The Gut Microbiome in Neurodevelopmental Psychology

A review of the literature

Justine Debelius, PhD
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

WHAT MAKES US HUMAN?

Biologically, not philosophically

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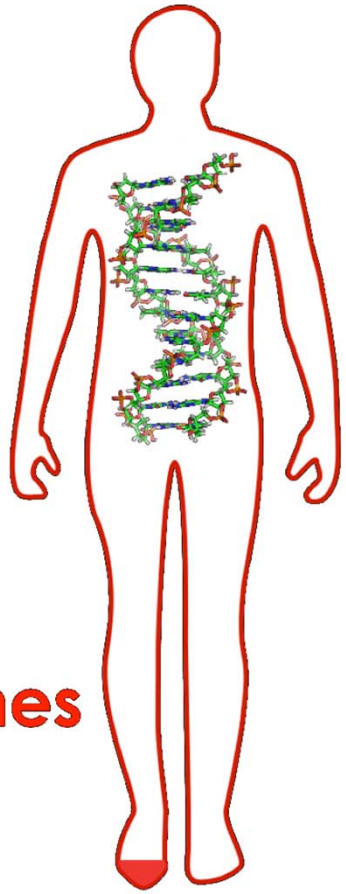

20,000
human genes

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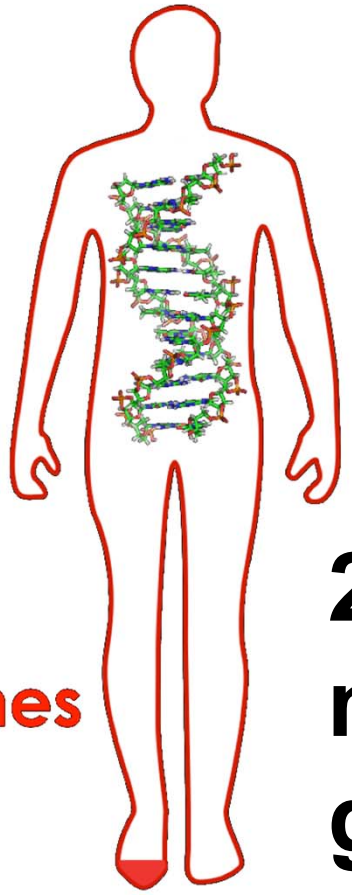
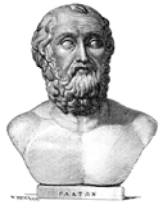
20,000
human genes



2 – 20 million microbial genes



Our microbial communities make us unique

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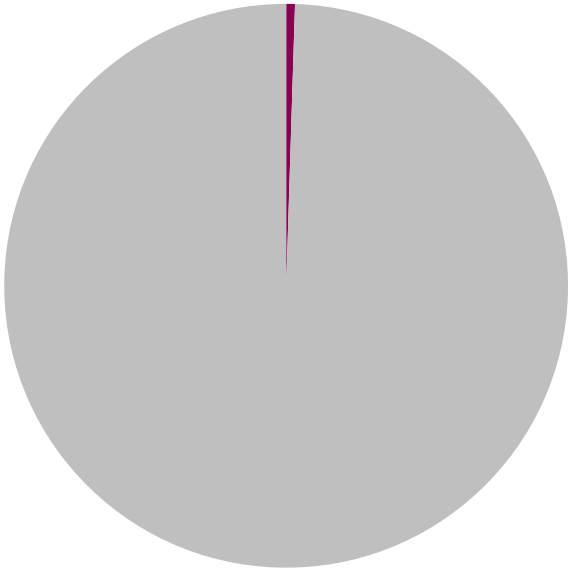
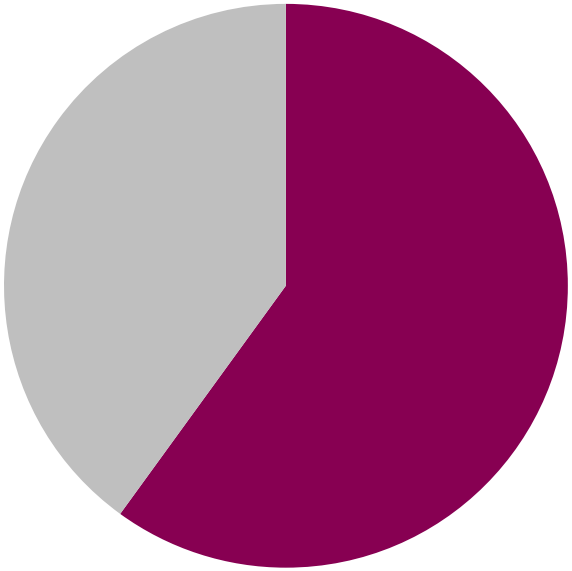
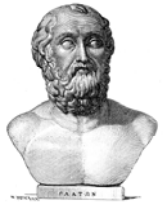
Genes



Microbial Lineages

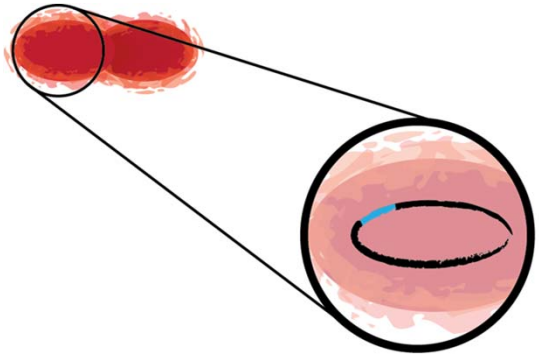


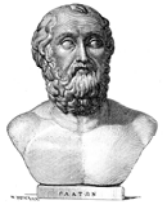


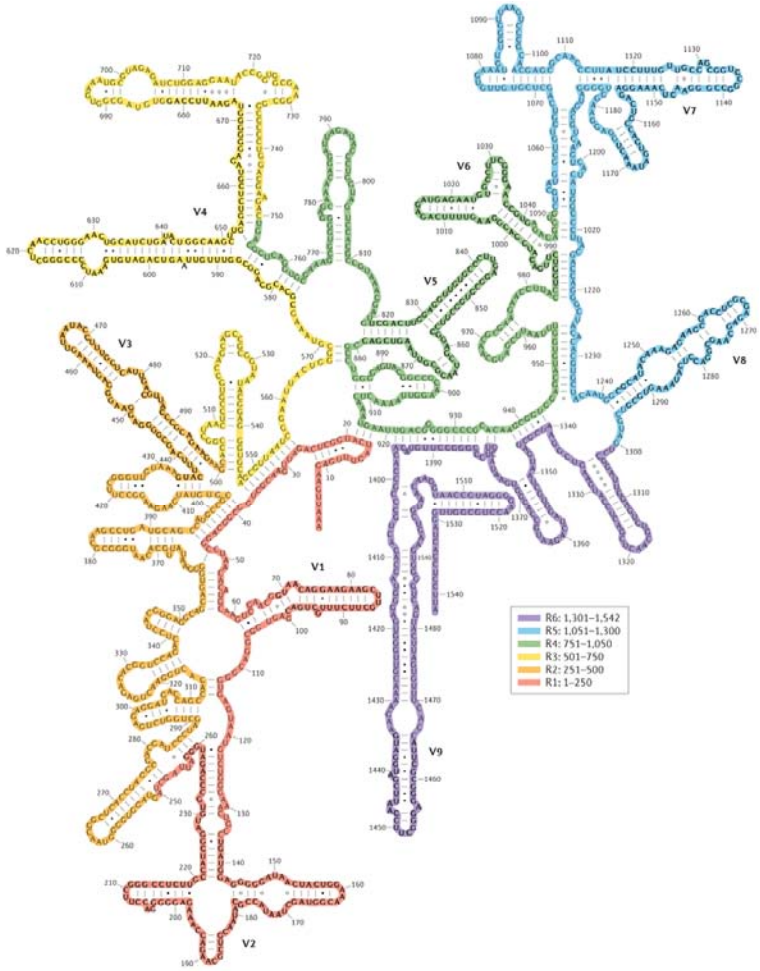
Shared

Unique

Anton et al (2015). *Nature* **526**:68; Turnbaugh (2010). *Nature*. **457**:480

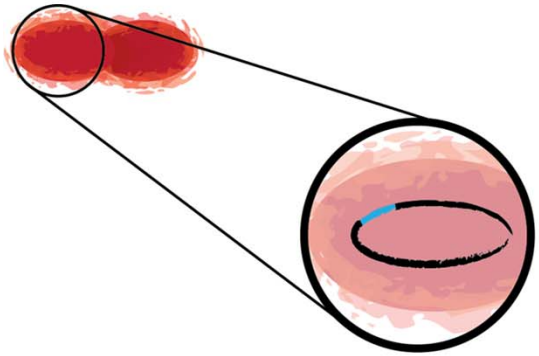


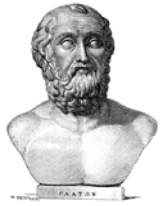


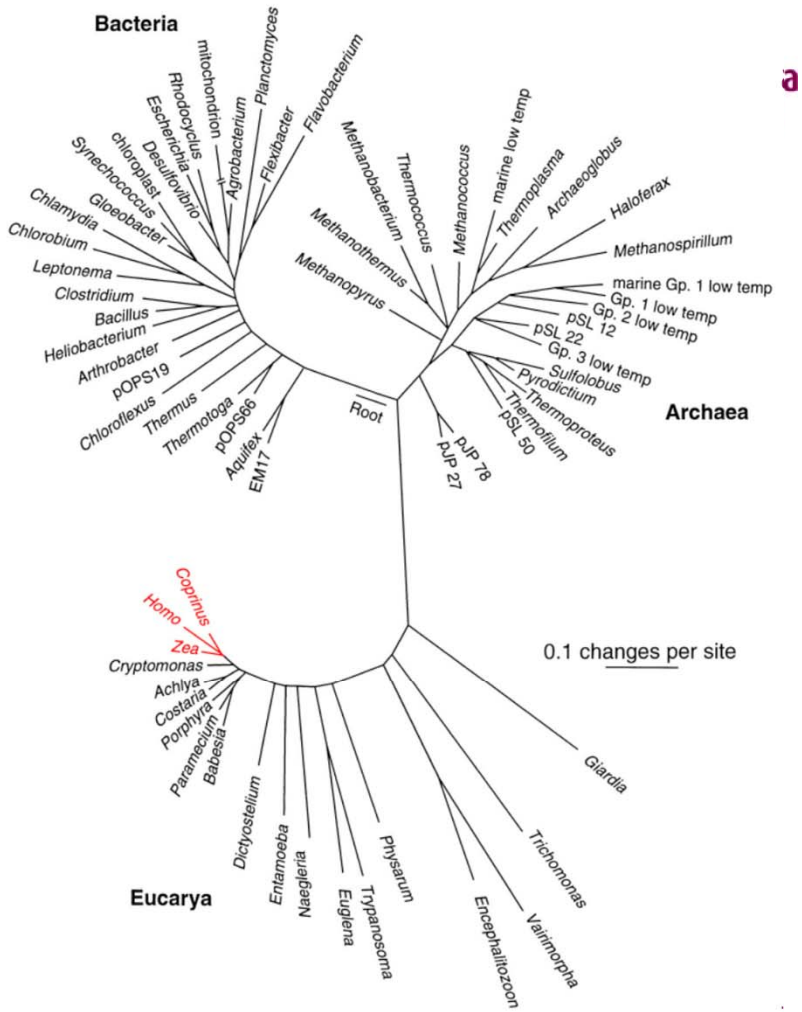


Nature Reviews | Microbiology

Yarza et al (2014) *Nature Reviews*. 12: 635

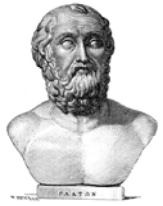






Pace. (2001). *PNAS*. 98: 805-808

You are more related to…

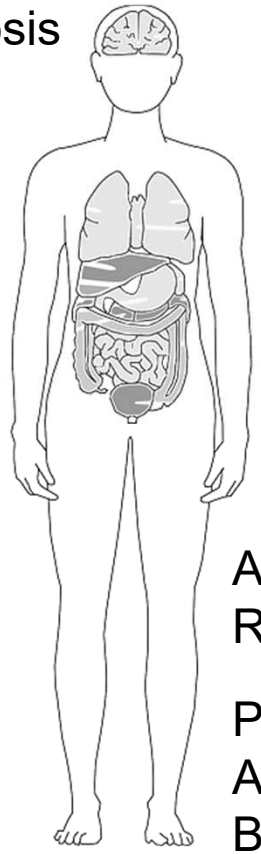


http://www.g4tv.com/attackoftheshow/blog/post/717271/velociraptor-riding-a-shark/

Multiple Sclerosis

Asthma
Allergies
Cystic Fibrosis

Crohn's and Colitis
Celiac disease
Colon Cancer
Gastric Ulcers
Kwashikor
Obesity
Short Bowel Syndrome
Food Allergies

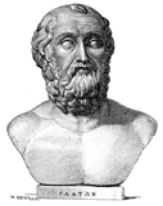


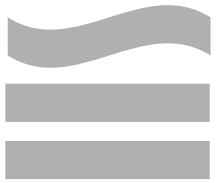
Anorexia Nervosa
Anxiety
Addiction
Autism
Depression
Parkinson's Disease
Schizophrenia

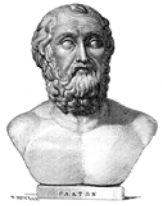
Diabetes
Sex hormone level (in mice)

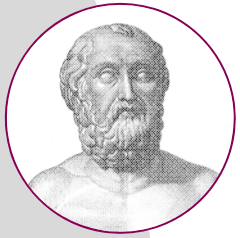
Ankylosing Spondylitis
Rheumatoid Arthritis

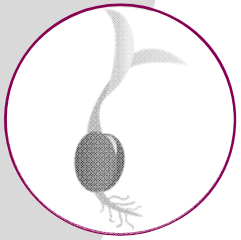
Psoriasis
Atopic Dermatitis
Body Odor











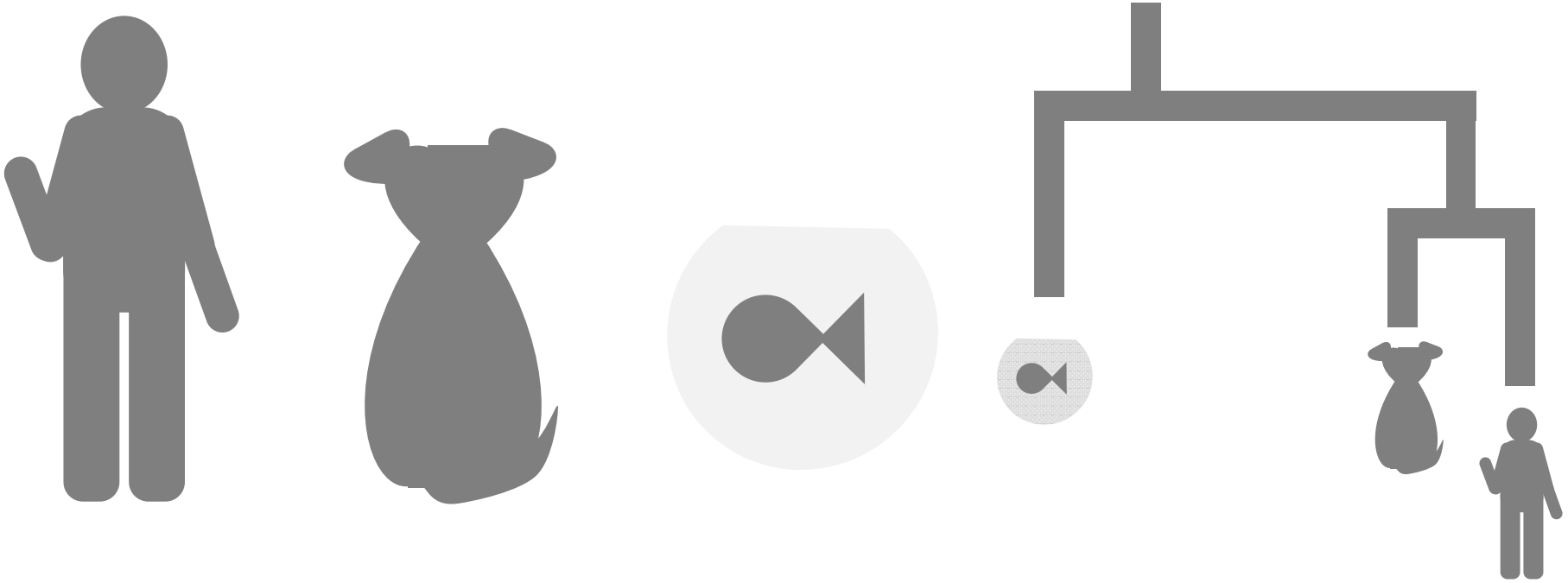
MICROBIAL CARTOGRAPHY

Tools for Exploration

g__Homo

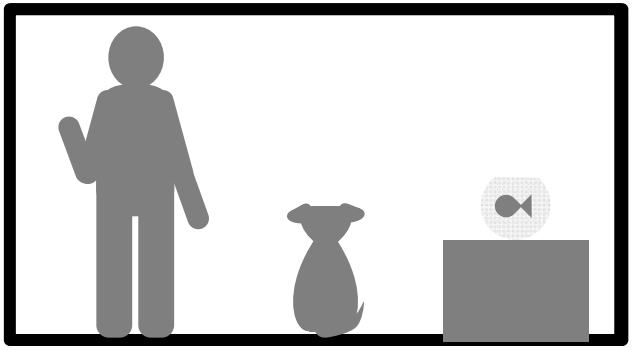
g__Canis

f__Cyprinidae; g__

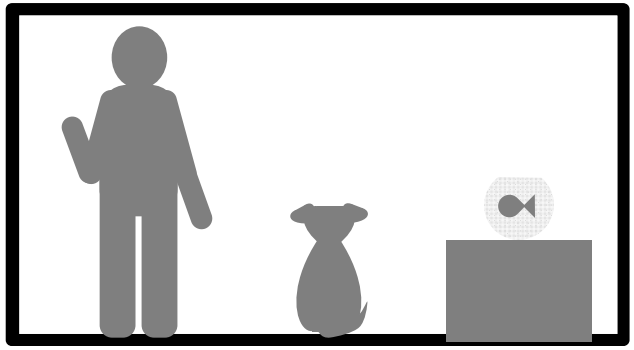


Disorder and culprits

Who ate the shoe?



Who made a mess?



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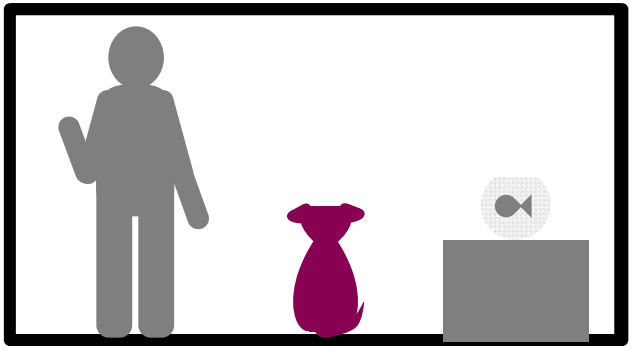

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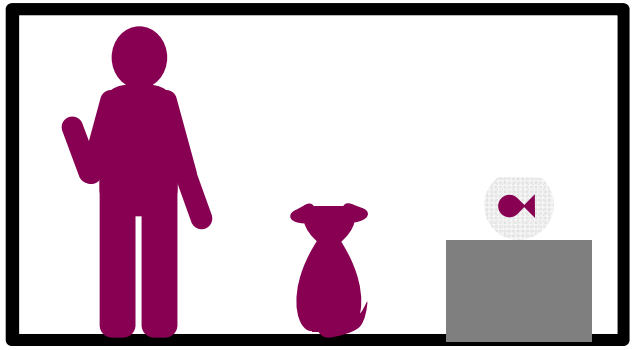


A community perspective in microbial measurements

- **Alpha Diversity**
  - → how may different types of organisms are there in a single microbial community?

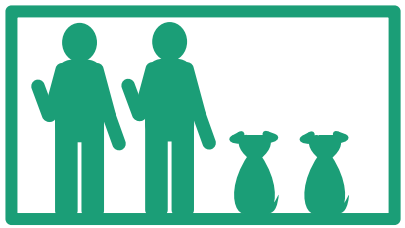
- **Beta Diversity**
  - → How similar (or dissimilar) are two microbial communities?

A community perspective in microbial measurements

- **Alpha Diversity**
  - → how may different types of organisms are there in a single microbial community?

- **Beta Diversity**
  - → How similar (or dissimilar) are two microbial communities?

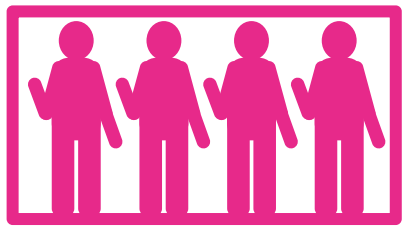
- If there is a difference in alpha and beta diversity,
  What distinguishes the two communities?



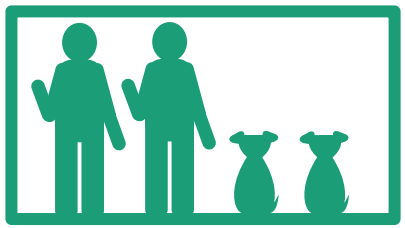
2 humans
2 dogs

3 humans
1 fish

2 humans
1 dog
1 fish



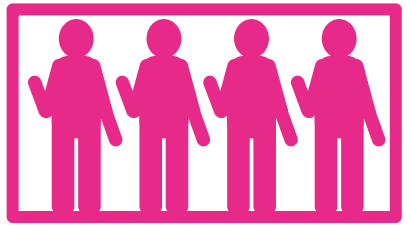
4 humans



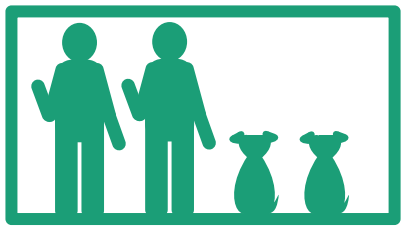
human
dog

human
fish

human
dog
fish



human



human
dog

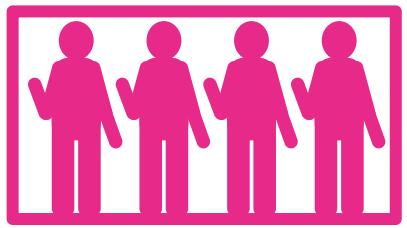
2

human
fish

2

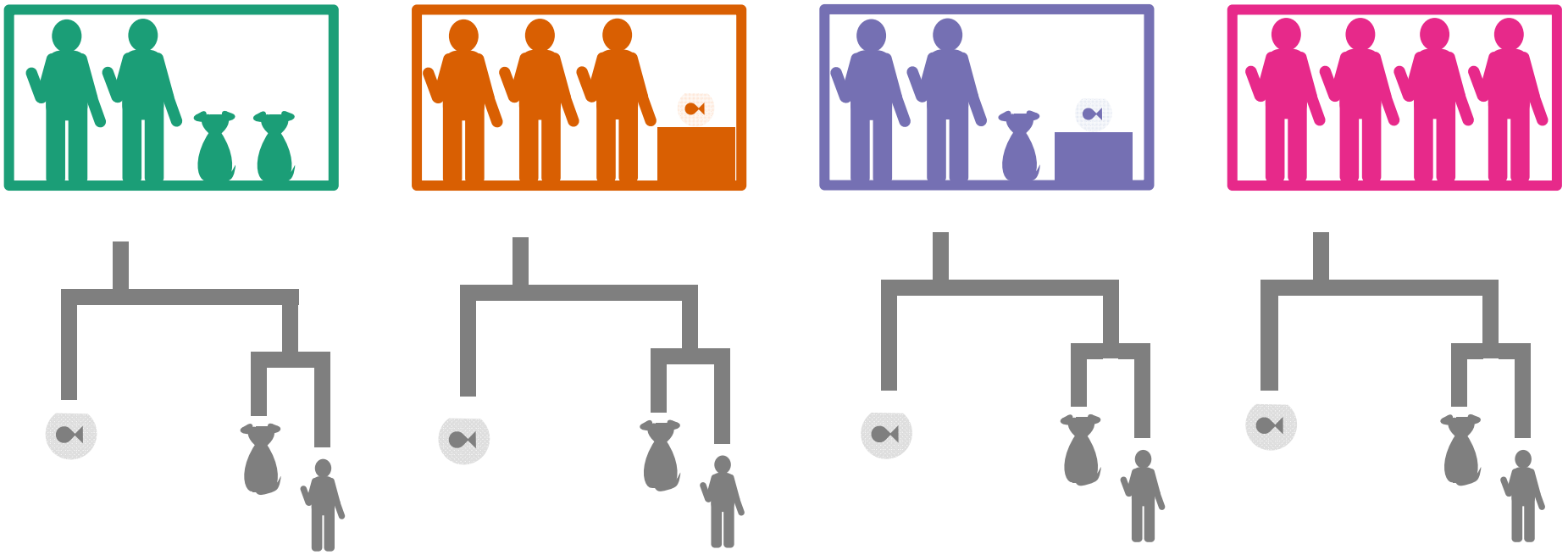
human
dog
fish

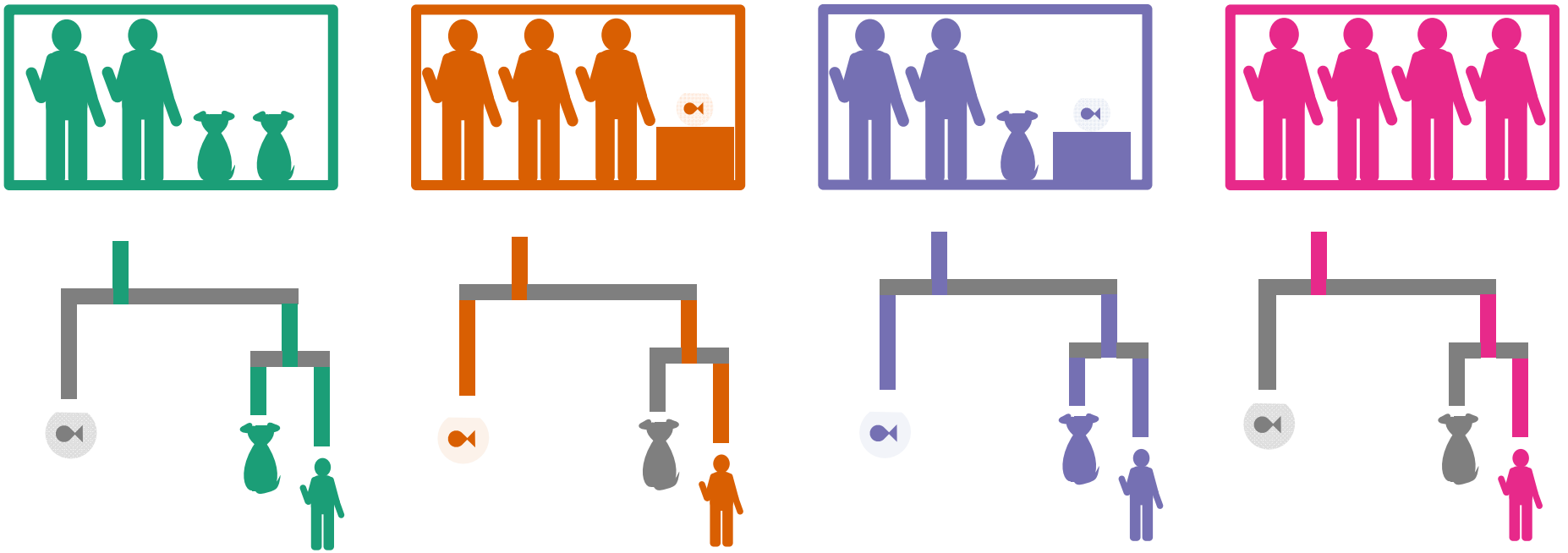
3



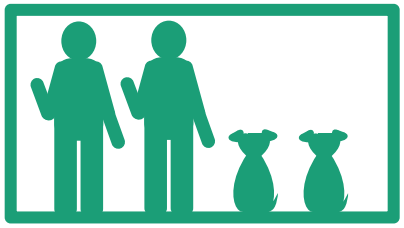
human

1

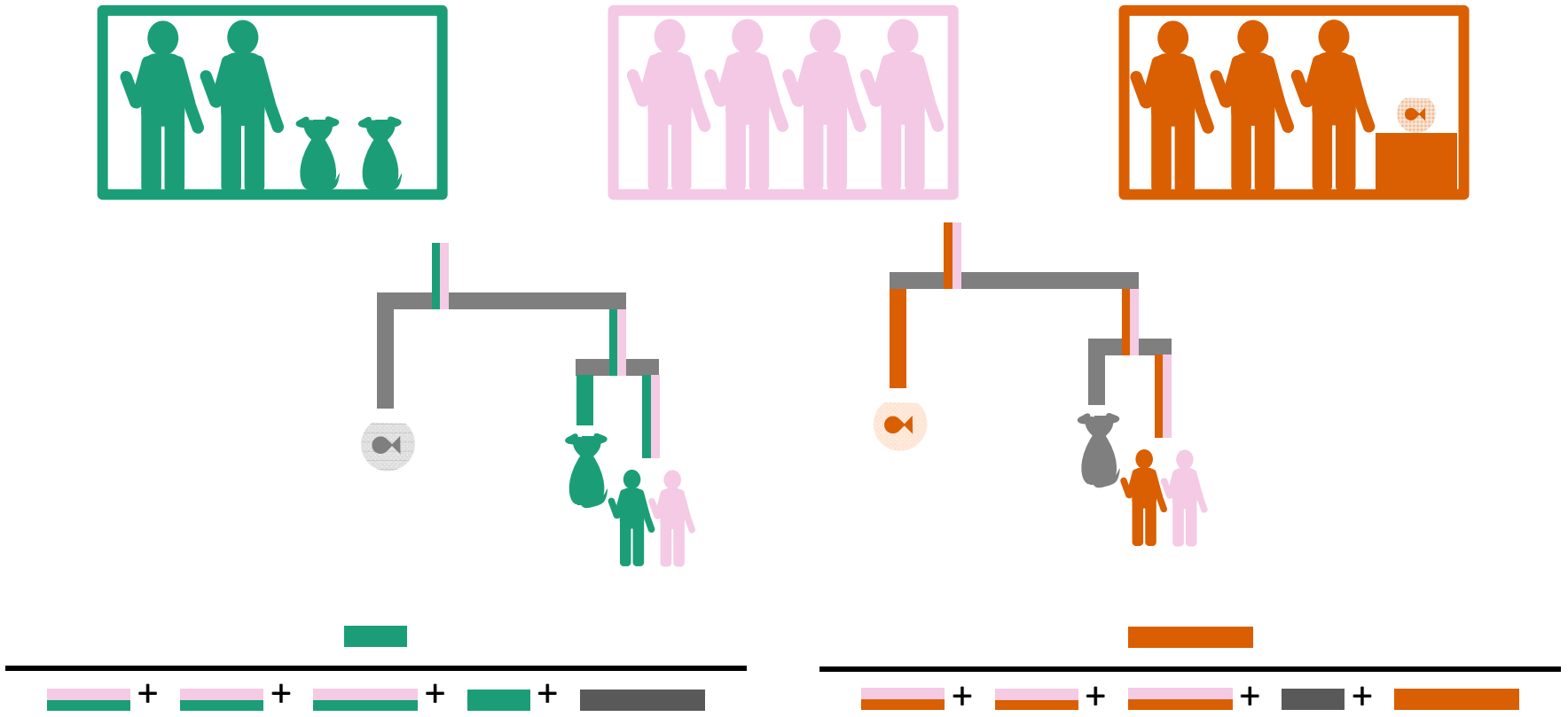




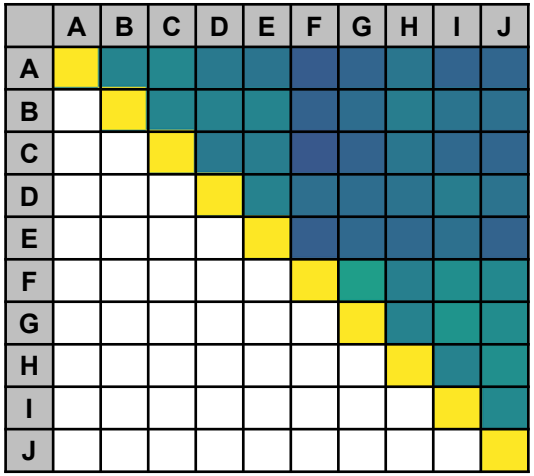
Between Sample (beta) Diversity



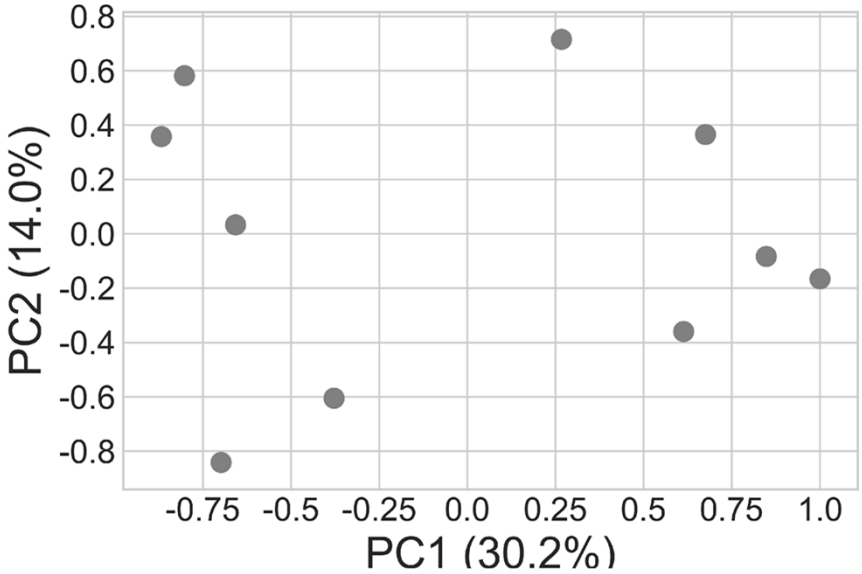
Unweighted UniFrac Distance



Lozupone and Knight (2005). Appl Env Microbol. **71**: 8228



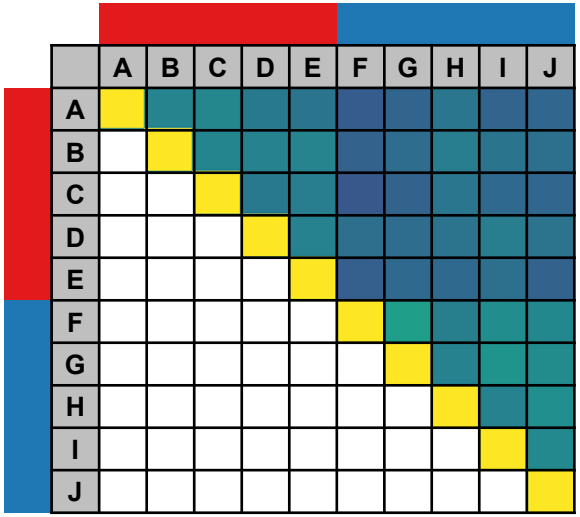
ordination



*Data from Yatsuneno et al (2012). *Nature*

United States

Venezuela



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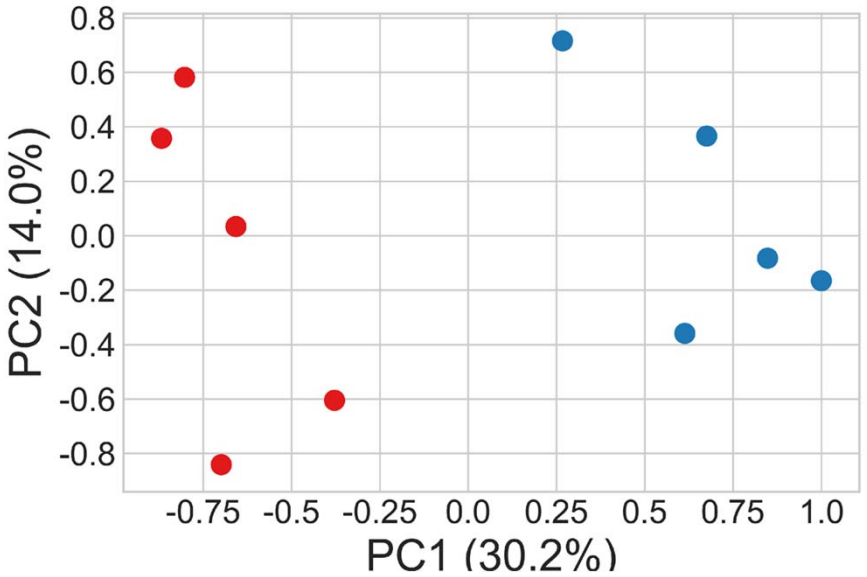

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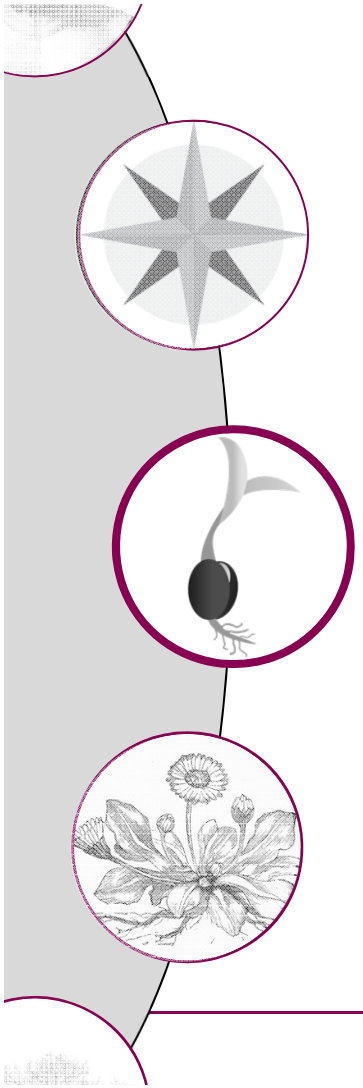


STARTING FROM SCRATCH

How do we seed the microbiome?

Where do we get our microbes?

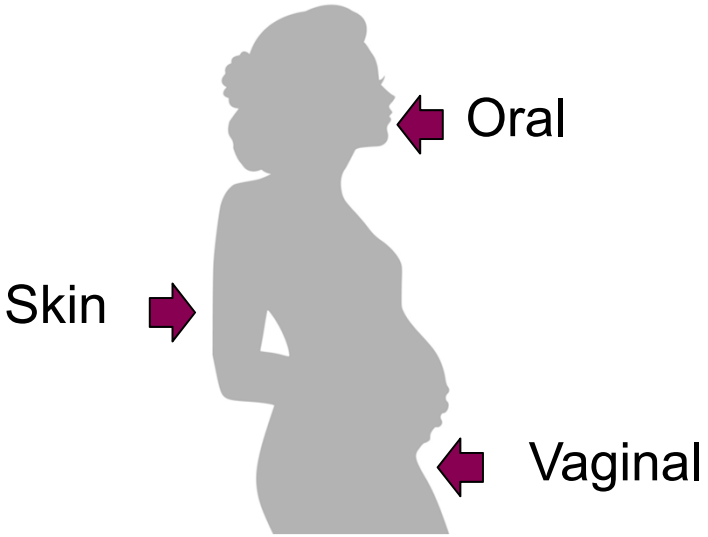
How does delivery method impact the neonatal microbiome?

9 Venezuelan Women

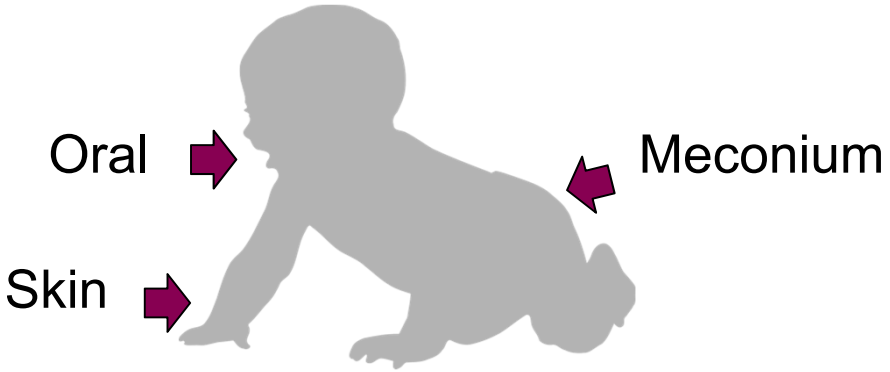
10 Infants

Dominguez-Bello et al. (2010) *PNAS*. 7, 11971-11975

How does delivery method impact the neonatal microbiome?



9 Venezuelan Women
4 Vaginal Deliveries
5 C-sections



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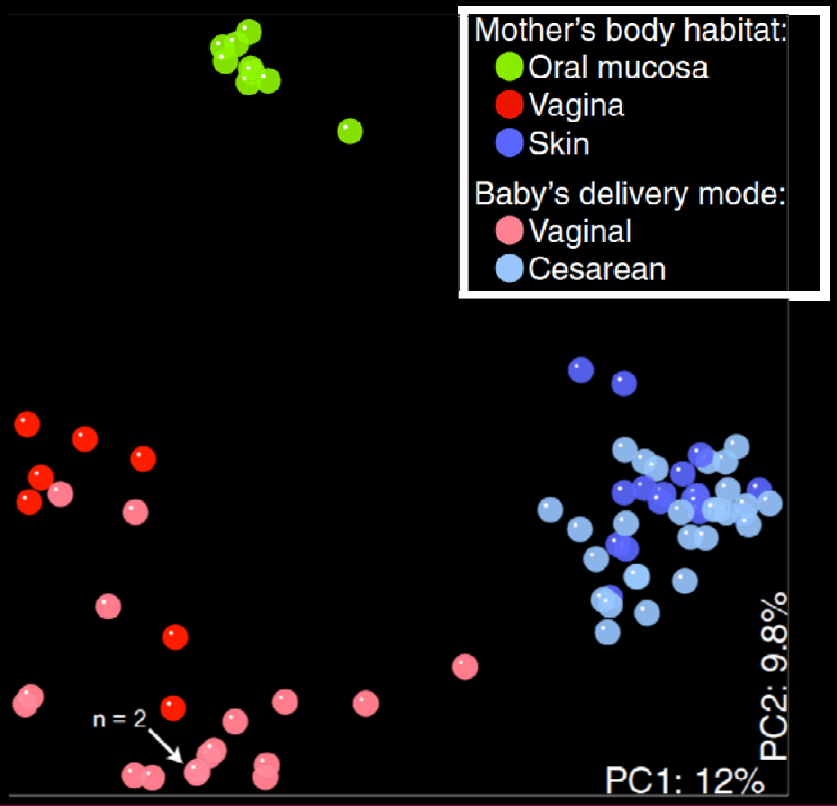


Dominguez-Bello et al. (2010) *PNAS*. 7, 11971-11975

How does delivery method impact the neonatal microbiome?

A baby's microbiome reflects the their delivery mode

Dominguez-Bello et al. (2010) *PNAS*. 7, 11971-11975

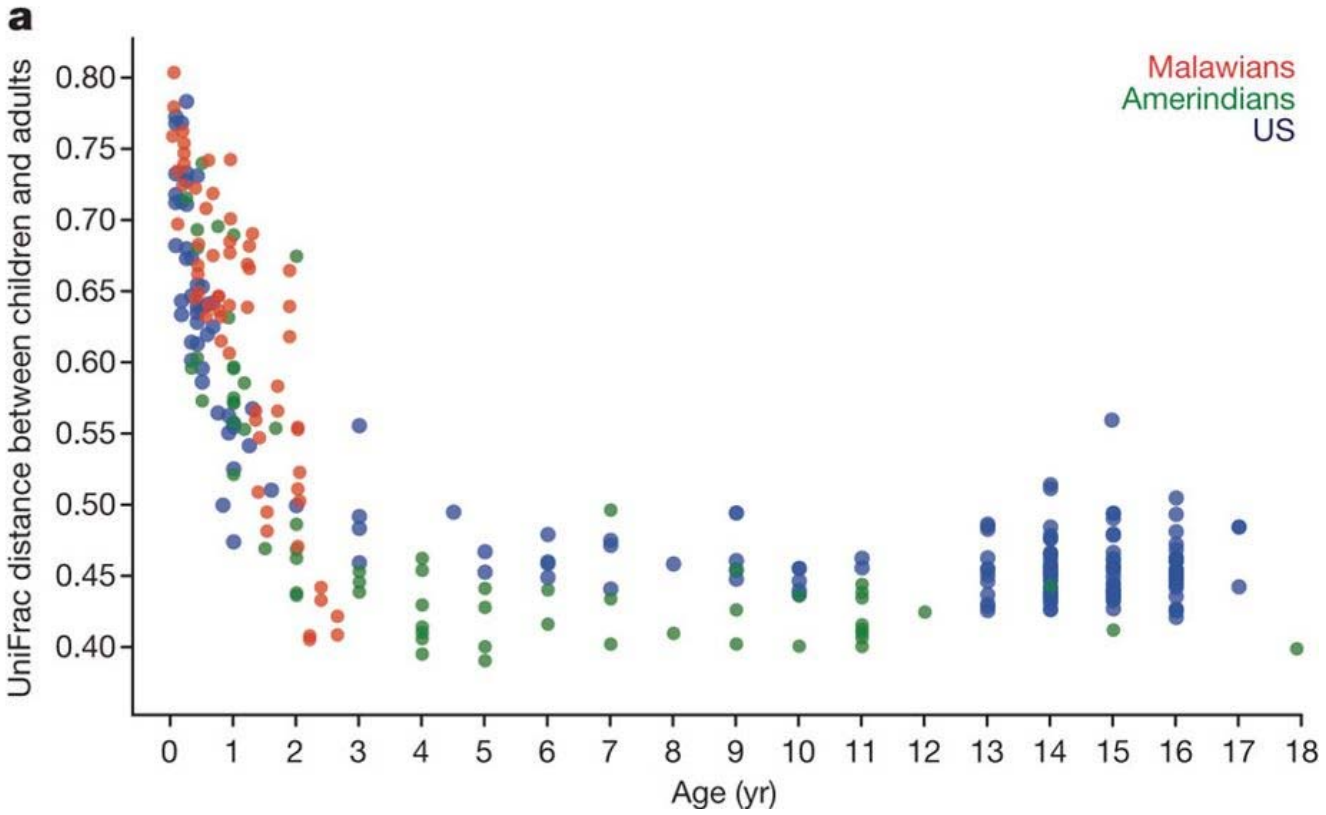
CULTIVATING A MICROBIAL GARDEN

Mary, Mary, Quite Contrary,
How do your microbes grow?

How do our microbes grow with us?

Yatsunenko et al. *Nature*. 2012 486(7402):222-7

A cross-sectional developmental growth



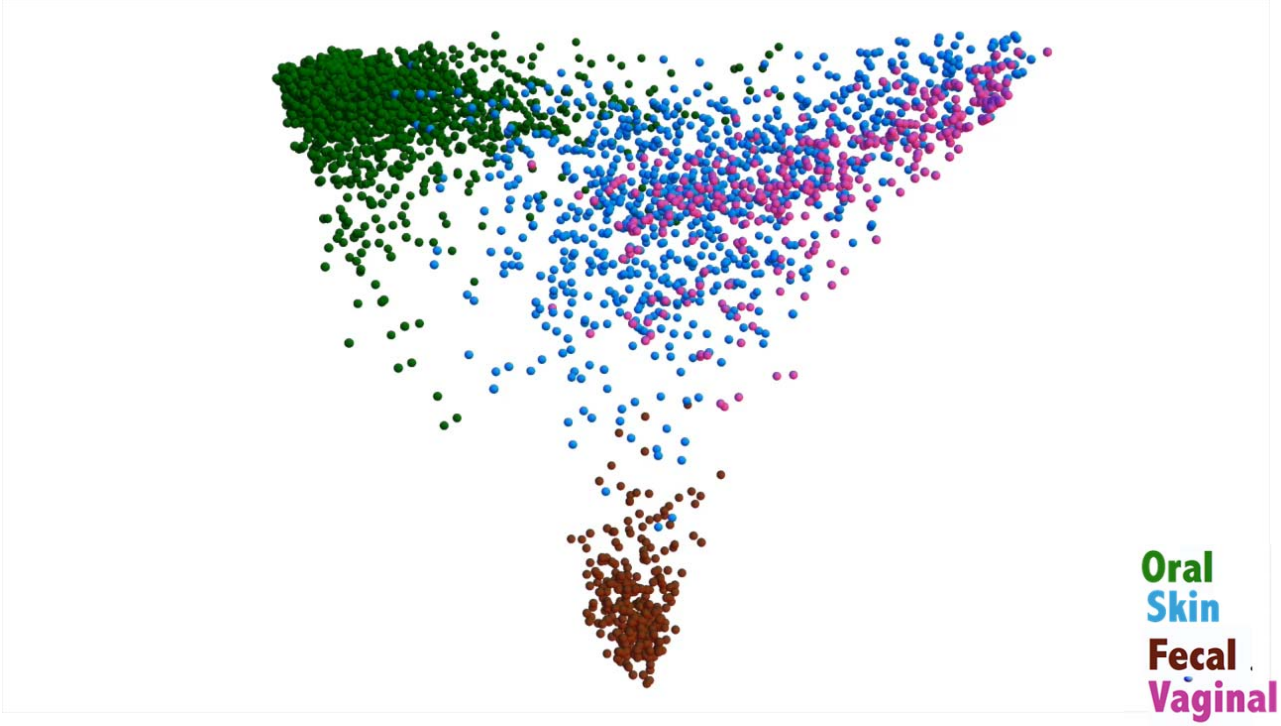
Yatsunenko et al. *Nature*. 2012 486(7402):222-7

What “microbiome growth” this look like in the first year?

1 mom, 1 baby, 1 sample/week for the first year

Koenig, et al. (2011) *PNAS*. 108 Suppl, 4578

What “microbiome growth” this look like in the first year?



Data: Koenig, et al. (2011) *PNAS*. 108 Suppl, 4578; Movie: Y. Vazquez-Baeza, A Gonzalez

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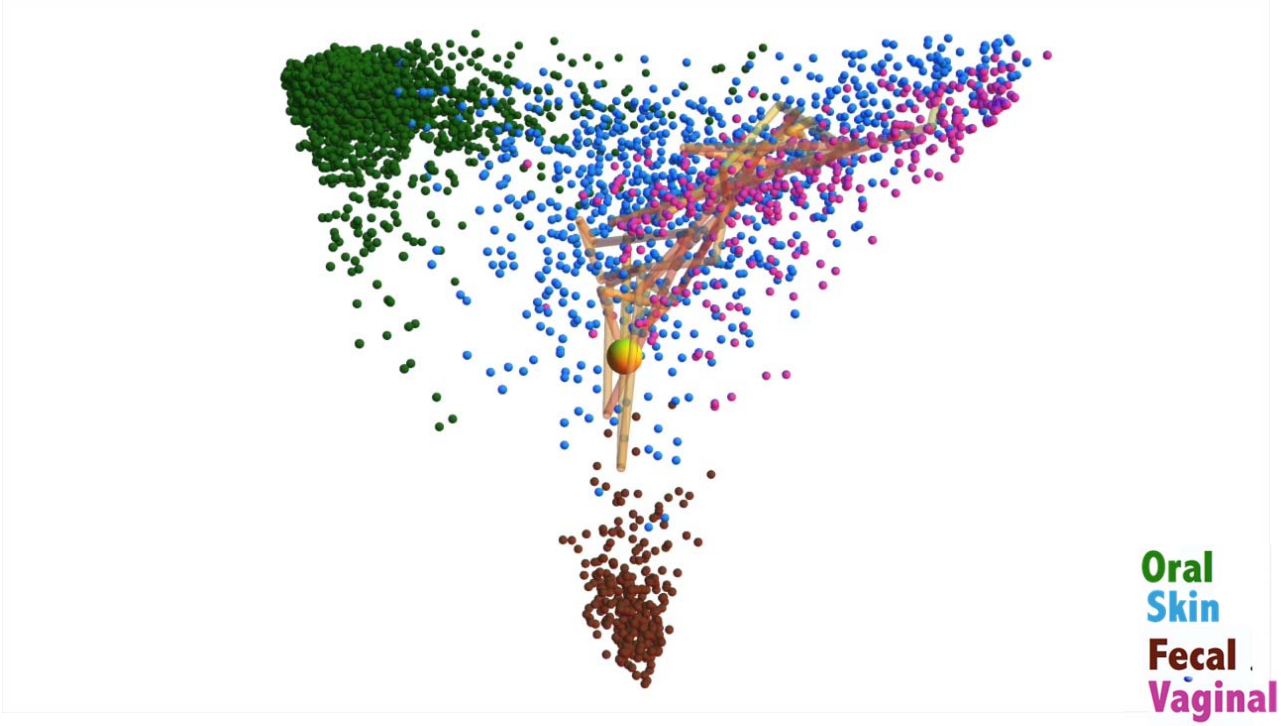

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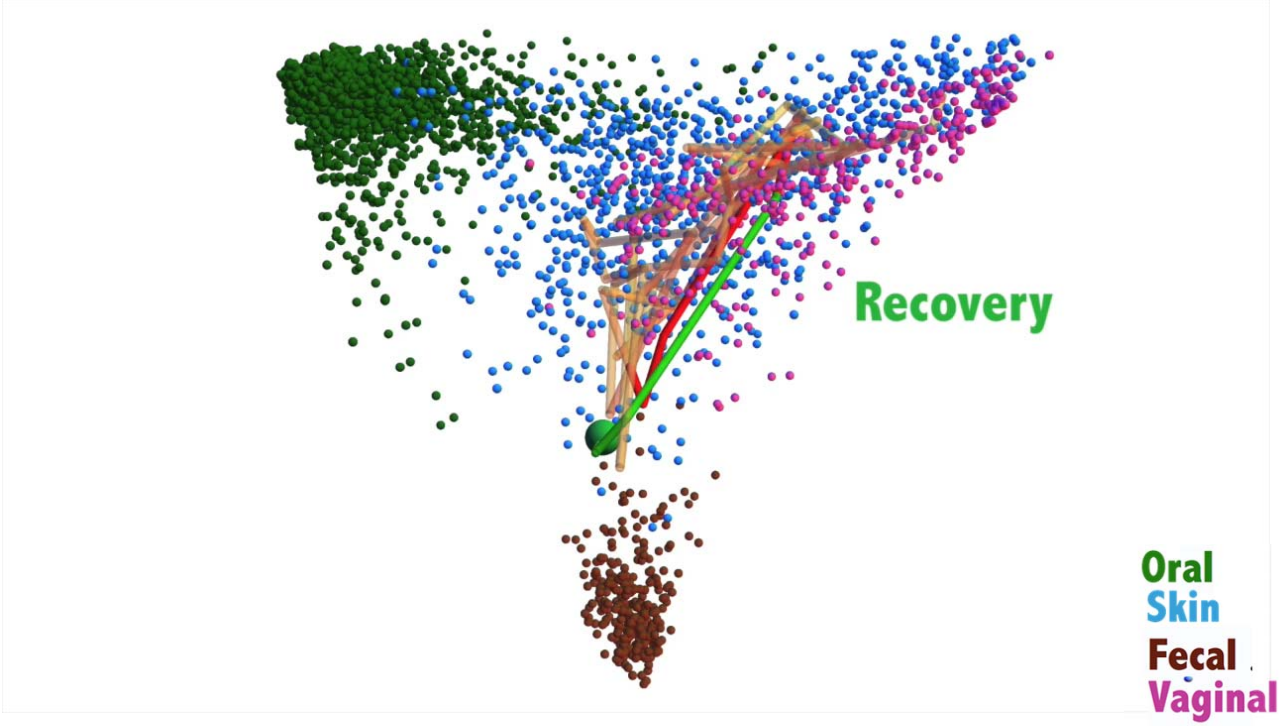

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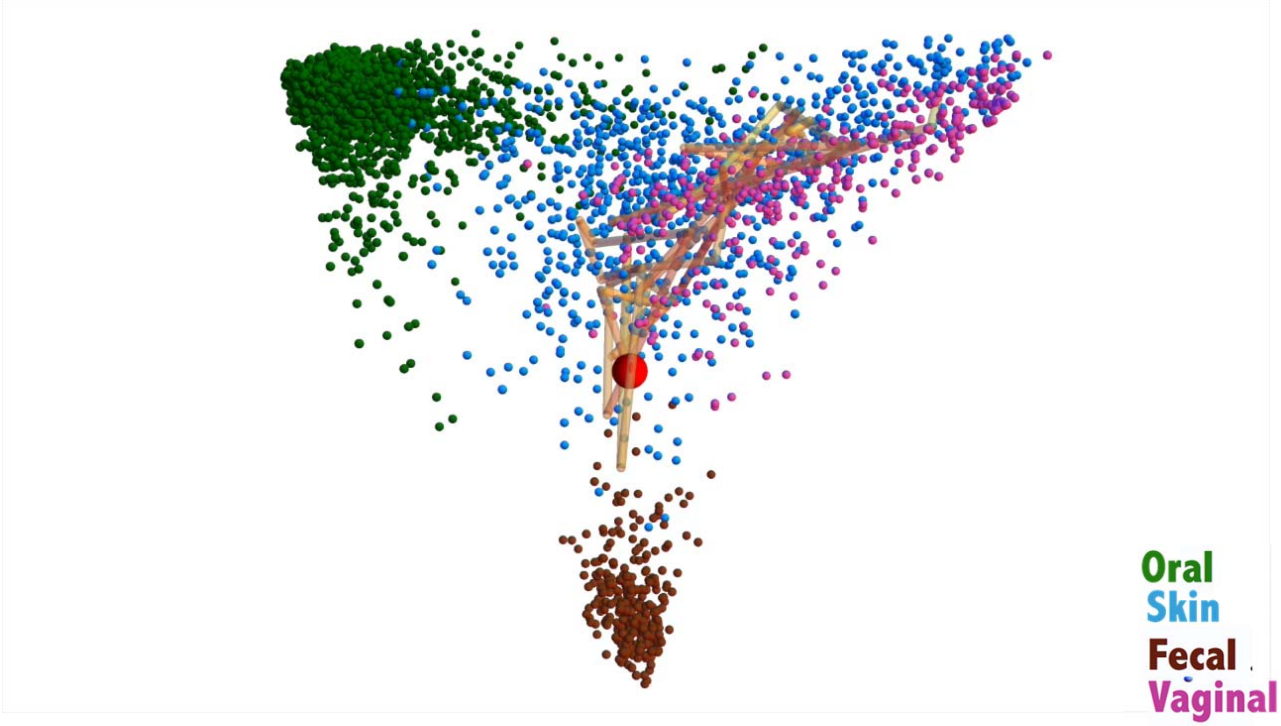
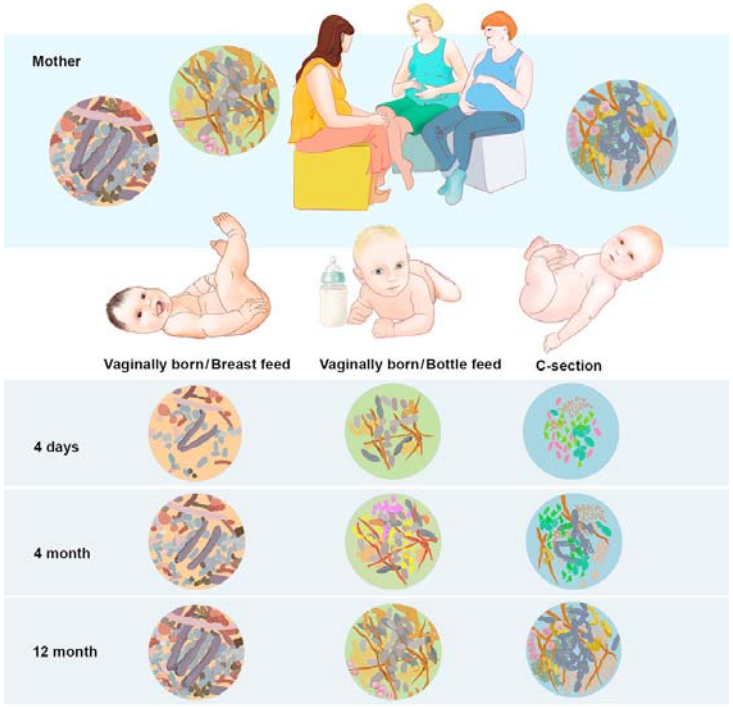


Data: Koenig, et al. (2011) *PNAS*. 108 Suppl, 4578; Movie: Y. Vazquez-Baeza, A Gonzalez

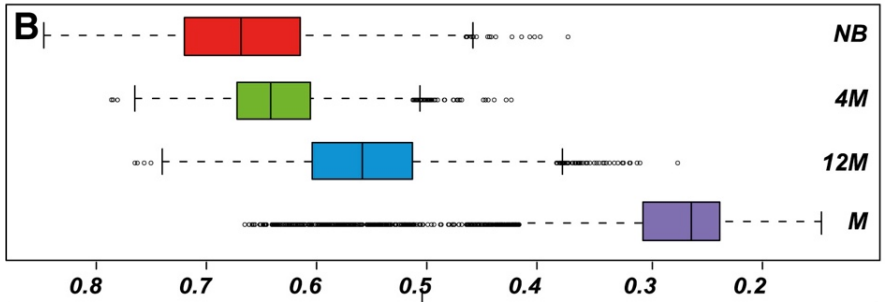
Is this pattern true at a larger scale?



98 mothers
15% C-section

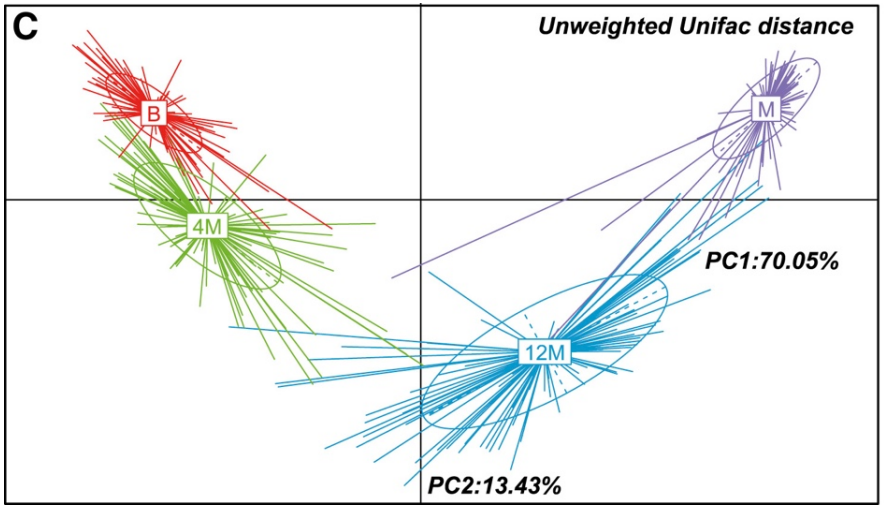
Information about diet
(breast feeding,
formula, and solid food)

Is this pattern true at a larger scale?



Unweighted UniFrac Distance
from Mother's gut

Birth
4 months
12 months
Mother



Bäckhed et al (2015) *Cell Host & Microbe*. **17**: 690

Karolinska Institutet

Rapid development early in life, but development continues into adulthood

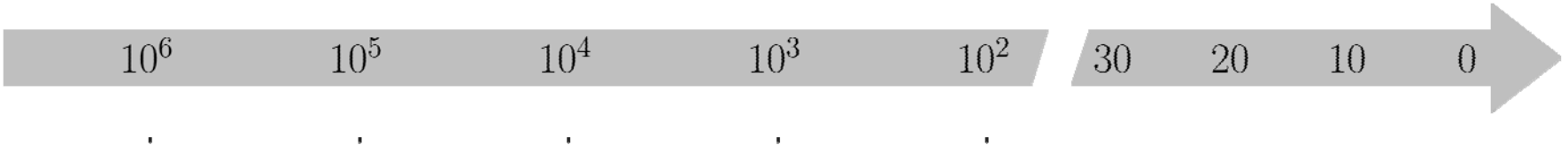
WHY IS THERE SO MUCH CHANGE?

An accidental evolutionary experiment

- Richard Lenski's evolutionary experiment:
- **60,000 generations** of laboratory E. coli in less than **30 years**
- (est. 66,000 generations in Nov 2016)

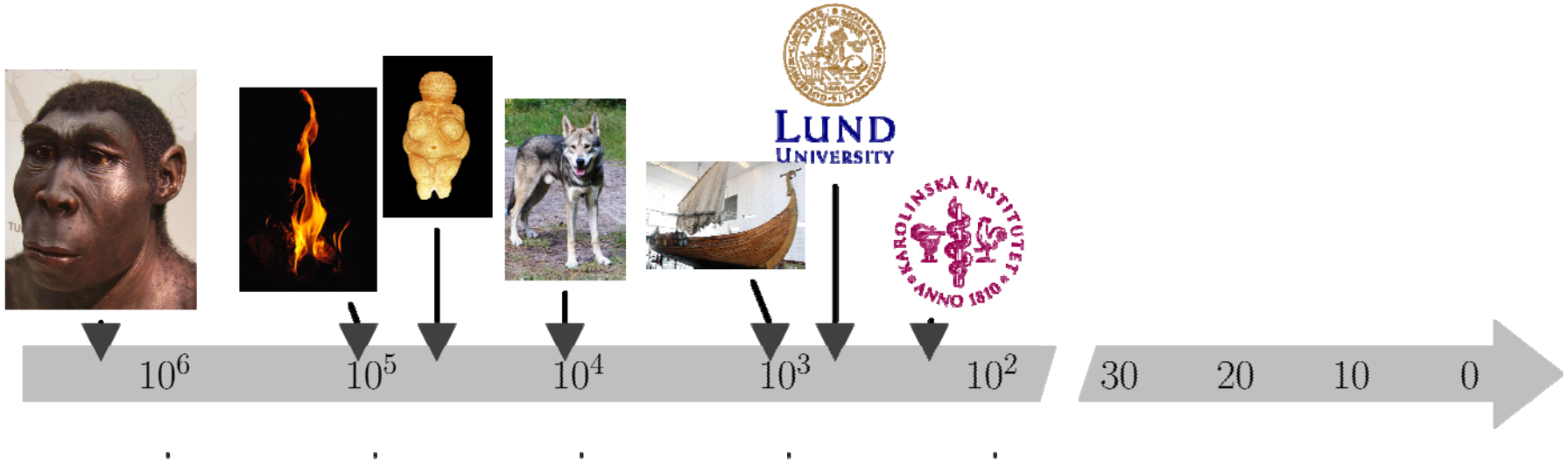
Lenski, R. (2017). ISME J. 11:2181-2194; *image*: G.L. Kohuth/Michigan State University

What's that in "human" years?*



*Assumes a 25 year generation

What's that in "human" years?*



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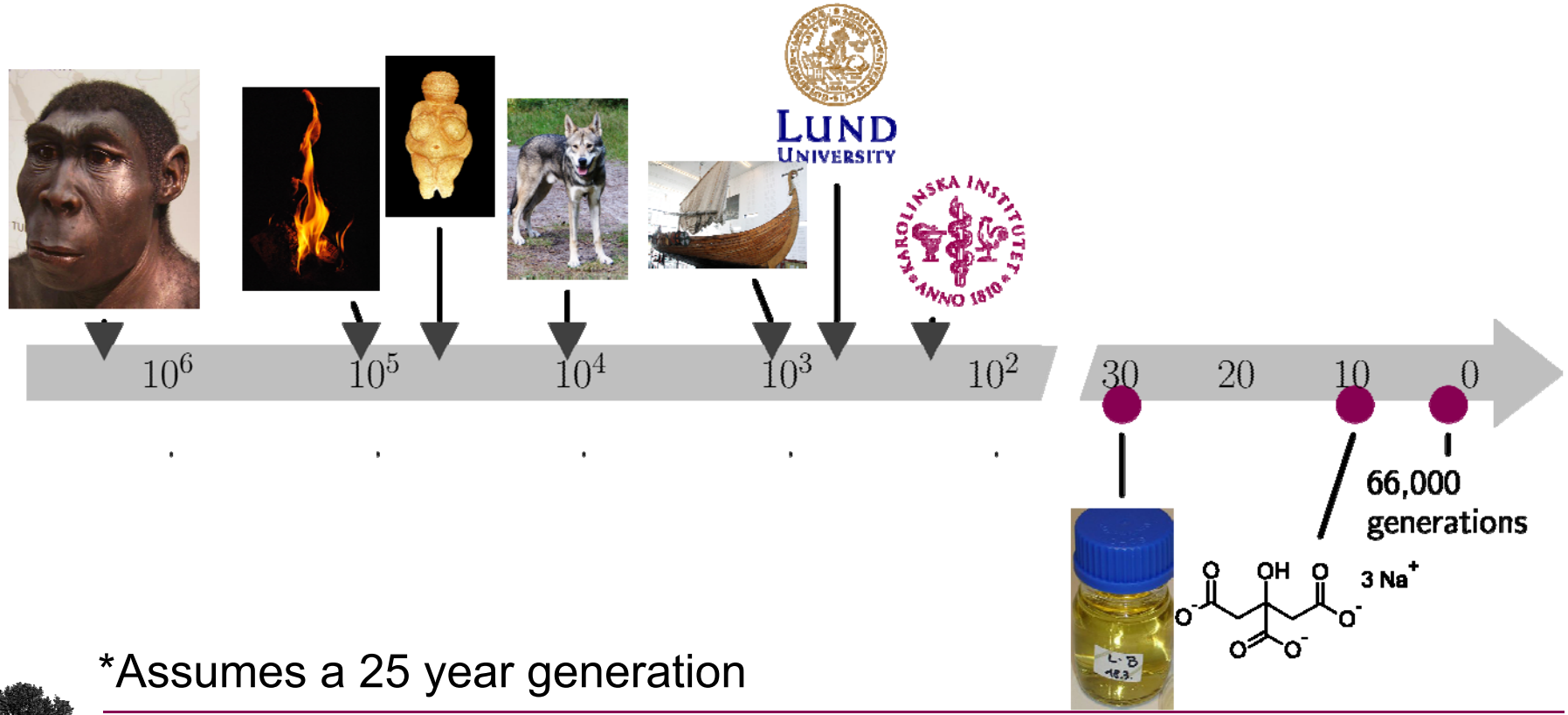

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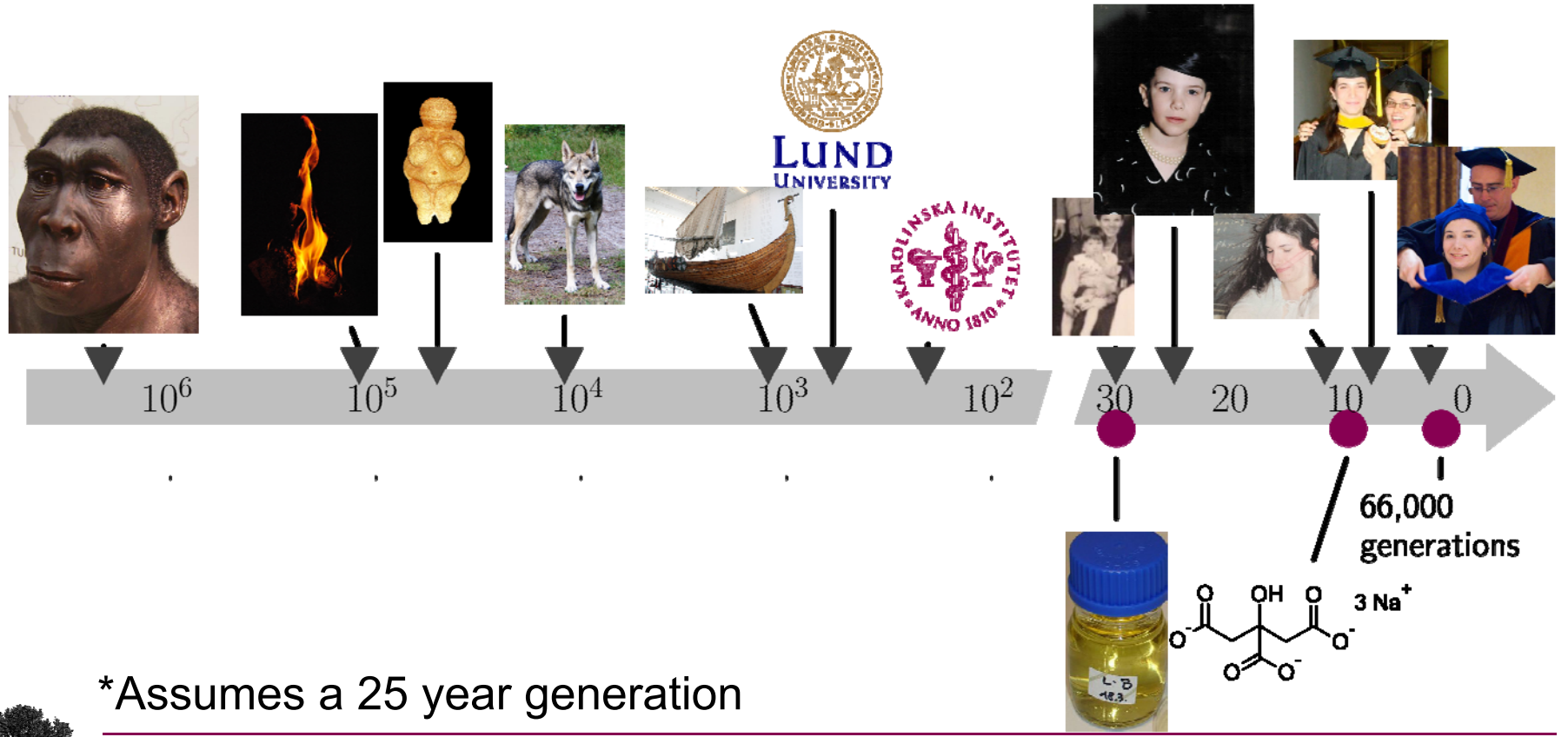

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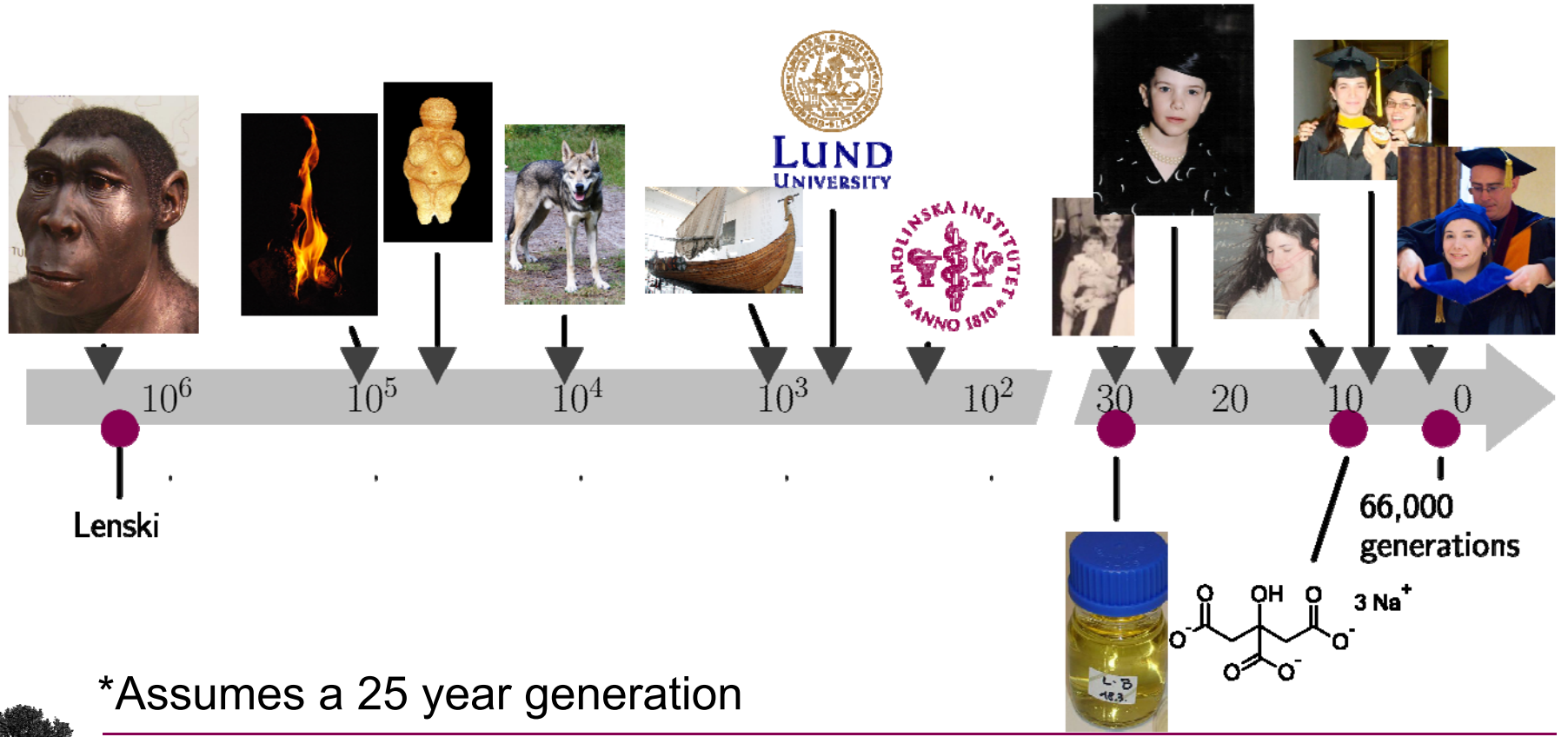

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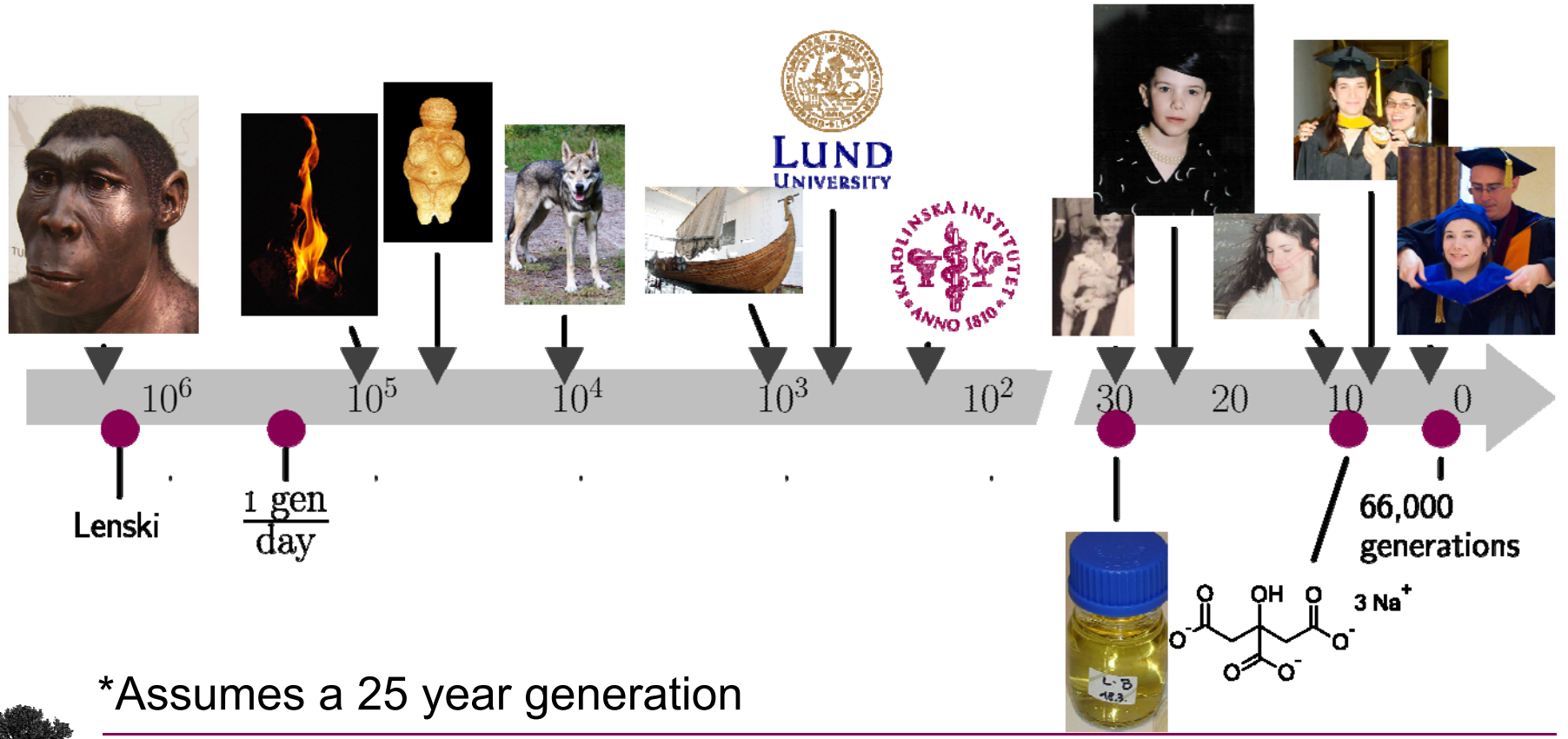

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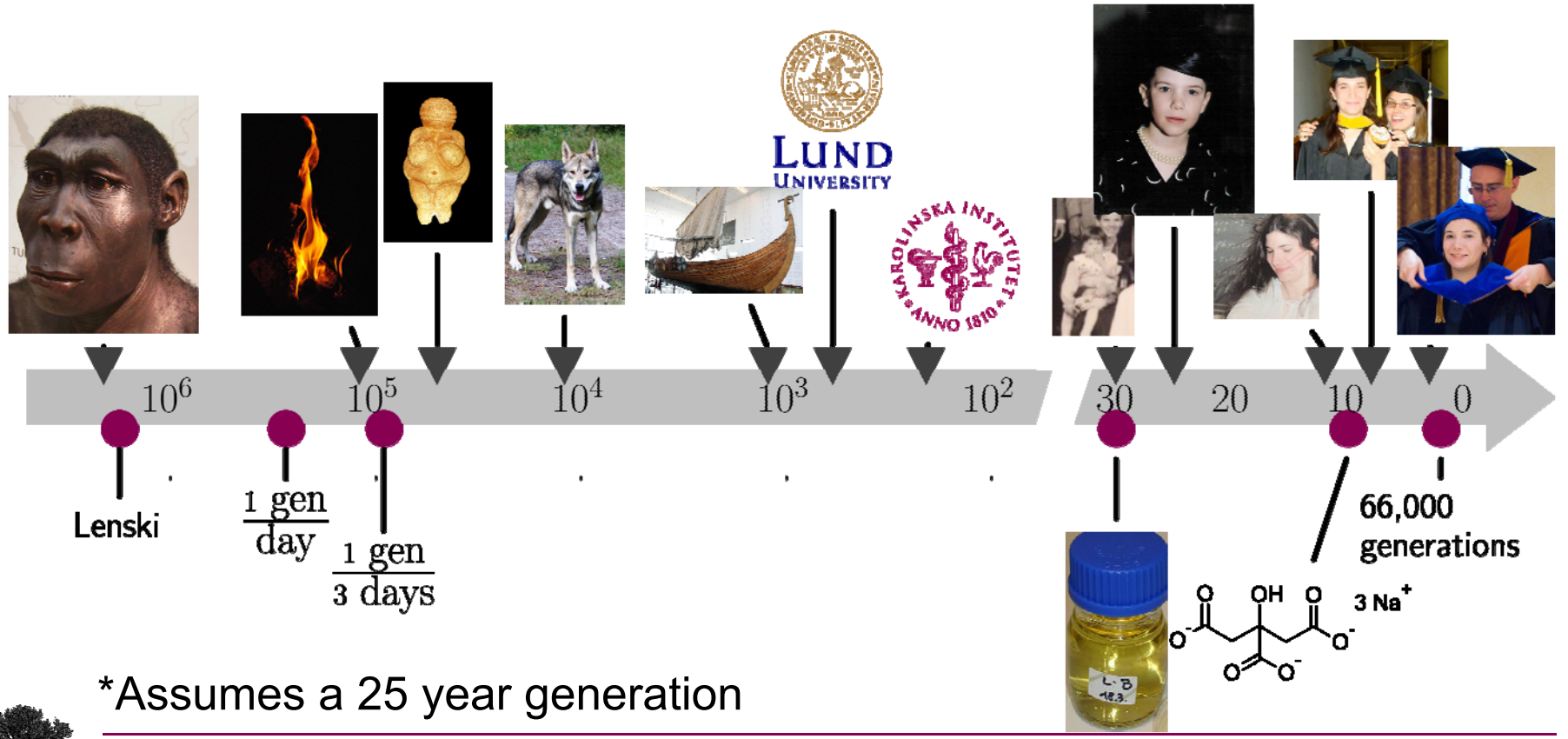

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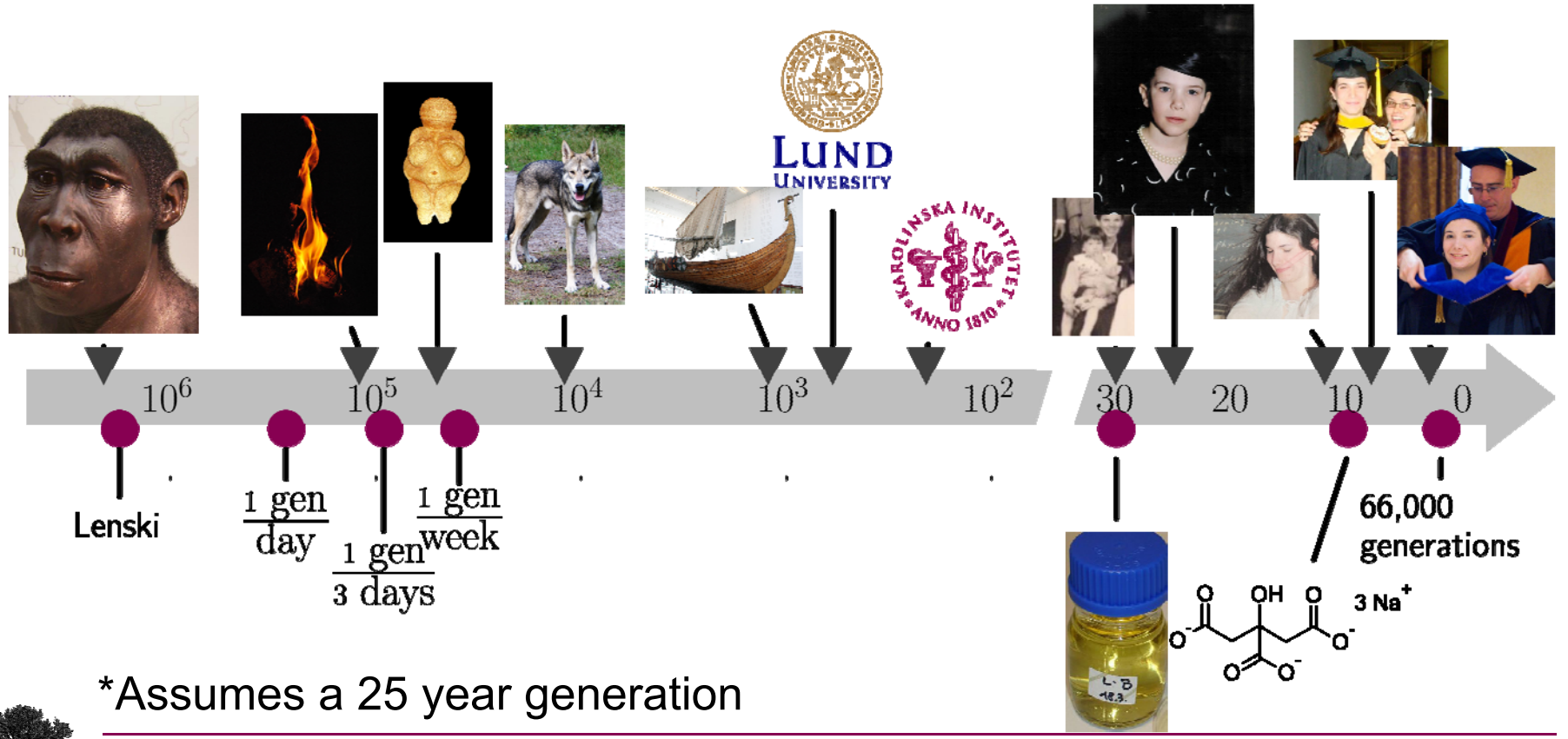
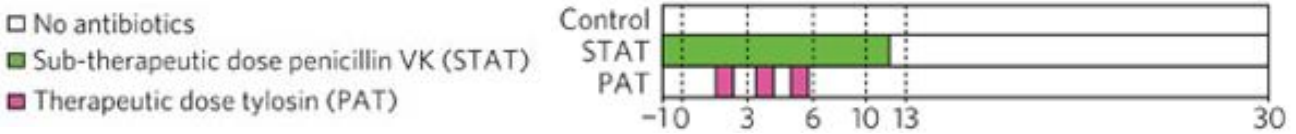


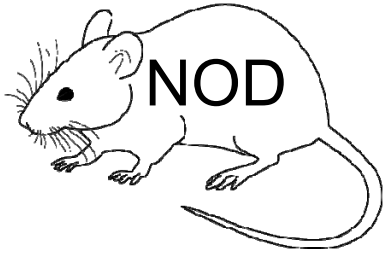
*Assumes a 25 year generation

WHY EARLY LIFE EXPOSURES MATTER

Small humans, big effects

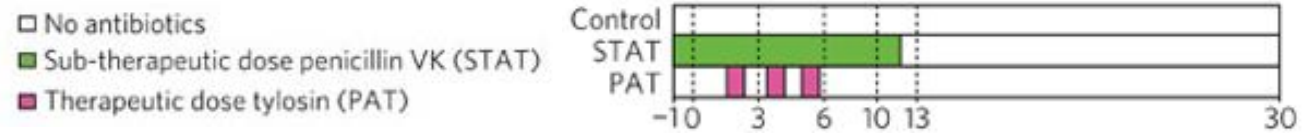
Do antibiotics affect immune development?

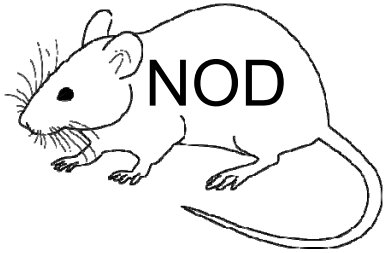


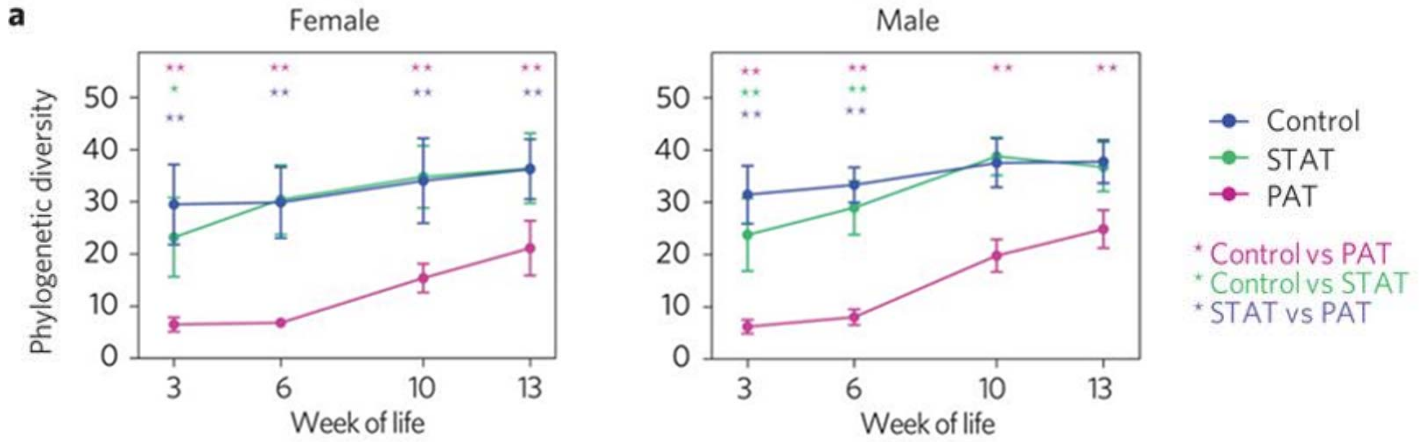


Livanos et al (2016) *Nature Microbiology*. **1**: 16140

Antibiotics increase alter microbiome development in a mouse model

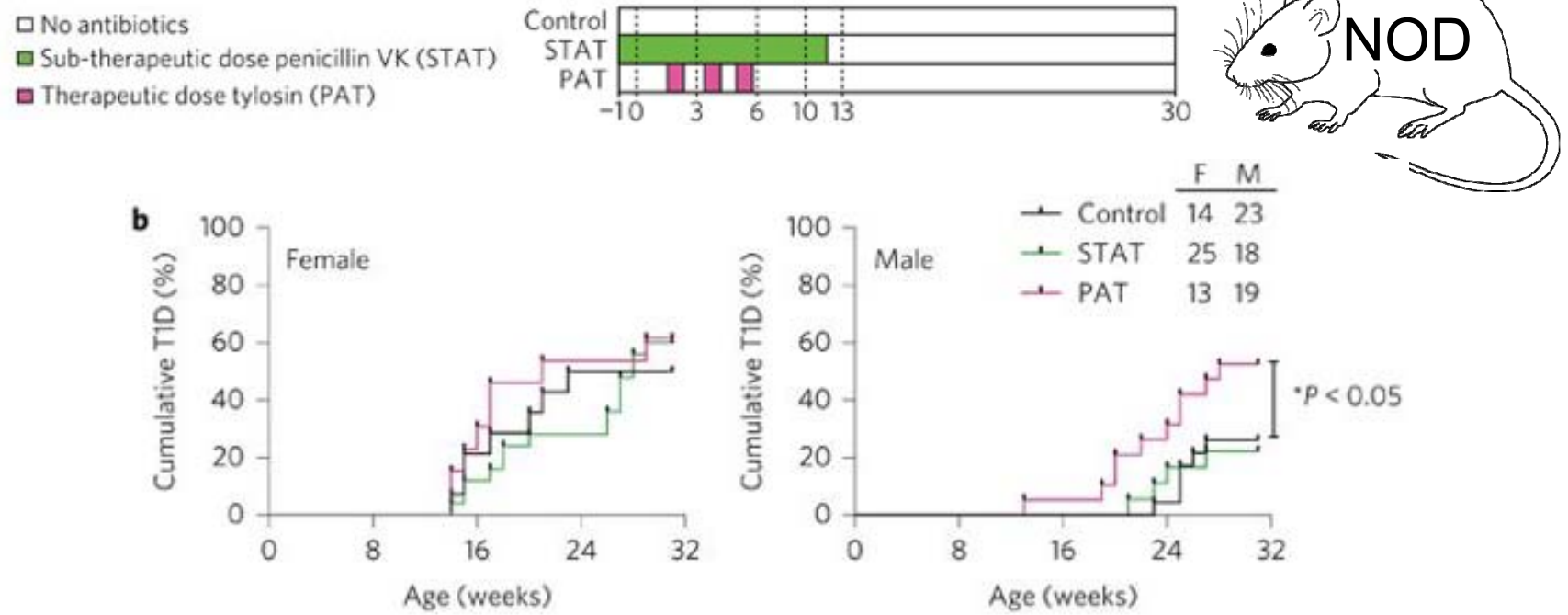






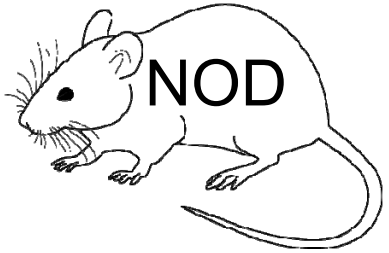
Livanos et al (2016) *Nature Microbiology*. **1**: 16140

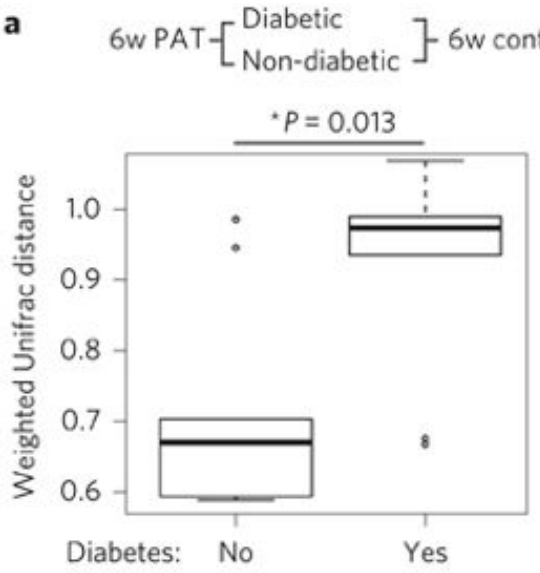
Antibiotics increase autoimmune events in a mouse model



Livanos et al (2016) *Nature Microbiology*. **1**: 16140

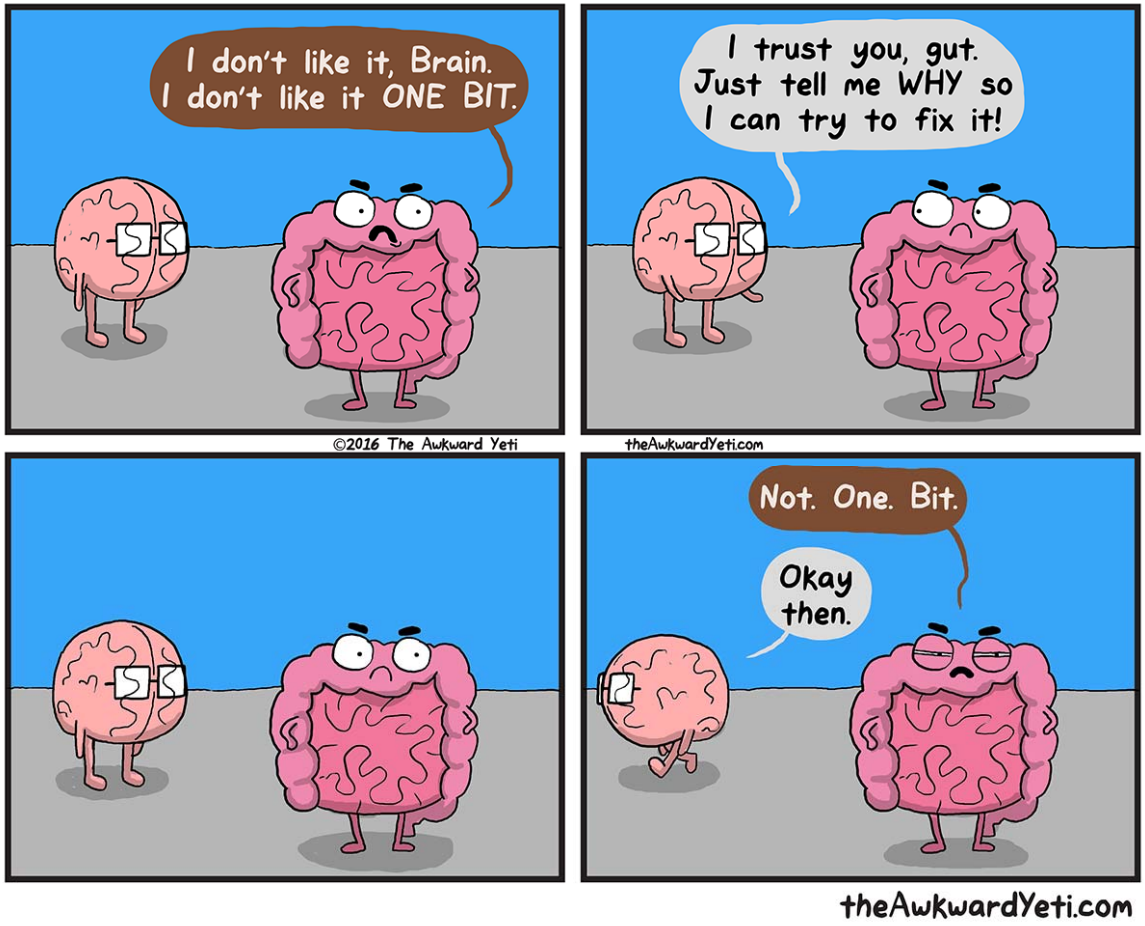
The microbiome at 6 weeks predicts autoimmunity



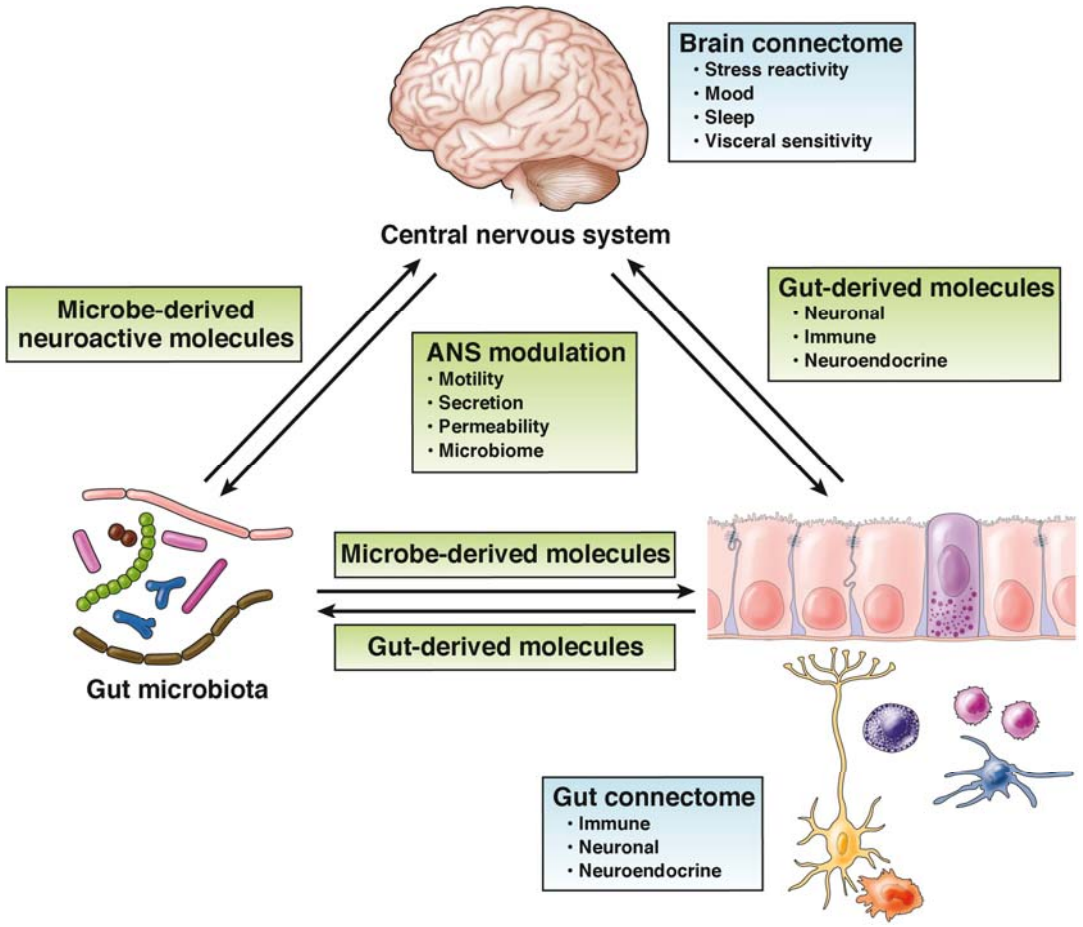


THE GUT-BRAIN AXIS

I’ve got a feeling about it



Seluk. (Dec 2016) "Gut Instincts" *The Ugly Yeti*. http://theawkwardyeti.com/comic/gut-instincts/



Martin et al (2018). *Cell Mol Gastroenterol and Hepatol* **6**: 133

Autism Spectrum Disorder

Table 1: DSM-5 Diagnostic Criteria for Autism Spectrum Disorder (ASD)1

Diagnostic Criteria of Autism Spectrum Disorder (ASD)

Severity is based on social communication impairments and restricted, repetitive patterns of behavior

A. Persistent deficits in Social Communication and Social Interaction across multiple contexts
B. Restrictive, repetitive pattern of behavior, interests or activities
C. Symptoms must be present in the early developmental period (may be masked by learned strategies in later life)
D. Symptoms cause clinically significant impairment in social, occupational or other important areas of current functioning
E. These disturbances are not explained by intellectual disability (intellectual developmental disorder) or global developmental delay

Specified further:
- With or without accompanying language impairment
- With or without accompanying intellectual impairment associated with a known medical or genetic condition or environmental factor
- With catatonia

American Psychiatric Association (2013) DSM V.

Is there a relationship between ASD and gastrointestinal problems?

Is there a relationship between ASD and gastrointestinal problems?

Risk of GI Problems in children with ASD

GI Symptom	Pooled OR
General Concerns	4.42
Diarrhea	3.63
Constipation	3.86
Abdominal Pain	2.45

McElhanon et al (2014) *Pediatrics* **133**: 872

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Risk of GI Problems in children with ASD

GI Symptom	Pooled OR
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Diarrhea	3.63
Constipation	3.86
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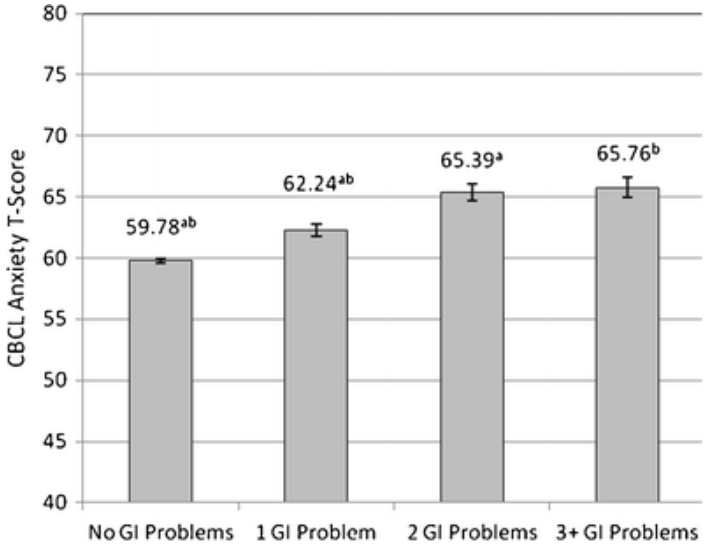
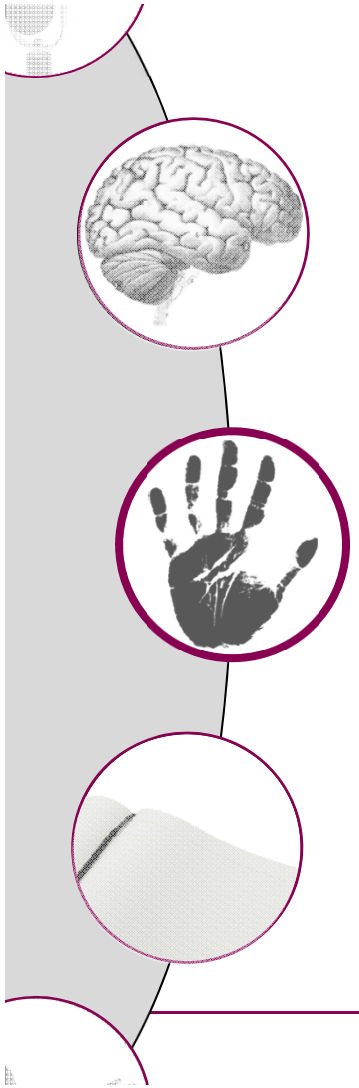
GI discomfort is associated with anxiety



McElhanon et al (2014) *Pediatrics* **133**: 872; Mazurek et al (2012) *J Abnorm Child Psych* **31**: 165



THE MICROBIOME AND AUTISM SPECTRUM DISORDER

The brain-gut-microbe connection in neurodevelopment

Karolinska Institutet

Is the microbiome different in individuals with Autism Spectrum Disorder?

Karolinska Institutet

ELSEVIER

Anaerobe

Volume 16, Issue 4, August 2010, Pages 444-453

PLOS ONE

PLOS ONE

Comparison of Fecal Microbiota in Children with Autism Spectrum Disorders and Neurotypical Siblings in the Simons Simplex Collection

idence of *Prevotella* and Other Fermenters in icroflora of Autistic Children

yoon Park, Zehra Esra Ilhan, Garrick Wallstrom, Joshua LaBaer, James B. Adams,

Journal of Pediatric Gastroenterology and Nutrition

Issue: Volume 64(5), May 2017, p e110–e116

Copyright: © 2017 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology,

Publication Type: [Original Article: Gastroenterology]

Analysis of the Duodenal Microbiome in Autistic Individuals: Association With Carbohydrate Digestion

Kushak, Rafail I.[*]; Winter, Harland S.[*]; Buie, Timothy M.[*]; Cox, Stephen B.[†]; Phillips, Caleb D.[†,‡]; Ward, Naomi L.[§,‖]

Brent L. W

Omar Jab

Published:

h Autism

rwise

Serrazzanetti,

Is the microbiome different in individuals with Autism Spectrum Disorder?

- General conclusion is **yes**

Is the microbiome different in individuals with Autism Spectrum Disorder?

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- HOWEVER …

Is the microbiome different in individuals with Autism Spectrum Disorder?

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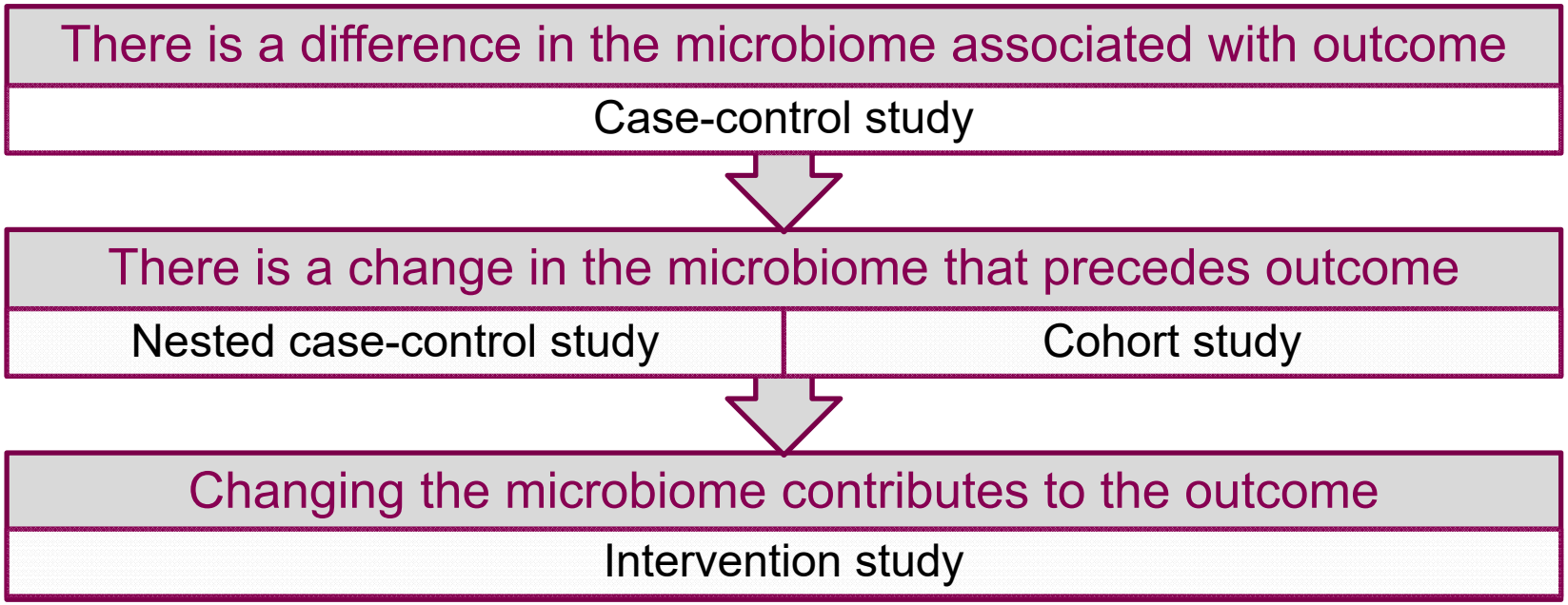
- HOWEVER …
  - → Studies of less than 100 children per group
  - → Inconsistent methods between studies

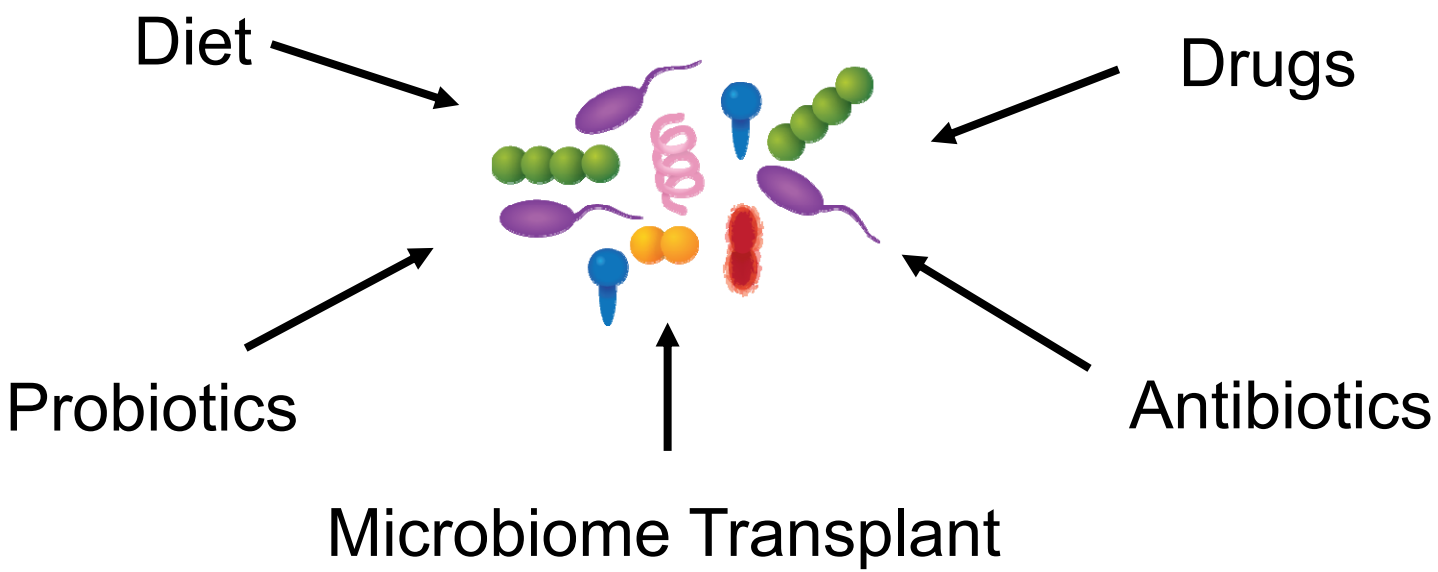
Is the microbiome different in individuals with Autism Spectrum Disorder?

- General conclusion is **yes**
- HOWEVER …
  - → Studies of less than 100 children per group
  - → Inconsistent methods between studies
- No way to measure directionality, temporality, or causality

How do you from correlation to causation?



Interventions for the microbiome



Is there a relationship between the microbiome in children with ASD and their behavior?

Kang et al (2017) *Microbiome*. **5:**10

Is there a relationship between the microbiome in children with ASD and their behavior?

Karolinska Institutet

Open label clinical trial of Fecal Material Transplant for ASD symptoms

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Open label clinical trial of Fecal Material Transplant for ASD symptoms

18 autistic children and 20 neurotypical children at one study site

- Fecal Material transplant in children with ASD

Kang et al (2017) *Microbiome*. **5:**10

Is there a relationship between the microbiome in children with ASD and their behavior?

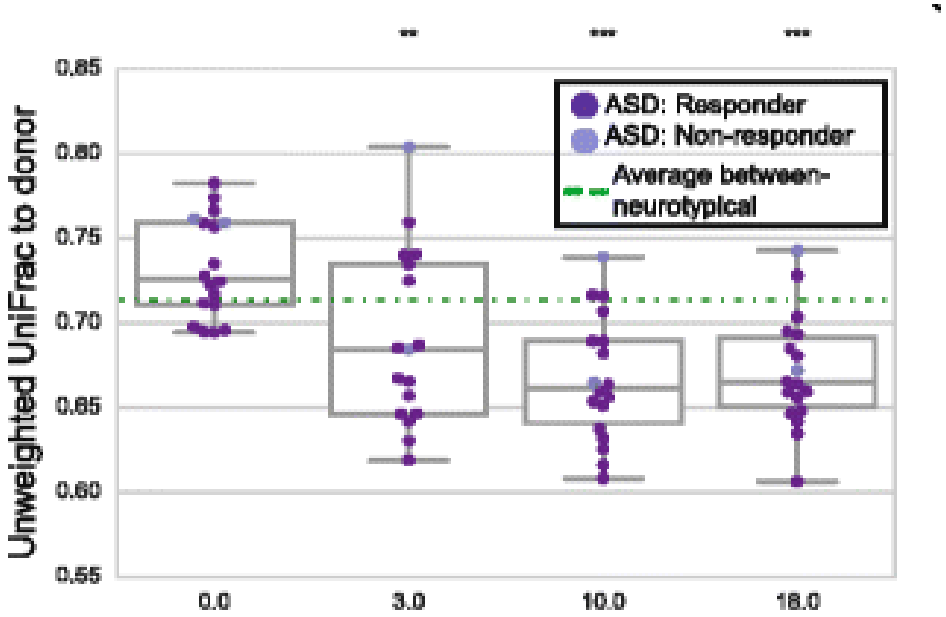
Open label clinical trial of Fecal Material Transplant for ASD symptoms

18 autistic children and 20 neurotypical children at one study site

- Fecal Material transplant in children with ASD
- GI function was measured with Gastrointestinal System Rating Scale
- Behavior was measured with the Parental Global Impressions-III (PGI III) scale
- Microbiomes were profiled with 16s rRNA sequencing

Kang et al (2017) *Microbiome*. **5:**10

Does the microbiome change in children with ASD following FMT?



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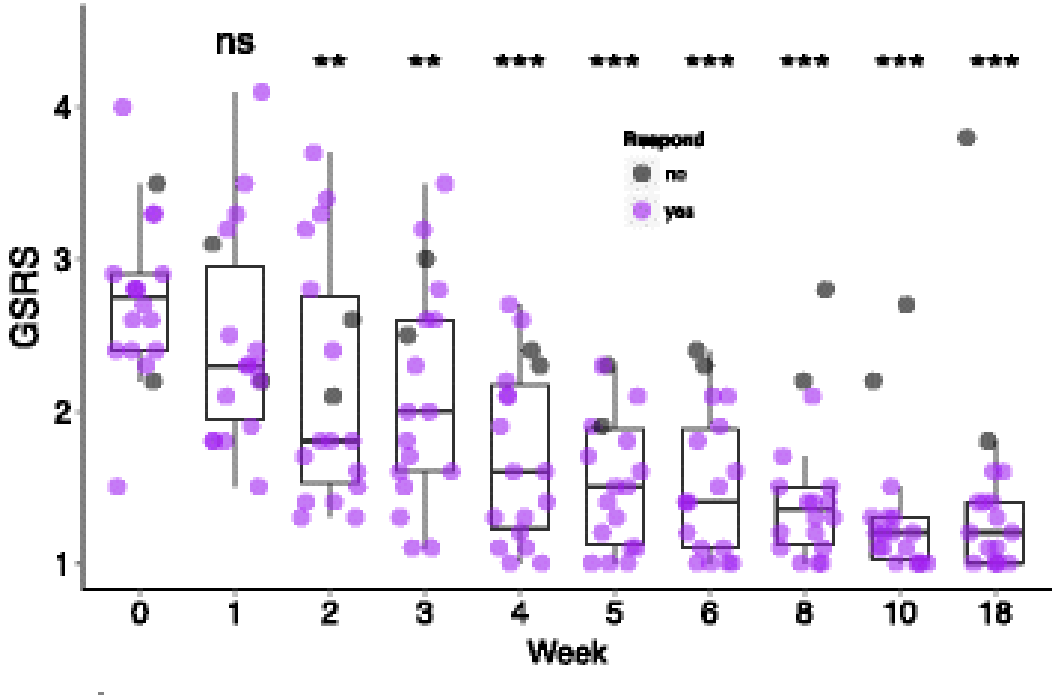
Can changing the microbiome affect gastrointestinal symptoms in children with ASD?



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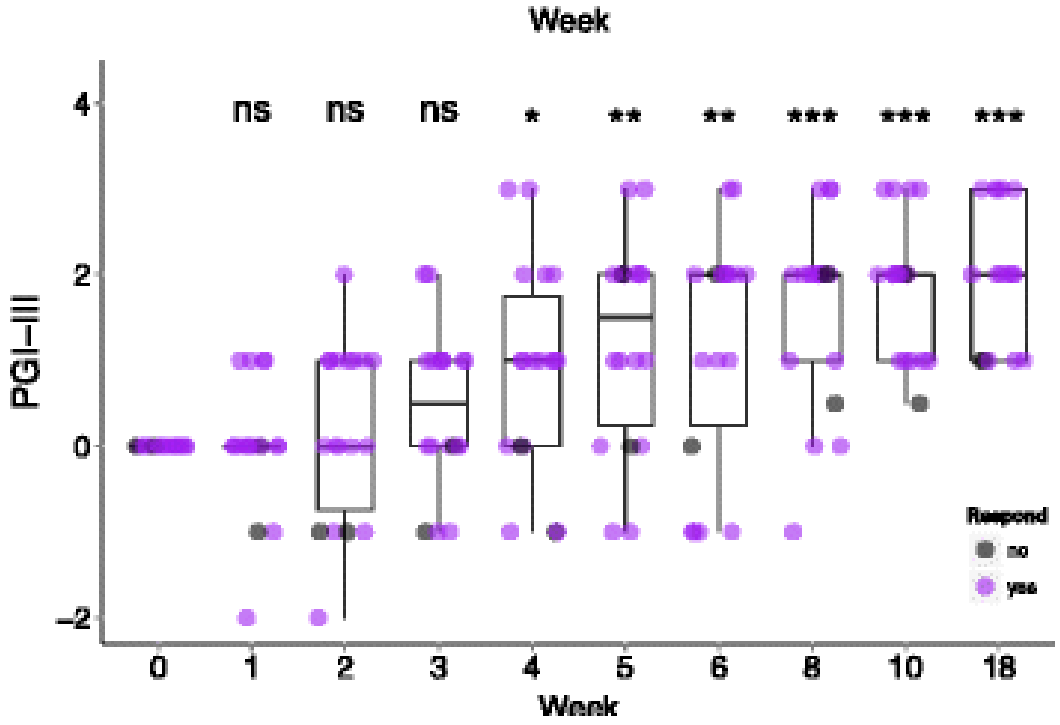
Can changing the microbiome affect behavior in children with ASD?



Kang et al (2017) *Microbiome*. **5:**10

Is there a relationship between the microbiome in children with ASD and their behavior?

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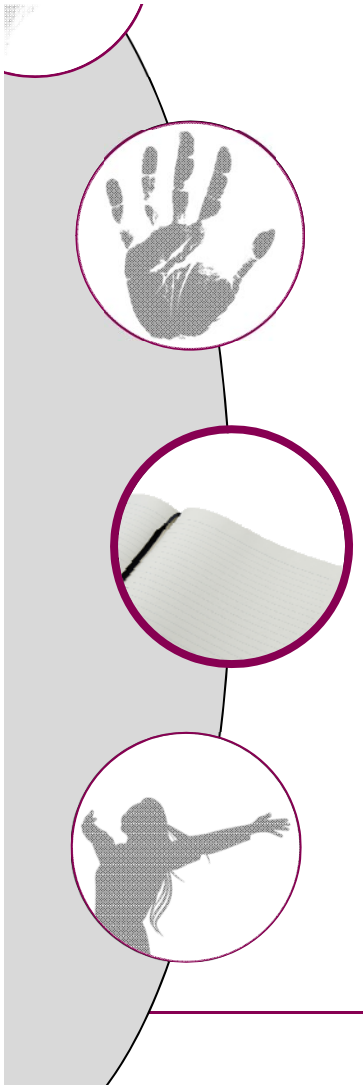
Yes, a small study suggest changing the microbiome may alleviate GI symptoms and alter behavior



THINKING ABOUT THE NEXT GENERATION OF STUDIES

"The only difference between screwing around and science is writing it down" -- Adam Savage

A role for the microbiome in ADHD?

Karolinska Institutet

A role for the microbiome in ADHD?

- 14 with ADHD; (11.2 yrs)
  17 controls (13.1 yrs)

- 10 on medication
  (9 stopped 48 hours before)

Prehn-Kristensen (2018). *PLoS One*. **13**: e0200728

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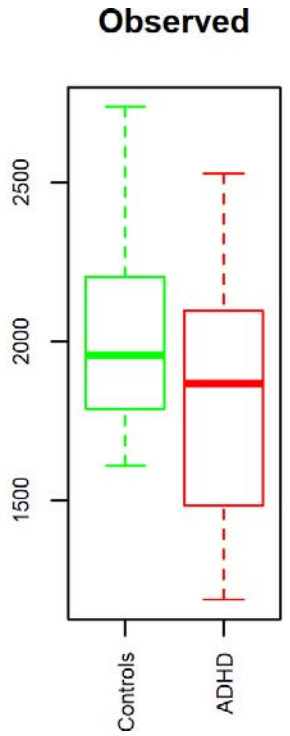

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How do we make the next iteration of this better?

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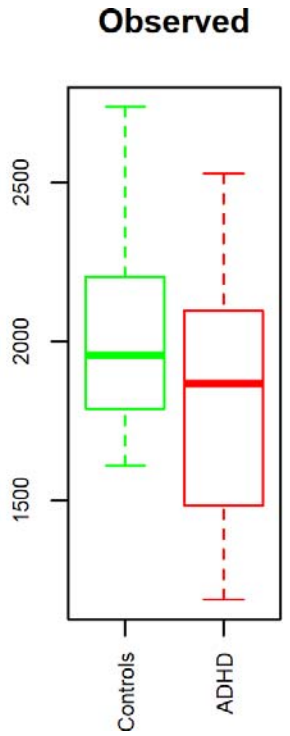


Prehn-Kristensen (2018). *PLoS One*. **13**: e0200728

How do we make the next iteration of this better?

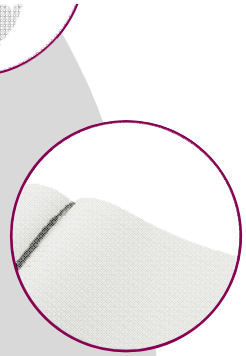
- Larger sample size
  → Large inter-individual
- Better consideration of confounders
- Consideration of longitudinal questions

Important confounders relevant for neurodevelopmental microbiome research

- Good age frequency matching is a must!
  → (Possibly even adjustment)
- Medication Use and History
  → Include a treated and untreated group? Treated and treatment naïve?
- Diet and interaction with diet
- Study Site Differences

Leveraging the Swedish Registers for better microbiome research

- Accurate phenotypic ascertainment
- Potential for long term history and follow up
- More complete medical history and family history
- Integration with additional data sources



THANK YOU!

(justine.debelius@ki.se)