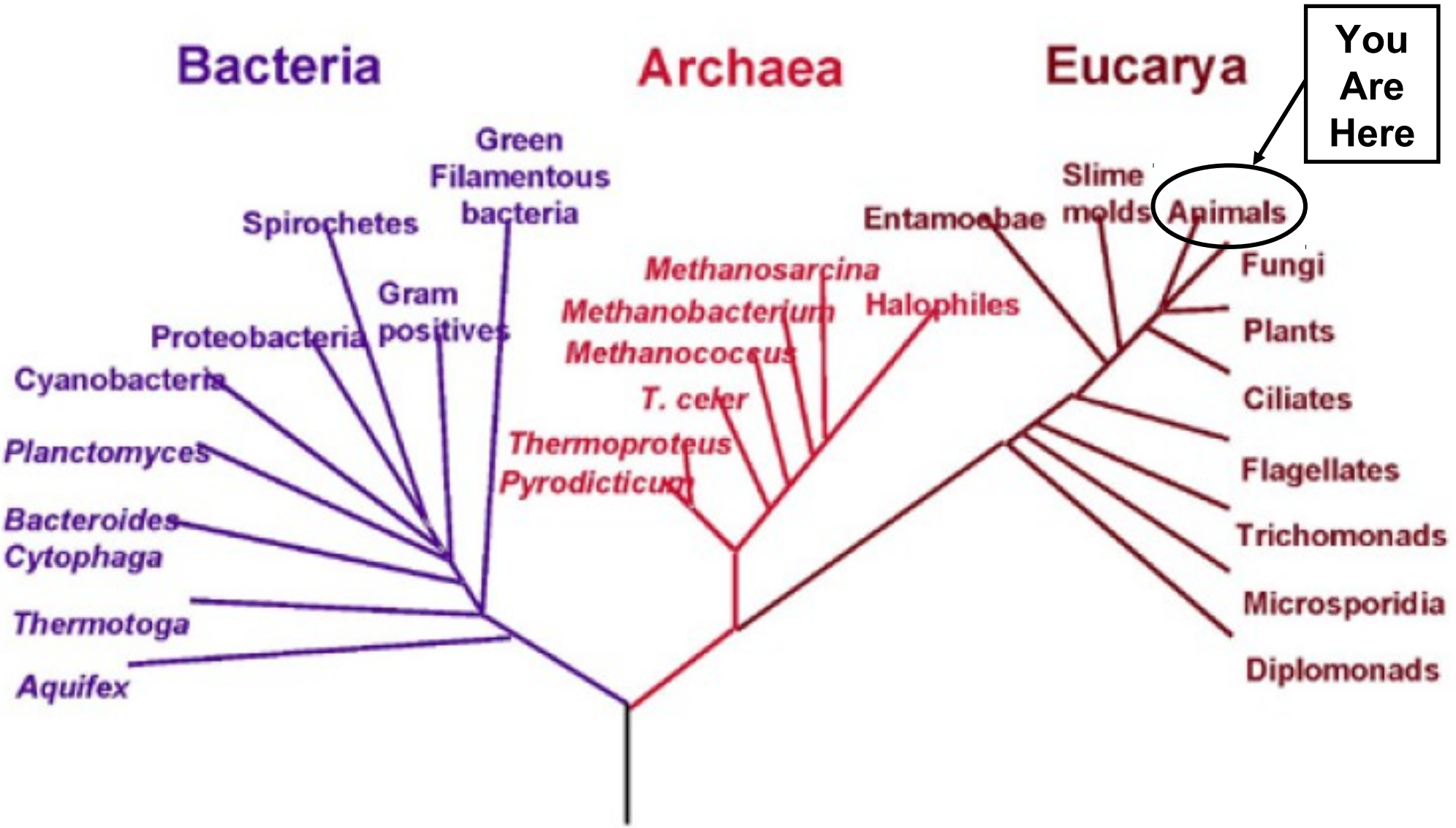
“Living in a Microbial World”

Global Health Program
Council on Foreign Relations
New York, NY
April 10, 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

Most Biological Diversity on Earth is in the Microbial World



Source: Carl Woese, et al

Humans Are Immersed in a Microbial World

Your Body Has 10 Microbe Cells For Every Human Cell

Earth Has 10 Million Microbe Cells For Every Human Cell

Major Projects are Genetically Sequencing The Two Realms



NIH HUMAN MICROBIOME PROJECT

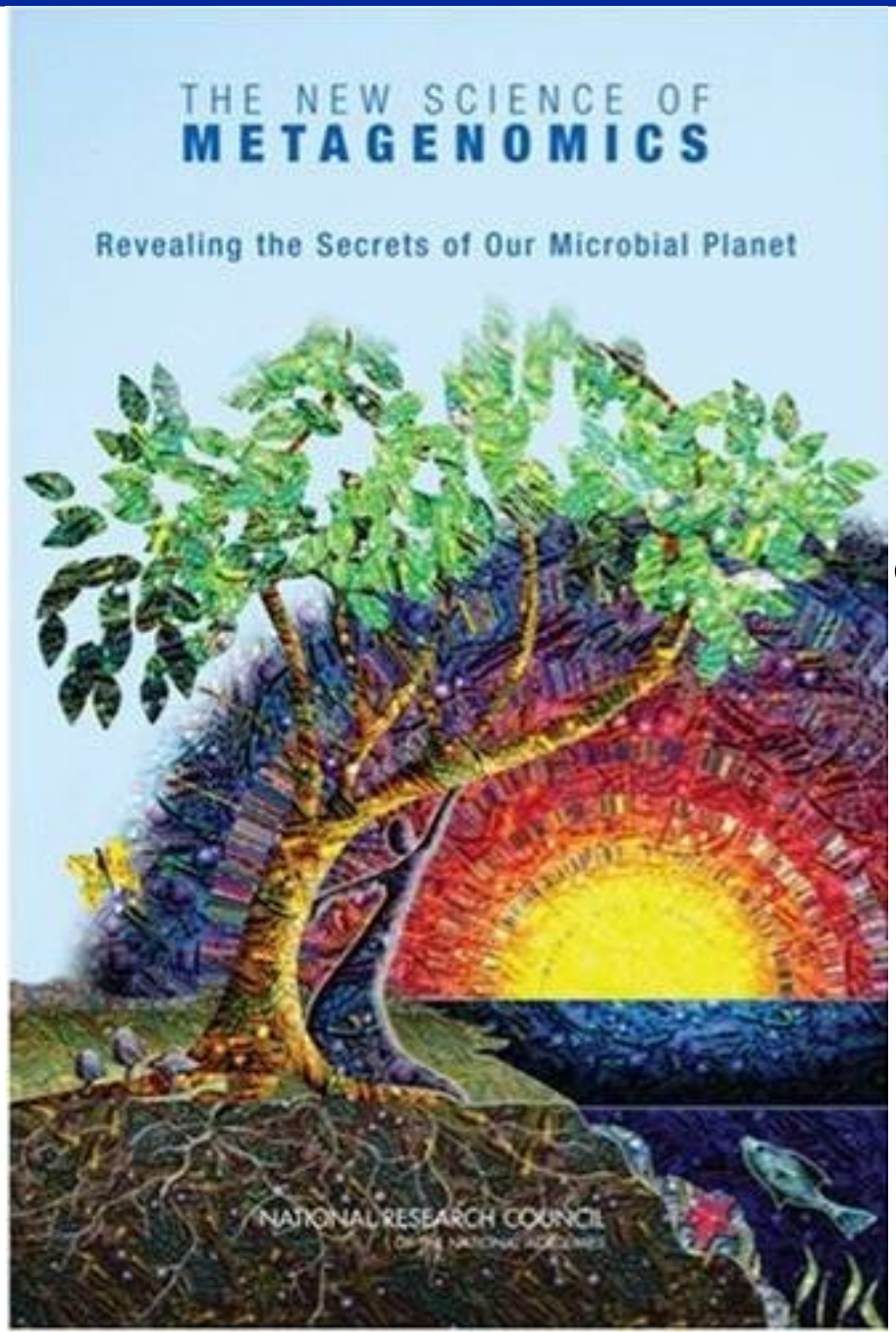


earth microbiome project

Using Genome Sequencing to Discover the Complex Dynamics of Microbial Communities

NRC Report:

Metagenomic data should be made publicly available in international archives as rapidly as possible.



"The emerging field of metagenomics, where the DNA of entire communities of microbes is studied simultaneously, presents the greatest opportunity -- perhaps since the invention of the microscope – to revolutionize understanding of the microbial world." –

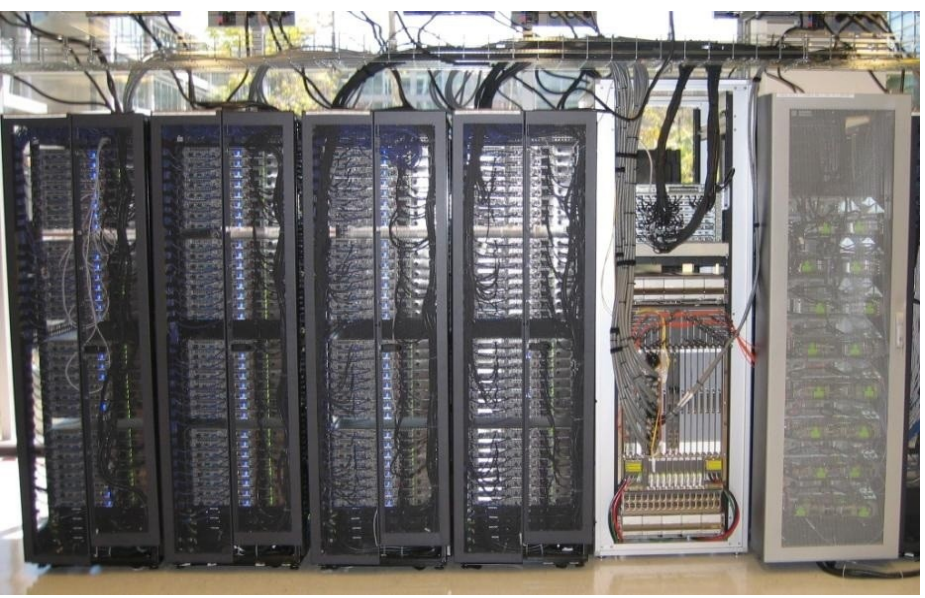
National Research Council
March 27, 2007

Community Cyberinfrastructure for Advanced Microbial Ecology Research and Analysis

http://camera.calit2.net/

camera
Marine Microbial Ecology

I Served as PI for the Grant Announced January 17, 2006





J. Craig Venter INSTITUTE

Gordon and Betty MOORE FOUNDATION

SDSC

5000 Users
90 Countries

it²

Marine Genome Sequencing Project – CAMERA Anchor Dataset Launched March 13, 2007



Each Sample ~2000 Microbial Species

MARINE MICROBIOLOGY INITIATIVE

camera
Marine Microbial Ecology

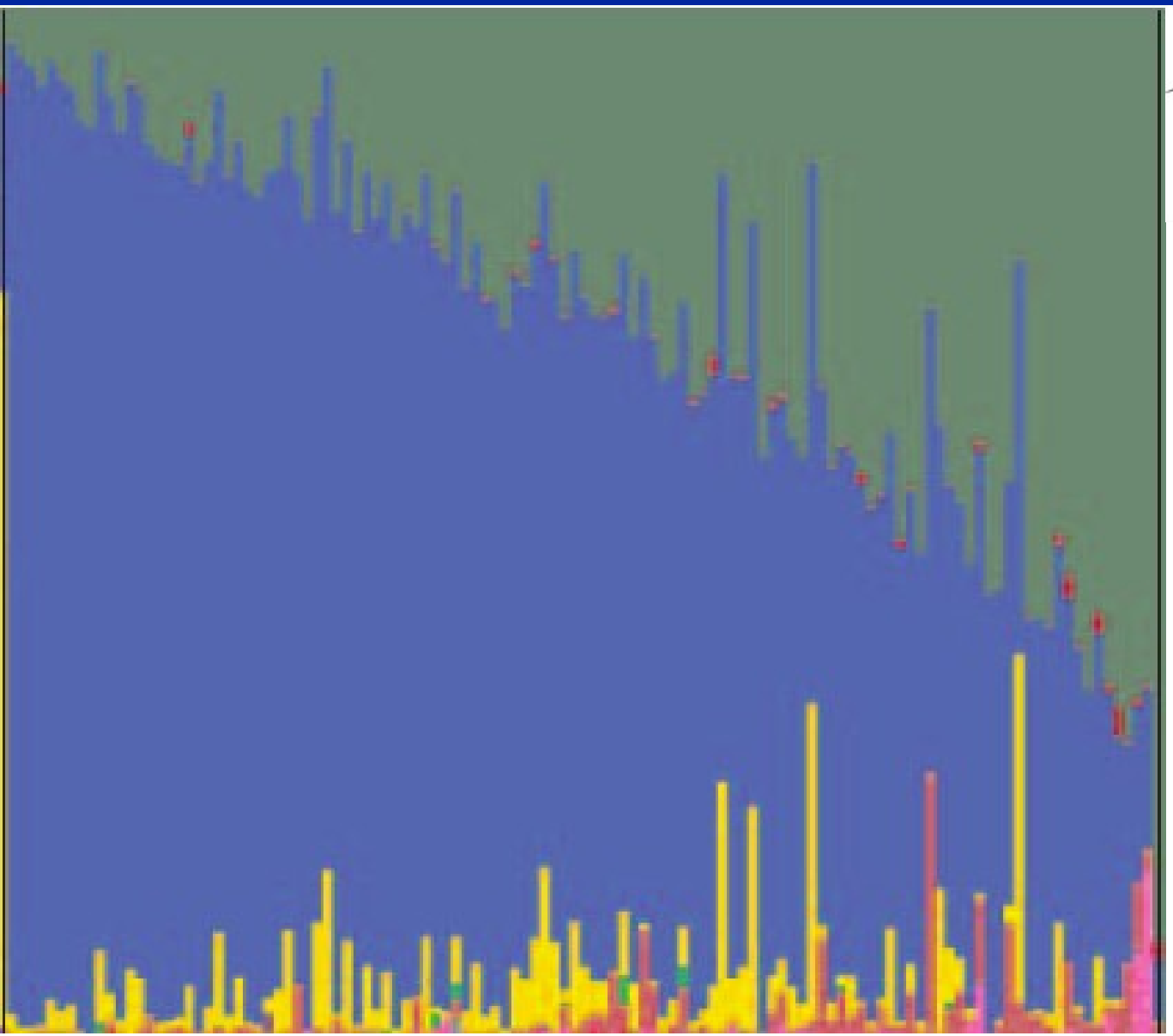
Gordon and Betty MOORE FOUNDATION

Measuring the Genetic Diversity of Ocean Microbes

J. Craig Venter INSTITUTE

it²

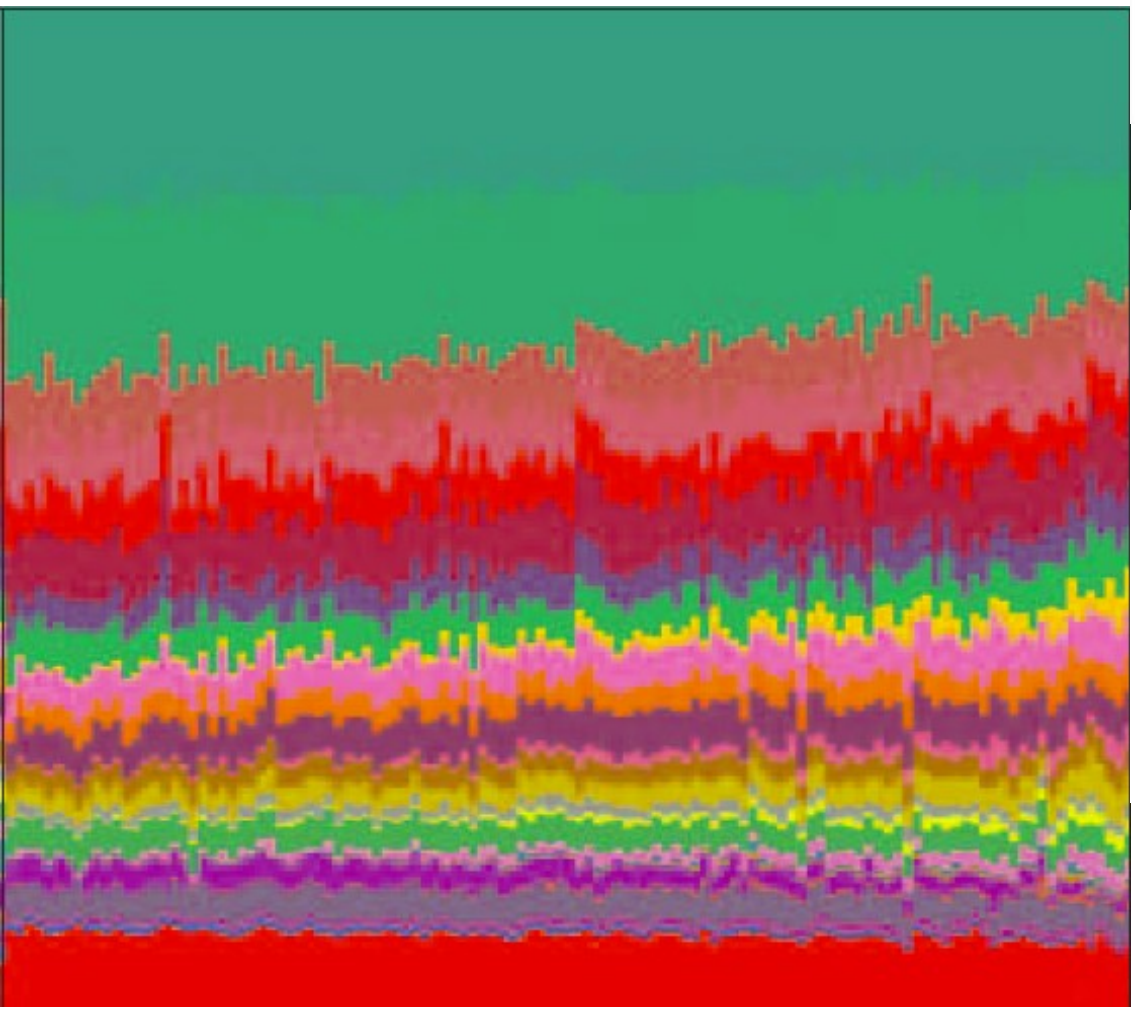
Mapping the "Healthy" Gut Microbiome: Considerable Phyla Variation Found in HMP



- Firmicutes
- Actinobacteria
- Bacteroidetes
- Proteobacteria
- Fusobacteria
- Tenericutes
- Spirochaetes
- Cyanobacteria
- Verrucomicrobia
- TM7

Source: "Structure, function and diversity of the healthy human microbiome," HMP Consortium, Nature, 486, 207-212 (2012)

However, Metabolic Pathways from Genes Vary Much Less Than Phyla Distribution in HMP

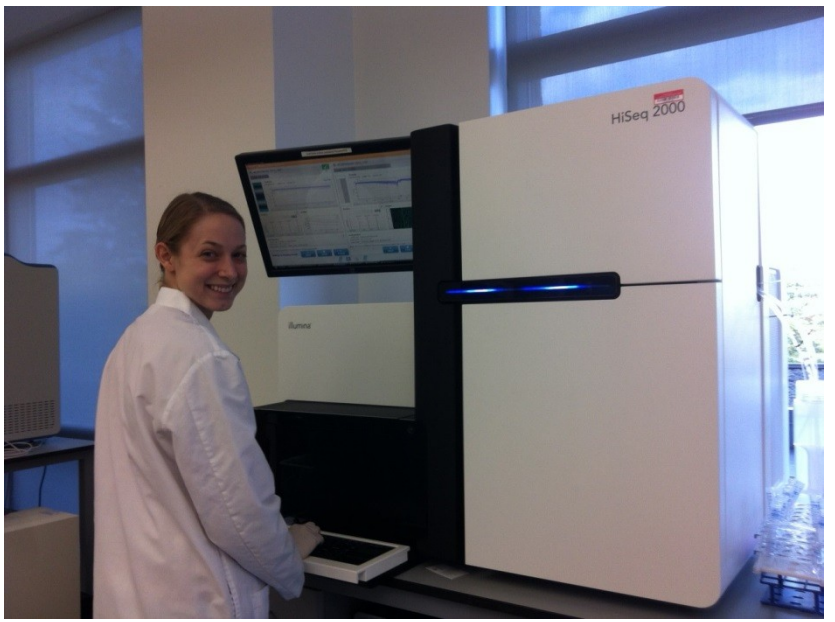


- Central carbohydrate metabolism
- Cofactor and vitamin biosynthesis
- Oligosaccharide and polyol transport system
- Purine metabolism
- ATP synthesis
- Phosphate and amino acid transport system
- Aminoacyl tRNA
- Pyrimidine metabolism
- Ribosome
- Aromatic amino acid metabolism

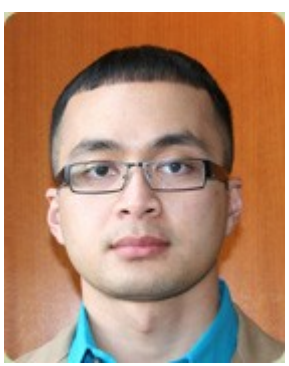
Source: "Structure, function and diversity of the healthy human microbiome," HMP Consortium, Nature, 486, 207-212 (2012)

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

- JCVI Did Metagenomic Sequencing on Seven of My Stool Samples Over 1.5 Years
- Sequencing on Illumina HiSeq 2000
  - Generates 100bp Reads
- JCVI Lab Manager, Genomic Medicine
  - Manolito Torralba
- IRB PI Karen Nelson
  - President JCVI



Illumina HiSeq 2000 at JCVI



Manolito Torralba, JCVI



Karen Nelson, JCVI

J. Craig Venter INSTITUTE

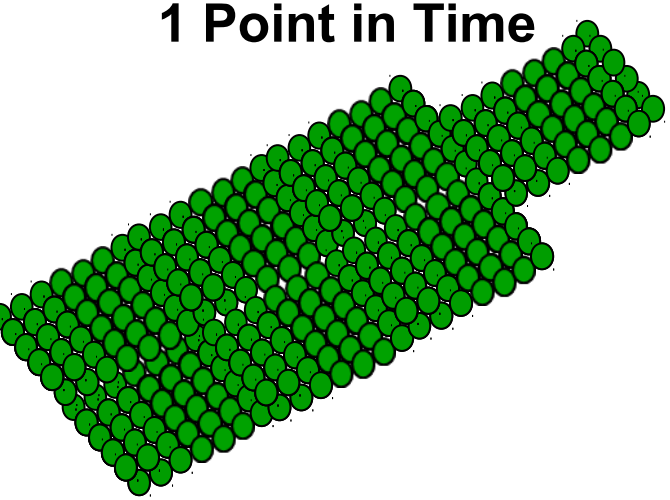
it²

We Downloaded Additional Phenotypes from NIH HMP For Comparative Analysis

Download Raw Reads
~100M Per Person

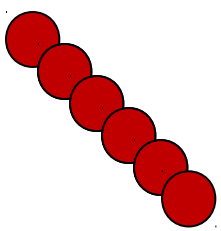
"Healthy" Individuals

250 Subjects
1 Point in Time



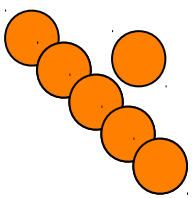
Larry Smarr

6 Points in Time

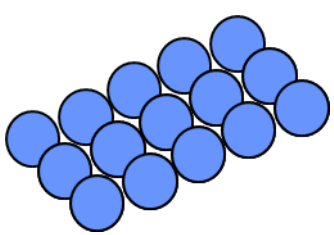


IBD Patients

2 Ulcerative Colitis Patients,
6 Points in Time



5 Ileal Crohn's Patients,
3 Points in Time



Total of 27 Billion Reads
Or 2.7 Trillion Bases

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

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**

NCBI National Center for Biotechnology Information

NIH

Now to Align Our 27 Billion Reads Against the Reference Database

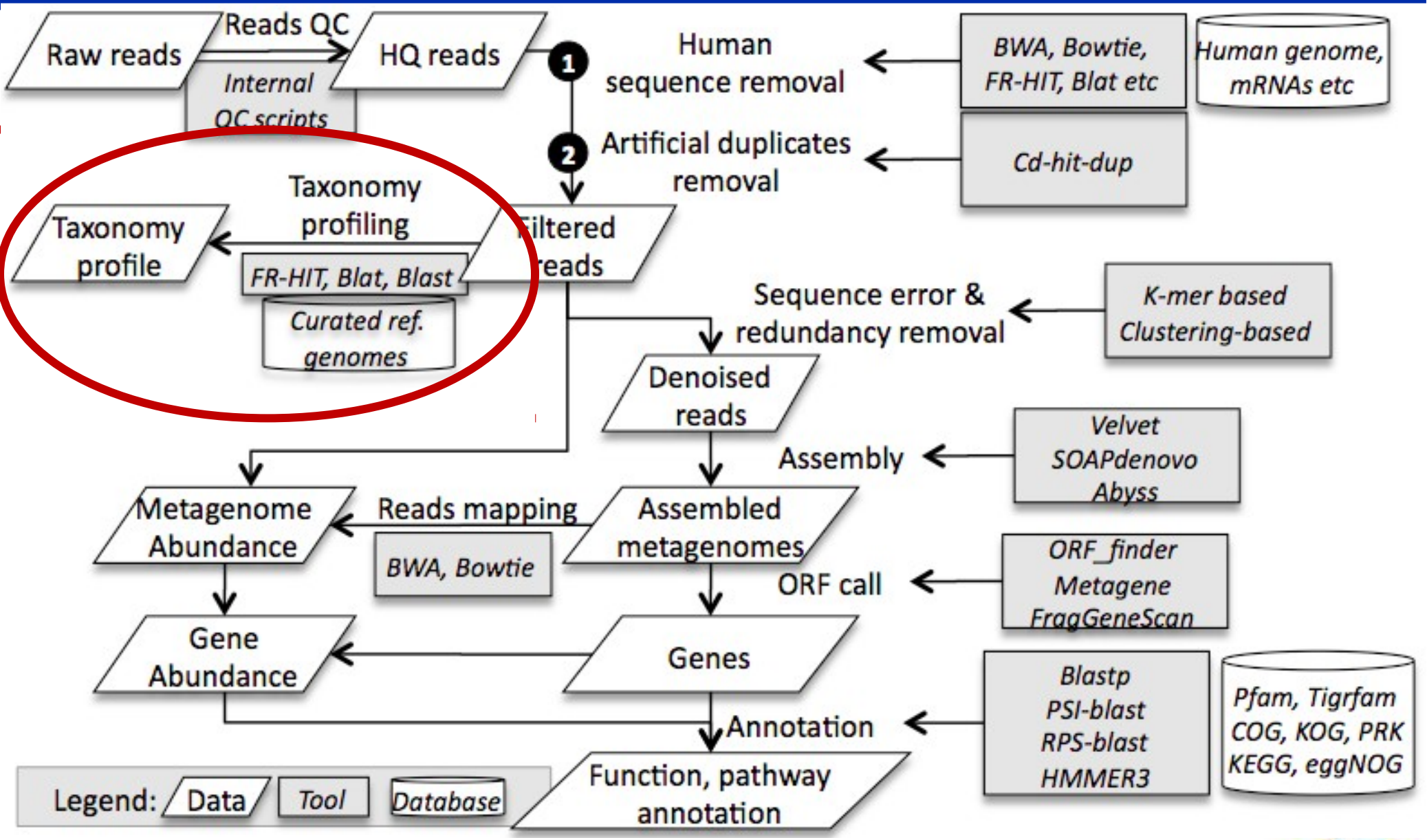
Used Over 25 CPU-Years on SDSC Gordon and DELL Cloud

J. Craig Venter INSTITUTE

Source: Weizhong Li, Sitao Wu, CRBS, UCSD

it²

Computational NextGen Sequencing Pipeline: From Sequence to Taxonomy and Function



National Human Genome Research Institute

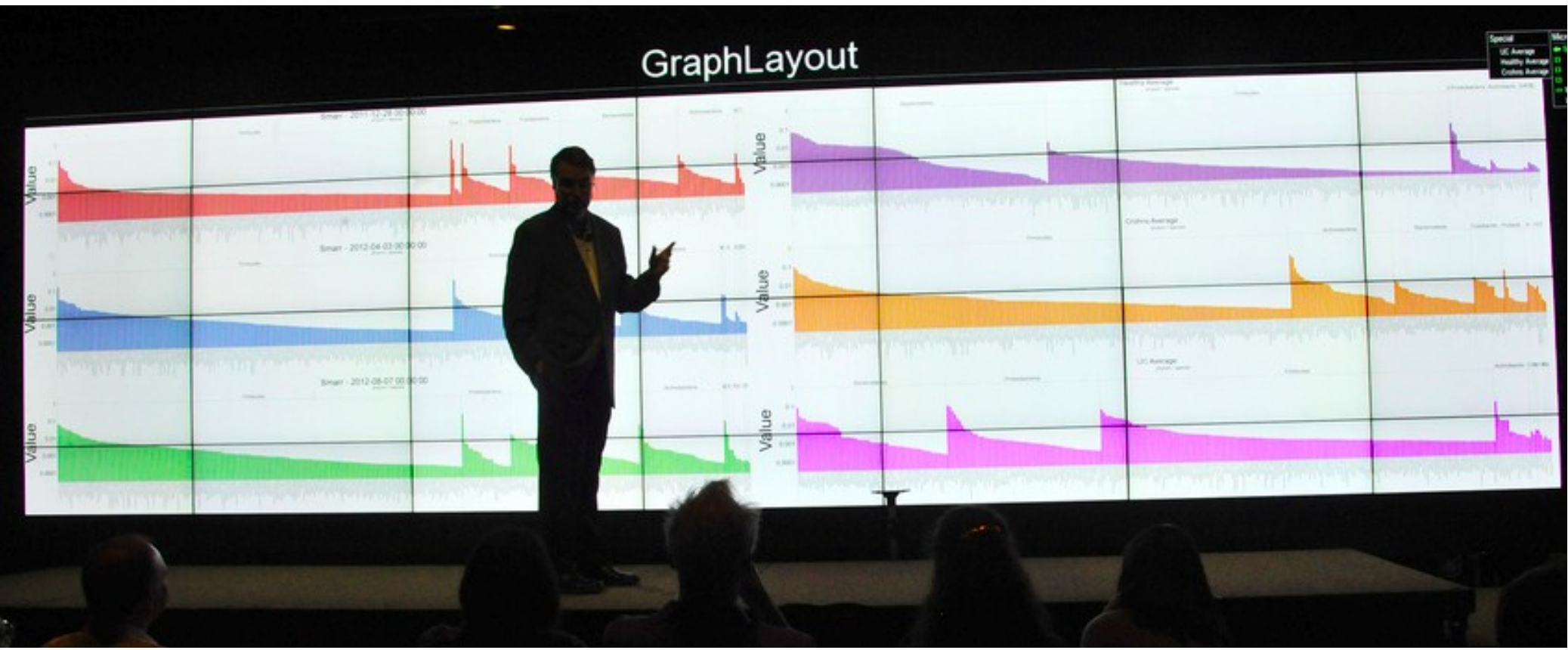
HMP

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

CRBS

it²

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



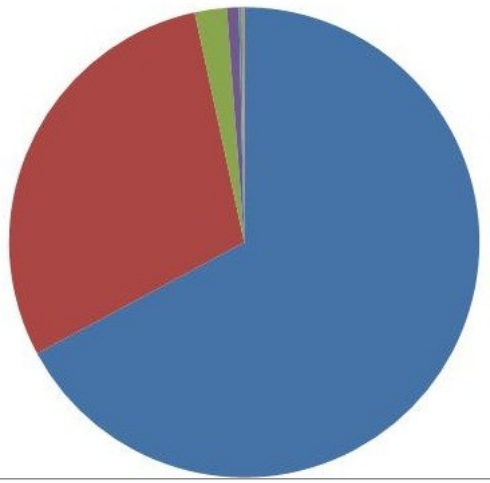
Comparing 3 LS Time Snapshots (Left)
with Healthy, Crohn's, UC (Right Top to Bottom)

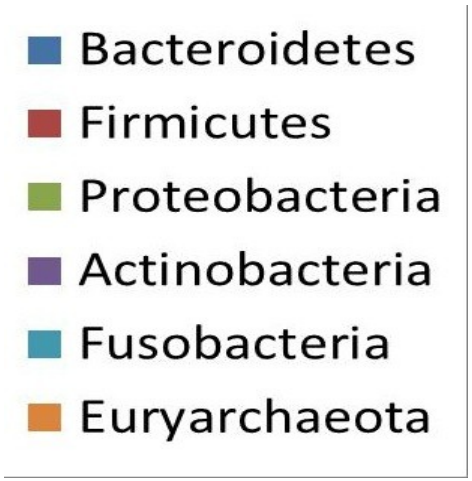
Calit2 VROOM-FuturePatient Expedition

We Find Major Shifts in Microbial Ecology Between Healthy and Two Forms of IBD

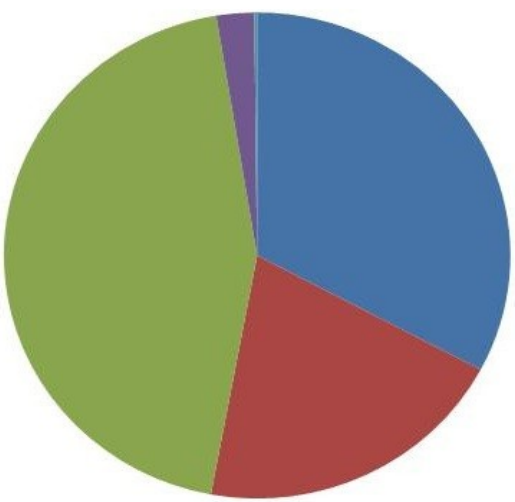
Microbiome "Dysbiosis" or "Mass Extinction"?

Ave. Healthy



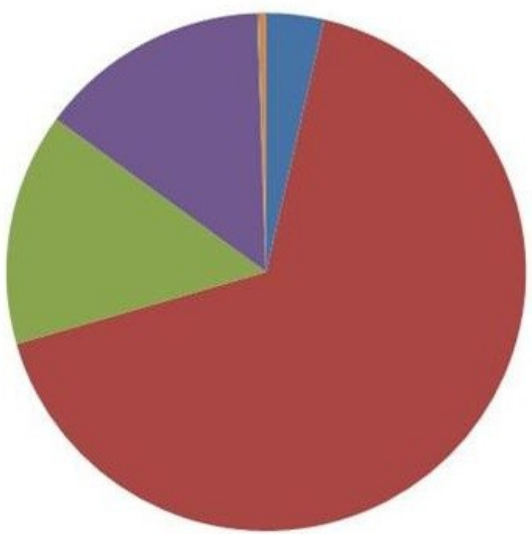


Ave. Ulcerative Colitis



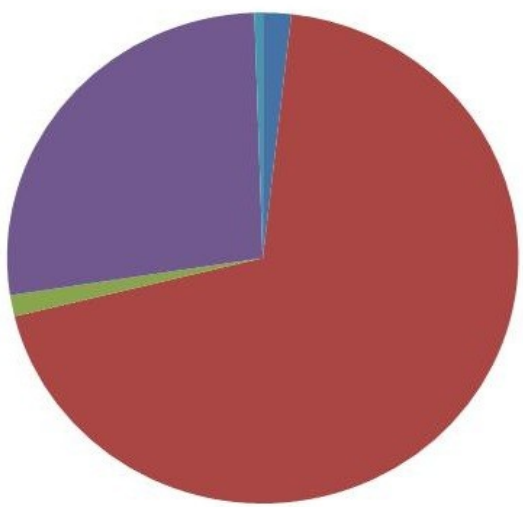
Explosion of Proteobacteria

LS Apr 2012



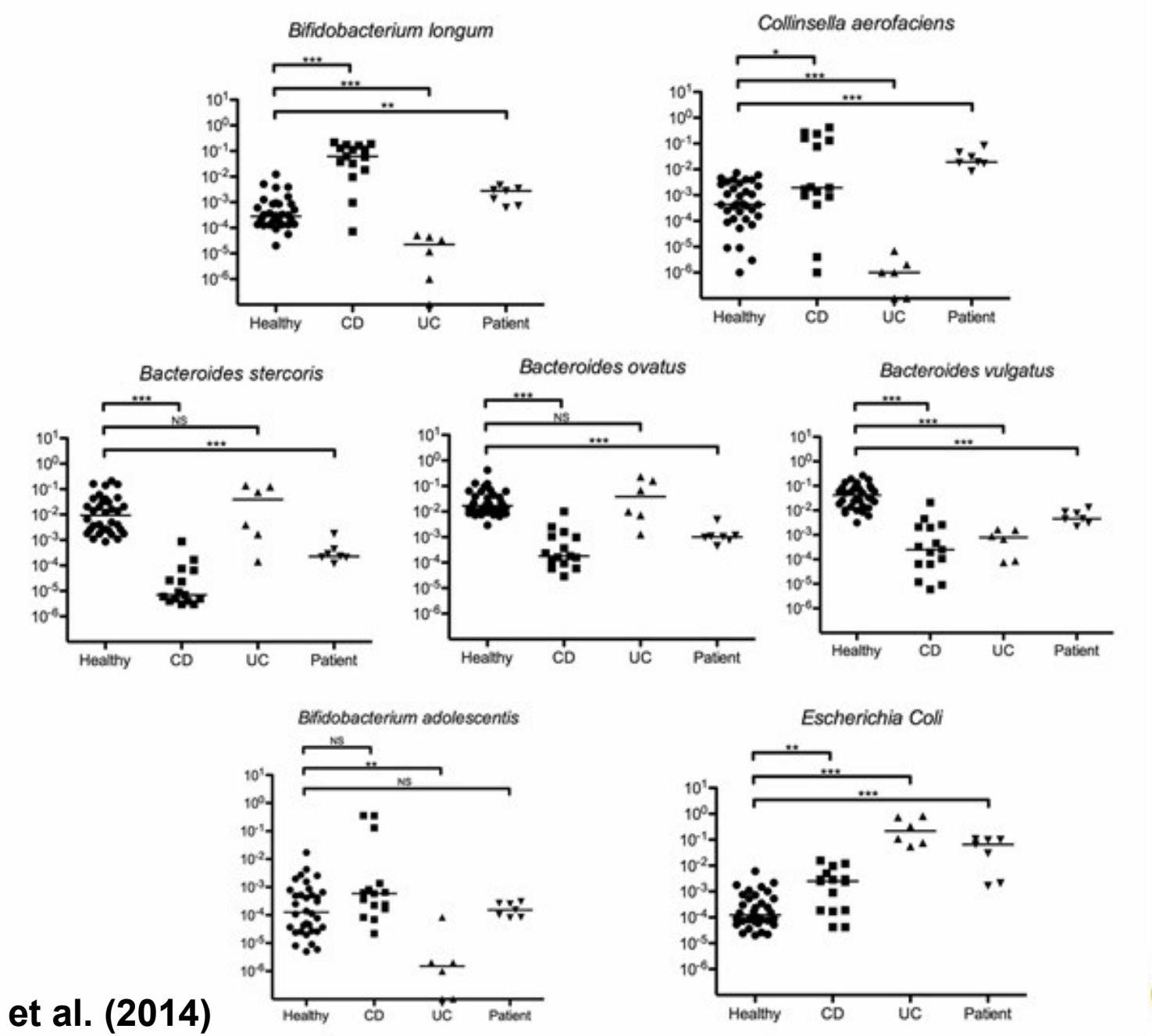
On the IBD Spectrum

Ave. Crohn's



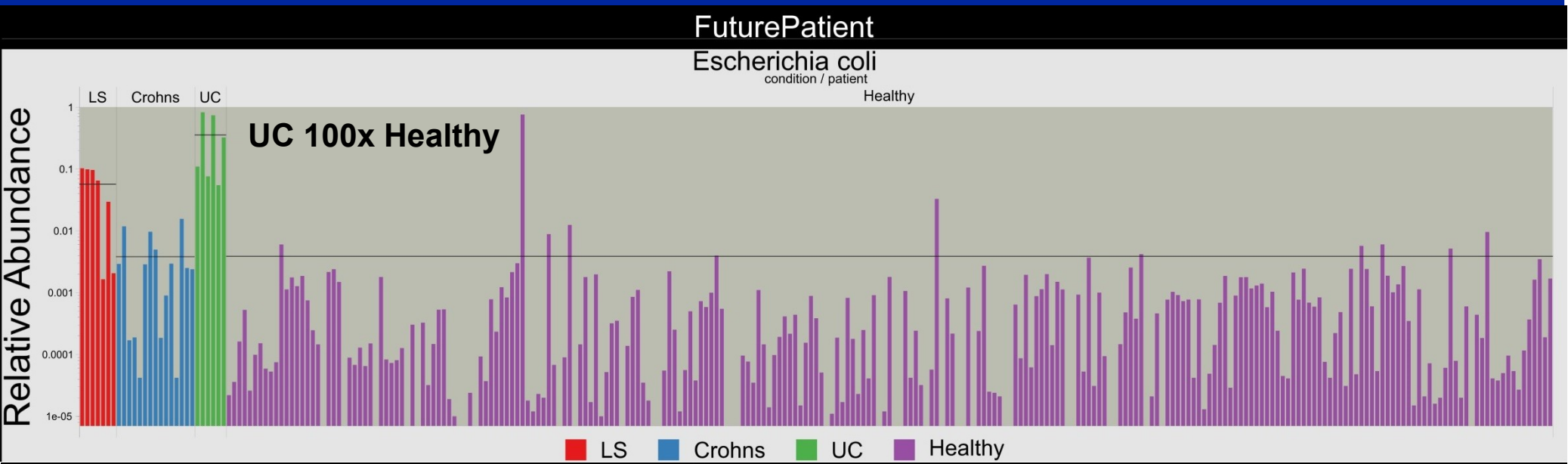
Collapse of Bacteroidetes

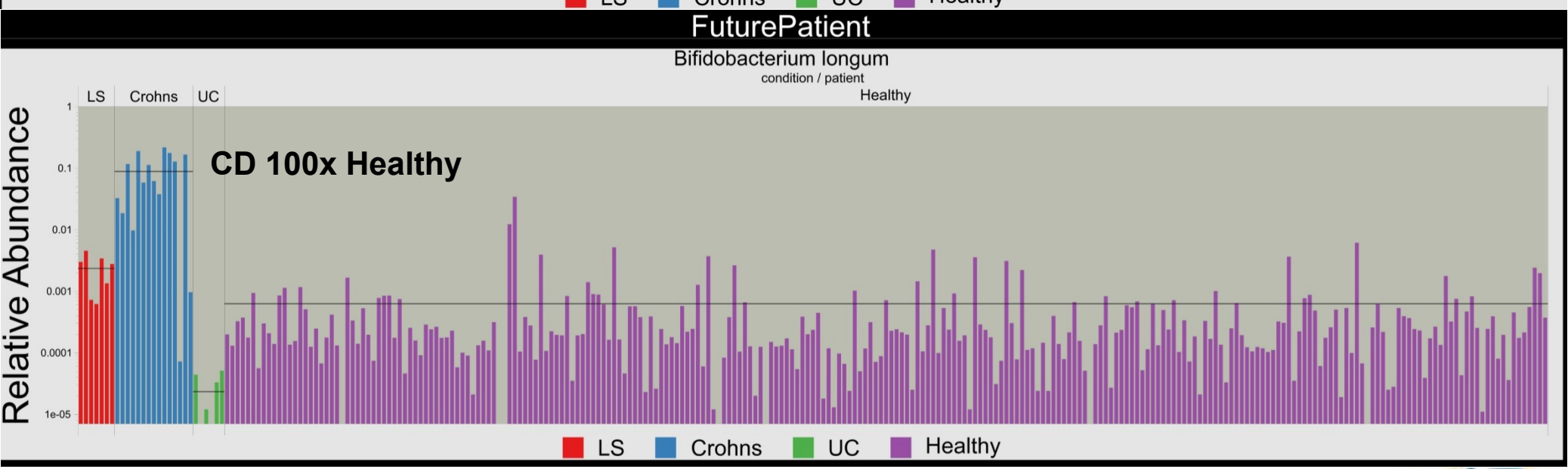
Bacterial Species Which PCA Indicates Best Separate the Four States



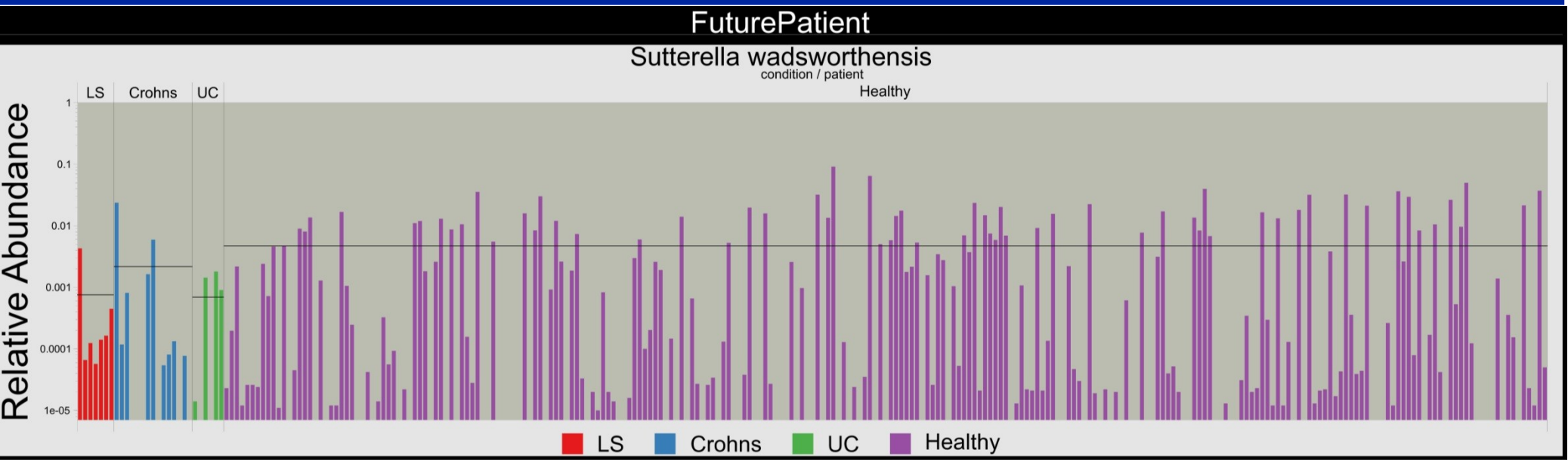
Source: Wu, et al. (2014)

Toward Microbiome Disease Diagnosis





Corellating Specific Microbes with Disease States: Sutterella wadsworthensis and Child Autism-GI

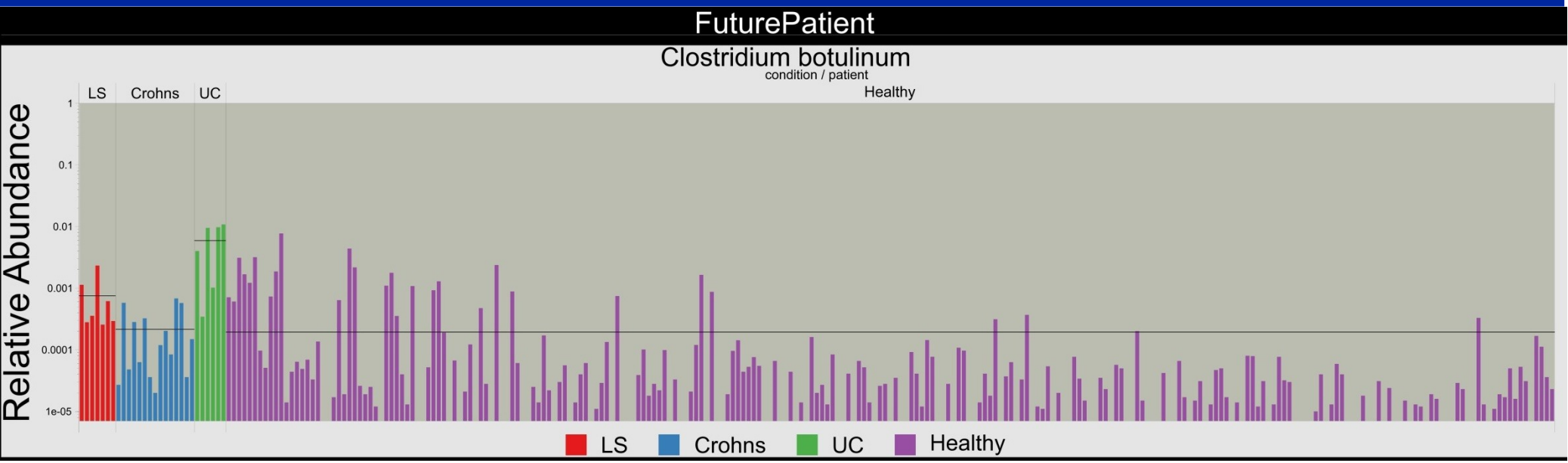


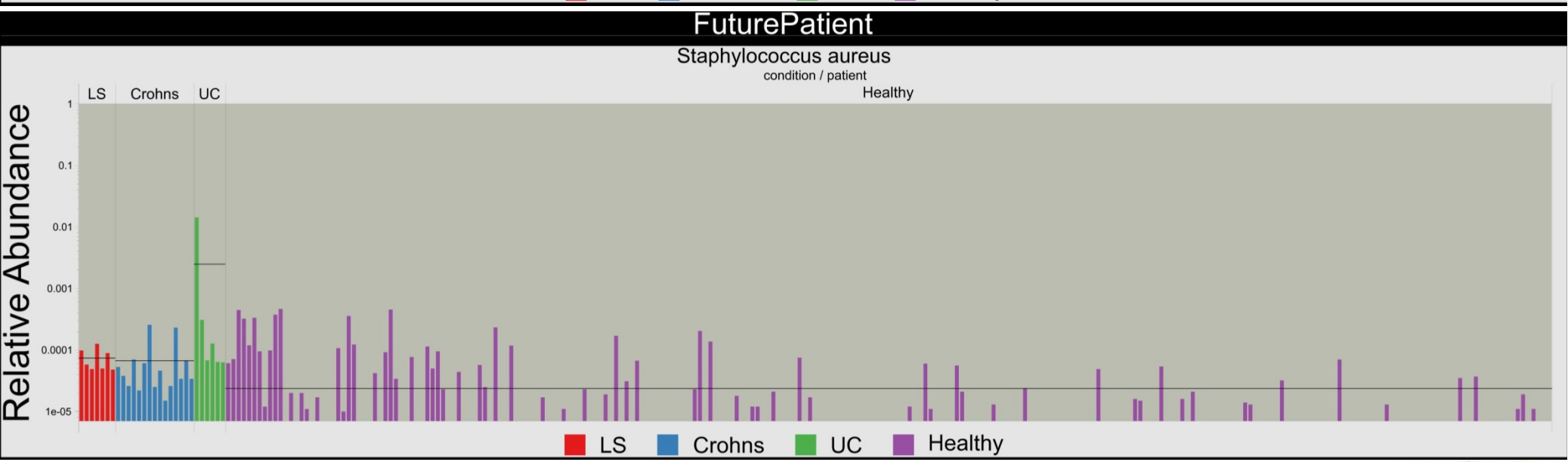
Application of Novel PCR-Based Methods for Detection, Quantitation, and Phylogenetic Characterization of *Sutterella* Species in Intestinal Biopsy Samples from Children with Autism and Gastrointestinal Disturbances

Brent L. Williams, Mady Hornig, Tanmay Parekh, and W. Ian Lipkin

"We have designed and applied novel Sutterella-specific PCR assays that confirmed high levels of Sutterella species in over half of from AUT-GI children and the complete absence of Sutterella in Control-GI children tested in this study."

Scanning for Potential Pathogens in Diseased Patients





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
Tom DeFanti
Kevin Patrick
Jurgen Schulze
Andrew Prudhomme
Philip Weber
Fred Raab
Joe Keefe
Ernesto Ramirez



SDSC Team

Michael Norman
Mahidhar Tatineni
Robert Sinkovits

UCSD Health Sciences Team

William J. Sandborn
Elisabeth Evans
John Chang
Brigid Boland
David Brenner