“How Do I Quantify My Body and Try to Improve its Health?”

Talk to Metagenics

June 18, 2019

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

SYSTEMS BIOLOGY RESEARCH GROUP

CENTER FOR microbiome INNOVATION

it²

“Know Thyself”
From the Temple of Apollo to the Quantified Self



From the Reichert-Haus in Ludwigshafen, Germany

“Knowing Me” Led Me to Become a Digitally-Enabled “Patient of the Future”: Measuring the State of My Body and “Tuning” It

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

Age 51





Age 61

HEALTH IT, PEOPLE, WIRELESS

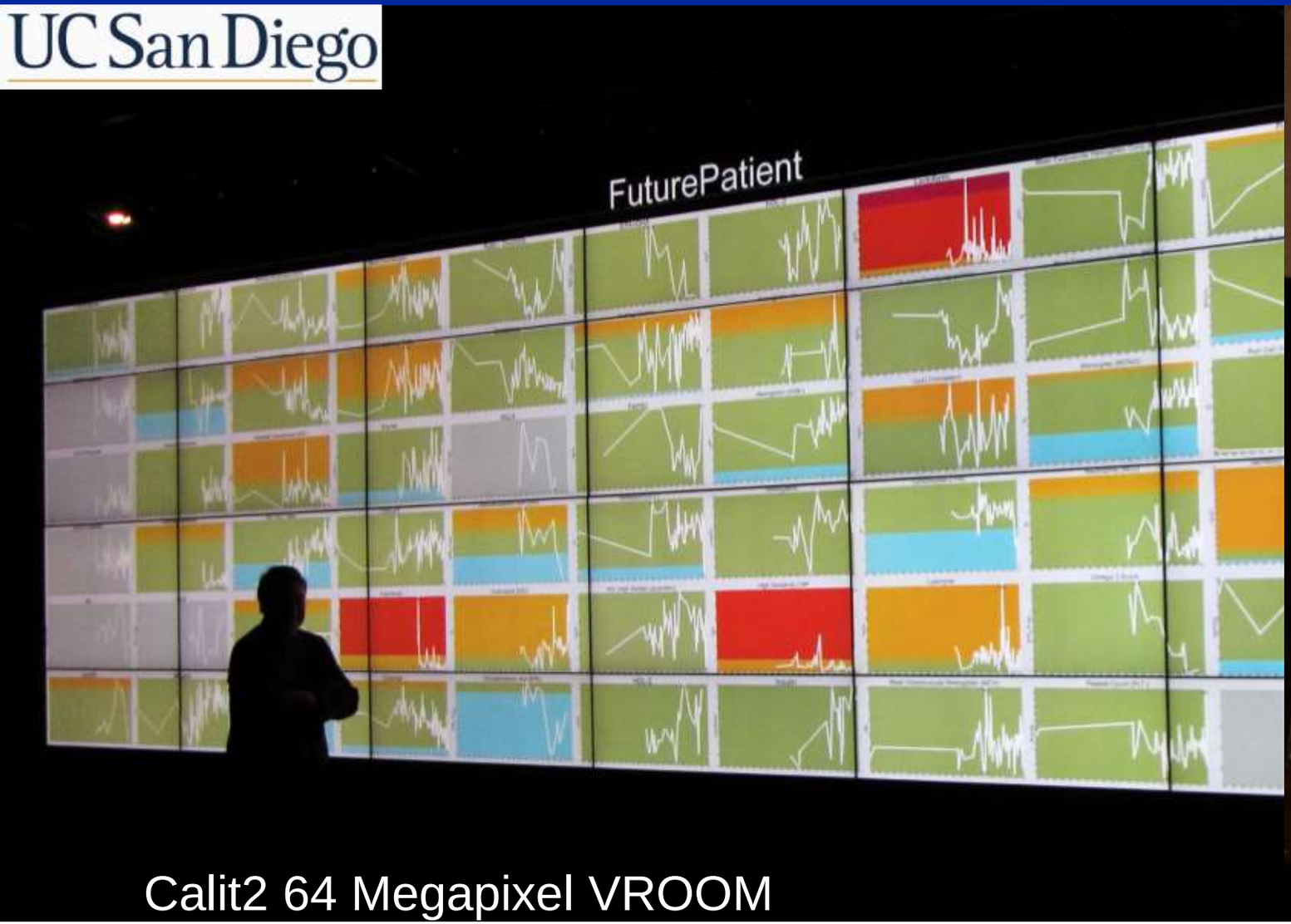
How Internet Pioneer Larry Smarr Lost 20 Pounds by Becoming a “Quantified Self”

Luke Timmerman 5/12/10

www.xconomy.com/san-diego/2010/05/12/how-internet-pioneer-larry-smarr-lost-20-pounds-by-becoming-a-quantified-self/

To Know Myself, I Began Tracking My Internal Biomarkers To Better Understand My Body's System Dynamics

UC San Diego



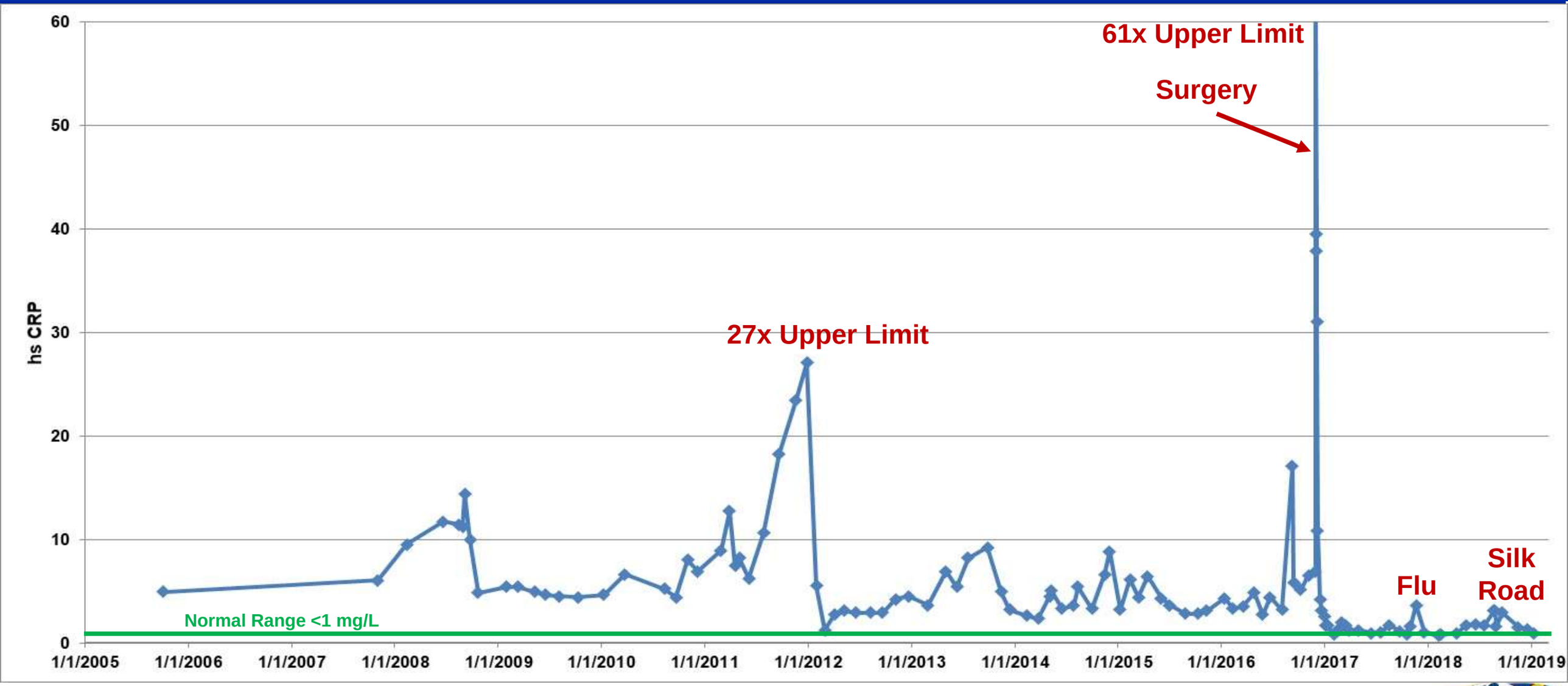
Calit2 64 Megapixel VROOM



My Quarterly Blood Draw

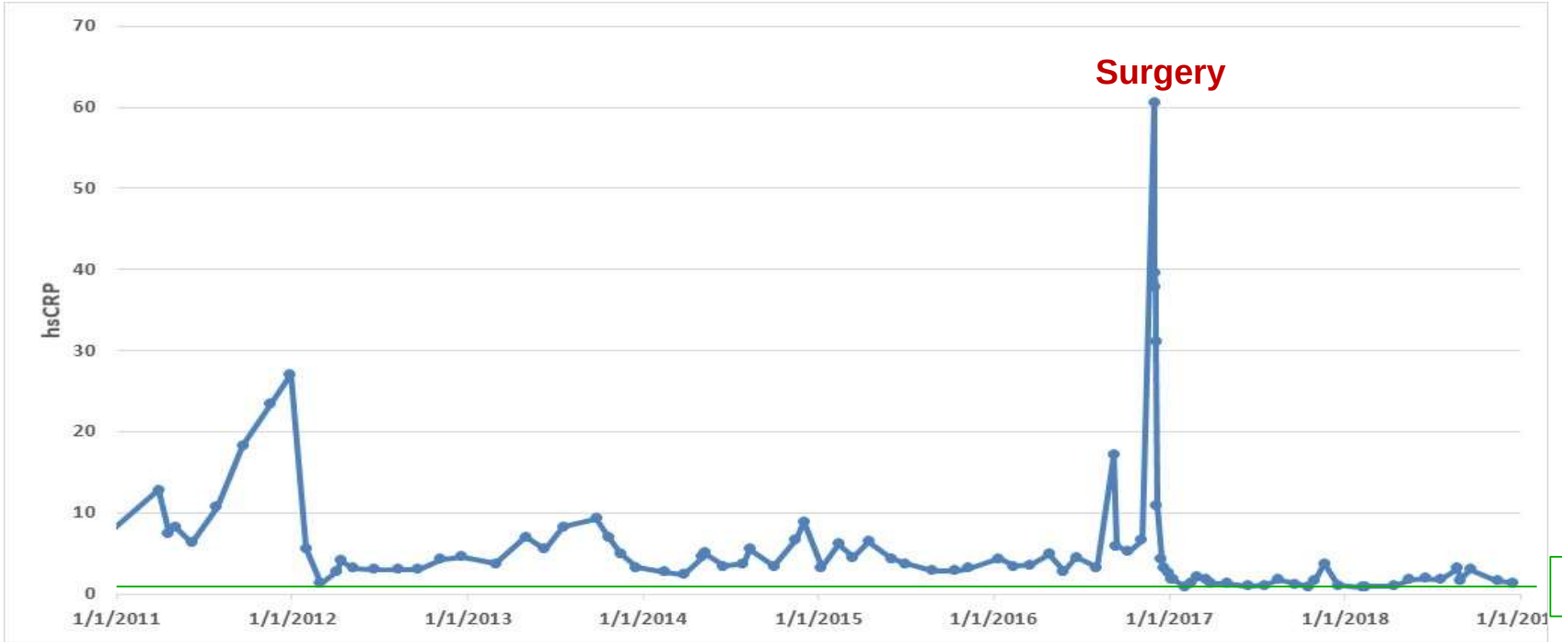
For a Detailed 45-Minute Video of Me Exploring My Biomarkers and Microbiome on the Wall, Google "Larry Smarr Future Patient"

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

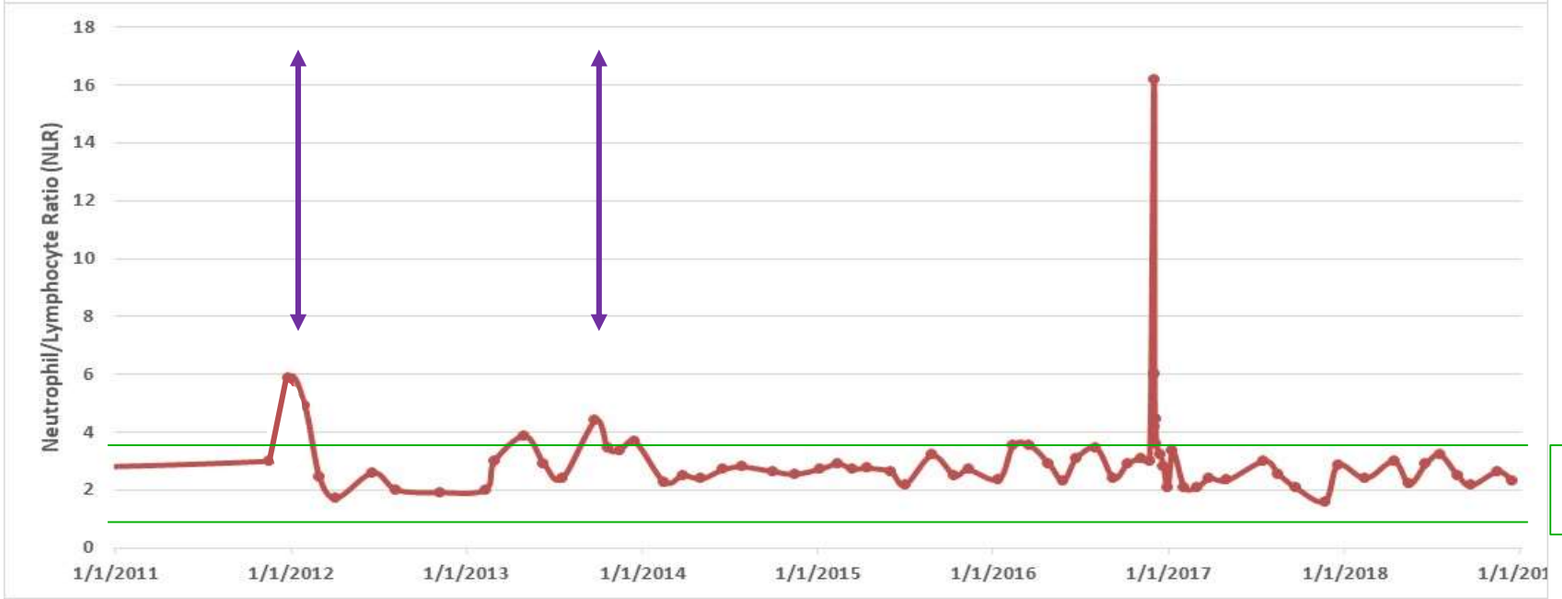


Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

Comparing Two Inflammation Blood Biomarkers: hs CRP and Neutrophil/Lymphocyte Ratio

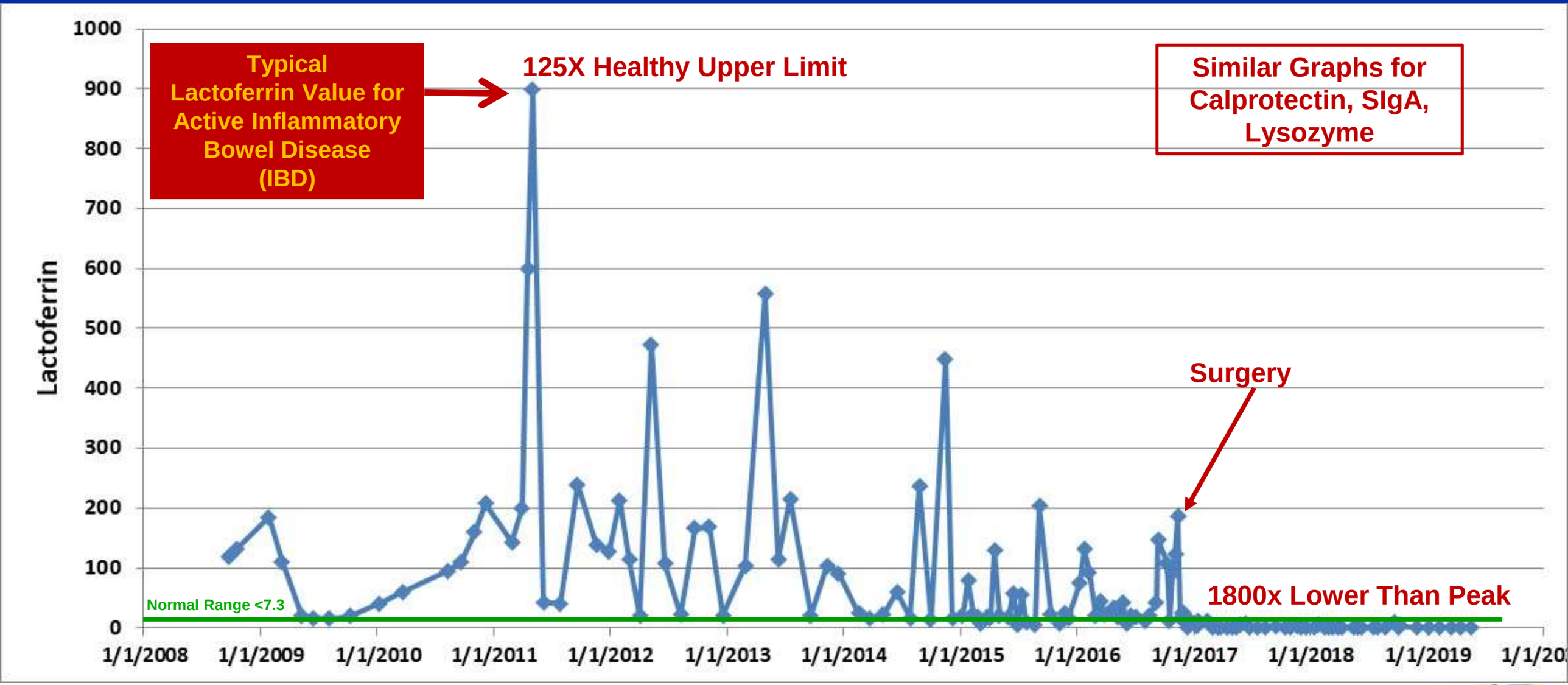


Healthy <1.0



Healthy
0.8<NLR<3.5

Colonic Inflammation:
Abrupt Shift to Healthy Following Surgical Resection



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

New Estimates In 2016 Estimate a Human Body Contains ~30 Trillion Human Cells and ~40 Trillion Microbes

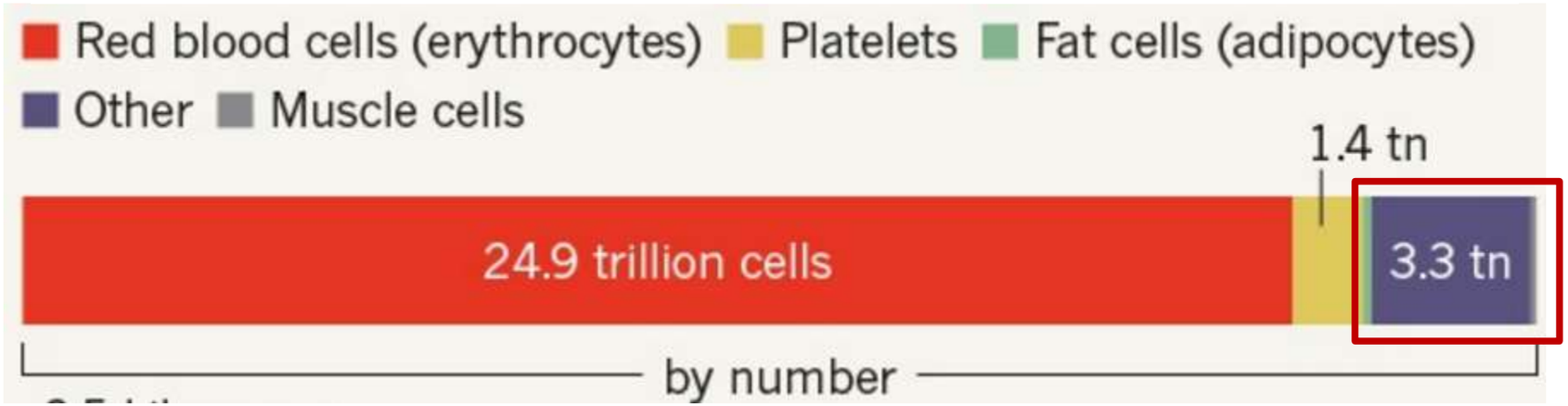
Scientists bust myth that our bodies have more bacteria than human cells

nature

Decades-old assumption about microbiota revisited.

Alison Abbott

08 January 2016



DNA-Bearing Cells

However, Red Blood Cells and Platelets Have No Nuclear DNA.
Therefore, Ratio of DNA-Bearing Cells for Human vs. Microbiome is Still >10:1

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

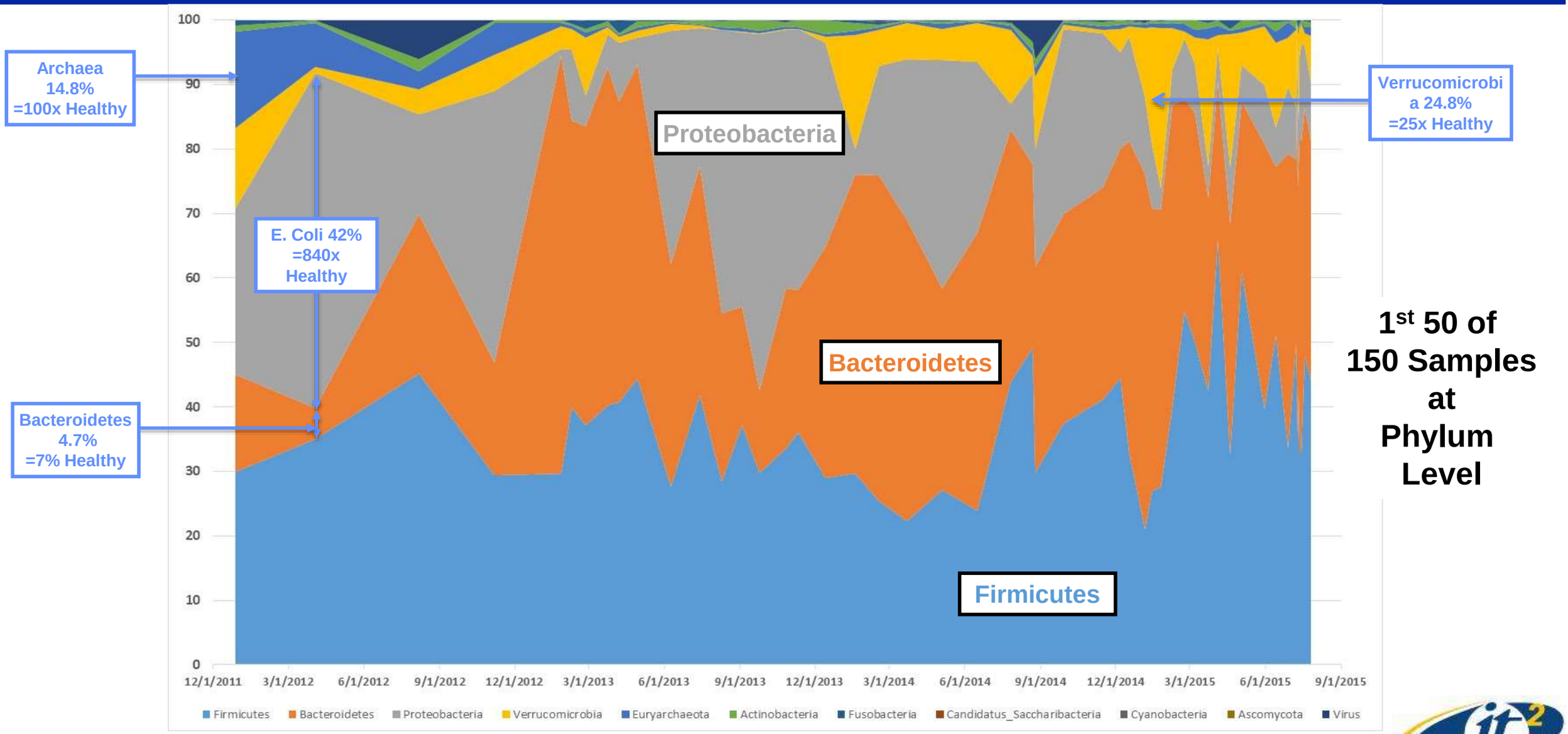
By Gary Robbins 1:30 P.M. JAN. 11, 2015 Updated 12:17 P.M. JAN. 12, 2015 PRINT COMMENTS 0





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

Metagenomically Sequencing Long Time Series Stool Samples to Reveal Patient Gut Microbiome Ecology Dynamics During Disease



1st 50 of 150 Samples at Phylum Level

Sequencing Rob Knight Lab; Analysis Xin Fang, UCSD

Rob Knight and My Team Analyzing The16S Sequencing of My 50 Gut MicrobiomeTime Series by Species

taxa-bar-plots.qzv | QIIME 2 View - Chromium

taxa-bar-plots.qzv | Color Schemes | Ve

Secure | https://view.qiime2.org/visualization/?type=html&src=8c779ab7-b14f-4a45-9170-c924145db3d9

qiime2view

File: taxa-bar-plots.qzv

Visualization | Peek | Provenance

Download

SVG (bars) | SVG (legend) | CSV

Taxonomic Level

Level 7

Color Palette

schemeAccent

Sort Samples By

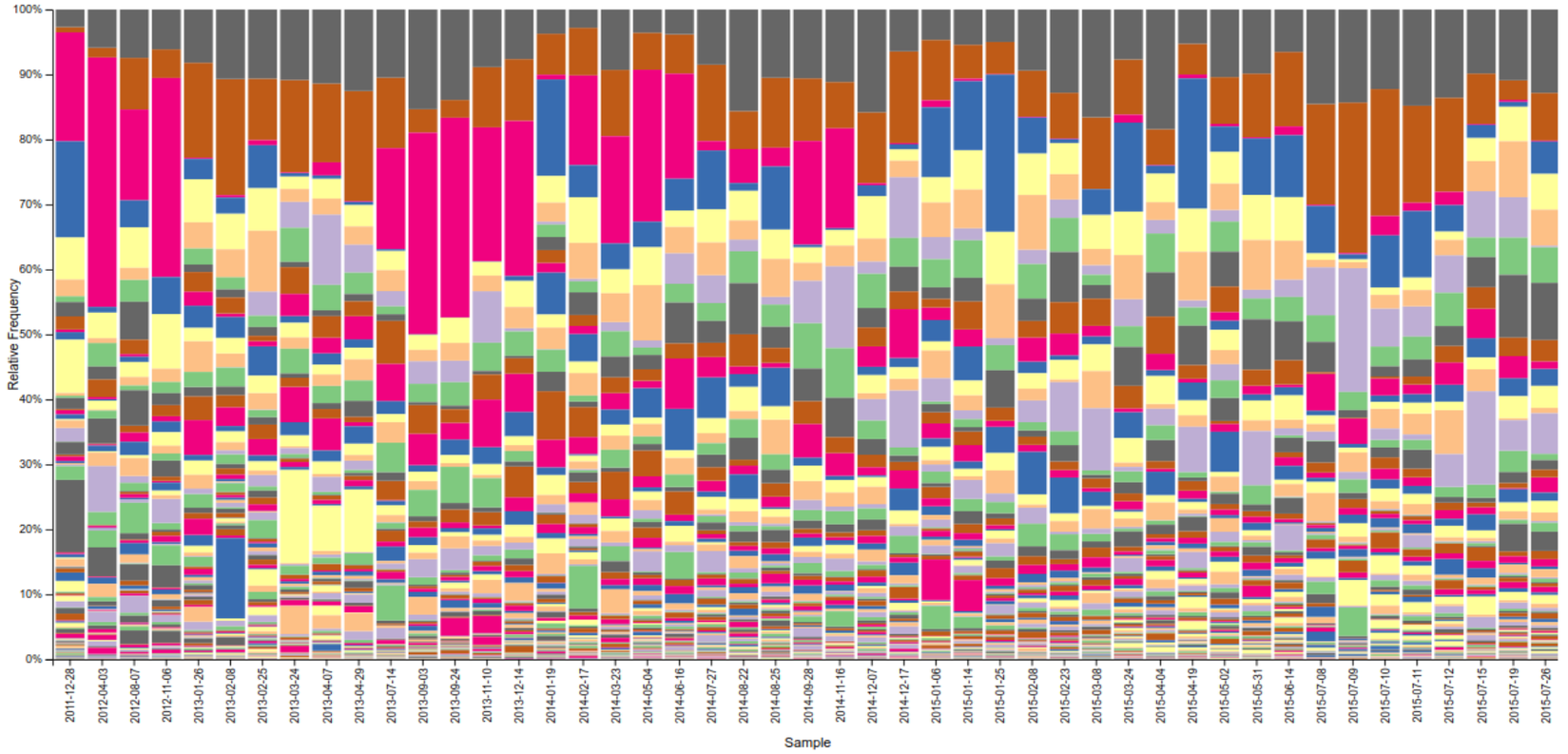
collection_timestamp

Ascending

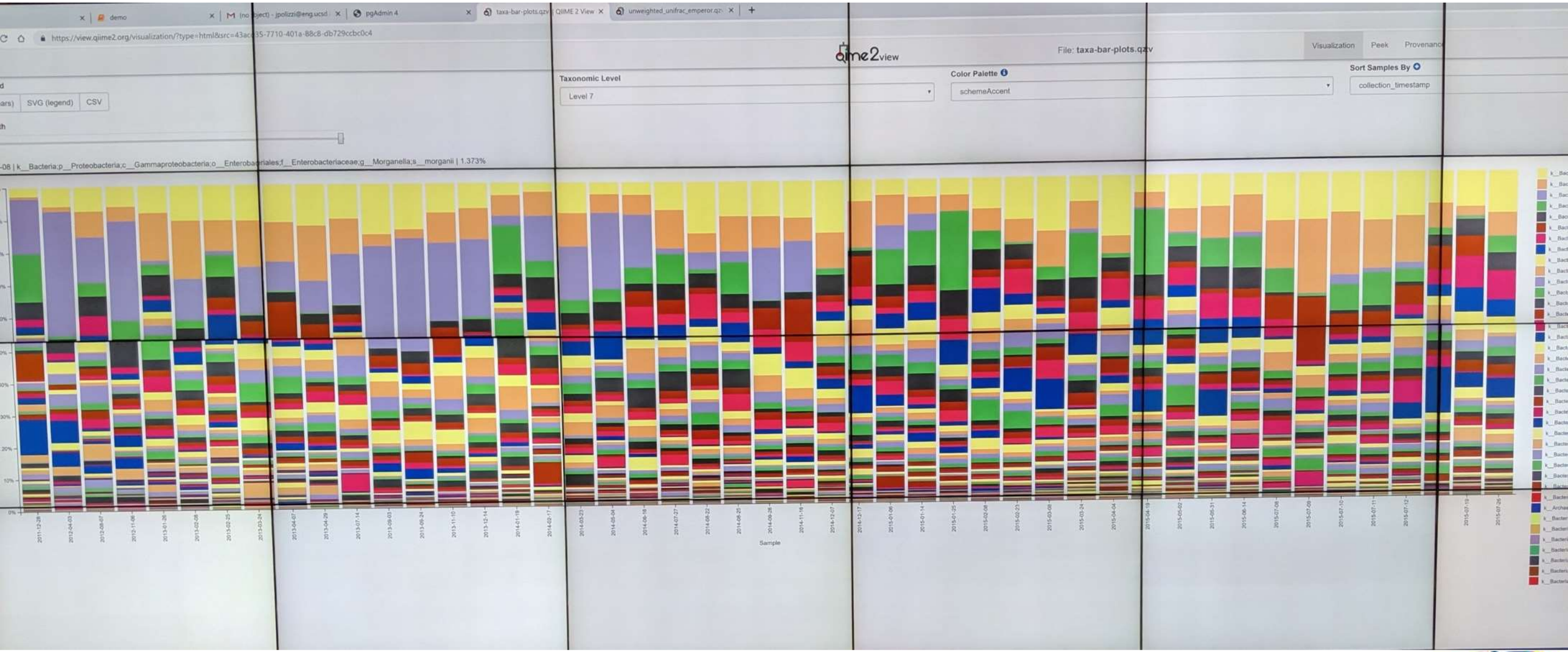
Relabel X?

Bar Width

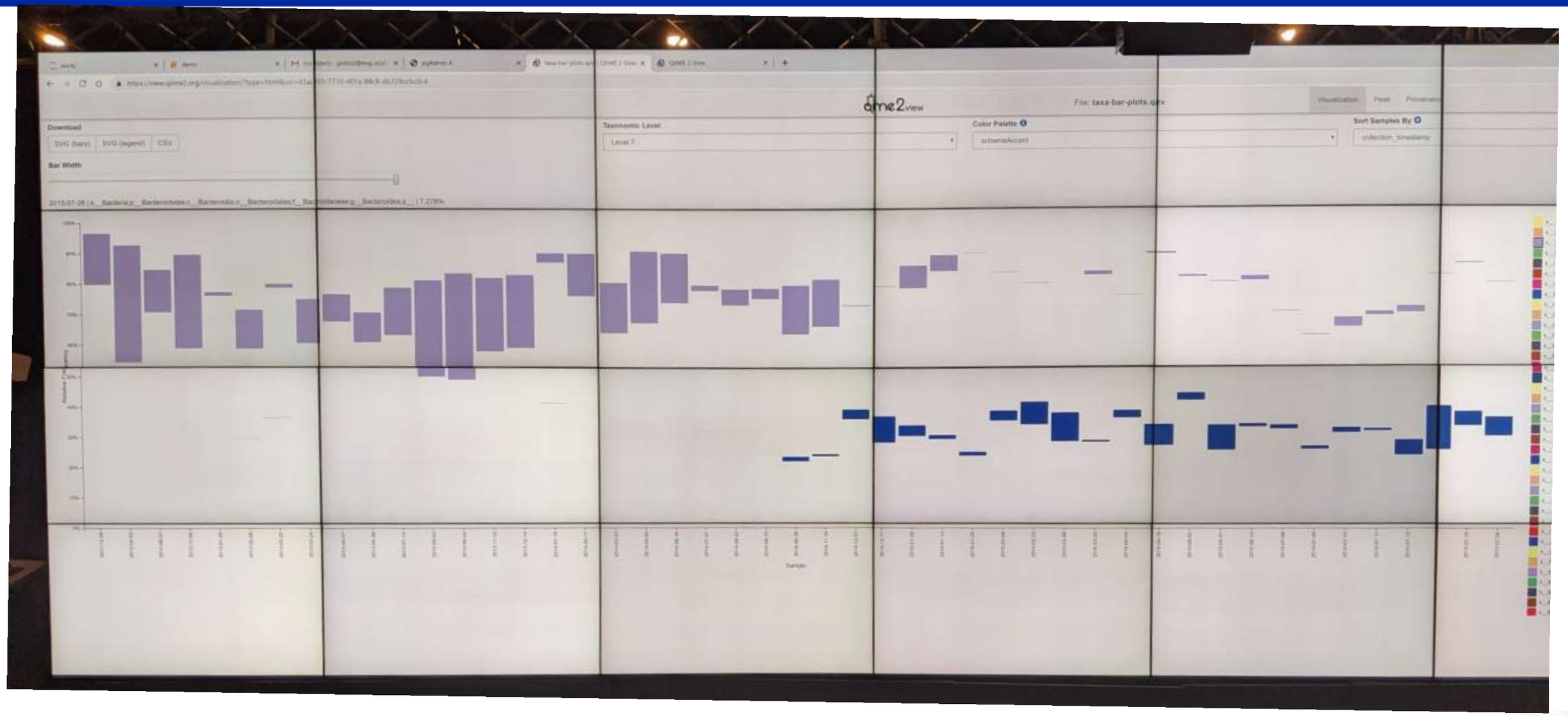
2015-07-26 | k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__[Mogibacteriaceae];g__;s__ | 0.119%



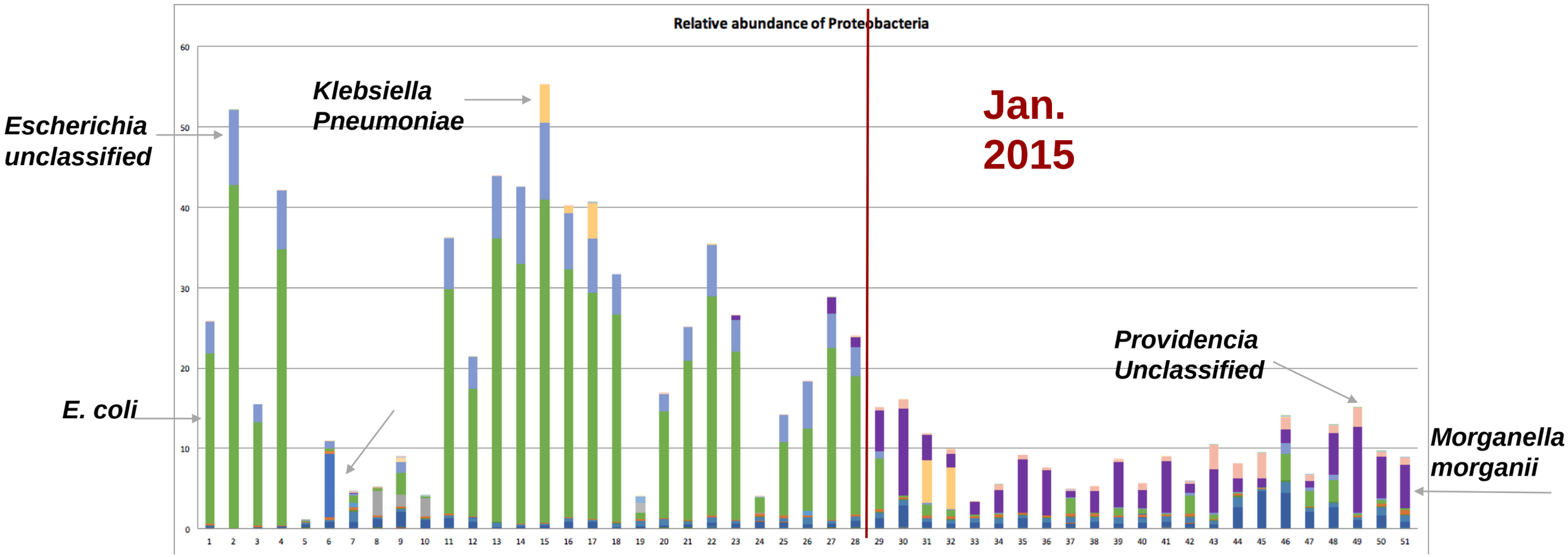
My Gut Microbiome 16S Time Series on the 64M Pixel VROOM



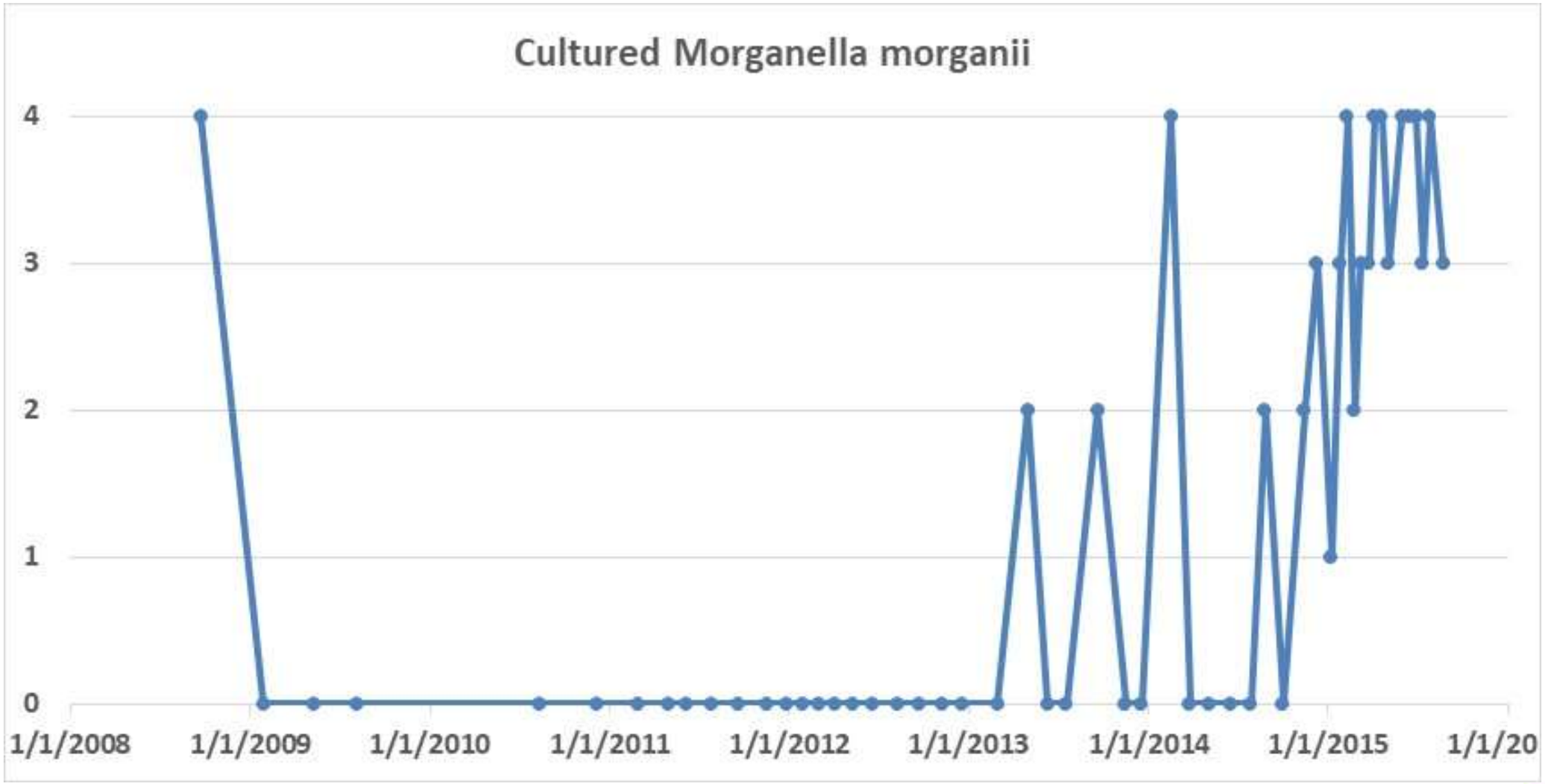
Discovery of Replacement of E. coli Within Proteobacteria by Morganella morganii-16S Sequencing on the 64M Pixel VROOM



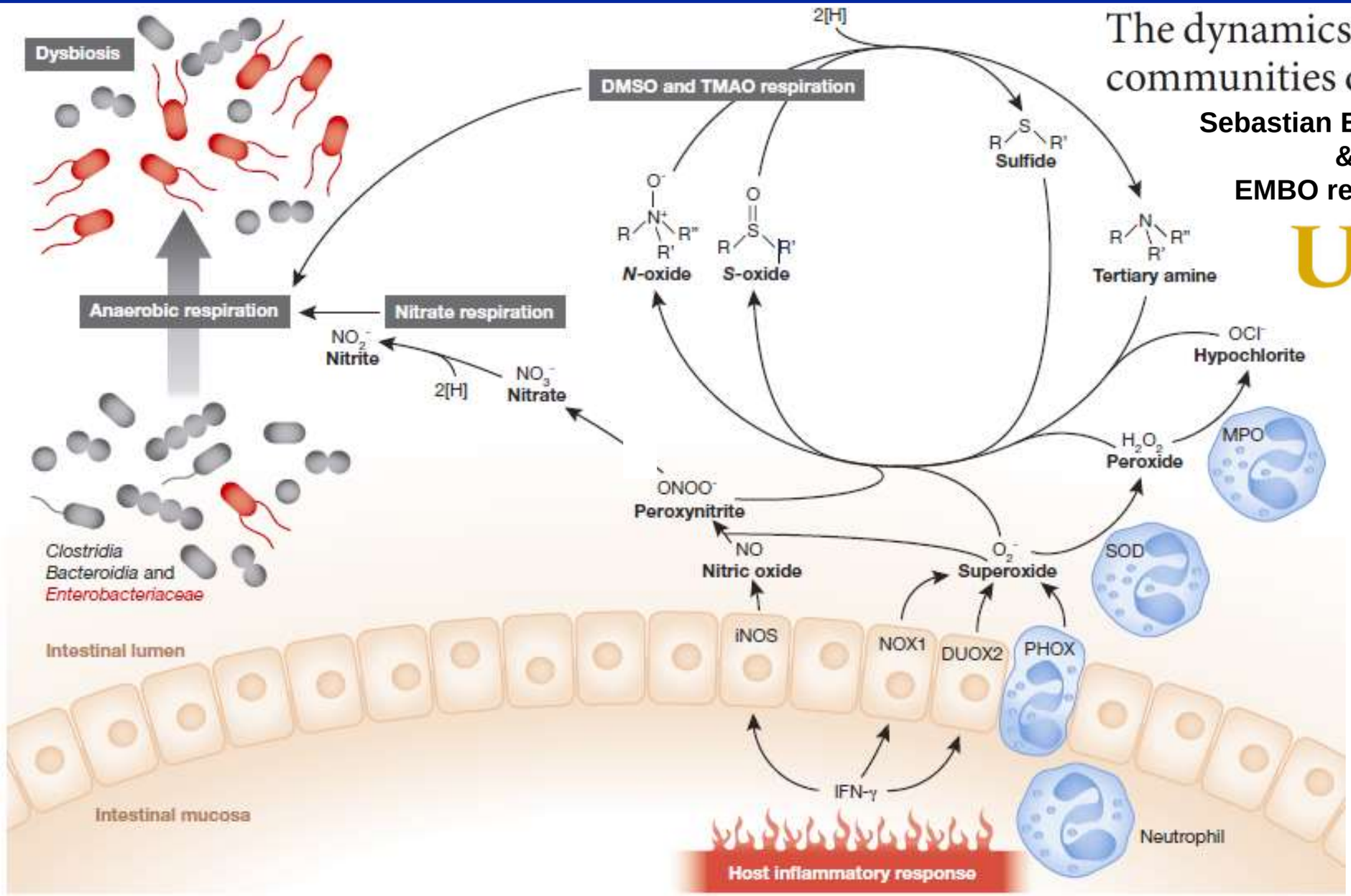
Proteobacteria Community Structure Changed Dramatically - Metagenomics Sequencing



Cultured Morganella Tracks Metagenomically and 16S Sequenced Microbiome Time Series



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

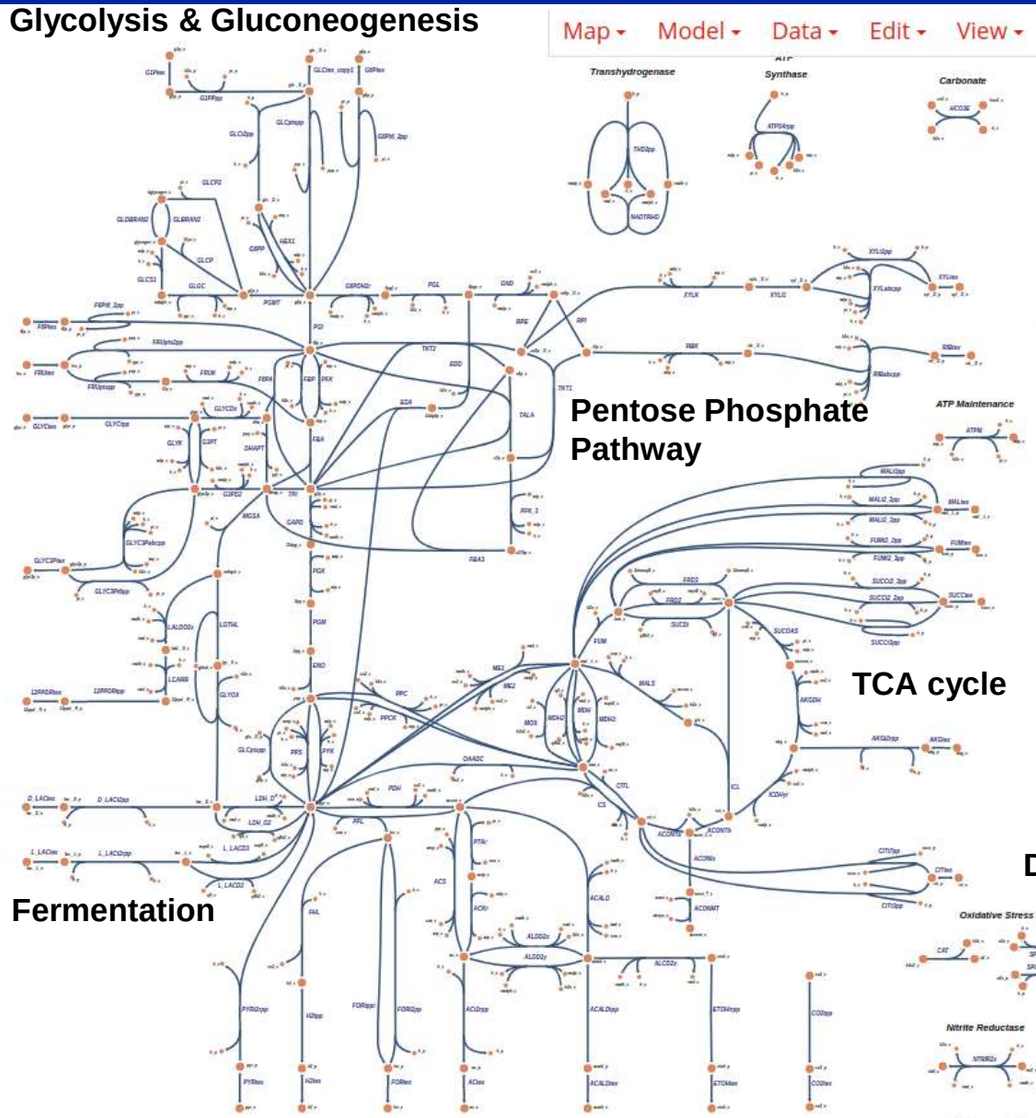


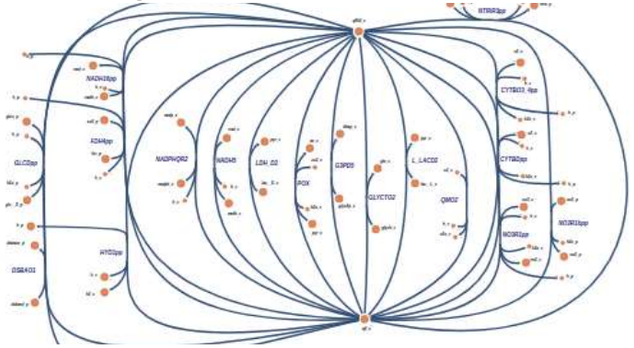
The dynamics of gut-associated microbial communities during inflammation

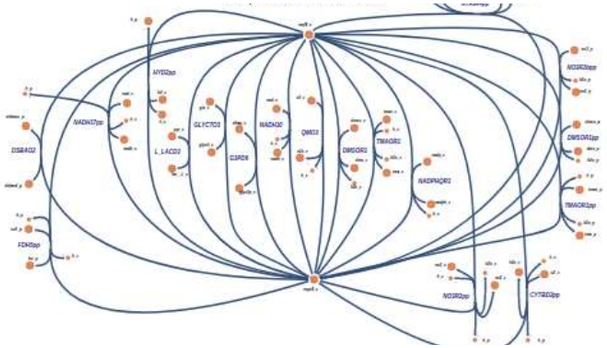
Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler,
EMBO reports v.14, p. 319-327 (2013)

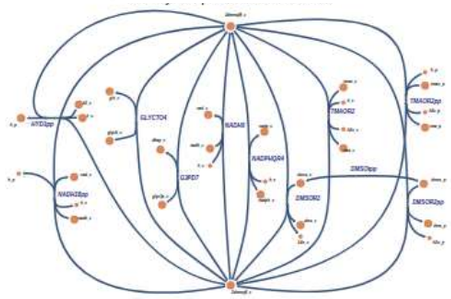
UCDAVIS

UC San Diego Has Constructed Genome-Wide Metabolic Computational Models for 110 E. Coli Strains (including 54 IBD isolates)







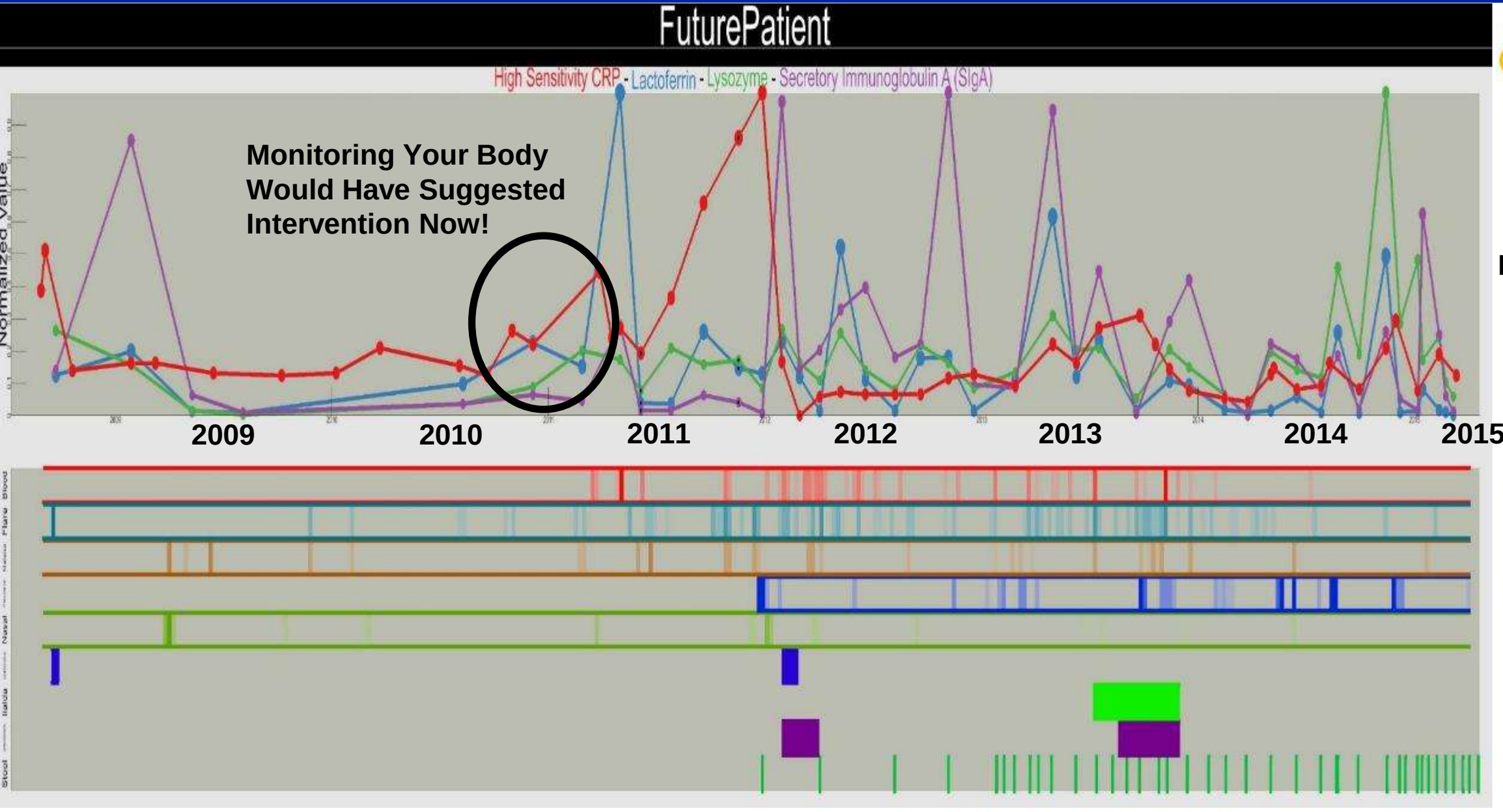


- Metabolic Network for Central Metabolism in *E.coli*
- Other Metabolic Pathways Not shown:
  - Amino Acid Metabolism
  - Fatty Acid Metabolism
  - Nucleotide Metabolism
  - ……
- Metabolic Network Varies For Different Strains

Bernhard Palsson Systems Biology Research Group-UC San Diego

King et al. PLOS Computational Biology (2015)

Time Series Reveals Oscillations in Immune Biomarkers Associated with Time Progression of Autoimmune Disease



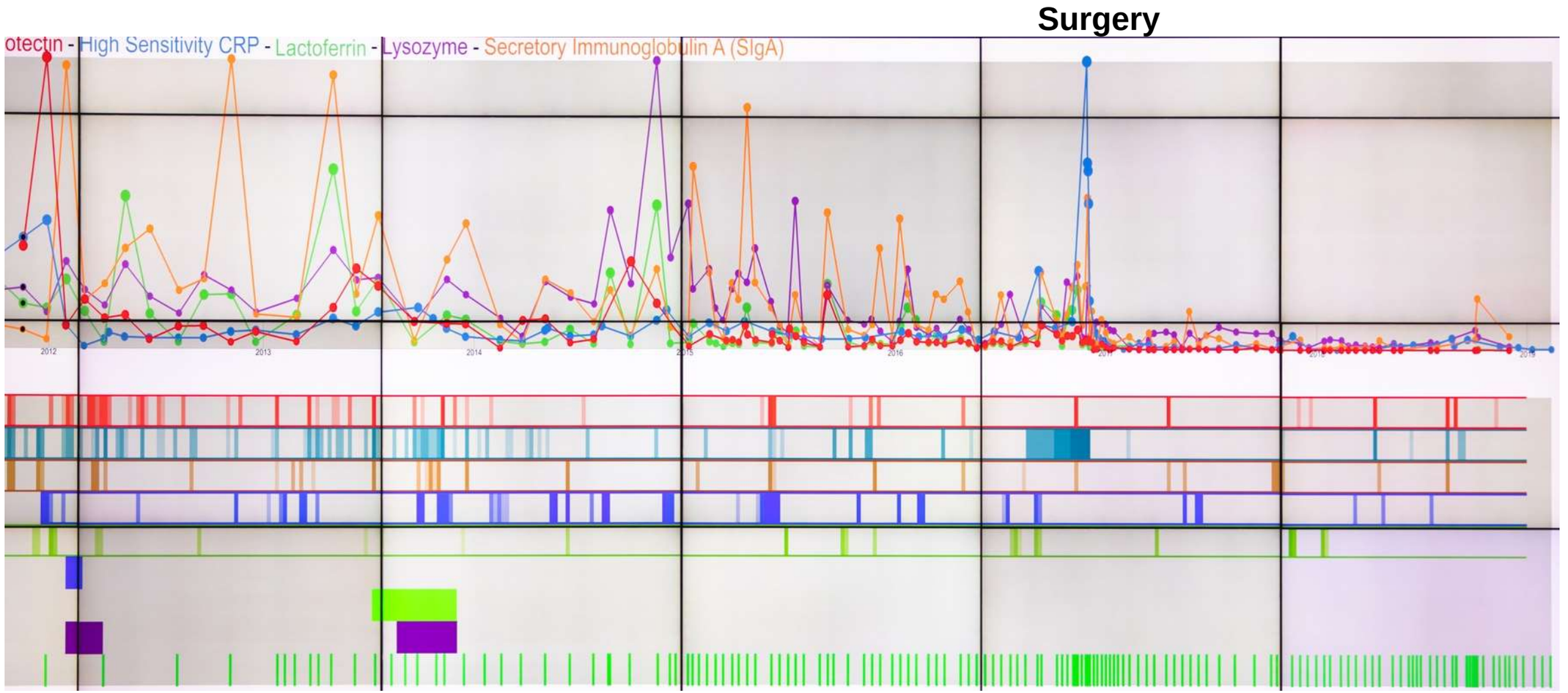
Immune & Inflammation Variables

Weekly Symptoms

Pharma Therapies

Stool Samples

Time Series Reveals Behavior Changes (Depression, Malaise) Associated with Time Progression of Autoimmune Disease



Immune & Inflammation Variables

Weekly Symptoms

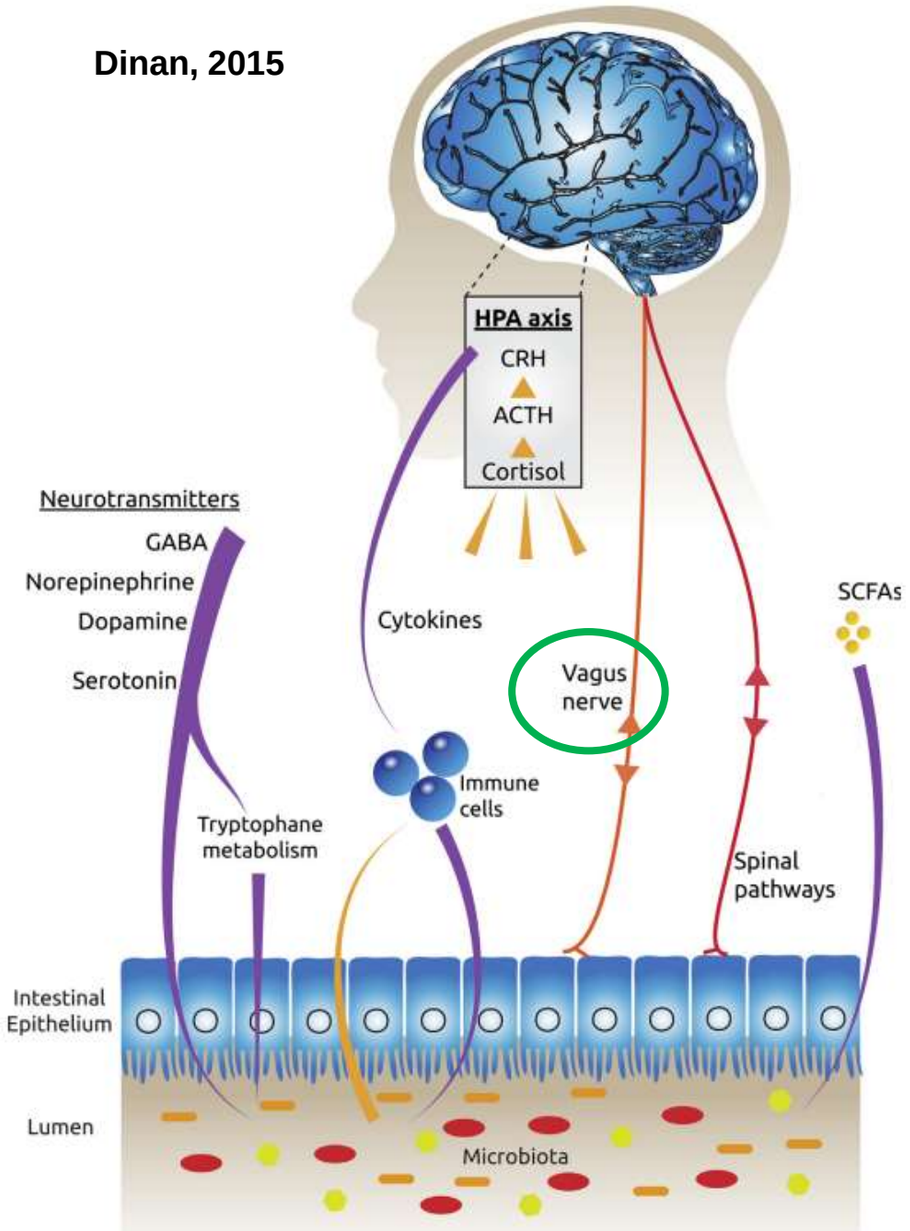
Mood Disorders

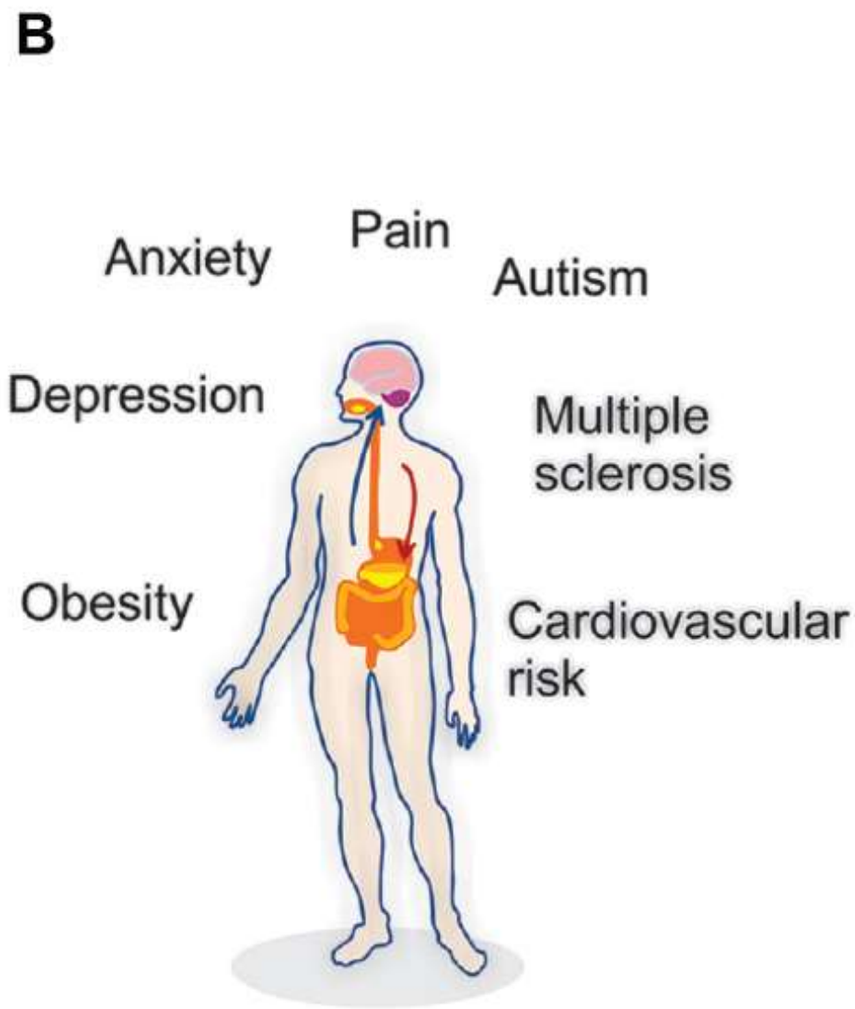
Pharma Therapies Stool Samples

To Understand Episodic Depression
One Needs to Sequence My Stool Samples
To Reveal Gut Microbiome Ecology Dynamics

The Microbiome–Gut–Brain Axis Provides New Systemic Insights into Shifts in Behavior and Disease

Dinan, 2015





Source: Montiel-Castro, et al.
Frontiers in Integrative Neuroscience 2013

Gut Microbes Regulate Serotonin Production, 90% of Which is in the Large Intestine

AMERICAN PSYCHOLOGICAL ASSOCIATION

“It's almost unthinkable that the gut is not playing a critical role in mind states," says gastroenterologist Emeran Mayer, MD, director of the Center for Neurobiology of Stress at UCLA

By Dr. Siri Carpenter
September 2012, Vol 43,

"More and more studies are showing that mice or other model organisms with changes in their gut microbes exhibit altered behaviours," noted senior author Dr Elaine Hsiao of Caltech.

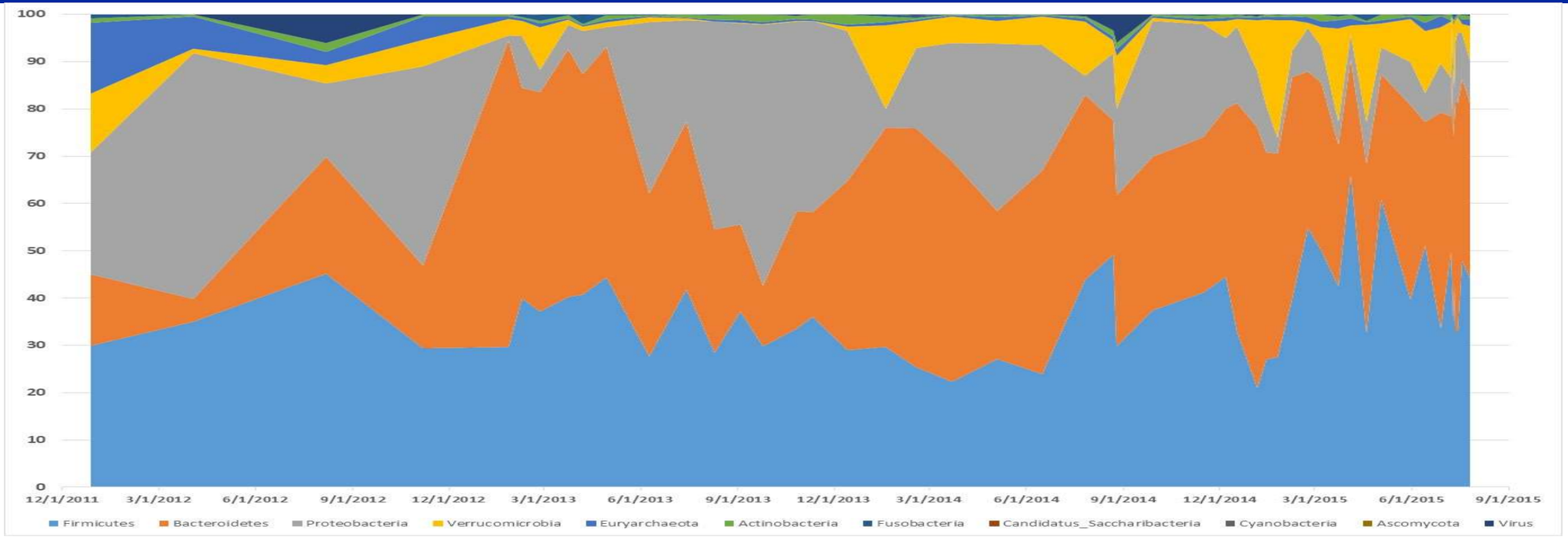
***Cell* 161 264-276 (2015)**

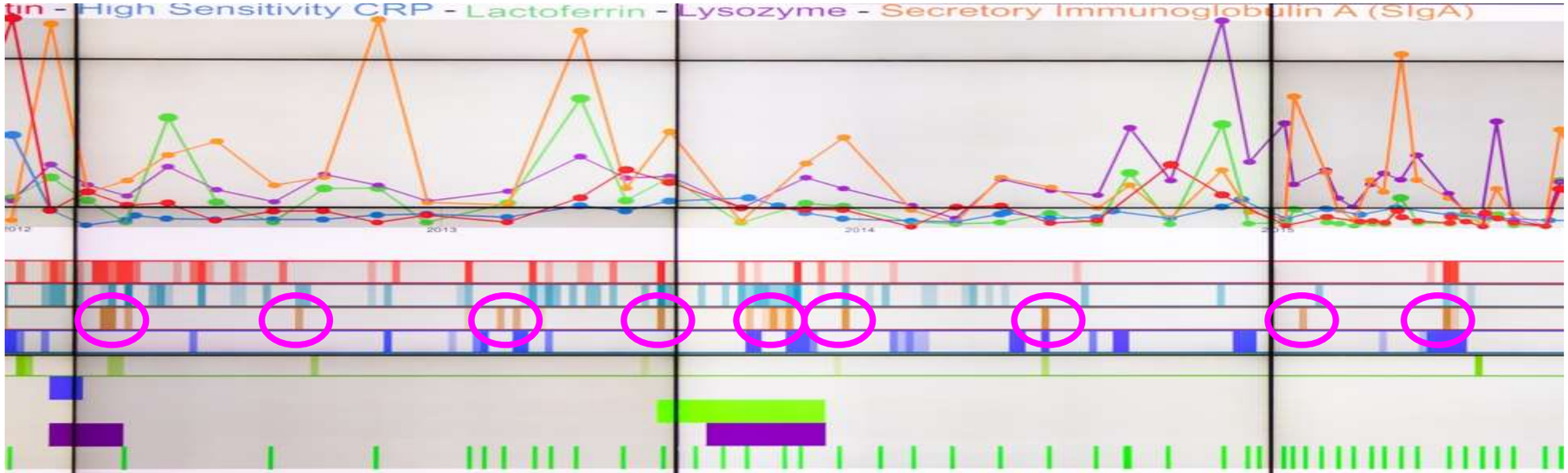
AMI American Microbiome Institute

April 13, 2015

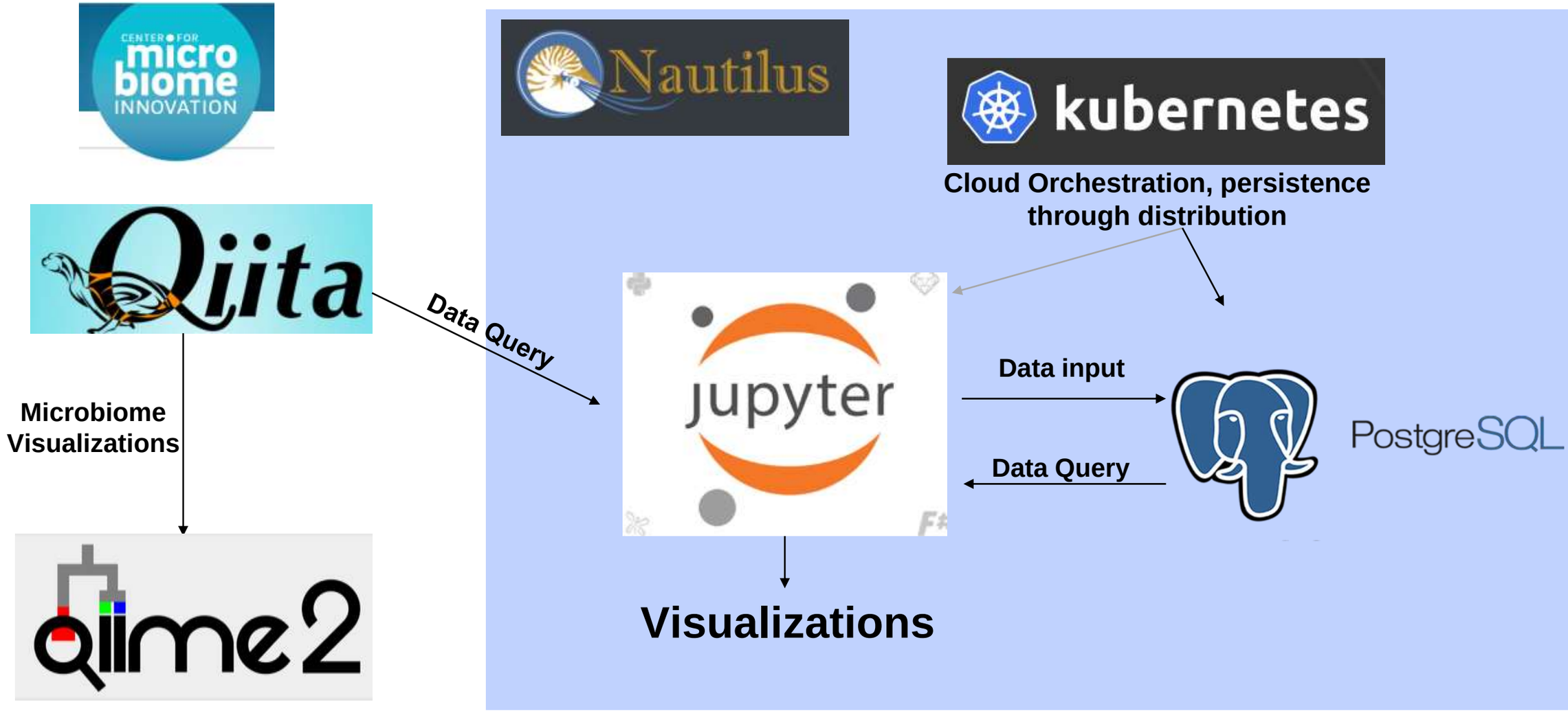
Gut bacteria help regulate serotonin levels

First Alignment of Microbiome Ecology with Inflammation and Immune Biomarkers, Pharma, and Symptoms

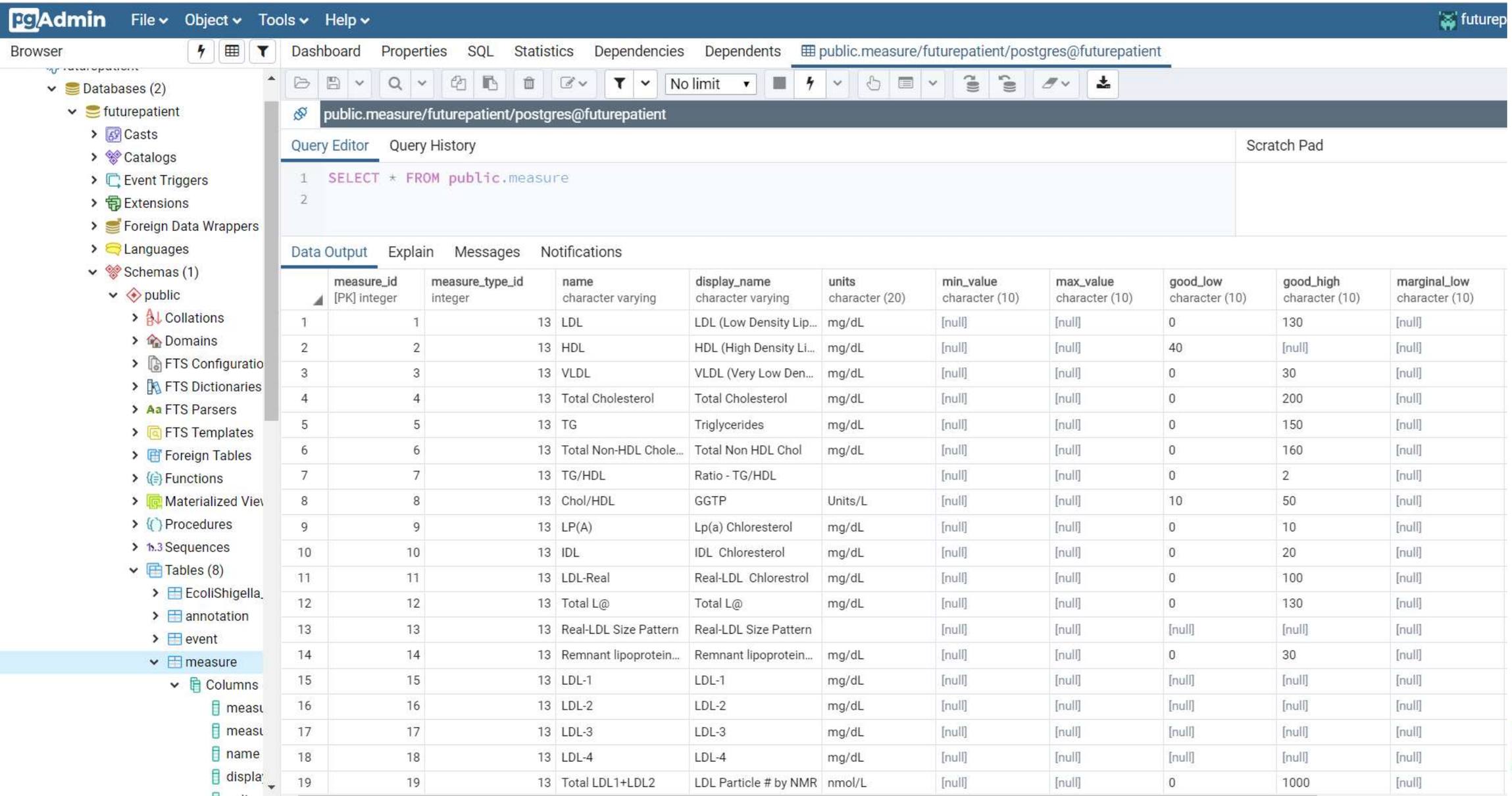




Personalized Medical Database with Distributed Jupyter Notebooks and Persistent PostgreSQl Database Working with Knight Lab's Qiita Database and Qiime2 viewer



PostgreSQL Personal Medical Database



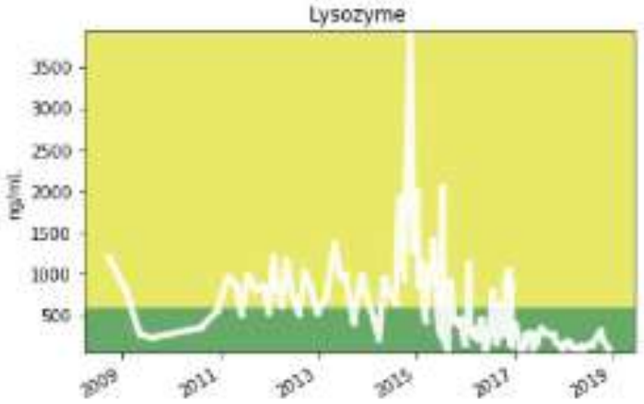
	measure_id [PK] integer	measure_type_id integer	name character varying	display_name character varying	units character (20)	min_value character (10)	max_value character (10)	good_low character (10)	good_high character (10)	marginal_low character (10)
1	1	13	LDL	LDL (Low Density Lip...	mg/dL	[null]	[null]	0	130	[null]
2	2	13	HDL	HDL (High Density Li...	mg/dL	[null]	[null]	40	[null]	[null]
3	3	13	VLDL	VLDL (Very Low Den...	mg/dL	[null]	[null]	0	30	[null]
4	4	13	Total Cholesterol	Total Cholesterol	mg/dL	[null]	[null]	0	200	[null]
5	5	13	TG	Triglycerides	mg/dL	[null]	[null]	0	150	[null]
6	6	13	Total Non-HDL Chole...	Total Non HDL Chol	mg/dL	[null]	[null]	0	160	[null]
7	7	13	TG/HDL	Ratio - TG/HDL		[null]	[null]	0	2	[null]
8	8	13	Chol/HDL	GGTP	Units/L	[null]	[null]	10	50	[null]
9	9	13	LP(A)	Lp(a) Chloresterol	mg/dL	[null]	[null]	0	10	[null]
10	10	13	IDL	IDL Chloresterol	mg/dL	[null]	[null]	0	20	[null]
11	11	13	LDL-Real	Real-LDL Chlorestrol	mg/dL	[null]	[null]	0	100	[null]
12	12	13	Total L@	Total L@	mg/dL	[null]	[null]	0	130	[null]
13	13	13	Real-LDL Size Pattern	Real-LDL Size Pattern		[null]	[null]	[null]	[null]	[null]
14	14	13	Remnant lipoprotein...	Remnant lipoprotein...	mg/dL	[null]	[null]	0	30	[null]
15	15	13	LDL-1	LDL-1	mg/dL	[null]	[null]	[null]	[null]	[null]
16	16	13	LDL-2	LDL-2	mg/dL	[null]	[null]	[null]	[null]	[null]
17	17	13	LDL-3	LDL-3	mg/dL	[null]	[null]	[null]	[null]	[null]
18	18	13	LDL-4	LDL-4	mg/dL	[null]	[null]	[null]	[null]	[null]
19	19	13	Total LDL1+LDL2	LDL Particle # by NMR	nmol/L	[null]	[null]	0	1000	[null]

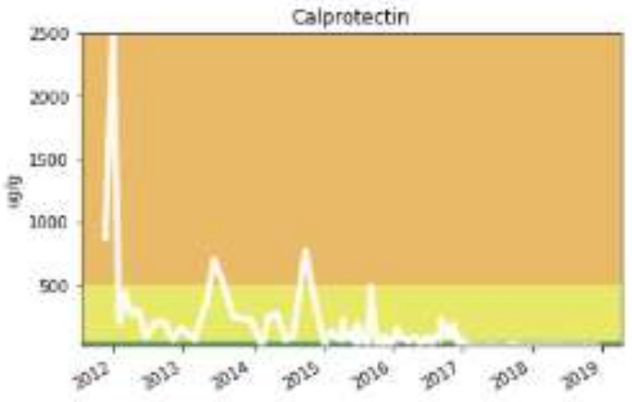
JupyterLab Python Notebook and Visualizations

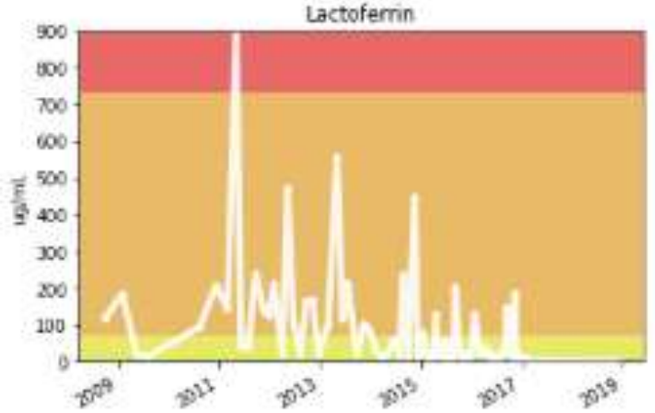


```
In [14]: for i in range(1, 7):
             graphBioMarker2D(i+170)
```

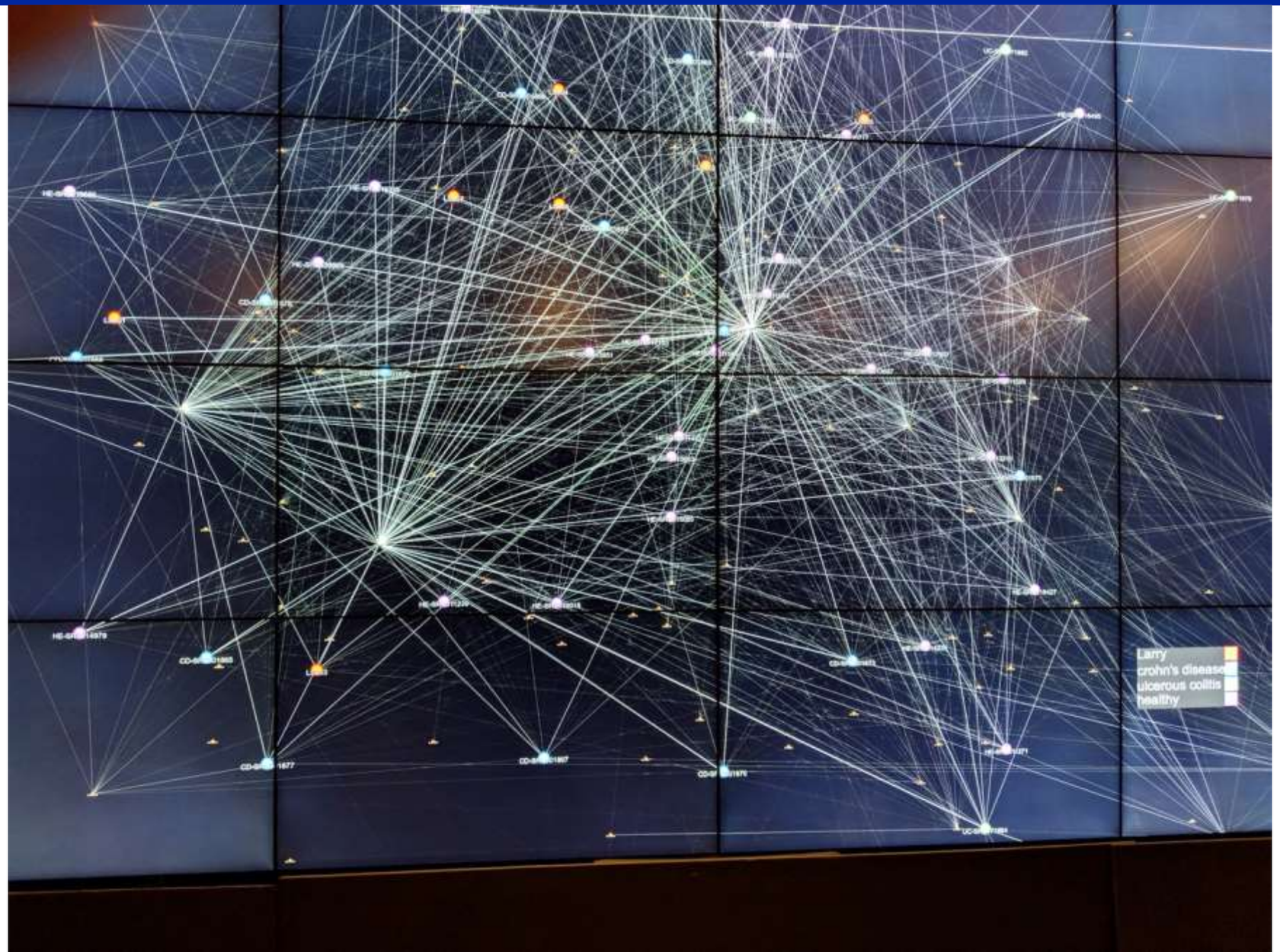




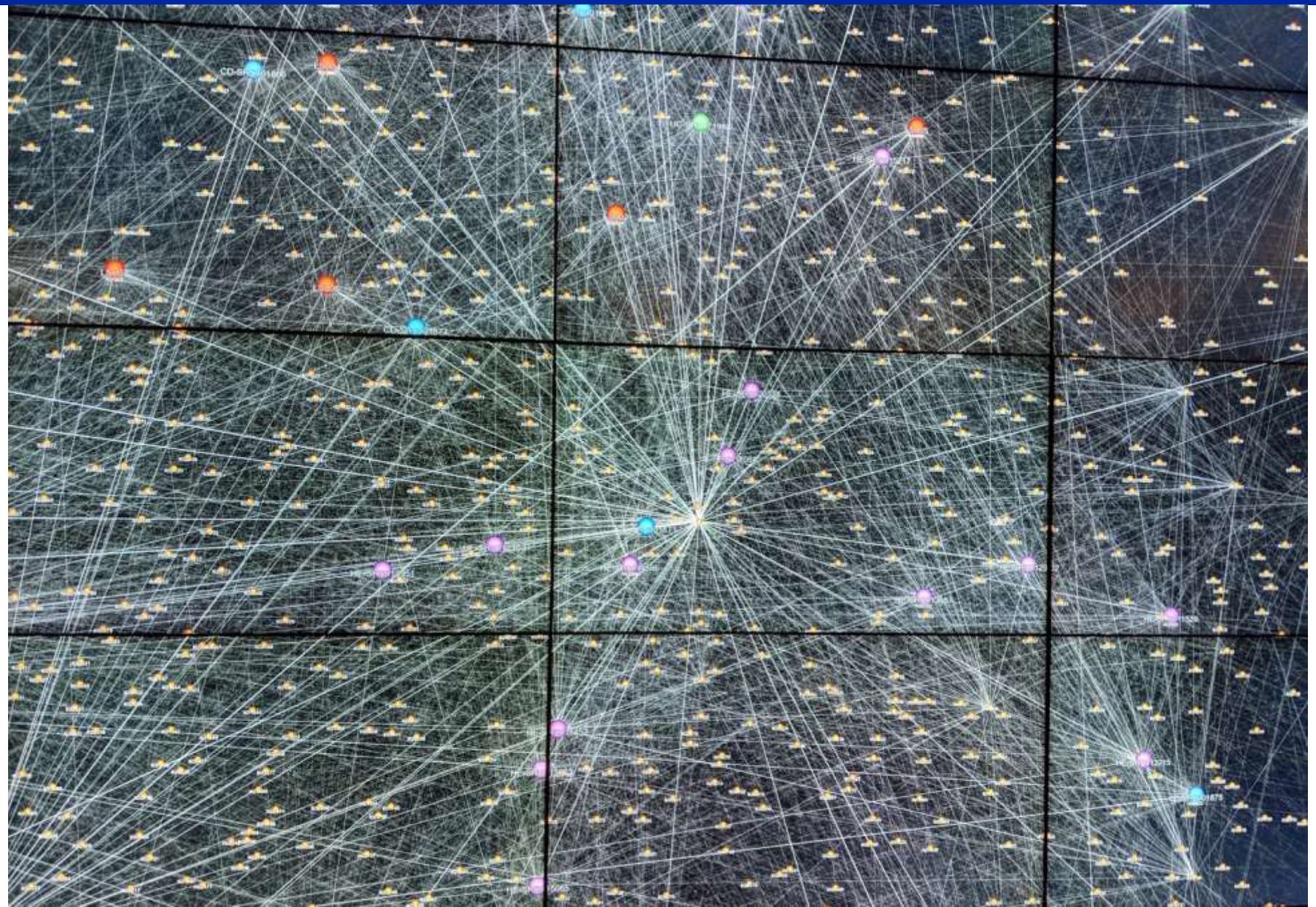




Exploring Many Parameters Per Person Using Network Visualization



10,000 Microbiome Protein Families Across 60 Patients



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

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

Reverse Insulin Resistance with Intermittent Fasting



By: COURTNEY SPERLAZZA, MPH

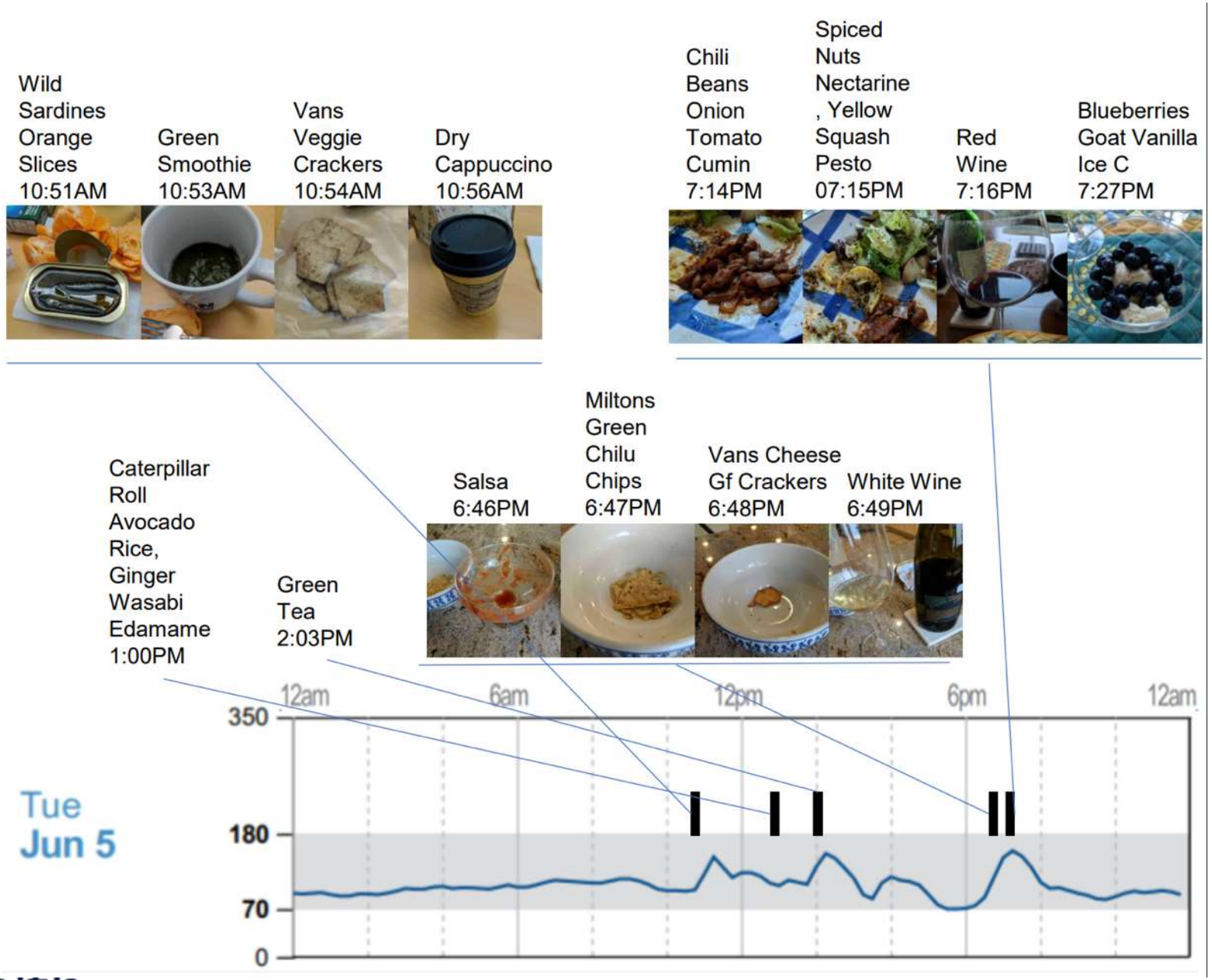
April 10, 2018

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

All Food/ Drink Photo/ Time-Stamped/ Annotated For 100-Days

Glucose Every 15 Minutes for Two Weeks Before and After 100-Day Trial





UC San Diego Health



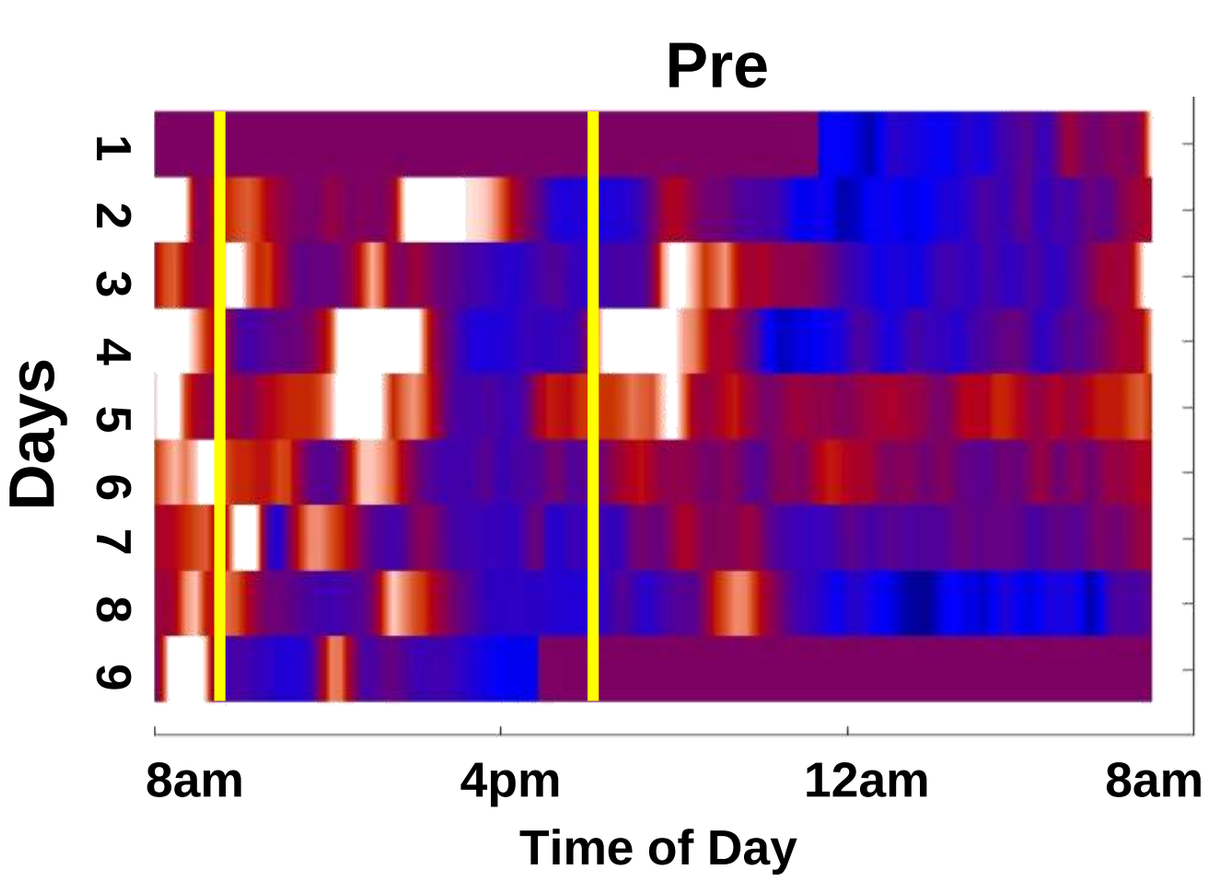
Pam Taub, MD
Cardiology

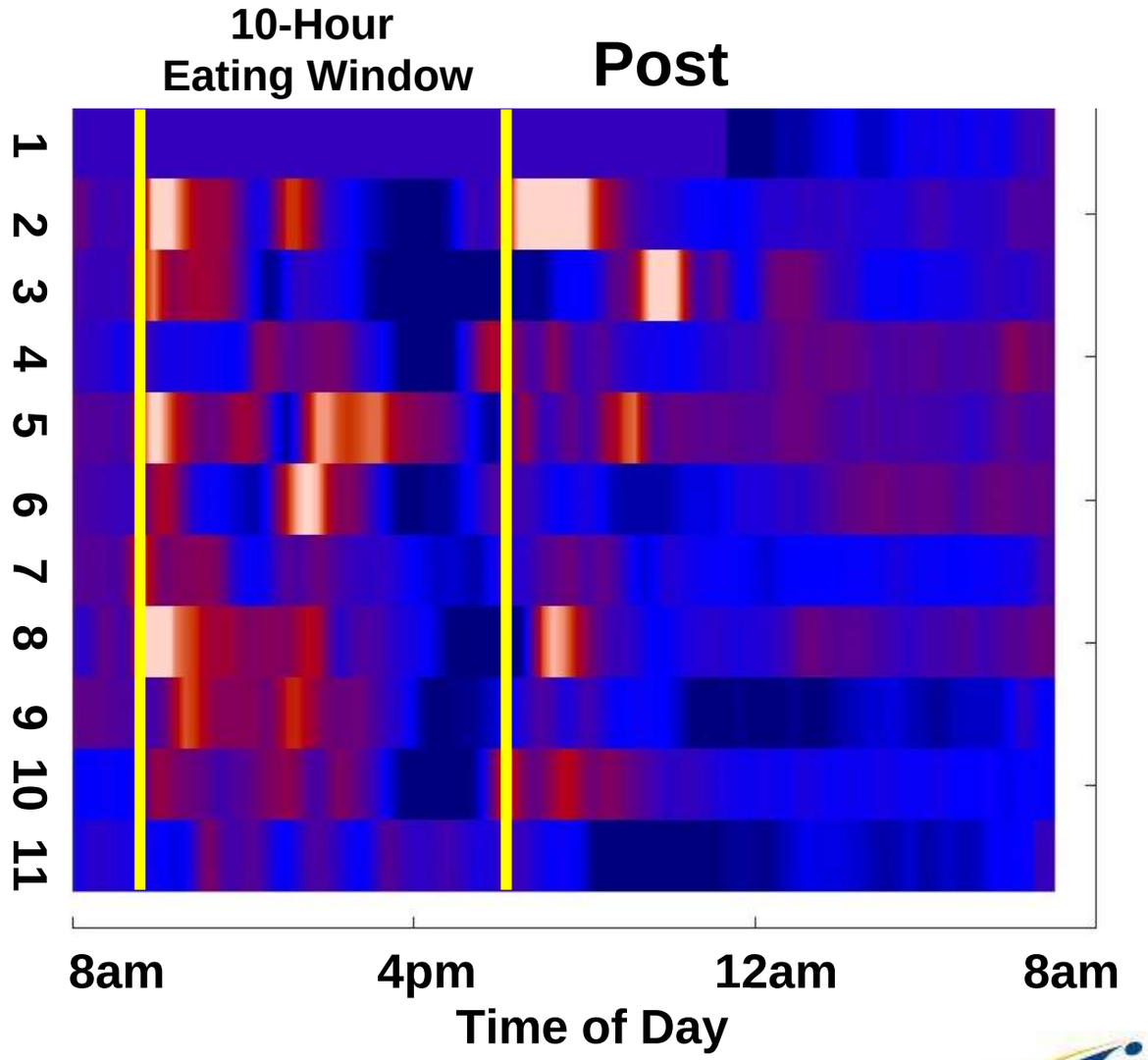


Satchin Panda, PhD
Circadian Biology

Emily Manoogian, Panda Lab, Salk Institute

Heat Map of Continuous Glucose Monitor Every 15 Minutes Before and After 3 Months of Time-Restricted Eating

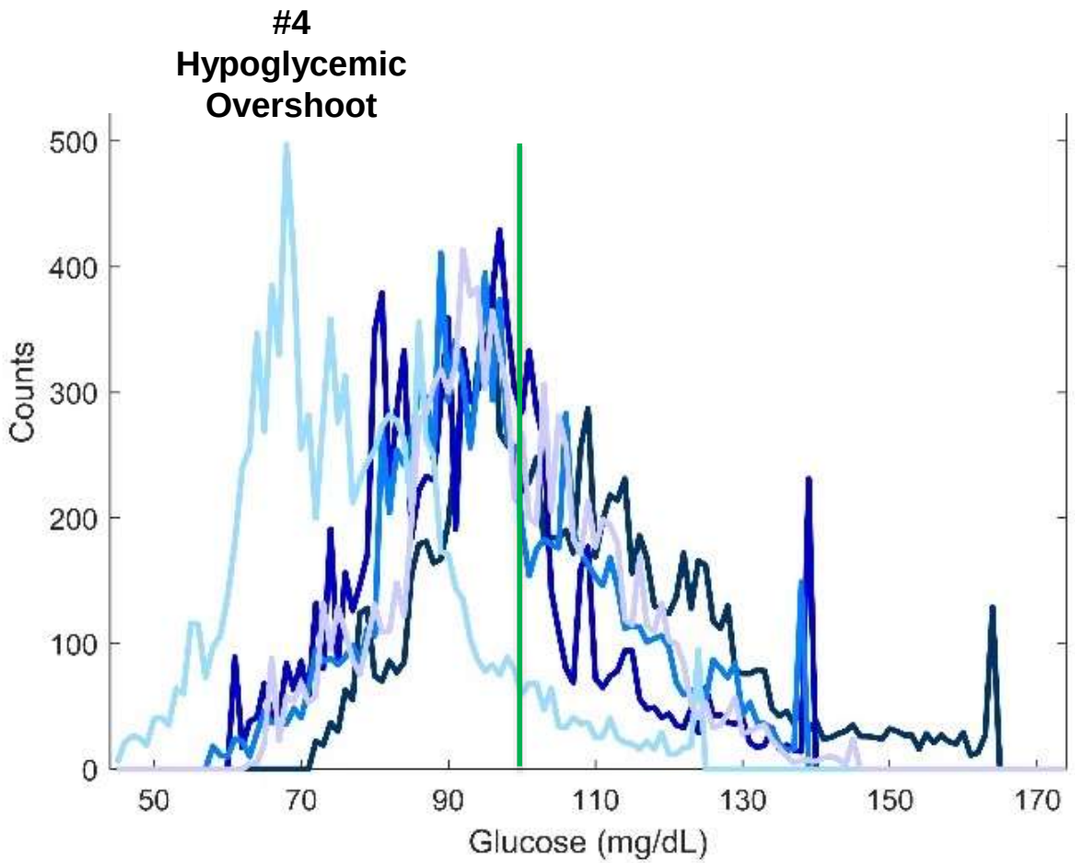


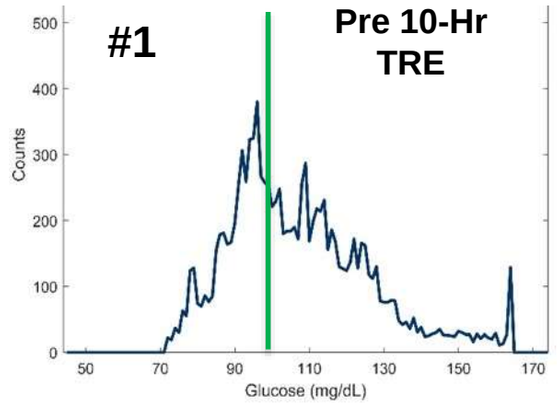


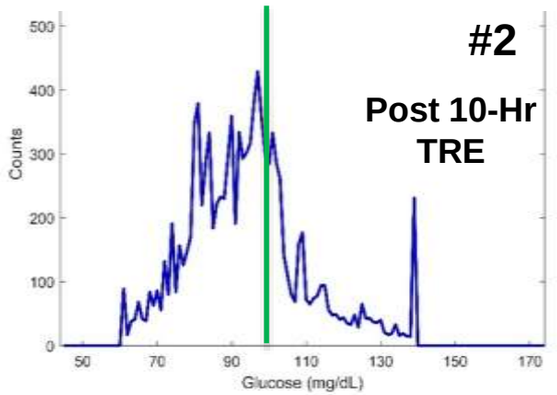
- **Other Improvements:**
  - **Waist 108cm to 102 cm**
  - **Weight 197 to 189**
  - **Blood Pressure 140/74 to 130/69**

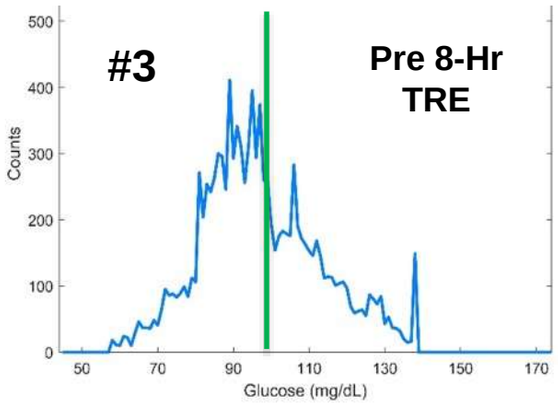
Data from Taub/Panda Clinical Trial
Graphics by Azure Grant, UC Berkeley

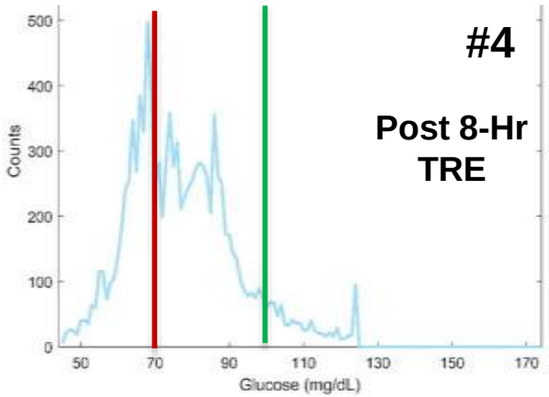
Time Evolution of CGM Normalized Distribution Function

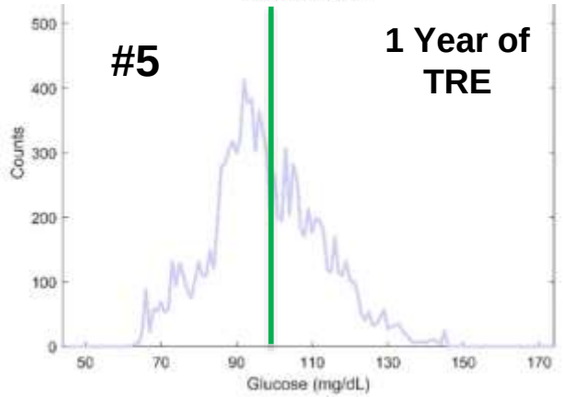






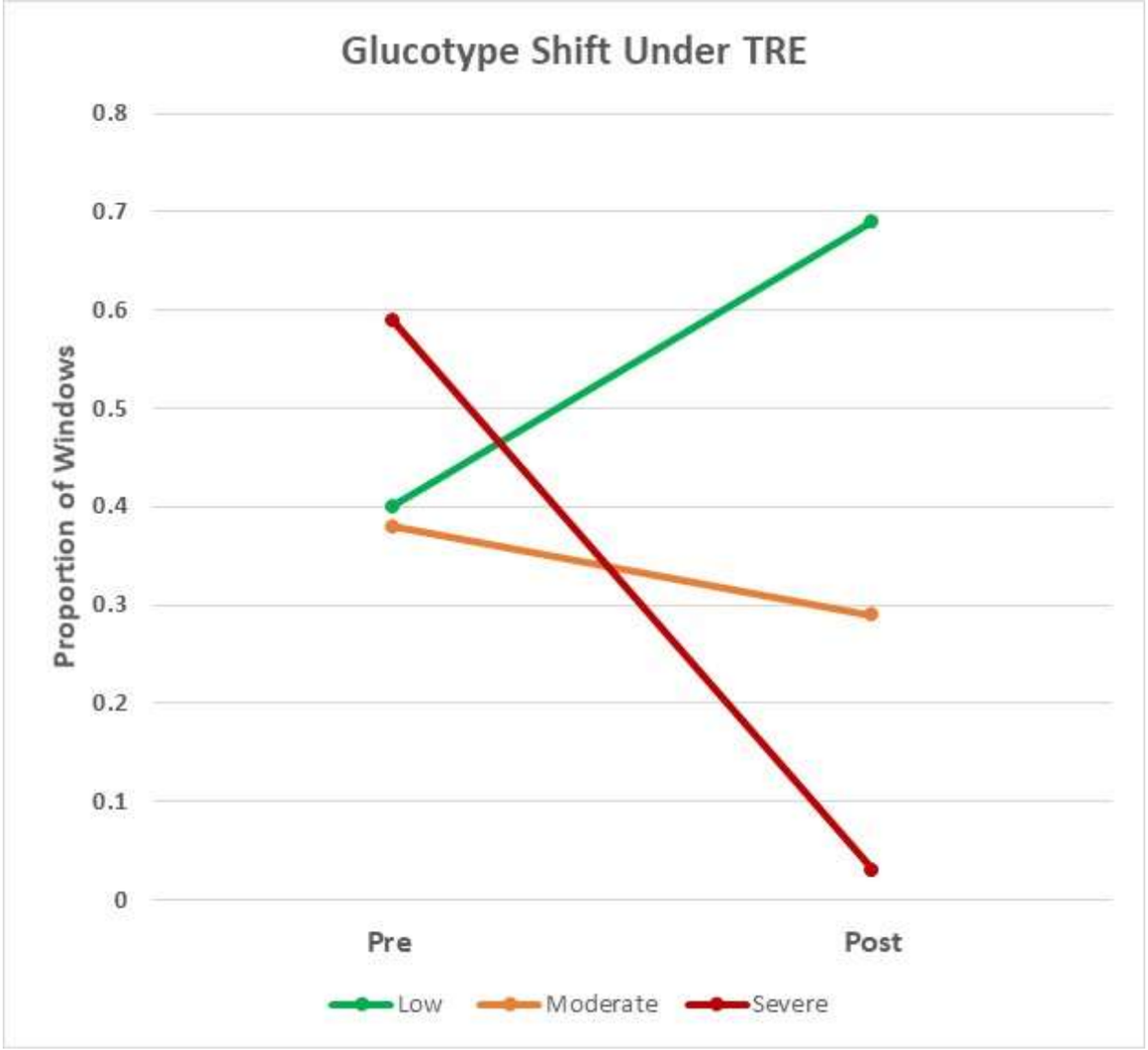






Data from Taub/Panda Clinical Trial
Graphics by Azure Grant, UC Berkeley

I Completely Reversed
My Glucotype Under Time Restricted Eating



Computations by Alessandra Breschi, Michael Snyder Lab, Stanford University

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

american gut

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

American Gut: an Open Platform for Citizen Science Microbiome Research

AMERICAN SOCIETY FOR MICROBIOLOGY | mSystems AN OPEN ACCESS JOURNAL PUBLISHED BY THE AMERICAN SOCIETY FOR MICROBIOLOGY May 15, 2018

it²

Can I Increase My Microbiome Diversity By Consuming ~50 Plant Species Per Day?







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

I Also Have Time-Stamped Annotated Photos of Everything I Consumed

UC San Diego

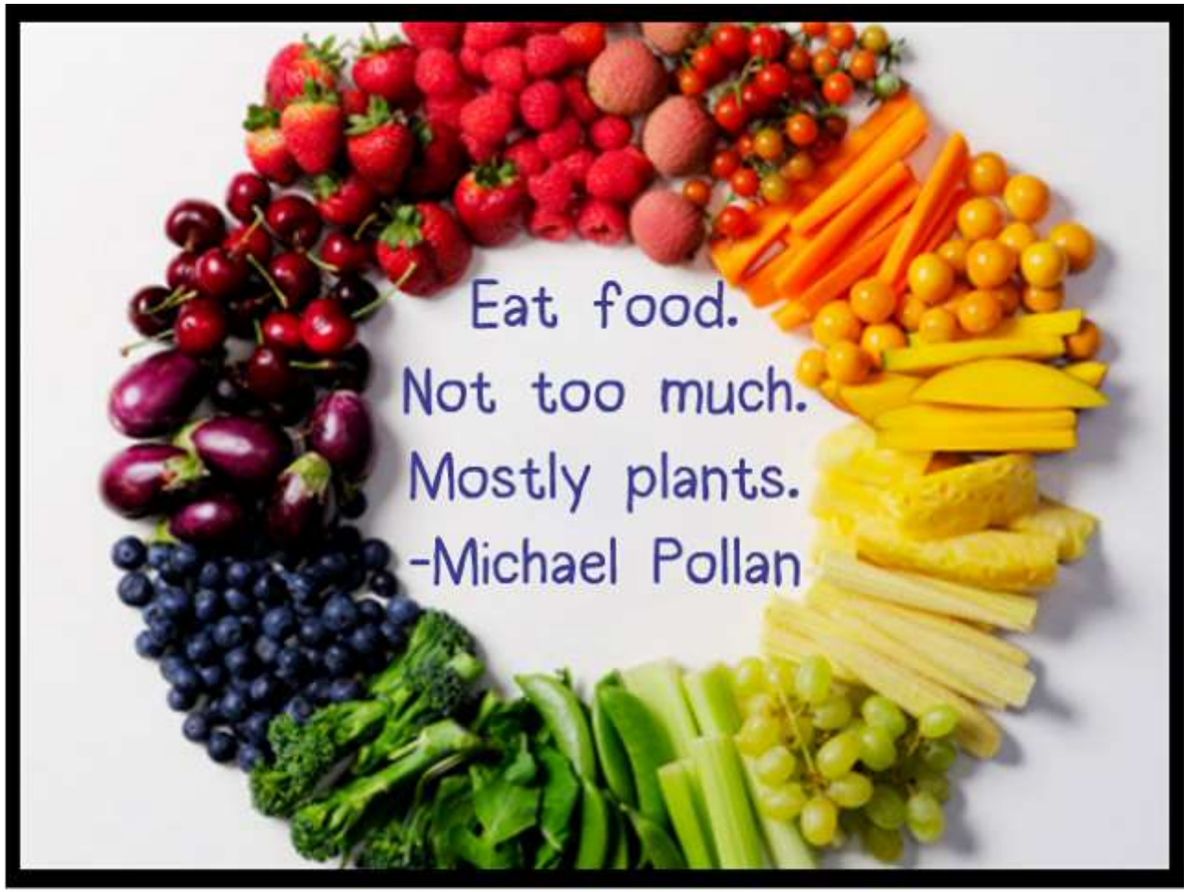
it²

200 Years of Food Wisdom:
Eat Mostly Plants

**"I have lived temperately,
eating little animal food,
& that, not as an aliment
so much as a condiment
for the vegetables,
which constitute my principal diet."
-Thomas Jefferson, age 76**

Jefferson to Dr. Vine Utley, March 21, 1819,

AN ARTICLE COURTESY OF THE
THOMAS JEFFERSON
ENCYCLOPEDIA MORE »



Michael Pollan, In Defense of Food, 2009

www.pinterest.nz/pin/573575702526997325/

Microbiome Ecology Shift Led to Transition to Metabolic Syndrome
Increasing Plant Diversity in Diet and Time Restricted Eating Reversed It



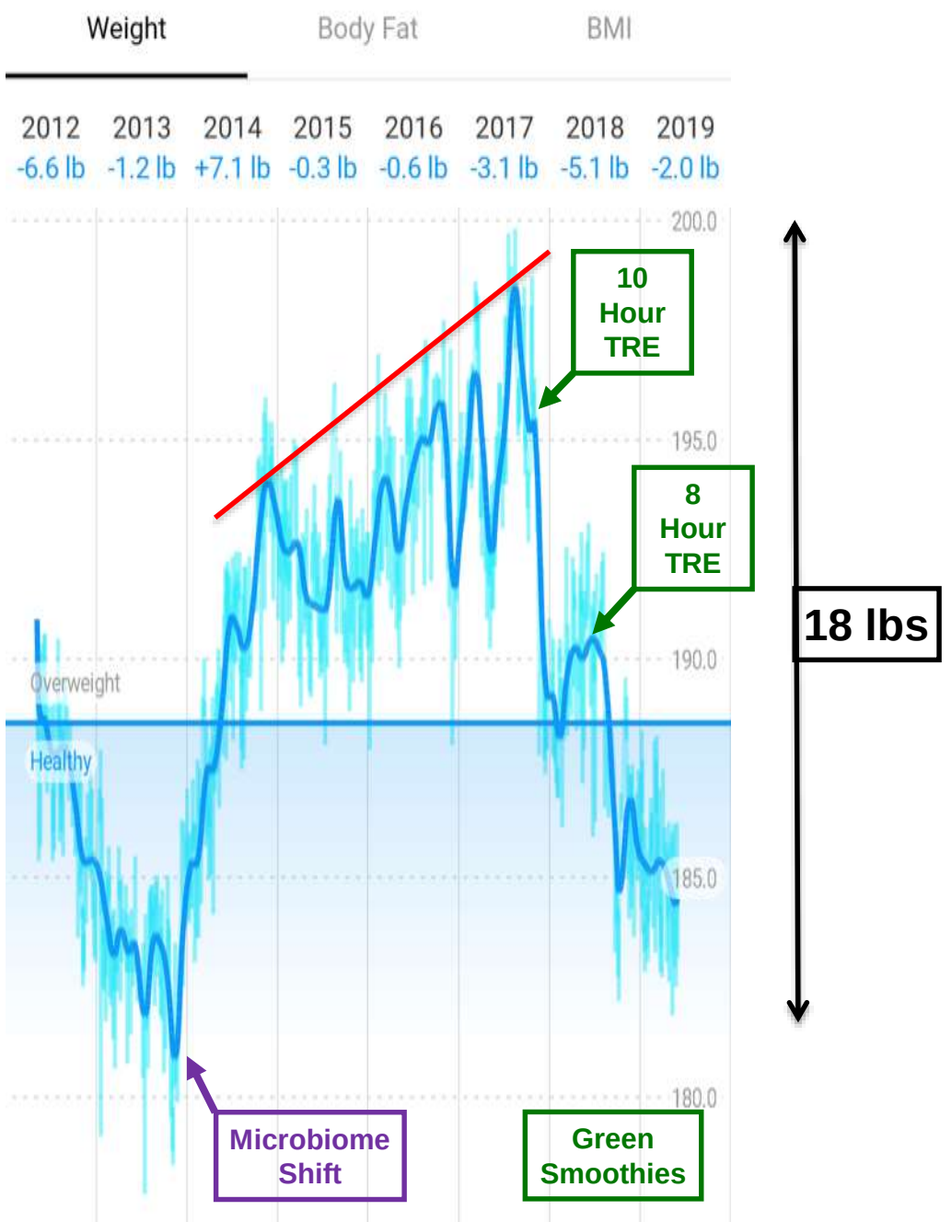
Grad Student Xin Fang

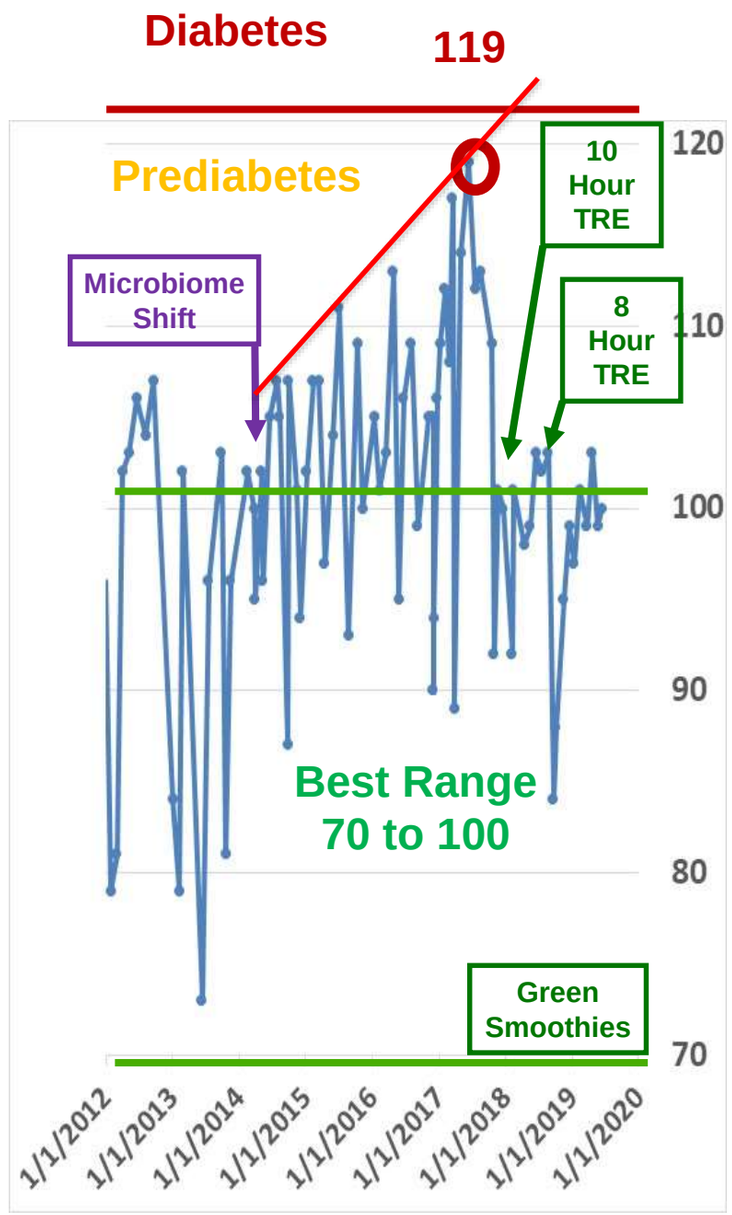
Next Step: Analyze Microbiome Dynamics

150 Frozen Stool Samples 2012-2019

Plus

100 Daily Frozen Stool Samples During 10-Hour Restricted Eating Trial

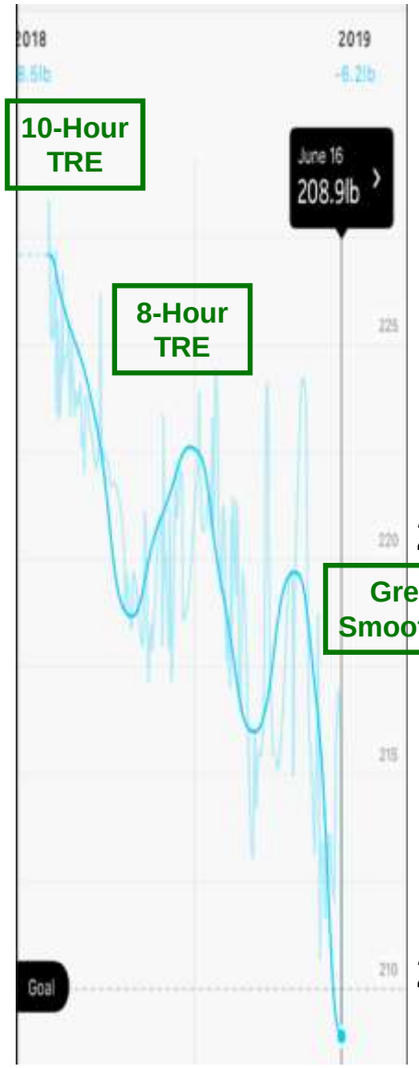




Three Weight Drops
Using Time Restricted Eating







Time and Weight Scales The Same

Goal: Measure My Body's Toxic Load

Stool and Red Blood Cell Mercury Are Historically High





Stool
Heavy Metals
Oct. 2018

3.6x Mercury
2.2x Arsenic
2.0x Bismuth
1.6x Cadmium
1.5x Lead
1.5x Nickel
1.2x Thallium

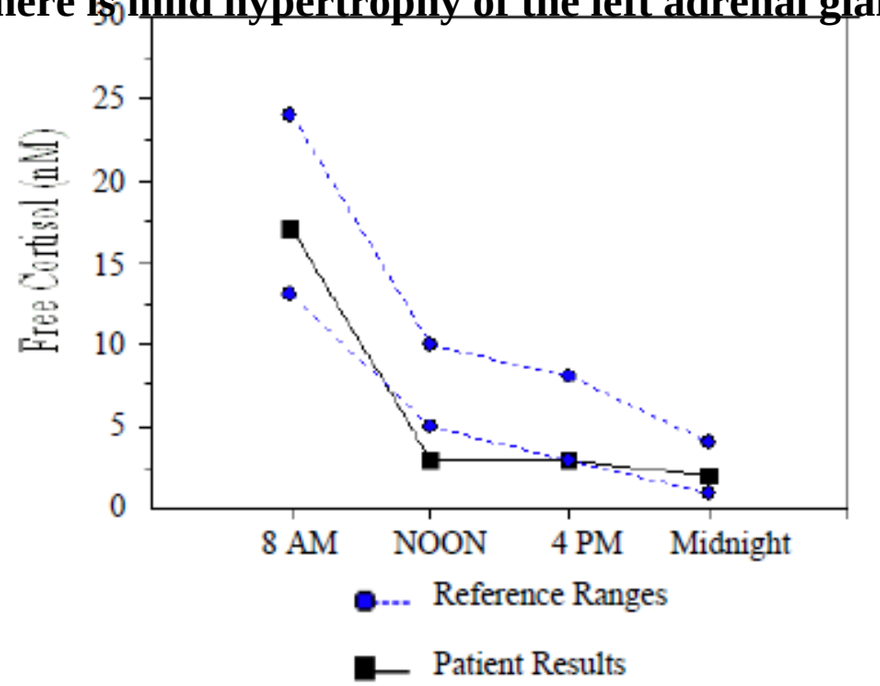
What Don’t I Know About My Body’s Toxin Load

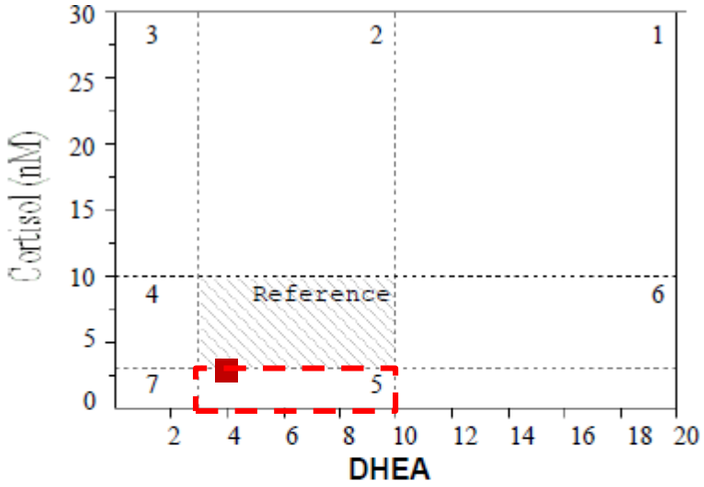
- Need to Test For:
  - Endrocrine Disrupters
    - Glyphosate
    - PCBs
    - BPA
    - Other Pesticides
  - Heavy Metals
    - Blood
    - RBC
    - WBC
    - Stool
  - Molds
  - Body Detoxifiers
    - Gluthathione
    - Selenium

Goal: Measure My Body’s Hormonal System

Cortisol-DHEA Tests 2008

There is mild hypertrophy of the left adrenal gland





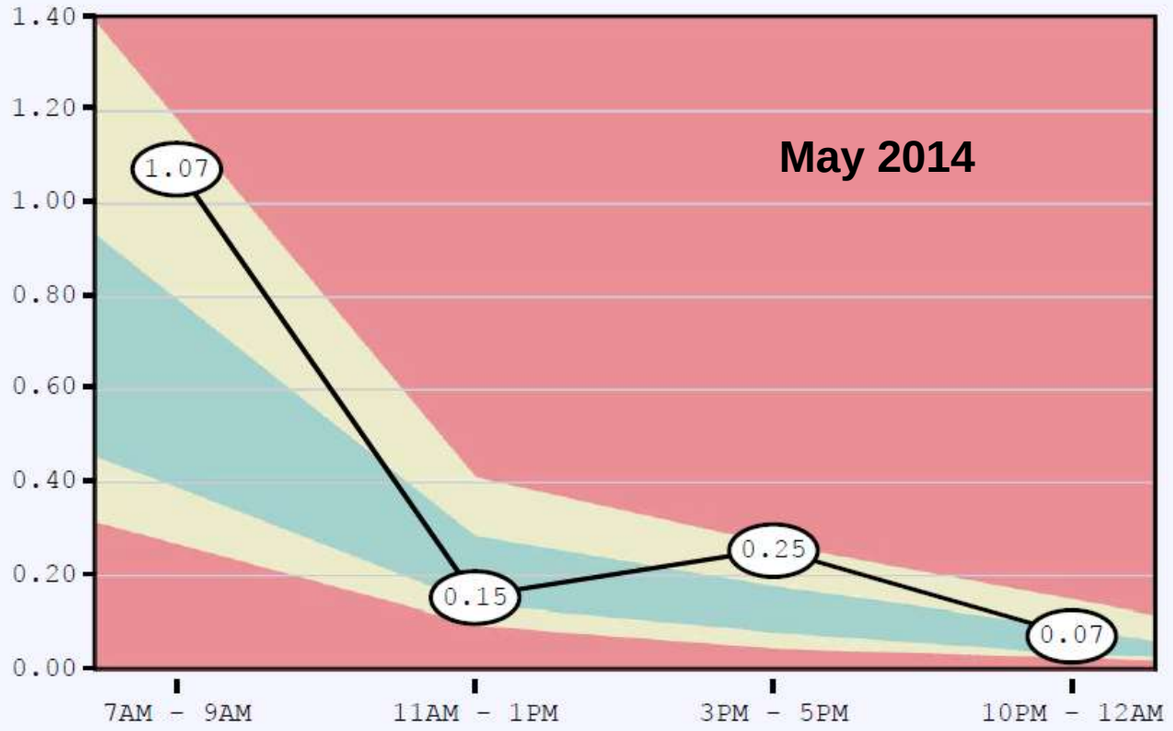
CORTISOL-DHEA CORRELATION SPECTRUM

1. Adapted to stress.
2. Adapted with DHEA slump.
3. Maladapted Phase I.
4. Maladapted Phase II.
5. **Non-adapted, Low Reserves.**
6. High DHEA.
7. Adrenal Fatigue.

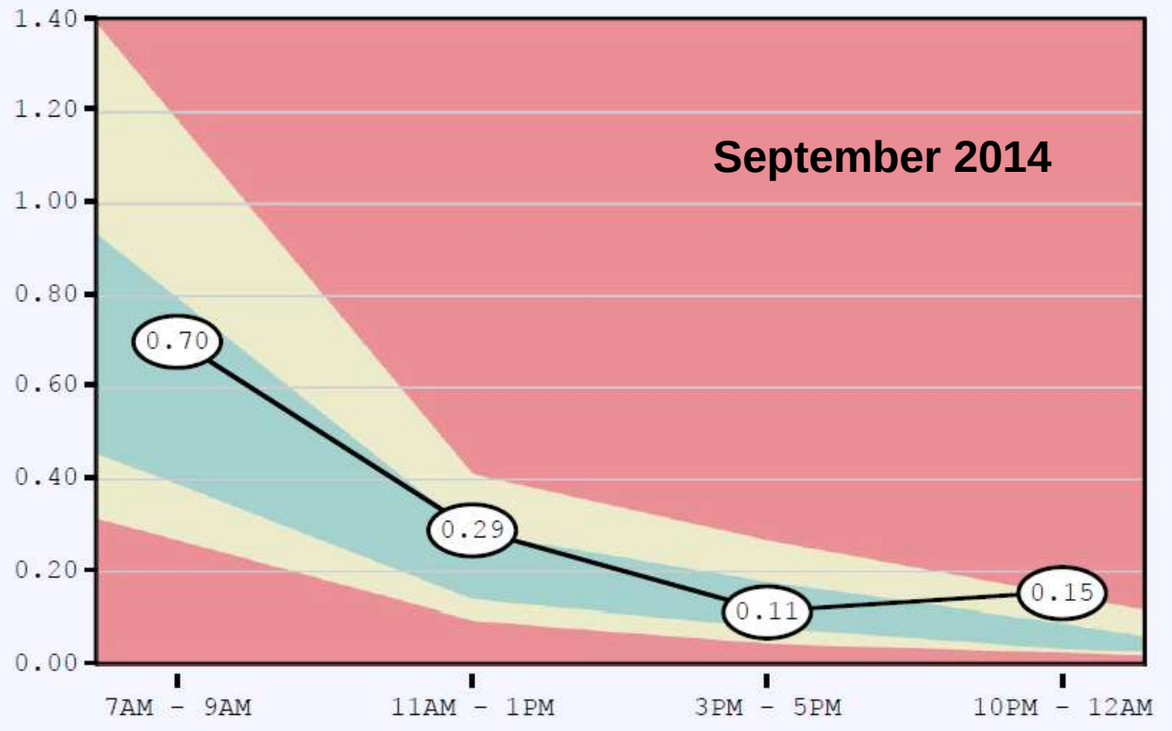
- **Surprising Result—Low Cortisol In Spite of My Stressful Life Style**
- **Hypothesis: Suboptimal Cortisol Output Reflects an Adrenal Decline or a Depleted Reserve Caused by Chronic and Protracted Exposure to Stressors**

Adrenal Glands Produce Cortisol, DHEA, and Adrenaline Coupled to Cholesterol Cycle

DHEA Continues Low

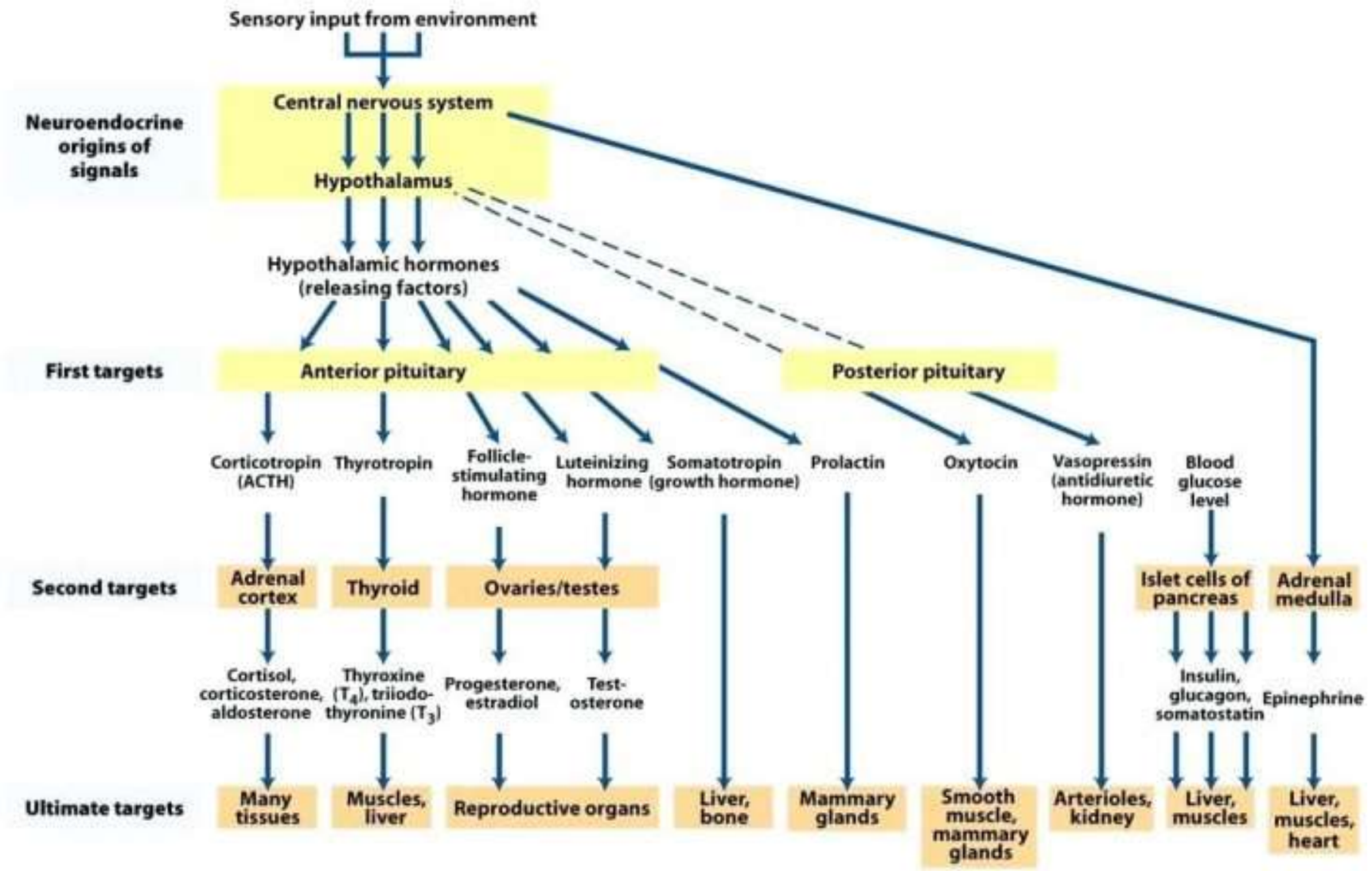


Hormone	Reference Range	Reference Range
DHEA 7am - 9am	50	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	47	115-1,188



Hormone	Reference Range	Reference Range
DHEA 7am - 9am	68	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	97	115-1,188

What Don't I Know
About My Body's Endocrine System



https://rbpaonline.com/endocrine-hormone-flow-chart/organization-endocrine-glands-system-hormone-flow-chart/

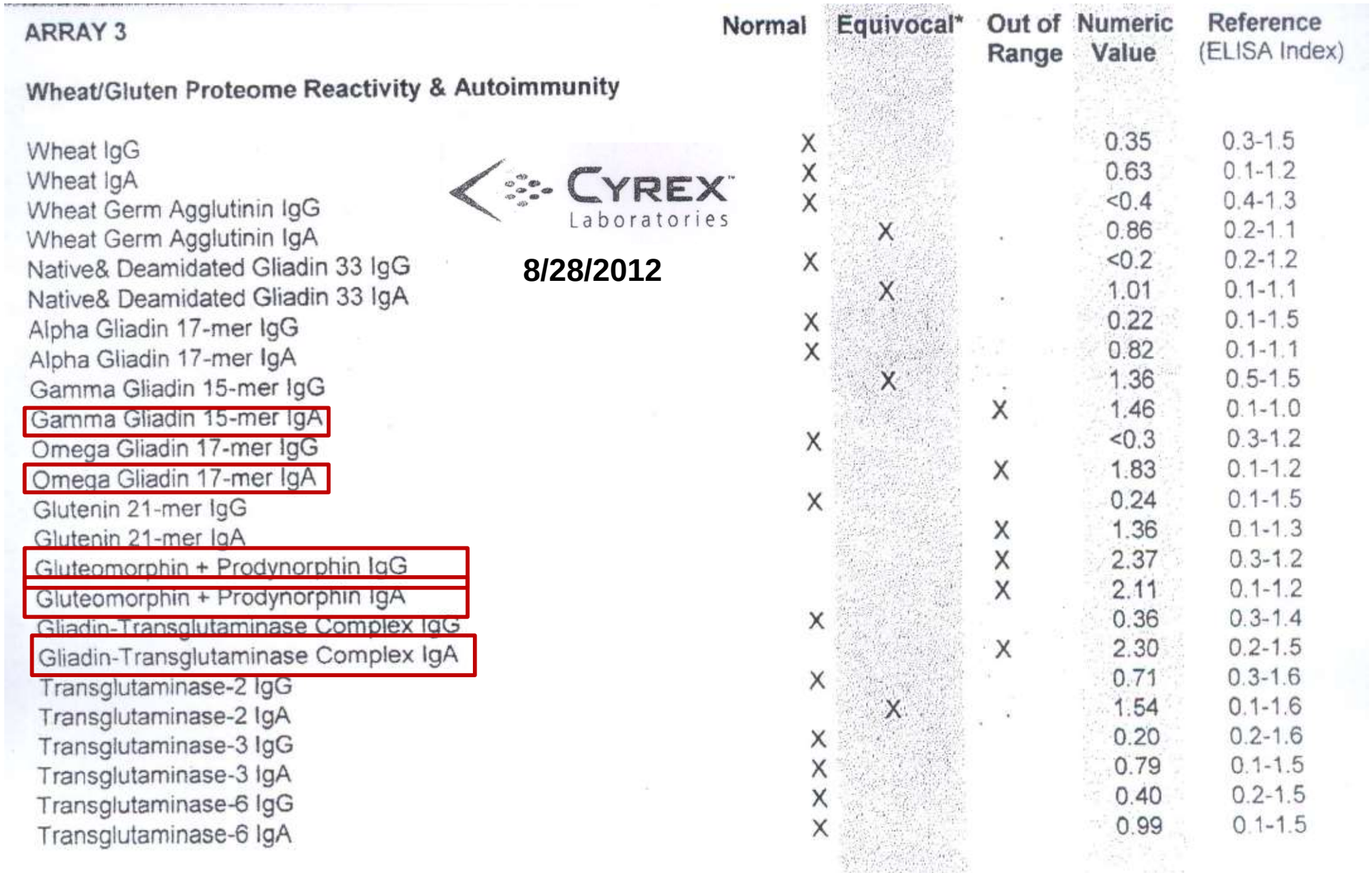
Goal: Measure My Body's Blood/Gut and Blood/Brain Permeability

Evidence of Gut Cell Lining Damage

ARRAY 2 Intestinal Antigenic Permeability Screen	Normal	Equivocal*	Out of Range	Numeric Value	Reference (ELISA Index)
Actomyosin IgA**			X	28.24	0.0-20.0
Occludin/Zonulin IgG	X			1.01	0.2-1.5
Occludin/Zonulin IgA	X			1.21	0.1-1.8
Occludin/Zonulin IgM			X	2.23	0.1-2.1
Lipopolysaccharides(LPS)IgG		X		1.26	0.1-1.6
Lipopolysaccharides(LPS)IgA			X	3.00	0.1-1.8
Lipopolysaccharides(LPS)IgM	X			0.57	0.1-2.0

CYREX Laboratories

Evidence of Gluten Intolerance



ARRAY 3

Wheat/Gluten Proteome Reactivity & Autoimmunity

CYREX Laboratories

8/28/2012

	Normal	Equivocal*	Out of Range	Numeric Value	Reference (ELISA Index)
Wheat IgG	X			0.35	0.3-1.5
Wheat IgA	X			0.63	0.1-1.2
Wheat Germ Agglutinin IgG	X			<0.4	0.4-1.3
Wheat Germ Agglutinin IgA		X		0.86	0.2-1.1
Native& Deamidated Gliadin 33 IgG	X			<0.2	0.2-1.2
Native& Deamidated Gliadin 33 IgA		X		1.01	0.1-1.1
Alpha Gliadin 17-mer IgG	X			0.22	0.1-1.5
Alpha Gliadin 17-mer IgA	X			0.82	0.1-1.1
Gamma Gliadin 15-mer IgG		X		1.36	0.5-1.5
Gamma Gliadin 15-mer IgA			X	1.46	0.1-1.0
Omega Gliadin 17-mer IgG	X			<0.3	0.3-1.2
Omega Gliadin 17-mer IgA			X	1.83	0.1-1.2
Glutenin 21-mer IgG	X			0.24	0.1-1.5
Glutenin 21-mer IgA			X	1.36	0.1-1.3
Gluteomorphin + Prodynorphin IgG			X	2.37	0.3-1.2
Gluteomorphin + Prodynorphin IgA			X	2.11	0.1-1.2
Gliadin-Transglutaminase Complex IgG	X			0.36	0.3-1.4
Gliadin-Transglutaminase Complex IgA			X	2.30	0.2-1.5
Transglutaminase-2 IgG	X			0.71	0.3-1.6
Transglutaminase-2 IgA		X		1.54	0.1-1.6
Transglutaminase-3 IgG	X			0.20	0.2-1.6
Transglutaminase-3 IgA	X			0.79	0.1-1.5
Transglutaminase-6 IgG	X			0.40	0.2-1.5
Transglutaminase-6 IgA	X			0.99	0.1-1.5

Other Foods Are Fine

ARRAY 4	Normal	Equivocal*	Out of Range	Numeric Value	REFERENCE (ELISA Index)
Gluten-Associated Cross-Reactive Foods & Foods Sensitivity**					
Rye,Barley,Spelt,Polish Wheat	X			<0.4	0.4-1.4
Cow's Milk	X			0.23	0.1-1.3
Casein (Alpha & Beta)	X			0.14	0.1-1.2
Casomorphin	X			0.48	0.2-1.6
Milk Butyrophilin	X			0.43	0.1-1.3
Whey Protein	X			0.16	0.1-1.3
Chocolate (Milk)	X			0.13	0.1-1.4
Oats	X			0.24	0.2-1.0
Yeast	X			0.39	0.2-1.2
Coffee	X			0.47	0.2-1.2
Sesame	X			0.95	0.1-1.3
Buckwheat	X			<0.4	0.4-1.5
Sorghum	X			<0.3	0.3-1.2
Millet	X			0.44	0.3-1.5
Hemp	X			0.77	0.3-1.5
Amaranth	X			0.29	0.2-1.3
Quinoa	X			<0.5	0.5-1.5
Tapioca	X			0.46	0.1-1.1
Teff	X			0.66	0.2-1.1
Soy	X			<0.5	0.5-1.5
Egg	X			0.55	0.2-1.7
Corn	X			0.30	0.3-1.4
Rice	X			1.13	0.4-1.6
Potato	X			<0.6	0.6-1.4

** All analytes are tested for IgG and IgA combined.

We Can Grow My Gut in a Dish



Pradipta Ghosh

thisweek@ucsandiego

By Judy Piercey and Alicia Clarke | May 09, 2019 | Subscribe

Helmsley Charitable Trust Grants UC San Diego $4.7M to Study Crohn's Disease

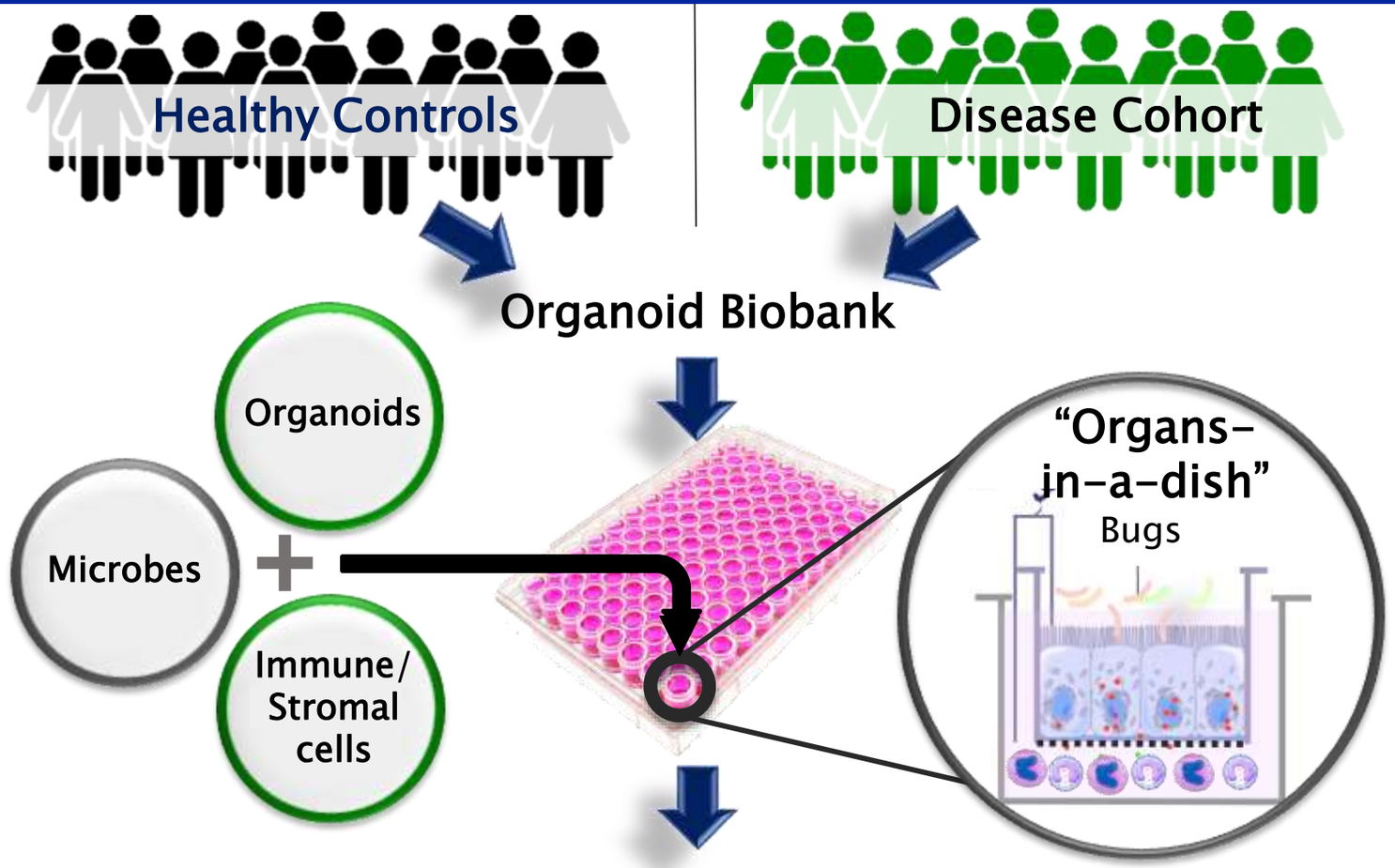
Two grants aim to advance more personalized treatments for patients

HUMANOID™

Human Organoid-based Center of Research Excellence (CoRE)

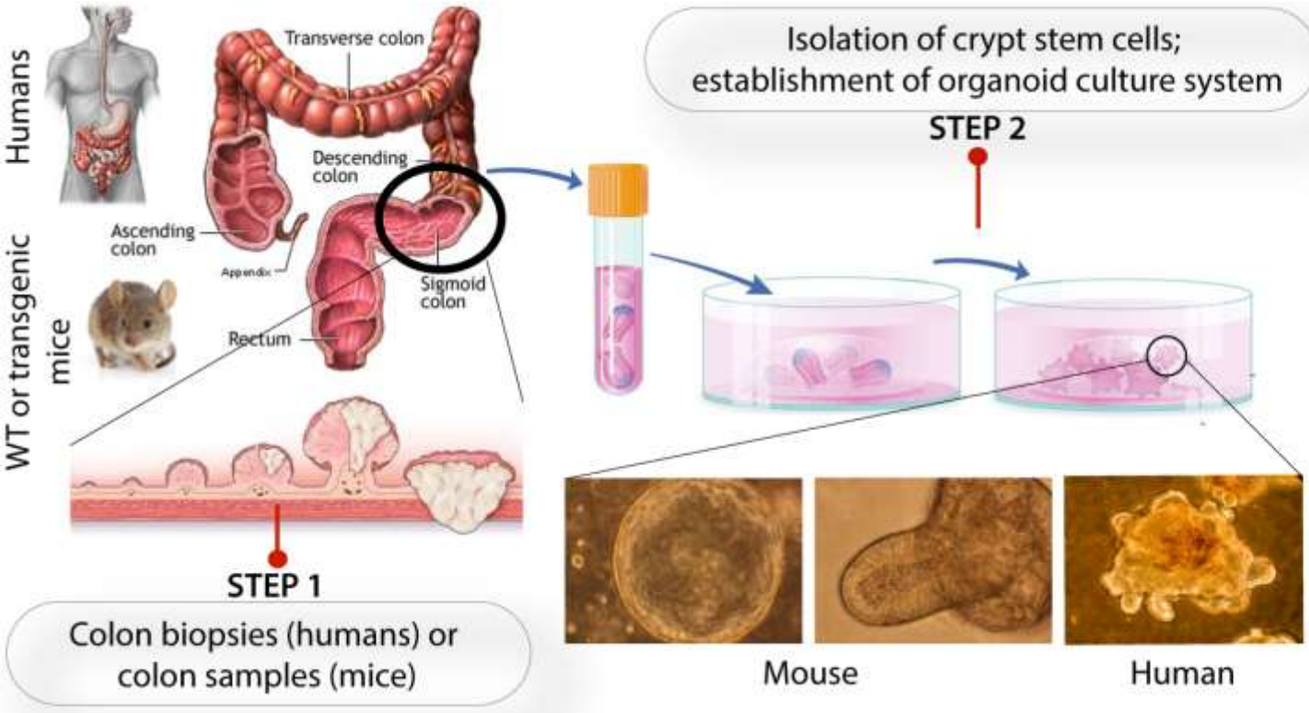
Creating an Organoid

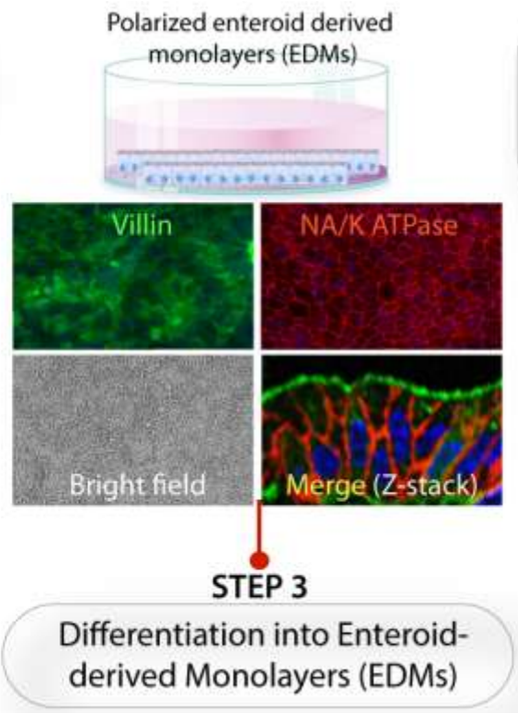
The stem cells will be derived from intestinal biopsies of patients with the disease and used to reverse-engineer the gut lining.
The model will encompass the microbes, immune cells and other complex cell types found in the gut.

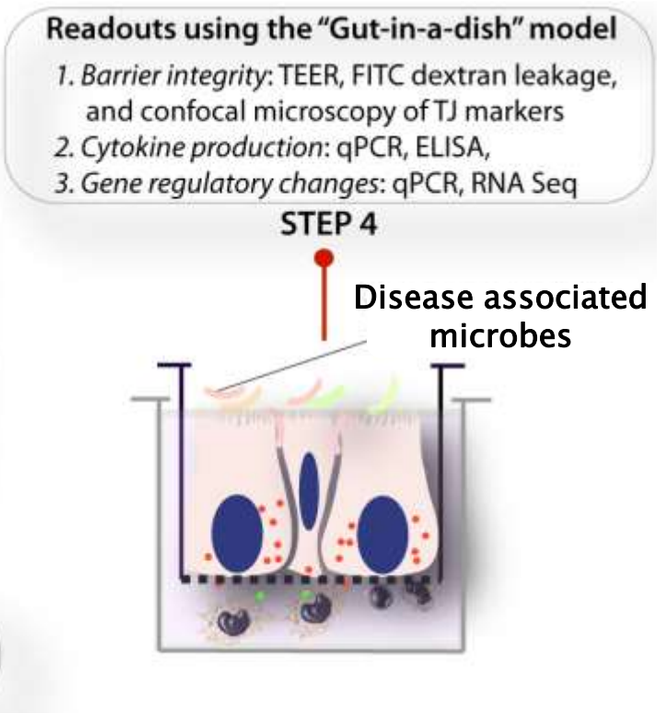


HUMANOID™
Human Organoid-based Center of Research Excellence (CoRE)

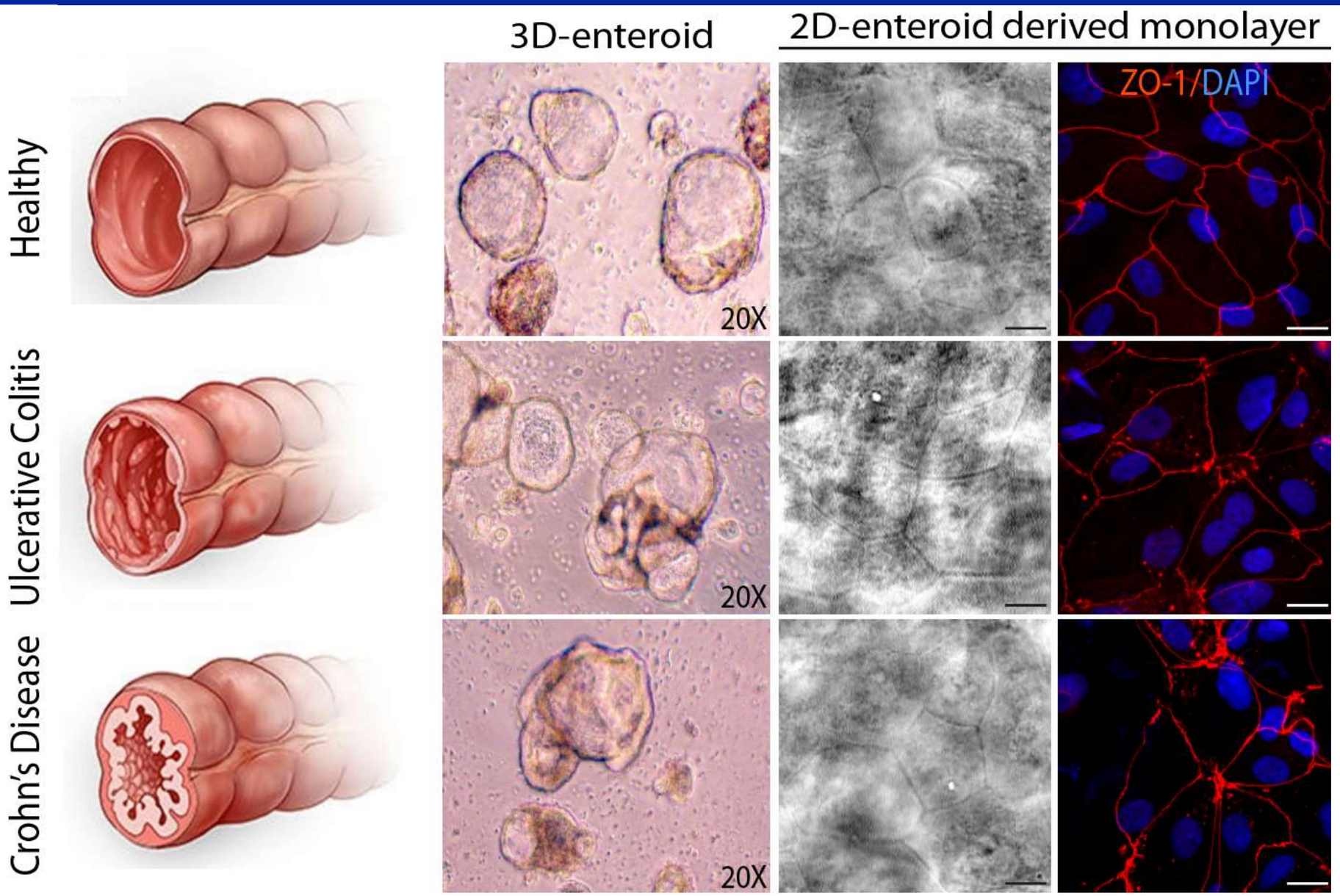
We Plan to Create a Smarrganoid From A Colonoscopy Biopsy This Year

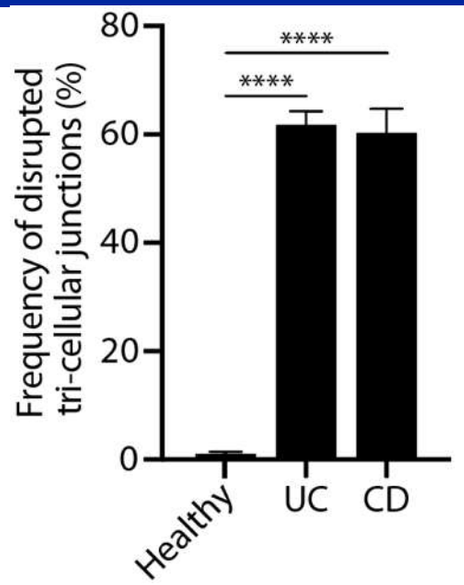


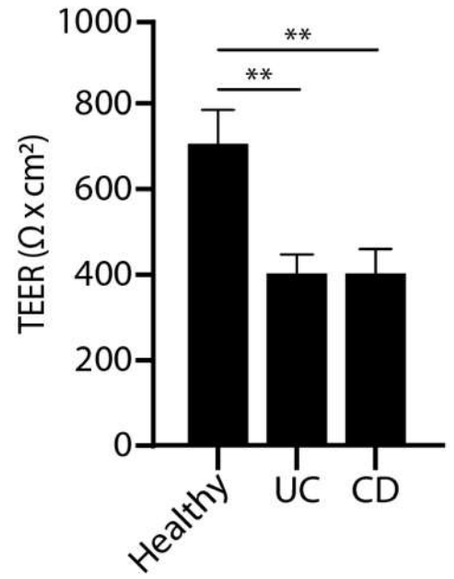




Enteroid Monolayers From IBD Patients are Leaky







What Don’t I Know
About My Gut’s Permeability

- **Leaky Gut Tests**
- **Food absorption**
- **Oxidative Stress**
- **Immunology Panel**
- **Blood Stool Metabolomics**

Goal: What Foods and Supplements Will Optimize an Individuals Health?

Goal: Quantify Your Food Intake So You Can "Tune" Your Glucose/Insulin System and Lower Inflammation

Computed Average Over 12 Days When at Home for Maximum Accuracy
Measure All Food and Drink Components,
Then Use USDA Lookup to Compute Each Item

calories	fat	carb	protein		fiber	sugar	sodium
kcal	g	g	g		g	g	mg
1441	46	122	80	0	26	53	1358

Still Need to Lower Sugar &
Increase Protein and Decrease Fat by 15%

- **Quality of Food**
  - **All Organic and Mostly Locally Grown**
  - **Carbs are Low Glycemic Index**
    - **No Added Sugar or Refined Flour – Mostly Fruits and Vegetables**
  - **Proteins are Lean**
    - **Meat is Grass Fed – No Corn or Antibiotics**
    - **Fish is Wild, Often Locally Caught**
  - **Fats are Omega-3 Rich**
    - **Supplemented by 7g Daily Pharmaceutically Purified Fish Oil Pills**

I Have Used Metagenics Products For Over a Decade

Ultra Inflammatory X360
Aug 12, 2008

I Need To Tune My Supplements and Green Smoothies

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

KNIGHTLAB

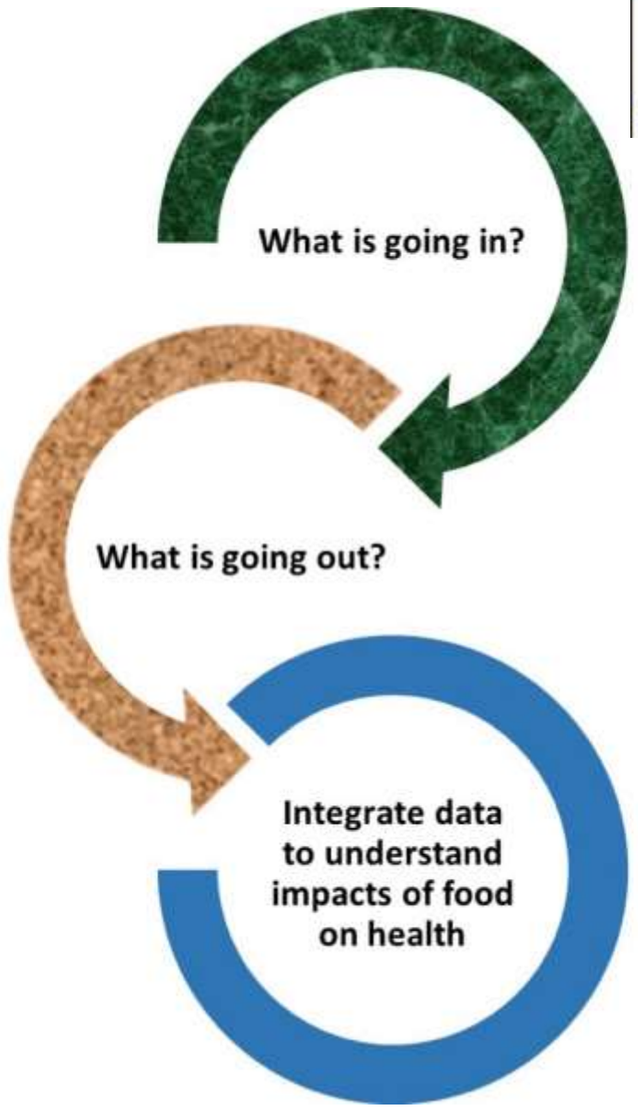
UC San Diego

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

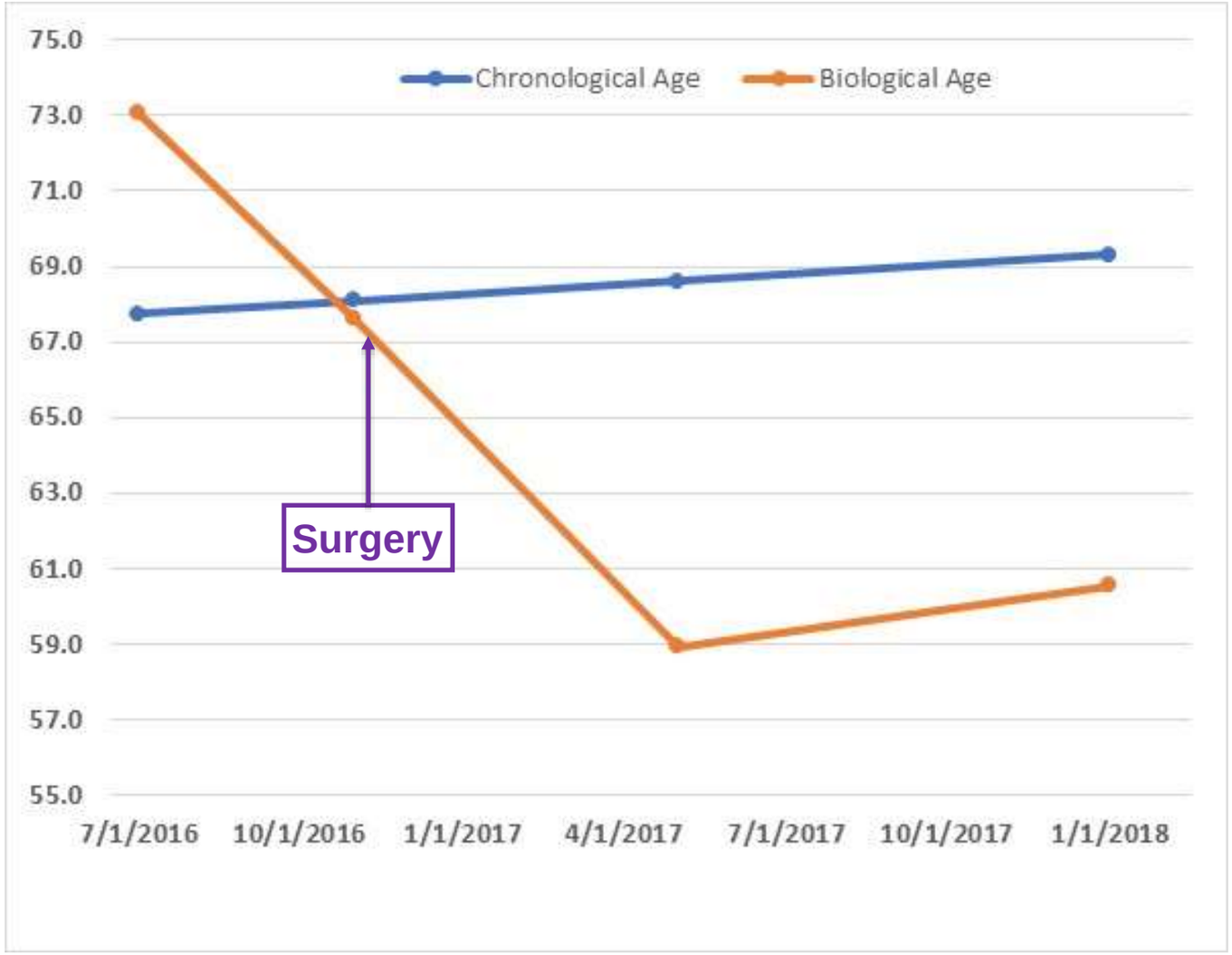
THE DUTTON LAB @ UCSD

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

Blood Tests I Do Quarterly to Annually
In Addition to hsCRP, Lipids, Minerals, & Omegas

- **Electrolytes**
  - **Sodium, Potassium, Chlorine, CO_2**
- **Blood Sugar Cycle**
  - **Glucose, Insulin, A1C Hemoglobin**
- **Bones**
  - **Alkaline Phosphatase**
- **Kidneys**
  - **Bun, Creatinine, Uric Acid**
- **Protein**
  - **Total Protein, Albumin, Globulin**
- **Liver**
  - **GGTP, SGOT, SGPT, LDH, Total and Direct Bilirubin**
- **Thyroid**
  - **T3 Uptake, T4, Free Thyroxine Index, FT4, 2nd Gen TSH**
- **Heart**
  - **Homocysteine**
- **Blood Cells**
  - **Complete Blood Cell Count**
  - **Red Blood Cell Subtypes**
  - **White Blood Cell Subtypes**
- **Cancer Screen**
  - **CEA, Total PSA, % Free PSA**
  - **CA-19-9**
- **Vitamins & Antioxidant Screen**
  - **Vit D, E; Selenium, ALA, coQ10, Glutathione, Total Antioxidant Fn.**
- **Others**
  - **Ferritin**
  - **Progesterone**
  - **Testosterone, Total and Free**
  - **FSH**
  - **Estradiol**

By Tuning My Body
I Seem to Be Aging Backwards



Analysis by John Earls, Institute for Systems Biology, Seattle, WA

Thanks to Our Great Team!

Calit2@UCSD
Future Patient Team

Joel Polizzi
Isaac Nealey
Jurgen Schulze
Tom DeFanti
Andrew Prudhomme
Philip Weber
Fred Raab
Jerry Sheehan
Kevin Patrick
Joe Keefe
Ernesto Ramirez



UCSD Health Sciences Team

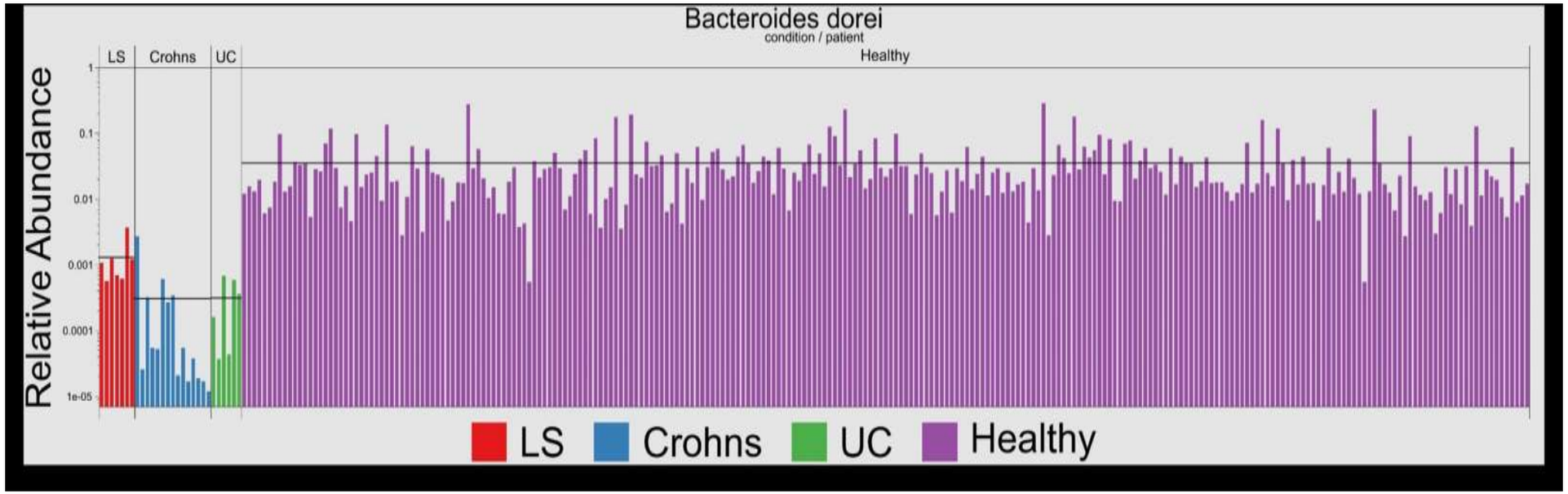
David Brenner, Dean
Rob Knight Lab
William J. Sandborn Lab
Bernhard Palsson Lab
Pieter Dorrestein Lab
Sonia Ramamoorthy
Radiology Department
Mike Kurisu/Hollis King DOs

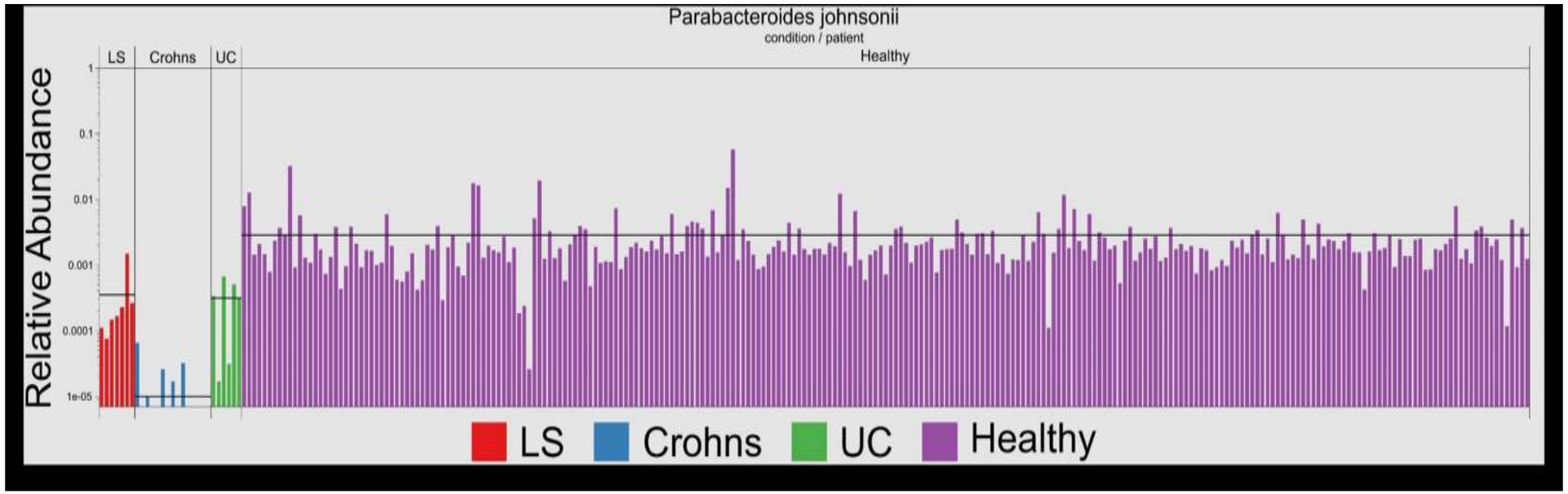
Osteopathic Center San Diego

Mike Kurisu/Hollis King DOs

Extra Slides

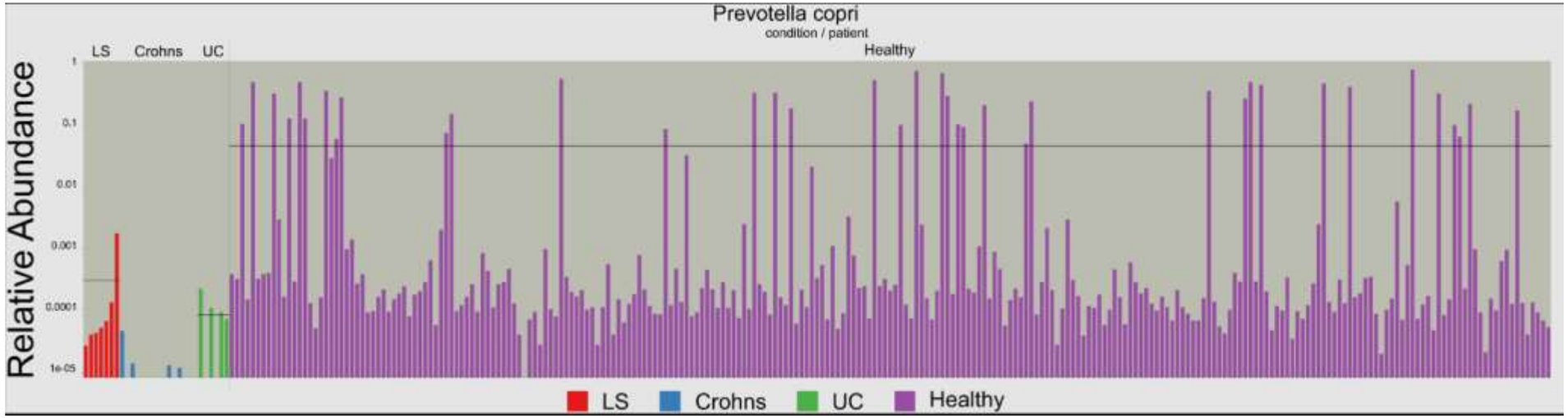
Can Microbial Metagenomics Diagnose Disease States? Some Species Can Differentiate IBD vs. Healthy Subjects





There is a Bimodal Distribution of Healthy People with High and Low Prevotella copri Relative Abundance

Ratio of High to Low Relative Abundance
Is 100-1000x!



CLINICAL AND TRANSLATIONAL REPORT

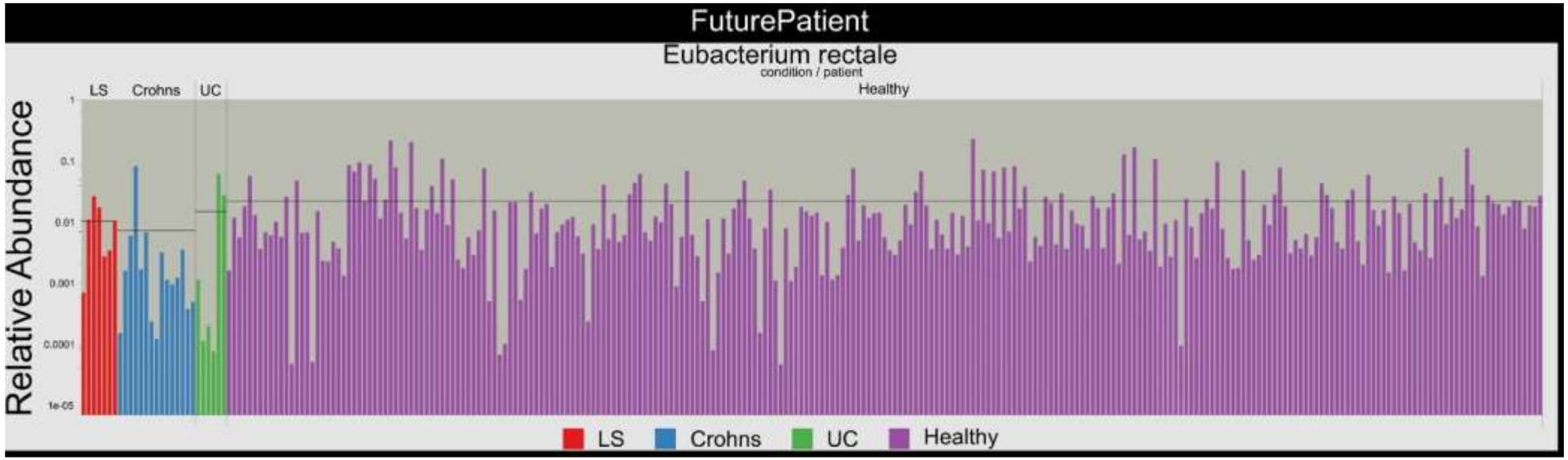
Cell Metabolism

Dietary Fiber-Induced Improvement in Glucose Metabolism Is Associated with Increased Abundance of *Prevotella*

Petia Kovatcheva-Datchary, Anne Nilsson, Rozita Akrami, Ying Shiuan Lee, Filipe De Vadder, Tulika Arora, Anna Hallen, Eric Martens, Inger Björck, Fredrik Bäckhed

Published Online: November 06, 2015

Eubacterium rectale,
A Firmicute Butyrate Producer



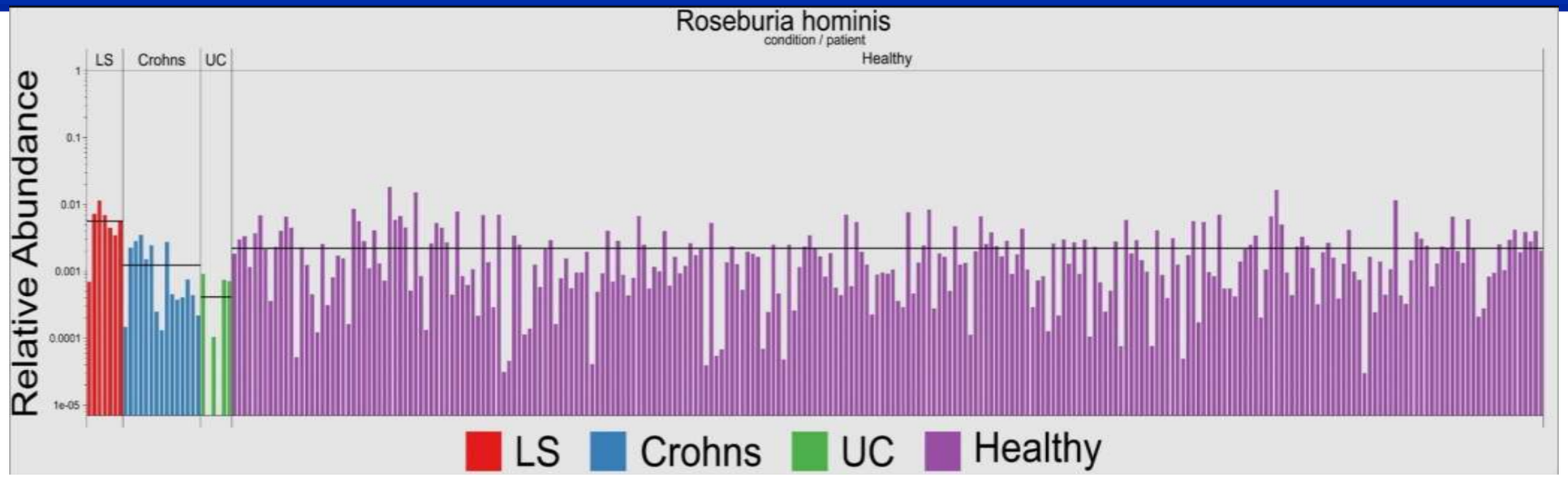
**"Human colonic butyrate producers are Gram-positive Firmicutes,
but are phylogenetically diverse,
with the two most abundant groups related to
Eubacterium rectale/Roseburia spp. and to Faecalibacterium prausnitzii."**

Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine

Petra Louis & Harry J. Flint

Trends in Microbiology 2012

Ulcerative Colitis Patients Seem to Have Reduced Abundance of *Roseburia hominis*

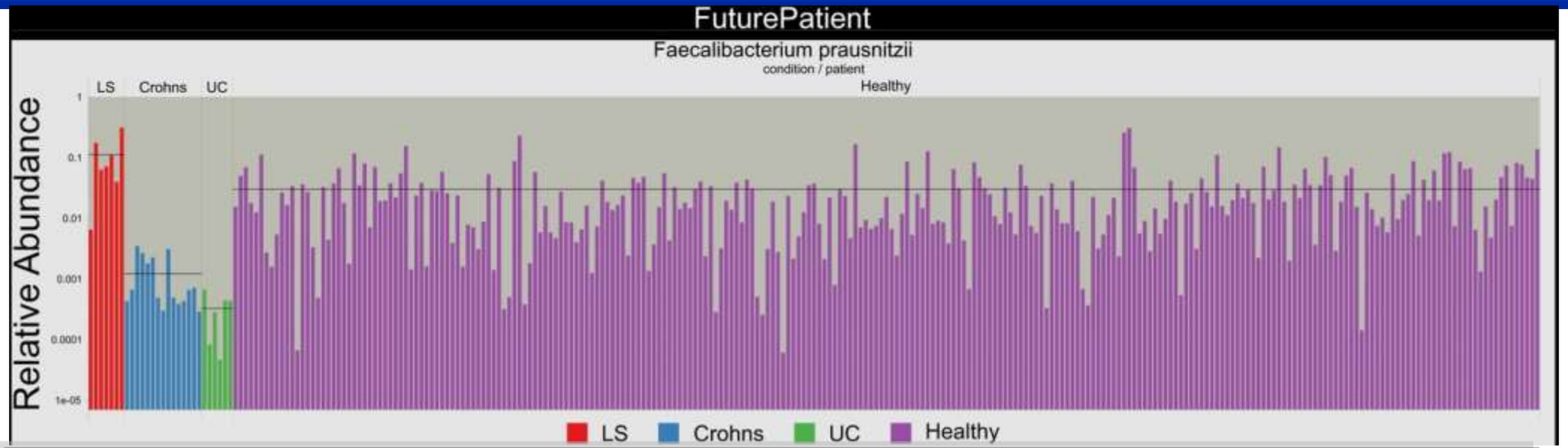


A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis

Gut, 2013

Kathleen Machiels,[1] Marie Joossens,[2,3] João Sabino,[1] Vicky De Preter,[4] Ingrid Arijs,[1] Venessa Eeckhaut,[5] Vera Ballet,[1] Karolien Claes,[1] Filip Van Immerseel,[5] Kristin Verbeke,[4] Marc Ferrante,[1] Jan Verhaegen,[6] Paul Rutgeerts,[1] Séverine Vermeire[1]

Ileal Crohn's and UC Patients Have Reduced Abundance of Anti-Inflammatory *Faecalibacterium prausnitzii*



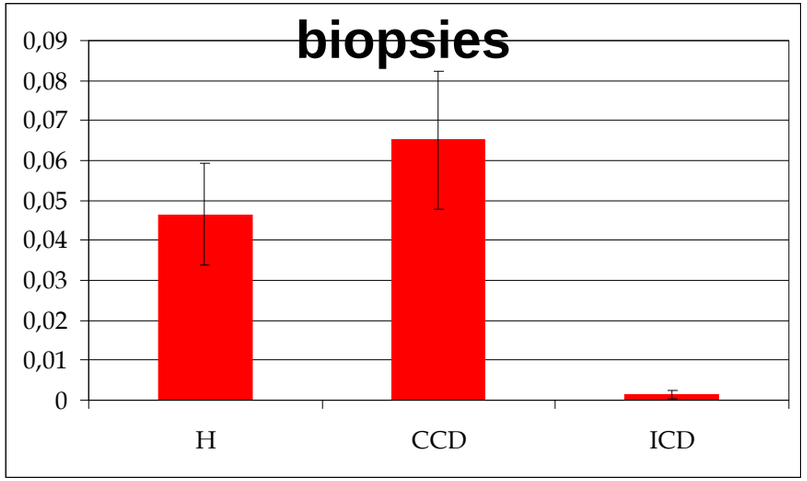
Decreased abundance of *Faecalibacterium prausnitzii* in the gut microbiota of Crohn's disease

Journal of Gastroenterology and Hepatology **28** (2013) 613–619

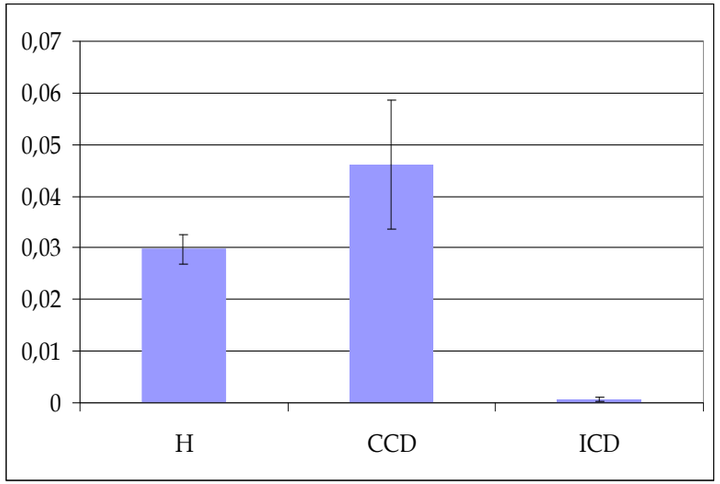
Takehide Fujimoto,* Hirotsugu Imaeda,† Kenichiro Takahashi,* Eiji Kasumi,* Shigeki Bamba,* Yoshihide Fujiyama† and Akira Andoh*

Faecalibacterium depleted in Ileal CD

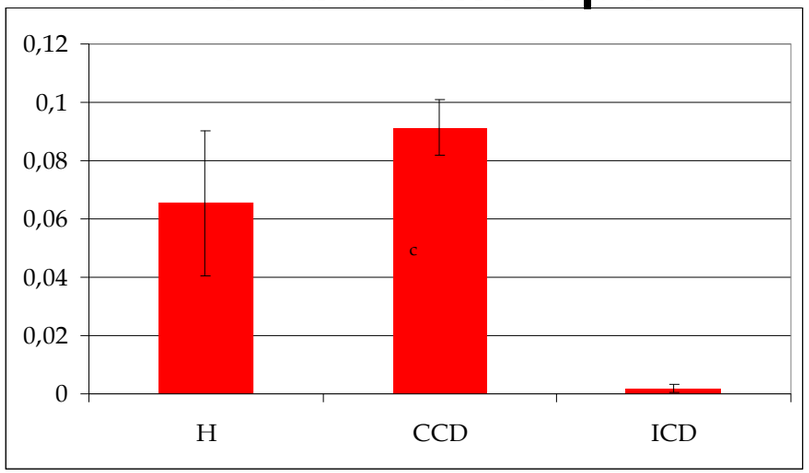
ileum biopsies



feces



distal colon biopsies



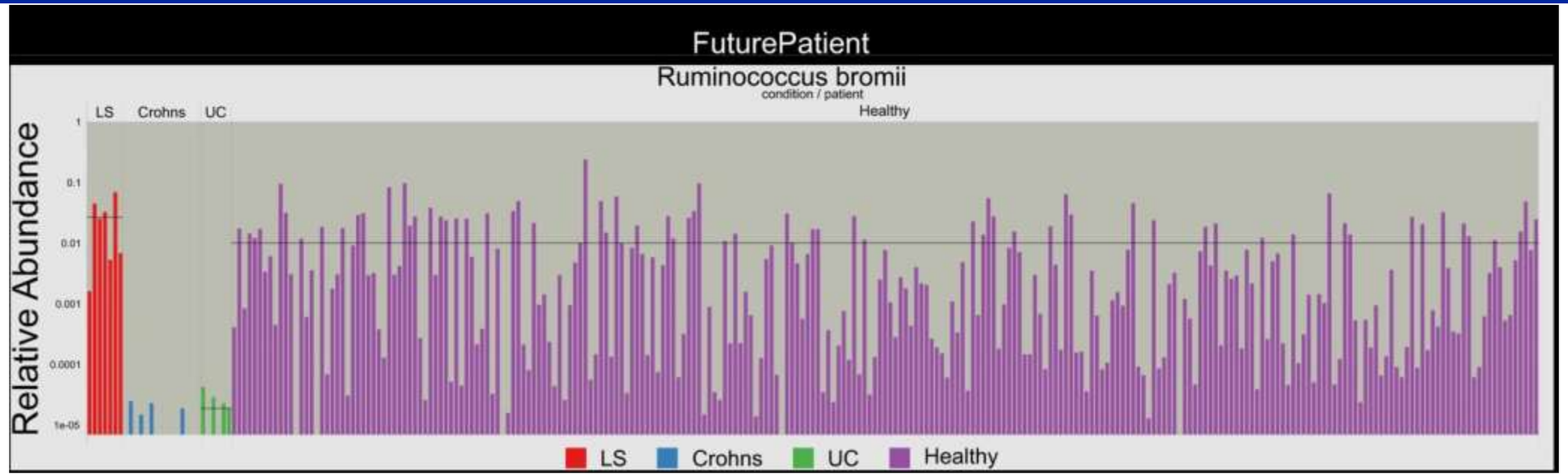
Willing et al., 2009.Inflammatory Bowel Diseases

Faecalibacterium prausnitzii

One of the main producers of butyrate Important for colonic health.

Slide from Janet Jansson, PNNL

Absence of Ruminococcus bromii May Impair Fermentation in IBD Patients



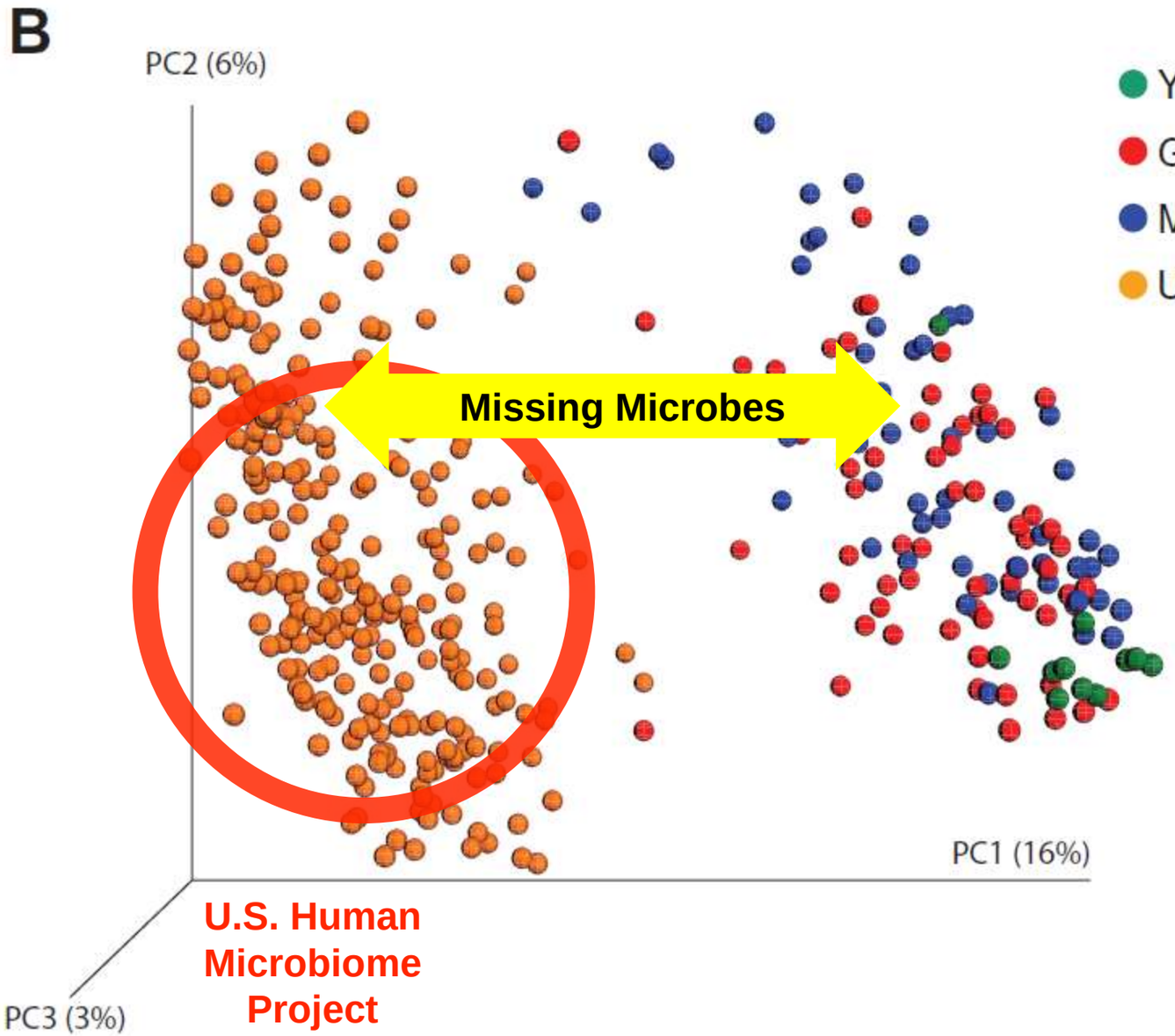
ISME J. 2012 Aug;6(8):1535-43. doi: 10.1038/ismej.2012.4. Epub 2012 Feb 16.

Ruminococcus bromii is a keystone species for the degradation of resistant starch in the human colon.

Ze X[1], Duncan SH, Louis P, Flint HJ.

"This argues strongly that R. bromii has a pivotal role in fermentation of [resistant starch] RS3 in the human large intestine, and that **variation in the occurrence of this species and its close relatives may be a primary cause of variable energy recovery** from this important component of the diet."

The United States Population's Human Gut Microbiome Has Diverged a Great Deal from Hunter-Gatherers



[Amerindians in Venezuela/Columbia]

[Africa]



"The microbiome of uncontacted Amerindians," J. C. Clemente, et al. Science Advances 1, e1500183 (2015).

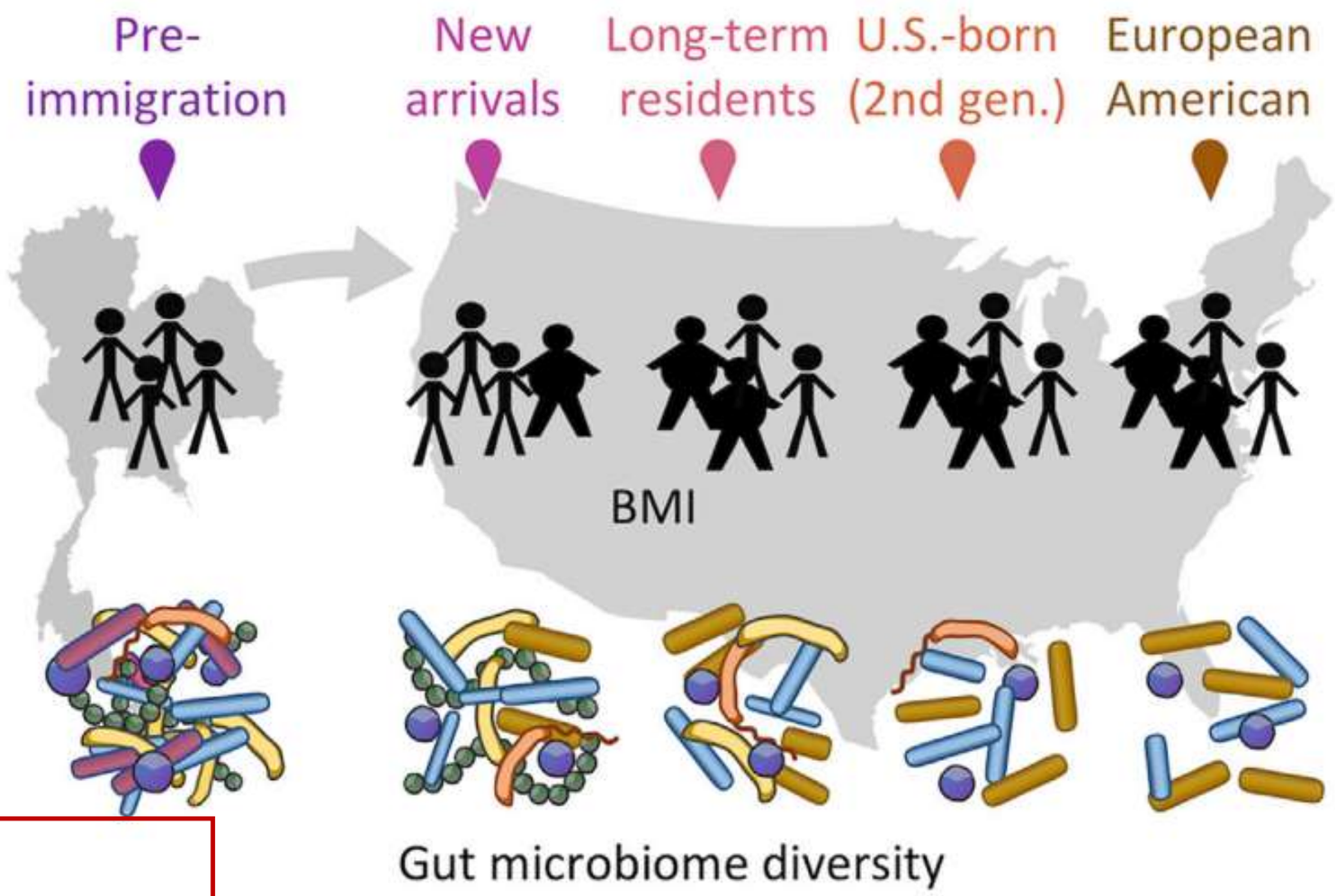
The “Western Diet” Seems to Increase Obesity and Reduce the Gut Microbiome Ecological Diversity

Cell

US Immigration Westernizes the Human Gut Microbiome

Pajau Vangay, …, Dan Knights

Cell *175*, 962–972, November 1, 2018



Highlights:

- **Loss of diversity increases with obesity**
- **US immigrants lose microbial plant fiber degradation**

Growing Evidence That Widely Used Artificial Food Additives Can Contribute to Obesity and Glucose Intolerance

nature
International journal of science
9 OCTOBER 2014 | VOL 514 | NATURE | 181

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

NATURE | NEWS

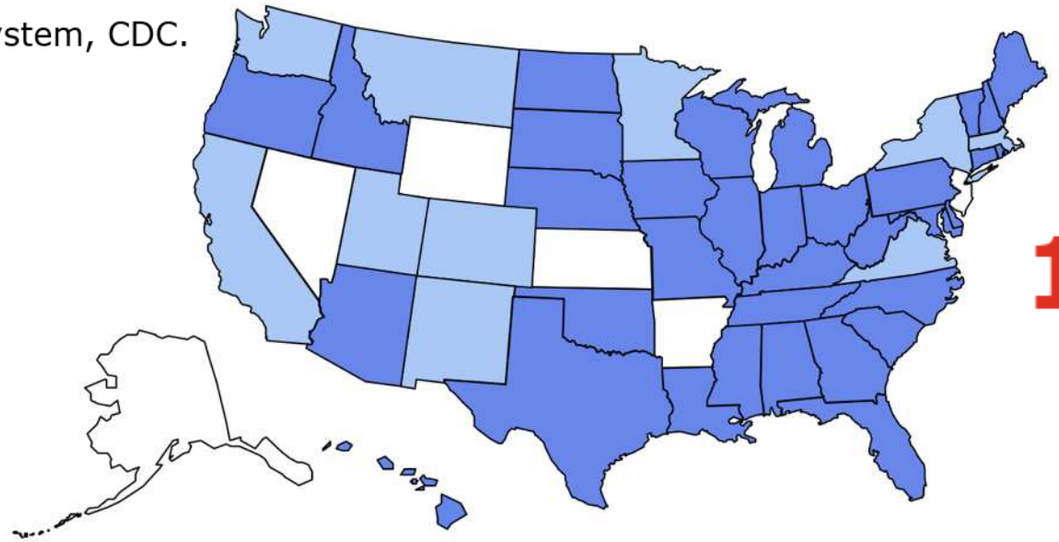
nature
International journal of science

Food preservatives linked to obesity and gut disease

Sara Reardon **February 25, 2015**

Could the Gut Microbiome Ecology Changes Shed New Light On The Obesity/Metabolic Syndrome Public Health Emergency?

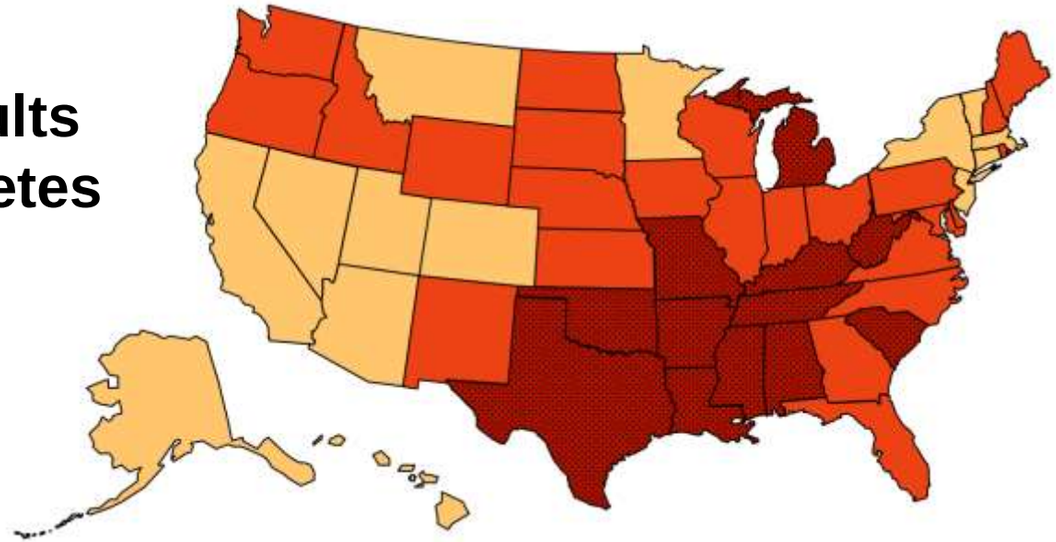
Source: Behavioral Risk Factor Surveillance System, CDC.



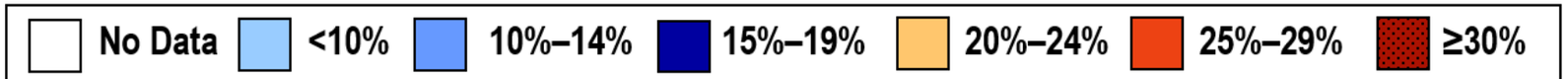
1990

% Obese
BMI ≥30

100 Million American Adults Have Diabetes or Prediabetes - CDC 2017



2010



Evidence is Mounting That There Is a Lean and an Obese Gut Microbiome

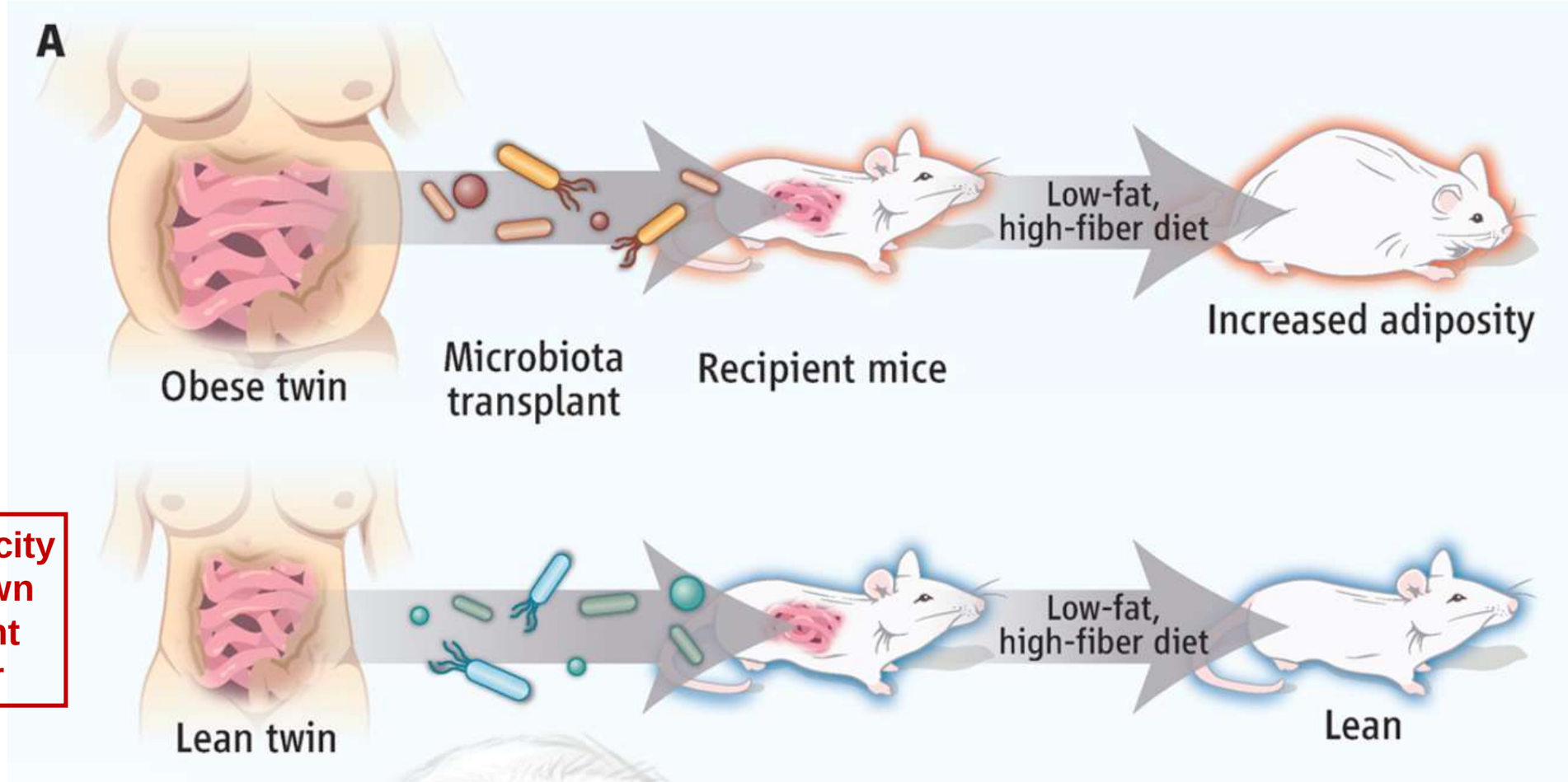
Science

PERSPECTIVE MICROBIOLOGY

Fighting Obesity with Bacteria

Alan W. Walker & Julian Parkhill

September 6, 2013



greater capacity to breakdown and ferment plant fiber

Are Changes in Our Microbiome Ecology Driving The Multi-Decadal Increase In Autoimmune and Other Non-Communicable Diseases?

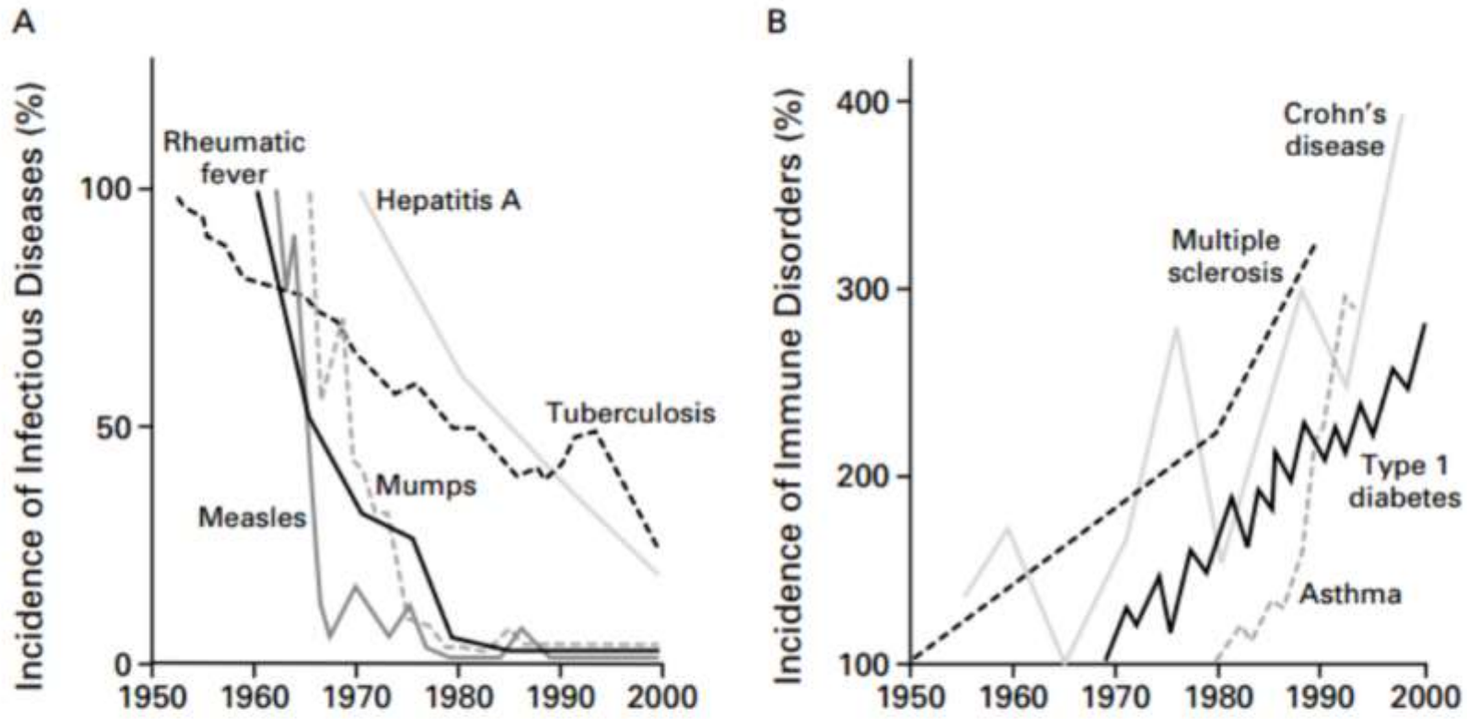
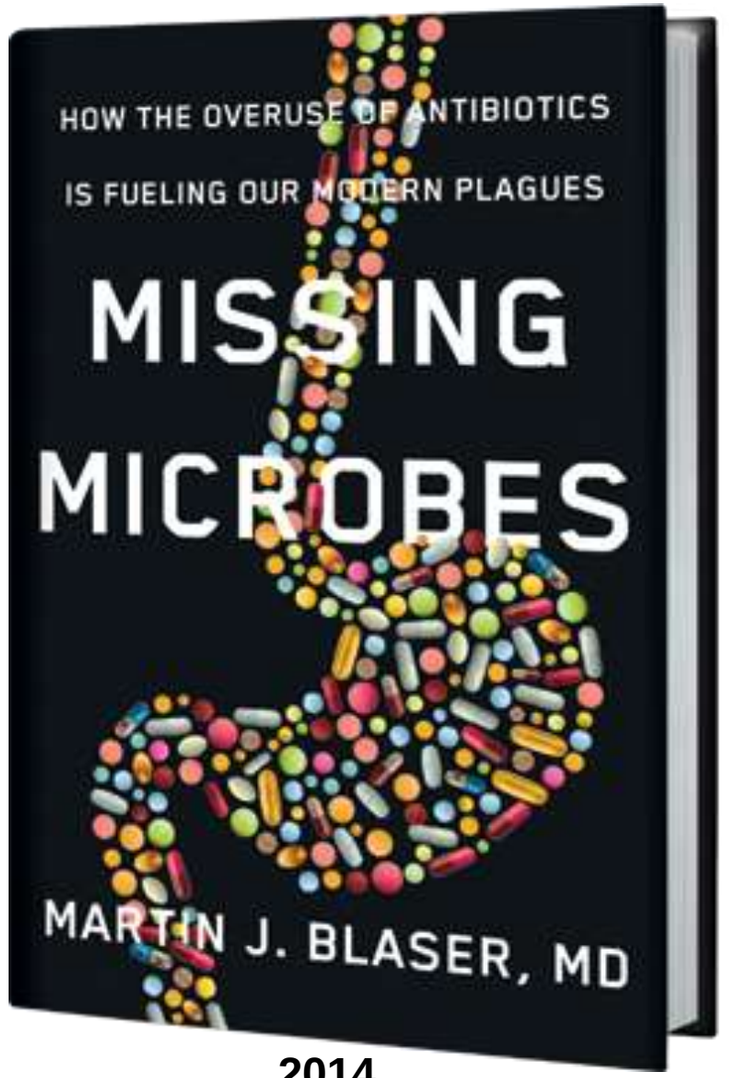


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

Bach (2002) N Engl J Med, Vol. 347, 911-920

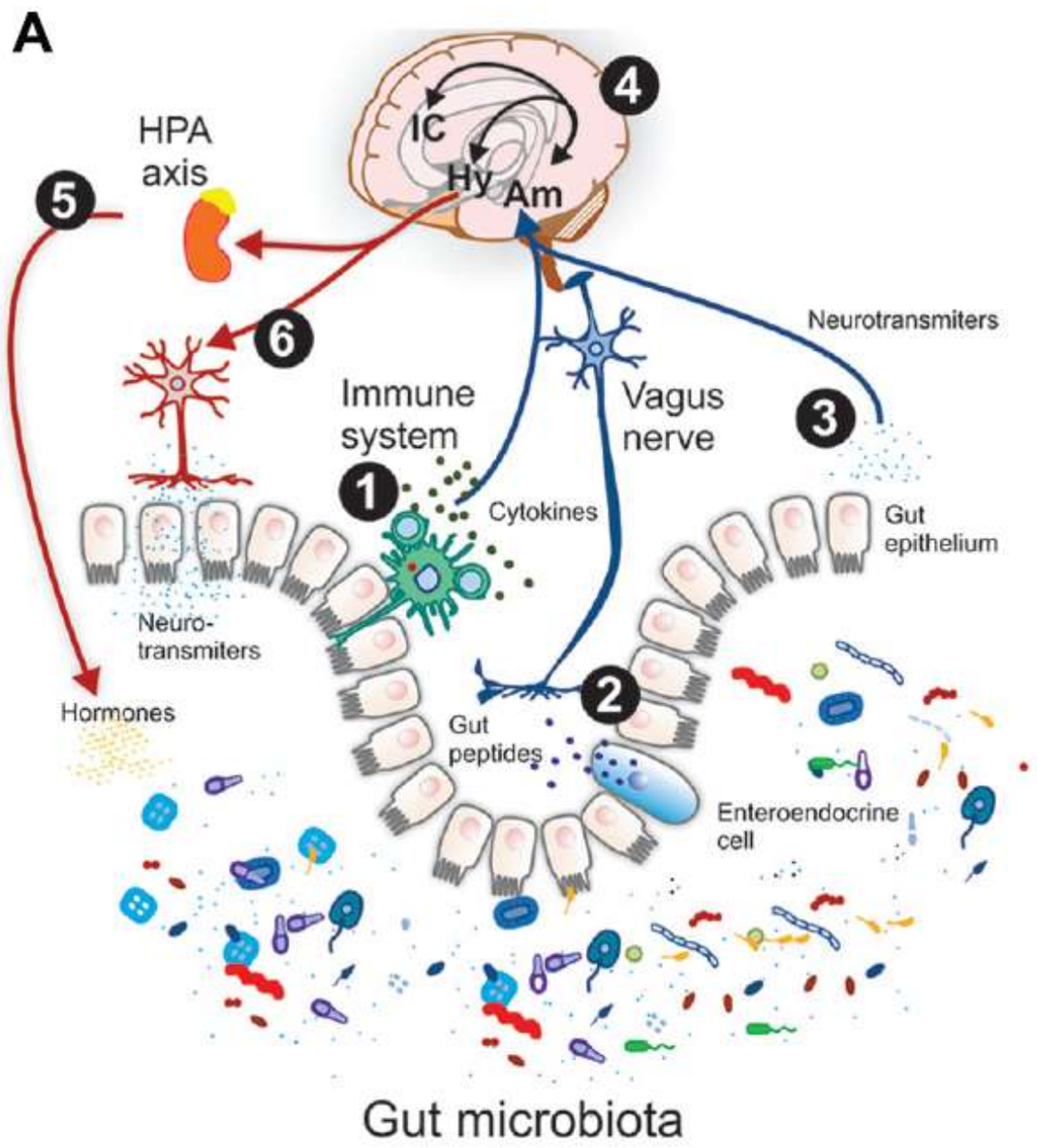


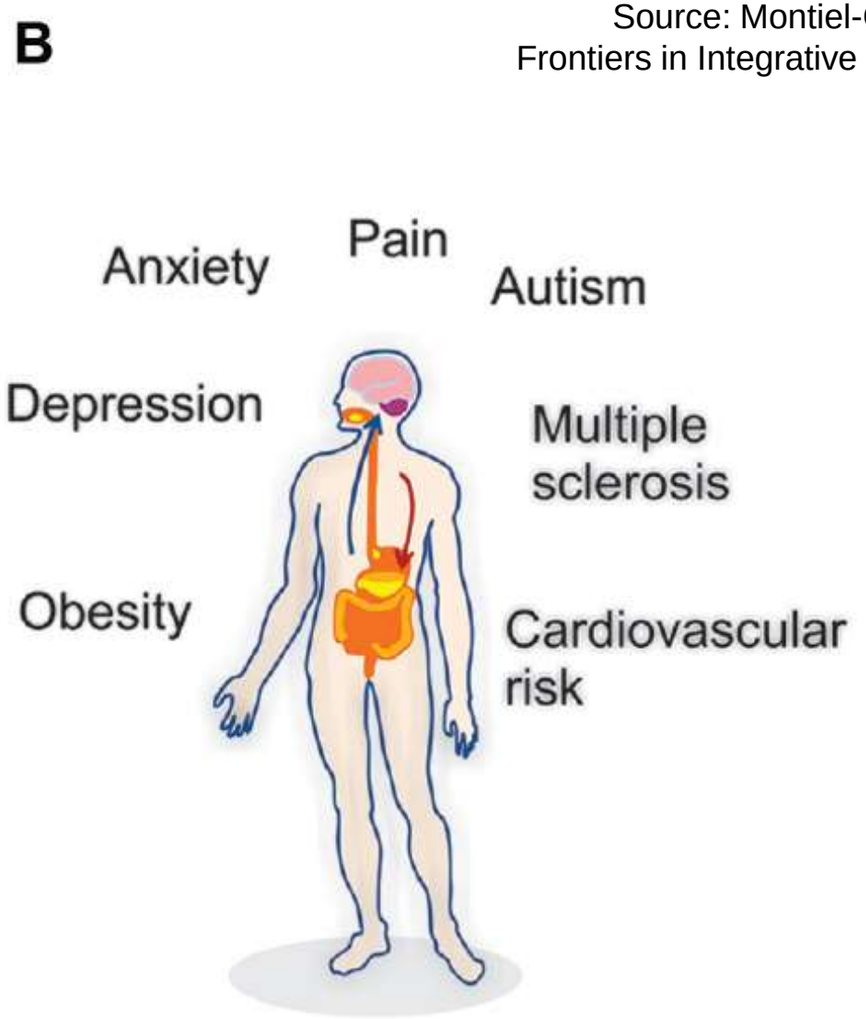
2014

Blaser Served as President of the Infectious Diseases Society of America and is a Member of the National Academy of Medicine

The Microbiome–Gut–Brain Axis Connects Altered Microbiome Ecology To Shifts in Behavior and Disease Throughout the Body

Source: Montiel-Castro, et al.
Frontiers in Integrative Neuroscience 2013



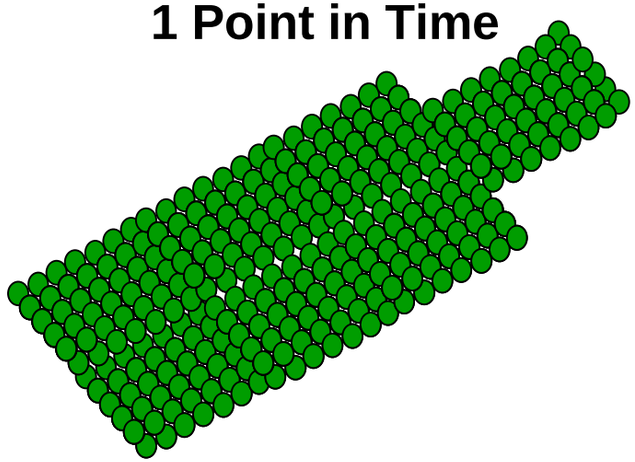


We Gathered Raw Illumina Reads on 275 Humans and Generated a Time Series of My Gut Microbiome

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

"Healthy" Individuals

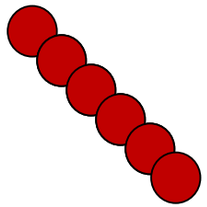
250 Subjects
1 Point in Time



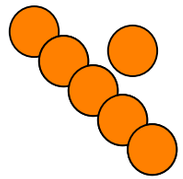
Inflammatory Bowel Disease (IBD) Patients

Larry Smarr
(Colonic Crohn's)

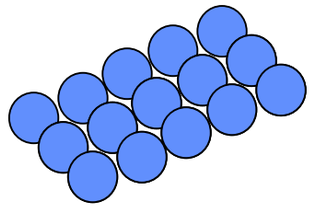
7 Points in Time



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 Time Series, IBD Patients, & Healthy Controls

Illumina HiSeq 2000 at JCVI



SDSC Gordon Data Supercomputer



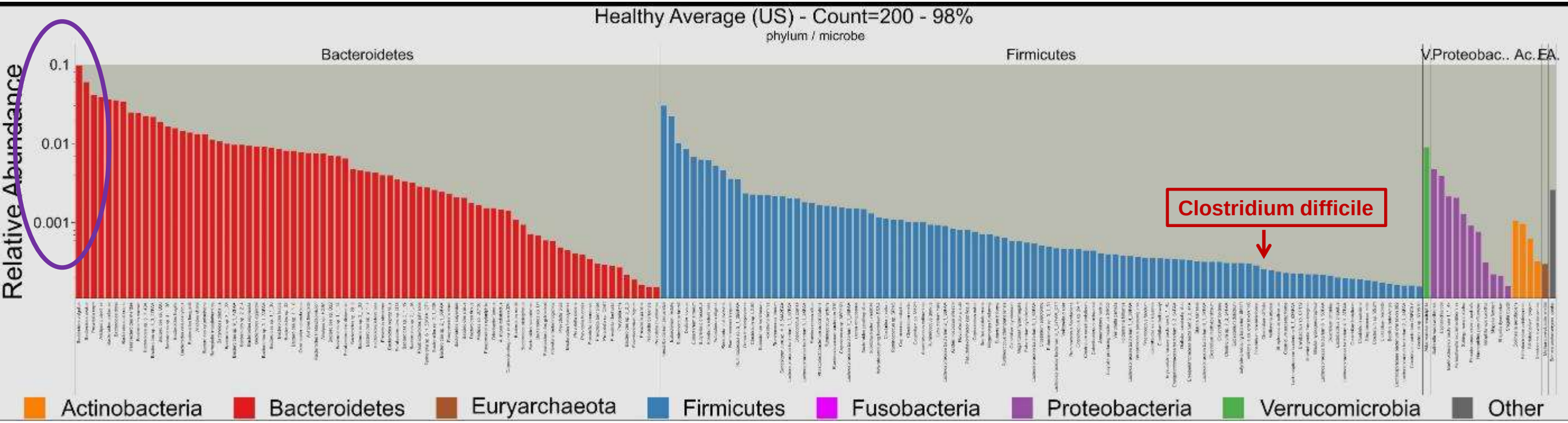
Dell Solutions Center
Industry Solutions Lab
SANGER DSU

J. Craig Venter INSTITUTE · SDSC · DELL · NIH · HMP · CRBS · it²

Results Include Relative Abundance of Hundreds of Microbial Species

Average Over 250 Healthy People
From NIH Human Microbiome Project

Note Log Scale



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

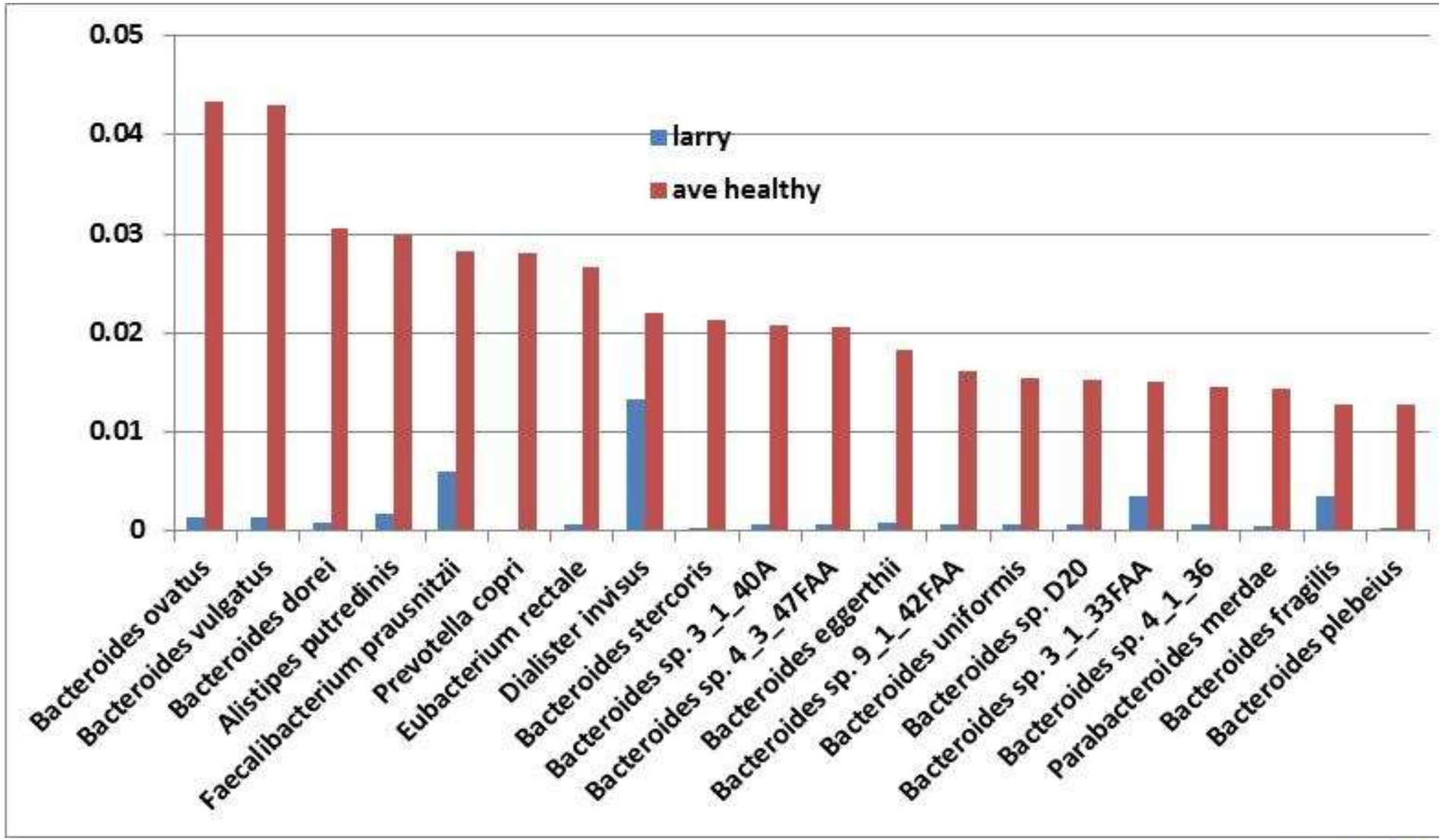


”In many areas following these burns invasive species are able to establish themselves, crowding out native species.”

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

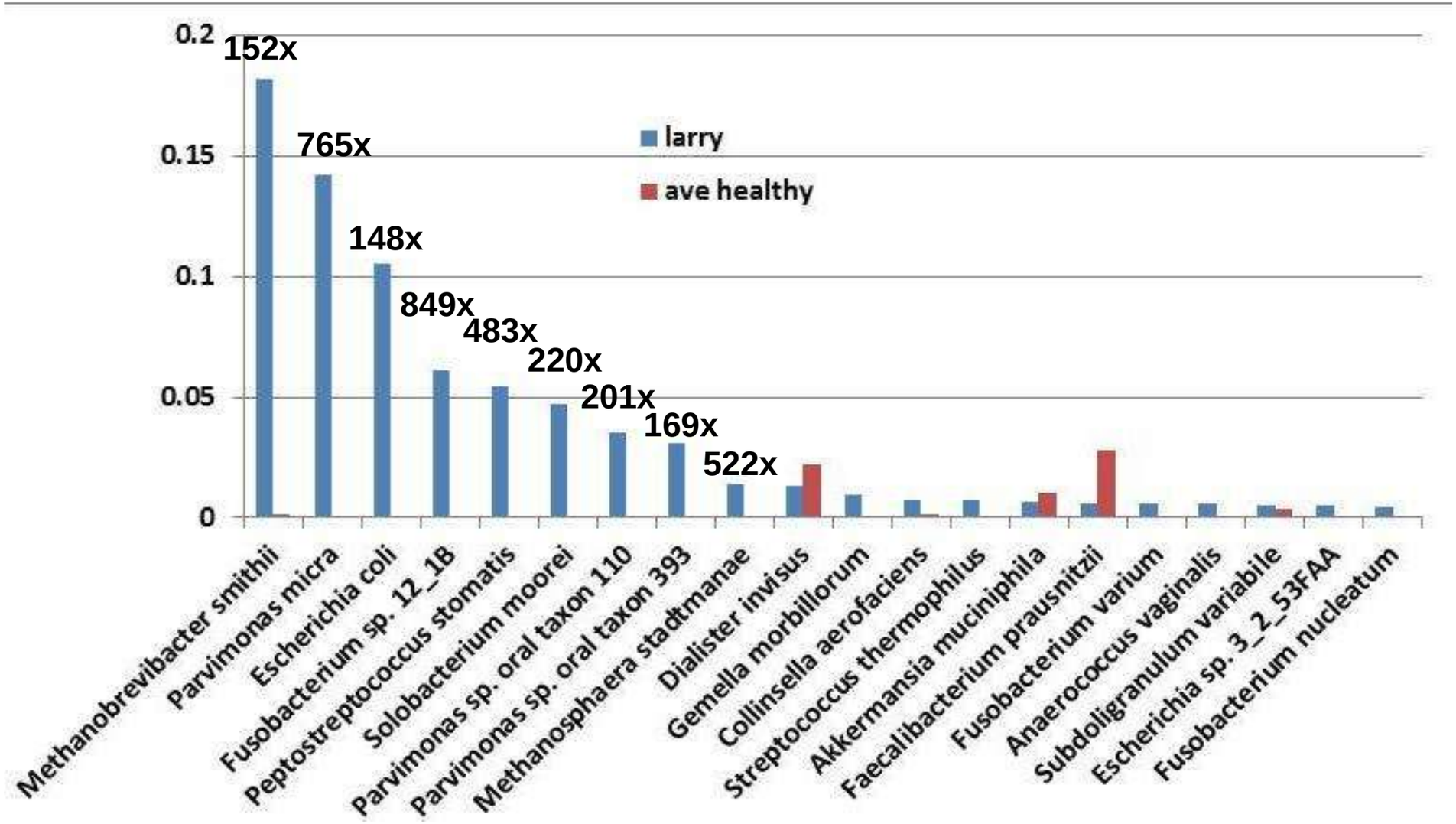
Almost All Abundant Species (≥1%) in Healthy Subjects Are *Severely Depleted* in Larry's Gut Microbiome

- **Red Bars** Are Relative Abundance of Top 20 Species in Healthy People
- **Blue Bars** Are Relative Abundance of Same Species in Larry Smarr When CRP=27 (12/28/2011)



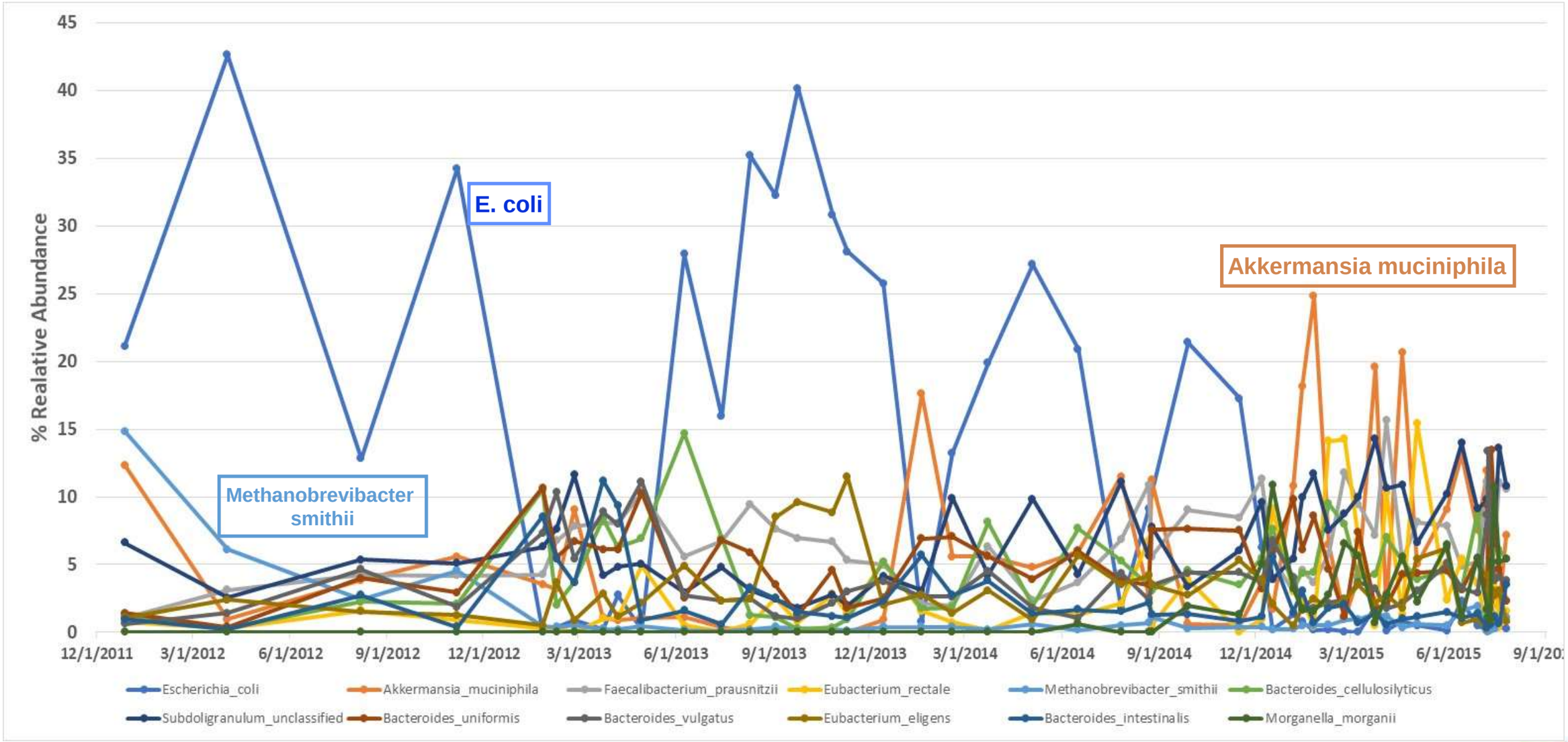
Invasive Species Take Over Gut Microbiome in Disease State

- **Blue Bars** Are Relative Abundance of Top 20 Species in Larry Smarr When CRP=27 (12/28/2011)
- **Red Bars** Are Relative Abundance of Same Species in Healthy People

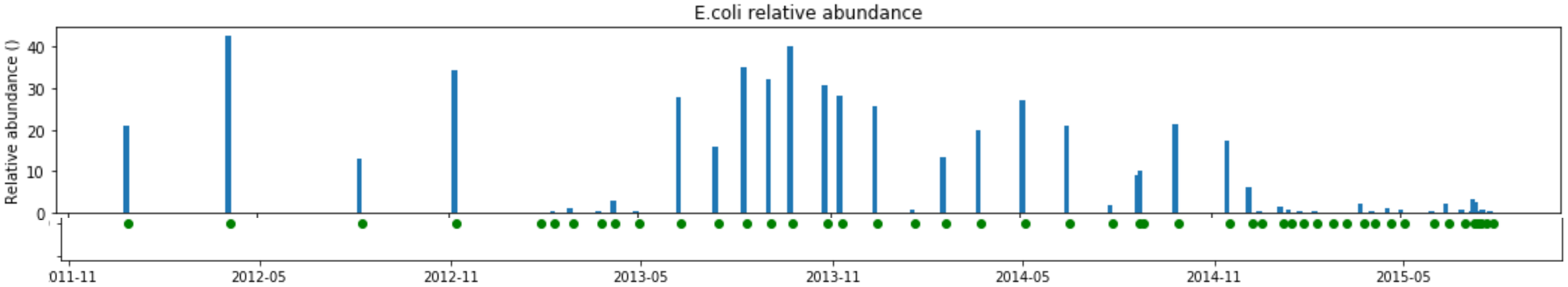


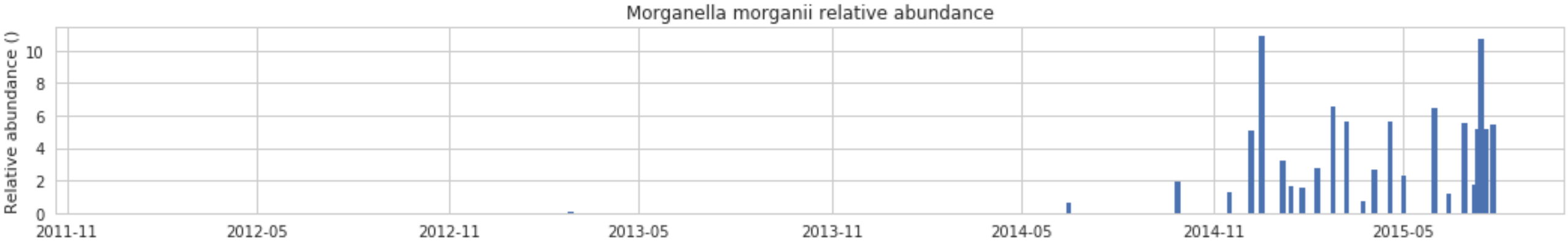
Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

Species That Exceeded 10% Total Abundance At Some Point in the 51 Time Samples

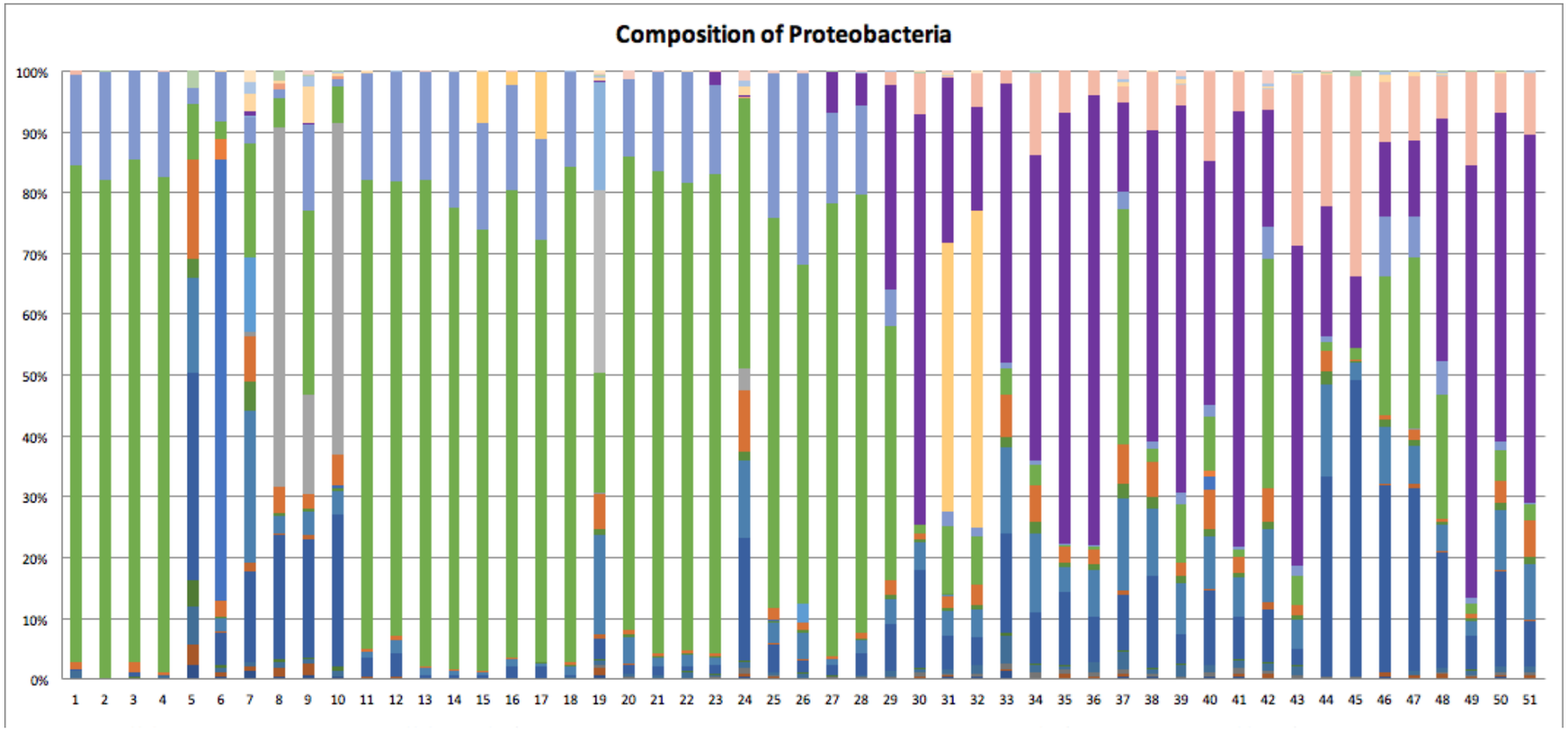


Proteobacteria Community Structure Changed Dramatically - Metagenomics Sequencing





Changes in Proteobacteria Composition



Discovery of Replacement of E. coli Within Proteobacteria by Morganella morganii-16S Sequencing

taxa-bar-plots.qzv | QIIME 2 View - Chromium

taxa-bar-plots.qzv × | Color Schemes | Ve ×

Secure | https://view.qiime2.org/visualization/?type=html&src=8c779ab7-b14f-4a45-9170-c924145db3d9

qiime2view

File: taxa-bar-plots.qzv

Visualization | Peek | Provenance

Download

SVG (bars) | SVG (legend) | CSV

Taxonomic Level

Level 7

Color Palette

schemeAccent

Sort Samples By

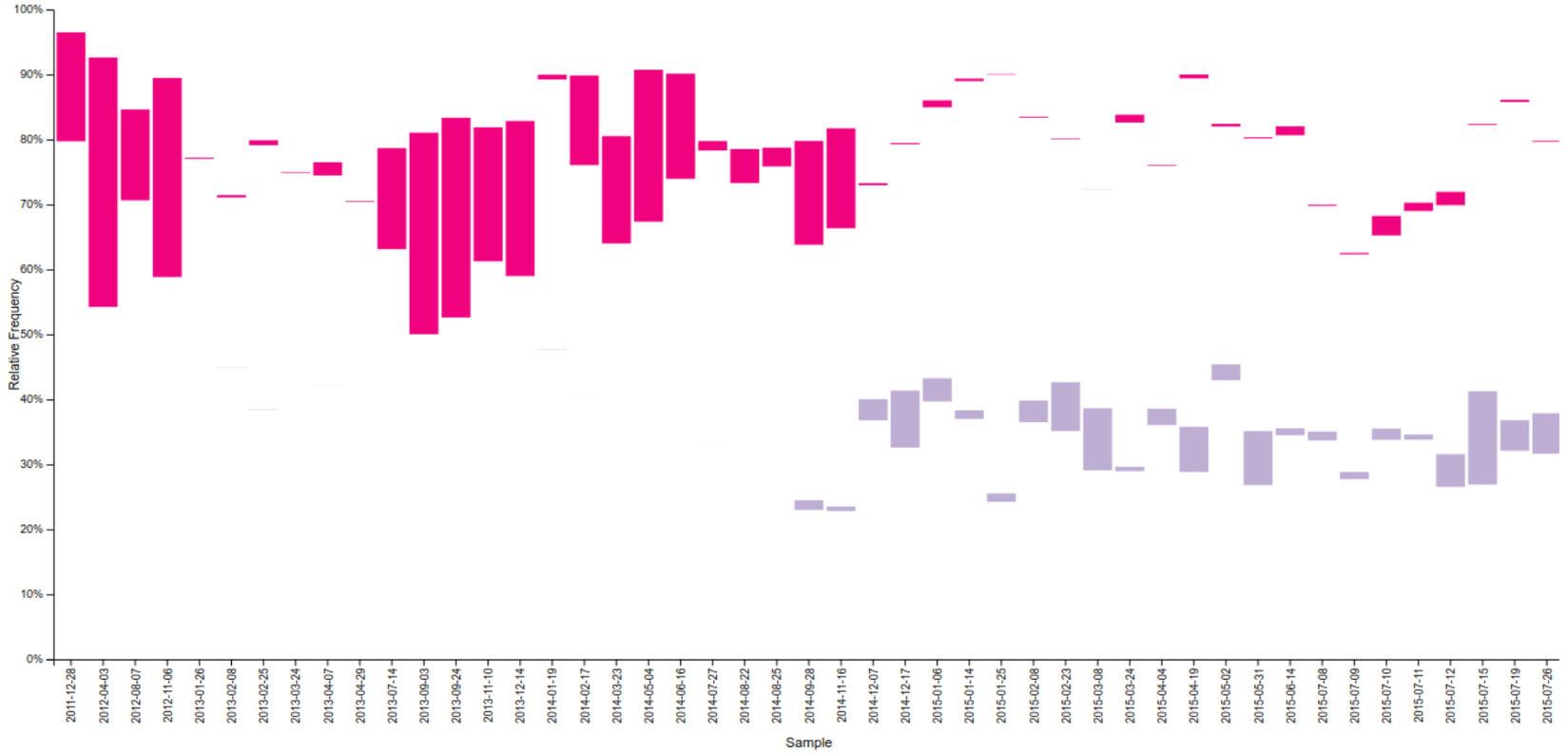
collection_timestamp

Ascending

Relabel X?

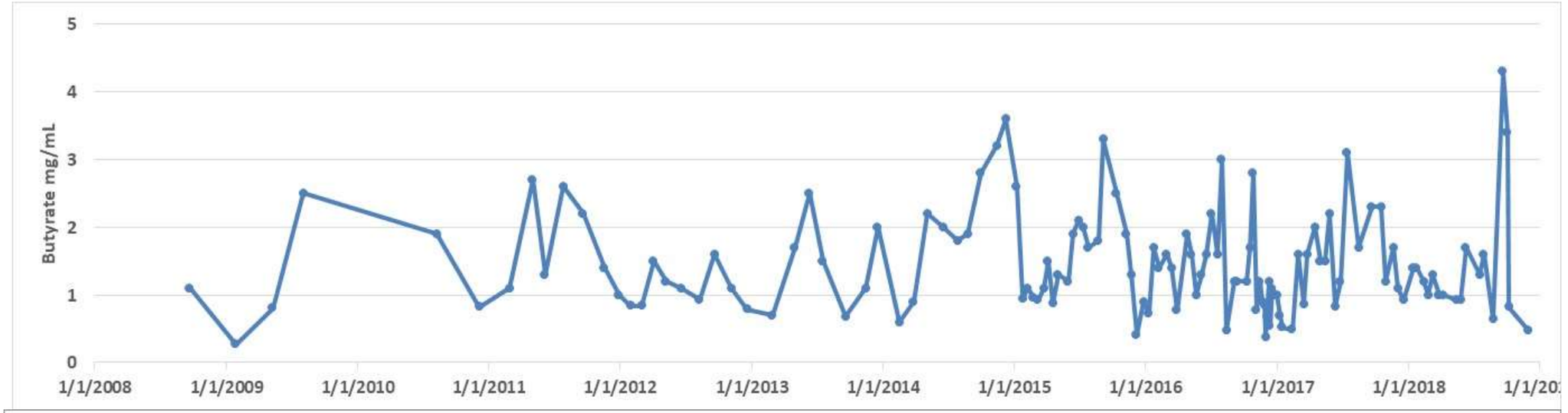
Bar Width

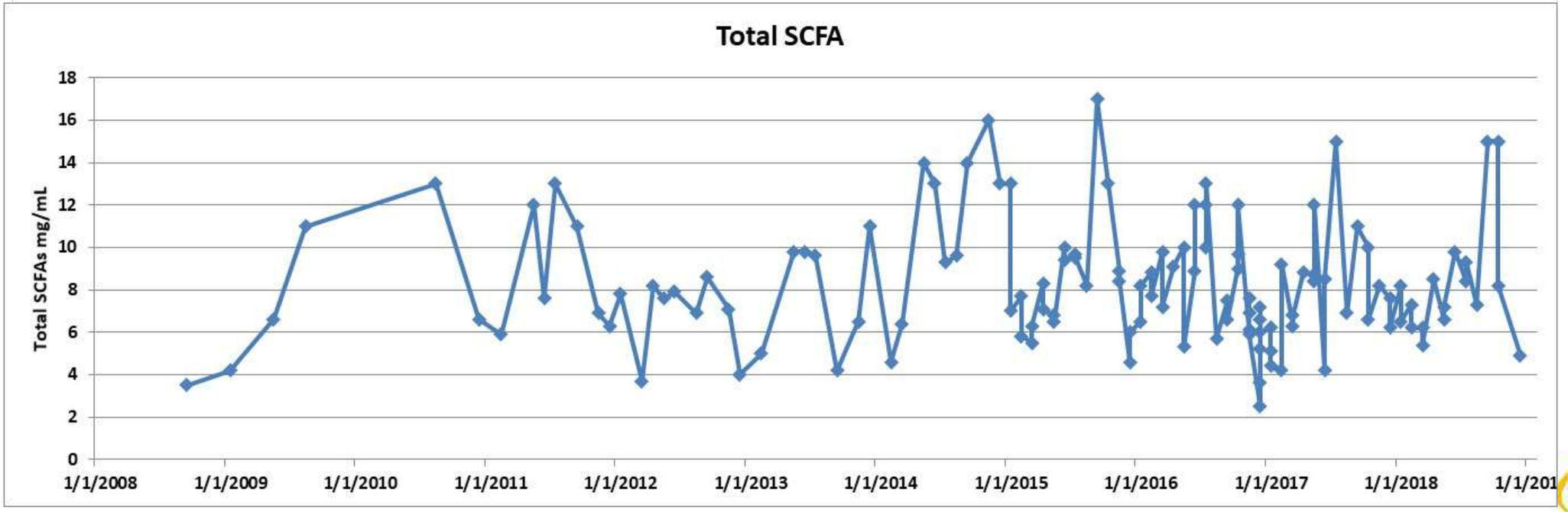
2015-07-19 | k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Morganella;s__morganii | 4.701%



k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Faecalibacterium;s__prausnitzii
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Escherichia;s__coli
k__Bacteria;p__Verrucomicrobia;c__Verrucomicrobiae;o__Verrucomicrobiales;f__Verrucomicrobiaceae;g__Akkermansia;s__muciniphila
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira;s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Prevotellaceae;g__Prevotella;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Coprococcus;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Ruminococcus;s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__[Paraprevotellaceae];g__[Prevotella];s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Rikenellaceae;g__human;s__gut metagenome
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__;g__;s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__uniformis
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Morganella;s__morganii
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Lachnospira;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Porphyromonadaceae;g__Parabacteroides;s__distasonis
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;__
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k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Porphyromonadaceae;g__Parabacteroides;s__
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k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Rikenellaceae;g__;s__
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Rikenellaceae;g__Alistipes;s__putredinis
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k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;__;__
k__Bacteria;p__Proteobacteria;c__Alphaproteobacteria;o__RF32;f__;g__;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Dorea;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Gemmiger;s__formicilis
k__Archaea;p__Euryarchaeota;c__Methanobacteria;o__Methanobacteriales;f__Methanobacteriaceae;g__Methanobrevibacter;s__
k__Bacteria;p__Proteobacteria;c__Betaproteobacteria;o__Burkholderiales;f__Alcaligenaceae;g__Sutterella;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Veillonellaceae;g__Phascolarctobacterium;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__[Ruminococcus];s__gnavus
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Providencia;s__
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Ruminococcus;s__bromii

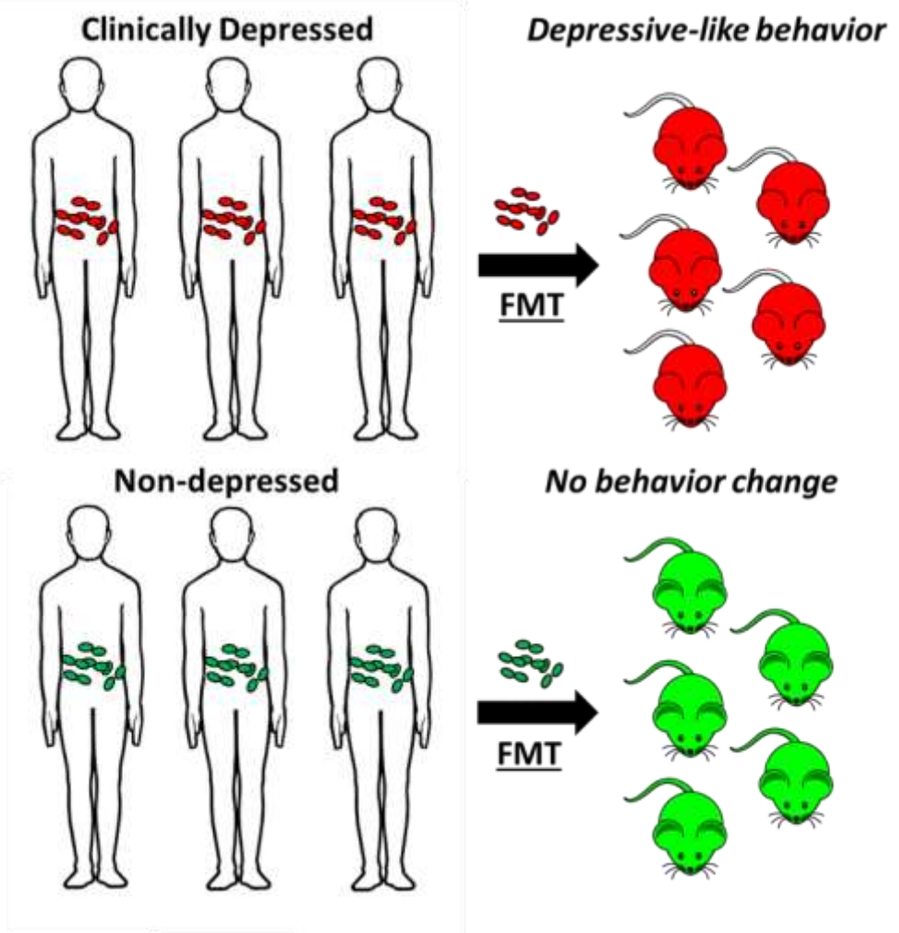
Total SCFAs and Butyrate





The Gut Microbiome and Mental Health

- **The Microbiome is Linked to Many Components of Mental Health**
  - **Brain Development**
  - **Mood/Behavior**
  - **Neurodegenerative Disorders**
- **Comorbidity is Common Between CNS and GI Disorders**
- **Antibiotics Use Has Been Linked To Behavioral Phenotypes (Depression + Anxiety)**
  - **But Not Antivirals or Antifungals**



Fecal Microbiome Transplant from Human to Animal Transmits Phenotype

Source: Jack Gilbert, UCSD

Gut Microbiome Dysbiosis
Is Being Linked to Irritable Bowel Syndrome and Depression

GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

The Role of Gut-Brain Interactions in Influencing Symptoms of Irritable Bowel Syndrome



Emeran A. Mayer, MD, PhD
Director, G. Oppenheimer Center for Neurobiology of Stress & Resilience
UCLA Vatche and Tamar Manoukian Division of Digestive Diseases
UCLA Microbiome Center
Los Angeles, California

January 2018

Viewpoint | Free Access

Melancholic microbes: a link between gut microbiota and depression?

T. G. Dinan, J. F. Cryan

Neurogastroenterology & Motility

01 August 2013

EDITORIAL · 04 FEBRUARY 2019

Links between gut microbes and depression strengthened

The once-wild idea that intestinal bacteria influence mental health has transformed into a major research pursuit.

nature
International journal of science

Combining Deep Metagenomics and Supercomputing Time to Map the Differences Between Health and Disease



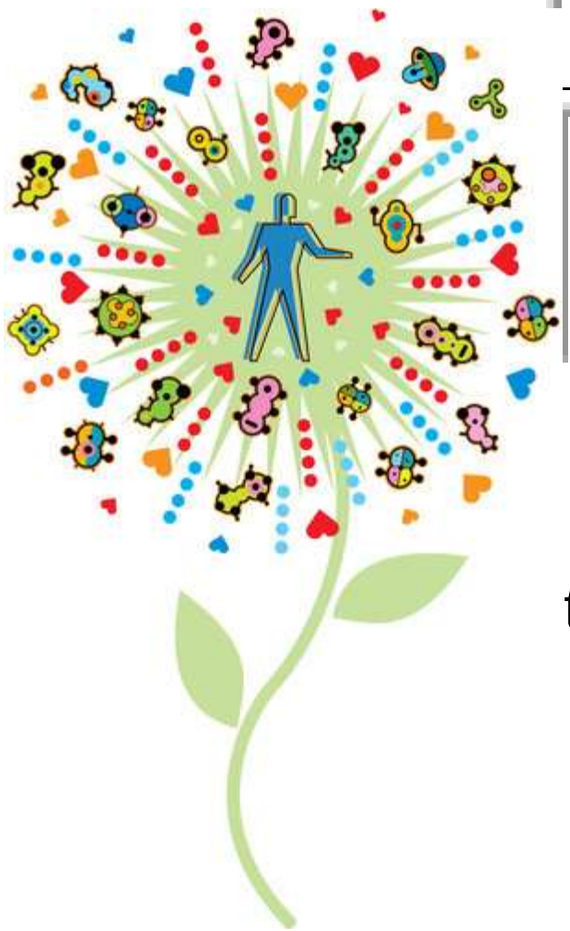
SDSC



- **Controls: 100s of Healthy Subjects**
- **Smarr Gut Microbiome Time Series**
  - **~80 Samples Over 5 Years**
- **Hundreds of IBD Patients**
  - **Phenotyped Patients Drawn from Sandborn BioBank**

Knight/Smarr Labs Using
100 CPU-Years of Supercomputer Time

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



The New York Times

Science

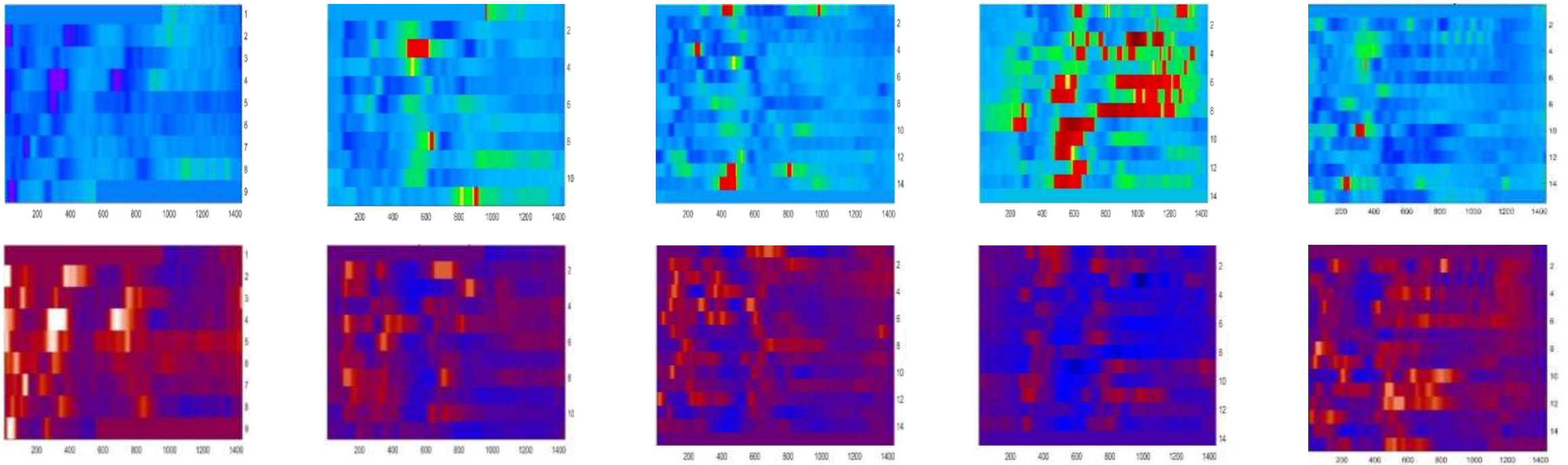
Tending the Body’s Microbial Garden

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.”

Heatmaps of CGM by Day Evolution Under TRE



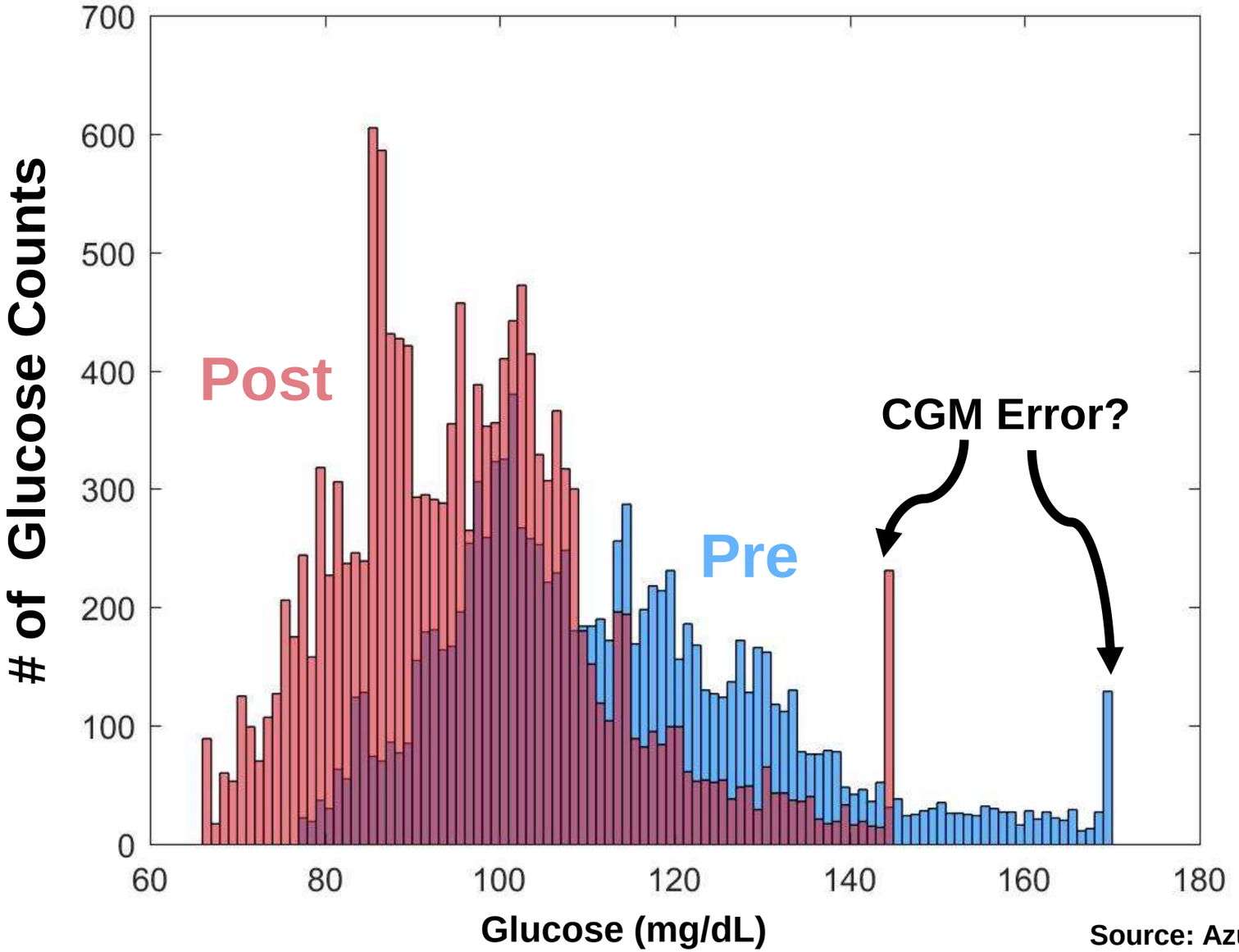




Minutes Since 0800 h

Data from Taub/Panda Clinical Trial
Graphics by Azure Grant, UC Berkeley

Glucose Profile Shifts Back to Healthy Range: Comparing Before and After 3 Months of 10-Hour Time-Restricted Eating



Source: Azure Grant, UCB

Monticello's Vegetable Garden Terrace: Jefferson Grew 330 Varieties of Over 70 Species of Vegetables



©Thomas Jefferson Foundation at Monticello. Photo by Robert Llewellyn

My Experiments in Personalized Wellness
Got Me Invited to Address the American Philosophical Society

AMERICAN PHILOSOPHICAL SOCIETY

275th ANNIVERSARY MEETING PROGRAM

Saturday Morning, November 10, 2018

Toward Personalized Wellness: An Ounce of Prevention Is Worth a Pound of Cure

Larry Smarr

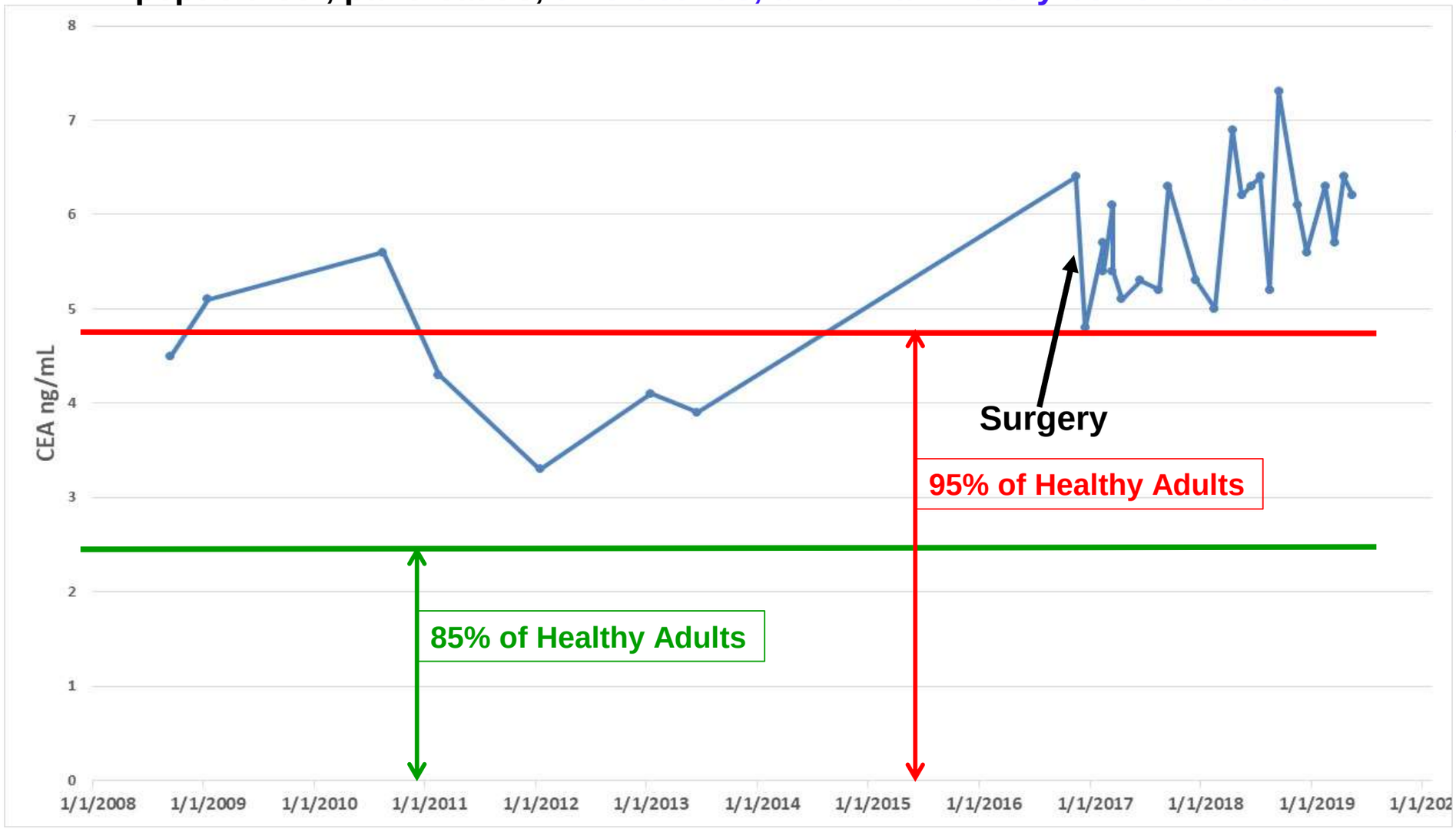
Founding Director, California Institute for Telecommunications and Information Technology

University of California at San Diego



Outlier: Carcinoembryonic Antigen (CEA) Screening Test for Colon Cancer Continues to Rise, Even After Sigmoid Colon Resection Surgery

"Elevated levels are also frequently seen in other gastrointestinal diseases including peptic ulcer, pancreatitis, diverticulitis, and inflammatory bowel disease."



Question: Why Didn't CEA Drop Into Normal Range Post-Surgery?

Ranges from Exeter Clinical Labs www.exeterlaboratory.com/test/carcinoembryonic-antigen-cea/

From N=1 Experiment to Clinical Tool: 3D Medical Imaging Pilot to Improve Surgical Outcomes for Patients with Crohn's Disease (CD)

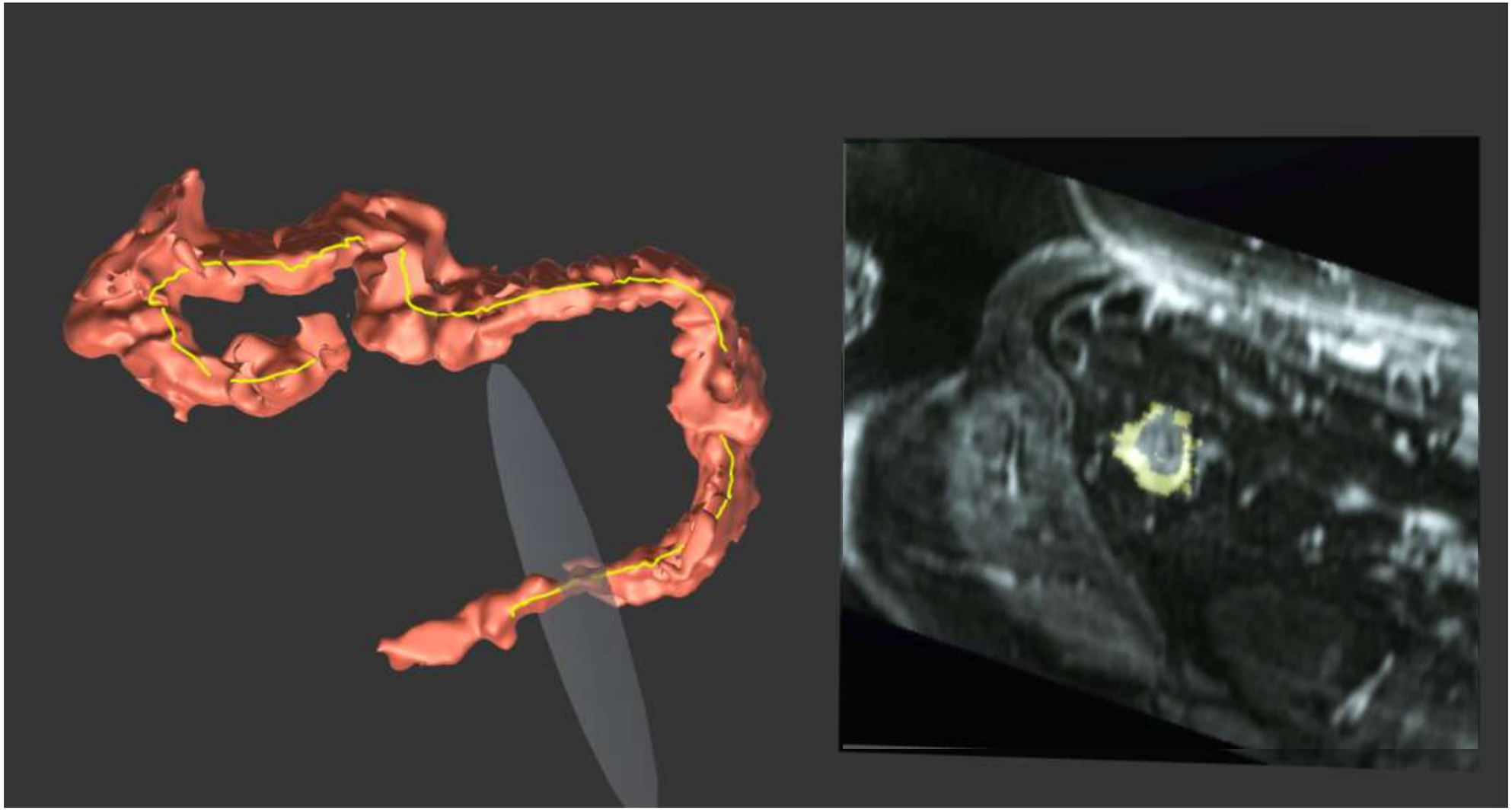
- **$1.2 M Grant From the Helmsley Charitable Trust**



- **UC San Diego Collaborative Team:**
  - PI Larry Smarr, PhD, Director Calit2
  - Jurgen Schulze, PhD, Virtual Reality Research Scientist, Calit
  - Ramesh Rao, PhD, Director, Calit2's Qualcomm Institute
  - Sonia Ramamoorthy, MD, Chief of Colorectal Surgery
  - Bill Sandborn, MD, Chief of Gastroenterology
  - Cynthia Santillan, MD, Chief of Body Imaging
  - Anders Dale, PhD, Co-Director of the Multimodal Imaging Laboratory

- **Pilot Will:**
  - Integrate 3D Medical Imaging Within Clinical Practice
  - Evaluate 10 CD Patients Having Small Bowel or Colonic Strictures Using 3D Imaging
  - Assess Software Usability in the UCSD IBD Clinic & Operating Room for Both Physician & Patient

Helmsley Grant Enables Use of Machine Learning on MRI Slices To Locate 3D Colon, Trace It's Centerline, and Get Colon Wall Cross-Section



Source: Jurgen Schultz, Russell Xie, Zifeng Li, Larry Smarr

Helmsley Grant Enabled
Undergraduate to Bring 3D MRI into Head Mounted Displays

UCSD Undergrad Trevor Hedstrom



Berkeley Grad Student Azure Grant



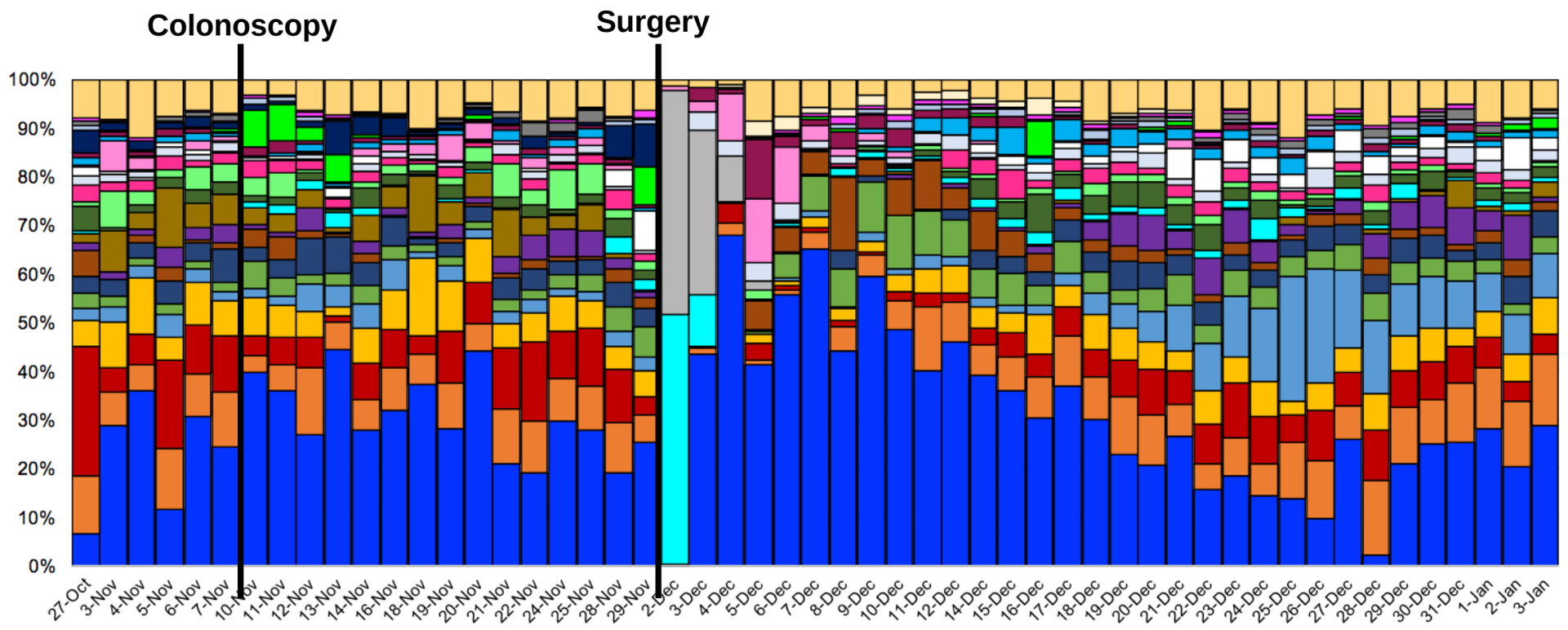
Larry's Spinal MRI Data

DICOM Volume Renderer

Look Inside Your Body With Your Phone

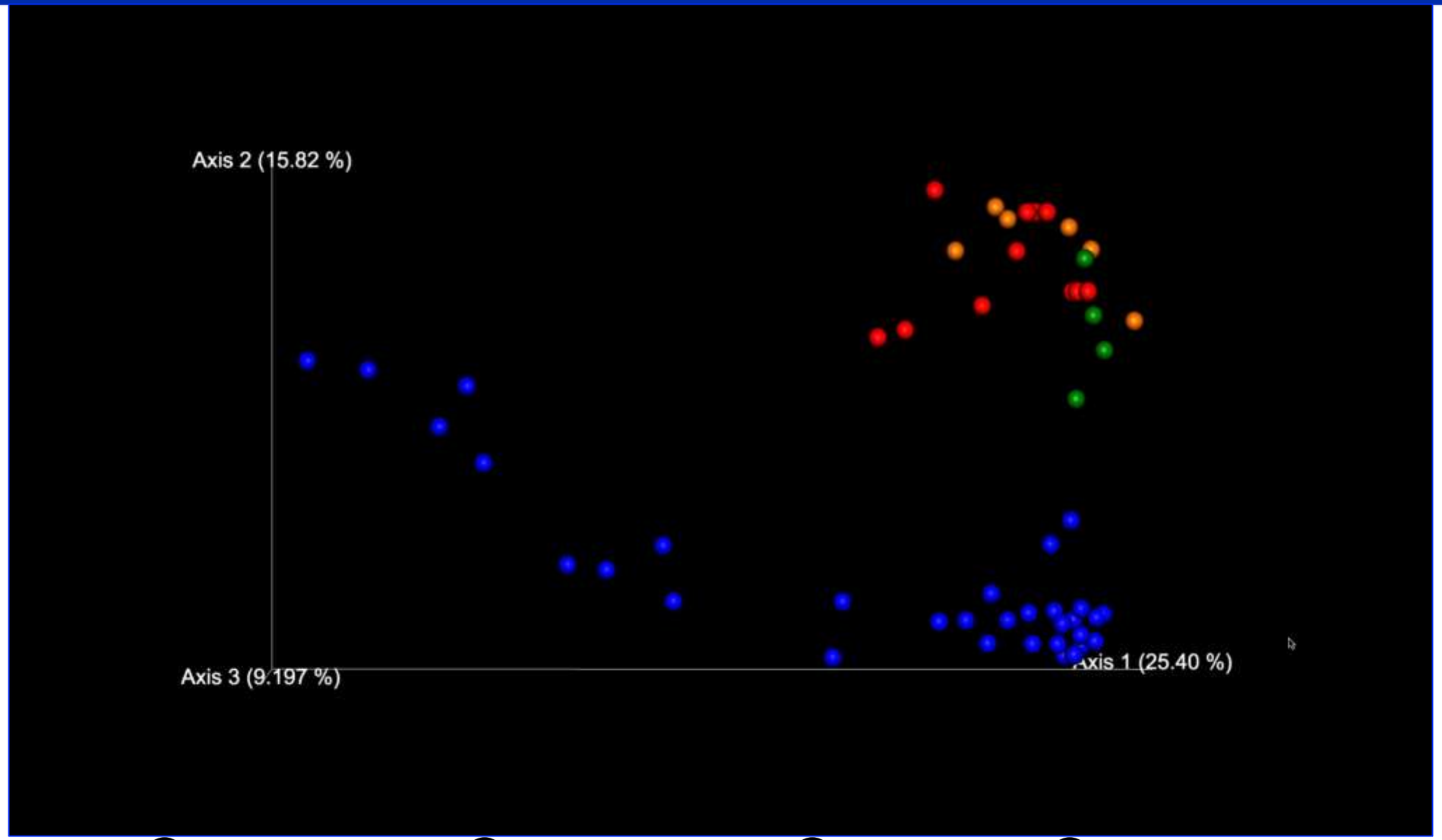


Gut Microbiome Genus-Level Profiles
Daily Samples Before and After Abdominal Surgery



Source: Embriette Hyde, UCSD

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



Inflamed Disease State

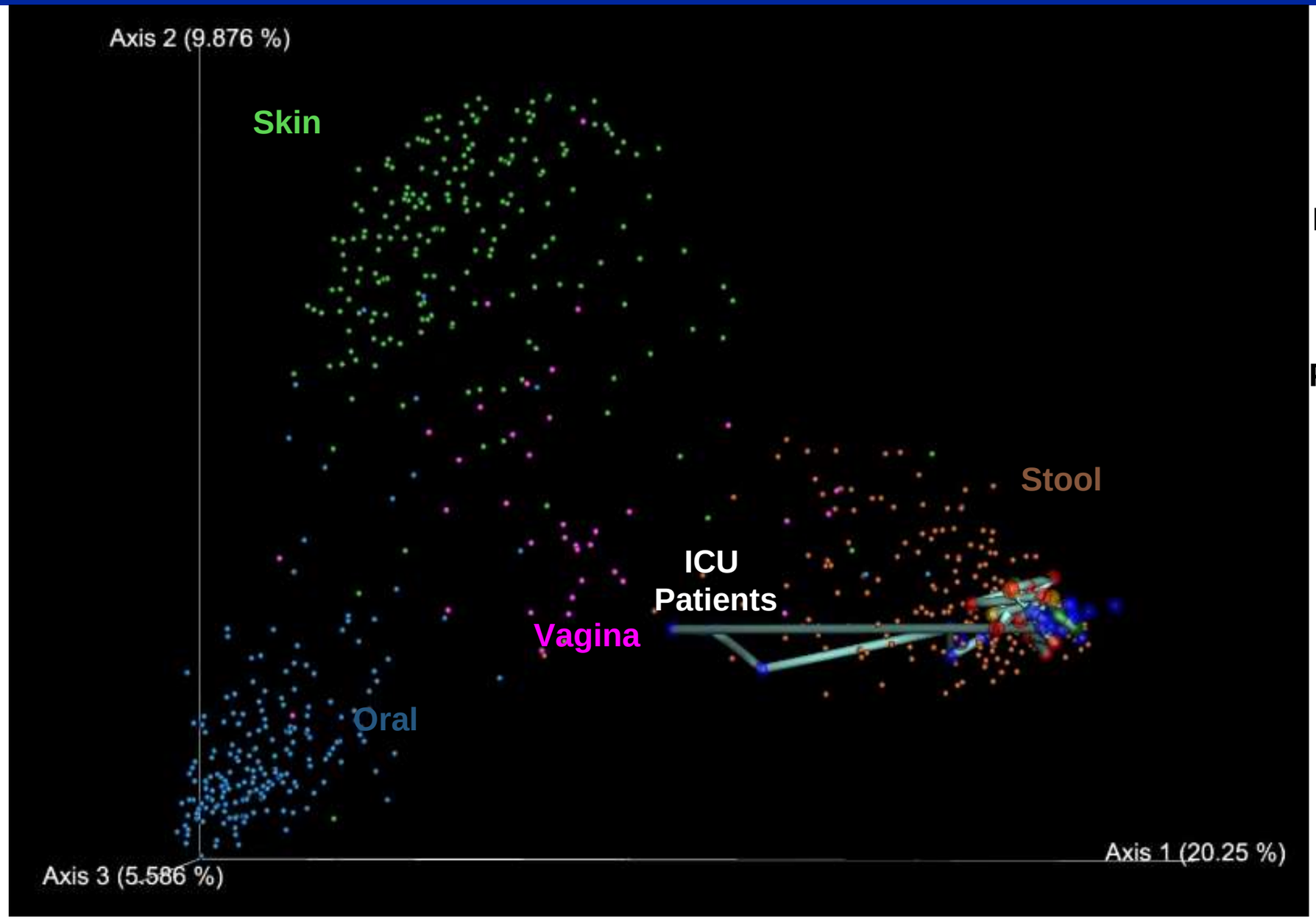
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Healthy Post-Surgery State

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

Published 2018 mSystems

LS Longitudinal Blood Tests of Vitamin D3

