

**MBIO**



**2018**

# L'alimentation, une alliée du microbiote en perte d'équilibre ?

Muriel Derrien, PhD

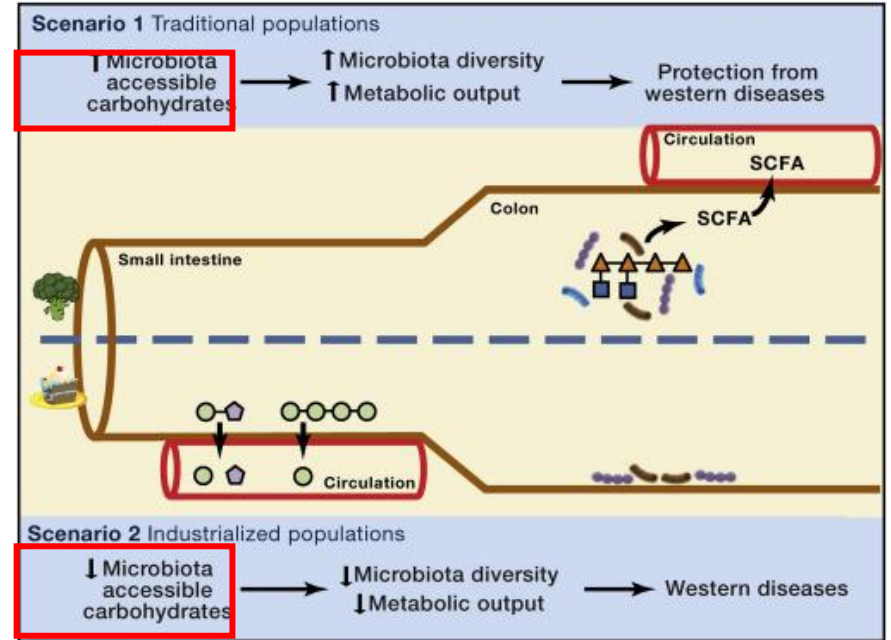
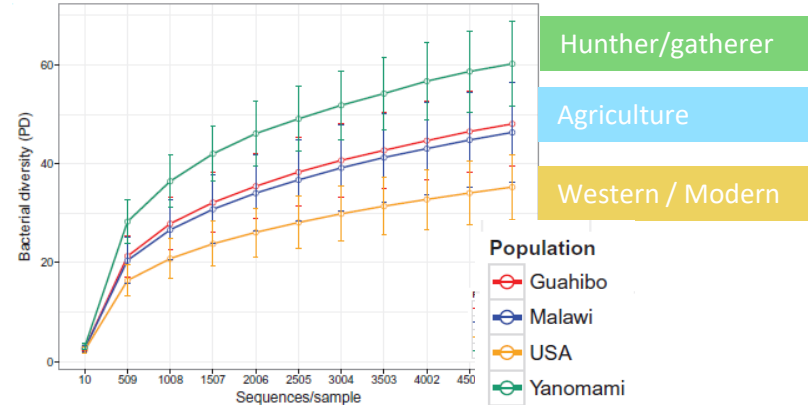
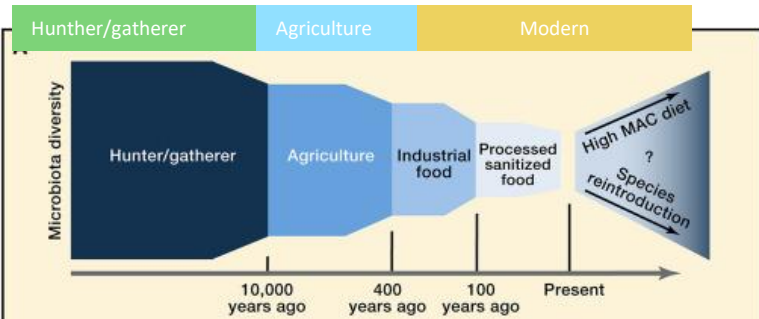
Danone Nutricia Research

Palaiseau

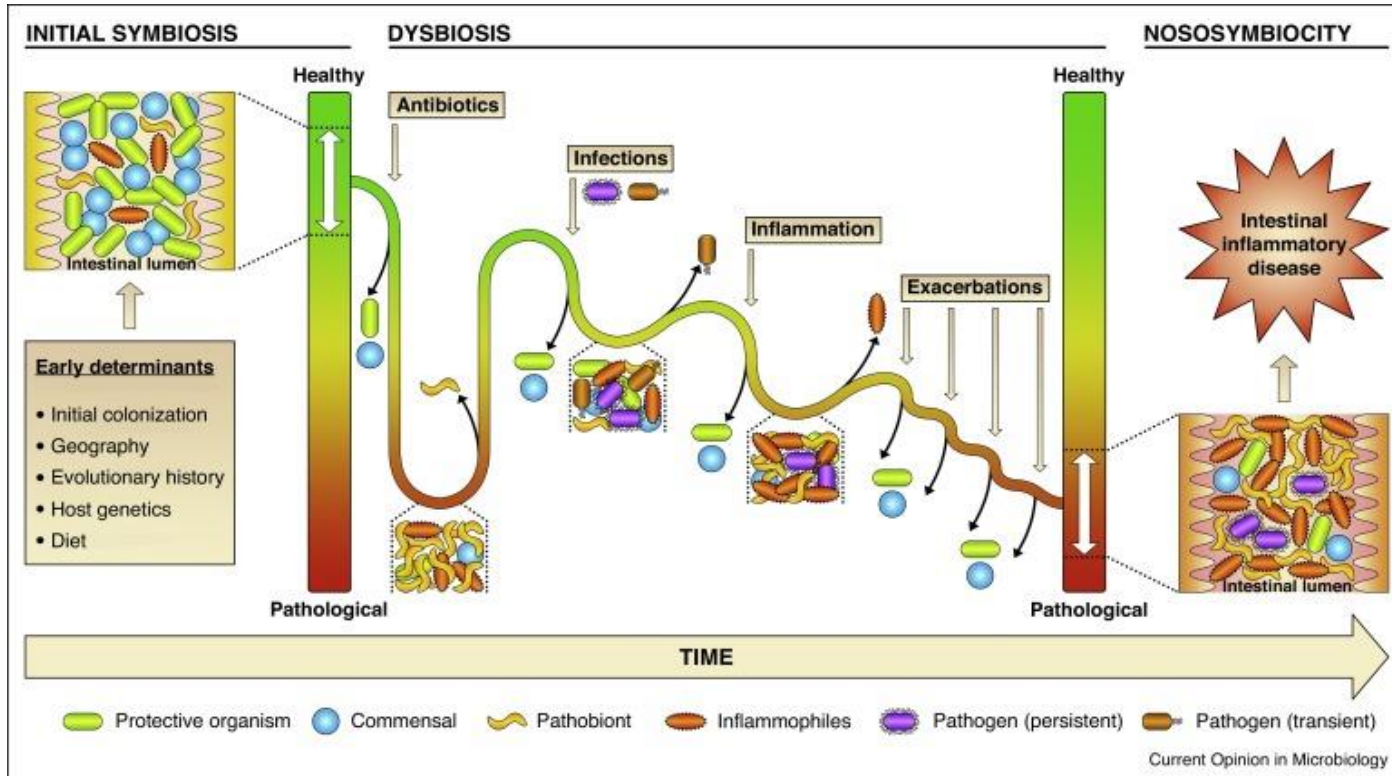
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# Human diet has drastically been reduced in fiber over last decades



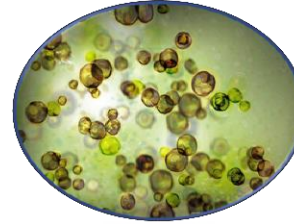
# Host- microbe interactions: for better and for worse



# Analogy with a current environmental issue : bleaching great barrier reef



Change in environmental conditions



Loss of symbiosis with Zooxanthella

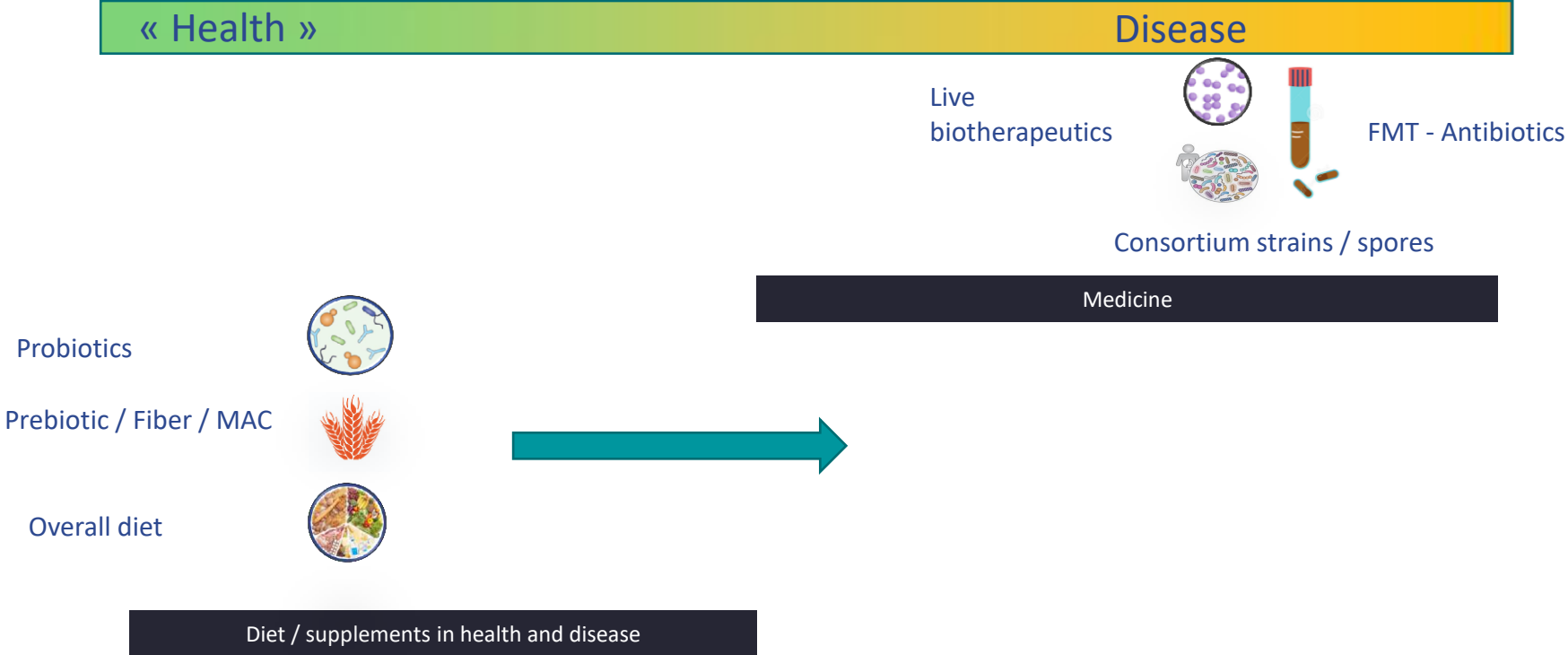


Bloom of predator *Acanthaster planci*



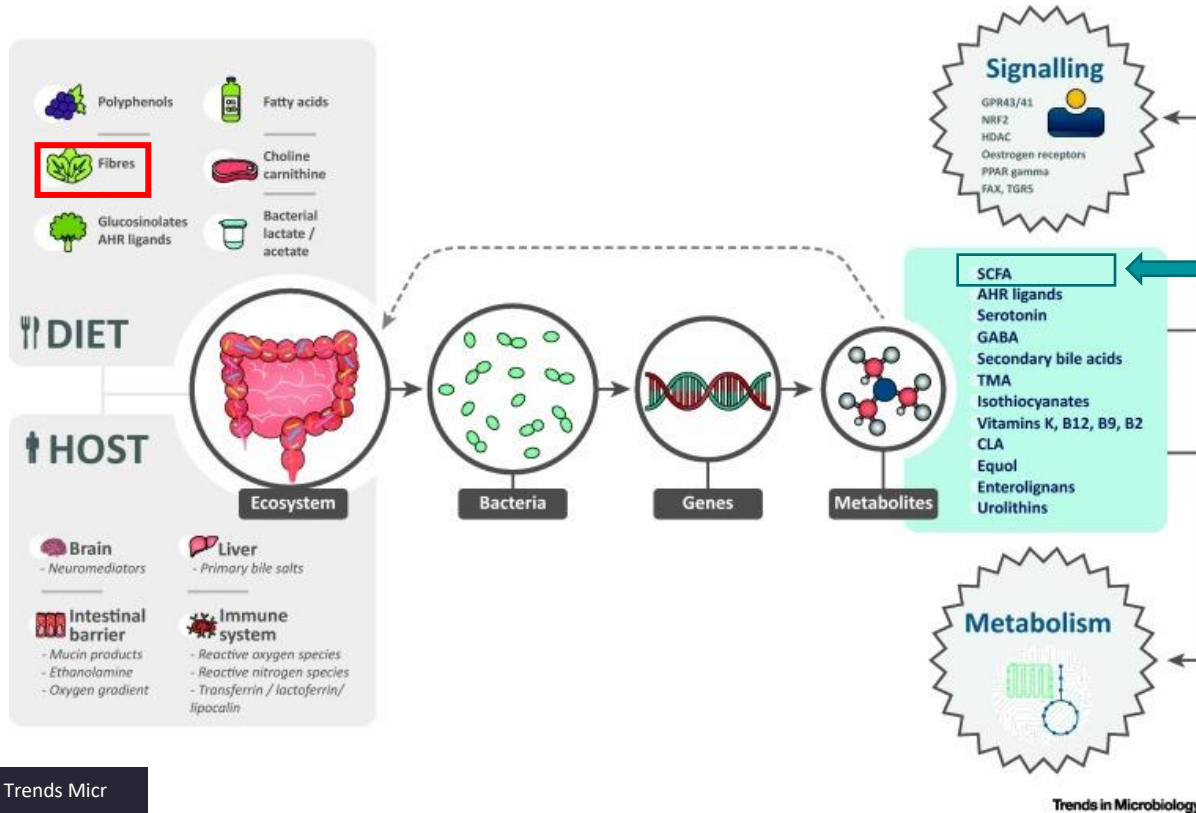
Awareness and some solution are currently being tested to slow down coral reefs bleaching

# Harnessing the plasticity of microbiota for human health





# Diet is a source of bioactives for host interaction





Targeted approaches to improve gut microbiota functioning

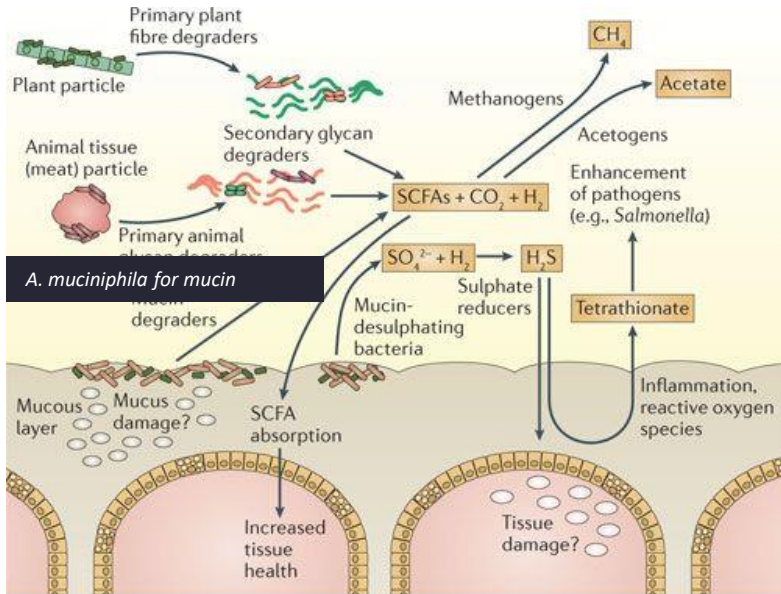
# Targeted approaches to improve microbiota functioning

- Optimisation of metabolism of dietary fibers by LAB / Bifidobacteria
- Identification of nutrients that fill needs of butyrate producers

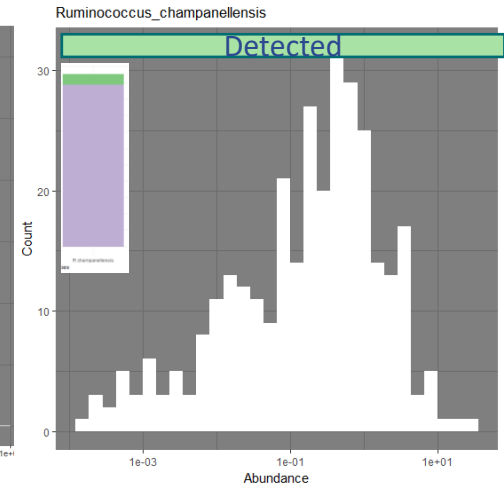
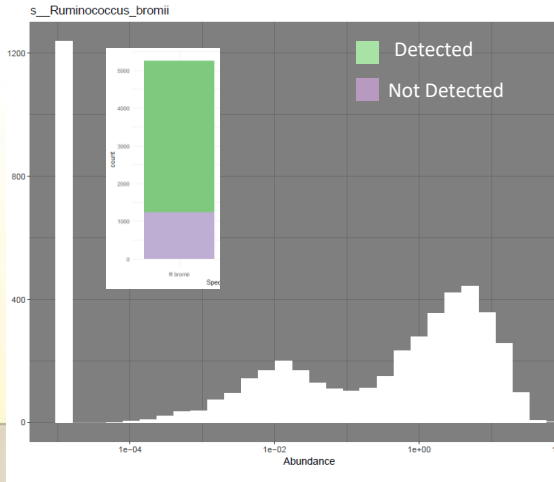


# Some keystone bacteria are dedicated to fibers

*R. bromii* – R Starch  
*R. champanellensis* - Cellulose



Nature Reviews | Microbiology

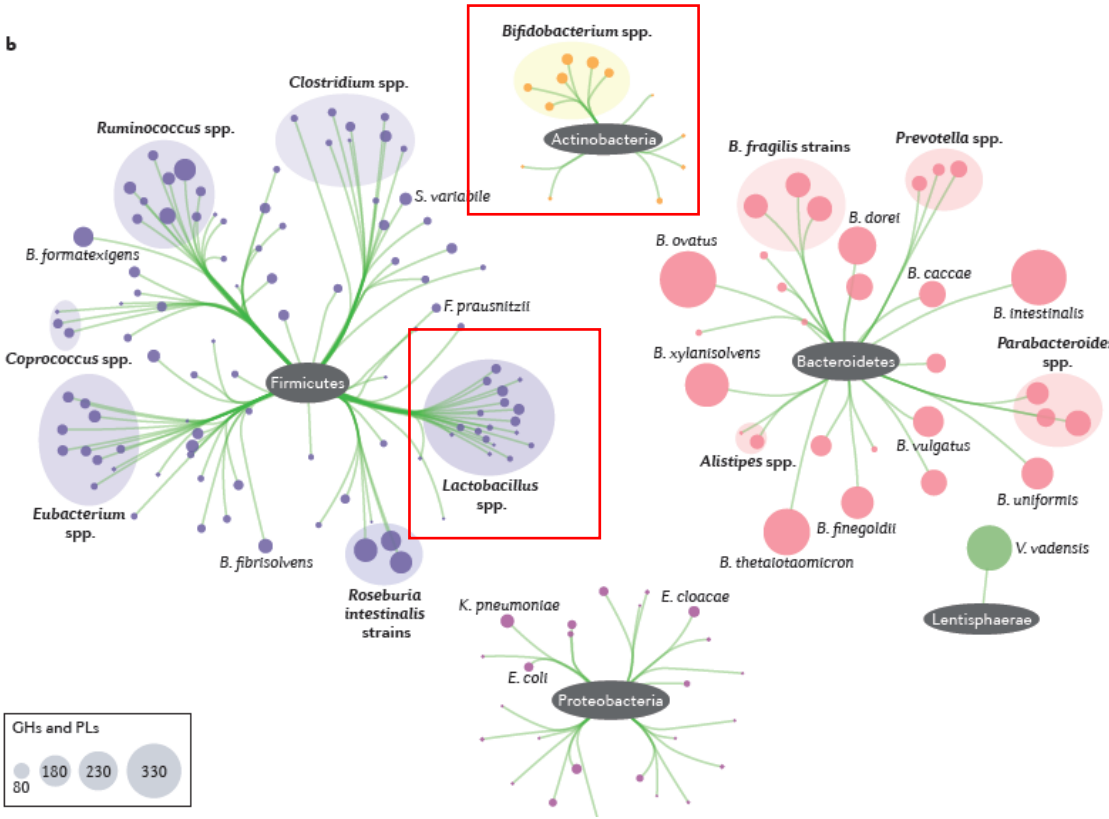


Variable prevalence / abundance in 5200 human fecal metagenomes (healthy + disease)

# LAB and Bifidobacteria have glycan-degrading repertoire

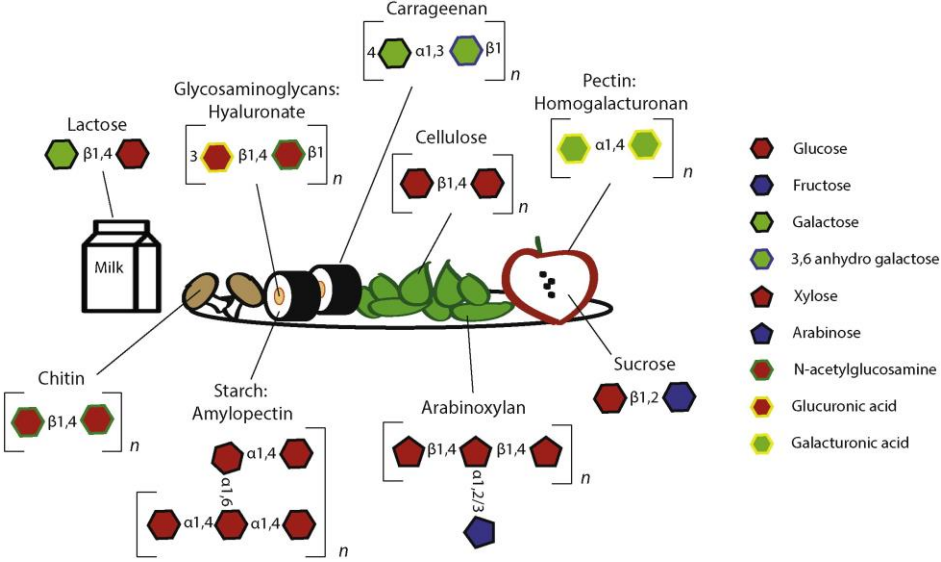
In search of their diversity

b



Our internal collection has > 1800 strains – Source of metabolic activity

# Dietary carbohydrates metabolism require wide range of enzymes



Major polysaccharides  
 Cellulose  
 Xylane  
 pectin

Heteropolysaccharides  
 Arabinogalactan  
 Galactomannane  
 Xyloglucan

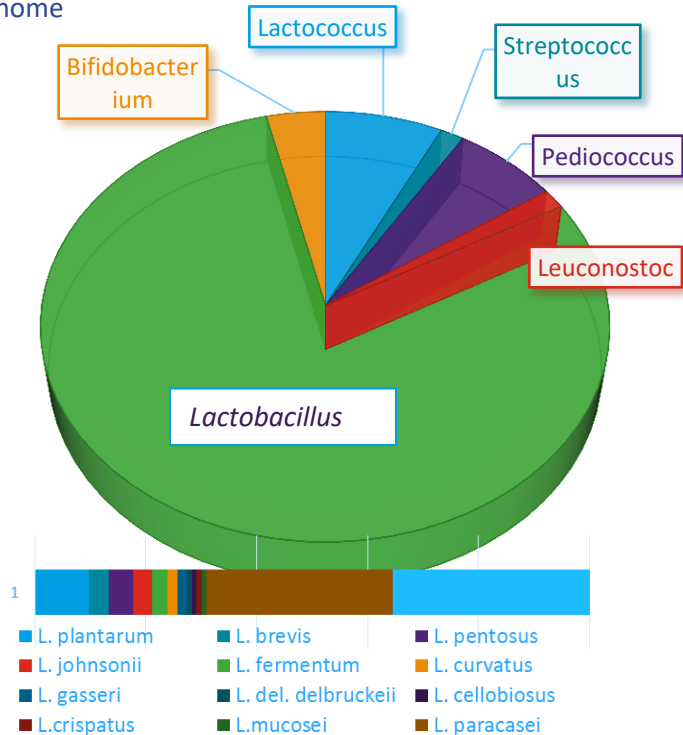
Amylopectin  
 Resistant Starch

Mix-linkage polysaccharides  
 Laminarin  
 Lichenan  
 B-glucan

Select mix of lactic acid bacteria and bifidobacteria strains degrading dietary fibers and producing lactate and acetate -> Enhance SCFA

# Identification of a bacterial consortium able to grow on dietary polysaccharides

142 strains –  
Genome



10 transferts- every 3.5 days in  
chemically defined medium



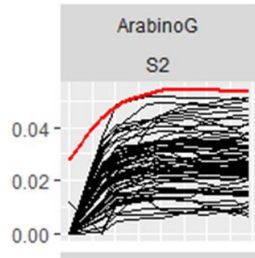
Growth + substrate degradation  
Strain tracking using metagenomic sequencing (de novo catalogue)



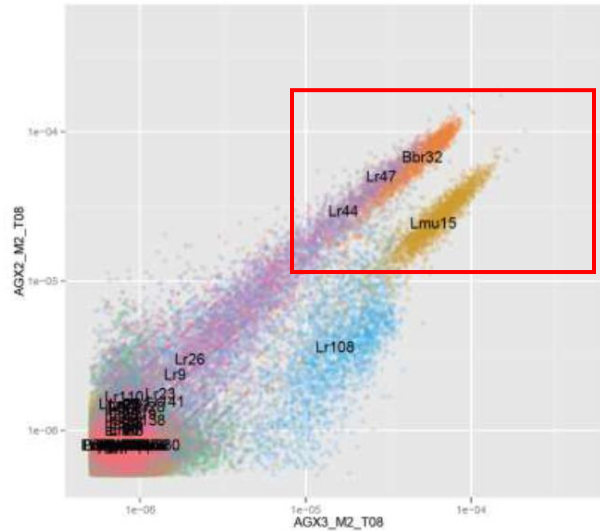
# A bacterial consortium is able to grow on heteropolysaccharides mix

## Heteropolysaccharides

Arabinogalactan  
Galactomannane  
Xyloglucan



No growth for individual  
strains



Final enriched culture of AXG

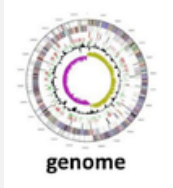
*L. mucosae*, *B. breve* and 2 strains of *L. rhamnosus*

- Done on several fibers mix (15 substrates) -> different strains and CAZy enriched depending on substrate
- Proof of concept to be tested in gut models and human

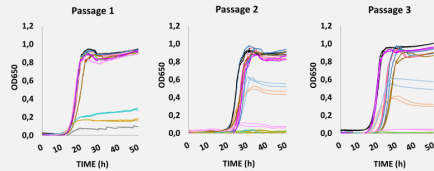
# Targeted approaches to improve microbiota functioning

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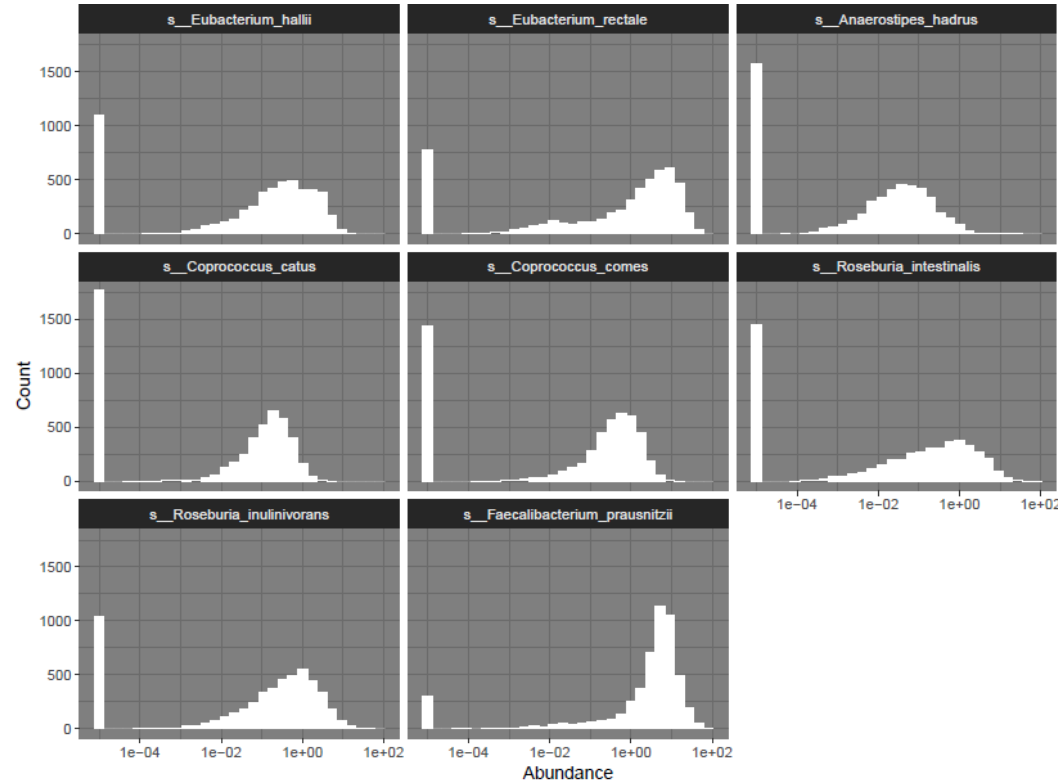
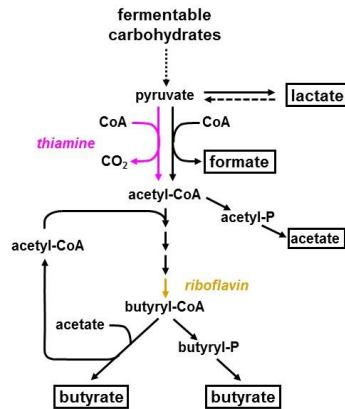
# Prediction of vitamin auxotrophy in butyrate producers



+



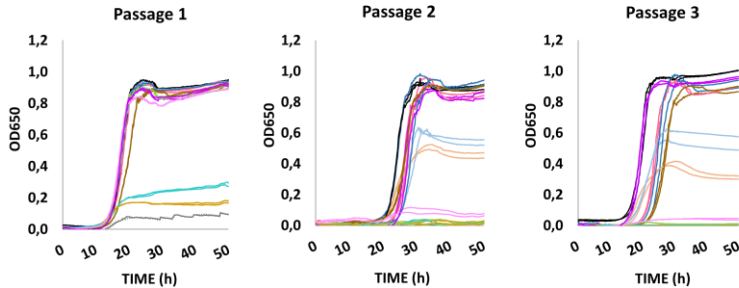
Genomic predictions of *In vitro* growth in chemically defined medium without vitamin precursor



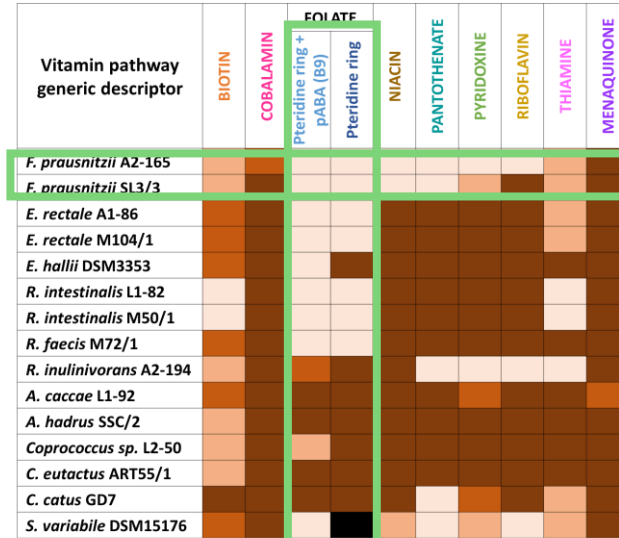
# Butyrate producers exhibit variability in vitamins needs



Each strain grown in triplicate for 3 passages in Chemically Defined Medium for each vitamin



*F. prausnitzii* and *R. inulinivorans* are unable to grow without several vitamins

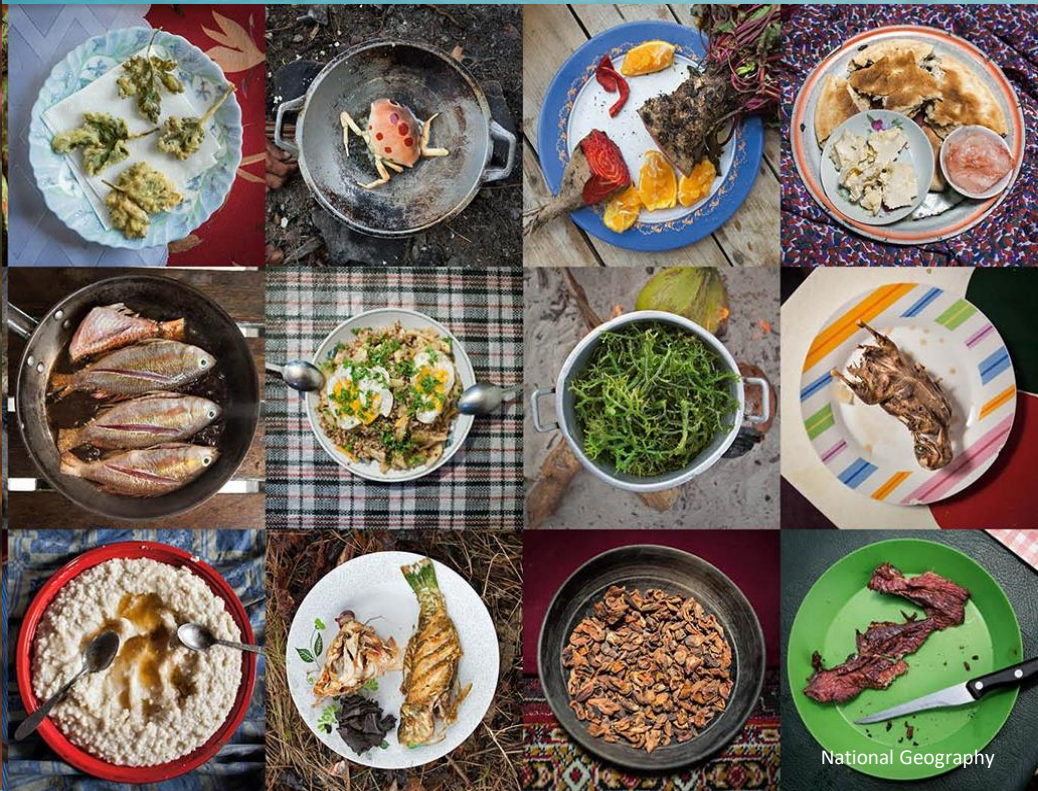


Percentage of growth in relation to the positive control with all vitamins:

- Dark Brown: 100 – 90 %
- Light Brown: < 90 – 50 %
- Medium Brown: < 50 – 10 %
- White: < 10 %
- Black: Non conclusive

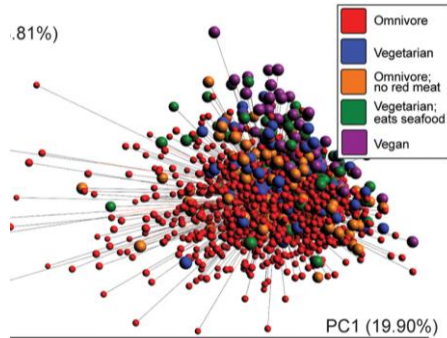
Figure 4. Heat map of vitamin biosynthesis based on *in vitro* growth experiments.



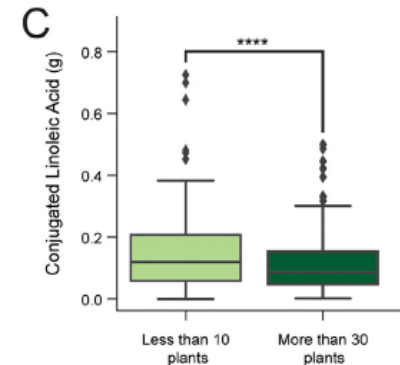
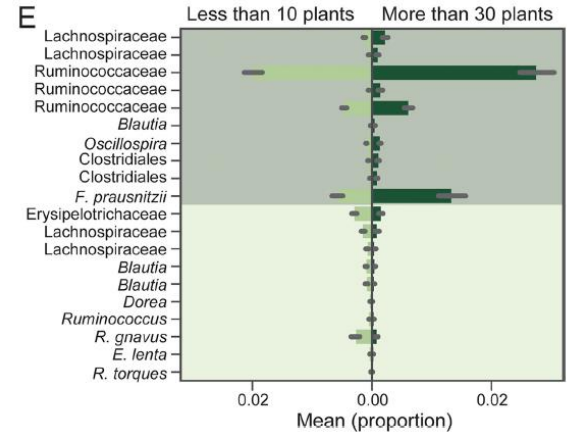


# Exploration of new diet -microbiota associations in human

# High resolution of microbiota – diet association is needed



American Gut database  
1,596 individuals



Within same population, no major difference between dietary habits using 16S

- **Increase resolution of microbiota**  
Metabolomic
- **Increase resolution of Diet**  
Number of plants

# Diet information is diverse



Tradition



Type of diet –  
(Omnivorous, vegan, vegetarian ...)  
Diet score

Food categories  
(Dairy, Fruit, Vegetables...)  
Food groups  
(Yogurt, Brocoli , Apples ...)



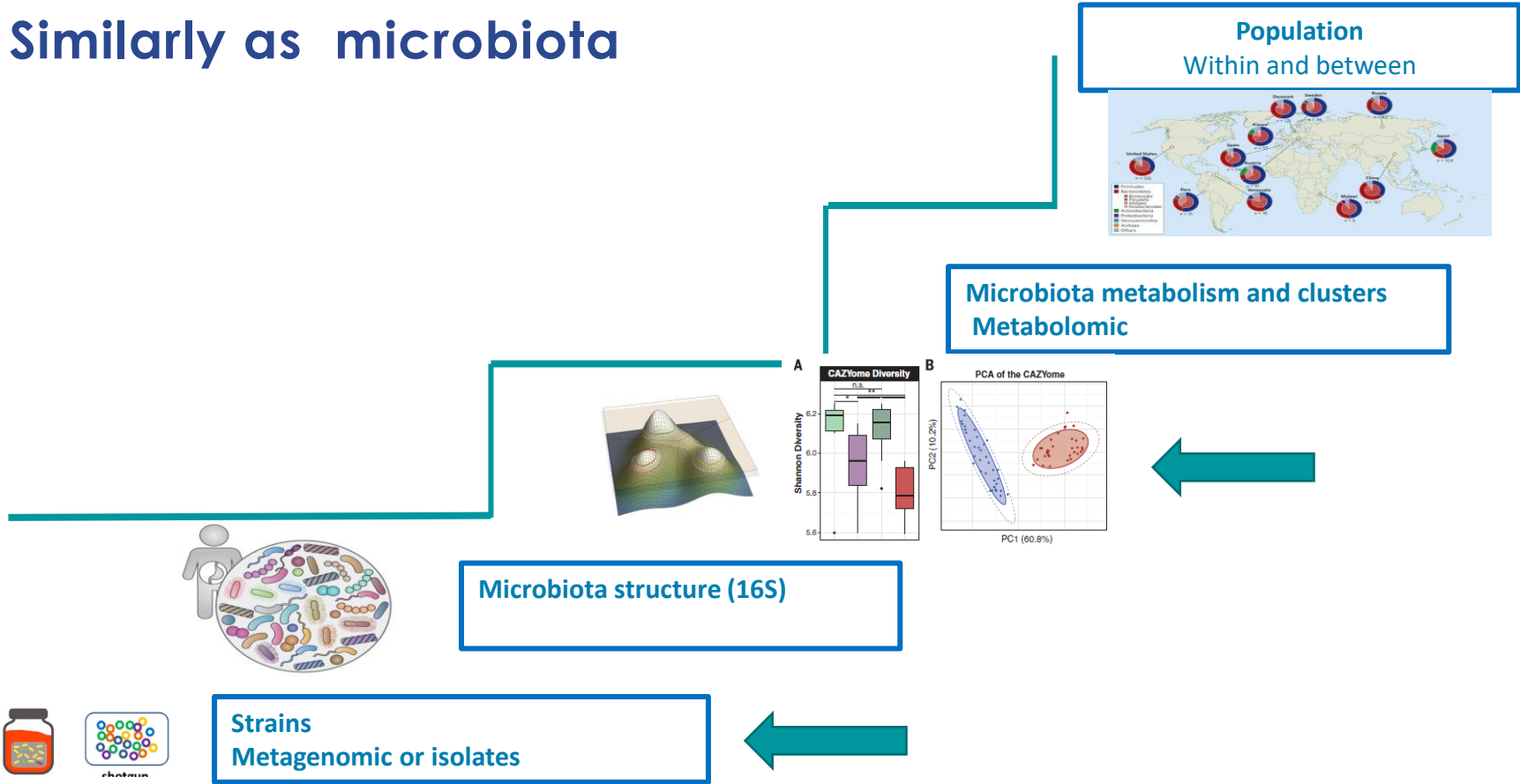
Micronutrient and macronutriments  
(Calcium, vitamins ...)



© Dan Stock Photo

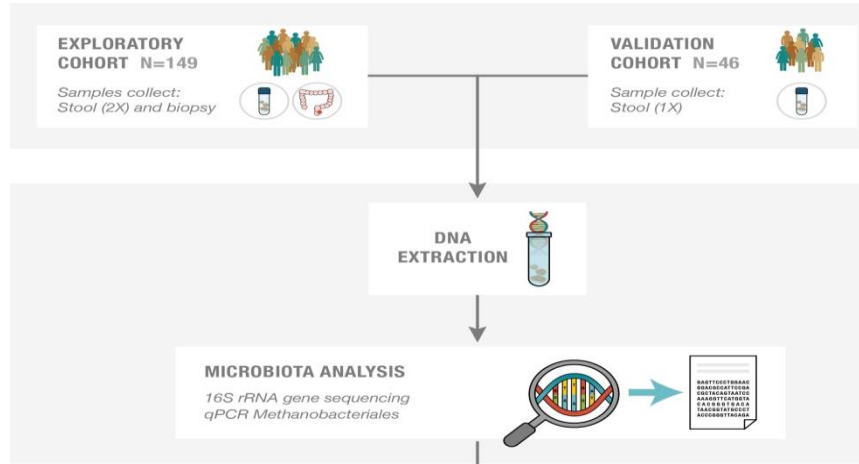


# Similarly as microbiota





# Well phenotyped cohort with high resolution microbiota and diet

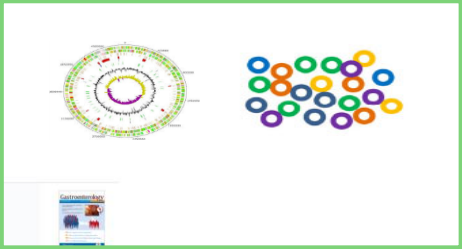


## 16S sequencing

```

OTU-001 GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
OTU-002 GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
OTU-003 GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
          GGTAAATCGGAGGATTC AAG...
    
```

## Metagenomic sequencing



## Diet - Clinical data and symptoms

**4-day food recall**

**HEALTH FORM**

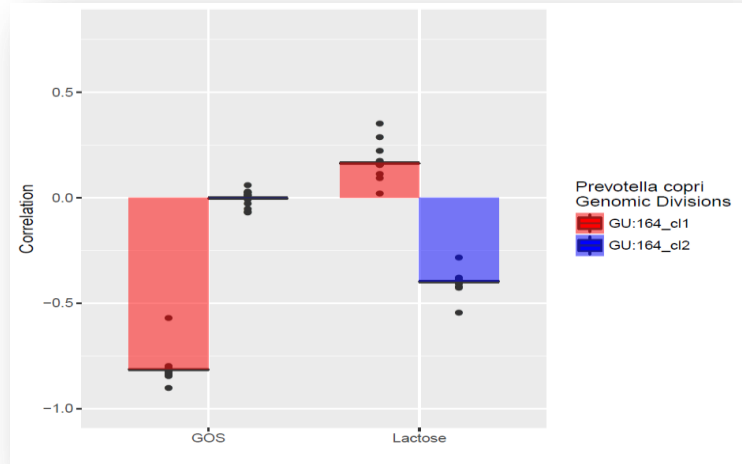
Oro-anal transit time, psychological and gastrointestinal symptom severity

Gastroenterology  
Available online 7 October 2016  
In Press, Accepted Manuscript — Note to users

Identification of an Intestinal Microbiota Signature Associated With Severity of Irritable Bowel Syndrome  
Julien Tap<sup>1,2,\*</sup>, Muriel Derrien<sup>1</sup>, Hans Törnblom<sup>3,4</sup>, Rémi Brazzelles<sup>1</sup>, Stéphanie Cools-Portier<sup>1</sup>, Joël Doré<sup>5</sup>, Stine Storsrud<sup>6</sup>, Boris Le Neve<sup>1</sup>, Lena Ohman<sup>1,5,6,8</sup>, Magnus Simén<sup>1,4,7</sup>

# Prevotella copri “subsp” associates differently with Fodmap

Example: *Prevotella copri* infraspecies



*Prevotella copri* cl1 negatively associated with GOS intake

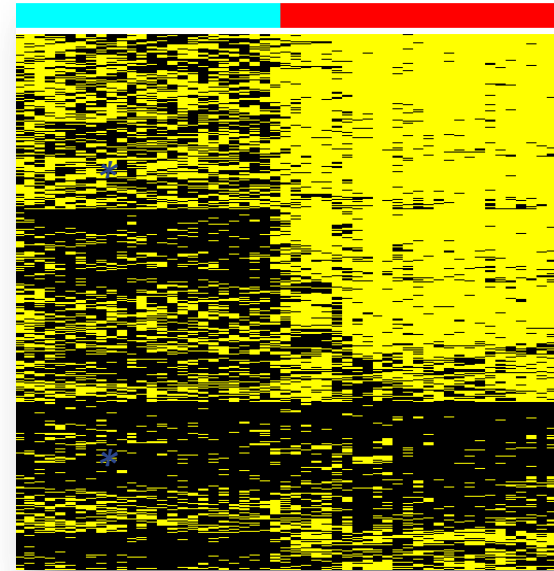
*Prevotella copri* cl2 negatively associated with lactose intake

*Prevotella copri* cl2

Amino acid degradation  
Succinate production

*Prevotella copri* cl1

Glycolyse hydrolase  
Sucrose degradation  
Sulfate reduction

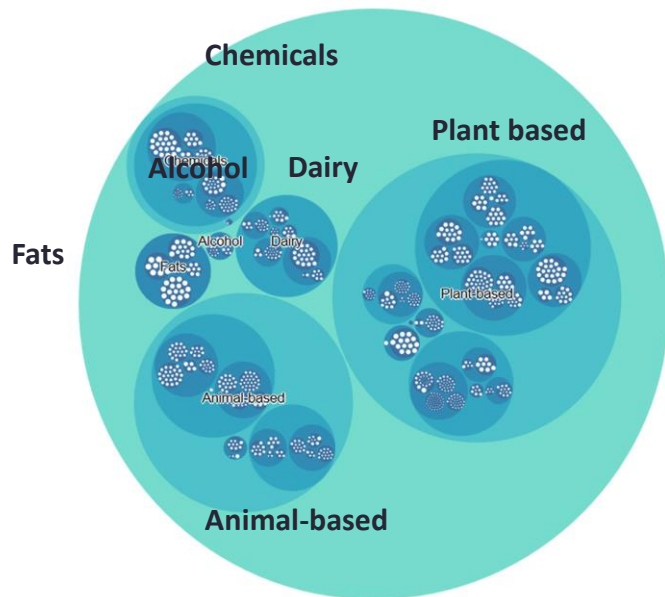


# Metagenomics is associated with food categories

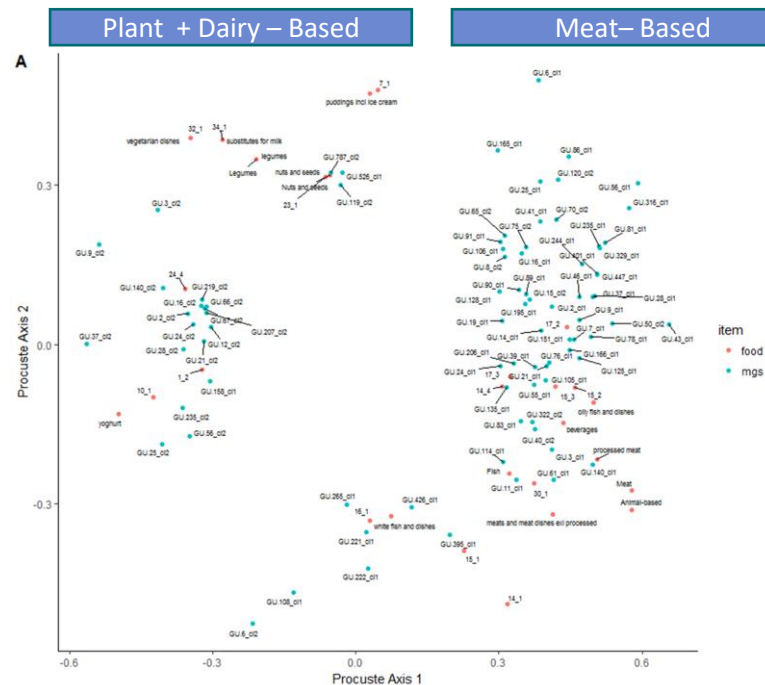
2,091 food items (white circle, Swedish database) clustered by nutrients value

Organised in 5 large food groups

Computed based on macro and micronutrients content

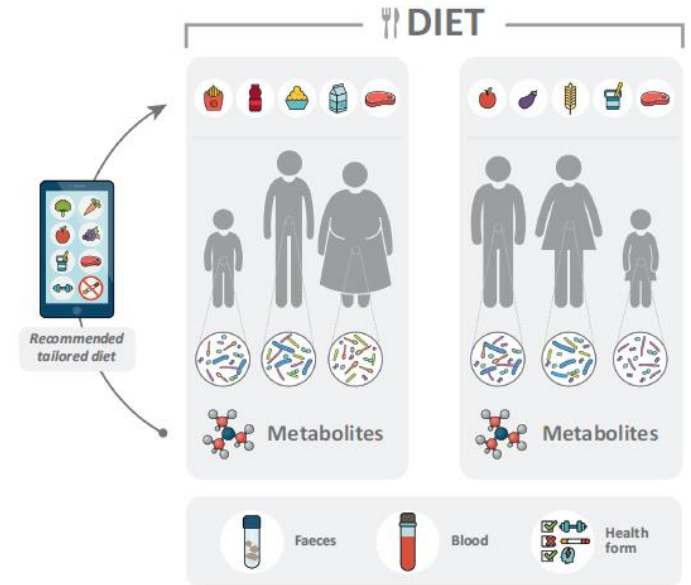


Procrustes analysis between Food and microbiota distance ( $p < 0.001$ ) -



# Conclusions and perspectives

- LAB and Bifidobacteria offer complementary and attractive metabolic function
- Diet offers many opportunities of enriching microbiota function
- Stratification of gut microbiota is an approach to optimise diet recommendation



Trends in Microbiology



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Harry Flint

