"The Human Microbiome and the Revolution in Digital Health"

The Florida Institute for Human and Machine Cognition

Pensacola Evening Lecture Series

Pensacola, FL

January 22, 2014

Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

Dept. of Computer Science and Engineering

Jacobs School of Engineering, UCSD

http://lsmarr.calit2.net

Abstract

The human body is host to 100 trillion microorganisms, ten times the number of cells in the human body and these microbes contain 100 times the number of DNA genes that our human DNA does. The microbial component of our “superorganism” is comprised of hundreds of species with immense biodiversity. Thanks to the National Institutes of Health’s Human Microbiome Program researchers have been discovering the states of the human microbiome in health and disease. To put a more personal face on the “patient of the future,” I have been collecting massive amounts of data from my own body over the last five years, which reveals detailed examples of the episodic evolution of this coupled immune-microbial system. To decode the details of the microbial ecology requires high resolution genome sequencing feeding Big Data parallel supercomputers. Since modern medicine has not taken into account the nature and changes in the human microbiome, we can look forward to revolutionary changes in medical practice over the next decade.

In My Teenage Years, I Spent Time Every Summer at Pensacola Beach



My Mother and Two Brothers, Photo by My Father

Pensacola Created My Life-Long Interest in the Living Ecology of the Sea



www.pinterest.com/pin/652318945754787 40/

I Spent Decades Studying the Ecological Dynamics of Coral Reefs



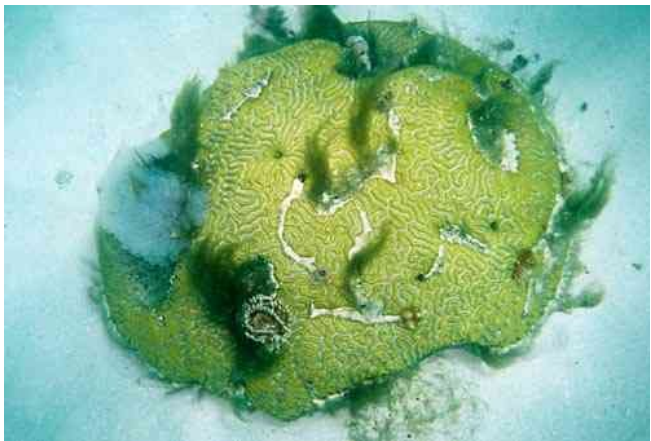


My 120 Gallon Home Salt Water Coral Reef Aquarium in Illinois



Pristine

Degraded



My Snorkeling Photos From Coral Reefs

Over the Last Decade I Have Been Studying the Ecological Dynamics of My Own Body

Age 41



Age 51



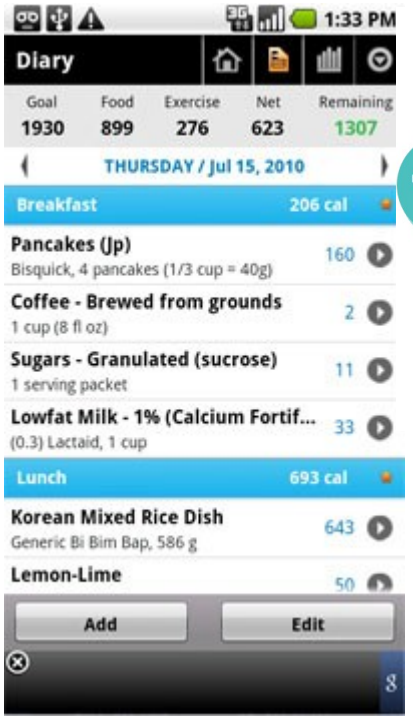
Age 61



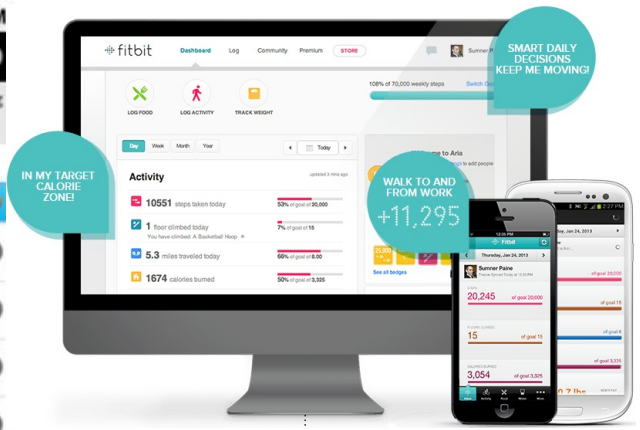
I Reversed My Body's Decline By Quantifying and Altering Nutrition and Exercise

http://lsmarr.calit2.net/repository/LS_reading_recommendations_FiRe_2011.pdf

I Used a Variety of Emerging Personal Sensors To Quantify My Body & Drive Behavioral Change



MyFitnessPal-
Calories Ingested



FitBit -
Daily Steps &
Calories Burned



Withings/iPhone-
Blood Pressure





Withings WiFi Scale -
Daily Weight



Zeo-Sleep



Azumio-Heart Rate

From Measuring Macro-Variables to Measuring My Internal Variables – What Did I Learn?

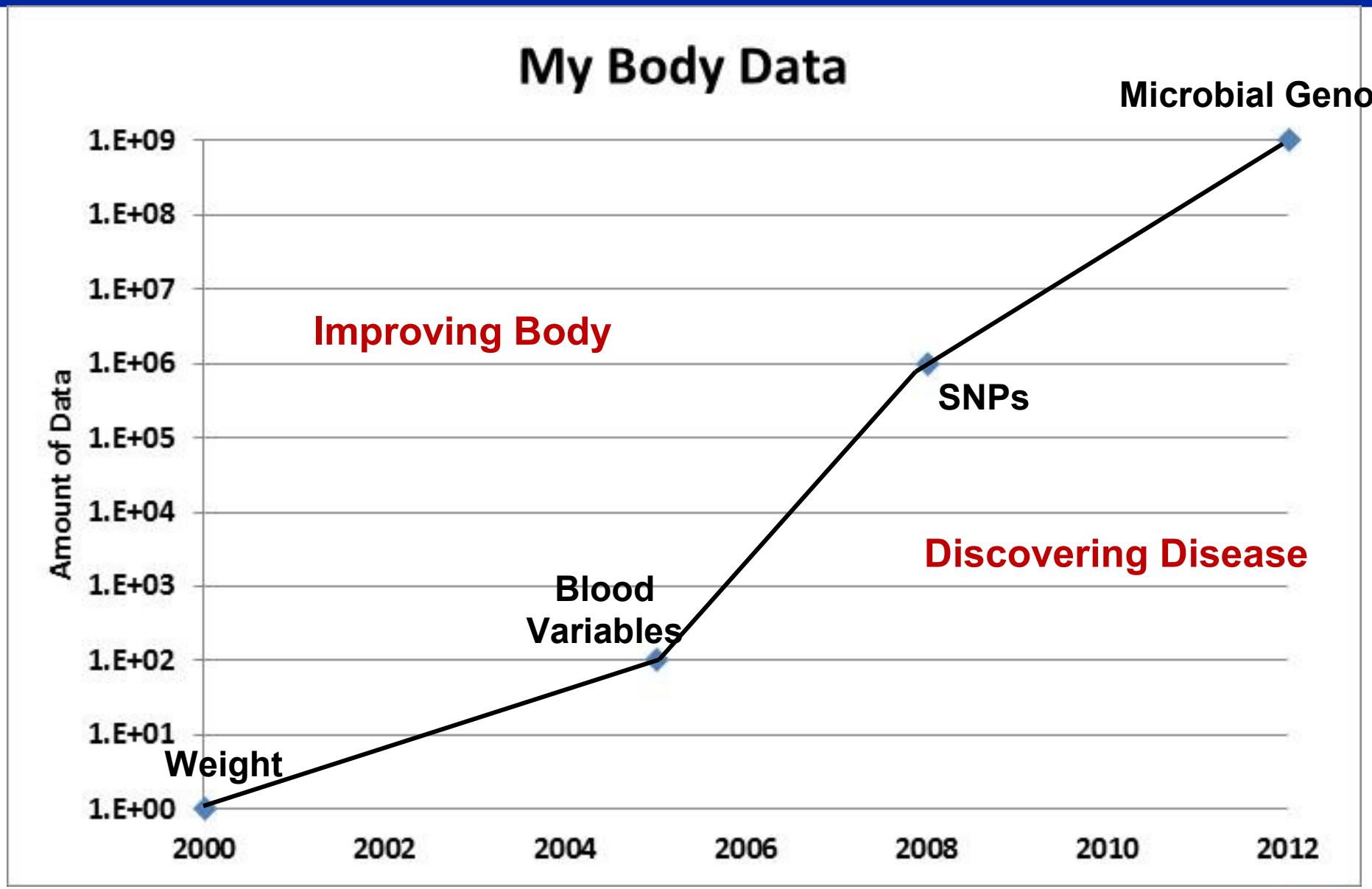


The Patient of the Future

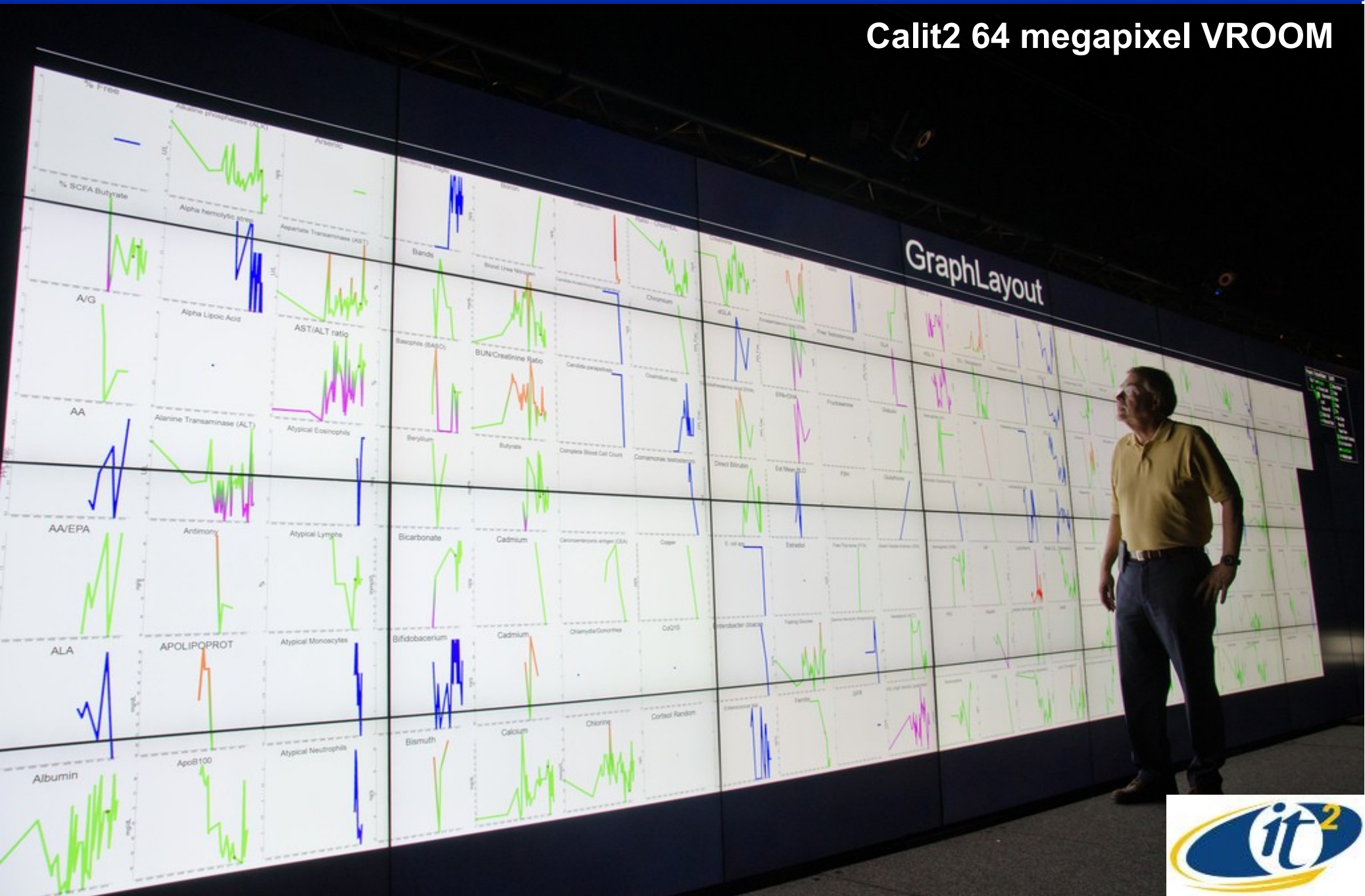
Internet pioneer Larry Smarr's quest to quantify everything about his health led him to a startling discovery, an unusual partnership with his doctor, and more control over his life.

www.technologyreview.com/biomedicine/39636

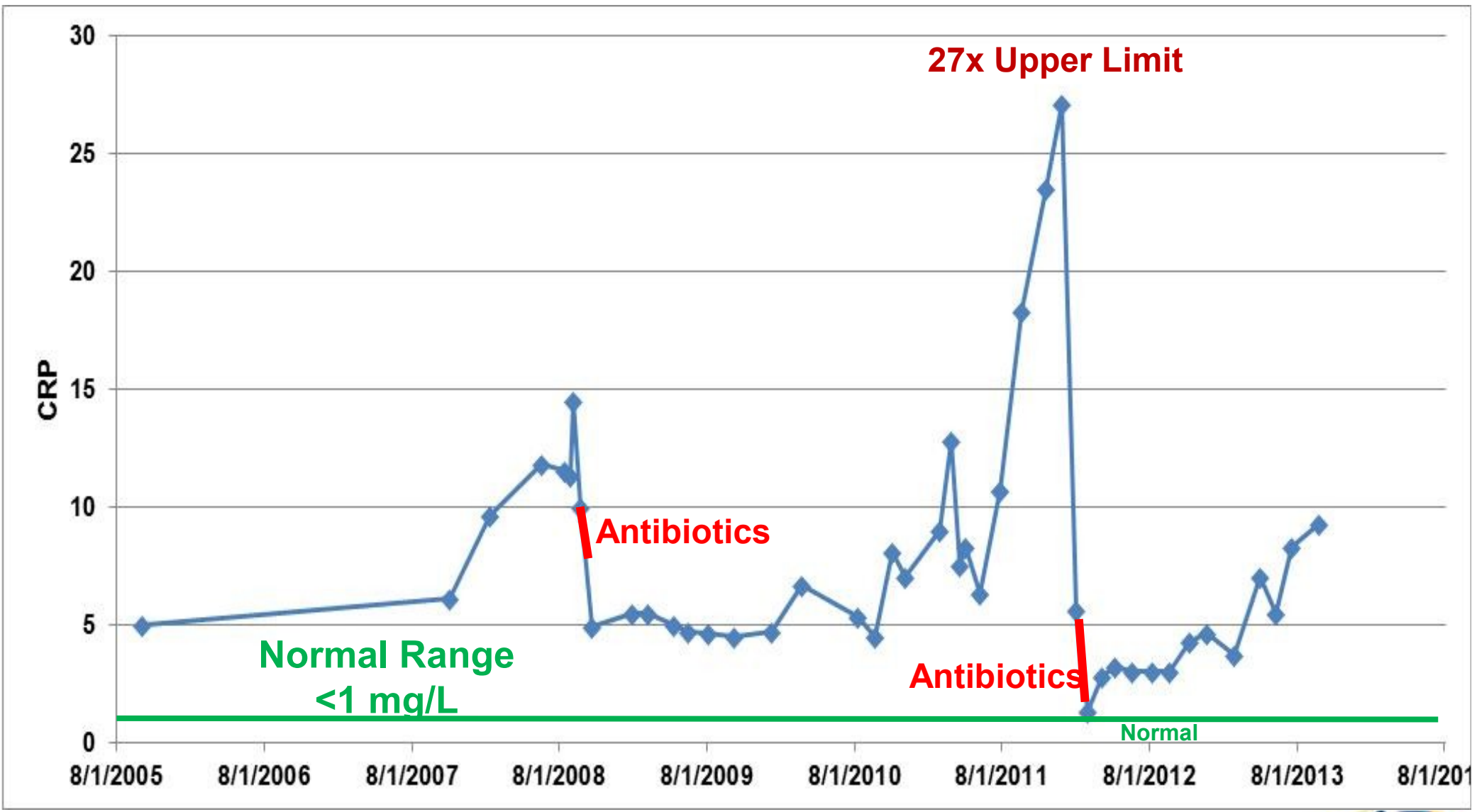
From One to a Billion Data Points Defining Me: The Exponential Rise in Body Data in Just One Decade!



Visualizing Time Series of 150 LS Blood and Stool Variables, Each Over 5-10 Years

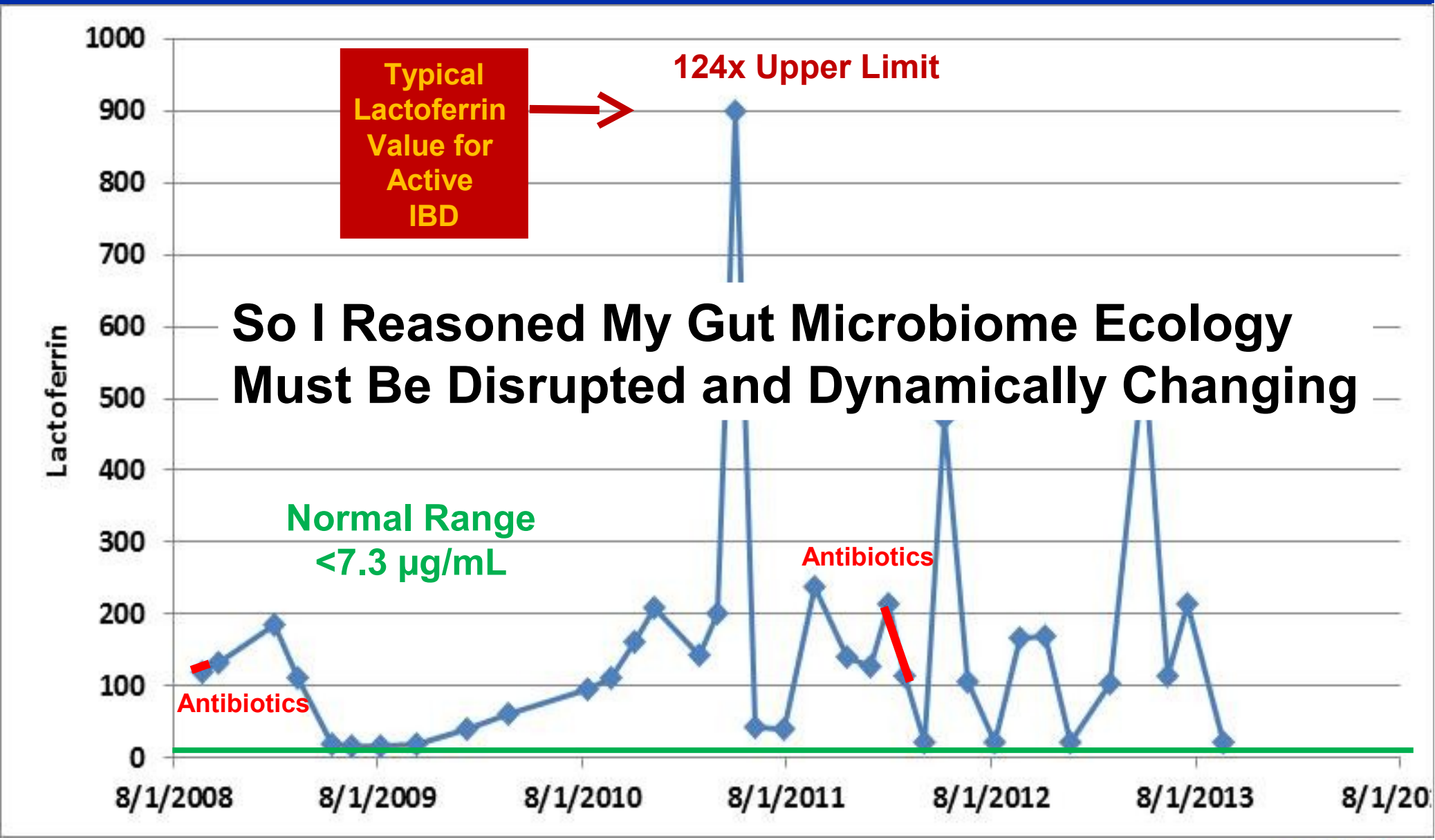


I Discovered I Had Chronic Inflammation by Tracking Complex Reactive Protein In My Blood Samples



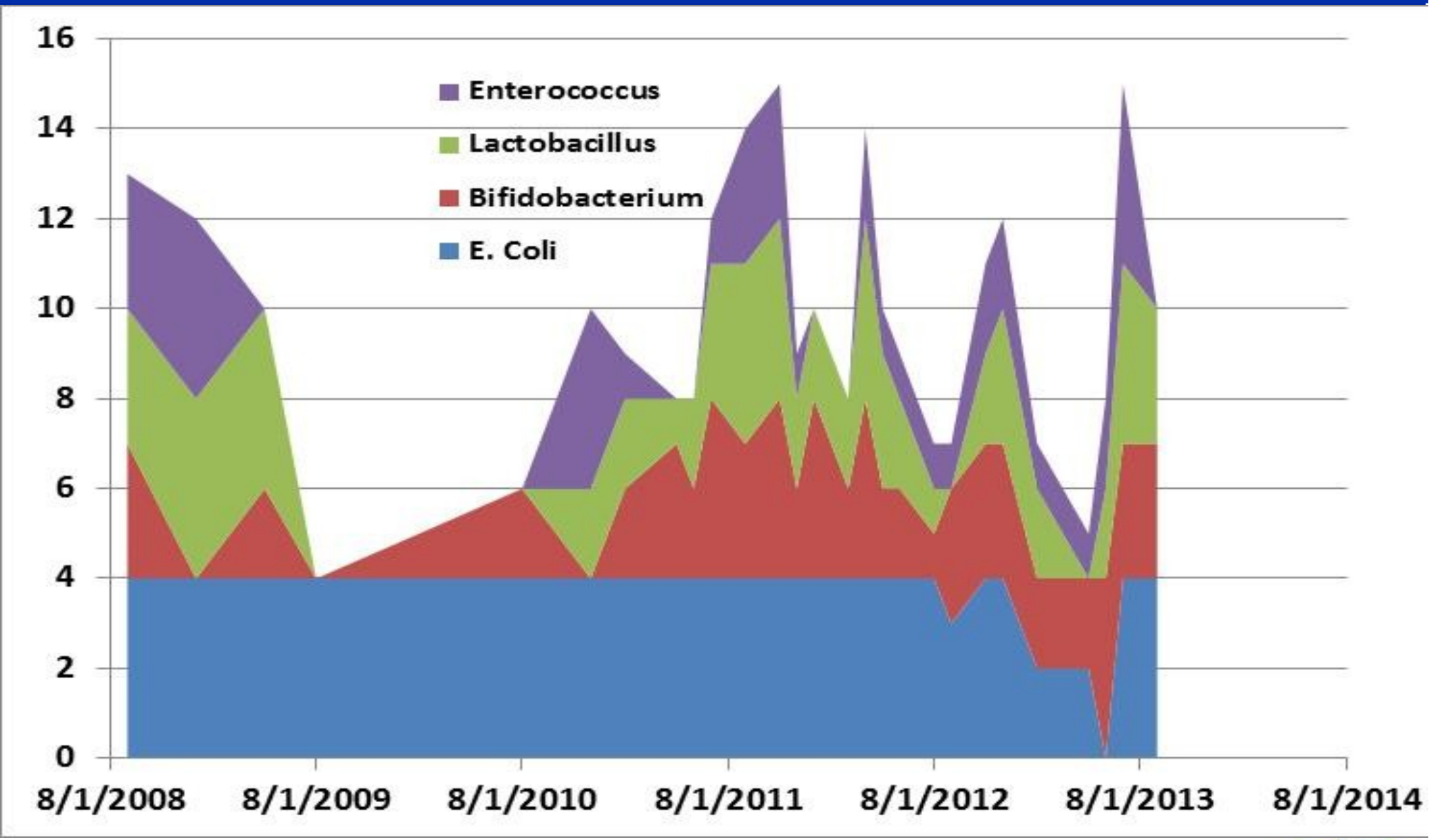
CRP is a Generic Measure of Inflammation in the Blood

But by Using Stool Analysis Time Series, I Discovered I Had Episodically Excursions of My Immune System



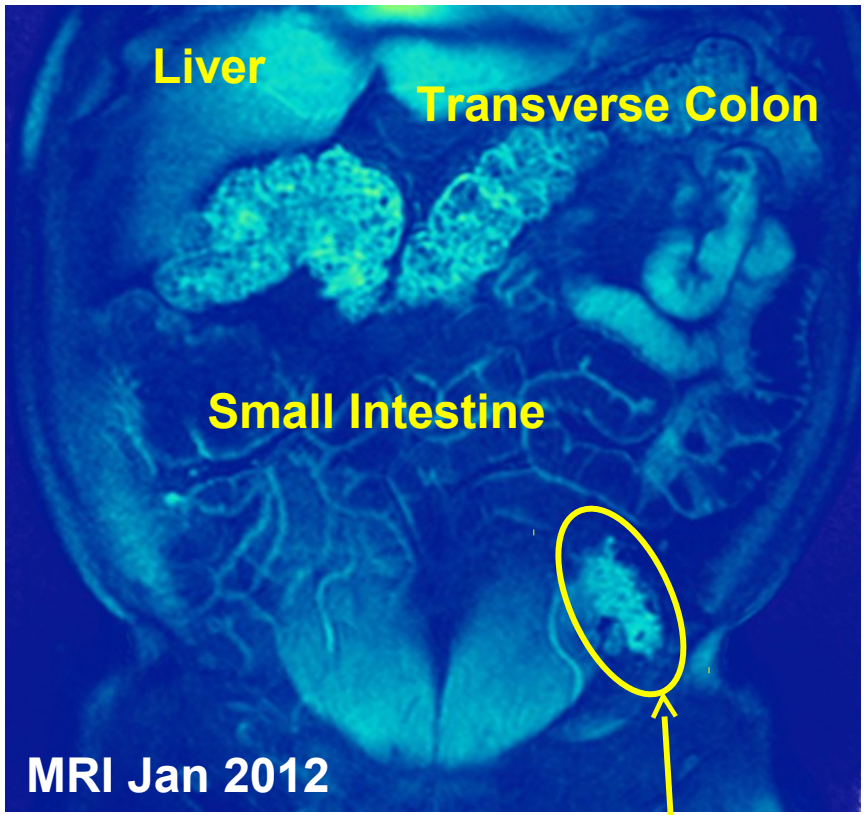
Lactoferrin is a Protein Shed from Neutrophils -
An Immune System Antibacterial that Sequesters Iron

Indeed, My Cultured Gut Bacterial Abundance Time Series Revealed an Oscillatory Microbiome Ecology



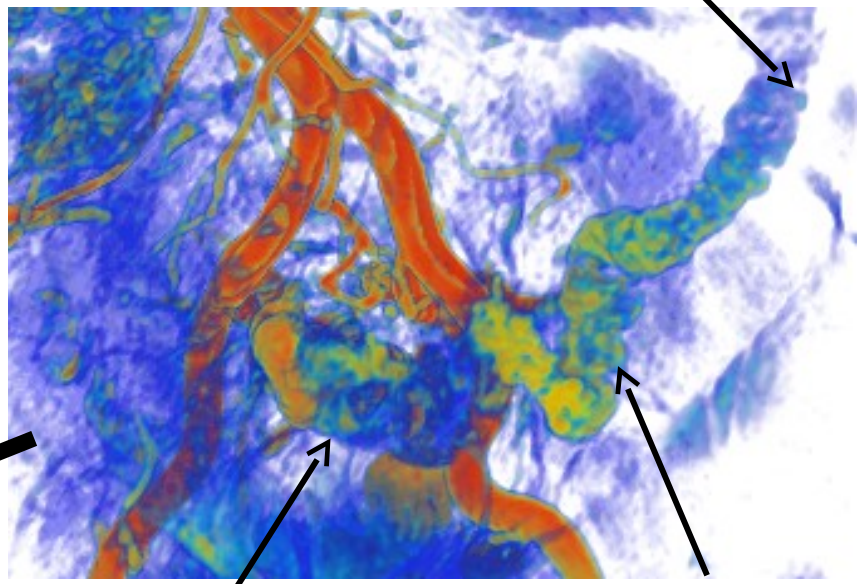
LS Data from Yourfuturehealth.com

Confirming the IBD Hypothesis: Finding the "Smoking Gun" with MRI Imaging



I Obtained the MRI Slices From UCSD Medical Services and Converted to Interactive 3D Working With Calit2 Staff & DeskVOX Software

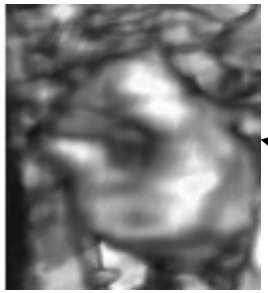
Descending Colon



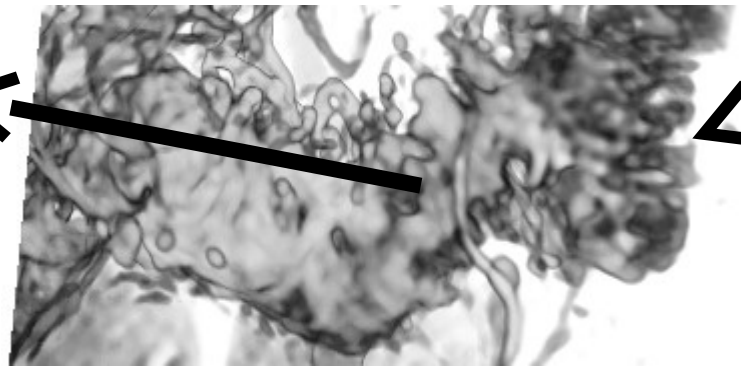
Major Kink

Sigmoid Colon Threading Iliac Arteries

Cross Section



Diseased Sigmoid Colon



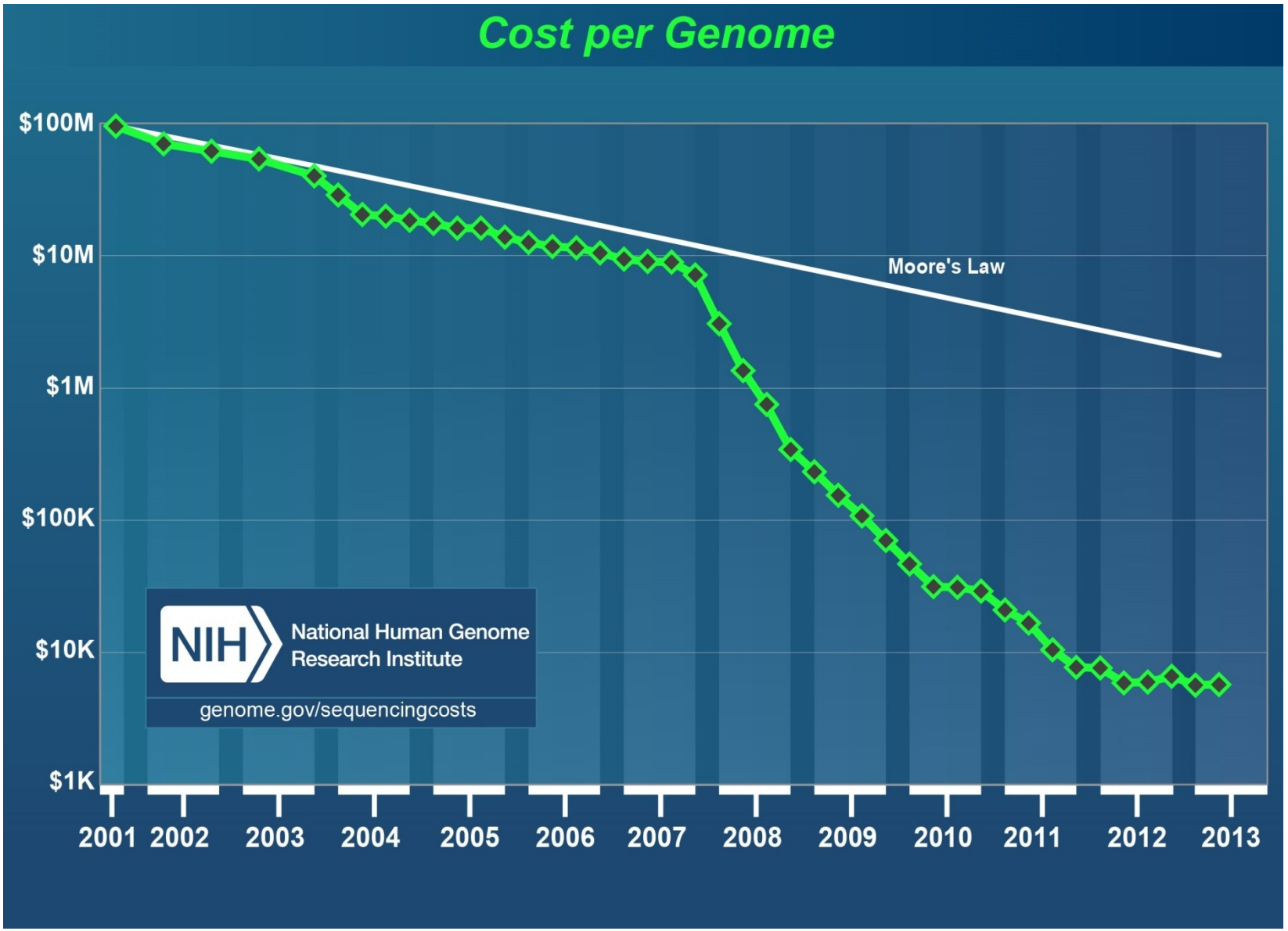
Why Did I Have an Autoimmune Disease like IBD?

Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.
--*The Role of Microbes in Crohn's Disease*

So I Set Out to Quantify All Three!

Paul B. Eckburg & David A. Relman
Clin Infect Dis. 44:256-262 (2007)

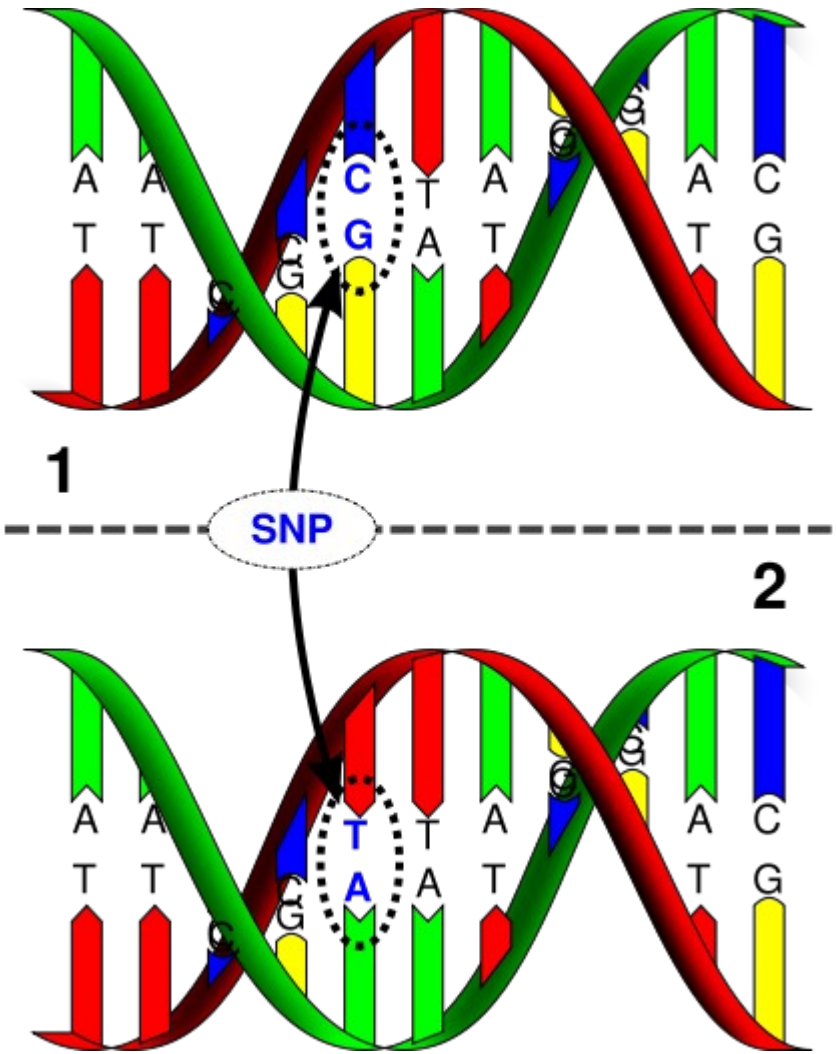
The Cost of Sequencing a Human Genome Has Fallen Over 10,000x in the Last Ten Years!



This Has Enabled Sequencing of Both Human and Microbial Genomes

Single Nucleotide Polymorphisms (SNPs) Make Up About 90% of All Human Genetic Variation

Person A

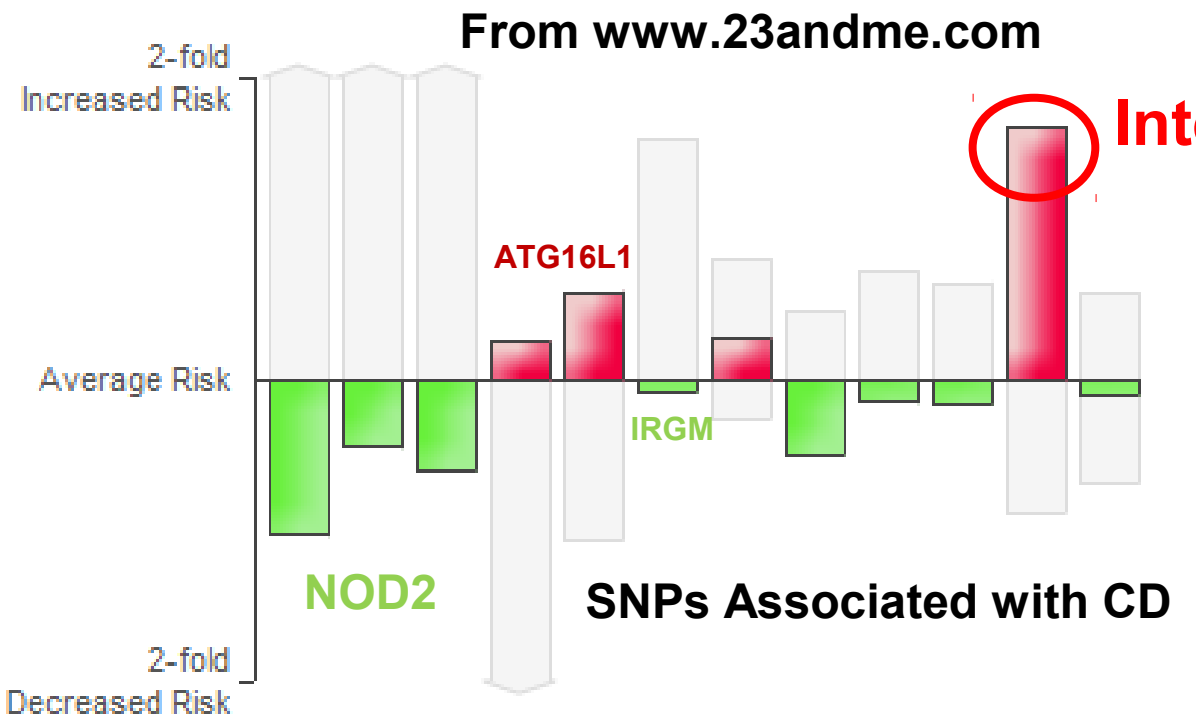


Person B

SNPs Occur Every 100 to 300 Bases Along Human DNA

www.23andme.com Tracks One Million SNPs

I Wondered if Crohn's is an Autoimmune Disease, Did I Have a Personal Genomic Polymorphism?



Polymorphism in Interleukin-23 Receptor Gene — 80% Higher Risk of Pro-inflammatory Immune Response

Now Comparing 163 Known IBD SNPs with 23andme SNP Chip and My Full Human Genome

News and Views

Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

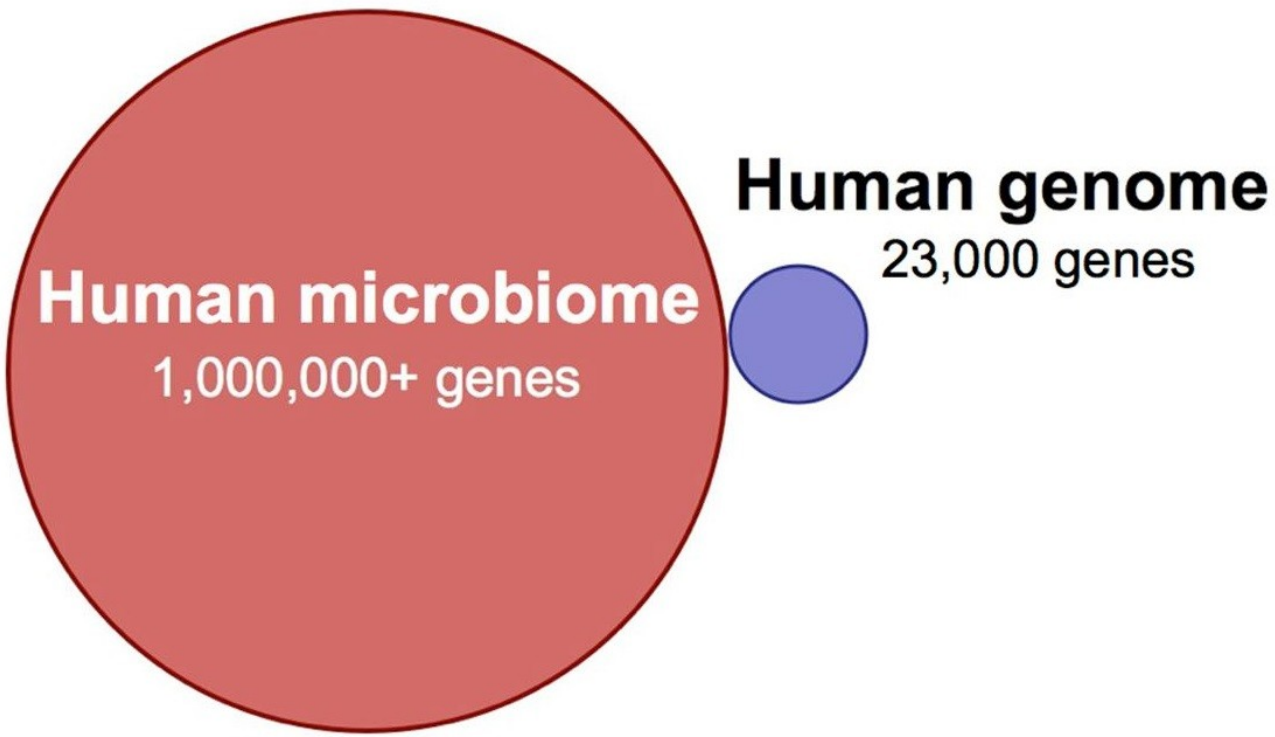
Markus F Neurath[1]

I Had Carried Out Observations in Optical, Radio, and X-Ray on the Andromeda Galaxy in the 1980s



Now I am Observing the 100 Trillion Non-Human Cells in My Body

Your Body Has 10 Times As Many Microbe Cells As Human Cells



99% of Your DNA Genes Are in Microbe Cells Not Human Cells

Inclusion of the Microbiome Will Radically Change Medicine

J. Craig Venter™ INSTITUTE

it²

2012 Was
the Year of Human Microbiome





When We Think About Biological Diversity We Typically Think of the Wide Range of Animals






But All These Animals Are in One SubPhylum Vertebrata of the Chordata Phylum

All images from Wikimedia Commons.
Photos are public domain or by Trisha Shears & Richard Bartz

Think of These Phyla of Animals When You Consider the Biodiversity of Microbes Inside You



Phylum Chordata



Phylum Cnidaria



Phylum Echinodermata



Phylum Annelida



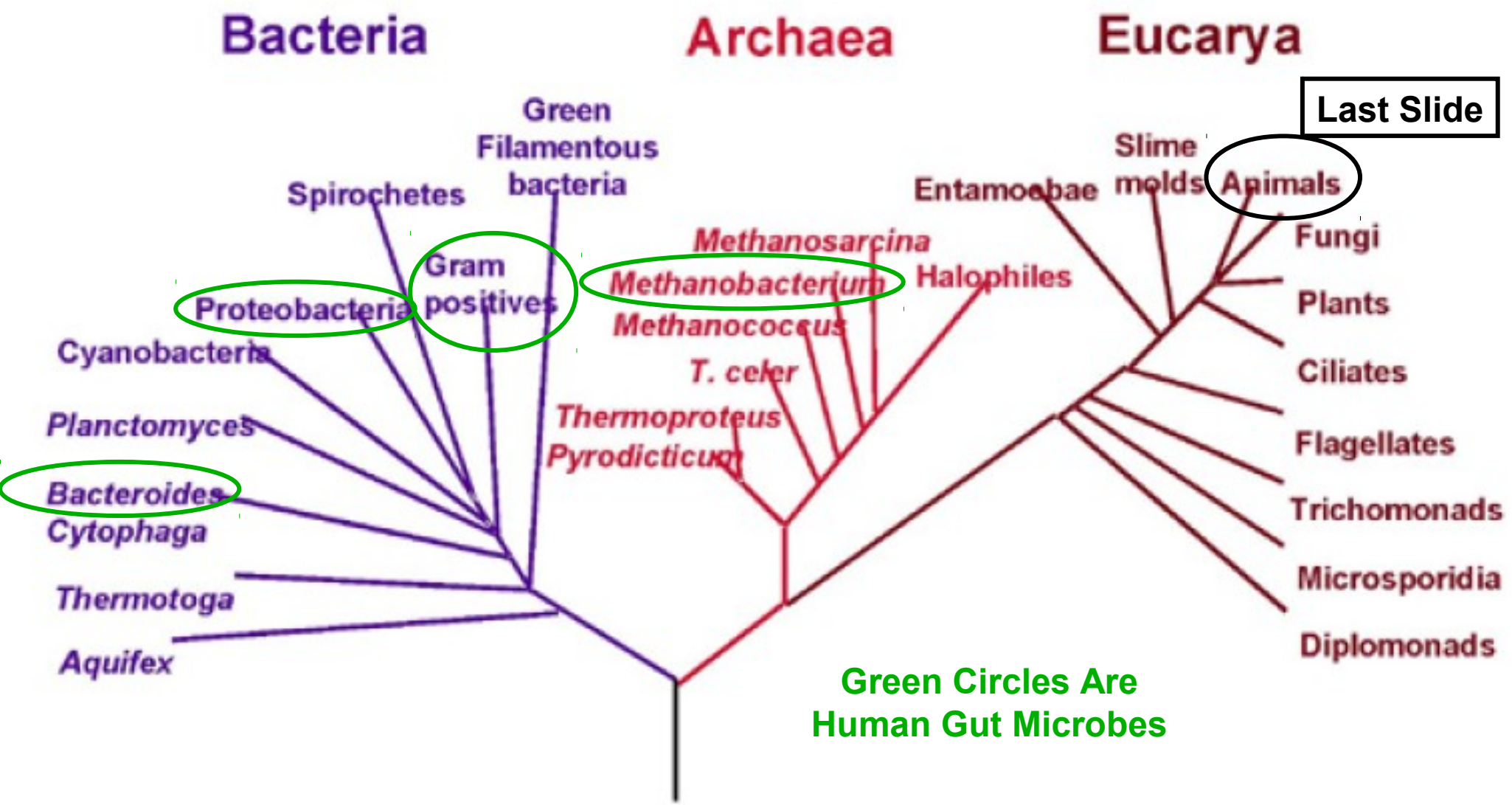
Phylum Mollusca



Phylum Arthropoda

All images from WikiMedia Commons.
Photos are public domain or by Dan Hershman, Michael Linnenbach, Manuae, B_cool

However, The Evolutionary Distance Between Your Gut Microbes Is Much Greater Than Between All Animals



Evolutionary Distance Derived from Comparative Sequencing of 16S or 18S Ribosomal RNA

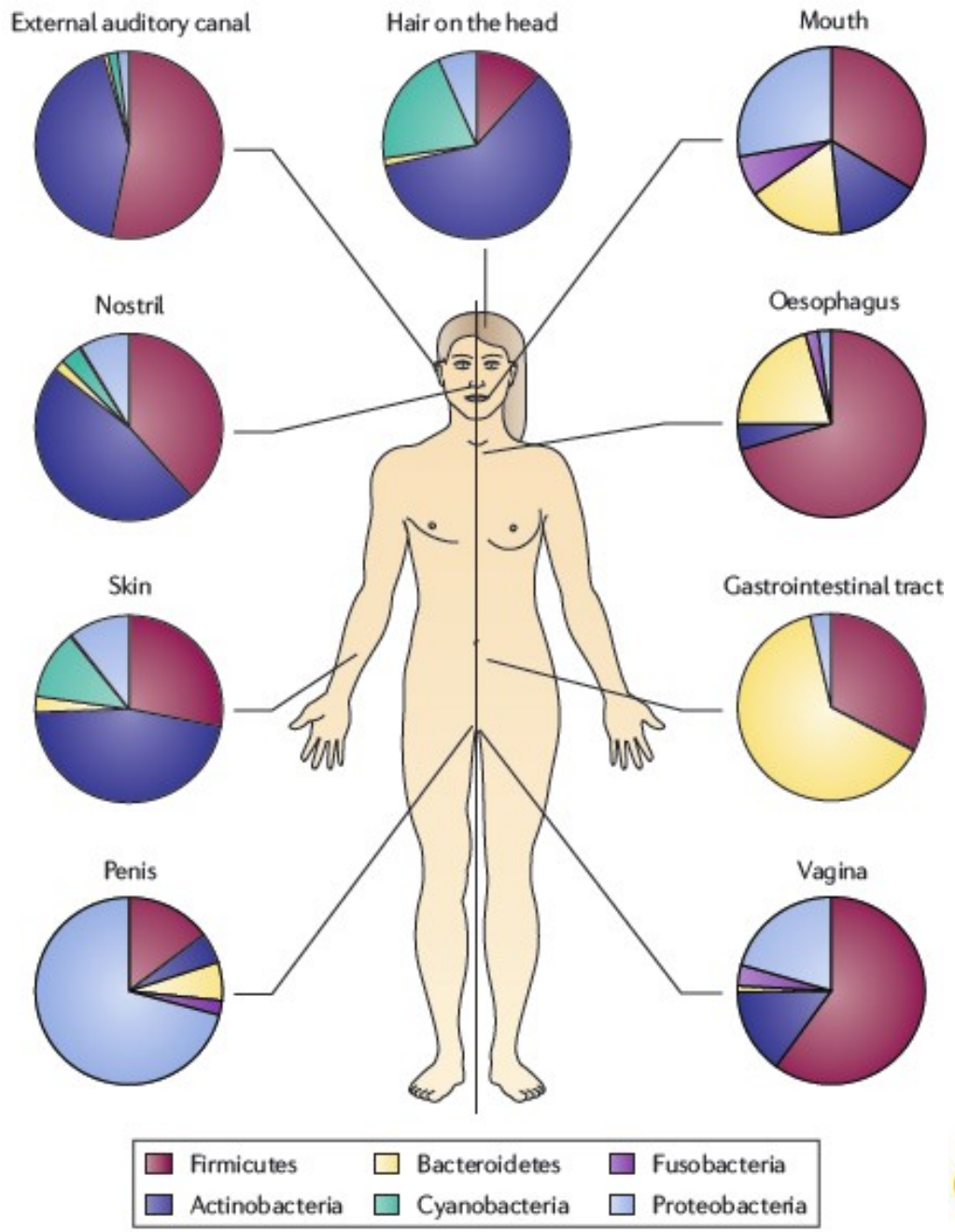
Source: Carl Woese, et al

Quantifying Our Human Superorganism: Distribution of Microorganism Ecology on Our Bodies

Human Microbiome Project

The NIH Common Fund
WE ACCELERATE DISCOVERY.

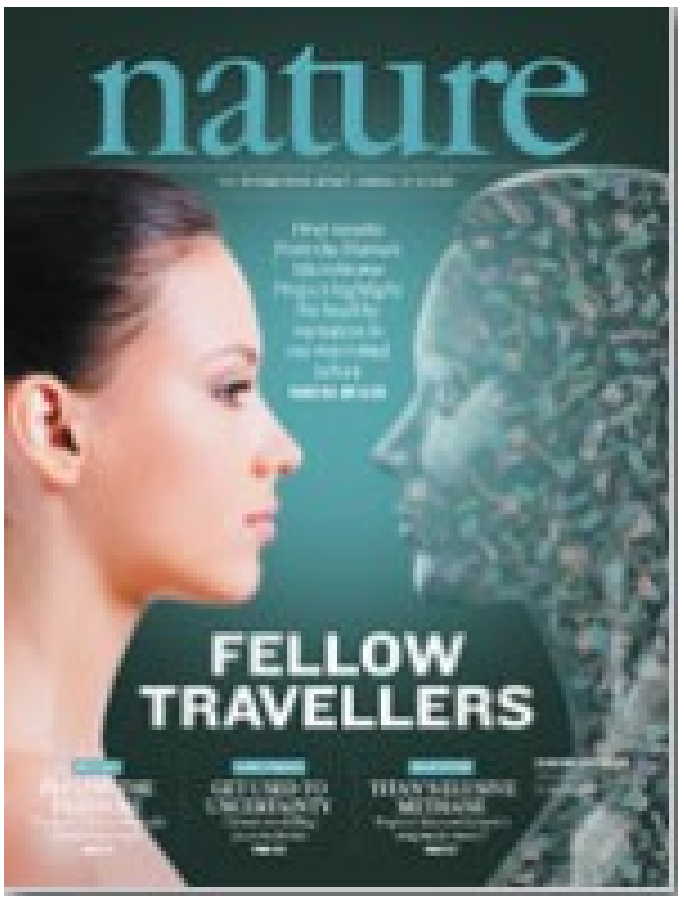
Nature Reviews Microbiology
v.9, p. 279 (2011)



Intense Scientific Research is Underway on Understanding the Human Microbiome



June 8, 2012



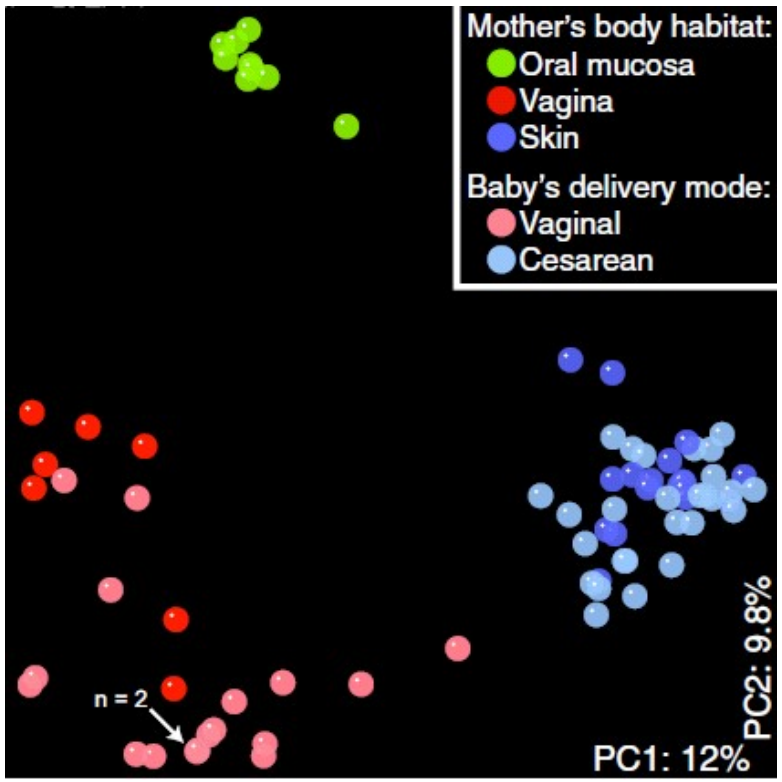
June 14, 2012

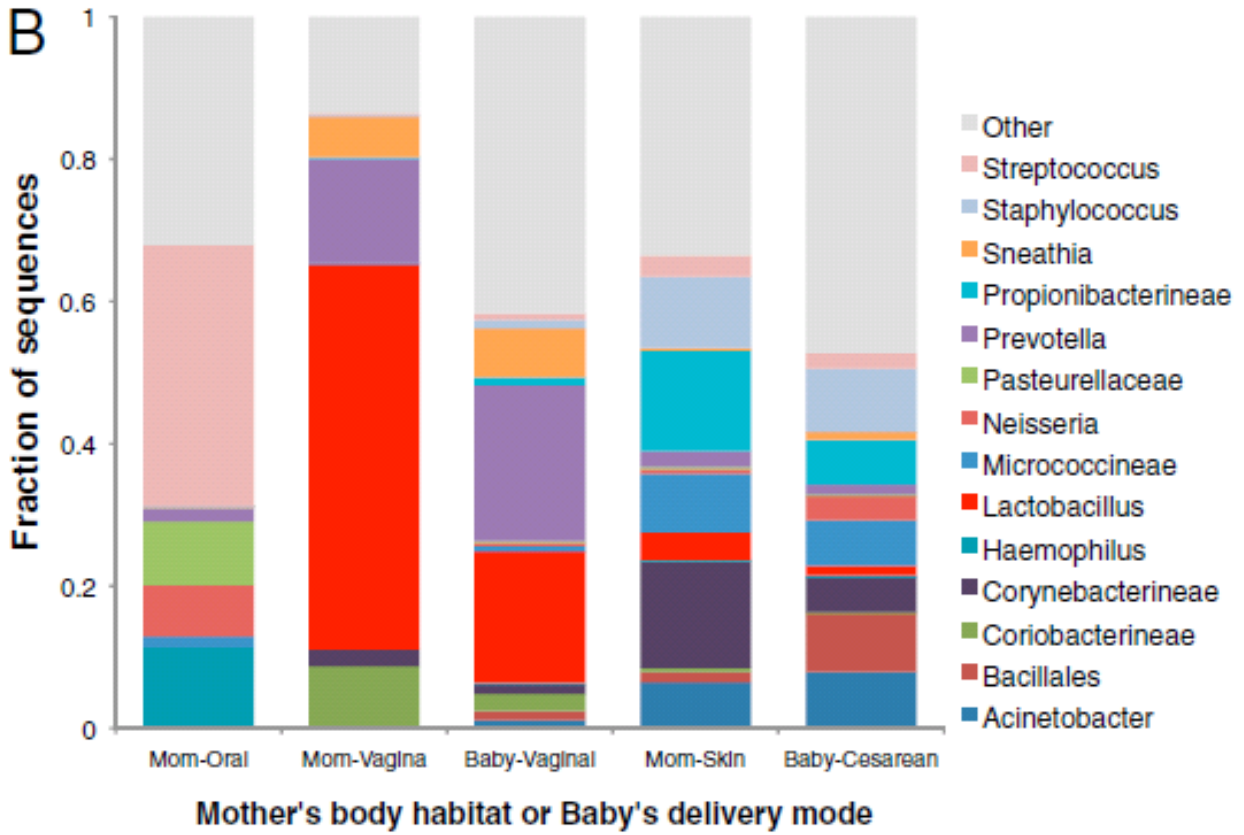
From Culturing Bacteria to Sequencing Them

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Early Medically Relevant Results: Delivery Mode Determines Infant's Initial Microbiome

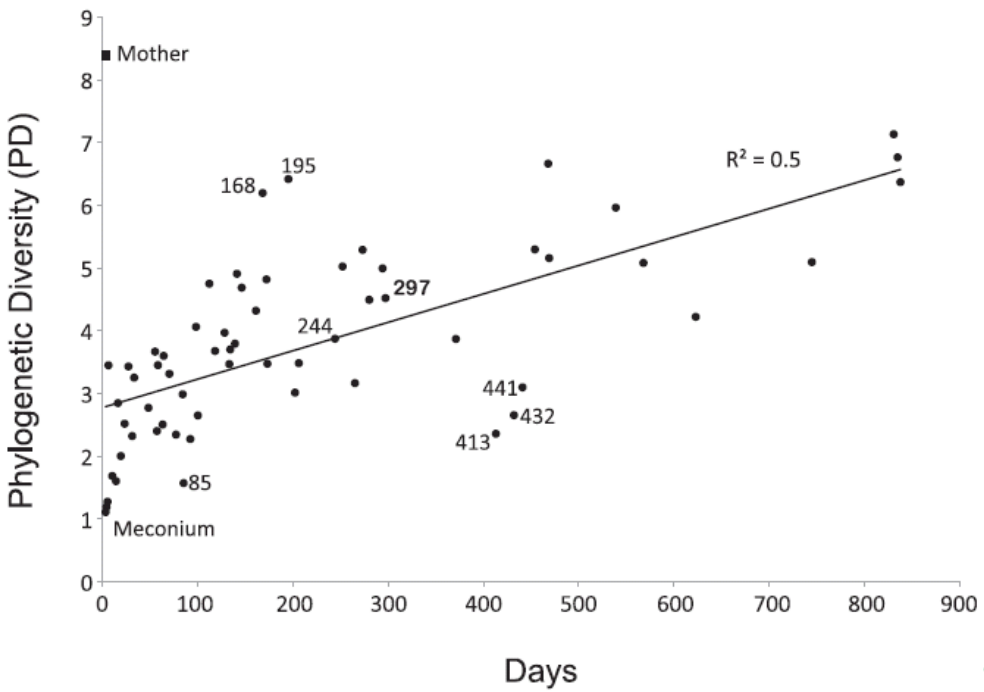


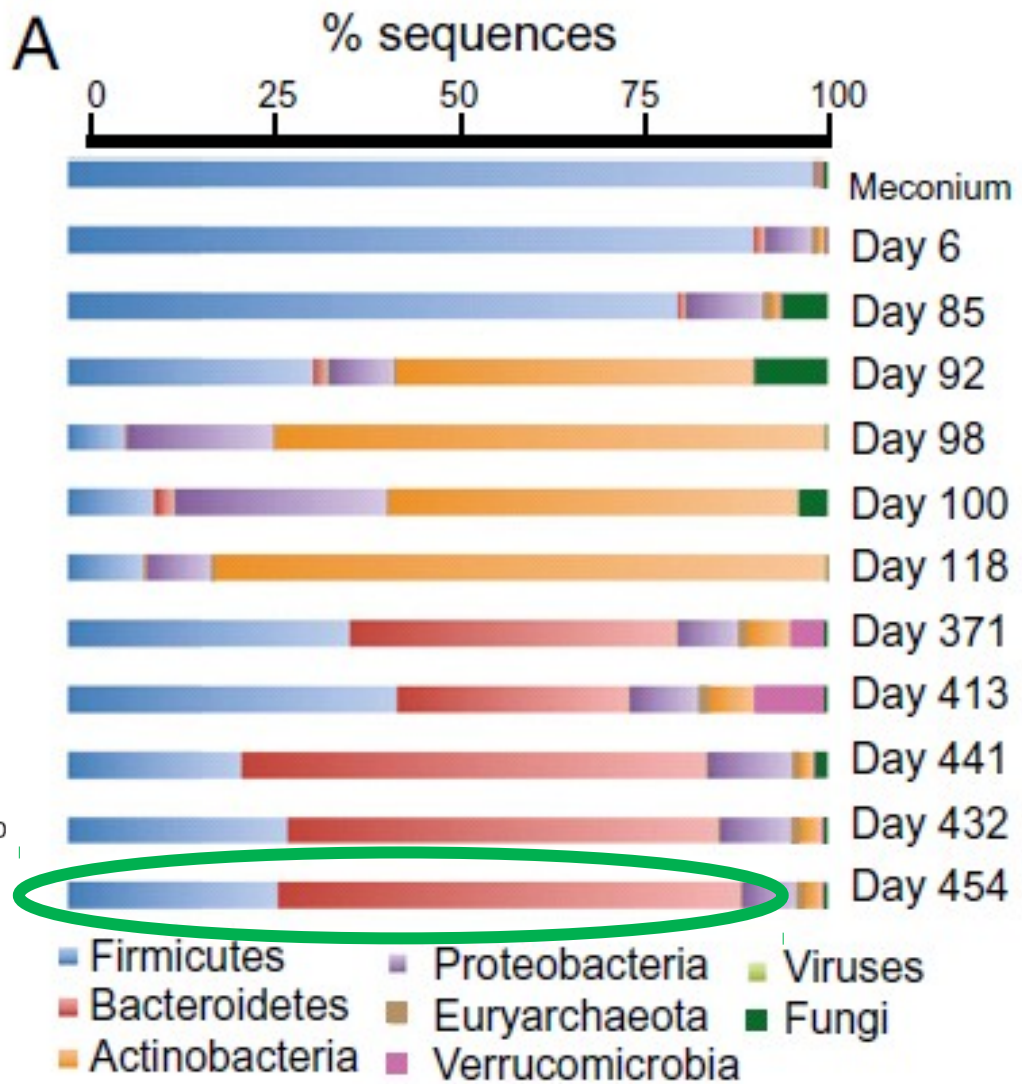


"The composition of the initial microbiota may have implications for nutritional and immune functions associated with the developing microbiota. For example, recent studies suggest that Cesarean-delivered babies may be more susceptible to allergies and asthma."

Maria Dominguez-Belloa, et al. PNAS (2010) 107 11971–11975

The Infant Gut Microbiome Rapidly Increases its Diversity After Birth



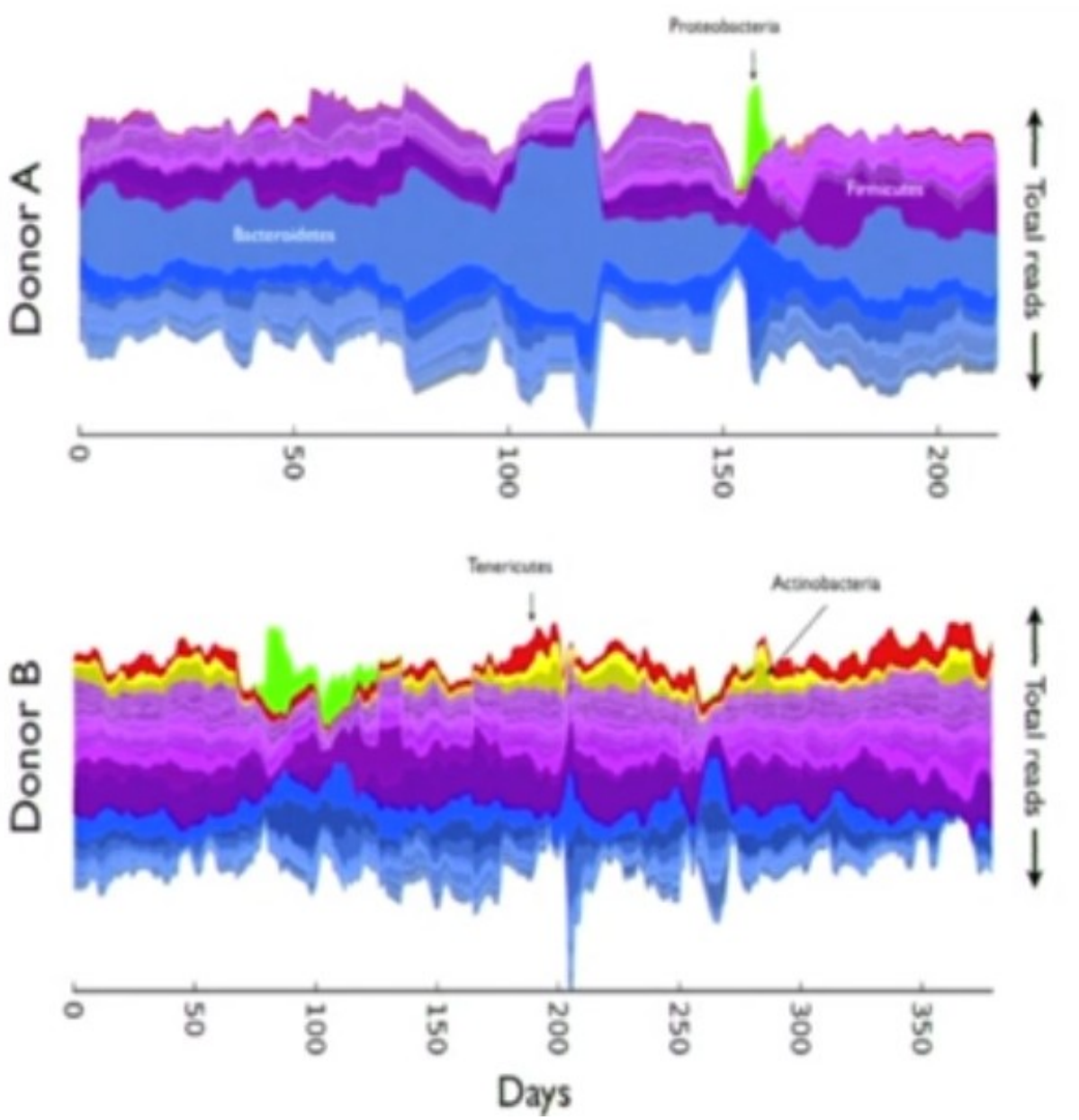


Adult Gut Microbiome Dominated By Bacteroidetes/Firmicutes

"Succession of microbial consortia in the developing infant gut microbiome," Jeremy Koeniga, et al. PNAS 108 Suppl 1:4578-85 (2011)

The Adult Healthy Gut Microbiome Is Remarkably Stable Over Time

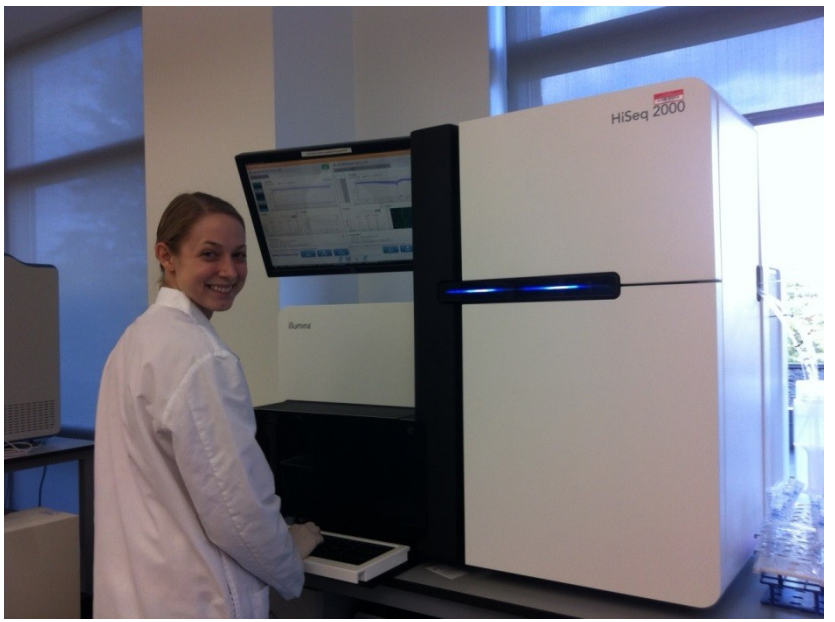
Gut communities over time



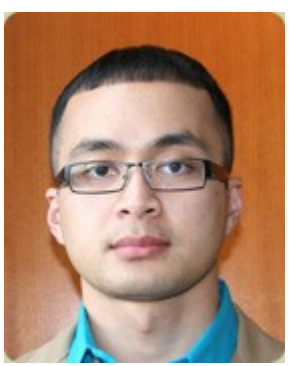
Source: Eric Alm, MIT

To Map Out the Dynamics of My Microbiome Ecology I Partnered with the J. Craig Venter Institute

- JCVI Did Metagenomic Sequencing on Six of My Stool Samples Over 1.5 Years
- Sequencing on Illumina HiSeq 2000
  - Generates Reads (100 Bases)
  - Run Takes ~14 Days
  - My 6 Samples Produced
    - 190.2 Gbases of Data
- JCVI Lab Manager, Genomic Medicine
  - Manolito Torralba
- IRB PI Karen Nelson
  - President JCVI



Illumina HiSeq 2000 at JCVI


Manolito Torralba, JCVI


Karen Nelson, JCVI

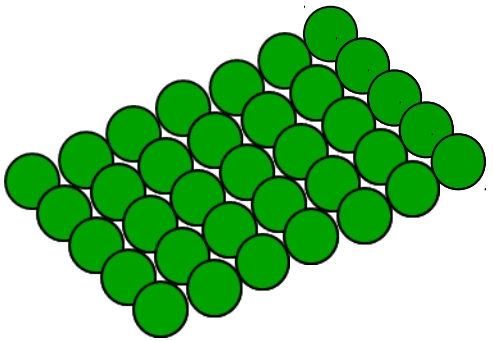
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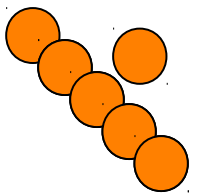
We Downloaded Additional Human Gut Microbiome Data from the NIH For Comparative Analysis



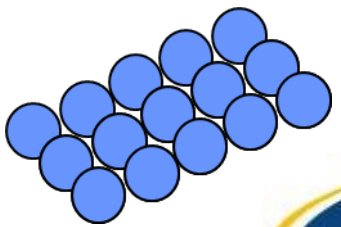
35 "Healthy" Individuals:
1 Point in Time



2 Ulcerative Colitis Patients:
1 Point in Time
and 5 Points in Time



5 Ileal Crohn's Patients:
3 Points in Time



Total of 5 Billion Illumina Reads

Source: Jerry Sheehan, Calit2; Weizhong Li, Sitao Wu, CRBS, UCSD

We Used SDSC's Gordon Data-Intensive Supercomputer to Analyze a Wide Range of Gut Microbiomes

Source: Weizhong Li, Sitao Wu, CRBS, UCSD

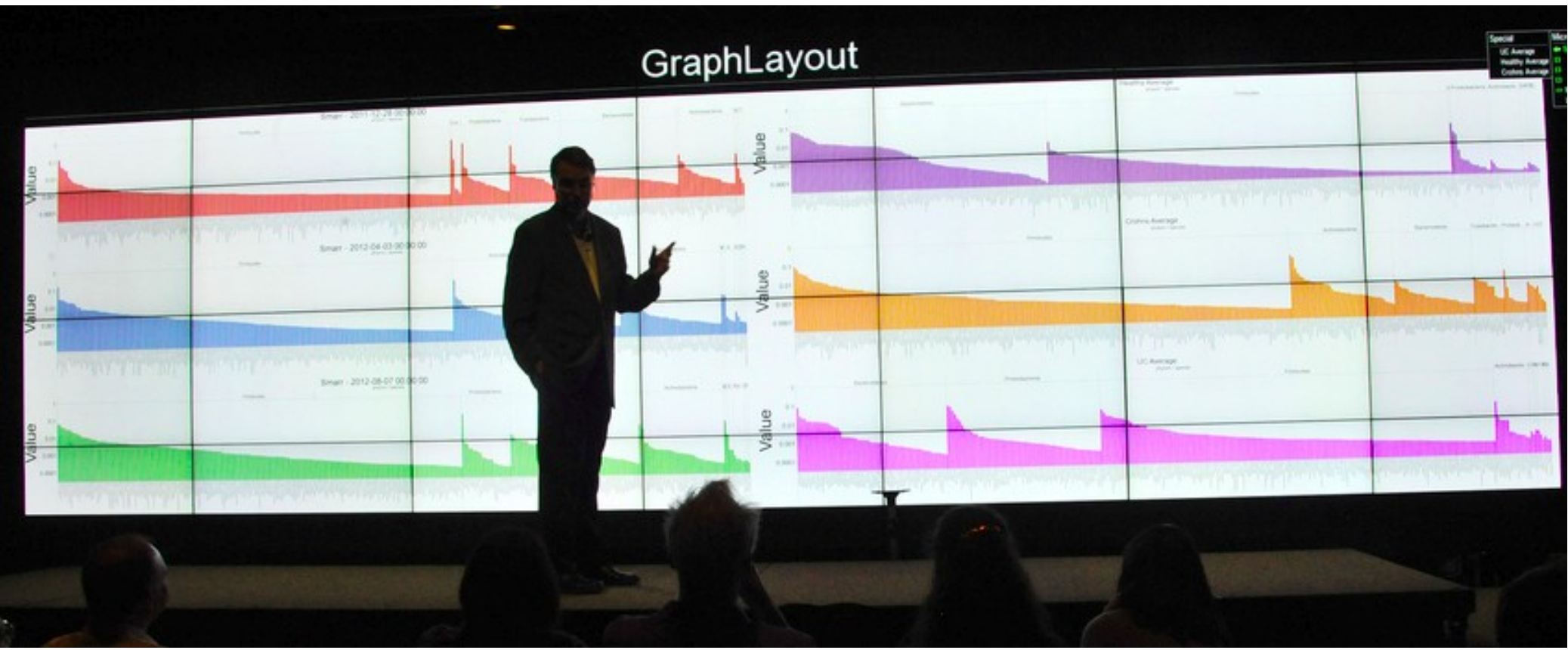


Our Team Used 25 CPU-Decades
To Compute
the Comparative Gut Microbiome
of My Time Samples
and Our Healthy and IBD Controls
Starting With
the 5 Billion Illumina Reads
Received from JCVI

Enabled by
a Grant of Time
on Gordon from SDSC
Director Mike Norman

NSF NIH HMP J. Craig Venter INSTITUTE CRBS SDSC it²

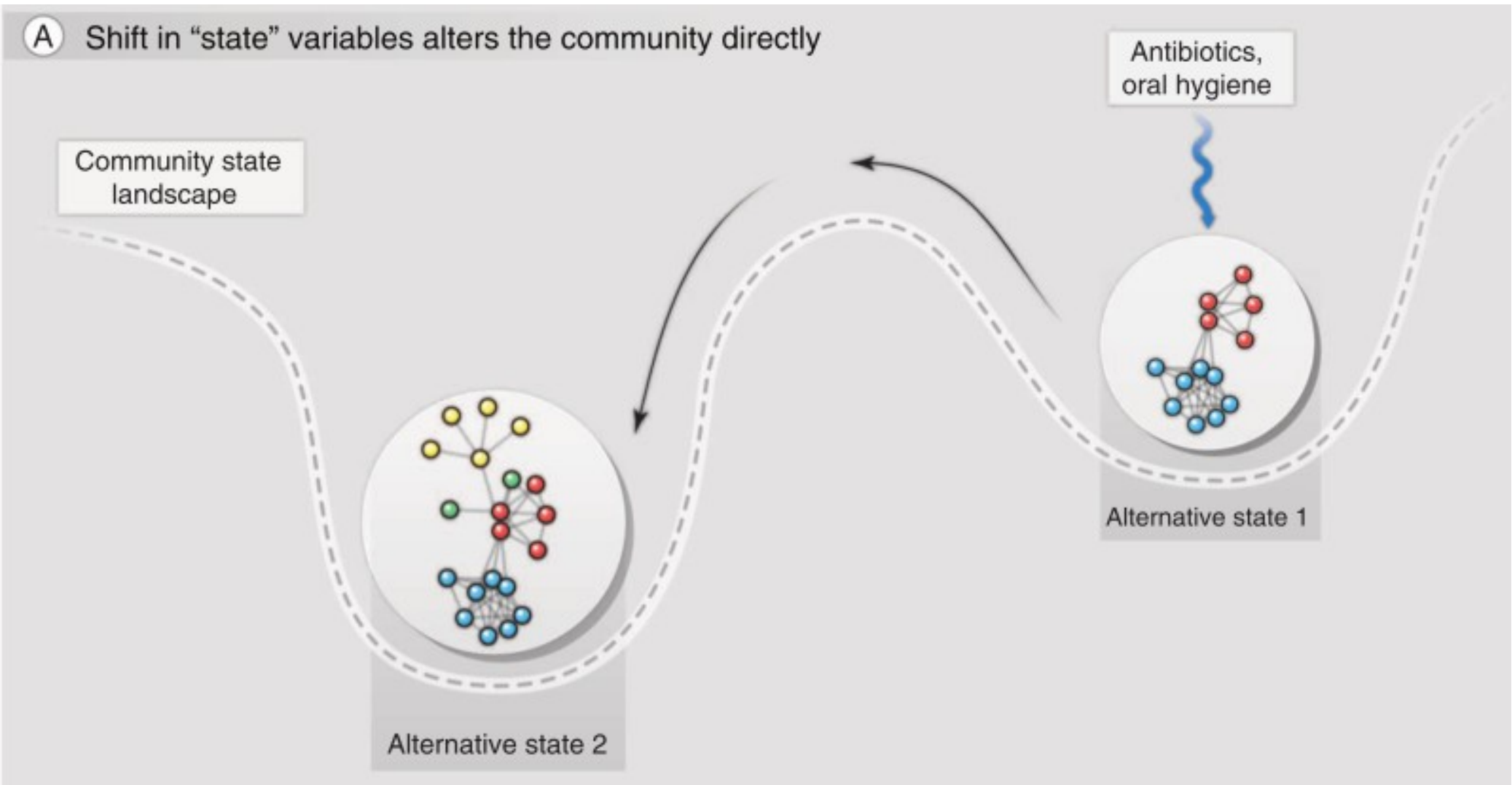
Using Scalable Visualization Allows Comparison of the Relative Abundance of 200 Microbe Species



Comparing 3 LS Time Snapshots (Left)
with Healthy, Crohn's, UC (Right Top to Bottom)

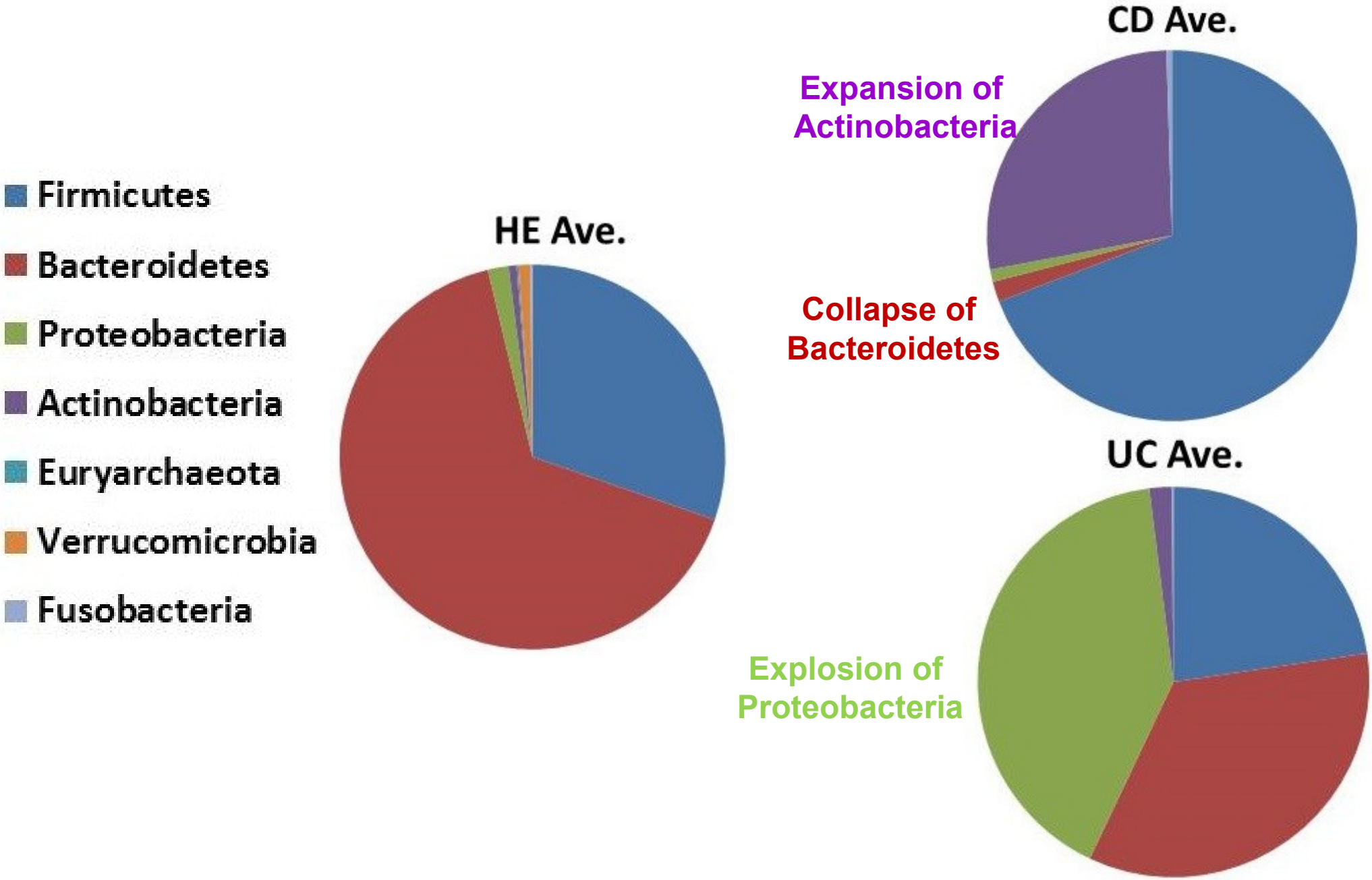
Calit2 VROOM-FuturePatient Expedition

Lessons from Ecological Dynamics I: Gut Microbiome Has Multiple Relatively Stable Equilibria



"The Application of Ecological Theory Toward an Understanding of the Human Microbiome,"
Elizabeth Costello, Keaton Stagaman, Les Dethlefsen, Brendan Bohannan, David Relman
Science 336, 1255-62 (2012)

Disease State Has a Different Microbiome Equilibrium Than Healthy



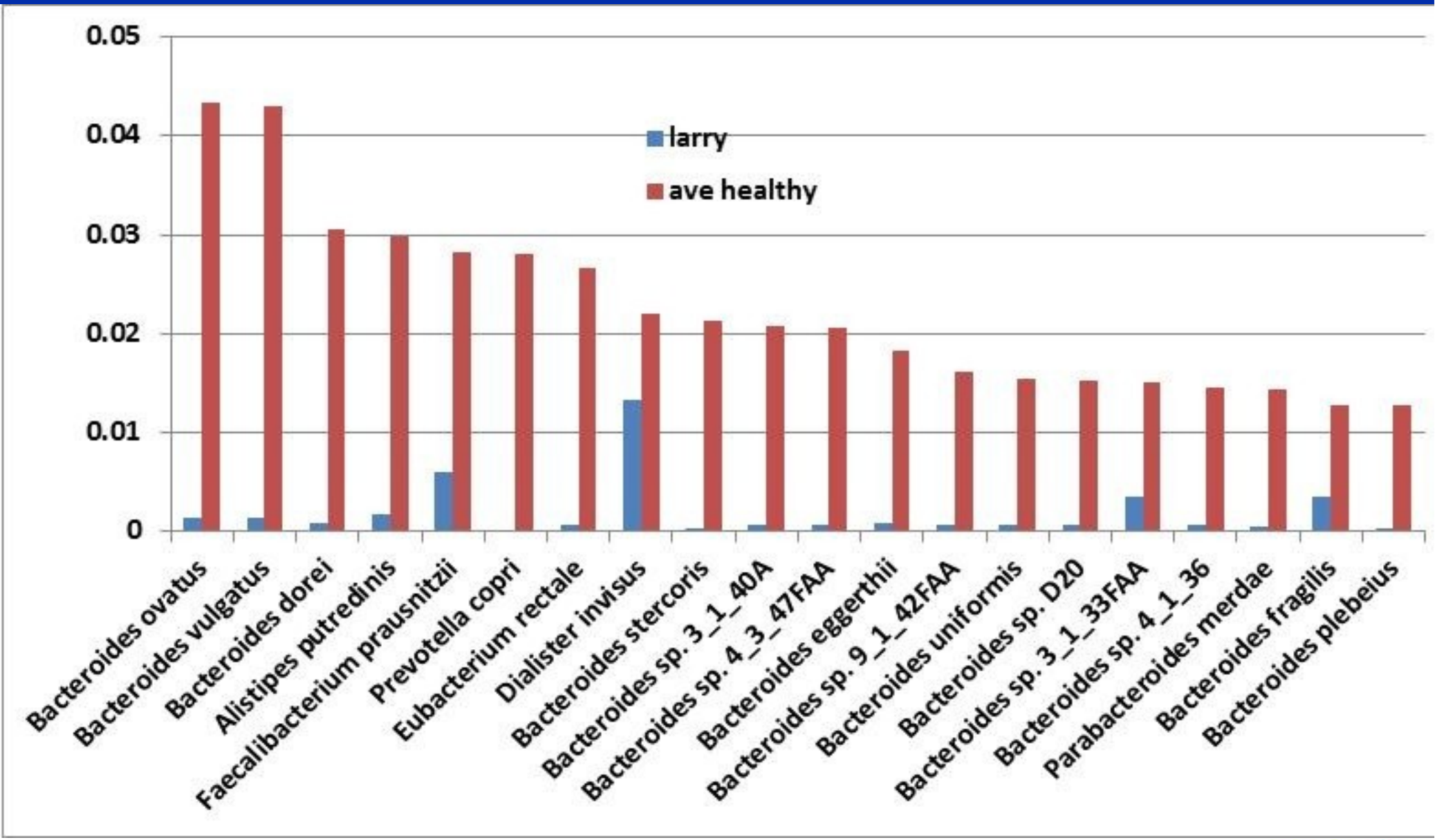
Lessons From Ecological Dynamics II:
Invasive Species Dominate After Major Species Destroyed



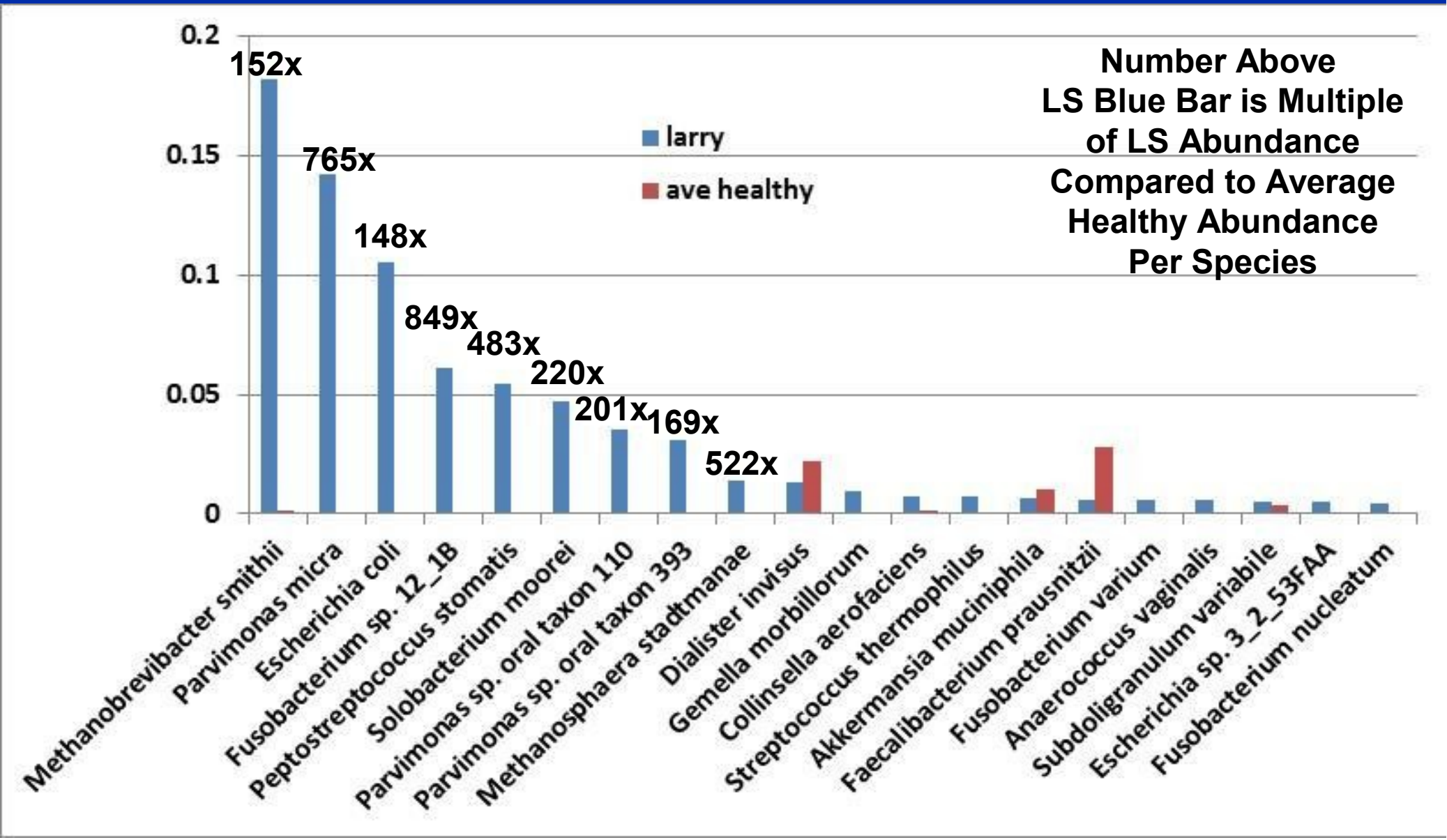
”In many areas following these burns invasive species are able to establish themselves, crowding out native species.”

Source: Ponderosa Pine Fire Ecology
http://cpluhna.nau.edu/Biota/ponderosafire.htm

Almost All Abundant Species (≥1%) in Healthy Subjects Are *Severely Depleted* in Larry's Gut Microbiome



Top 20 Most Abundant Microbial Species In LS vs. Average Healthy Subject



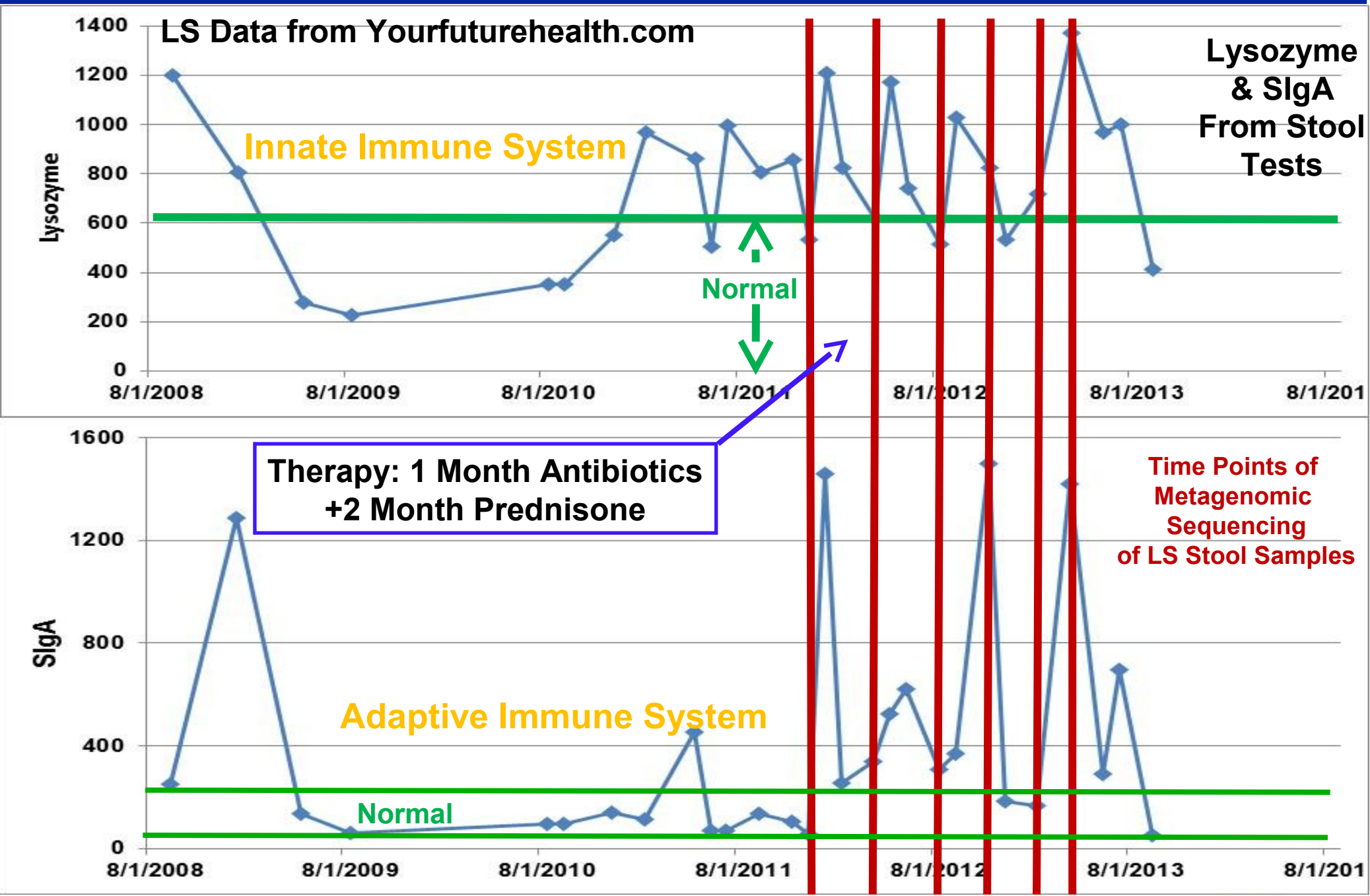
Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

Homing in on the Dynamic Interactions of the Coupled Human Immune System & Gut Microbiome

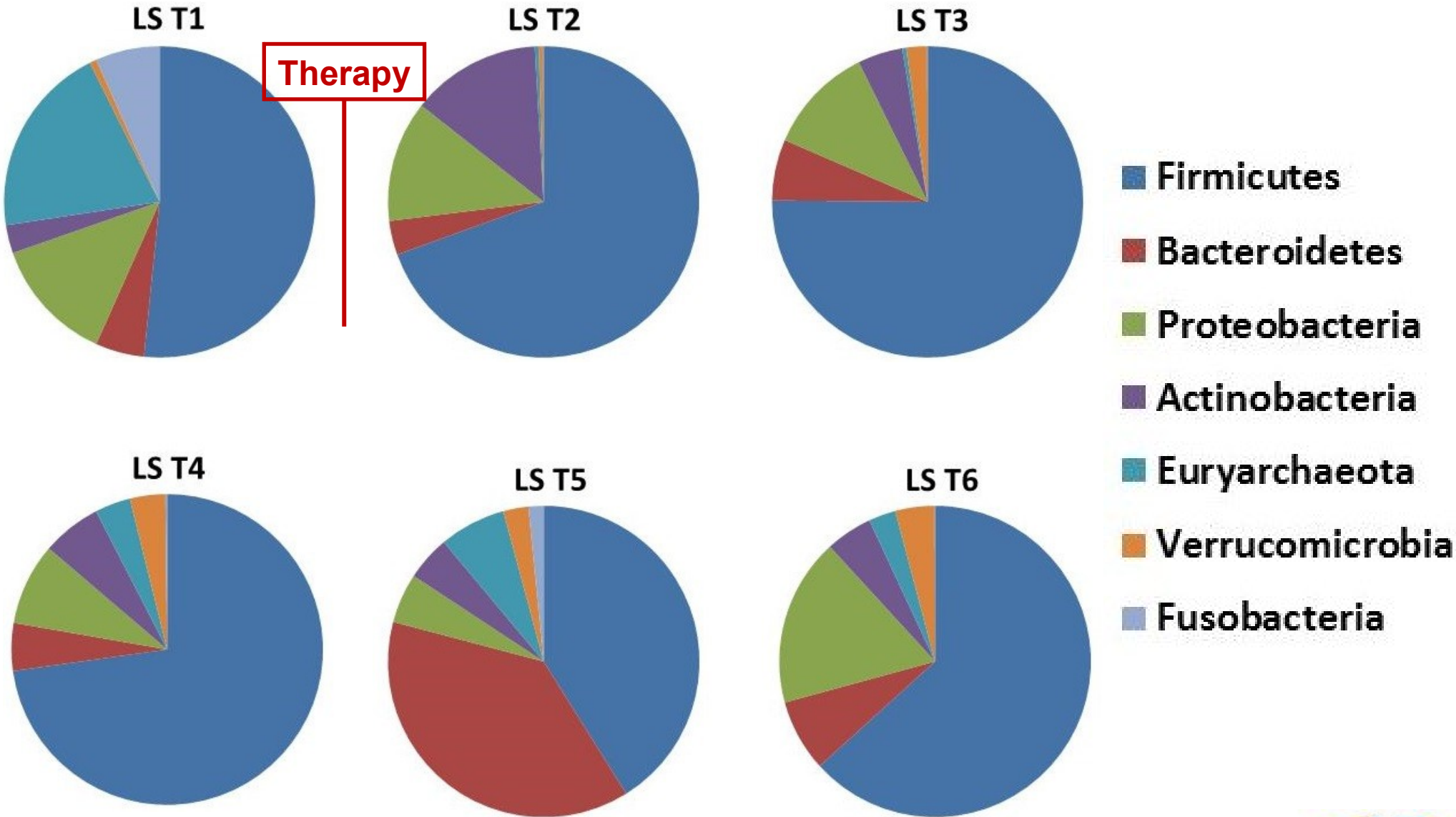
"Advances in our understanding of the interplay between components of the innate and adaptive arms of the immune system will be central to future progress."

-Judy H. Cho,
The Genetics and Immunopathogenesis of Inflammatory Bowel Disease,
***Nature Reviews Immunology* (2008)**

Fine Time Resolution Sampling Revealed Regular Oscillations of the Innate and Adaptive Immune System



Time Series Reveals Autoimmune Dynamics of Gut Microbiome by Phyla



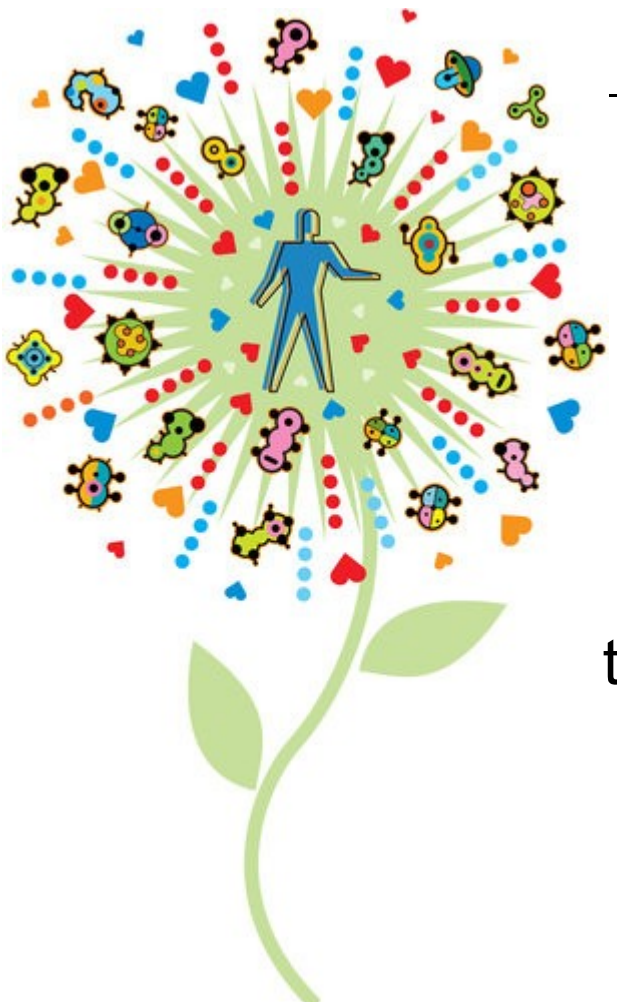
Six Metagenomic Time Samples Over 16 Months

Next Step: Time Series of Metagenomic Gut Microbiomes and Immune Variables in an N=100 Clinic Trial

Goal: Understand
The Coupled Human Immune-Microbiome Dynamics
In the Presence of Human Genetic Predispositions

Drs. William J. Sandborn, John Chang, & Brigid Boland
UCSD School of Medicine, Division of Gastroenterology

From War to Gardening: New Therapeutical Tools for Managing the Microbiome



The New York Times

Science

Tending the Body's Microbial Garden

By CARL ZIMMER
Published: June 18, 2012

"I would like to lose the language of warfare," said Julie Segre, a senior investigator at the National Human Genome Research Institute. "It does a disservice to all the bacteria that have co-evolved with us and are maintaining the health of our bodies."

Where I Believe We are Headed: Predictive, Personalized, Preventive, & Participatory Medicine

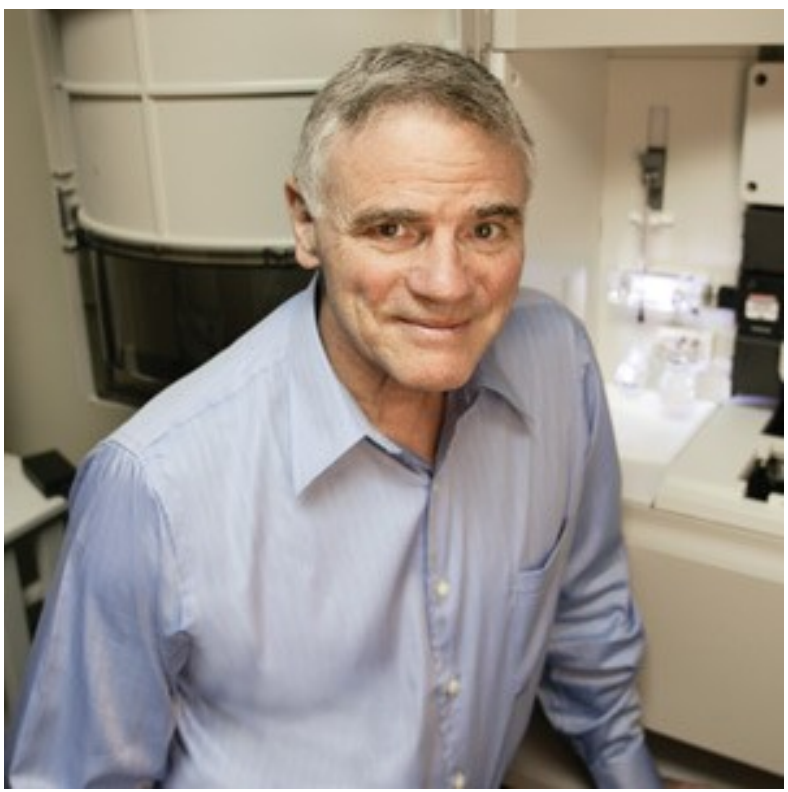
Newsweek

I am Lee Hood's Lab Rat!

A Doctor's Vision of the Future of Medicine

Leroy Hood
NEWSWEEK

From the magazine issue dated Jul 13, 2009



www.newsweek.com/2009/06/26/a-doctor-s-vision-of-the-future-of-medicine.html

Thanks to Our Great Team!

UCSD Metagenomics Team

Weizhong Li
Sitao Wu

JCVI Team

Karen Nelson
Shibu Yooseph
Manolito Torralba

Calit2@UCSD Future Patient Team

Jerry Sheehan
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