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HEALTH SCIENCES

The Microbiome: Methods, Tools, and Examples

W. Evan Johnson, PhD

Professor of Medicine, Division of Infectious Disease

Director, Center for Data Science

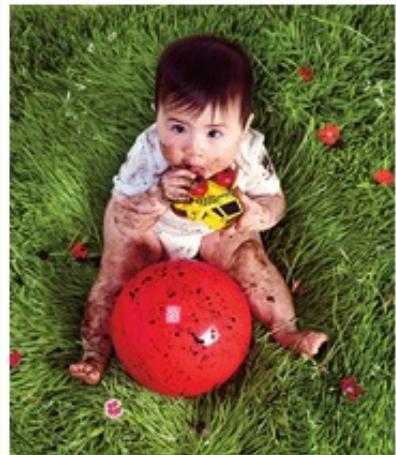
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Magazine

Some of My Best Friends Are Germs



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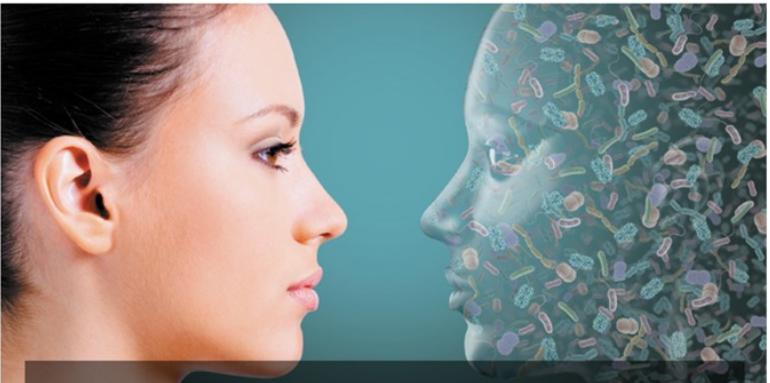
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SPECIAL

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HUMAN MICROBIOTA

The human body is colonized by a vast number of microbes, collectively referred to as the human microbiota. The link between these microbes and our health is the focus of a growing number of research initiatives, and new insights are emerging rapidly, some of which we are proud to present in this special collection.

Credit: Steven H. Lee / Studio Graphiko

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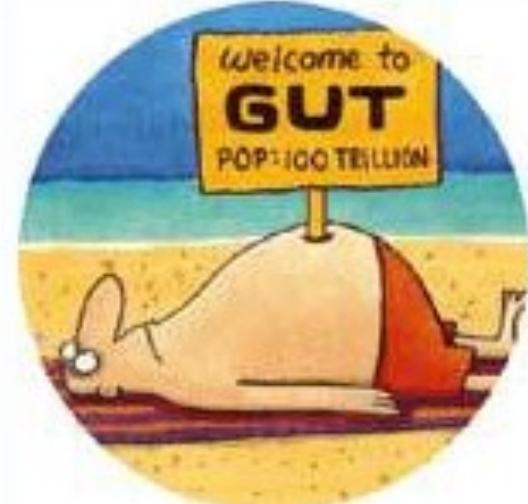
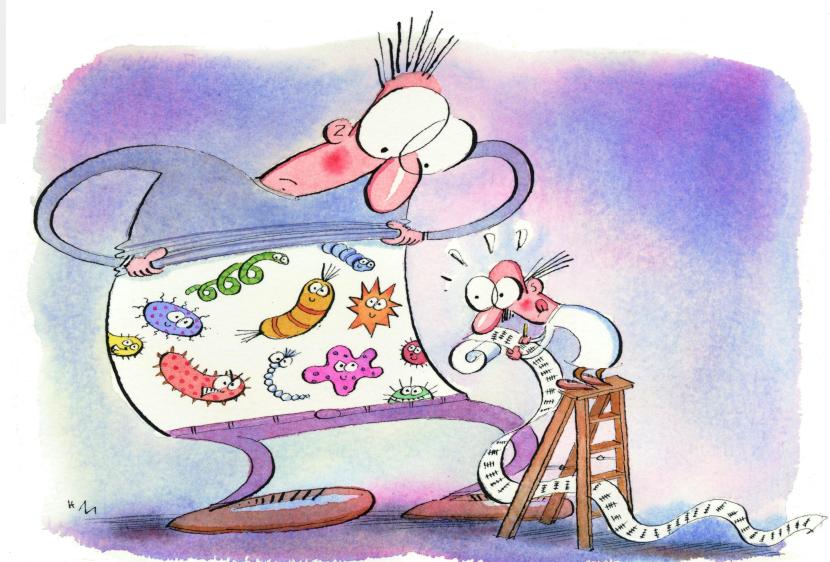
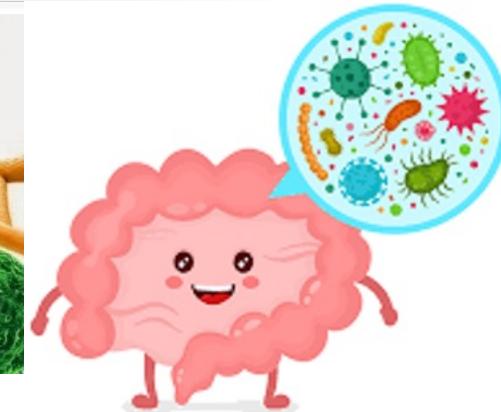
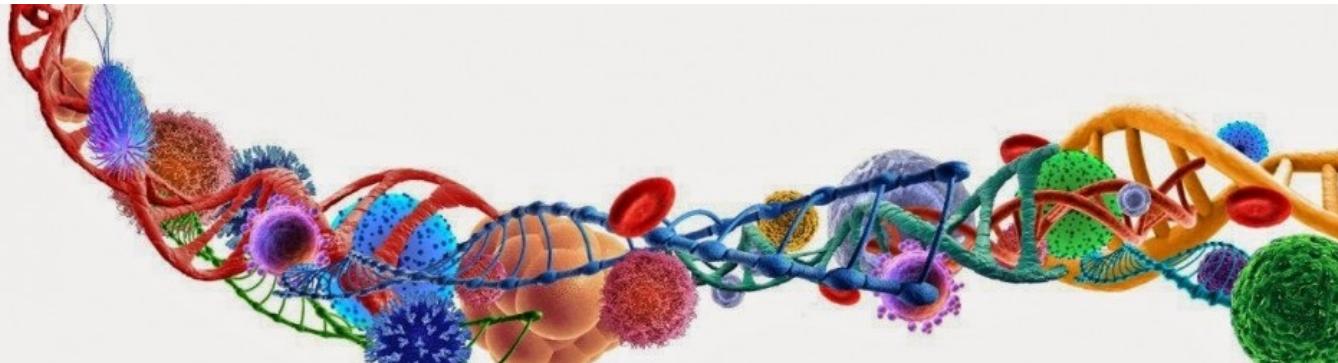
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SPECIAL ISSUE
**MICROBIOTA
AT WORK**



Our human cells are outnumbered!



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Scientists bust myth that our bodies have more bacteria than human cells

Decades-old assumption about microbiota revisited.

Alison Abbott

08 January 2016

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Red blood cells dominate our total cell count by number (though not by mass).

It's often said that the bacteria and other microbes in our body outnumber our own cells by about ten to one. That's a myth that should be forgotten, say researchers in Israel and Canada. The ratio between resident microbes and human cells is more likely to be one-to-one, they calculate.

A 'reference man' (one who is 70 kilograms, 20–30 years old and 1.7 metres tall) contains on average about 30 trillion human cells and 39 trillion bacteria, say Ron Milo and Ron Sender at the Weizmann Institute of

Science in Rehovot, Israel, and Shai Fuchs at the Hospital for Sick Children in Toronto, Canada.

Those numbers are approximate — another person might have half as many or twice as many bacteria, for example — but far from the 10:1 ratio commonly assumed.



Bacteria bonanza found in remote Amazon village



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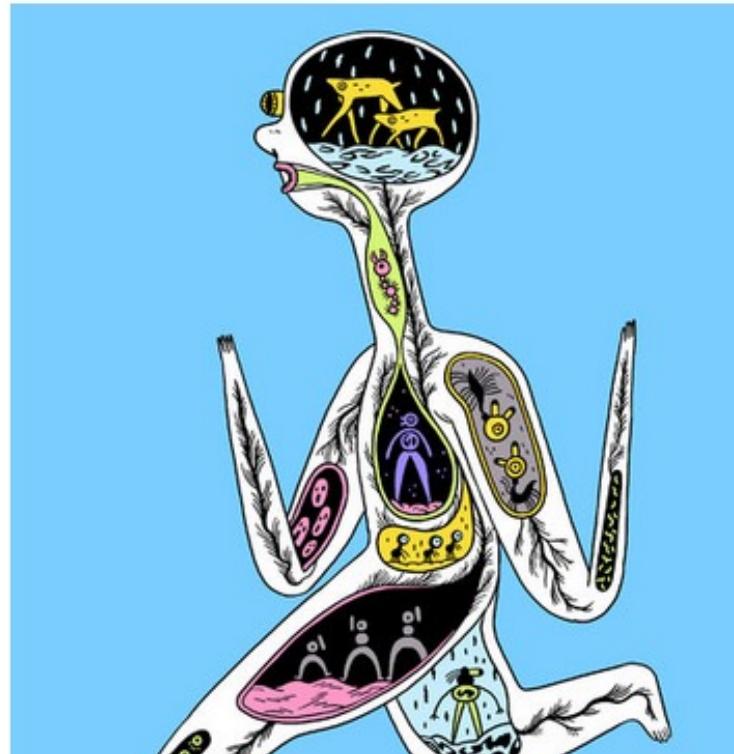
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There Is No ‘Healthy’ Microbiome

By ED YONG NOV. 1, 2014



LONDON — IN the late 17th century, the Dutch naturalist Anton van Leeuwenhoek looked at his own dental plaque through a microscope and saw a world of tiny cells “very prettily a-moving.” He could not have predicted that a few centuries later, the trillions of microbes that share our lives — collectively known as the microbiome — would rank among the hottest areas of biology.

These microscopic partners help us by digesting our food, training our immune systems and crowding out other harmful microbes that could

NOSOCOMIAL INFECTION

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing

Evan S. Snitkin,¹ Adrian M. Zelazny,² Pamela J. Thomas,¹ Frida Stock,²

NISC Comparative Sequencing Program,³ David K. Henderson,²

Tara N. Palmore,^{2*} Julia A. Segre^{1*}

The Gram-negative bacteria *Klebsiella pneumoniae* is a major cause of nosocomial infections, primarily among immunocompromised patients. The emergence of strains resistant to carbapenems has left few treatment options, making infection containment critical. In 2011, the U.S. National Institutes of Health Clinical Center experienced an outbreak of carbapenem-resistant *K. pneumoniae* that affected 18 patients, 11 of whom died. Whole-genome sequencing was performed on *K. pneumoniae* isolates to gain insight into why the outbreak progressed despite early implementation of infection control procedures. Integrated genomic and epidemiological analysis traced the outbreak to three independent transmissions from a single patient who was discharged 3 weeks before the next case became clinically apparent. Additional genomic comparisons provided evidence for unexpected transmission routes, with subsequent mining of epidemiological data pointing to possible explanations for these transmissions. Our analysis demonstrates that integration of genomic and epidemiological data can yield actionable insights and facilitate the control of nosocomial transmission.



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Open-Source Genomic Analysis of Shiga-Toxin–Producing *E. coli* O104:H4

Holger Rohde, M.D., Junjie Qin, Ph.D., Yujun Cui, Ph.D., Dongfang Li, M.E., Nicholas J. Loman, M.B., B.S., Moritz Hentschke, M.D., Wentong Chen, B.S., Fei Pu, B.S., Yangqing Peng, B.S., Junhua Li, B.E., Feng Xi, B.E., Shenghui Li, B.S., Yin Li, B.S., Zhaoxi Zhang, B.S., Xianwei Yang, B.S., Meiru Zhao, M.S., Peng Wang, B.M., Yuanlin Guan, B.E., Zhong Cen, M.E., Xiangna Zhao, B.S., Martin Christner, M.D., Robin Kobbe, M.D., Sebastian Loos, M.D., Jun Oh, M.D., Liang Yang, Ph.D., Antoine Danchin, Ph.D., George F. Gao, Ph.D., Yajun Song, Ph.D., Yingrui Li, B.S., Huanming Yang, Ph.D., Jian Wang, Ph.D., Jianguo Xu, M.D., Ph.D., Mark J. Pallen, M.D., Ph.D., Jun Wang, Ph.D., Martin Aepfelbacher, M.D., Ruifu Yang, M.D., Ph.D., and the *E. coli* O104:H4 Genome Analysis Crowd-Sourcing Consortium

N Engl J Med 2011; 365:718-724 | August 25, 2011 | DOI: 10.1056/NEJMoa1107643

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Human nutrition, the gut microbiome and the immune system

Andrew L. Kau, Philip P. Ahern, Nicholas W. Griffin, Andrew L. Goodman & Jeffrey I. Gordon

[Affiliations](#) | [Corresponding author](#)

Nature 474, 327–336 (16 June 2011) | doi:10.1038/nature10213

Published online 15 June 2011



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Richness of human gut microbiome correlates with metabolic markers

Emmanuelle Le Chatelier, Trine Nielsen, Junjie Qin, Edi Prifti, Falk Hildebrand, Gwen Falony, Mathieu Almeida, Manimozhiyan Arumugam, Jean-Michel Batto, Sean Kennedy, Pierre Leonard, Junhua Li, Kristoffer Burgdorf, Niels Grarup, Torben Jørgensen, Ivan Brandslund, Henrik Bjørn Nielsen, Agnieszka S. Juncker, Marcelo Bertalan, Florence Levenez, Nicolas Pons, Simon Rasmussen, Shinichi Sunagawa, Julien Tap, Sebastian Timmer et al.

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Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease

Luke Jostins, Stephan Ripke, Rinse K. Weersma, Richard H. Duerr, Dermot P. McGovern, Ken Y. Hui, James C. Lee, L. Philip Schumm, Yashoda Sharma, Carl A. Anderson, Jonah Essers, Mitja Mitrovic, Kaida Ning, Isabelle Cleynen, Emilie Theatre, Sarah L. Spain, Soumya Raychaudhuri, Philippe Goyette, Zhi Wei, Clara Abraham, Jean-Paul Achkar, Tarig Ahmad

Editor's summary

العربية

Genetic studies have implicated unsuspected mechanisms in the pathogenesis of Crohn's disease and ulcerative colitis, two of the most common forms of inflammatory bowel disease. This paper presents a ...



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Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis

Robert A Koeth, Zeneng Wang, Bruce S Levison, Jennifer A Buffa, Elin Org, Brendan T Sheehy, Earl B Britt, Xiaoming Fu, Yuping Wu, Lin Li, Jonathan D Smith, Joseph A DiDonato, Jun Chen, Hongzhe Li, Gary D Wu, James D Lewis, Manya Warrier, J Mark Brown, Ronald M Krauss, W H Wilson Tang, Frederic D Bushman, Aldons J Lusis & Stanley L Hazen

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Nature Medicine 19, 576–585 (2013) | doi:10.1038/nm.3145

Received 07 December 2012 | Accepted 27 February 2013 | Published online 07 April 2013

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by Bäckhed

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in 2013

Mark S Butler,
Mark A Blaskovich
and Matthew A Cooper

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ORIGINAL ARTICLE

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Jen-Shan Chin, Ph.D., Jon Sorenson, Ph.D., Jason B. Harris, M.D., William P. Robins, Ph.D., Richelle C. Charles, M.D., Roger R. Jean-Charles, M.D., James Bullard, Ph.D., Dale R. Webster, Ph.D., Andrew Kasarskis, Ph.D., Paul Peluso, Ph.D., Jen E. Paxinos, Ph.D., Yoshiharu Yamaichi, Ph.D., Stephen B. Calderwood, M.D., John J. Mekalanos, Ph.D., Eric E. Schaefer, M.D., and Matthew K. Waldor, M.D., Ph.D.



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Cohabiting family members share microbiota with one another and with their dogs



Se Jin Song, Christian Lauber, Elizabeth K Costello, Catherine A Lozupone, Gregory Humphrey, Donna Berg-Lyons, J Gregory Caporaso, Dan Knights, Jose C Clemente, Sara Nakielny, Jeffrey I Gordon, Noah Fierer, Rob Knight 

University of Colorado, Boulder, United States; Stanford University School of Medicine, United States; Northern Arizona University, United States; Institute for Genomics and Systems Biology, United States; University of Minnesota, United States; BioTechnology Institute, University of Minnesota, United States; Howard Hughes Medical Institute, University of California, San Francisco, United States; Washington University School of Medicine, United States; Howard Hughes Medical Institute, University of Colorado, Boulder, United States; Biofrontiers Institute, University of Colorado, Boulder, United States

DOI: <http://dx.doi.org/10.7554/eLife.00458>

Published April 16, 2013

Cite as eLife 2013;2:e00458



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Letter

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David, Corinne F. Maurice, Rachel N. Carmody, David B. Gootenberg, Julie E. Button, Benjamin E. Wolfe, Alisha V. Ling, A. Sloan Devlin, Yug Varma, Michael A. Fischbach, Sudha B. Biddinger, Rachel J. Dutton & Peter J. Turnbaugh

Nature **505**, 559–563 (23 January 2014)

doi:10.1038/nature12820

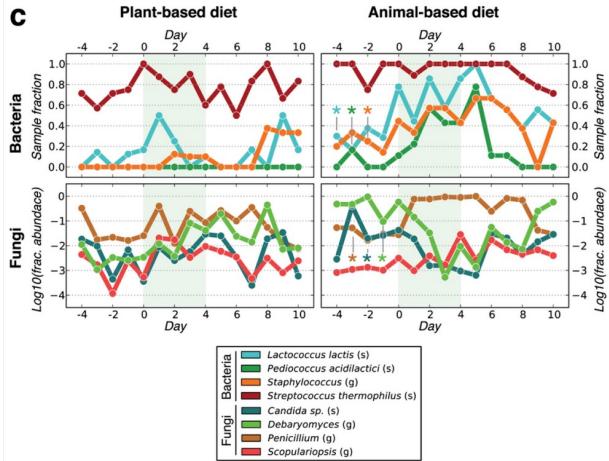
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Accepted: 29 October 2013

Published online: 11 December 2013

Inflammatory bowel disease Microbiome





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Shaping the oral microbiota through intimate kissing

Remco Kort , Martien Caspers, Astrid van de Graaf, Wim van Egmond, Bart Keijser and Guus Roeselers

Microbiome 2014 2:41 | DOI: 10.1186/2049-2618-2-41 | © Kort et al.; licensee BioMed Central Ltd. 2014

Received: 18 July 2014 | Accepted: 20 October 2014 | Published: 17 November 2014

Abstract

Background

The variation of microbial communities associated with the human body can be the cause of many factors, including the human genetic makeup, diet, age, surroundings, and sexual behavior. In this study, we investigated the effects of intimate kissing on the oral microbiota of 21 couples by self-administered questionnaires about their past kissing behavior and by the evaluation of tongue and salivary microbiota samples in a controlled kissing experiment. In addition, we quantified the number of bacteria exchanged during intimate kissing by the use of marker bacteria introduced through the intake of a probiotic yoghurt drink by one of the partners prior to a second intimate kiss.

Results

Similarity indices of microbial communities show that average partners have a more similar oral microbiota composition compared to unrelated individuals, with by far most pronounced similarity for communities

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- Abstract
- Background
- Results and discussion
- Conclusions
- Methods
- Availability of supporting data
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Some beards contain more poo than a toilet shocking study reveals

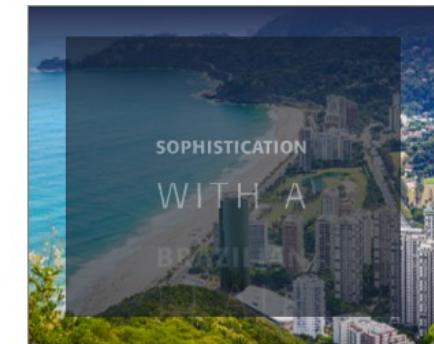
According to microbiologists, hairy faces could actually be dirtier than a loo because of the rancid bacteria that beards collect



BY HAYLEY COYLE

21:01, 3 MAY 2015 | UPDATED 21:14, 3 MAY 2015

NEWS



STEPHEN HAWKING
Professor Stephen Hawking says humans will be WIPED OUT in 1,000 years unless we find new planet



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Bearded men have poop on their faces | New York Post

nypost.com/2015/05/04/science-proves-that-beards-contain-fecal-matter/ ▾

May 4, 2015 - Apparently the key to a poo-free beard is to make sure you wash your ... that some of the bacteria "are the kind of things that you find in feces".

Fecal Matter in Your Beard - Men's Health

www.menshealth.com/health/no-poop-in-beard ▾

May 7, 2015 - No, Your Beard Doesn't Have Poop in It. Your facial hair is probably dirtier than you thought, but you don't need to panic. You've probably seen the gross headline this week: There's **feces** in your beard!

Does Your Beard Really Contain More Poo Than A Toilet? | IFLScience

www.iflscience.com/health-and-science/your-beard-does-not-contain-more-poo-toilet/ ▾

Contrary to what you have seen in the media, **beards** do not harbor more poo than a ... He told the presenter that these bacteria are usually found in **feces**, but ...

No, your beard isn't full of poop (probably) - The Washington Post

<https://www.washingtonpost.com/news/health/wp/2015/05/04/no-your-beard-isnt-full-of-poop-probably/> ▾

May 4, 2015 - No, your **beard** isn't full of poop (probably) ... gut bacteria to the detection of poo bacteria to the dangerous and gross presence of **fecal matter**.

Your Hipster Beard May Have More Fecal Matter Than A Dirty Toilet ...

www.medicaldaily.com/your-hipster-beard-may-have-more-fecal-matter-dirty-toilet-it... ▾

May 5, 2015 - A man's **beard** may be a breeding ground for bacteria found in **fecal matter**.



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Longer Contact Times Increase Cross-Contamination of *Enterobacter aerogenes* from Surfaces to Food

Robyn C. Miranda and Donald W. Schaffner

C. A. Elkins, Editor

[Author Affiliations](#)

ABSTRACT

Bacterial cross-contamination from surfaces to food can contribute to foodborne disease. The cross-contamination rate of *Enterobacter aerogenes* on household surfaces was evaluated by using scenarios that differed by surface type, food type, contact time (<1, 5, 30, and 300 s), and inoculum matrix (tryptic soy broth or peptone buffer). The surfaces used were stainless steel, tile, wood, and carpet. The food types were watermelon, bread, bread with butter, and gummy candy. Surfaces (25 cm^2) were spot inoculated with 1 ml of inoculum and allowed to dry for 5 h, yielding an approximate concentration of 10^7 CFU/surface. Foods (with a 16-cm^2 contact area) were dropped onto the surfaces from a height of 12.5 cm and left to rest as appropriate. Posttransfer, surfaces and foods were placed in sterile filter bags and homogenized or massaged, diluted, and plated on tryptic soy agar. The transfer rate was quantified as the log percent transfer from the surface to the food. Contact time, food, and surface type all had highly significant effects ($P < 0.000001$) on the log percent transfer of bacteria. The inoculum matrix (tryptic soy broth or

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This Article

Accepted manuscript posted online 2 September 2016, doi: 10.1128/AEM.01838-16

Appl. Environ. Microbiol., November 2016, vol. 82 no. 21 6490–6496

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Written by Julie Wolf

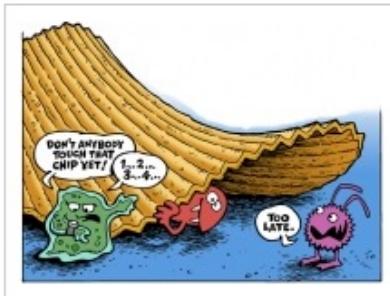
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While walking through your house, you drop a granola bar you were eating. Quick – do you pick it up and eat it? Is the ground too dirty to eat from? Does the amount of time the food sits on the ground matter? Will more microbes gather onto the snack as you decide whether or not to continue noshing?

This last question refers to **the five-second rule**, a colloquial rule that holds that food touching the ground for five seconds or less has less contamination and is therefore okay to eat, while food touching the ground for over five seconds has to be discarded. This commonly understood rule (even known to most five-year-olds) was

put to systematic examination in a recent *Applied and Environmental Microbiology* report.

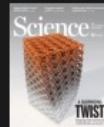
The authors, Robyn Miranda and Donald Schaffner, examined the effect of time during bacterial transfer from one of four different surfaces: stainless steel, tile, wood, or carpet. Each surface was coated with the same amount of bacteria and allowed to dry before food was exposed to the surface for 1, 5, 30, or 300 seconds. If the five-second rule held up, the scientists expected to see less bacteria transferred during 1 and 5 second exposures than in 30 or 300 second exposures.

Across all different surfaces and using several different food types, the authors found that more exposure time led to



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Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy^{1,2,3}, Emmanuelle Le Chatelier⁴, Lisa Derosa^{1,2,3}, Connie P. M. Duong^{1,2,5}, Maryam Tidjani Alou^{1,2,3}, Romain ...

[+ See all authors and affiliations](#)

Science 02 Nov 2017:
eaan3706
DOI: 10.1126/science.aan3706

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Abstract

Immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis induce sustained clinical responses in a sizeable minority of cancer patients. Here, we show that primary resistance to ICI can be due to abnormal gut microbiome composition. Antibiotics (ATB) inhibited the clinical benefit of ICI in patients with advanced cancer. Fecal microbiota transplantation (FMT) from cancer patients who responded to ICI (but not from non-responding patients) into germ-

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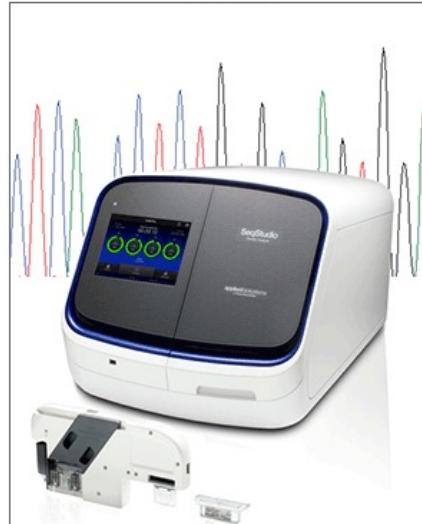


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Research Article | Host-Microbe Biology

Alzheimer's Disease Microbiome Is Associated with Dysregulation of the Anti-Inflammatory P-Glycoprotein Pathway

John P. Haran, Shakti K. Bhattacharai, Sage E. Foley, Protiva Dutta, Doyle V. Ward, Vanni Bucci, Beth A. McCormick

Melinda M. Pettigrew, *Editor*

DOI: 10.1128/mBio.00632-19

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ABSTRACT

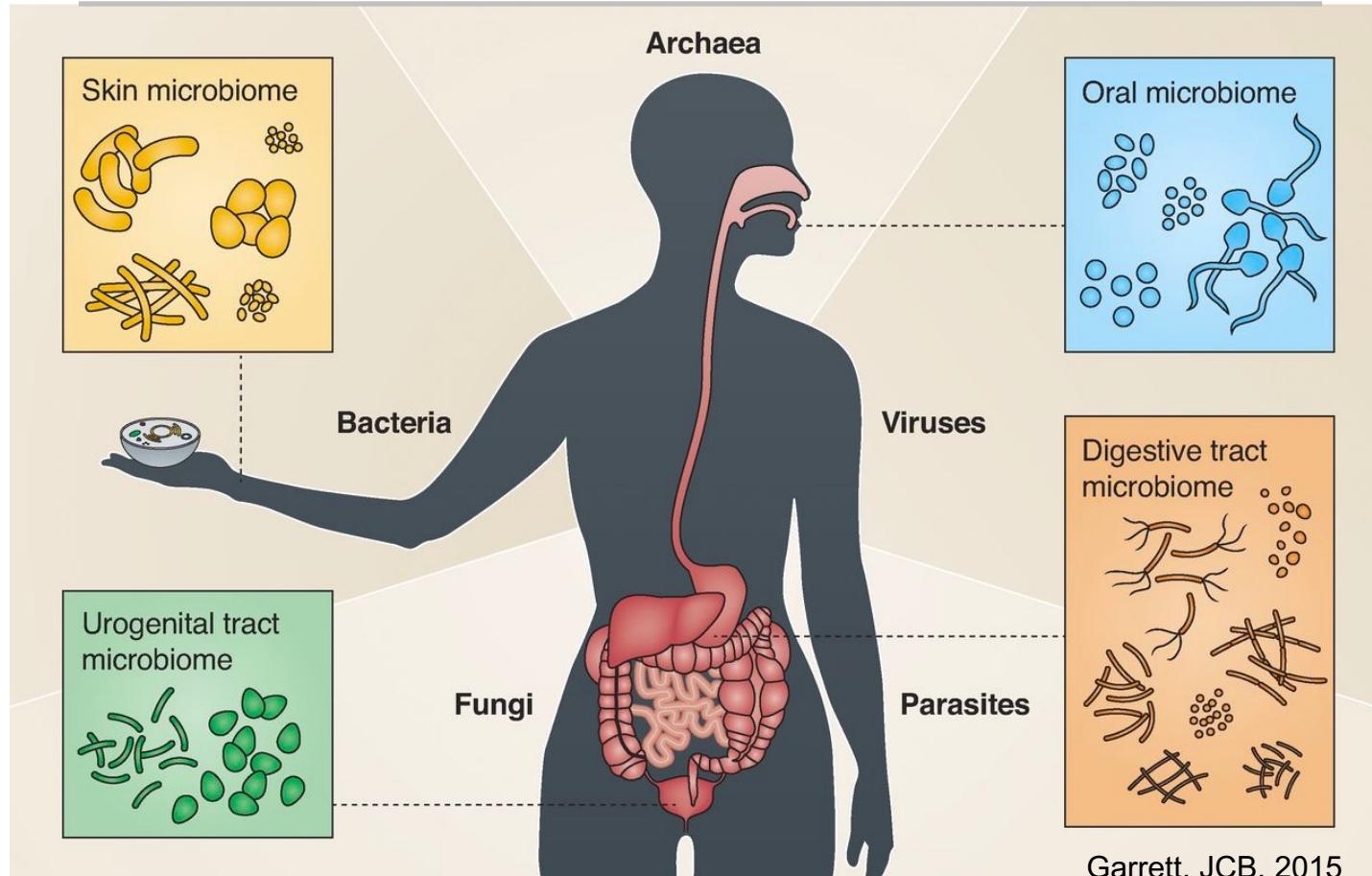
The microbiota-gut-brain axis is a bidirectional communication system that is poorly understood. Alzheimer's disease (AD), the most common cause of dementia, has long been associated with bacterial infections and inflammation-causing immunosenescence. Recent studies examining the

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We depend on microbes and their metabolism



Garrett. JCB, 2015

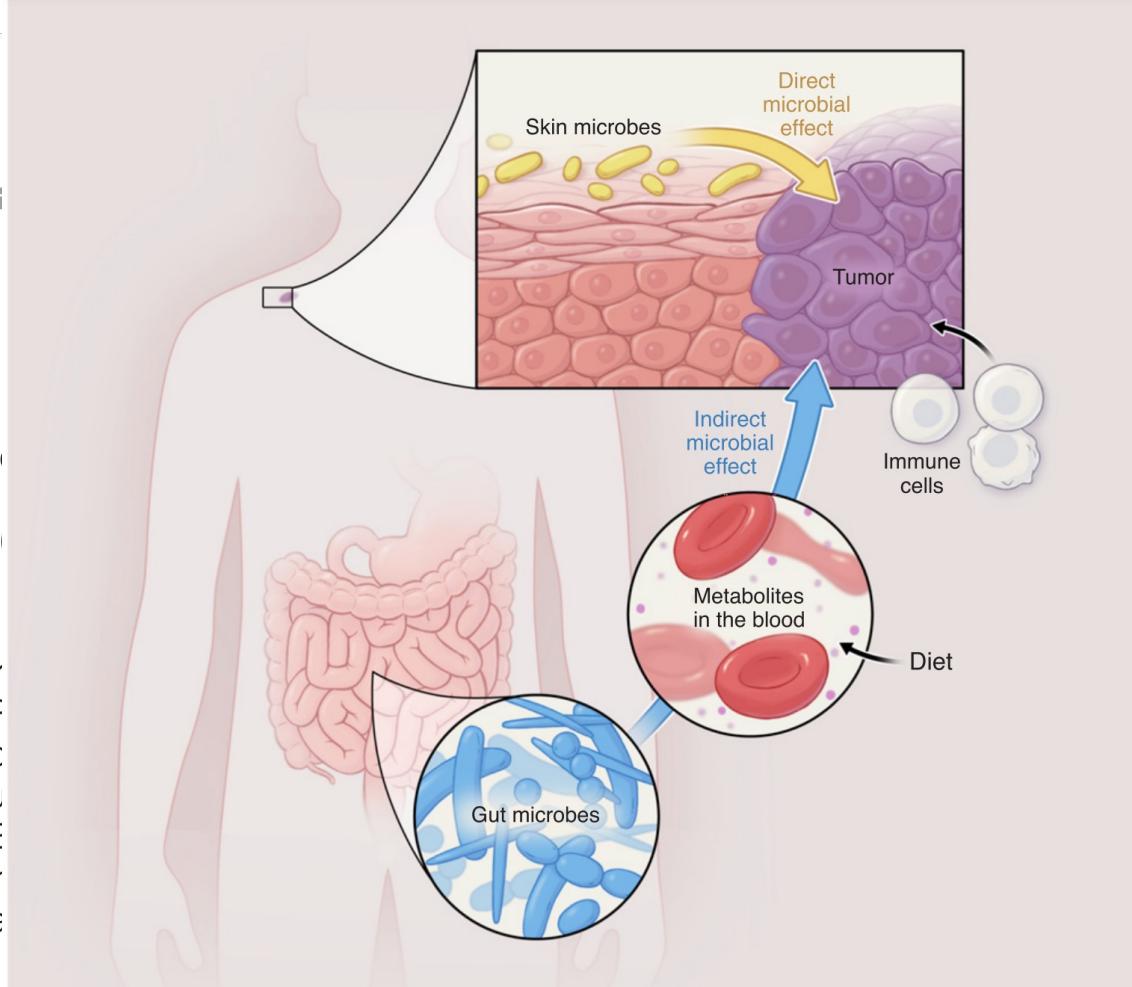


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L. Whiteson,¹⁶
njo,²⁰

Current state of the microbiome

The Madness of Microbiome: Attempting To Find Consensus “Best Practice” for 16S Microbiome Studies

 Jolinda Pollock,^{a,b}  Laura Glendinning,^b Trong Wisedchanwet,^b  Mick Watson^b



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NATURE | COMMENT



Microbiology: Microbiome science needs a healthy dose of scepticism

William P. Hanage

20 August 2014



How the co-discovery of CRISPR explosively



RUTGERS “Metagenomics” Etymology

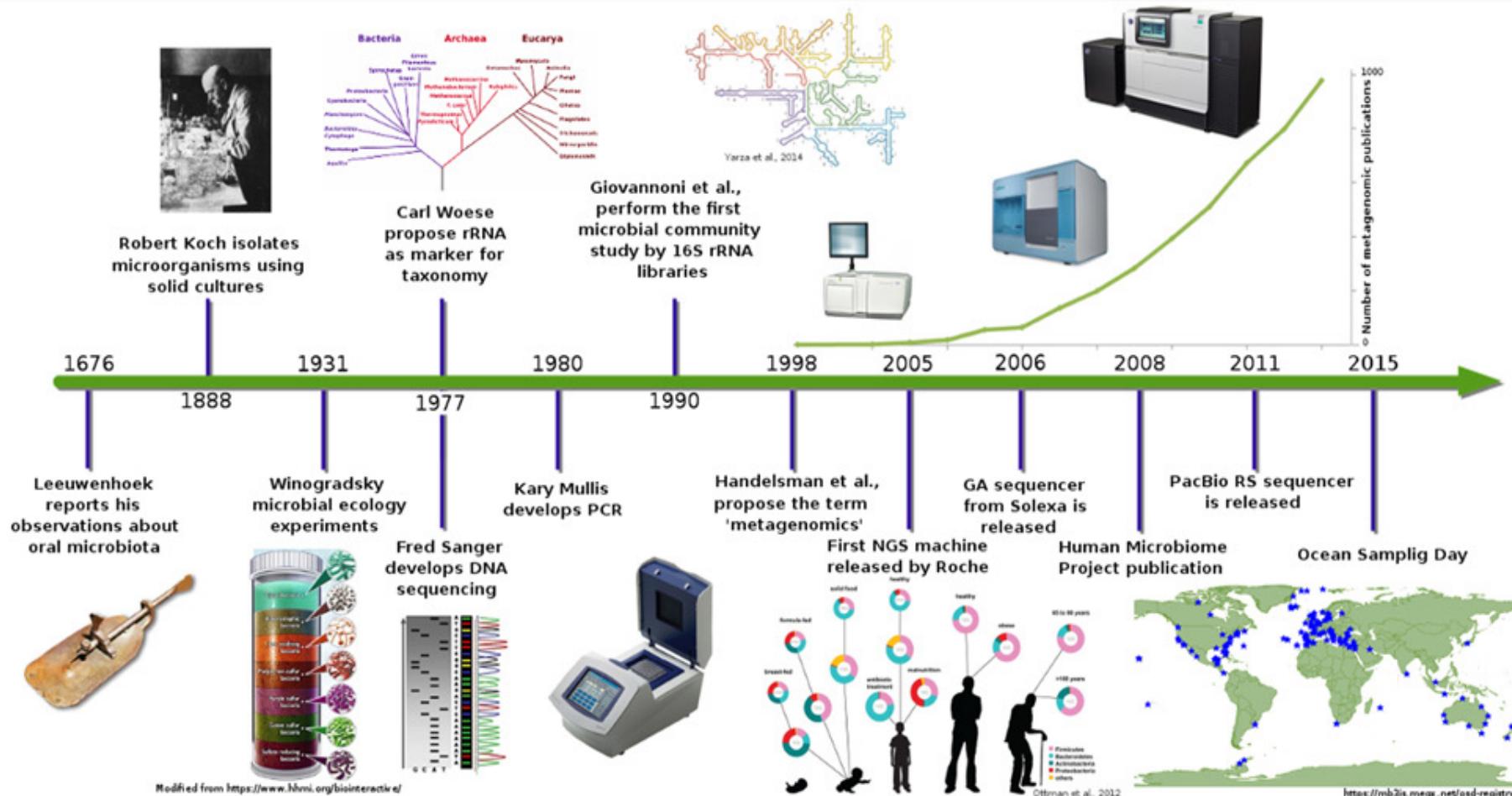
- Coined in 1998, collection of genetic material from multiple organisms, analyzed as if one genome
- In Greek, meta means “transcendent”
- 2005: “the application of modern genomics techniques without the need for isolation and lab cultivation of individual species”



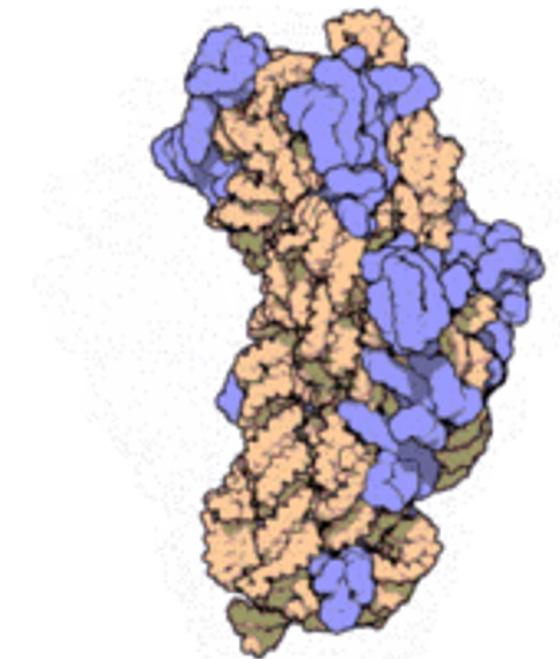
ATCCGGACTAGC



RUTGERS The History of the Microbiome

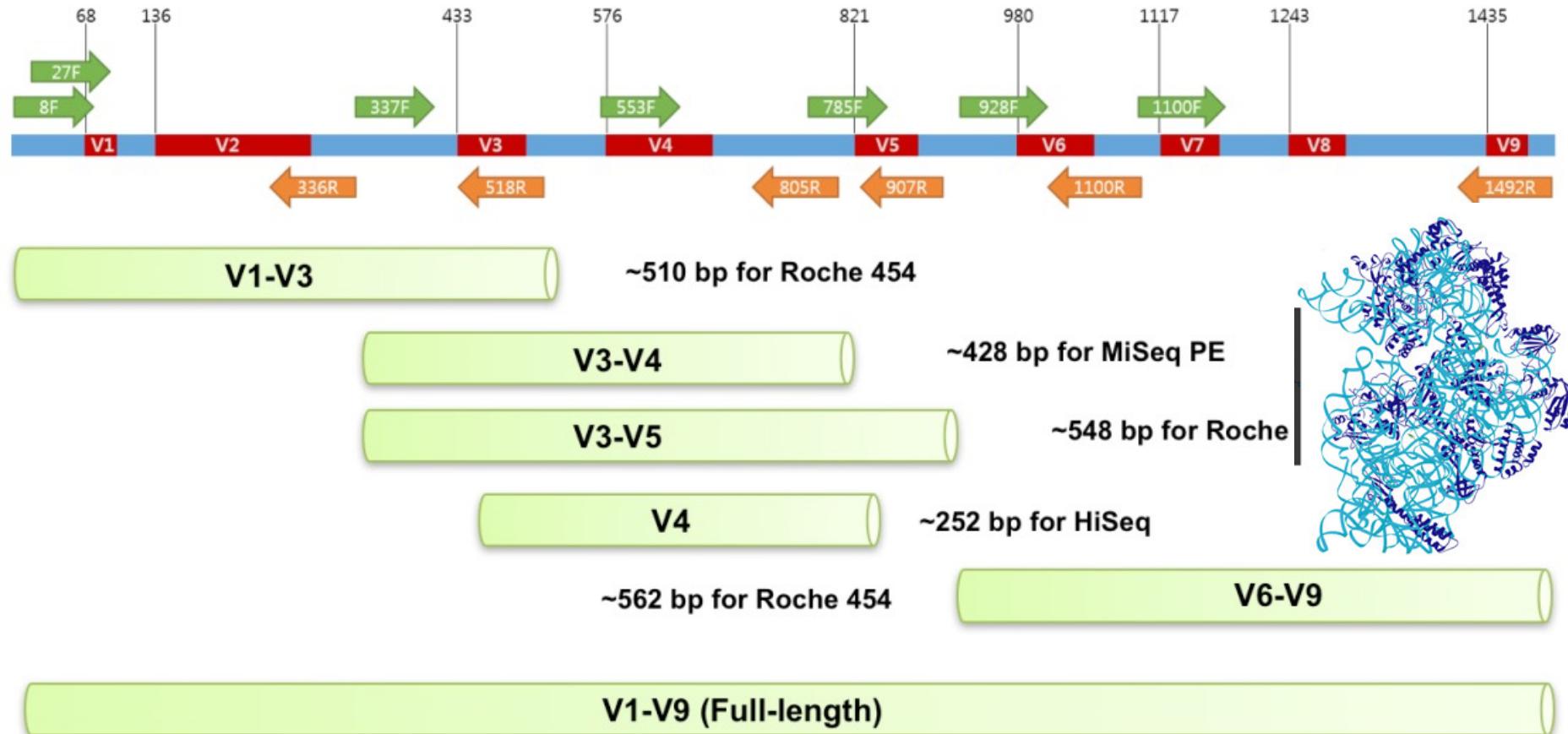


- PCR amplify and sequence ~1.5kbp
- Advantages
 - Conserved in bacteria (all have one)
 - Highly variable regions: identify taxonomy and phylogeny
 - Established and affordable
- Disadvantages
 - Neglects viruses, fungi, parasites, etc
 - No strains or sometimes species identification
 - PCR bias?

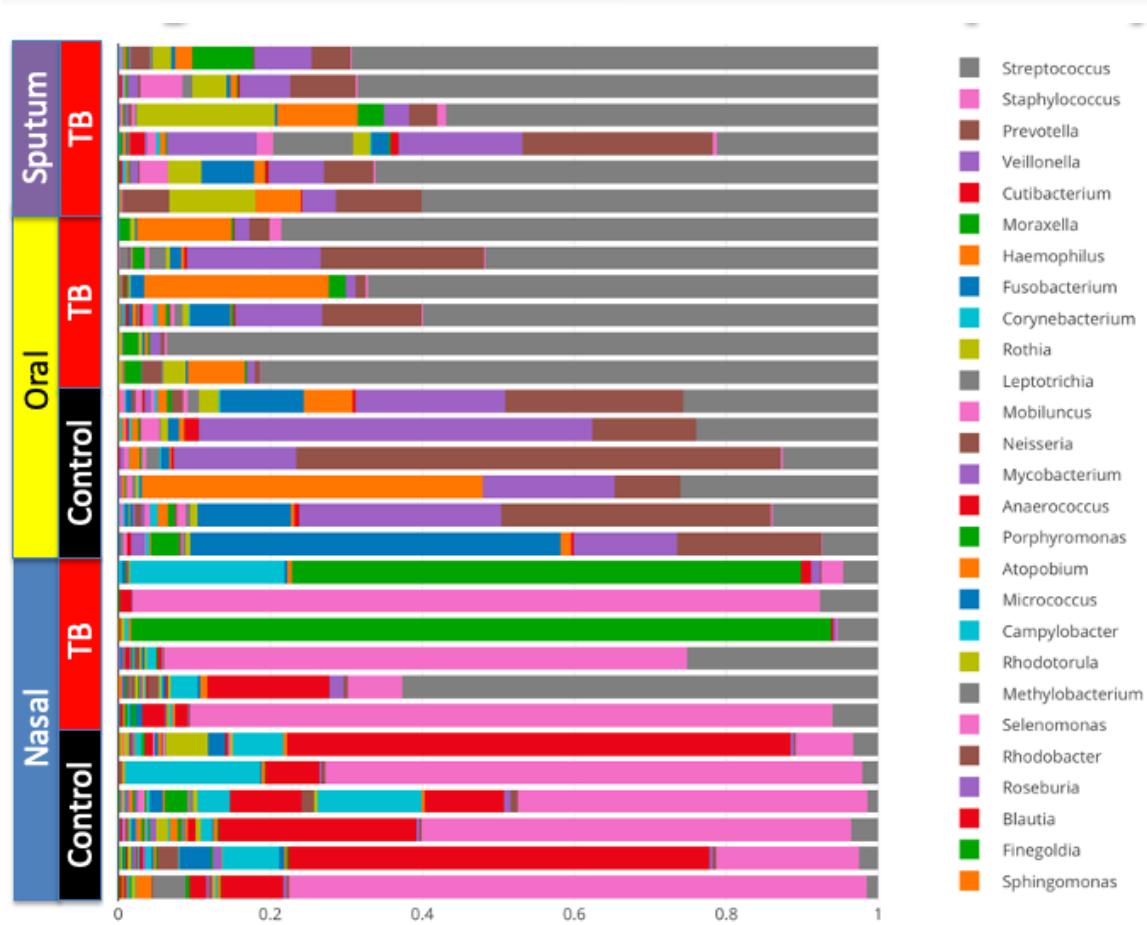


The 16S subunit

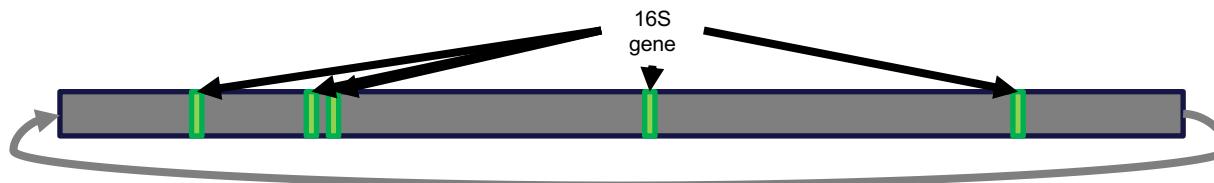
16S Ribosomal Sequencing



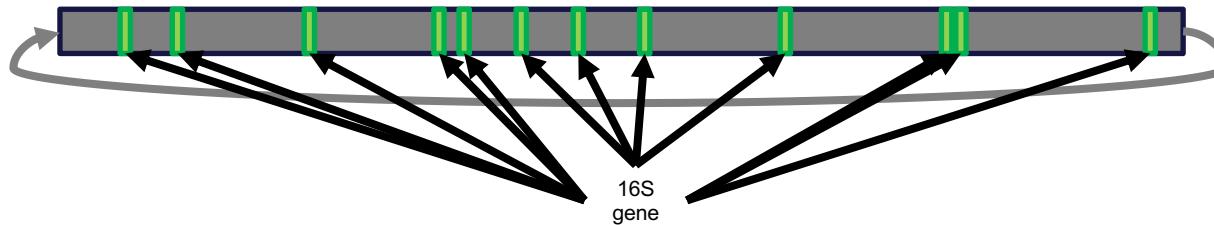
AIRWAY MICROBIOME OF TB (16S)



16S Genomic Diversity



Different species have different copy numbers of 16S rDNA





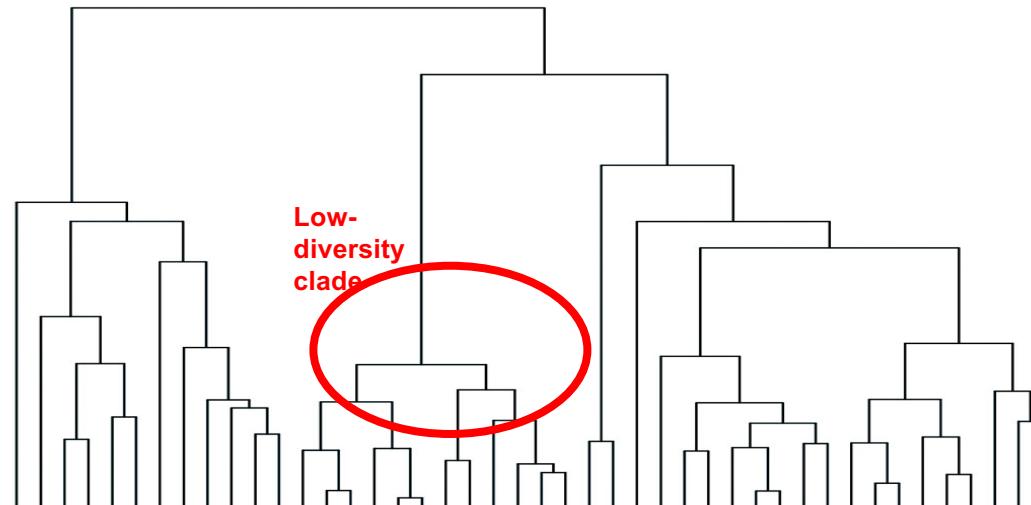
...and each copy has a unique sequence!



Ambiguous Alignments

When do ambiguous alignments appear?

Species 1	C	A	T	T	T	A	G	G	T	C	C	A	G
Species 2	C	A	T	T	T	A	A	G	T	C	C	A	G
Species 3	C	A	T	T	T	A	T	G	T	C	C	A	G

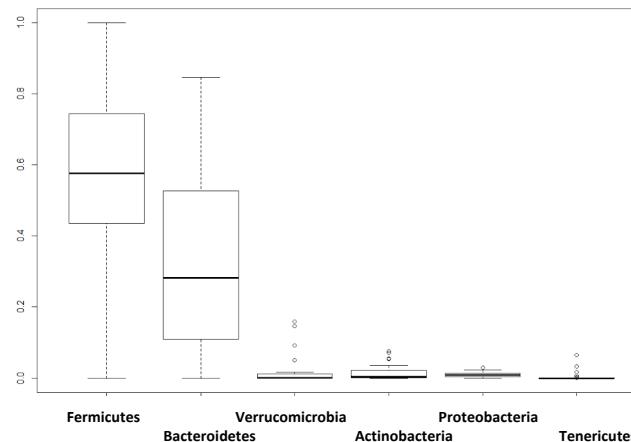


 RUTGERS Whole Metagenome Sequencing

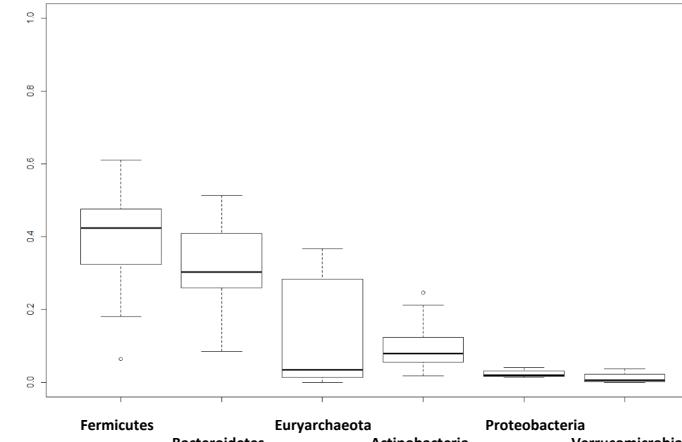
- Sequence whole (fragmented) DNA
- Advantages:
 - Not limited to bacteria (viruses, fungi, parasites)
 - No PCR amplification bias
- Disadvantages:
 - Host contamination in reads
- Analysis:
 - Align to whole genome library
 - Need to filter host reads

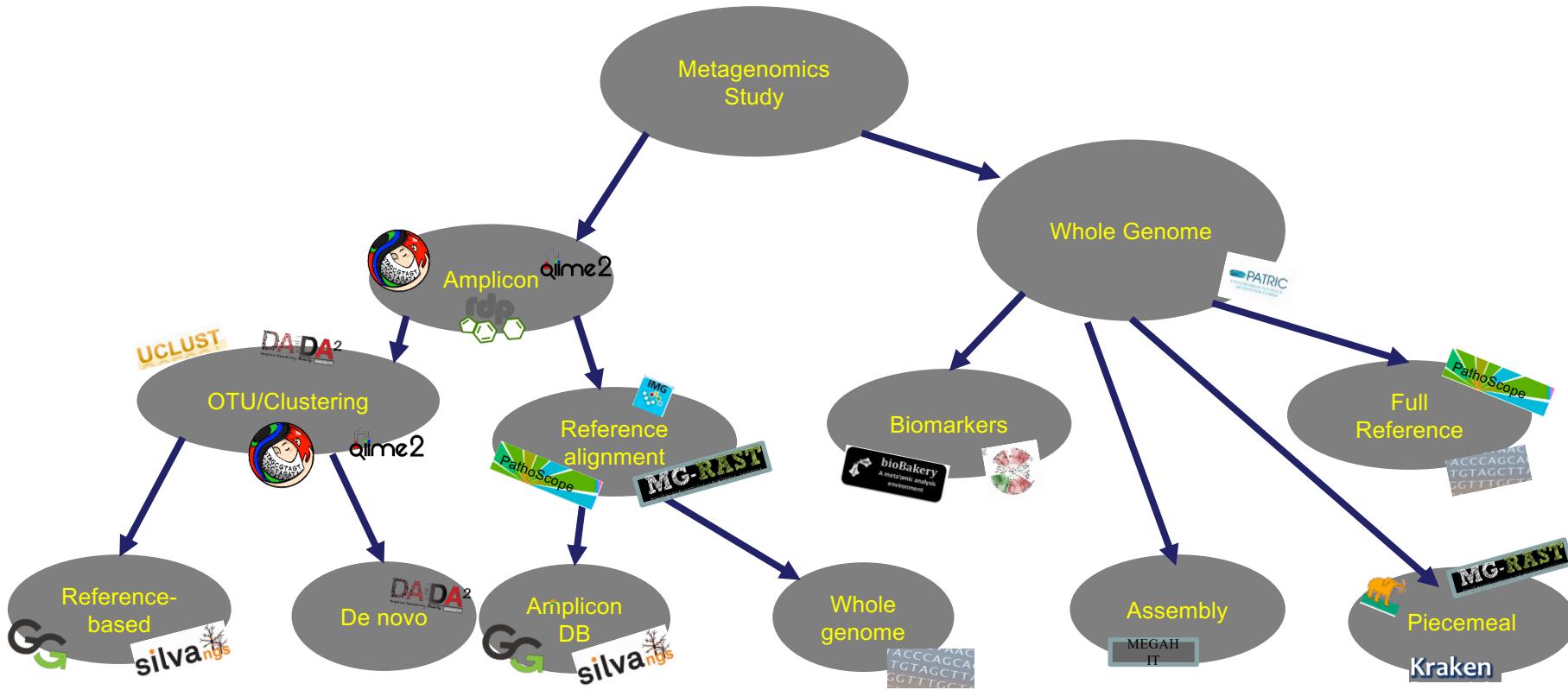
- Sequence total RNA (deplete ribosomal RNA)
- Get host transcription AND microbiome profile
- Measures *activity* NOT *abundance*

Top Phyla in 16S rDNA-seq



Top Phyla in whole RNA-seq





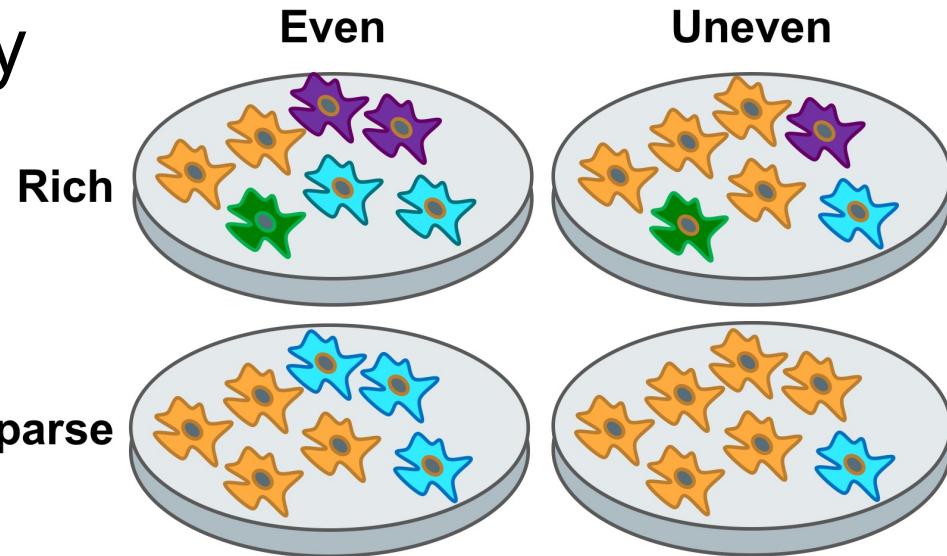
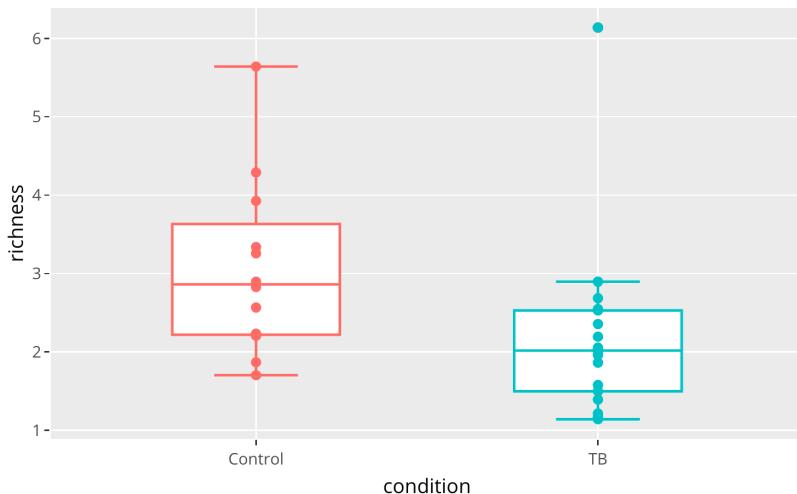


RUTGERS

Alpha Diversity

- Measures ‘richness’ of the microbiome
- Number of species relative proportions

Alpha diversity between Disease (inverse_simpson)



Simpson Index:

$$\lambda = \sum_{i=1}^R p_i^2$$

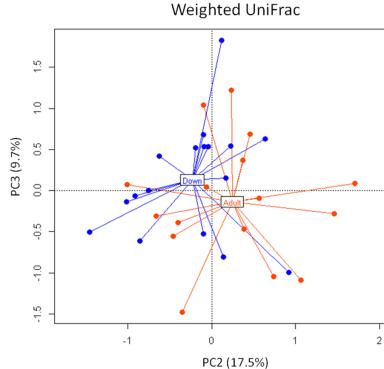
Shannon Index:

$$H' = - \sum_{i=1}^R p_i \ln(p_i)$$

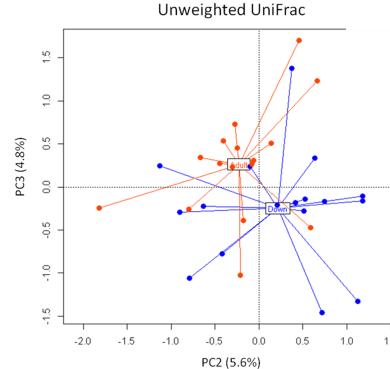


- Measures similarity between two samples
- Microbiome equivalent for ‘correlation’

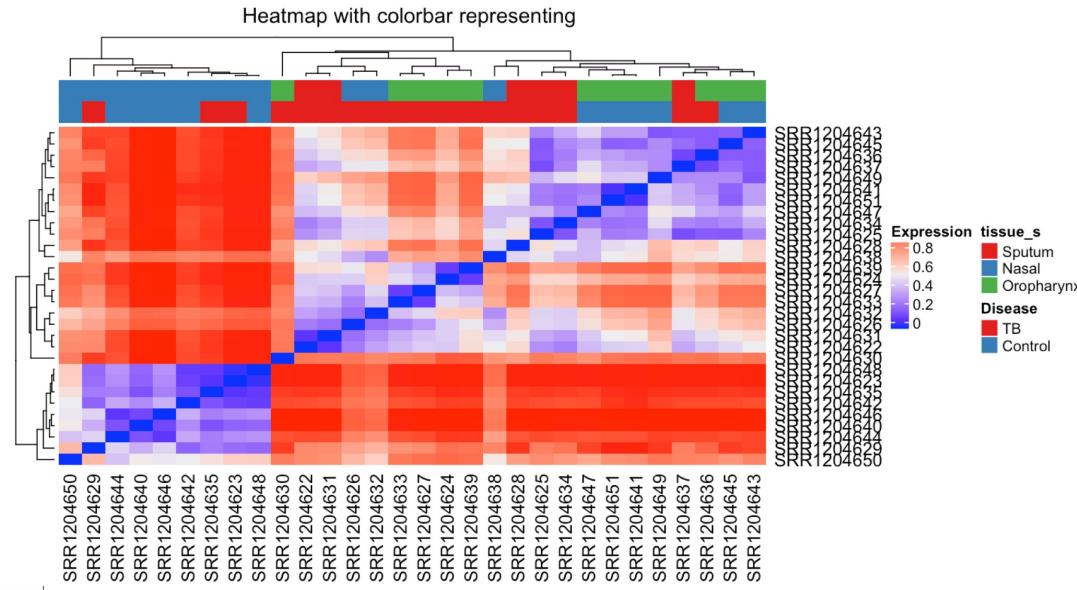
3 A



3 B



Biagi, et al., PLOS One 2014



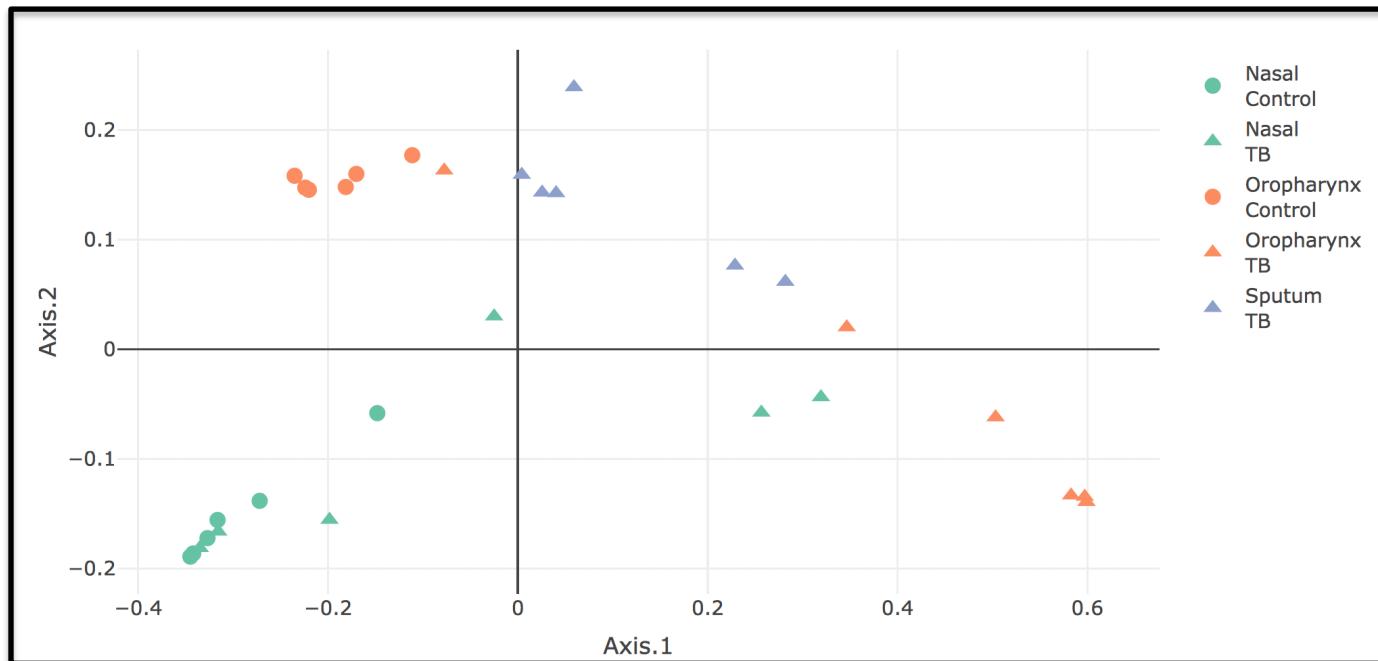
Weighted UniFrac:

$$d^W = \frac{\sum_{i=1}^n b_i |p_i^A - p_i^B|}{\sum_{i=1}^n b_i (p_i^A + p_i^B)}$$



RUTGERS Principal Coordinate Analysis

- Dimension reduction for metagenomic data
- Example TB microbiome in multiple tissues:



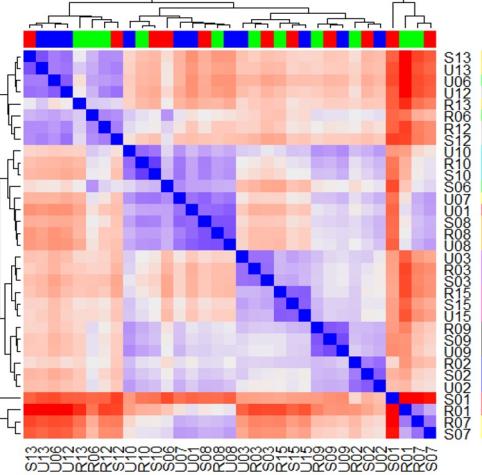
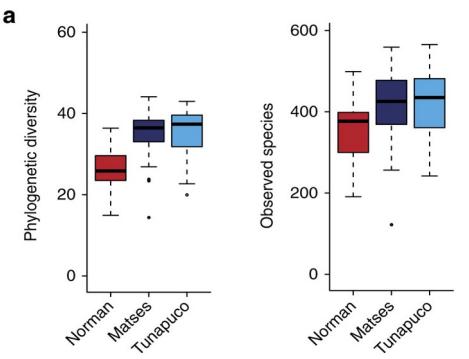
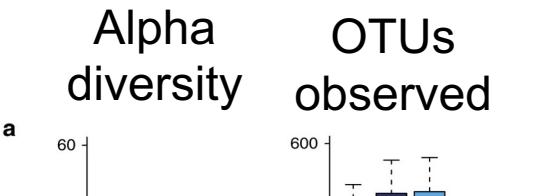
OTU Tables

- Organization Taxonomic Units (OTUs)
- Rows are microbes; columns are samples

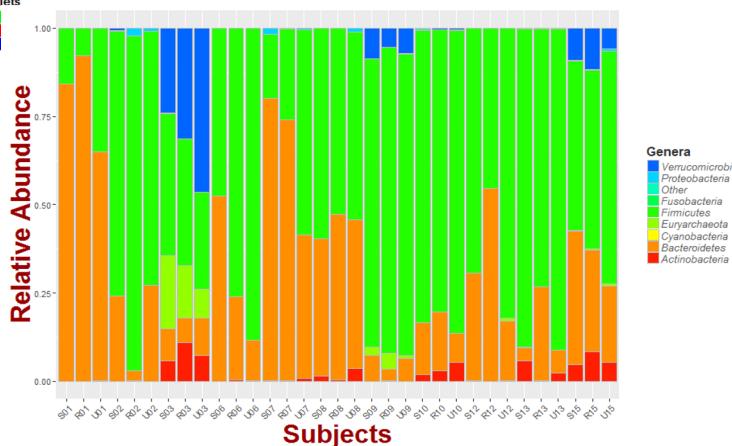
no rank	taxid	Sample_01_1	Sample_01_2	Sample_01_3	Sample_02_1
Megasphaera_elssdenii_DSM_20460	1064535	0	0	0	0
Streptococcus_infantarius_subsp._infantarius_CJ18	1069533	0	0	0	0
Ruminococcus_champanellensis_18P13	213810	0	0	0	0
Bacteroides_thetaiotaomicron_VPI-5482	226186	0	0	0	0
butyrate-producing_bacterium_SM4/1	245012	0	0	0	4284
butyrate-producing_bacterium_SSC/2	245018	3717	2898	145	22545
Bacteroides_fragilis_NCTC_9343	272559	5392	6083	14925	57773
Streptococcus_thermophilus_CNRZ1066	299768	0	0	21	0
Streptococcus_thermophilus_LMD-9	322159	353	0	21	0
Streptococcus_salivarius_JIM8777	347253	0	0	0	2303
Akkermansia_muciniphila_ATCC_BAA-835	349741	0	0	0	0

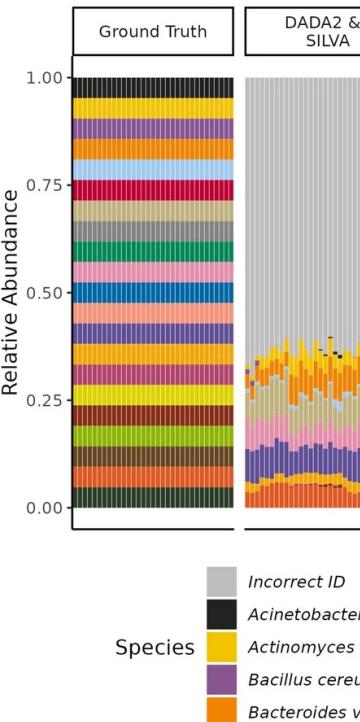
16S rDNA analysis

Qiime is a standard 16S analysis toolkit. It used PyNAST to align reads to a reference (probably greengenes) and can automatically spit out summary metrics and plots.



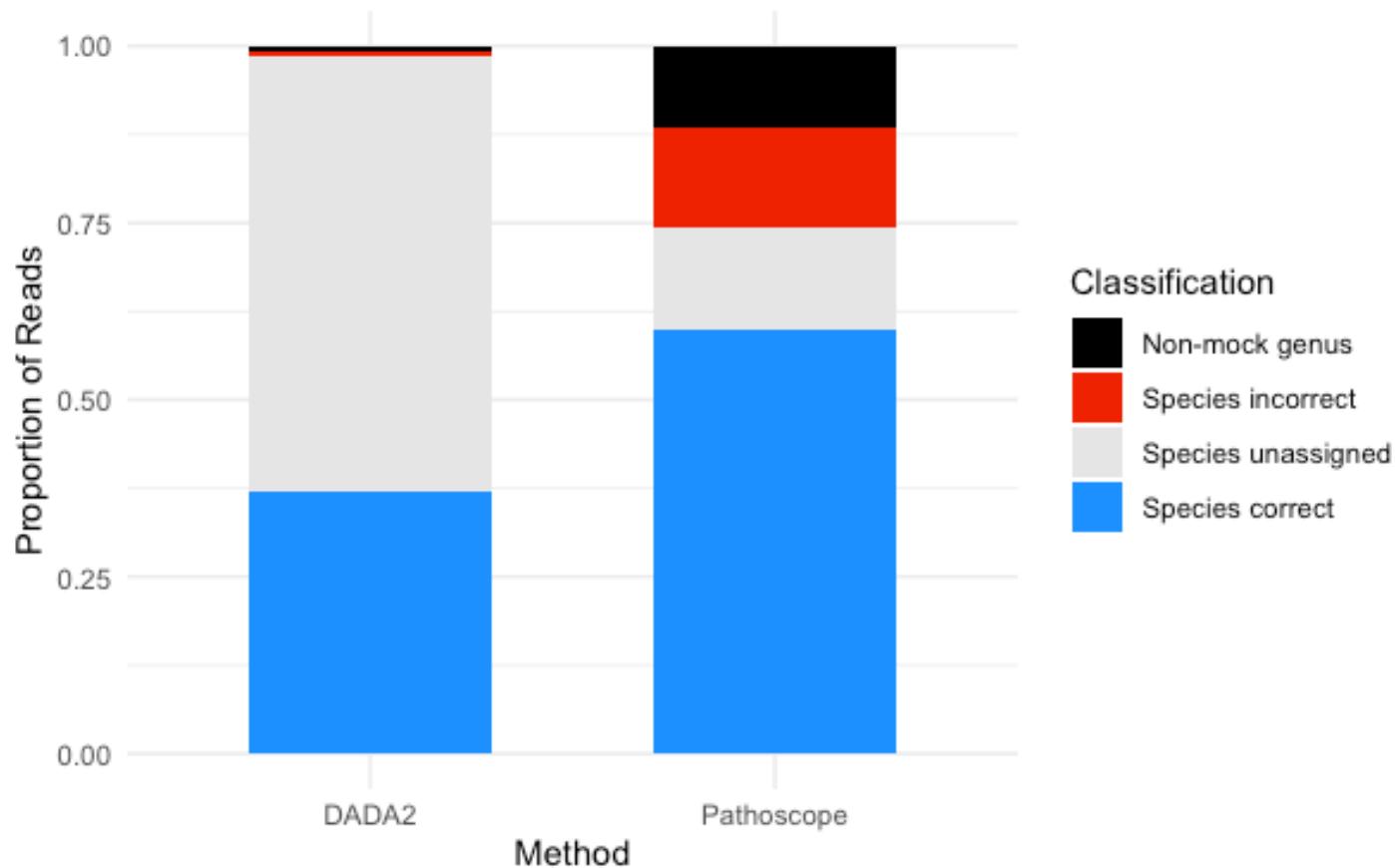
Taxa abundance

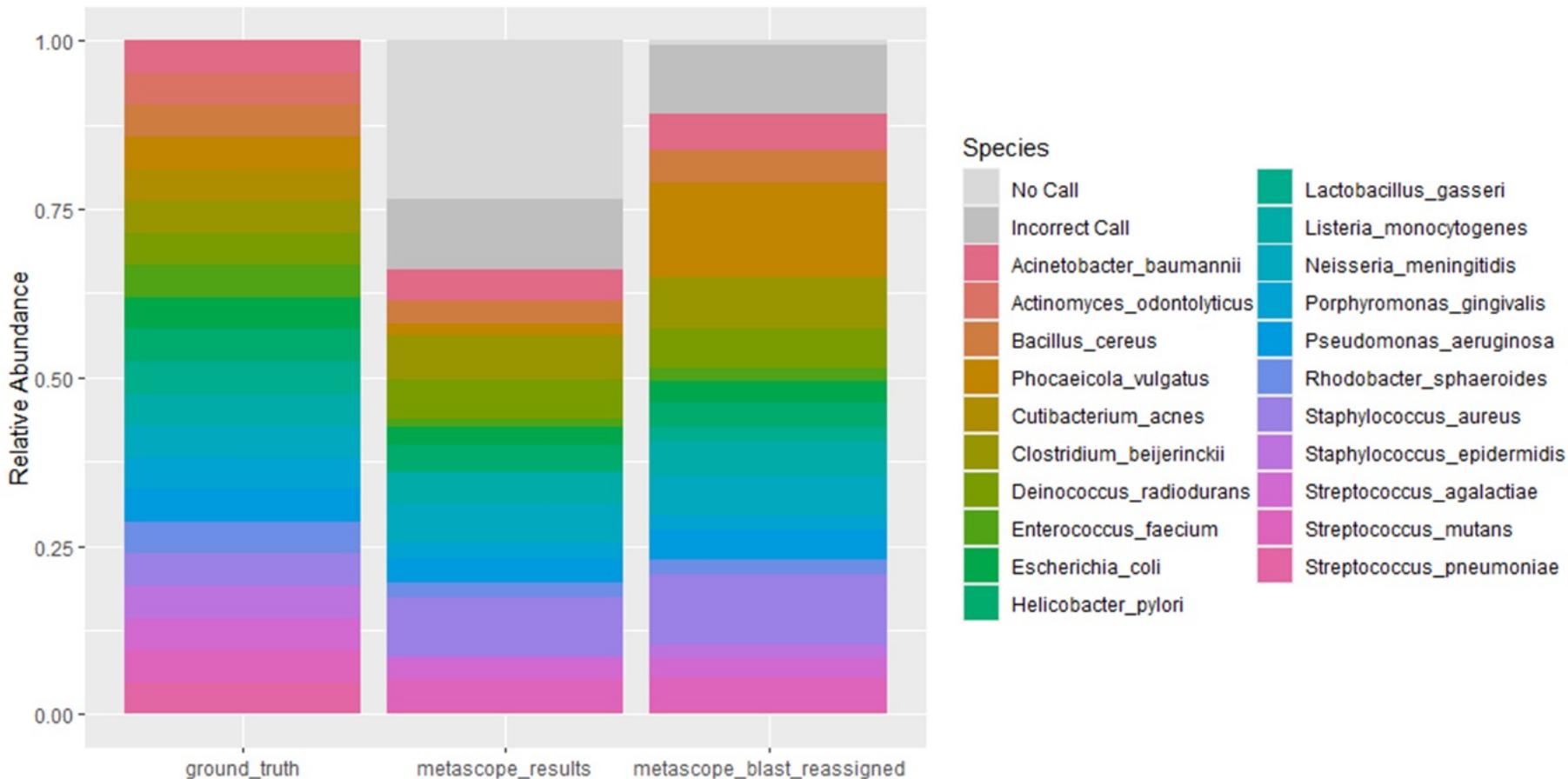


Stacked bar plot of 16S rRNA
Kozich et al. (2013) samplesAubrey (Brie)
Odom-Mabey

Tyler Faits

Kozich 130403_A, SILVA DB







RUTGERS

Collect specimen



Microbiome Profiling

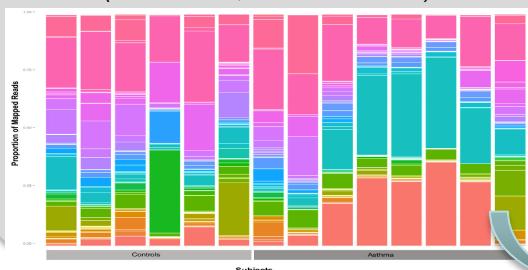
Align to Microbial Genomes (*PathoScope*; Hong et al., 2014)



Bayesian Mixture Modeling (PahOLD; Francis et al., 2013)

$$\mathcal{L}(\pi, \theta, \eta) = \prod_{i=1}^R \prod_{j=1}^G q_{ij} \pi_j^{x_{ij}} \theta_j^{(1-y_i)x_{ij}}$$

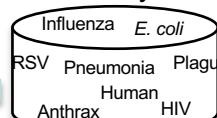
Microbial Abundance (animalcules; Zhao et al. 2021)



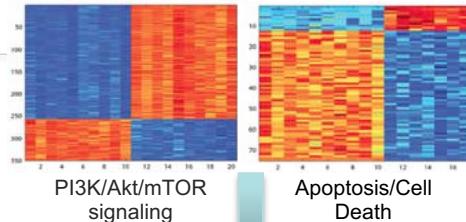
DNA/RNA Sequencing



Genome Sequence Library



Host Response Pathways



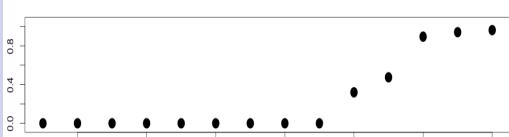
Host Profiling

Align to Human Genome

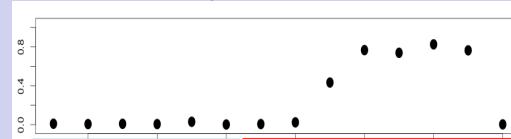


Integrate Results (*animalcules*; Zhao et al. 2021)

Pathway Activation

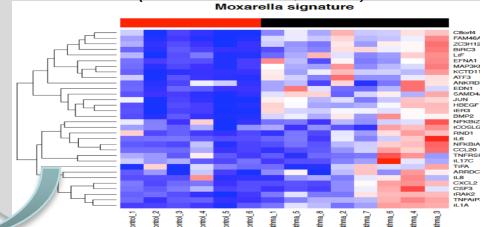


Pathogen Abundance



Control Asthma
Castro-Nallar et al., 2015

Immune Pathway Activity
(Johnson et al., 2021)



PathoScope:

'Plug and Play' Metagenomic Framework

- **PathoScope Core Modules:**

- PathoLib: Automatic genome library extraction and optimization
- PathoMap: Align reads and filter reads from host, etc.
- PathoID: Reassign ambiguous reads, identify strains present, and estimate proportions of RNA/DNA
- PathoReport: Summary reports, XML report, contigs, annotations etc

- **PathoScope Optional Modules:**

- PathoQC: Parallel quality control wrapper for multiple QC programs.
- PathoDB: Extract annotation from NCBI (name, genes, products, lineage, etc)



Changjin Hong



Solaiappan Manimaran

Let $i = 1, \dots, R$ index the reads and let $j = 1, \dots, G$ index genome. Our likelihood is as follows:

$$\mathcal{L}(\pi, \theta, \eta) \propto \prod_{i=1}^R \prod_{j=1}^G \left(q_{ij} \pi_j \theta_j^{(1-y_i)} \right)^{x_{ij}}$$

Data:

$x_{ij} = 1$ if read i is from genome j . (not observed)

$y_i = 1$ if read i is unique. 0 if non-unique.

q_{ij} = The likelihood that read i is from genome j .



Keith Crandall



Owen Leete (Francis)

Parameters:

π_j = Overall proportion of reads from genome j .

θ_j = Proportion of non-unique reads from genome j .

MetaScope (New!)

- “PathoScope-like pipeline” fully integrated into R
- Features and functions
 - download_refseq: Downloads genome libraries/indexes
 - align_target: aligns reads to multiple reference genomes using Bowtie2 or Rsubread, combines and orders results
 - filter_host: removes reads that align to host genomes
 - metascope_id: reassigned ambiguous read alignments (Bayesian mixture modeling)



Rahul Varki



Aubrey (Brie) Odom-Mabey



Why GitHub?  Team Enterprise Explore  Marketplace Pricing 

Sear

 [compbioimed / MetaScope](#) 

<https://github.com/compbioimed/MetaScope>


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```
if (!requireNamespace("BiocManager", quietly = TRUE))
  install.packages("BiocManager")

BiocManager::install("animalcules")
```

<http://127.0.0.1:6877> | [Open in Browser](#) | [Publ](#) <http://127.0.0.1:6877> | [Open in Browser](#) | [Publ](#)

animalcules v1.7.0 Upload Summary and Filter Abundance Dimension Reduction Differential Analysis Biomarker animalcules v1.7.0 Upload Summary and Filter Abundance Dimension Reduction Differential Analysis Biomarker

Filter Categorize Assay Dashboard

Filter By

Metadata

Select a Condition

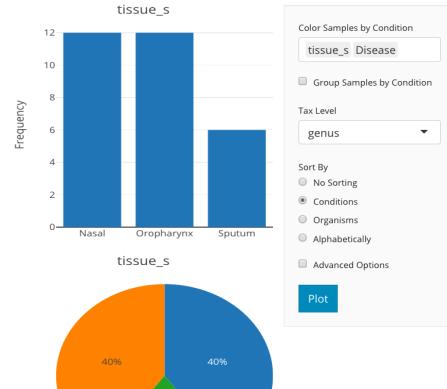
tissue_s

Include

Sputum Nasal Oropharynx

Advanced Options

Summary Statistics	
Number of Samples	30
Number of Covariates	5
Number of Organisms	427
Sample Mean Counts	20561
Sample Median Counts	18573
Organism Mean Counts	1445
Organism Median Counts	25



Color Samples by Condition

tissue_s Disease

Group Samples by Condition

Tax Level

genus

Sort By

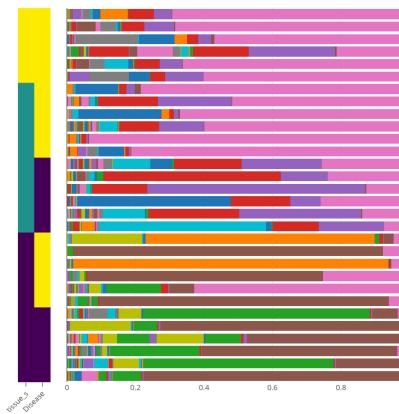
No Sorting

Conditions

Organisms

Alphabetically

Advanced Options



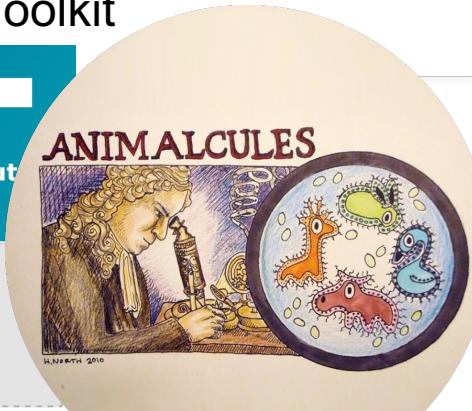
Streptococcus
Staphylococcus
Prevotella
Vellonella
Cultibacterium
Moraxella
Haemophilus
Fusobacterium
Corynebacterium
Rothia
Leptotrichia
Mobiluncus
Neisseria
Mycobacter
Anerococci...
Porphyromonas
Atopobium
Microccus
Campylobacter
Rhodotorula
Methylobacterium
Selenomonas
Roseburia
Blaertia
Finegoldia
Sphingomonas



Yue (Jason) Zhao



Anthony Federico



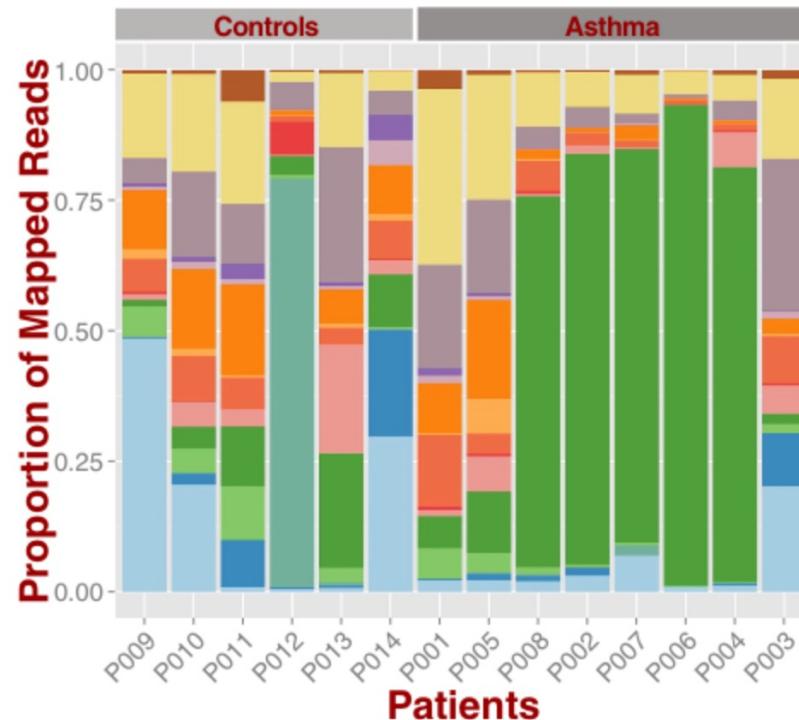
(animalcules: Interactive Microbiome Analytics and Visualization in R, Zhao et al., *Microbiome*, 2021)



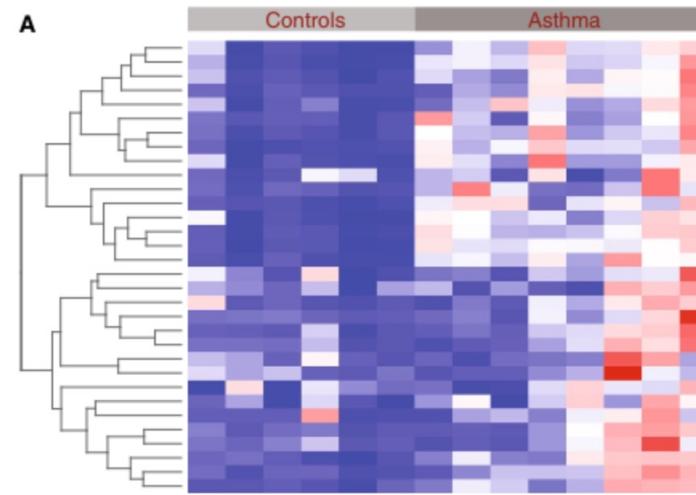
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Asthma Nasal Metatranscriptomics

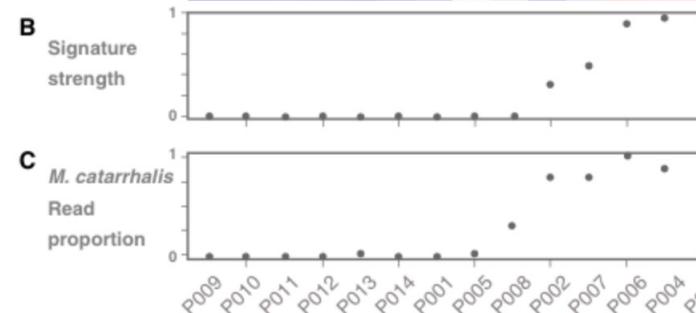
- Nasal brushings, Total RNA-seq
- 'Healthy' asthmatic (n=8) and control children (n=6)



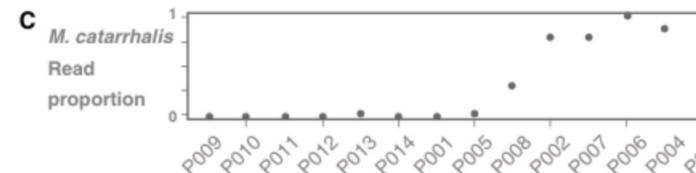
A



B



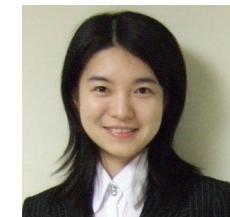
C



Eduardo Castro-Nallar



Keith Crandall



Ying Shen



RUTGERS Aperiomics (metagenomics)

Metagenome sequencing to solve hard-to-diagnose infections

REQUEST A FREE CUSTOMER PORTFOLIO

APERIOMICS

The **ONLY** Company Identifying **EVERY** Bacteria, Virus, Fungus & Parasite in **ONE** Test

CLINICIAN INFORMATION

PATIENT INFORMATION

Saving Lives by Discovering the Unknown™

Reimagining the Way the Medical Field Tests for Pathogens

Standardized laboratory testing fails, up to 75% of the time, to identify pathogens that cause infection..

11 Years Old, Multiple Tests, Years of Suffering and an Elusive Treatment

At the age of 11, and after 6 years of suffering illness after illness, Vincent – a young man in Wamego, Kansas, had been tested and tested but no one seemed to be able to pinpoint the cause of his extreme discomfort and frightening symptoms. Mario suffered from ADHD, OCD, moderate Asperger's Syndrome, severe sensory problems, rages, trouble swallowing and even lesions on his hands as the skin would crack and peel.

[READ HIS STORY](#)

22 Years of Needless Pain Resolved in Just a Few Weeks

Starting at the age of 15, Lori felt miserable...fatigue, insomnia, mood swings, difficulty thinking, mild GI issues...but it was not until she was 26 years old that she'd had enough of the pain that she finally went to see a doctor to do something about it. Unfortunately, she went through an ever-rotating carousel of doctors that started years of endless testing and misdiagnoses.

[READ HER STORY](#)

After 6 Years of Abdominal Pain, Finally Answers

Barbara's son John, 19, woke up one morning complaining about extreme stomach pain. Despite a number of examinations, the pain persisted for many weeks and, when he was scoped, his doctor diagnosed him with Celiac disease, a serious autoimmune disorder in which the ingestion of gluten can lead to damage in the small intestine.

[READ HIS STORY](#)

Ruling Out Infection

The trouble began in September 2016 after he had had a new pacemaker implanted. Within a week of the procedure, his surgery site was not healing and had begun to exude blood and other fluid. Naturally, everyone assumed it was an infection and his doctors prescribed antibiotics. After a couple of months the wound still wasn't healing and infection-like symptoms continued.

[READ HIS STORY](#)

Aperiomics Case Study

- 68 year old woman from West Virginia
- Unexplained pain much of her adult life
- Diagnoses: chronic Lyme, arthritis, pain unknown origin
- Blood test, metagenomic profiling
- 30M DNA seqs, 270 matched Mtb
- Not Lyme, she had extrapulmonary TB!

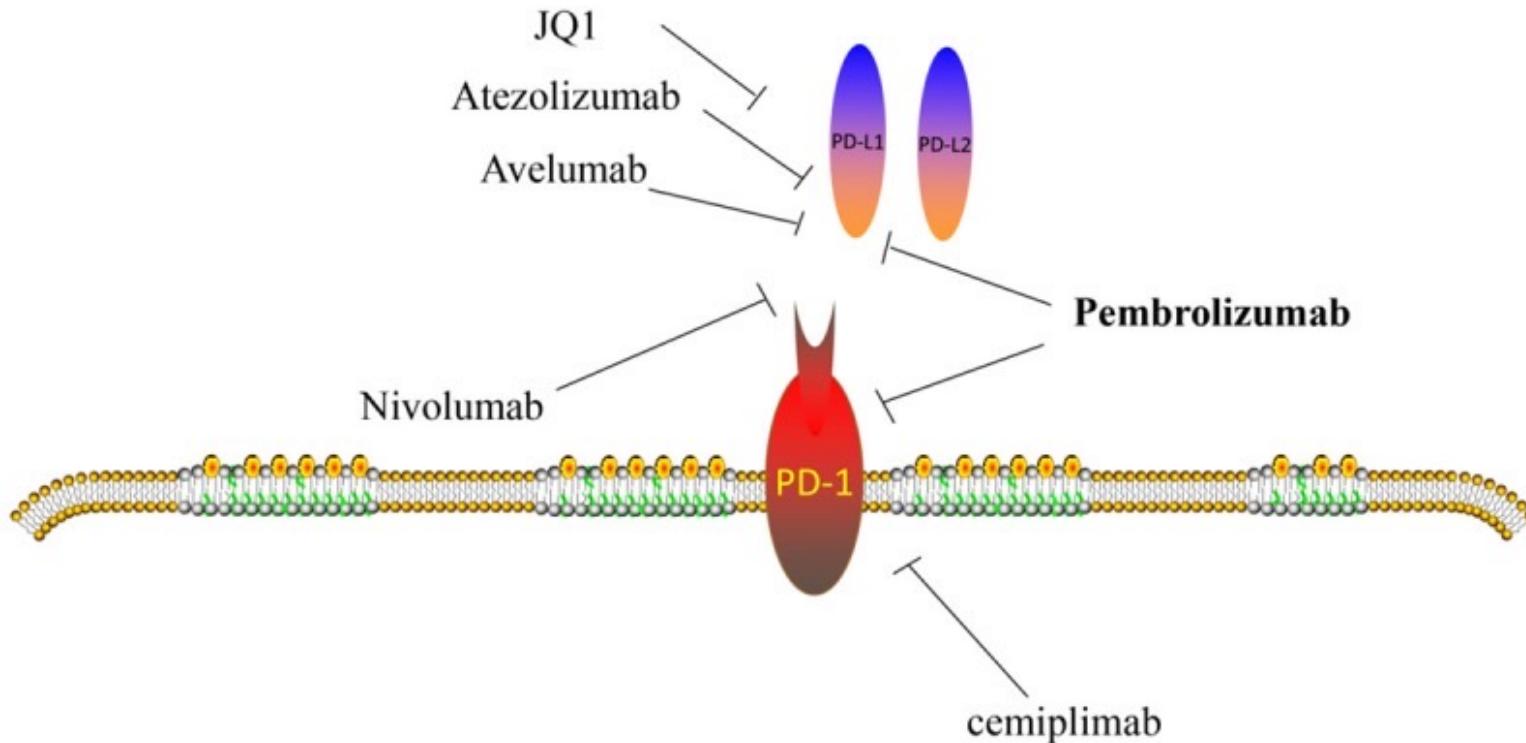


History of microbes and cancer immunotherapy

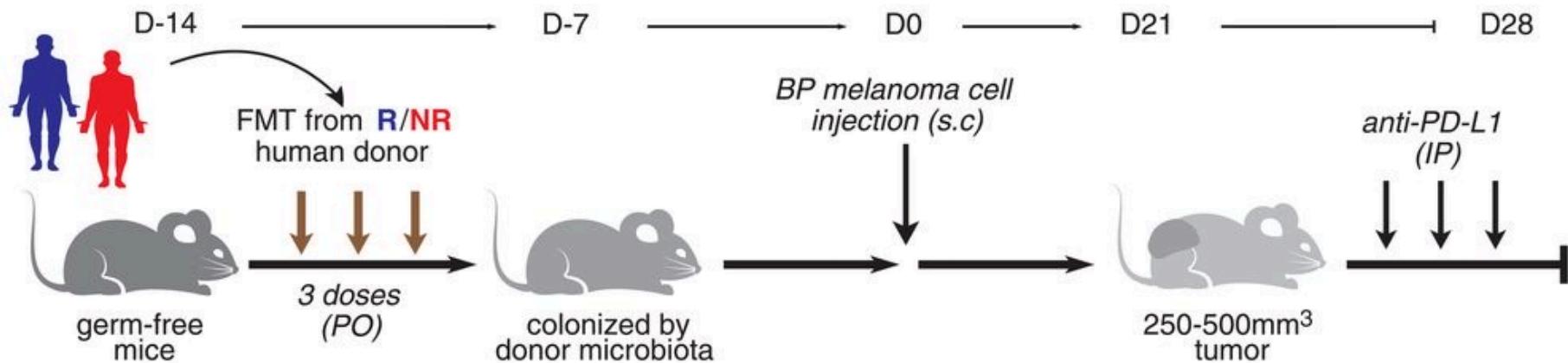
- **2600 B.C.: Imhotep**, Egyptian physician (and architect/ engineer) treated tumors with a poultice to induce infection designed to induce regression of tumors
- **13th century**: St. Peregrine (“The Cancer Saint”) experienced spontaneous regression of tumor, after the tumor became infected
- **18th and 19th centuries**: deliberate infection of tumors after surgery was common practice. Many physicians reported successful treatment of cancer with infection
- **1891**: William Coley developed “Coley’s Toxins” comprised of a milieu of heat-killed bacteria



Inhibitors of PD-1/PD-L1 in cancers



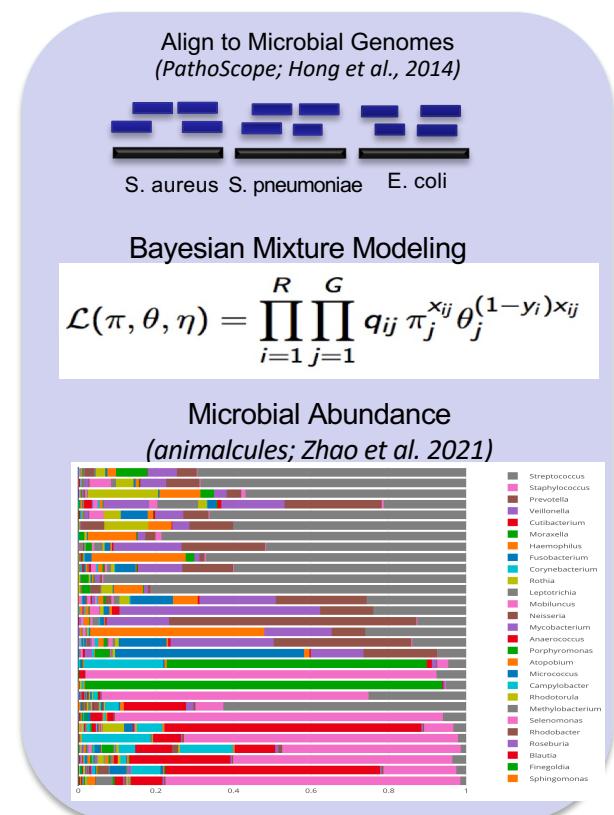
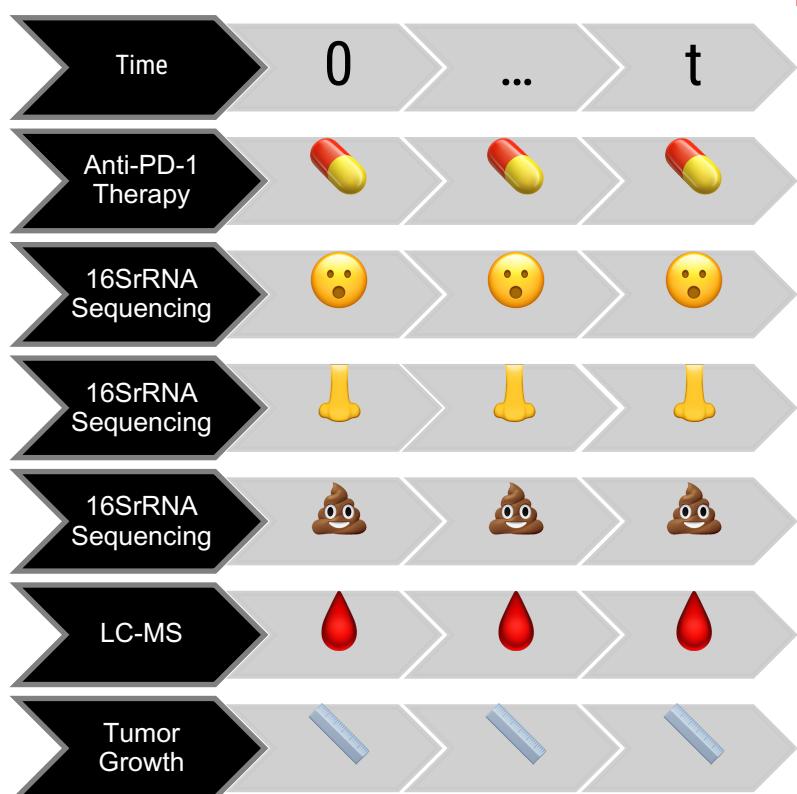
Gut microbiome is associated antitumor immunity.



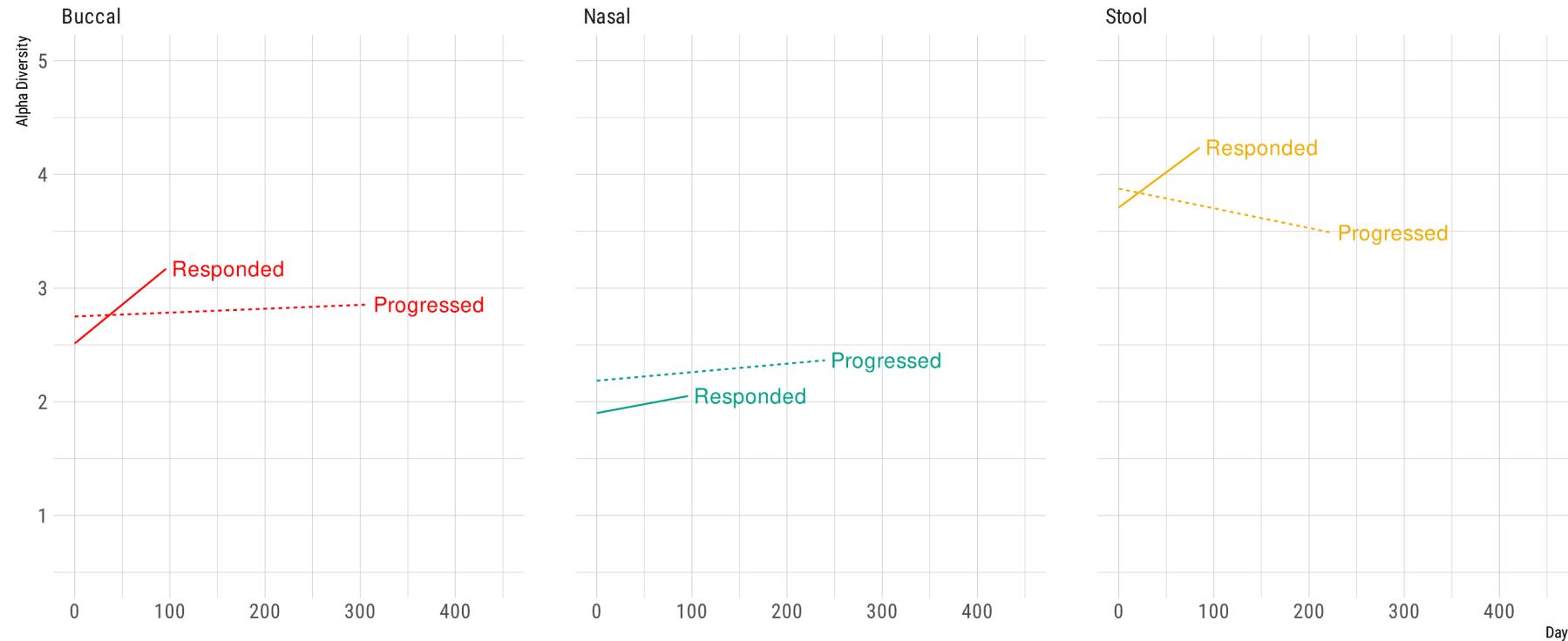
Gopalakrishnan, V. et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 359, 97–103 (2018)



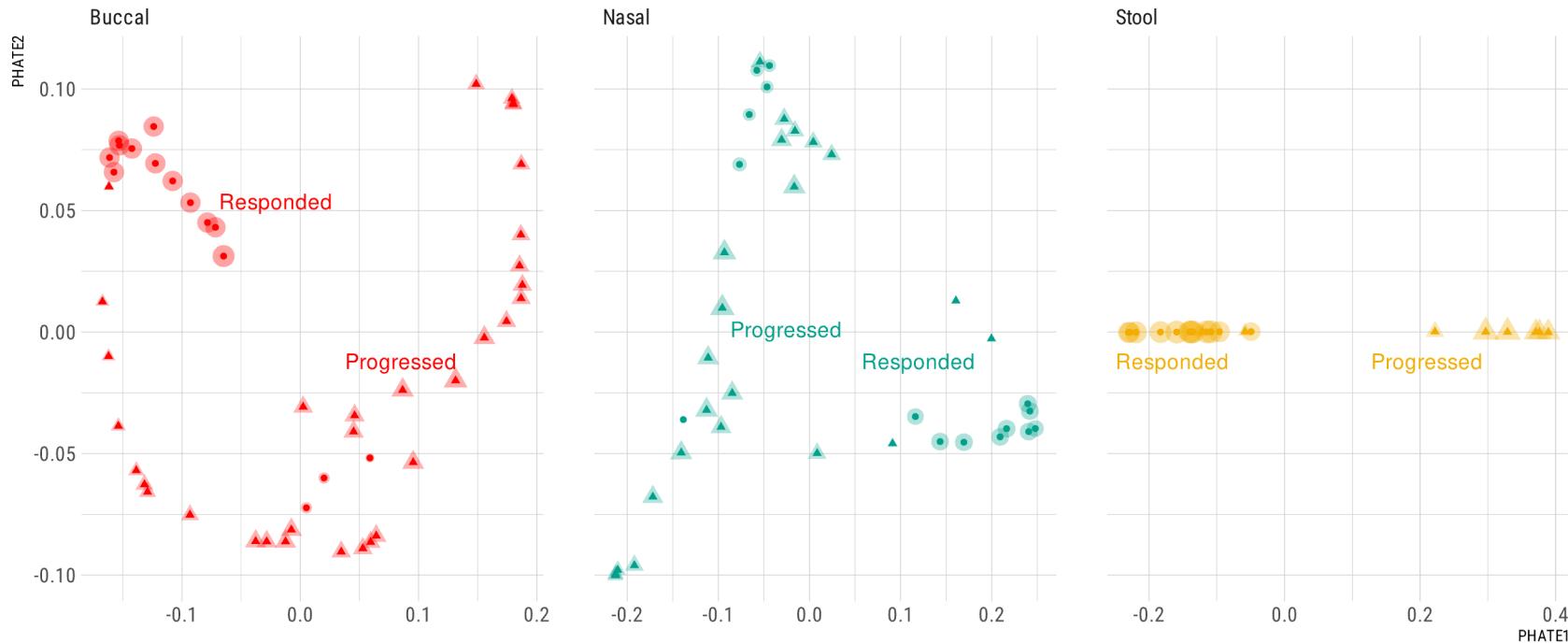
Study Design Summary



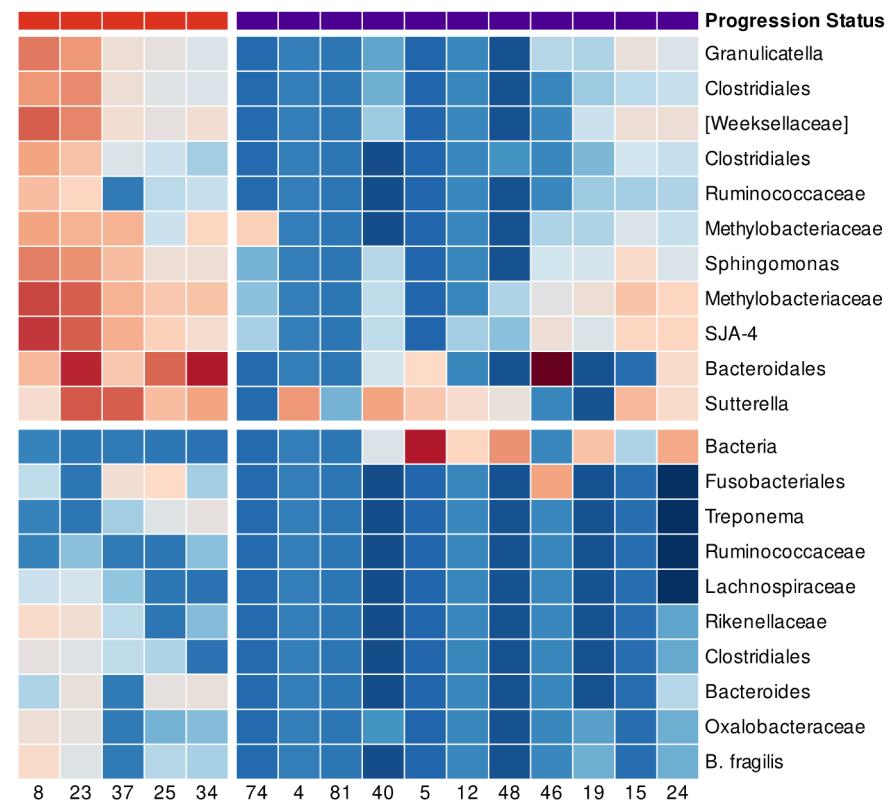
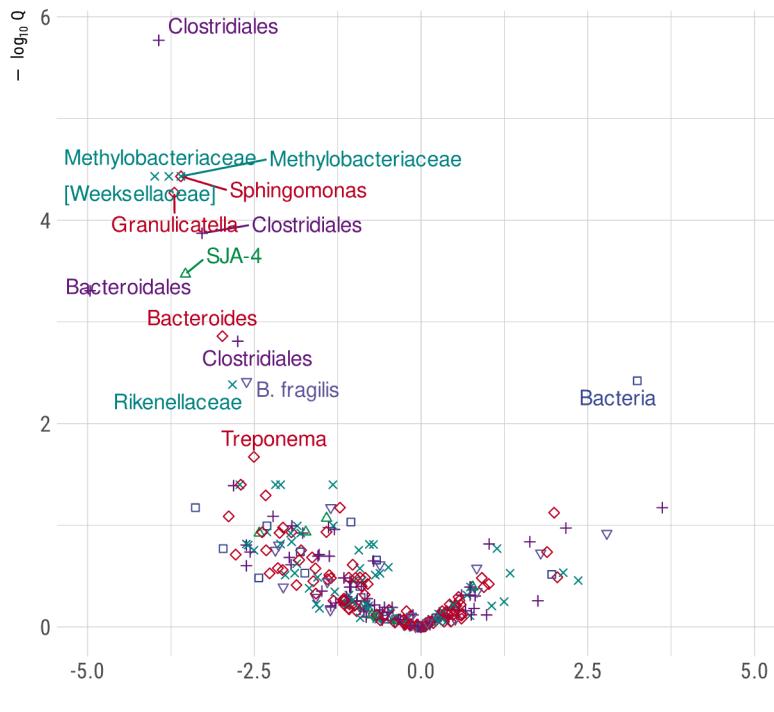
Alpha Diversity, Shannon Index Over Time



Beta Diversity, PHATE Embedding



Buccal Samples, Significant OTUs, Baseline





Examining the maternal/infant health and HIV exposure in Zambia

- Southern Africa Mother Infant Pertussis Study (**SAMIPS**)
- A small Zambian cohort could provide insight into HIV exposure phenomenon in NP
- Characterize NP microflora over 14 weeks

Left inset: Images of Chawama compound, a slum in Lusaka, Zambia where infants were enrolled.
Images by Britta Pedersen

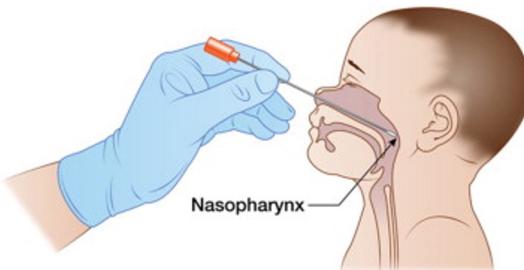


Chris Gill

Infant Respiratory Health and HIV Exposure in Zambia

Nasal swabs from infants at birth and at 2-week intervals for 12 weeks

Nasal swabs from mothers at (infant's) birth and at 12 weeks



	HIV- Mother	HIV+ Mother
Healthy infant (for at least 3 months)	 N=17	 N=13
Infant respiratory illness in first 3 months	 N=7	 N=3



Chris Gill



Aubrey (Brie)
Odom-Mabey



Rotem Lapidot



Jessica McClintock

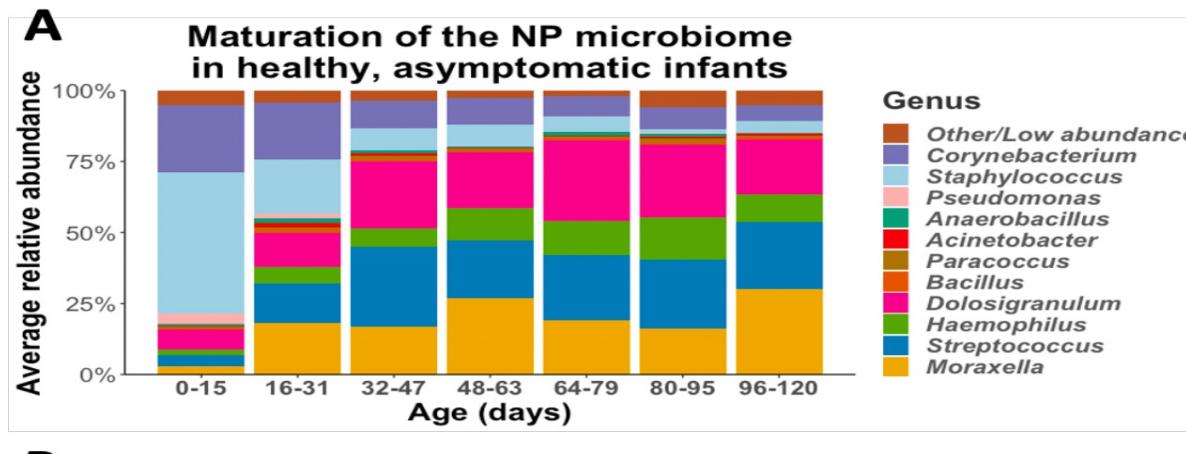


Tyler Faits



RUTGERS

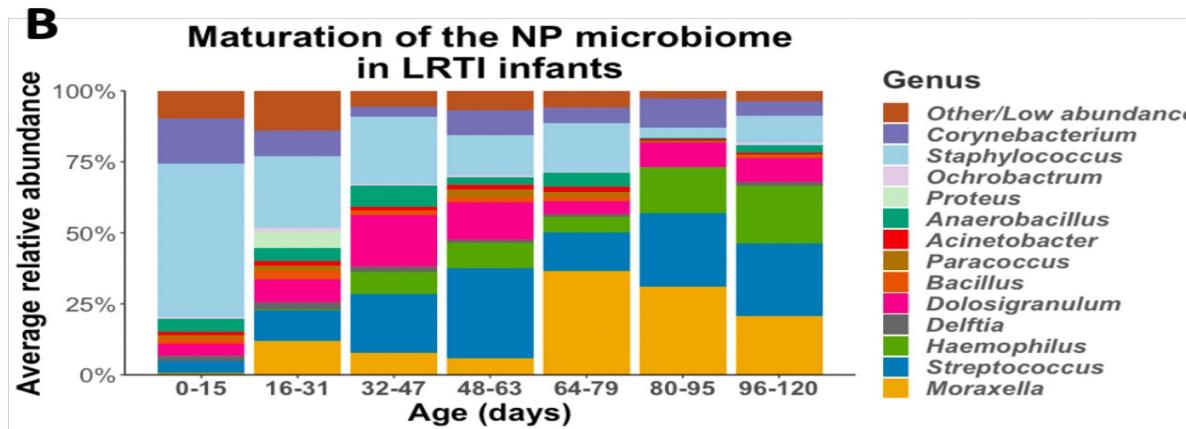
Development of microbiota over time



Chris Gill



Rotem Lapidot



Tyler Faits

GEE background: Generalized linear models

- Relate mean of Y to *linear predictor* through **link function**

$Y \sim \text{Normal}$

- Mean of Y is center of the distribution, μ
- Identity link

$Y \sim \text{Bernoulli}$

- Mean of Y is p , probability of success
- Logit link

$Y \sim \text{Poisson}$

- Mean of Y is λ , rate per unit time of events
- Log link

$$\mu = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

$$\log(\lambda) = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

Generalized Estimating Equations (GEEs)

- Extends GLM to accommodate correlated Ys
 - Abundance of a taxon*
- Longitudinal
 - 7 timepoints*
 - AR(1) correlation structure*
- Link function
 - Identity link - normal distribution*
- No distribution/lielihood assumption
 - Wald hypothesis tests*

First-order Auto Regressive/AR(1) correlation structure:

Correlation among responses within clusters (infants) decays exponentially with time

	Time 0	Time 1	Time 2	Time 3
Time 0	1	ρ	ρ^2	ρ^3
Time 1	ρ	1	ρ	ρ^2
Time 2	ρ^2	ρ	1	ρ
Time 3	ρ^3	ρ^2	ρ	1

- Over-dispersed, zero-inflated, high dimensional, compositional data
- For example, model for Batch effects:

$$Y_{ijg} \sim NB(\mu_{ijg}, \phi_{ig})$$

$$\log \mu_{ijg} = \alpha_g + X_j \beta_g + \gamma_{ig} + \log N_j$$

$$var(Y_{ijg}) = V_{ij}^{1/2} R_m V_{ij}^{1/2}$$

$$V_{ij} = diag_m(\mu_{ijm} + \phi_{im} \mu_{ijm}^2)$$

R_m describes compositional nature

- Methods and tools for longitudinal microbiome data



Yuqing Zhang



Brie Odom-Mabey



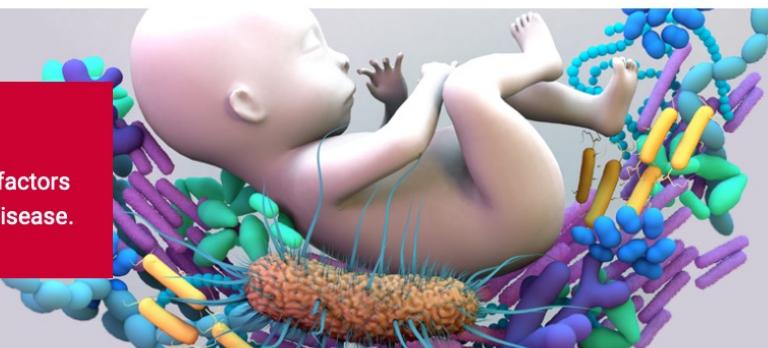
Howard Fan



Lucas Schiffer

Welcome

The New Jersey Kids Study is a statewide initiative that aims to better understand the many factors influencing healthy childhood growth and development as well as risk factors for childhood disease.

[Learn More about NJKS >](#)

Participants

Find out how to be part of the study.

[About](#)[How to Get Involved](#)[Partners](#)

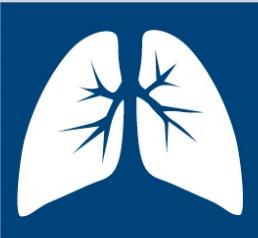
Researchers

Find current NJKS resources and more information.

Coming Soon:[Researcher Resources](#)

News & Updates

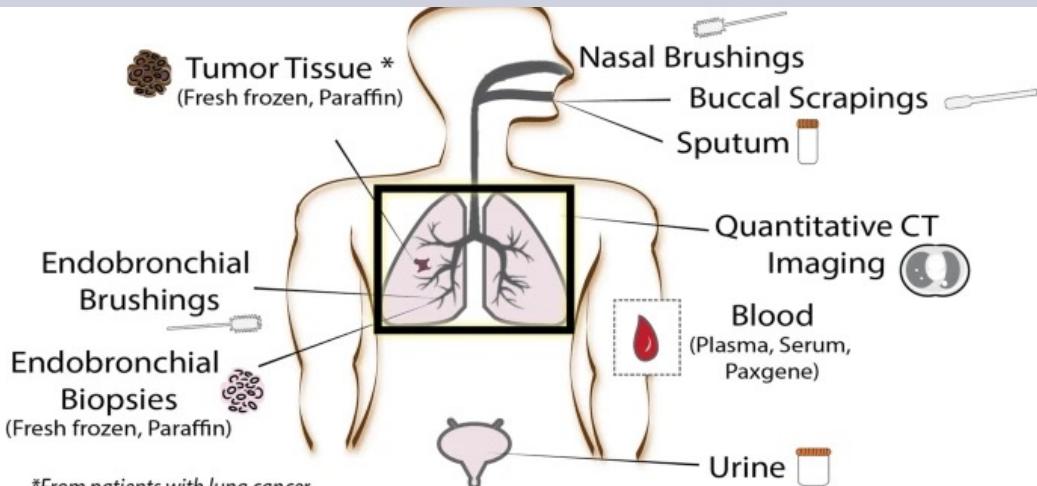
[NJKS in the News](#)



DECAMP

Biomarker Research

Detection of Early Lung Cancer among Military Personnel



Biomarkers to Test
Blood: Plasma Protein, Exosomal miRNA
Endobronchial biopsies: Gene expression
Endobronchial brushings: Gene expression
Nasal brushings: Gene expression
Urine: Metabolomics
Imaging: Densitometry, Body composition, Airway features and Phenotype



VOLUNTEERS ARE INVITED TO
PARTICIPATE IN THE STUDY:

DECAMP 1 - DETECTION of EARLY LUNG
CANCER AMONG MILITARY PERSONNEL

- ✓ Are you 45 years or older?
- ✓ Are you a current or former heavy smoker*?

* Defined as ≥20 pack years ... pack years are determined by:
number of packs smoked/day X number of years smoked

- ✓ Have you been told you have a lung nodule?

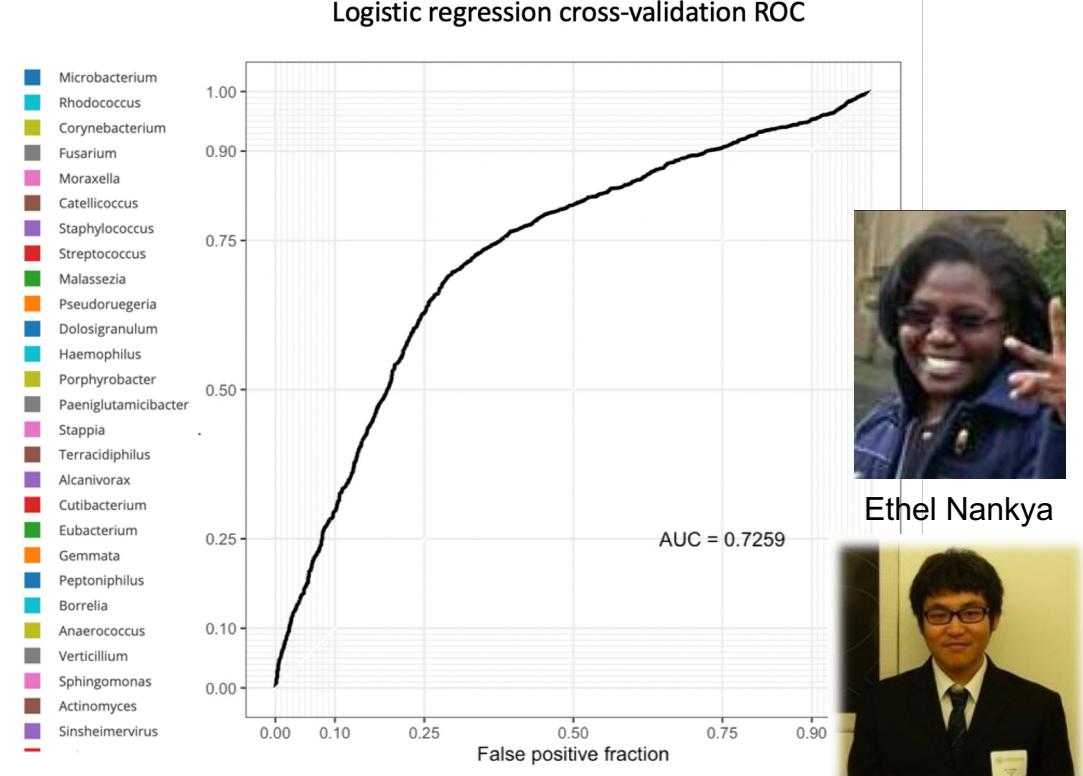
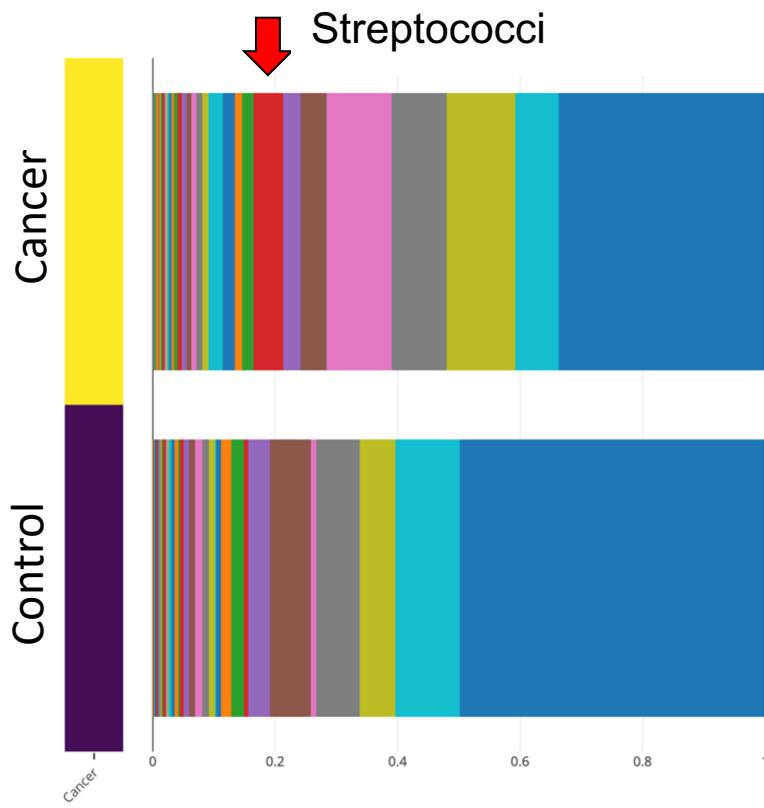
You may be eligible to participate in a study aimed at
helping diagnose lung cancer in the future.

If interested, please contact:



Detection of Early Lung Cancer among Military Personnel

Microbiome Biomarker for Cancer Interception



Yue (Jason) Zhao



RUTGERS

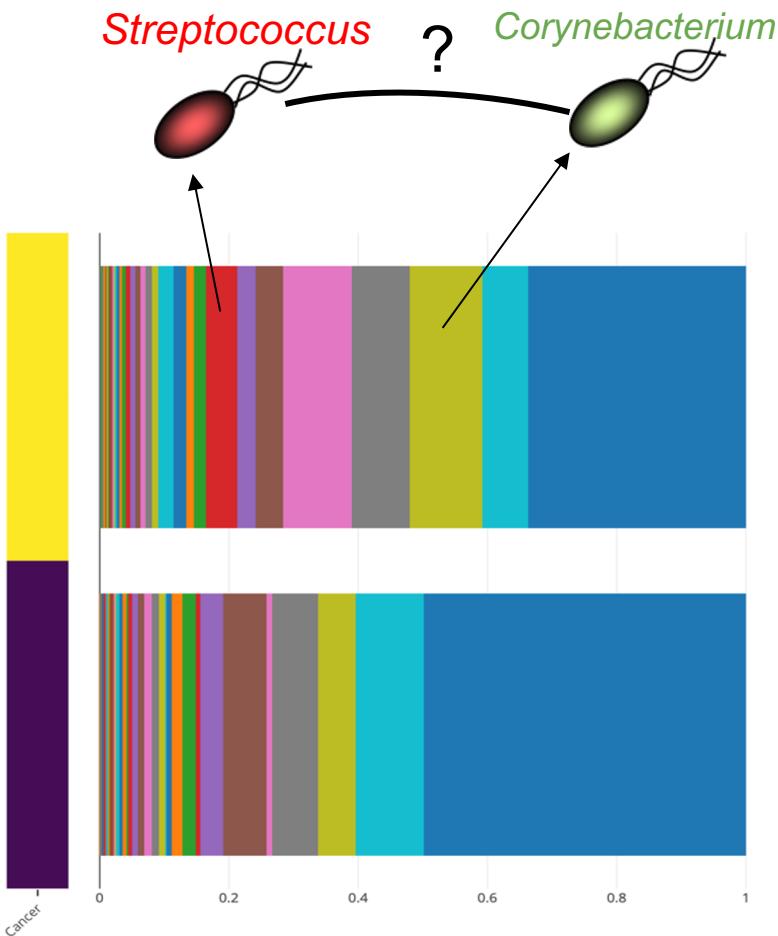
Microbial Interactions in Cancer



Daniel Segre

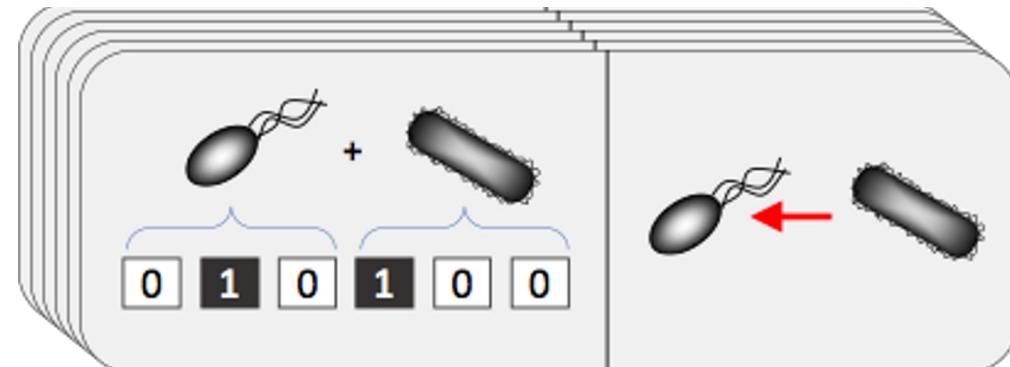
RESEARCH ARTICLE

Ecological and Evolutionary Science



Machine Learning Reveals Missing Edges and Putative Interaction Mechanisms in Microbial Ecosystem Networks

Demetrius DiMucci,^{a,b} Mark Kon,^{a,c} Daniel Segre^{a,b,d,e,f}



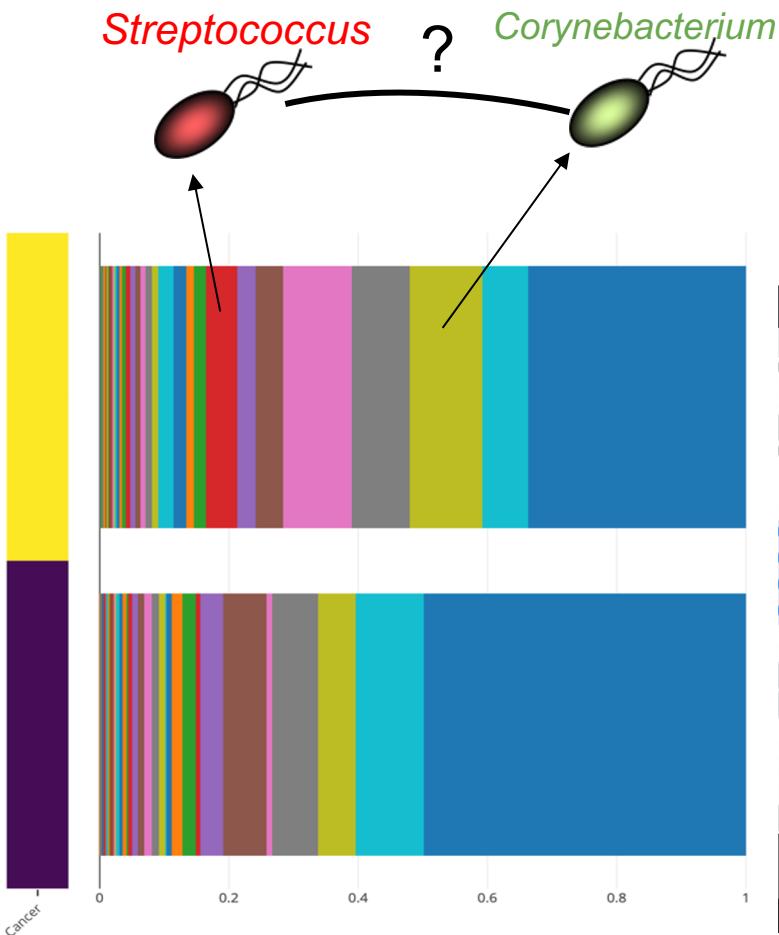


RUTGERS

Microbial Interactions in Cancer



Daniel Segre



Microbial Interaction Network Database (MIND)

The screenshot shows the MIND Web 1.0 interface. On the left, there's a search bar with "Moraxella" entered and a database search button. Below it are taxonomy and edge filters. The main area features a network graph where nodes represent microorganisms and edges represent interactions. A legend at the bottom right defines the edge colors: green for Gut, pink for Skin, black for Correlation, and dashed black for Anticorrelation. The graph shows a central cluster of nodes with many outgoing edges to other nodes, primarily in the gut and skin habitats.

MIND - Web 1.0 File Edit Filters Nodes Layout Samples Documents Login Register

Labels Auto Fit Tooltip

Clear Reset

Moraxella Enter microbial name

Search database

Taxonomy Filters: All

1. phylum 2. class

3. order 4. family

5. genus 6. species

7. subspecies 8. no rank

Edge Filters:

Weight cutoff 0.5

Number of Links 2

Networks: All

Human microbiome

Conditions Inter. types Habitats

Enter keywords of networks

C0006 Gut

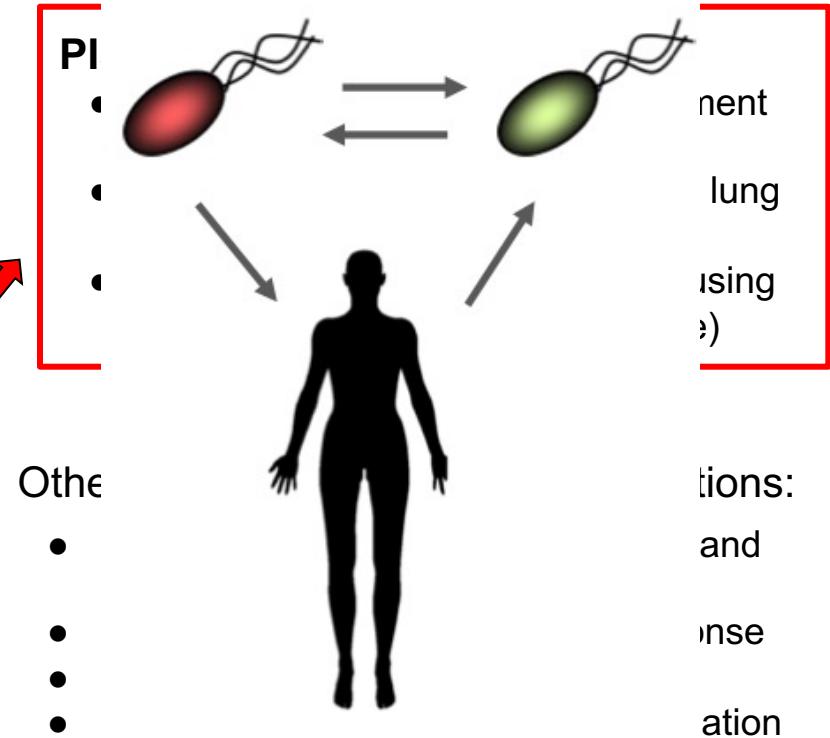
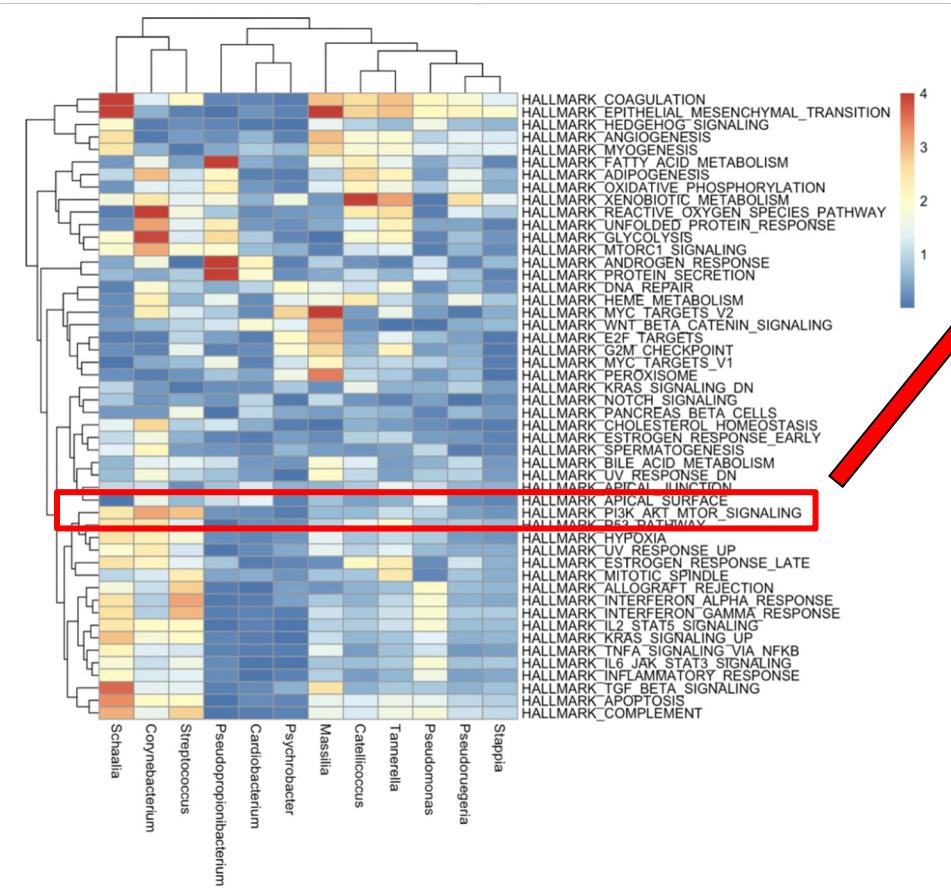
C0007 Toot

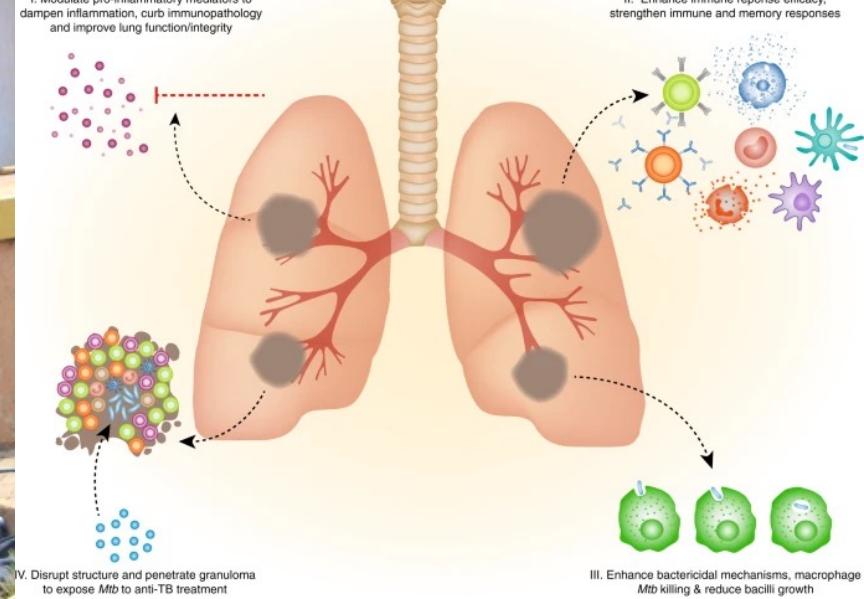
C0008 Toot

©2017- MIND-VisANT | Nodes: 90 | Selected Nodes: 0 | Edges: 195 | 0.00% nodes are selected...

Gut
Skin
Correlation
Anticorrelation

Host-Microbe Interactions in Cancer

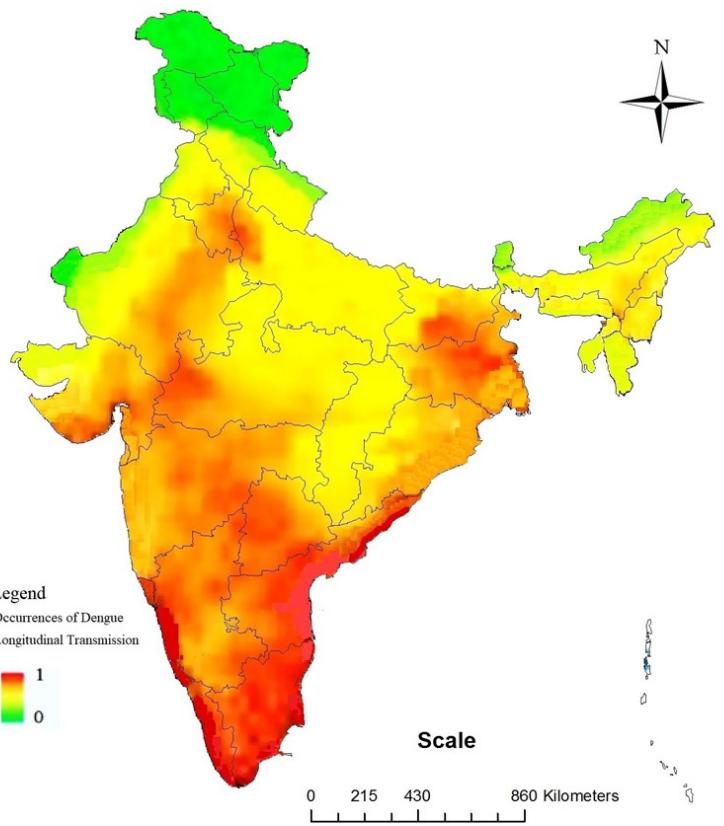






RUTGERS

Probability of Dengue Transmission in India



Thank you!

