The human gut microbiome in health and disease

Peer Bork
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EMBL, Heidelberg

Aiming at a functional understanding of biological systems

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How to study microbes: Until recently via growing them

…but 99% cannot be easily cultured, so only a few were studied individually

Petri dishes with agarose (nutrient cocktail)…invented 1887!

From toilet air

From the hand of an 8 year old

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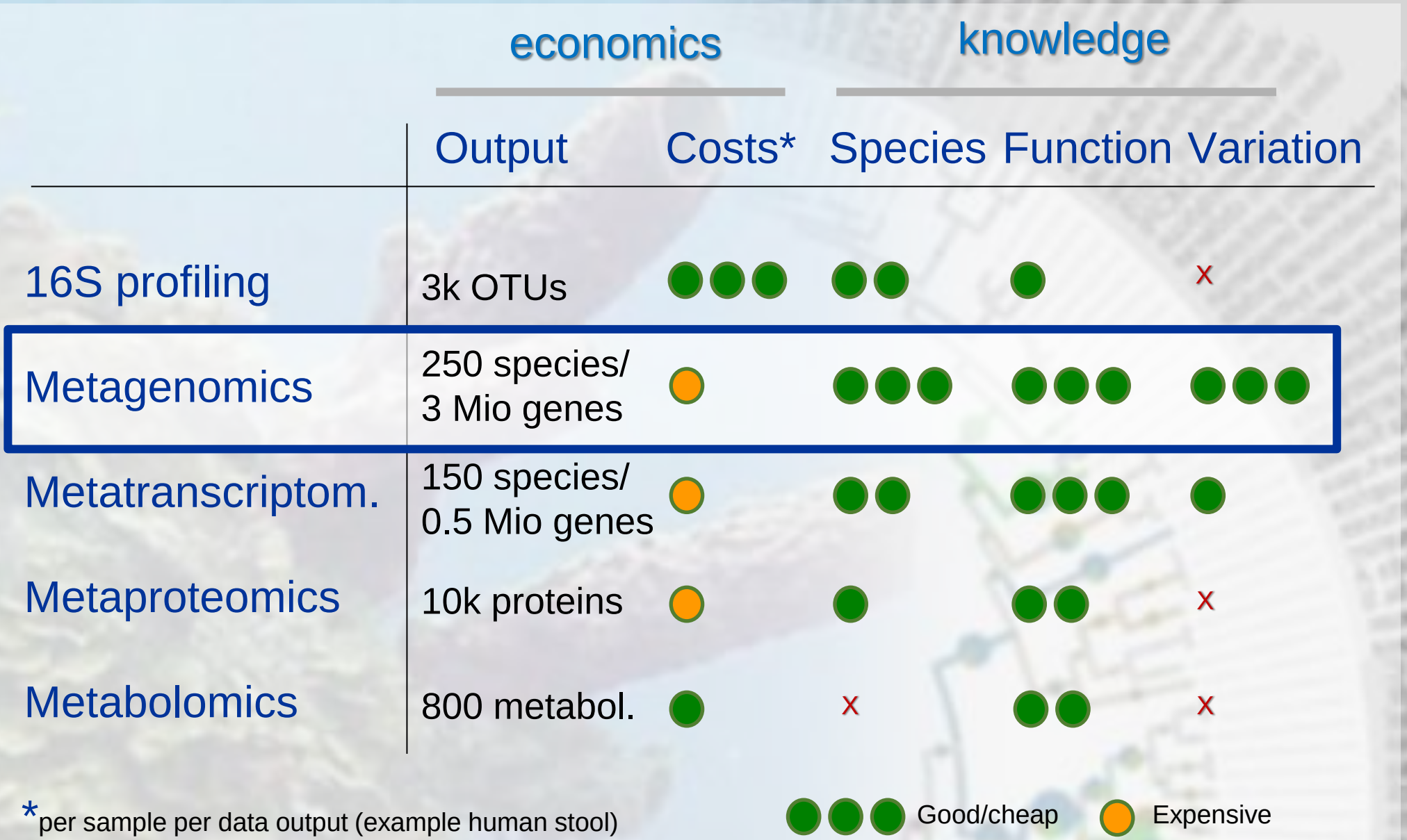
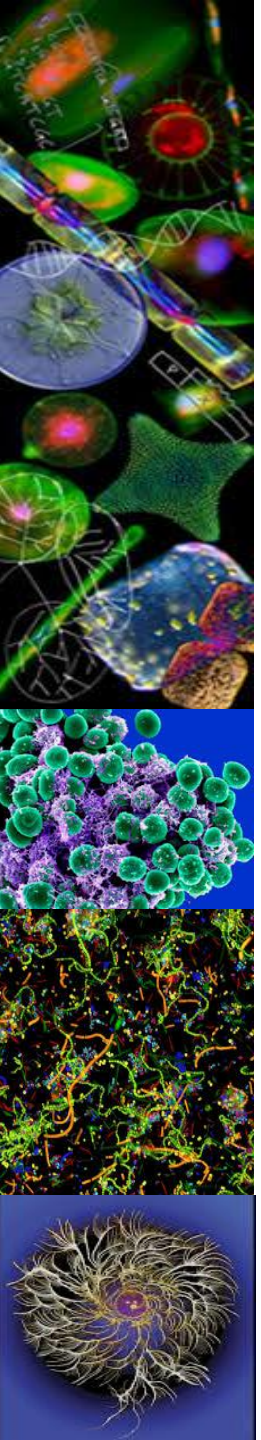
Towards structure and function of a microbiome

Molecular approaches to access a microbiome





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III. From associations to diagnostics
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The Milky Way harbours ca. 100 Billion (10^{11}) stars...
We have ca. 40 Trillion ($4x10^{13}$), i.e. ca 400x more, microbial cells in our gut, more than human cells

Which and how many microbes are in the gut?

In 2010 already hope for diagnostics, but not even basics where known

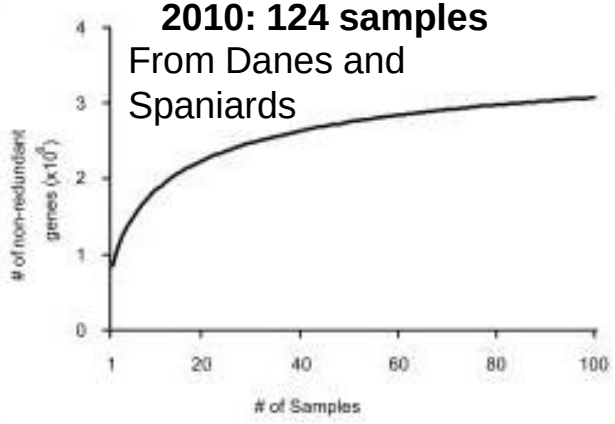
Mostly bacteria, >1000 species per person, exact number unclear

More bacterial than human cells, biomass together up to ca 1.5kg (brain 1.3kg)

With metagenomics wee see ca 250 species/pers: in 2010 together 3.3 Mio genes

2010: 124 samples

From Danes and Spaniards



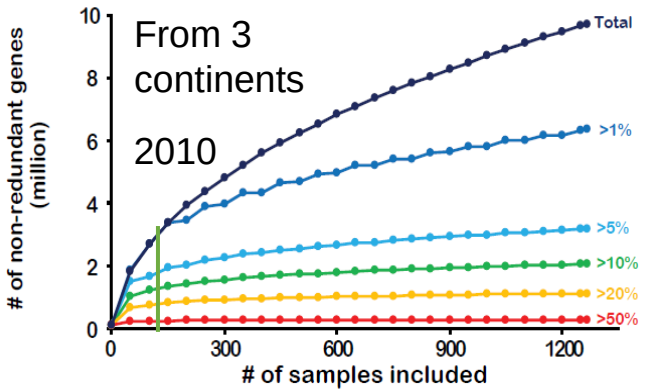
3.3 Mio genes, 4Gb per sample

Qin et al, Nature 464(2010)59

2014: 1267 samples

From 3 continents

2010



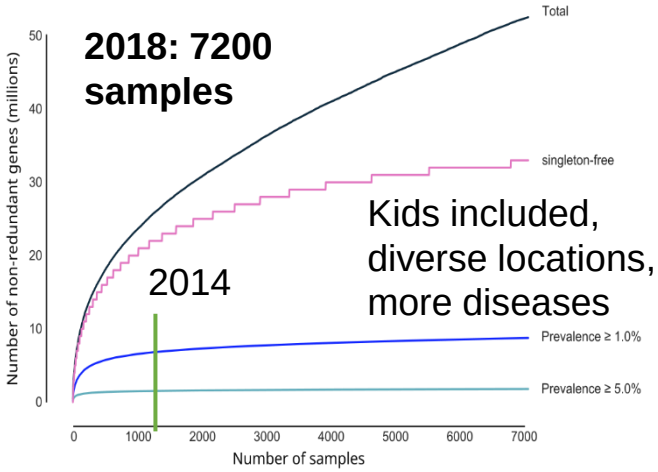
10 Mio genes, 5GB per sample

Li et al, Nat.Biotech. 32(2014)834

2018: 7200 samples

Kids included, diverse locations, more diseases

2014



56Mio genes, 10GB per sample

Coelho et al., in revision

Some mispredicted genes aside, each of us carries a lot of unique genes (or rare species)!

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How different are our gut microbes?

Lots of biological variation in taxonomic composition, yet there is structure in the data

ARTICLE Nature 473(2011)174
doi:10.1038/nature09944

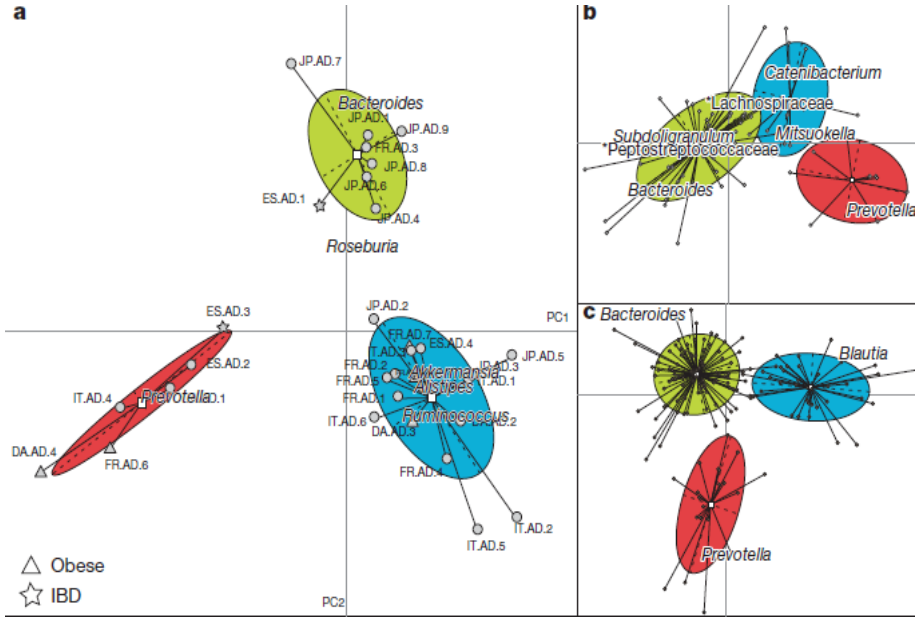
Enterotypes of the human gut microbiome

Manimozhiyan Arumugam[1]*, Jeroen Raes[1,2]*, Eric Pelletier[3,4,5], Denis Le Paslier[3,4,5], Takuji Yamada[1], Daniel R. Mende[1], Gabriel R. Fernandes[1,6], Julien Tap[1,7], Thomas Bruls[3,4,5], Jean-Michel Batto[7], Marcelo Bertalan[8], Natalia Borruel[9], Francesc Casellas[9], Leyden Fernandez[10], Laurent Gautier[8], Torben Hansen[11,12], Masahira Hattori[13], Tetsuya Hayashi[14], Michiel Kleerebezem[15], Ken Kurokawa[16], Marion Leclerc[7], Florence Levenez[7], Chaysavanh Manichanh[9], H. Bjørn Nielsen[8], Trine Nielsen[11], Nicolas Pons[7], Julie Poulain[3], Junjie Qin[17], Thomas Sicheritz-Ponten[8,18], Sebastian Tims[15], David Torrents[10,19], Edgardo Ugarte[3], Erwin G. Zoetendal[15], Jun Wang[17,20], Francisco Guarner[9], Oluf Pedersen[11,21,22,23], Willem M. de Vos[15,24], Søren Brunak[8], Joel Doré[7], MetaHIT Consortium†, Jean Weissenbach[3,4,5], S. Dusko Ehrlich[7] & Peer Bork[1,25]

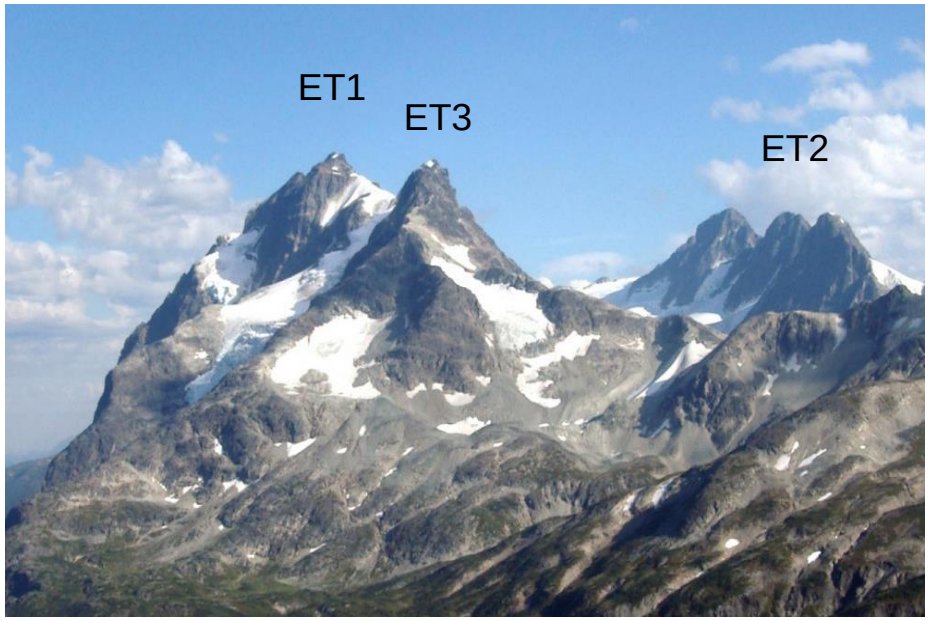
Enterotypes in the landscape of gut microbial community composition

Paul I. Costea[1], Falk Hildebrand[1,2,3], Manimozhiyan Arumugam[4], Fredrik Bäckhed[5,6], Martin J. Blaser[7], Frederic D. Bushman[8], Willem M. de Vos[9,10], S. Dusko Ehrlich[11,12], Claire M. Fraser[13], Masahira Hattori[14], Curtis Huttenhower[15], Ian B. Jeffery[16], Dan Knights[17,18], James D. Lewis[19], Ruth E. Ley[20], Howard Ochman[21], Paul W. O'Toole[16], Christopher Quince[22], David A. Relman[23,24,25], Fergus Shanahan[16], Shinichi Sunagawa[1,26], Jun Wang[5,27,28,29,30], George M. Weinstock[31], Gary D. Wu[32], Georg Zeller[1], Liping Zhao[33], Jeroen Raes[2,3,34]*, Rob Knight[35,36,37,38]* and Peer Bork[1,39,40]*

Nature Microbiol. 3(2018)8



3 distinct community types at genus level…



…now in context of a complex composition landscape

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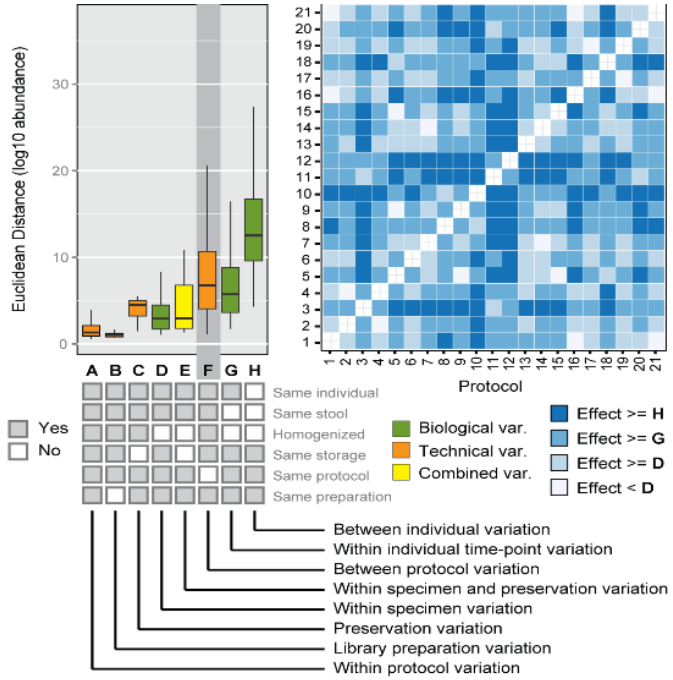
There are still limitations, e.g. little comparability or resolution

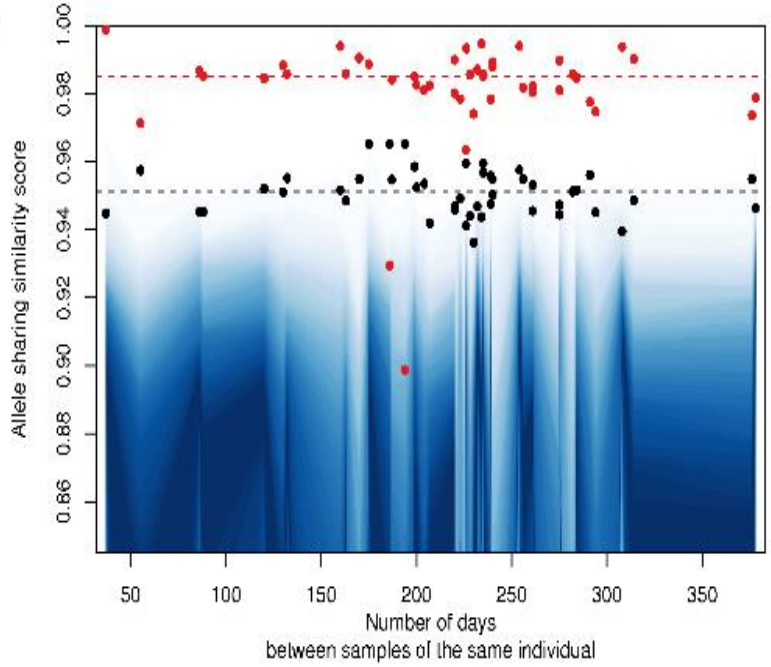
Lots of technical variation as standards are still emerging



Voigt et al., Genome Biol. 16(2015)73
Costea et al., Nature Biotech 35(2017)1069

Different protocols but also same protocol in in different labs vary considerably

Taxonomic resolutions towards strain populations



Schloissnig et al., Nature 493(2013)45
Zhu et al, Genome Biol. 16(2015)82

Two individuals differ in conspecific strains, even monozygotic twins have individual strains

Numerous 16S profiling and metagenomic association studies (MWAS), but difficult to compare

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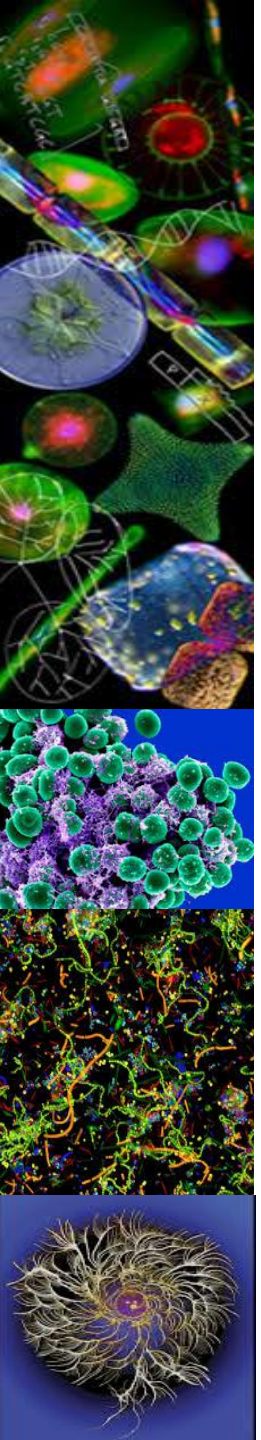

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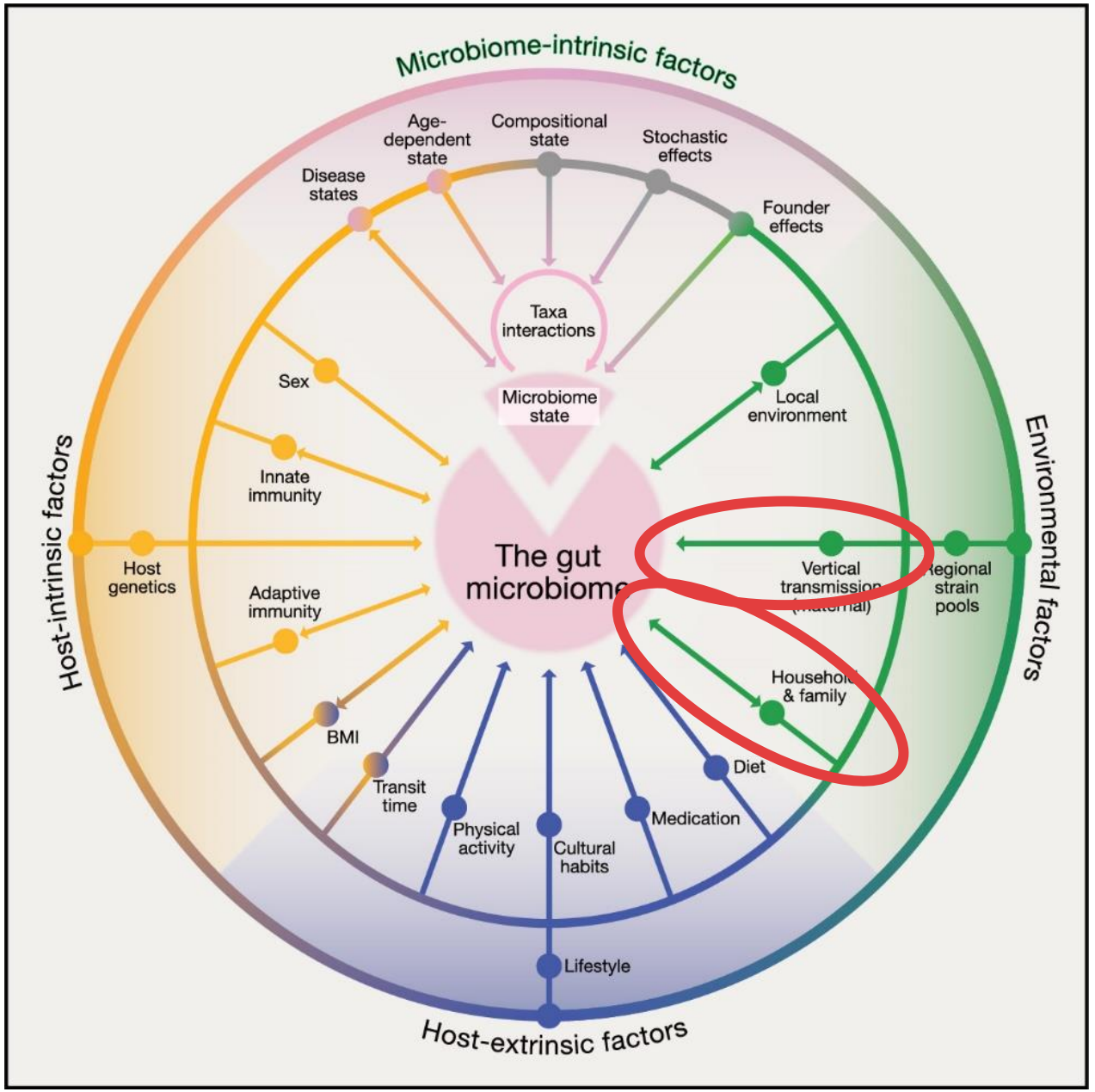
The human gut microbiome variation and associated factors

Effect size of host genetics <2%!

Rothschild et al.. Nature (2018)



Association studies do not reveal causality…does not matter for diagnostics though

Transmission from mother?

Schmidt, Raes# and Bork#, Cell 172(2018)1298

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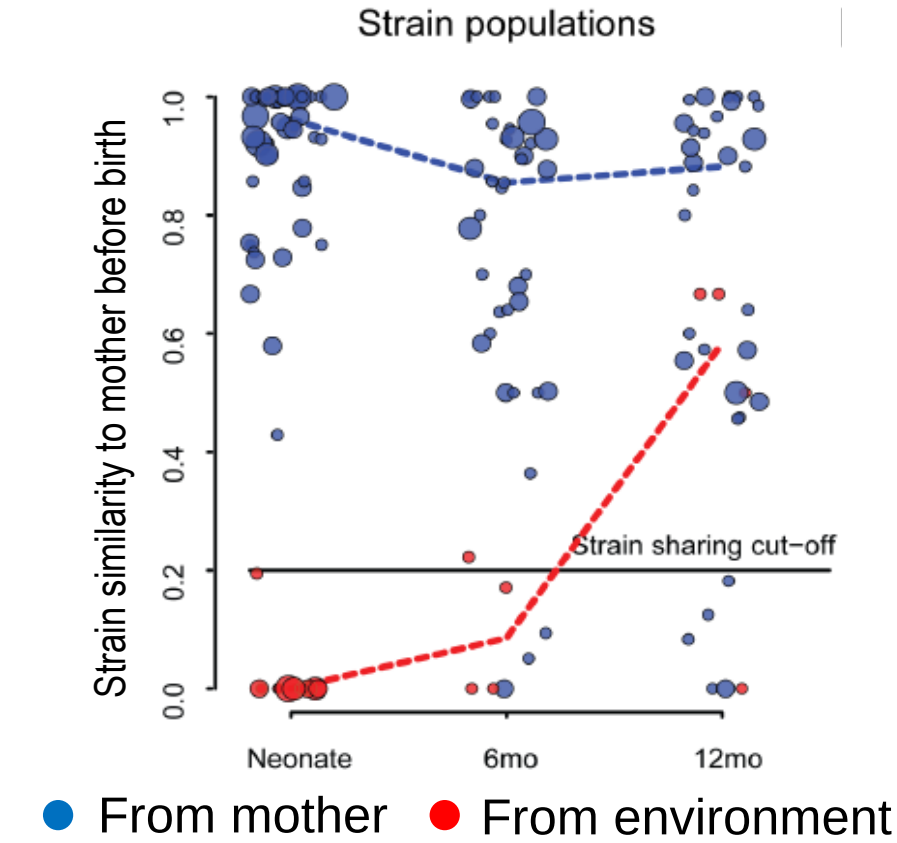
Where do our bugs come from and do we keep them ?

At birth? All from the mother and father has no impact (microbe-wise)?

Baby strains in comparison to their mothers



Cohort: 400 Families from 5 countries:

Most species and strains come from mother via the birth channel

Ferretti et al., Cell Host Mic 24(2018)133

At Caesarean birth bugs come from environment

Also after birth some transmission from mother to baby (more than from father)

Bacterial strains from mother are a kind of protection, as “proven” in mother

Korpela et al., Genome Res. 28(2018)561

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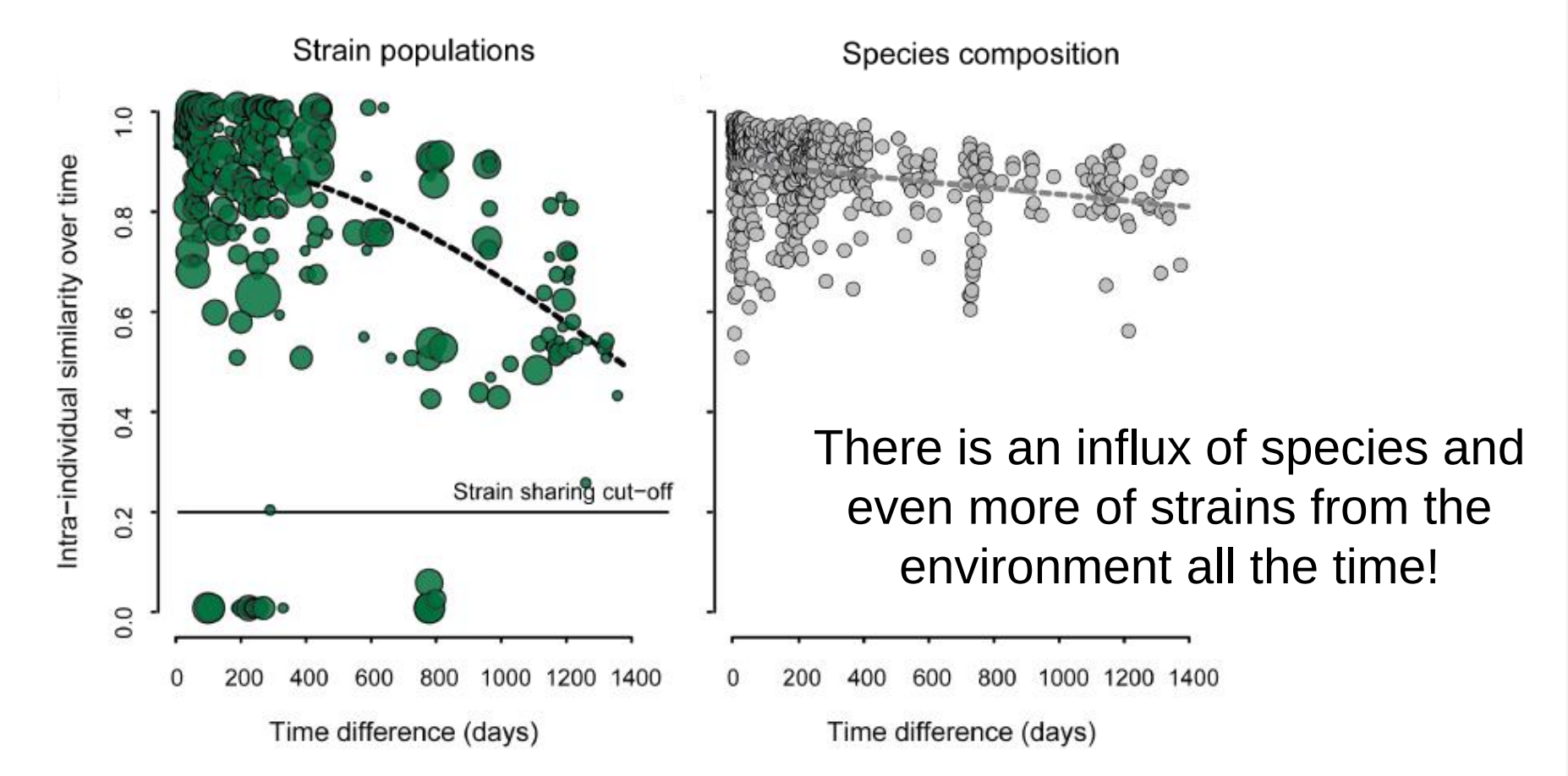
Strain pools change faster than species composition over time



There is an influx of species and even more of strains from the environment all the time!

Environment impacts conspecific strain composition, even species can change

Korpela et al., Genome Res. 28(2018)561

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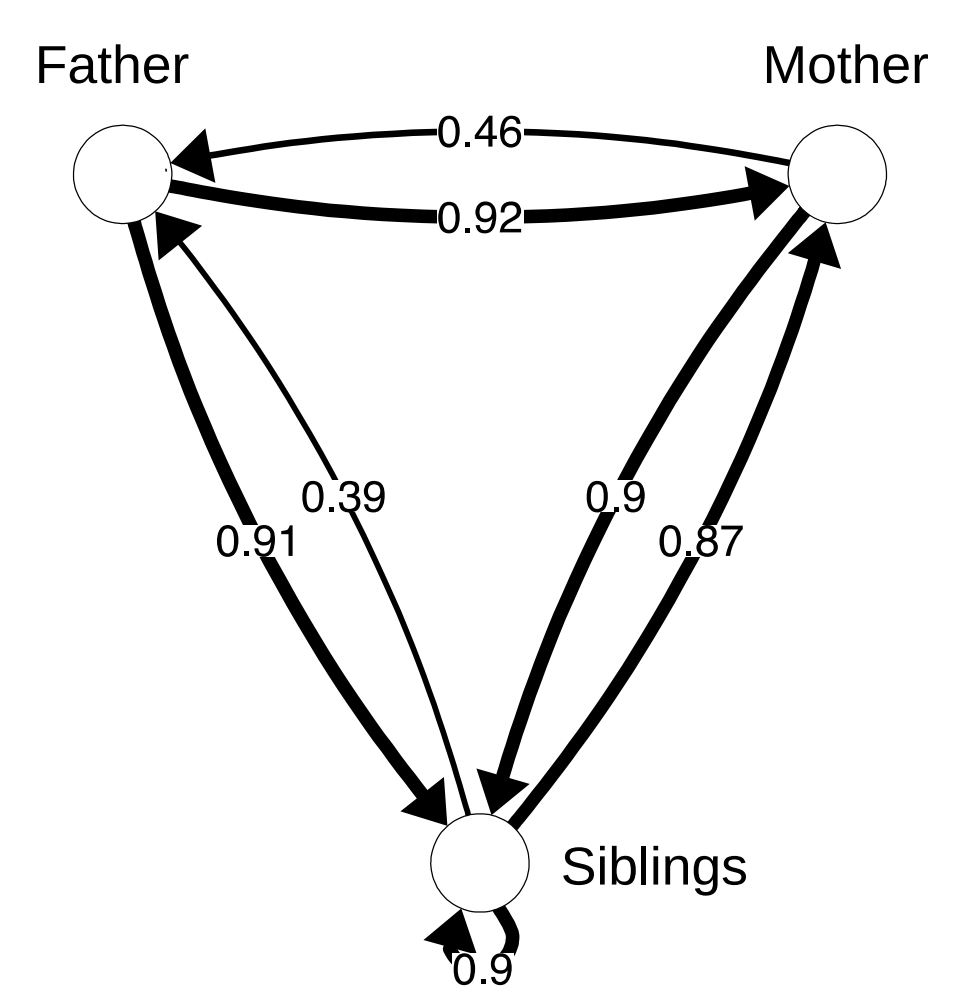
Transmission of gut microbial strains between family members



Longitudinal sampling of family members allows to infer directionality of transfer (first in one person, than in another)

Fathers spread most strains to family members !

Korpela et al., Genome Res. 28(2018)561

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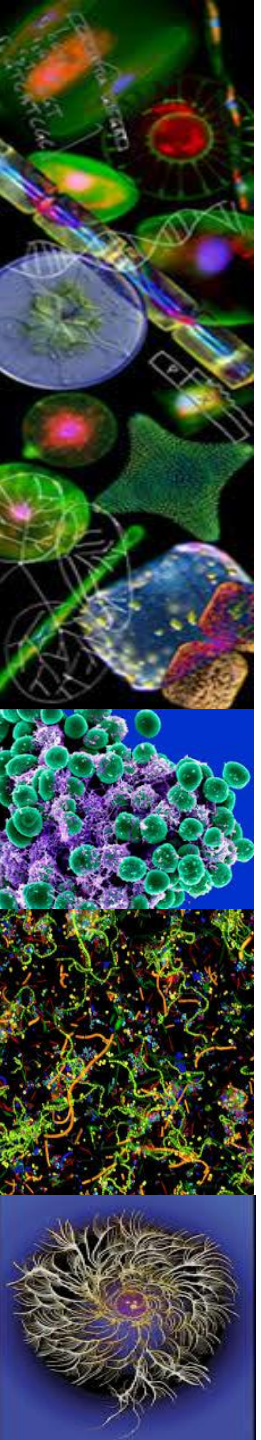

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Medical relevance of the gut microbiome

- **Diagnosis of diseases**: First microbiome-based tests soon applied

- **Personalized medication** after gut microbiome assessment:
  choice of drug (response, resistance awareness), dose, drug combinations, side effect assessment

- **Microbial therapies**: (1) Fecal microbiota transplantation, little understood; needs improvements to be widely applicable, (2) probiotics, (3) prebiotics or combinations of (2) and (3) (synbiotics)

Still many issues due to limited knowledge, e.g.

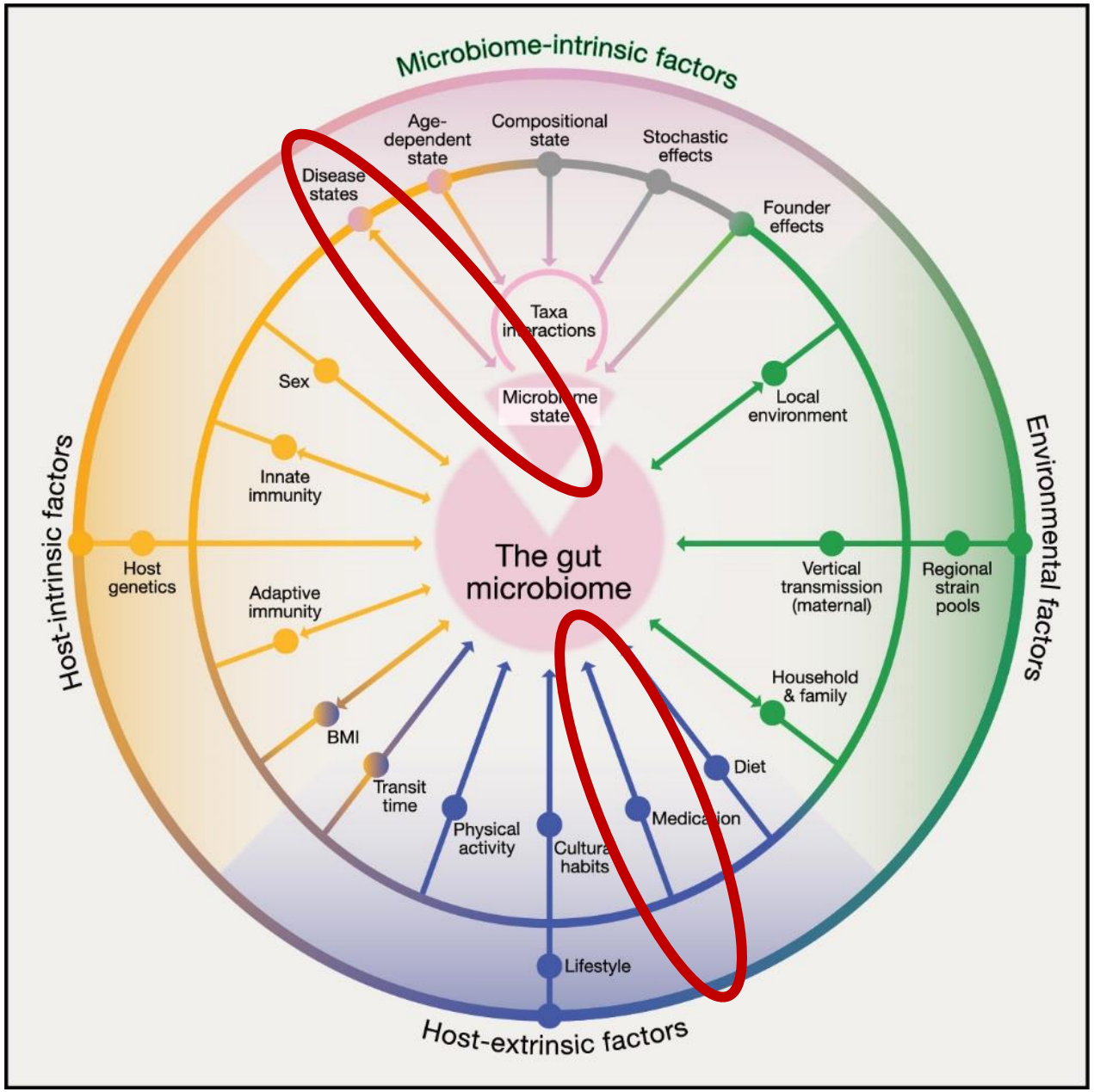
- Due to large individual variations, we still don't know what a "healthy" microbiome is and in how many flavors it can come

- Gut bugs can be "good" or "bad" depending on environment

Microbial biomarkers need to take co-variation into account

Effect size of host genetics <2%!

Rothschild et al.. Nature (2018)



Biomarkers for diagnosis have to be sensitive and (disease-) specific

Medication has effect on microbiome and *vice versa*

Schmidt, Raes# and Bork#, Cell 172(2018)1298

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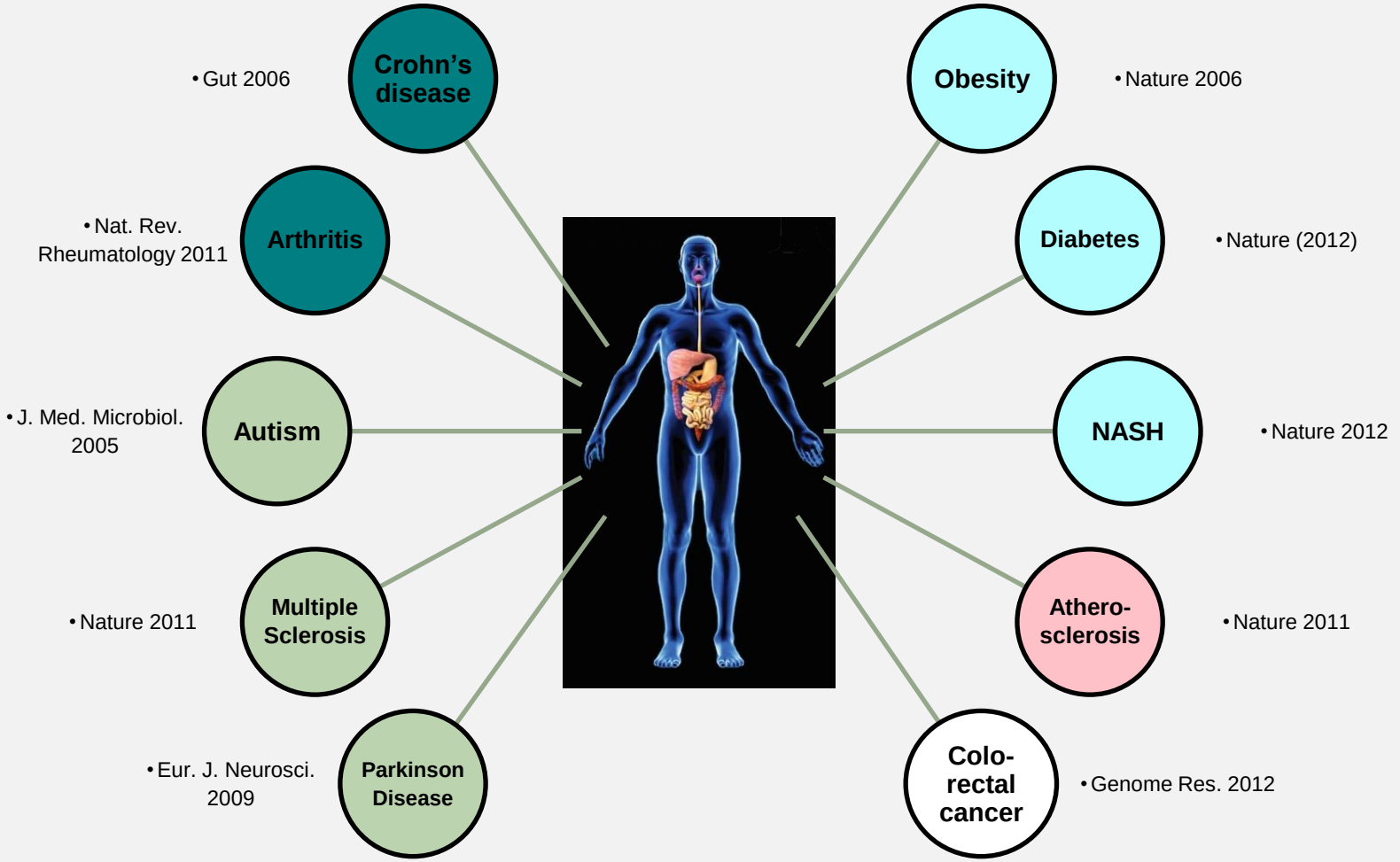
Metagenome-wide association studies (MWAS) link gut microbiome to a multitude of diseases



Yet, we still don't know what „healthy" is!

Indication areas

- Inflammatory diseases
- Neurological disorders
- Metabolic diseases
- Cardiovascular diseases
- Cancer

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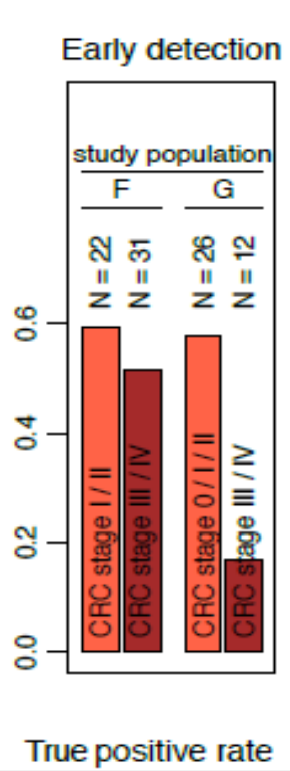
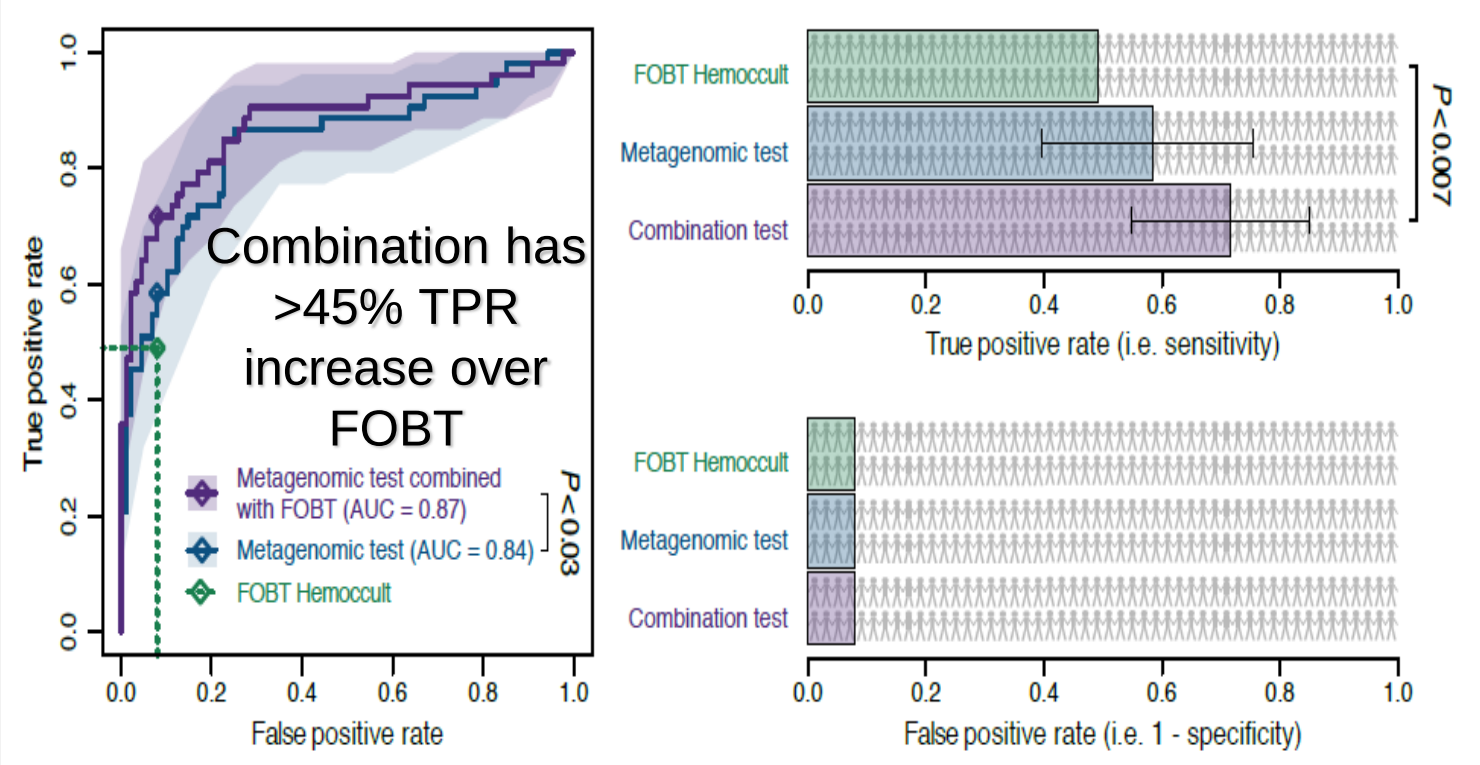
Colon cancer: Early stage detection and complementarity to Fecal occult blood test (FOBT)

French cohort (N=156) with external validation on a German cohort reveals 20+ marker species





Marker species detect stage I/II, not adenomas though

FOBT and microbial signals complementary, a combination thus enhances prediction accuracy…

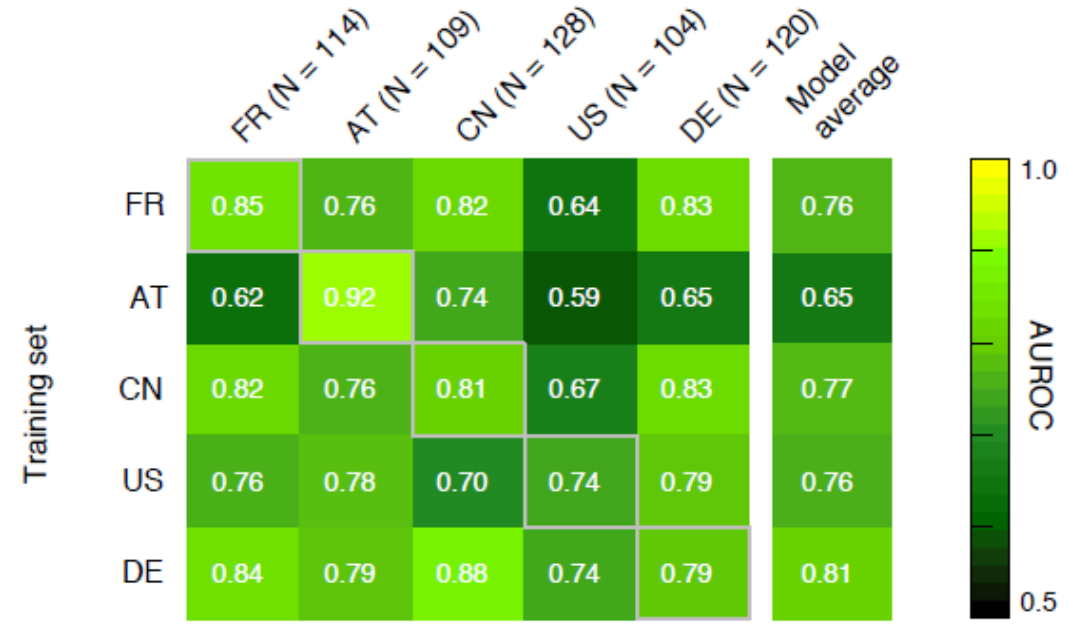
Zeller, Tap*, Voigt* et al, Mol.Sys.Biol. 10(2014)766*

patent granted in 2018

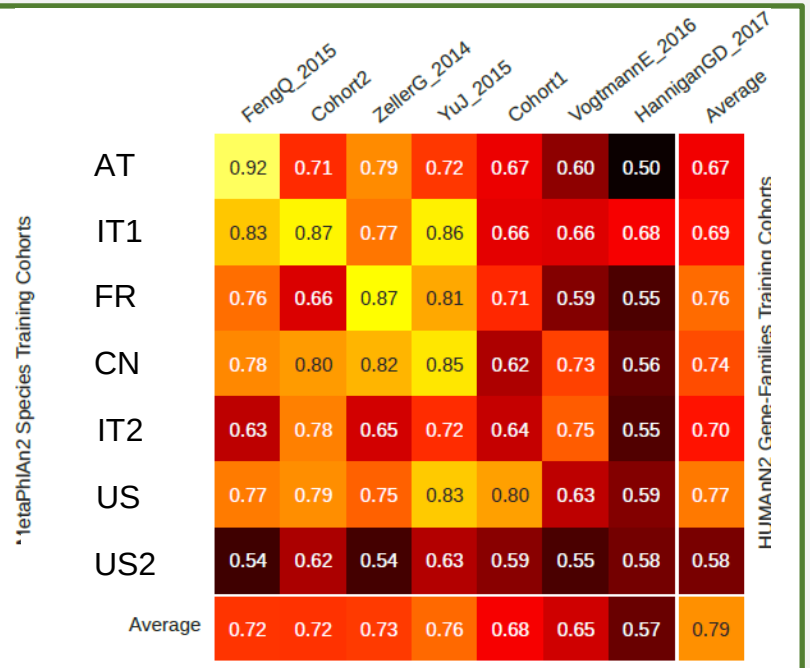
Marker species stand out across country and study biases

Consistency despite different processing and analysis

Several cohorts in 2 studies with consistent signal, additionally validated by 3 external cohorts



Wirbel et. al., Nat. Med. 25(2019)679



Thomas et. al., Nat. Med. 25(2019)667

Two different species-calling approaches (mOTU and metaphlan), different stats etc

Combination of cohorts gains statistical power

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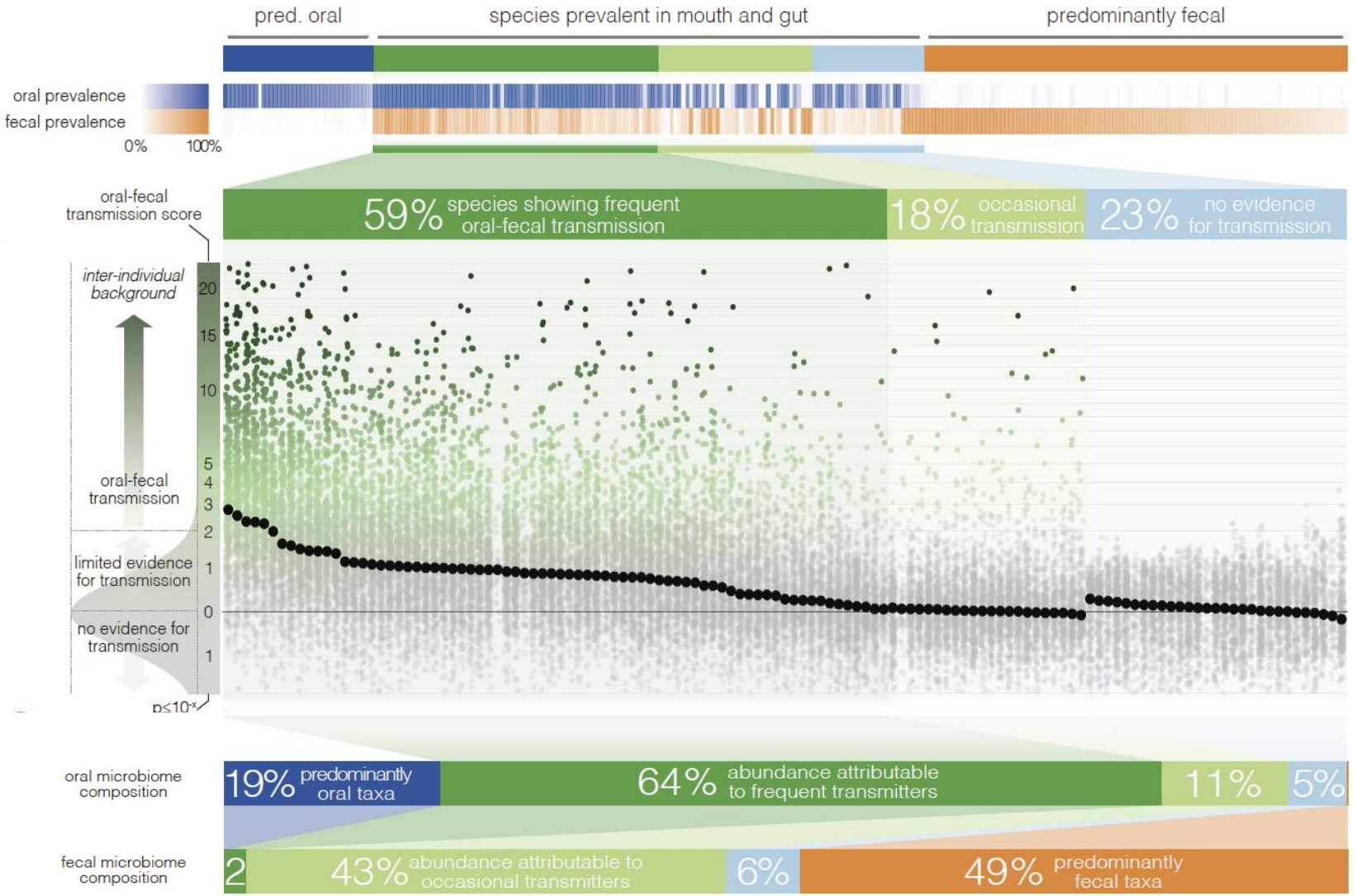
Many oral species are transmitted to gut in healthy individuals



SNV-based identification of transmission:

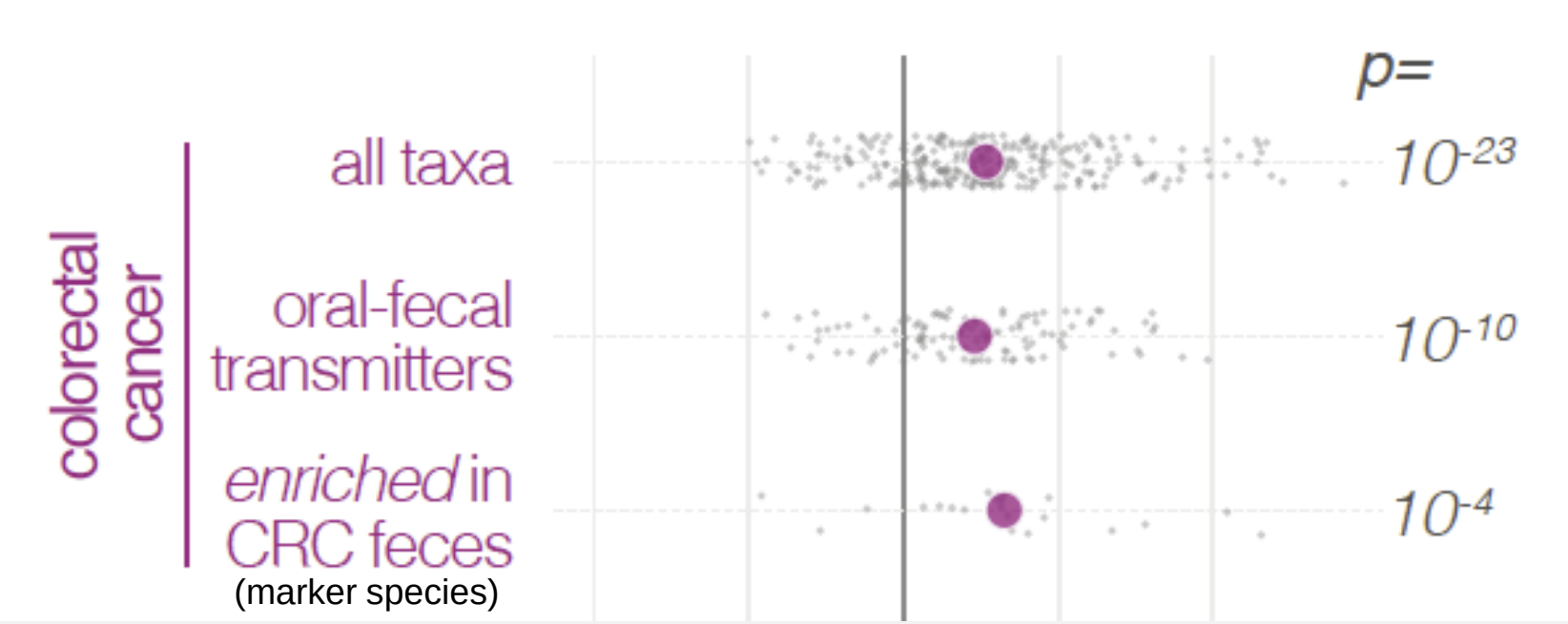
Out of 310 species from 470 healthy individuals, **77% show evidence of transmission**

45% of fecal species are at least occasionally replaced by oral strains

Schmidt, Hayward et. al., eLife (2019) e42693

Many CRC marker species are oral, transmitted and from patient

In CRC patients, transmission is increased over healthy, even more so for marker species



Schmidt, Hayward et. al., eLife (2019) e42693

…all great, but metagenomics 500 EURO, FOBT 5 Euro…

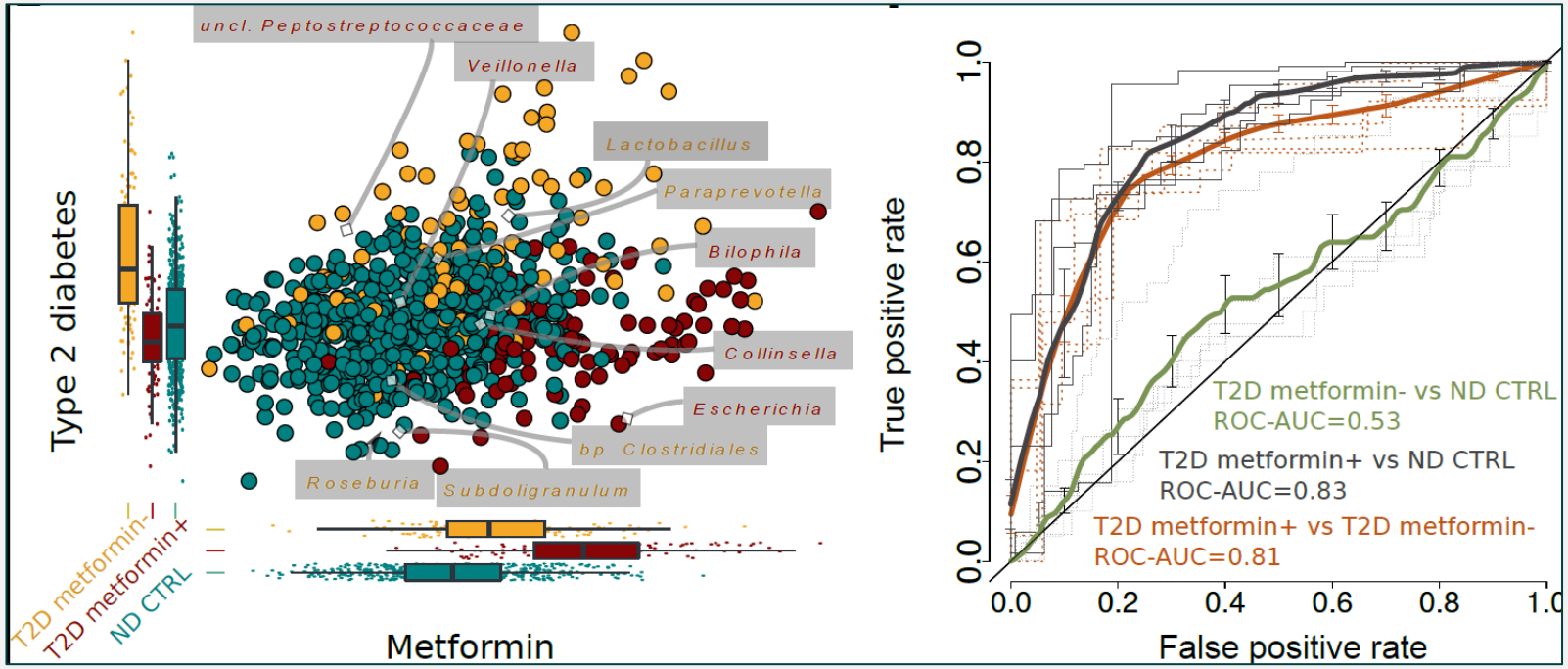
Associations can be unspecfic, confounded or indirect

(What if all CRC patients have inflammation and we developed an unspecific inflammation test?)

“The gut microbiome is associated with type 2 diabetes”

Qin et al., Nature 2012, AUC 0.81 (Chinese cohort) *Karlsson et al., Nature 2013* AUC 0.83 (Swedish cohort)

BUT the drug metformin is a major confounder that needs to be disentangled



Forslund, Hildebrand et al., Nature 228(2015)262

(with EU Metahit consortium)

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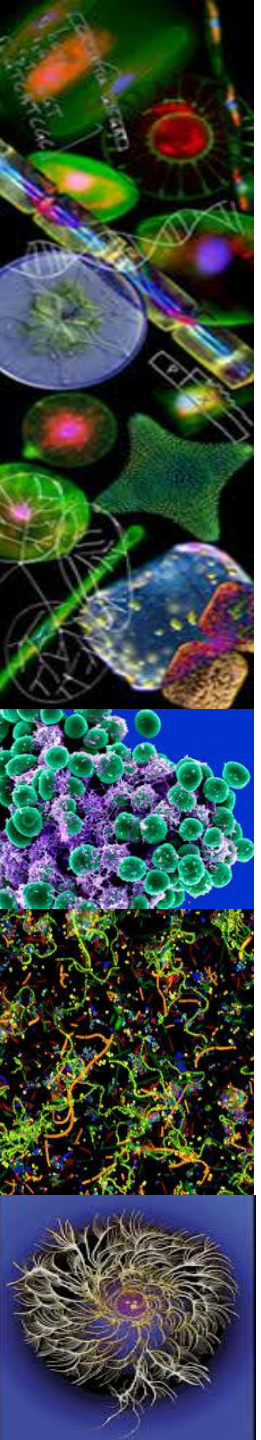

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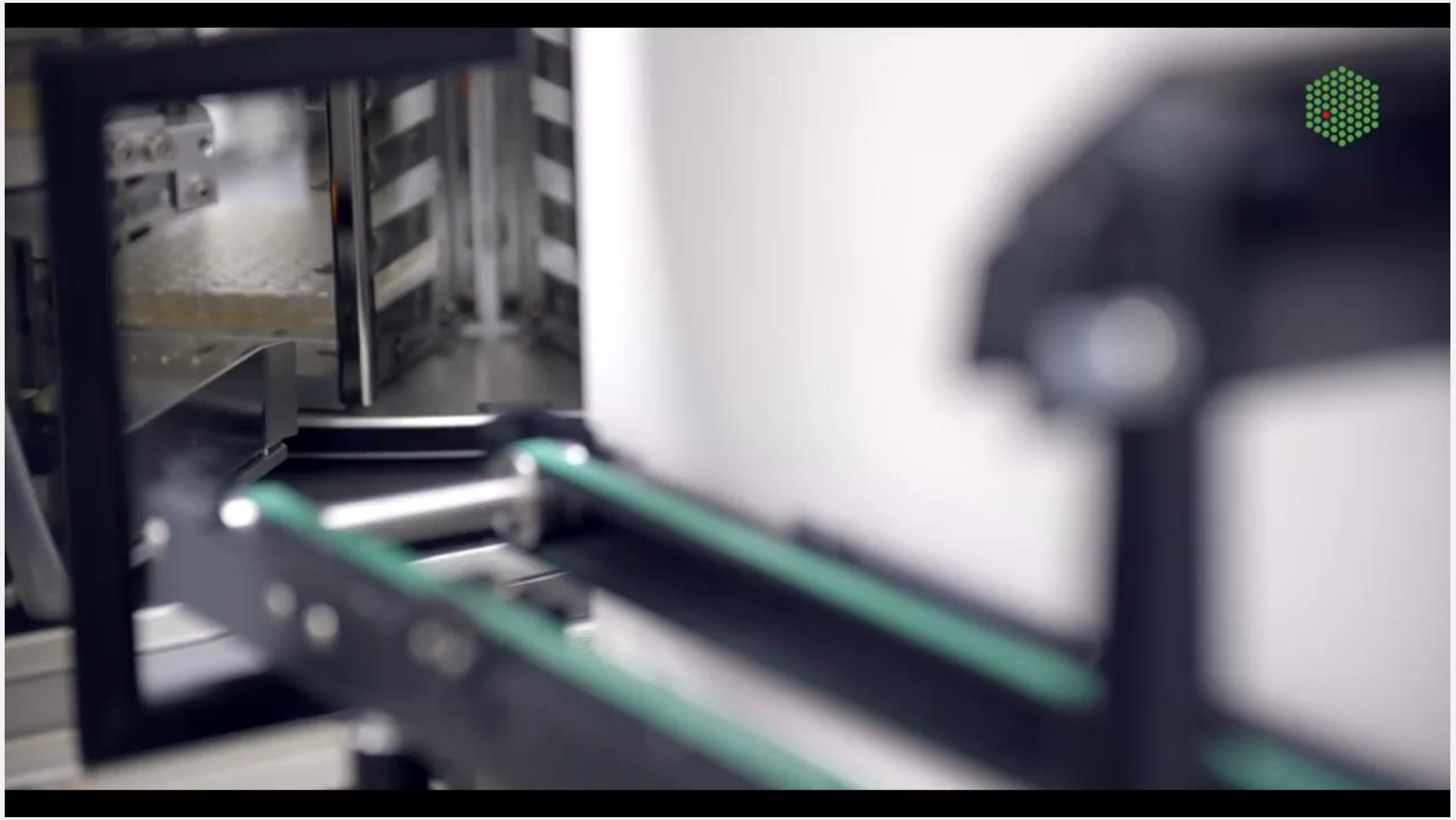
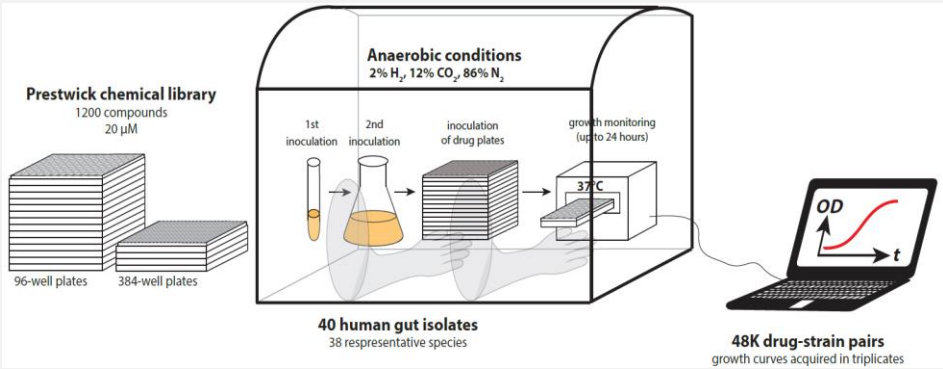
(1) Therapy by medicinal drugs

In vitro drug-bug screen for direct interactions

1200 medicinal drugs vs 40 representative gut strains





Automation of work flow at EMBL, robotics also in anaerobic chamber; 1200 drugs vs 1 bug in 1 day

Movie by EICAT

With Typas, Patil and Zeller groups at EMBL

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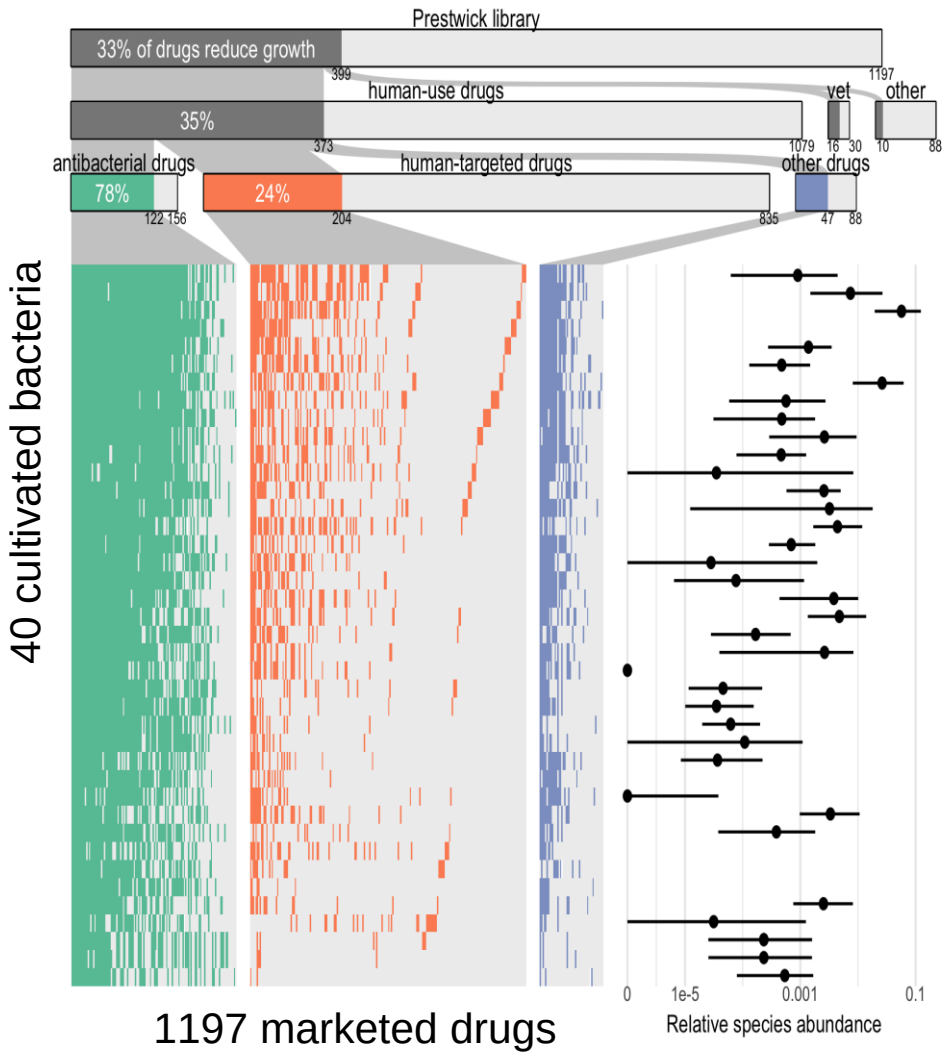
Many “human targeted” therapeutic drugs change our gut microbiome



- Antibacterial
- Human-targeted
- Antifungal and antiviral

>24% of the human-targeted drugs deplete at least one gut bacterium

This fraction is probably much higher
(low doses, only 40 of 1000+ tested)

Some changes part of drug action,
most lead to unwanted side effects

With Typas, Patil and Zeller groups at EMBL

Maier, Pruteanu, Kuhn et al., Nature 555(2018)623

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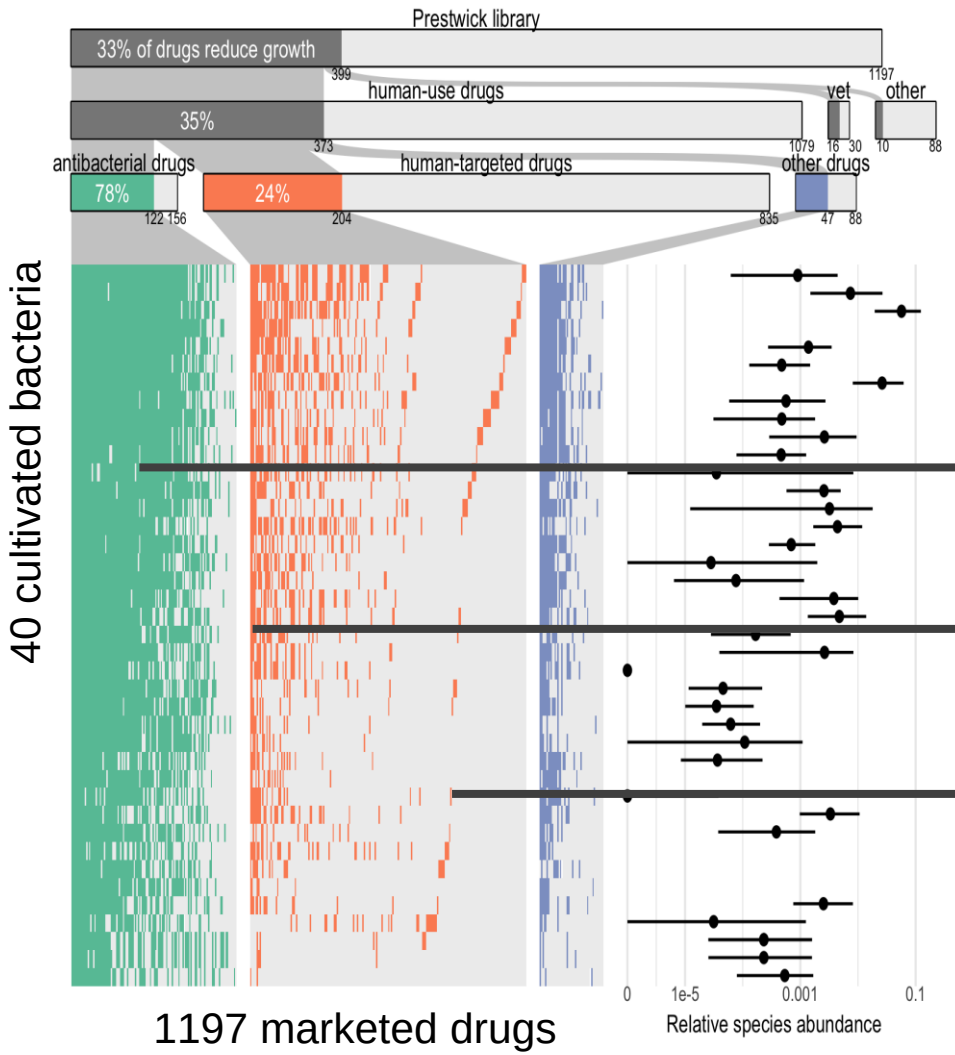
Many “human targeted” therapeutic drugs change our gut microbiome



- Antibacterial
- Human-targeted
- Antifungal and antiviral

Drugs as baseline for new antibiotics?

Antibiotics are designed against pathogens, not against commensals

Some human-targeted drugs act like broad-spectrum antibiotics

Some drugs only inhibit one specific species

With Typas, Patil and Zeller groups at EMBL

Maier, Pruteanu, Kuhn et al., Nature 555(2018)623

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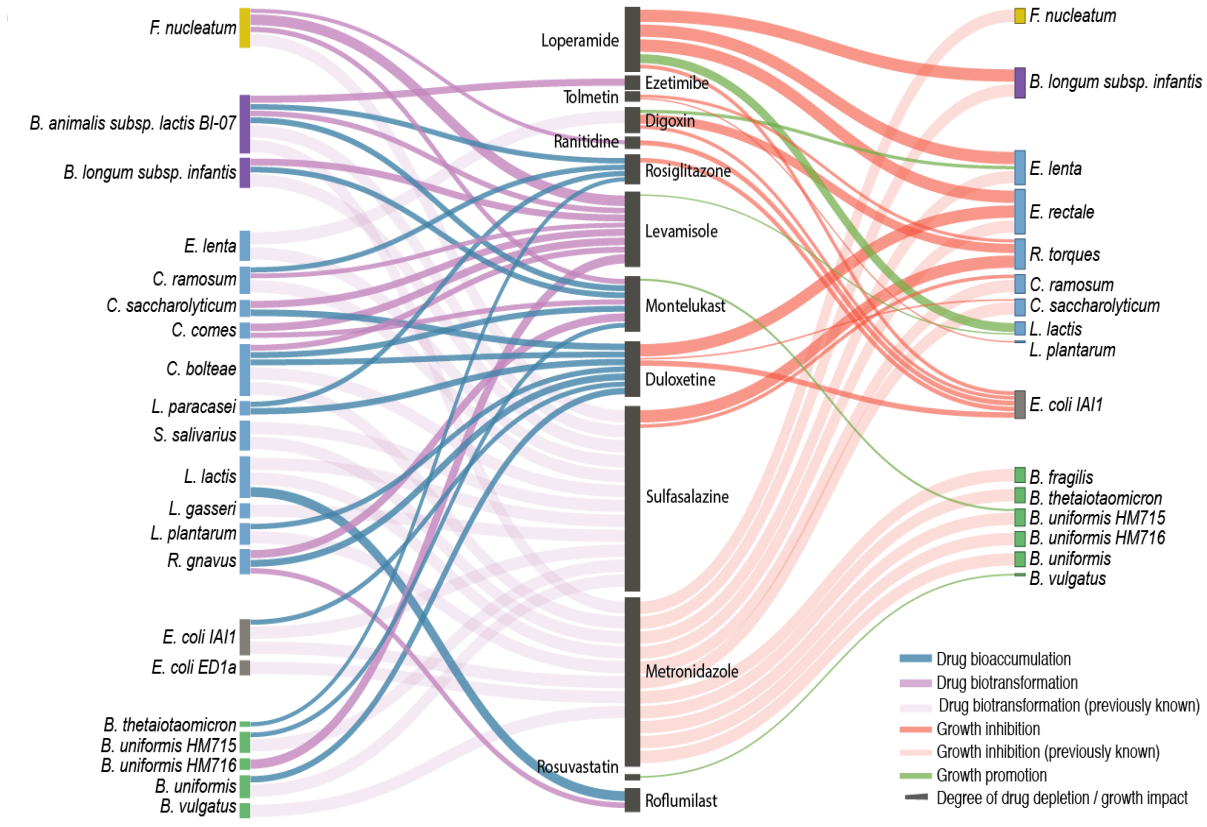
Quantifying the impact of bug on drugs
(in addition to drugs on bugs)

Gut bacteria interact with drugs and food (e.g. biotransformation)



Pilot: 25 bugs vs 15 drugs

Bacteria can modify or accumulate drugs, thus changing pharmacology of drugs

Bioaccumulation is a considerable drug-bug interaction category

Emerging individual drug-bug and drug-chemical interaction networks

Goal: individual microbiome status guides medication

With Patil and Typas groups (EMBL); Brochado et al., Nature 2018, Klünemann et al., Nature, in revision

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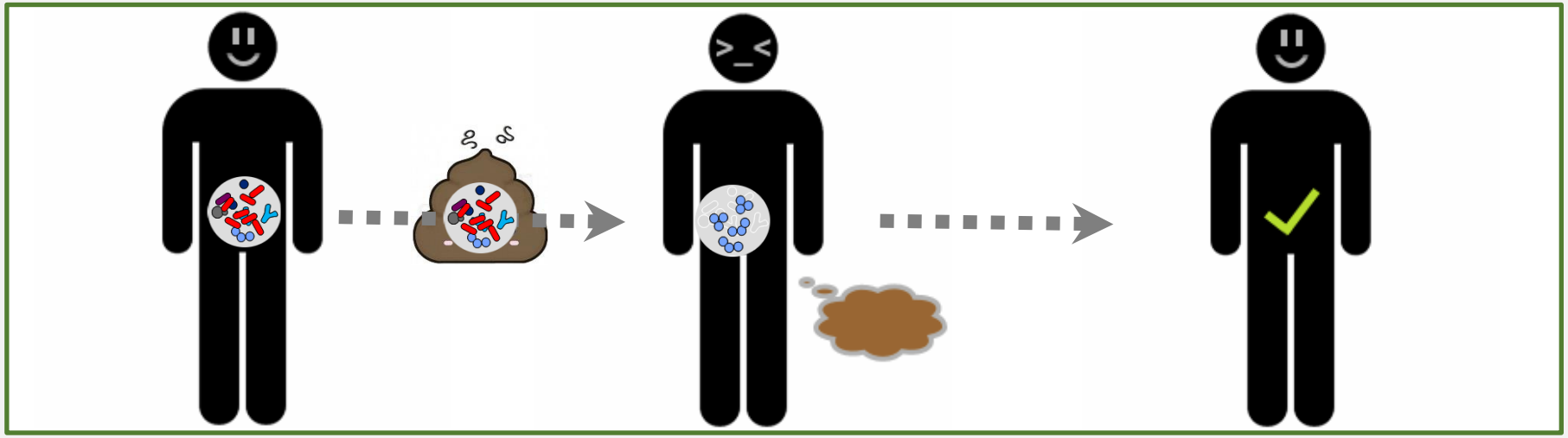
(1) Microbial therapy:
Tracing strain transfer in Fecal Microbiota Transplantation (FMT)



Analysis usually at species/OTU level, but most species are shared

- Transfer of stool from a healthy donor to patient
  - Usually following antibiotics treatment or bowel lavage
- Positive effects reported in GI and non-GI diseases
  - Over 90% success in treating *Clostridium difficile* infection
  - Not so straight forward in other diseases
- Mechanism is still unknown

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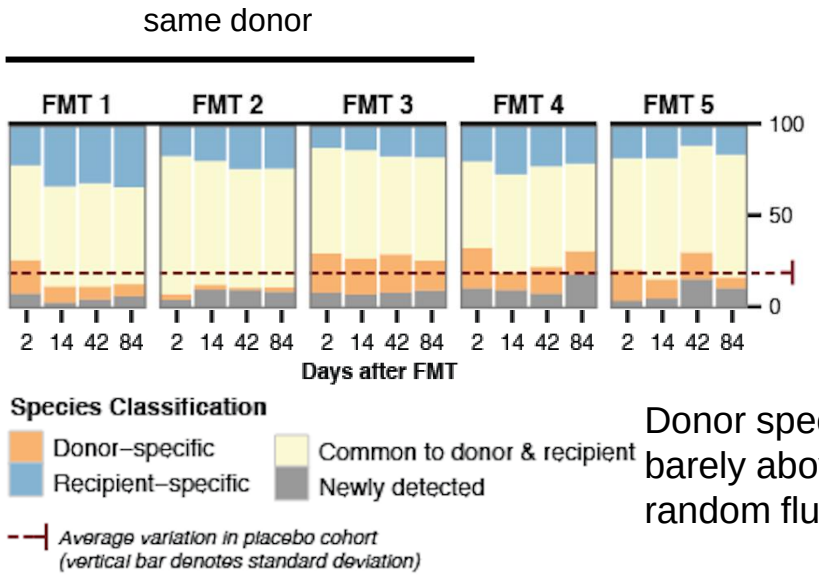
Strain replacement after FMT for metabolic syndrome

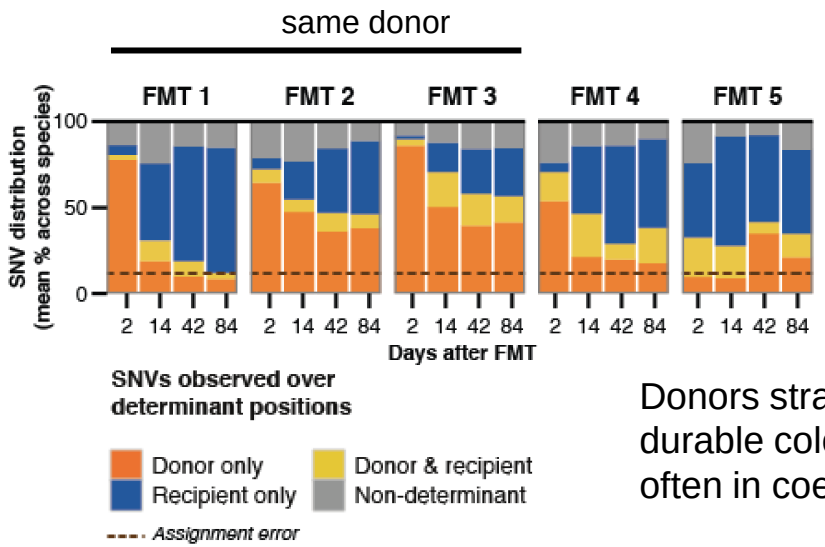
The need of donor-recipient microbiome “compatibility”

Species



Donor species barely above random fluctuation

Strains



Donors strains with durable colonization, often in coexistence

1. There is no “superdonor” – 1 donor has different outcomes
2. Donor strains can colonise and persist over at least 3 months
3. New donor strains colonise better than donor species, perhaps by hiding from the immune system
4. Extensive donor and recipient strain coexistence

Strain replacement implies personalized treatment options, e.g. by replacing multidrug resistance.
Thus, microbiome census first, then treatment

With W. de Vos, M. Nieuwdorp

Li et al., Science 352(2016)586

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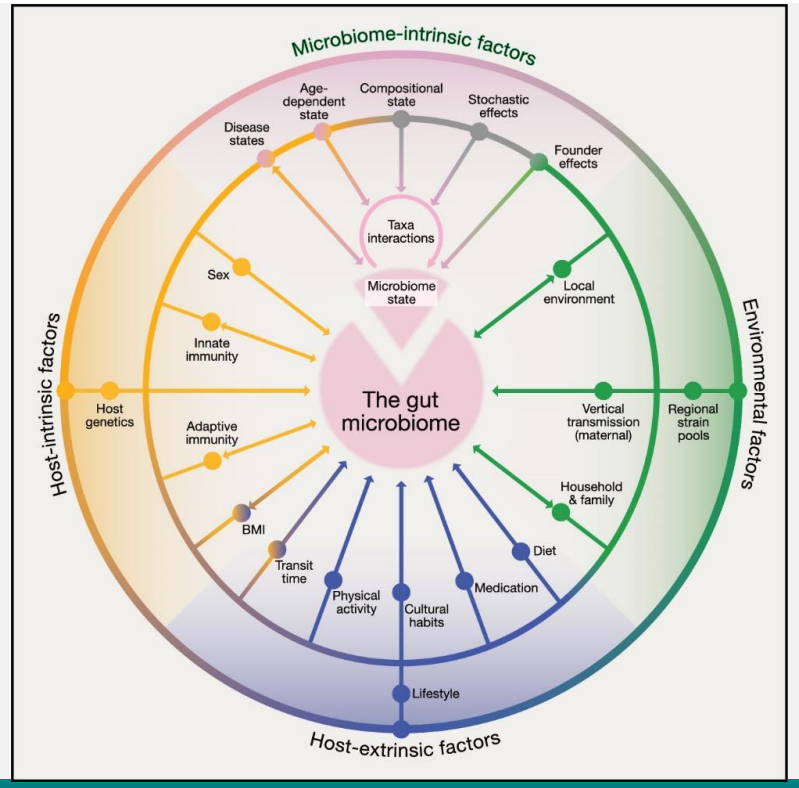
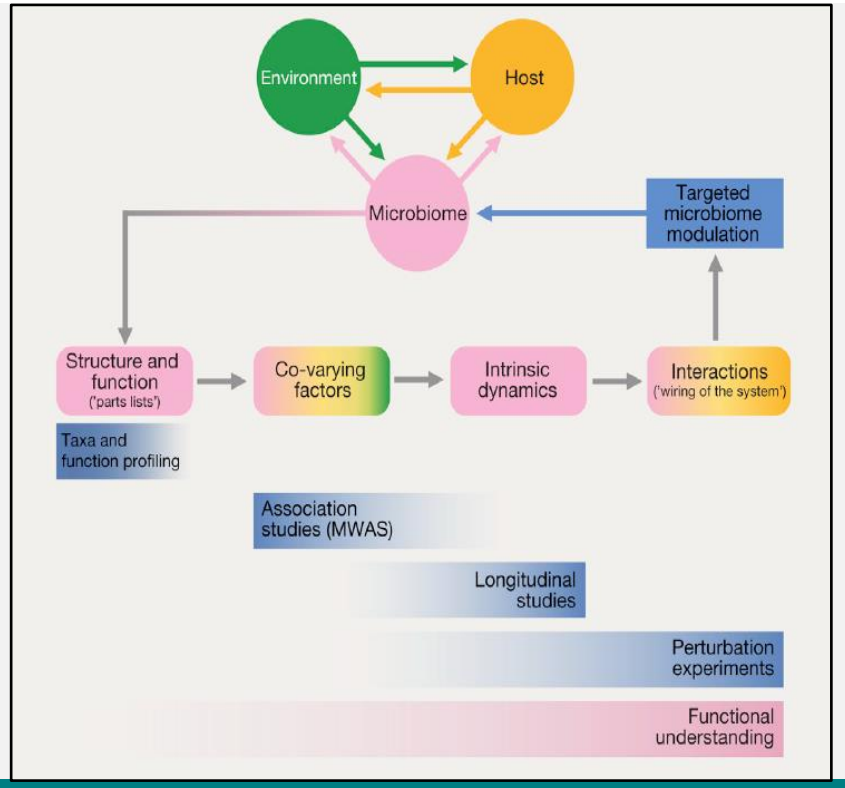
The human gut microbiome and its clinical relevance





Metagenome-wide association studies (MWAS) still reveal basics and are sufficient for diagnostics

MWAS need to be coupled with *in vitro* microbiomics for mechanistic insights enabling individual modulation

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Deciphering function and evolution of biological systems

The main focus of this **Computational Biology** group is to predict function and to gain insights into evolution by comparative analysis of complex molecular data. The group currently works on three different scales:

- **genes and proteins,**
- **protein networks and cellular processes, and**
- **phenotypes and environments.**

They require both tool development and applications. Some selected projects include comparative gene, genome and metagenome analysis, mapping interactions to proteins and pathways as well as the study of temporal and spatial protein network aspects. All are geared towards the bridging of genotype and phenotype through a better understanding of molecular and cellular processes.

The group is partially associated with Max Delbrück Center for Molecular Medicine (MDC), Berlin.

Selected recent publications and News

Disentangling Genetic and Environmental Effects on the Proteotypes of Individuals.
Romanov N, Kuhn M, Aebersold R, Ori A, Beck M, Bork P
Cell 177, 1-11, 2019 Apr 25, doi: 10.1016/j.cel..2019.03.015
Abstract+PDF

Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer.
Wirbel J, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, Fleck JS, Voigt AY, Palleja A, Ponnudurai R, Sunagawa S, Coelho LP, Schrotz-King P, Vogtmann E, Habermann N, Niméus E, Thomas AM, Manghi P, Gandini S, Serrano D, Mizutani S, Shiroma H, Shiba S, Shibata T, Yachida S, Yamada T, Waldron L, Naccarati A, Segata N, Sinha R, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G.
Nature Medicine, Epub 2019 Apr 1; 25(4):679-689, doi: 10.1038/s41591-019-0406-6
Abstract

Structure and function of the global topsoil microbiome.
Bahram M, Hildebrand F, Forslund SK, Anderson JL, Soudzilovskaia NA, Bodegom PM, Bengtsson-Palme J, Anslan S, Coelho LP, Harend H, Huerta-Cepas J, Medema MH, Maltz MR, Mundra S, Olsson PA, Pent M, Pölme S, Sunagawa S, Ryberg M, Tedersoo L, Bork P
Nature, 2018 Aug 1, 10.1038/s41586-018-0386-6
Abstract

Pervasive Protein Thermal Stability Variation during the Cell Cycle
Becher I, Andrés-Pons A, Romanov N, Stein F, Schramm M, Baudin F, Helm D, Kurzawa N, Mateus A, Mackmull MT, Typas A, Müller CM, Bork P, Beck M, Savitski MM
Cell, 2018 Apr 26, doi:10.1016/j.cell.2018.03.053
Abstract

Extensive impact of non-antibiotic drugs on human gut bacteria.
Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, Fernandez KC, Dose H, Mori H, Patil KR, Bork P & Typas A.
Nature, SharedIt link 2018 March 19, doi:10.1038/nature25979
Abstract

The Human Gut Microbiome: From Association to Modulation.
Schmidt TSB, Raes J, & Bork P.
Cell, View it online 2018 March 8, Volume 172, Issue 6, p1198–1215 doi:10.1016/j.cell.2018.02.044

For details see: www.bork.embl.de

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