“Capturing the Interactive Dynamics of the Human Host/Microbiome System”

John Lawrence Lecture
Lawrence Berkeley National Laboratory
Berkeley, CA
June 12, 2018

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

I will report on results from a decade of quantification of my body (including its gut microbiome), using longitudinal measurements of the gut microbiome composition and of over a hundred blood and stool biomarkers. These are contextualized using human genome sequencing and MRI/CAT imaging. As a system scientist, my goal is to illuminate the interactive dynamics of the human host/microbiome system in health and disease, as well as to illustrate how medical interventions can drastically alter the internal dynamics of the host/microbiome system. These N=1 experiments are a rapidly growing addition to the traditional approach of averaging over large numbers of individuals and give us glimpses into the future of personalized precision medicine.

Your Body Has 10 Times
As Many Microbe Cells As DNA-Bearing Human Cells

Your Body Hosts 40 Trillion Microbes

Your Microbiome is
Your "Near-Body" Environment
and its Cells
Contain ~100x as Many DNA Genes
As Your Human DNA-Bearing Cells

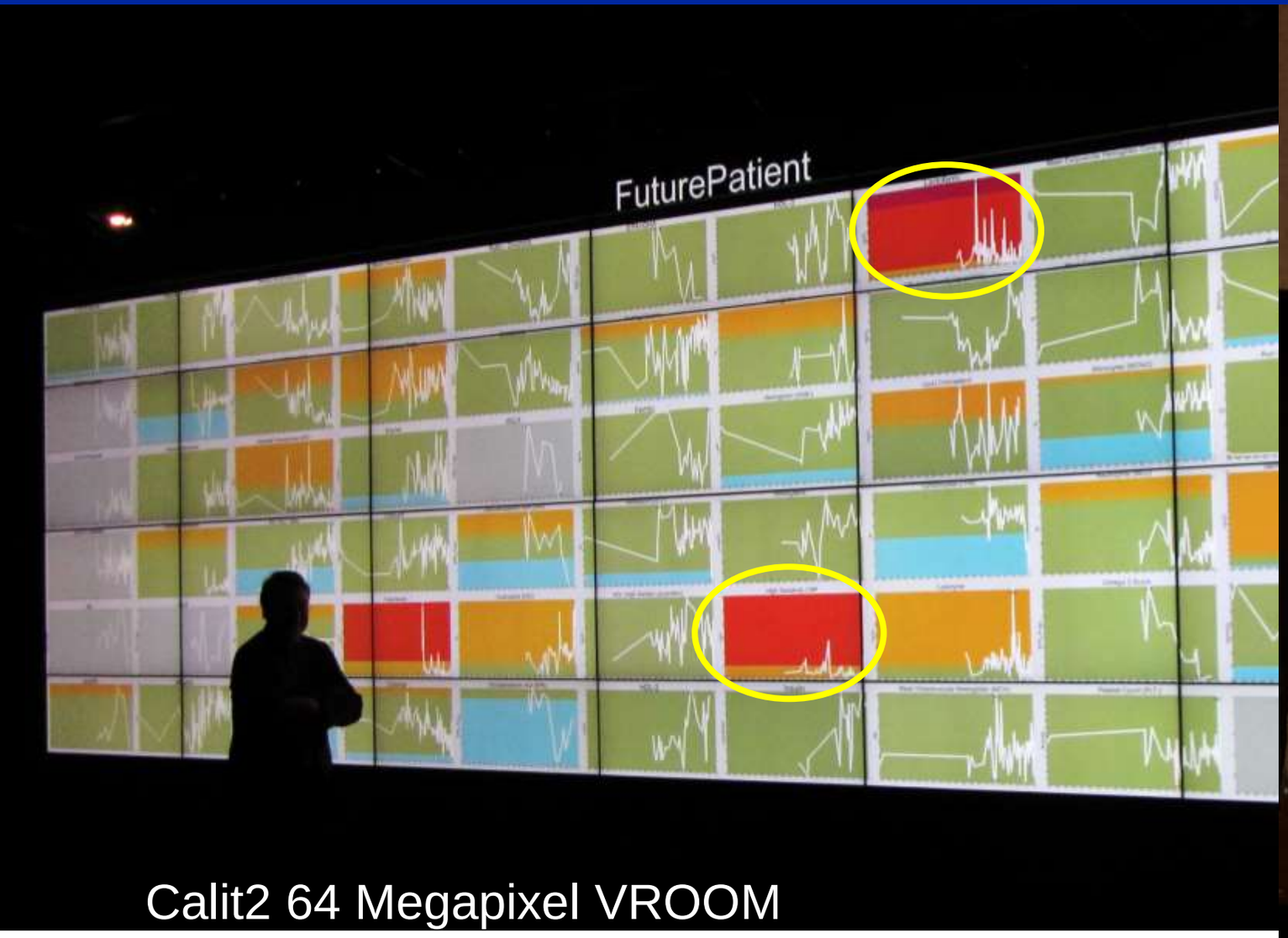
Inclusion of this "Dark Matter" of the Body
Will Radically Alter Medicine

The Human Gut
as a Super-Evolutionary Microbial Cauldron

- **Enormous Density**
  - 1000x Ocean Water
- **Highly Dynamic Microbial Ecology**
  - Hundreds to Thousands of Species
- **Horizontal Gene Transfer**
- **Phages**
- **Adaptive Selection Pressures (Immune System)**
  - Innate Immune System
  - Adaptive Immune System
  - Macrophages and Antimicrobial proteins
- **Constantly Changing Environmental Pressures**
  - Diet
  - Antibiotics
  - Pharmaceuticals

How Can Data Science Elucidate This Dynamical System?

Since Humans Are Not Mice, I Have Been Tracking My Internal Biomarkers For A Decade To Understand Human Host/Microbiome Dynamics



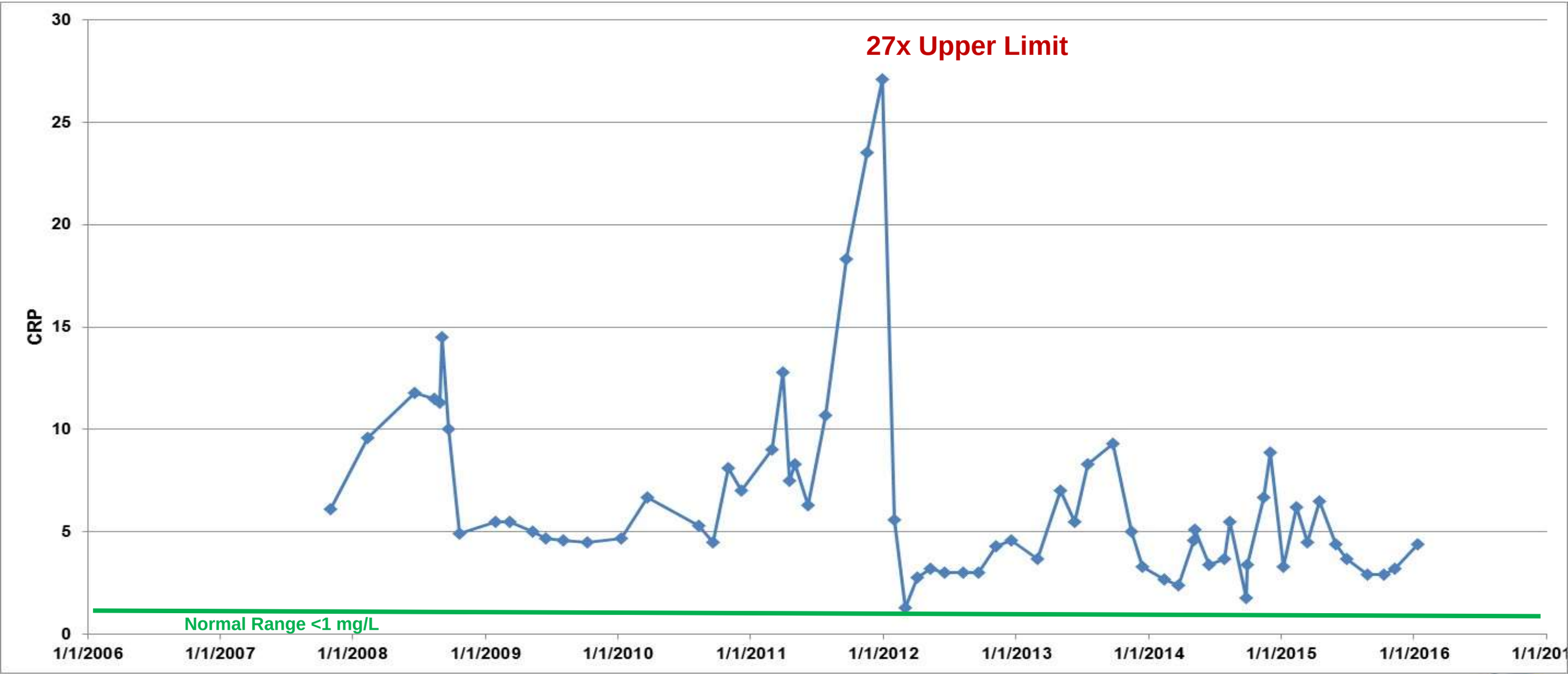
Calit2 64 Megapixel VROOM



My Quarterly Blood Draw

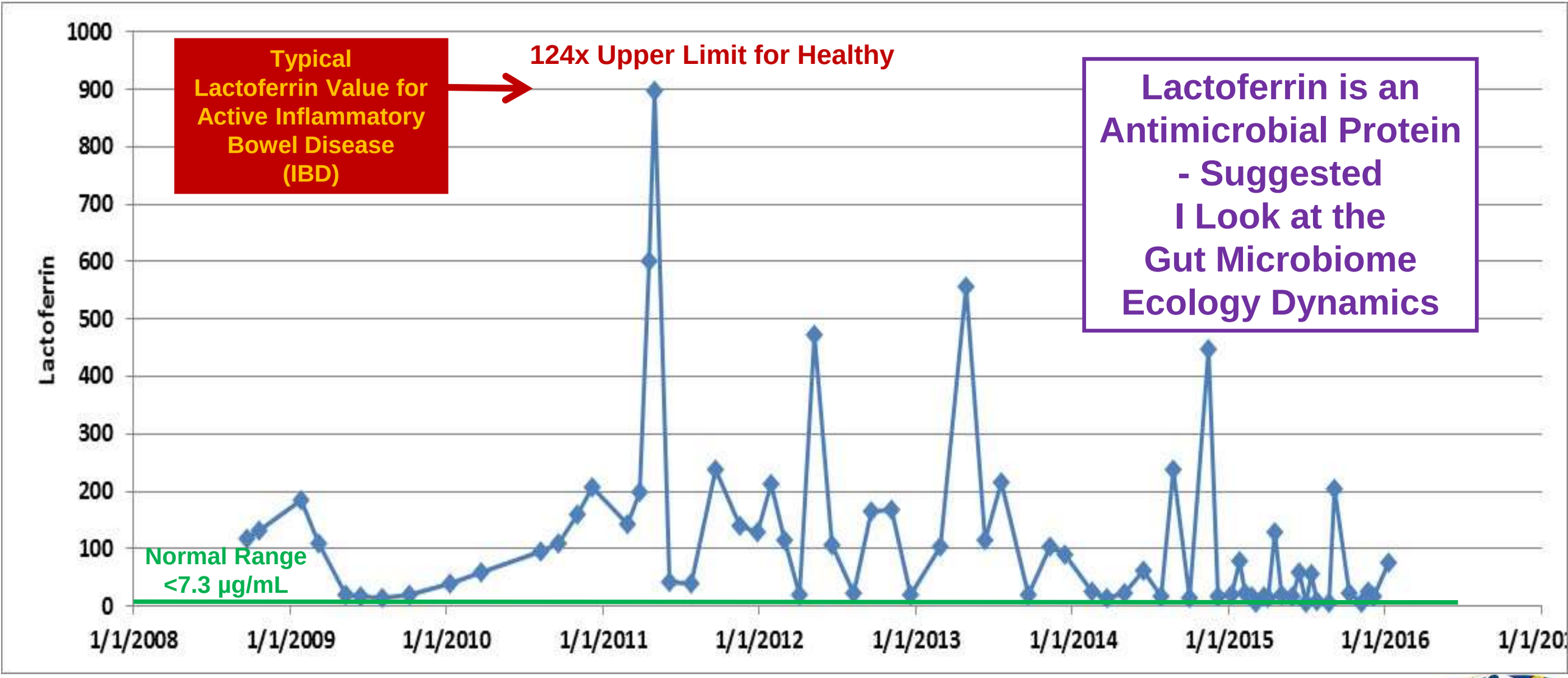
UC San Diego

Only One of My Blood Measurements Was Far Out of Range--Indicating Chronic Inflammation



Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

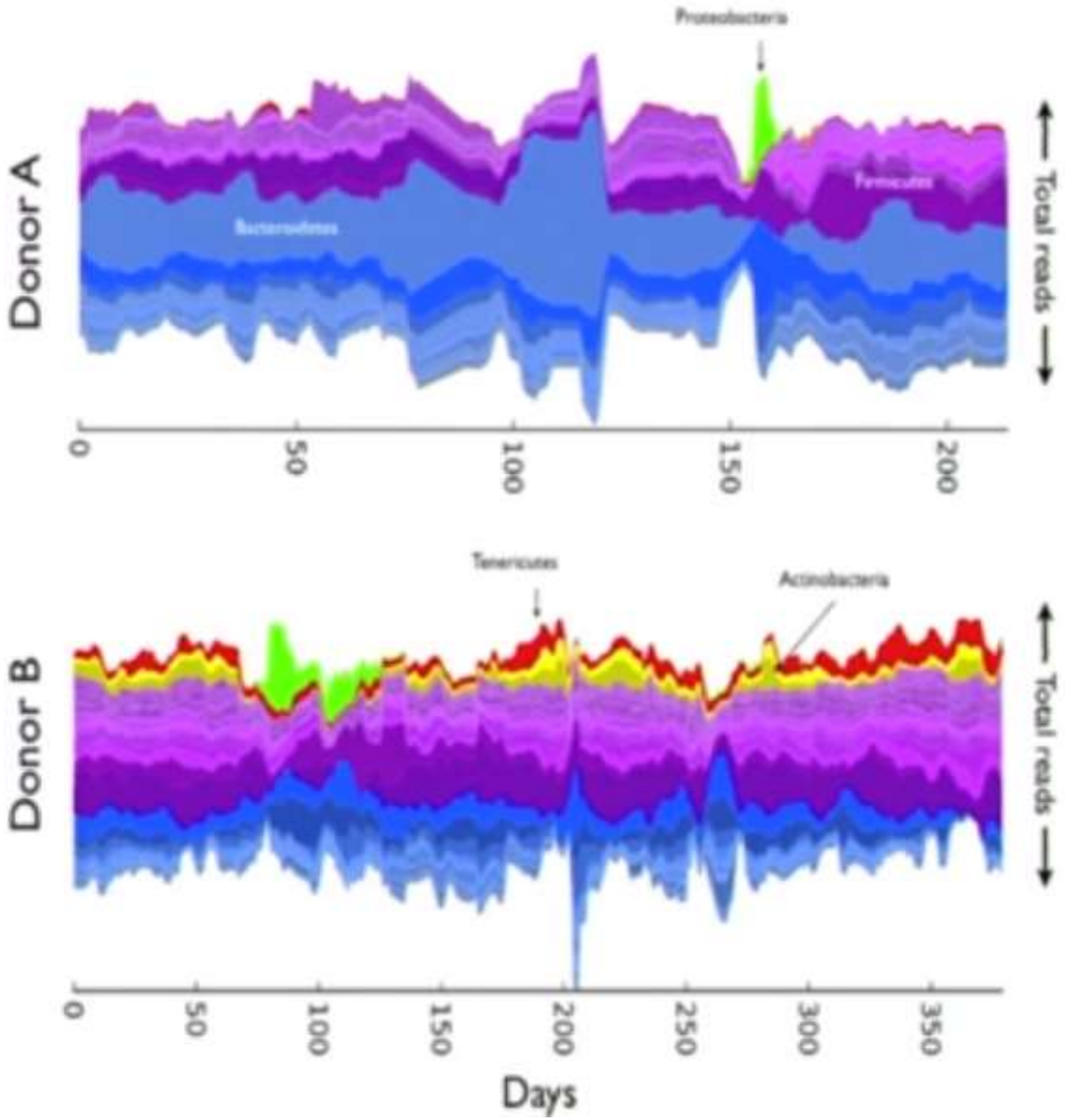
Longitudinal Stool Tests Revealed Large Excursions in My Immune System: Inflammatory Bowel Disease (IBD)



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

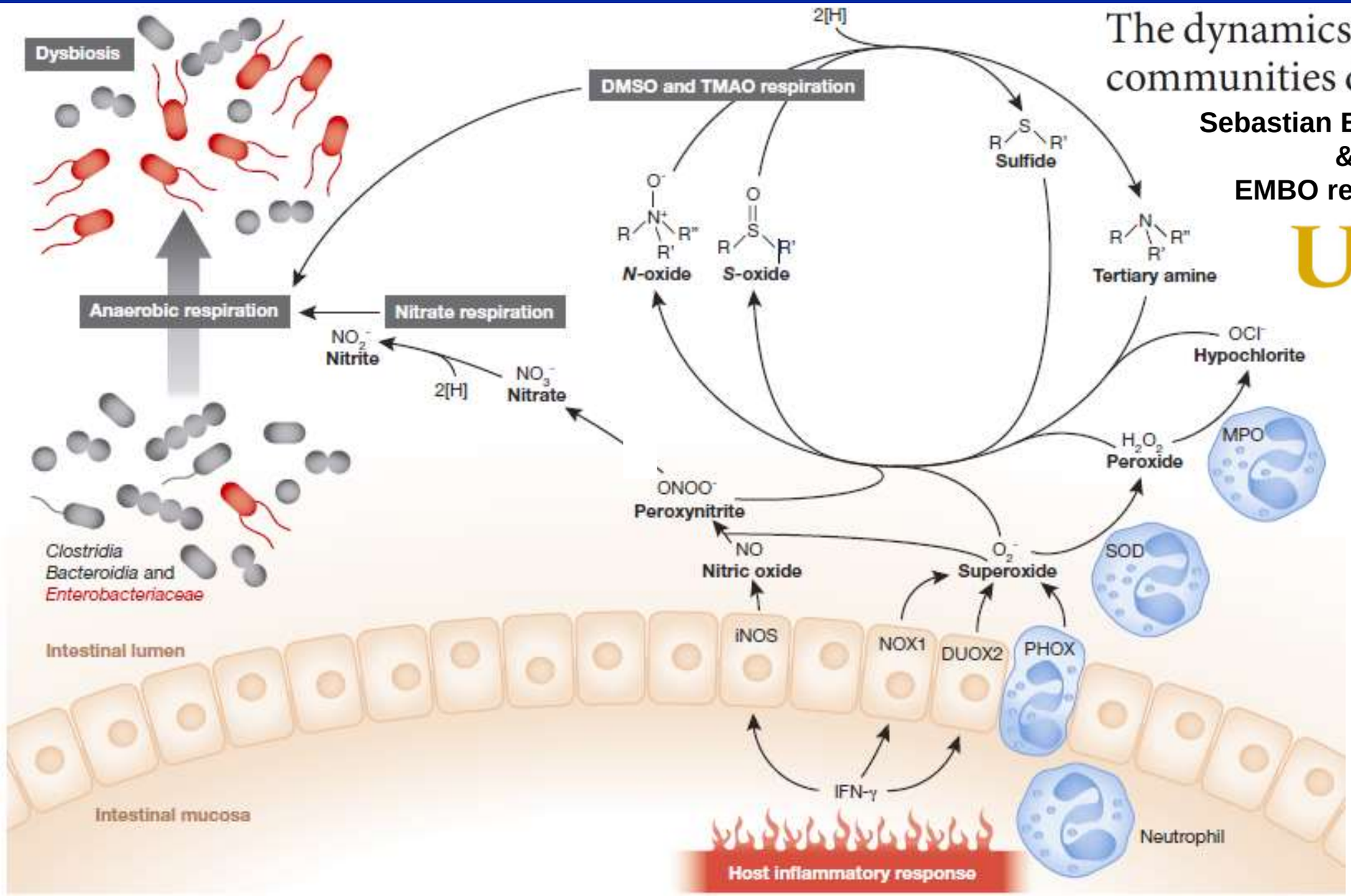
The Adult Healthy Gut Microbiome Is Remarkably Stable Over Time

Gut communities over time



Source: Eric Alm, MIT

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

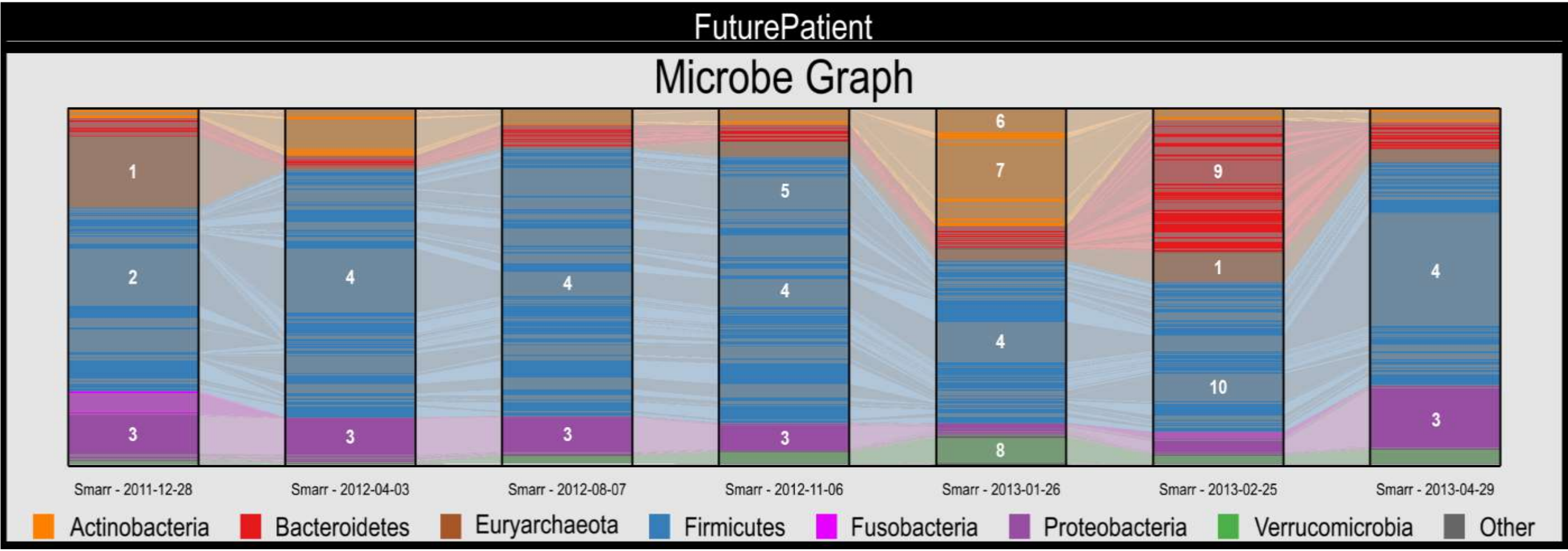


The dynamics of gut-associated microbial communities during inflammation

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

UCDAVIS

In Contrast to a Healthy Person, With Inflammation My Gut Microbiome Was Quite Unstable With High Levels of E. coli



1. Methanobrevibacter smithii (Euryarchaeota)
2. Parvimonas micra (Firmicutes)
3. Escherichia coli (Proteobacteria)
4. Faecalibacterium prausnitzii (Firmicutes)
5. Dorea longicatena (Firmicutes)
6. Actinomyces odontolyticus (Actinobacteria)
7. Bifidobacterium animalis (Actinobacteria)
8. Akkermansia muciniphila (Verrucomicrobia)
9. Bacteroides intestinalis (Bacteriodetes)
10. Ruminococcus bromii (Firmicutes)

Source: Smarr, Hyde, McDonald, Sandborn, Knight

Why Did I Have an Autoimmune Disease like IBD?

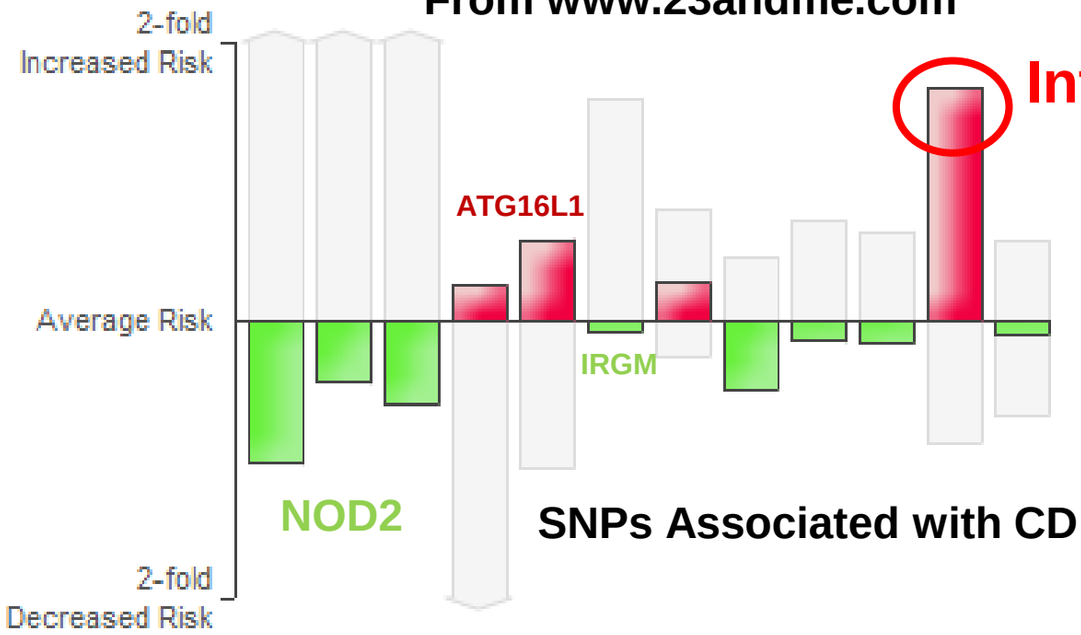
Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.
--The Role of Microbes in Crohn's Disease

So I Set Out to Quantify All Three!

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

I Found I Had One of the Earliest Known SNPs Associated with Crohn's Disease

From www.23andme.com



Polymorphism in Interleukin-23 Receptor Gene — 80% Higher Risk of Pro-inflammatory Immune Response rs1004819

A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene

Richard H. Düerr, *et al.*
Science **314**, 1461 (2006)

News and Views

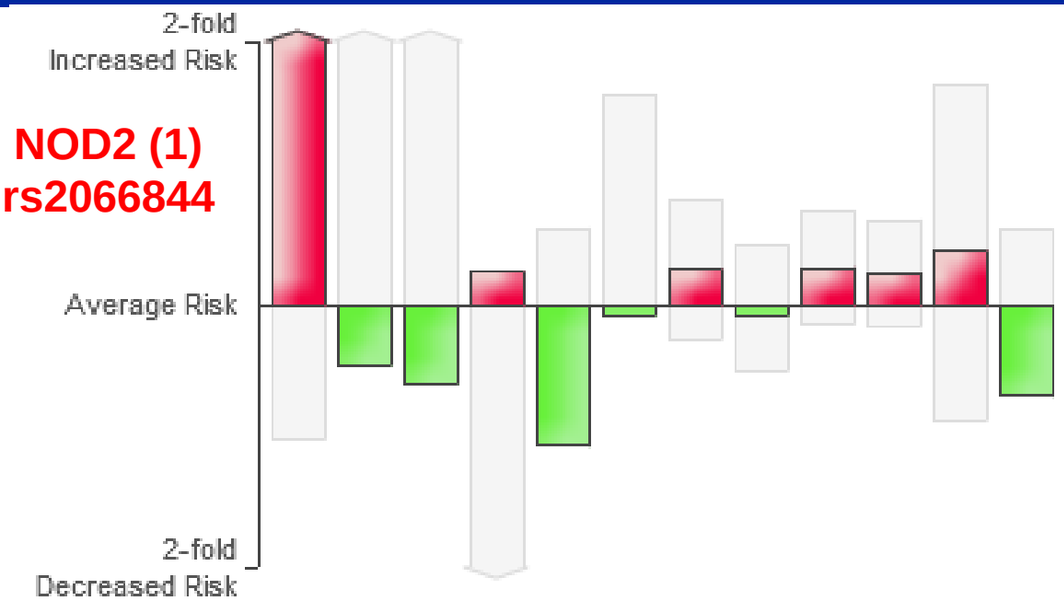
Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

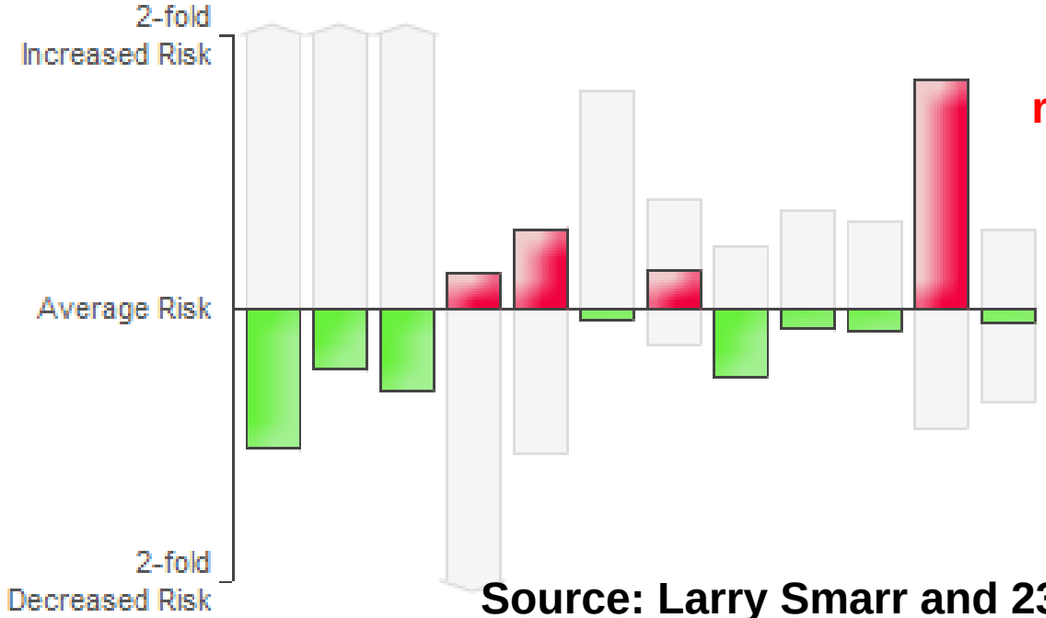
There Is Likely a Correlation Between CD SNPs and Where and When the Disease Manifests

Subject with Ileal Crohn's



Female
CD Onset
At 20-Years Old

Subject with Colon Crohn's



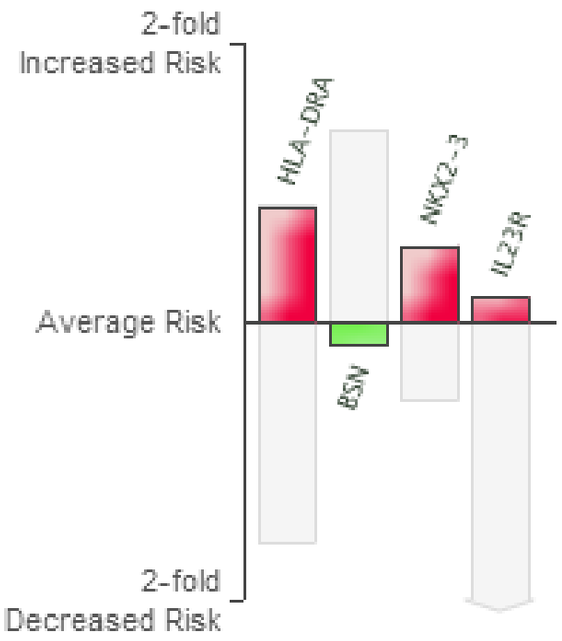
Me-Male
CD Onset
At 60-Years Old

Source: Larry Smarr and 23andme

I Also Had an Increased Risk for Ulcerative Colitis, But a SNP that is Also Associated with Colonic CD



I Have a 33% Increased Risk for Ulcerative Colitis HLA-DRA (rs2395185)



I Have the Same Level of HLA-DRA Increased Risk as Another Male Who Has Had Ulcerative Colitis for 20 Years

"Our results suggest that at least for the SNPs investigated [including HLA-DRA], colonic CD and UC have common genetic basis."
-Waterman, et al., IBD 17, 1936-42 (2011)

~35,000 IBD Patients Genotyped
From 49 Centres in 16 Countries in Europe, North America, and Australasia

Lancet 2016; 387: 156–67

Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study

Isabelle Cleynen, Gabrielle Boucher*, Luke Jostins*, L Philip Schumm, Sebastian Zeissig, Tariq Ahmad, Vibeke Andersen, Jane M Andrews, Vito Annese, Stephan Brand, Steven R Brant, Judy H Cho, Mark J Daly, Marla Dubinsky, Richard H Duerr, Lynnette R Ferguson, Andre Franke, Richard B Gearry, Philippe Goyette, Hakon Hakonarson, Jonas Halfvarson, Johannes R Hov, Hailang Huang, Nicholas A Kennedy, Limas Kupcinskas, Ian C Lawrance, James C Lee, Jack Satsangi, Stephan Schreiber, Emilie Théâtre, Andrea E van der Meulen-de Jong, Rinse K Weersma, David C Wilson, International Inflammatory Bowel Disease Genetics Consortium†, Miles Parkes, Severine Vermeire, John D Rioux, John Mansfield, Mark S Silverberg, Graham Radford-Smith, Dermot P B McGovern*, Jeffrey C Barrett*, Charlie W Lees**

Our data support a continuum of disorders within inflammatory bowel disease, much better explained by three groups (ileal Crohn's disease, colonic Crohn's disease, and ulcerative colitis) than by Crohn's disease and ulcerative colitis as currently defined.

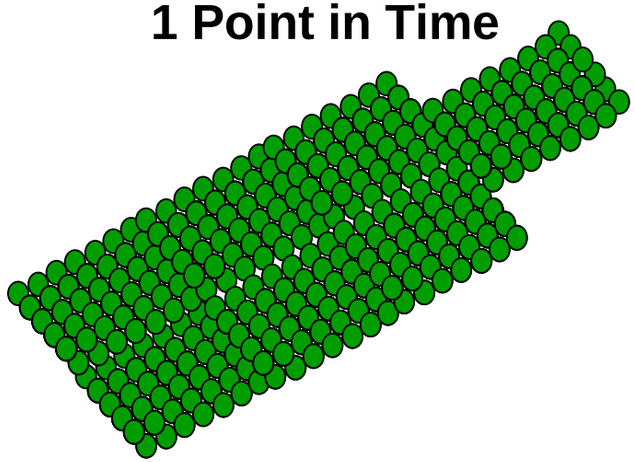
THE LANCET

Using Metagenomics to Compare Healthy Subjects with IBD Patients From 3 Subtypes

Each Sample Has 100-200 Million Illumina Short Reads (100 bases)

"Healthy" Individuals

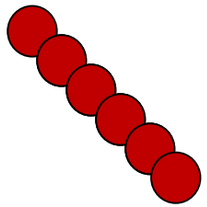
250 Subjects
1 Point in Time



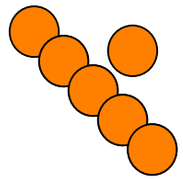
Inflammatory Bowel Disease (IBD) Patients

Larry Smarr
(Colonic Crohn's)

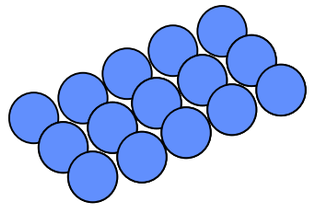
7 Points in Time



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

To Map Out the Dynamics of Autoimmune Microbiome Ecology Couples Next Generation Genome Sequencers to *Big Data* Supercomputers

Source: Weizhong Li, UCSD

Our Team Used 25 CPU-years to Compute Comparative Gut Microbiomes Starting From 2.7 Trillion DNA Bases of My Samples and Healthy and IBD Controls

Illumina HiSeq 2000 at JCVI



SDSC Gordon Data Supercomputer



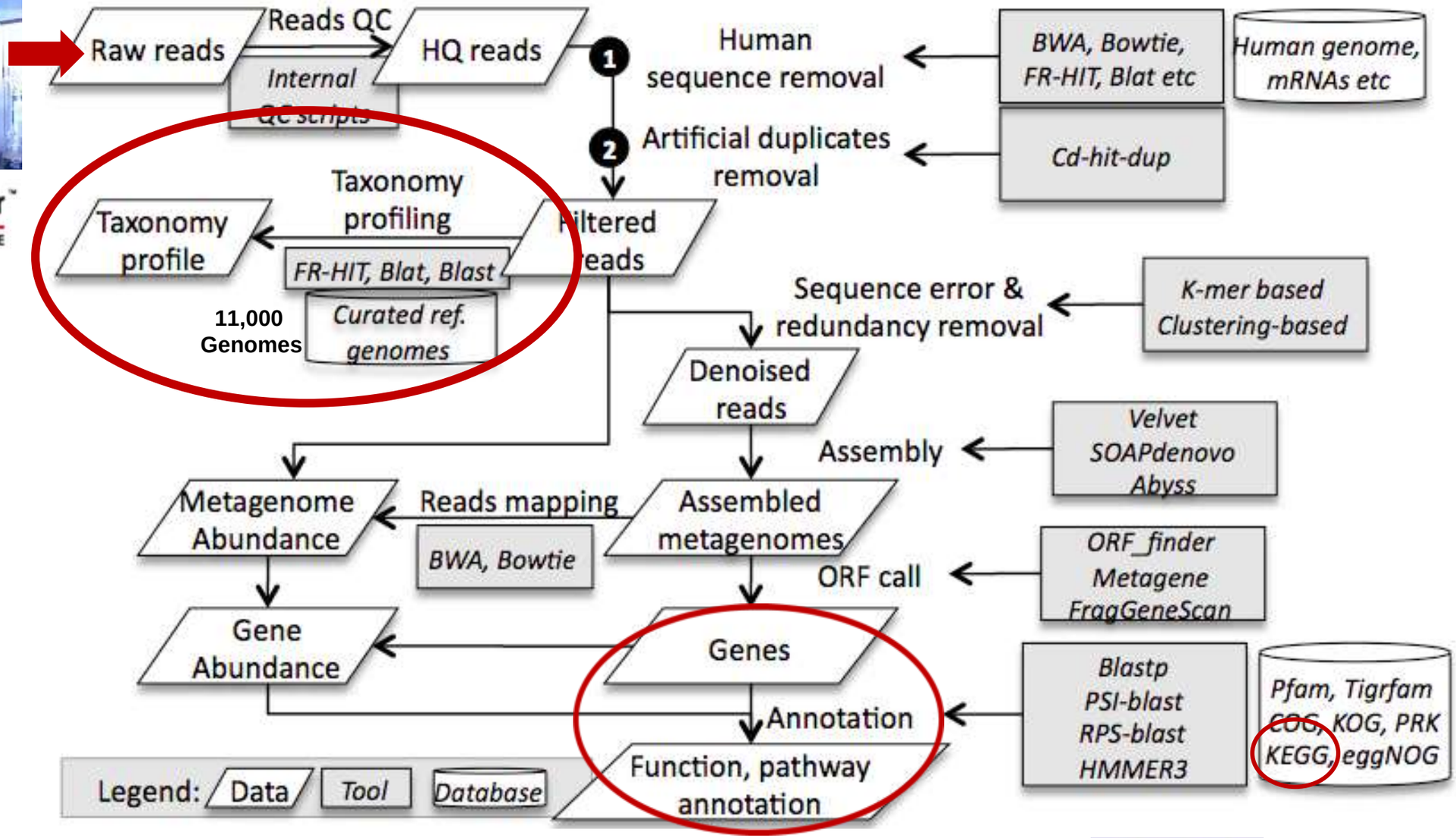
Dell Solutions Center
Industry Solutions Lab
SANGER DSU

J. Craig Venter INSTITUTE SDSC DELL NIH HMP CRBS it²

Computational NextGen Sequencing Pipeline: From Sequence to Taxonomy to Function



J. Craig Venter INSTITUTE



National Human Genome Research Institute

HMP

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

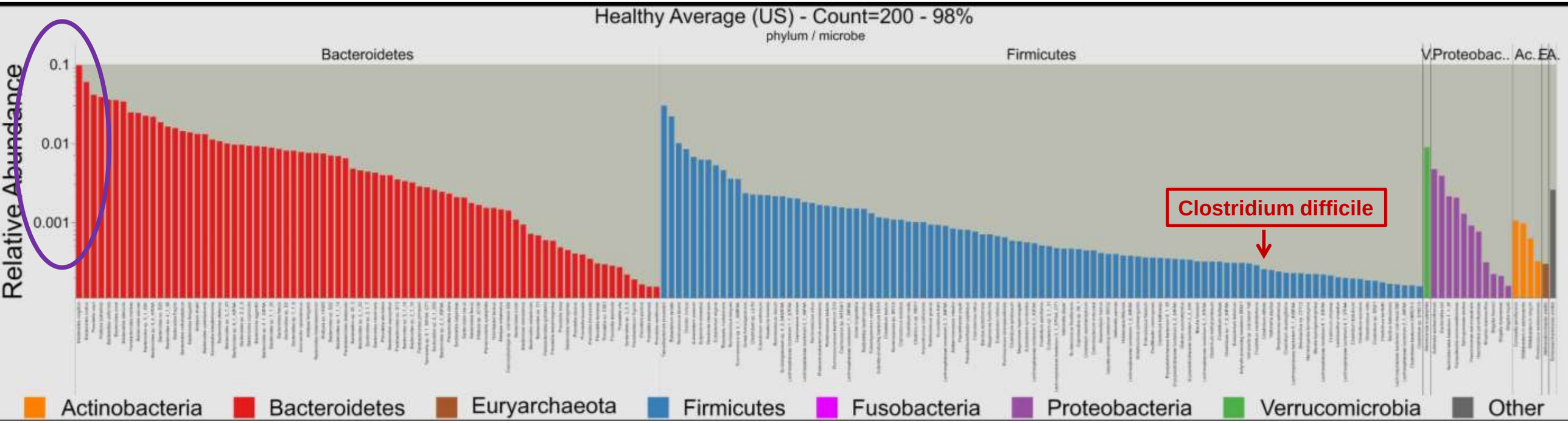
CRBS

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Supercomputer Metagenomics Produces Relative Abundance of Hundreds of Microbial Species

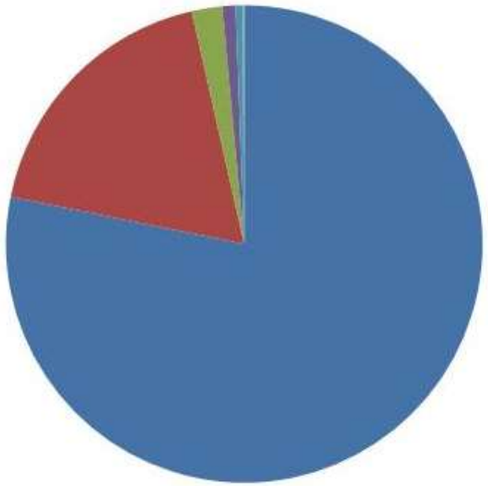
Average Over 250 Healthy People
From NIH Human Microbiome Project

Note Log Scale

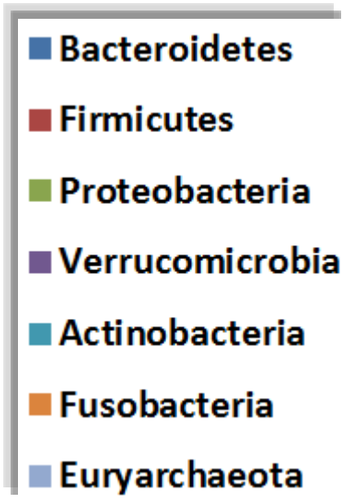


We Found Major State Shifts in Microbial Ecology Phyla Between Healthy and Three Forms of IBD

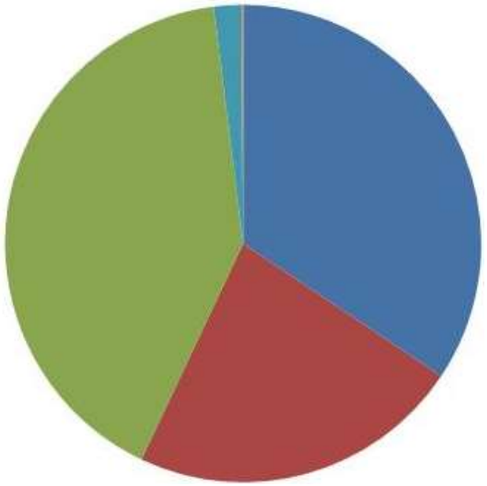
Average HE



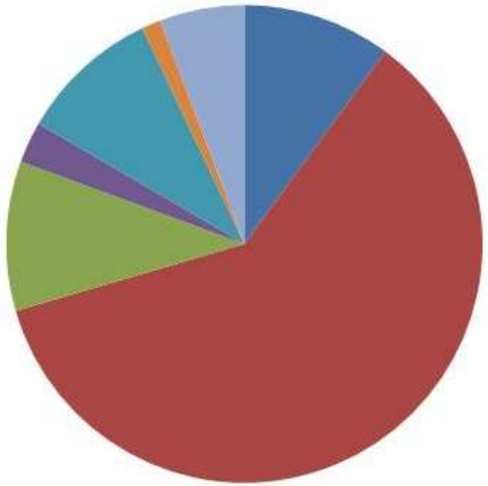
Most Common Microbial Phyla



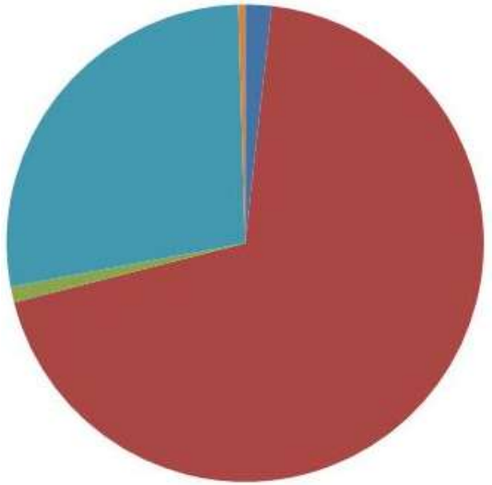
Average Ulcerative Colitis



Average LS Colonic Crohn's Disease



Average Ileal Crohn's Disease



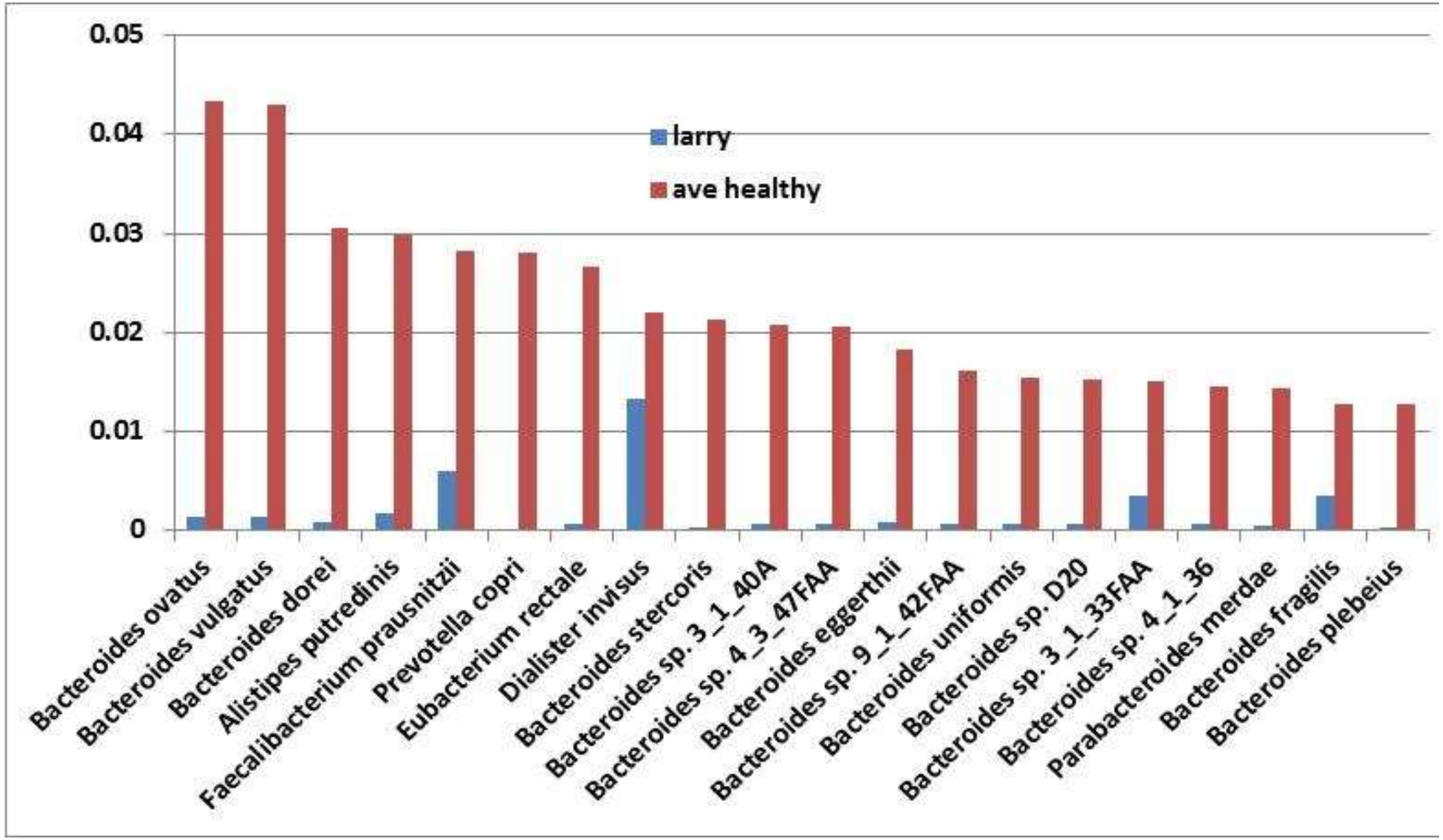
Lessons From Ecological Dynamics I:
Invasive Species Dominate After Major Species Destroyed



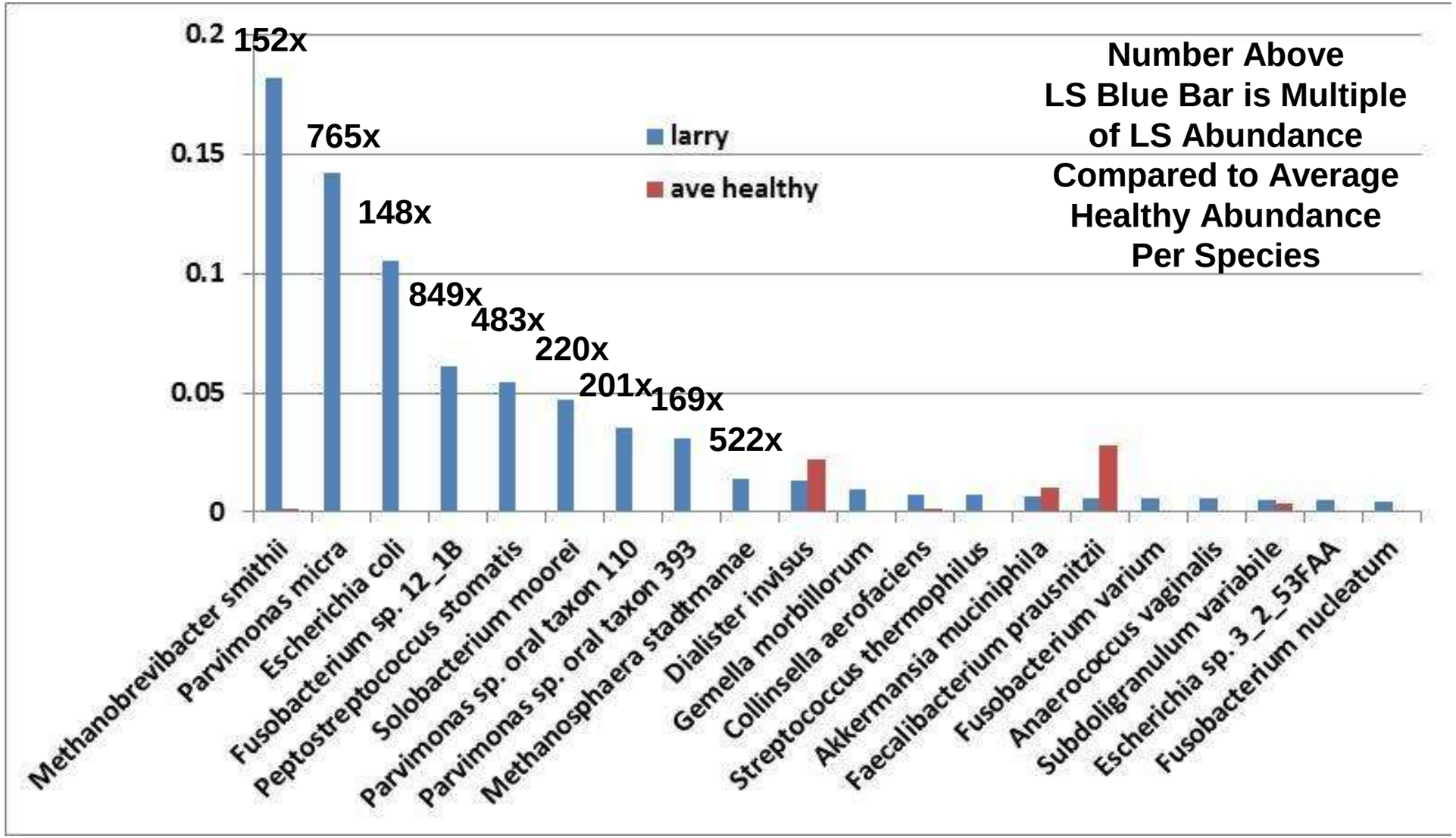
”In many areas following these burns invasive species are able to establish themselves, crowding out native species.”

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



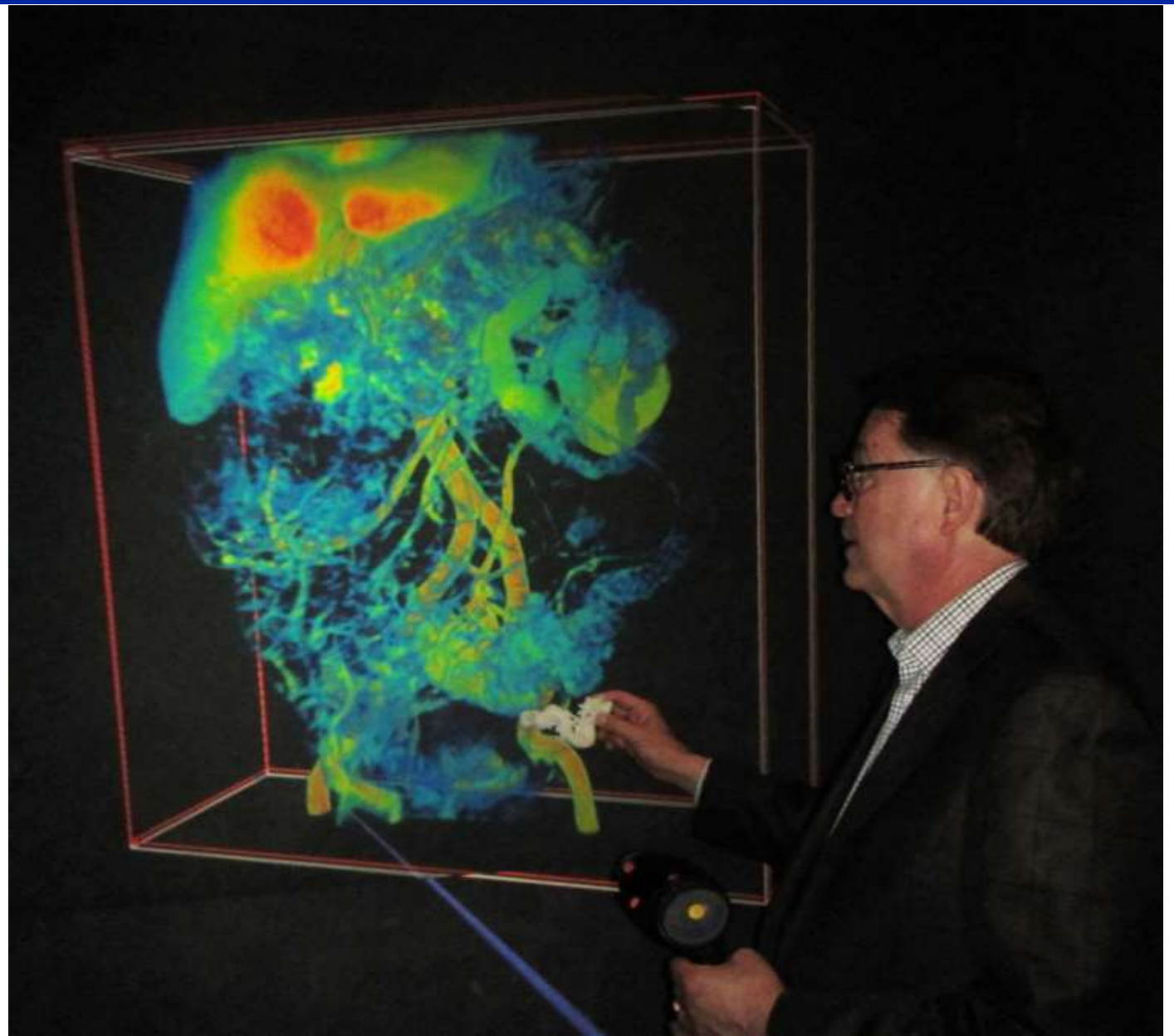
In Place of the Depleted Common Microbes in Healthy People Are Rare Microbes in My Gut



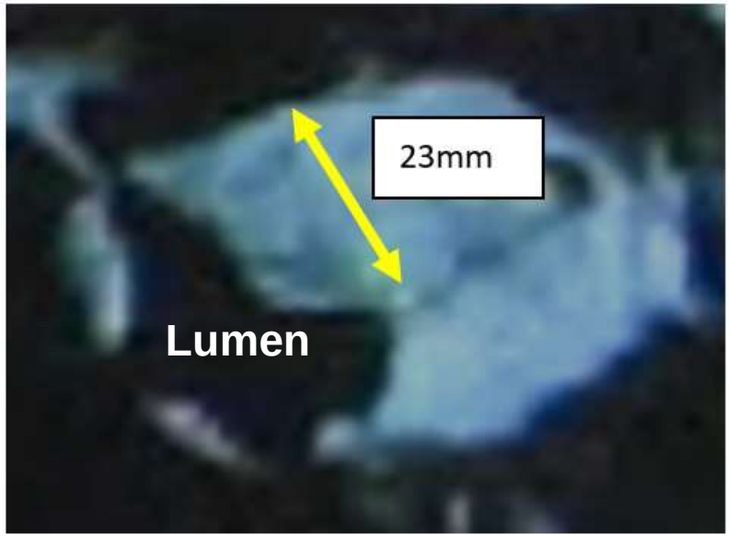
Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

I Had Been Giving Virtual Reality Tours of “Transparent Larry” for Six Years at Calit2

3D Volumetric Visualization Created by Calit2’s Jurgen Schulze from January 2012 MRI

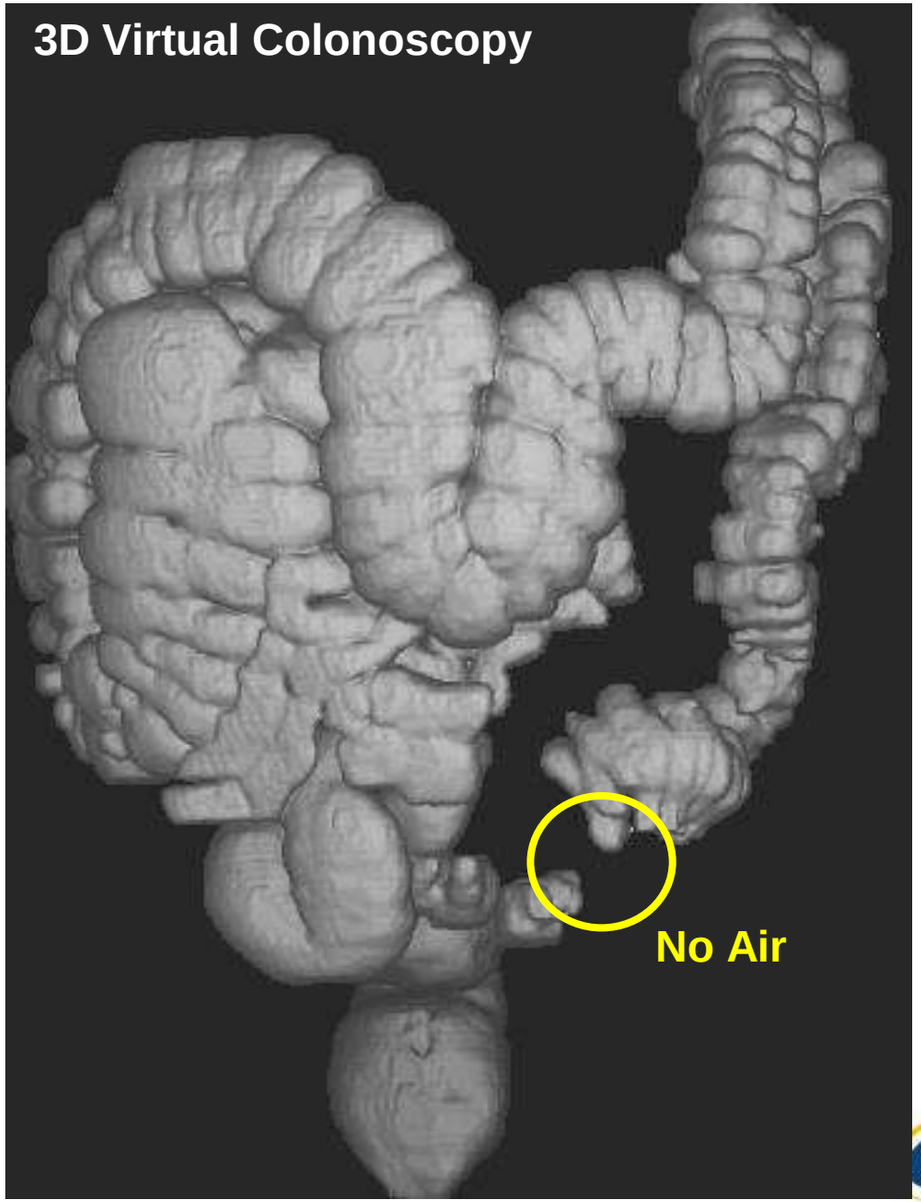


Full Body CAT Scan at mm Resolution, Including Virtual Colonoscopy June 2016 Convinced Me Time Had Come for Surgery



**“I would take it out.
All it can do is cause you trouble.”
-Harvey Eisenberg, MD
June 2016**

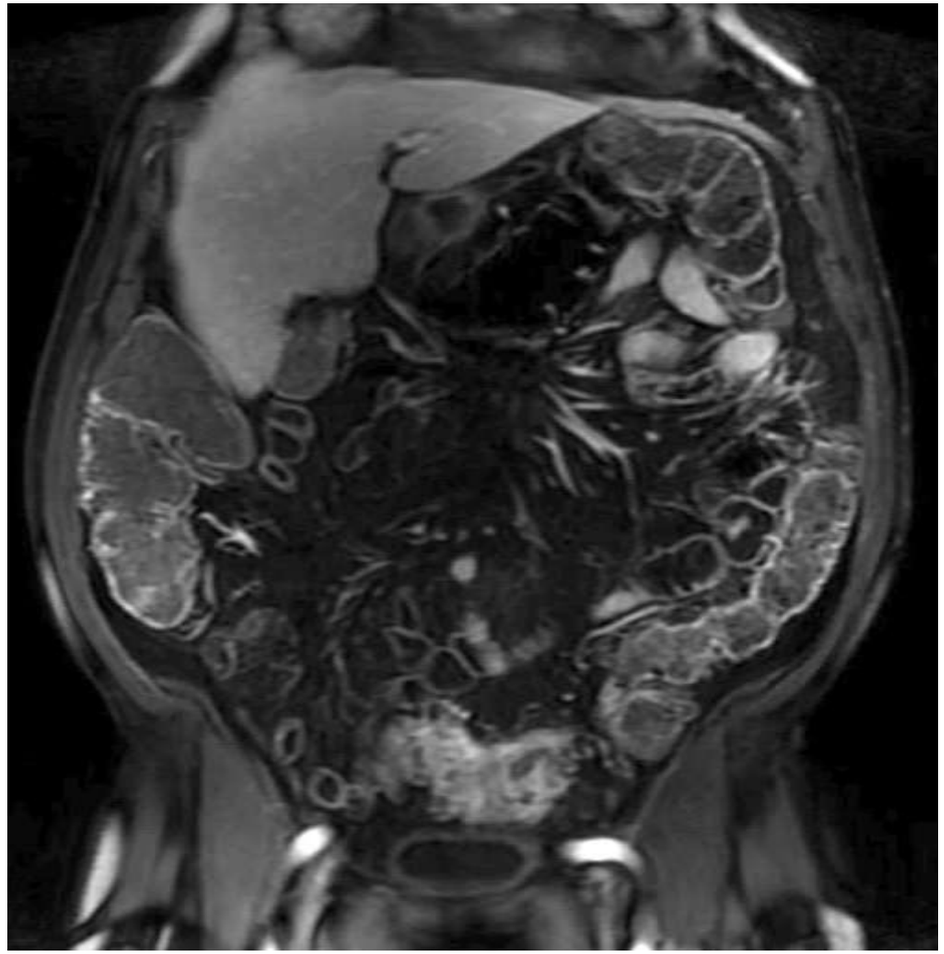
**Smarr Met with Dr. Sandborn Sept 12, 2016
Then With Dr. Ramamoorthy Oct 6, 2016**



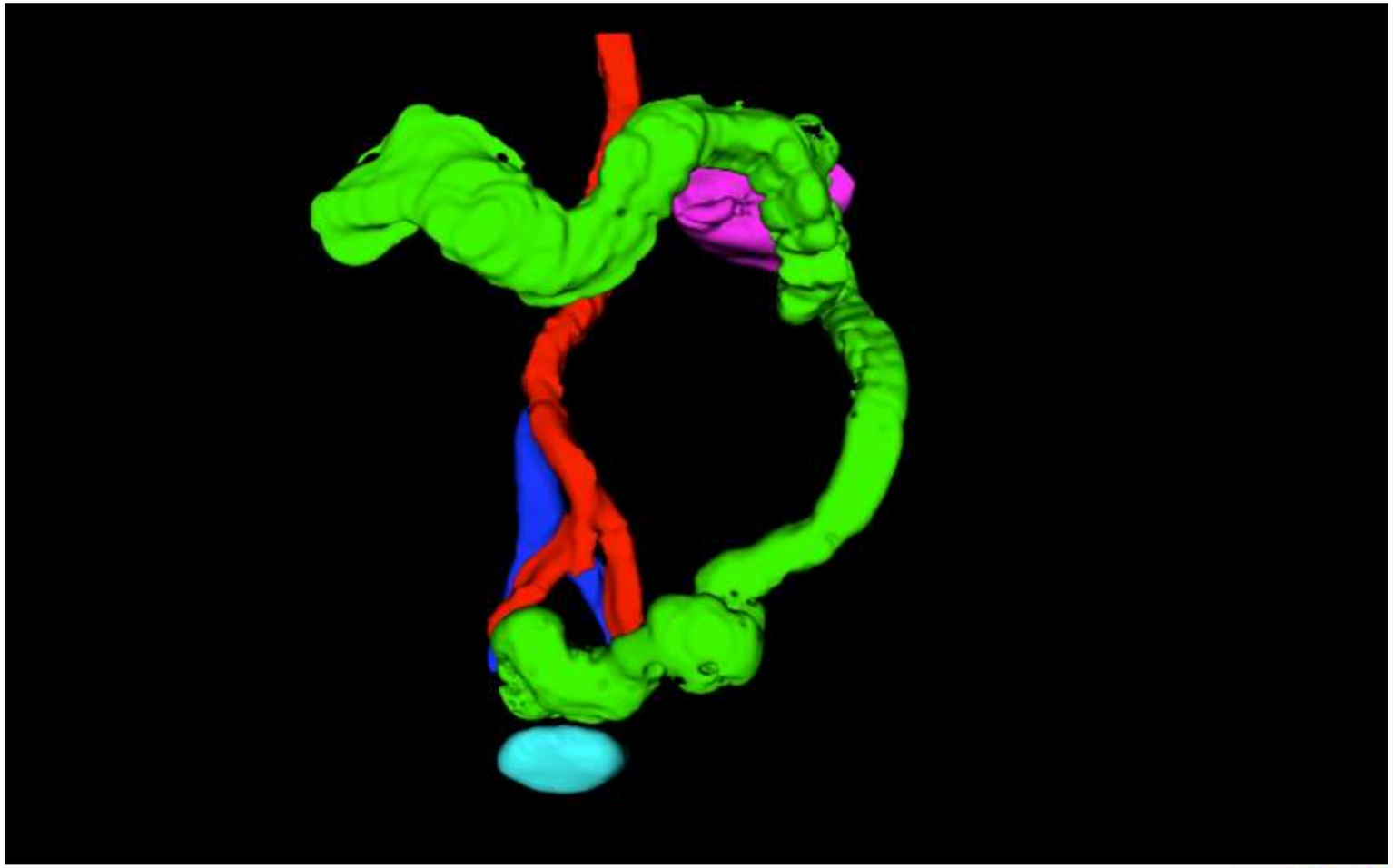
Source: Body Scan Intl., Irvine, CA

From Quantified Self to Quantified Surgery: Converting MRI Slices to 3D Organ Segmentation for Surgical Pre-Planning

Images of Dr. Smarr's Abdomen
To Support Sigmoid Colon Resection Surgery



MRI Slice from Dr. Cynthia Santillan



3D Organ Segmentation Made by Dr. Jurgen Schulze from Dr. Santillan's 150-Slice MRI

Smarr Became the First Robotic Colo-Rectal Surgery in the Jacobs Medical Center on Tuesday November 29, 2016



UC San Diego Health

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I Have Been Collaborating with the UCSD Knight Lab To Analyze My Gut Microbiome Dynamics

LOCAL TOPICS | SCIENCE & ENVIRONMENT | SCIENCE

UCSD hires star biologist Rob Knight

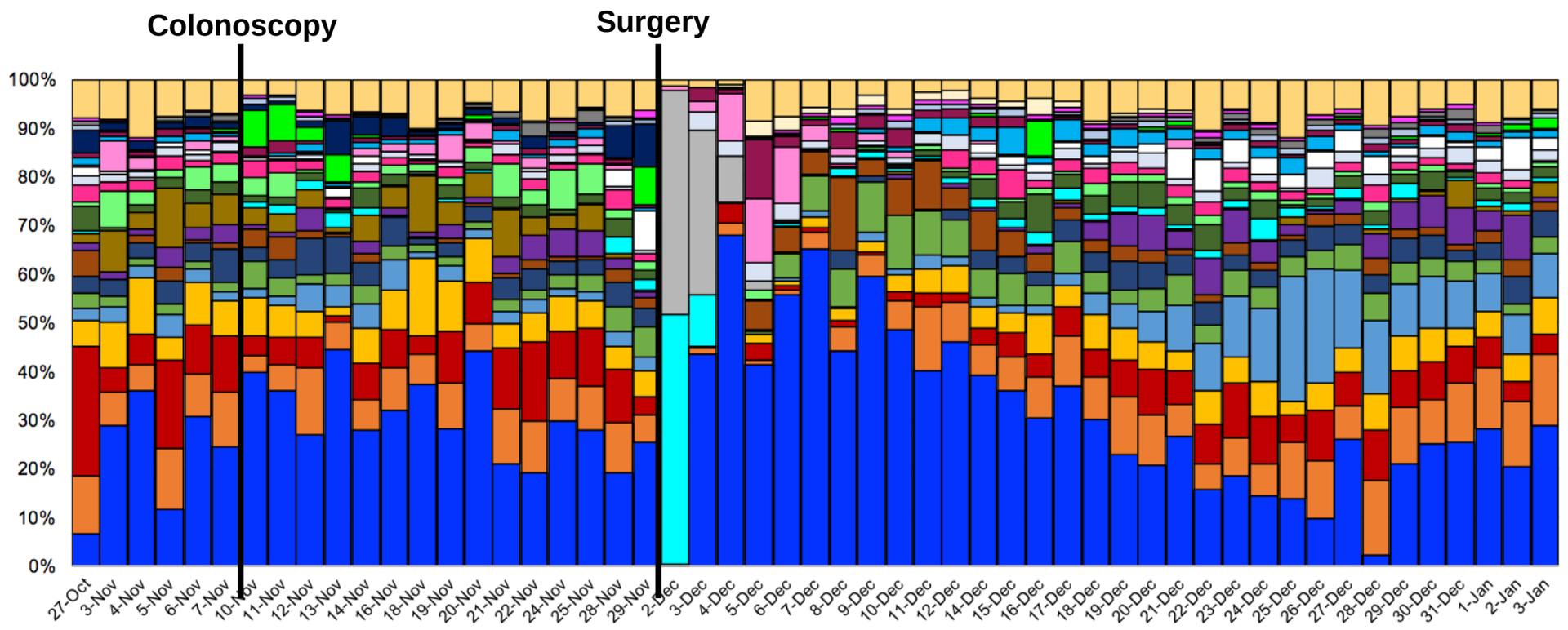
By Gary Robbins 1:30 P.M. JAN. 11, 2015 Updated 12:17 P.M. JAN. 12, 2015 PRINT COMMENTS 0





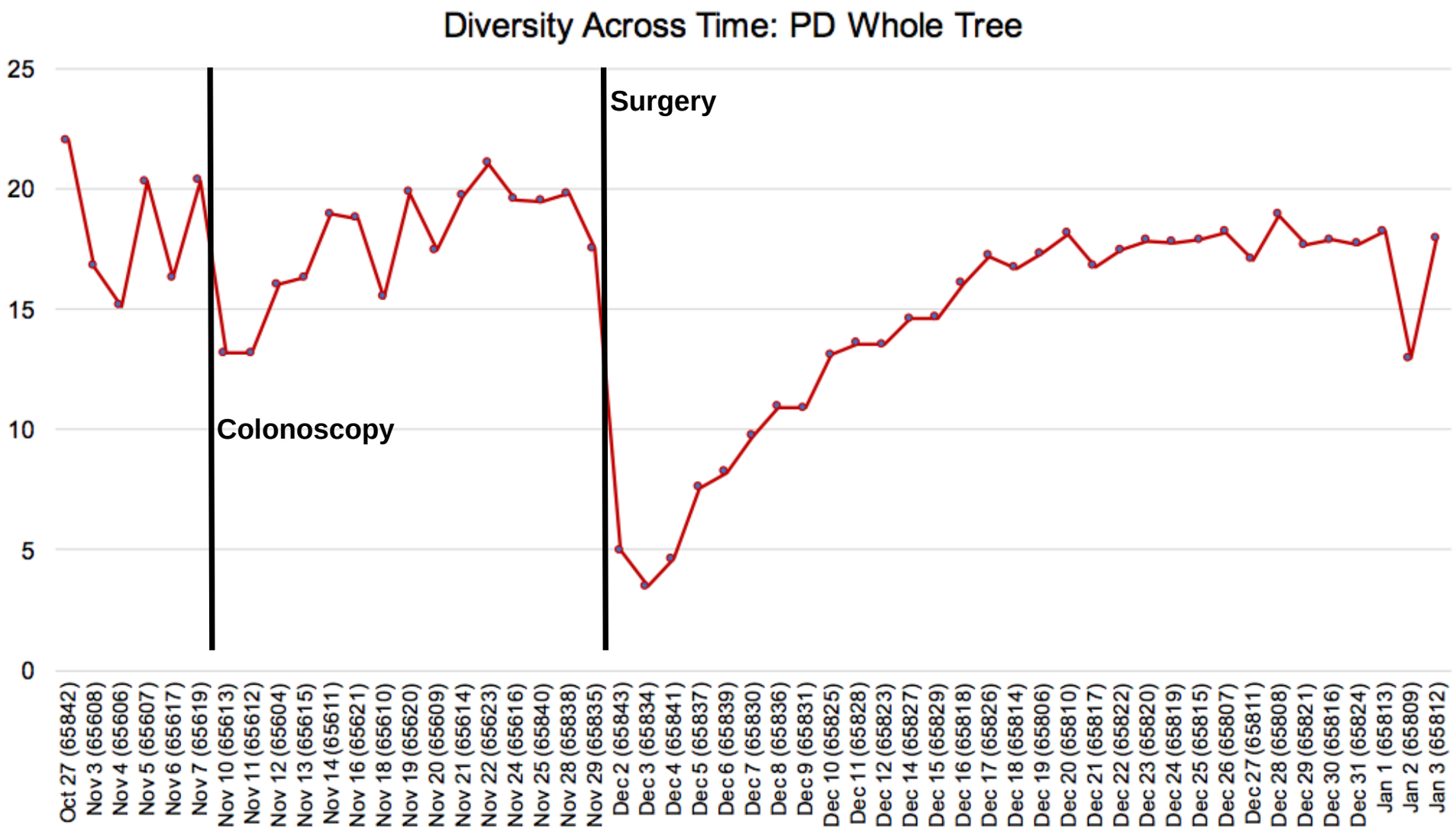
Larry's 40 Stool Samples Over 3.5 Years
to Rob's lab on April 30, 2015

Gut Microbiome Genus-Level Profiles
Daily Samples Before and After Abdominal Surgery



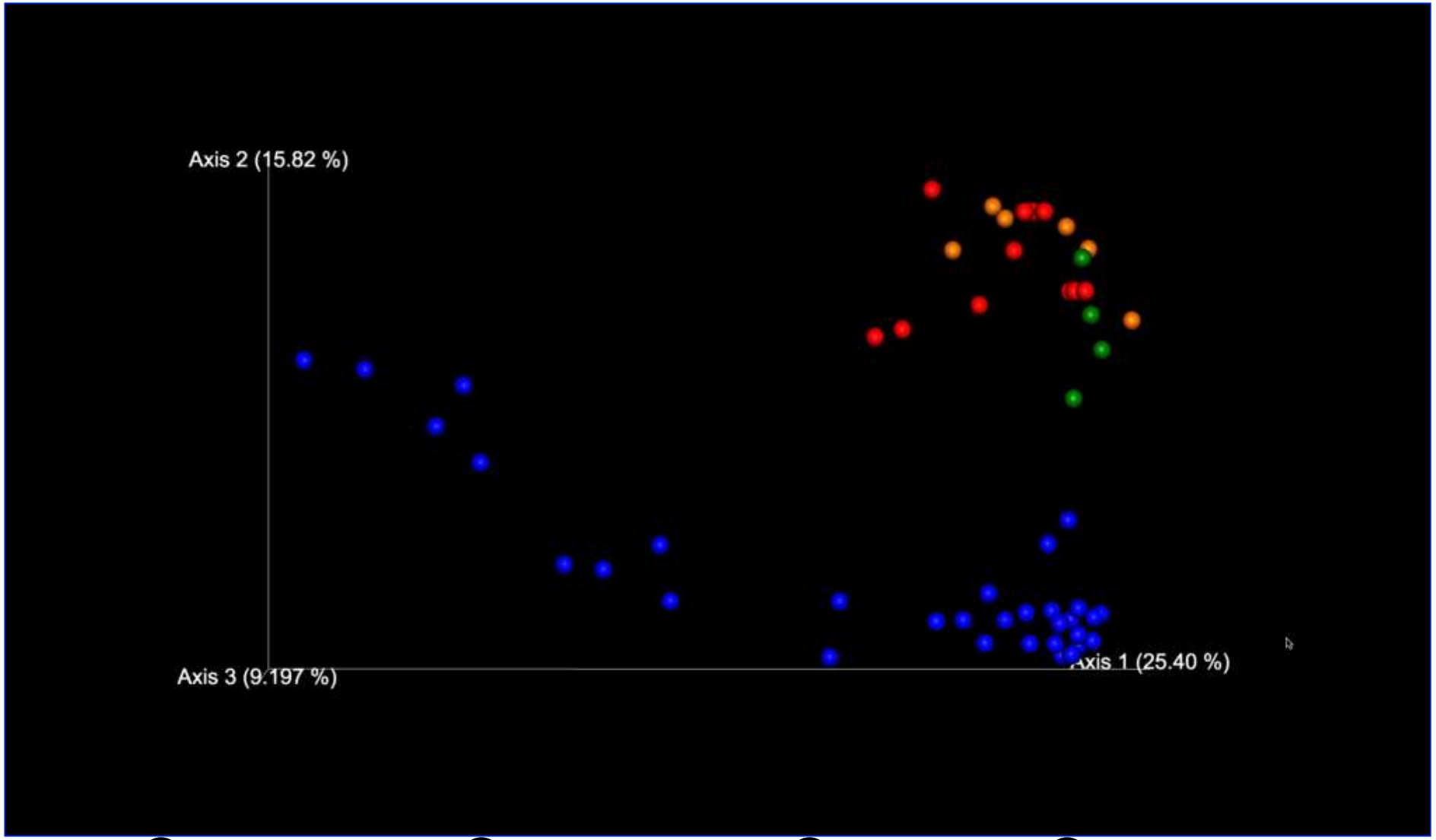
Source: Embriette Hyde, UCSD

Much Larger Drop in Microbiome Ecology Diversity Following Surgery Than Following Colonoscopy



Source: Embriette Hyde, UCSD

Major Shift in Gut Microbiome Ecology Following Abdominal Surgery With Return to New Equilibrium State



Inflamed Disease State

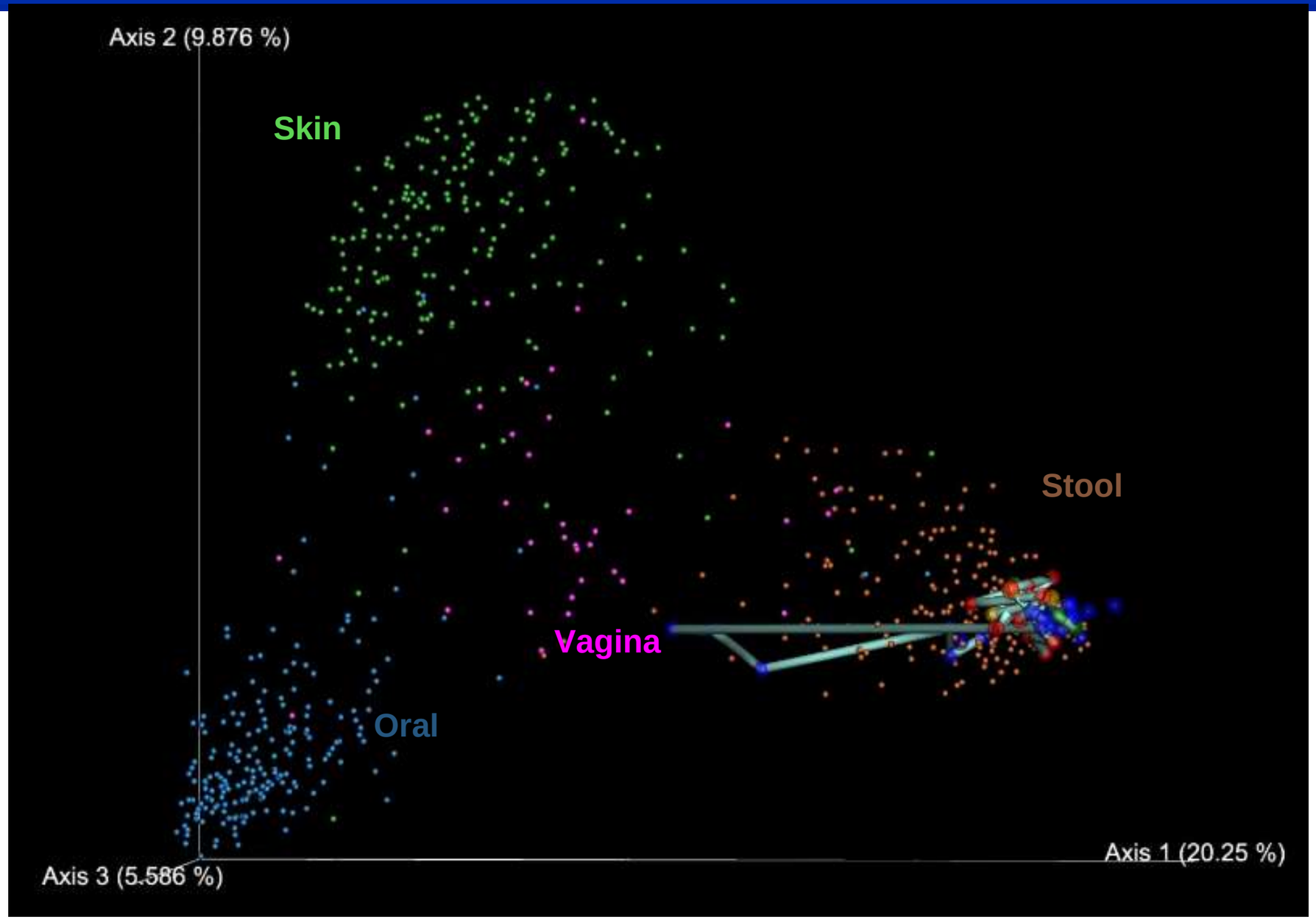
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Healthy Post-Surgery State

Pre-colonoscopy Post-colonoscopy Pre-surgery Post-surgery

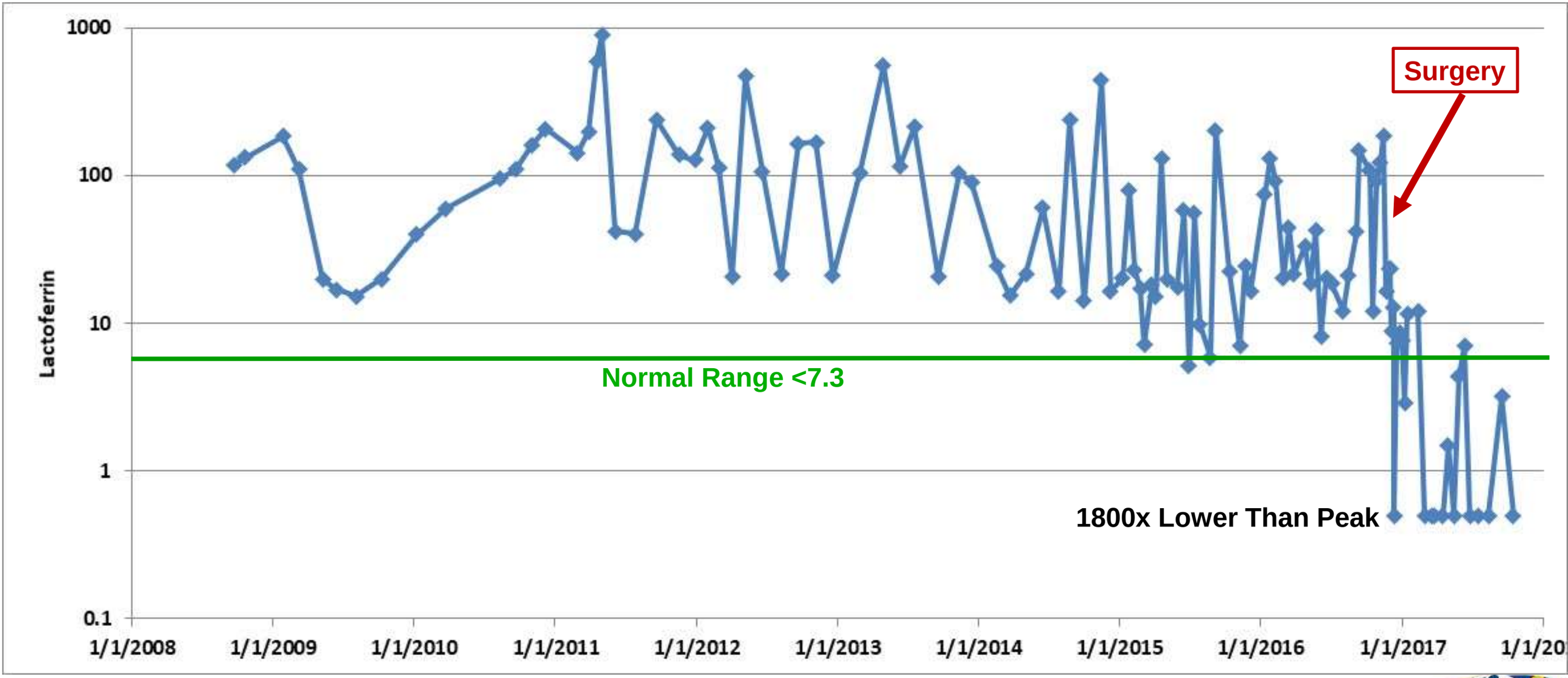
Source: Embriette Hyde, Yoshiki Vázquez Baeza, Knight Lab, UCSD

My Gut Microbiome Changed More After Surgery Than the Difference Between 10,000 Individuals!

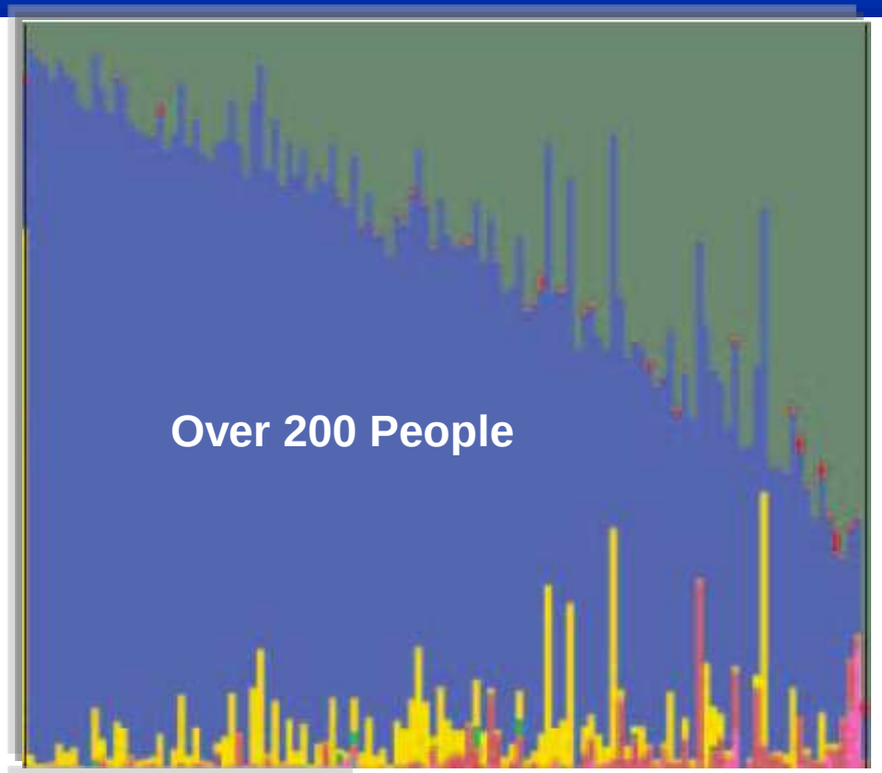


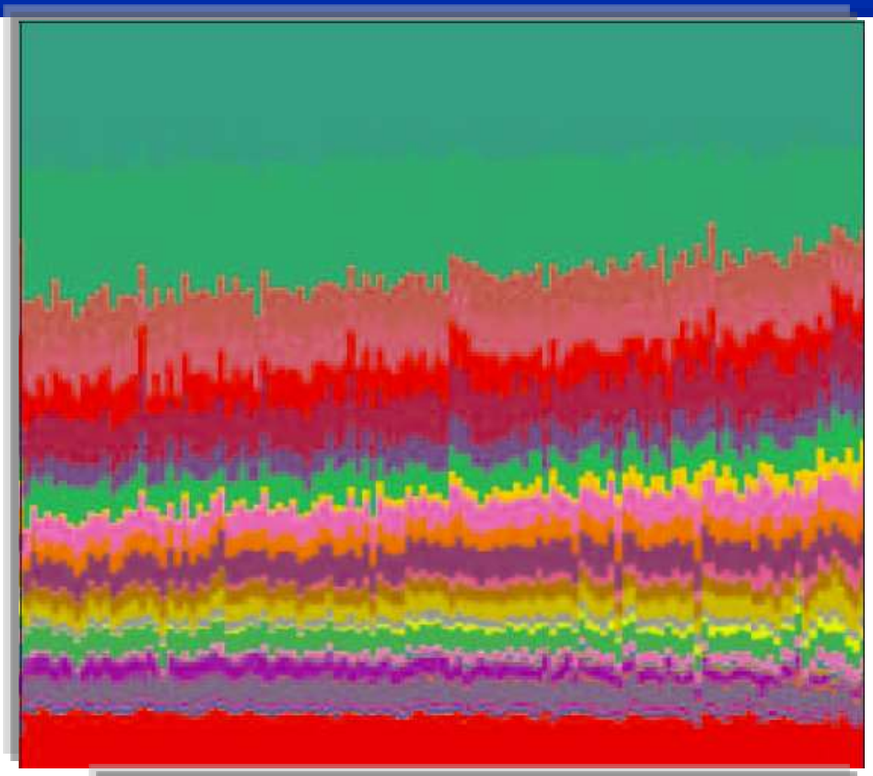
Data From American Gut Project, UCSD. Rob Knight, Director

Colonic Inflammation: Abrupt Shift to Healthy Following Surgical Resection (Note Logarithmic Scale)



In a “Healthy” Gut Microbiome:
Large Taxonomy Variation Between Individuals, Low Protein Family Variation





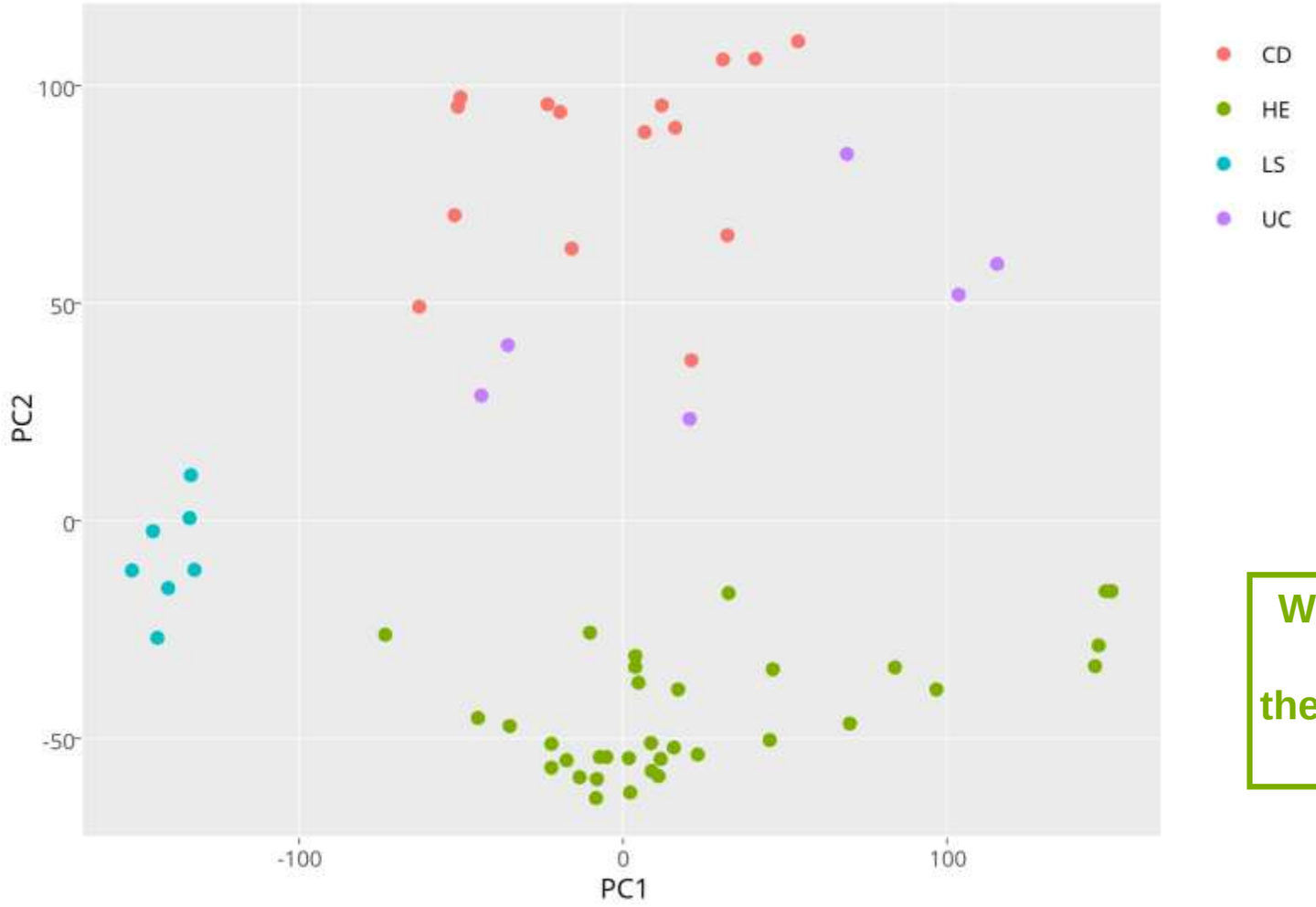
- Firmicutes
- Actinobacteria
- Bacteroidetes
- Proteobacteria
- Fusobacteria
- Tenericutes
- Spirochaetes
- Cyanobacteria
- Verrucomicrobia
- TM7

- 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: Nature, 486, 207-212 (2012)

We Supercomputed ~10,000 Microbiome Protein Families (KEGGs) Which Cleanly Separate Disease Subtypes Using PCA

Implies That Disease Subtypes Have Distinct Protein Distributions



We Used a 35 Person Subset of the 255 Healthy Person HMP Study

Center for Microbiome Innovation

SDSC

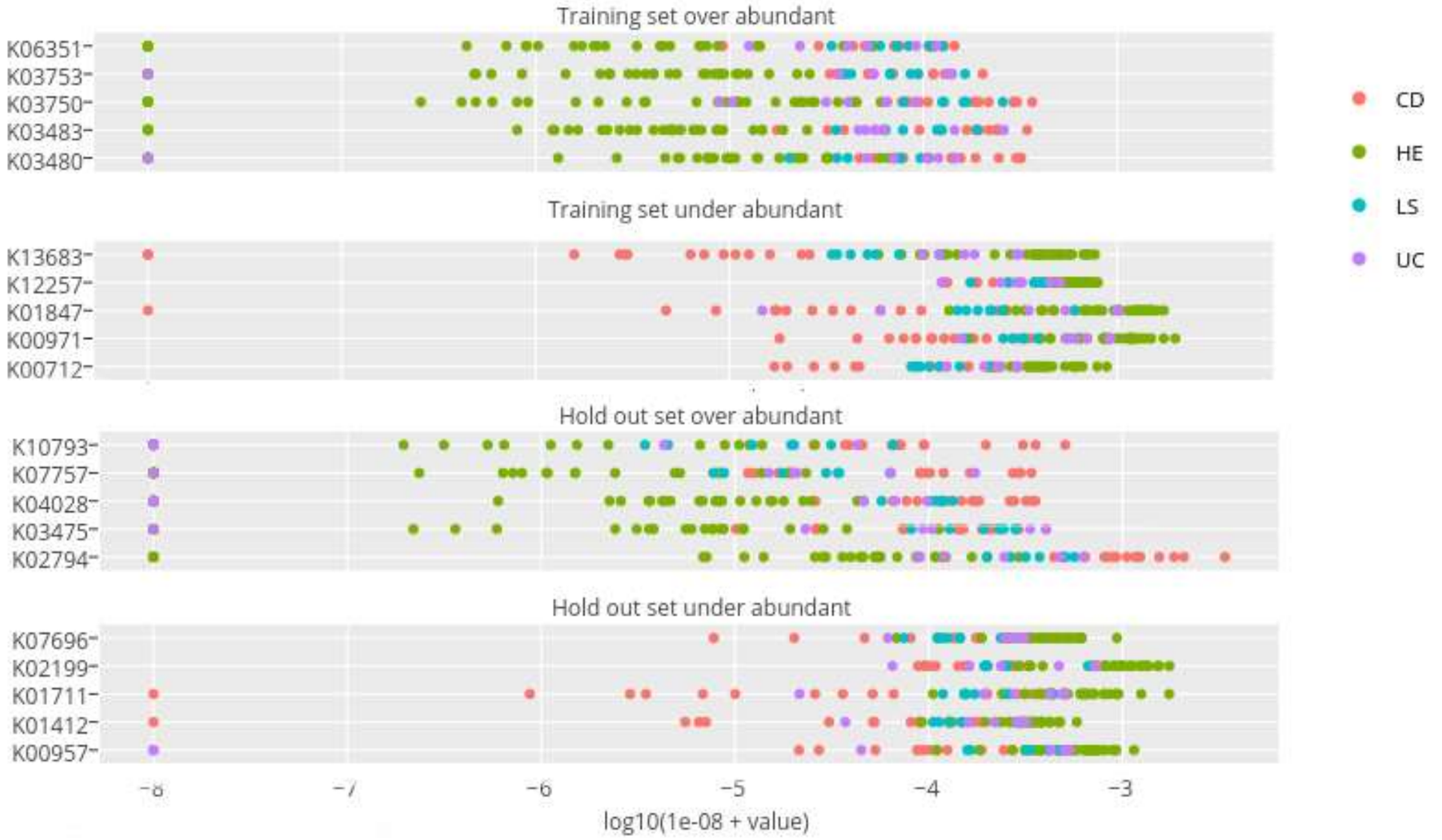
From Yazdani, Taylor, Debelius, Li, Knight, Smarr in IEEE International Conference on Big Data (December 5-8, 2016)

it²

Using Machine Learning (Random Forest) to Discover the Protein Families That Differentiate Between the Disease and Healthy Cohorts

Selected from Top 100 KS Scores

Selected by Random Forest Classifier From Holdout Set



Next Step: Investigate Biochemical Pathways of KEGGs That Differentiate Disease States

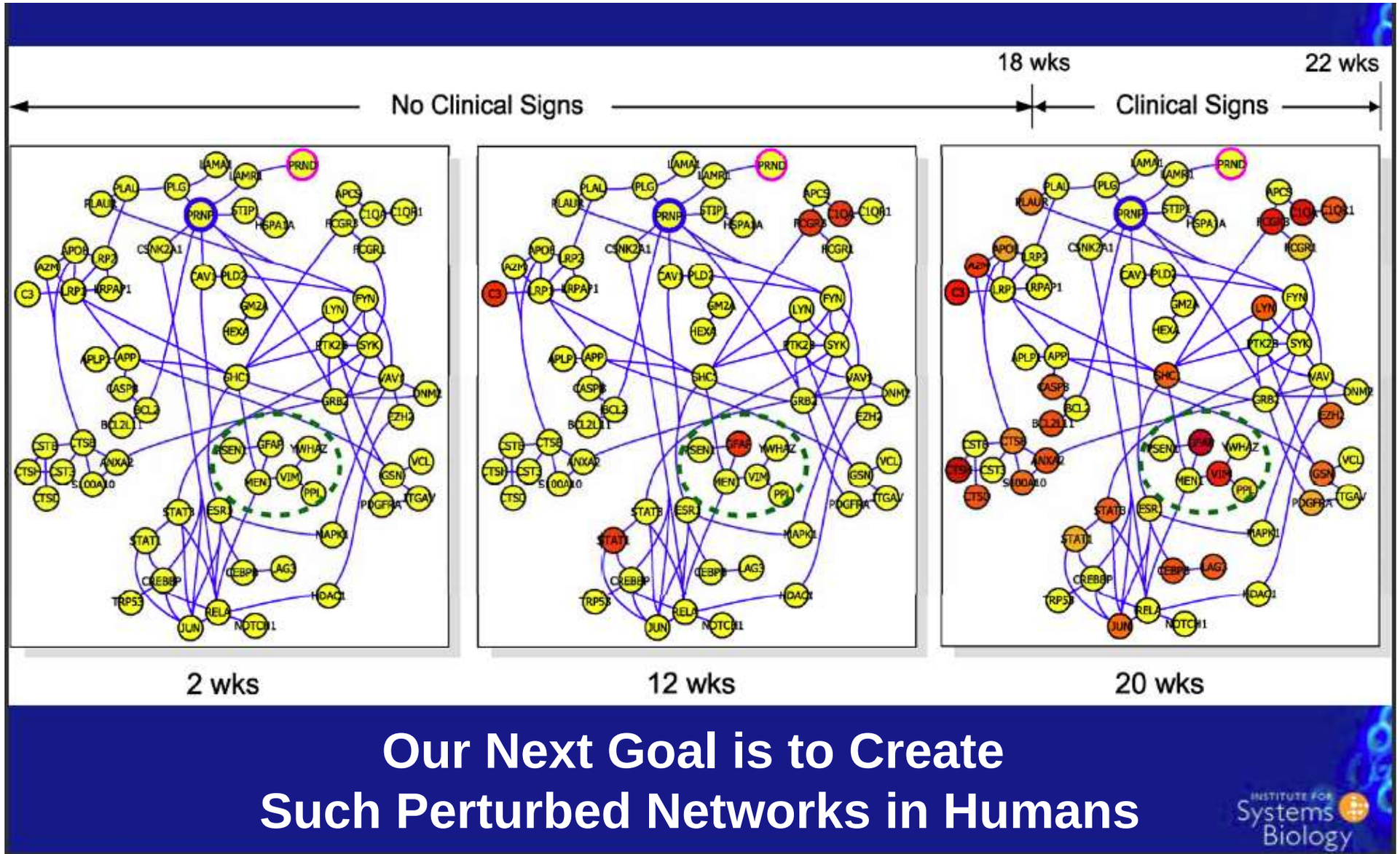
From Yazdani, Taylor, Debelius, Li, Knight, Smarr in
IEEE International Conference on Big Data
(December 5-8, 2016)

Center for Microbiome Innovation

Disease Arises from Perturbed Protein Family Networks: Dynamics of a Prion Perturbed Network in Mice

Source: Lee Hood, ISB





Our Next Goal is to Create Such Perturbed Networks in Humans

Institute for Systems Biology

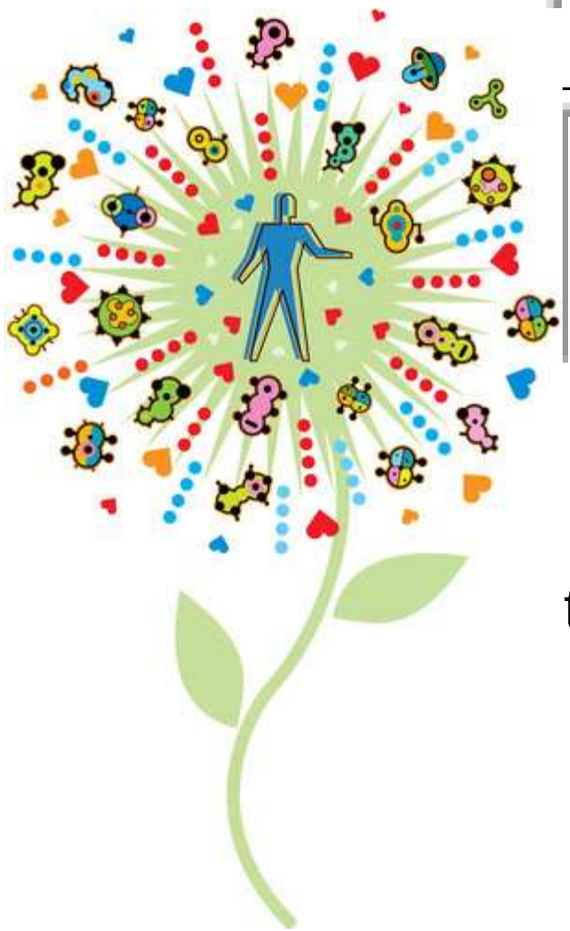
it²

Toward a Novel Microbiome Disease Diagnostic

We Need Machine Learning Tools Because This Year
10,000 Protein Families → One Million Microbiome Genes
and
50 Subjects →500
Leading to ~1000 Times Larger Datasets

Center for Microbiome Innovation

Can We “Garden” Our Way Back to Health?
New Tools for Managing the Microbiome



The New York Times

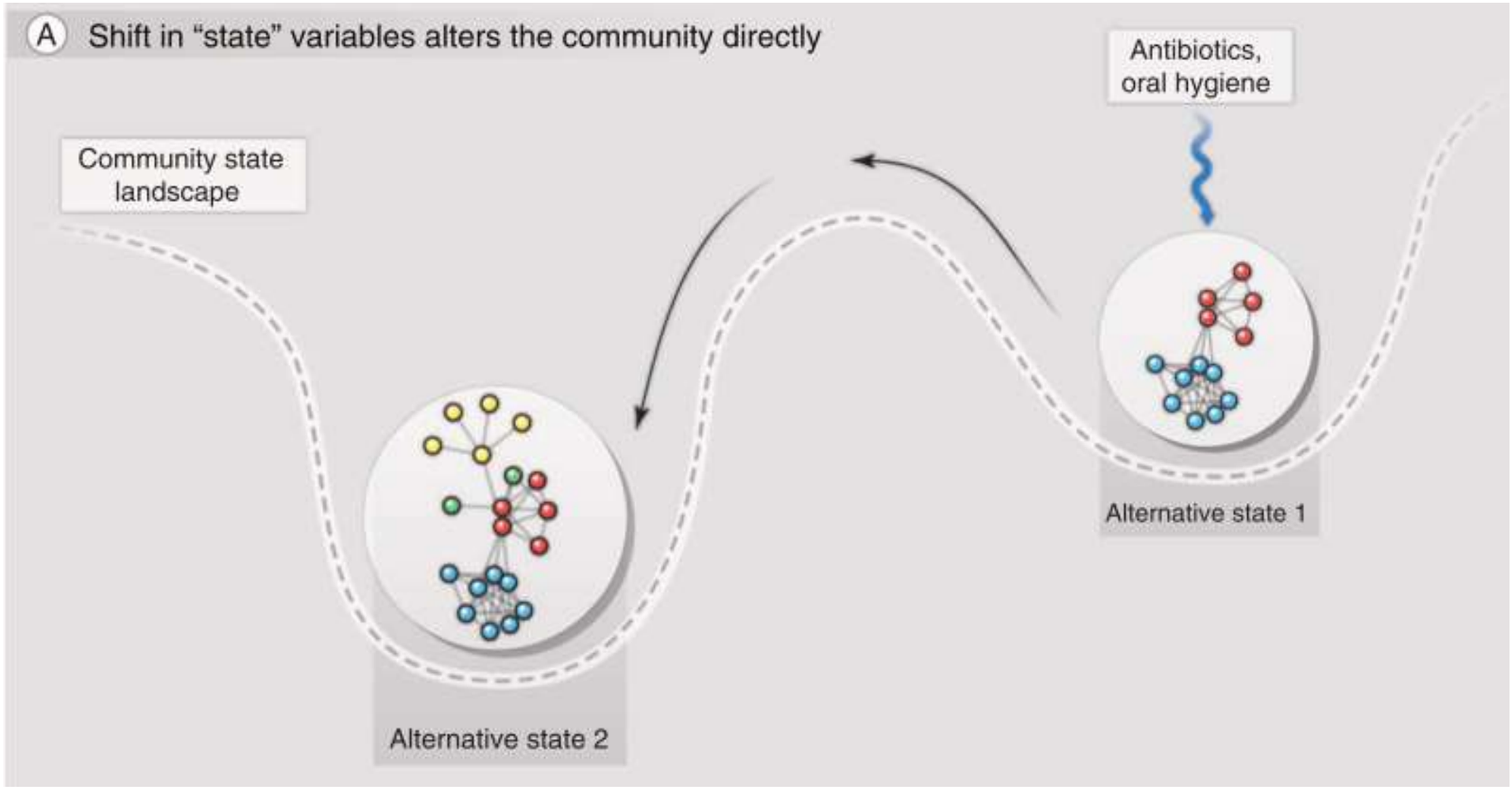
Science

Tending the Body’s Microbial Garden

By CARL ZIMMER
Published: June 18, 2012

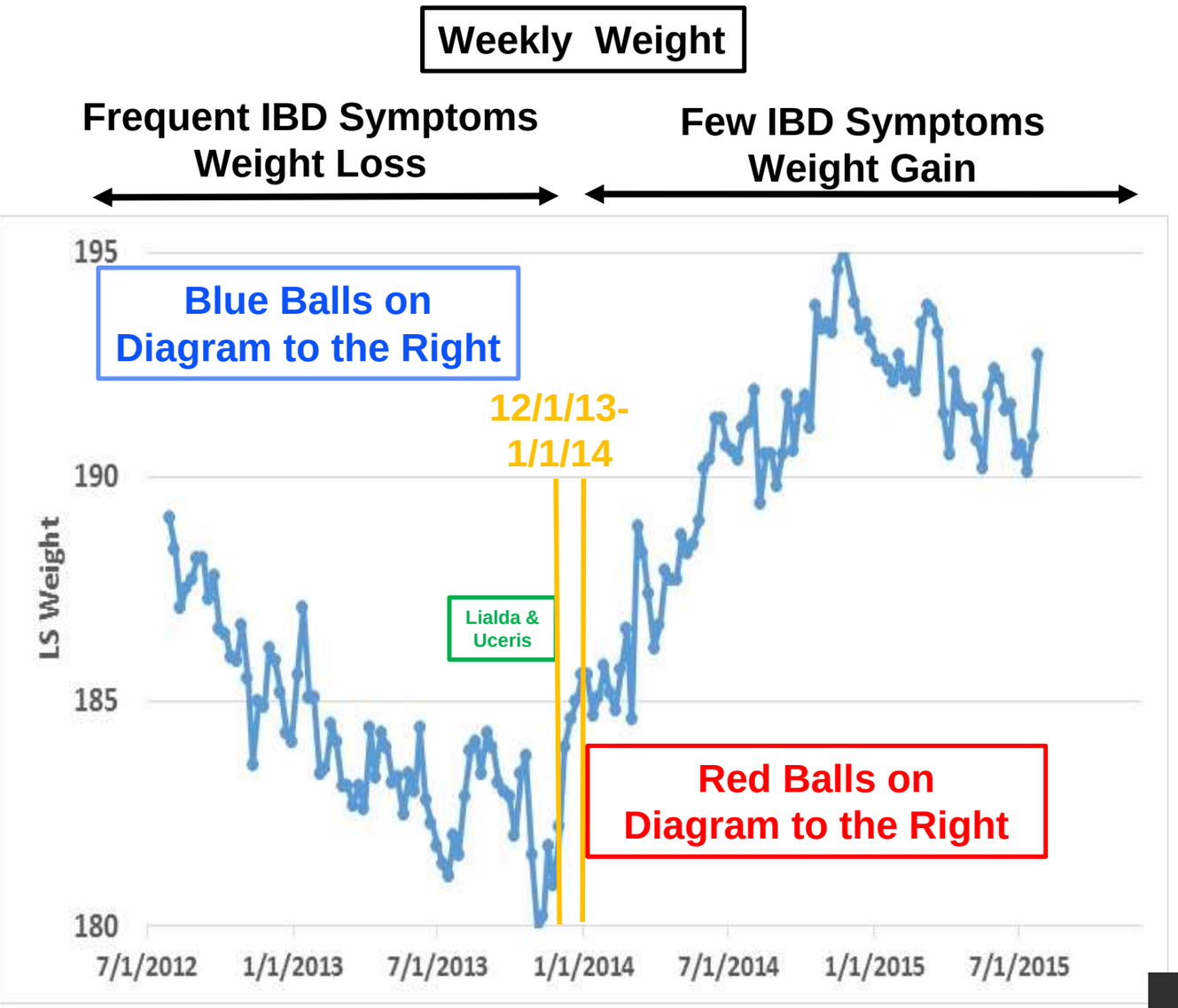
“I would like to lose the language of warfare,”
said Julie Segre, a senior investigator at
the National Human Genome Research Institute.
”It does a disservice to all the bacteria
that have co-evolved with us
and are maintaining the health of our bodies.”

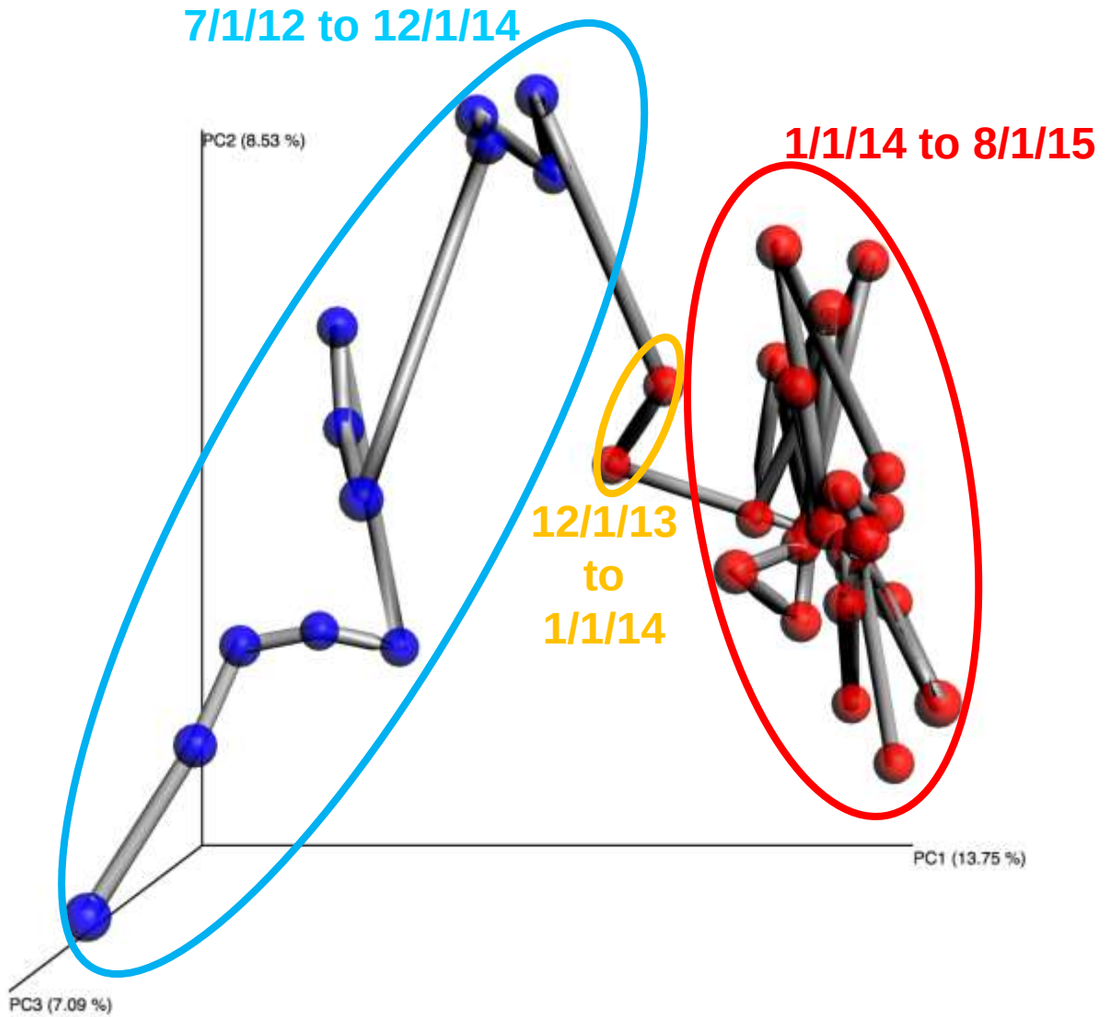
Lessons from Ecological Dynamics II: Gut Microbiome Has Multiple Relatively Stable Equilibria



"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)

My Gut Microbiome Ecology Shifted After Drug Therapy Leading to Rapid Weight Gain, But Drop in IBD Symptoms

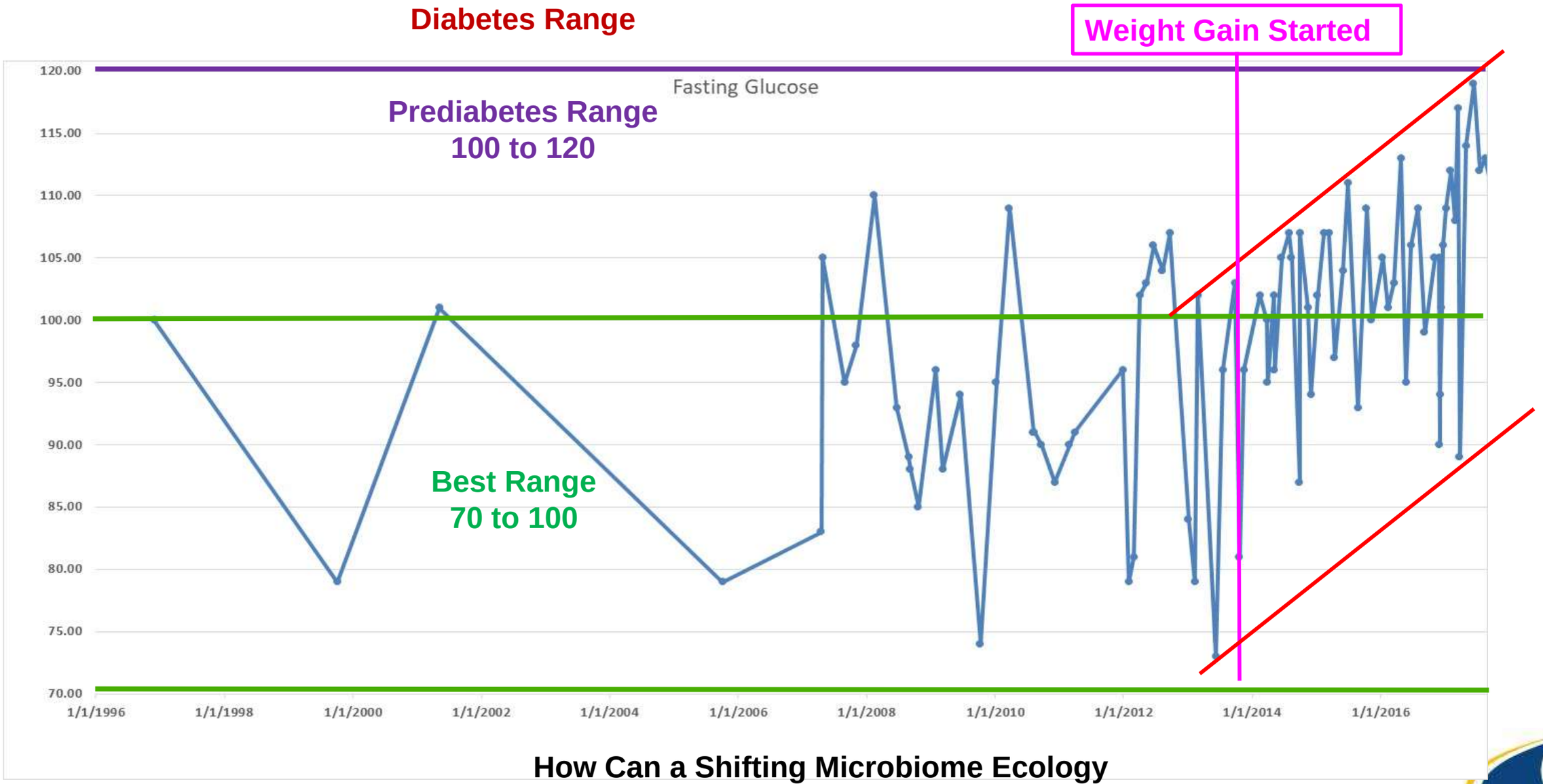




Weight Data from Larry Smarr, Calit2, UCSD

PCoA by Justine Debelius and Jose Navas, Knight Lab, UCSD

My Fasting Glucose Level Began to Rise After the Microbiome Shift – I Was Developing Metabolic Syndrome and Prediabetes



How Can a Shifting Microbiome Ecology Alter Your Glucose Pathway?

Aligning Your Eating Pattern With Your Body's Circadian Rhythm Is As Important As What You Eat

Reverse Insulin Resistance with Intermittent Fasting



By: COURTNEY SPERLAZZA, MPH

Time-Restricted Feeding Is a Preventative and Therapeutic Intervention against Diverse Nutritional Challenges

Cell Metabolism
December 2, 2014

Amandine Chaix,[1] Amir Zarrinpar,[1,2] Phuong Miu,[1] and Satchidananda Panda[1,*]
[1]Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[2]Division of Gastroenterology, University of California, San Diego, La Jolla, CA 92093, USA

I Volunteered to Become a Patient in the UCSD/Salk Pilot Study of Time-Restricted Eating (TRE) in Metabolic Syndrome

- Hypothesis
  - In patients with metabolic syndrome who eat for ≥ 14 hours per day, limiting daily oral intake to 10 hours per day for 3 months while using a smartphone application will result in:
    - Weight loss
    - Improved glucose metabolism
    - Improved biomarkers associated with cardiovascular disease risk
- First study of TRE in metabolic syndrome
- First use of continuous glucose monitoring during TRE
- November 2017 to February 2018

- My Improvements:
  - Fasting Glucose Peak Dropped From 119 to 101
  - Waist 108cm to 102 cm
  - Weight 197 to 189
  - Blood Pressure 140/74 to 130/69

UC San Diego

salk
Where cures begin.

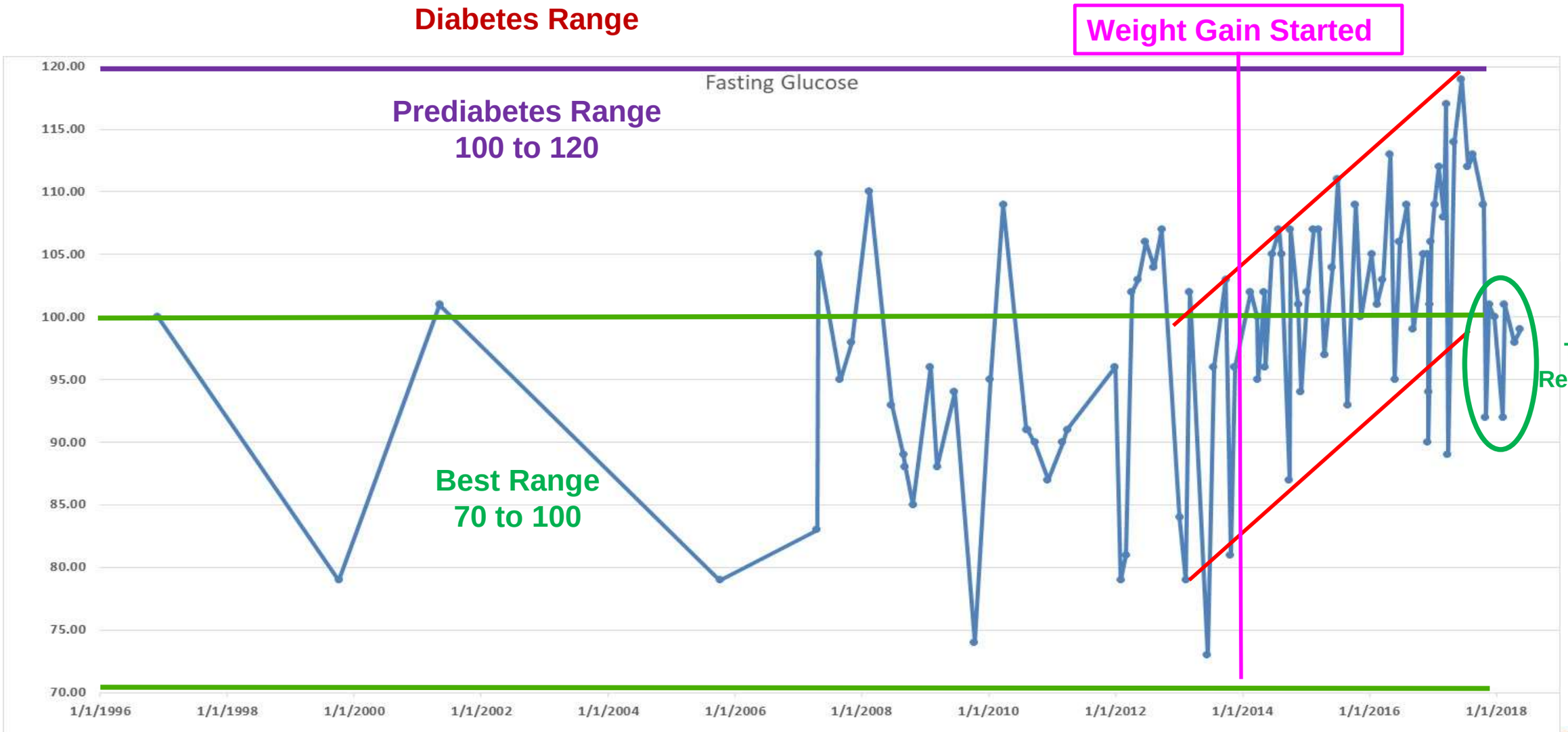


Pam Taub, MD
Cardiology



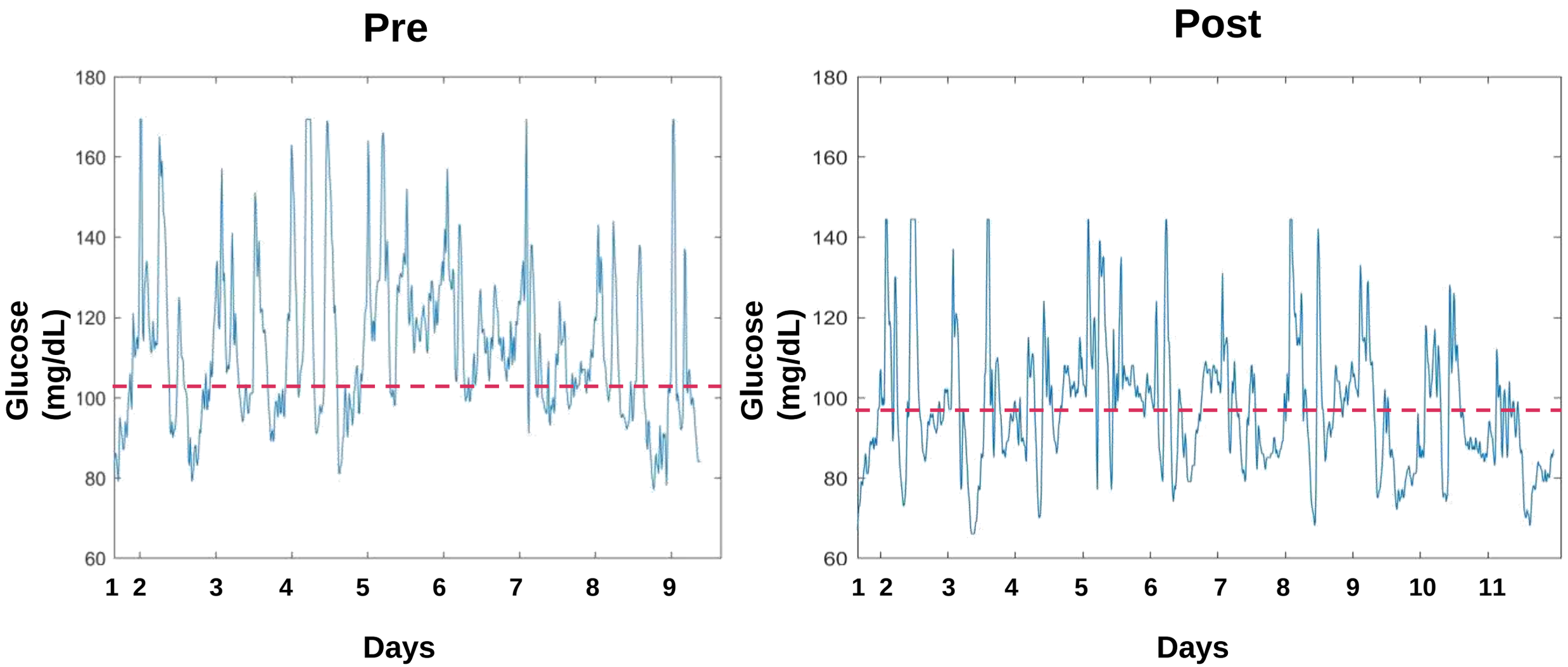
Satchin Panda, PhD
Circadian Biology

My Fasting Glucose Level Dropped Abruptly Into Normal Level During Time Restricted Diet



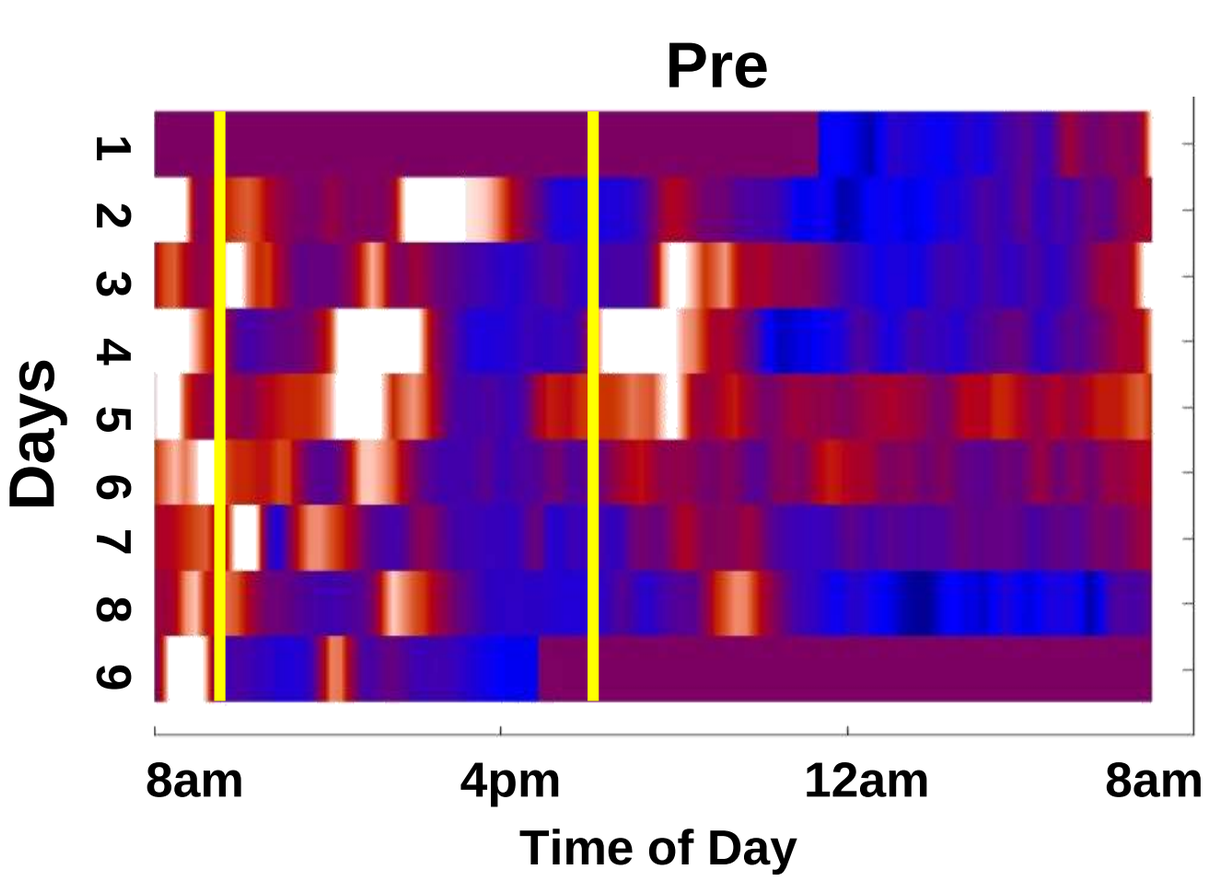
How Can a Shifting Microbiome Ecology Alter Your Glucose Pathway?

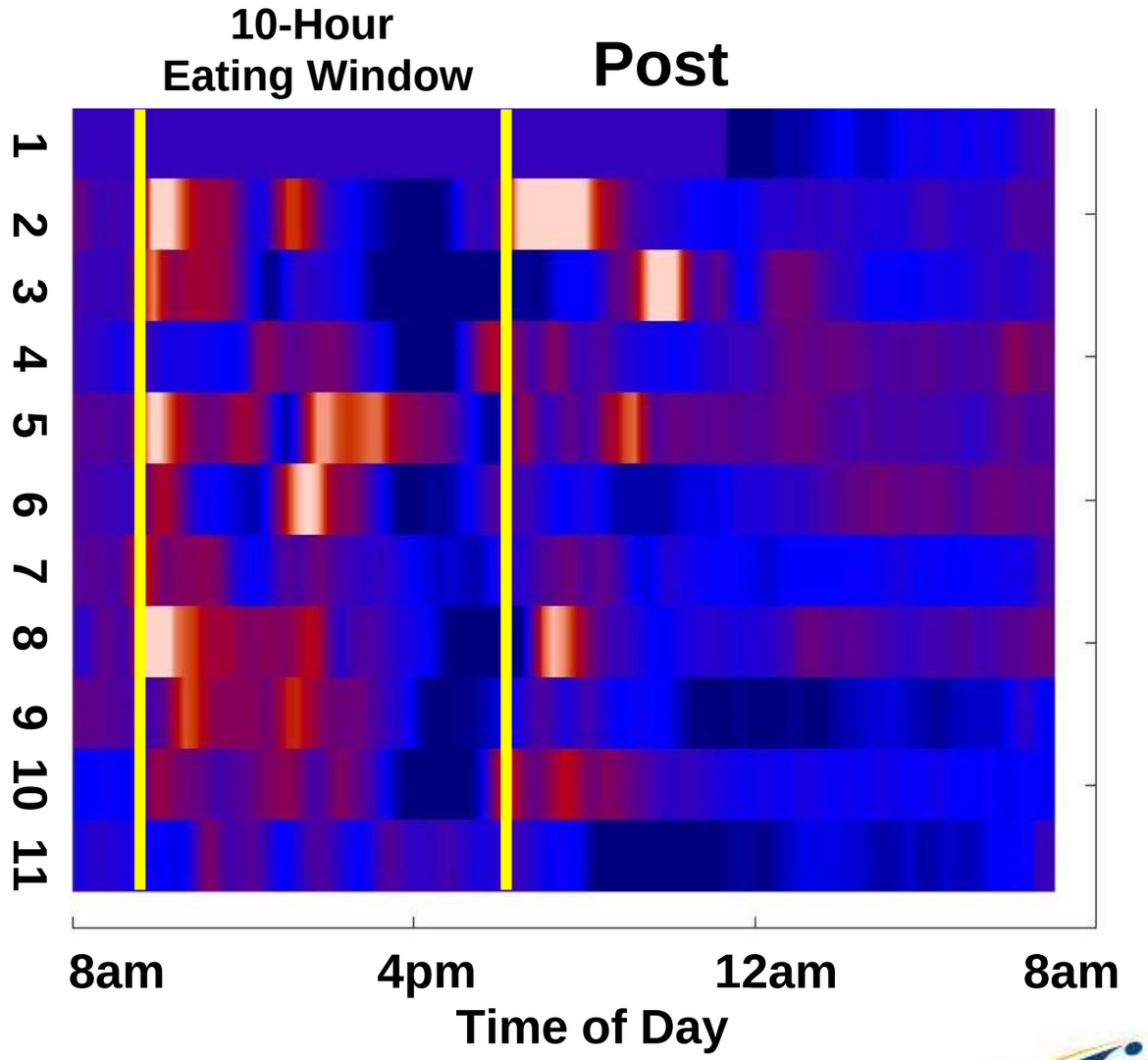
Time-Restricting My Food Intake to Ten Hours Improved My Glucose Spiking Without Changing Diet



Data from Taub/Panda Clinical Trial
Graphics by Azure Grant, QuantifiedSelf.com

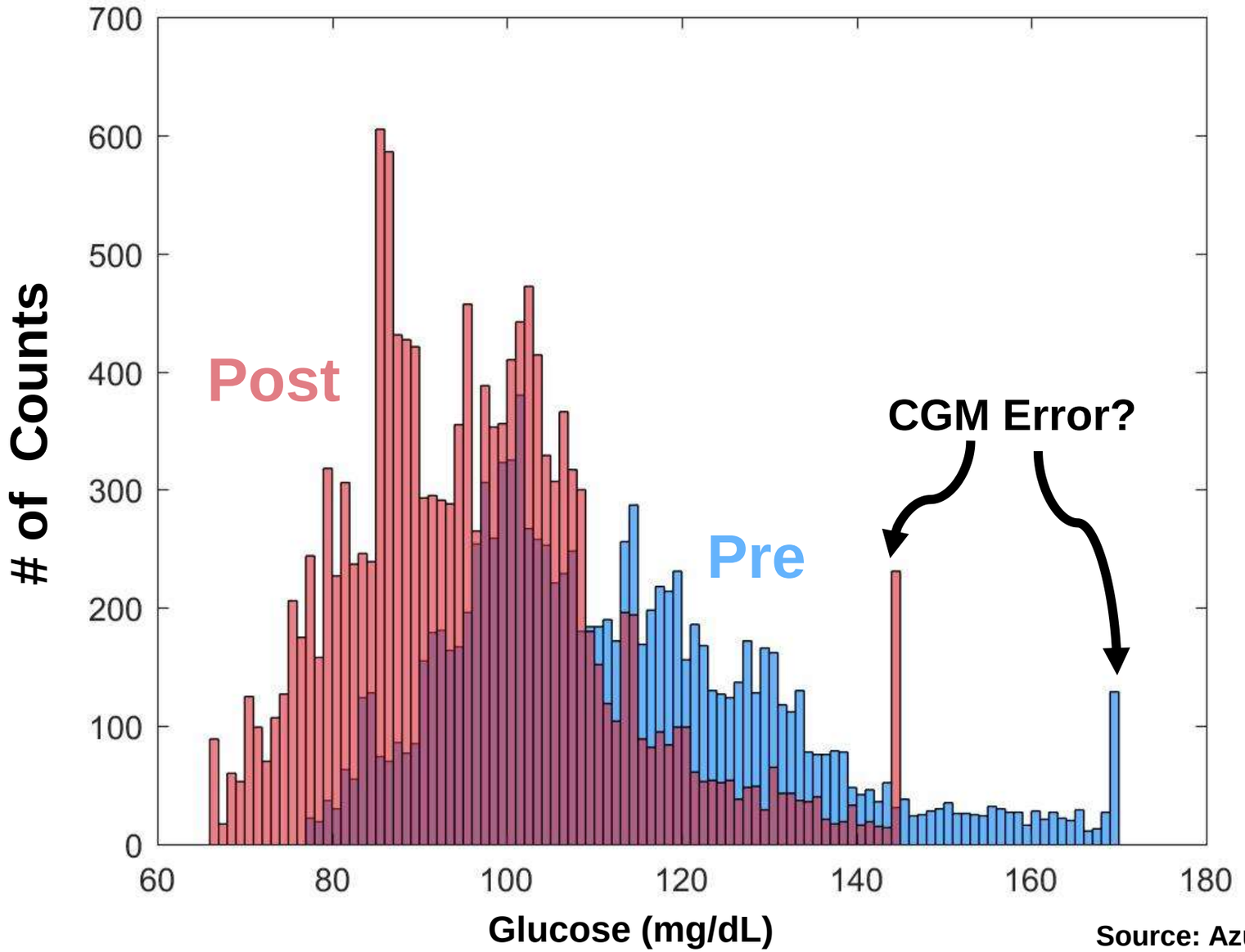
Heat Map of Continuous Glucose Monitor Every 5 Minutes Before and After 3 Months of Time-Restricted Eating





Data from Taub/Panda Clinical Trial
Graphics by Azure Grant, QuantifiedSelf.com

Major Changes in Glucose Profile
Before and After 3 Months of Time-Restricted Eating



Source: Azure Grant, UCB

Adding Vegetable Fiber to the Diet Seems to Counter Obesity By Increasing Microbiome Diversity

Cell Host & Microbe 10 January 2018

Fiber-Mediated Nourishment of Gut Microbiota Protects against Diet-Induced Obesity by Restoring IL-22-Mediated Colonic Health

Jun Zou, Benoit Chassaing, Vishal Singh, Michael Pellizzon, Matthew Ricci, Michael D. Fythe, Matam Vijay Kumar, Andrew T. Gewirtz[5]

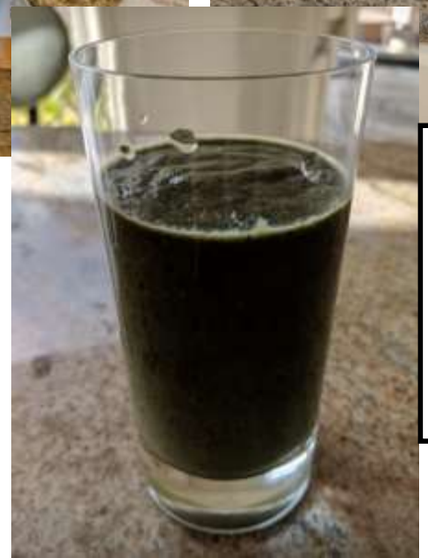
american gut

The more different types of plants a person eats, the higher their gut microbiome diversity.

Can I Increase My Microbiome Diversity By Consuming 3 Dozen Plant Species Per Day?







UC San Diego's Rob Knight Lab is Currently Sequencing 100 Days of My Stool Samples

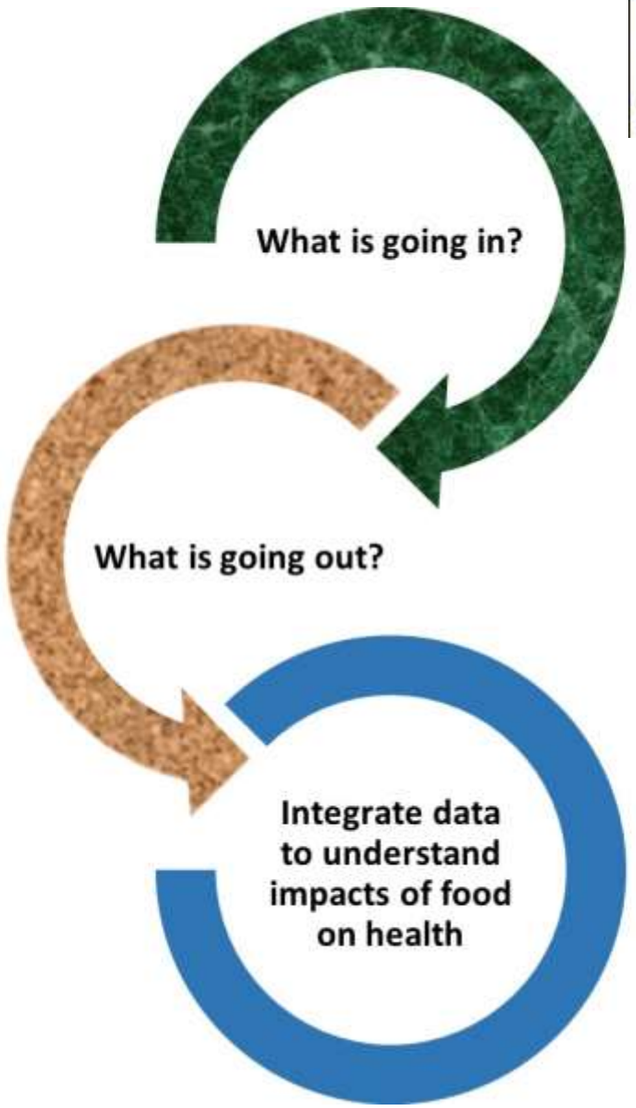
I Also Have Over 500 Time-Stamped Photos of Everything I Consumed During the 100 Days

UC San Diego

UC San Diego Is Carrying Out Detailed Input/Output Research Connecting Metagenomics and Metabolomics of Food and Gut Microbiome

KNIGHTLAB
UC San Diego

UCSD
the Dorrestein Lab.
The Skaggs School of Pharmacy and Pharmaceutical Sciences,
The Departments of Pharmacology, Chemistry and Biochemistry.
UNIVERSITY OF CALIFORNIA, SAN DIEGO



Global FoodOmics Project

American Gut Project

american gut

Meta-Analyses

CENTER FOR microbiome INNOVATION

THE DUTTON LAB @ UCSD

Projects Leaders: Julia Gauglitz, Rob Knight, Pieter Dorrestein, Rachael Dutton, UC San Diego

Thanks to Our Great Team!

Calit2@UCSD

Future Patient Team

Jerry Sheehan
Tom DeFanti
- Joe Keefe
- John Graham

Kevin Patrick
Mehrdad Yazdani
Jurgen Schulze
- Andrew Prudhomme
- Philip Weber
- Fred Raab

Ernesto Ramirez



JCVI Team

Karen Nelson
- Shibu Yooseph
- Manolito Torralba

Ayasdi

Devi Ramanan
Gunnar Carlsson

UCSD Metagenomics Team

Weizhong Li
- Sitao Wu

SDSC Team

Michael Norman
- Mahidhar Tatineni
- Robert Sinkovits

UCSD Health Sciences Team

David Brenner
Rob Knight Lab
- Bryn Taylor
- Daniel McDonald
- Yoshiki Vázquez Baeza
- Gail Ackermann
- Greg Humphrey
- Embriette Hyde
- Justine Debelius
- Jose Navas

William J. Sandborn Lab
- Elisabeth Evans
- John Chang
- Brigid Boland