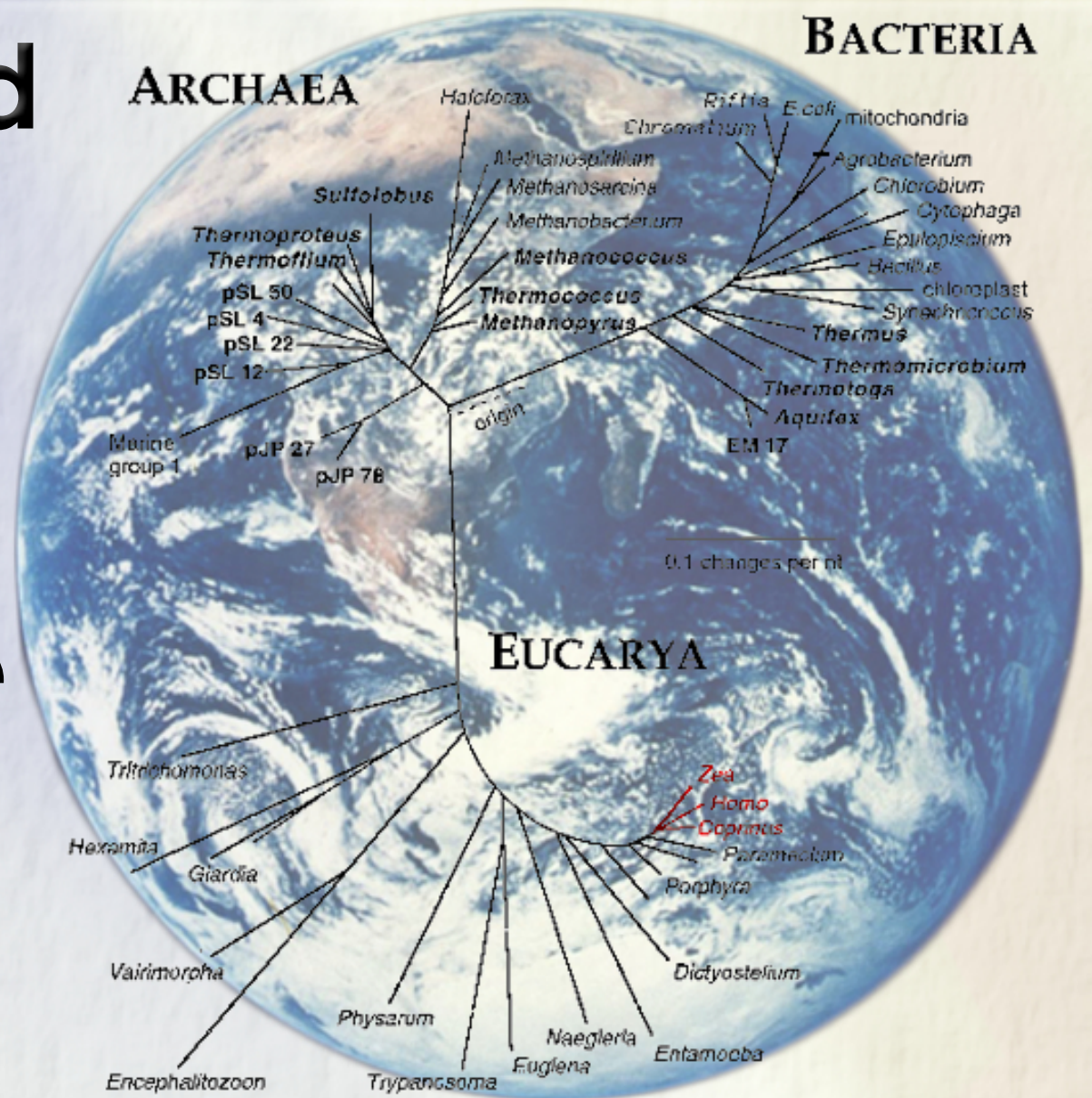


Why you should care about microbial community ecology (in the context of bioinformatics)



Rob Knight

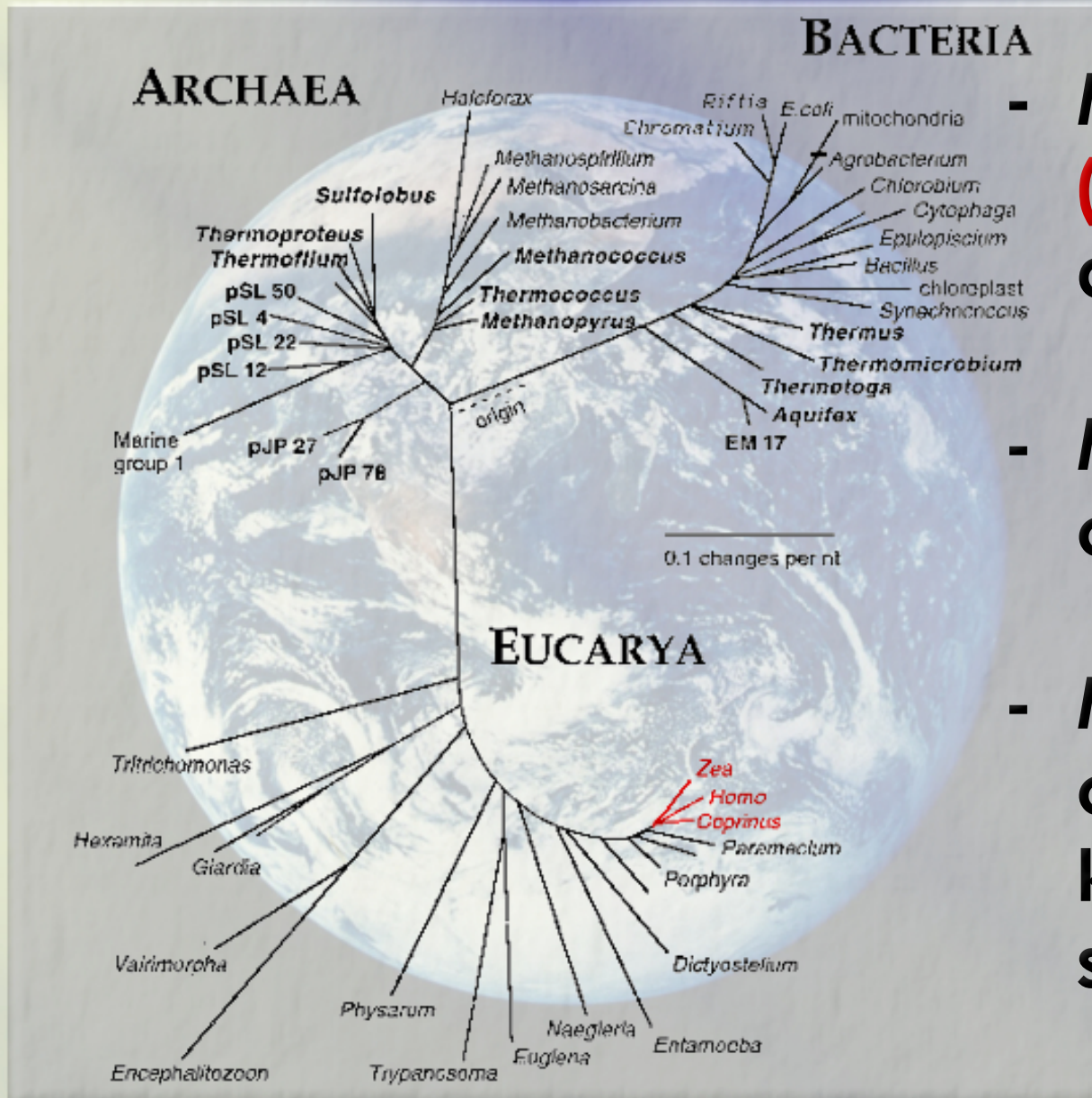
**HHMI, and Dept. Chemistry & Biochemistry
University of Colorado, Boulder**

**It's important to remember that
our world...**



NASA: Earth from Apollo

...is a microbial world

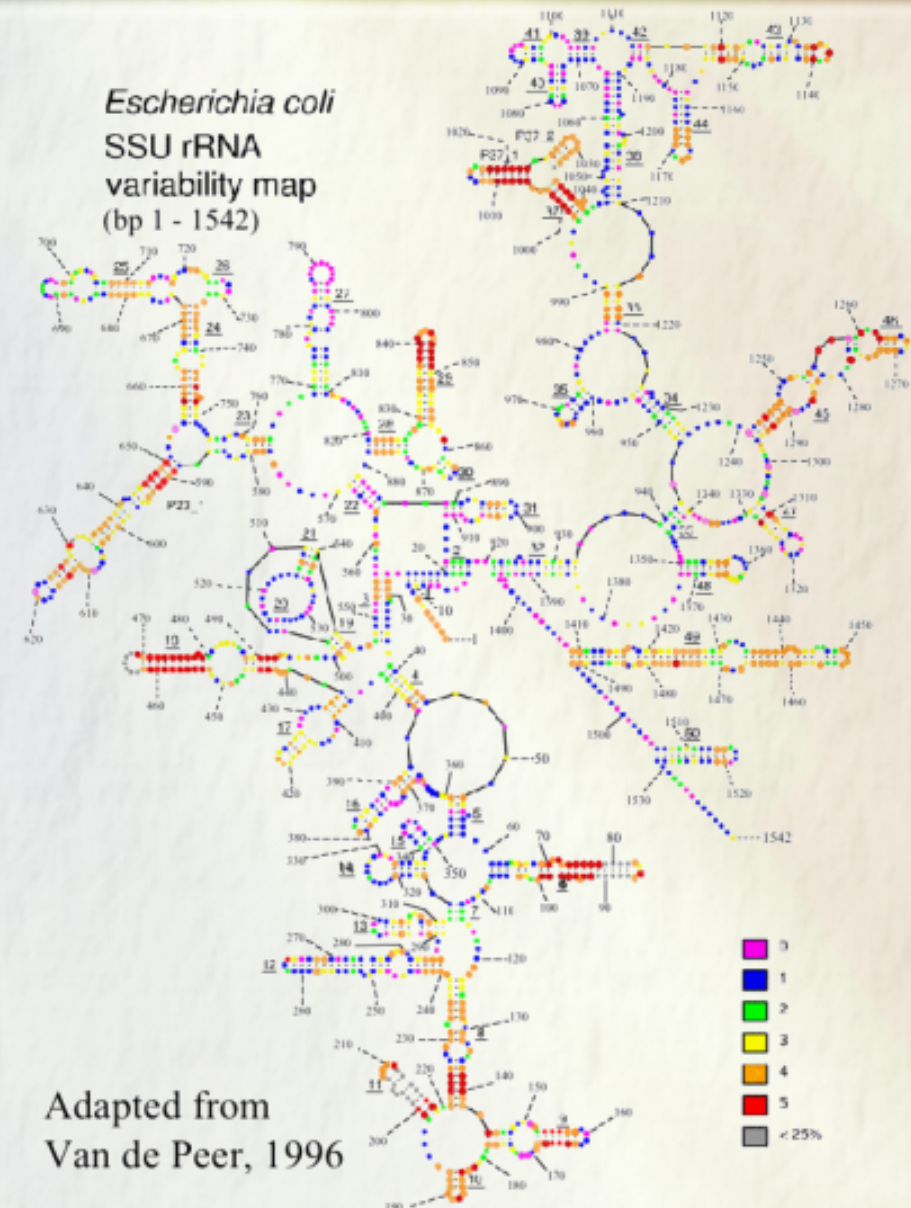


- Multicellular lineages (red) rare, not diverse as measured by SSU rRNA
- Most molecular diversity can be found in microbes
- Most (99%+) microbes can't be cultured: known only from sequences

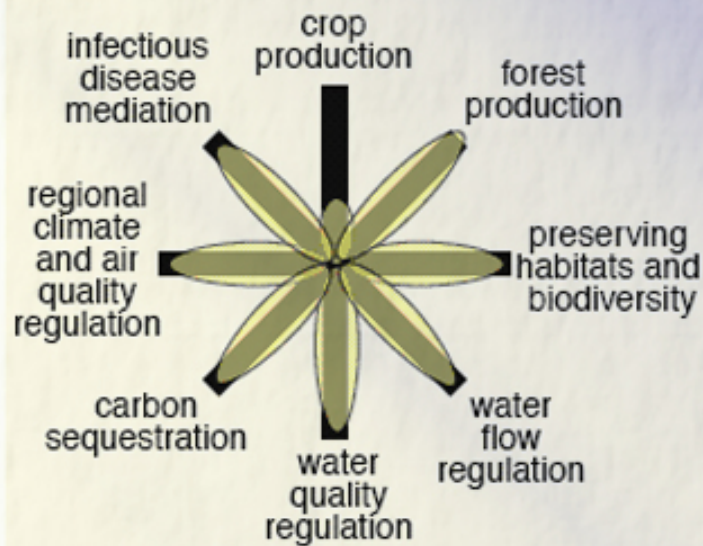
Tree adapted from Pace 1997 Science 276:734-740.

Ribosomal RNA is an excellent phylogenetic marker

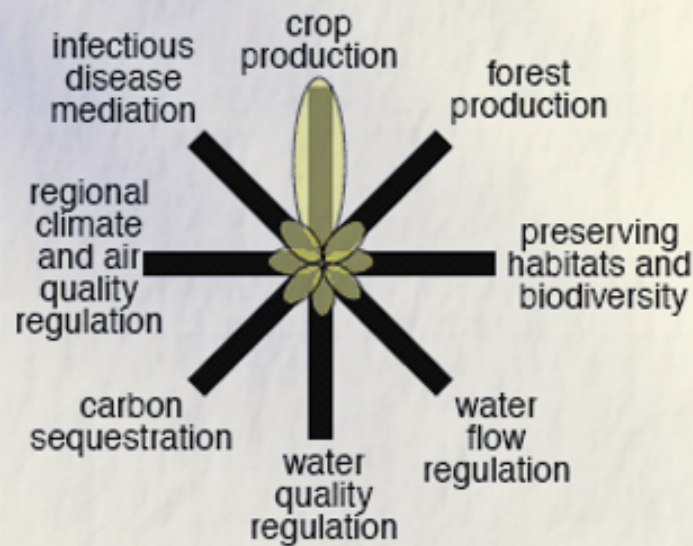
- Found in all species
- Has fast- and slow-evolving regions so can reconstruct relationships at different depths
- Large pre-existing databases for comparison



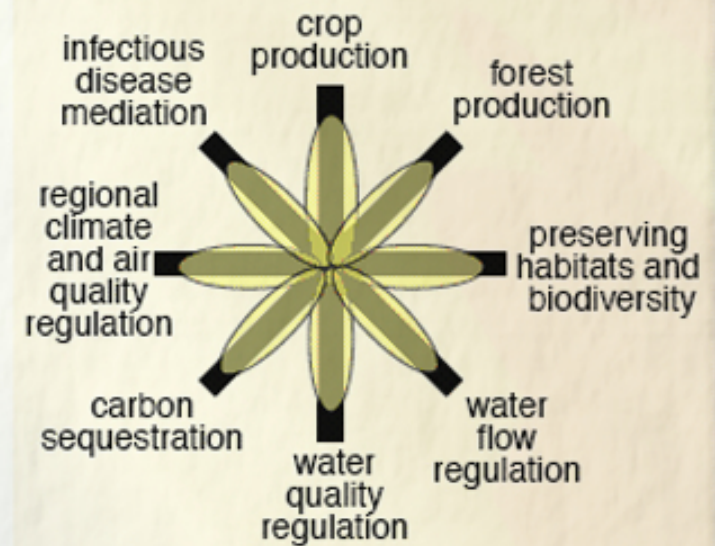
Microbes are ubiquitous, provide key ecosystem services



natural ecosystem



intensive cropland



cropland with restored ecosystem services

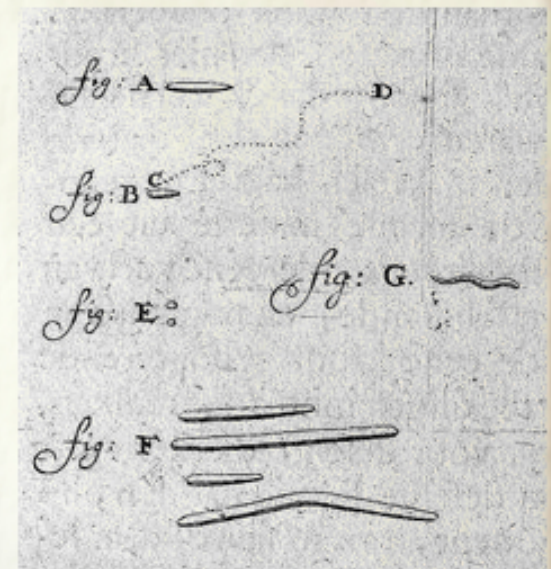
Early observations: body teeming with microbial life



+



=



“...animalcules were in such enormous numbers, that all the water...seemed to be alive.” — van Leeuwenhoek (1683)

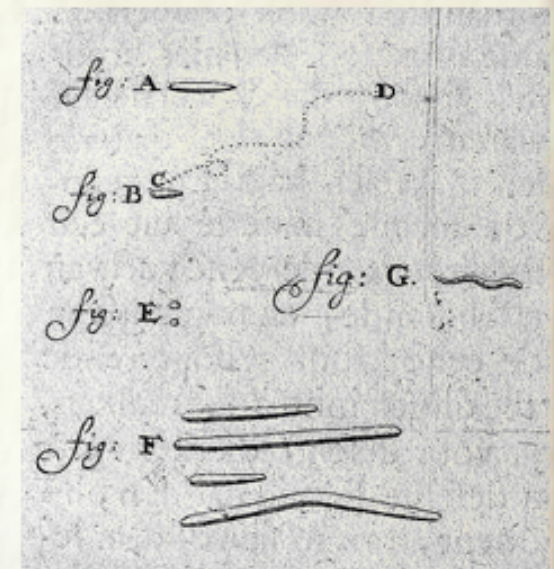
Early observations: body teeming with microbial life



+



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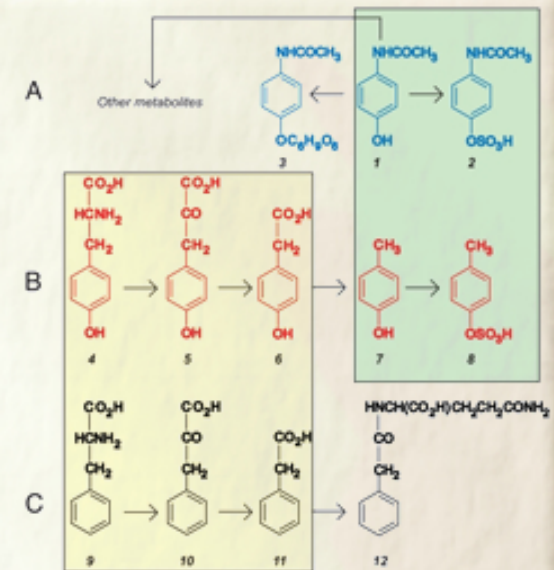


“...animalcules were in such enormous numbers, that all the water...seemed to be alive.” — van Leeuwenhoek (1683)

Why should you care about your microbes?

Why should you care about your microbes?

They determine whether Tylenol is toxic to your liver...



Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism

T. Andrew Clayton^a, David Baker^b, John C. Lindon^a, Jeremy R. Everett^c, and Jeremy K. Nicholson^{a,1}

^aBiomolecular Medicine, SORA Division, Faculty of Medicine, Sir Alexander Fleming Building, Imperial College London, South Kensington, London SW7 2AZ, United Kingdom; ^bPfizer Inc., 50 Pequot Avenue, New London, CT 06320; and ^cPfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

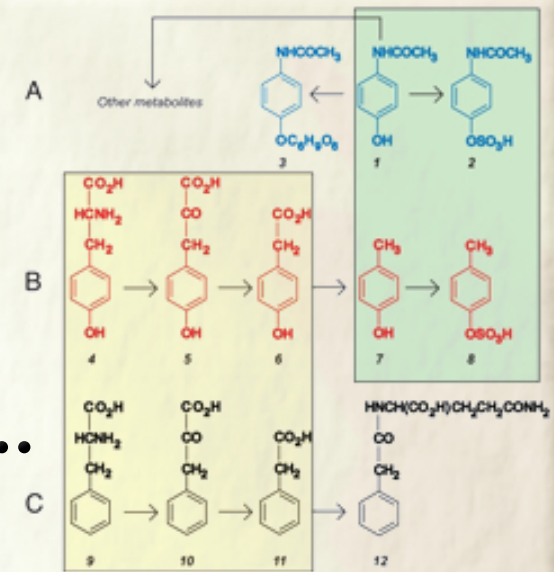
Communicated by Burton H. Singer, Princeton University, Princeton, NJ, April 29, 2009 (received for review December 8, 2008)

Why should you care about your microbes?

They determine whether Tylenol is toxic to your liver...



...they tell you who to have sex with (if you're a fruit fly)...



Pharmacometabonomic identification of a significant

Commensal bacteria play a role in mating preference of *Drosophila melanogaster*

Gil Sharon^a, Daniel Segal^a, John M. Ringo^b, Abraham Hefetz^c, Ilana Zilber-Rosenberg^d, and Eugene Rosenberg^{a,1}

^aDepartment of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv 69978, Israel; ^bSchool of Biology and Ecology, University of Maine, Orono, ME 04469; ^cDepartment of Zoology, Tel Aviv University, Tel Aviv 69978, Israel; and ^d18 Radhavat Ilan St., Givat Shmuel 51905, Israel

Edited by R. John Collier, Harvard Medical School, Boston, MA, and approved September 28, 2010 (received for review July 12, 2010)

PNAS
NAS

Why should you care about your microbes?

They determine whether Tylenol is toxic to your liver...



...they tell you who to have sex with (if you're a fruit fly)...

...and they steal genes from your food to help you digest it



nature

Vol 464 | 8 April 2010 | doi:10.1038/nature08937

LETTERS

Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota

Jan-Hendrik Hehemann^{1,2,†}, Gaëlle Correc^{1,2}, Tristan Barbeyron^{1,2}, William Helbert^{1,2}, Mirjam Czejek^{1,2} & Gurvan Michel^{1,2}

There are about as many *E. coli* in your gut...



...as there are humans on Earth!



=



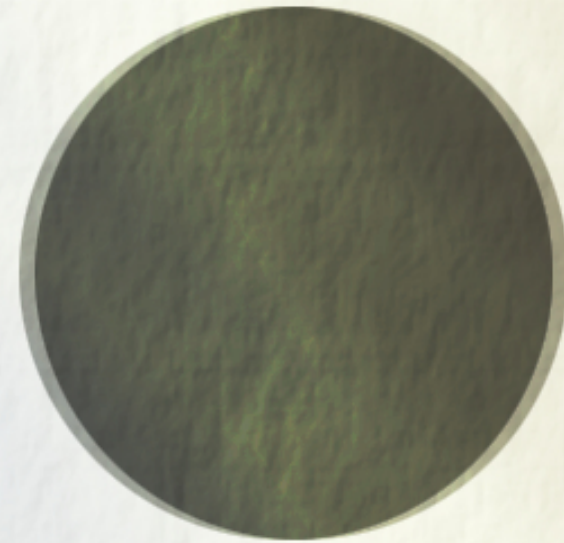
We think of *E. coli* as a classic gut microbe...



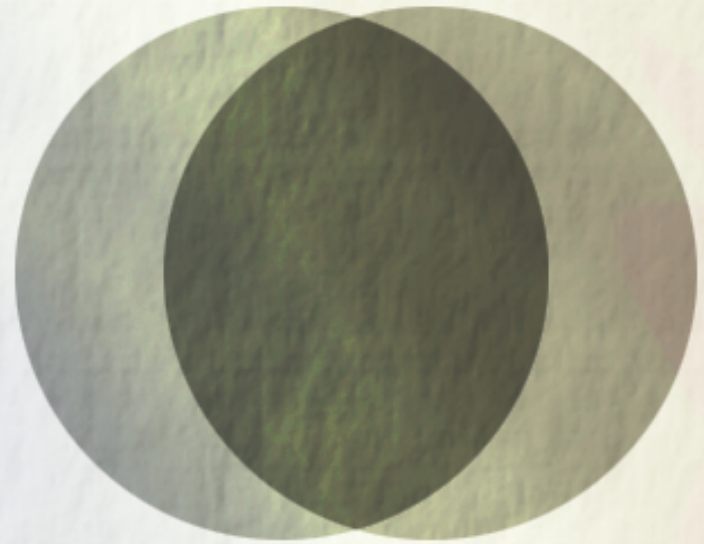
....but only because it is easy to grow in captivity, unlike most



...and any two humans you pick
have 99.9% identical genomes...



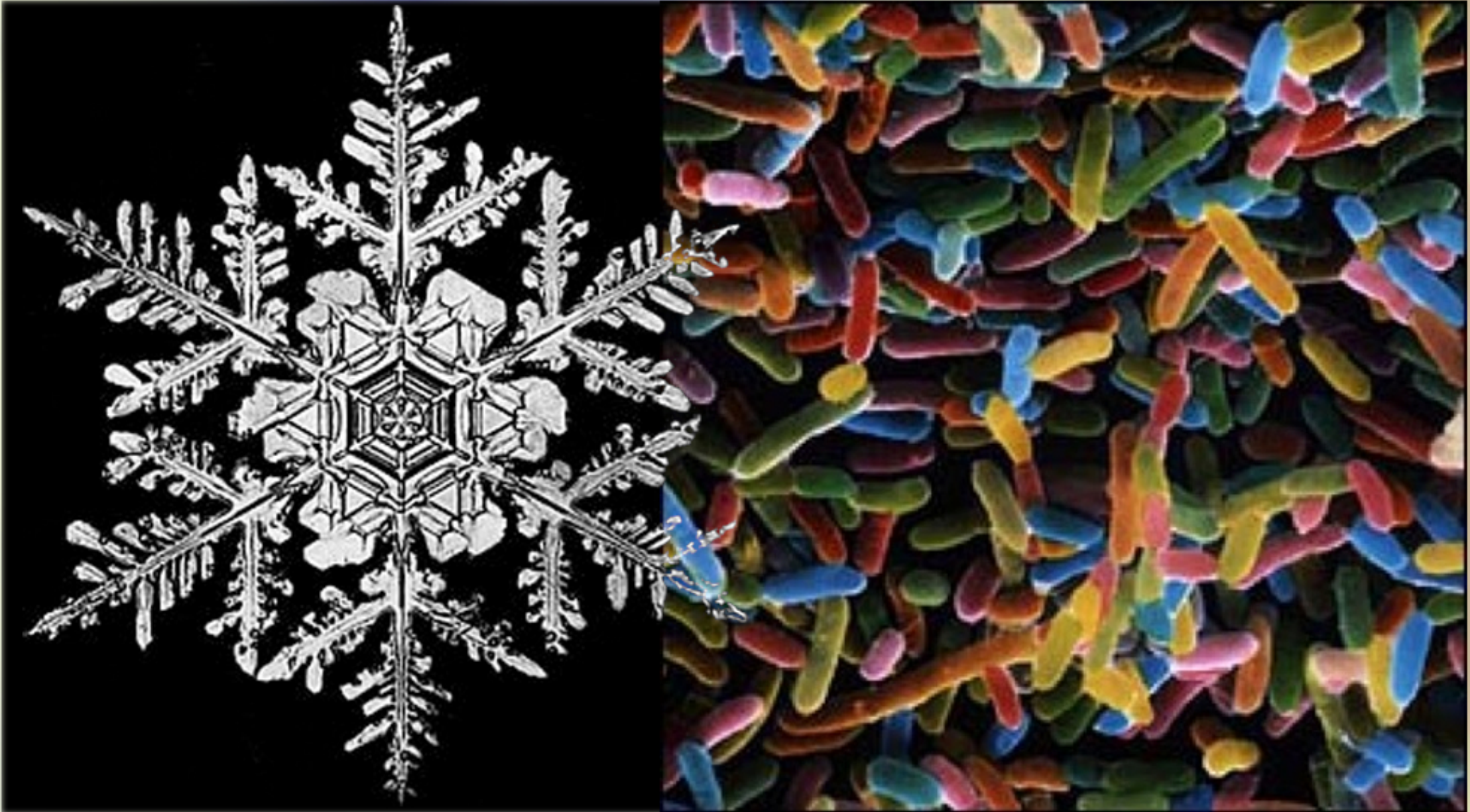
...but two E. coli cells can have genomes that are 40% different.



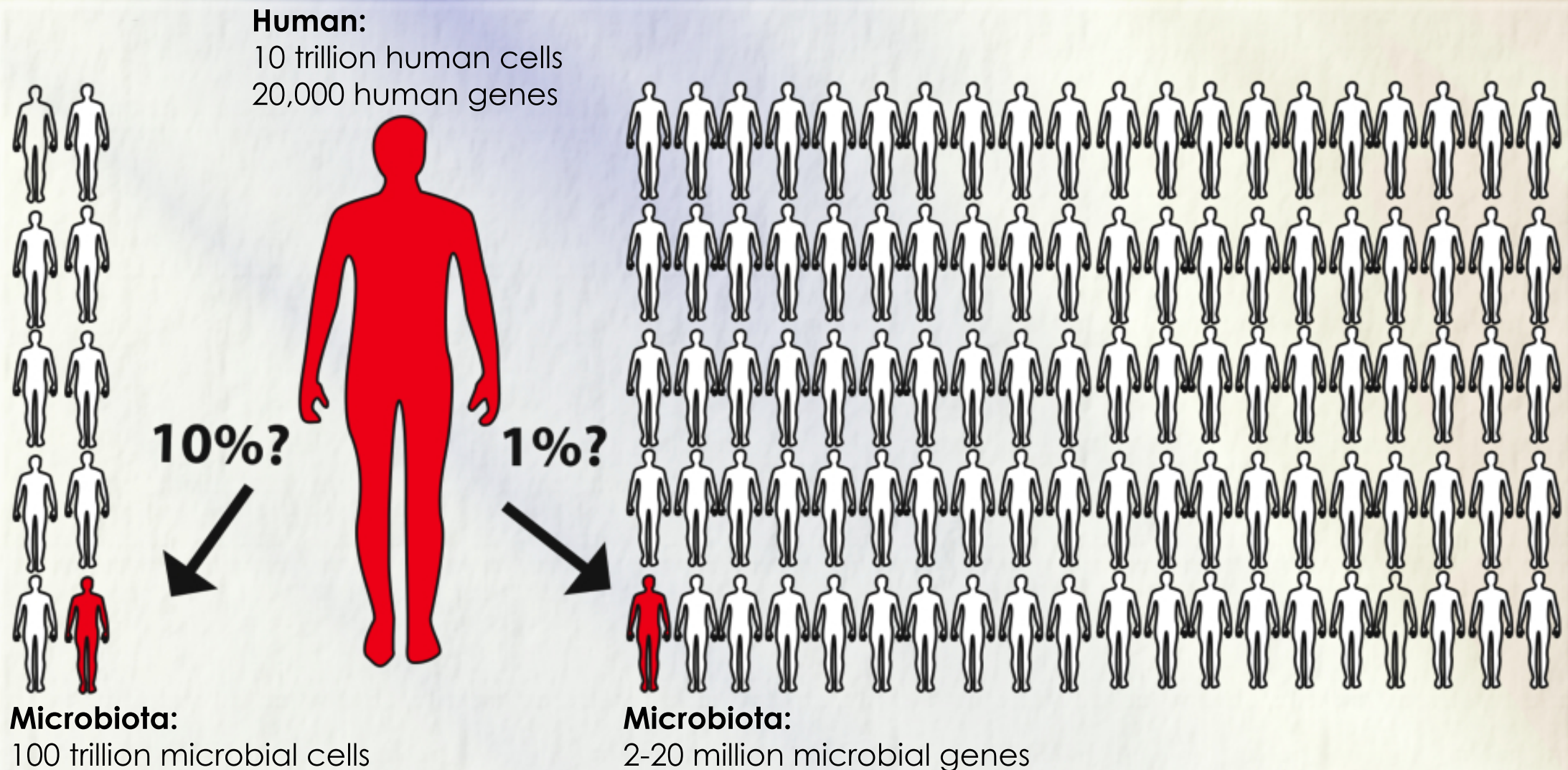
**So you are not a beautiful and
unique snowflake...**



...but your microbial symbionts are!



All this microbial diversity raises question: how human are we?



99.9% of our genomes the same, but our microbes...?

Micah Hamady, PhD thesis, 2009

We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

- How are microbes distributed over our bodies?**



We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

- How are microbes distributed over our bodies?
- How do our microbes change over time?



We are poised to answer key questions about our microbial selves

Overarching question: How can we develop technologies that manipulate our microbiota to improve health?

- How are microbes distributed over our bodies?**
- How do our microbes change over time?**
- How can we translate between humans and animal models?**

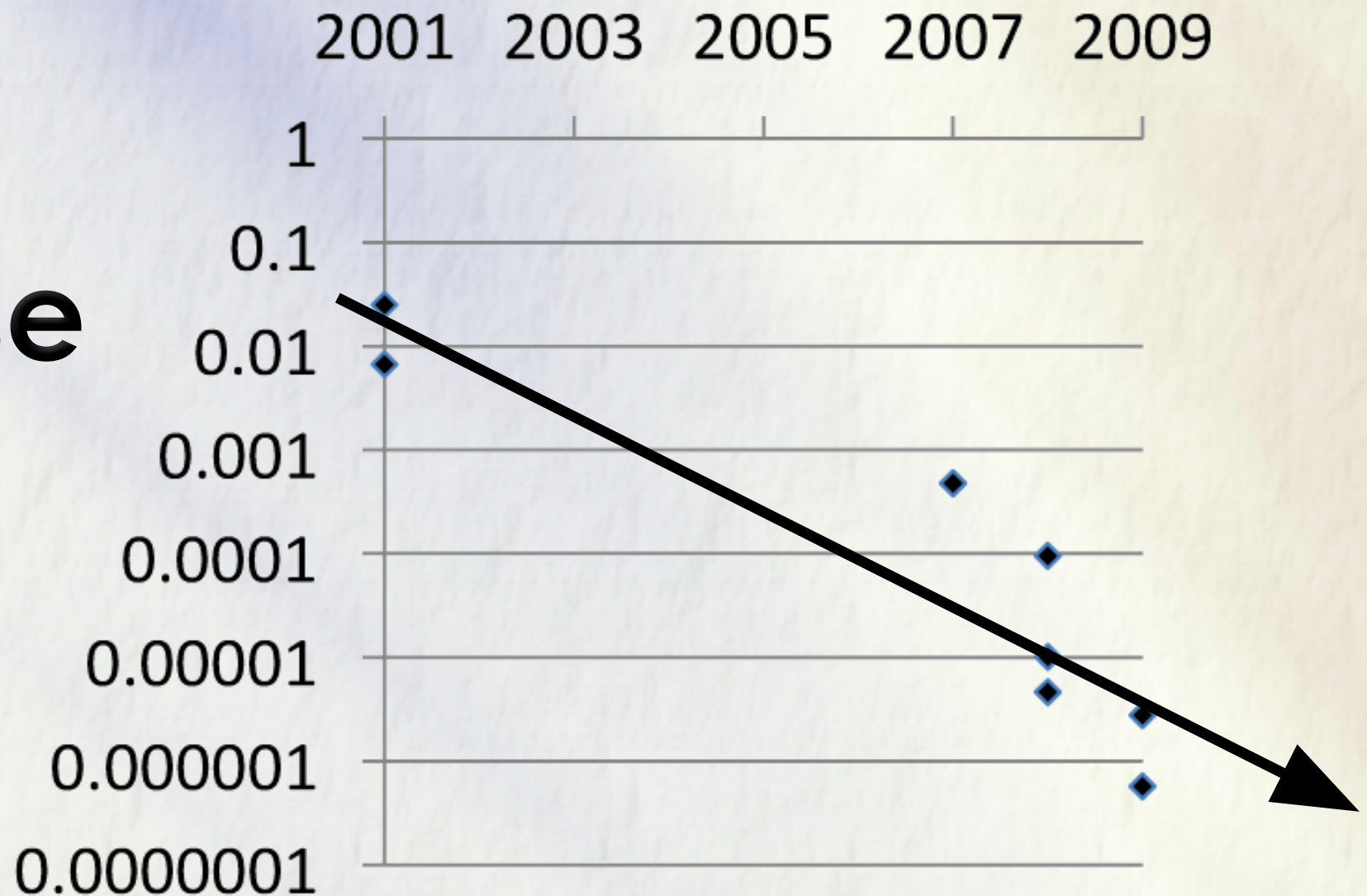


Microbiome studies motivate a broad range of bioinformatics

- Homology search**
- Sequence alignment**
- Phylogenetic trees**
- Assembly**
- Functional assignment**
- Distance metrics**
- Dimensionality reduction**
- Supervised and unsupervised classification**
- Networks (interaction, biochemical, regulatory)**
- Data visualization**

Sequencing is getting so cheap...

\$/base



The issue: need to interpret vast amounts of sequence/tree data

```
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first 9 of 130,000 sequences

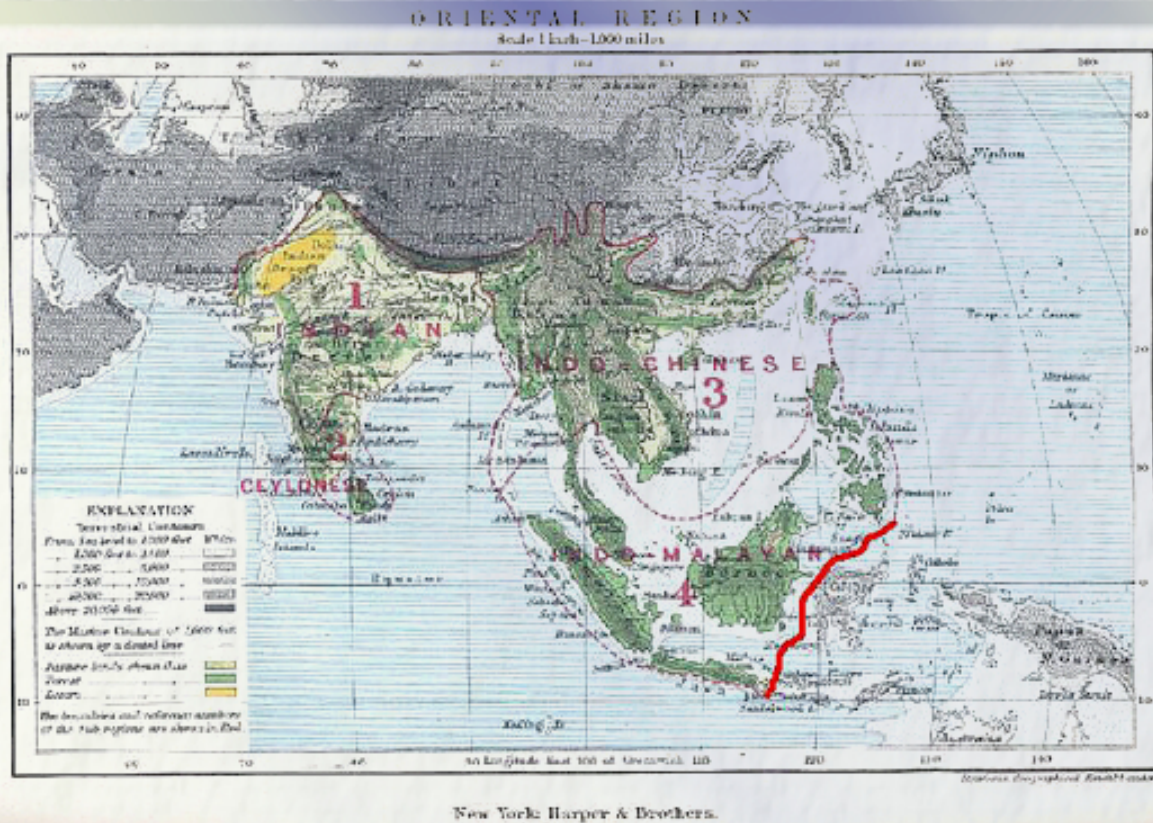
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~0.1% of the tree file



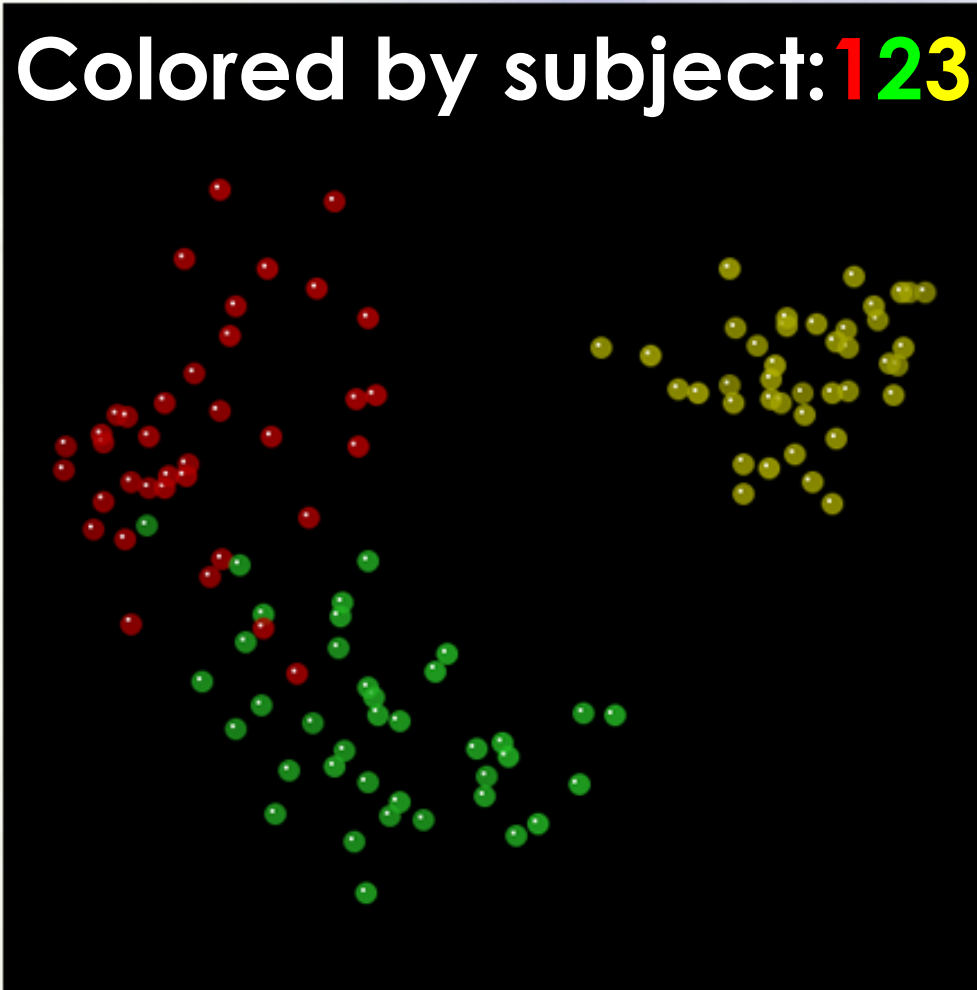
naive visualization of tree...

Microbial biogeography on the keyboard?

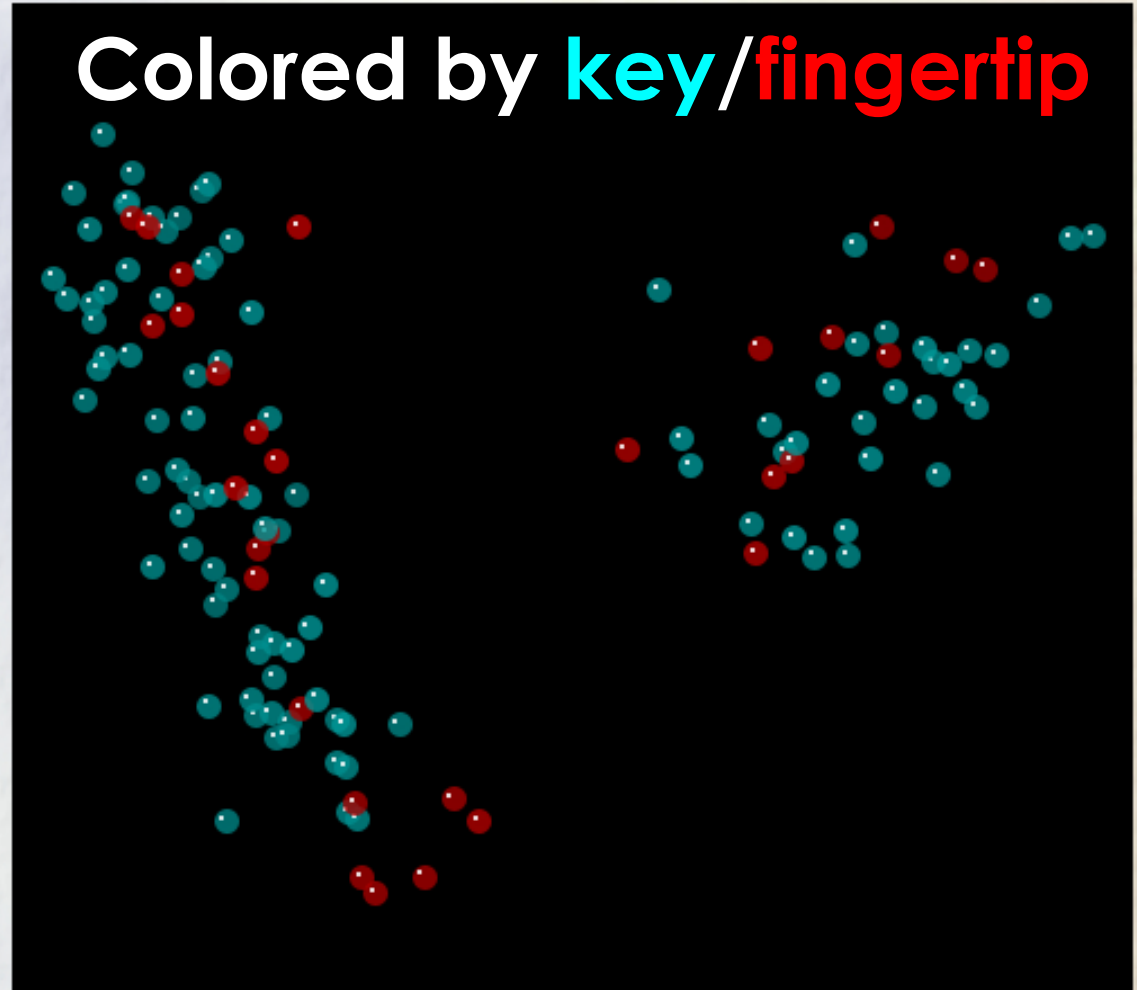


Two other views of these same data make patterns clear...

Colored by subject: **1** **2** **3**

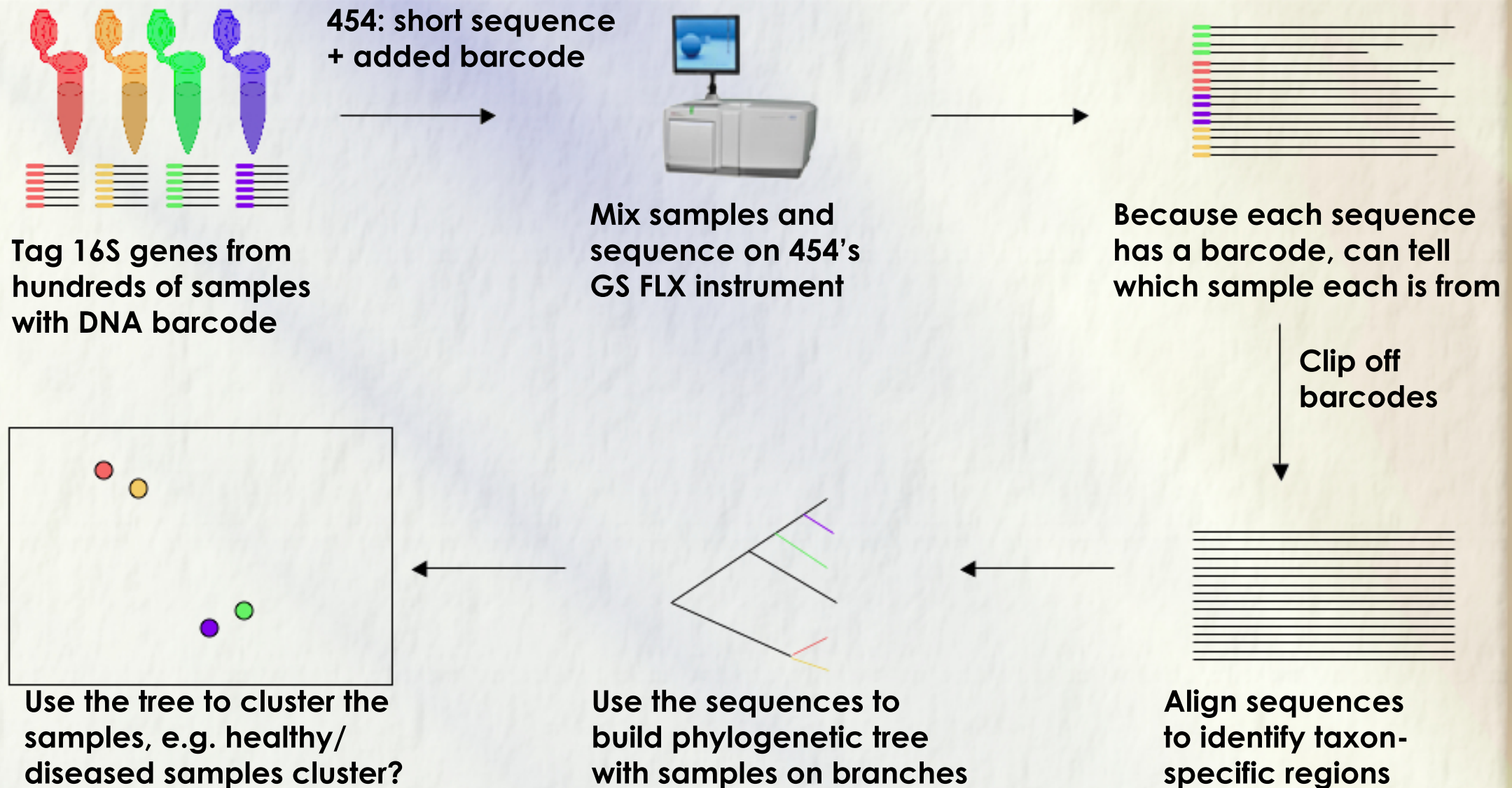


Colored by **key**/**fingertip**



...i.e., each individual has a unique skin community that is transferred from fingertips to keyboards

QIIME: integrating analysis of hundreds of samples

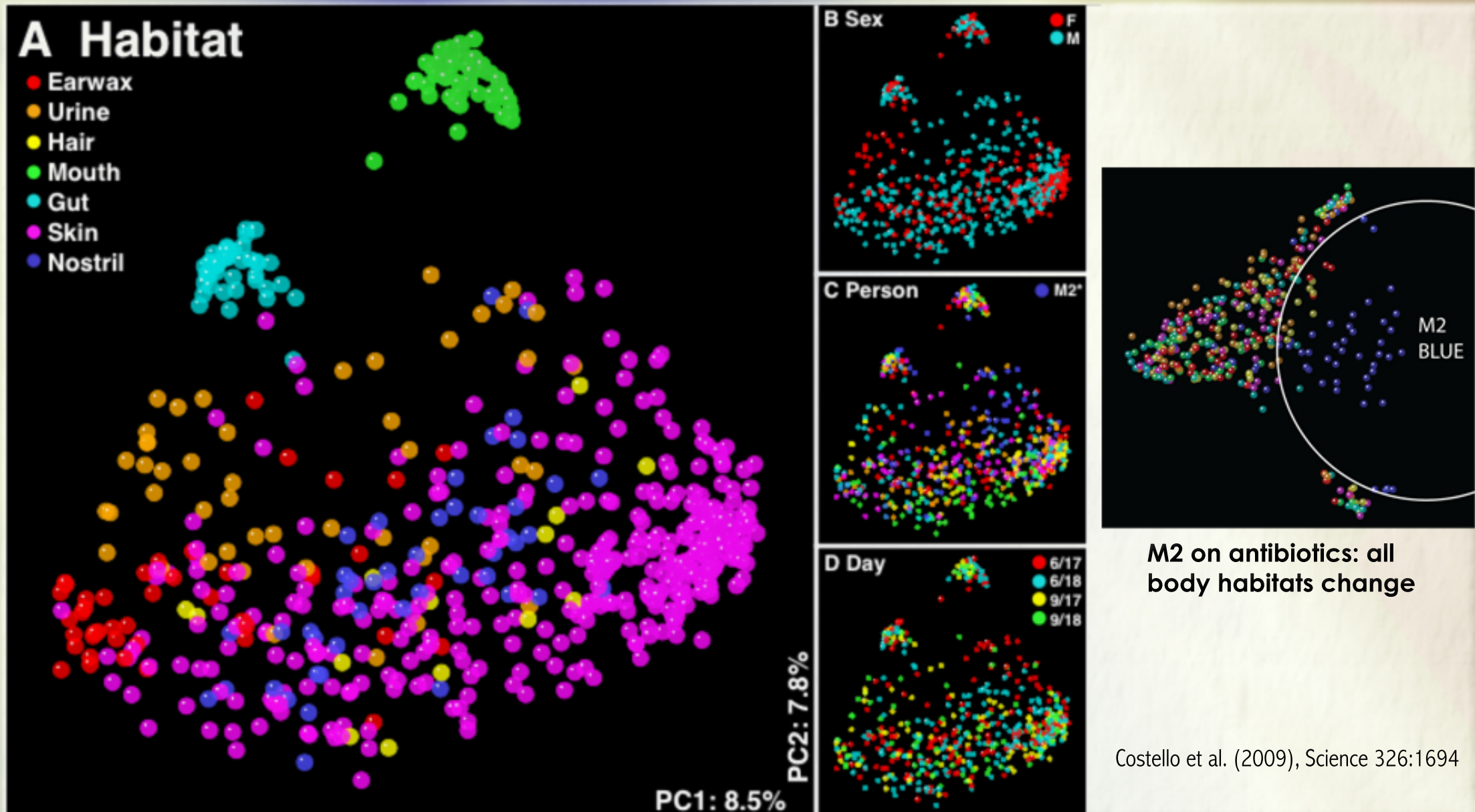


Why is it called “454”?

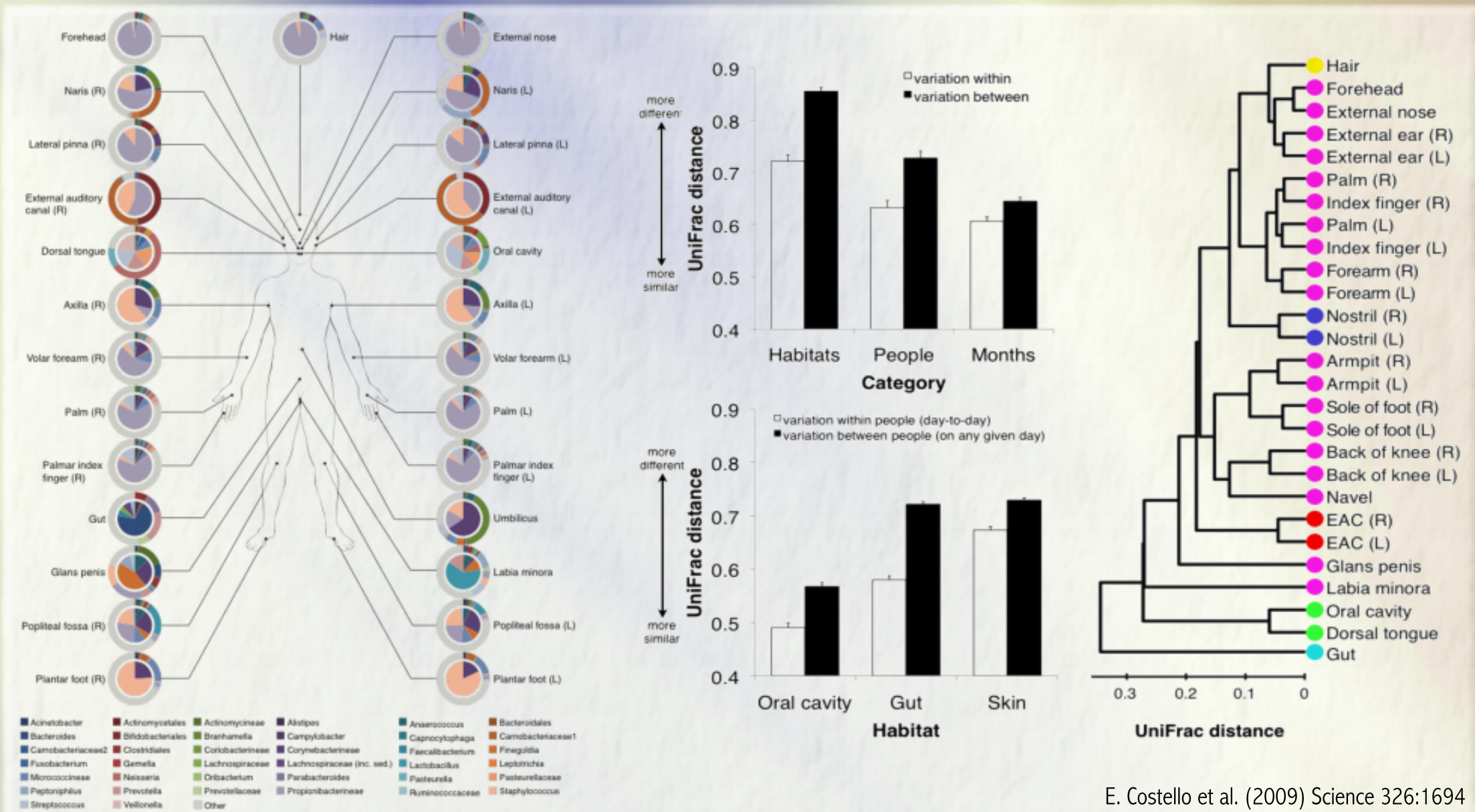
Why is it called “454”?



Different body habitats are very different from one another



Now getting first picture of overall human microbiome variability



**But a handful of timepoints isn't
really sufficient...**

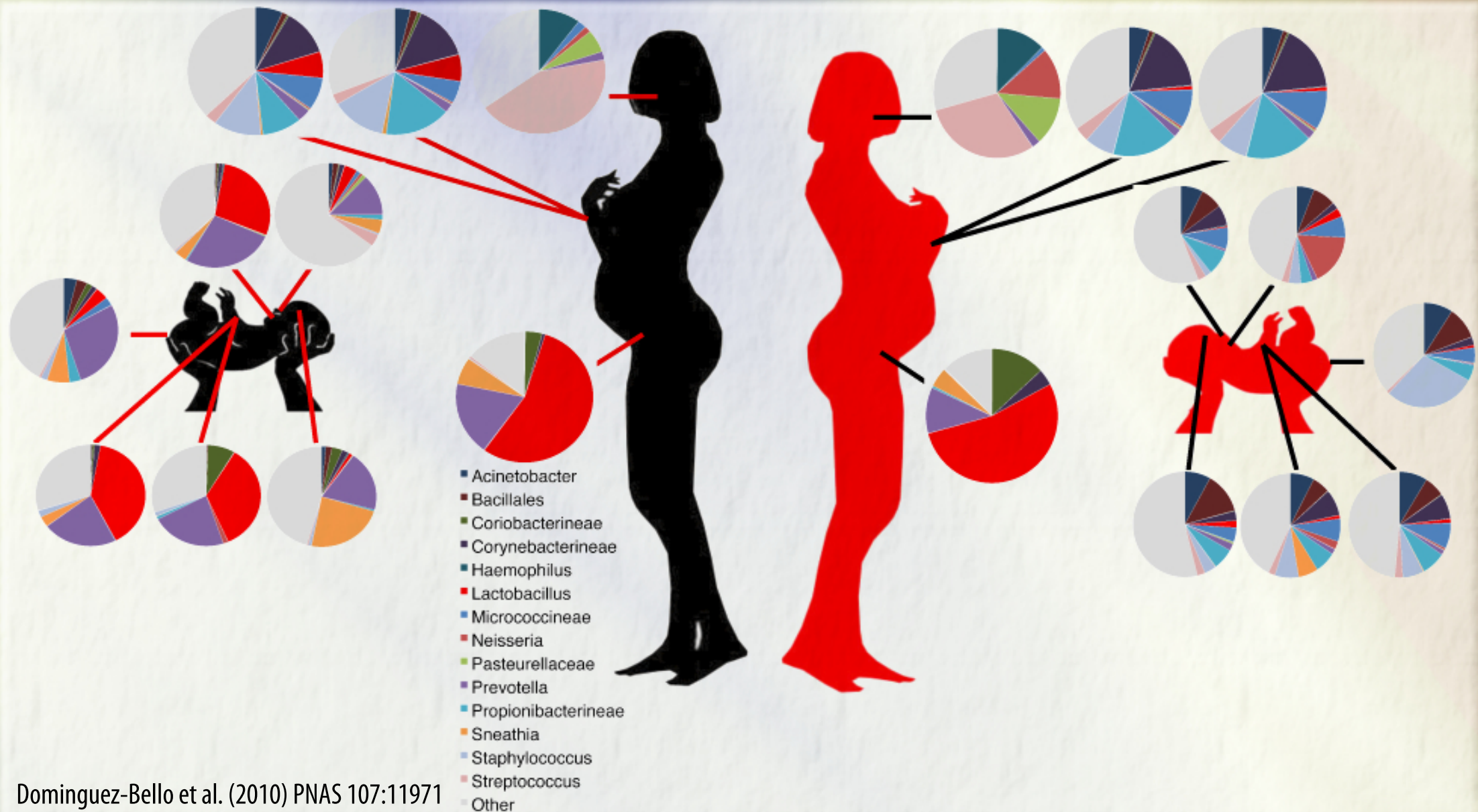
So where do our microbes come from?



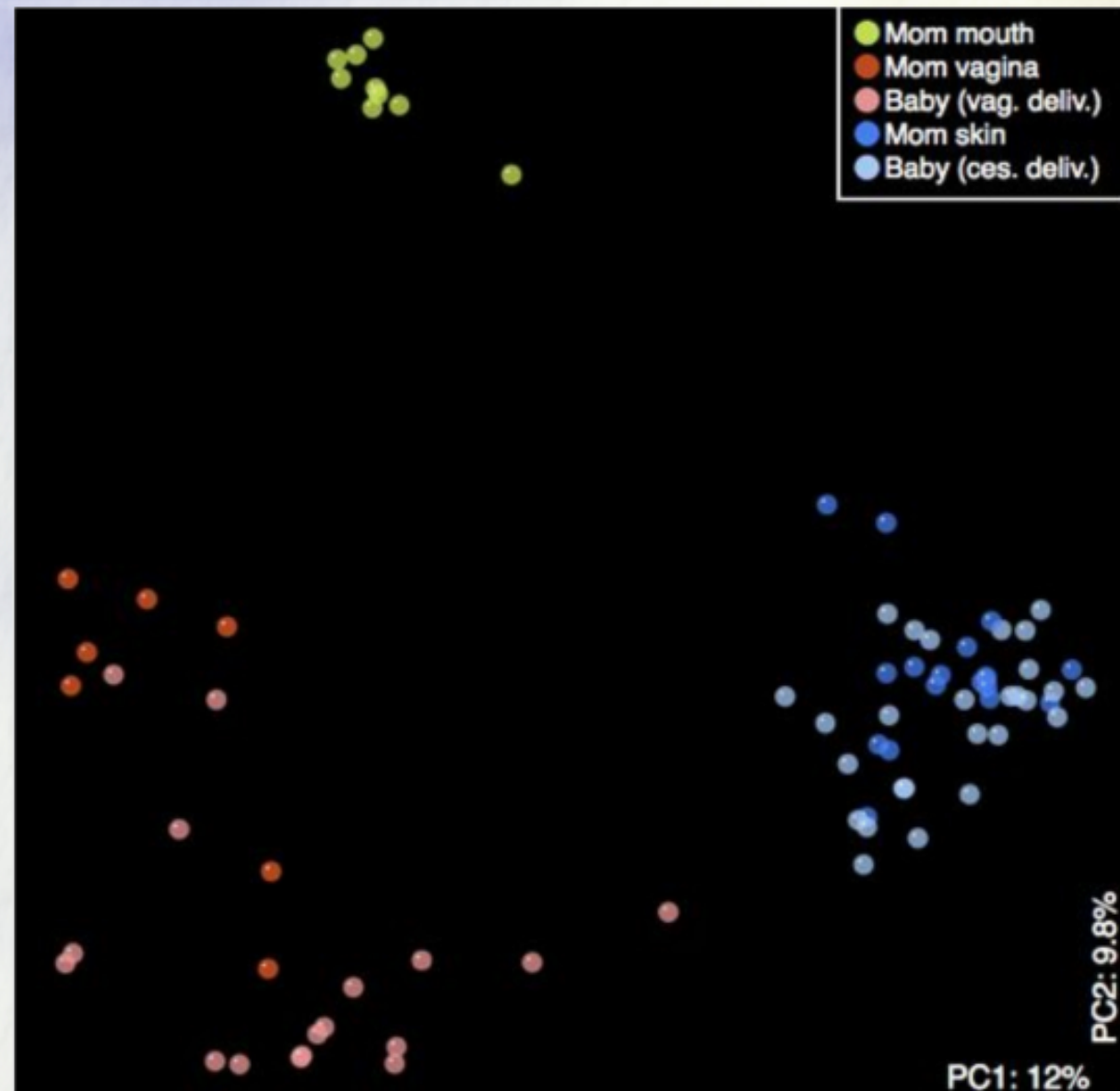
So where do our microbes come from?



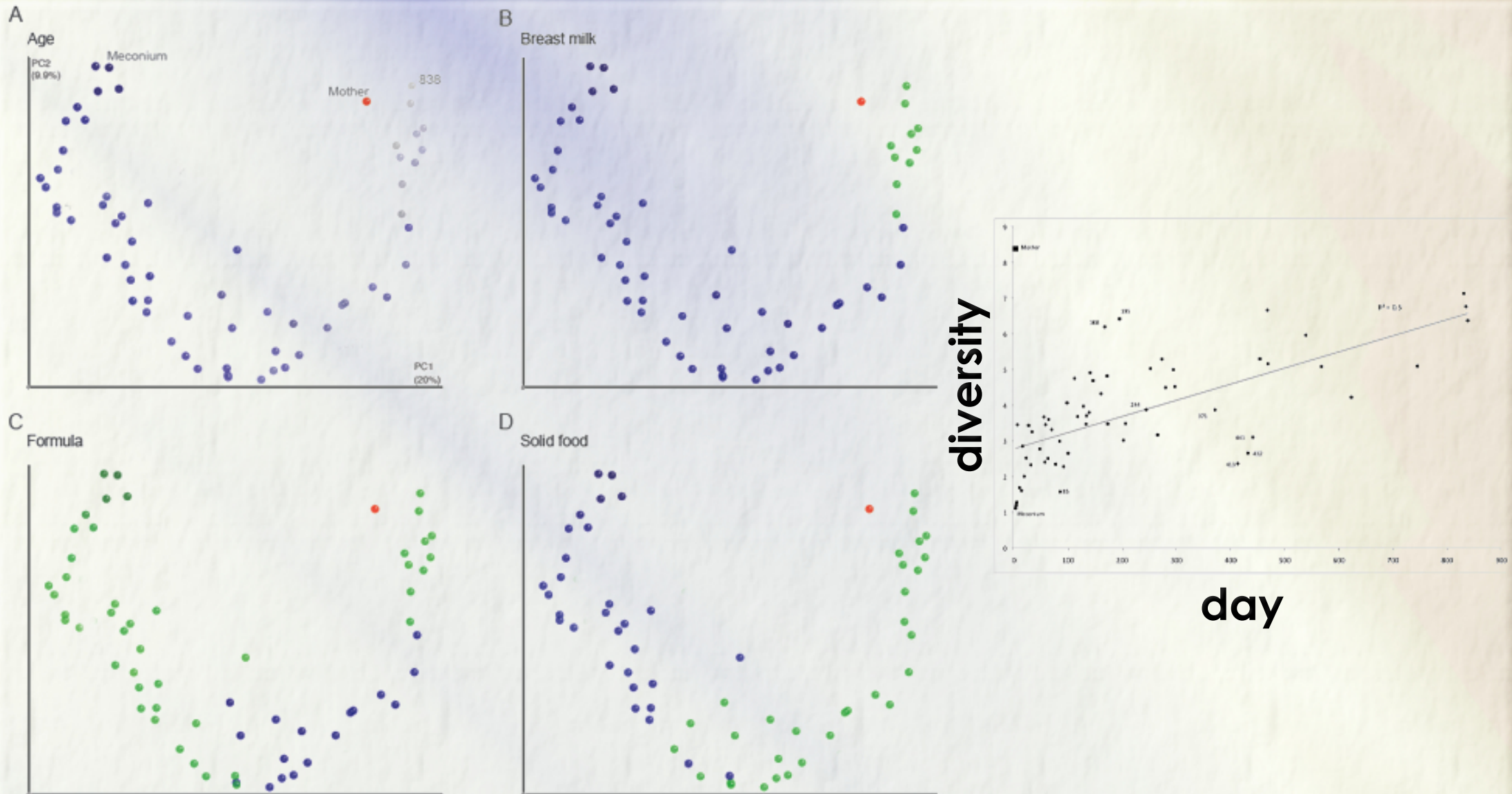
Sampling of the microbiota 20 minutes after birth



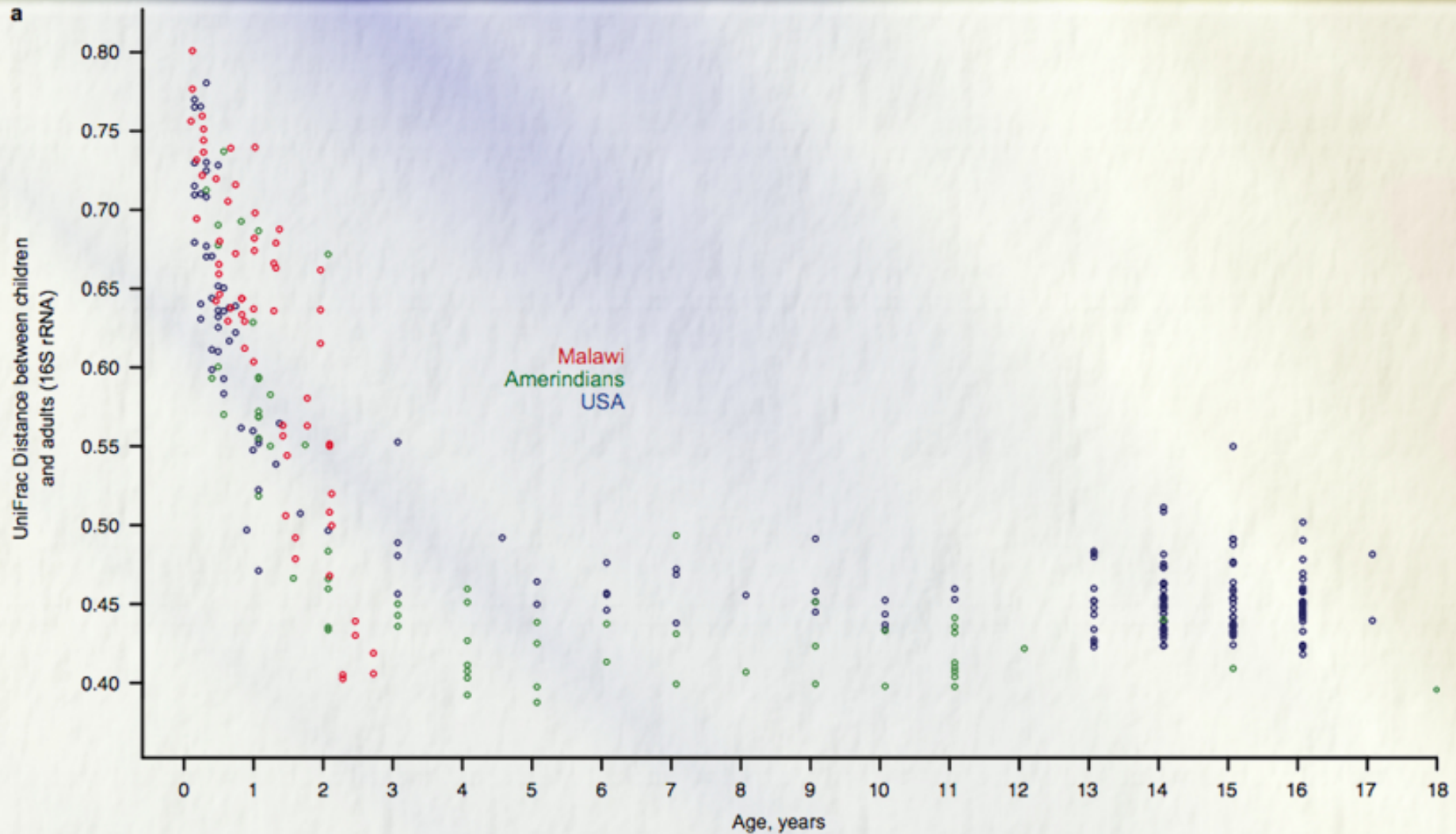
Sampling of the microbiota after birth... (alternative view)



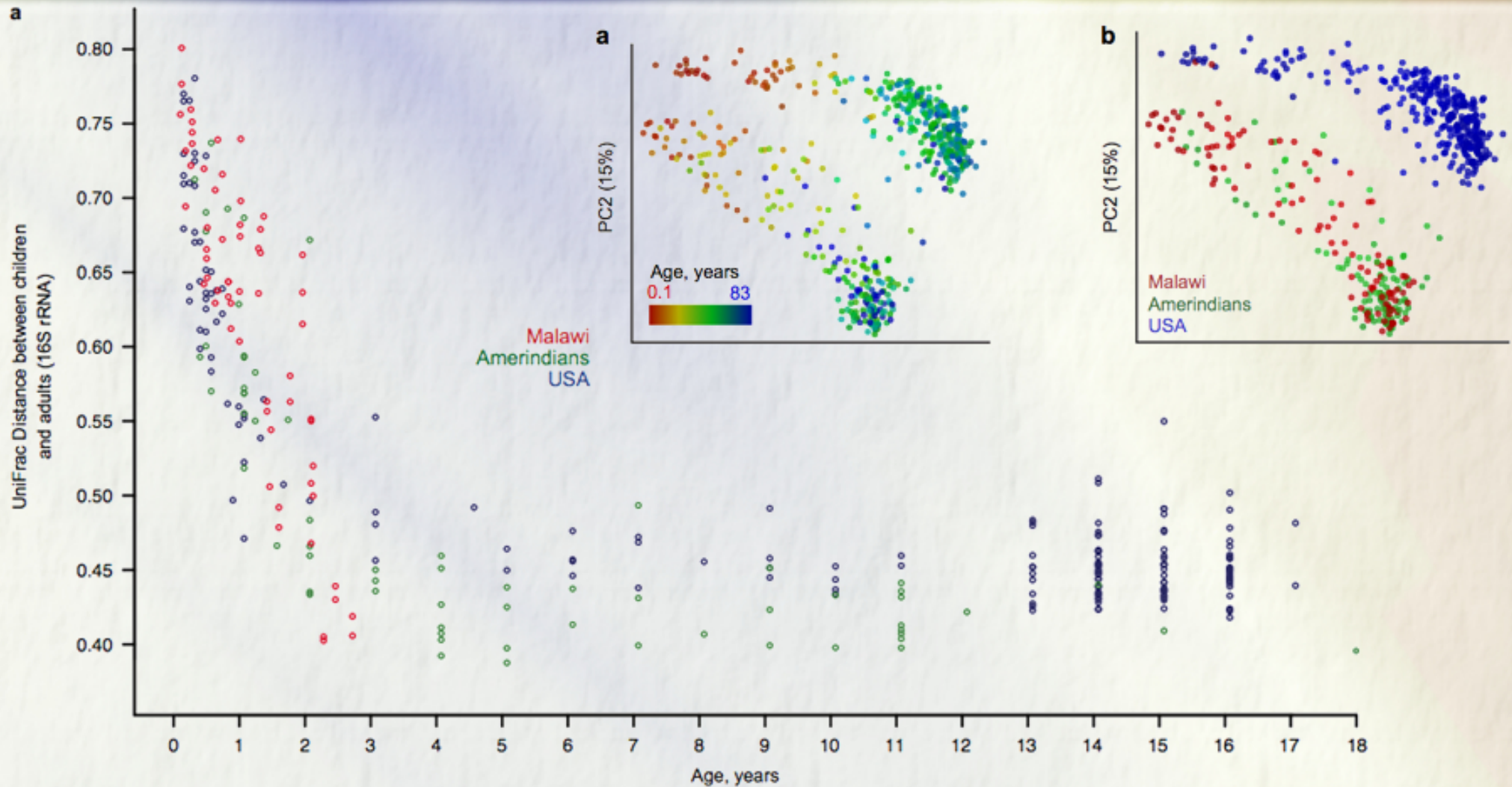
We can understand how the microbiome develops in infants...



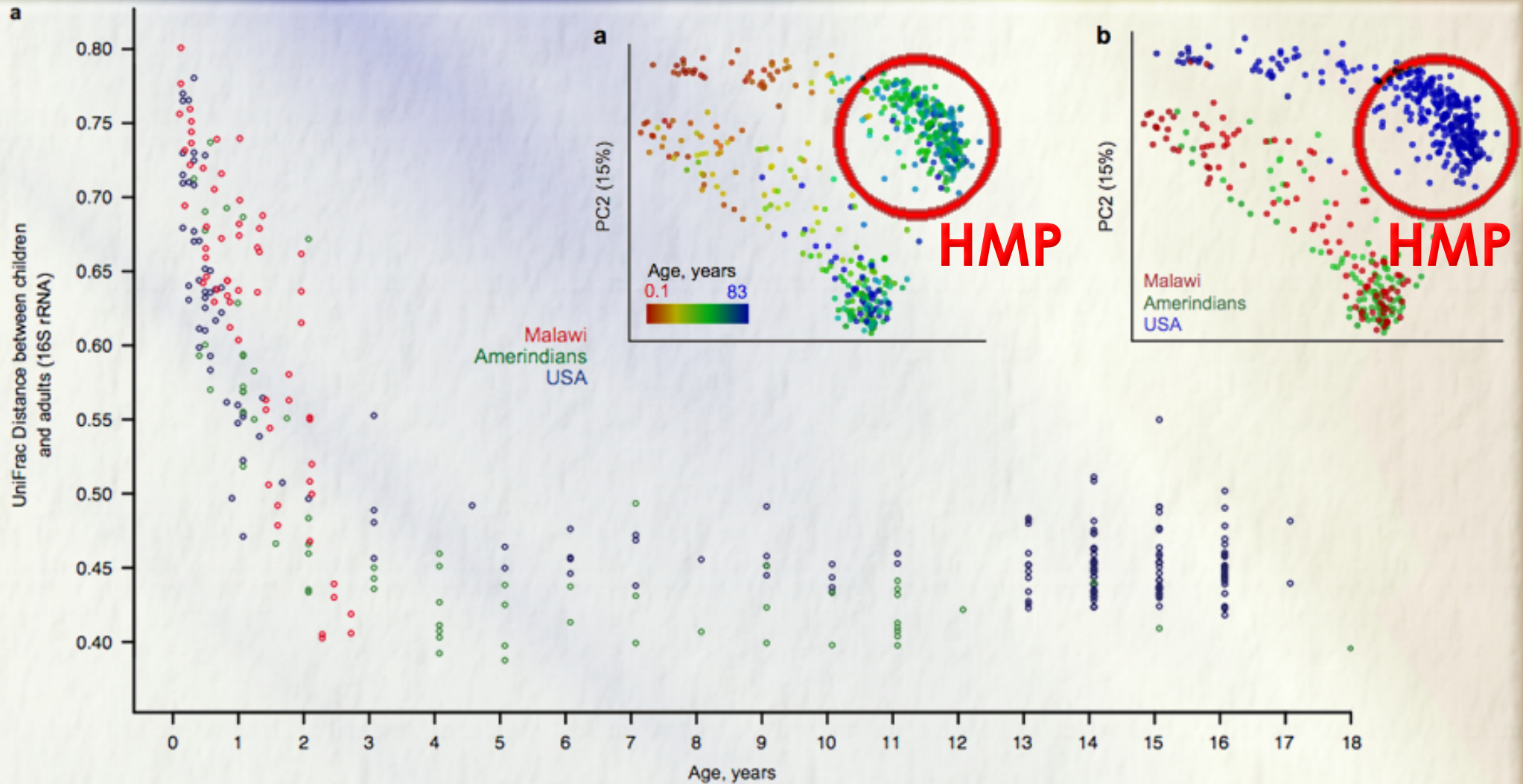
...and across cultures...



...although converging on very different endpoints!



And the HMP only covers the start of this diversity



Starting to cover rest of diversity by crowdfunding, with American Gut

American Gut - what's in your gut? | Indiegogo

www.indiegogo.com/americangut

Want crowdfunding tips and tricks? Download Indiegogo's free Crowdfunding Field Guide! [LEARN MORE](#)

American Gut - what's in your gut?
World's LARGEST open-source, community driven effort to characterize the microbial diversity of the Global Gut. All US and International participants welcome.
[Health - New Orleans, Louisiana, United States](#)

[Campaign Home](#) [Updates / 15](#) [Comments / 286](#) [Funders / 1993](#) [Gallery / 10](#)



What's in your gut?

\$339,114
Raised of \$400,000 Goal

0 time left

Flexible Funding campaign

This campaign received all of the funds contributed by Sat 02 Feb.

Perks for your contribution

\$49
Add One More Body Site

This is a Flexible Campaign and the project proceeds whether or not we reach our funding goal. Join us!

Share This Campaign: <http://igg.me/at/americangut1> [Follow](#)

American Gut: you can get involved!



>\$500k
>6000 people
>1200 kits
returned incl
400 PGP
samples...

...but we
need more!

Of course, not everyone wants to know what's in there...



Data just released into EBI for first 1080 American Gut samples

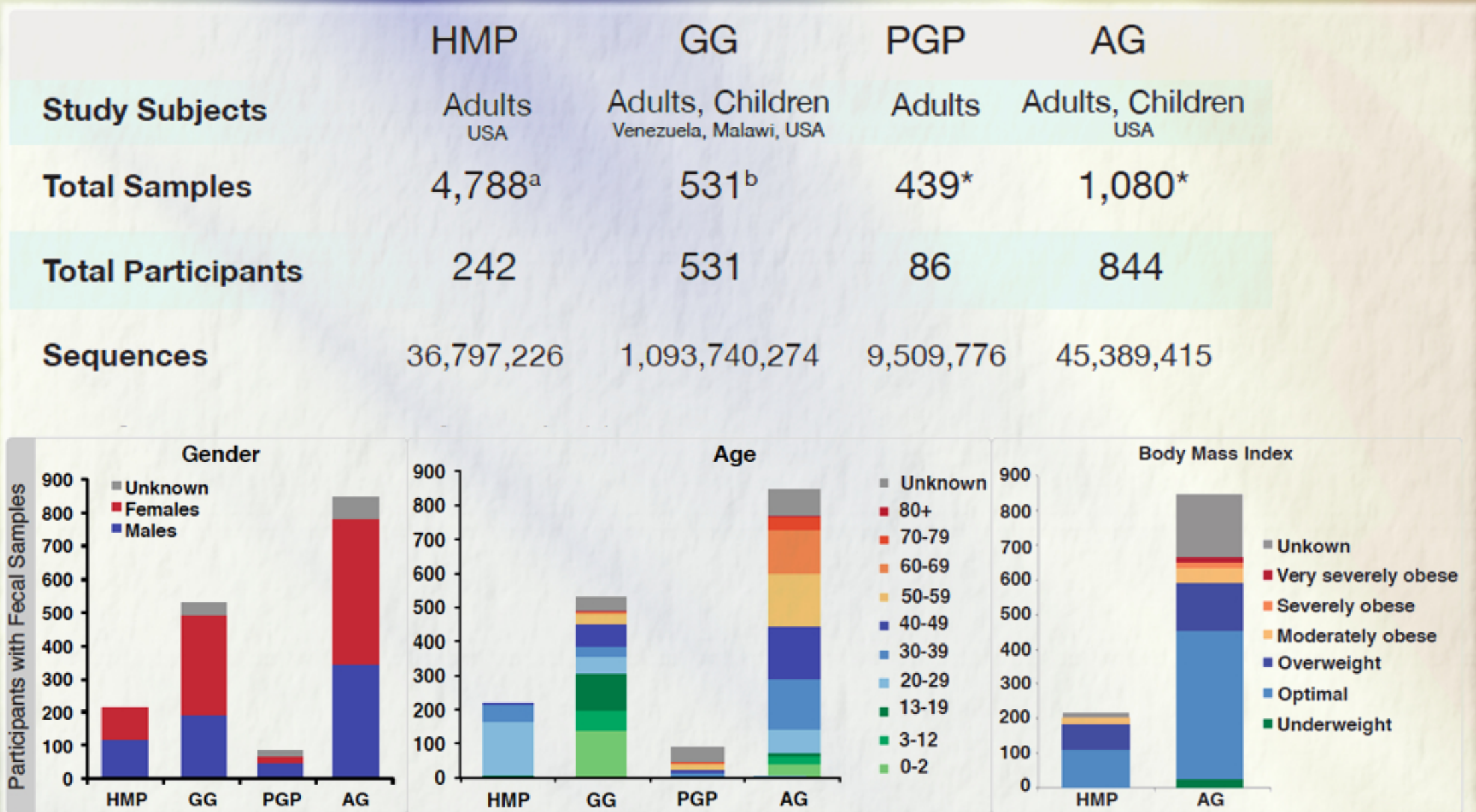
american Preliminary Characterization of the gut American Gut Population

We have, as of September 5, 2013, completed sequencing and quality control of the gut bacteria from the first 1080 samples from 844 participants in the American Gut study. This document gives a first look at results for the whole population. Your individual results (if your sample is among these first 1080 samples) will be available shortly.

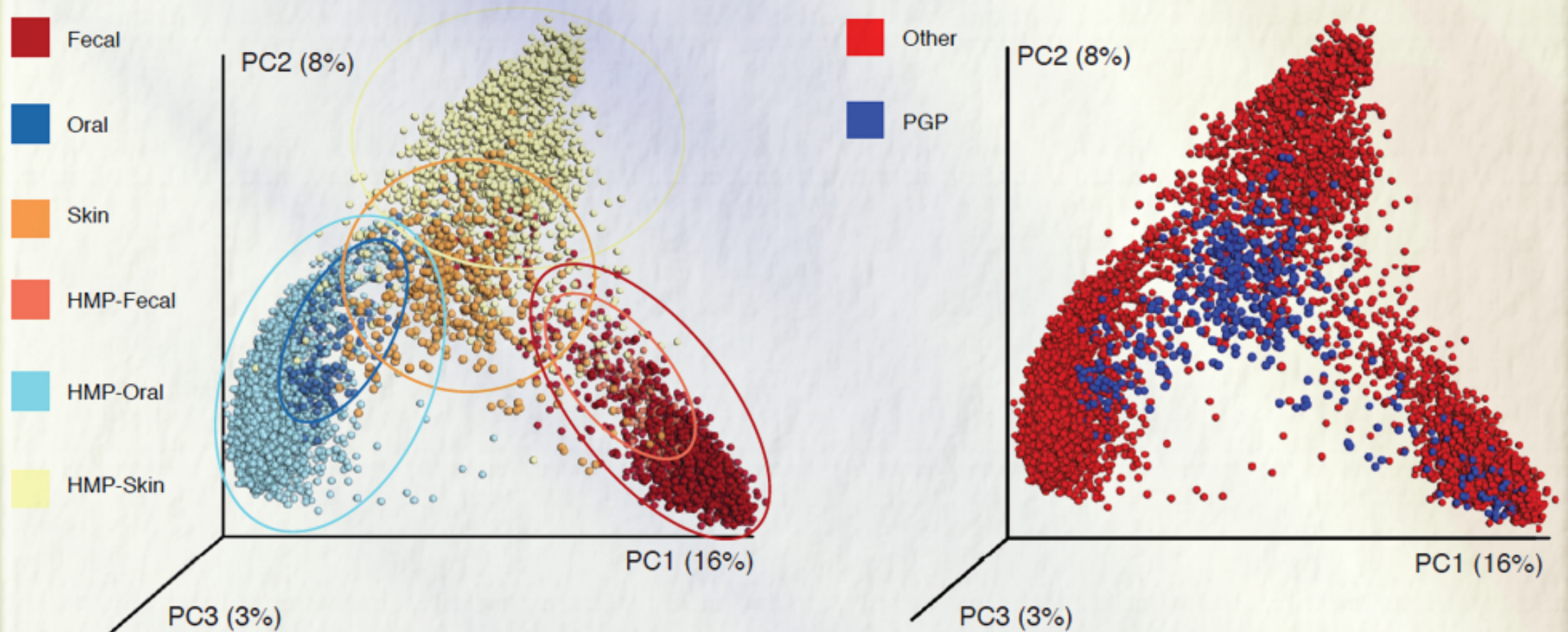
Here we compare the American Gut population to other populations who have had their gut bacteria characterized, describe the participants in the study, show the major kinds of bacteria in the gut microbiota of the American Gut population, and provide some information about what affects the gut bacteria (as well as show that some variables such as sex have surprisingly little effect).

Technical note: “microbiota” refers to a particular community of microbes, including bacteria (e.g. the human gut microbiota); “microbiome” refers to the genes those microbes contain (e.g. the human gut microbiome). Most participants in American Gut have signed up for characterization of the microbiota.

Demographics cover more range than previous studies

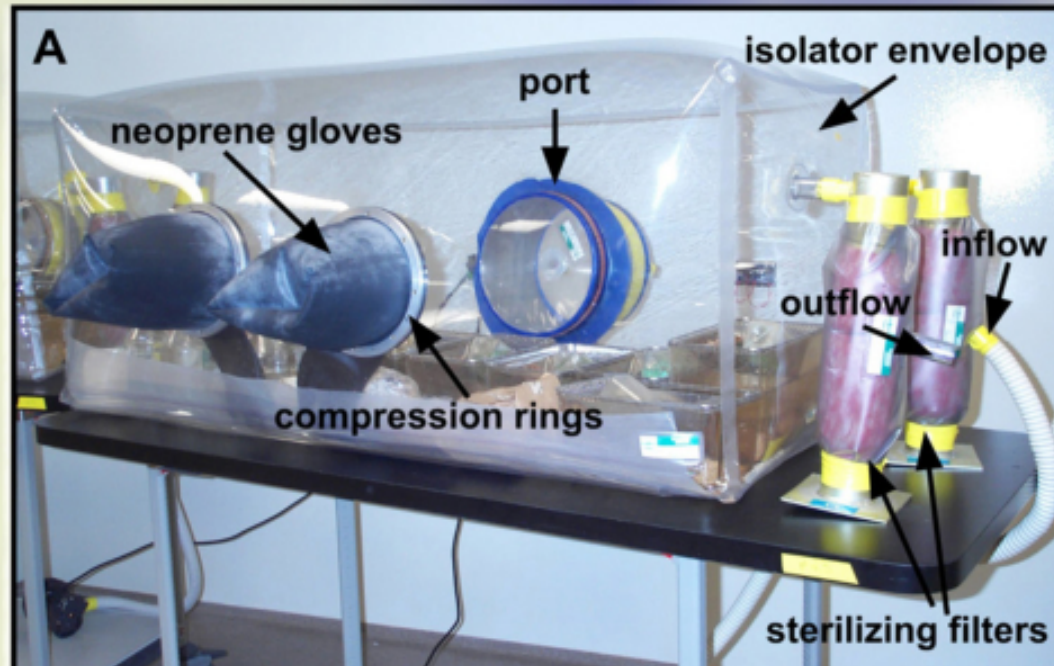


Overall results very consistent with prior studies at overall level...



**How can I tell
cause from
effect?**

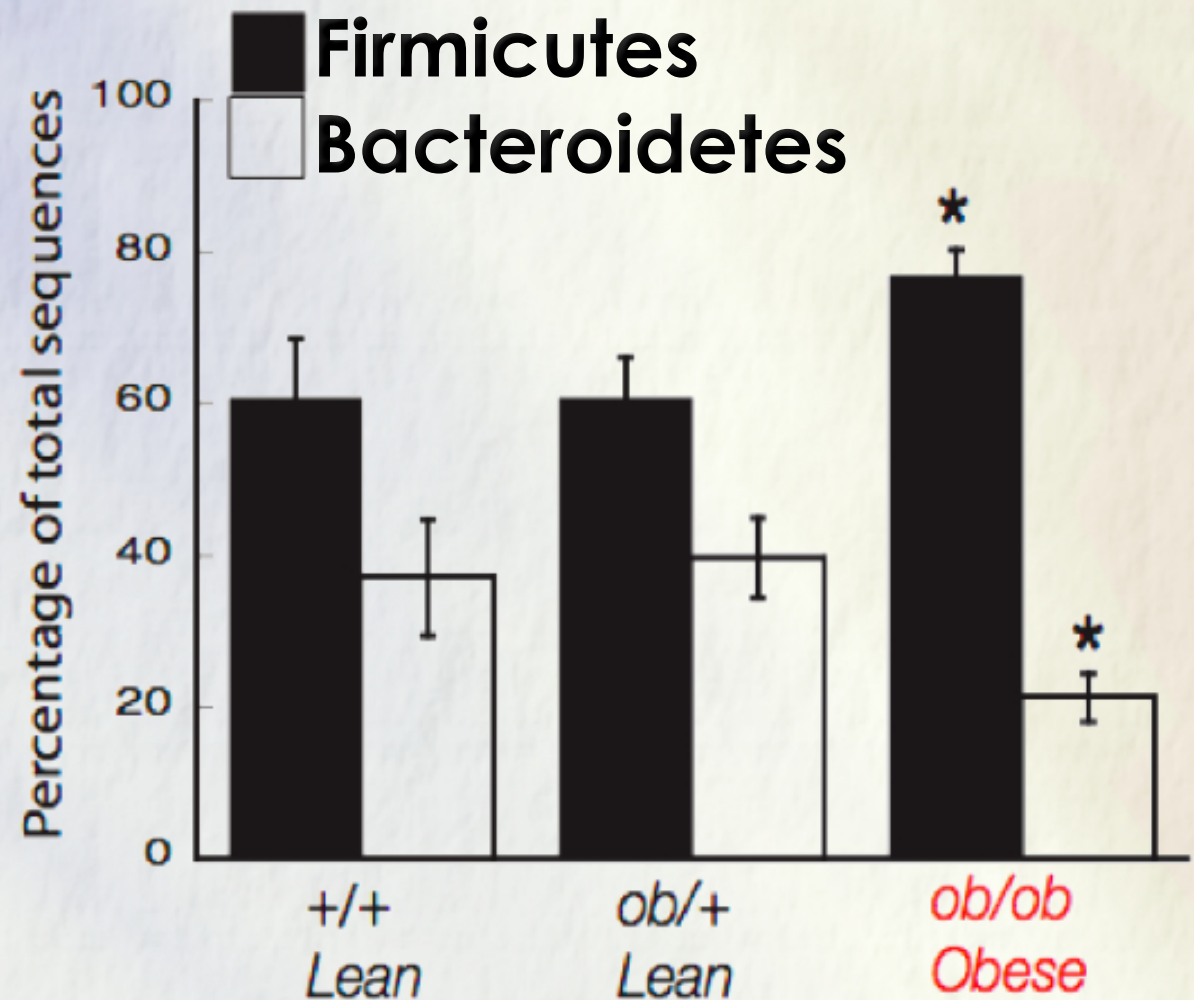
Can't do Koch's Postulates in humans, but can use mice



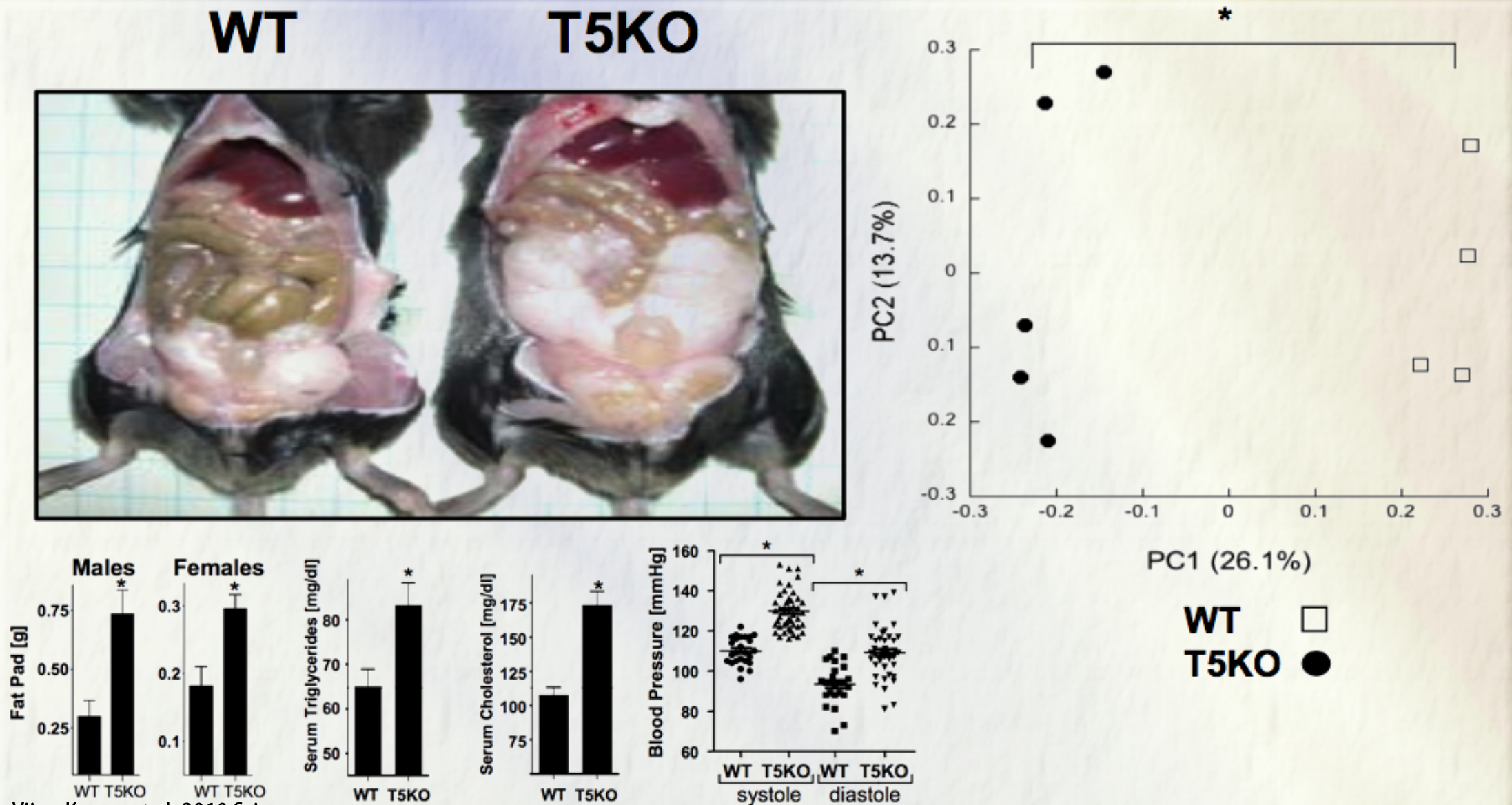
**Gnotobiotic isolation units
in Jeff Gordon's lab at
Wash U**



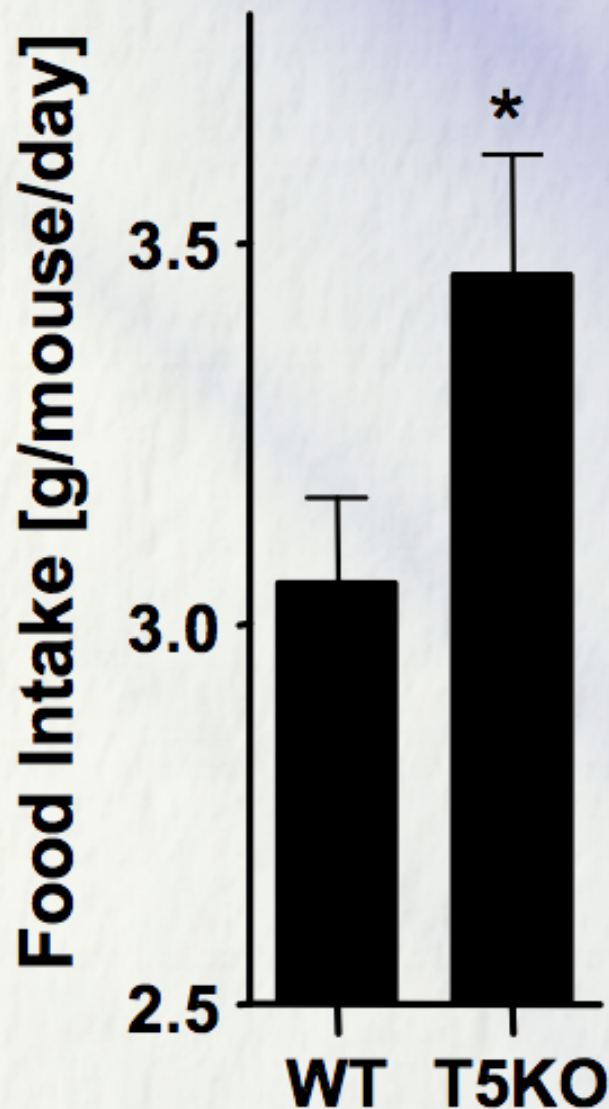
Do differences in the microbiome matter? Ask a fat mouse...



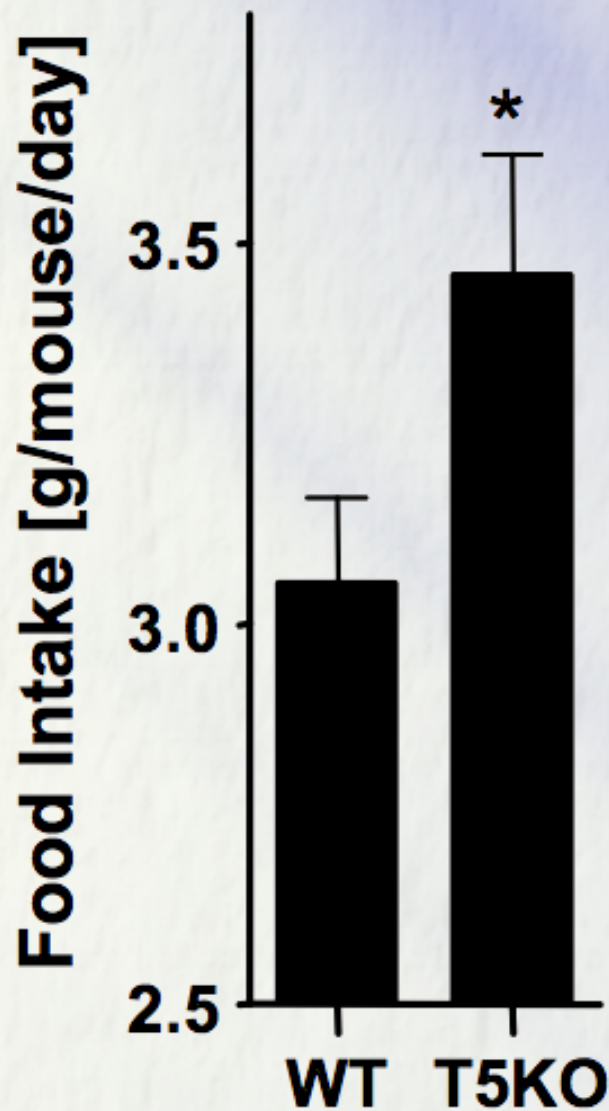
TLR5 mutant mice get fat for a different reason...



**...their transmissible gut microbes
make them want to eat more!**



...their transmissible gut microbes make them want to eat more!

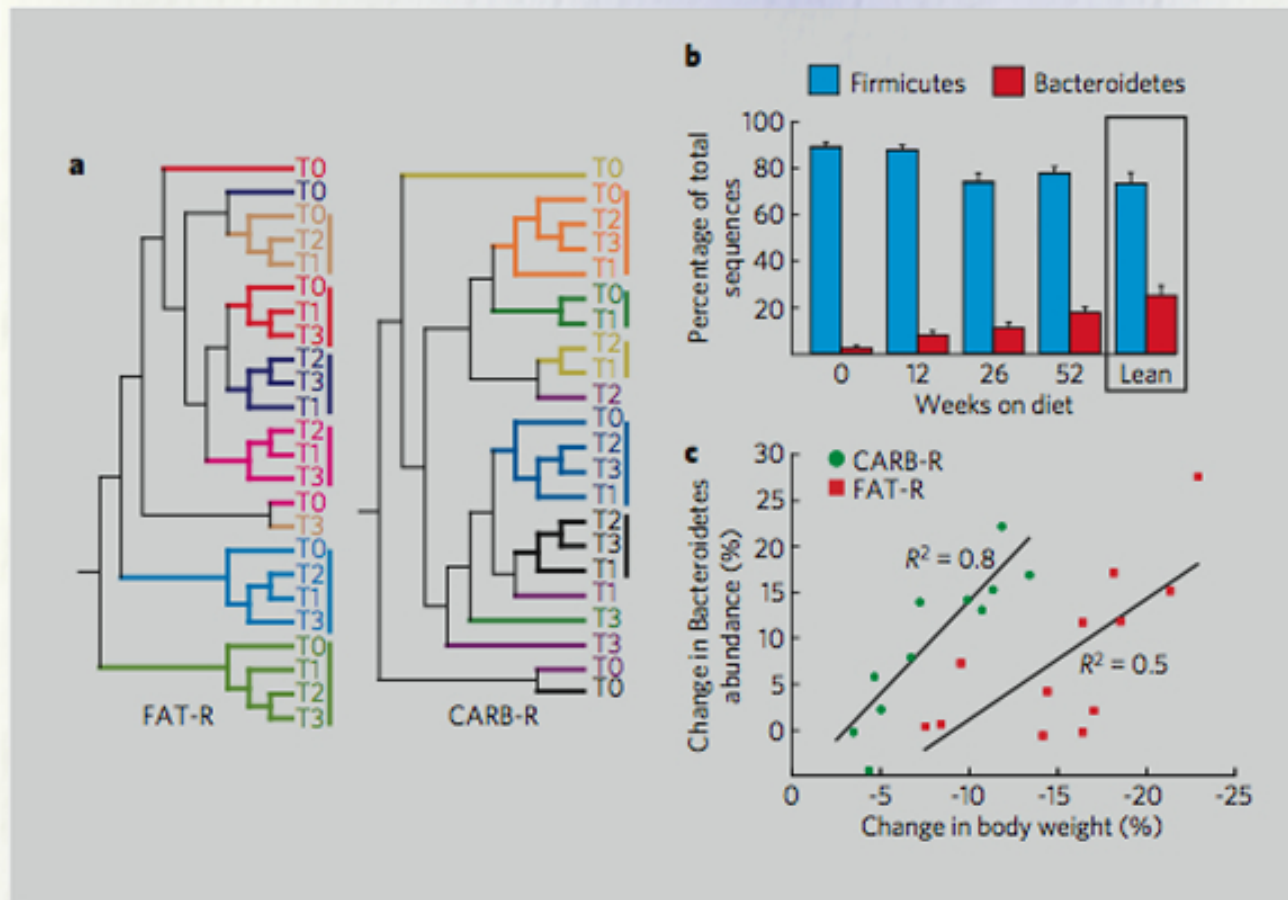


Do the results extend to humans?

Apparently so...

MICROBIAL ECOLOGY

Human gut microbes associated with obesity



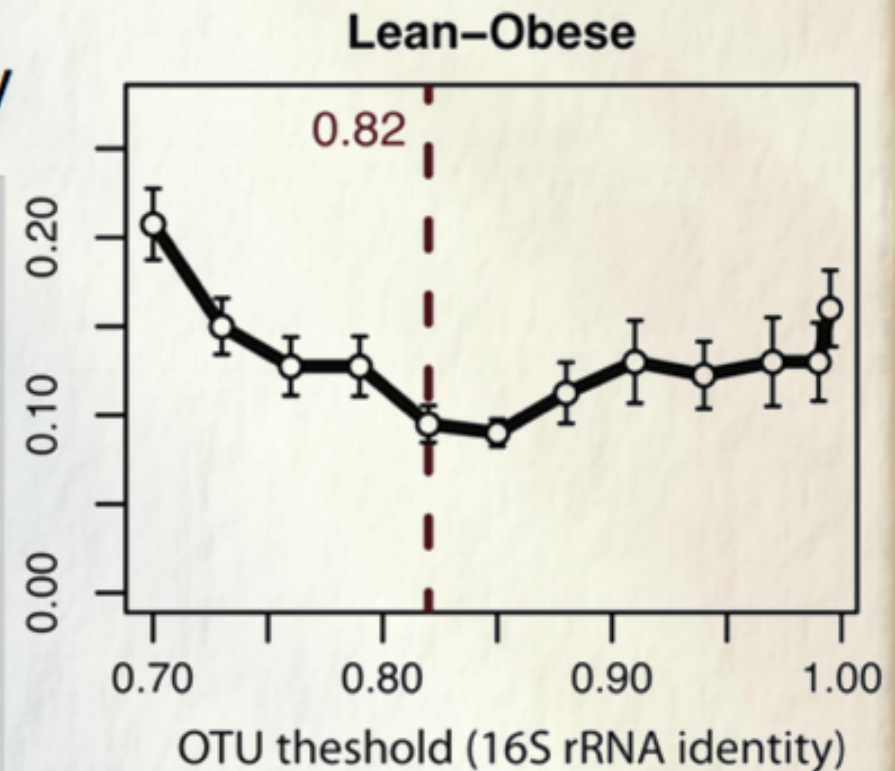
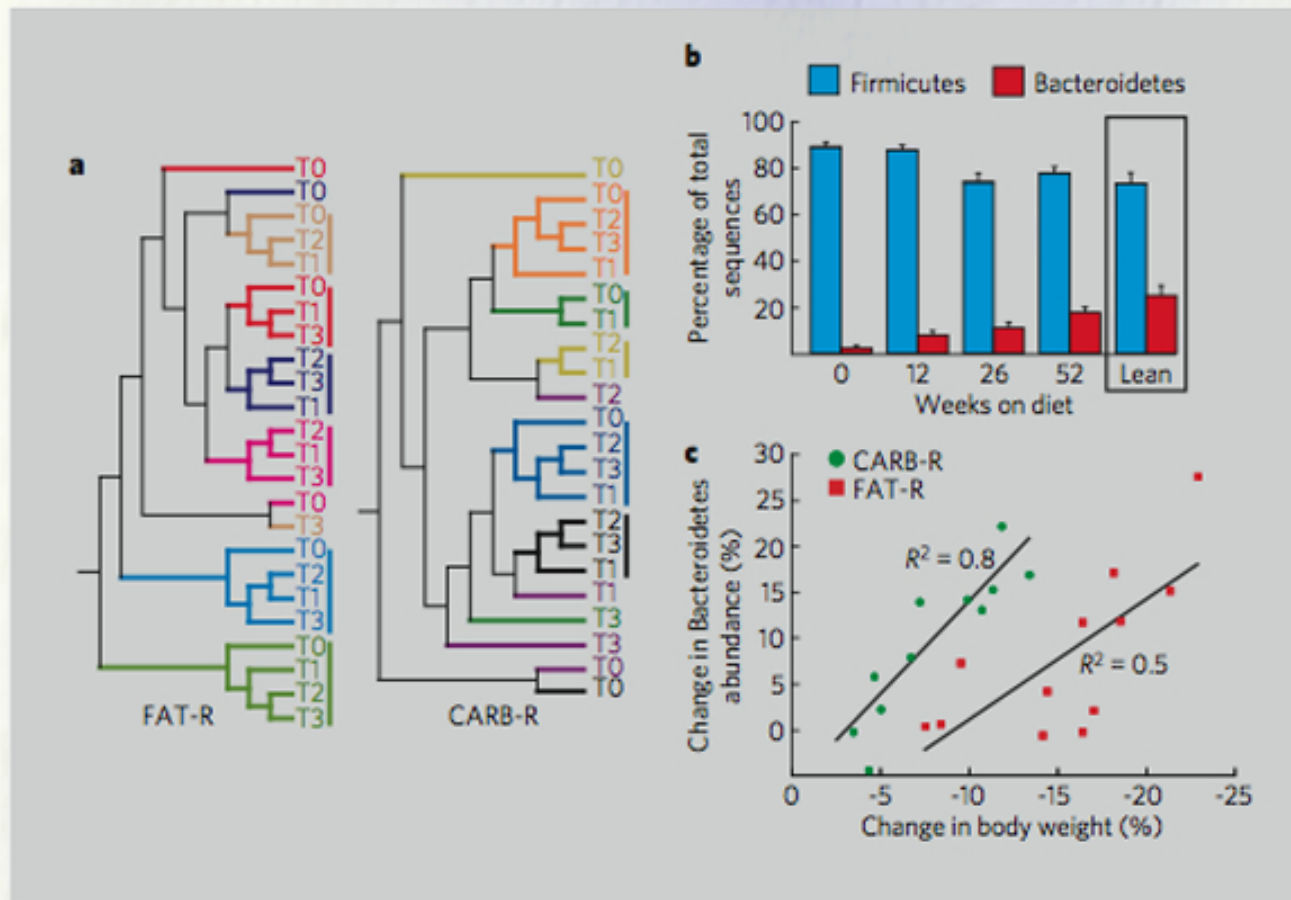
Ruth E. Ley, Peter J. Turnbaugh, Samuel Klein,
Jeffrey I. Gordon

Do the results extend to humans?

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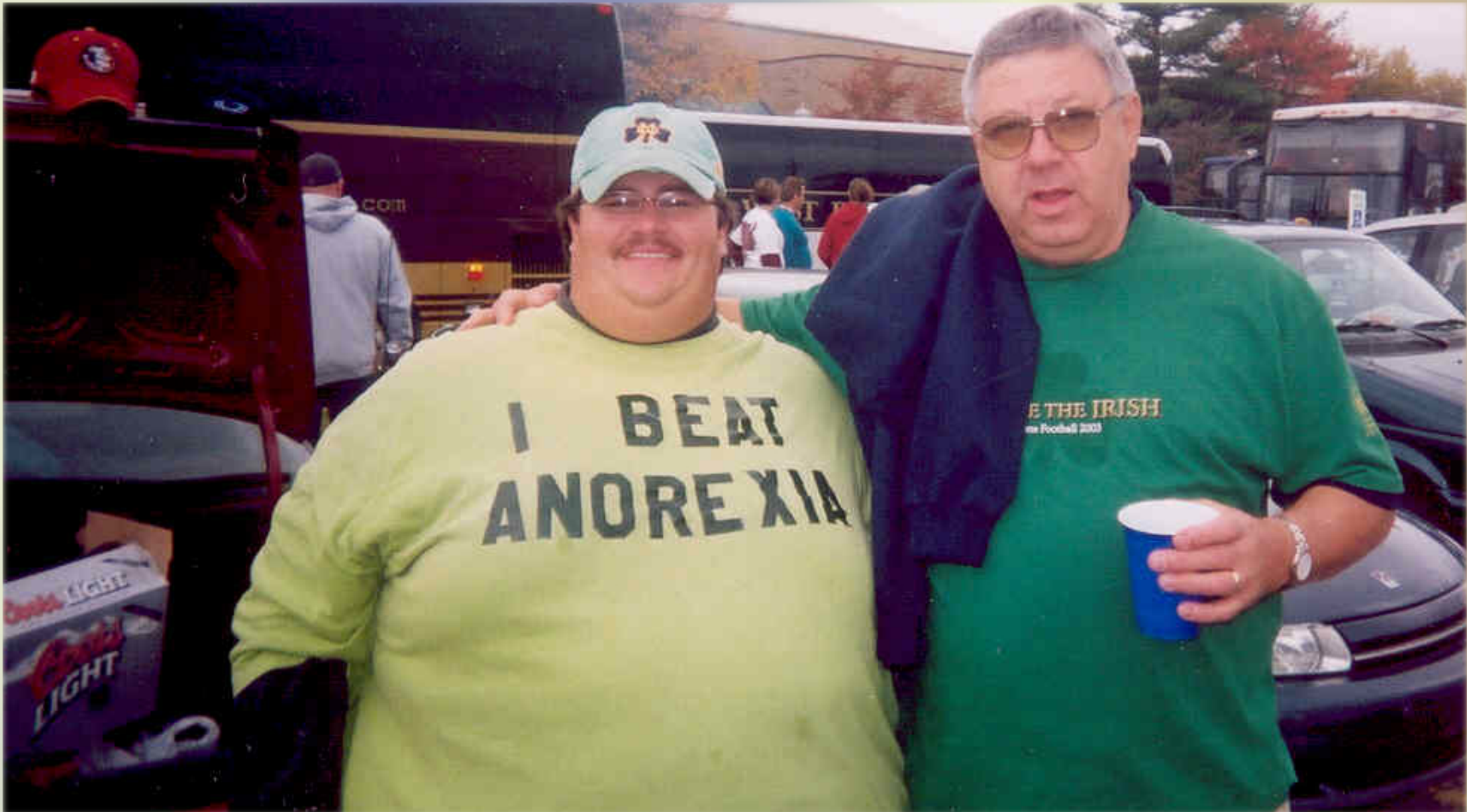
MICROBIAL ECOLOGY

Human gut microbes associated with obesity



Classify lean/obese with 90% accuracy by microbiome

...so can we change the
microbiome to cure disease...?



Future directions: personalized medicine in developing nations?



Photo: Tanya Yatsunenko, Malawi 2009

Future directions: personalized medicine in developing nations?



Photo: Tanya Yatsunenko, Malawi 2009



Cell phones
ubiquitous in
Malawi due to
Moore's Law...

Future directions: personalized medicine in developing nations?



Photo: Tanya Yatsunenko, Malawi 2009



**Cell phones
ubiquitous in
Malawi due to
Moore's Law...**

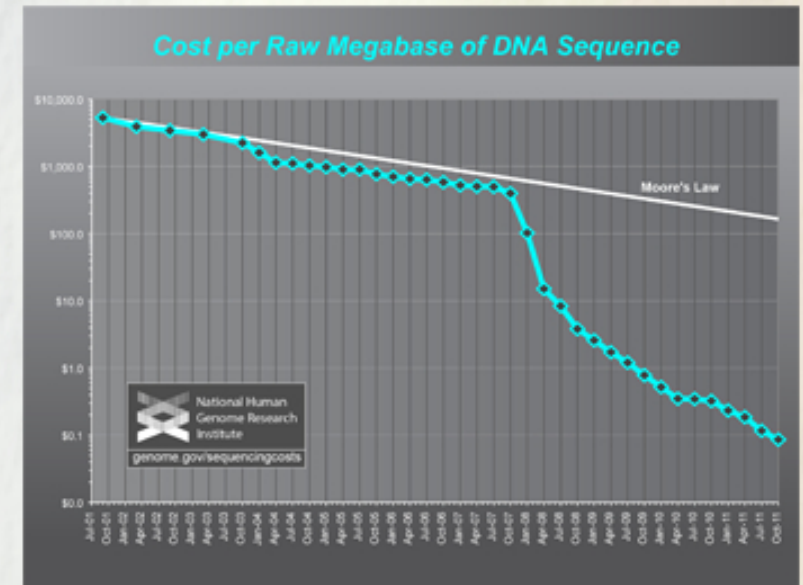
**...and not just
in Malawi, but
everywhere...**



Future directions: personalized medicine in developing nations?



Cell phones ubiquitous in Malawi due to Moore's Law...



...will DNA sequencing follow?

Pilot studies in humanized mice

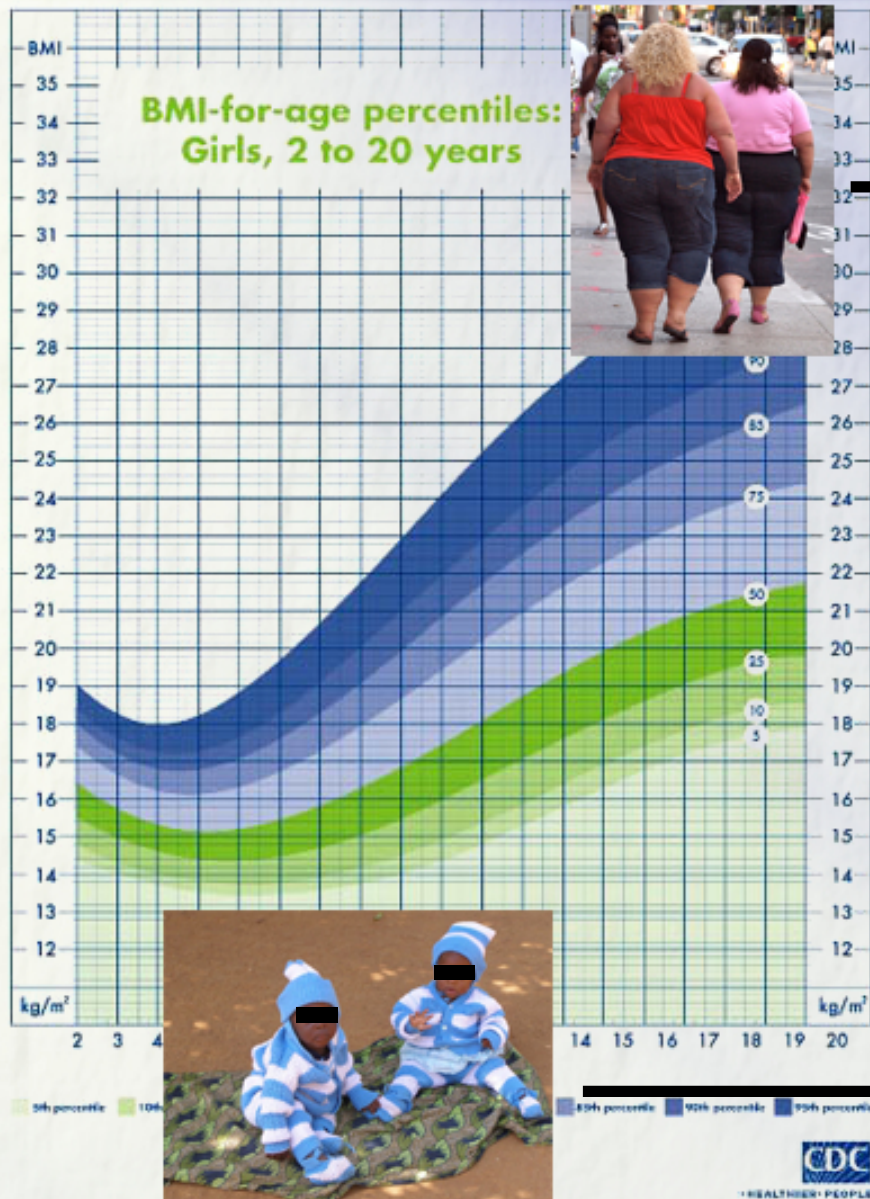


Photo: Tanya Yatsunenکو, Malawi 2009; collaboration with Gordon lab

Pilot studies in humanized mice: input microbes, diet change BMI

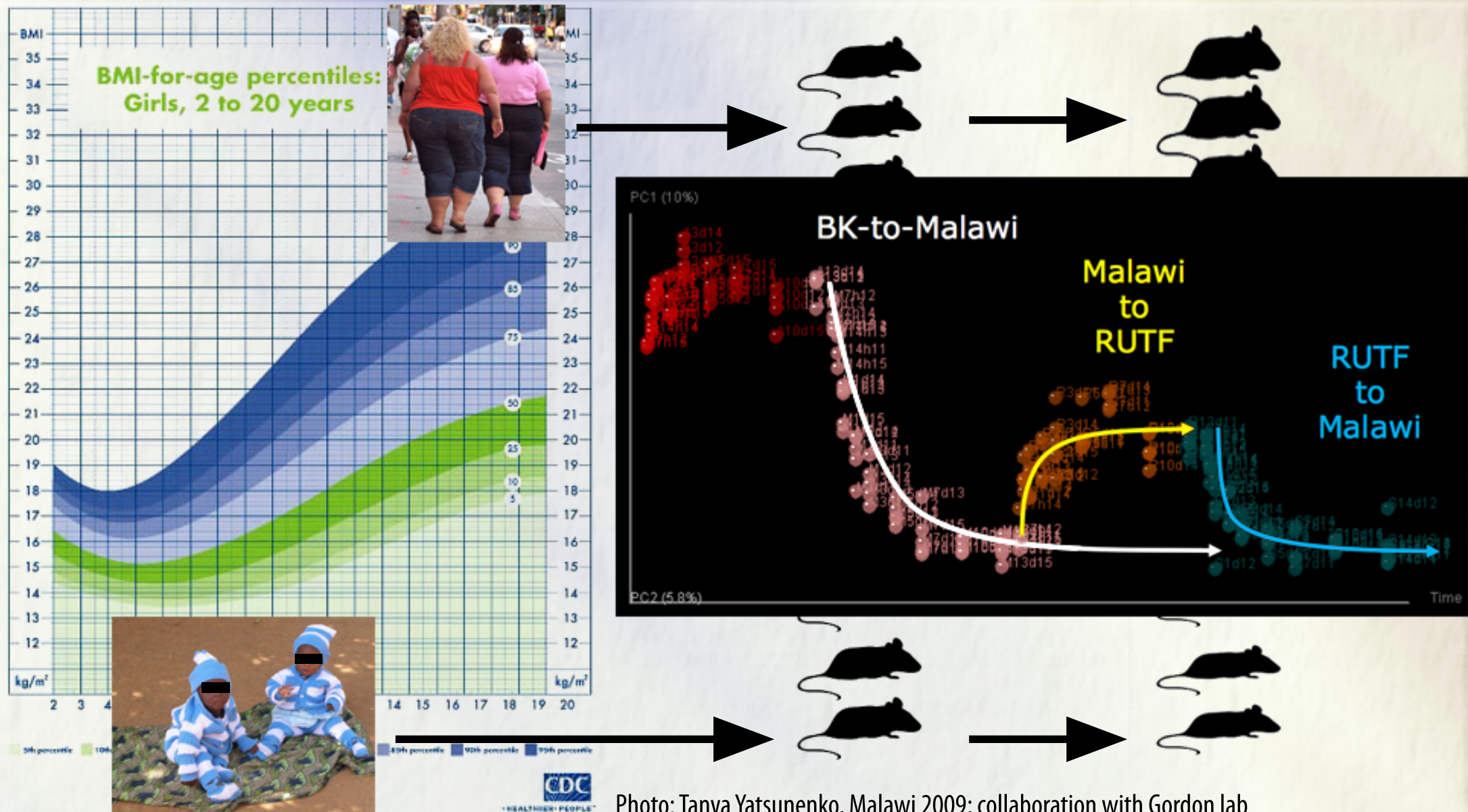
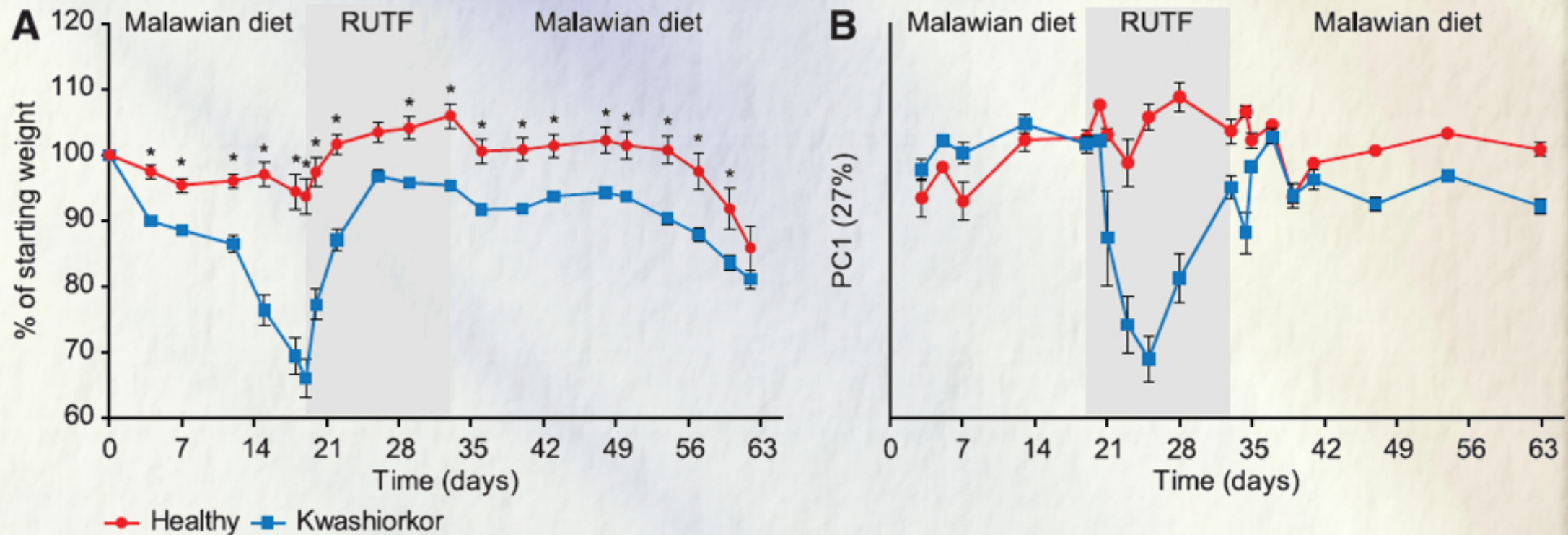


Photo: Tanya Yatsunenکو, Malawi 2009; collaboration with Gordon lab

...and individual phenotypes can be transplanted into mice



Culture collections permit mechanistic hypothesis tests

PNAS

Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice

Andrew L. Goodman¹, George Kallstrom, Jeremiah J. Faith, Alejandro Reyes, Aimee Moore, Gautam Dantas, and Jeffrey I. Gordon²

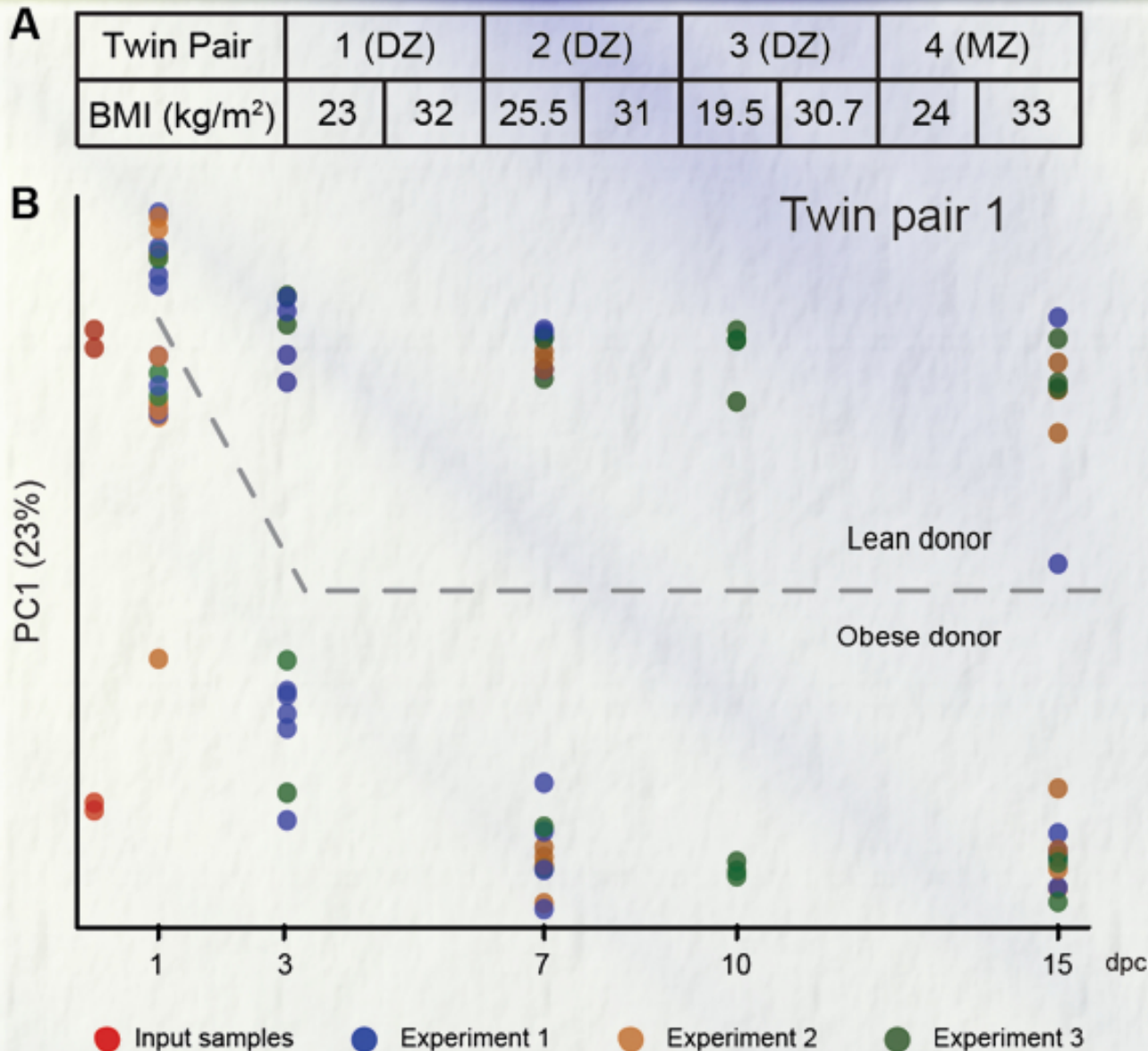
Center for Genome Science and Systems Biology, Washington University School of Medicine, St. Louis, MO 63108

Contributed by Jeffrey I. Gordon, February 24, 2011 (sent for review January 21, 2011)

The Long-Term Stability of the Human Gut Microbiota

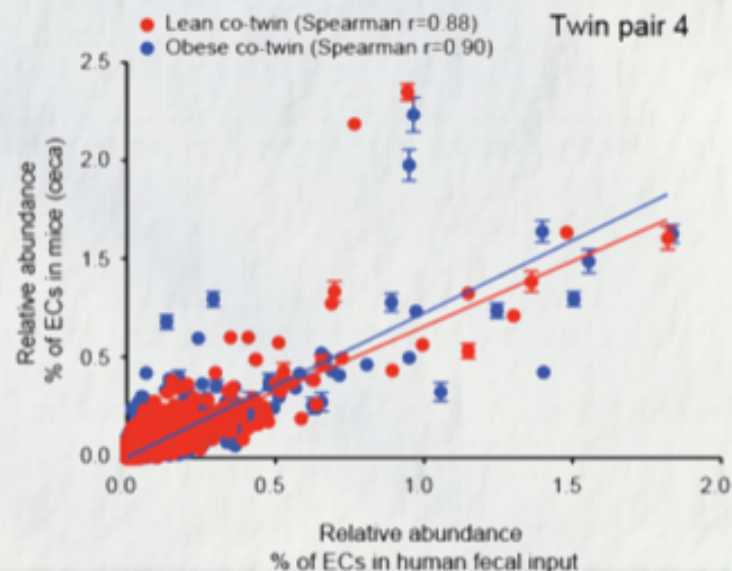
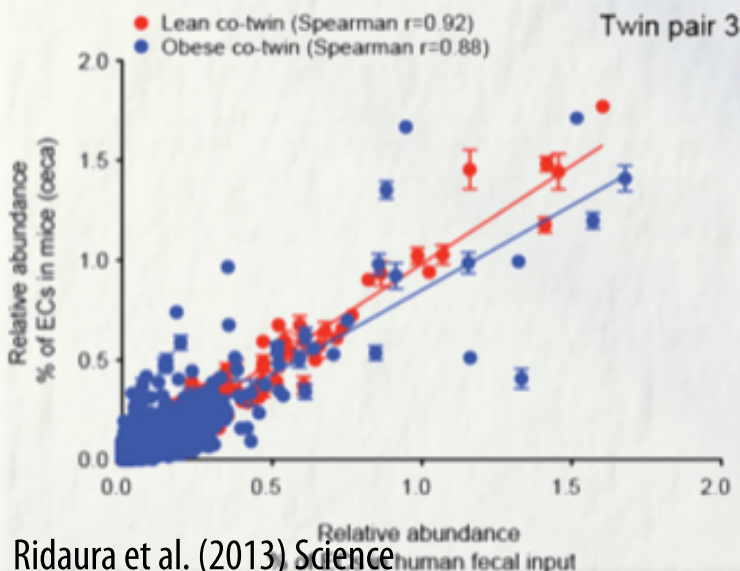
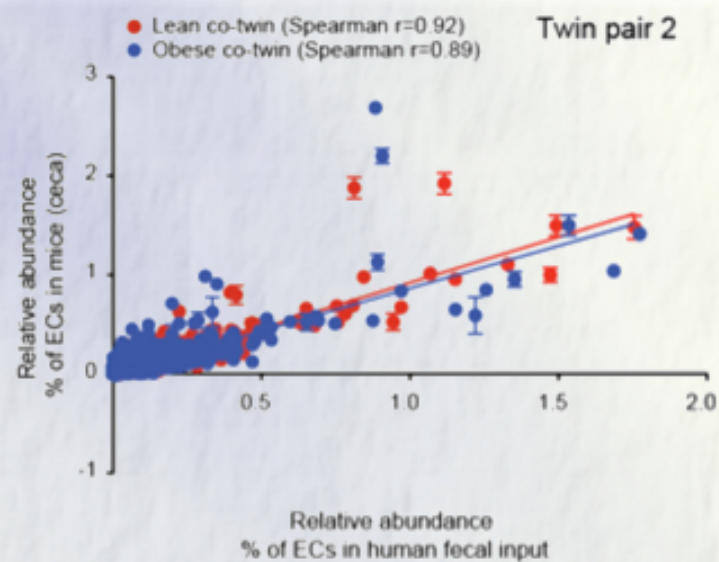
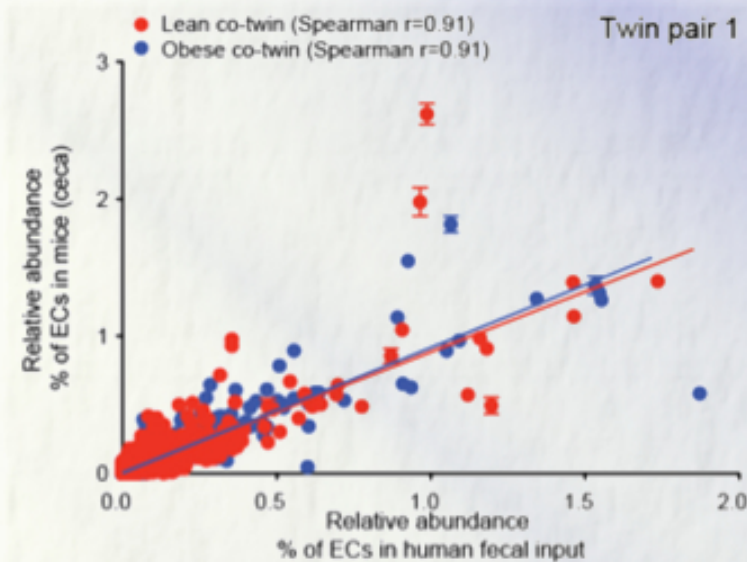
Jeremiah J. Faith,^{1*} Janaki L. Guruge,¹ Mark Charbonneau,¹ Sathish Subramanian,¹ Henning Sedorf,¹ Andrew L. Goodman,^{1†} Jose C. Clemente,^{3*} Rob Knight,^{3,4,5} Andrew C. Heath,² Rudolph L. Leibel,⁶ Michael Rosenbaum,⁶ Jeffrey I. Gordon^{1‡}

The same type of transplant also works for obesity phenotypes



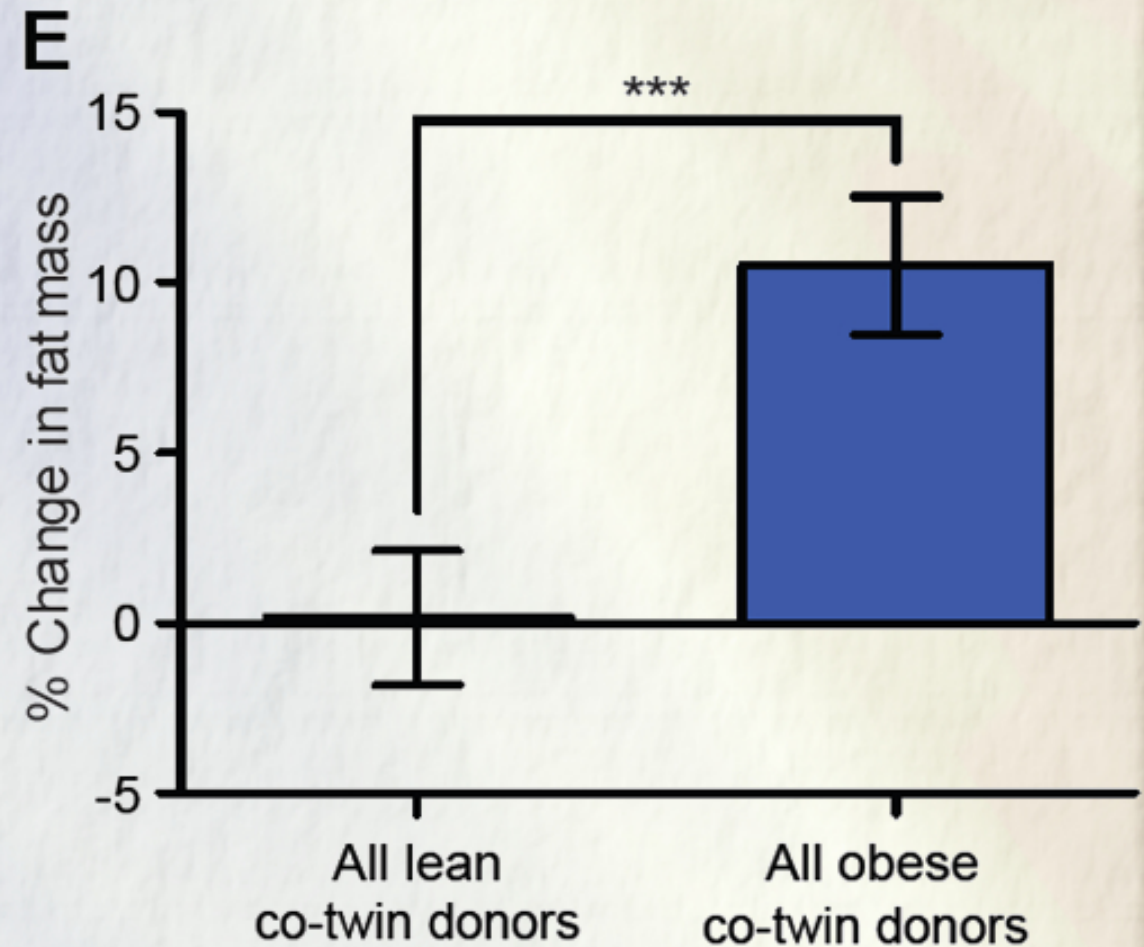
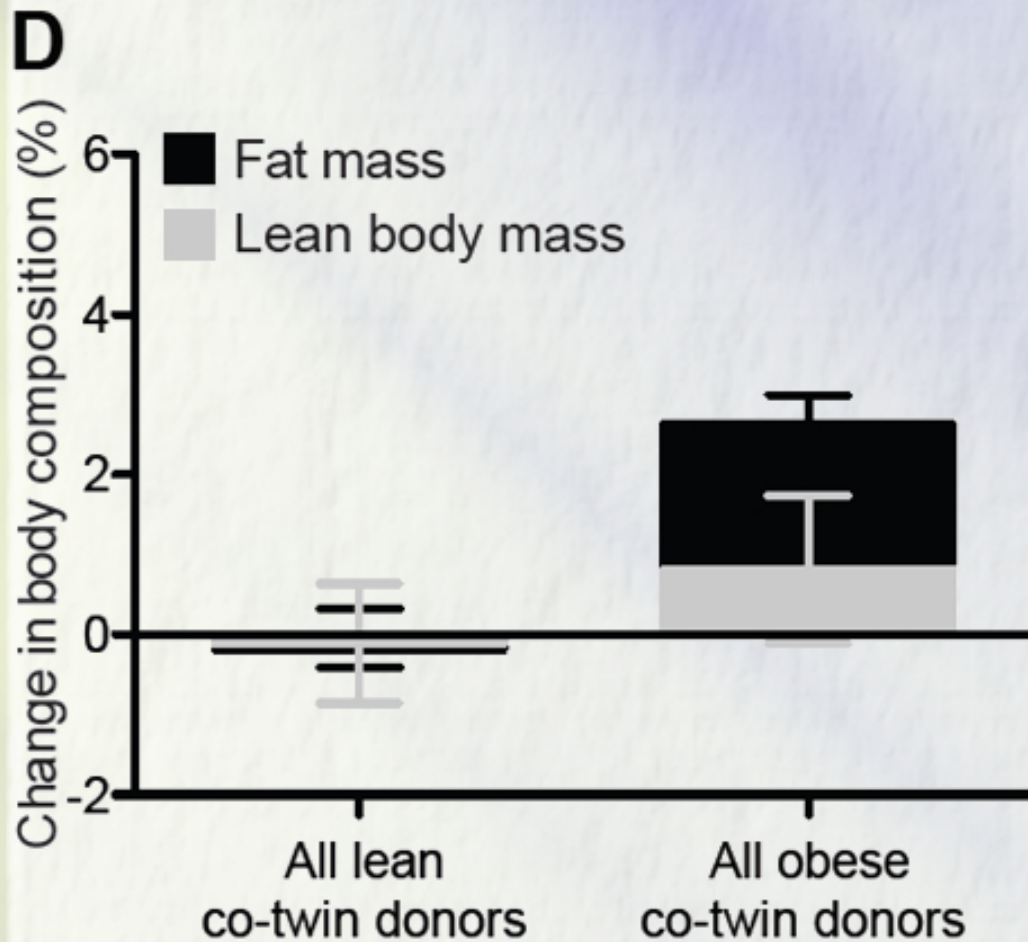
Twins discordant for obesity stably transplant different microbes into germ-free mice

The functional stability of the transplant is excellent



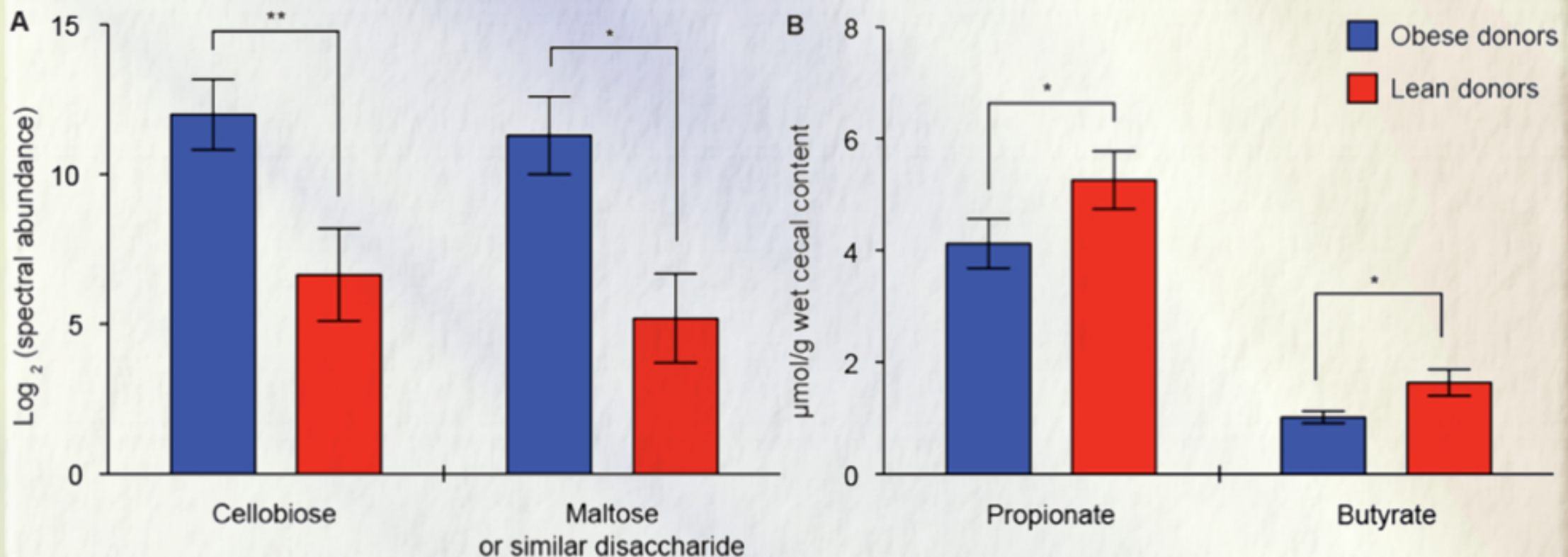
ECs are highly correlated in donor and recipient for all individuals

Body composition and fat mass depend on donor

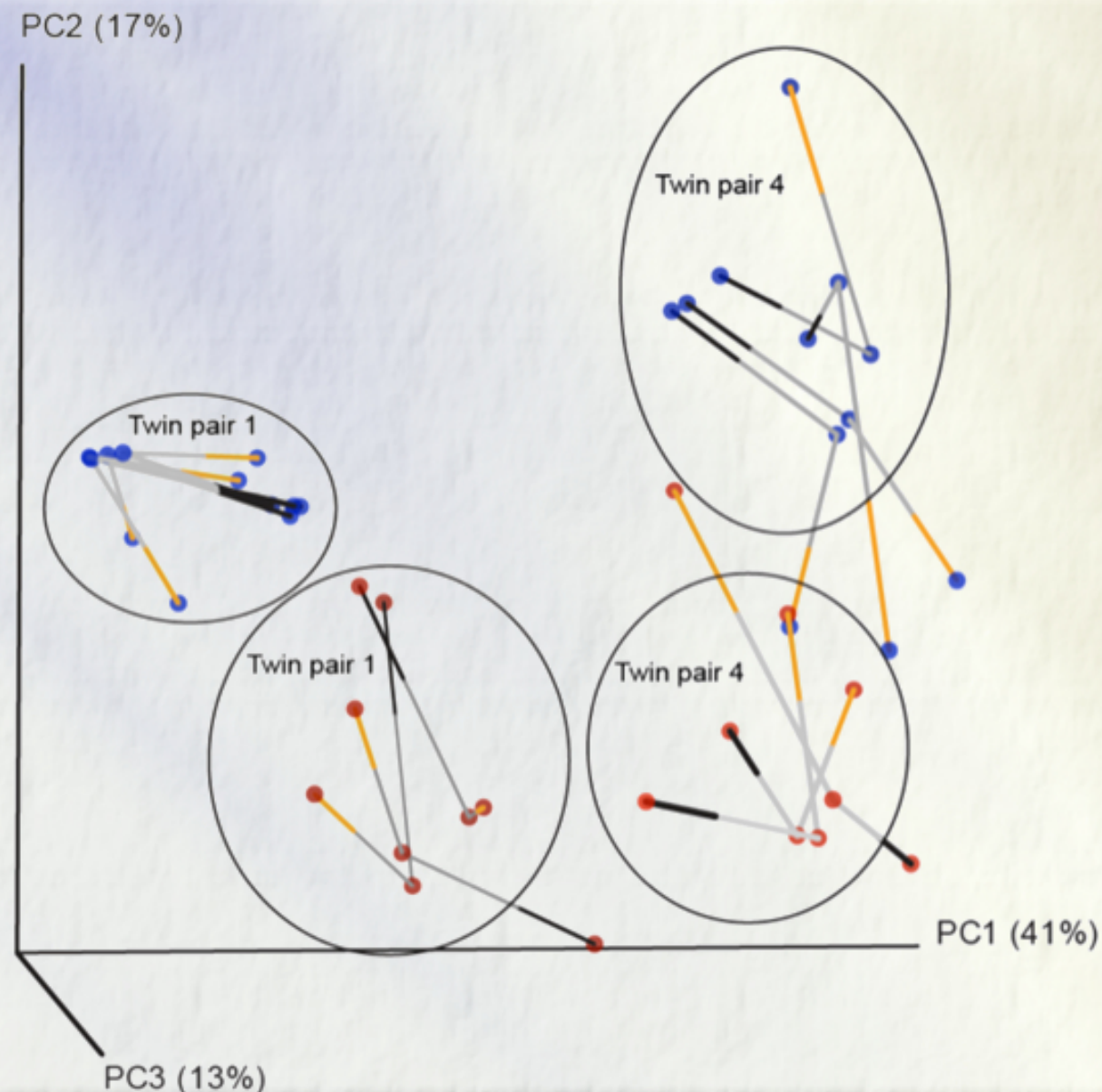


* Two-Way ANOVA, significant donor effect driven by the difference in adiposity

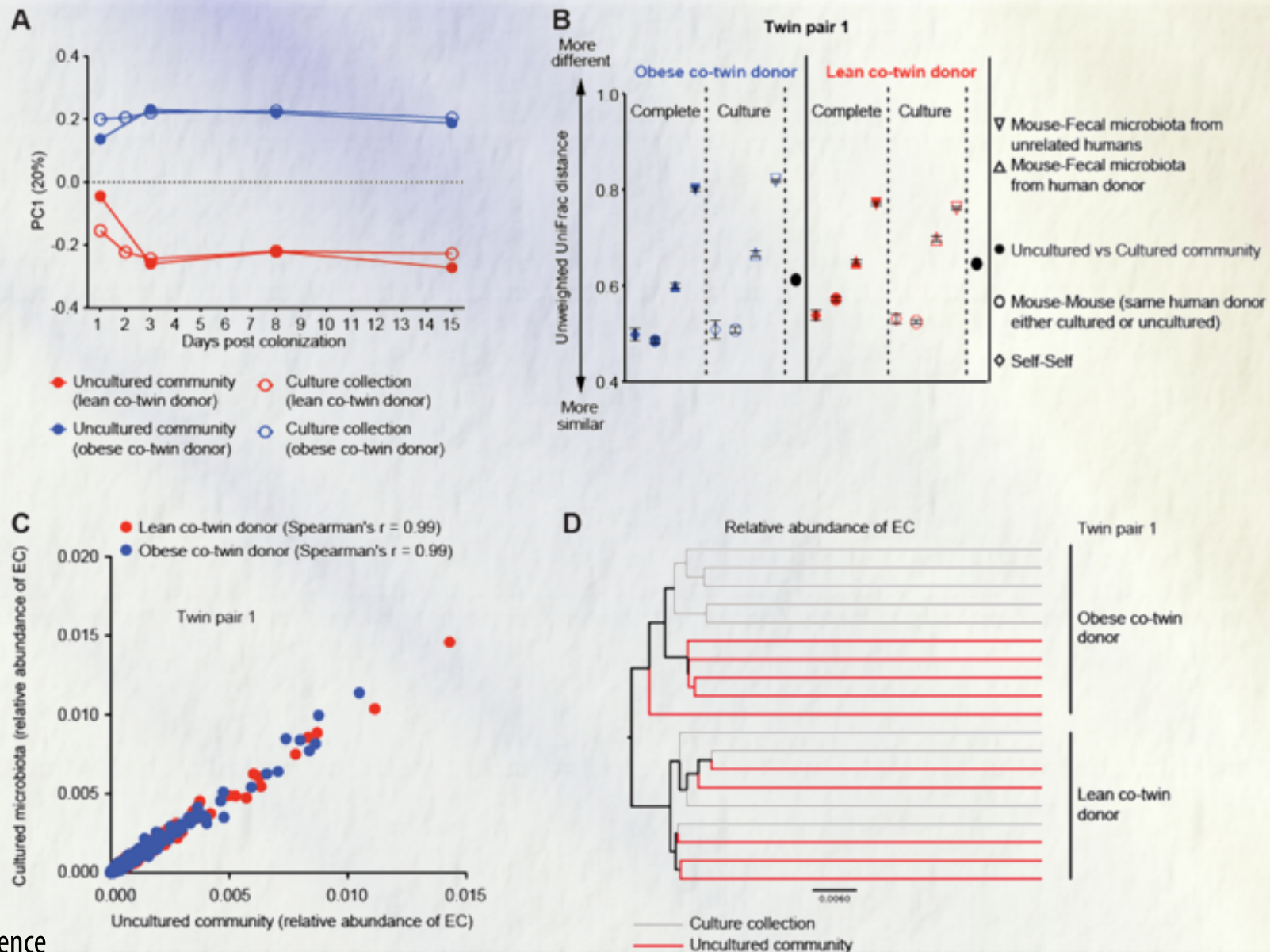
SCFAs upregulated in mice with lean donor



Multi-omics levels agree with each other to surprising degree



Results from culture collections agree with primary specimens



How can we extend this vision to the entire microbial world?

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**G. Evelyn
Hutchinson**

How can we extend this vision to the entire microbial world?



**G. Evelyn
Hutchinson**

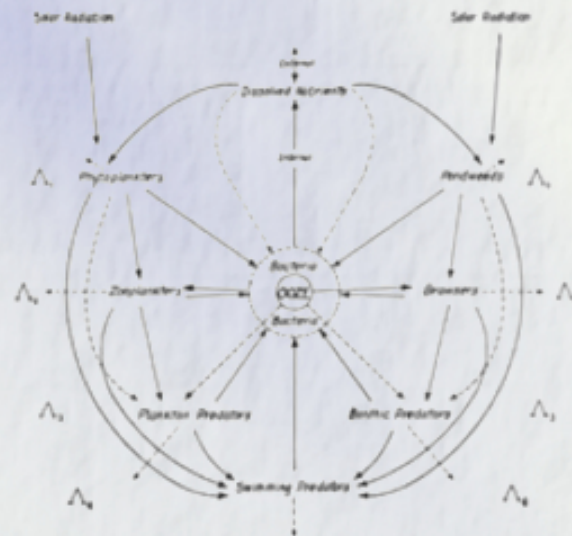


FIG. 1. Generalized invasion feedback relationships (after Lindeman, '41b).

**Niche space:
hypervolume**

How can we extend this vision to the entire microbial world?



**G. Evelyn
Hutchinson**

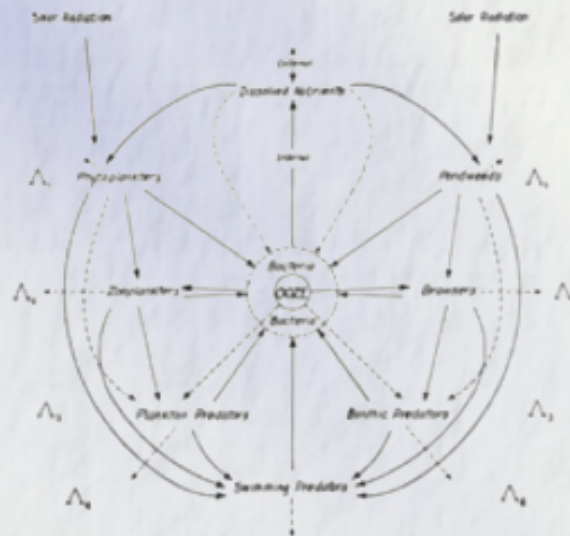


FIG. 1. Generalized lacustrine food-cycle relationship (after Lindeman, '41b).

**Niche space:
hypervolume**



Predict dynamics

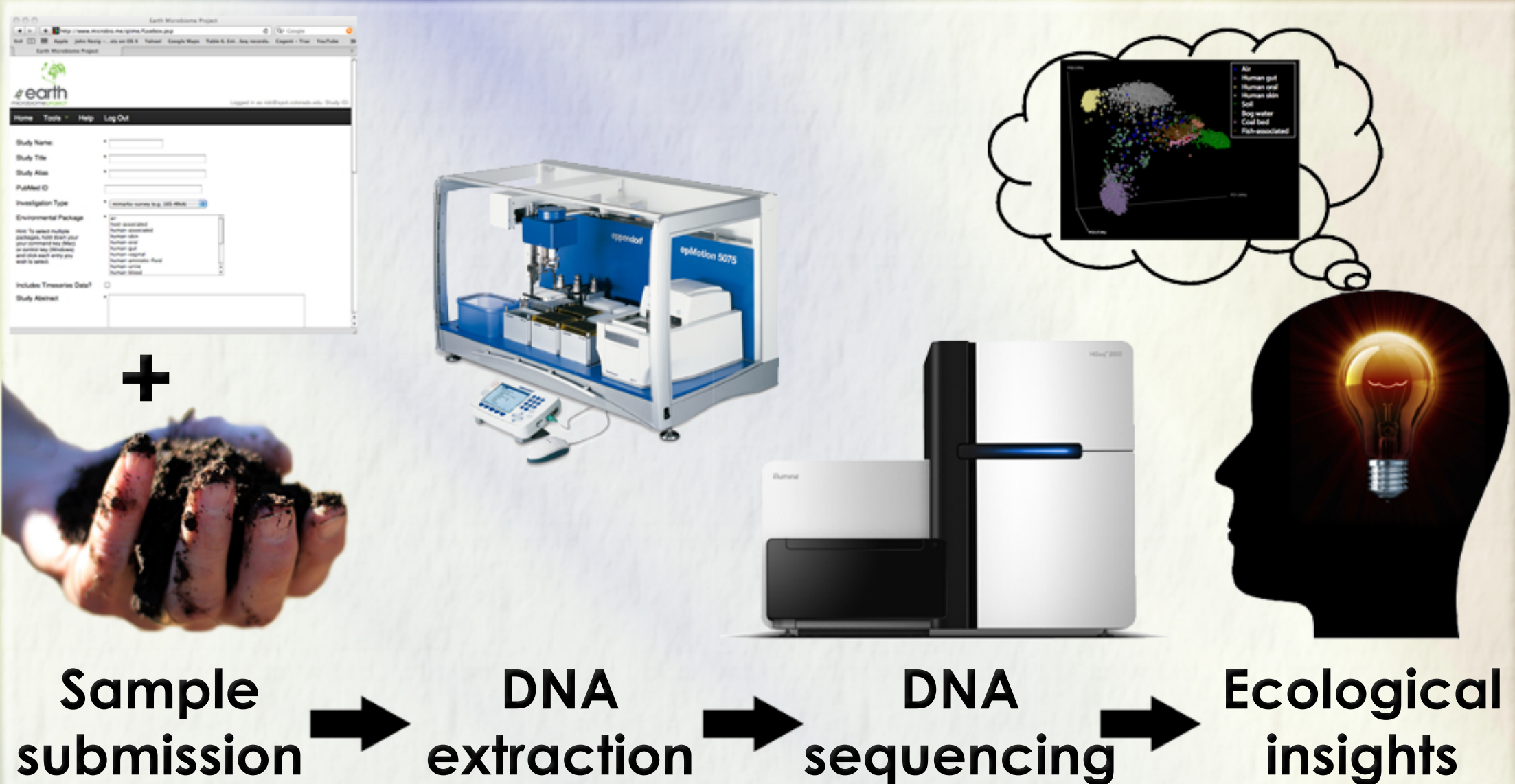
To address these questions, we held series of EMP meetings

The First International EMP (Earth Microbiome Project) Conference

13th-15th, June, 2011 Shenzhen, China



EMP now provides framework for samples through data analysis



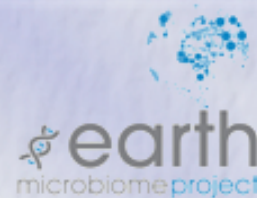
The community response to the EMP has been truly inspiring

EMP Structure:

Steering committee (10 members)

Advisory committee (45 members)

Participants (>100 members)



>100 members, 30 institutes, 12 countries

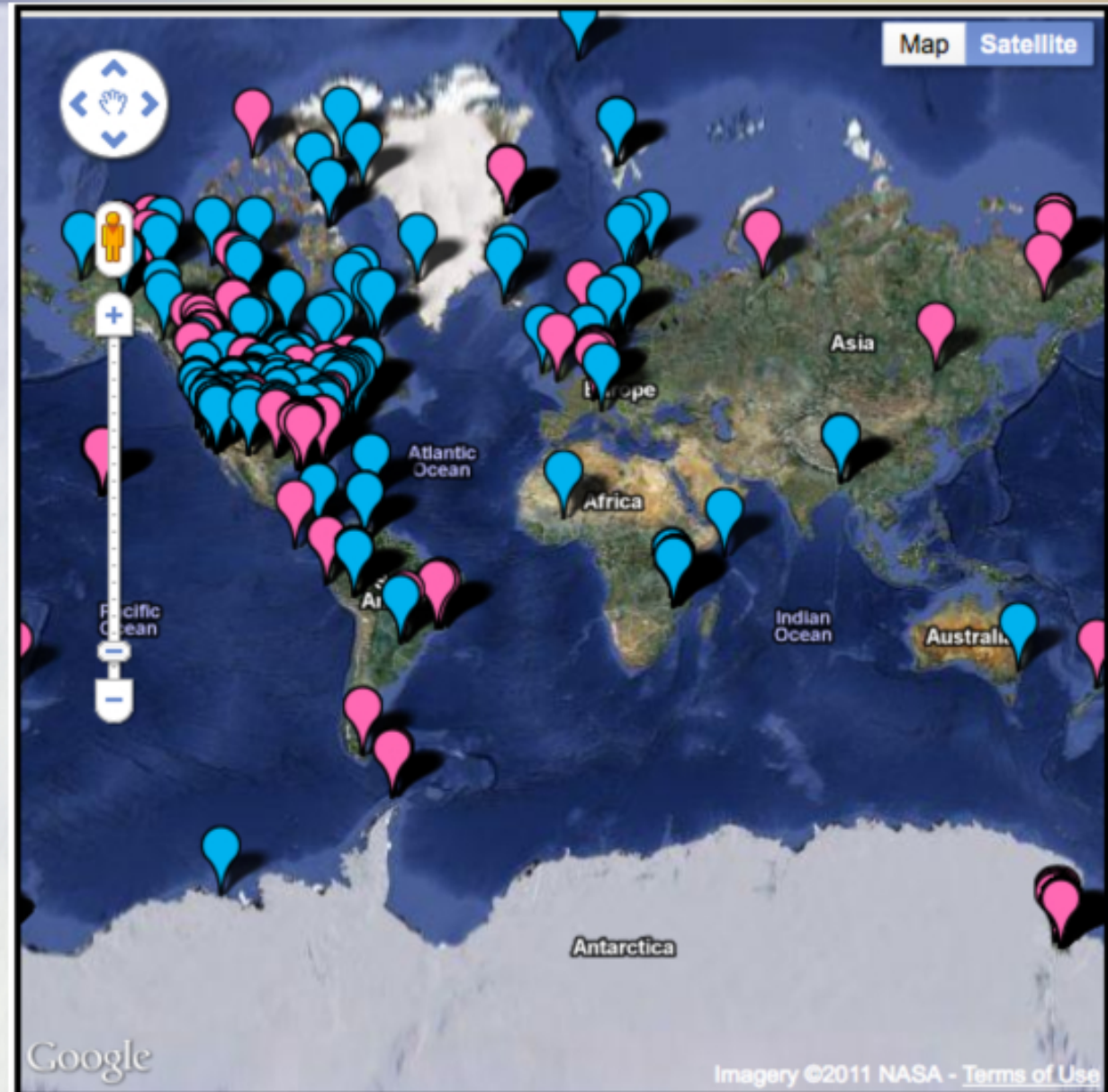
Janet Jansson, Rob Knight, Jack A. Gilbert, Bin Hu, Noah Fierer, Folker Meyer, Rick Stevens, Jonathan A Eisen, Jed Furhman, Mark Bailey, Jeff Gordon, Norman Pace, Jeroen Raes, James Tiedje, Ruth Ley, Noah Fierer, Dawn Field, Nikos Kyrpides, Frank-Oliver Glockner, Hans-Peter Klenk, K. Eric Wommack, Elizabeth M. Glass, Kathryn Docherty, Rachel Gallery, George Kowalchuk, Mark Bailey, Dion Antonopoulos, Pavan Balaji, C. Titus Brown, Christopher T. Brown, Narayan Desai, Dirk Evers, Wu Feng, Daniel Huson, James Knight, Eugene Kolker, Kostas Konstantindis, Joel Kostka, Rachel Mackelprang, Alice McHardy, Christopher Quince, Alexander Sczyrba, Ashley Shade, And you?



We have processed thousands of samples from around the world

Currently >60,000 samples pledged from >100 researchers

Selected based on rich standards-compliant metadata, ability to inform about processes on different spatial and temporal scales



...what principles can we derive that cross systems and scales?



Grinnell Glacier from Mt. Gould



1938
Hileman
photo/ GNP
Archives

1981
Key/ USGS
photo

1998
Fagre/ USGS
photo

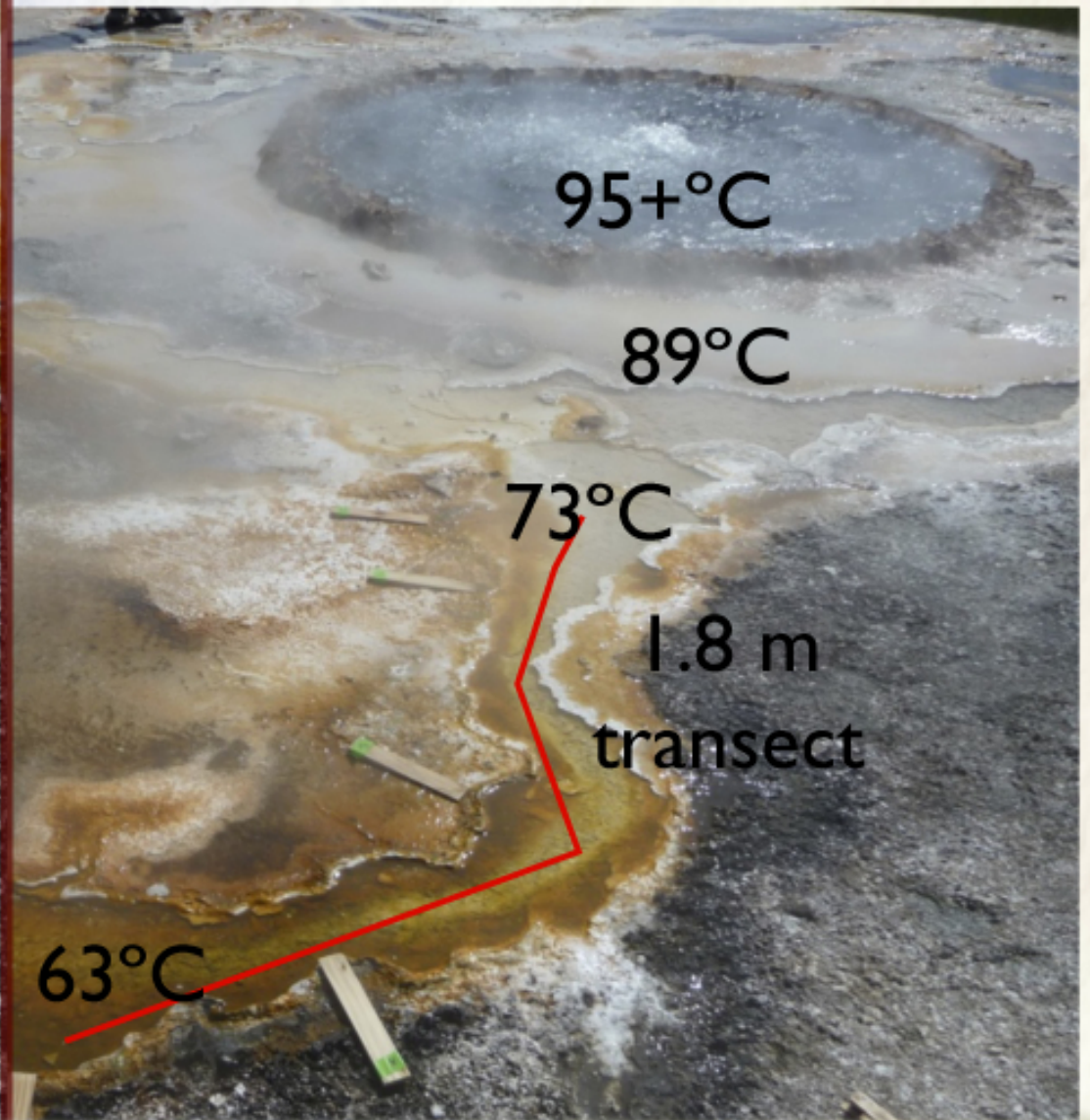
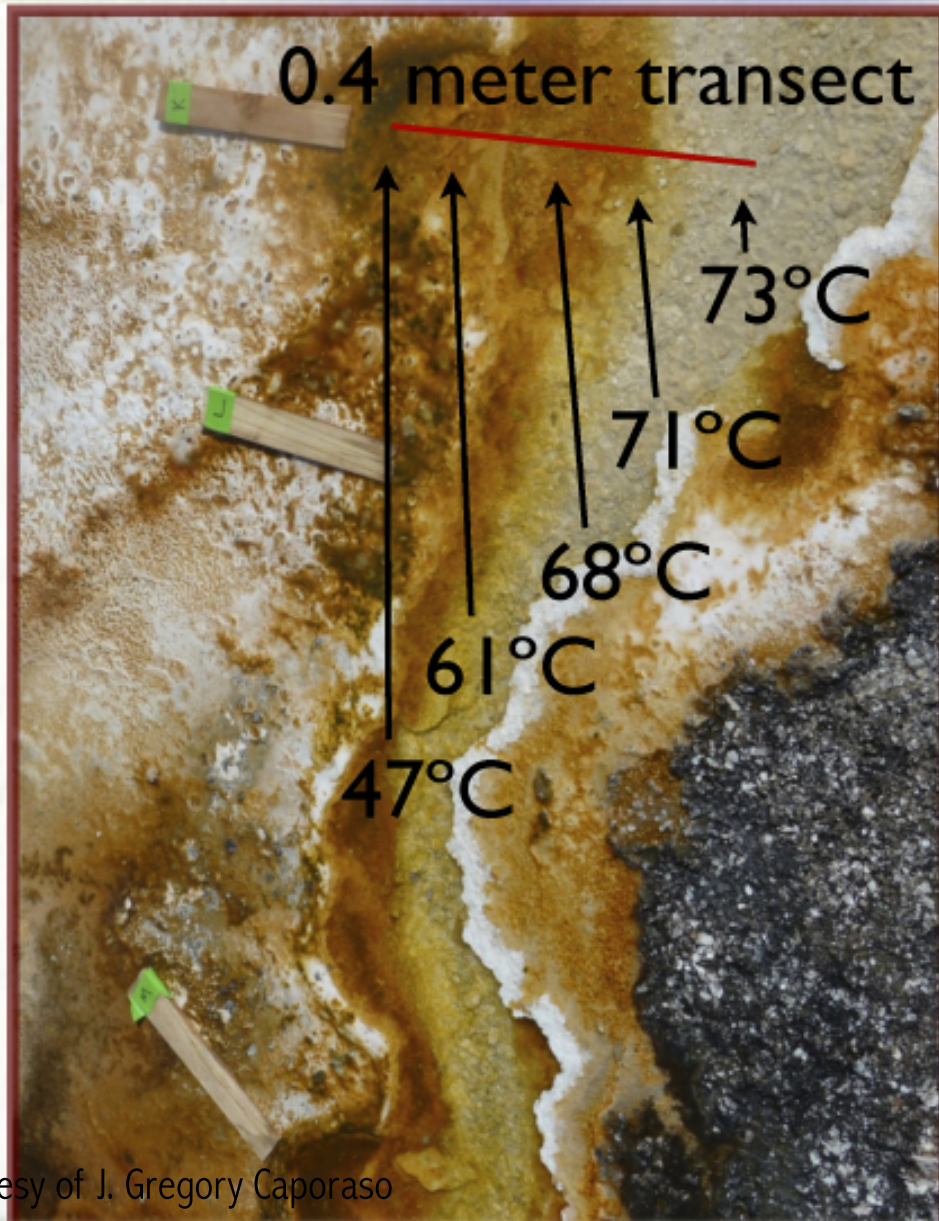
2005
Reardon/
USGS photo

Gradients in environments such as Yellowstone...



Courtesy of J. Gregory Caporaso

...are reproducible across highly variable spatial scales...



**...including the scale transformations
critical for translational medicine**



David Deen © 2006



GSC standards and EMP allow unprecedented data integration



EMP pilot studies

Annie Moore & Colleagues sampling cenote gradients, Yucatan, Mexico



EMP pilot studies



Extreme environments:
Acidic hot springs, Yellowstone—
contributed by Greg Caparoso

Merlot Microbiome:
High school volunteers
Long Island



EMP pilot studies



Chris Meyer, French Polynesia, sampling water and sediment at the LTER sites on the tropical island and reefs of Moorea.



EMP pilot studies



Contributed by Josh Neufeld Univ. Waterloo, Canada

EMP pilot studies

Thar Desert (Great Indian Desert)



Arctic Permafrost



Sampling desert sand, Subramanya Rao



Antarctica Dry Valleys



EMP pilot studies

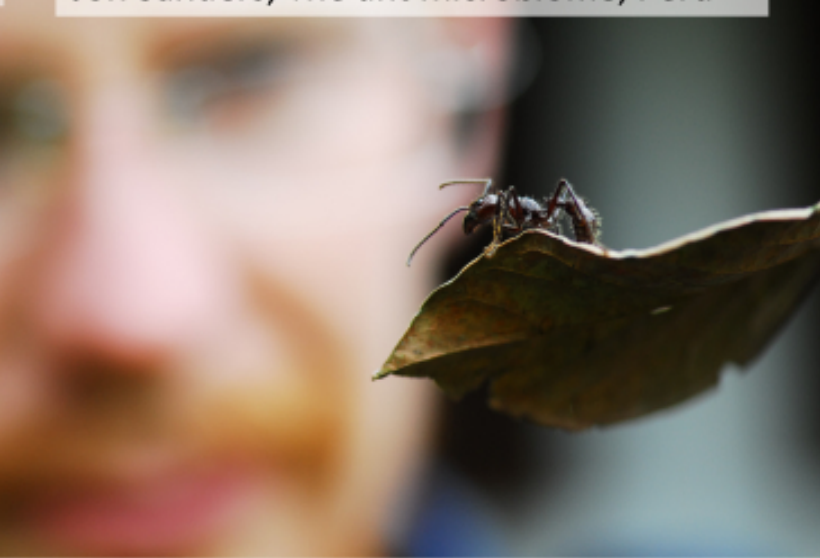
Beck Wehrle, The Iguana Microbiome



Corrie Moreau, The ant microbiome - Brazil

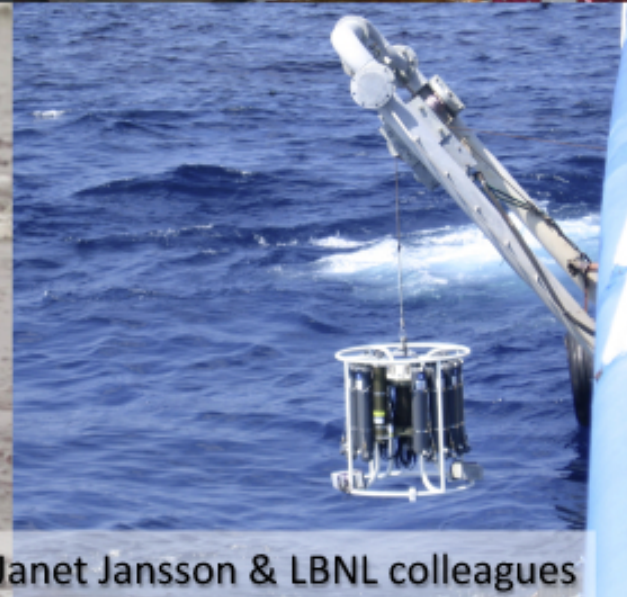
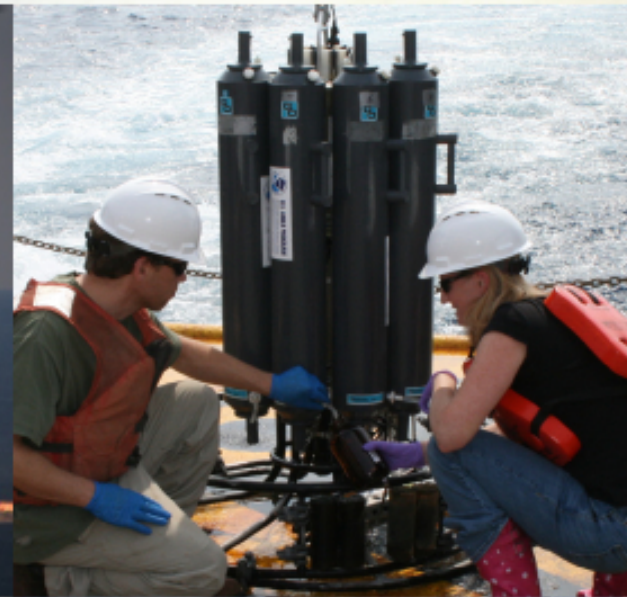


Jon Sanders, The ant microbiome, Peru



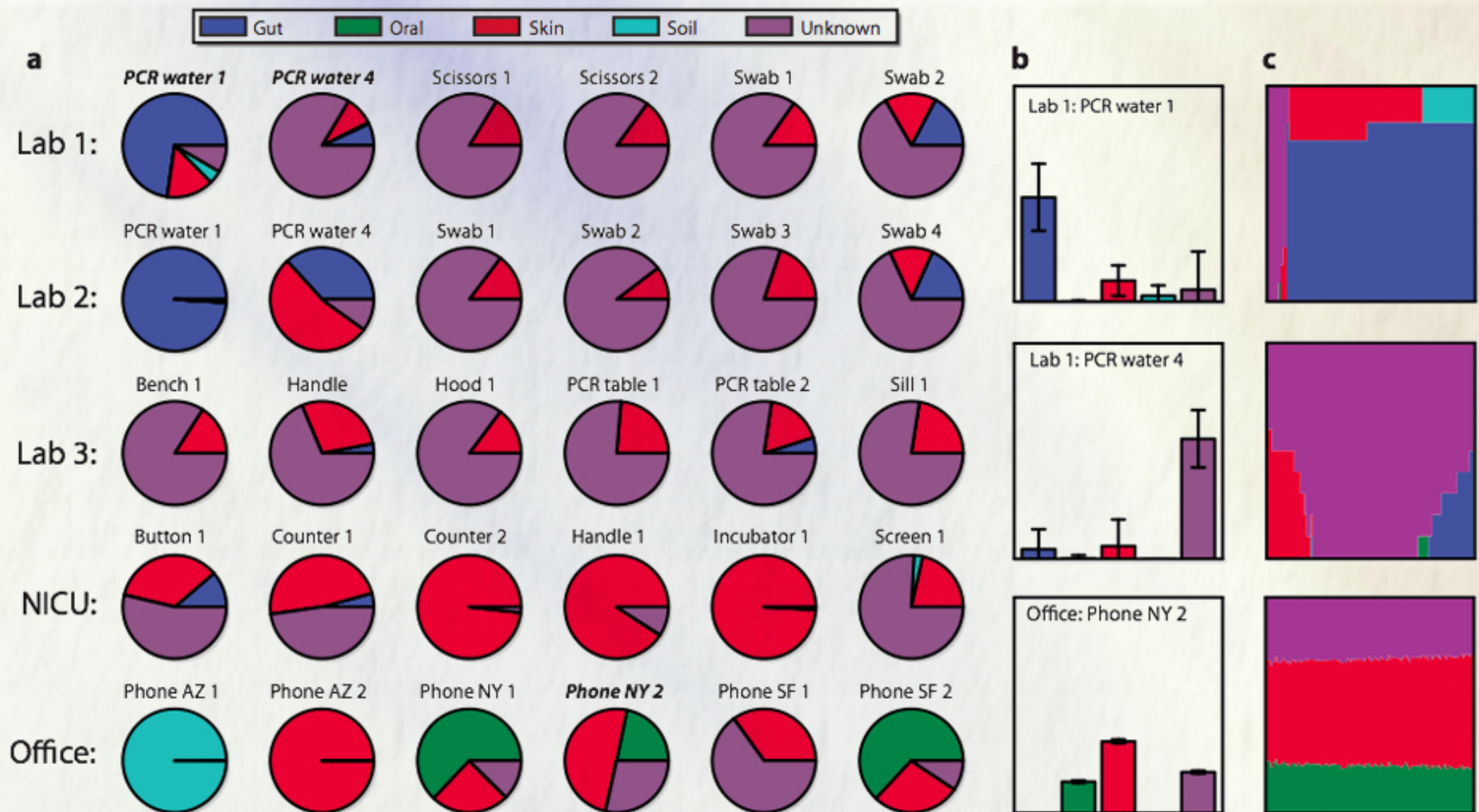
EMP pilot studies

Deepwater Horizon oil spill

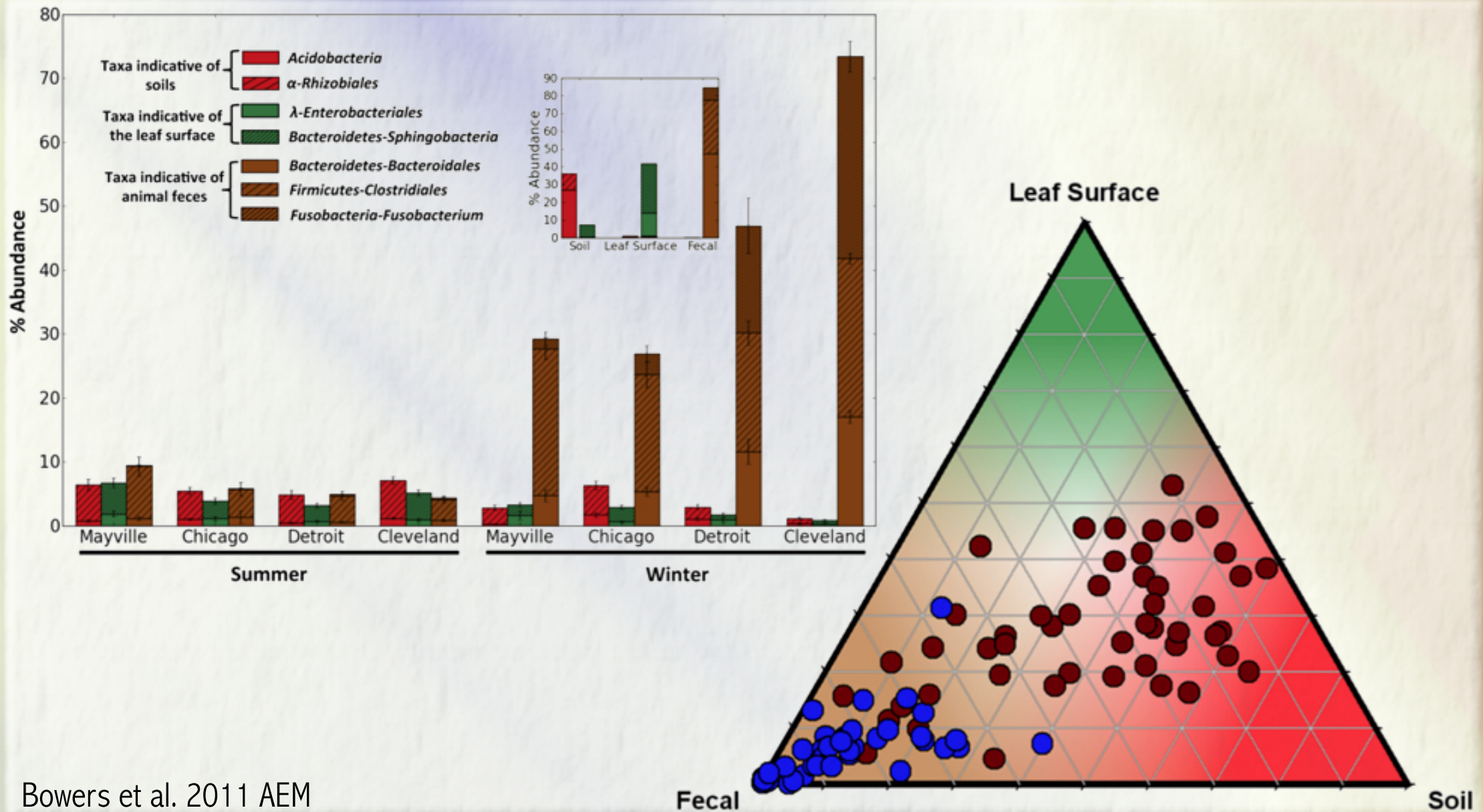


Terry Hazen, Janet Jansson & LBNL colleagues

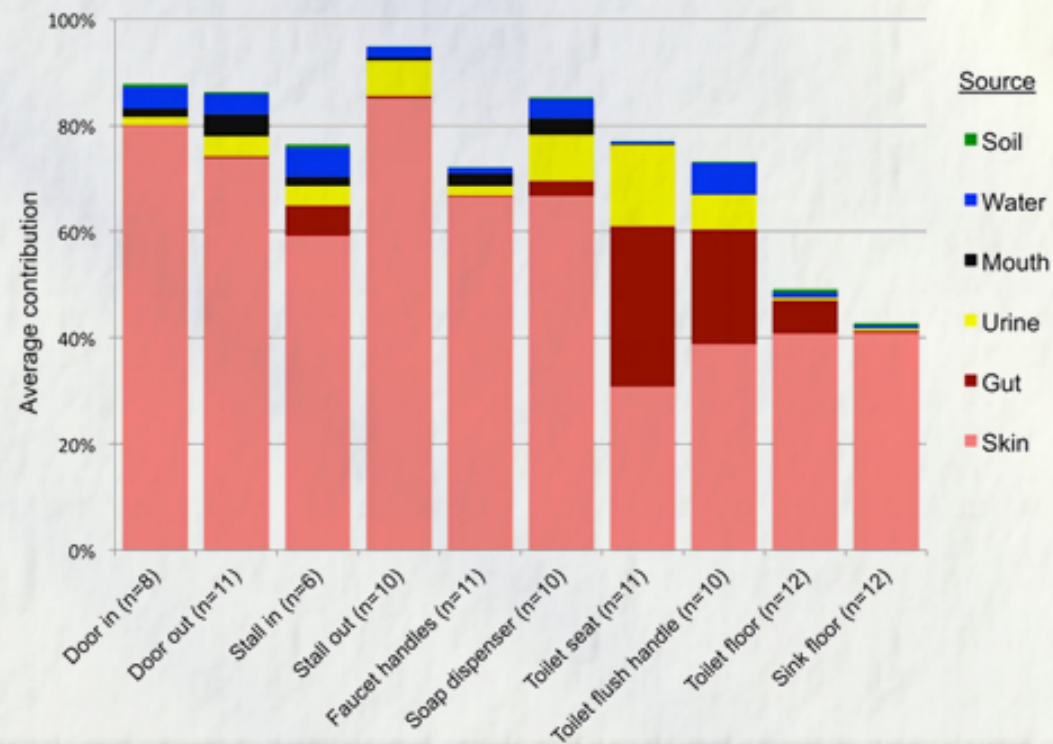
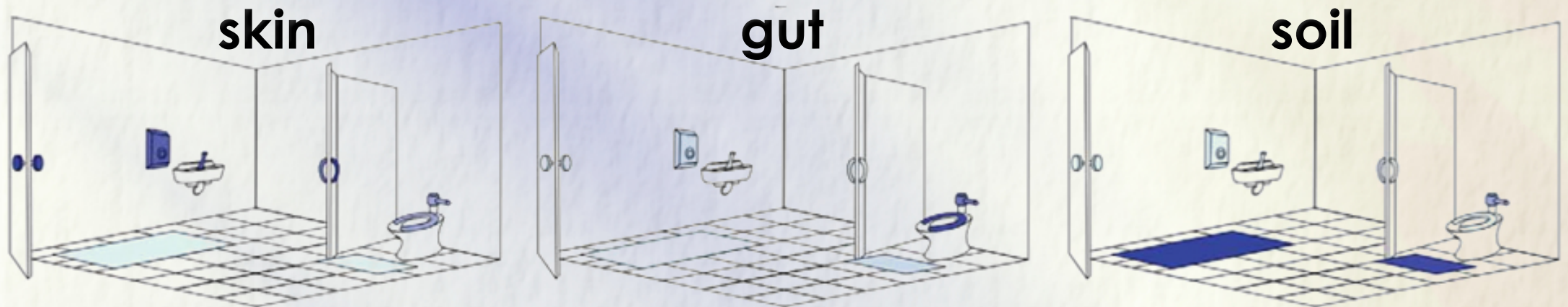
Database enables unanticipated benefits, e.g. source tracking



...to outdoor air...



...to public restrooms



Wolves have profound effect on Yellowstone ecosystem...

Before & After Wolves

Restoring wolves to Yellowstone after a 70-year absence as a top predator—especially of elk—set off a cascade of changes that is restoring the park's habitat as well.

YELLOWSTONE WITHOUT WOLVES 1926-1995

ELK overbrowsed the stream side willows, cottonwoods, and shrubs that prevent erosion. Birds lost nesting space. Habitat for fish and other aquatic species declined as waters became broader and shallower and, without shade from streamside vegetation, warmer.

ASPEN trees in Yellowstone's northern valleys, where elk winter, were seldom able to reach full height. Elk ate nearly all the new sprouts.

COYOTE numbers climbed. Though they often kill elk calves, they prey mainly on small mammals like ground squirrels and voles, reducing the food available for foxes, badgers, and raptors.

ART BY FERNANDO G. BAPTISTA, NO STAFF;
ANANDA MOHAI, NO STAFF
SOURCES: ROBERT L. BERSCHTA AND
WILLIAM J. RIPLEY, OREGON STATE
UNIVERSITY; DOUGLAS W. SMITH,
YELLOWSTONE NATIONAL PARK



YELLOWSTONE WITH WOLVES 1995-PRESENT

ELK population has been halved. Severe winters early in the reintroduction and drought contributed to the decline. A healthy fear of wolves also keeps elk from lingering at streamsides, where it can be harder to escape attack.

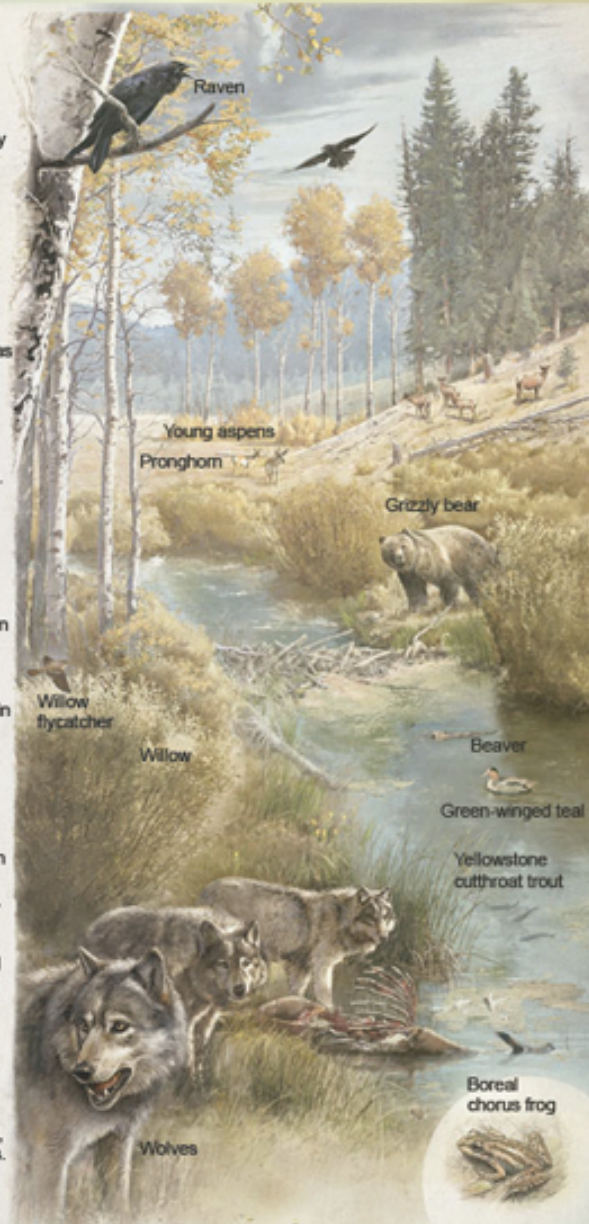
ASPENS The number of new sprouts eaten by elk has dropped dramatically. New groves in some areas now reach 10 to 15 feet tall.

COYOTES Wolf predation has reduced their numbers. Fewer coyote attacks may be a factor in the resurgence of the park's pronghorn.

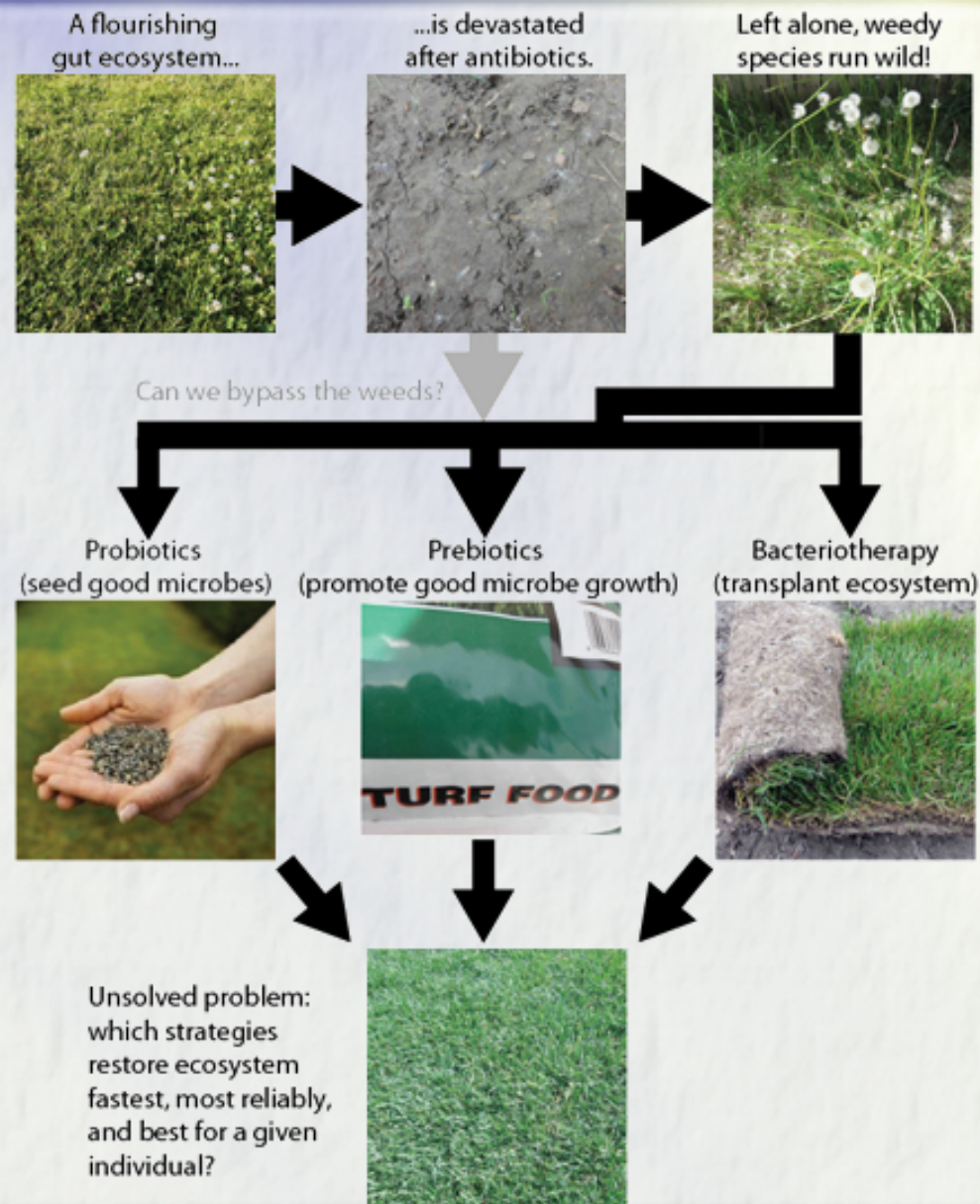
WILLOWS, cottonwoods, and other riparian vegetation have begun to stabilize stream banks, helping restore natural water flow. Overhanging branches again shade the water and welcome birds.

BEAVER colonies in north Yellowstone have risen from one to 12, now that some stream banks are lush with vegetation, especially willows (a key beaver food). Beaver dams create ponds and marshes, supporting fish, amphibians, birds, small mammals, and a rich insect population to feed them.

CARRION Wolves don't cover their kill, so they've boosted the food supply for scavengers, notably bald and golden eagles, coyotes, ravens, magpies, and bears.



Can we develop a restoration ecology for microbes?



Acknowledgments

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Tony Walters

Daniel McDonald

Nigel Cook

Dan Knights

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Jens Reeder -> Genentech

Julia Goodrich -> Cornell

Ryan Kennedy -> Penn

Zongzhi Liu -> Yale

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Jerry Kennedy

Greg Humphrey

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Will van Treuren

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Gail Ackermann

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Jo Handelsman (Yale), Lars Angenent (Cornell), George Church (Harvard)

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Ridaura, Alejandro Reyes, J Faith, Henning Seedorf, Liz Hansen, Nate McNulty, Jill Manchester, Sabrina Wagoner, Jessica Hoisington-Lopez

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