than that of host bacteria
- No serious side effect
- Phage therapy is faster and more economical than antibiotic therapy.





Phage therapy- limitations

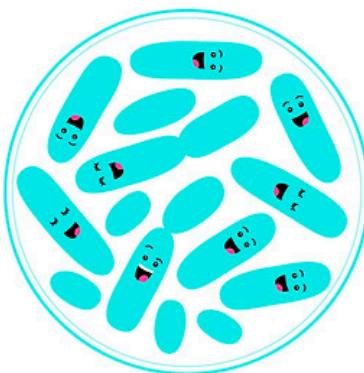
- The narrow lysis spectrum limits the effectiveness of bacteriophages in killing a variety of bacteria.
- Encapsulating and stabilizing bacteriophages
- Bacteria lysed by a phage may release endotoxins and super antigens that cause inflammation, which may potentially cause serious complications



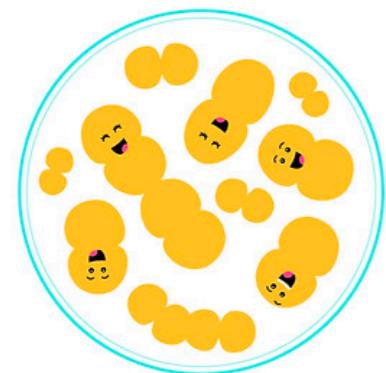
Prebiotics - Probiotics



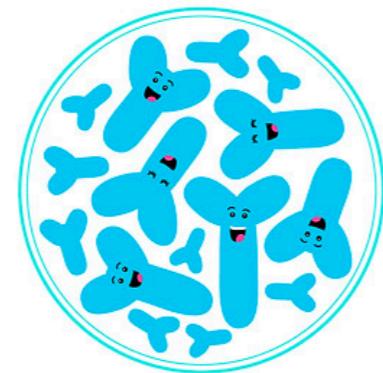
PROBIOTICS BACTERIA FAMILY



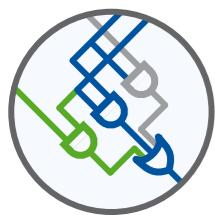
LACTOBACILLUS



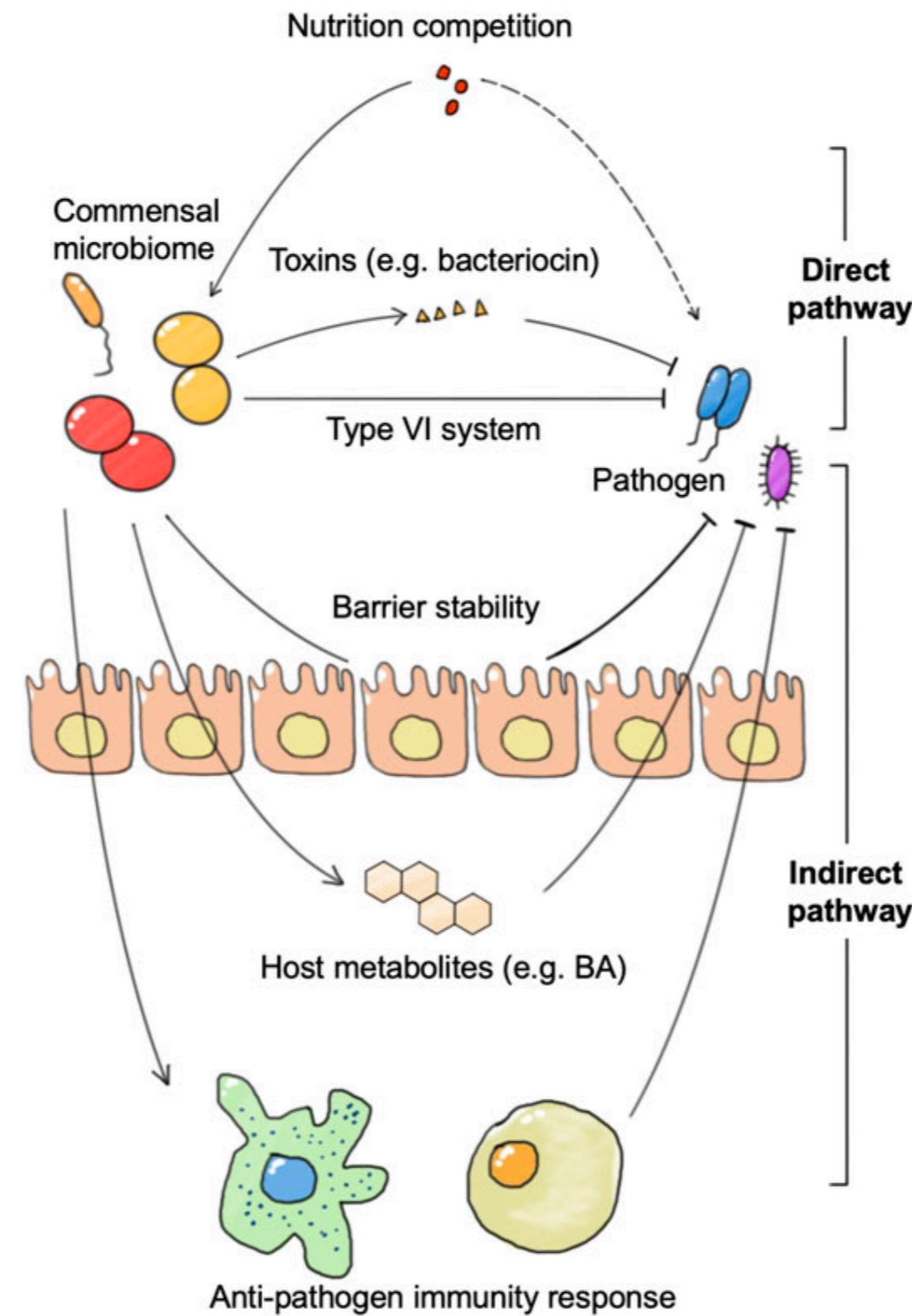
LACTOCOCCUS



BIFIDOBACTERIUM



High demand of probiotic bacteria



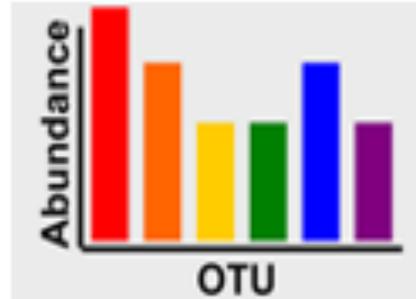


How do we study the microbiome?

Who is there?
What can they do?

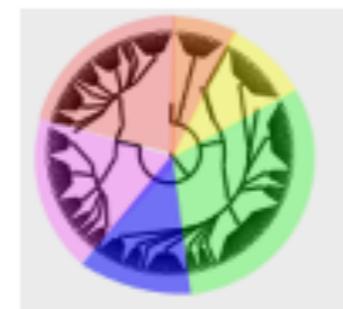
16S rRNA

Composition



Metagenomics

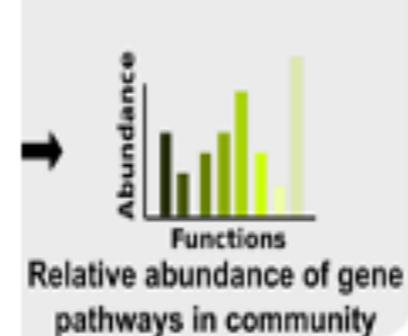
Functional capacity



What pathways/
genes are
active?

Metatranscriptomics

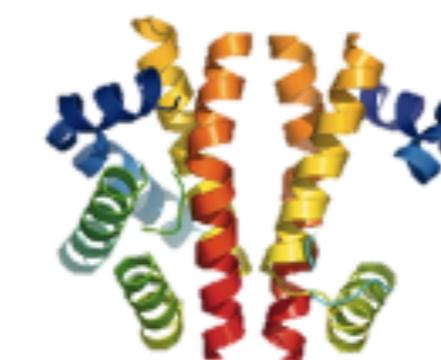
Gene expression



How do they
interact with
host?

Metaproteomics

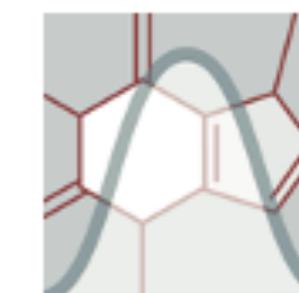
Catalytic Function



What are the
chemical
outcomes?

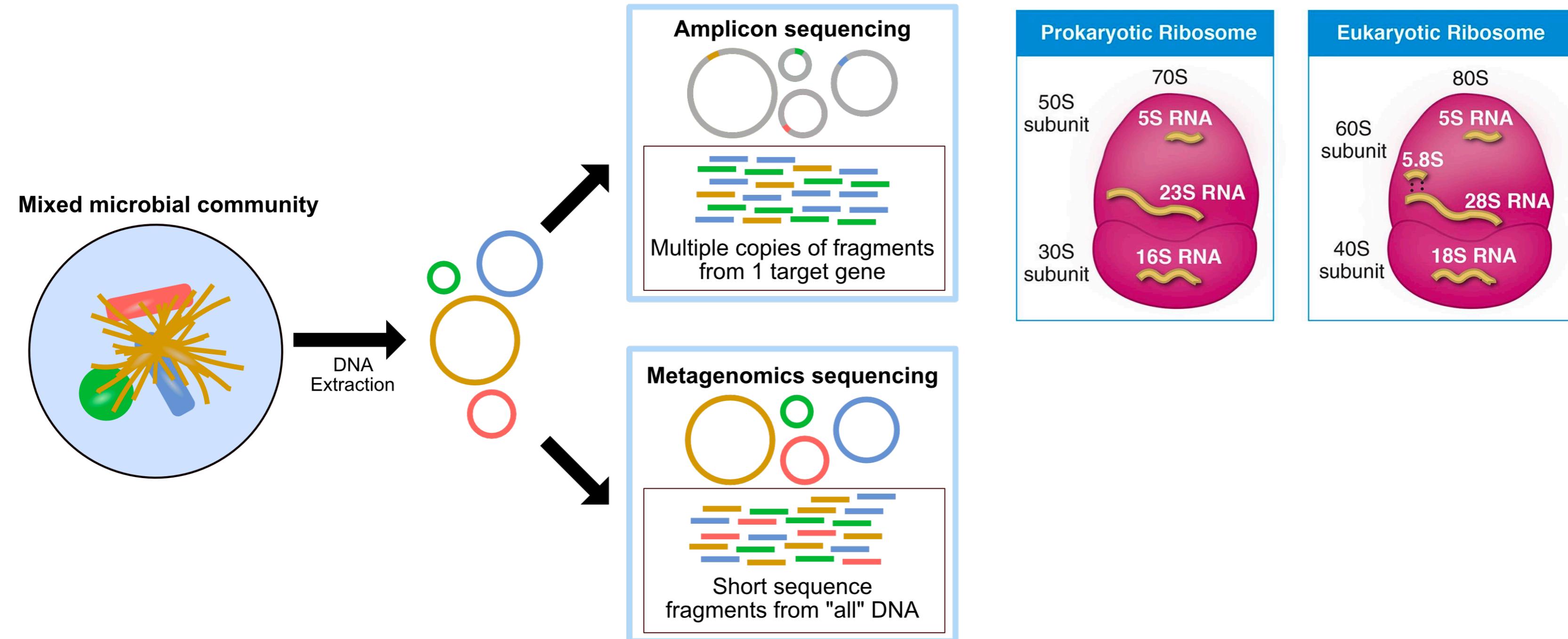
Metabolomics

Metabolic activity



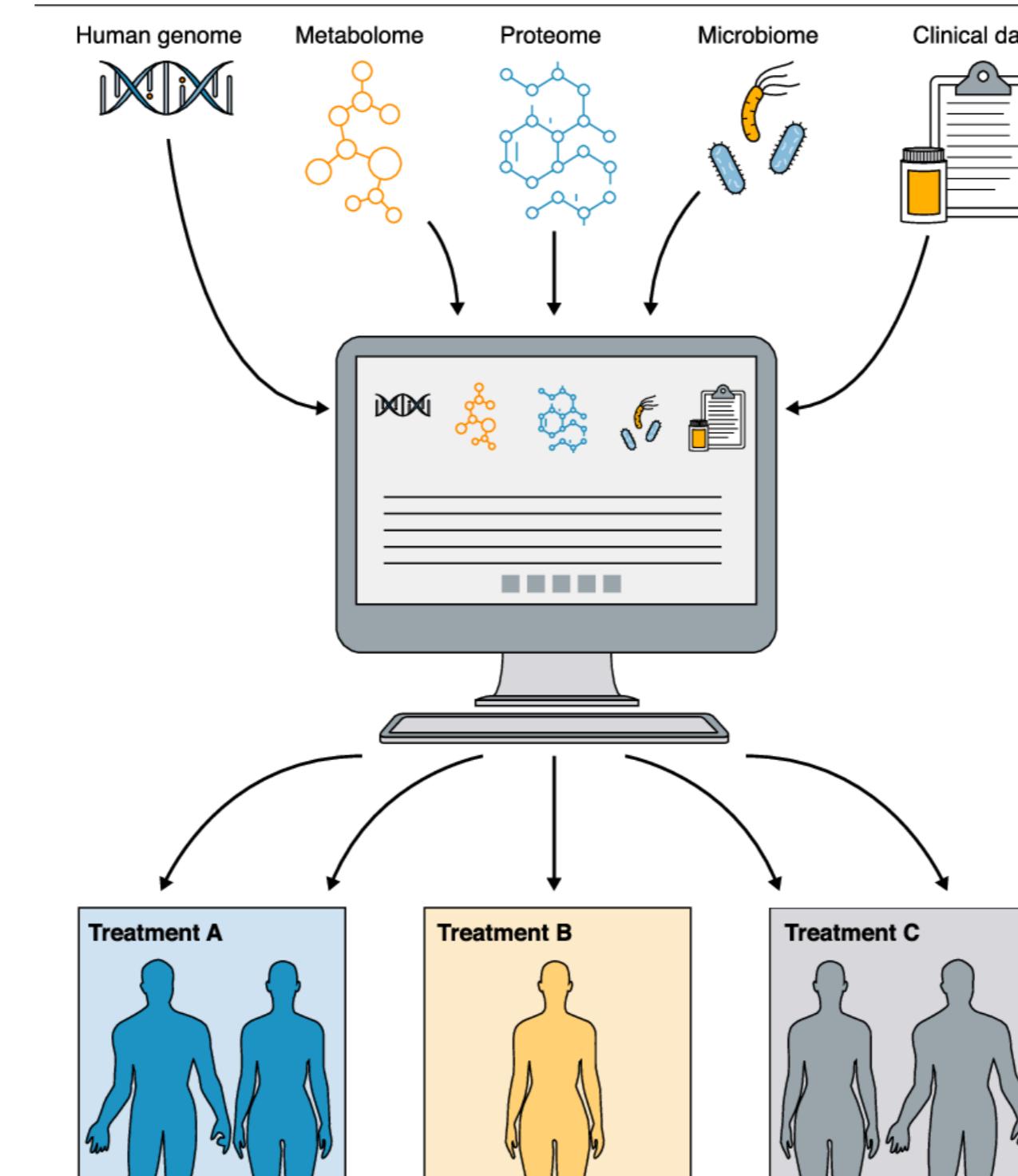


How do we study the microbiome?



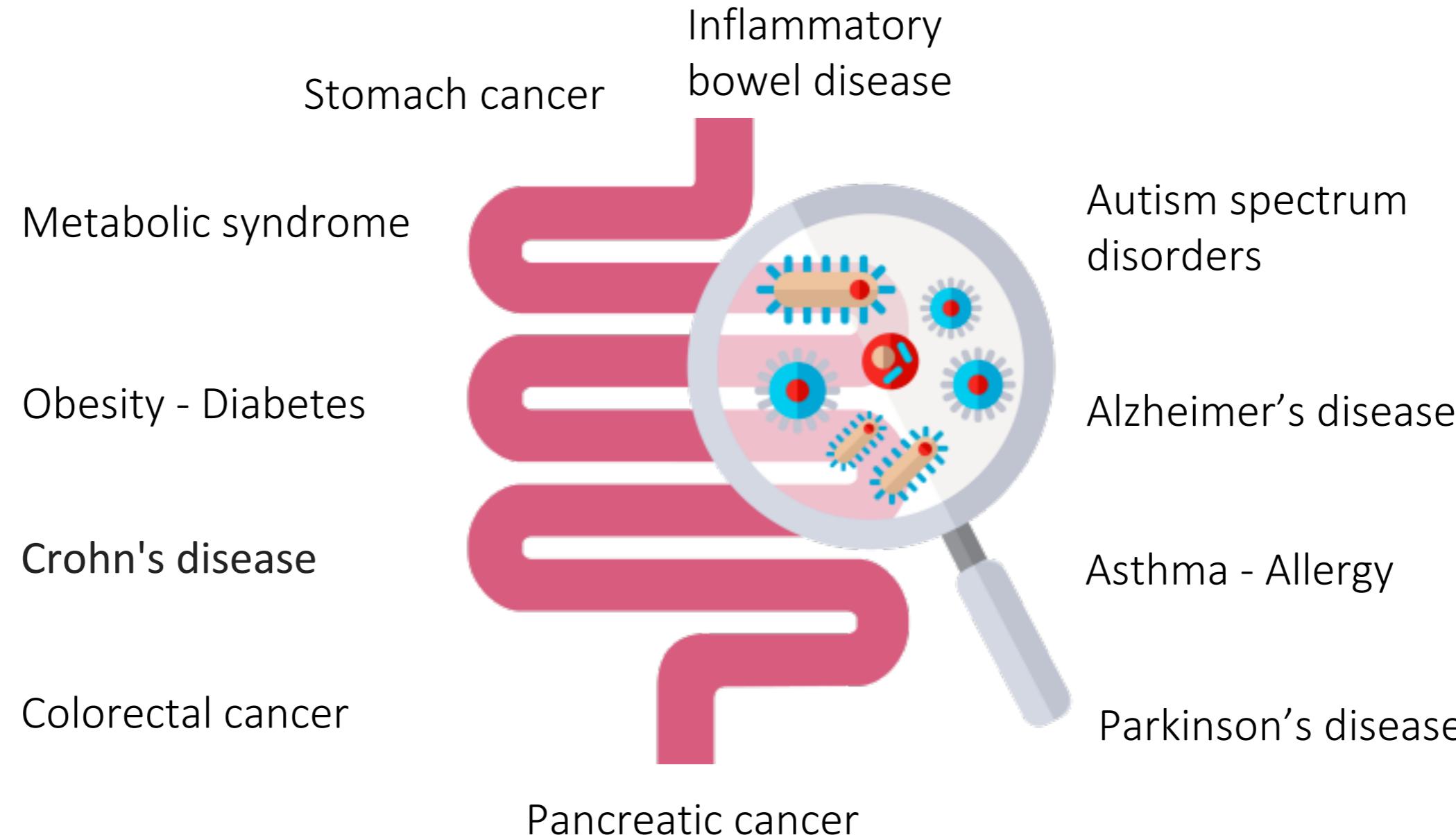


Combining different omics data



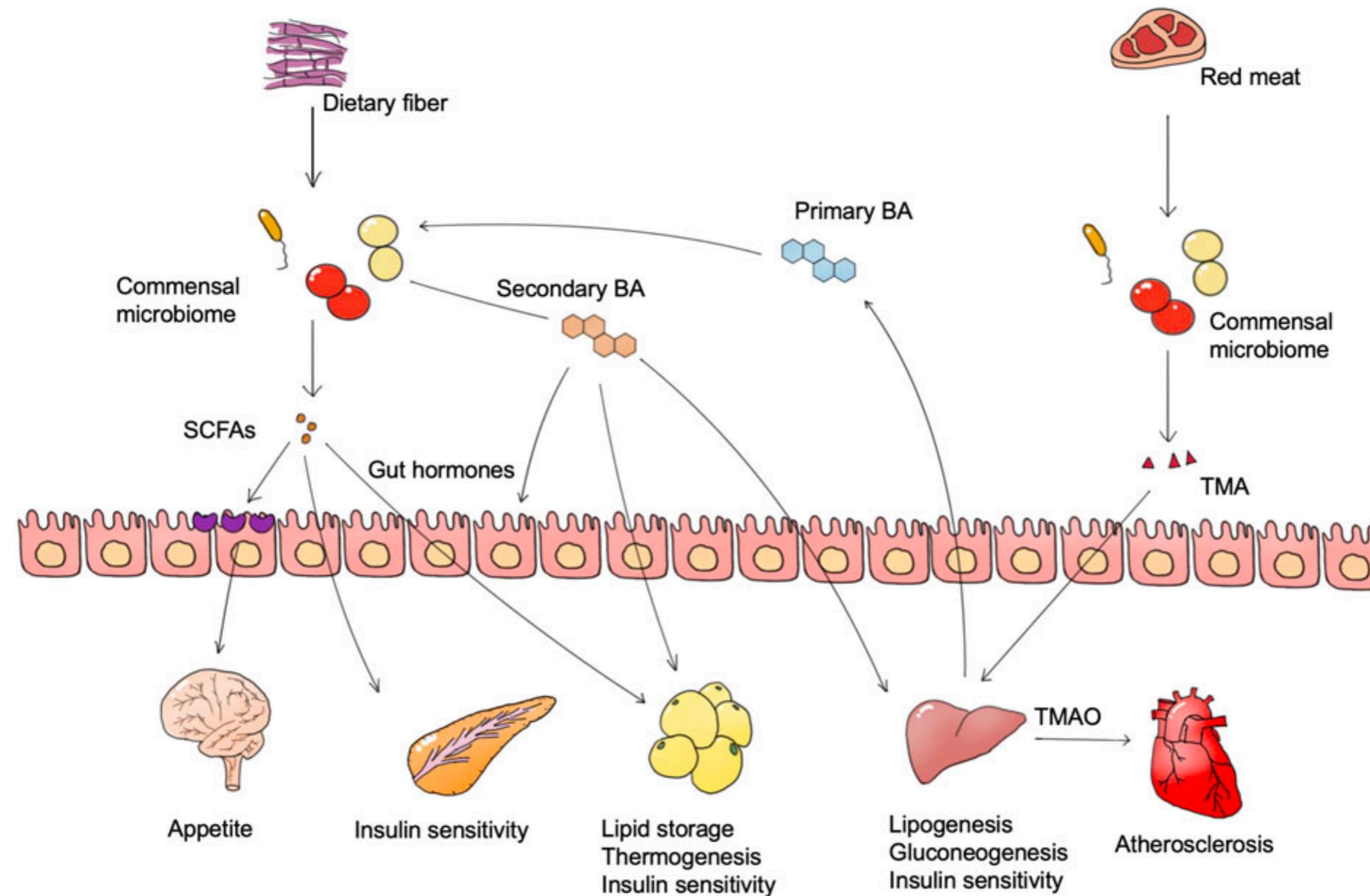


The link between the human microbiome and human health

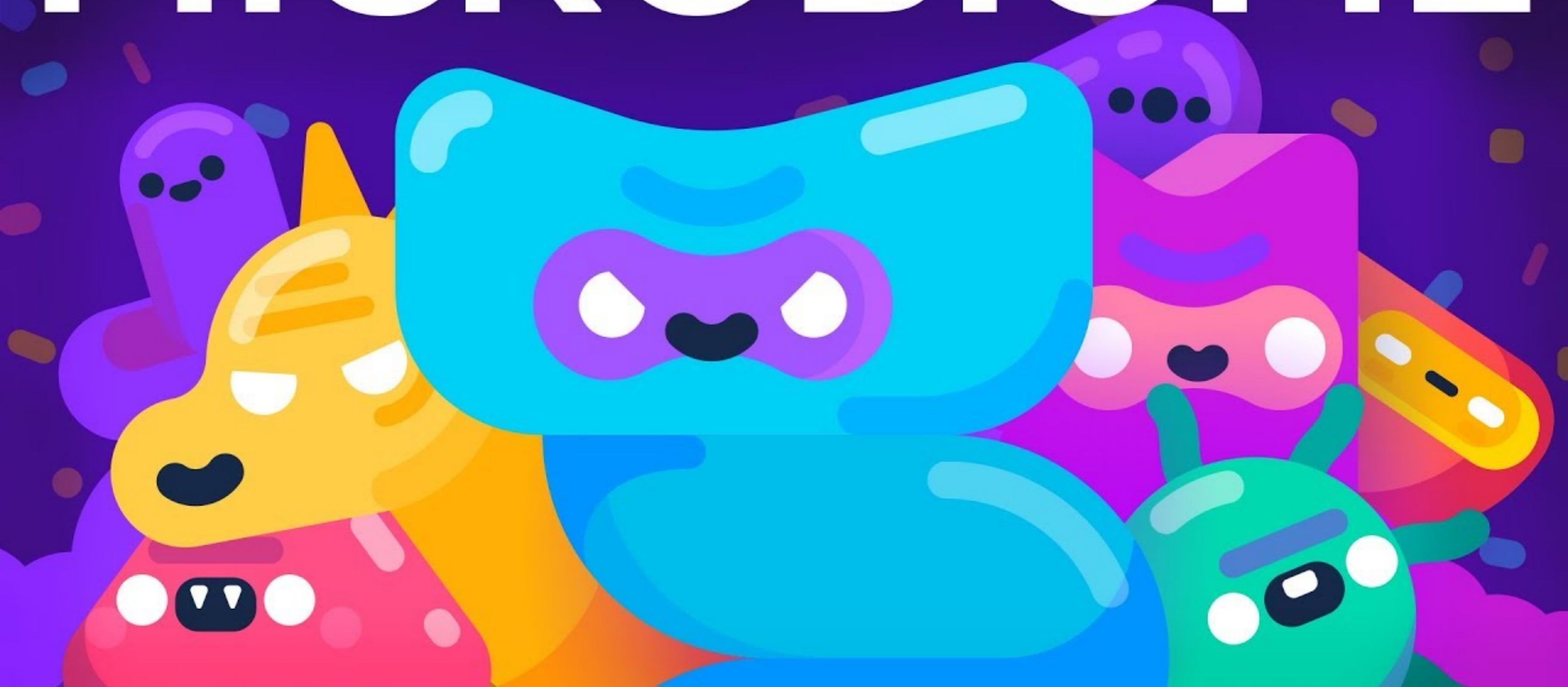


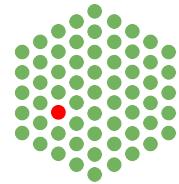


Microbiome-derived metabolites and metabolic diseases



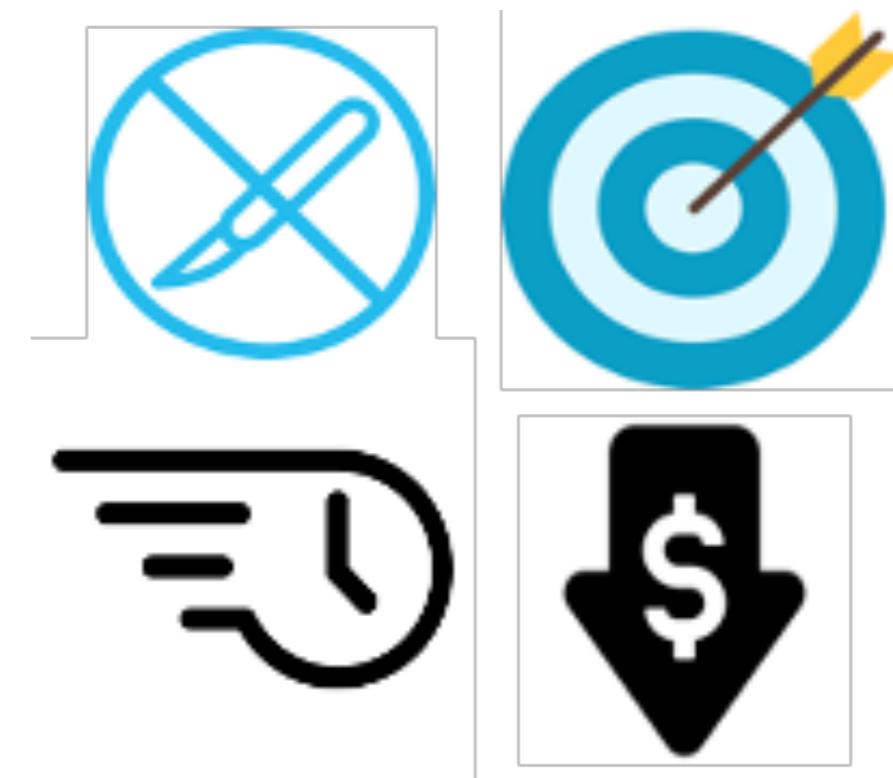
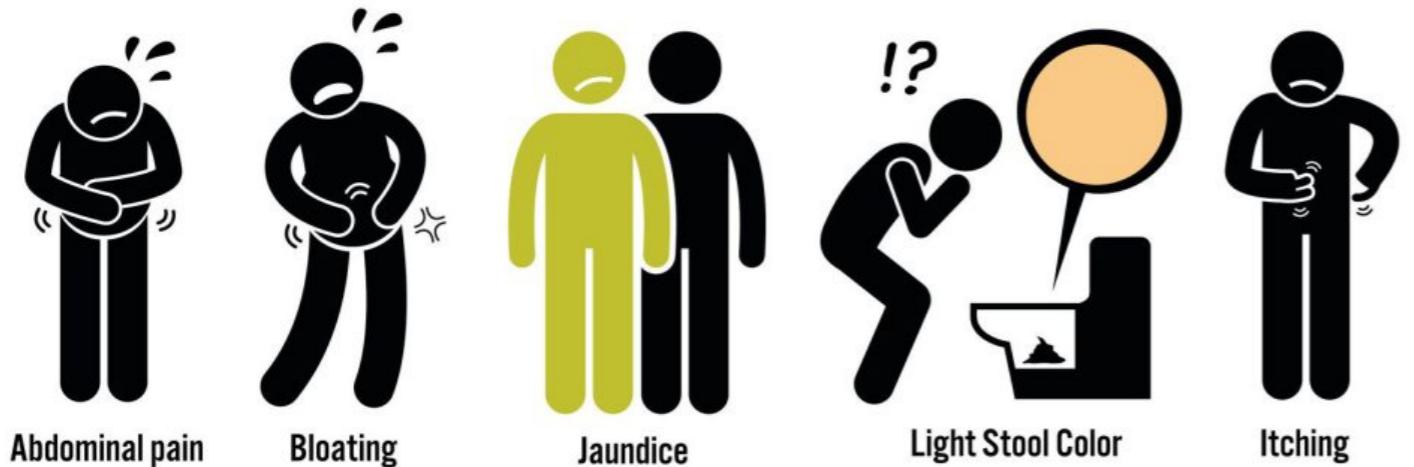
MICROBIOME

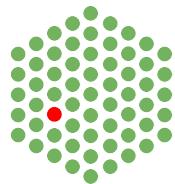




Pancreatic Ductal Adenocarcinoma (PDAC)

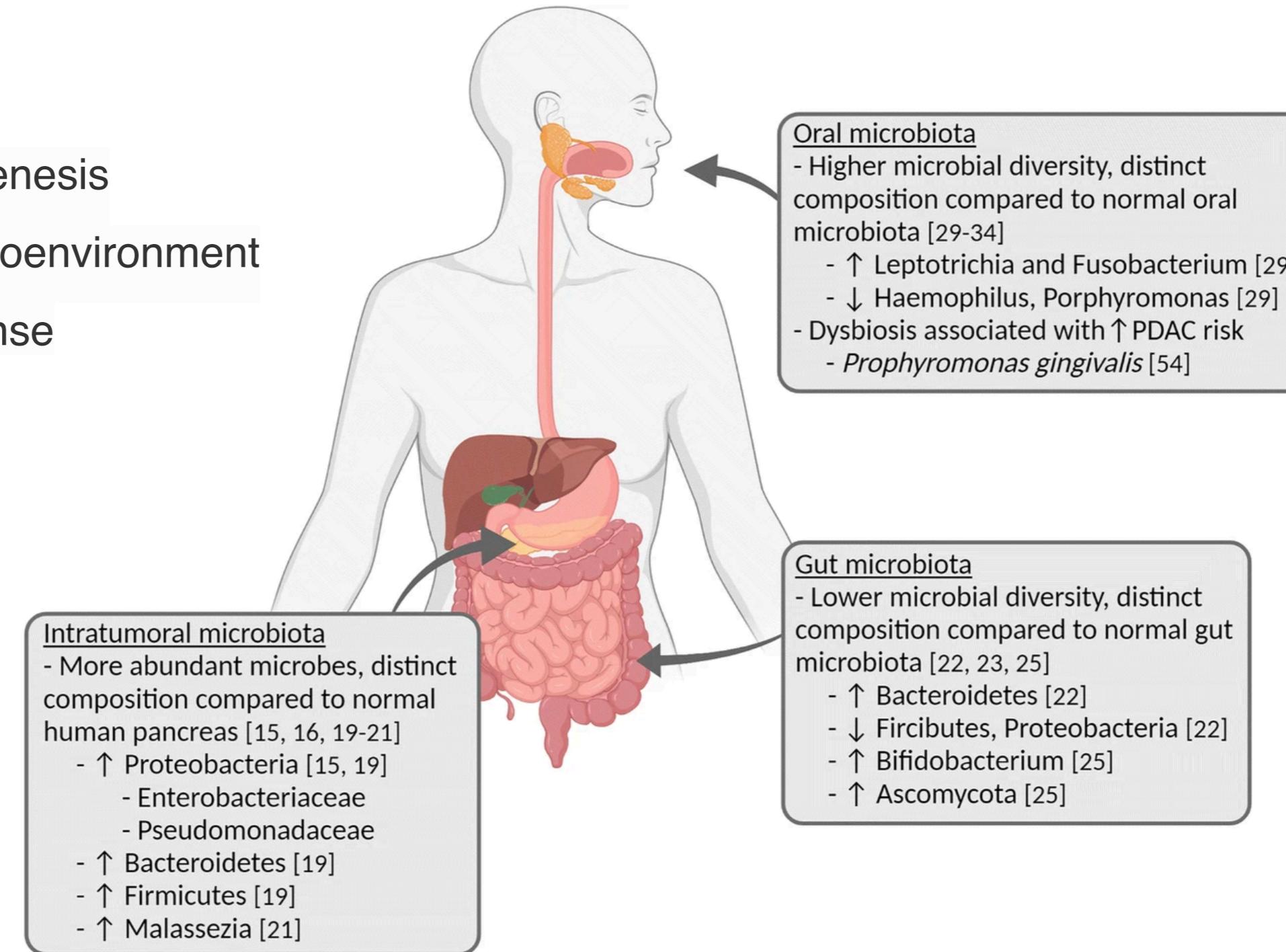
- 8th deadliest cancer worldwide
- **5 year survival rate is <10%**
- The only FDA approved marker: CA19-9 antigen in serum (low PDAC specificity)

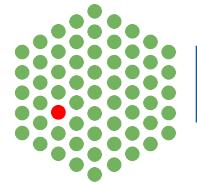




The PDAC microbiome

- Modulates PDAC risk
- Contributes to tumorigenesis
- Impacts the tumor microenvironment
- Alters treatment response





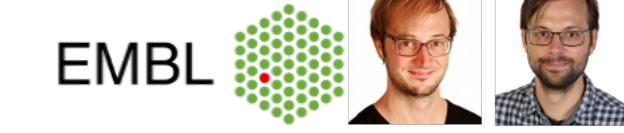
Potential of fecal microbiota for specific detection of PDAC



PanGen & MAGIC Consortiums



GOETHE
UNIVERSITÄT
FRANKFURT AM MAIN



Bork & Zeller Groups



Original research

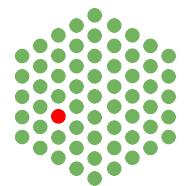
A faecal microbiota signature with high specificity for pancreatic cancer

Ece Kartal ^{1,2} Thomas S B Schmidt ¹, Esther Molina-Montes ^{3,4}, Sandra Rodríguez-Perales ^{4,5}, Jakob Wirbel ^{1,2}, Oleksandr M Maistrenko ¹, Wasiu A Akanni ¹, Bilal Alashkar Alhamwe ⁶, Renato J Alves ¹, Alfredo Carrato ^{4,7,8}, Hans-Peter Erasmus⁹, Lidia Estudillo ^{3,4}, Fabian Finkelmeier^{9,10}, Anthony Fullam ¹, Anna M Glazek,¹ Paulina Gómez-Rubio,^{3,4} Rajna Hercog,¹¹ Ferris Jung ¹¹, Stefanie Kandels ¹, Stephan Kersting ^{12,13}, Melanie Langheinrich ¹³, Mirari Márquez,^{3,4} Xavier Molero,^{14,15,16} Askarbek Orakov ¹, Thea Van Rossum ¹, Raul Torres-Ruiz ^{4,5}, Anja Telzerow ¹¹, Konrad Zych ¹, MAGIC Study investigators, PanGenEU Study investigators, Vladimir Benes ¹¹, Georg Zeller ¹, Jonel Trebicka ^{9,17}, Francisco X Real ^{4,18,19}, Nuria Malats ^{1,3,4}, Peer Bork ^{1,20,21,22}



- Picked up by **55** news outlets
- Blogged by **3**
- Tweeted by **264**
- On **1** Facebook pages
- Redditied by **1**
- Highlighted by **1** platforms
- 39** readers on Mendeley

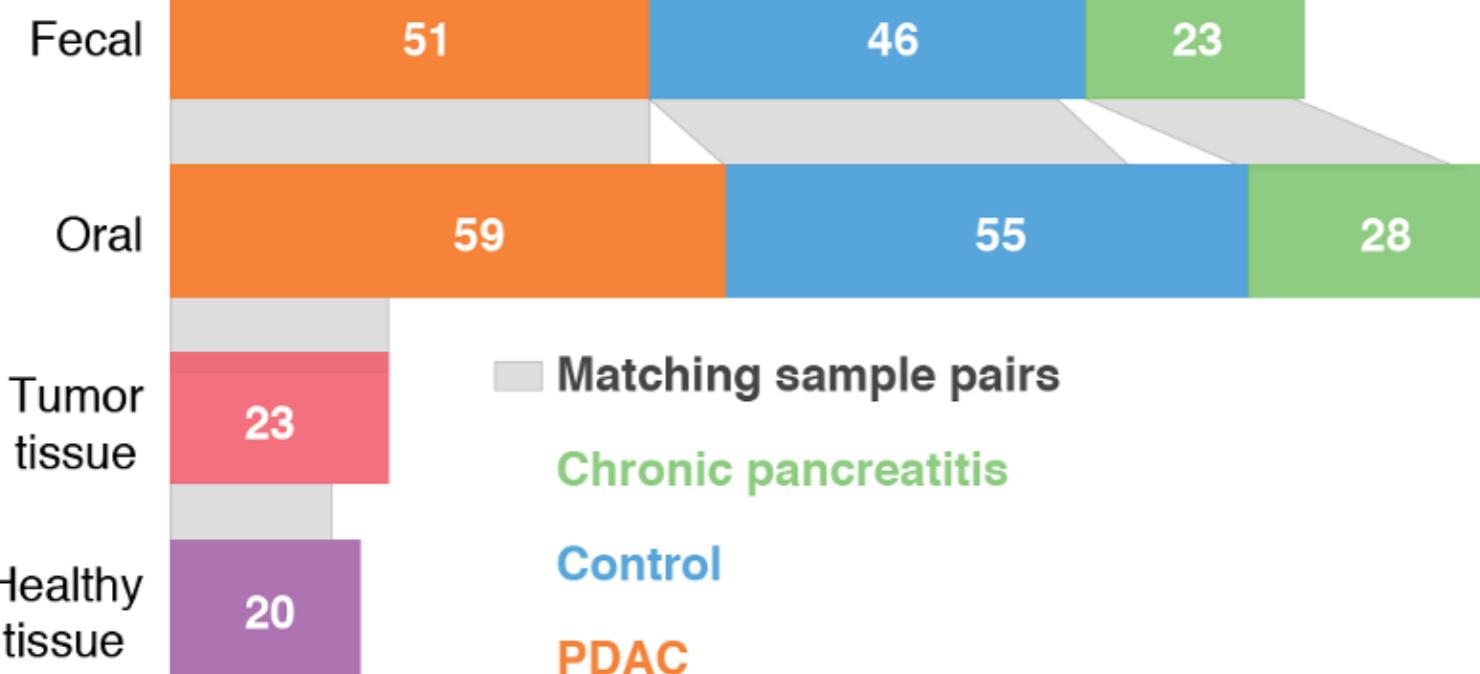




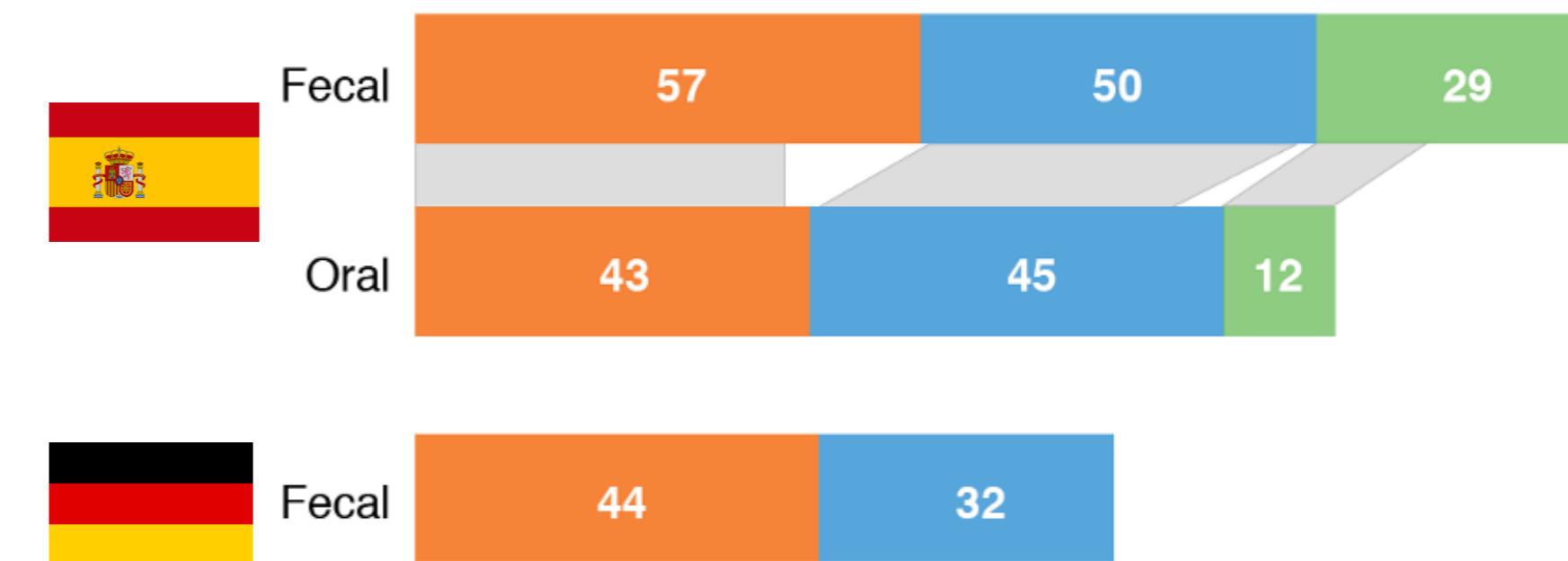
Potential of fecal microbiota for specific detection of PDAC

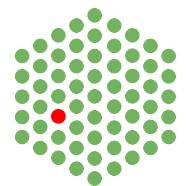
a Cohort overview

16S rRNA Amplicon

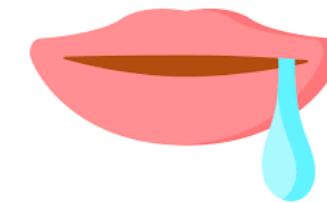
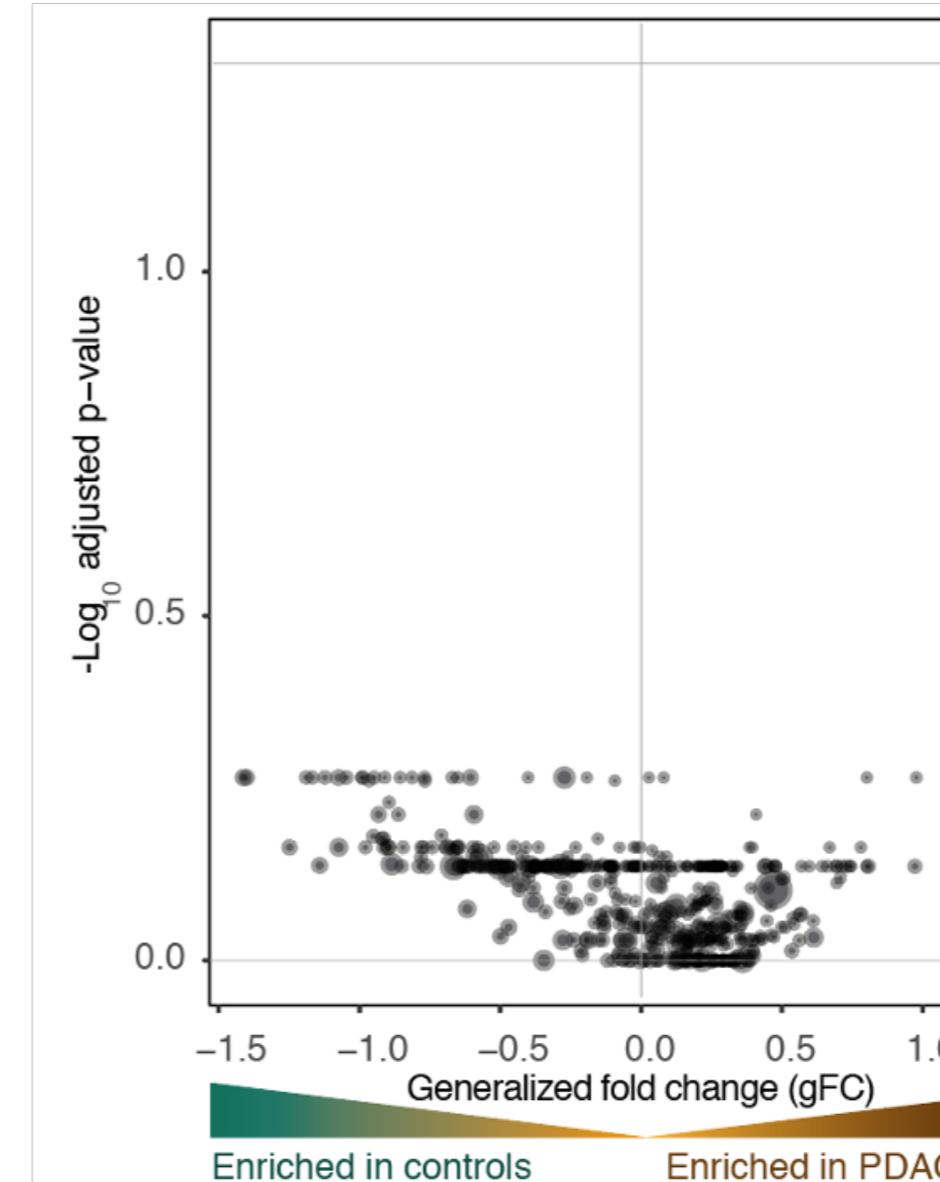
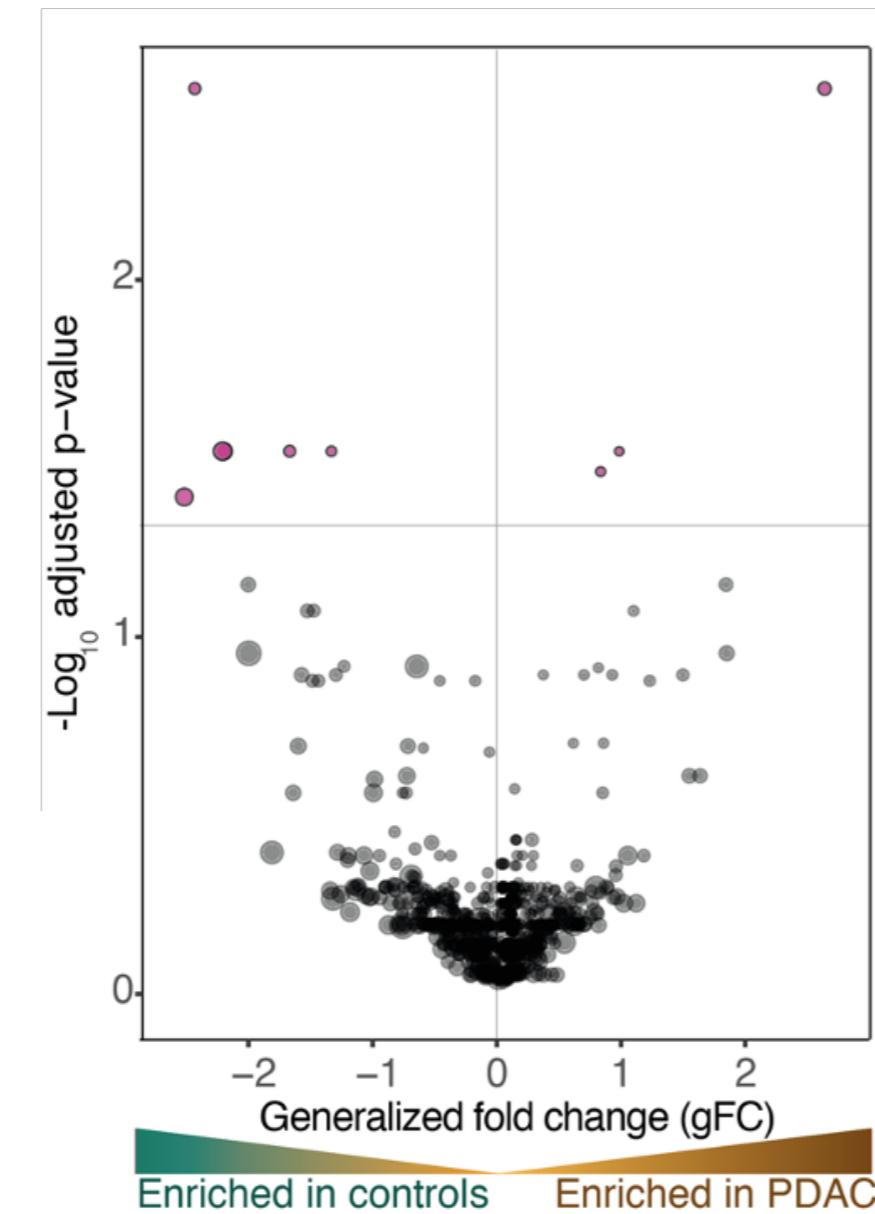
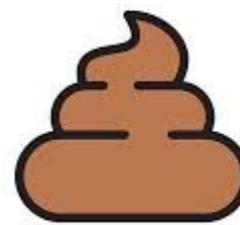


Shotgun Metagenomics

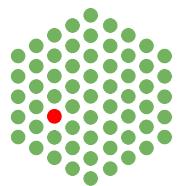




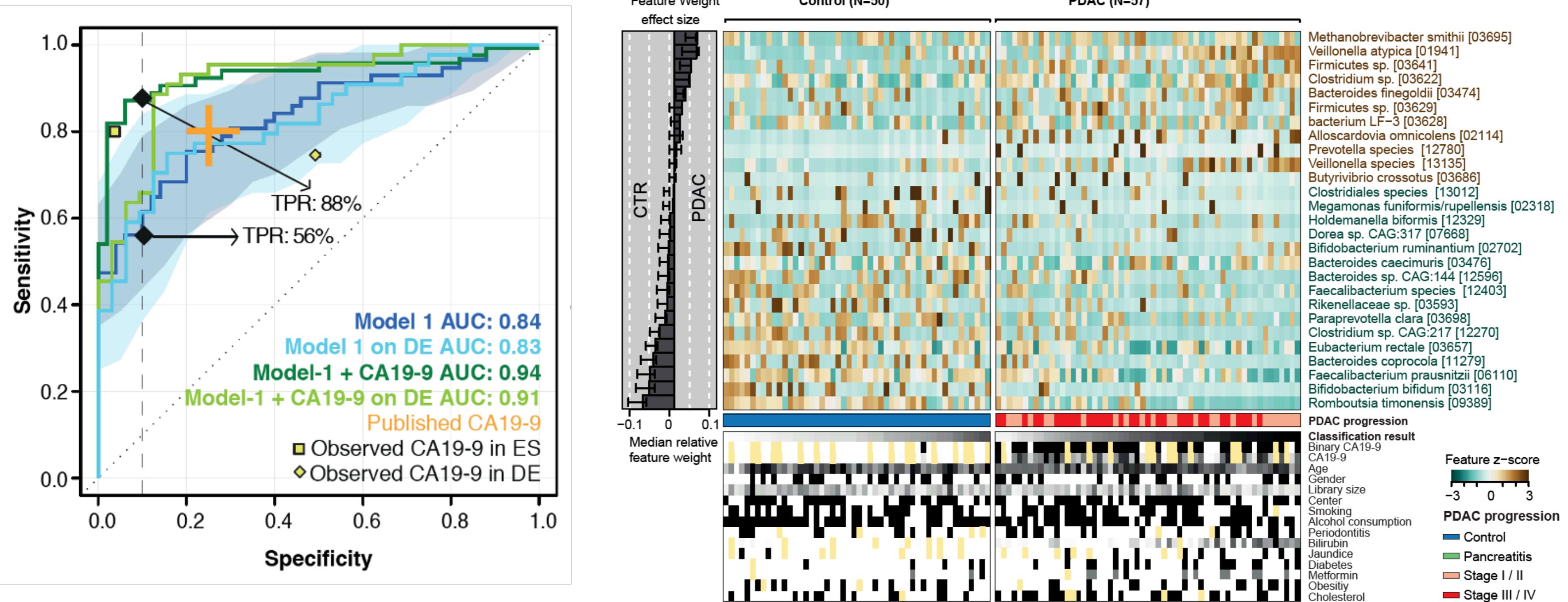
Differential abundant species between PDAC & CTR

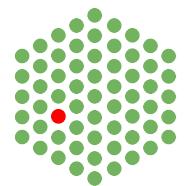


- Not significant
- Adjusted p-value < 0.05
- Relative abundance ● 0.01 ● 0.03 ● 0.05

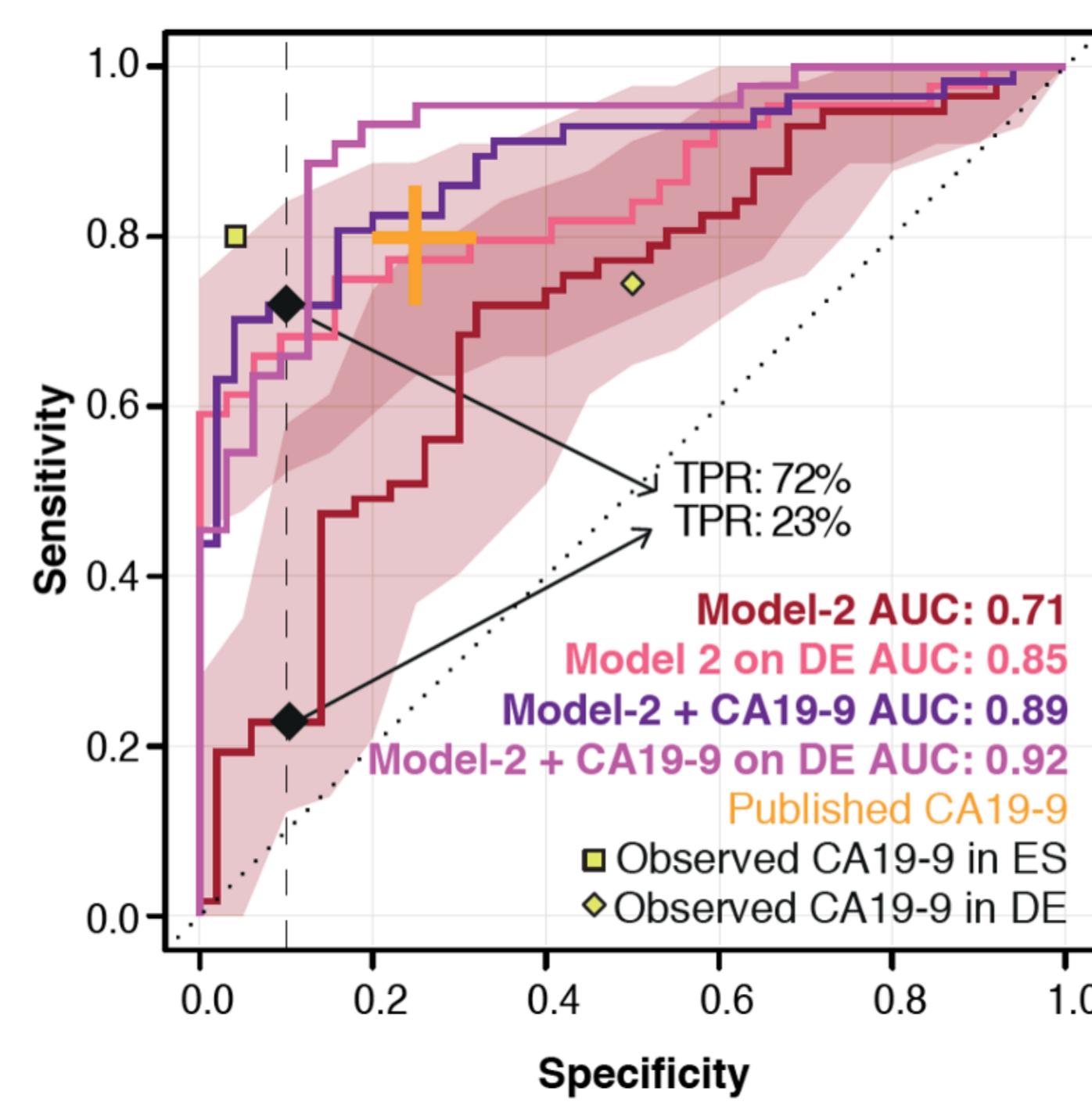


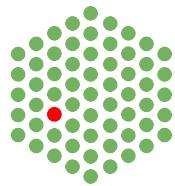
Unconstrained Model 1





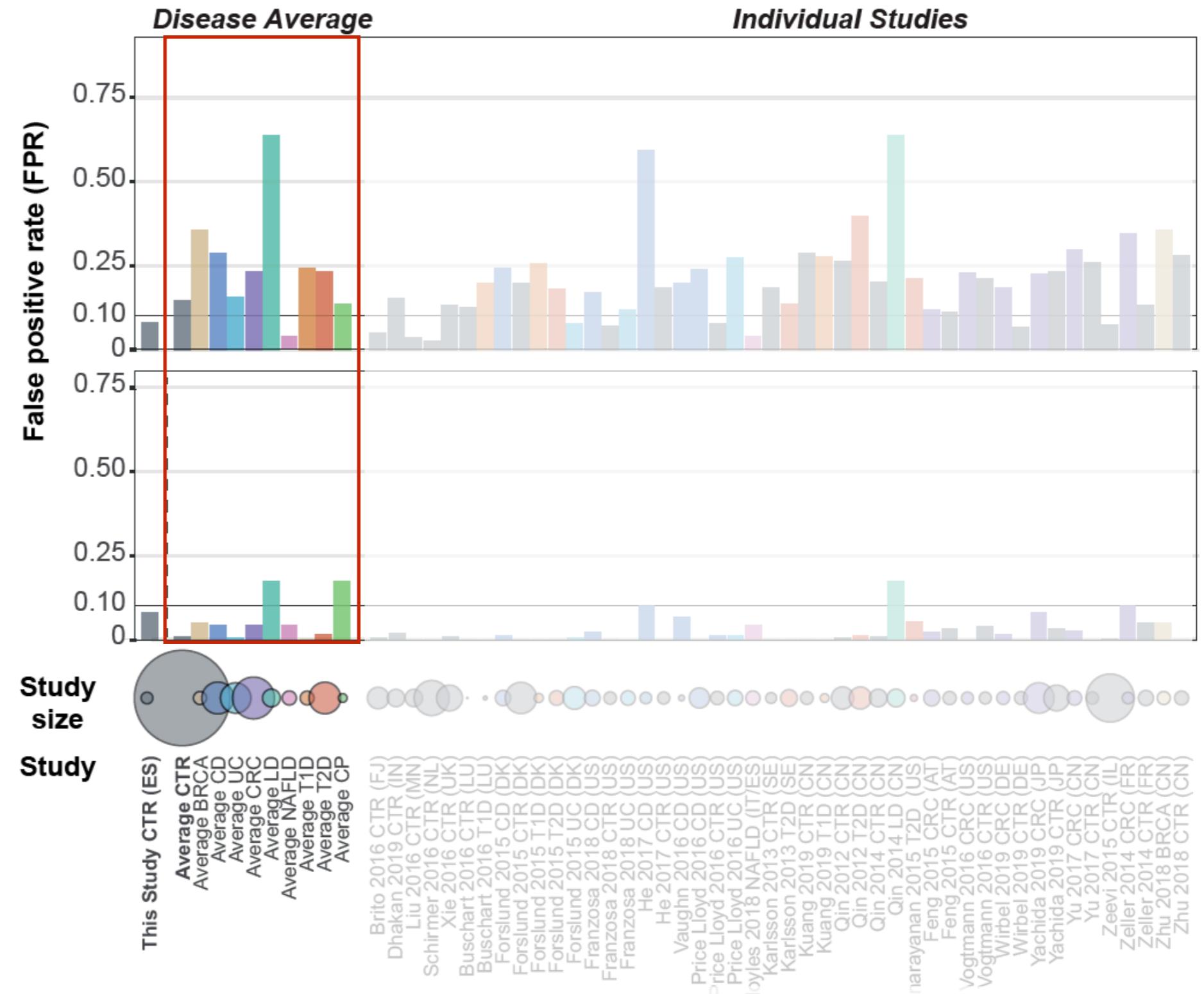
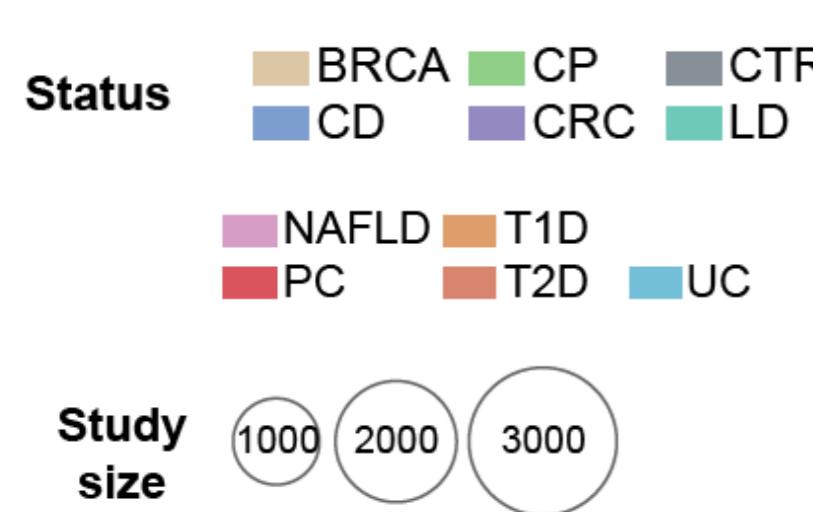
Enrichment-constrained model 2

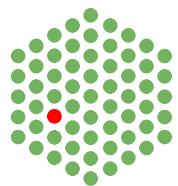




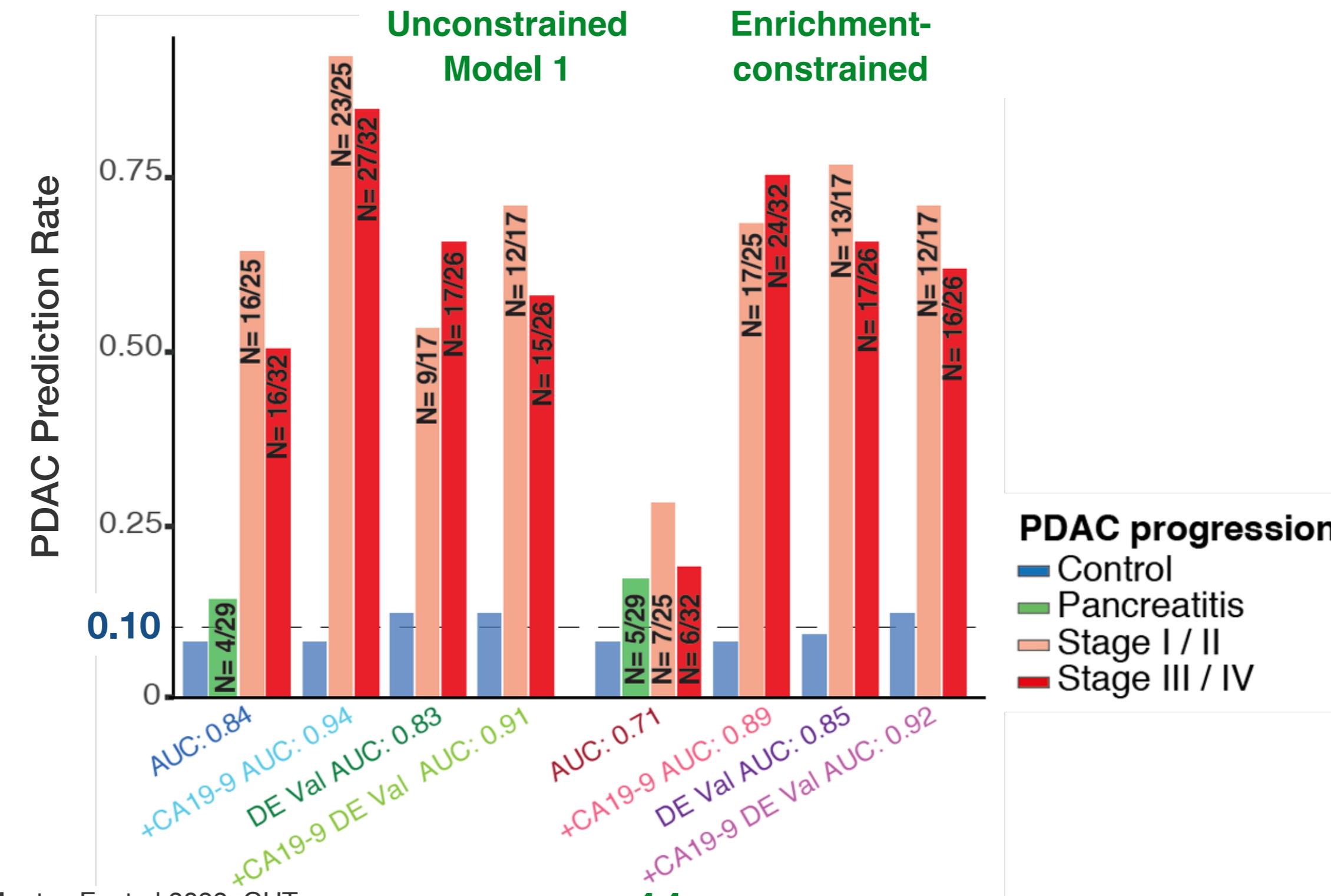
Validation of the PDAC fecal microbiome models in external

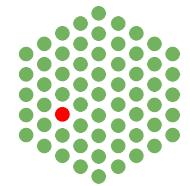
25 studies
5,792 samples
18 countries
9 diseases





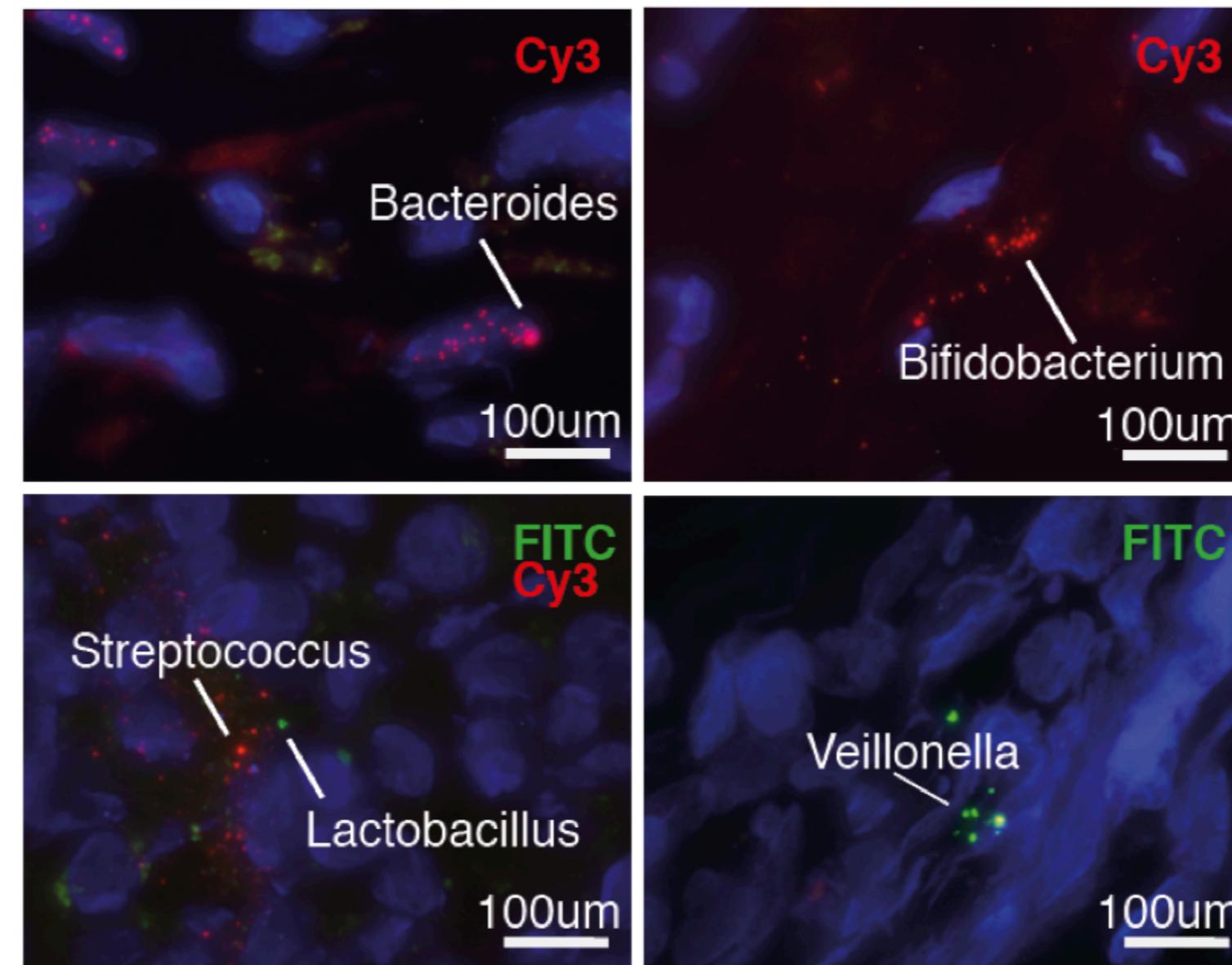
PDAC models do not show a bias for late stages

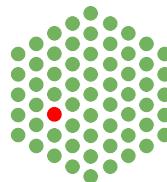




Presence of key genera in different body sites & sections of

Fluorescent in-situ hybridization





Summary

- We developed stool microbiota-based classifiers to predict PDAC with high accuracy and specificity, independent of disease stage.
- We validated the classifiers in an independent German cohort and verified it in 25 metagenomic studies.
- We confirmed marker taxa enriched in faecal, healthy and tumour pancreatic tissues by FISH.
- Further studies are needed to optimise the model performance.



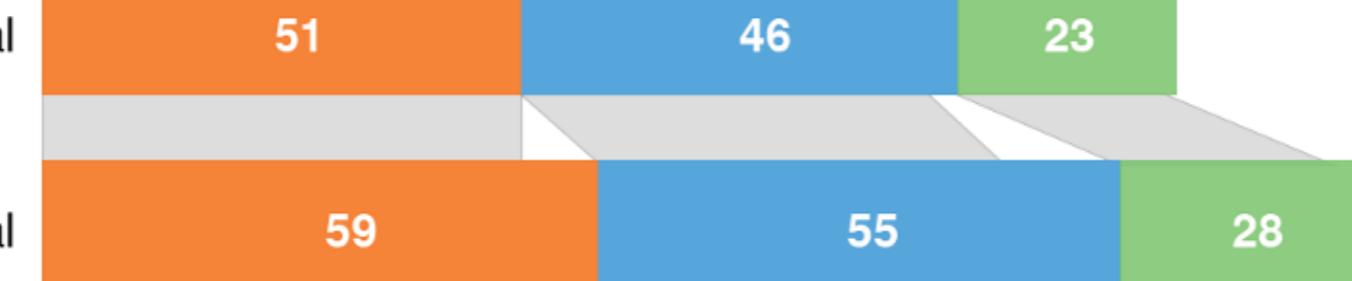
The plan for the practical session

a

Cohort overview

16S rRNA Amplicon

Fecal



Oral

Tumor tissue

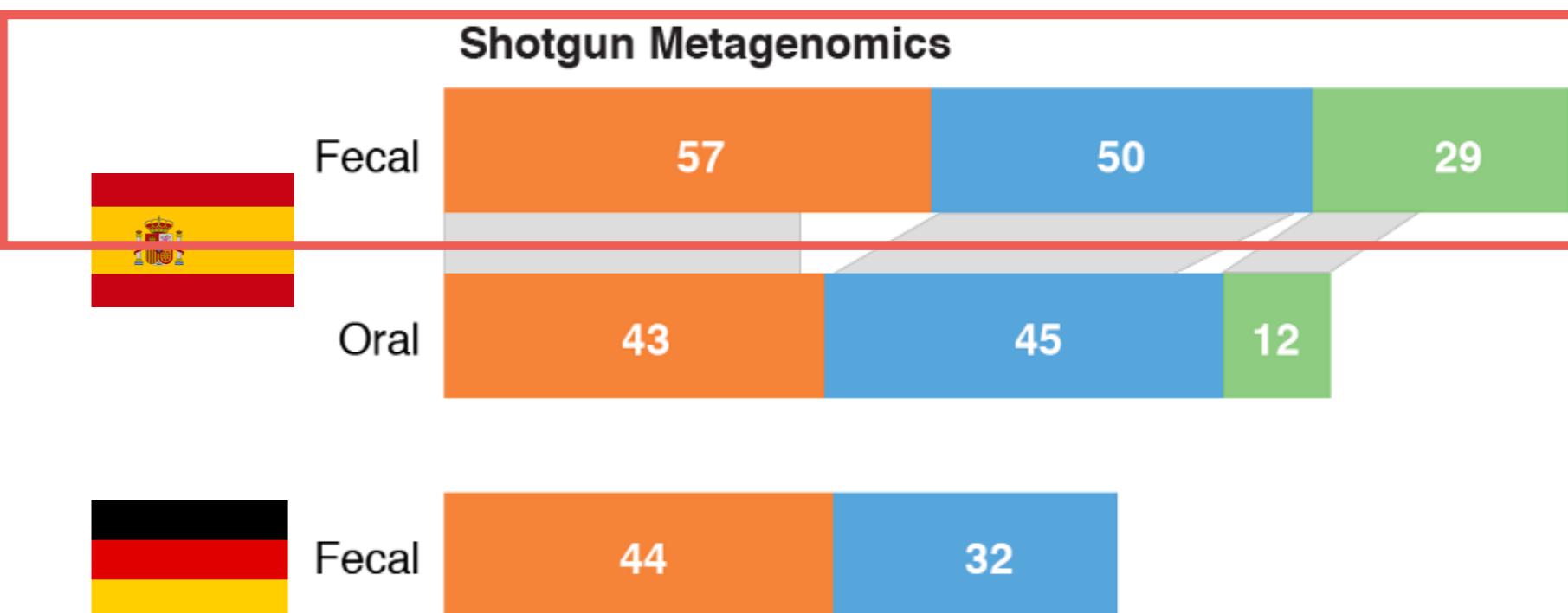
Healthy tissue

Matching sample pairs

Chronic pancreatitis

Control

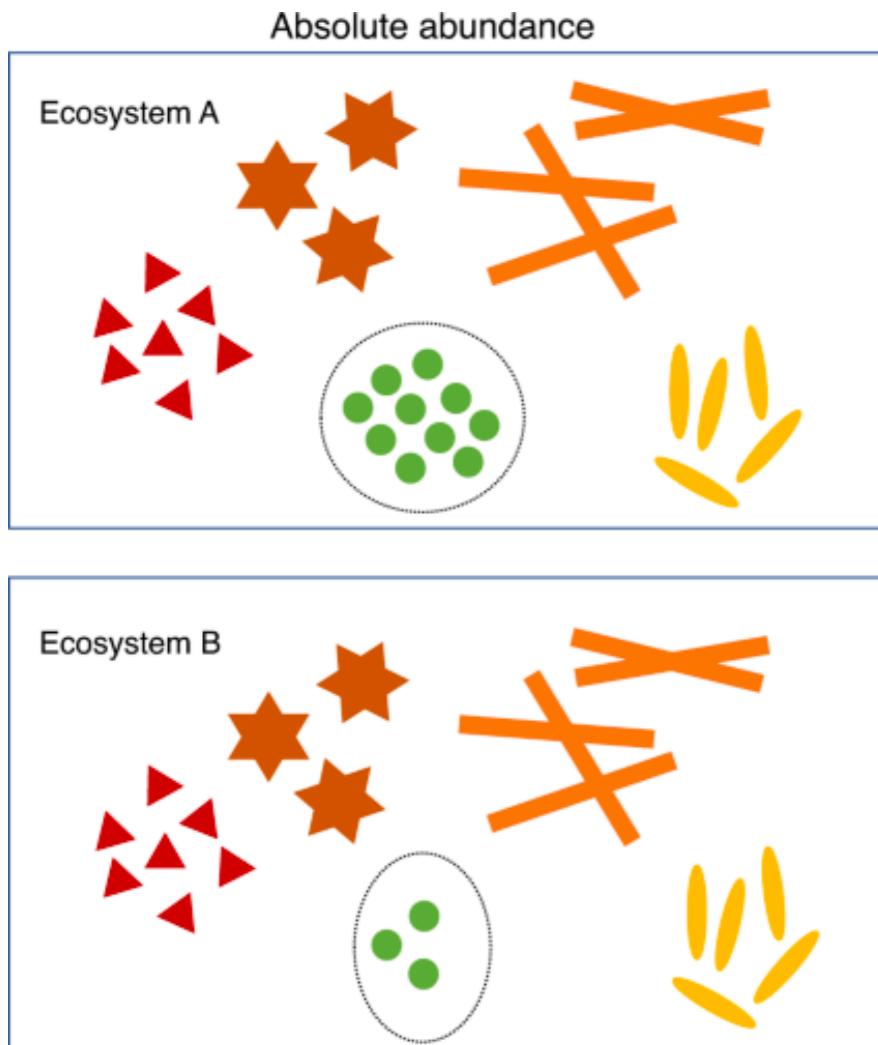
PDAC



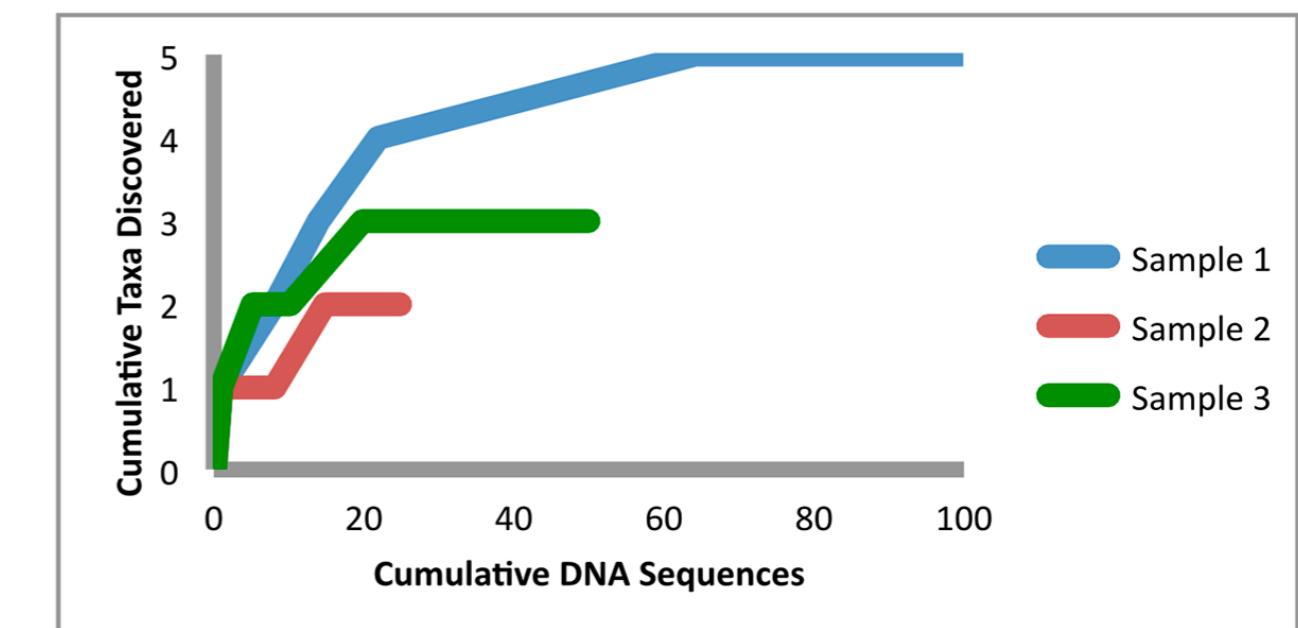


Data normalisation

- Relative abundance



- Rarefying normalizes library sizes by subsampling from observed sequences

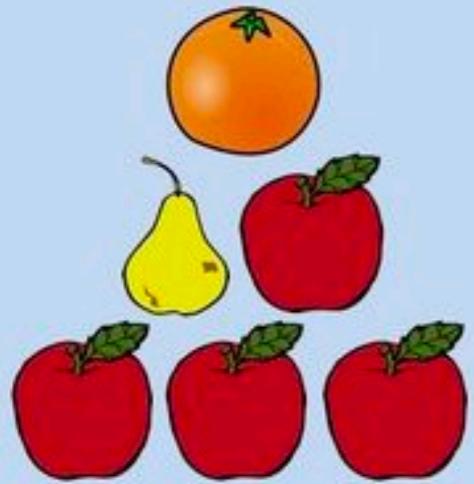




Diversity measures: alpha (within sample)

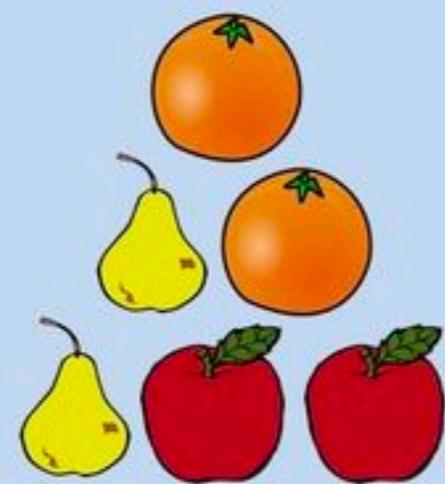
Being rich is good!

Being diverse is good!



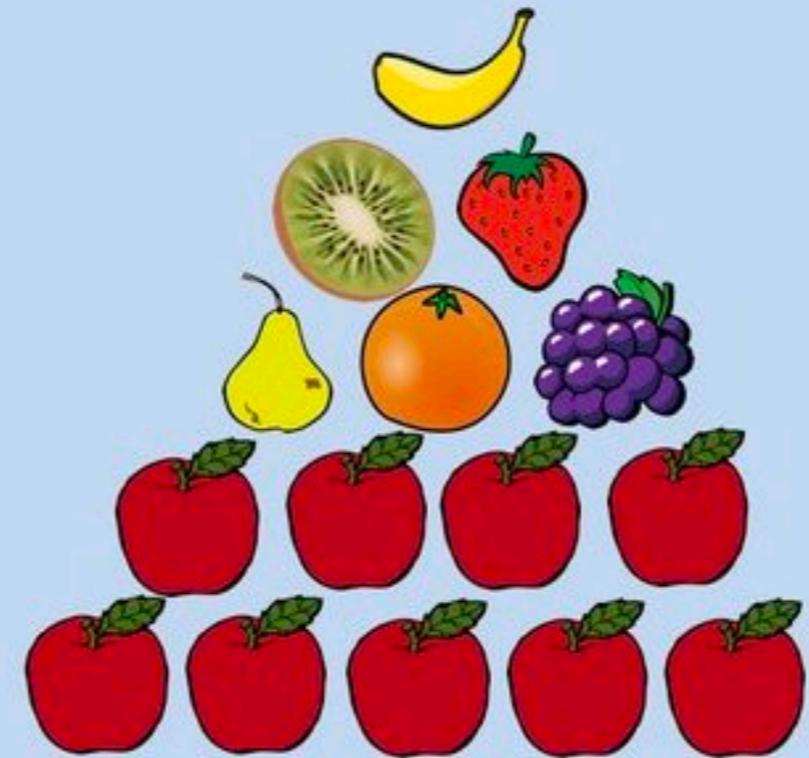
Low richness

3 types fruit



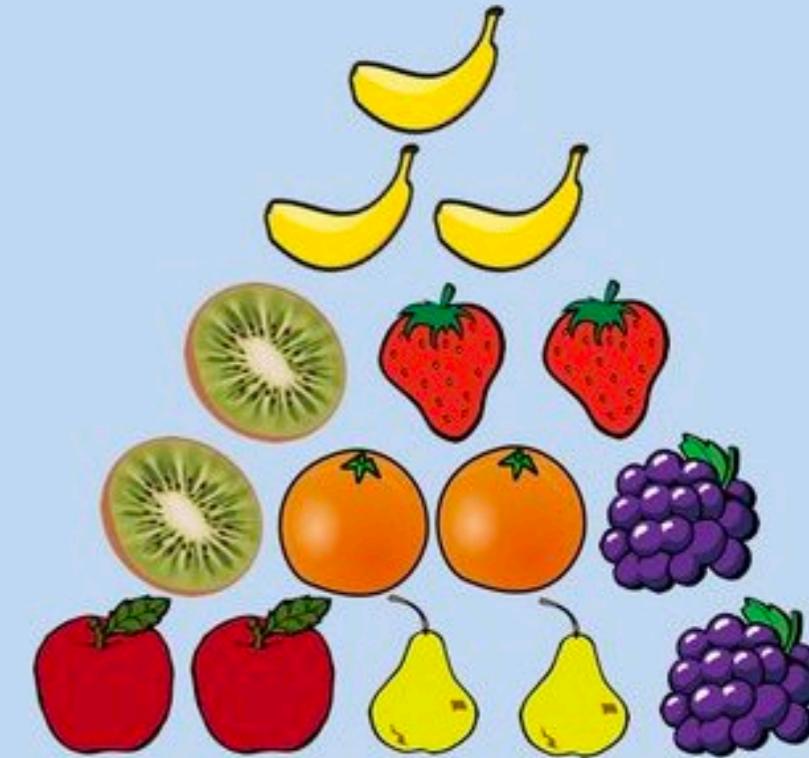
Low richness

3 types fruit



High richness

7 types fruit



High richness

7 types fruit

Low evenness

Lots of (common) types
Few of (rare) types

High evenness

Similar abundance of
each type

Low evenness

Lots of (common) types
Few of (rare) types

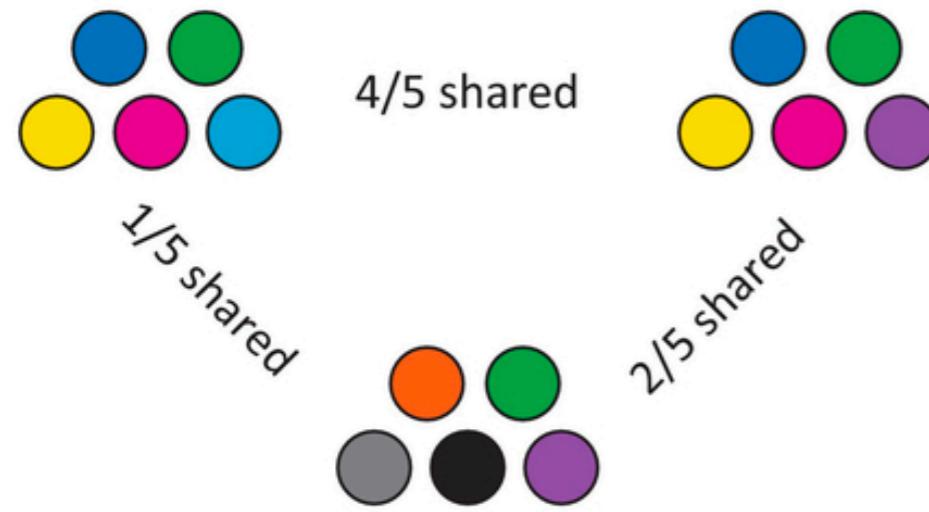
High evenness

Similar abundance of
each type

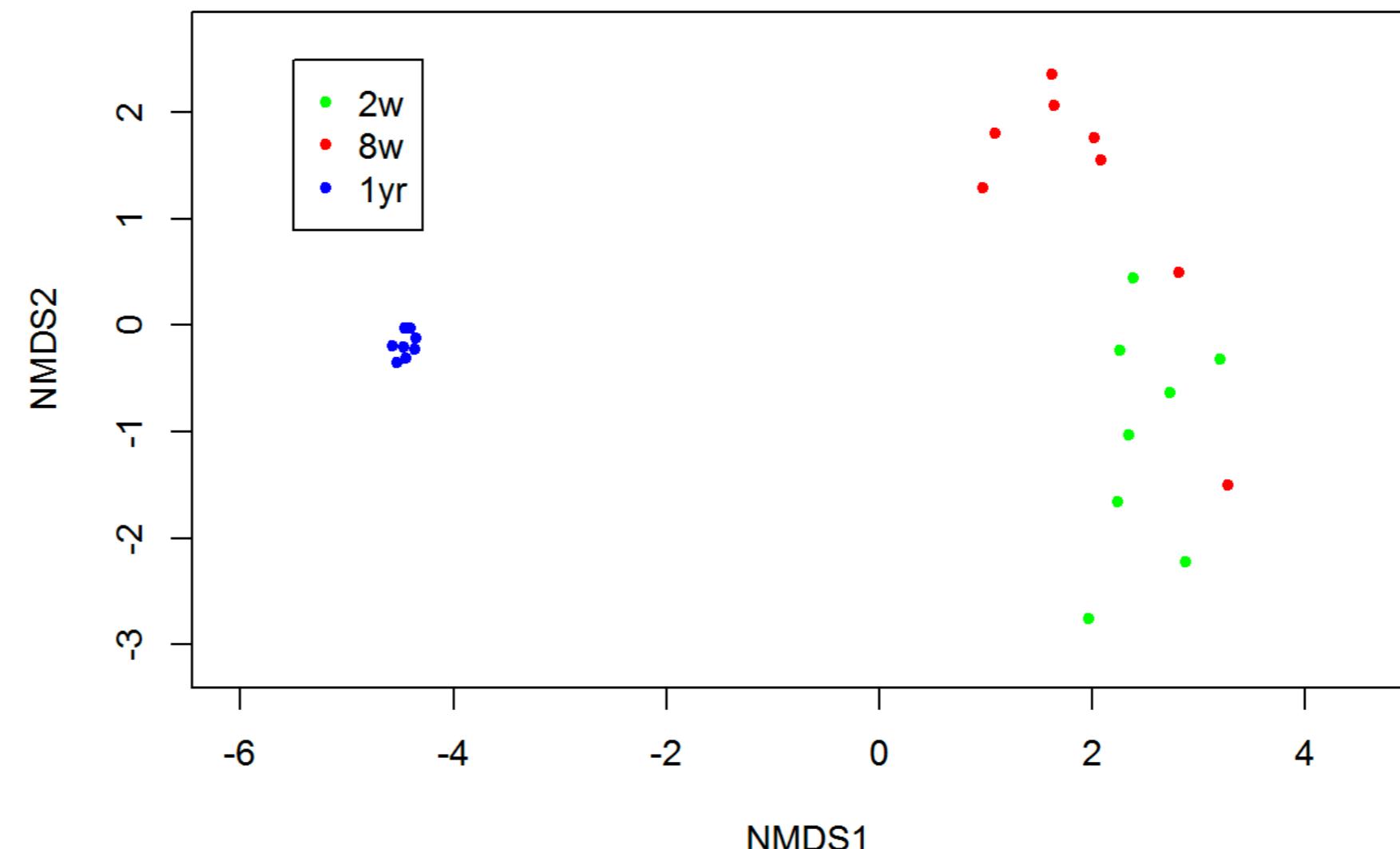


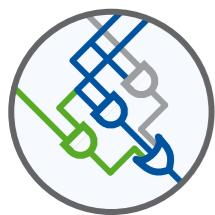
Diversity measures: beta (between samples)

Beta diversity: similarity between samples

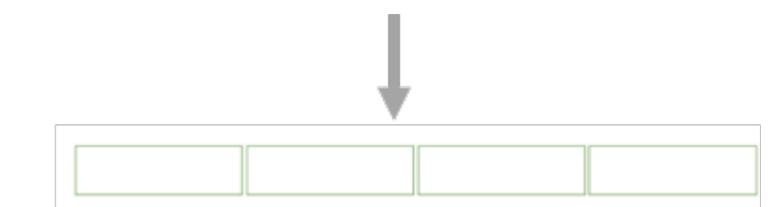
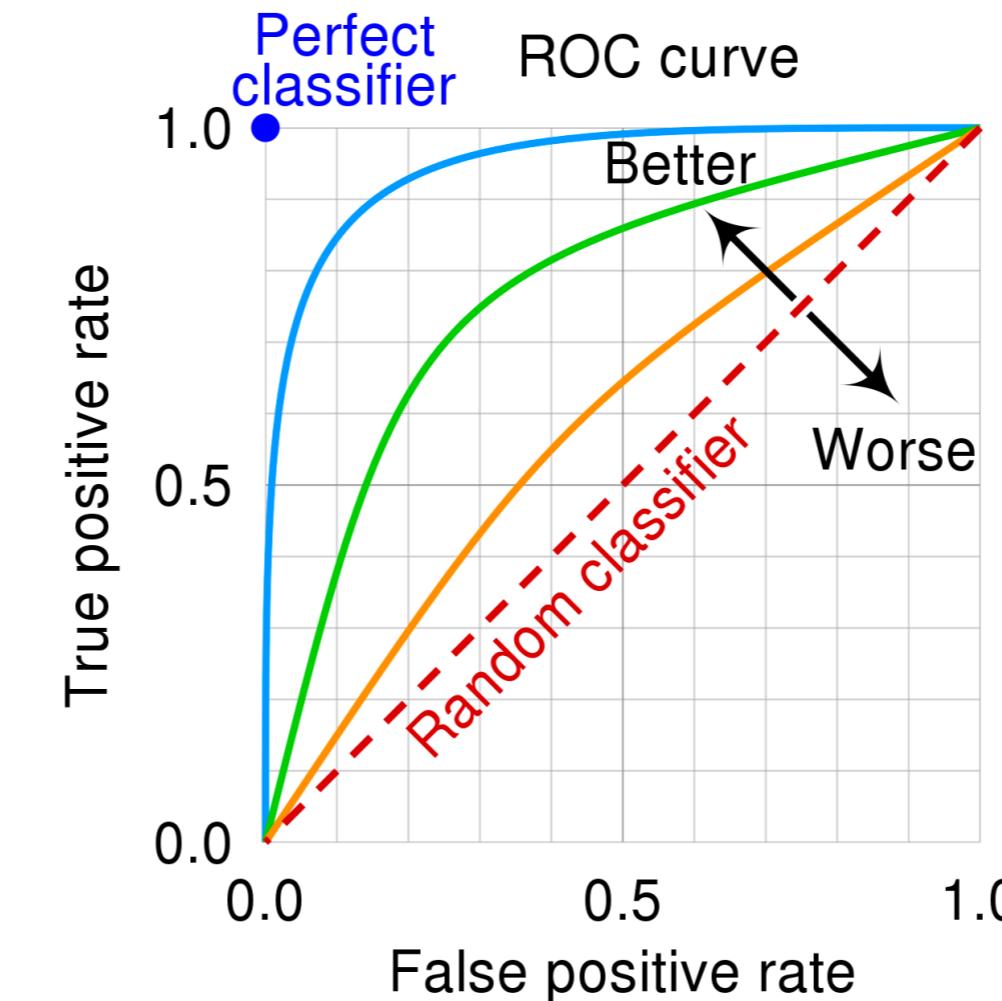
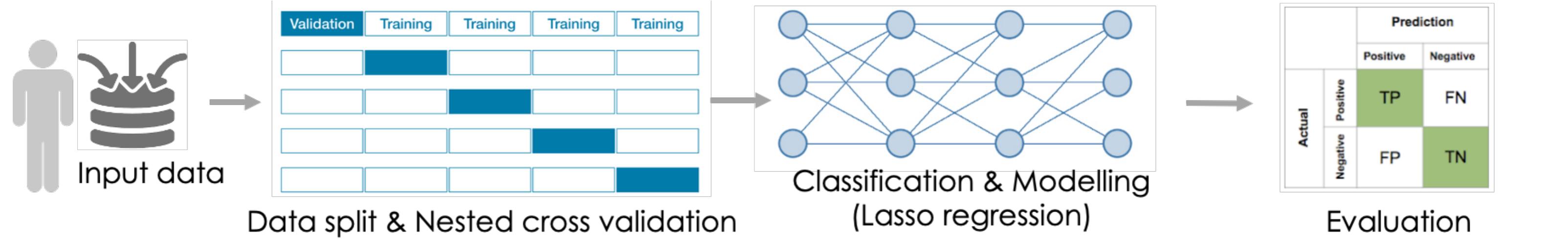


Bray-Curtis





Modelling





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NATIONALES CENTRUM
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www.saezlab.org  **@saezlab**

Julio Saez-Rodriguez

Daniel Dimitrow
Jovan Tavenki
Attila Gabor
Martin Cordoba

Lets go!

