"The Systems Biology Dynamics of the Human Immune System and Gut Microbiome"

Invited Talk

UCI Systems Biology Seminar Series

Irvine, CA

October 14, 2013

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

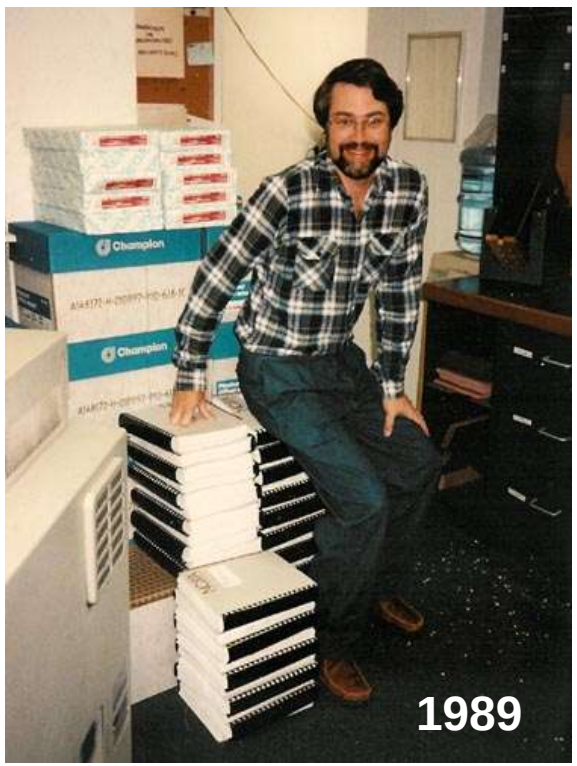
http://lsmarr.calit2.net

Abstract

In the last few years great progress has been made on using genetic sequencing to reveal the extraordinary microbial ecology that co-habits our human bodies. Indeed, ~90% of the cells in our superorganism are microbial and they contain ~99% of the DNA genes contained in our body. After birth, the growing diversity of gut bacterial species acts as a series of training sets to "boot up" the human immune system, leading to a lifetime coupled system of immune components and microbial ecology. In health the constant feedback between the immune system and microbiome leads to homeostasis in the gut. However, in autoimmune diseases this balance fails leading to large oscillations in immune variables and massive disruption of the microbial ecology. I will demonstrate this dysbiotic state with data taken from my own gut over the last five years. Deep metagenomic sequencing of the my gut microbiome reveals system dynamics at the species or even strain level. After exhibiting the ability to read out the immune system-microbiome dynamics, I will review current efforts to model this important biological system computationally or in vitro.

I Arrived in La Jolla in 2000 After 20 Years in the Midwest and Decided to Move Against the Obesity Trend

Age 41



Age 51



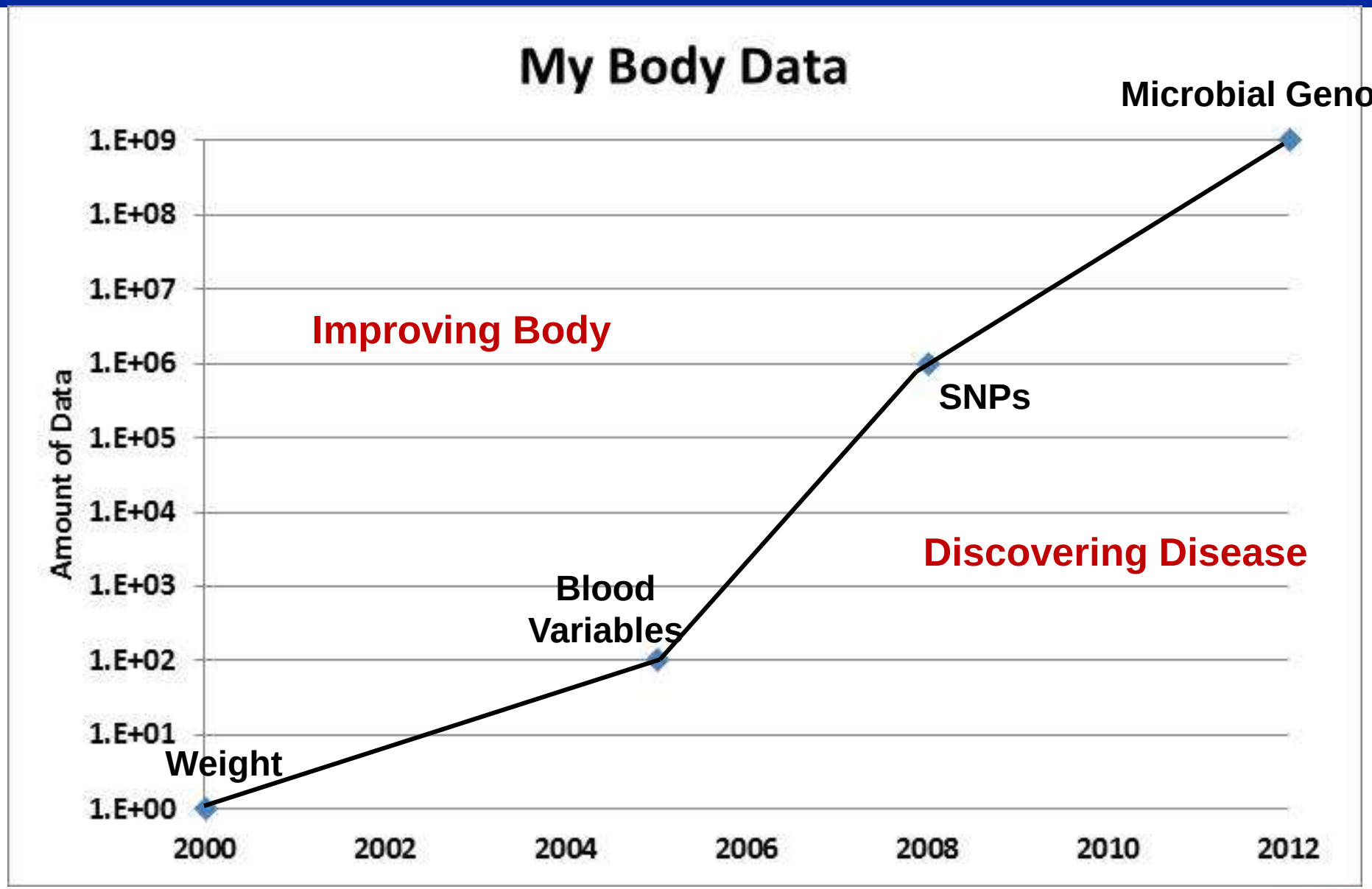
Age 61



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

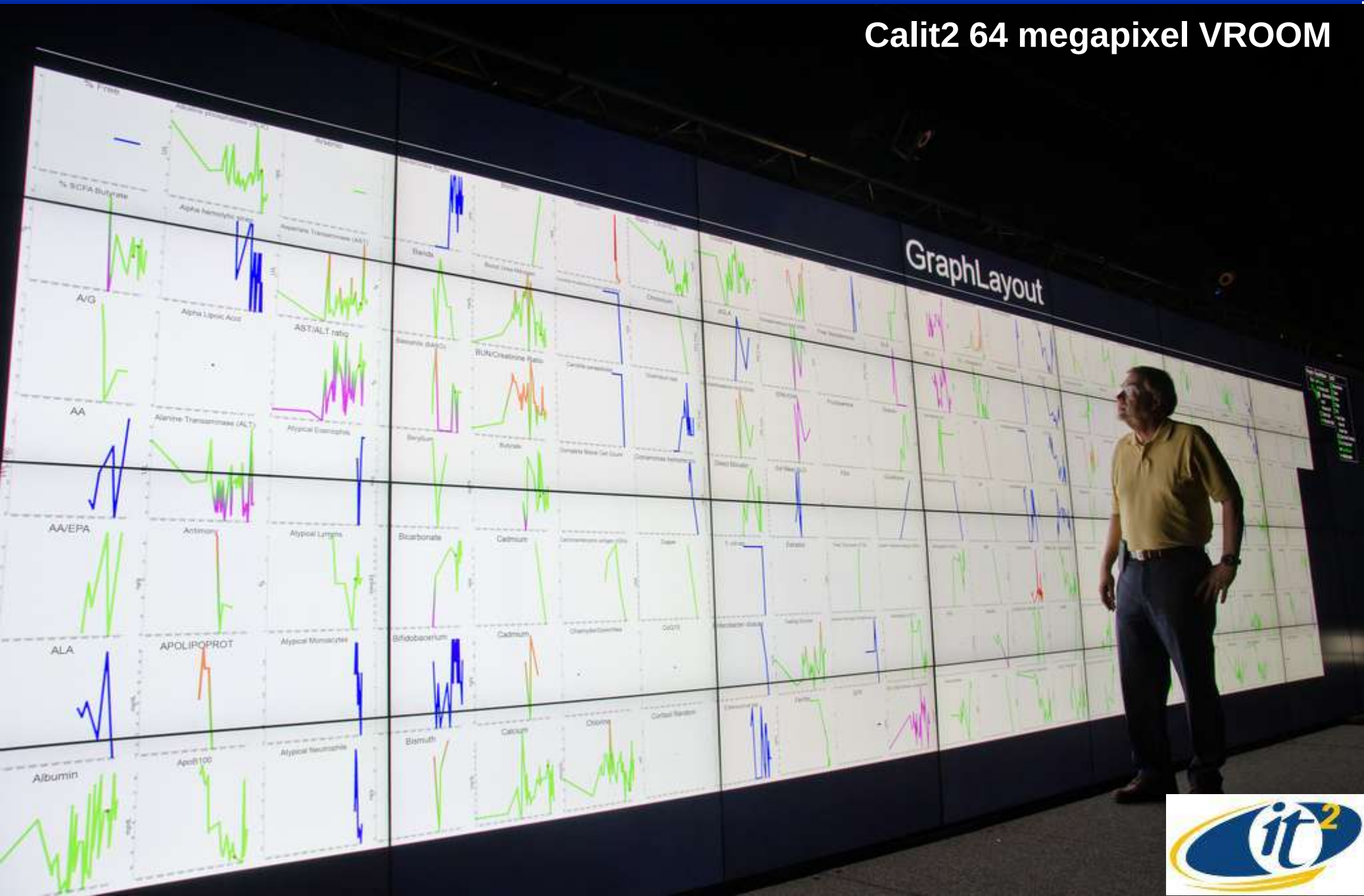
http://lsmarr.calit2.net/repository/LS_reading_recommendations_FiRe_2011.pdf

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

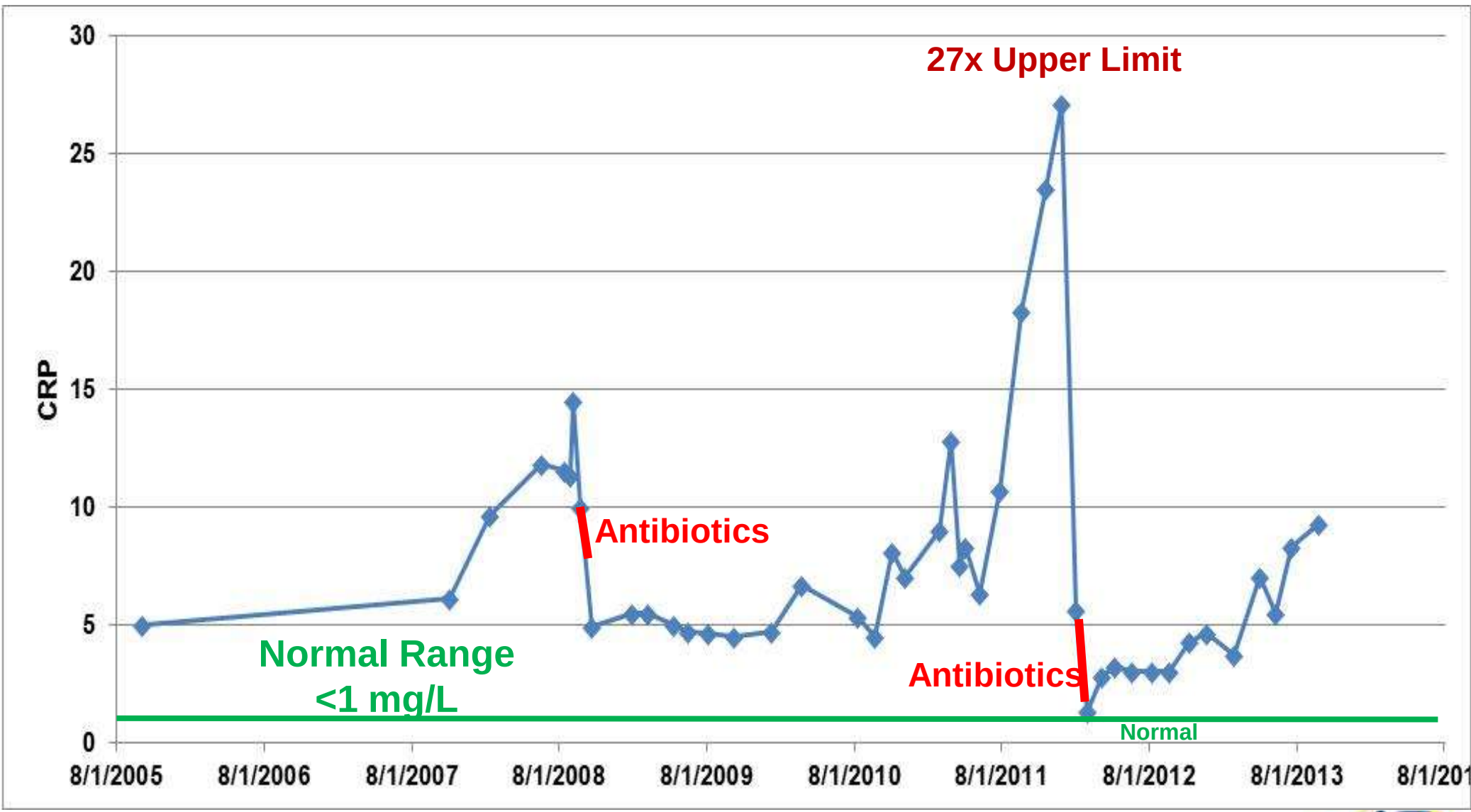


Each is a Personal Time Series
And Compared Across Population

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

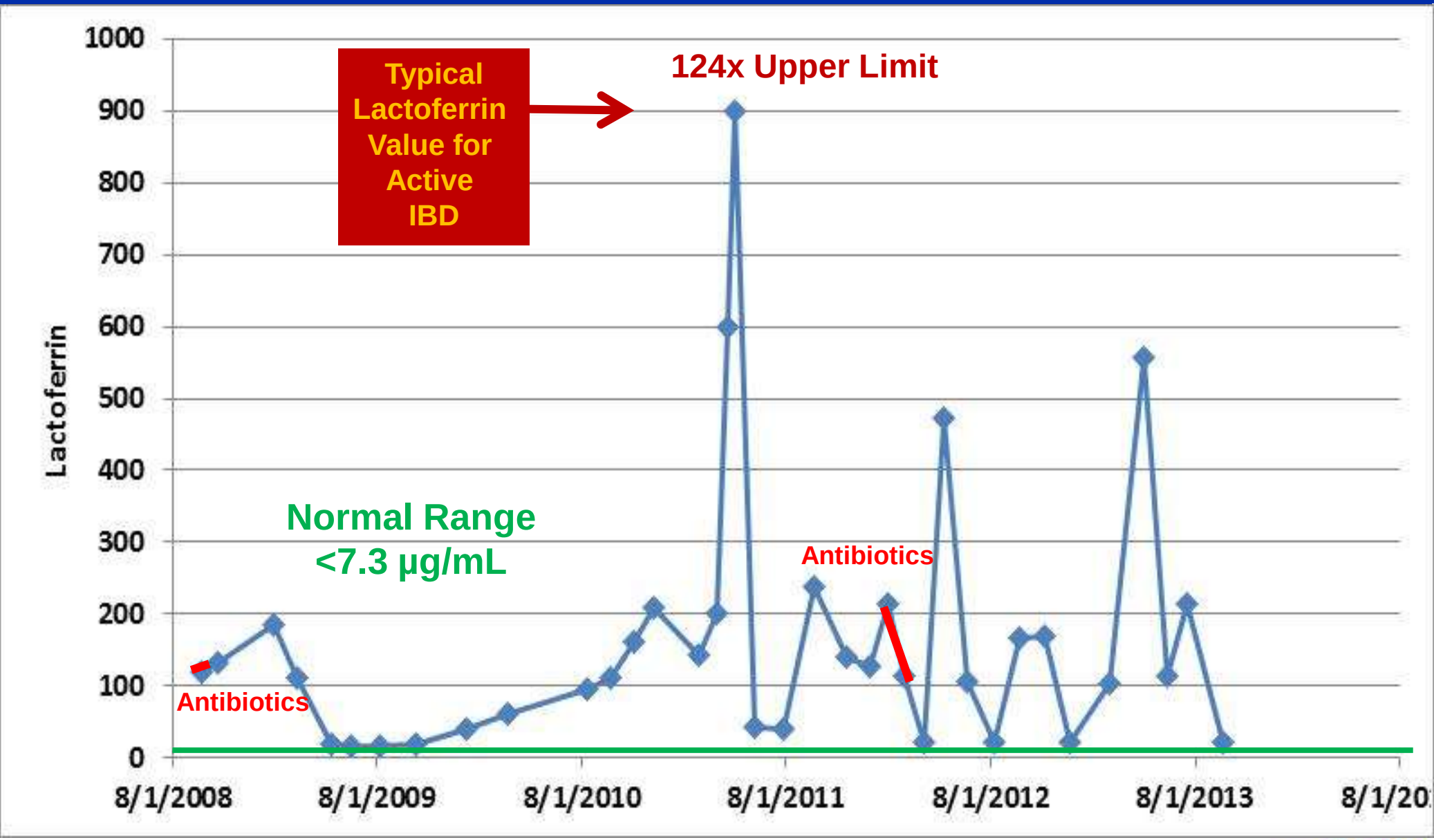


I Discovered I Had Episodic Chronic Inflammation by Tracking Complex Reactive Protein In My Blood Samples



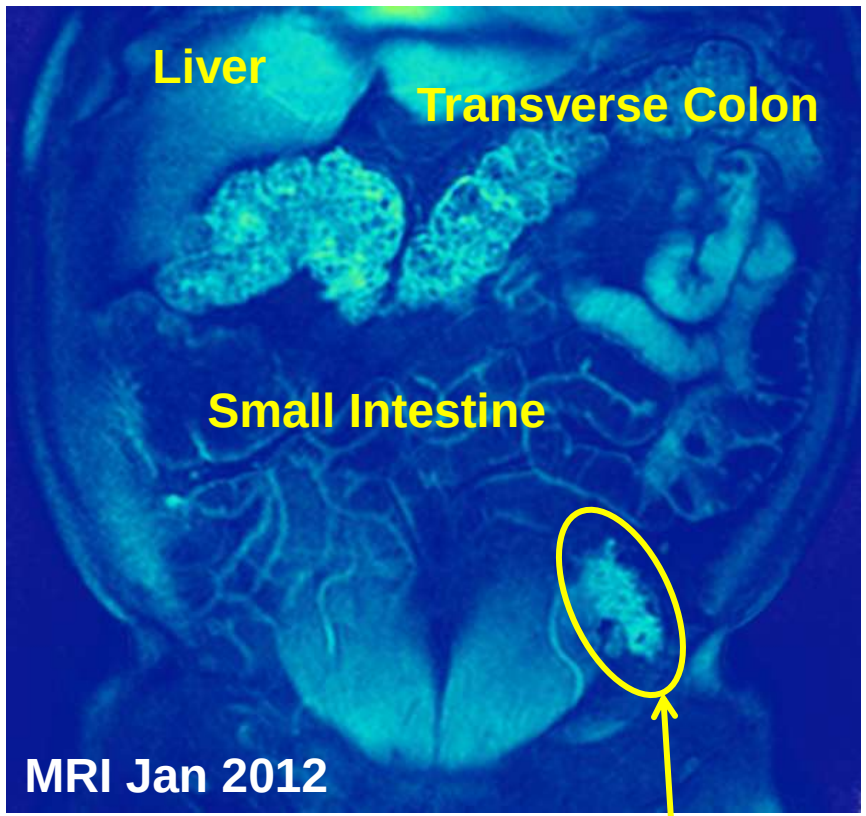
CRP is a Generic Measure of Inflammation in the Blood

By Adding Stool Samples, I Discovered I Had High Levels of the Protein Lactoferrin Shed from Neutrophils



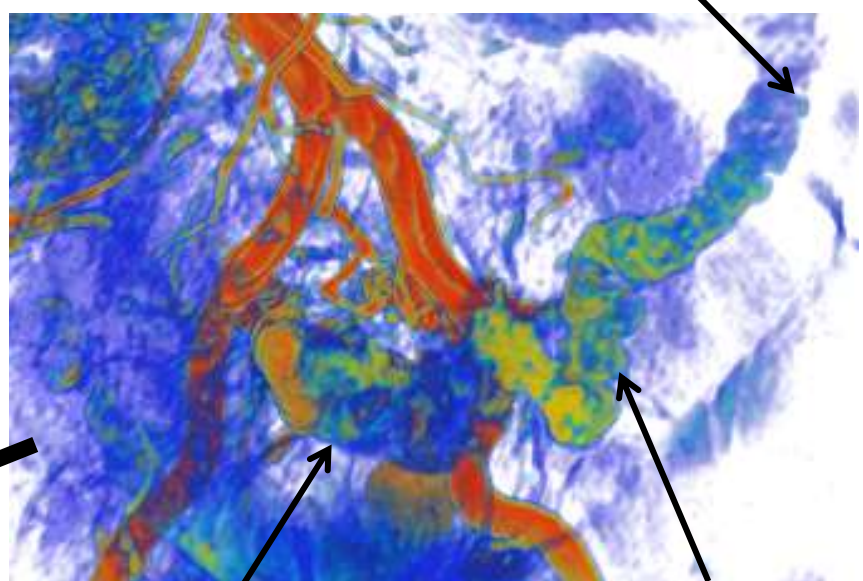
Lactoferrin is a Protein Shed from Neutrophils - An Antibacterial that Sequesters Iron

Confirming the IBD (Crohn's) 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

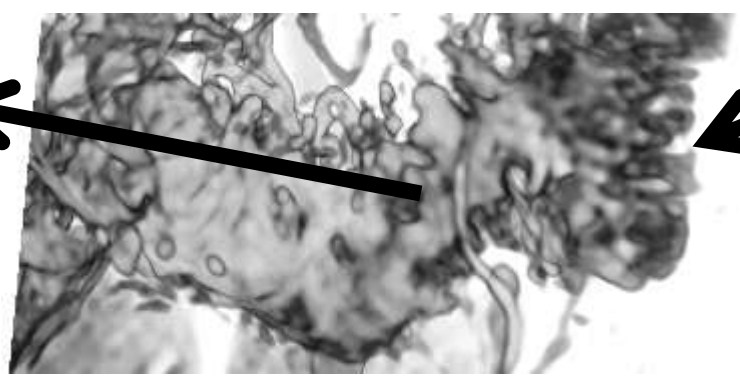
Descending Colon



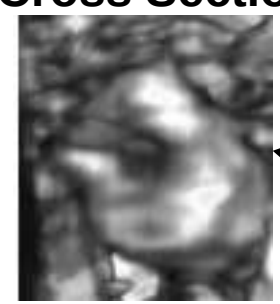
Major Kink

Sigmoid Colon Threading Iliac Arteries

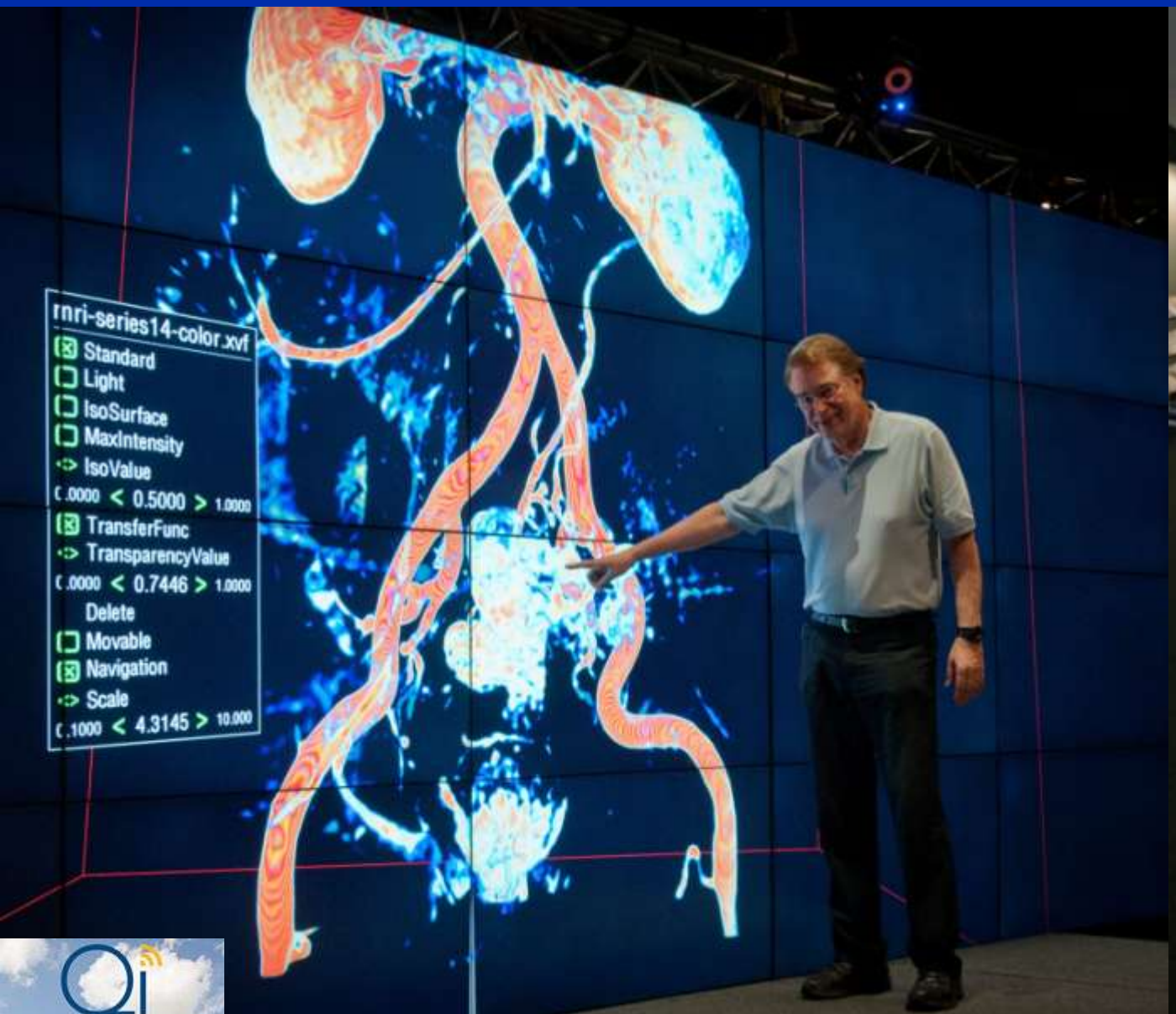
Diseased Sigmoid Colon



Cross Section



Converting MRI Slices Into 3D Interactive Virtual Reality AND 3-D Printing







Research: Calit2 FutureHealth Team

Why Did I Have an Autoimmune Disease like IBD?

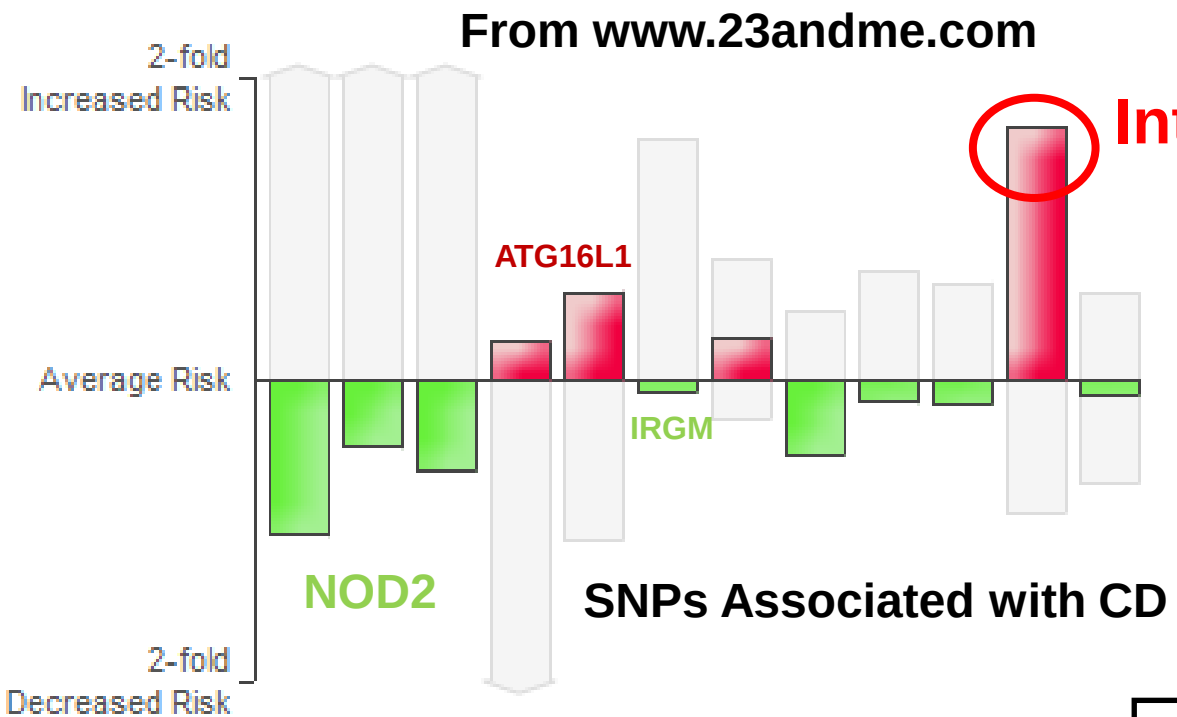
Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.

--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)

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

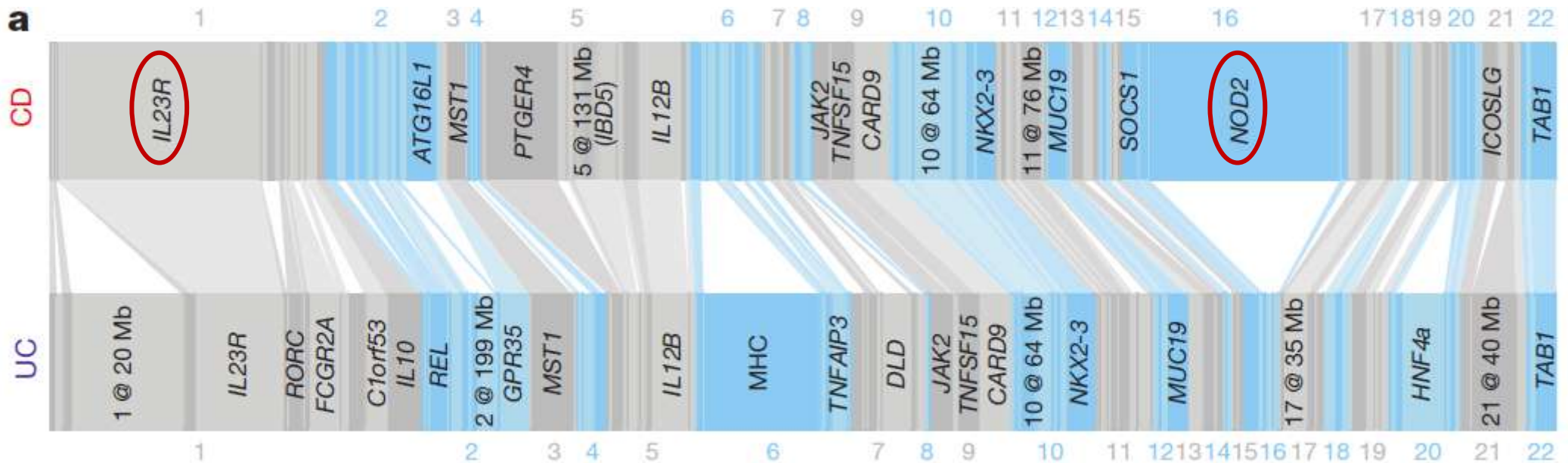
News and Views

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

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

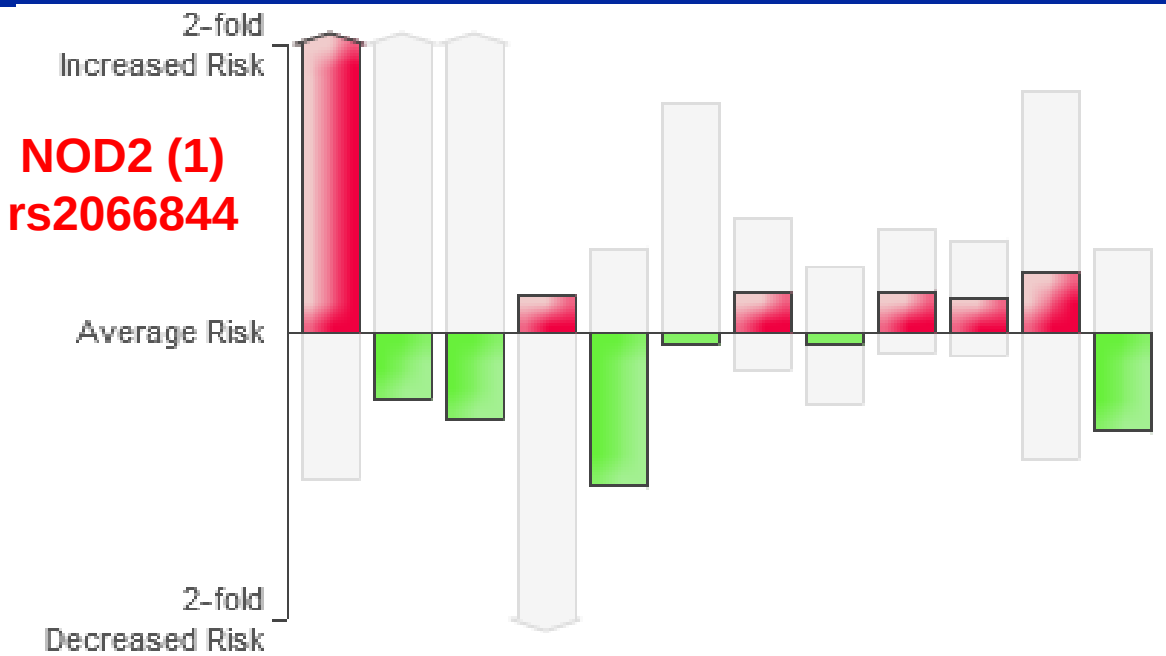
Variance Explained by Each of the 163 SNPs Associated with IBD



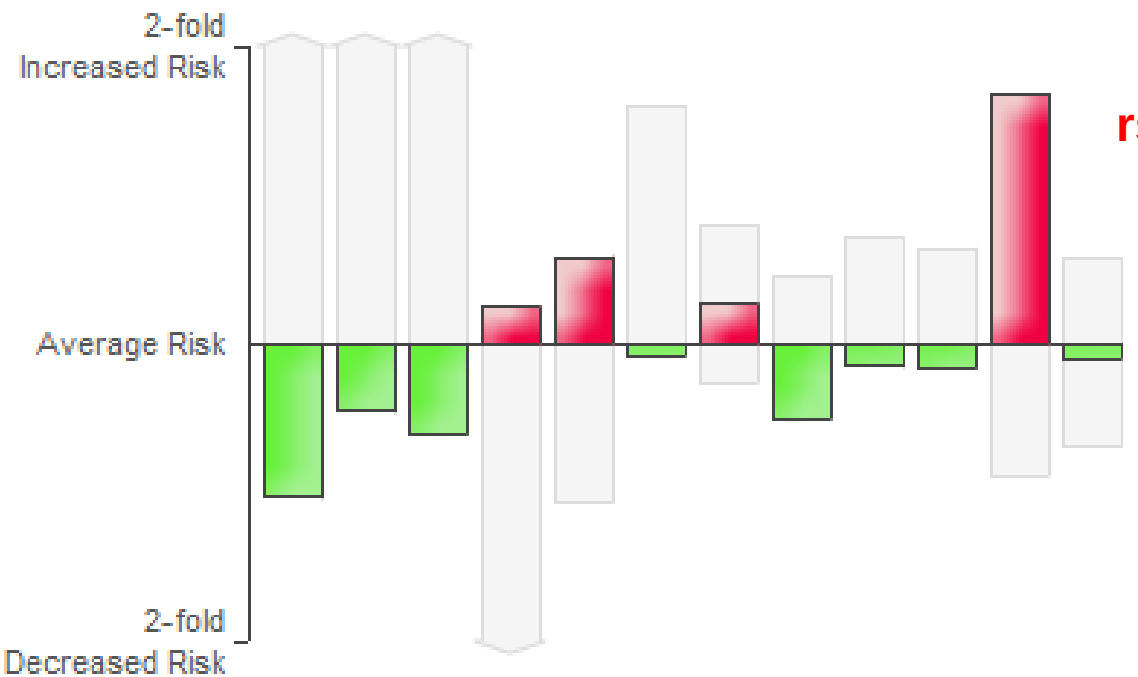
- The width of the bar is proportional to the variance explained by that locus
- Bars are connected together if they are identified as being associated with both phenotypes
- Loci are labelled if they explain more than 1% of the total variance explained by all loci

"Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease," Jostins, et al. Nature 491, 119-124 (2012)

Crohn's May be a Related Set of Diseases Driven by Different SNPs



Female
CD Onset
At 20-Years Old



Il-23R
rs1004819

Me-Male
CD Onset
At 60-Years Old

I Had My Full Human Genome Sequenced in 2012 - 1 Million/Year by 2015

Next Step: Compare Full Genome With IBD SNPs



PGP Used Complete Genomics, Inc. to Sequence my Human DNA

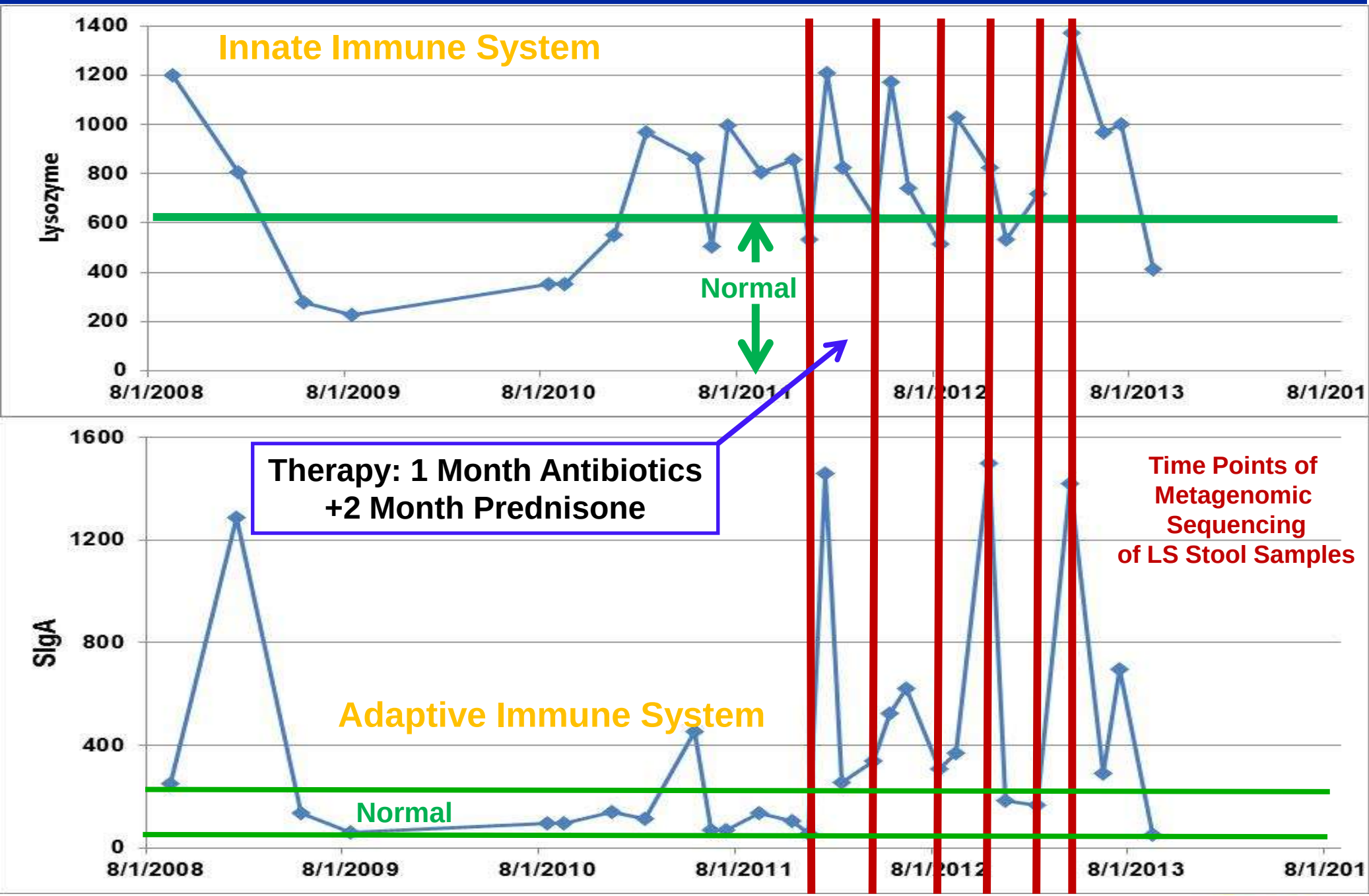
My Anonymized Human Genome is Available for Download

Personal Genome Project

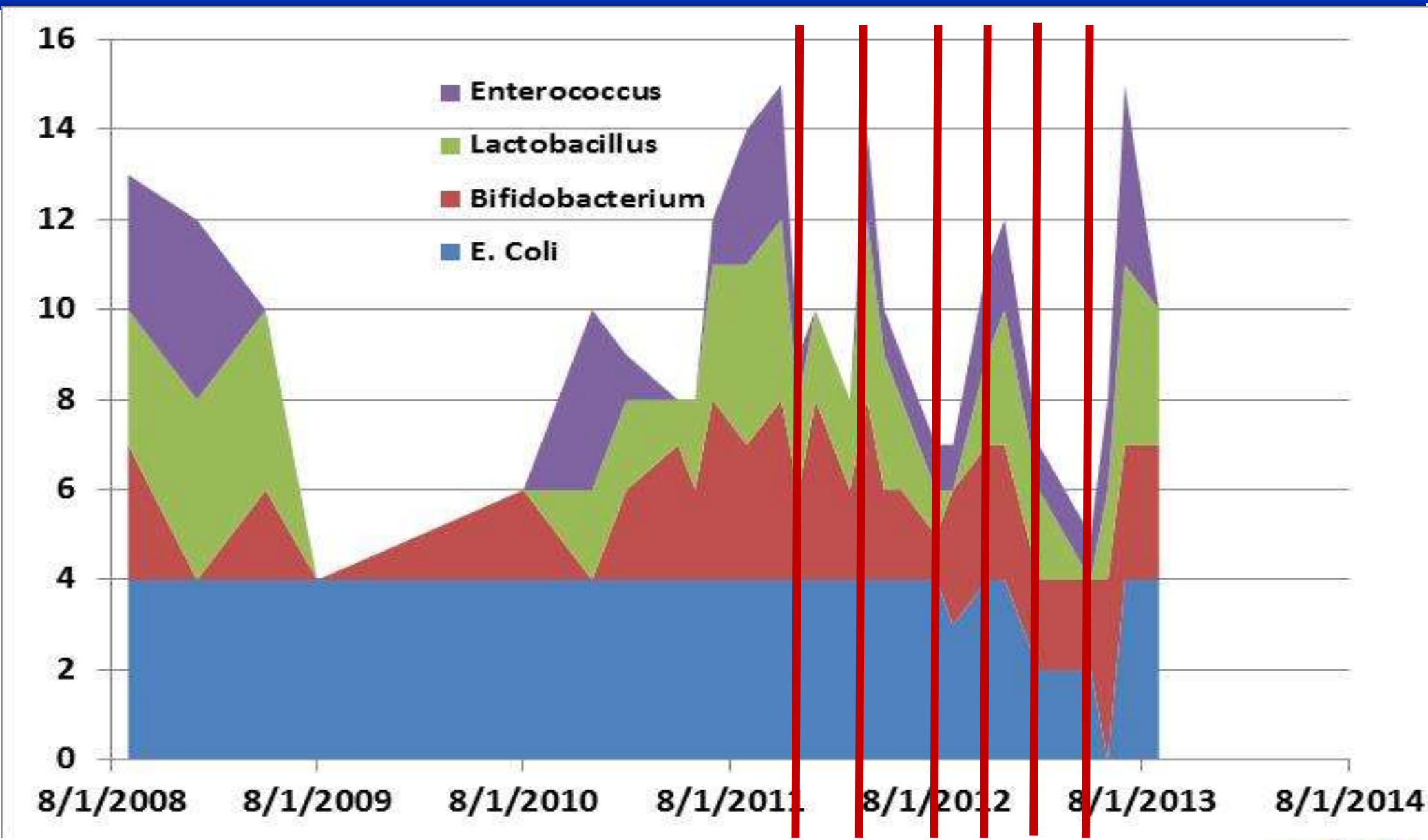


www.personalgenomes.org

Fine Time Resolution Sampling Reveals Unexpected Dynamics of Innate and Adaptive Immune System



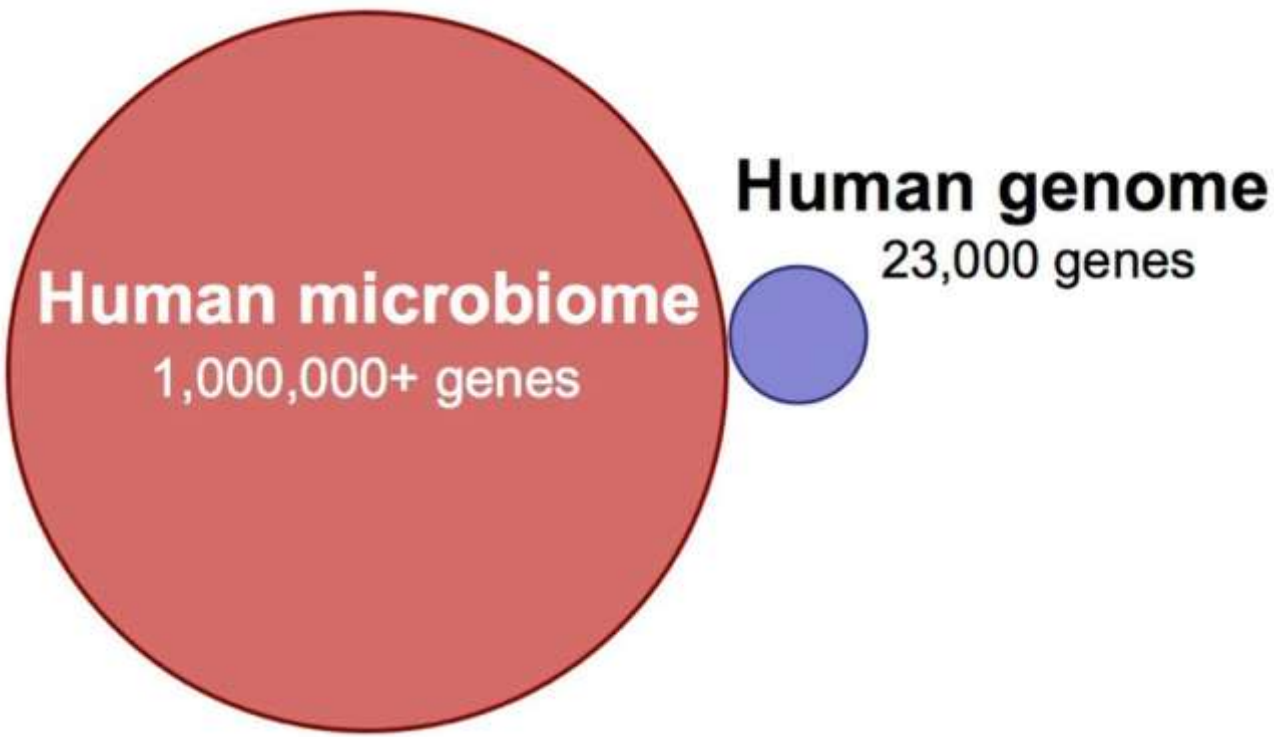
LS Cultured Bacterial Abundance Reveals Dynamic Microbiome Dysfunction



Time Points of Metagenomic Sequencing of LS Stool Samples

Next: Analyze the Dynamics of My Microbiome Ecology- 85% of the Species Can Not Be Cultured

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

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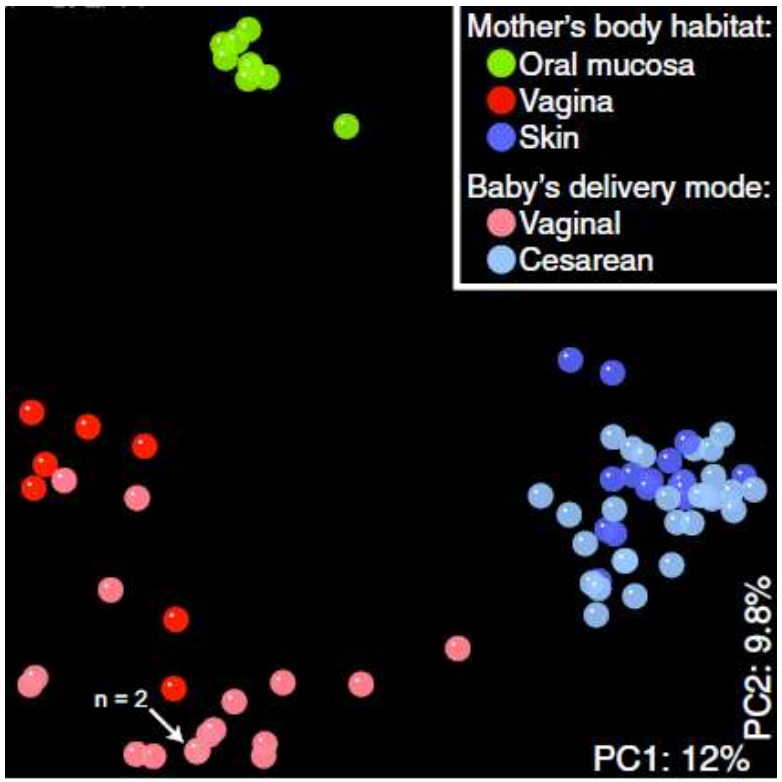
The Increasing Diversity of the Infant Gut Microbiome "Boots Up" the Infant's Immune System

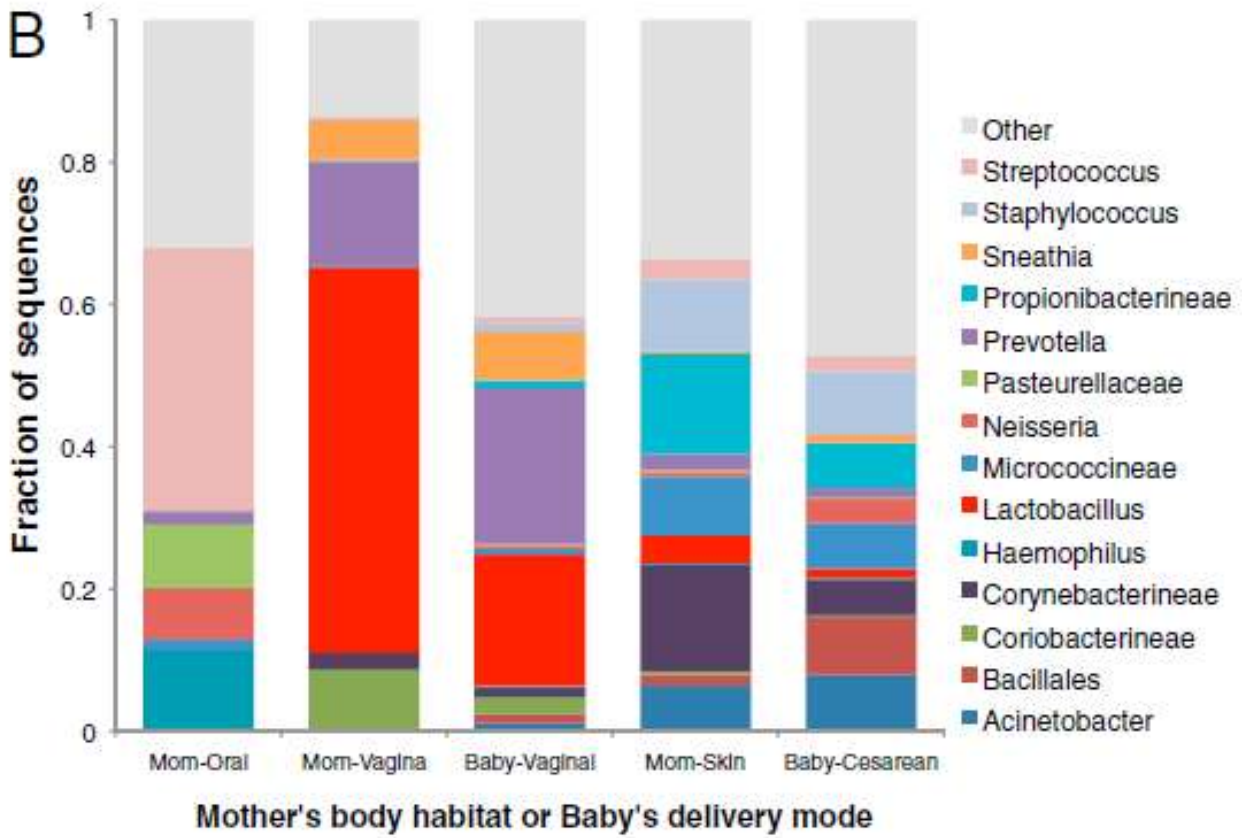
"The neonatal microbiota varies erratically until about 1-year-old when it stabilizes, establishing a consortium that resembles that of adults.

During this initial period, the neonatal immune system rapidly matures under the influence of the microbiota."

"Reciprocal interactions of the intestinal microbiota and immune system," Craig Maynard, et al. Nature 489, 231-241 (2012)

Delivery Mode Determines Infant's Initial Microbiome

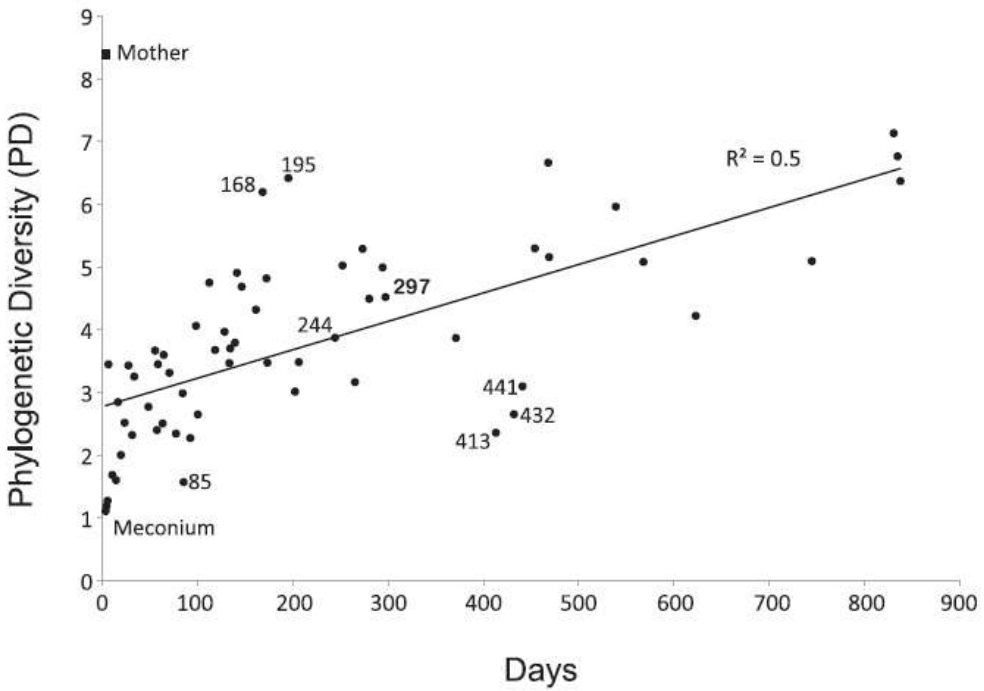


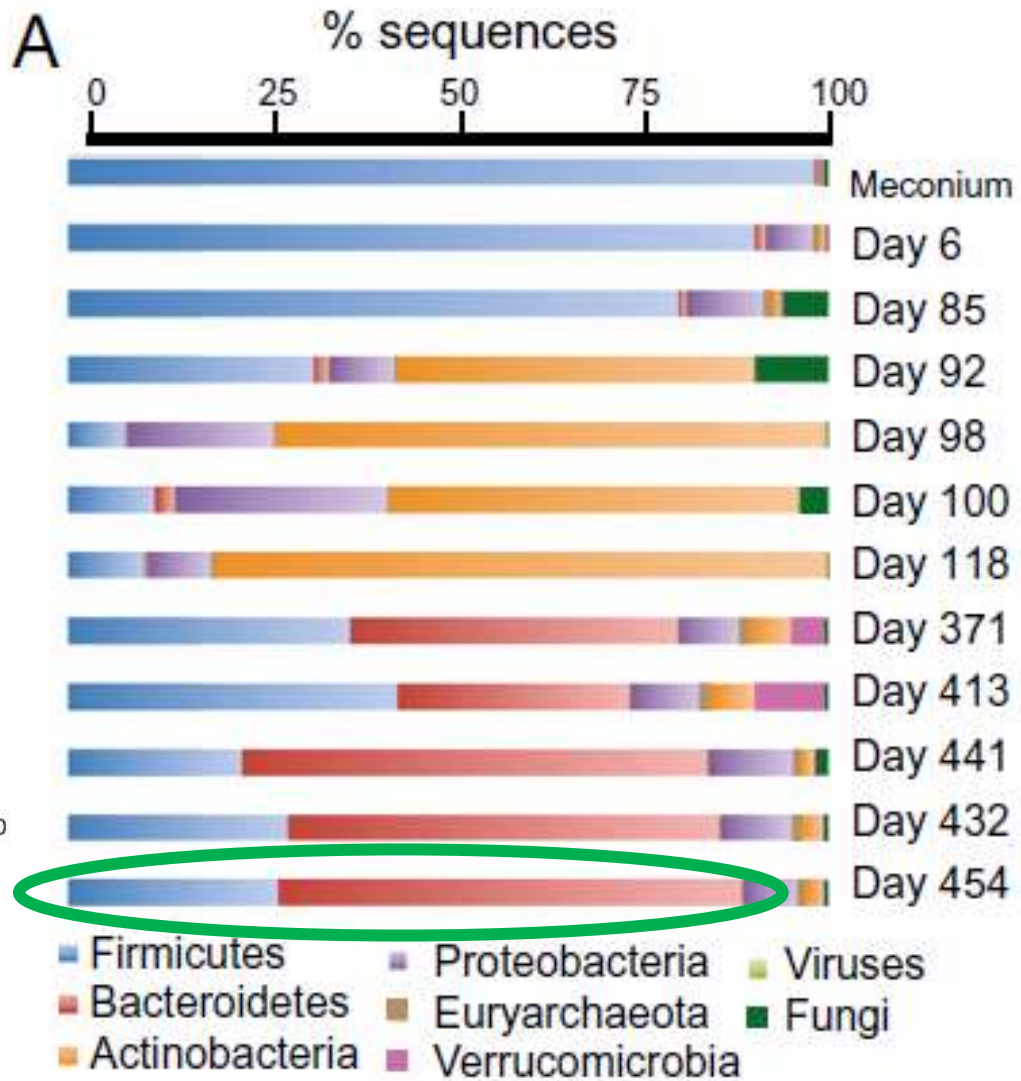


"The composition of the initial microbiota may have implications for nutritional and immune functions associated with the developing microbiota. For example, recent studies suggest that Cesarean-delivered babies may be more susceptible to allergies and asthma."

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

The Infant Gut Microbiome Rapidly Increases its Diversity After Birth

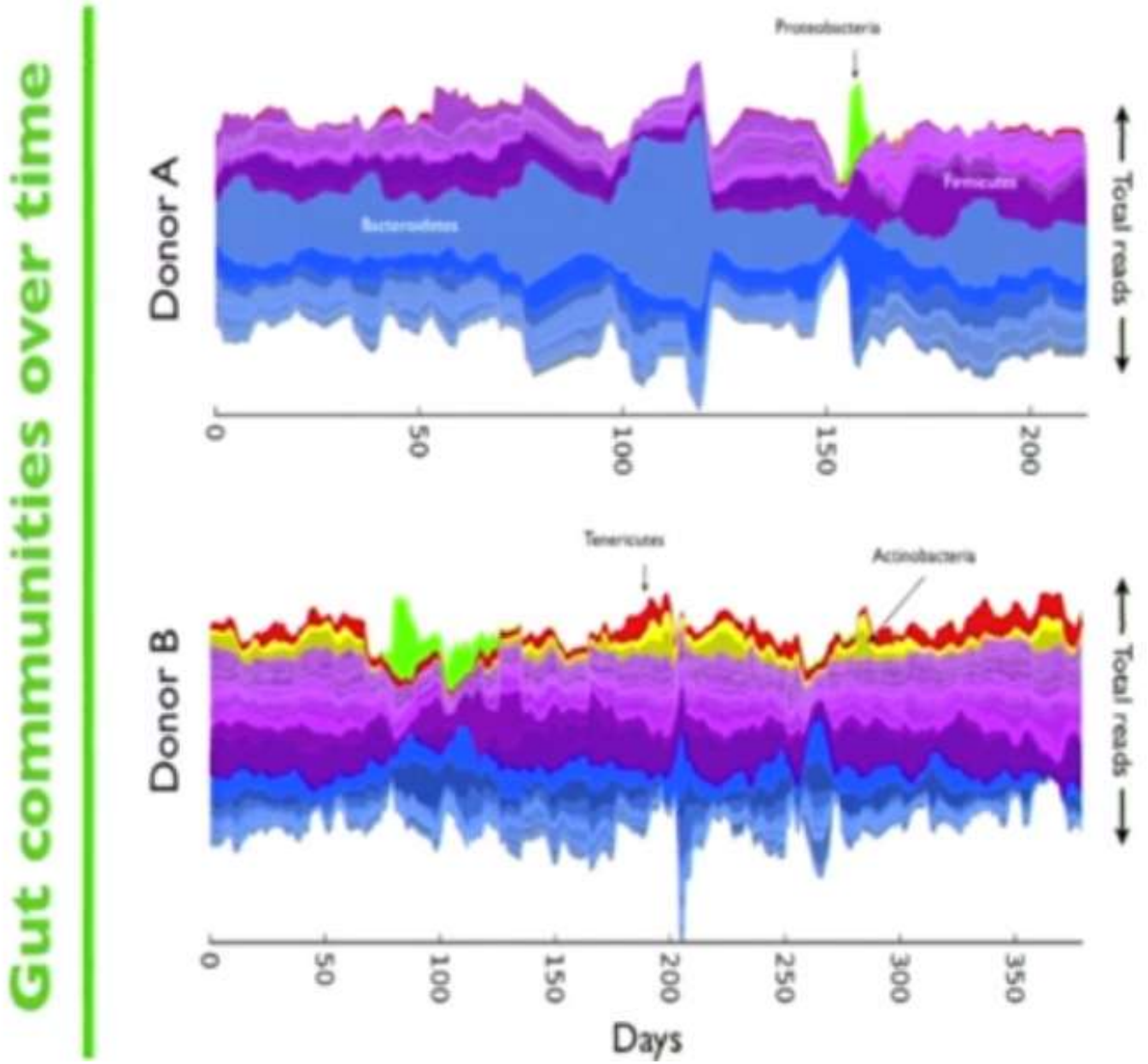




Adult Gut Microbiome Dominated By Bacteroidetes/Firmicutes

"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



Source: Eric Alm, MIT

To Map My Gut Microbes, I Sent a Stool Sample to the Venter Institute for Metagenomic Sequencing

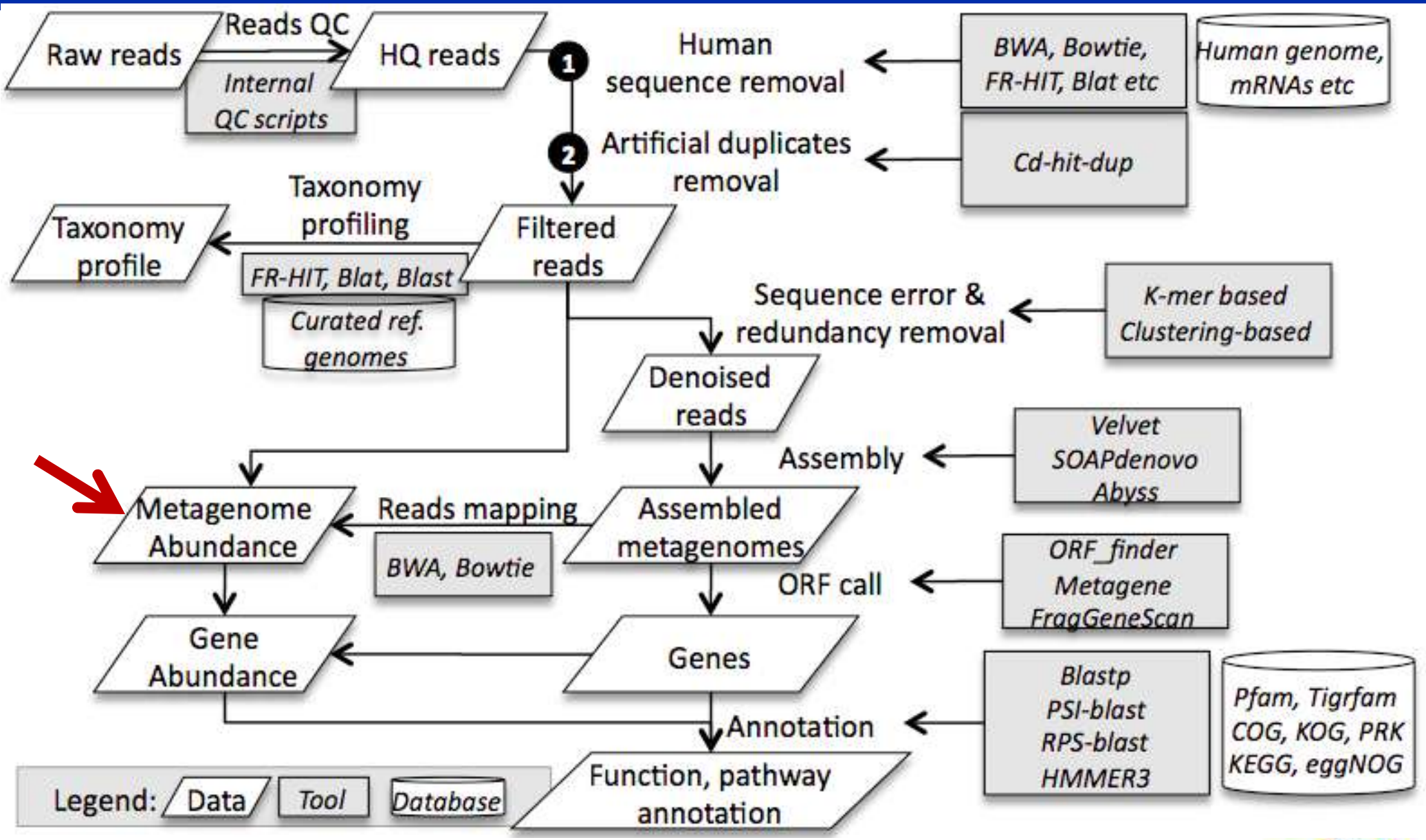


Gel Image of Extract from Smarr Sample-Next is Library Construction

Manny Torralba, Project Lead - Human Genomic Medicine
J Craig Venter Institute

January 25, 2012

Computational NextGen Sequencing Pipeline: From "Big Equations" to "Big Data" Computing



National Human Genome Research Institute

HMP

PI: (Weizhong Li, CRBS, UCSD):
NIH R01HG005978 (2010-2013, $1.1M)

CRBS

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We Created a Reference Database Of Known Gut Genomes

- **NCBI April 2013**
  - **2471 Complete + 5543 Draft Bacteria & Archaea Genomes**
  - **2399 Complete Virus Genomes**
  - **26 Complete Fungi Genomes**
  - **309 HMP Eukaryote Reference Genomes**
- **Total 10,741 genomes, ~30 GB of sequences**

Now to Align Our 12.5 Billion Reads Against the Reference Database

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Source: Weizhong Li, Sitao Wu, CRBS, UCSD

it²

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

- **~180,000 Core-Hrs on Gordon**
  - KEGG function annotation: 90,000 hrs
  - Mapping: 36,000 hrs
    - Used 16 Cores/Node and up to 50 nodes
  - Duplicates removal: 18,000 hrs
  - Assembly: 18,000 hrs
  - Other: 18,000 hrs
- **Gordon RAM Required**
  - 64GB RAM for Reference DB
  - 192GB RAM for Assembly
- **Gordon Disk Required**
  - Ultra-Fast Disk Holds Ref DB for All Nodes
  - 8TB for All Subjects



SDSC

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

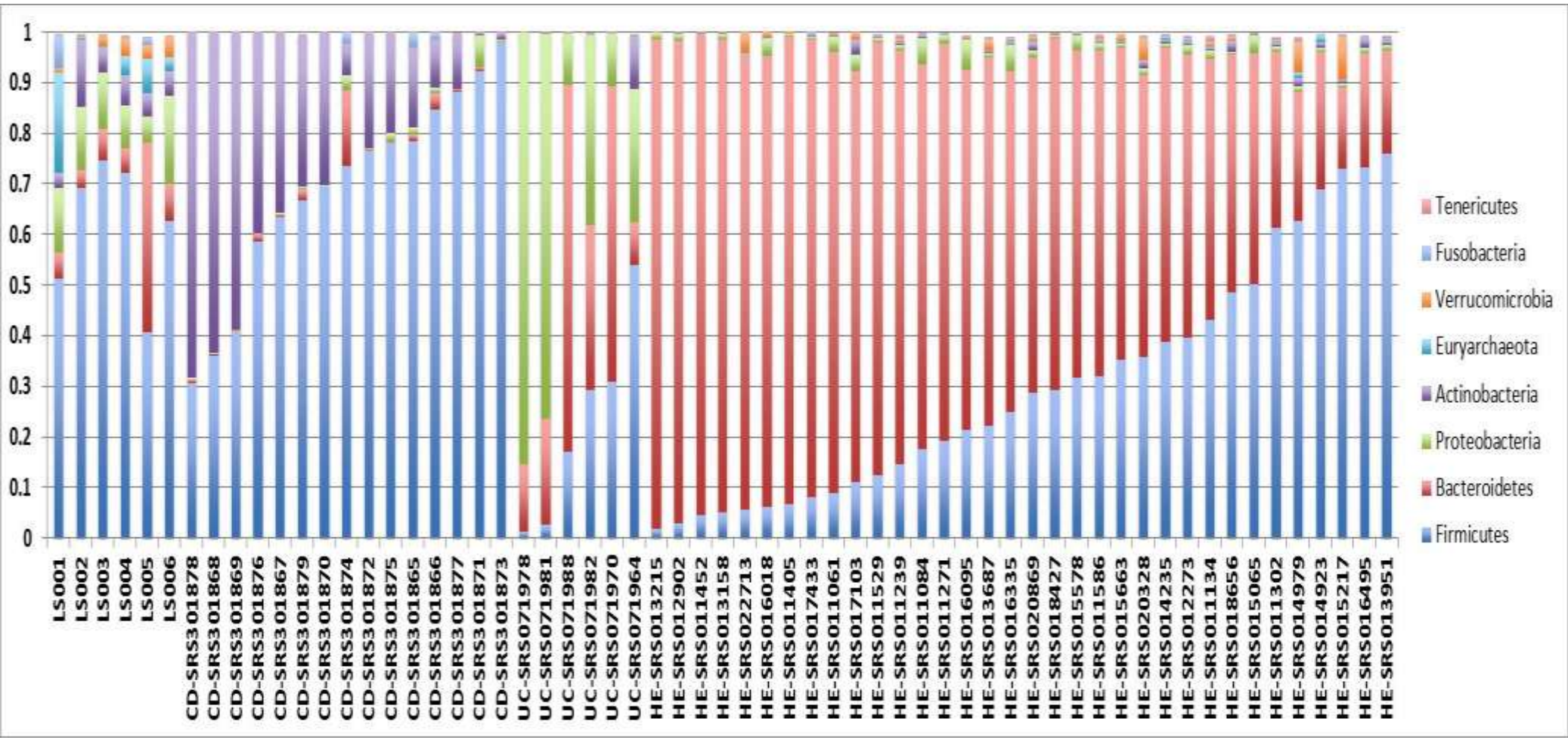
NSF NIH HMP

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CRBS it²

Phyla Gut Microbial Abundance Without Viruses: LS, Crohn's, UC, and Healthy Subjects

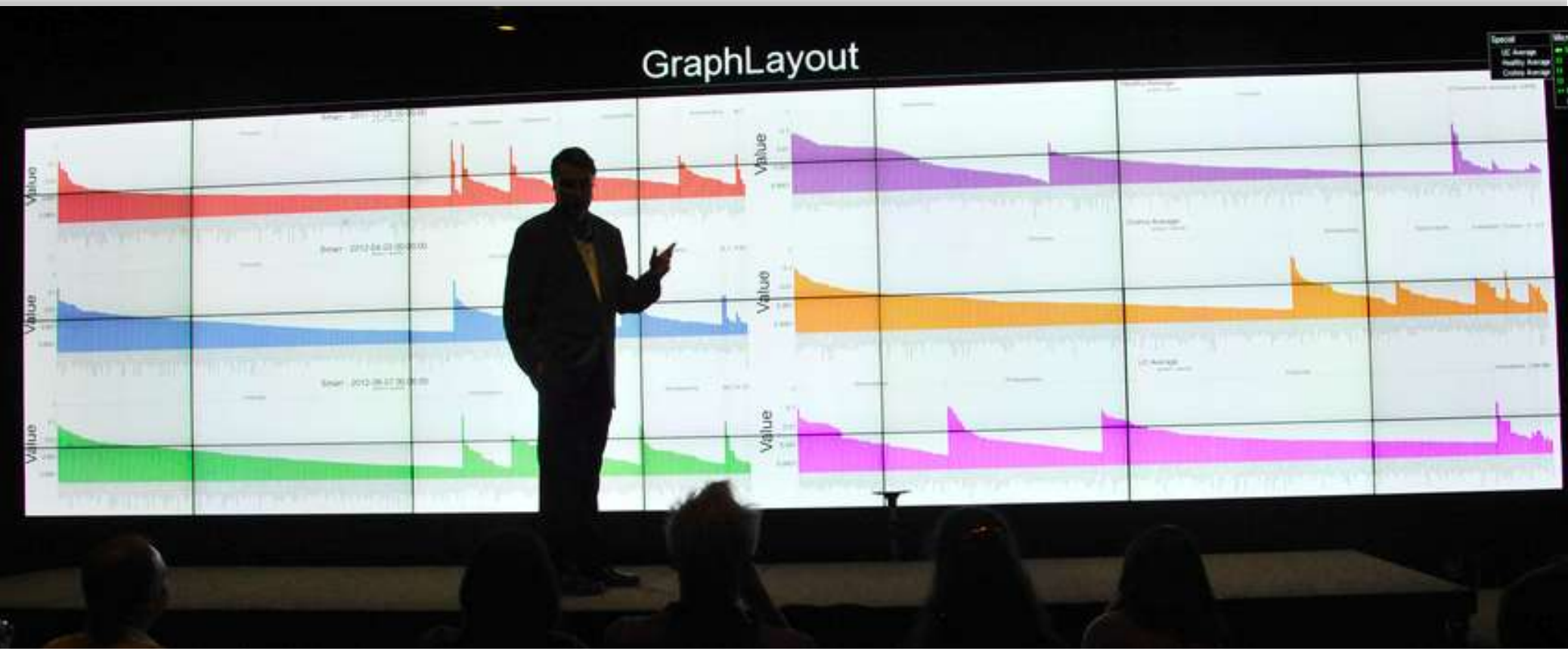
Source: Weizhong Li, Sitao Wu, CRBS, UCSD



LS **Crohn's** **Ulcerative Colitis** **Healthy**

Toward Noninvasive Microbial Ecology Diagnostics

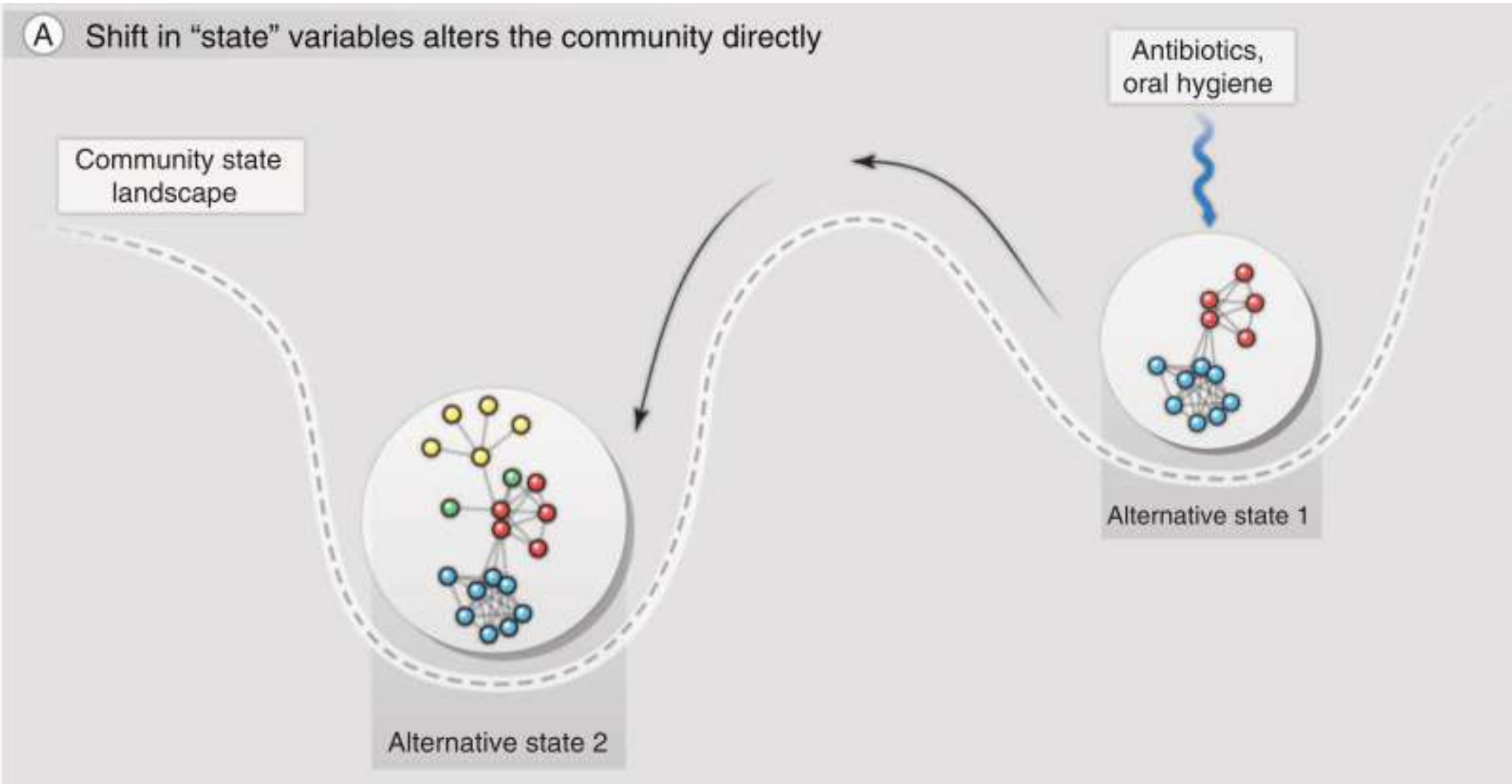
Using Scalable Visualization Allows Comparison of the Relative Abundance of 200 Microbe Species



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)

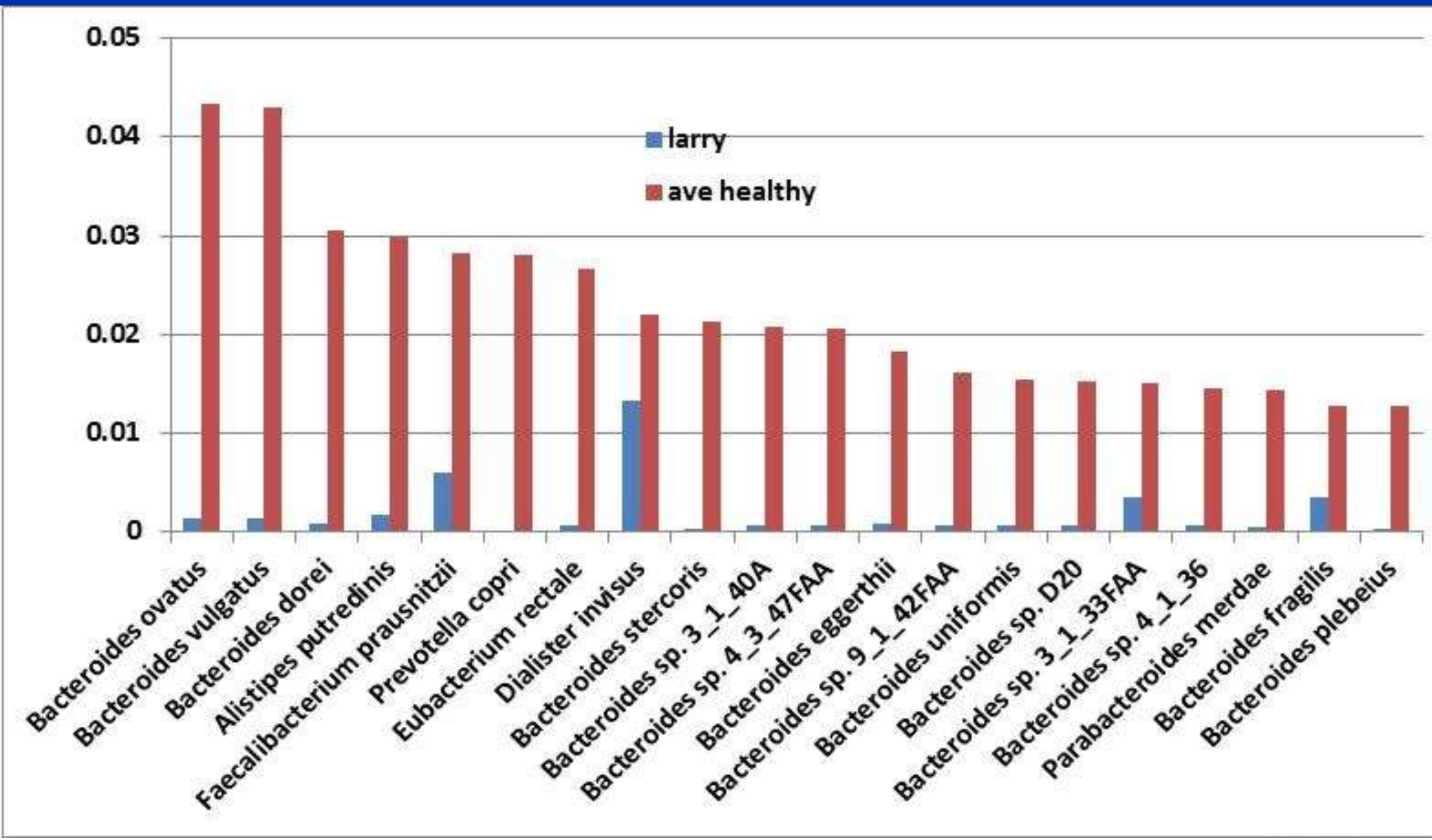
Lessons From Ecological Dynamics II:
Invasive Species Dominate After Major Species Destroyed



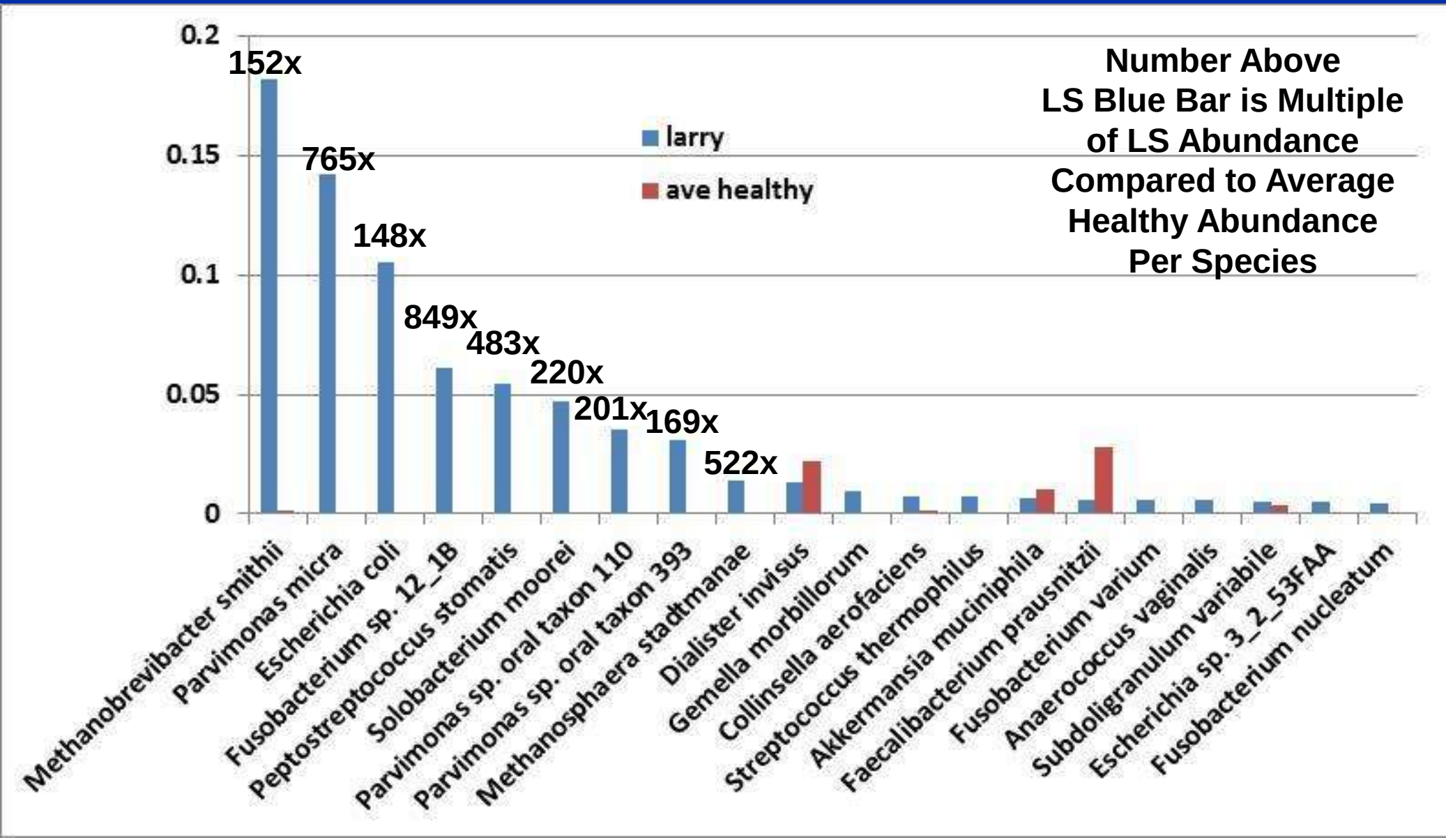
”In many areas following these burns invasive species are able to establish themselves, crowding out native species.”

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

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

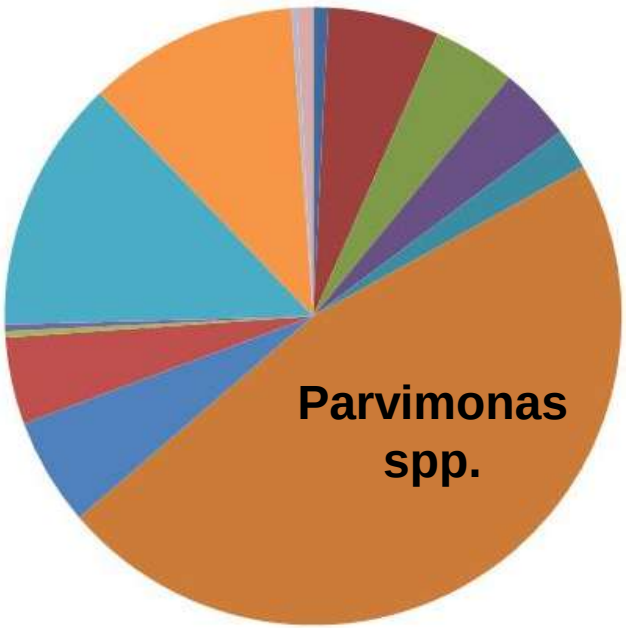


Blooms of Rare Species for Top 20 Most Abundant In LS vs. Average Healthy Subject

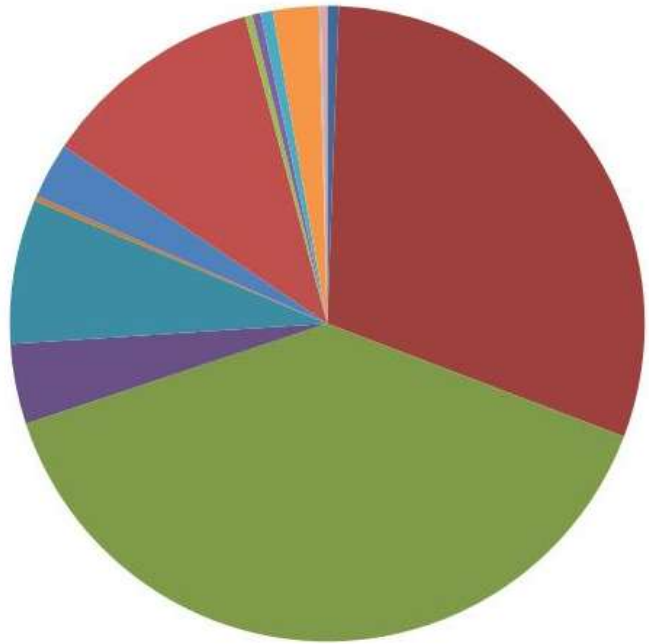


Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

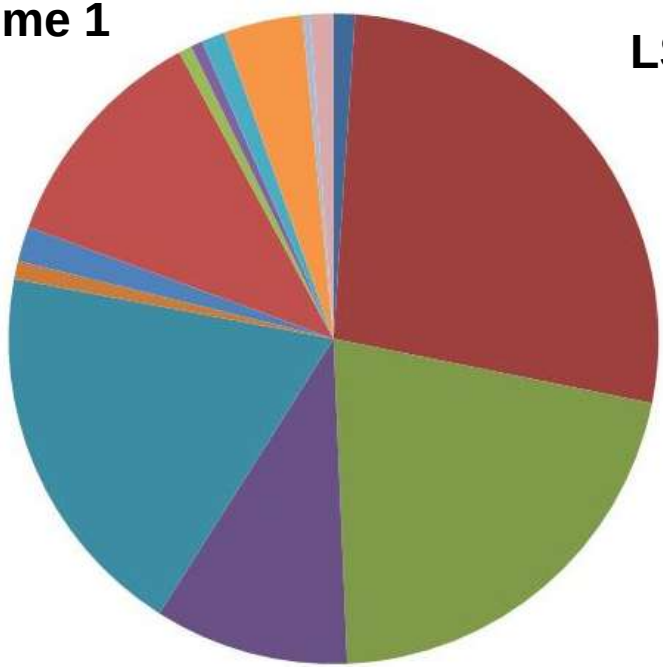
Rare Firmicutes Bloom in Colon Disappearing After Antibiotic/Immunosuppressant Therapy



LS Time 1



LS Time 2



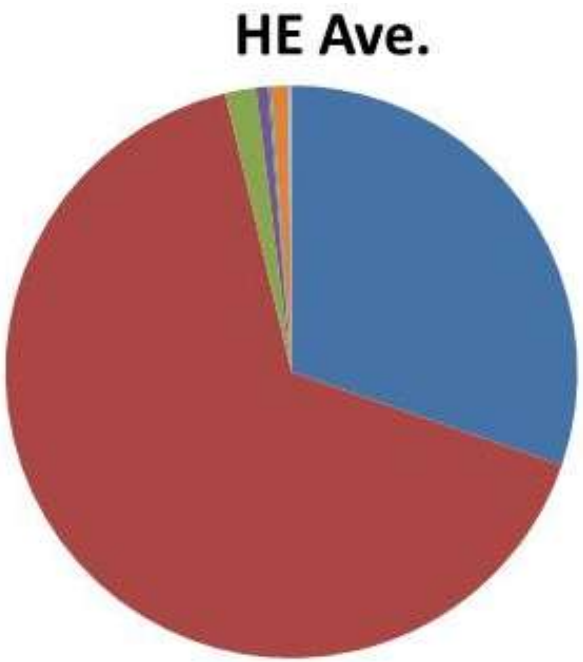
Healthy Average

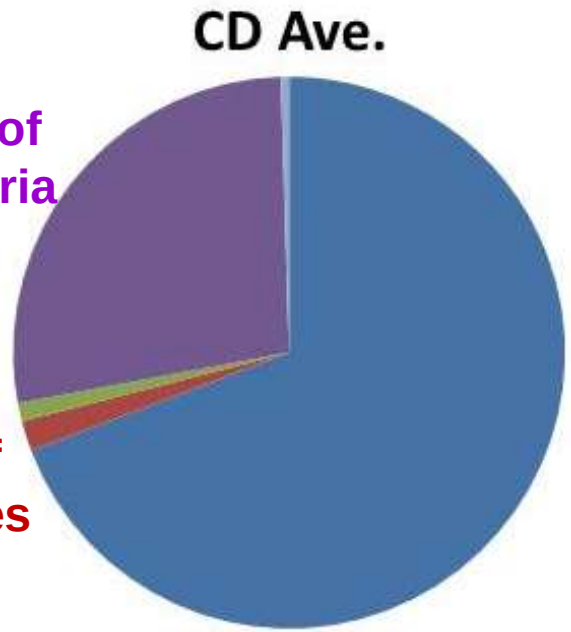
Firmicutes Families

- Lactobacillaceae
- Lachnospiraceae
- Ruminococcaceae
- Veillonellaceae
- Eubacteriaceae
- Clostridiales Family XI. Incertae Sedis
- Streptococcaceae
- Clostridiaceae
- Enterococcaceae
- Bacillaceae
- Peptostreptococcaceae
- Erysipelotrichaceae
- Staphylococcaceae
- Acidaminococcaceae

Comparison of 35 Healthy to 15 CD and 6 UC Gut Microbiomes

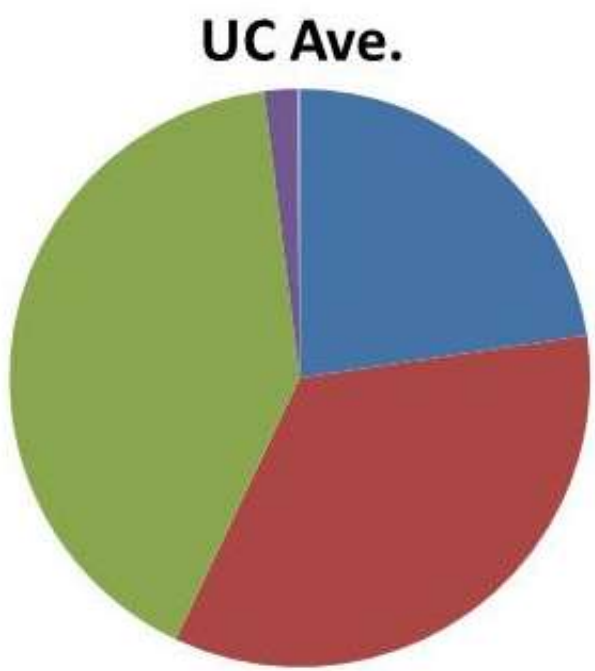






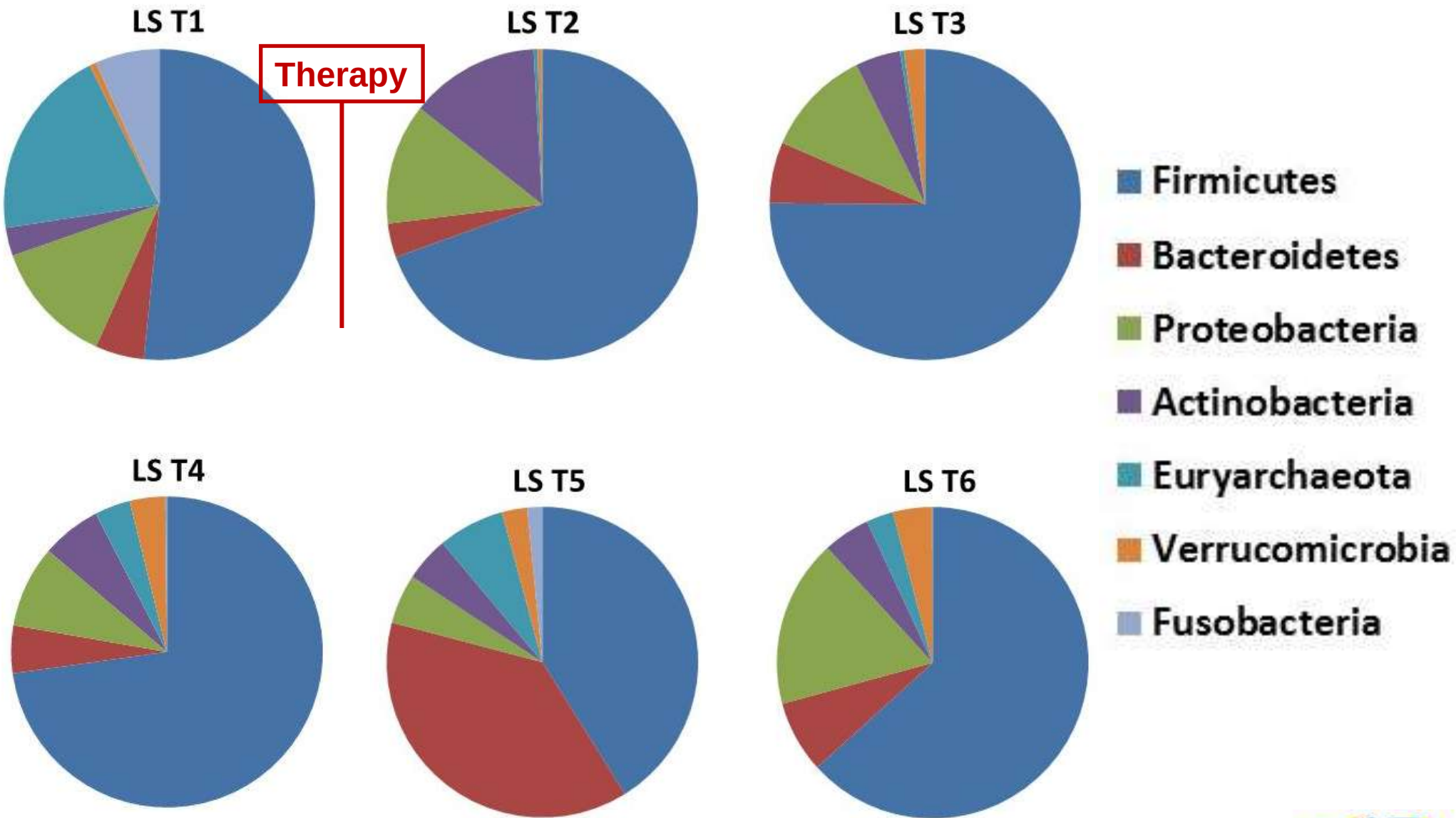
Expansion of Actinobacteria

Collapse of Bacteroidetes



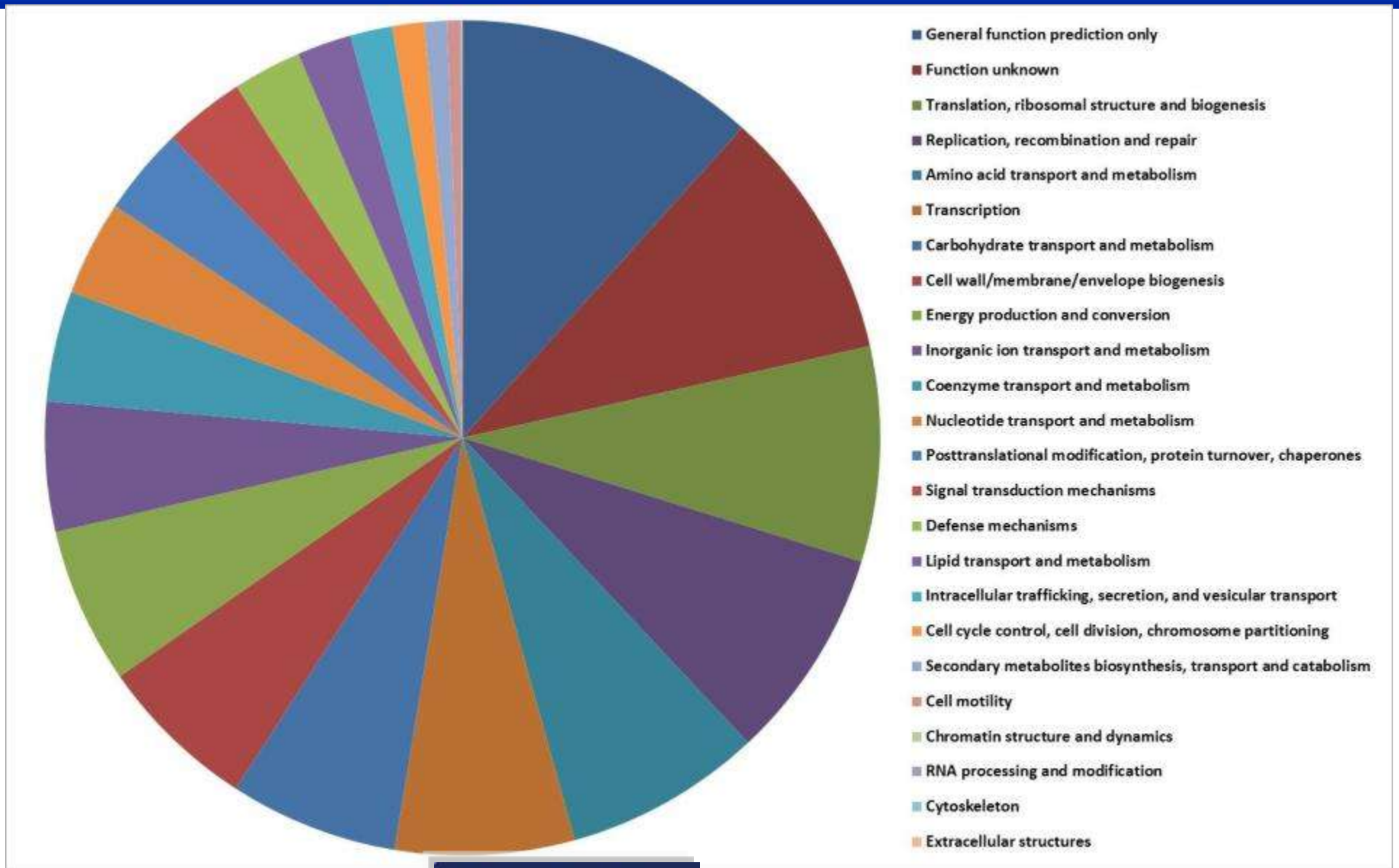
Explosion of Proteobacteria

Six LS Gut Microbiome by Phyla



Six Metagenomic Time Samples Over 16 Months

From Taxonomy to Function: Analysis of LS Clusters of Orthologous Groups (COGs)



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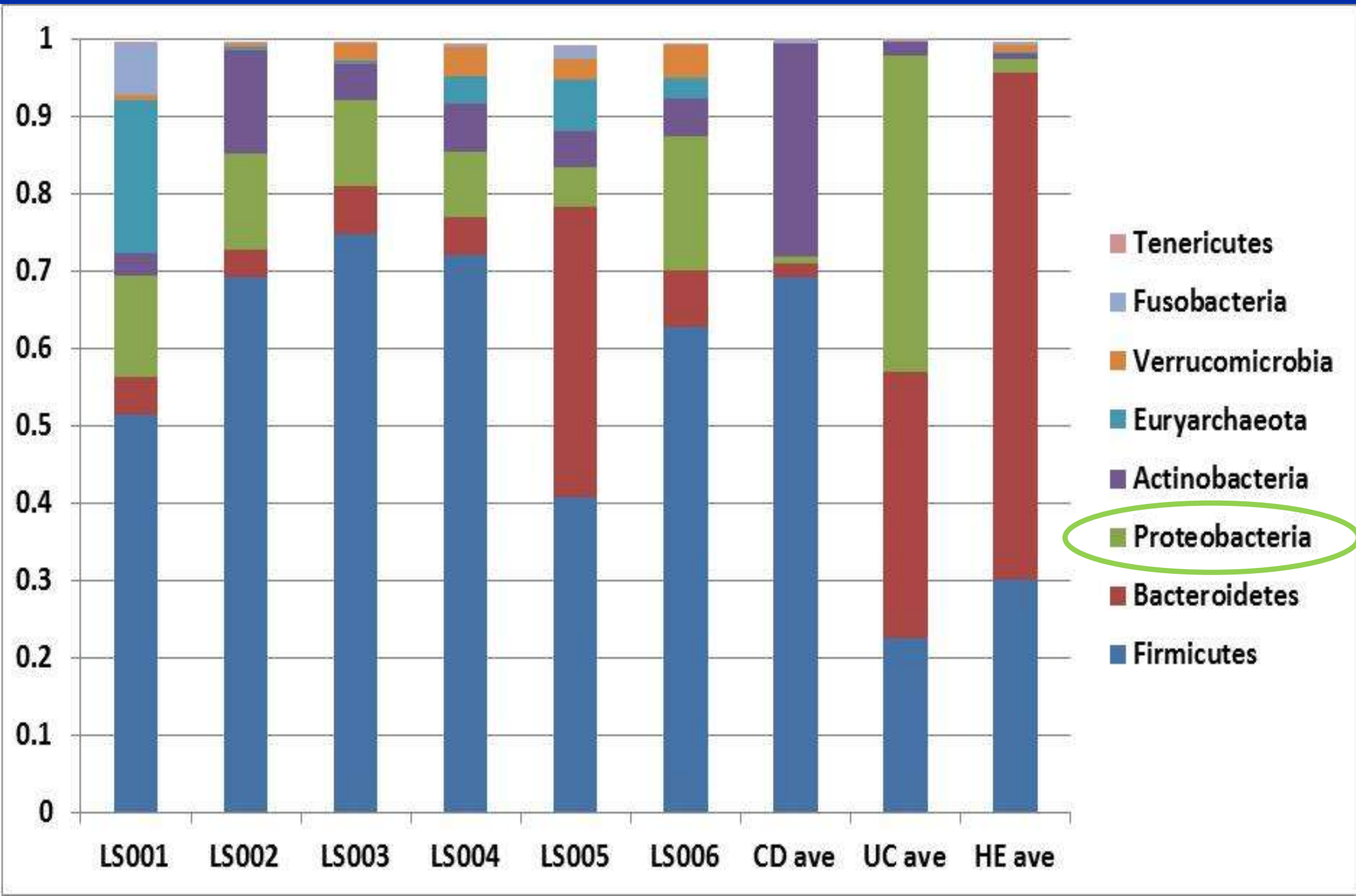
UC San Diego Health Sciences

SDSC

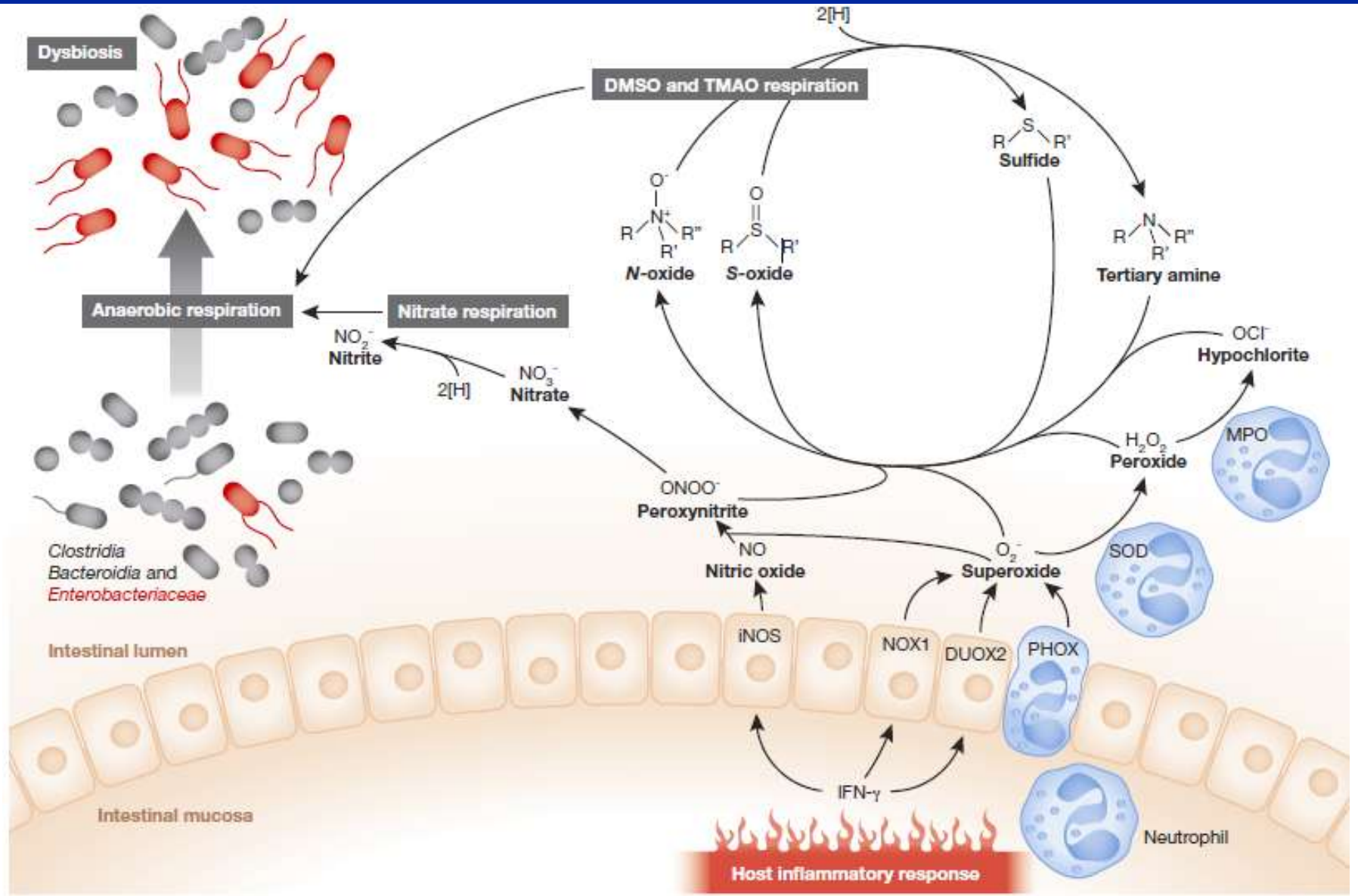
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Analysis: Weizhong Li & Sitao Wu, UCSD

Variation in Phyla Abundance in Health and IBD Plus My Time Series



Inflammation Enables Anaerobic Respiration Which Leads to Phylum-Level Shifts in the Gut Microbiome



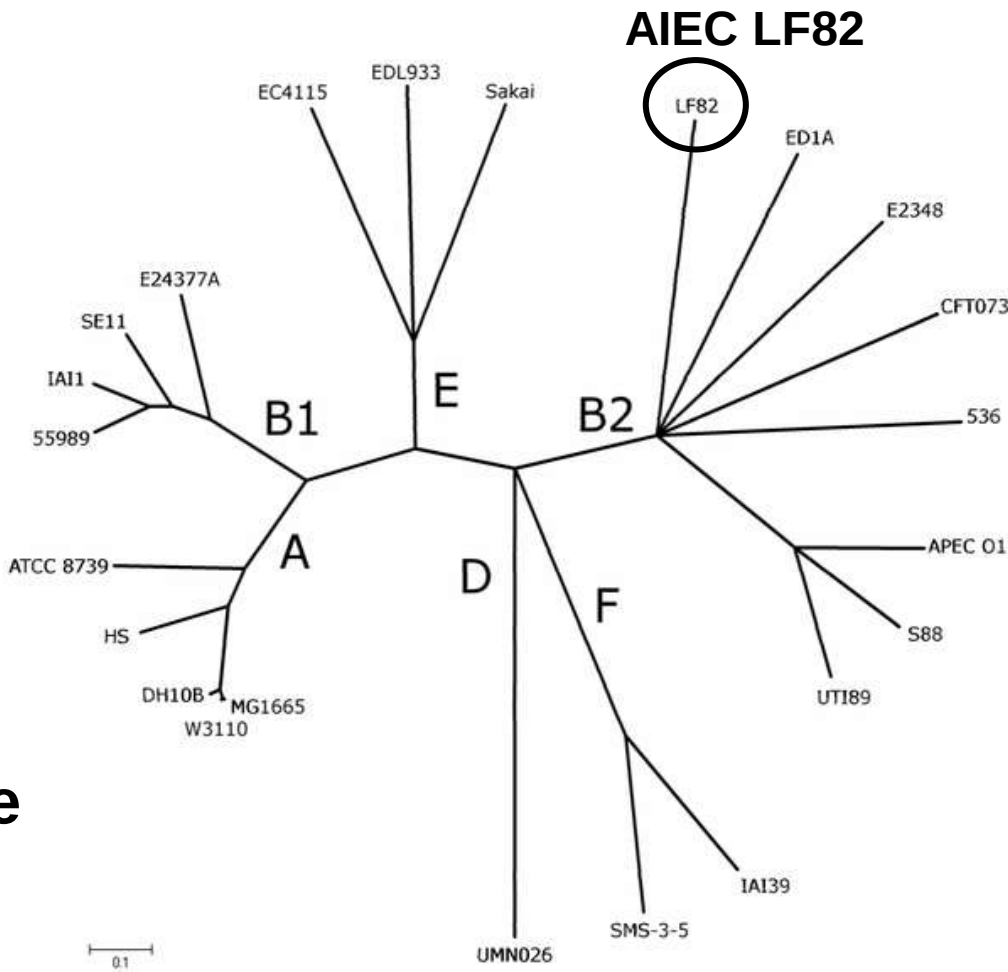
Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler,
EMBO reports VOL 14, p. 319-327 (2013)

Does Intestinal Inflammation Select for Pathogenic Strains That Can Induce Further Damage?

"Adherent-invasive E. coli (AIEC) are isolated more commonly from the intestinal mucosa of individuals with Crohn's disease than from healthy controls."

"Thus, the mechanisms leading to dysbiosis might also select for intestinal colonization with more harmful members of the Enterobacteriaceae* —such as AIEC— thereby exacerbating inflammation and interfering with its resolution."

Sebastian E. Winter , et al.,
EMBO reports VOL 14, p. 319-327 (2013)

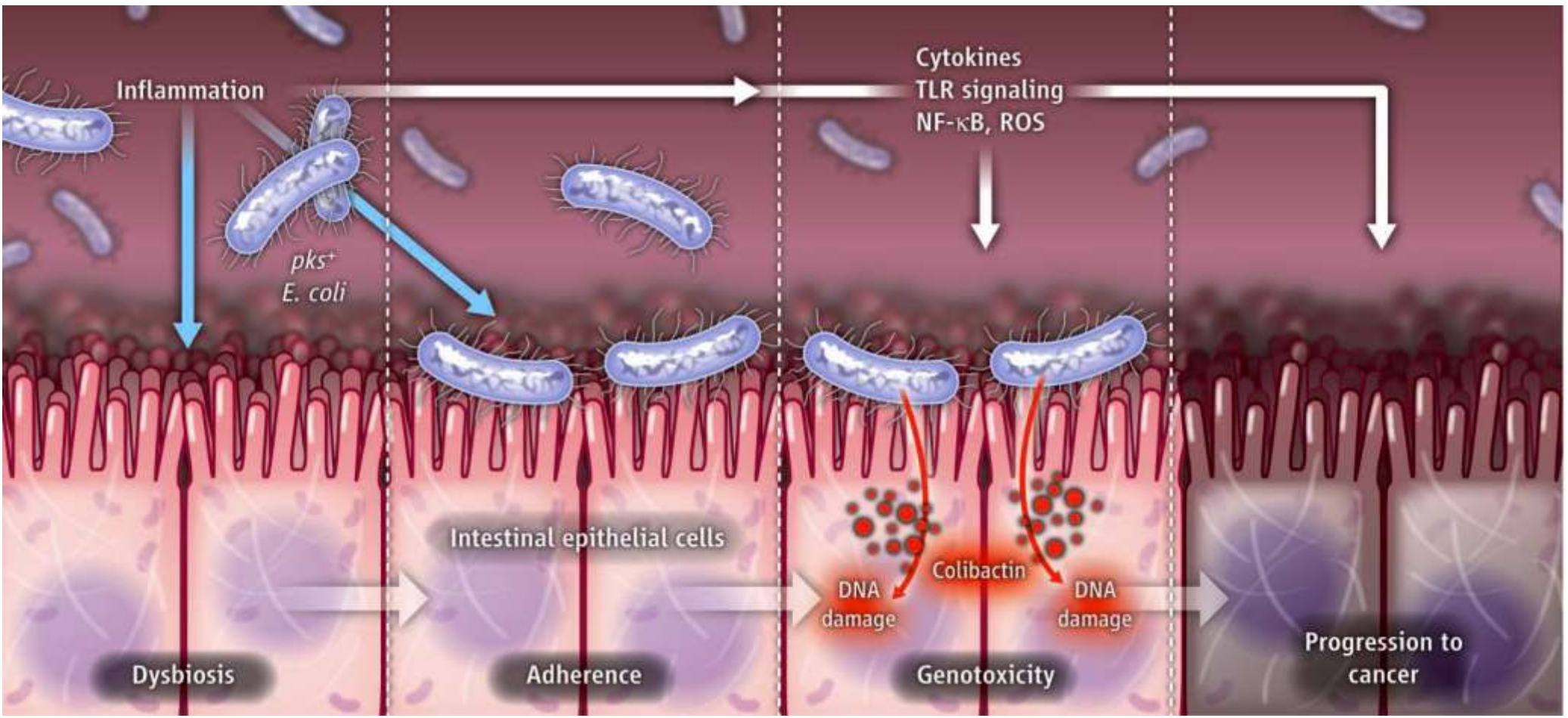


E. coli/Shigella Phylogenetic Tree
Miquel, et al.
PLOS ONE, v. 5, p. 1-16 (2010)

*Family Containing E. coli

Chronic Inflammation Can Accumulate Cancer-Causing Bacteria in the Human Gut

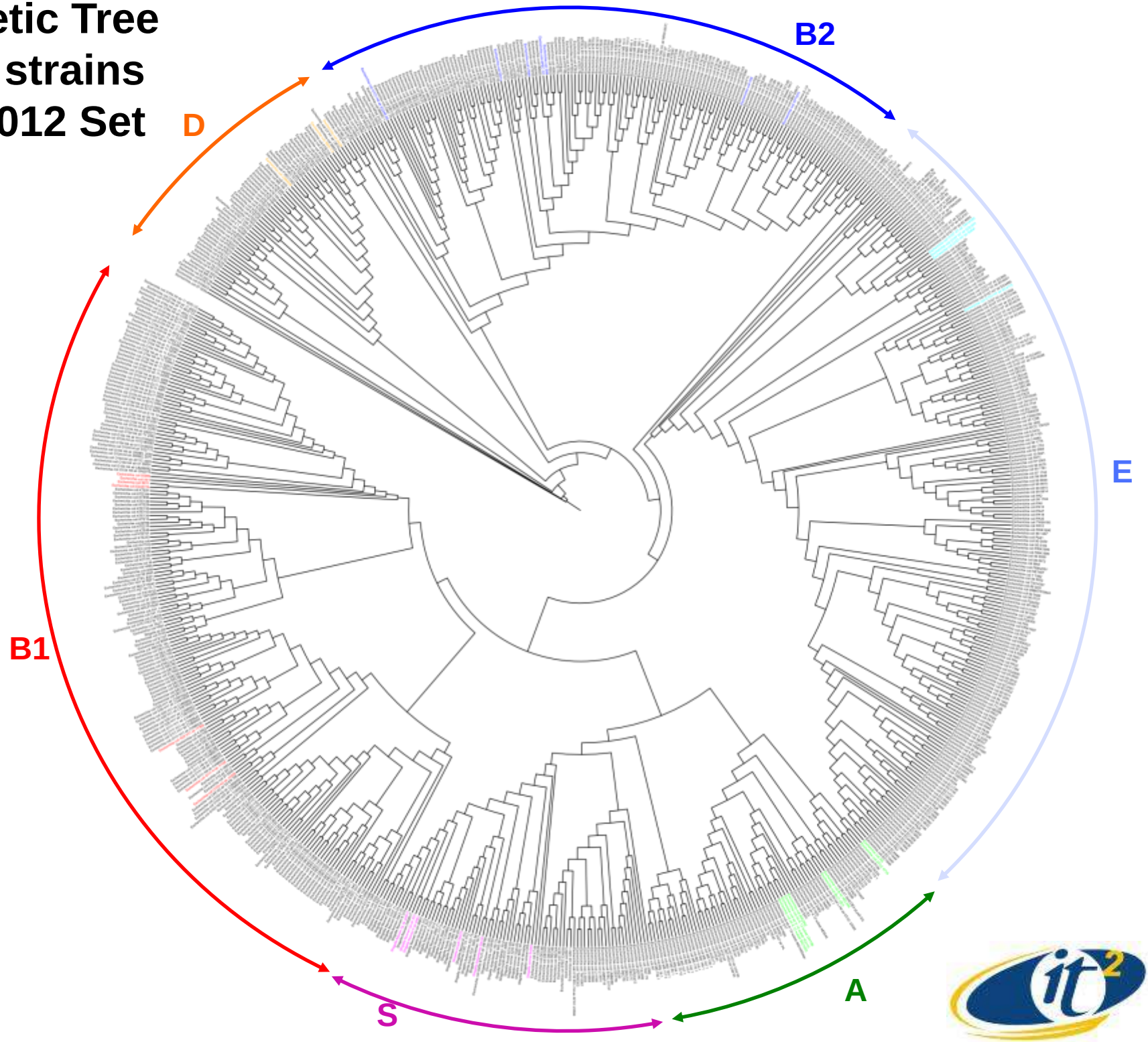
Escherichia coli Strain NC101



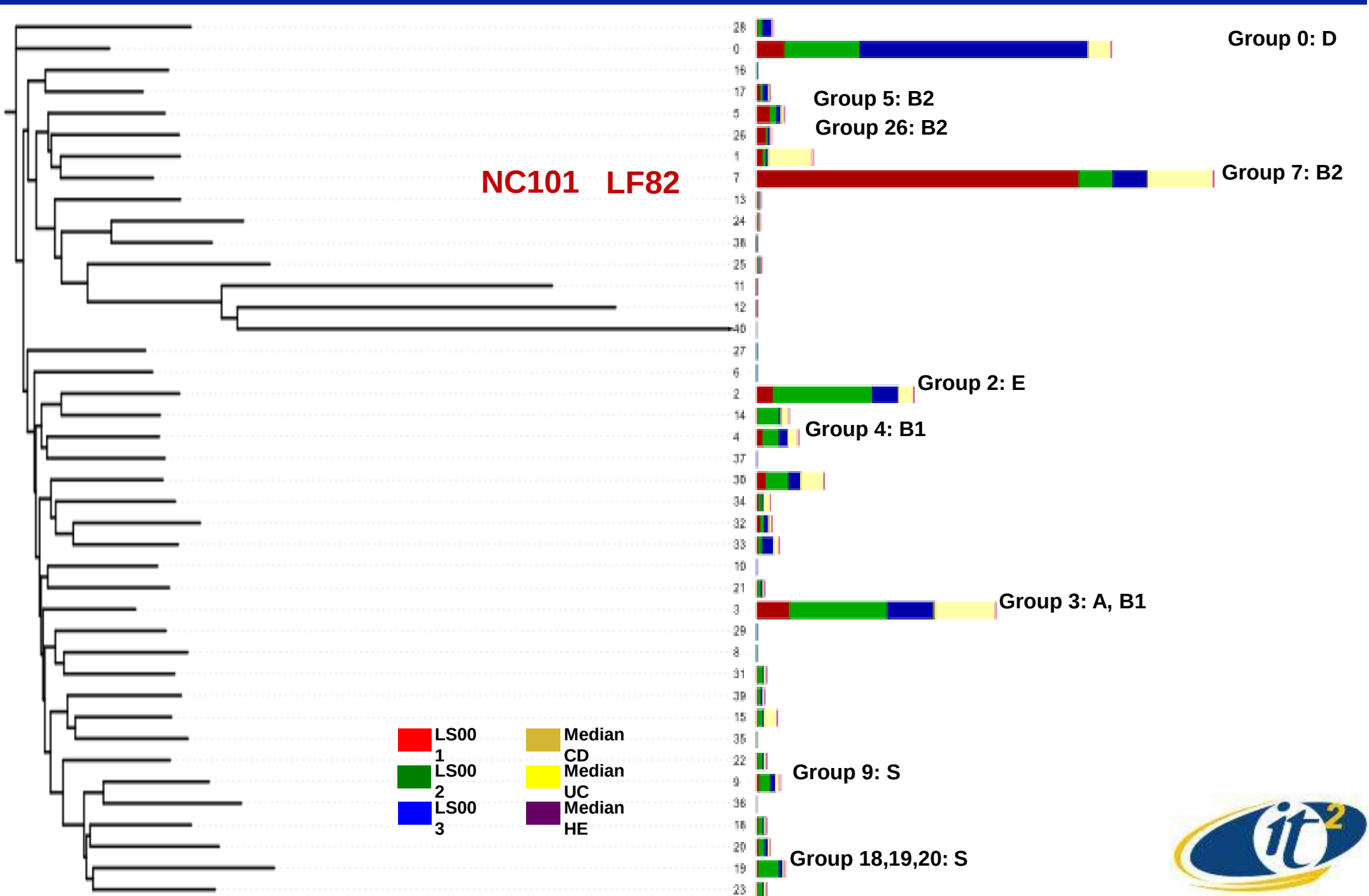
Science
AAAS

Bacteria Deliver a Genotoxic Hit
Robert F. Schwabe and Timothy C. Wang
Science **338**, 52 (2012);
DOI: 10.1126/science.1229905

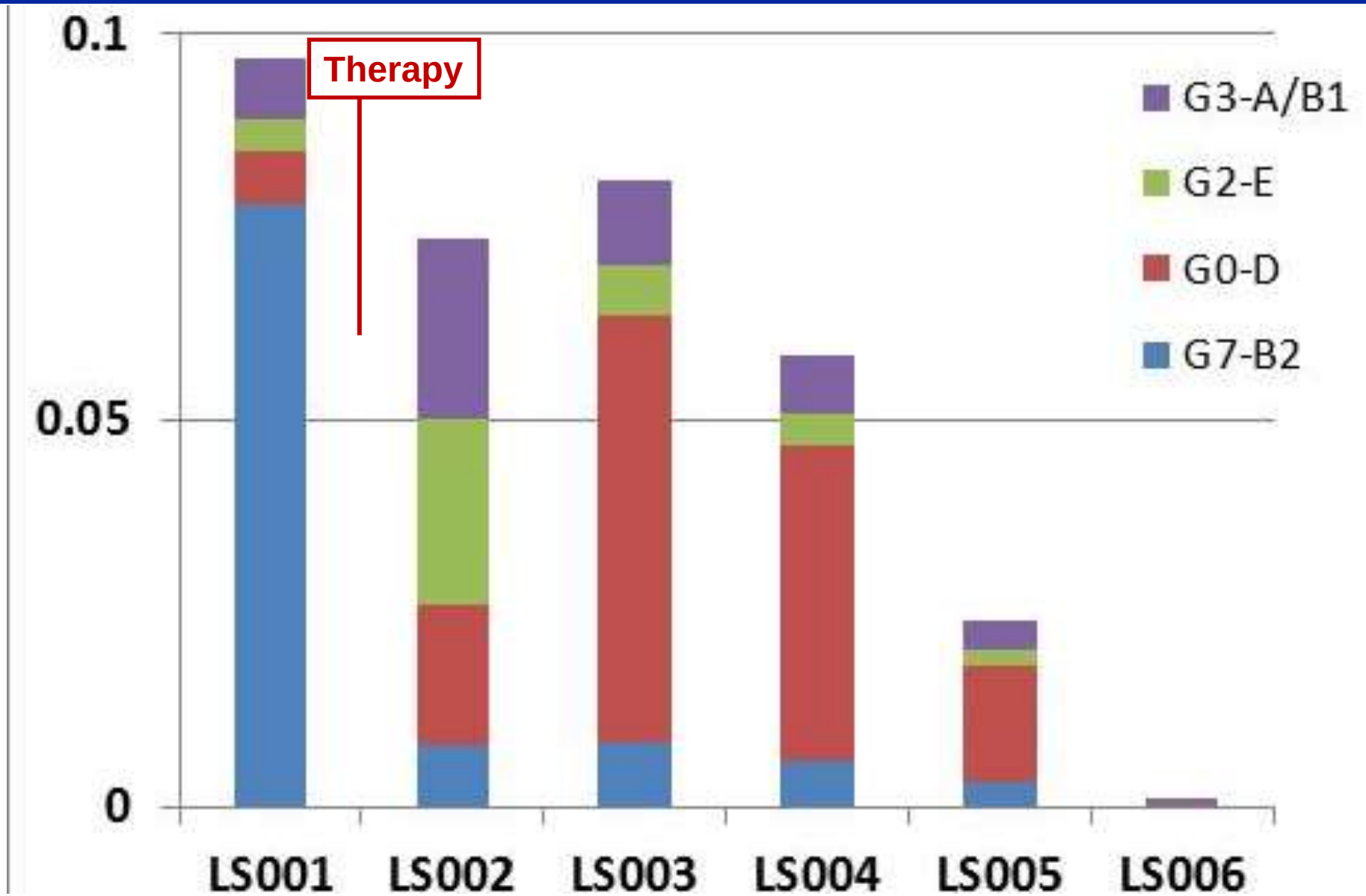
Phylogenetic Tree
778 Ecoli strains
=6x our 2012 Set



We Divided the 778 E. coli Strains into 40 Groups, Each of Which Had 80% Identical Genes



Reduction in E. coli Over Time
With Major Shifts in Strain Abundance



Strains >0.5% Included

Systems Biology Immunology Modeling: An Emerging Discipline

Systems immunology: a survey of modeling formalisms, applications and simulation tools

Vipin Narang · James Decraene · Shek-Yoon Wong · Bindu S. Aiswarya · Andrew R. Wasem · Shiang Rong Leong · Alexandre Gouaillard

Immunol Res 53:251–265 (2012)

Systems Biology in Immunology – A Computational Modeling Perspective

Ronald N. Germain*, **Martin Meier-Schellersheim**, **Aleksandra Nita-Lazar**, and **Iain D. C. Fraser**
Program in Systems Immunology and Infectious Disease Modeling, National Institute of Allergy and Infectious Disease, Laboratory of Immunology, National Institutes of Health, Bethesda, MD 20892

Annu Rev Immunol. 29: 527–585 (2011)

Early Attempts at Modeling the Systems Biology of the Gut Microbiome and the Human Immune System

Trends in Biotechnology June 2011, Vol. 29, No. 6

Prospects for systems biology and modeling of the gut microbiome

Fredrik H. Karlsson, Intawat Nookaew, Dina Petranovic and Jens Nielsen

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2012 IEEE 26th International Parallel and Distributed Processing Symposium

High-Performance Interaction-Based Simulation of Gut Immunopathologies with ENteric Immunity SImulator (ENISI)

Keith Bisset*, Md. Maksudul Alam*, Josep Bassaganya-Riera*, Adria Carbo*, Stephen Eubank*, Raquel Hontecillas*, Stefan Hoops*, Yongguo Mei*, Katherine Wendelsdorf*, Dawen Xie*, Jae-Seung Yeom*†, and Madhav Marathe*†

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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

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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Philip Weber
Fred Raab
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