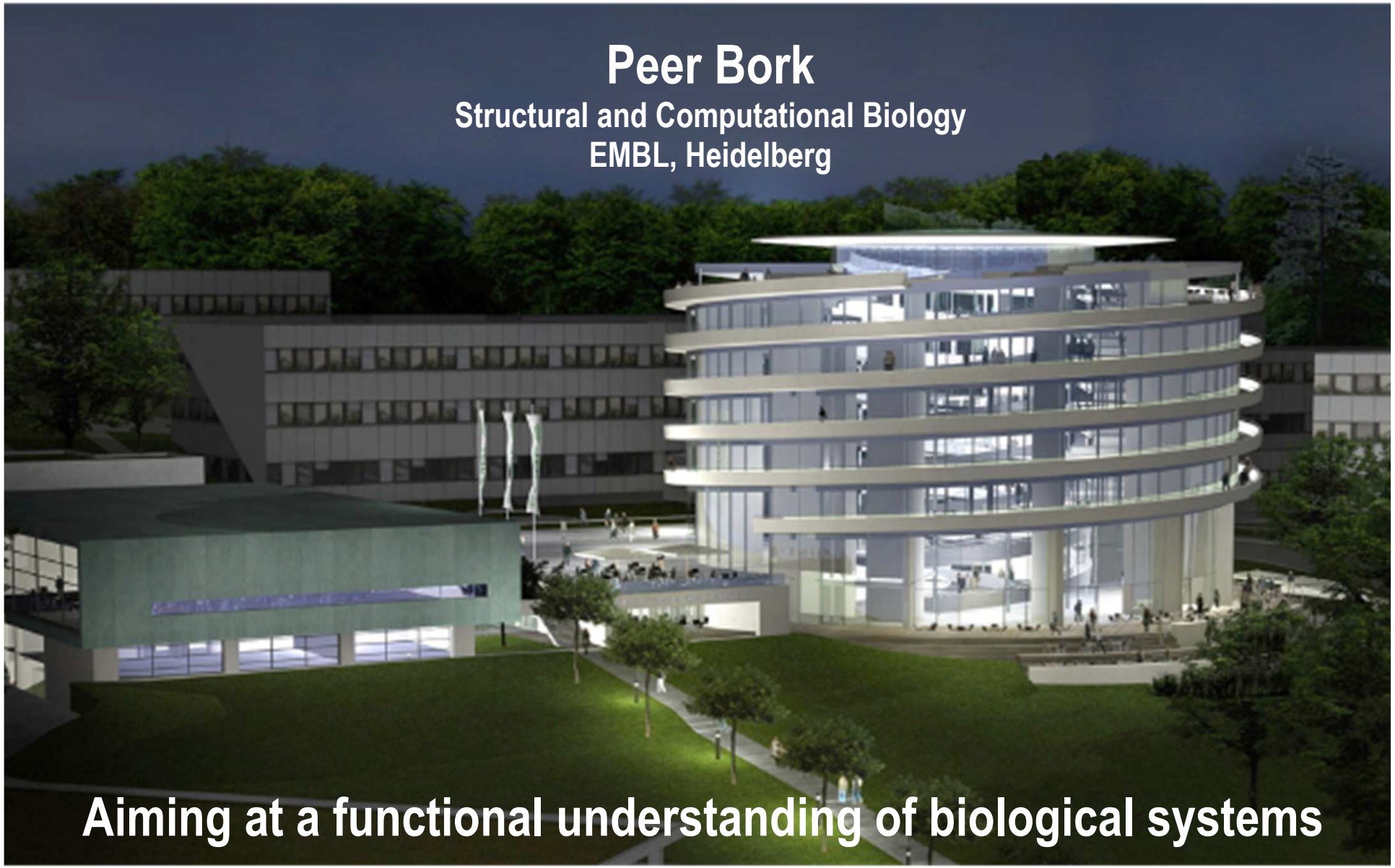
Clinical microbiomics
Towards diagnostics and personalised intervention

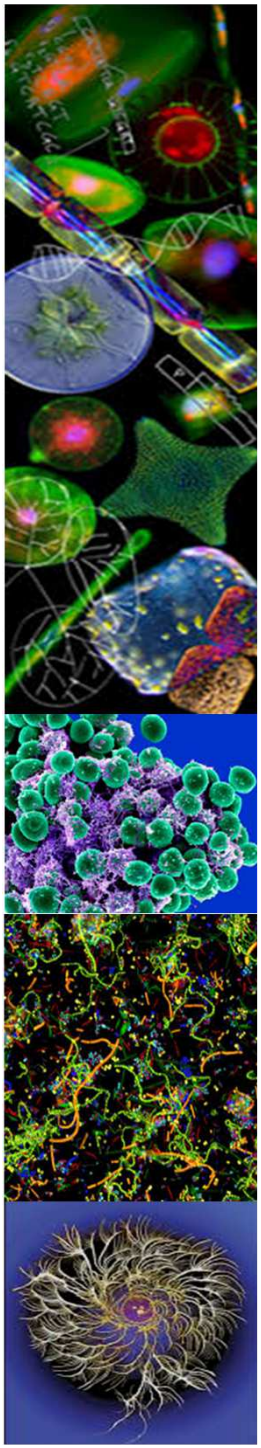


Clinical microbiomics
Towards diagnostics and personalised intervention

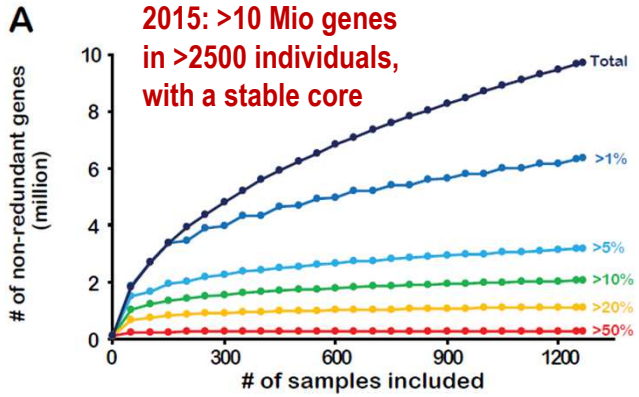
I. Association of the human microbiome with diseases
- Colon cancer: From biomarker discovery to diagnostics

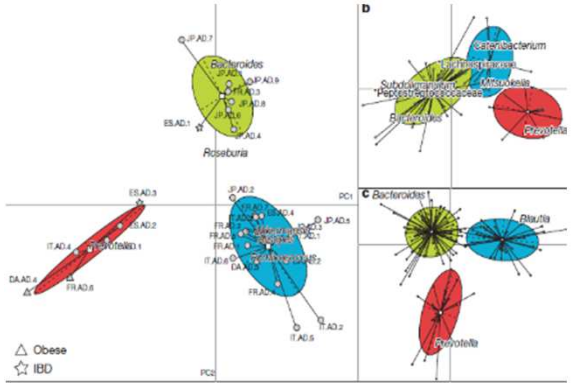
II. Effects of marketed drugs on gut microbes
- From observations to screening

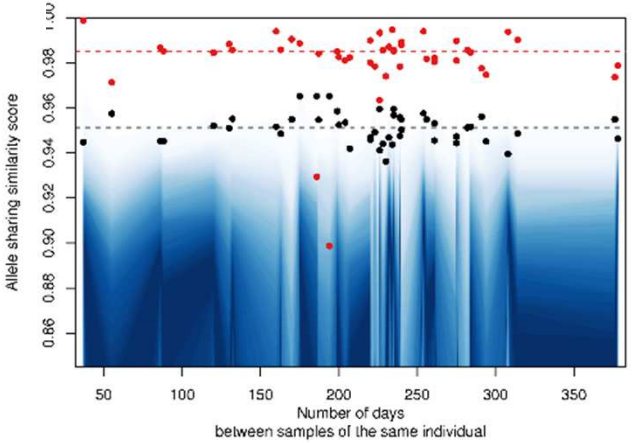
III. First interventions: Faecal microbiota transplantation
- Towards mechanistic understanding



Community structure of the gut and disease associations are being established…







Structure and function of gut microbiomes, provision of gene reference catalogs

Qin et al., Nature 464(2010)59
Li et al., Nature Biotech. 32(2014)834

ca 250 of > species per sample seen, gene count not saturating due to increase of rare genes

Stratification of the population (enterotypes)

Arumugam et al. Nature 473(2011)174
Costea et al., in revision (white paper)

Microbiota landscape with 2-3, perhaps more, density areas with still unclear cause (diet contributes)

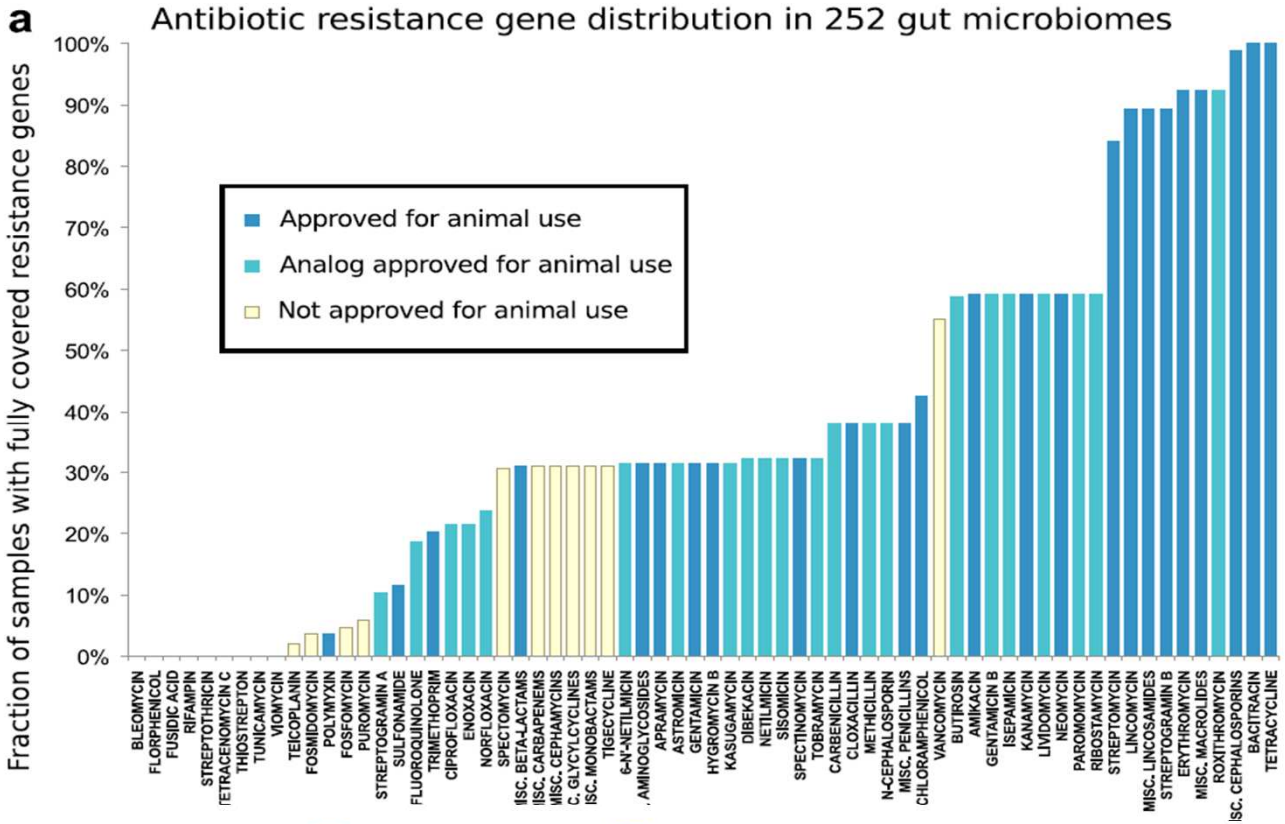
Strain-level resolution

Schloissnig et al., Nature 493(2013)45
Zhu et al, Genome Biol. 16(215)82

Two individuals differ in >4% SNPs and >13% gene content in a species they share

…but most published studies are statistically underpowered

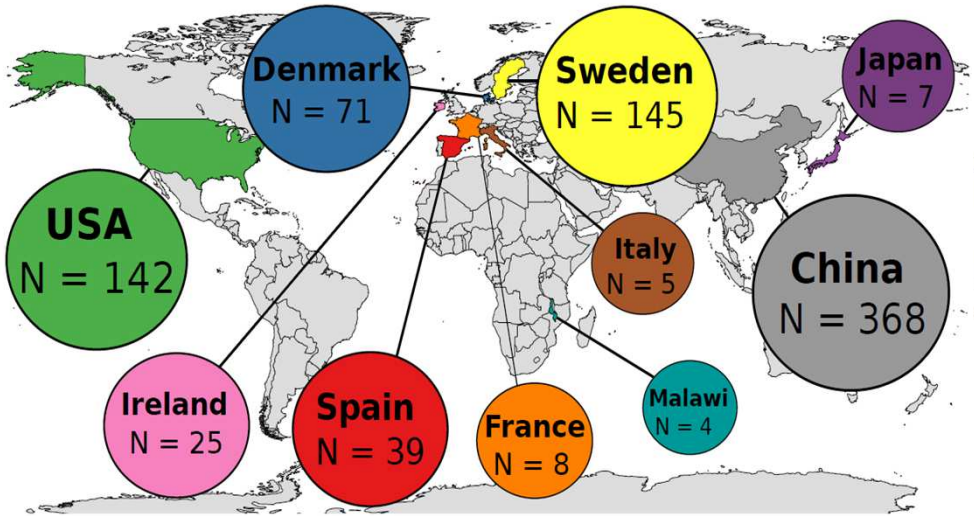
All kind of features (here antibiotic resistance) are being profiled…

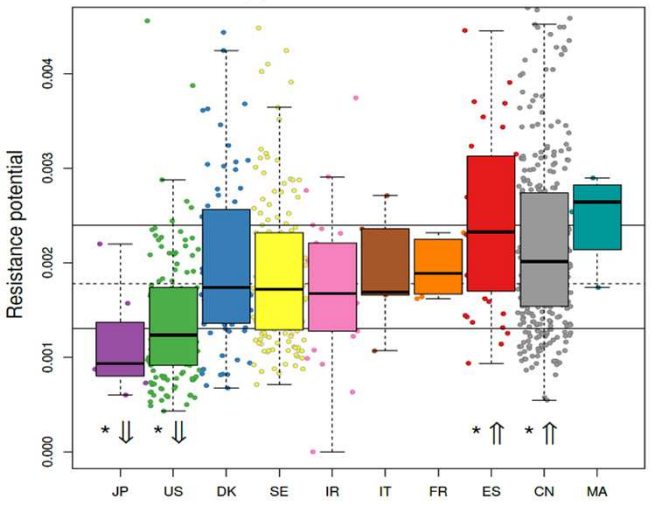


Ca 5Gb per individual mined for 370 genes that are known to provide resistance to 68 antibiotics classes

Antibiotic resistance potential in gut microbiota is associated with use in animals

Forslund et al.
Genome Res. 23(13)1163
Bioessays 36 (14)316





Regional differences

Goal is 5000 samples

500k Euro so far

Operates since Sep. 2011

Currently 550 Euro

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Cutting-edge Approach

Join an exciting scientific study and help to explore the ecosystems living within us.

Welcome to **my.microbes**

Microbes live in, on and around us all the time, contributing approximately 2 kilograms to our

Latest News

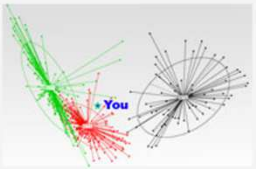
Enterotypes

Sampling DNA extraction Sequencing Analysis

Our Concept

Using samples collected non-invasively from different parts of human body, we will analyze

Individual Results



As a participant in our studies, you will have direct, free access to your personal analysis

A Global Network

Participants can (but don't have to) contact people with similar microbial profiles around the

If you would like to receive more details and be notified when we begin the public stage of our studies, please contact us.

my.microbes.eu

Donate or participate!

Personalized my.microbes report

Raw DNA amount:	6,604,063,163 bases (6.60 Gb)	which is 32.1% above average
High quality DNA:	5,346,005,086 bases (5.35 Gb)	which is 6.9% above average
Human DNA contamination:	0.175082%,	which is very low

Version 2

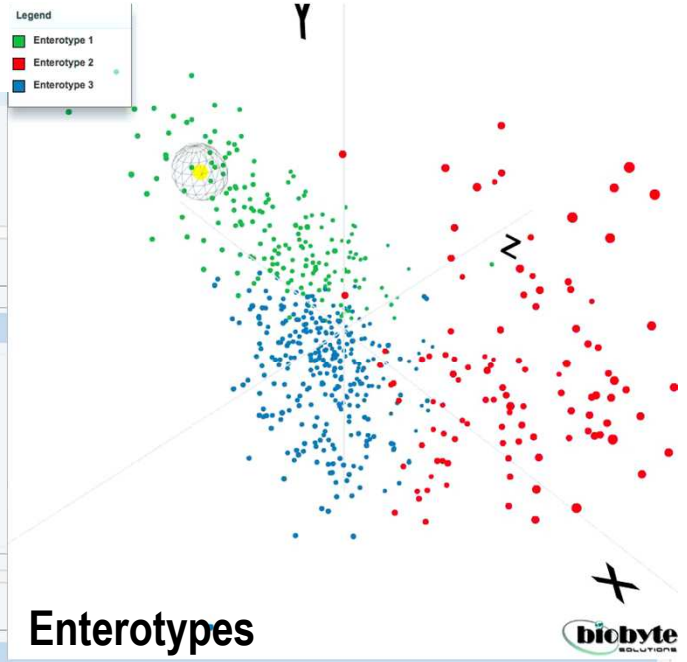
Highlights of detected deviations in your sample

Microbial genera/species with highest deviation from population average

The following microbial genera/species are present in high abundance in your sample, compared to our current participant population (**921** samples).

Detailed information and disclaimers

Genus	Deviation
Faecalibacterium	+11.44%
Roseburia	+6.4%
Bifidobacterium	+4.4%



Enterotypes

biobyte SOLUTIONS

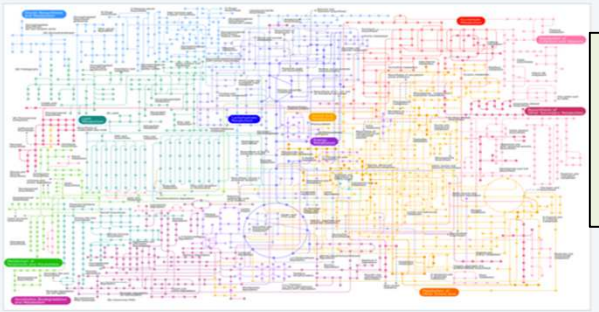
Genome/proteome functional analysis

KEGG orthologous group mapping

The genes predicted in your sample were mapped onto KEGG orthologous groups. The table below shows the top 10 most abundant KO groups detected. Click the KO identifiers to display further information about them at the KEGG web site.

To visualize all detected KOs in the interactive Pathways Explorer v2, click the map image below. Edges in the map which contain KOs detected in your sample will be colored red. Their widths will be directly proportional to the KO abundance in your sample.

Abundance	KEGG ID	Orthologous group name
0.643 %	K06147	ABCB-BAC; ATP-binding cassette, subfamily B, bacterial
0.586 %	K02004	ABC.CD.P; putative ABC transport system permease protein
0.535 %	K03088	SIG3.2, rpoE; RNA polymerase sigma-70 factor, ECF subfamily
0.507 %	K02003	ABC.CD.A; putative ABC transport system ATP-binding protein
0.352 %	K05349	bglX; beta-glucosidase [EC:3.2.1.21]
0.344 %	K03169	topB; DNA topoisomerase III [EC:5.99.1.2]
0.33 %	K01190	lacZ; beta-galactosidase [EC:3.2.1.23]
0.306 %	K07024	K07024
0.298 %	K03496	parA, soj; chromosome partitioning protein
0.292 %	K00850	pfkA, PFK; 6-phosphofructokinase 1 [EC:2.7.1.11]



approved by EMBL-ethics commission

Other microbiota-related properties

Nucleotide variation analyses

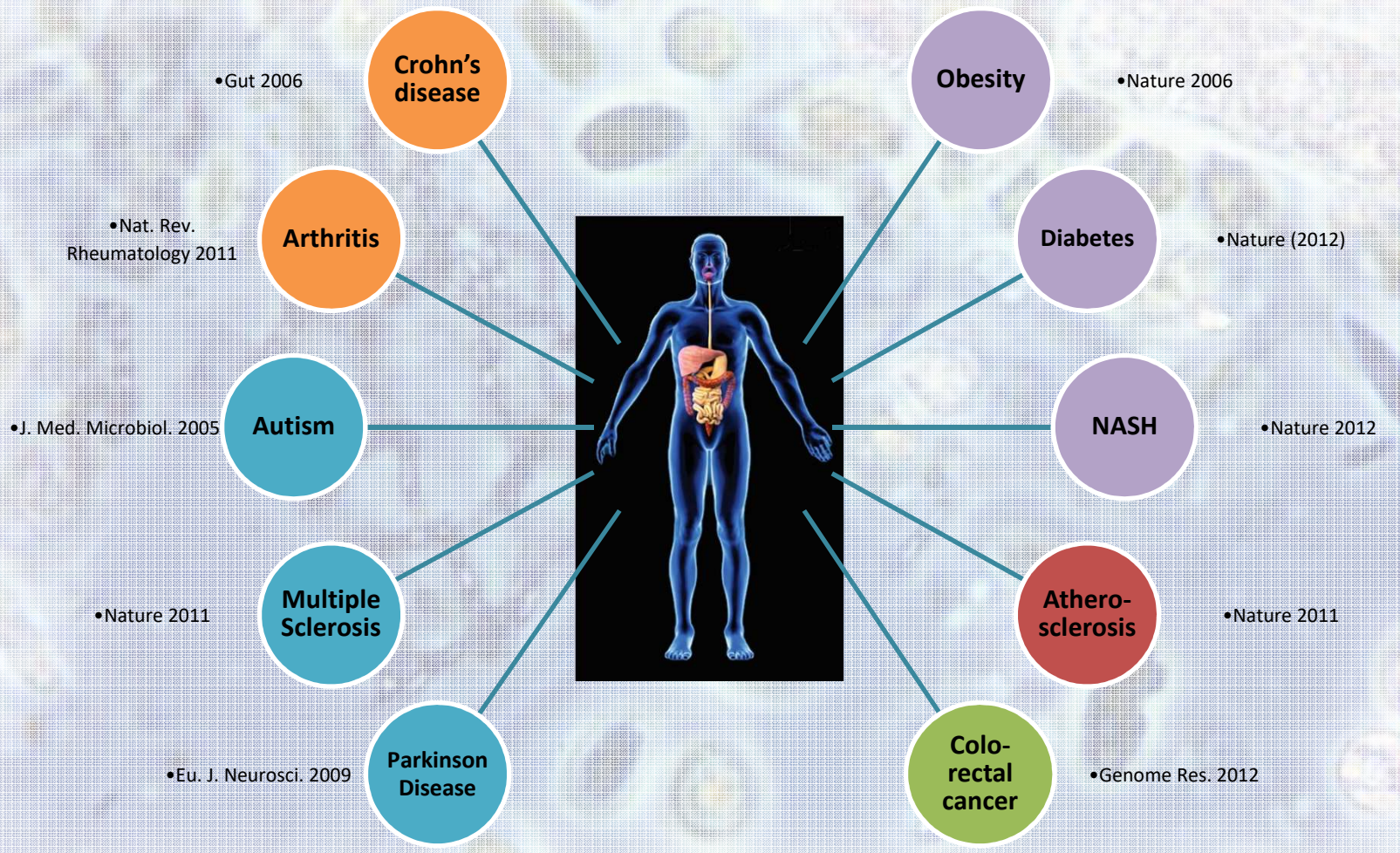
Feature	Value
Number of unique SNPs	
Species with most unique SNPs	*Parabacteroides merdae ATCC 43184*
Closest geographic match	Germany

Individual diseases tested for association with your microbiota

Disease	Association
Colon cancer	within average population risk

No approval for reporting antibiotics resistances, pathogen detection und some diseases

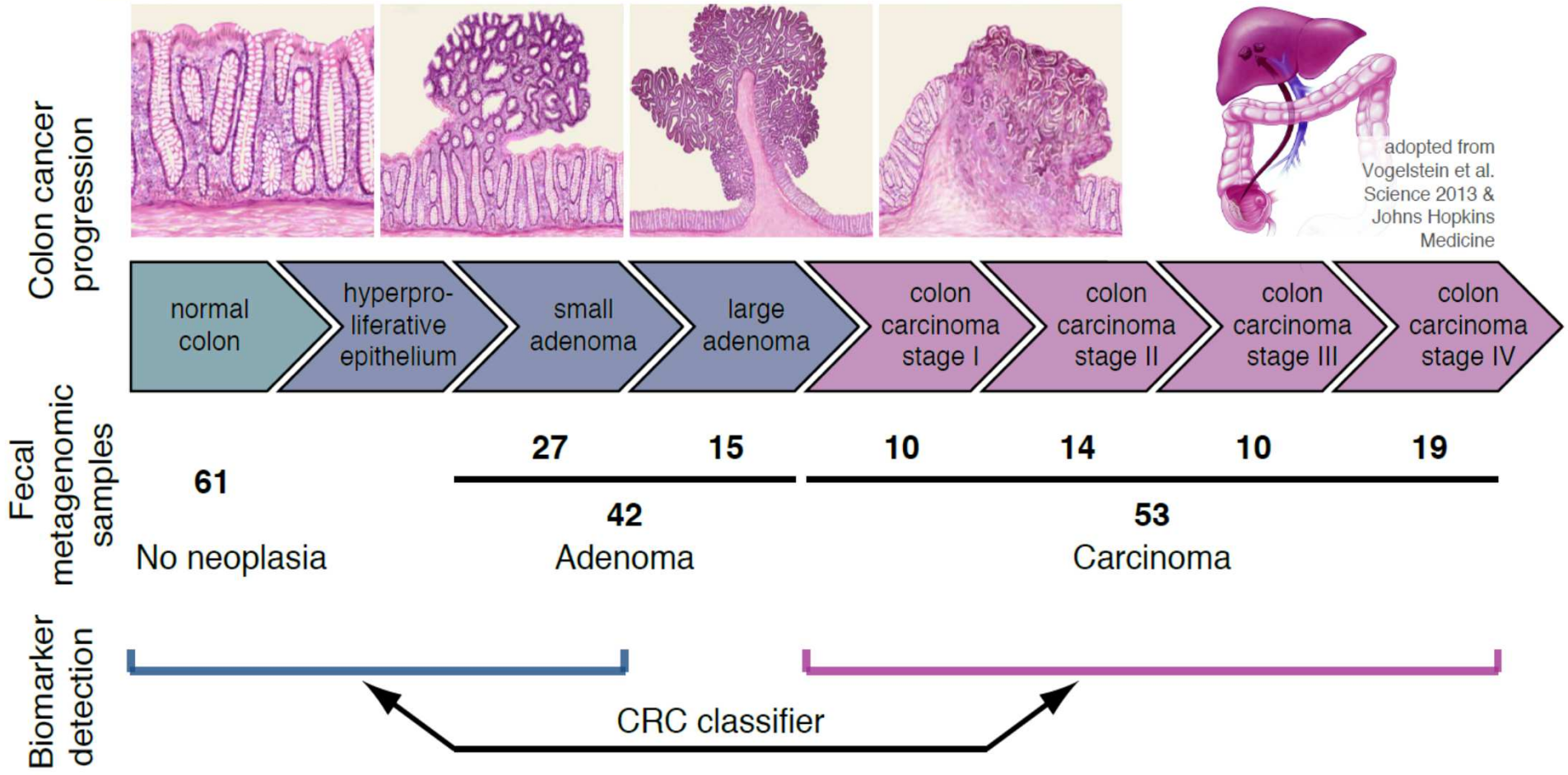
Our gut microbiome is linked to a multitude of different diseases



Association of microbiota with colon cancer

Stool samples from 156 French individuals provided by Iradj Sobhani

Study design (cancer detection)

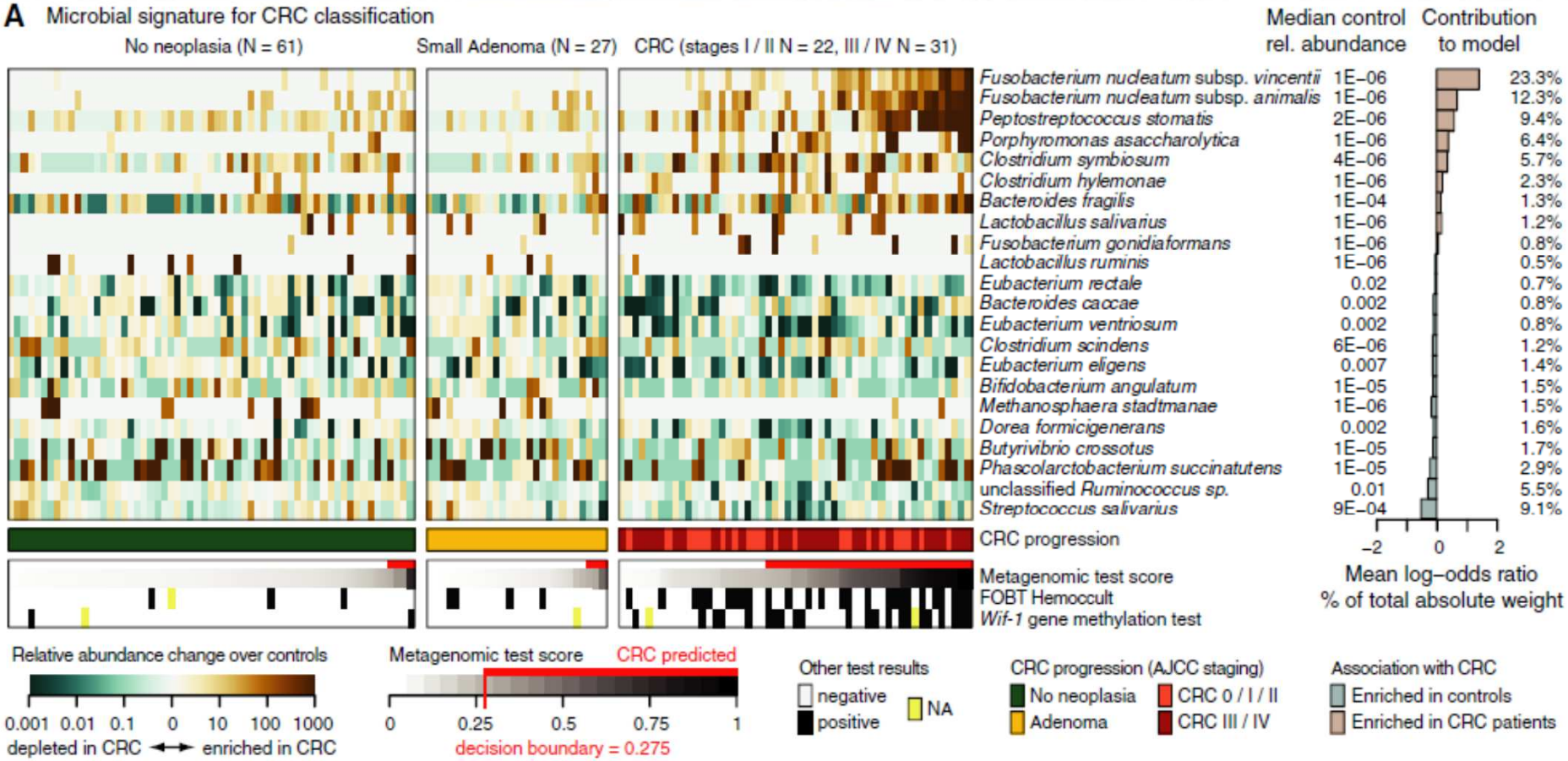


Per individual: on av. 9 Gb are currently sequenced, i.e. almost 3 human genome equivalents

Association of microbiota with colon cancer

A predictor based on faecal metagenomes from a French study population

Consensus model based on 22 differentially abundant species



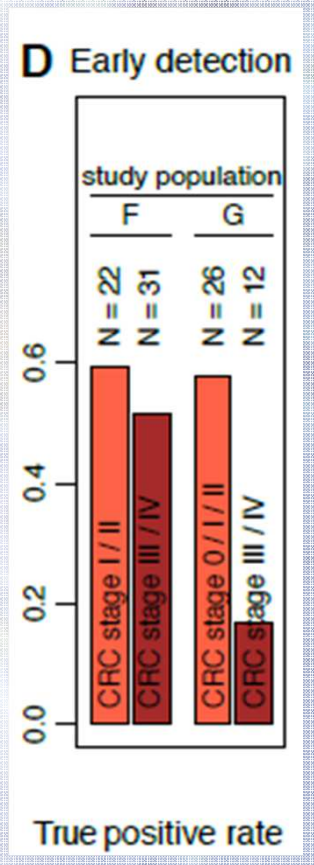
Fusobacterium nucleatum known to be involved at tumor itself, its also prevalent in stool

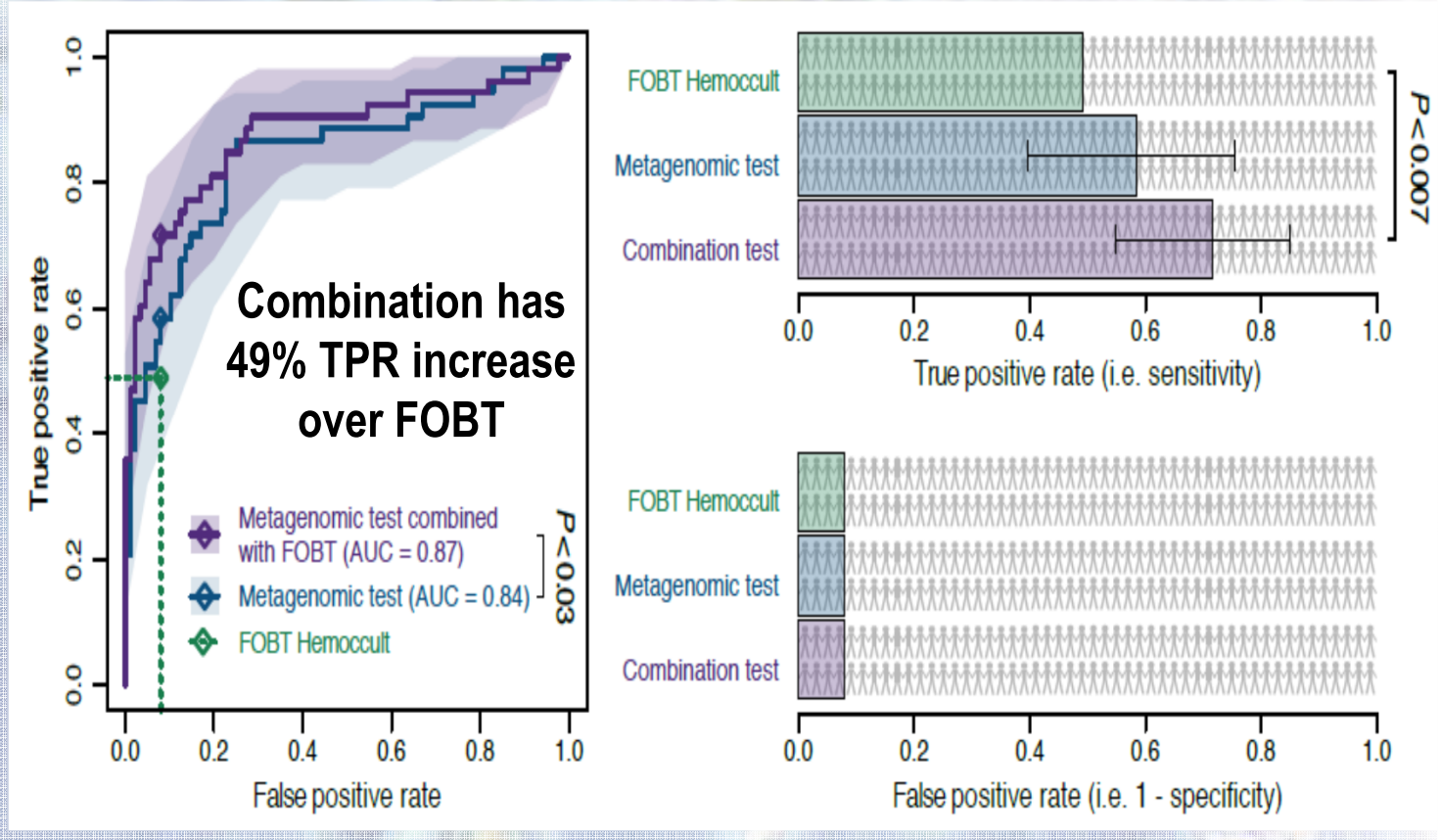
The signal is better than the commercially available FOBT test and a wif-1 based test

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

Association of microbiota with colon cancer

Biomarkers work well in early stages and detects features different from FOBT





Signal also holds for early cancer stages, also pre-cancer ones?

As FOBT correlates with inflammation, indeed a combination with FOBT greatly enhances prediction accuracy

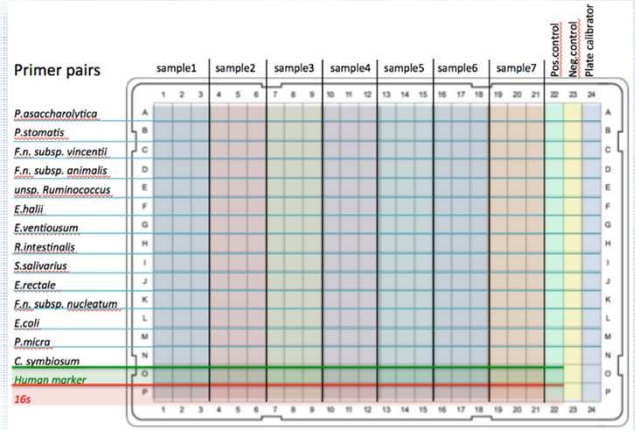
Association of microbiota with colon cancer

From metagenomics to cost effective, sensitive and specific CRC markers

Utilizing specific primers from several marker genes per marker species

Cancer risk groups:
>50 years or >40 years,
if obese etc.

Stool sampling,
preparation



384 well plate screening for
marker genes of 20 species

qPCR based
readout

To be combined with standard FOBT test (ca 6 Euro per sample)

Currently: ca 40 Euro costs per sample (but can still be reduced)

A deluge of studies on fecal CRC microbiomes from different regions

Since 2014 many more CRC associated metagenomes and 16S profiles from fecal samples published and more to come soon … but are they consistent?

Many possible confounding factors (inflammation, diet, drug treatment etc.)

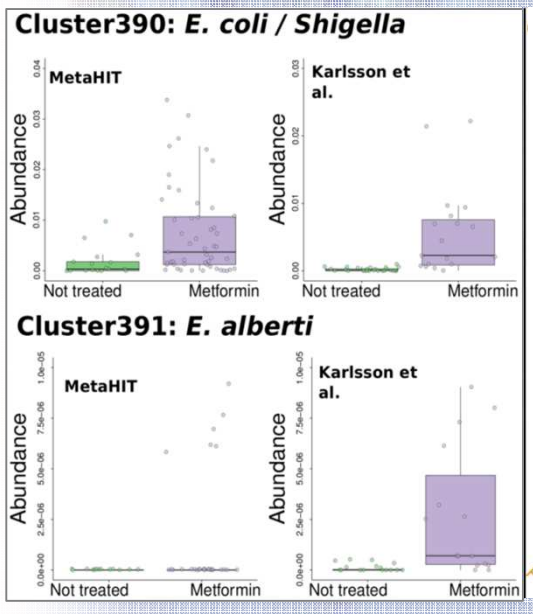
Example type II diabetes: Metformin induces gut microbial composition changes

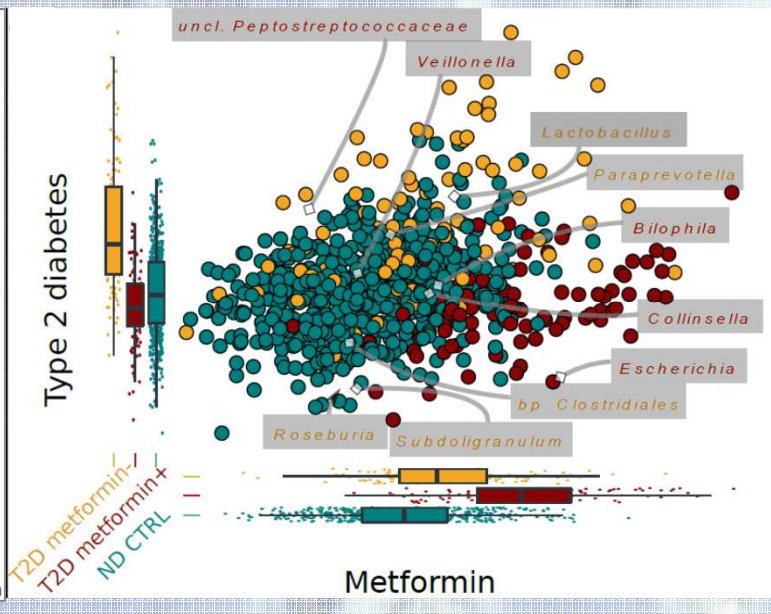
Chinese: Qin et al., Nature 2012; AUC 0.81

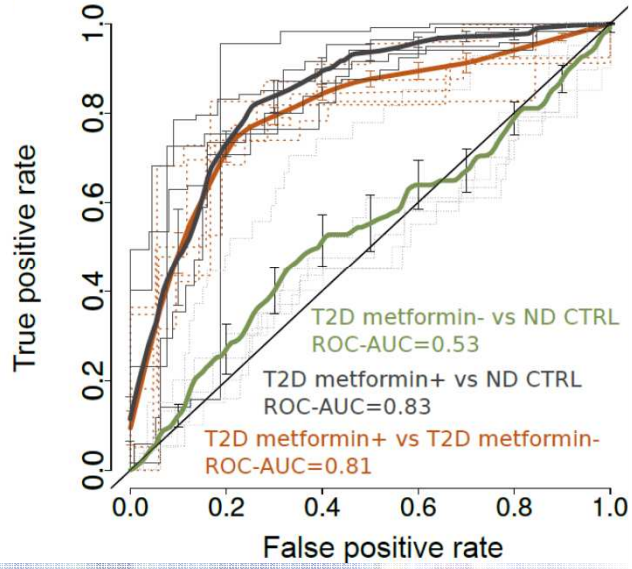
Swedish: Karlsson et al., Nature 2013; AUC 0.83

Danish: unpublished (54 T2D+75Ctrl); AUC 0.81

Combined cohort after omission of metformin-treated individuals: AUC = 0.53





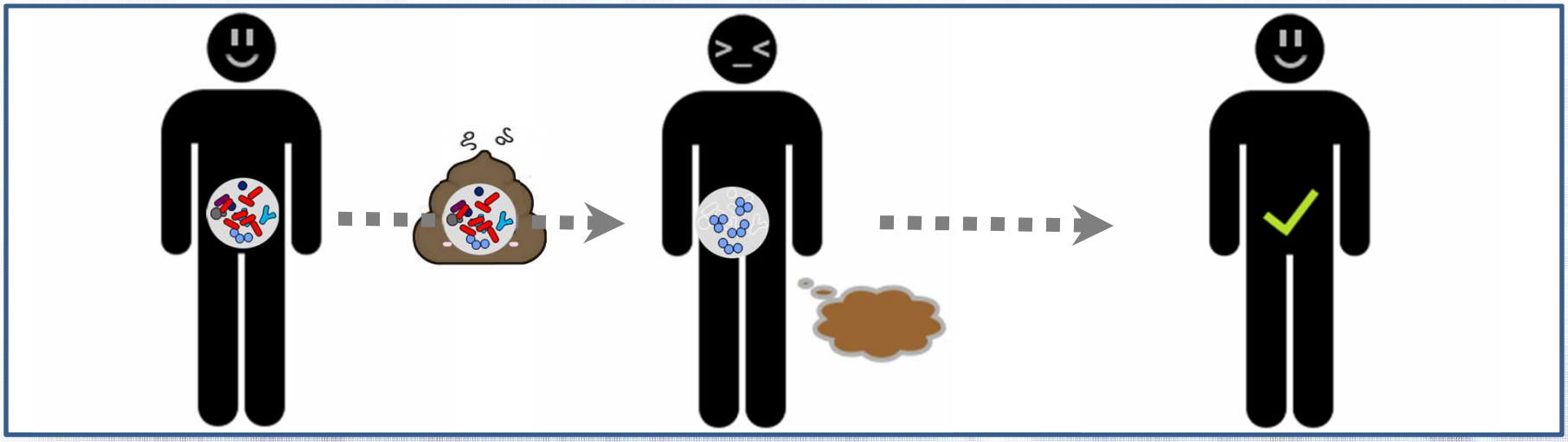


Some proteobacteria up after/during metformin treatment

Metformin is strongest signal, distinct from T2D which alone is weak

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

Faecal Microbiota Transplantation (FMT)



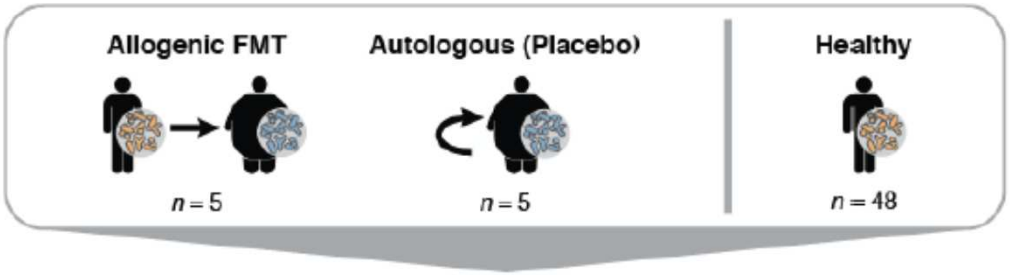
- Transfer of stool from a healthy donor to patient
  - Usually following antibiotics treatment or bowel lavage
- Positive effects reported in GI and non-GI diseases
  - Over 90% success in treating *Clostridium difficile* infection[1]
- Mechanism is currently unknown, e.g. fate of native and introduced strains
  - Specific bacteria introduced in patient[2]
  - Replacement or 'repair' of 'bad' microbial species

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

1. ***van Nood, E. et al. (2013). N Engl J Med, 368, 407-15.***
2. ***Lawley, TD., et al. (2012). PloS Pathog, 8, e1002995.***

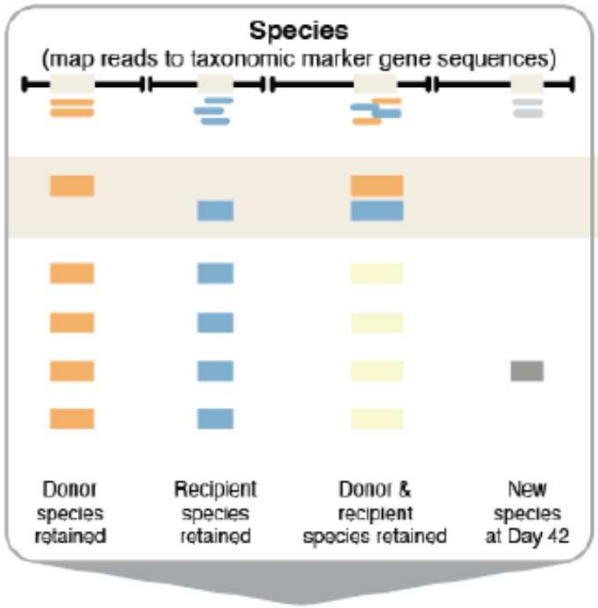
Donor species and strain colonization after FMT for metabolic syndrome

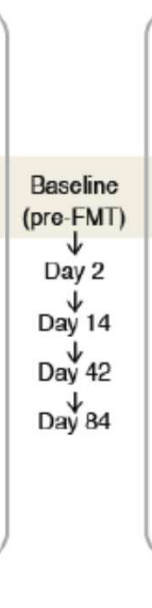
5 time points up to 3 months after FMT, 164 metagenomes incl. donors

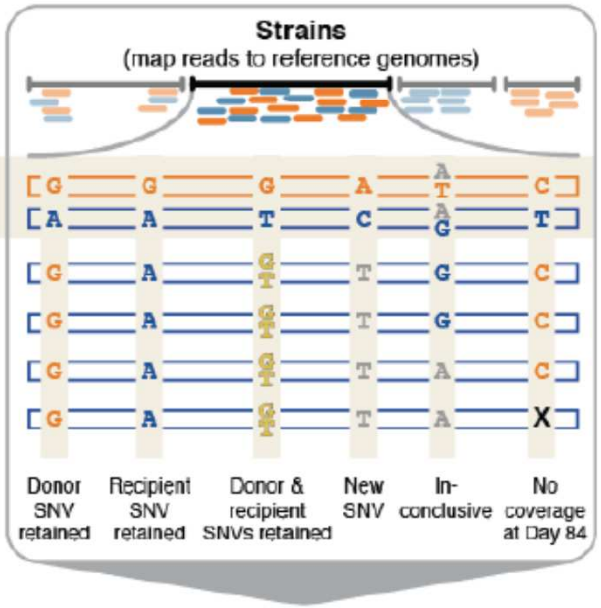


Collab. with W. de Vos and M. Nieuwdorp

Species



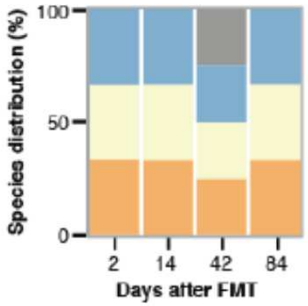


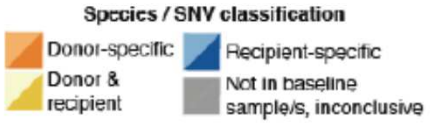


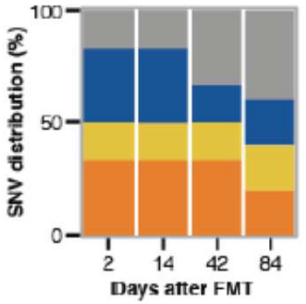
Strains

Measured using marker genes (mOTUs)

Sunagawa et al., Nature Meth. 10(2013)1196





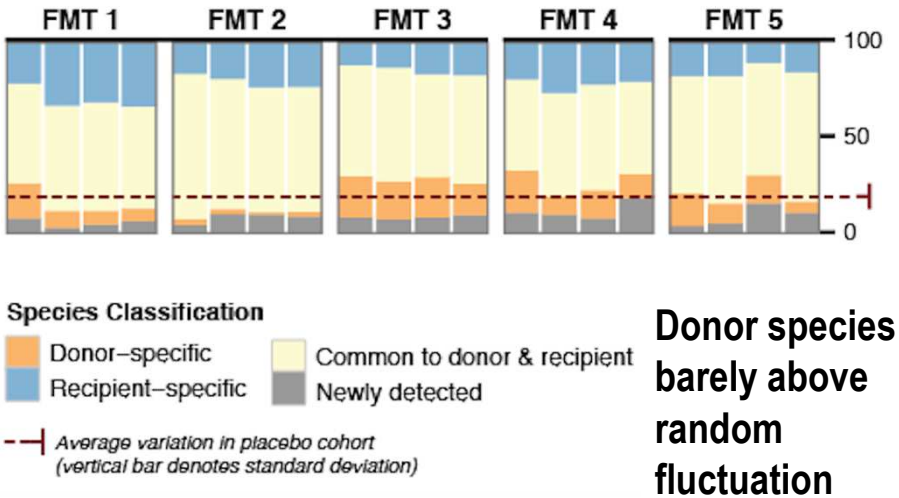


Measured using discriminative SNVs, modified from

Schloissnig et al., Nature 493(2013)45

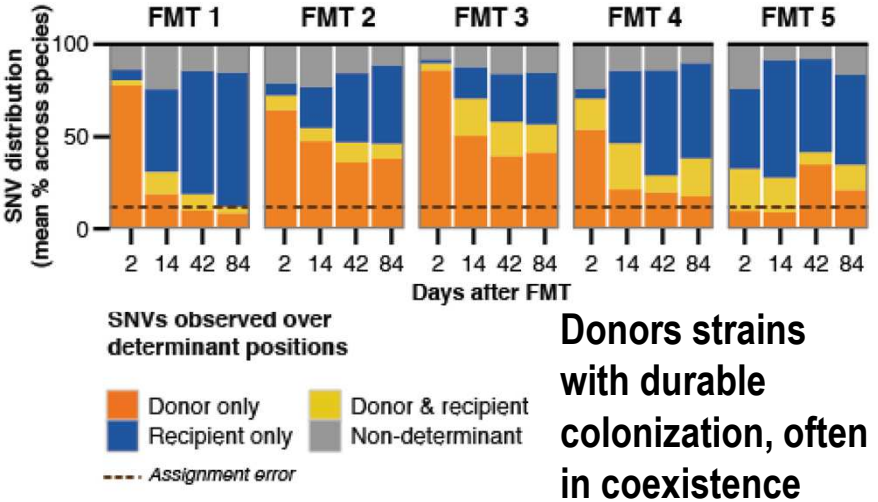
Strain replacement after faecal microbiota transplantation (FMT) is easier than acquisition of new species

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.

Li et al., Science 352(2016)586

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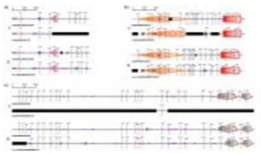
MDC Berlin-Buch EMBL

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

Human gut microbes impact host serum metabolome and insulin sensitivity
Pedersen HK, Gudmundsdottir1 V, Nielsen1 HB, Hyotylainen T, Nielsen T, Jensen BAH, Forslund K, Hildebrandi F, Prifti E, Falony G, Le Chatelier E, Levenez F, Doré J, Mattila I, Plichta DR, Pöhö P, Hellgren LI, Arumugam M, Sunagawa S, Vieira-Silva S, Jørgensen T, Holm JB, Trošt K, MetaHIT Consortium, Kristiansen K, Brix S, Raes J, Wang J, Hansen T, Bork P, Brunak S, Oresic M, Ehrlich SD & Pedersen O
Nature 2016 July 13. DOI: 10.1038/nature18646. PubMed: 27409811
Abstract

Plankton networks driving carbon export in the oligotrophic ocean
Guidi L, Chaffron S, Bittner L, Eveillard D, Larhlimi A, Roux S, Darzi Y, Audic S, Berline L, Brum J, Coelho LP, Espinoza JC, Malviya S, Sunagawa S, Dimier C, Kandels-Lewis S, Picheral M, Poulain J, Searson S, Stemmann L, Not F, Hingamp P, Speich S, Follows M, Karp-Boss L, Boss E, Ogata H, Pesant S, Weissenbach J, Wincker P, Acinas SG, Bork P, De Vargas C, Iudicone D, Sullivan MB, Raes J, Karsenti E, Bowler C, Gorsky G.
Nature 2016 Apr 28. 532, 465-70. PubMed:26863193
Abstract

Felix Burda Award for Medicine & Science
Felix Burda Award, Muenchen, 2016 Apr 17
Media echoes

Durable coexistence of donor and recipient strains after fecal microbiota transplantation
SS Li, A Zhu, V Benes, PI Costea, R Hercog, F Hildebrand, J Huerta-Cepas, M Nieuwdorp, J Salojärvi, AY Voigt, G Zeller, S Sunagawa, WM de Vos, P Bork
Science 2016 Apr 29. 586 - 589
Abstract

Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota
K Forslund, F Hildebrand, T Nielsen, G Falony, E Le Chatelier, S Sunagawa, E Prifti, S Vieira-Silva, V Gudmundsdottir, HK Pedersen, M Arumugam, K Kristiansen, AY Voigt, H Vestergaard, R Hercog, PI Costea, JR Kultima, JH Li, T Jørgensen, F Levenez, J Dore, MetaHIT consortium, HB Nielsen, S Brunak, J Raes, T Hansen, Jun Wang, SD Ehrlich, P Bork & O Pedersen.
Nature 2015 Dec 10;528(7581):262-6. doi: 10.1038/nature15766. Epub 2015 Dec 2. PMID: 26633628
Abstract

SCIENCE special issue: TARA OCEANS, 2015 May 22

Tara Oceans studies plankton at planetary scale
P. Bork, C. Bowler, C. de Vargas, G. Gorsky, E. Karsenti, and P. Wincker
Science 2015 May 22. Vol. 348 no. 6237 p. 873 DOI: 10.1126/science.aac5605

For details see:
www.bork.embl.de

Thank you!