



Metagenomics exploration of the gut microbiome in irritable bowel syndrome

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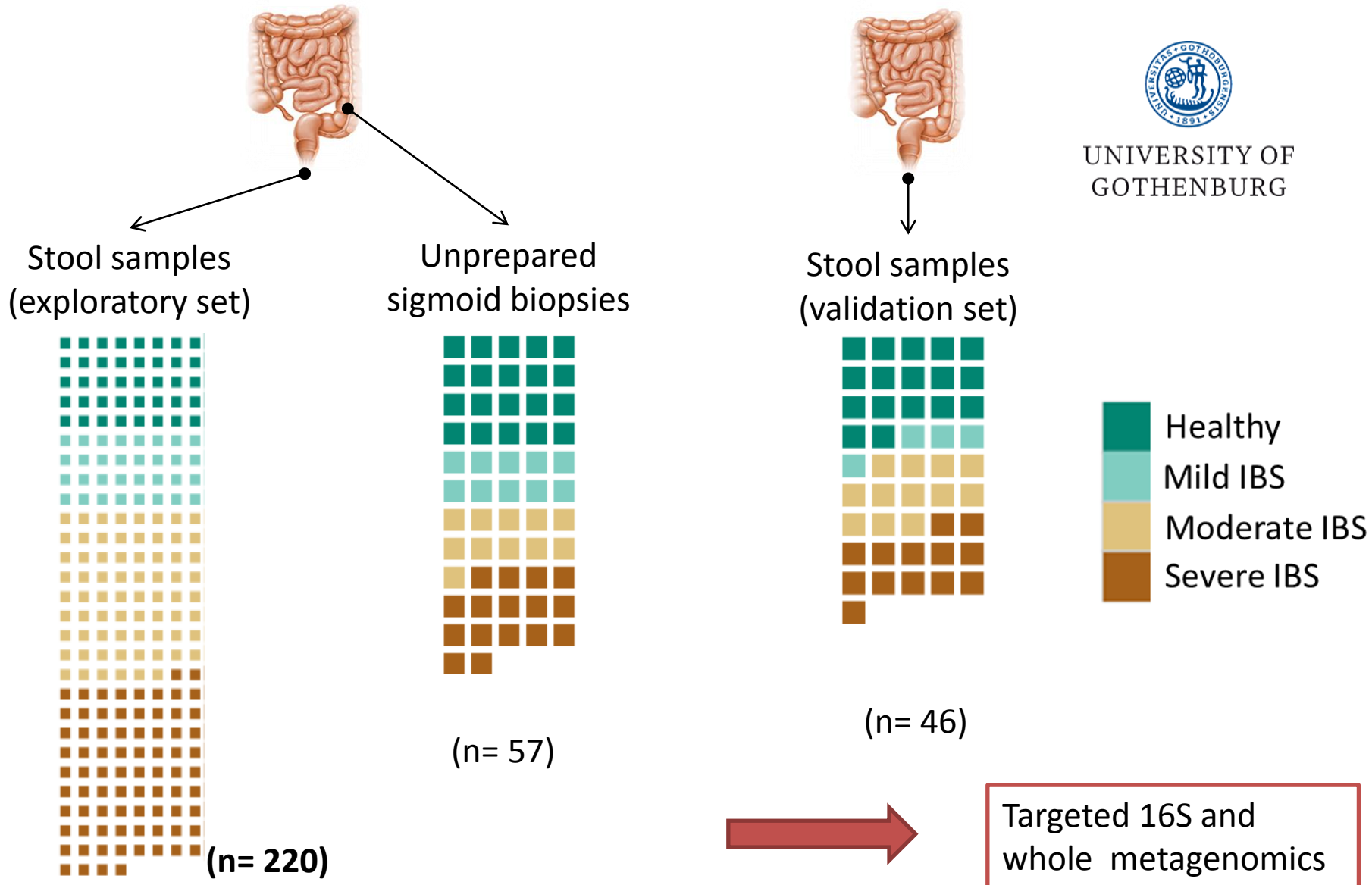
DANONE
NUTRICIA
RESEARCH

Metagenomics exploration of the gut microbiome in irritable bowel syndrome

Julien Tap

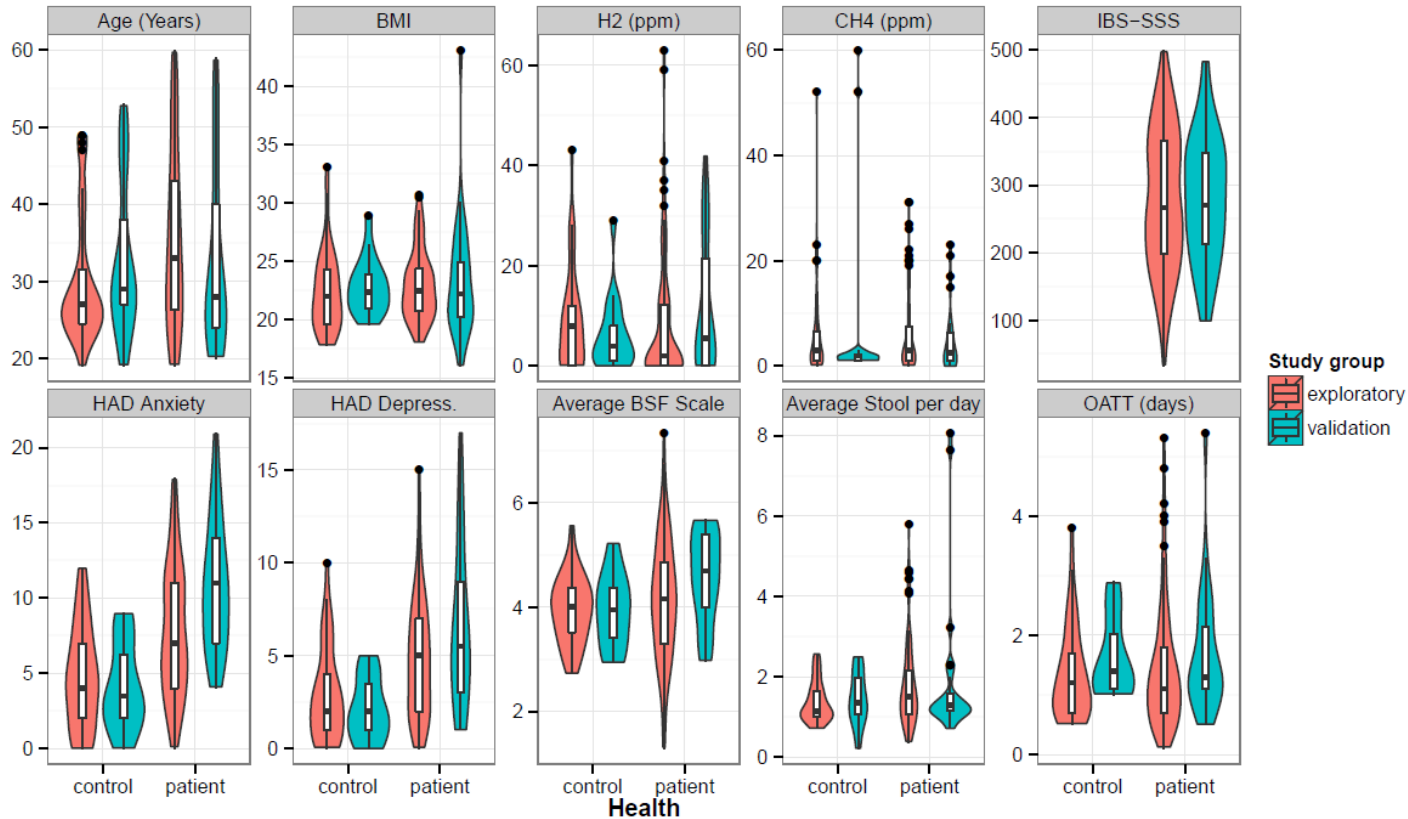
Muriel Derrien, Hans Törnblom, Rémi Brazeilles, Stéphanie Cools,
Joël Doré, Boris Le Nevé, Lena Öhman, Magnus Simrén

Healthy and IBS dataset

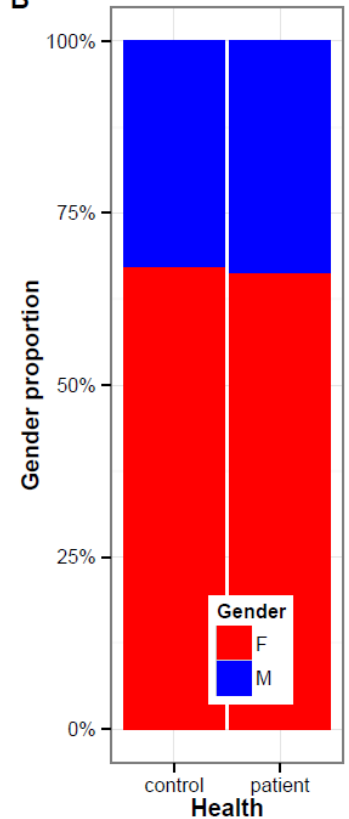


Clinical metadata

A

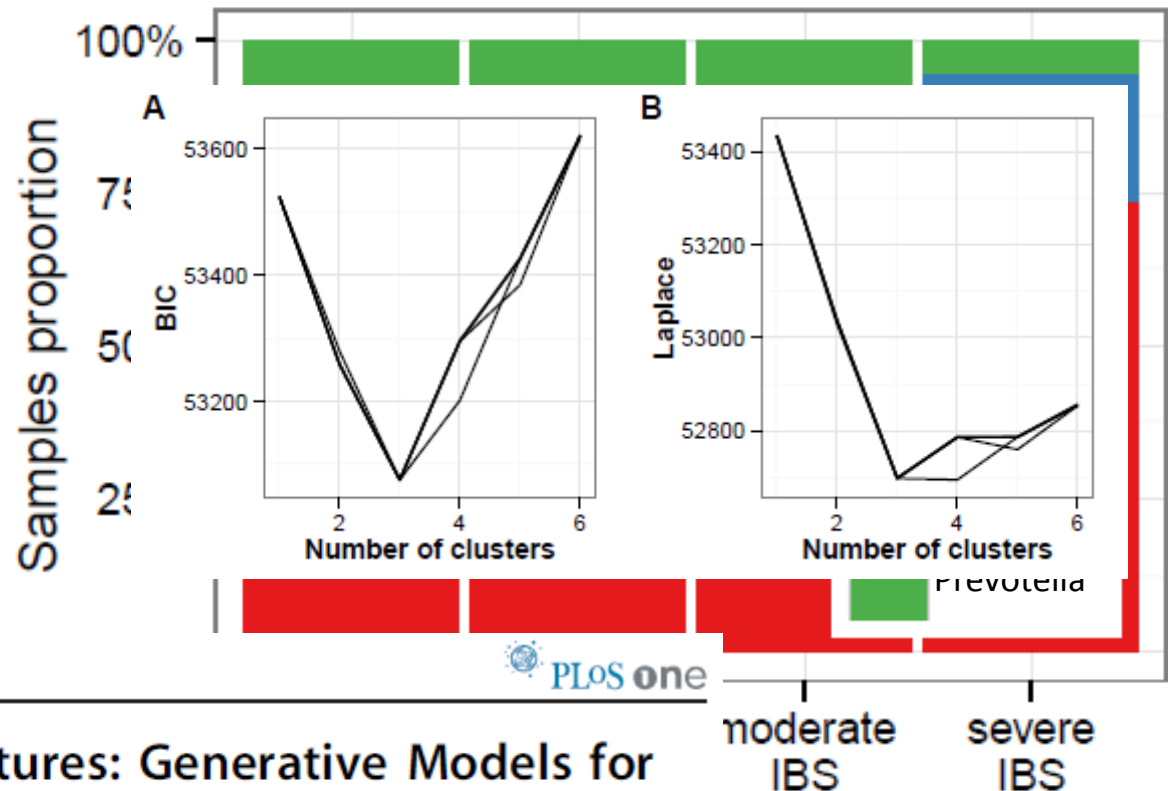


B



Link between IBS severity score and enterotypes distribution

3 enterotypes found in the stool dataset equivalent to those published elsewhere



OPEN ACCESS Freely available online

PLoS one

Dirichlet Multinomial Mixtures: Generative Models for Microbial Metagenomics

Ian Holmes¹, Keith Harris², Christopher Quince^{2*}

¹ Department of Bioengineering, University of California, Berkeley, California, United States of America, ² School of Engineering, University of Glasgow, Glasgow, United Kingdom

Higher Severity

LESS *Prevotella*-type More *Bacteroides*-type

Towards a gut microbial signature for IBS severity

Microbiota
2,900
bacterial species
(OTU)

Feature transformation: log10
and centering/scaling

10-fold stratified cross validation
(resampled 10 times)

Article



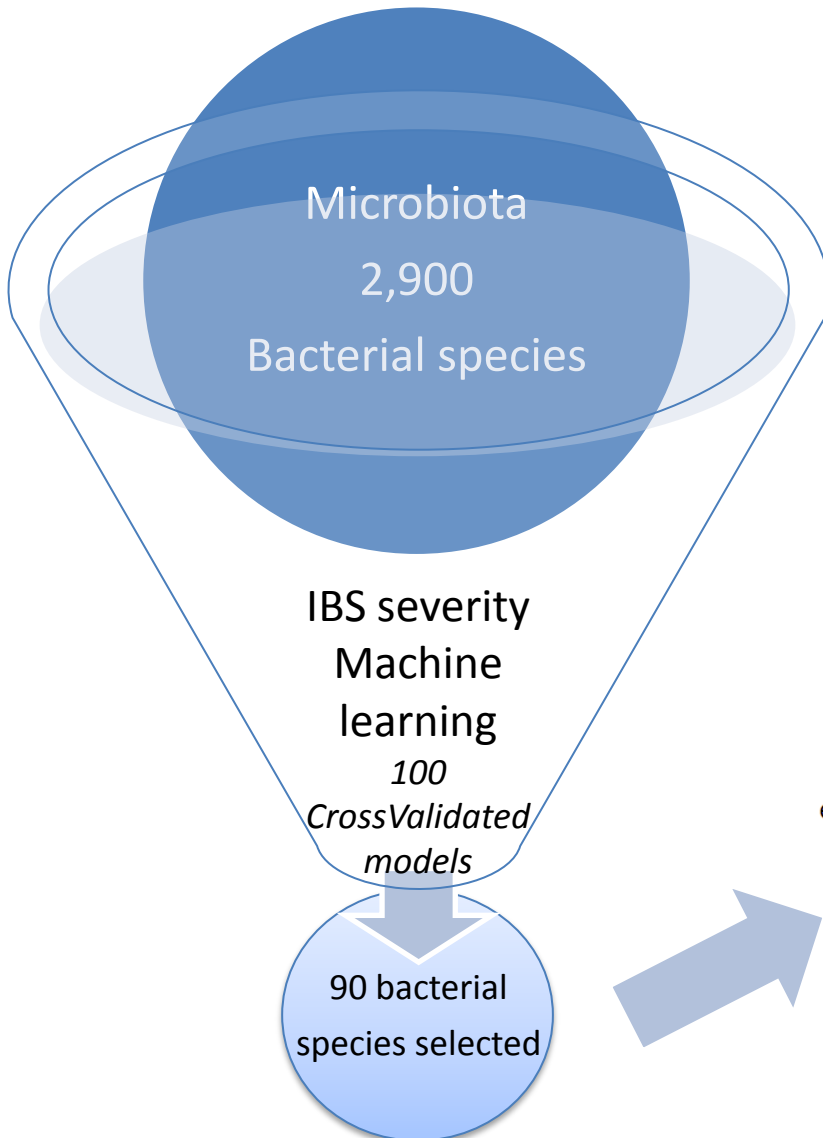
molecular
systems
biology

Potential of fecal microbiota for early-stage
detection of colorectal cancer

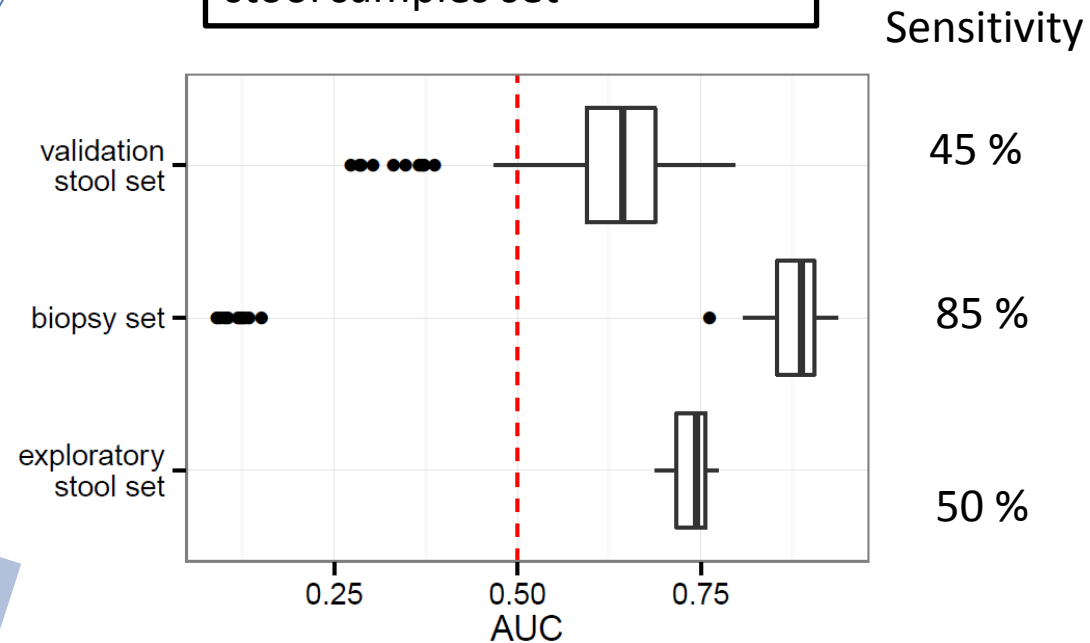
Georg Zeller^{1,†}, Julien Tap^{1,2,†}, Anita Y Voigt^{1,3,4,5,†}, Shinichi Sunagawa¹, Jens Roat Kultima¹, Paul I

Model evaluation: AUC,
sensitivity, ...

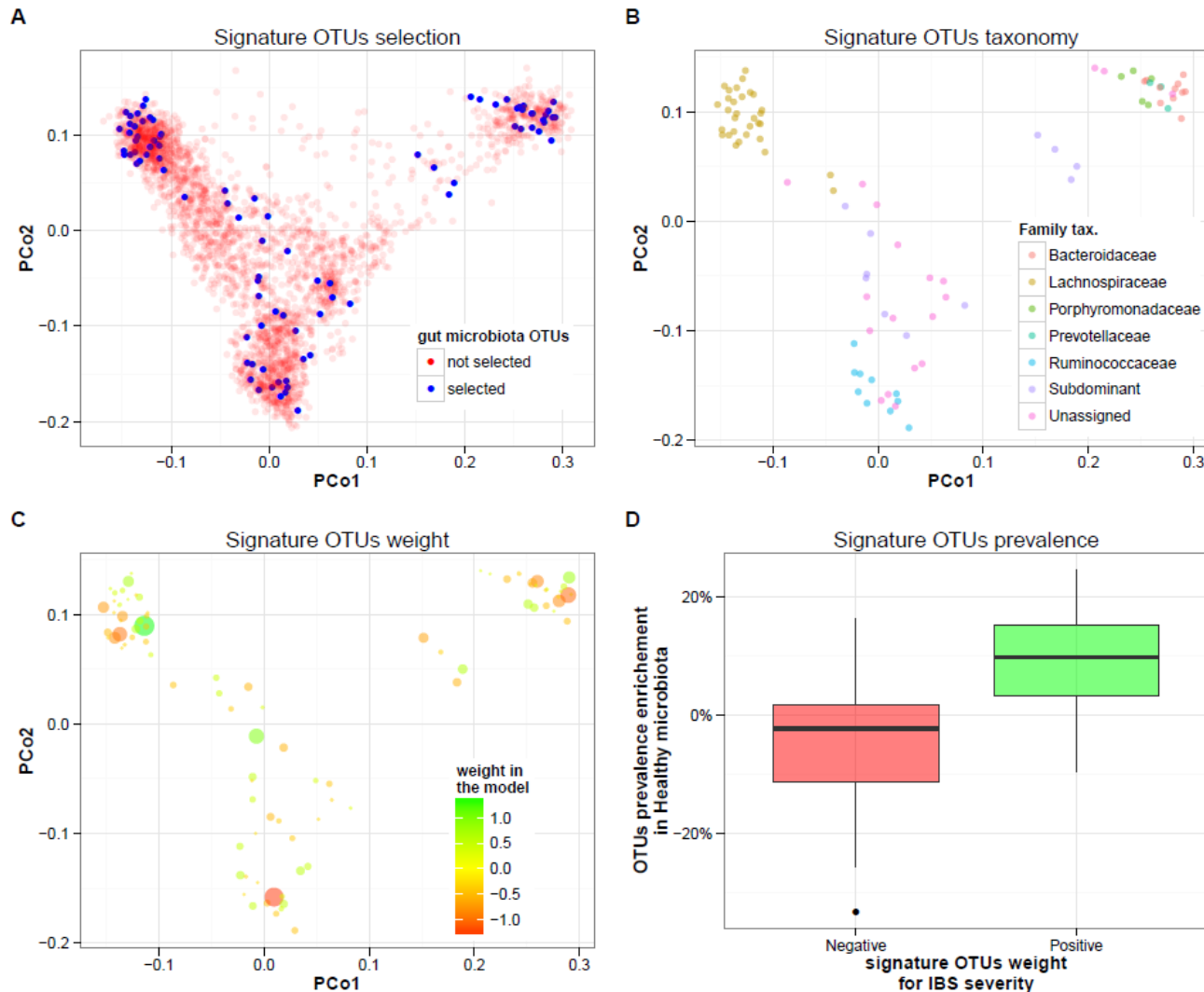
Towards a gut microbial signature for IBS severity



This signature is validated in biopsies and an independent stool samples set



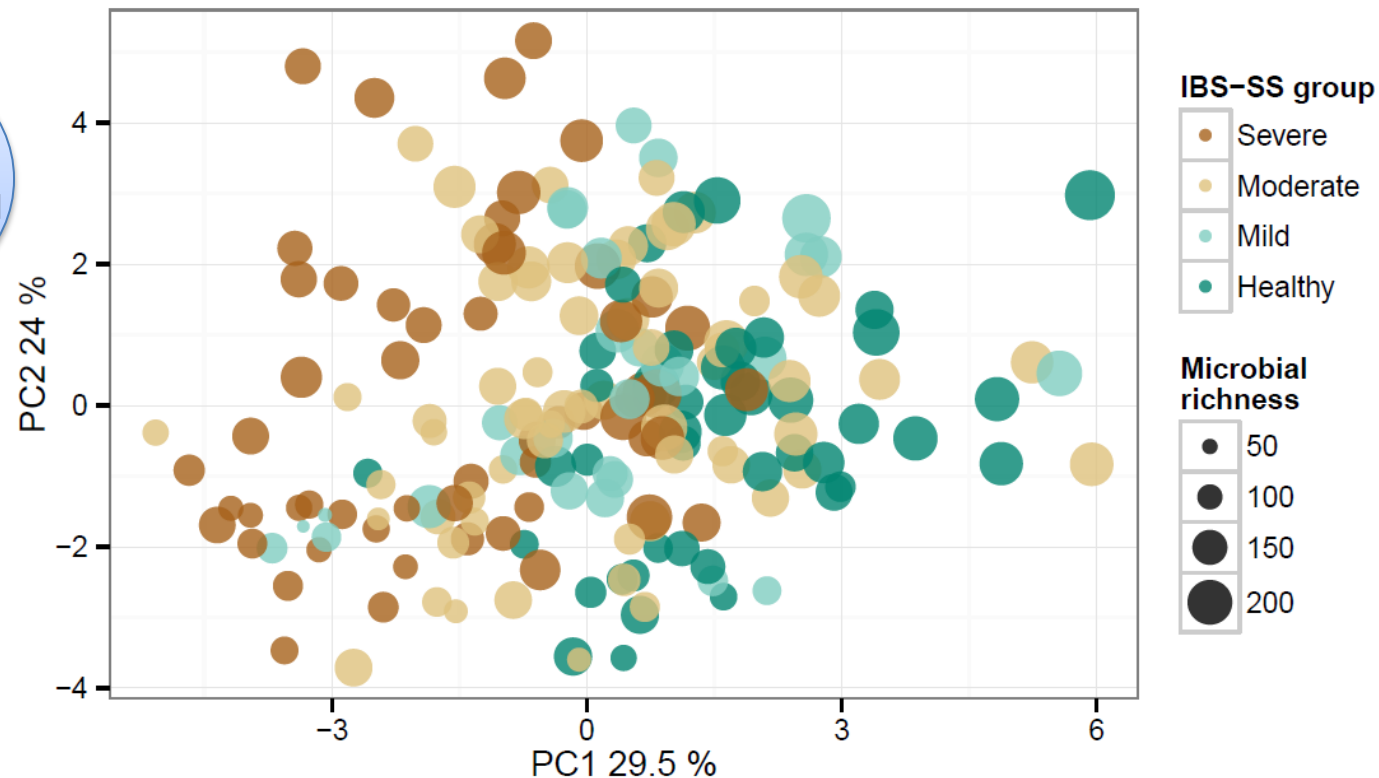
Taxonomic characterization of microbial IBS severity signature



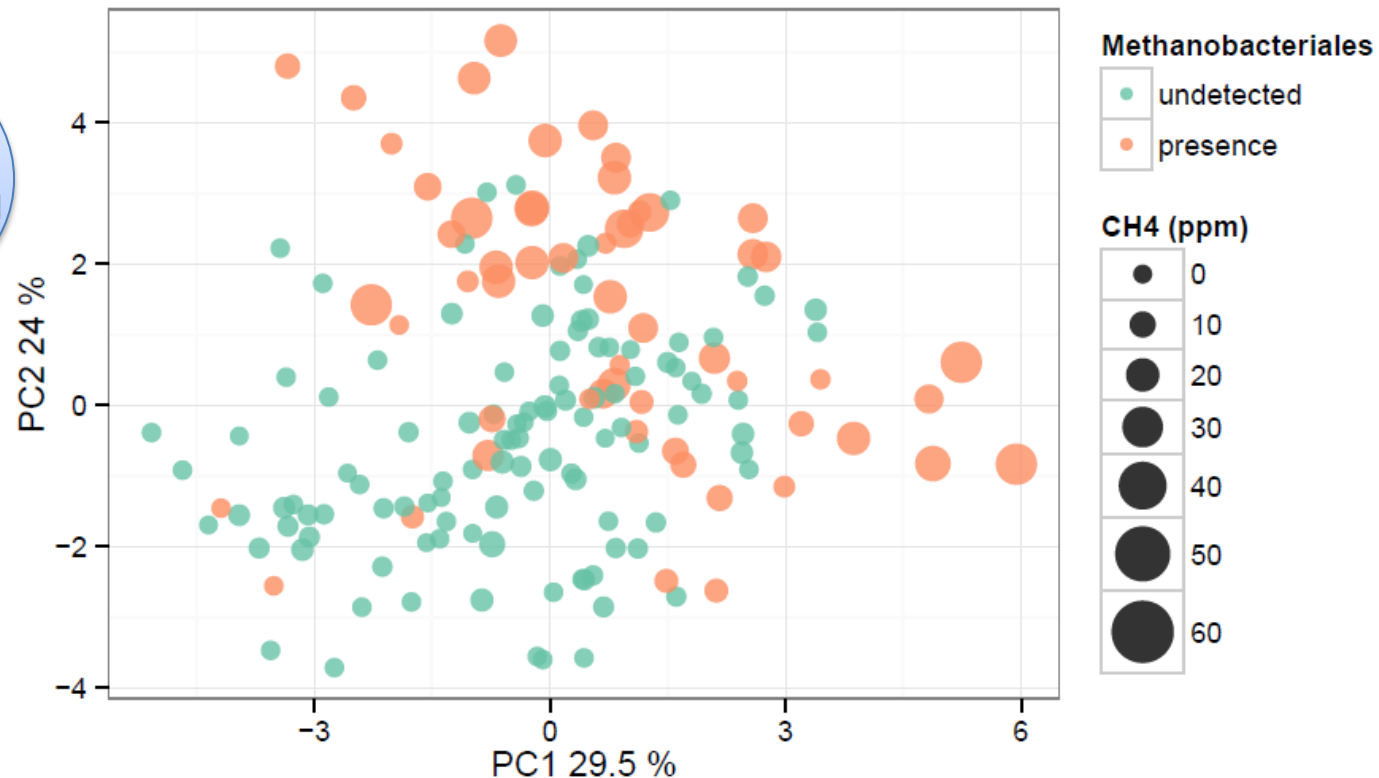
The signature was not specific to a specific taxa

Healthy associated taxa were more known and more frequent

Gut microbial signature for IBS severity is linked with lower microbial richness



Gut microbial signature for IBS severity is linked with exhaled methane

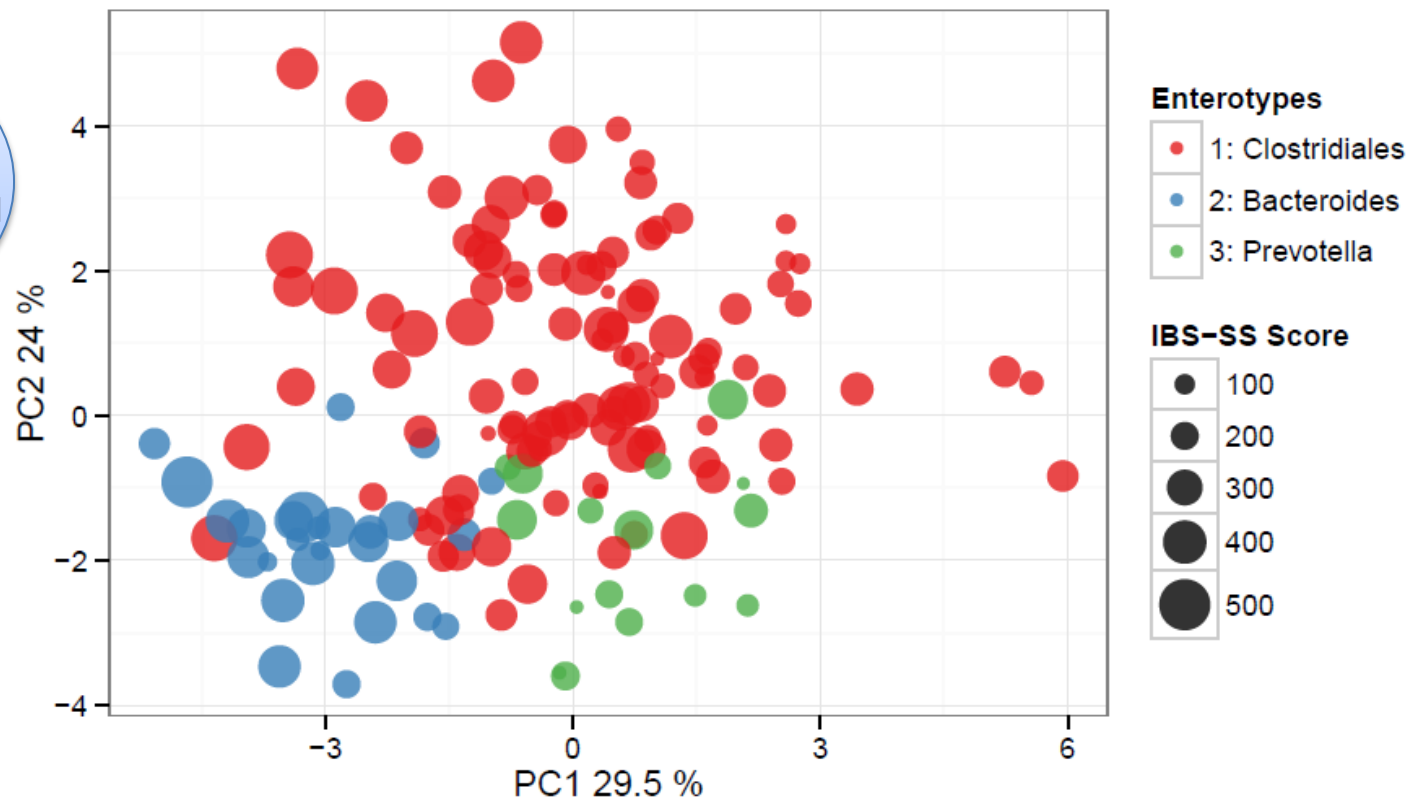


Severe IBS  Healthy

Low microbial richness  High microbial richness

Low CH₄ exhaled  High CH₄ exhaled

Gut microbial signature for IBS severity is linked with enterotypes



Severe IBS  Healthy

Low microbial richness  High microbial richness

Low CH₄ exhaled  High CH₄ exhaled

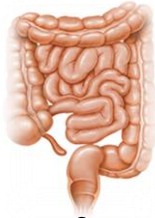
Bacteroides-type  *Clostridiales* & *Prevotella*-types

Messages from 16S set

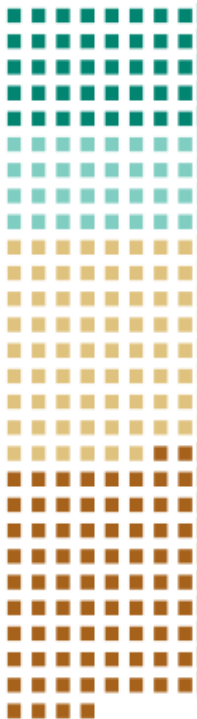
- IBS symptom severity is associated with a distinct signature at fecal microbiota level
- Gut microbial signature for IBS severity is linked with
 - low microbial richness
 - *Bacteroides* enriched enterotype
 - low Archea methanogens and exhaled CH₄



Going further with metagenomics



Stool samples
(exploratory set)

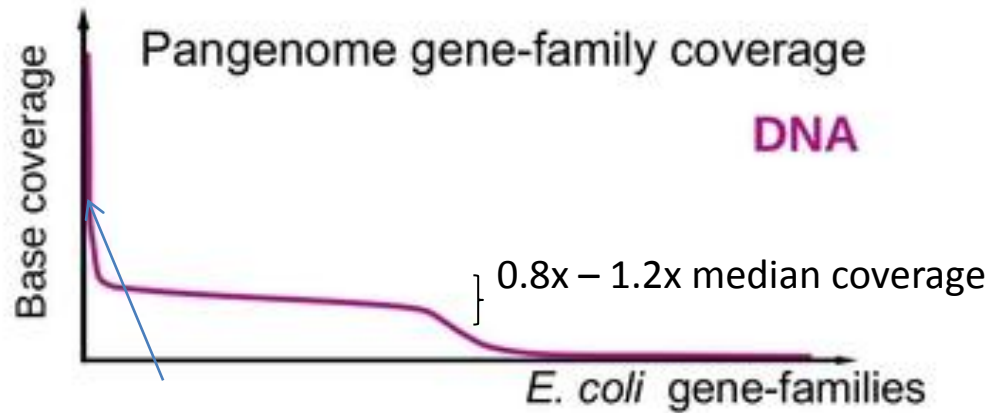


- A subset of 144 samples were subjected to whole metagenomics sequencing (MetaGenoPolis)
 - Solid 35 bases
- Mapping against the 3.9M MetaHIT genes catalog annotated by Nielsen et al.
 - Bowtie1 (csfasta) parsed in Meteor
 - 3 mismatch allowed
- Genes clustered into Metagenomics species (MGS)
 - MGS associated with small genes clusters (dependencies)

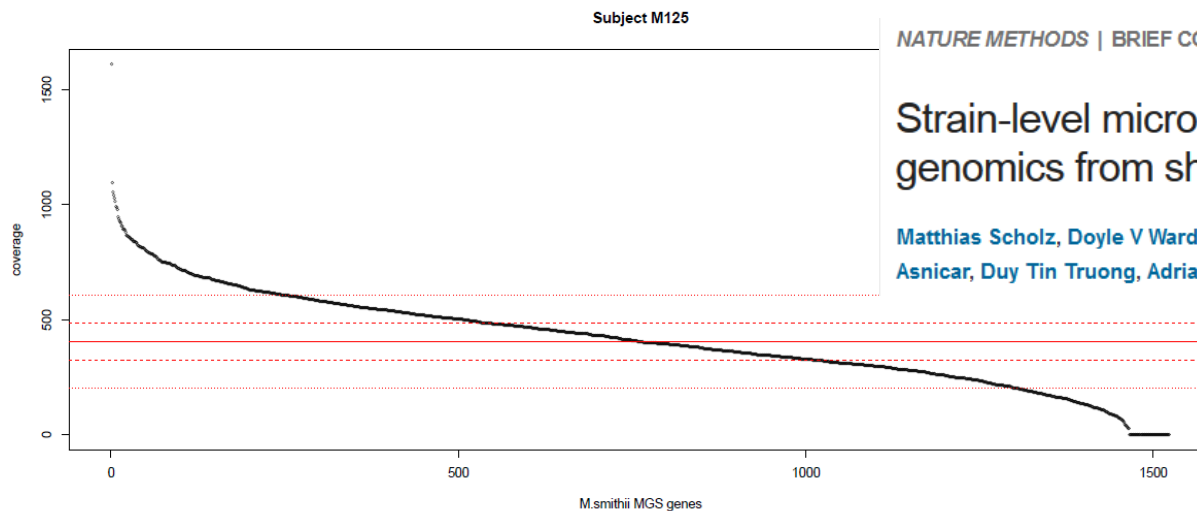


From MGS species to genomic division

PanPhlan method



Multi copy genes



NATURE METHODS | BRIEF COMMUNICATION

Strain-level microbial epidemiology and population genomics from shotgun metagenomics

Matthias Scholz, Doyle V Ward, Edoardo Pasolli, Thomas Tolio, Moreno Zolfo, Francesco Asnicar, Duy Tin Truong, Adrian Tett, Ardythe L Morrow & Nicola Segata

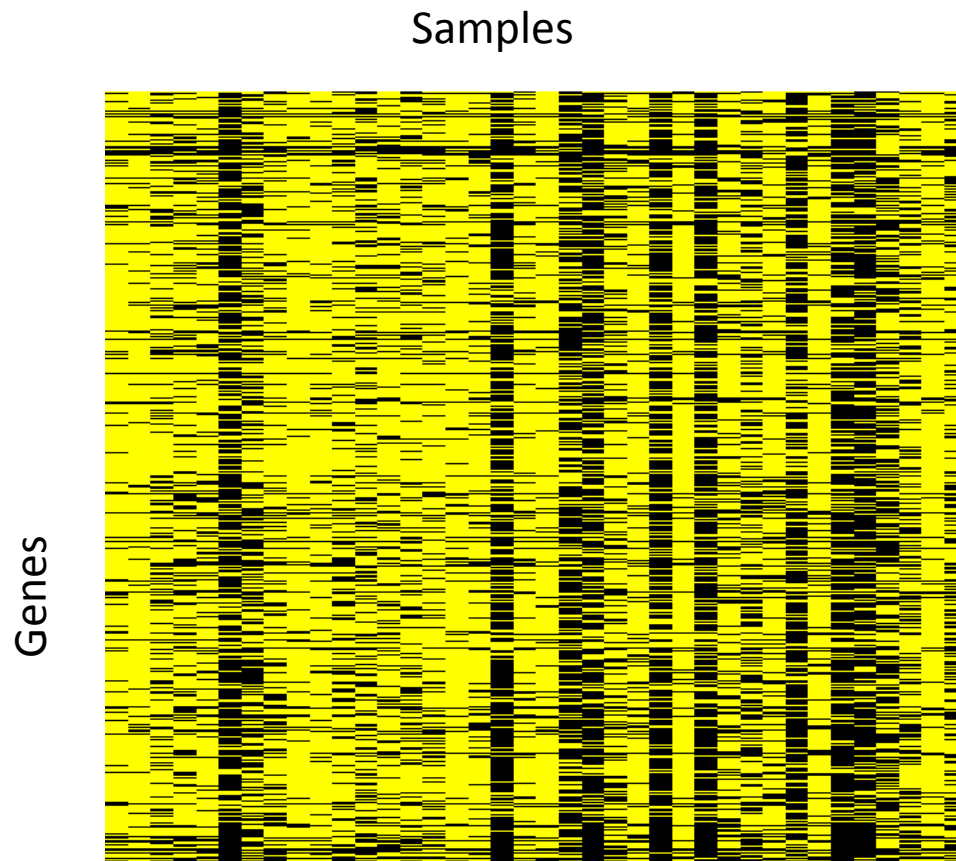
0.5x – 1.5x median coverage

Adaptation to
Solid mapped
data

Breaking MGS into genomic division

- Convert abundance matrix to presence/absence
- Partition around medoids to detect samples clusters
 - Cluster validity using silhouette coefficient
 - Cluster stability assessed with Jaccard coef. through resampling (partition max = 75%)
- Heatmap plot for visualization

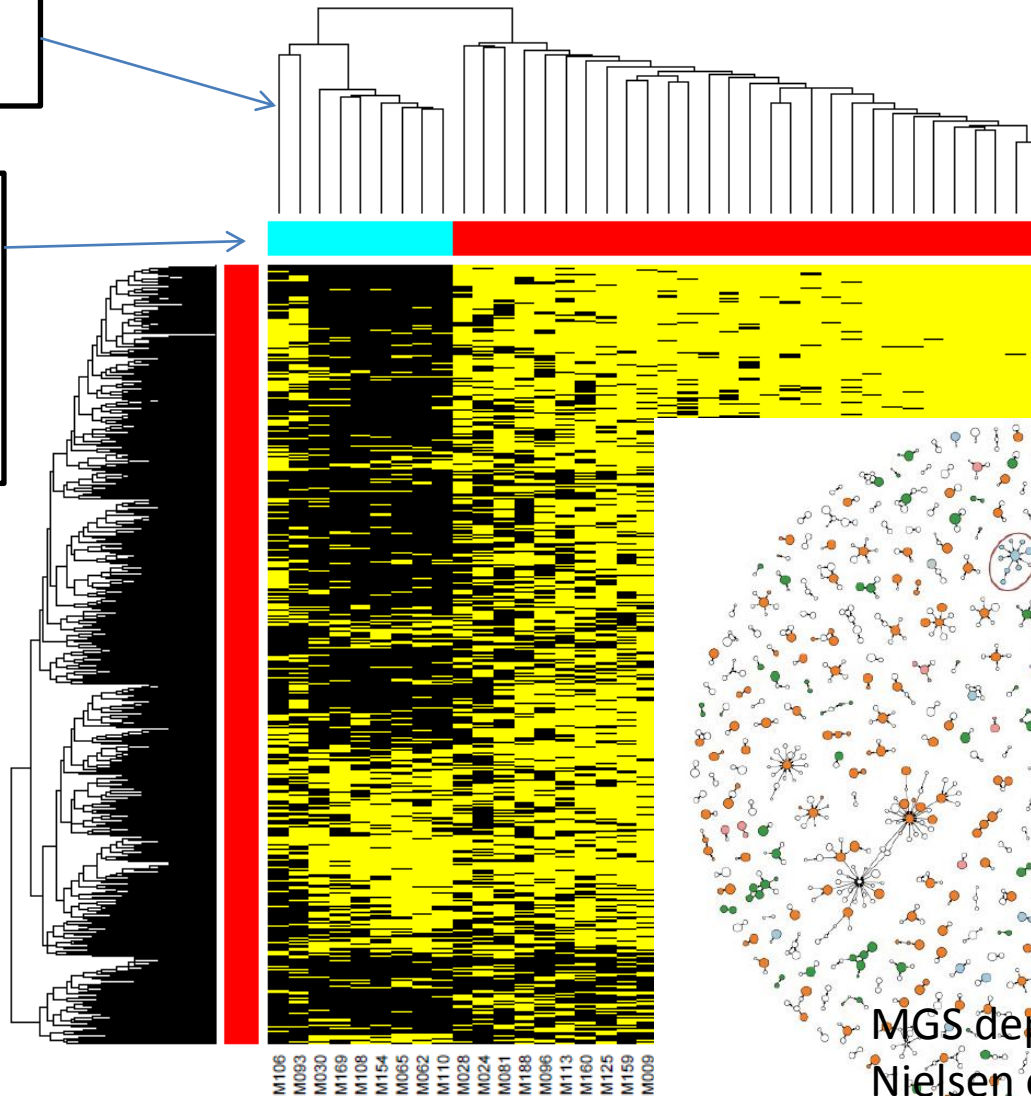
Methanobrevibacter smithii example



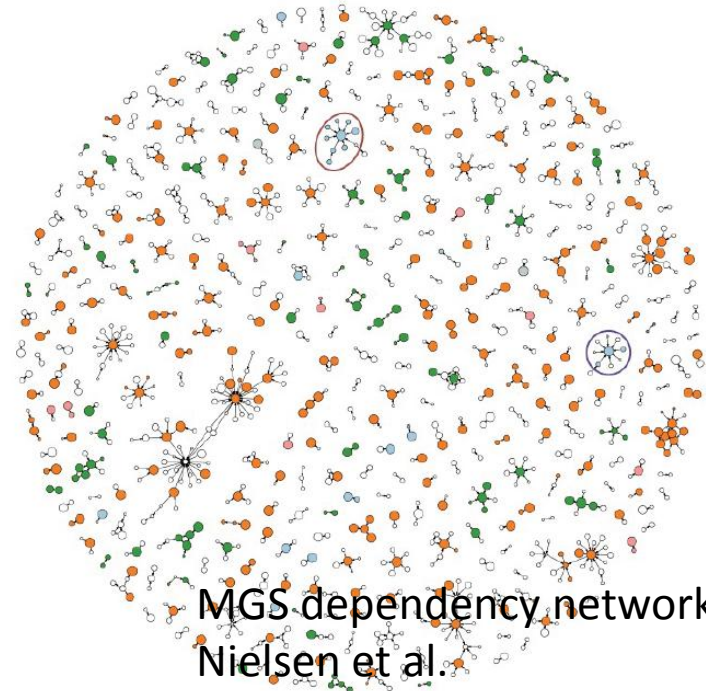
Methanobrevibacter smithii example

hierarchical
clustering

PAMk
clustering
+
Cluster
validation

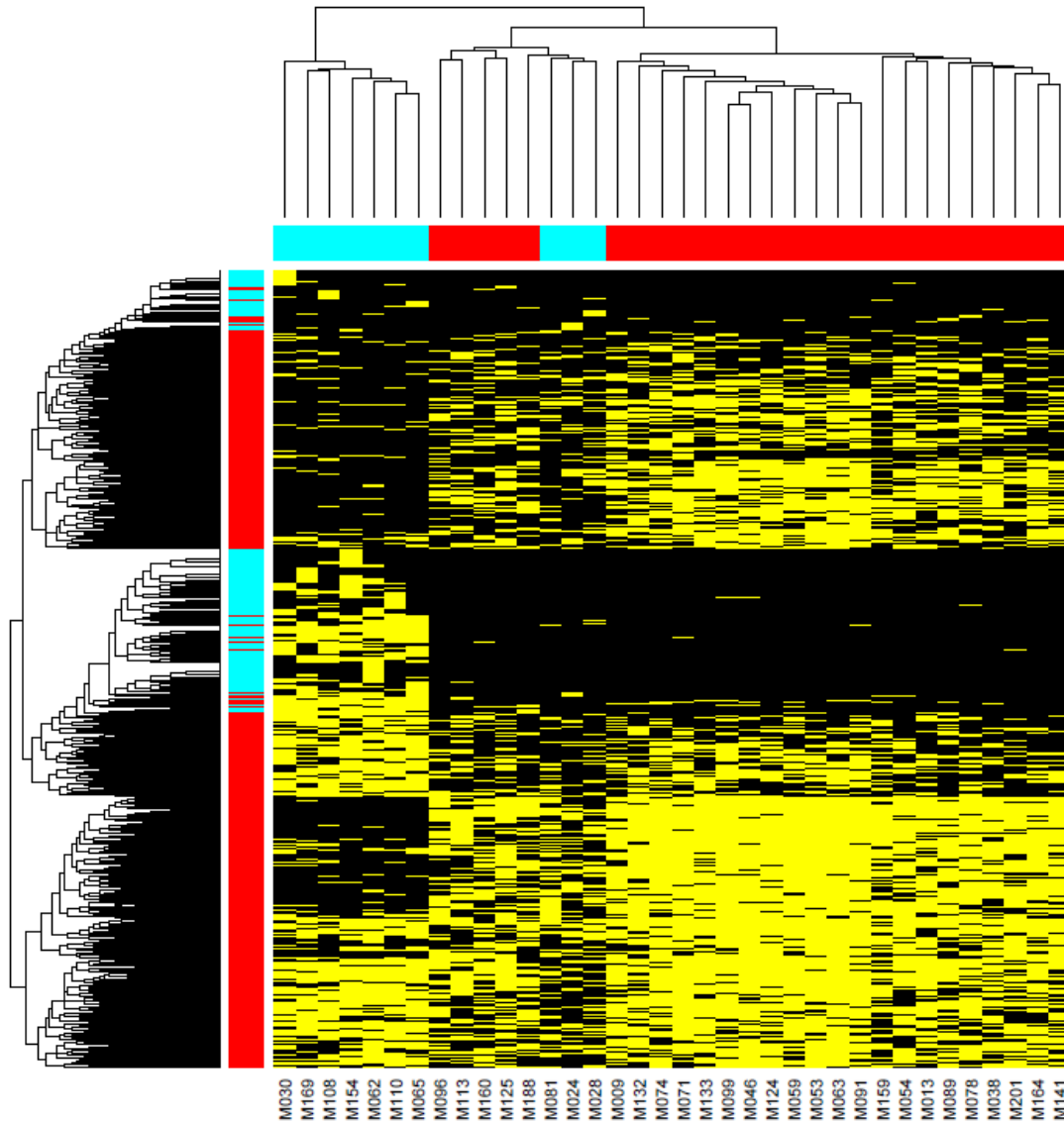


2 clusters are found
in the dataset



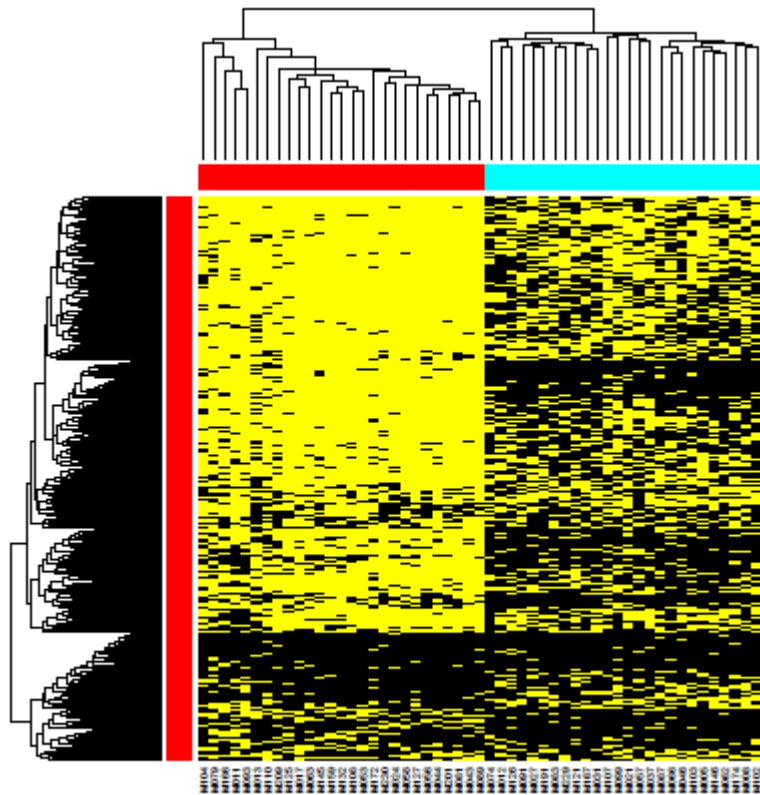
MGS dependency network
Nielsen et al.

Methanobrevibacter smithii example

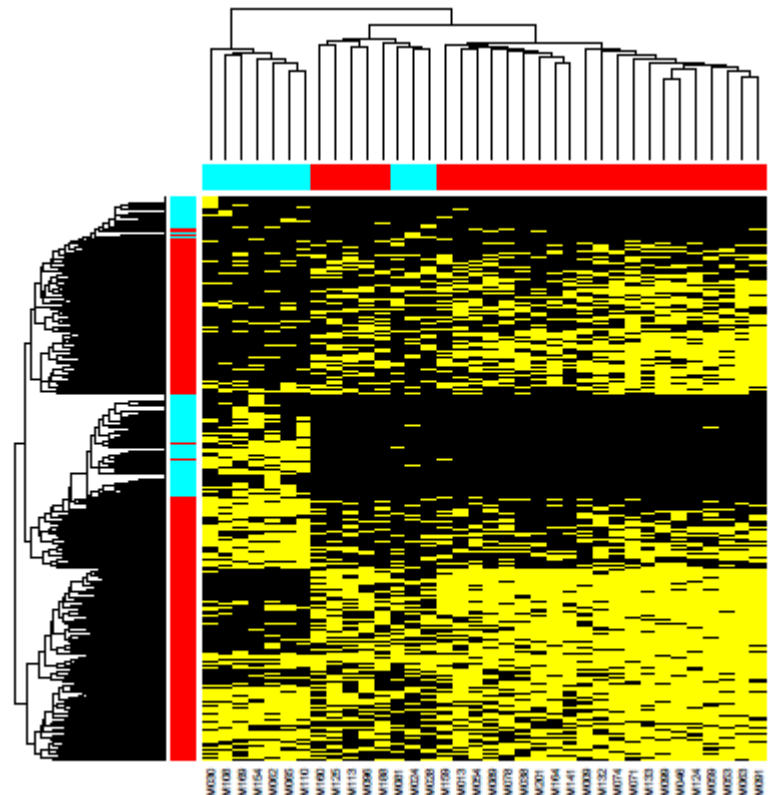


Small
dependency
cluster linked
with one
M.Smithii division

MGS genomic division



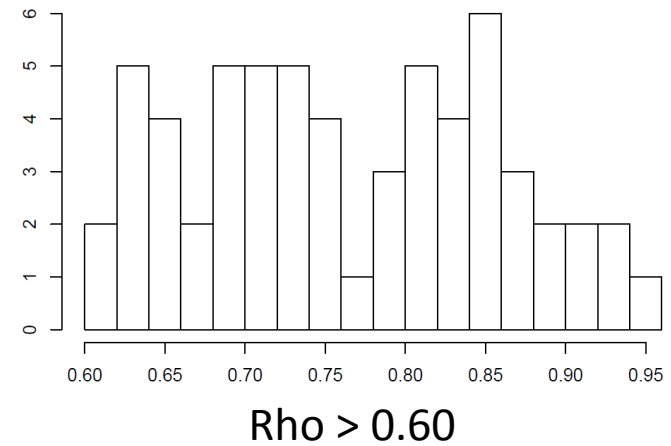
Prevotella copri “clades”



M. smithii “clades”

From IBS severe OTUs to MGS

Paired correlation analysis
allowed to find MGS from
severity OTU signature with a
good taxonomic agreement



OPEN

The ISME Journal (2016), 1–9
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www.nature.com/ismej



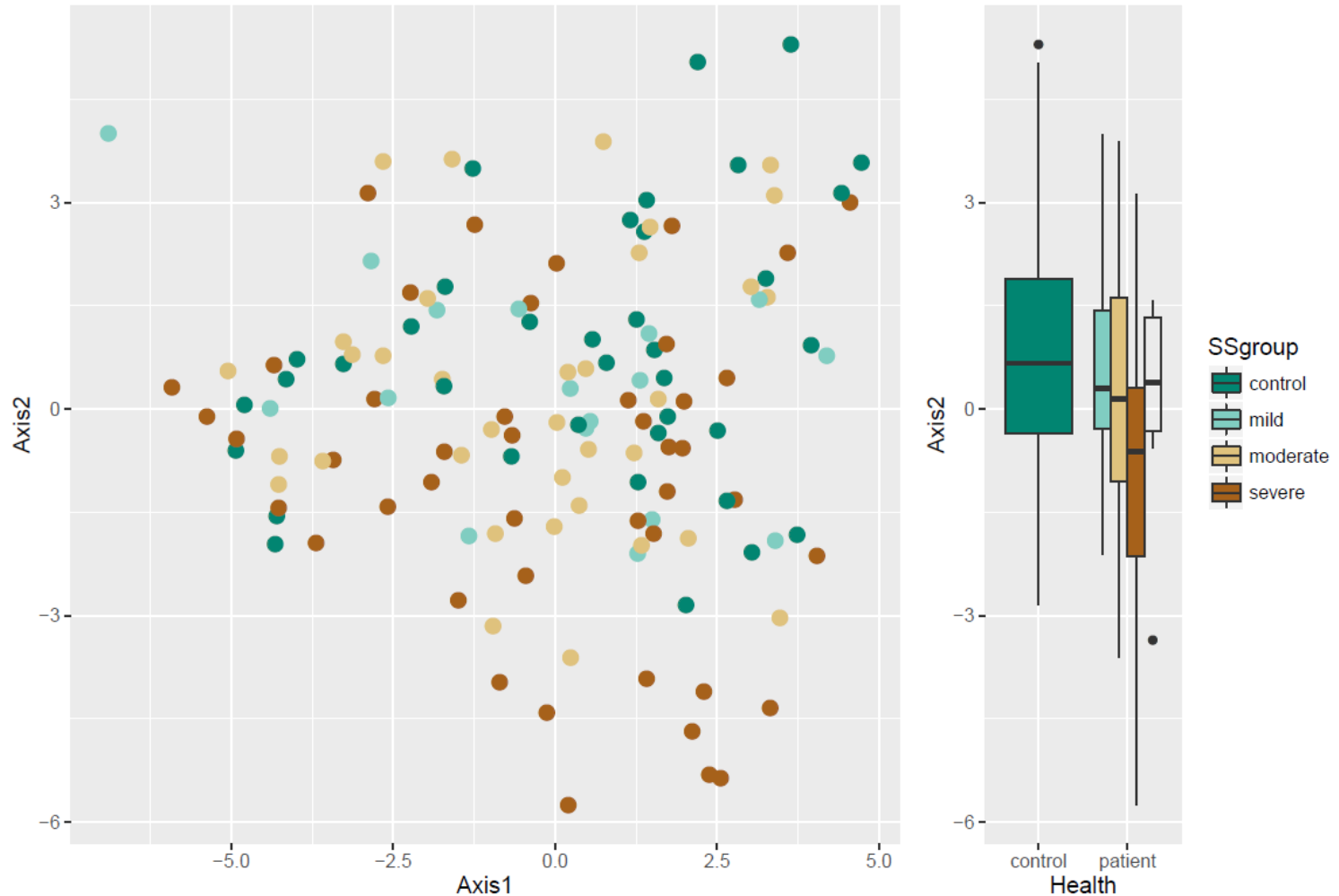
ORIGINAL ARTICLE

Capturing the most wanted taxa through cross-sample correlations

Mathieu Almeida¹, Mihai Pop^{1,2}, Emmanuelle Le Chatelier³, Edi Prifti³, Nicolas Pons³,
Amine Ghoulane³ and S Dusko Ehrlich³

55 MGS
were found
20 could be divided

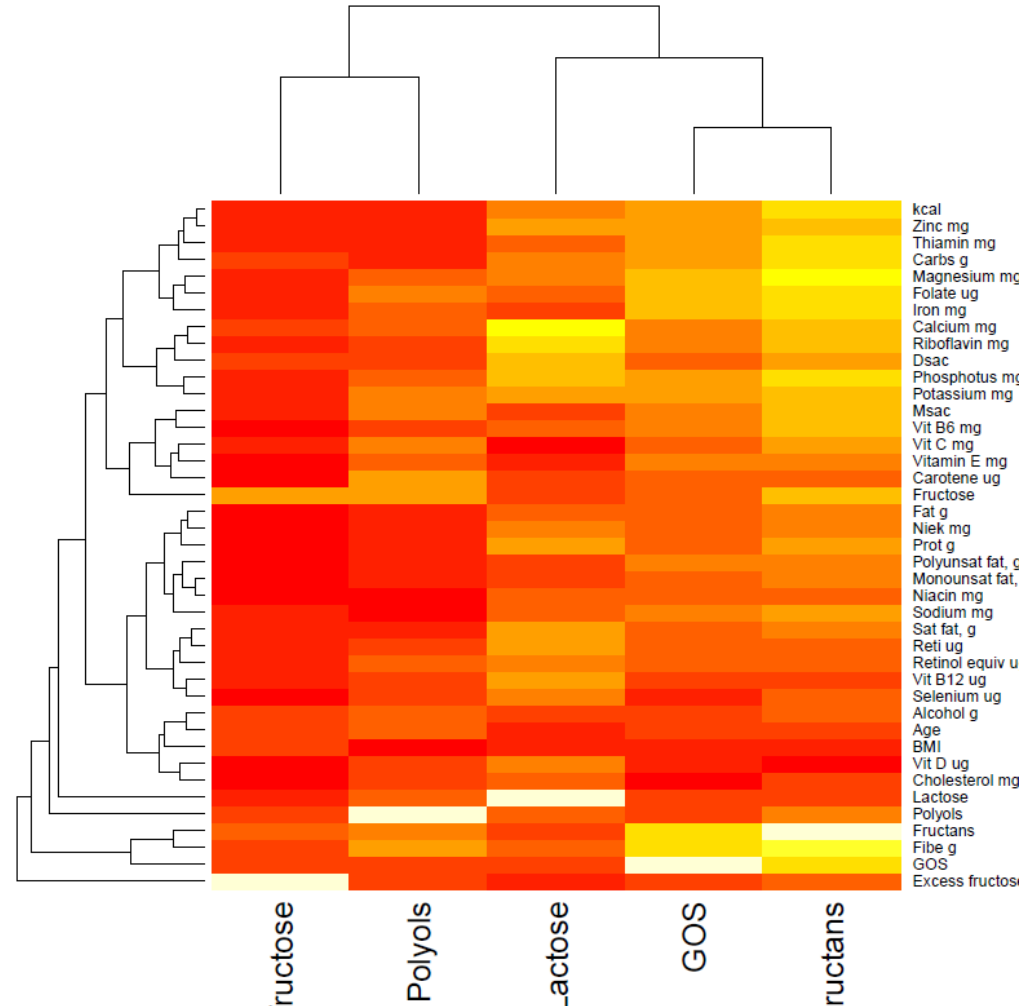
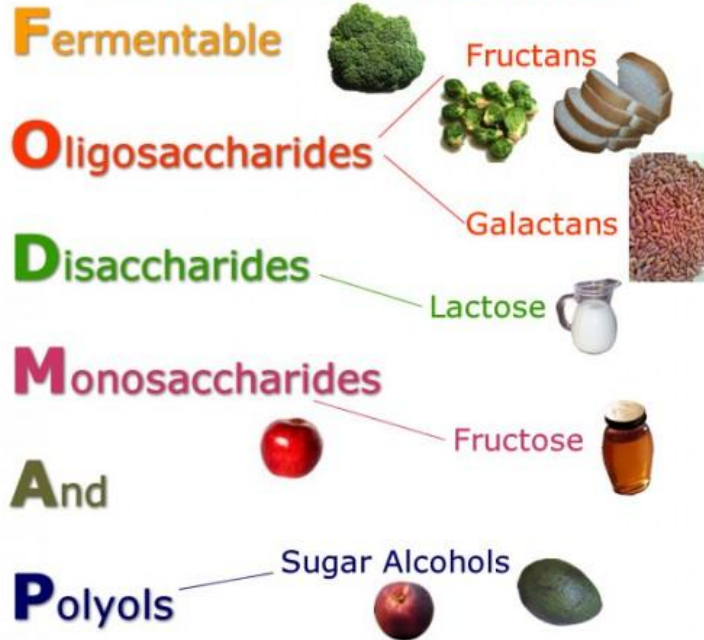
Severity MGS division



Severity associated MGS & their division still allowed to catch the severity signal

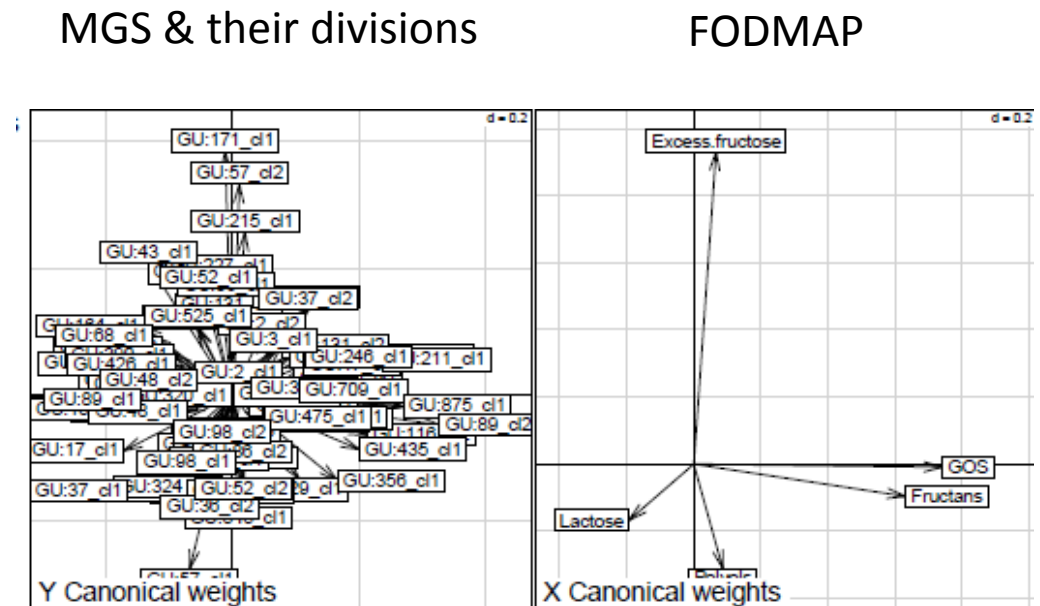
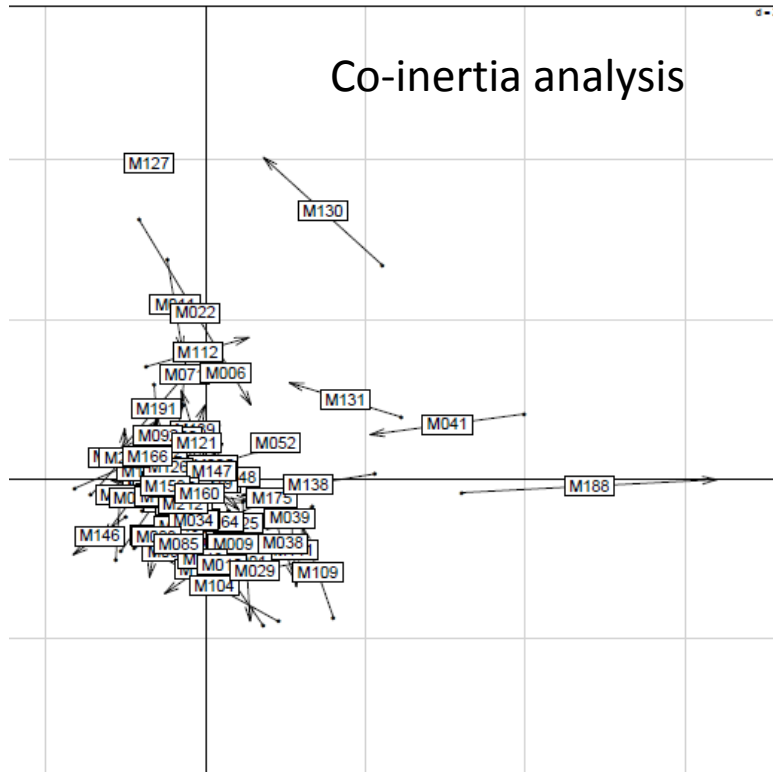
FODMAP diet

*IBS may be helped by keeping these
FODMAPs food to a minimum*
<http://blissfulwriter.hubpages.com/t/31f135>



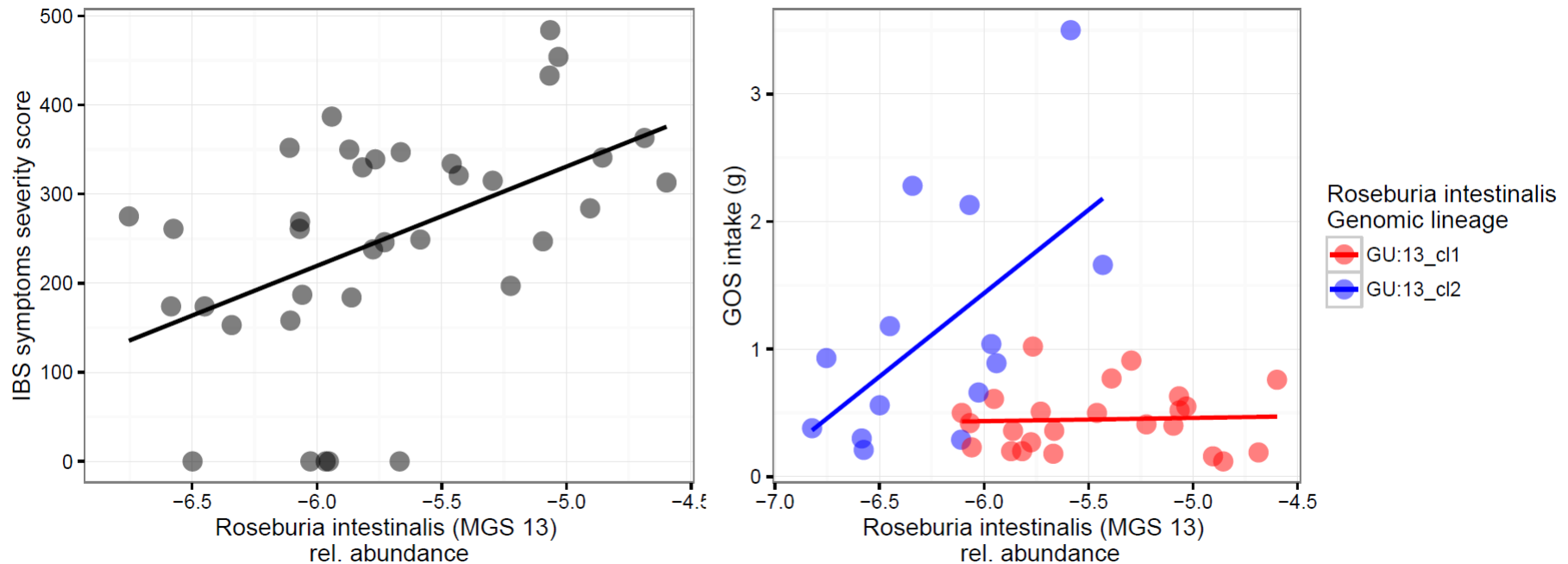
Fodmap diet correlation with other nutrient;
Lactose associated with calcium for example. Fructans with fibers.

Association between IBS severity MGS with FODMAP diet intake



17% of severity associated MGS inertia
is linked to FODMAP diet intake

Different diet association regarding genomic lineage



An example with *Roseburia intestinalis* MGS n°13

Take home messages for clinical microbiome analysis

1. Check confounding factors
2. Use classical ecology metrics
3. “Enterotype” your data
4. Do not forget Archaea and Eukaryota
5. Reduce de complexity (e.g. machine learning)
6. Classical multivariate analysis can still work
7. Go toward strain levels analysis

Acknowledgments



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INRA
SCIENCE & IMPACT

J. Doré
N. Pons



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RESEARCH**

R. Brazeilles
S. Cools-Portier
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