“Revealing the Dynamics within an Individual Human Body and Its Gut Microbiome”

Guest Lecture for Professor Ben Smarr’s Graduate Course Bioengineering 211: Systems Biology and Bioengineering I: Biological Components

UCSD

November 19, 2025

Dr. Larry Smarr

Founding Director Emeritus, California Institute for Telecommunications and Information Technology;

Distinguished Professor Emeritus, Dept. of Computer Science and Engineering

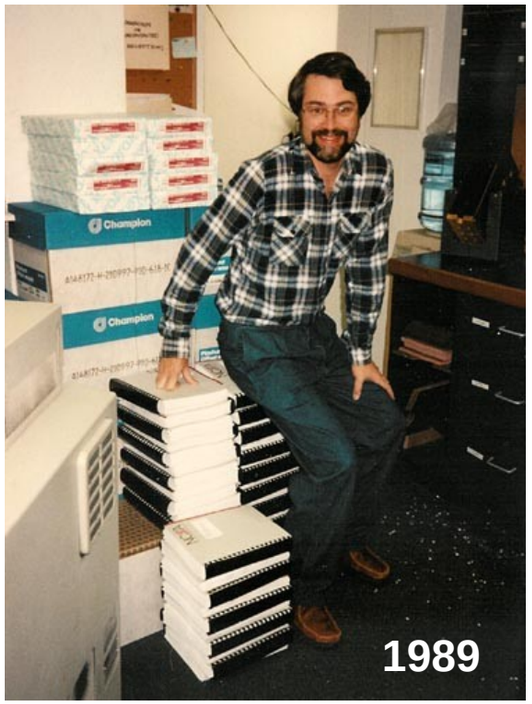
Jacobs School of Engineering, UCSD

http://lsmarr.net

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

Age 41



Age 51



Age 61



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

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

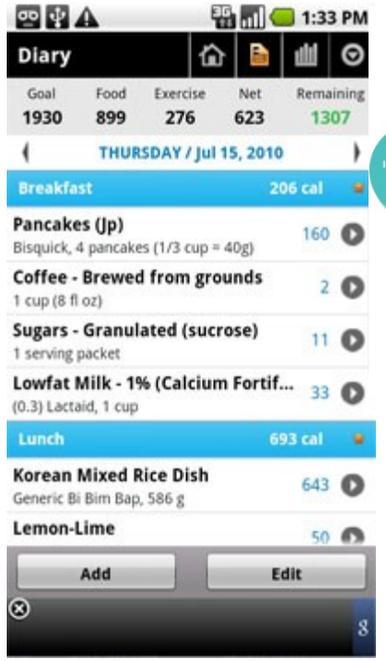
“Know Thyself”
From the Temple of Apollo to the Quantified Self



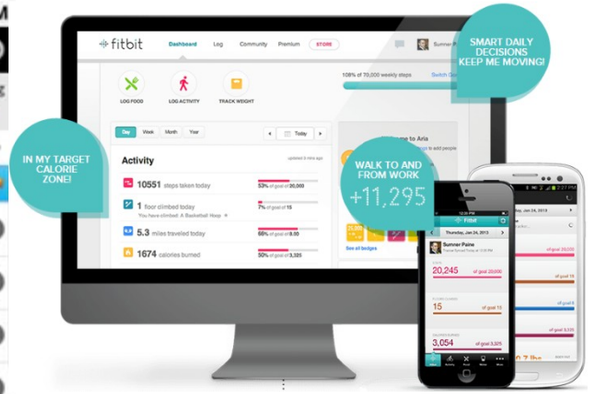
From the Reichert-Haus in Ludwigshafen, Germany

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



MyFitnessPal-
Calories Ingested



FitBit -
Daily Steps &
Calories Burned



Withings/iPhone-
Blood Pressure





Azumio-Heart Rate



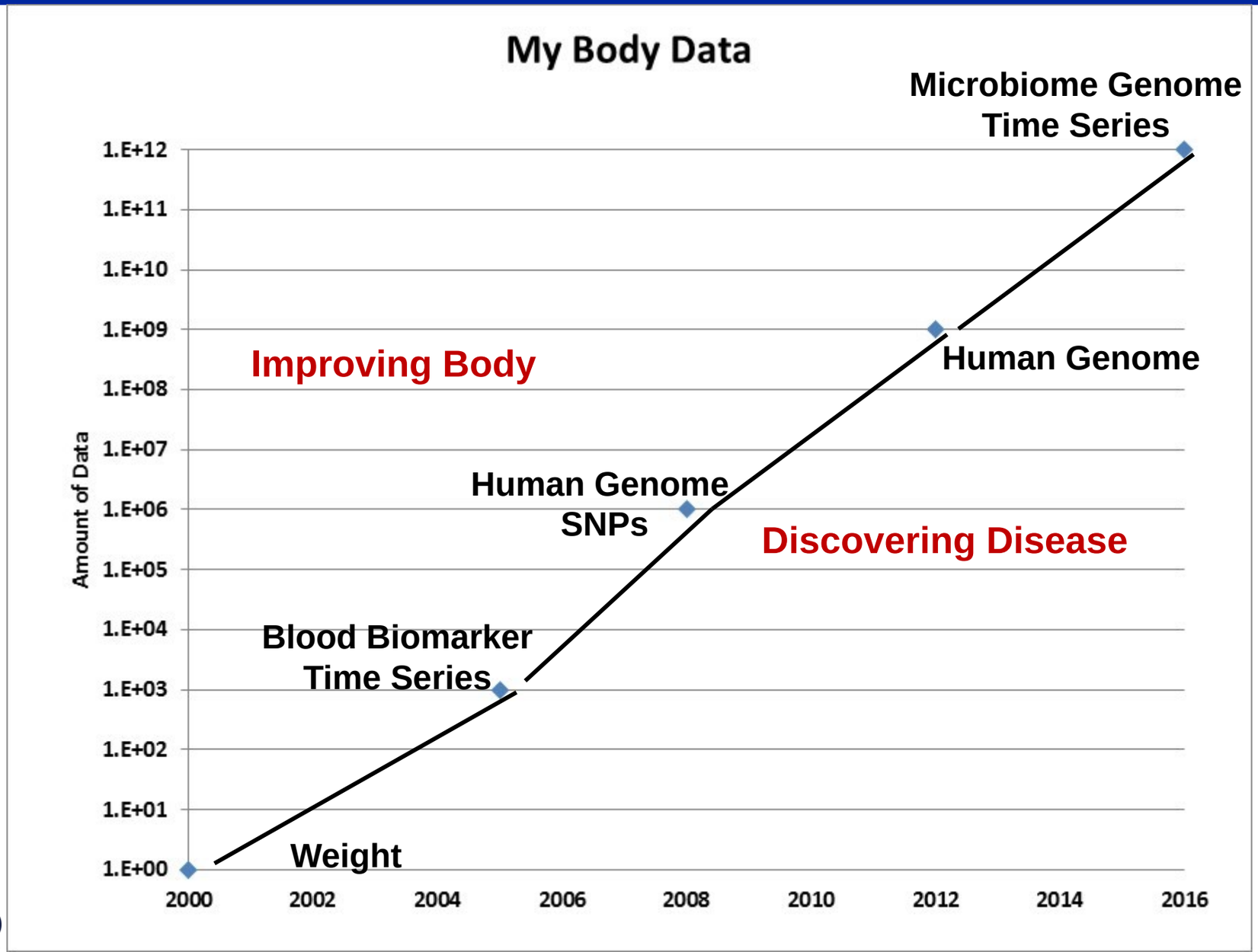
Withings WiFi Scale -
Daily Weight



Zeo-Sleep

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From One to One Trillion Data Points Defining Me in 15 Years: The Exponential Rise in Body Data



500 Time Steps
X 400 Microbe Types
x 5 Million Bases/Microbe Genome
= 1 Trillion

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

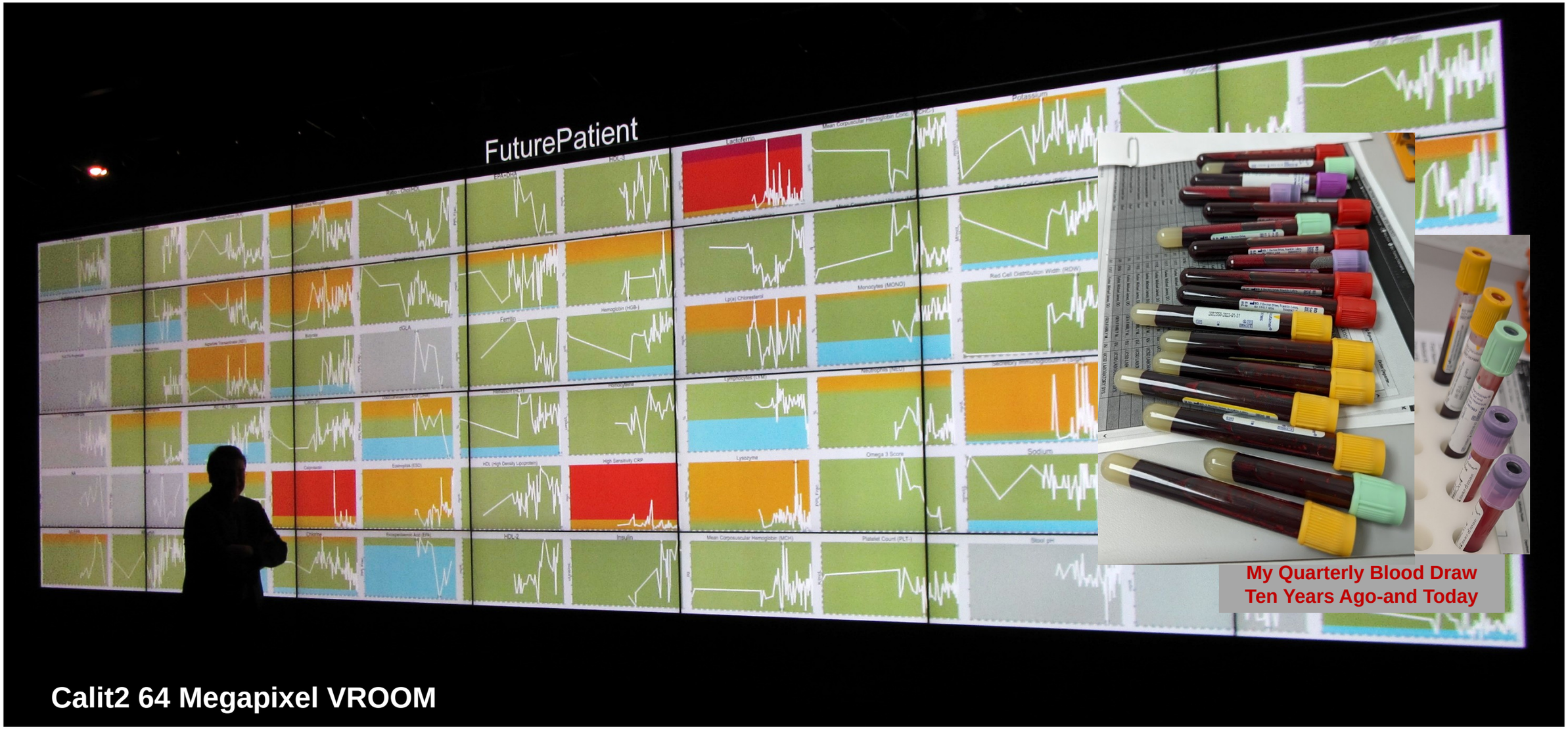


The Patient of the Future

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

www.technologyreview.com/biomedicine/39636

For the Last 20 Years I Have Been Exploring the Application of Data Science to My Blood and Stool Biomarkers Time Series in a Clinical Setting



My Quarterly Blood Draw
Ten Years Ago-and Today

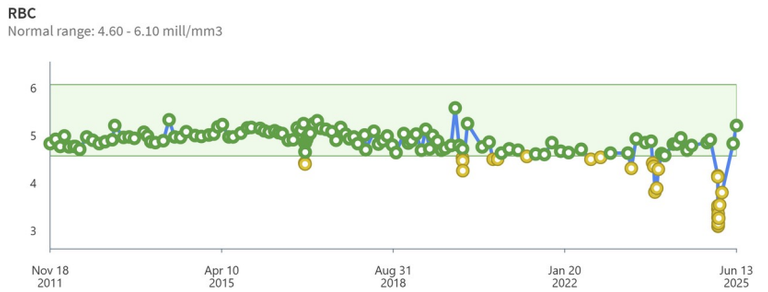
Calit2 64 Megapixel VROOM

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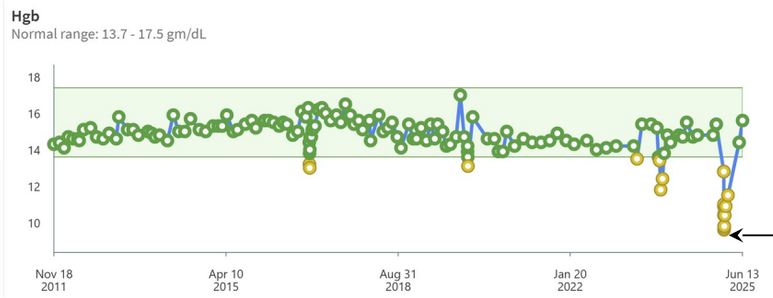
Watch video: https://lsmarr.net/futurepatient-larry-smarr-phd/

Blood Time Series Reveal Extreme Time Synchronous Changes: Colon Bleed Led to Lowest RBC, HGB, HCT and Iron in 14 Years

Red Blood Cell Count

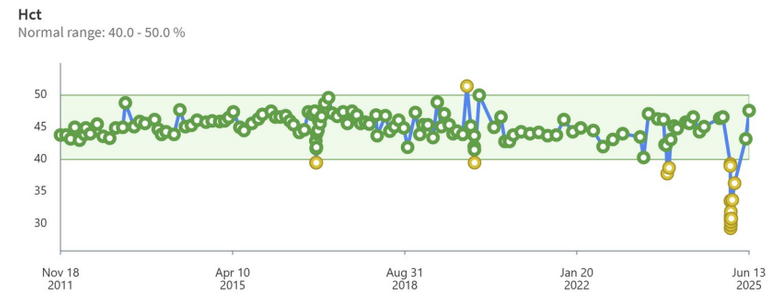


Hemoglobin

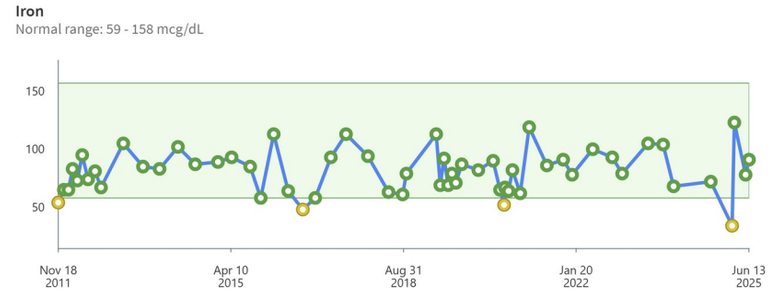


Jan 31, 2025

Hematocrit



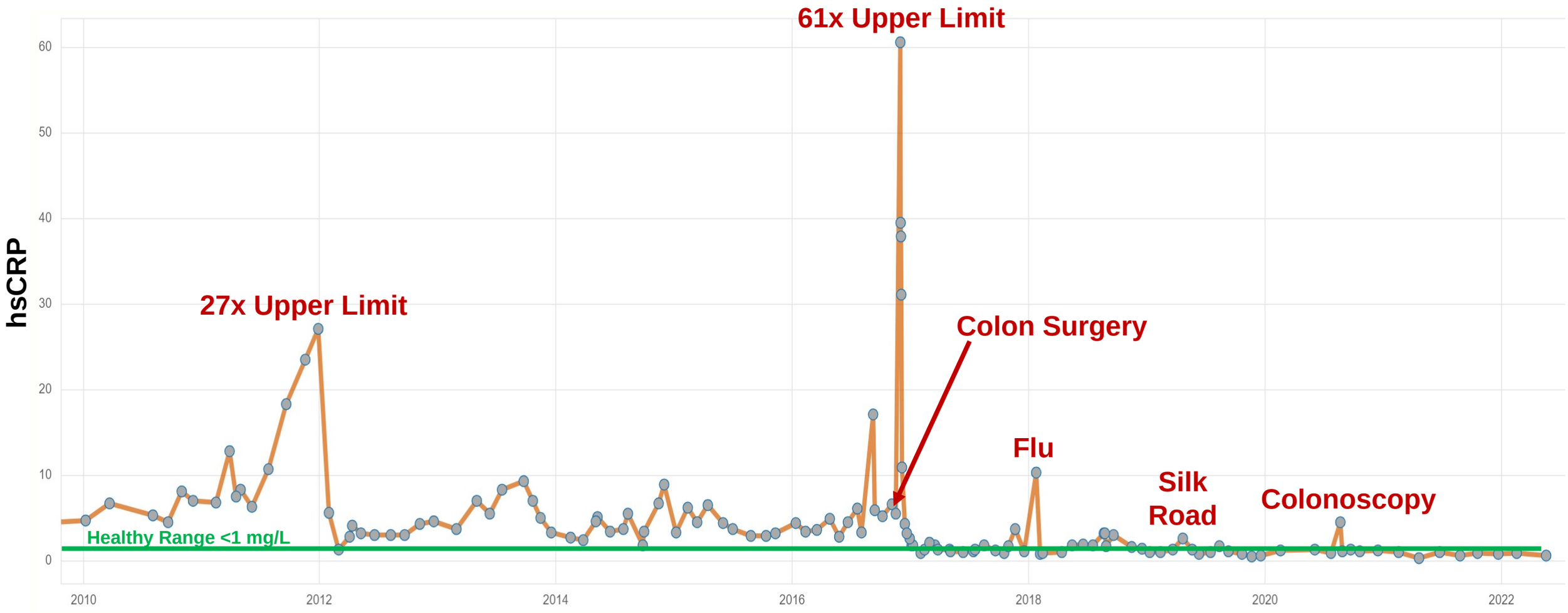
Iron



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Data and Graphs From: UCSD MyChart

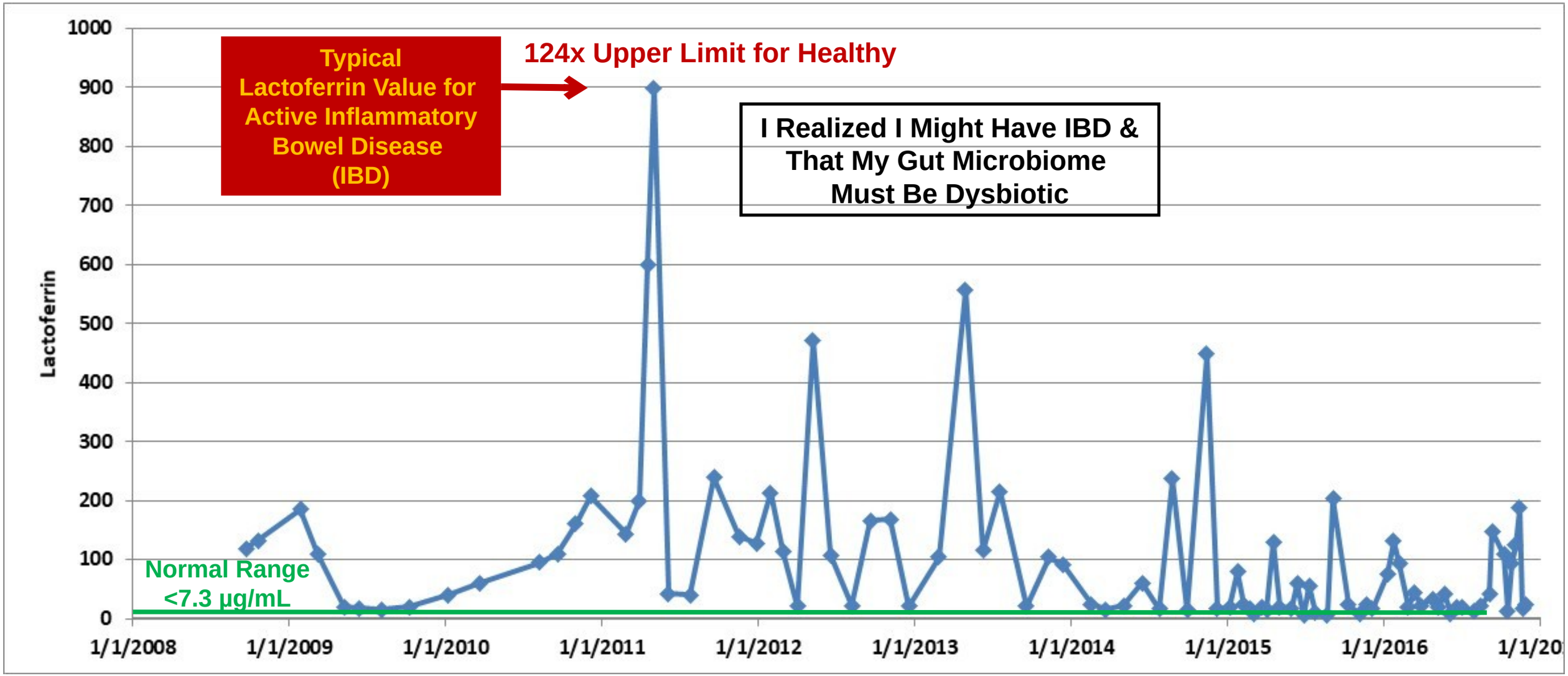
My Blood hsCRP Had Been Consistently High, Indicating Episodic Chronic Inflammation, But After Surgery It Reverted to Normal



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

Adding Stool Tests Revealed
Oscillatory Behavior in an Human Immune Variable Which is Antibacterial



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

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

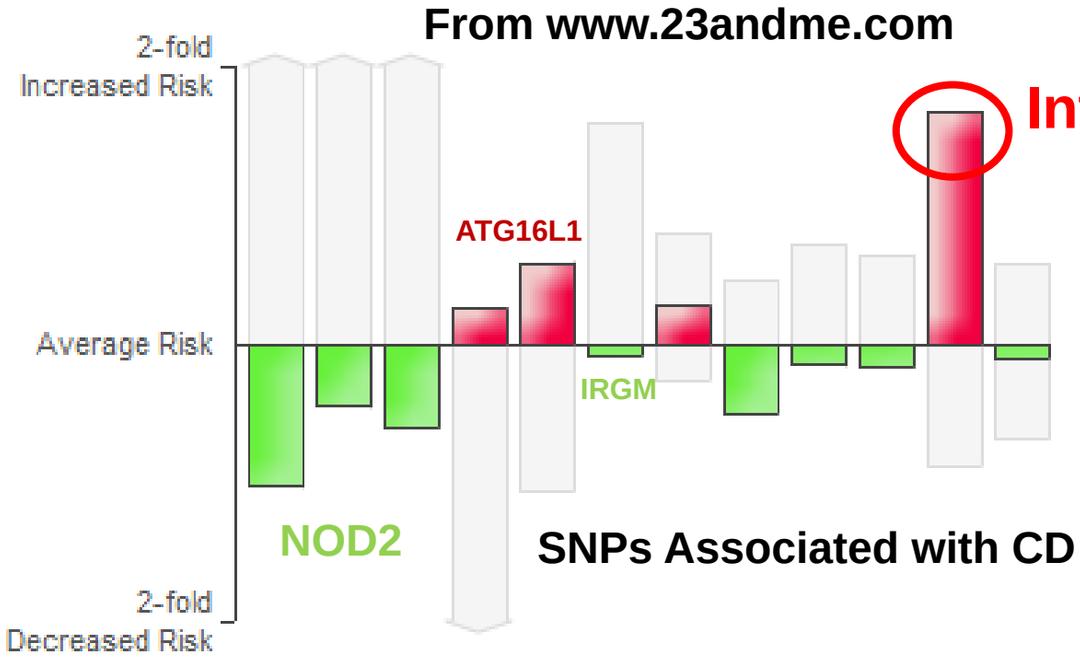
So I Set Out to Quantify All Three!

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

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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

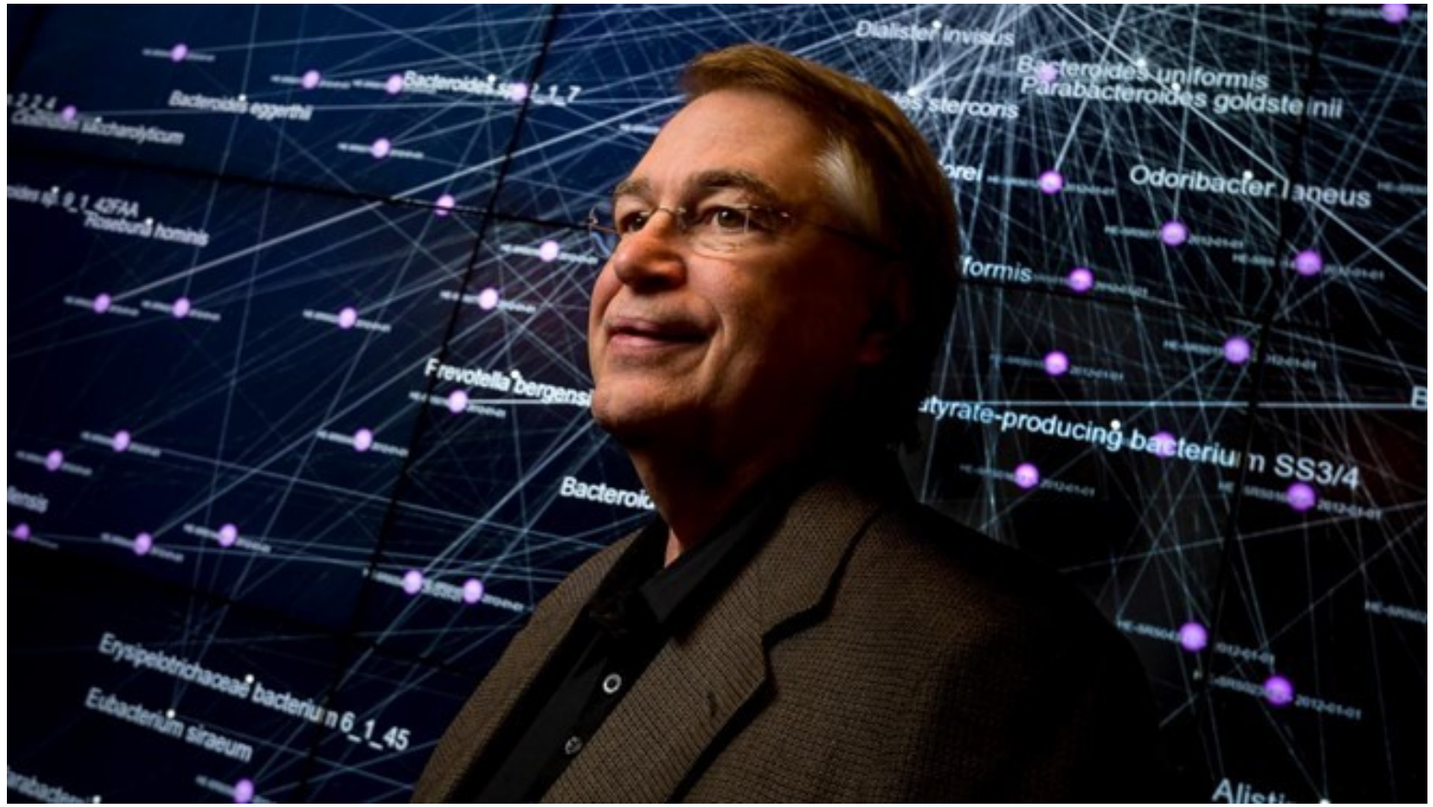
IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

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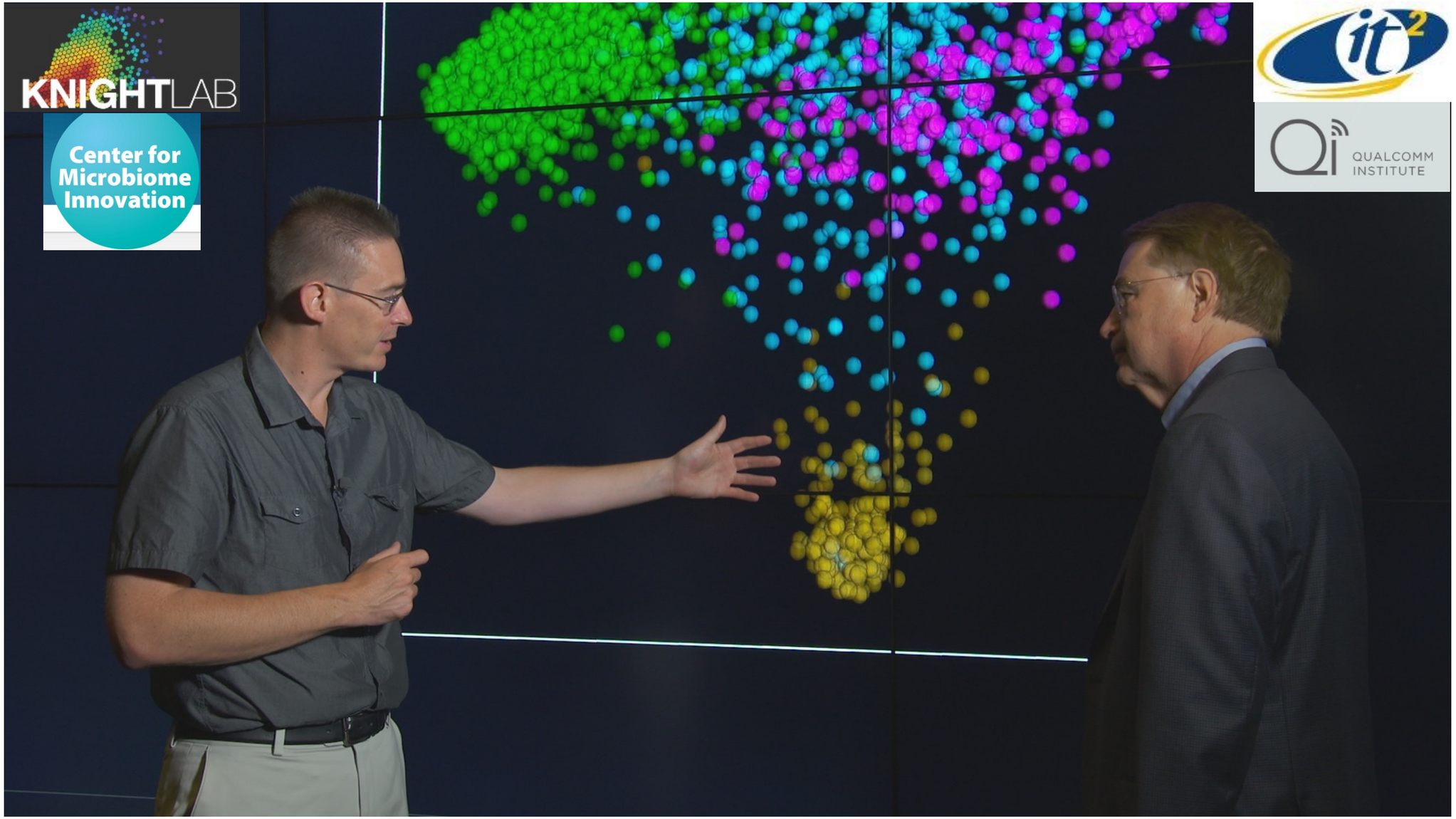
This Led to the “Future Patient” Project:
An N=1 High Time-Frequency Multi-Variable Time Series

- **Over 600 Daily Frozen (-80º) Stool Samples From One Individual Over 12 Years**
  - **~150 16S Sequenced Samples**
  - **~50 Metagenomics Sequenced Samples**
  - **~8 Metaproteomic Mass Spec Samples**
  - **Stored and Sequenced in the UCSD Knight Lab**
- **~186 Days of Stool Lab Results**
  - **Immune/Inflammatory Biomarkers**
  - **SCFA**
- **~168 Days of Blood Samples**
  - **~150 Biomarkers**
- **A lot of dietary/medical history**
- **...and more!**



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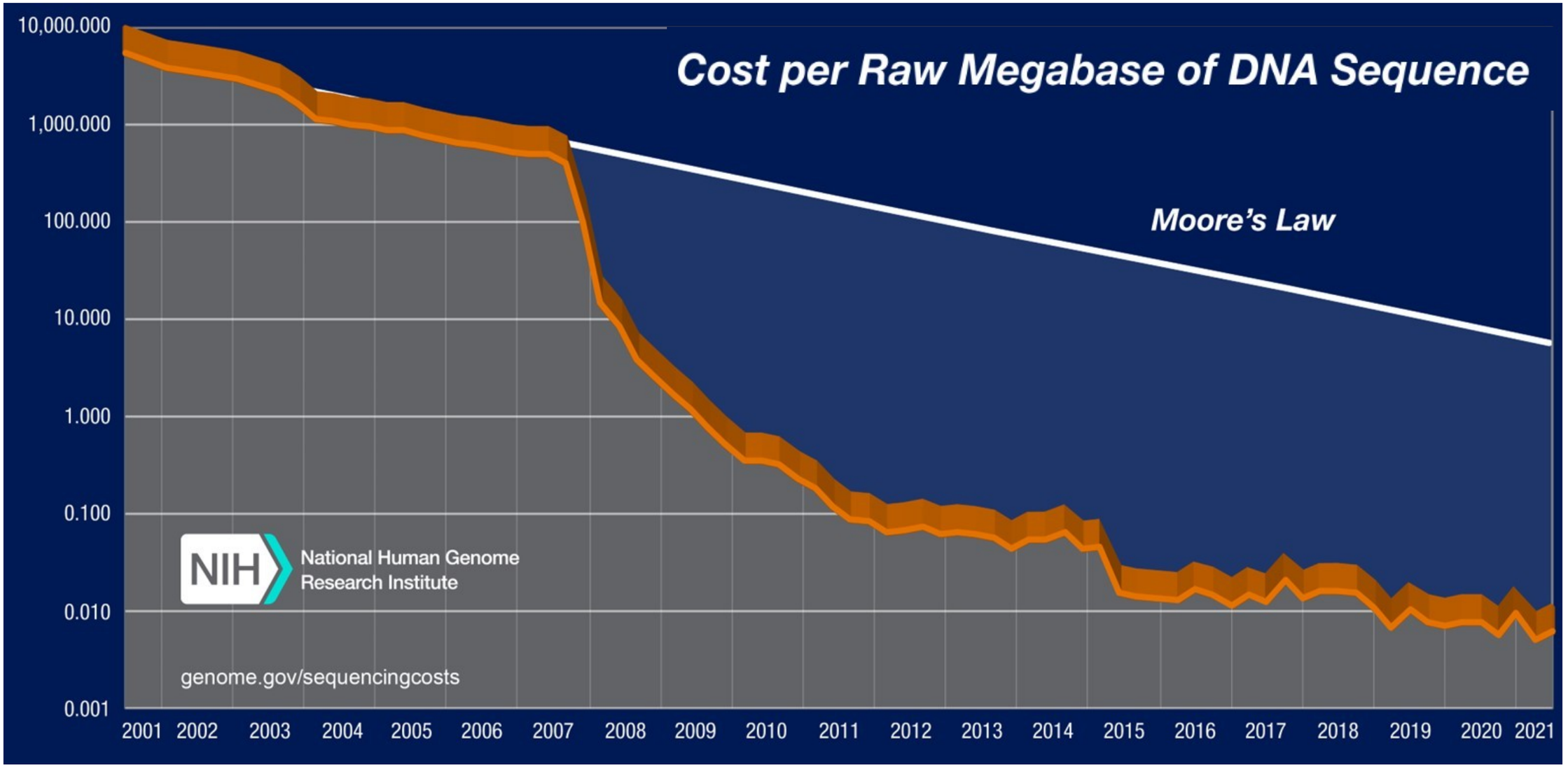
After 2015, We Have Combined the Resources of the Knight Lab and Calit2's Qualcomm Institute's Visualization Facilities Within the Center for Microbiome Innovation



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Watch video: https://lsmarr.net/discovering-human-gut-microbiome-dynamics/

Analysis of the Gut Microbiome Became Possible Because The Cost of Sequencing DNA Has Fallen Over 1,000,000x in the Last Twenty Years

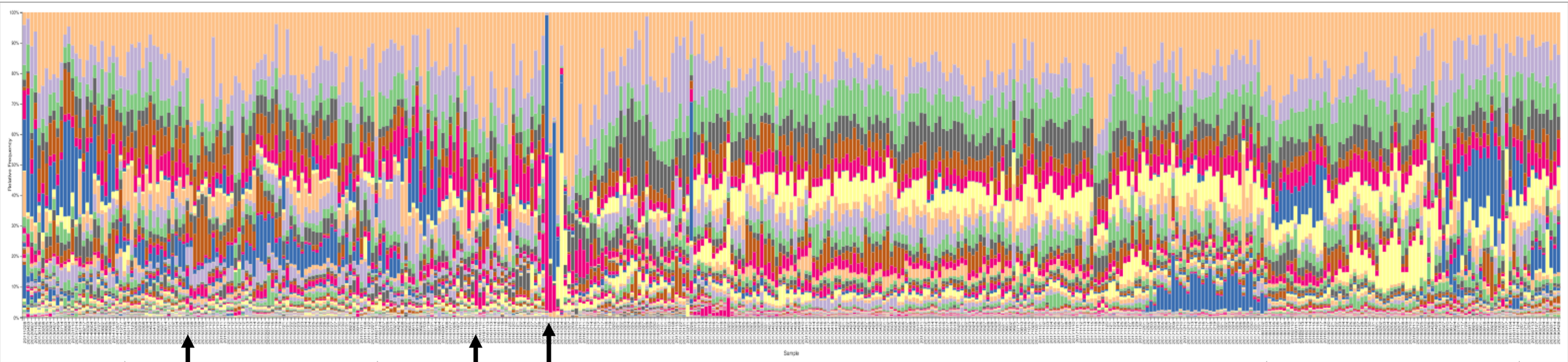


This Has Enabled a "Golden Age" of Discovery in Both Human and Microbiome Genetics

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Gut Microbiome Ecological Dynamics Revealed by 16S Genomic Sequencing of ~124 Smarr Daily Stool Samples Over 8 Years

Taxonomic Stacked Bar Plot of 16S Relative Abundance (Colors Represent Different Genus)



2015

2016

2017

2018

Colonoscopy
(July 7, 2015)

Resection Surgery
(November 29, 2016)

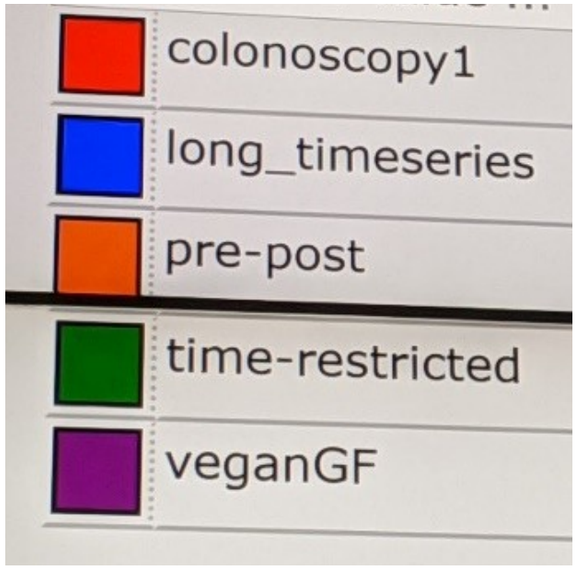
Colonoscopy
(November 8, 2016)

December 28, 2011

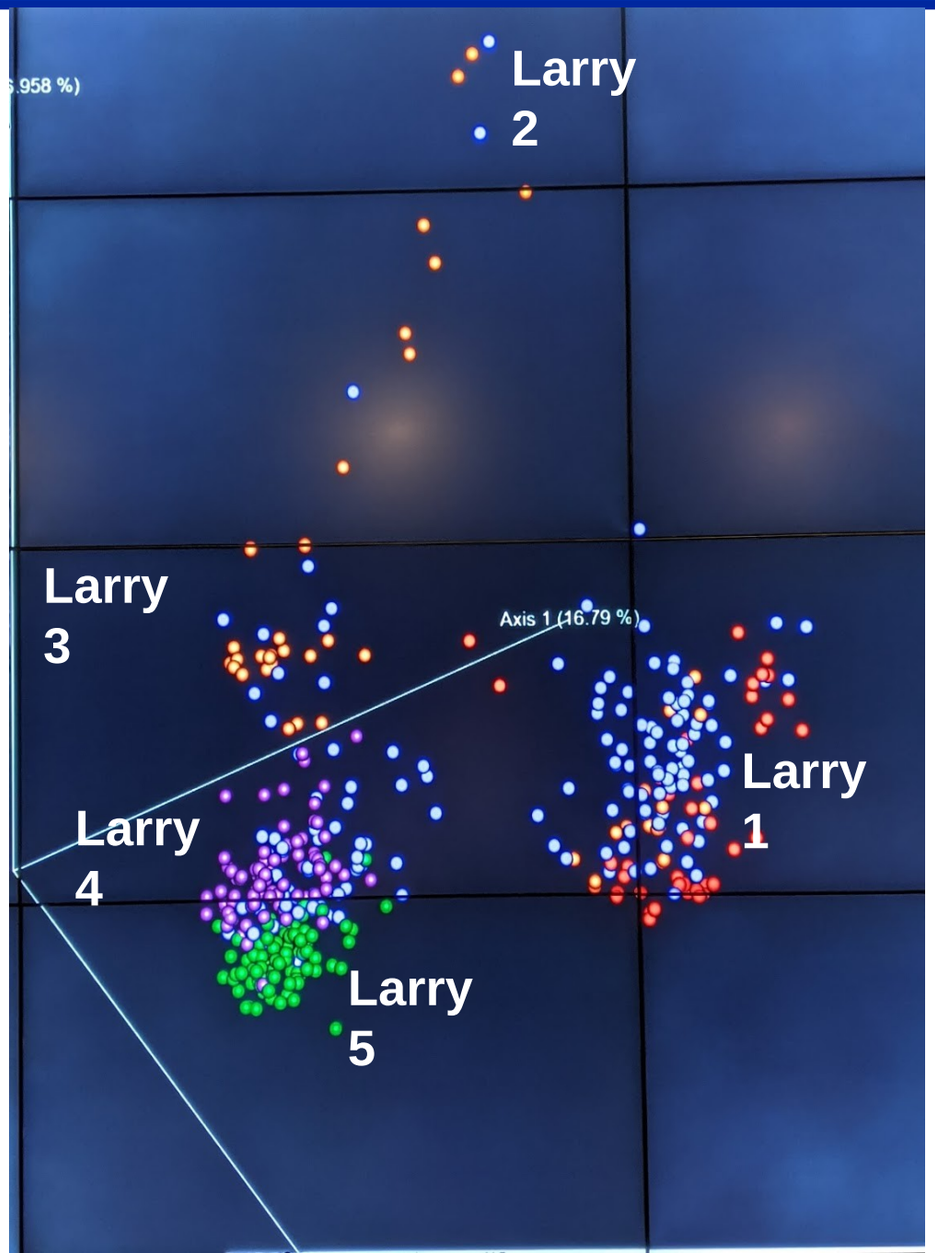
April 28, 2019

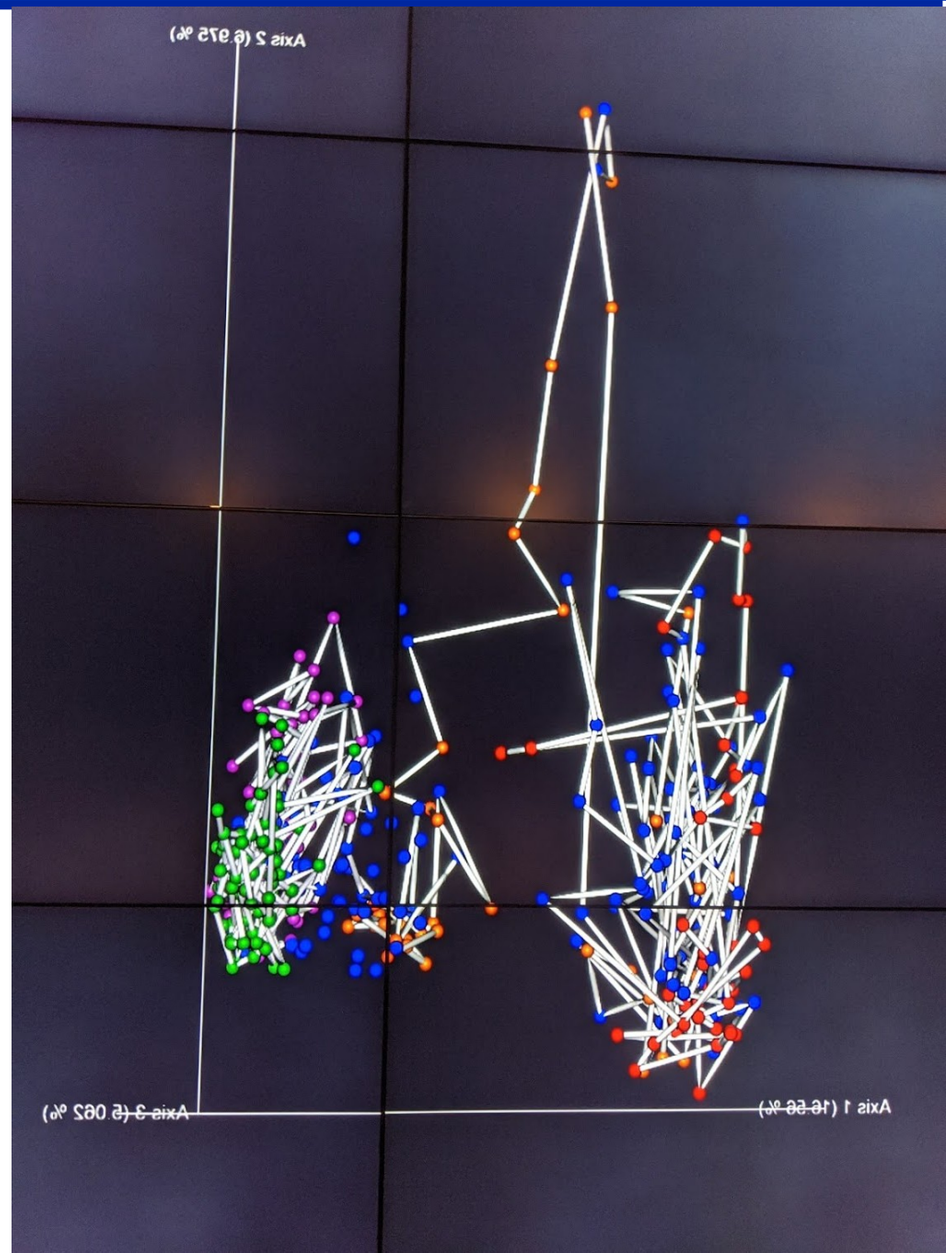
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Machine Learning (PCA) on 16S Time Series Reveals I Became 5 Different People Over 8 Years: First Three Were IBD Pre- and Post Surgery, Last Two From Dietary Changes



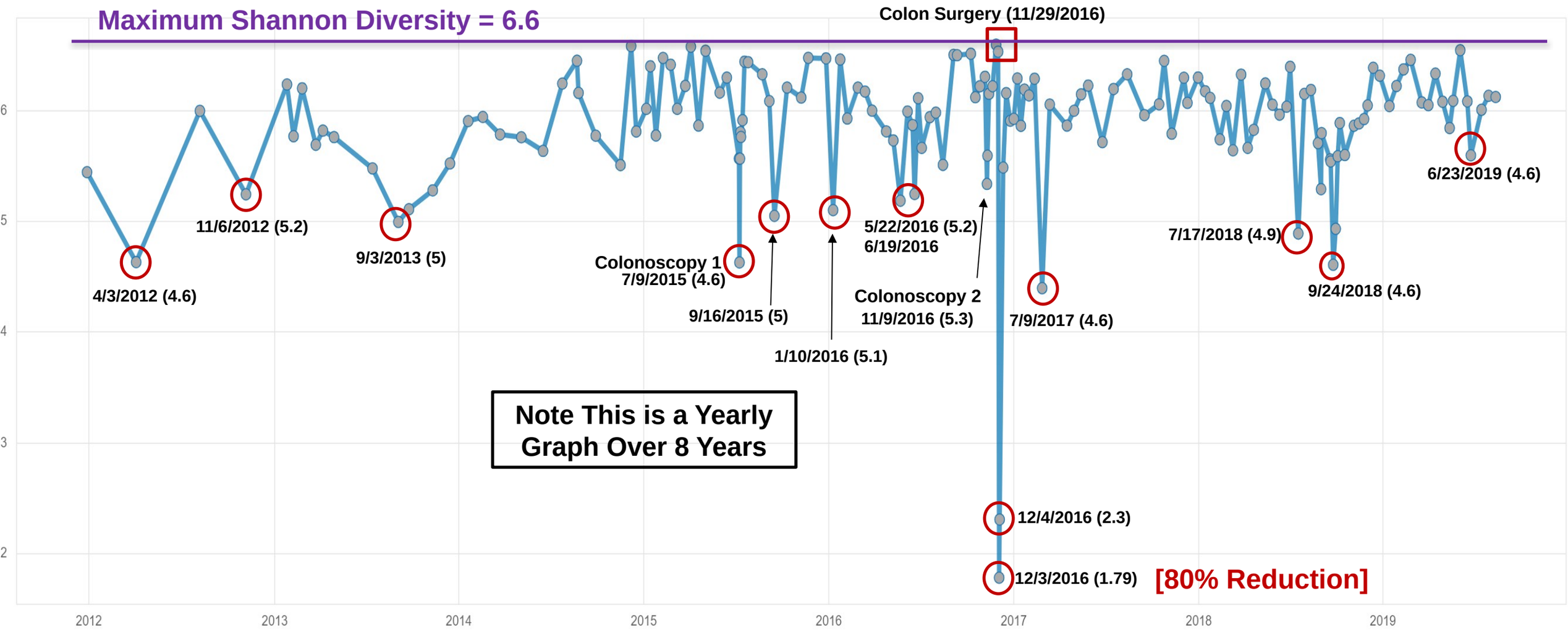
Note: Each Dot is a Single Day with a Full Gut Microbiome Ecology Consisting of 50 Genus, Each with a Relative Abundance





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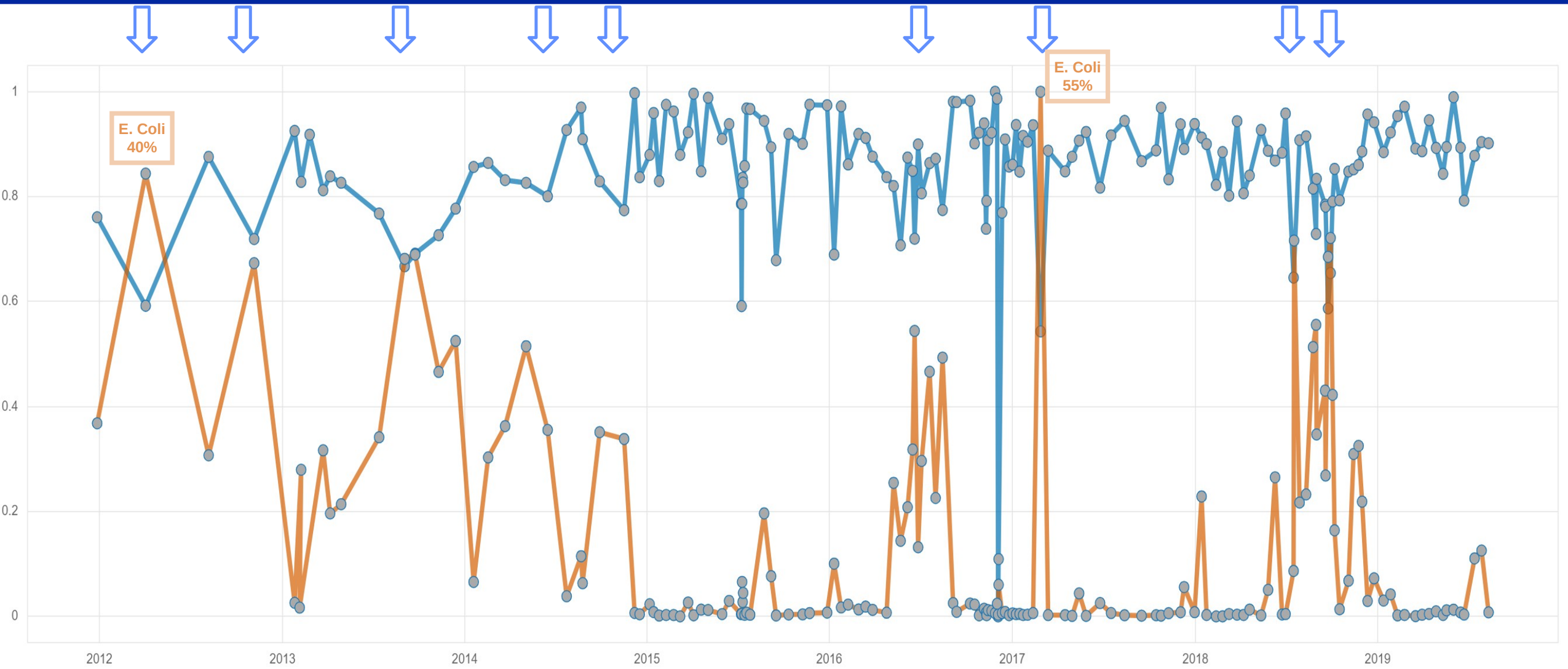
The Shannon Diversity of My Gut Microbiome Ecology Has Many Abrupt Drops-Some Caused by Medical Interventions



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Previous Graph

A Number of Shannon Diversity Dips Are Associated with E. coli blooms



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Experiment #1
Discovering Impact of Colonoscopy on Gut Microbiome Ecology

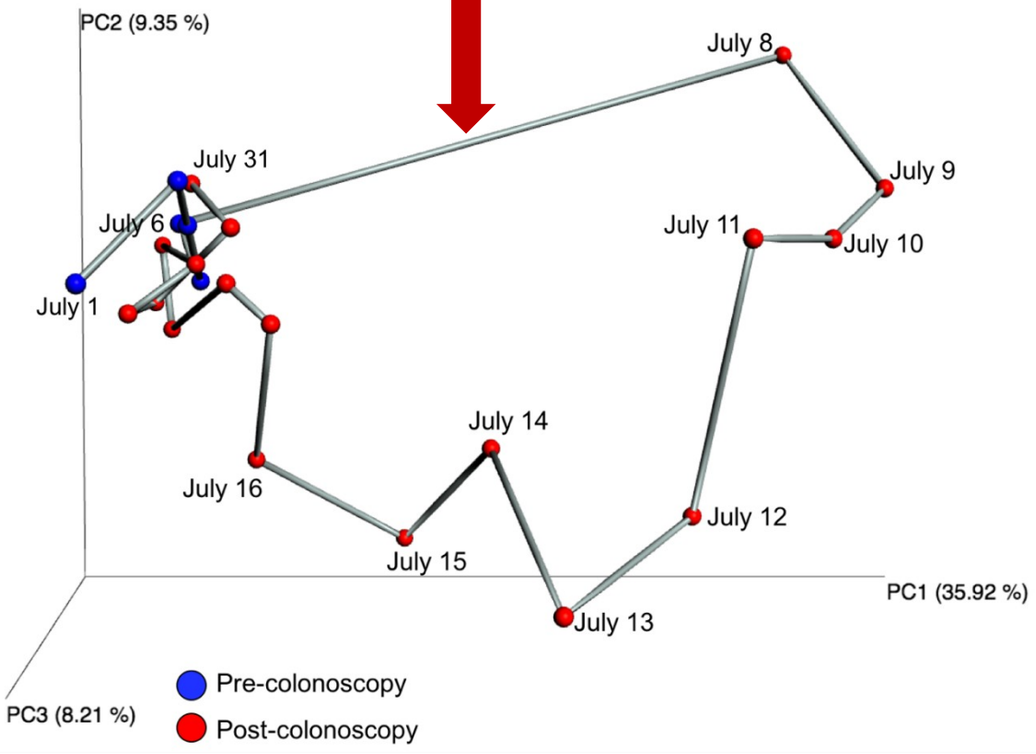
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My Microbiome Ecology Was Highly Disrupted by a Common Medical Intervention, But Eventually Returned to the Prior State

16 Million Colonoscopies Per Year in the US

July 2015 Colonoscopy

Shift Induced By Bowel Cleanse



Machine Learning Principal Component Analysis: Each Dot is a Single Day with a Full Gut Microbiome Ecology Consisting of 50 Genus, Each with a Relative Abundance

Tracking Human Gut Microbiome Changes Resulting from a Colonoscopy

Larry Smarr[1,2,5]; Embriette R. Hyde[4]; Daniel McDonald[4]; William J. Sandborn[2,3]; Rob Knight[2,4,5]

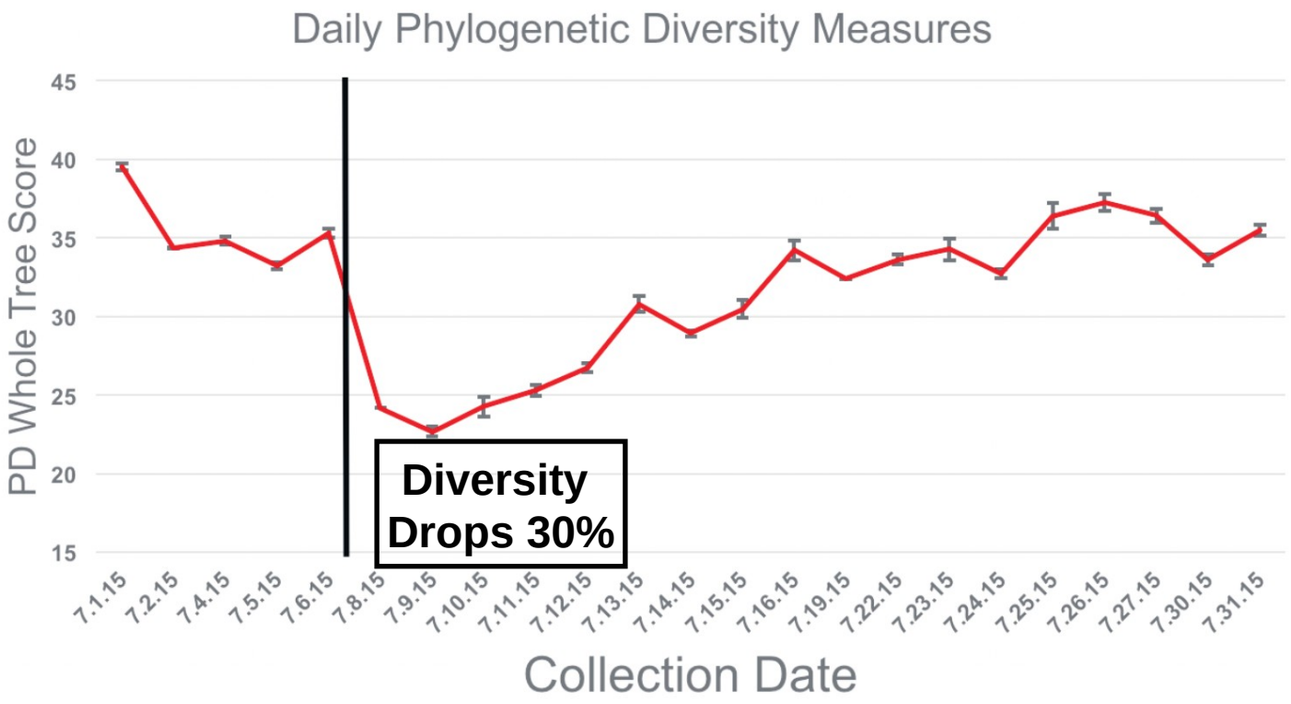
[1]University of California San Diego, Calit2, La Jolla, CA, USA; [2]University of California San Diego, Center for Microbiome Innovation, La Jolla, CA, USA; [3]University of California San Diego, Gastroenterology, San Diego, CA, USA; [4]University of California San Diego, Pediatrics, La Jolla, CA, USA; [5]University of California San Diego, Computer Science and Engineering, La Jolla, CA USA

Methods Inf Med. 56, 442-447 (2017)

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In the 2-3 Days Following Colon Cleanse There is a 50% Drop in Ecological Diversity and Major Changes in Microbial Genus Relative Abundance

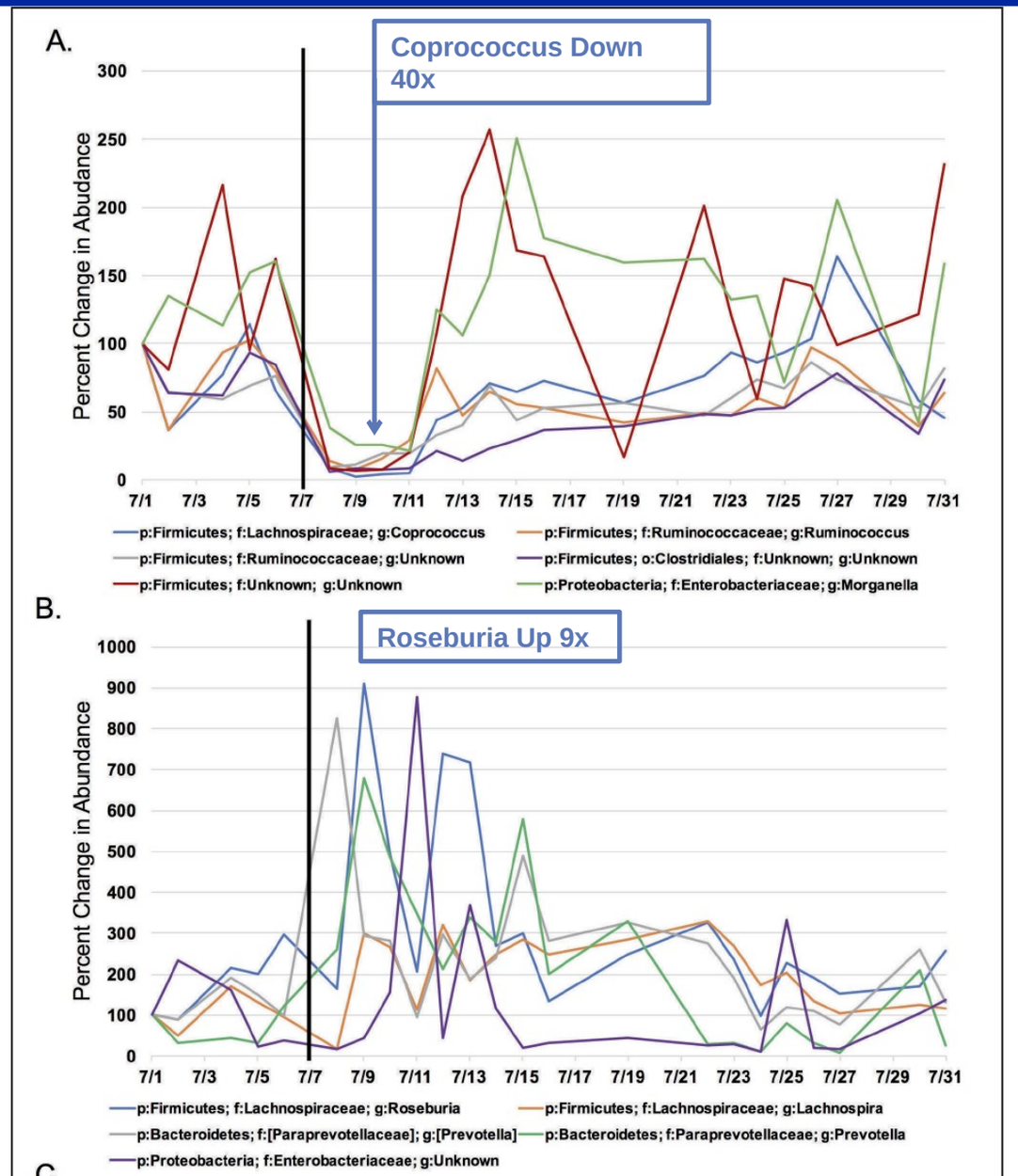
Prior Literature Concluded:
“Changes in Taxon Relative Abundance Up to 3X Were Observed Post-Colonoscopy”



Diversity Drops 30%

15 Million Colonoscopies Are Performed in the US Each Year

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Experiment #2
Discovering Microbe Strain Dynamics Using Metagenomics

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Published Paper on First 27 of Larry's 51 Metagenomically Sequenced Stool Samples

Metagenomics-Based, Strain-Level Analysis of *Escherichia coli* From a Time-Series of Microbiome Samples From a Crohn's Disease Patient

frontiers in Microbiology

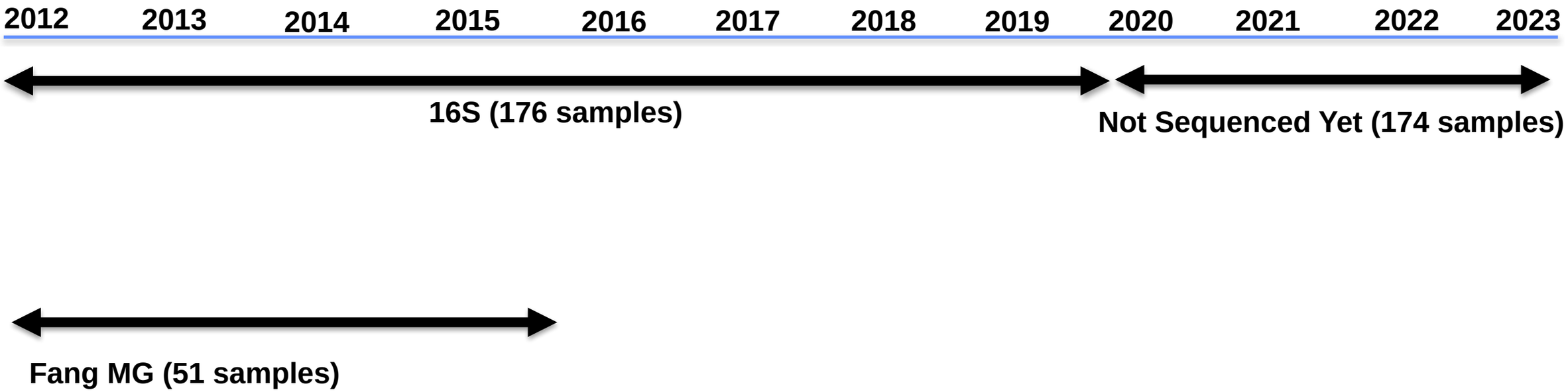
October 2018

Xin Fang[1], Jonathan M. Monk[1], Sergey Nurk[2], Margarita Akseshina[3], Qiyun Zhu[4], Christopher Gemmell[5], Connor Gianetto-Hill[5], Nelly Leung[6], Richard Szubin[1], Jon Sanders[6], Paul L. Beck[7], Weizhong Li[8,9], William J. Sandborn[10,11], Scott D. Gray-Owen[6], Rob Knight[4,12,13], Emma Allen-Vercoe[5], Bernhard O. Palsson[1,2,13,14] and Larry Smarr[12,13,15]**

[1] Department of Bioengineering, University of California, San Diego, La Jolla, CA, United States
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[4] Department of Pediatrics, University of California, San Diego, La Jolla, CA, United States
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[6] Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada
[7] Division of Gastroenterology, University of Calgary, Calgary, AB, Canada
[8] Human Longevity Inc., San Diego, CA, United States
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[10] Department of Medicine, University of California, San Diego, La Jolla, CA, United States
[11] Inflammatory Bowel Disease Center, University of California, San Diego, La Jolla, CA, United States
[12] Department of Computer Science and Engineering, University of California, San Diego, La Jolla, CA, United States
[13] Center for Microbiome Innovation, University of California, San Diego, La Jolla, CA, United States
[14] The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Lyngby, Denmark
[15] California Institute for Telecommunications and Information Technology, University of California, San Diego, La Jolla, CA, United States

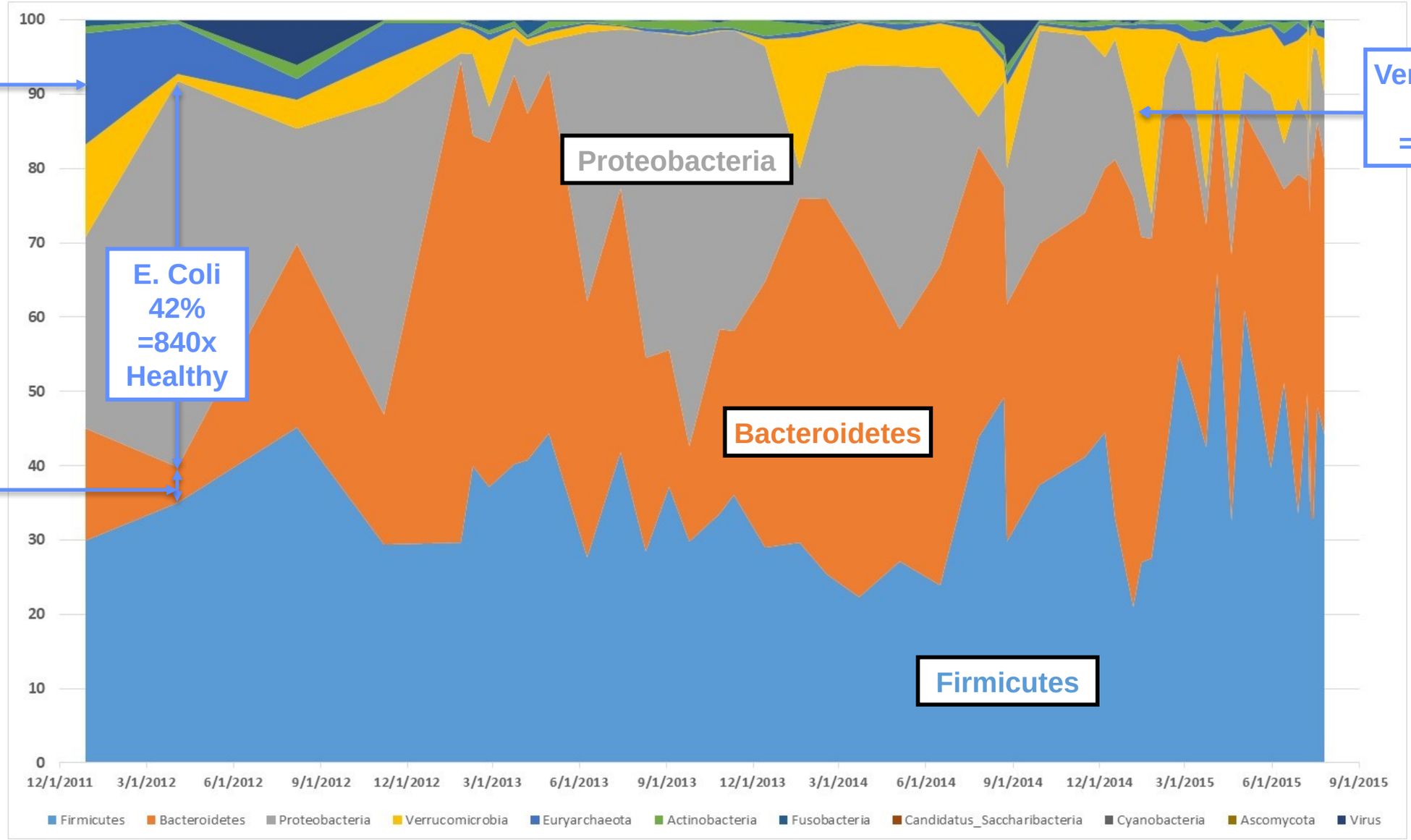
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16S and Metagenomic Sequencing of Smarr Long Time Series



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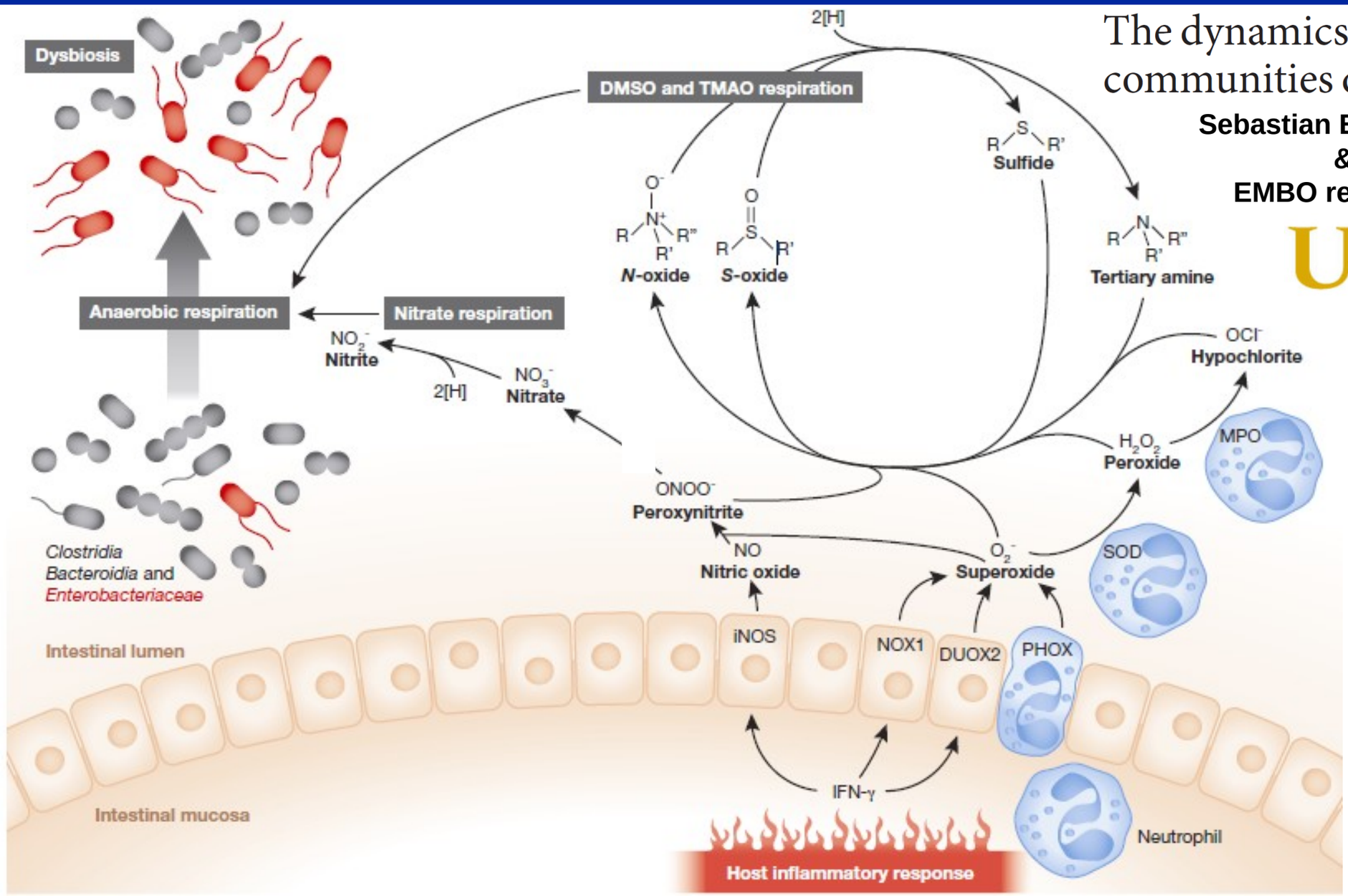
We Metagenomically Sequenced 51 of My Stool Samples Over 2.5 Years: Phylum Level Taxonomic Evolution Reveals Major Divergence from Healthy



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Sequencing Rob Knight Lab; Analysis Xin Fang, UCSD

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

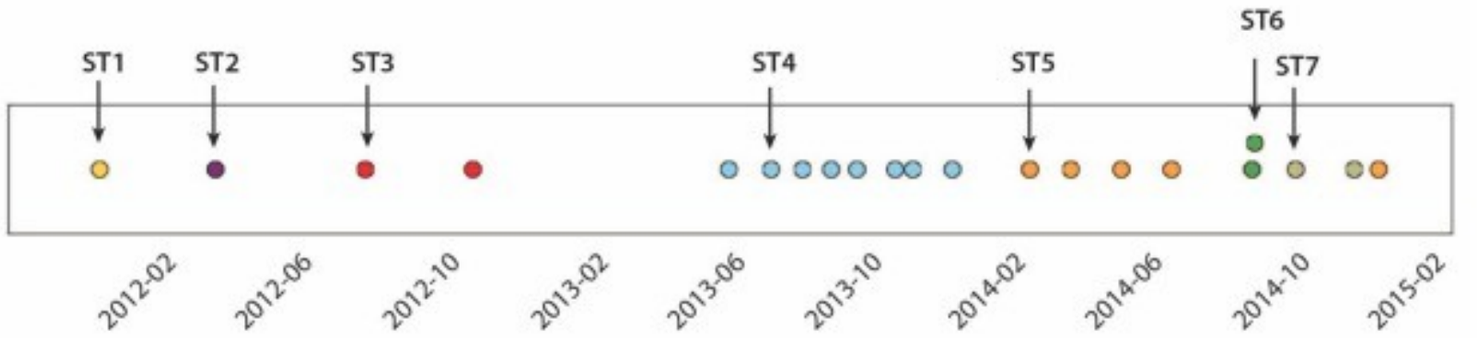


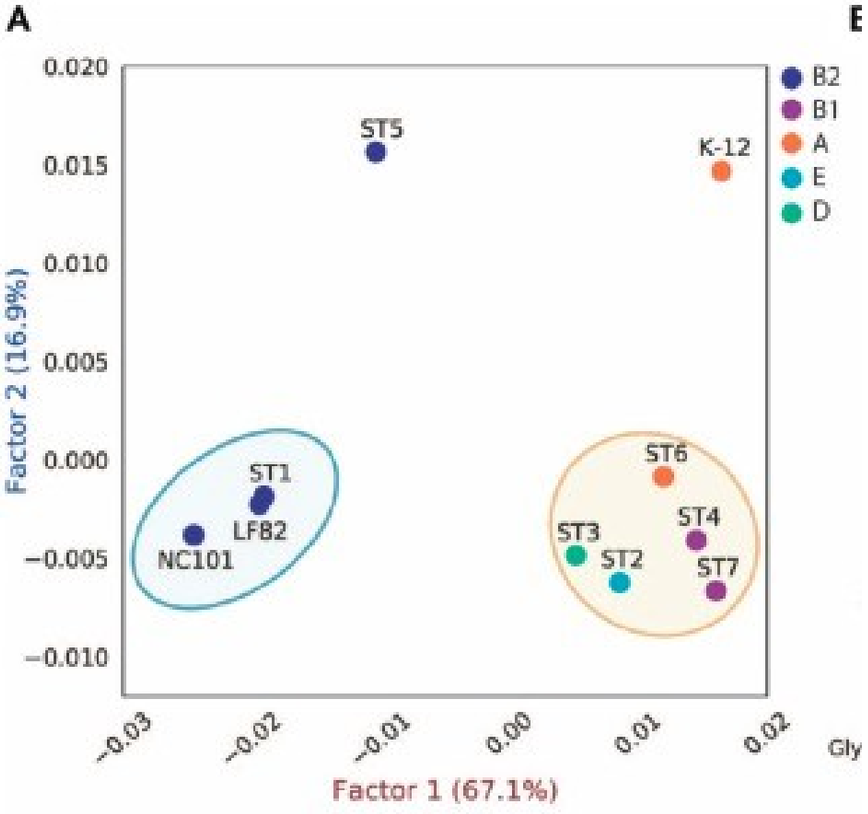
The dynamics of gut-associated microbial communities during inflammation

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

UCDAVIS

Strain-Specific Analysis of E. coli Demonstrating Evolution in Strain Space





- For 27 samples collected before 2015 with abundant *E. coli*, we performed strain-level analysis based on SNP profiles
- Seven different *E. coli* strain were dominating at different time points
- Analysis of the *de novo* assemblies of the 7 strains showed that ST1 collected at peak inflammation is the most similar to pathogenic strains in virulence factor and metabolic capabilities

Xin Fang, et al. Frontiers in Microbiology

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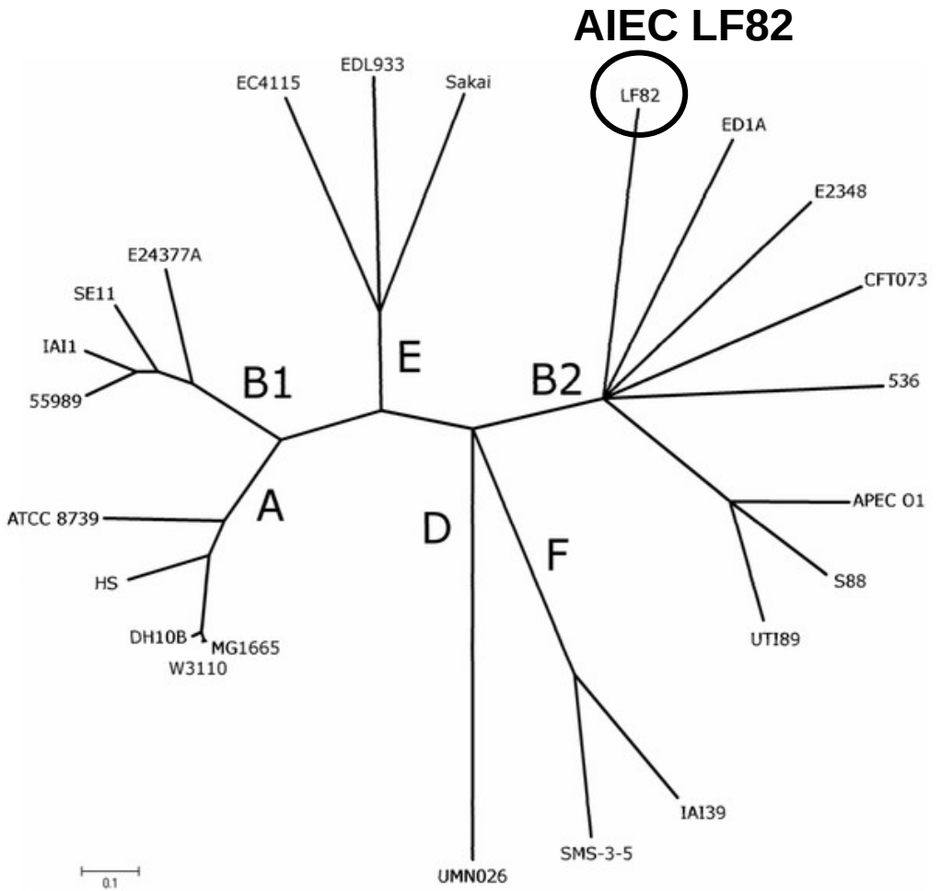
Does Intestinal Inflammation Select for Pathogenic Strains That Can Induce Further Damage?

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

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

***Family Containing E. coli**

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

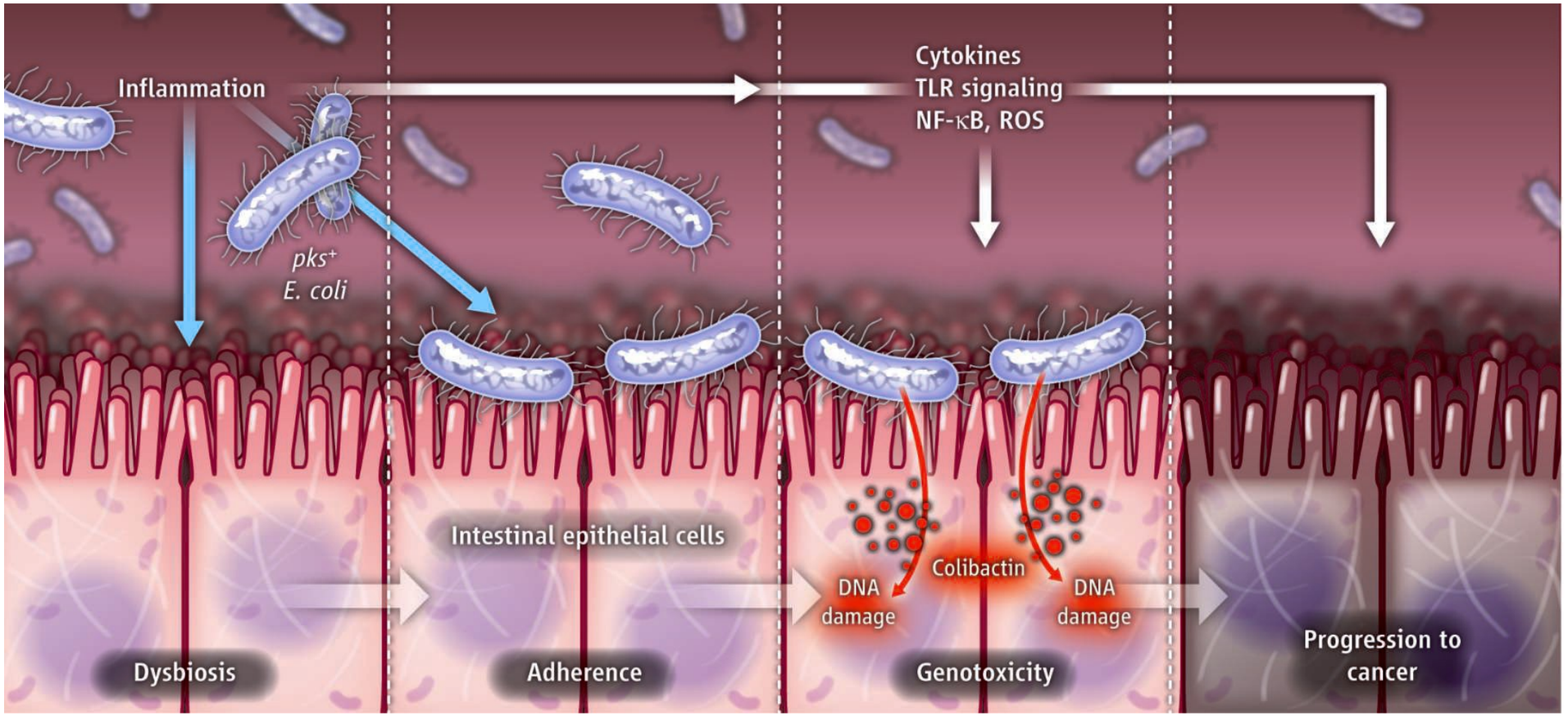


E. coli/Shigella Phylogenetic Tree
Miquel, et al.
PLOS ONE, v. 5, p. 1-16 (2010)

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

Escherichia coli Strain NC101 (Closely Related to LF82 & ST1)



Science
AAAS

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

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Experiment #3
Discovering Impact of Colon Surgery on Gut Microbiome Ecology

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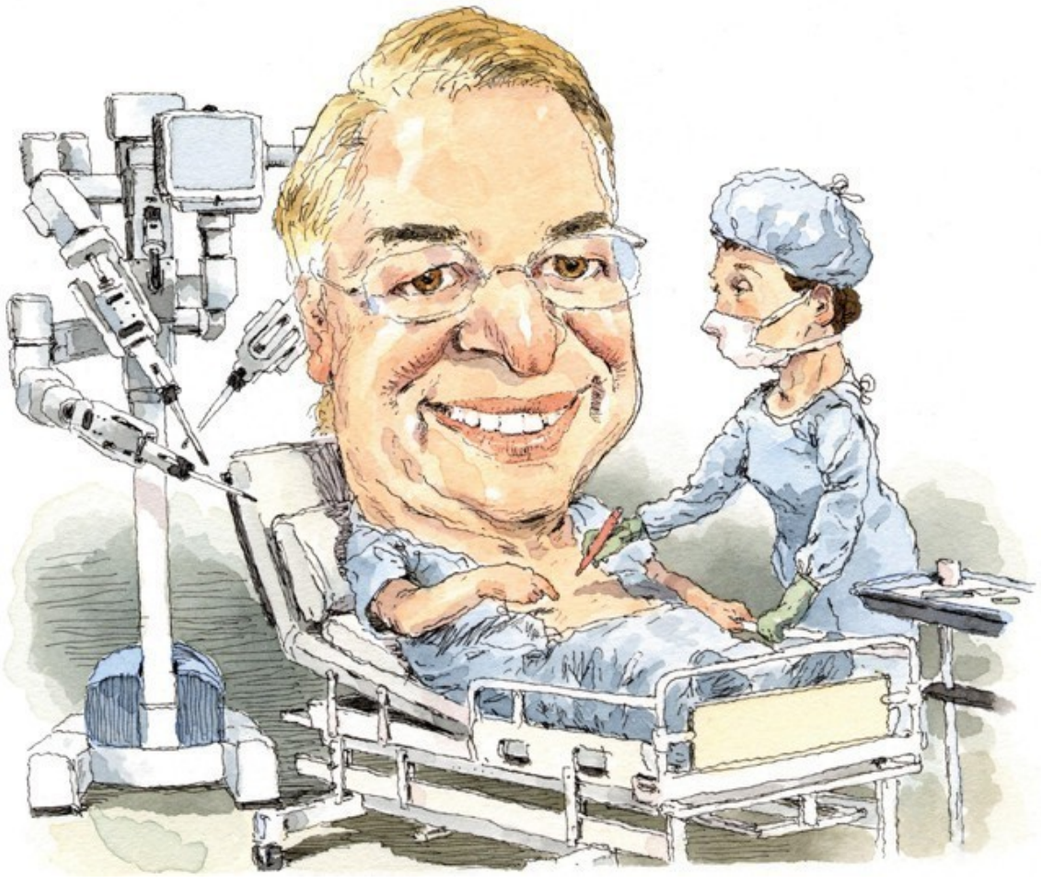
The Ability to See Inside Myself Led to My Co-Planning My Own Surgery

The Atlantic

The Man Who Saw Inside Himself

For years, Larry Smarr has used a supercomputer to monitor his health and peer at his organs. Recently, he used his knowledge to help direct his own surgery.

MARK BOWDEN | MARCH 2018 ISSUE | HEALTH



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2012 MRI Video Reveals Diseased Sigmoid Colon



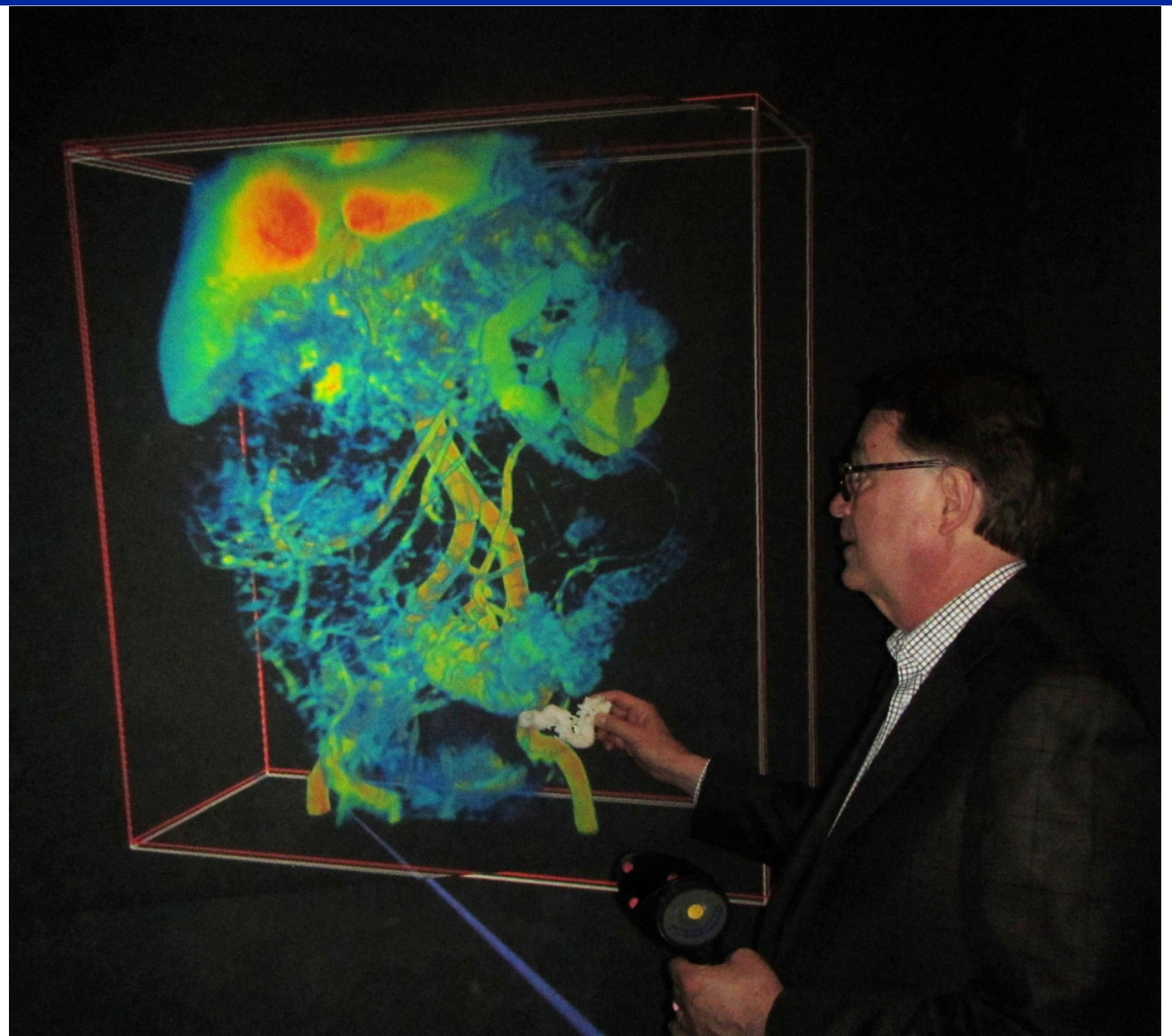
Note-This Portion of My Sigmoid Colon Doesn't Move

Source: Cynthia Santillan, MD Radiologist, UCSD

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3D Volumetric Visualization From MRI In Calit2 Virtual Reality StarCAVE

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

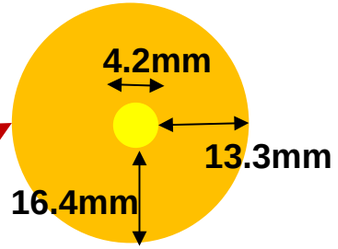


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MRI Slice Through Sigmoid Colon Reveals Thick Walls and Very Narrow Lumen



Source: Smarr MRI Oct. 25, 2016
Reading by Cynthia Santillan,
MD Radiologist, UCSD



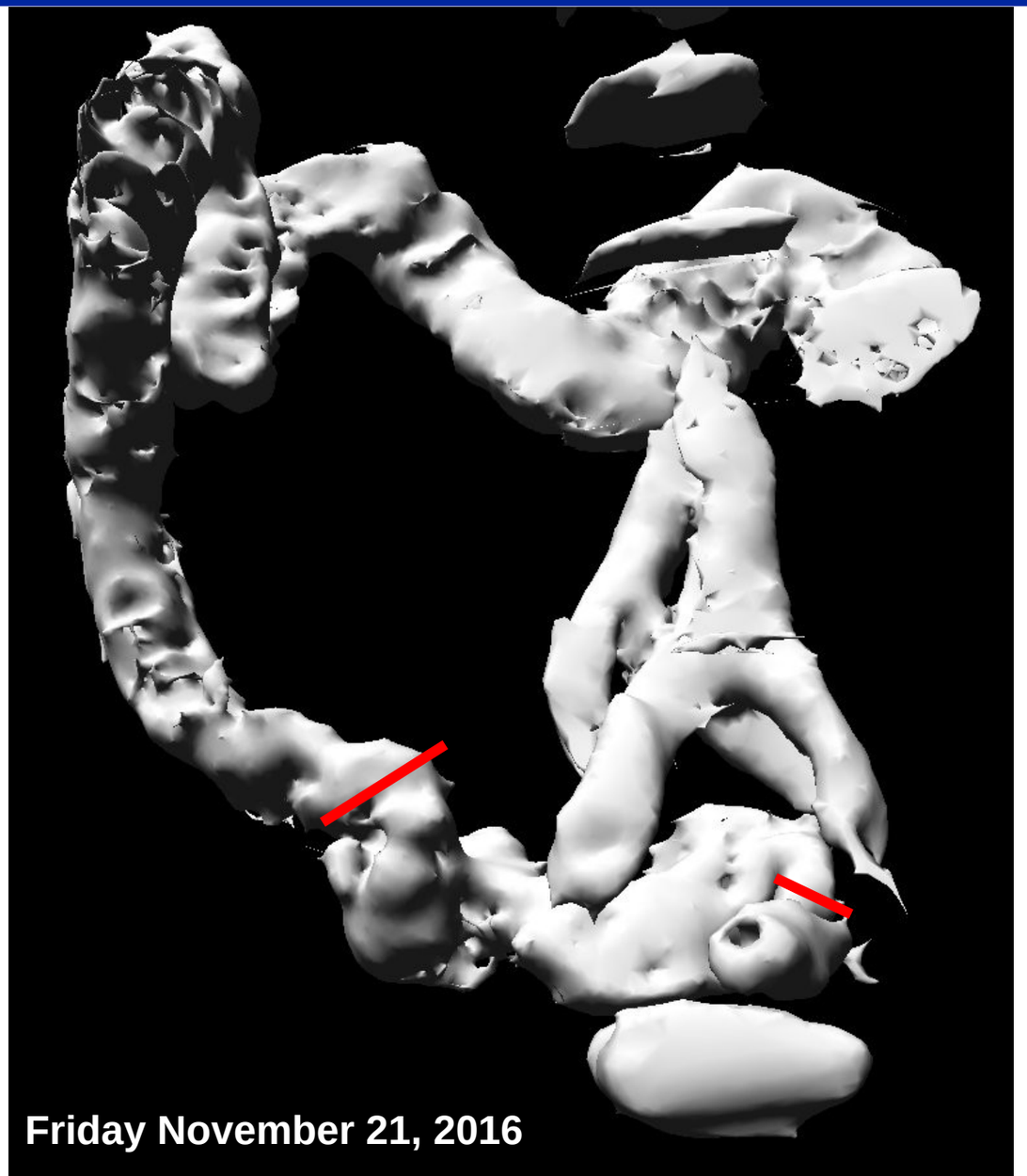
Normal opening (bright yellow) is 40mm; mine is 1/10 the diameter it should be.

Normal wall thickness (dark yellow) is 3mm, so wall thickness is 4-5 times as thick as it should be.

Patient & Surgeon Doing Pre-Surgical Planning in QI Virtual Reality: Using Virtual Reality As Input for Positioning The Two Resection Cuts



Surgeon Sonia Ramamoorthy, MD
in Calit2 Virtual Reality CAVE



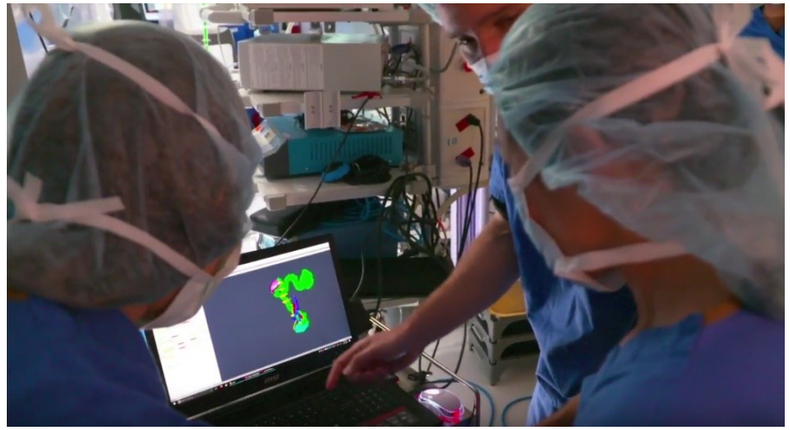
Friday November 21, 2016

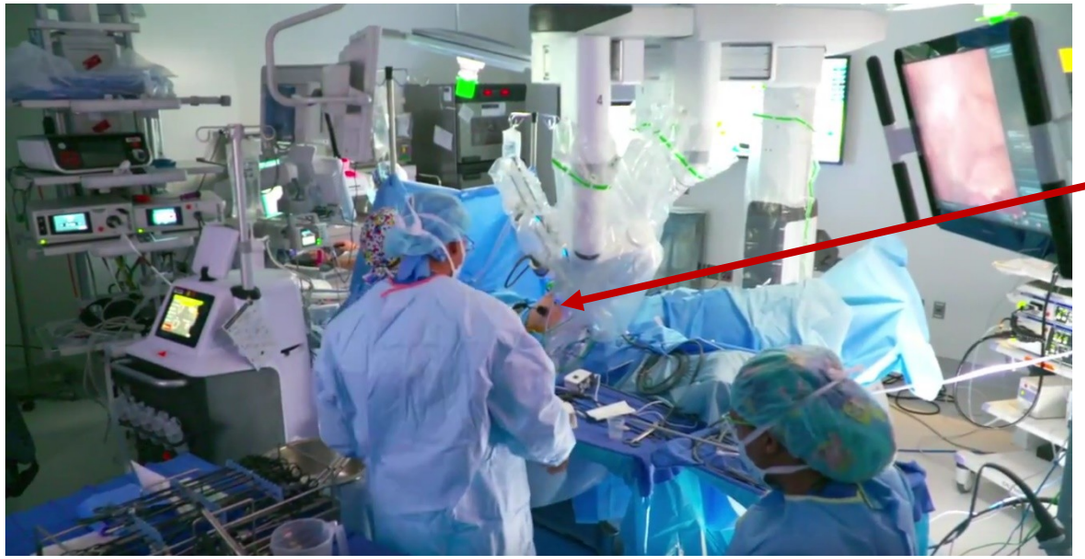
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Colon visualization by Jurgen Schulze, Calit2;
Photo credit Tom DeFanti, Calit2

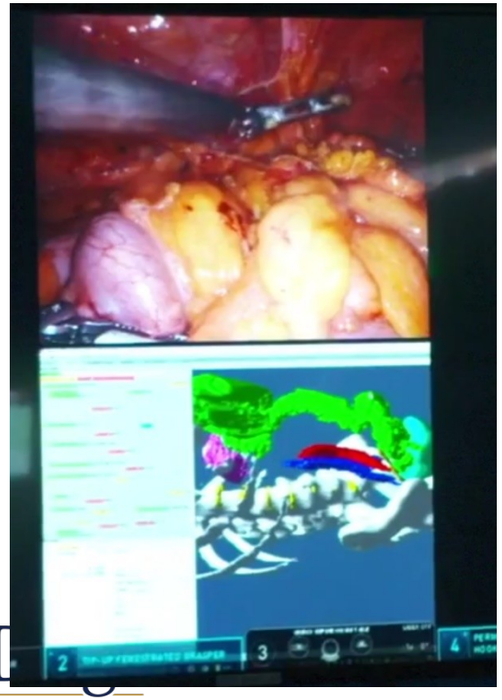
Dr. Ramamoorthy Used Calit2 Interactive 3D Anatomy To Guide Her Surgical Team During My Sigmoid Colon Resection on November 29, 2016

Dr. Schulze Rotating 3D Organs To Match Up With da Vinci Arms and Internal Camera



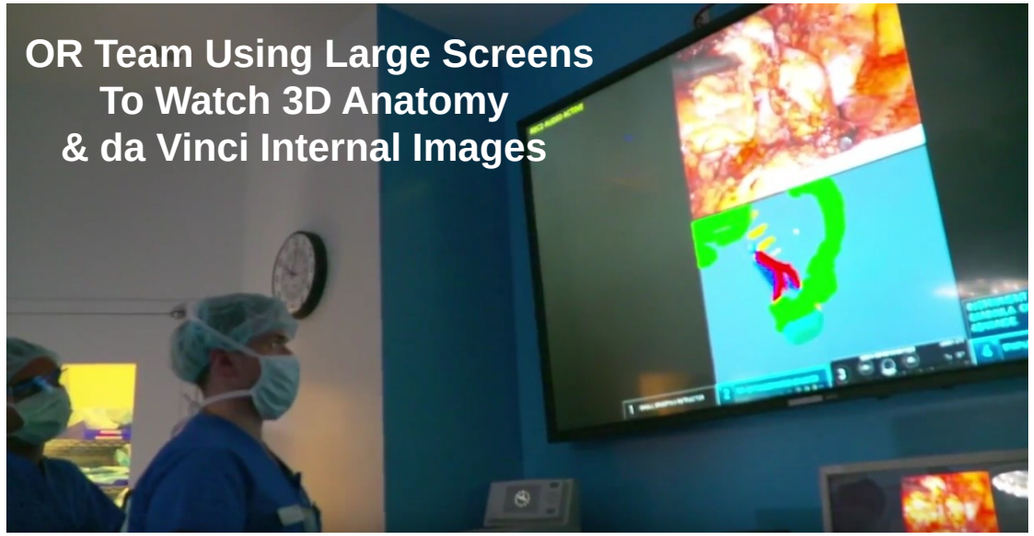


Patient Smarr With da Vinci Robot Arms Inside Him





Dr. Ramamoorthy Operating da Vinci Xi Robot During Surgery

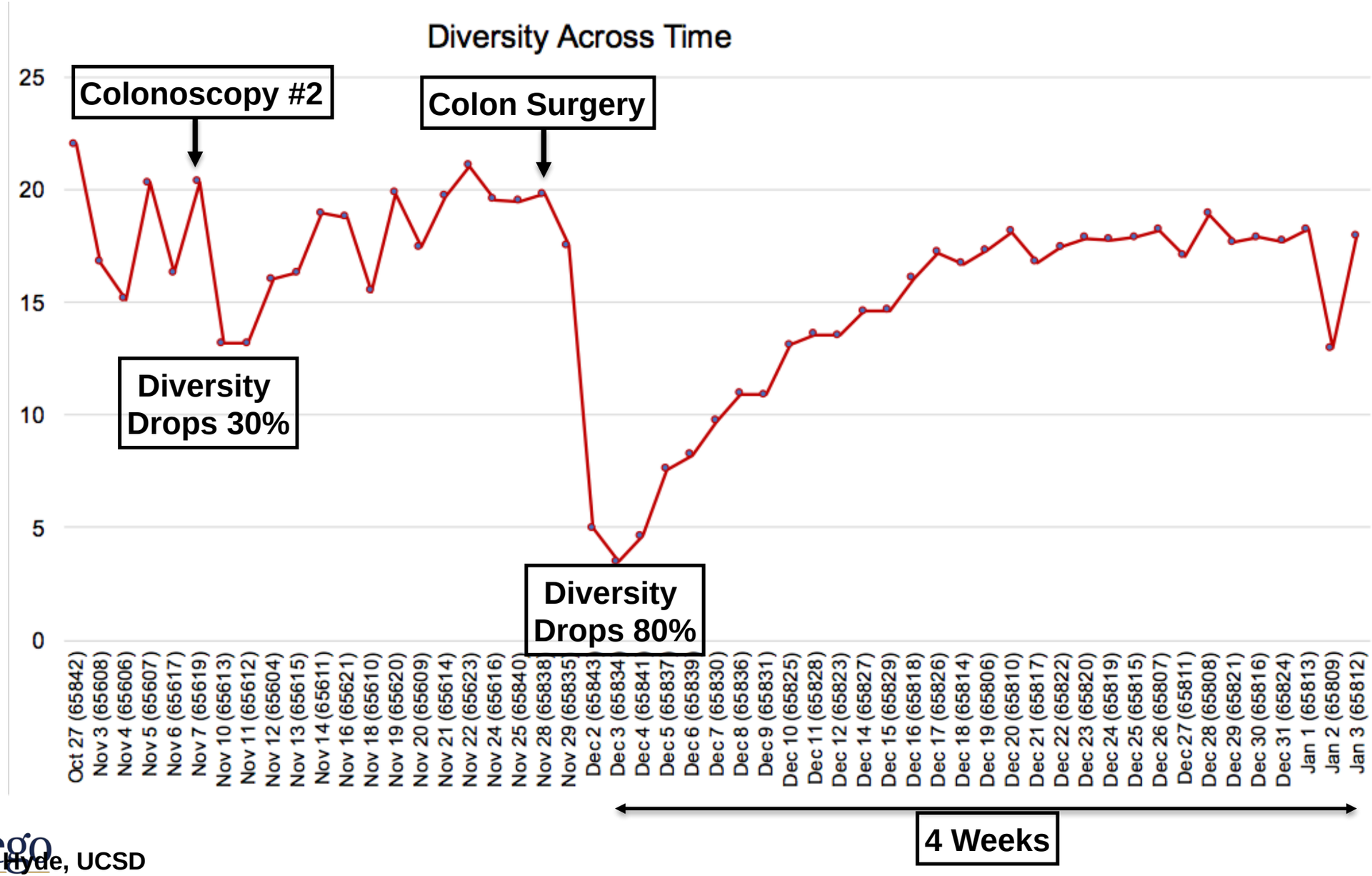


OR Team Using Large Screens To Watch 3D Anatomy & da Vinci Internal Images

https://lsmarr.net/look-twice-cut-once/

UC San D

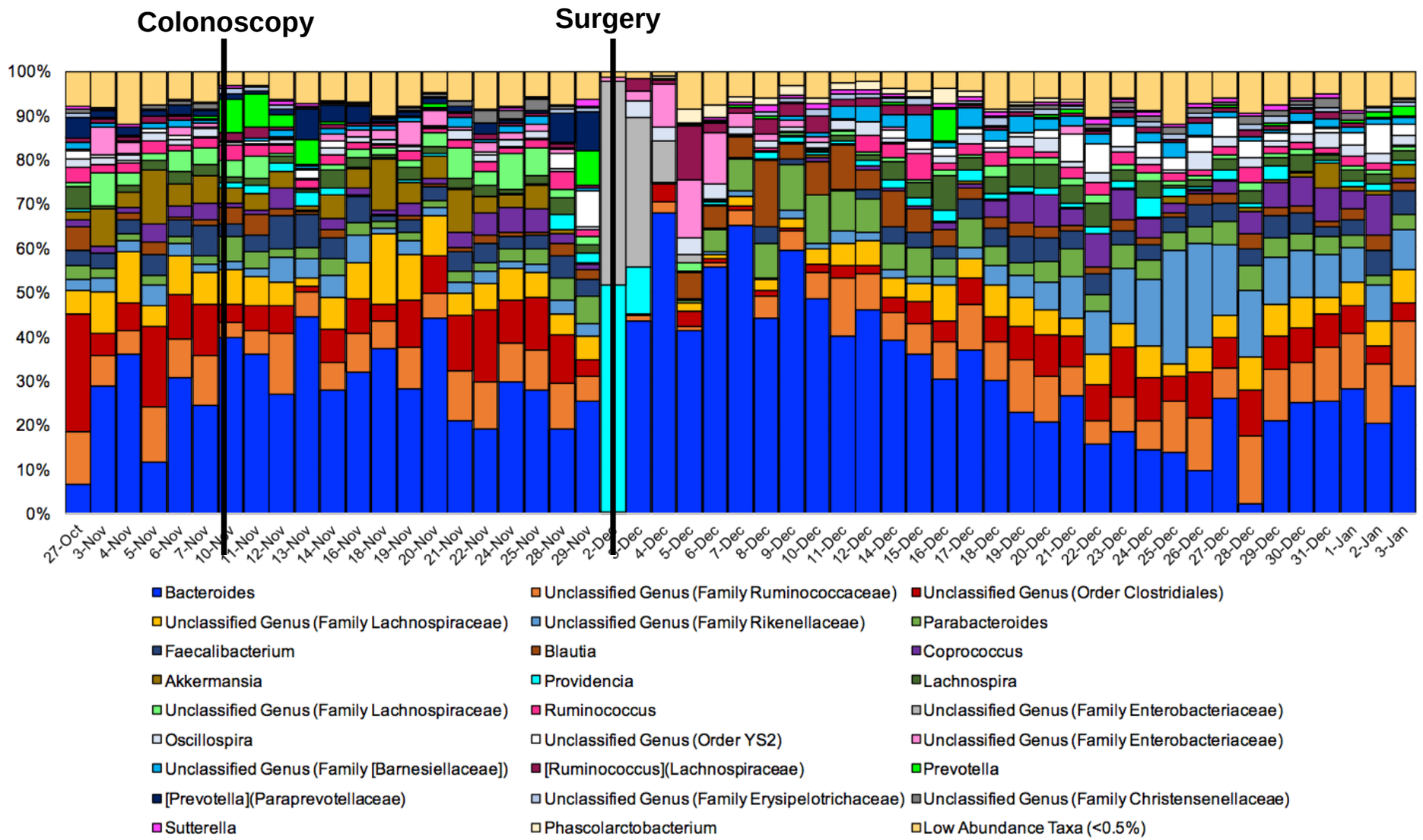
Sigmoid Colon Resection Surgery Wiped Out My Gut Microbiome Ecological Diversity: It Slowly Recovered Over a Month, But To a New State



UC San Diego

Source: Embriette Hyde, UCSD

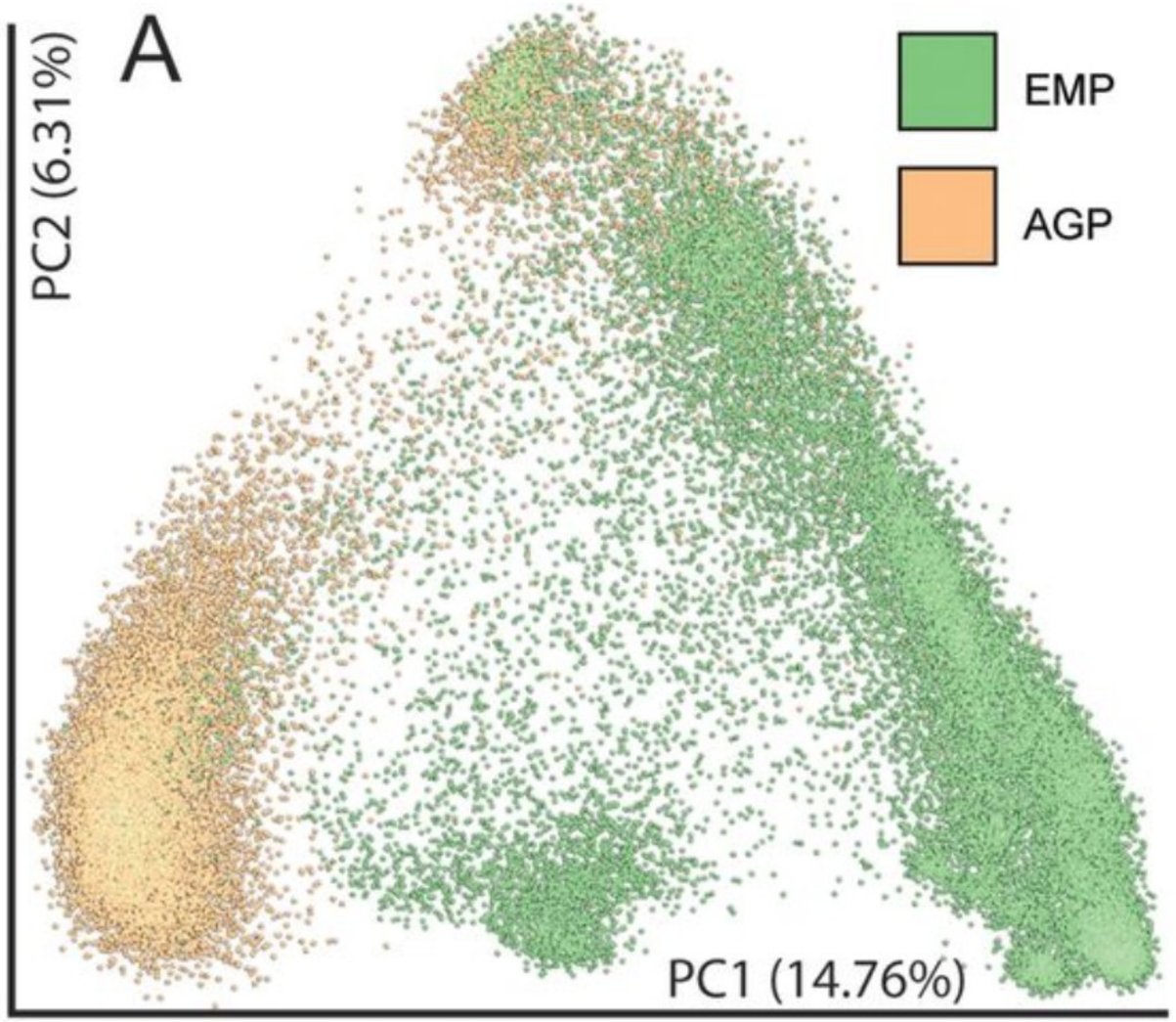
Major Gut Microbiome Drop in Diversity Seen from 16S Genus Profiles: Daily Samples Before and After Abdominal Surgery

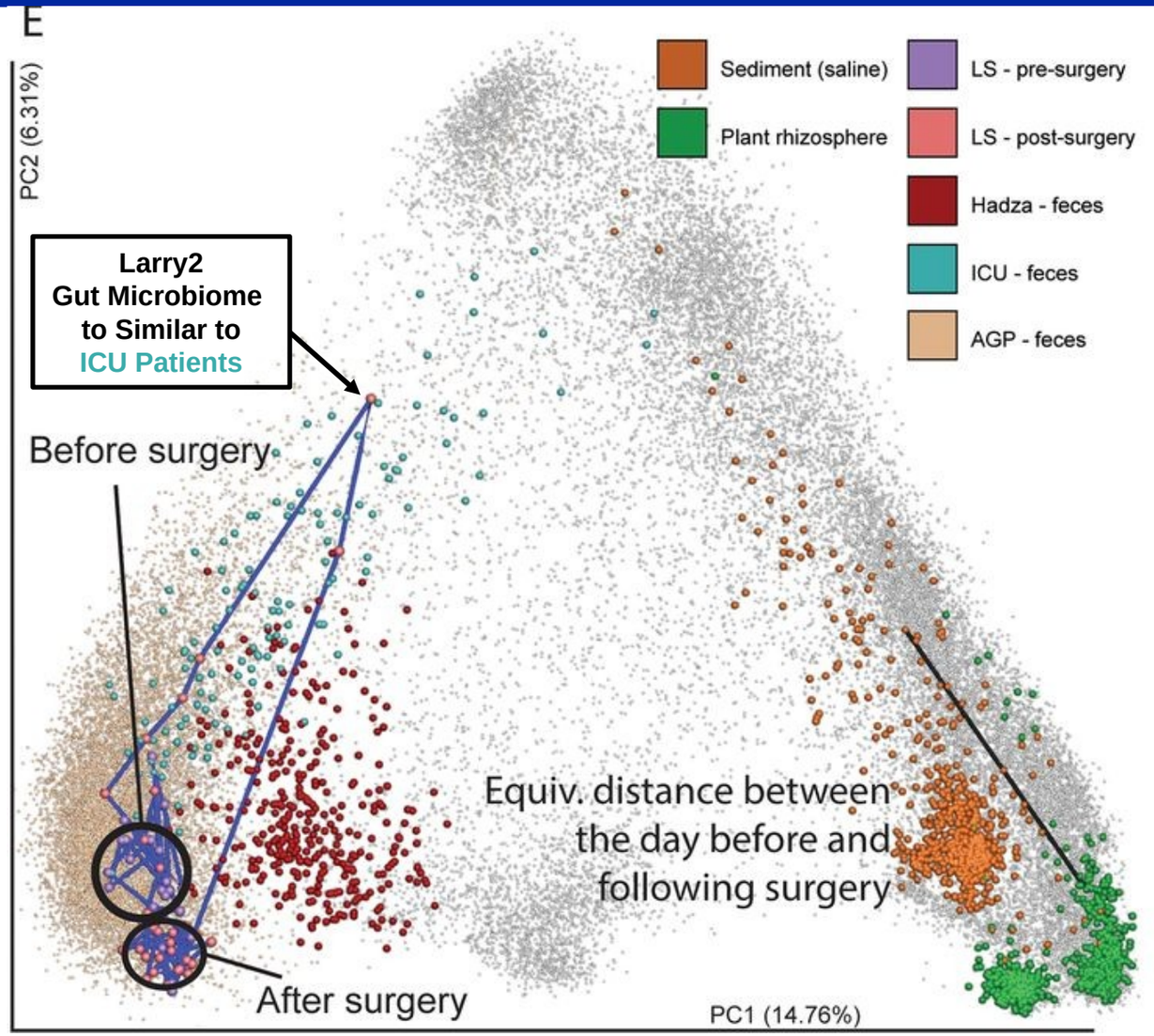


UC San Diego

Source: Embriette Hyde, UCSD

My Gut Microbiome Changed More After Colon Resection Surgery Than the Difference Between 10,000 Individuals in the American Gut Project!





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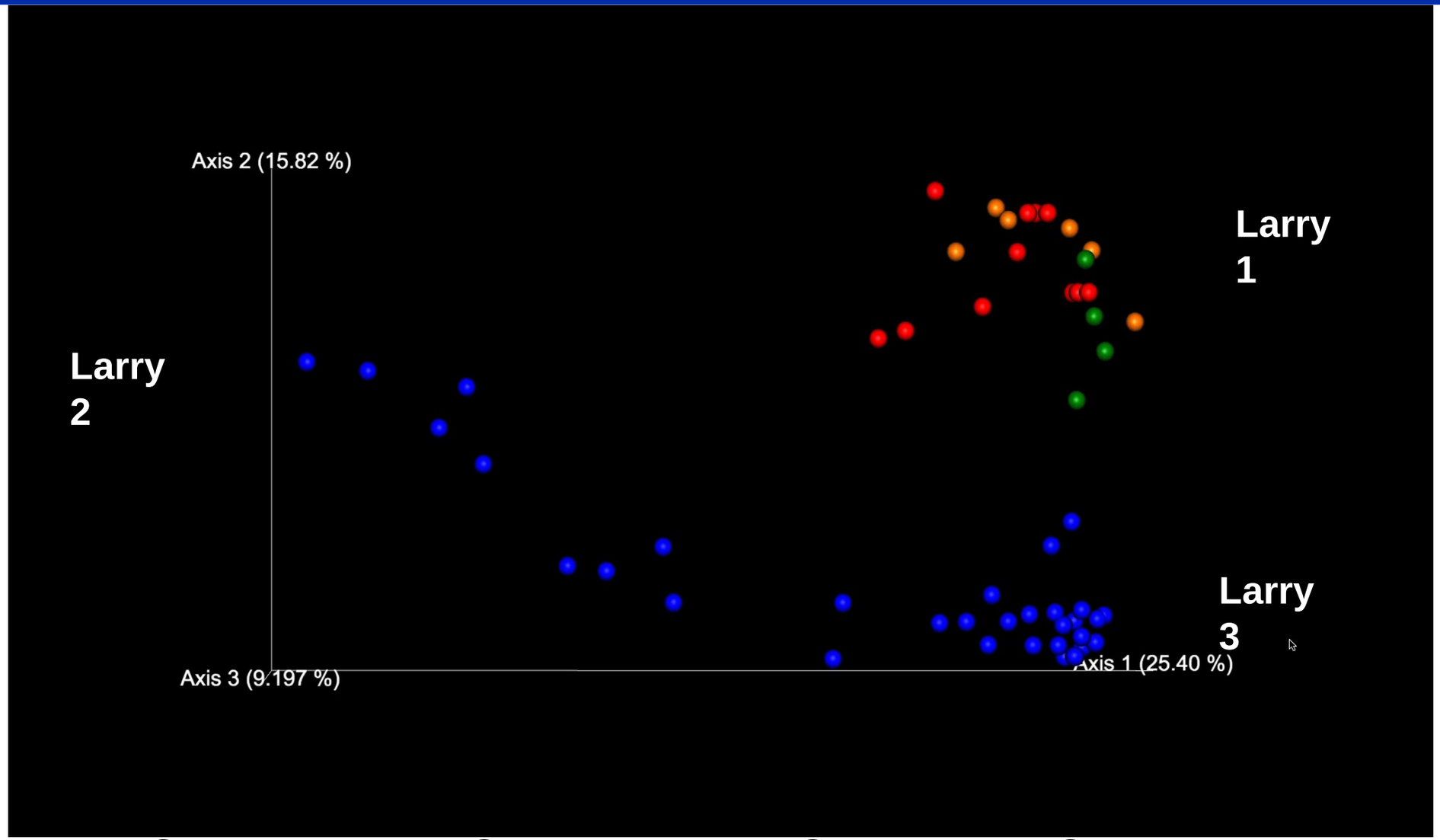
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American Gut: an Open Platform for Citizen Science Microbiome Research

Daniel McDonald et al. mSystems 2018; doi:10.1128/mSystems.00031-18

Principal Component Analysis (PCA) Reveals Major Shift in Gut Microbiome Ecology Following Abdominal Surgery With Return to Different Equilibrium State

Each Dot is That Day's Microbiome Ecology Projected Into 3-Space Using PCA Dimensional Reduction to Reveal Clusters Of Similar Ecologies



58 Samples 10/27/2016 -1/3/2017

Inflamed Disease State

⇩

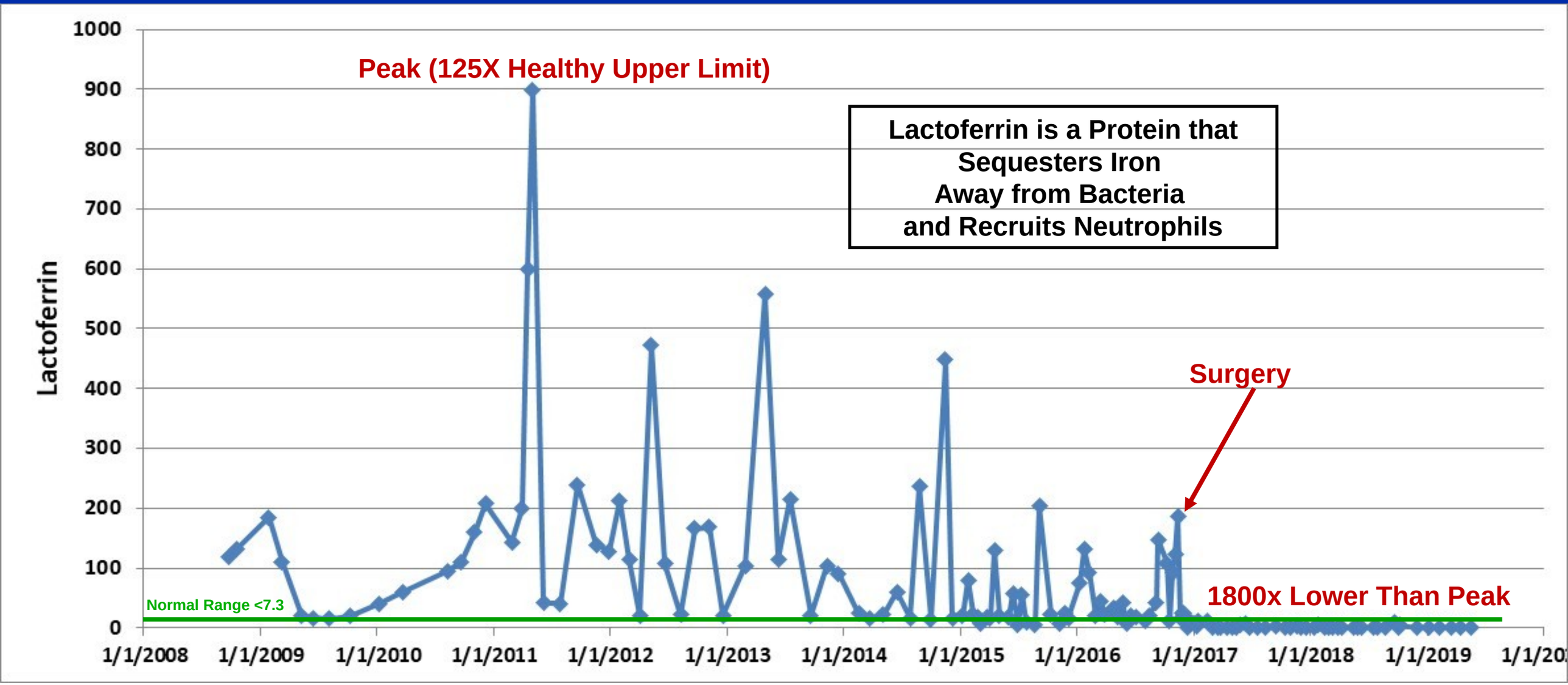
Non-Inflamed Healthy Post-Surgery State

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

UC San Diego

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

Lactoferrin Colonic Inflammation: Abrupt Shift to Healthy Following Surgical Resection



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Student Question: What Microbe Species Are Correlated With This Sudden Drop Post-Surgery?

Sequestering Iron from Enterobacteriaceae Is a Key Host Response

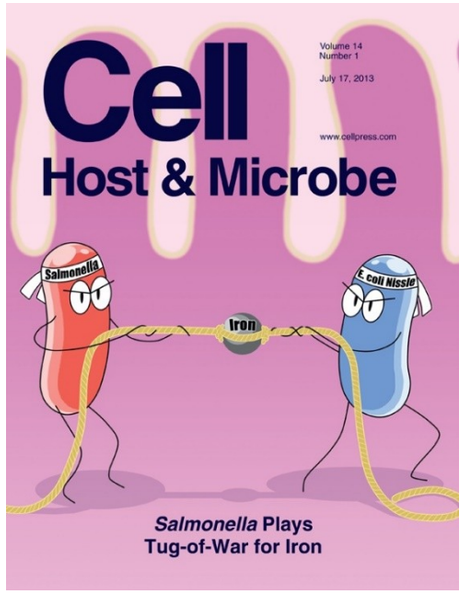
The Journal of Infectious Diseases

SUPPLEMENT ARTICLE 2021

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Harnessing Iron Acquisition Machinery to Target *Enterobacteriaceae*

Artur Sargun,[1] Romana R. Gerner,[2] Manuela Raffatellu,[2,3,4,a] and Elizabeth M. Nolan,[1,a]



Cell Host Microbe. 2013 Jul 17;14(1):26-37. doi: 10.1016/j.chom.2013.06.007.

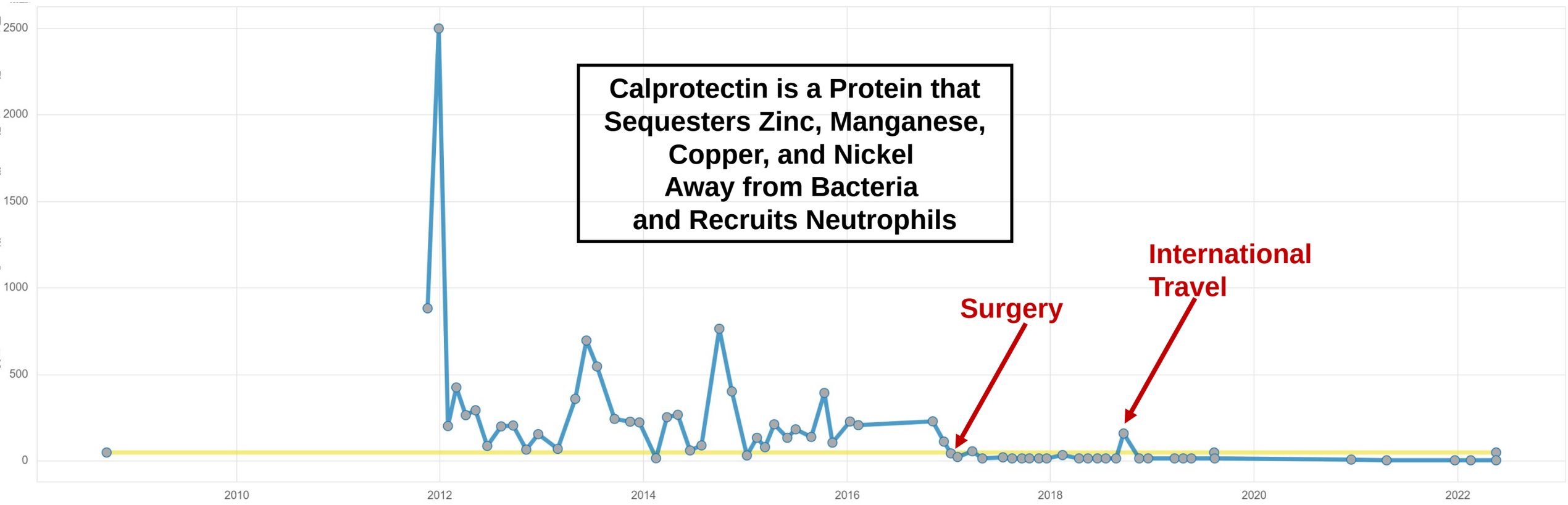
Probiotic bacteria reduce salmonella typhimurium intestinal colonization by competing for iron

Elisa Deriu [1], Janet Z Liu, Milad Pezeshki, Robert A Edwards, Roxanna J Ochoa, Heidi Contreras, Stephen J Libby, Ferric C Fang, Manuela Raffatellu

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LS Calprotectin Time Series From Stool Samples

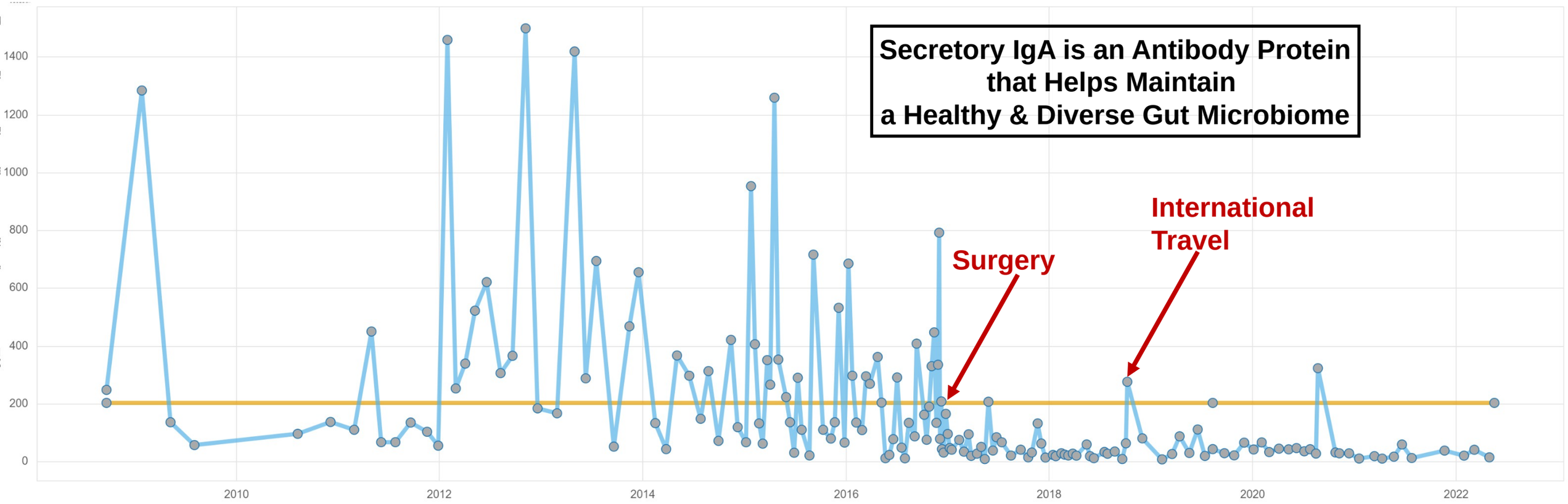
Student Question: What Microbe Species Are Correlated With This Sudden Drop Post-Surgery?



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LS Secretory IgA Time Series

Student Question: What Microbe Species are Correlated with the Sudden Drop Post Surgery?



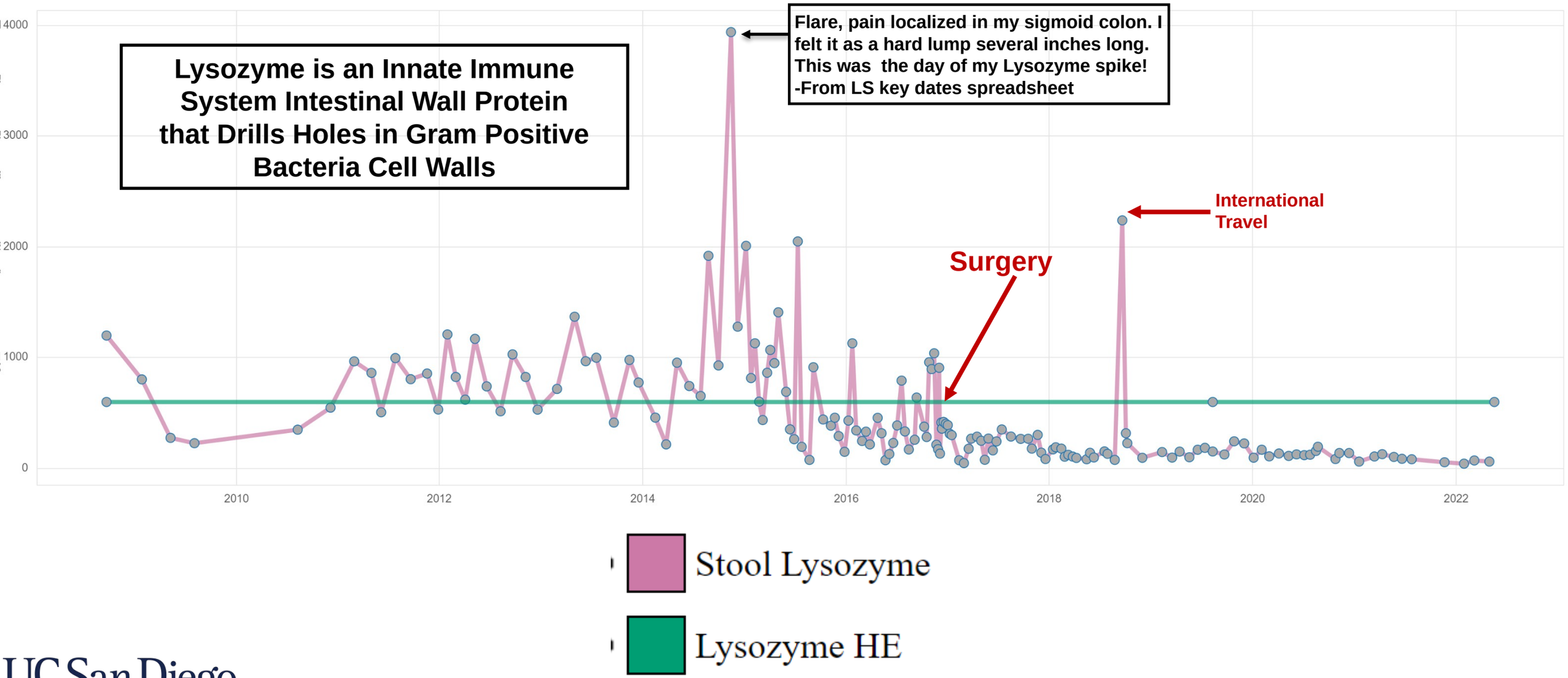
SIGA HE

Stool SIgA

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LS Lysozyme Time Series

Student Question: What Microbe Species, Particularly Gram Positive, are Correlated with the Sudden Drop Post Surgery?



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Future Directions

Discovering Human Host and Gut Microbiome Metaproteomics Dynamics

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Adding Metaproteomics to Metagenomics and Metabolomics of My Stool Time Series

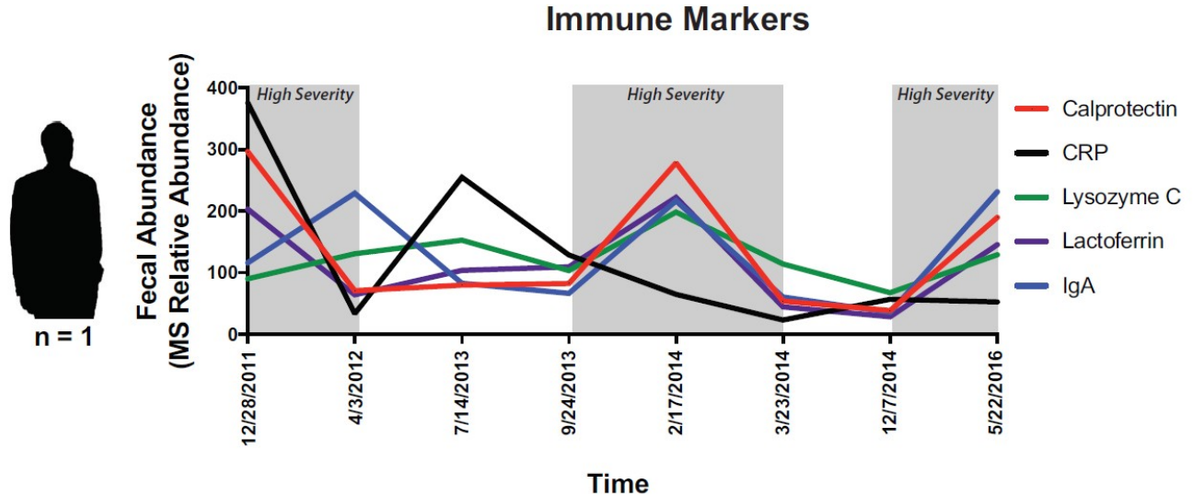
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RESEARCH ARTICLE
Host-Microbe Biology

Evaluating Metagenomic Prediction of the Metaproteome in a 4.5-Year Study of a Patient with Crohn's Disease

Robert H. Mills, Yoshiki Vázquez-Baezac, Qiyun Zhuc, Lingjing Jiang, James Gaffney, Greg Humphrey, Larry Smarr, Rob Knight, David J. Gonzalez
UCSD

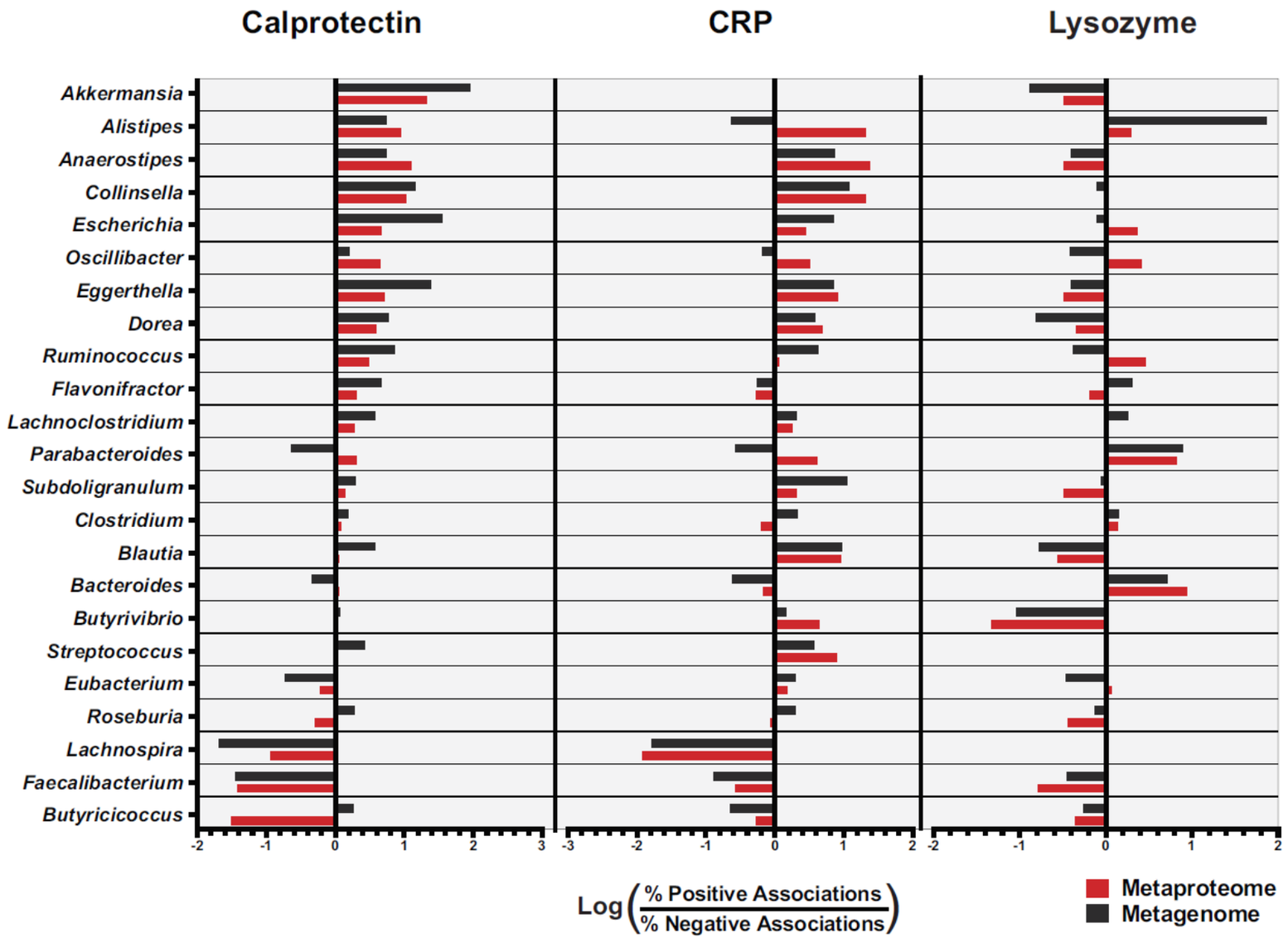
"Utilizing multiplexed quantitative proteomics and shotgun metagenomic sequencing of 8 time points, we quantified over 29,000 protein groups and 110,000 [microbe] genes and compared them to five protein biomarkers of disease activity."



https://journals.asm.org/doi/10.1128/msystems.00337-18

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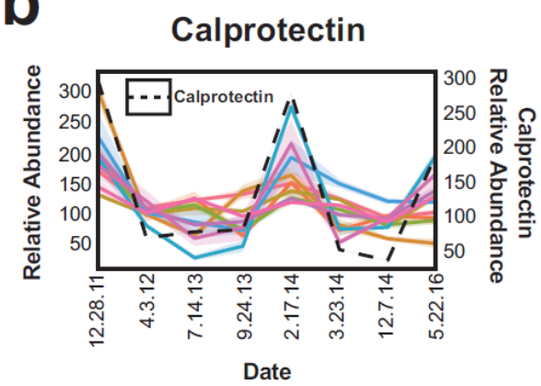
Correlating Gut Microbiome Taxonomy With Human Inflammation/Immune Biomarkers

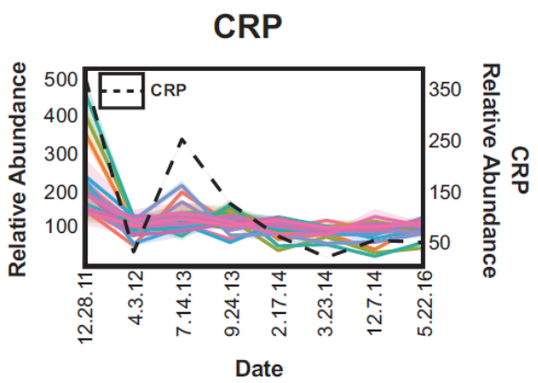


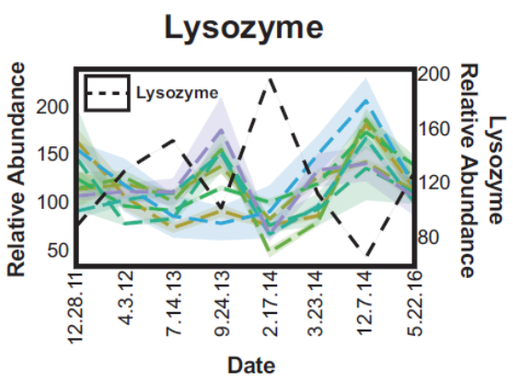
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Finding Proteins That Correlate or Anti-Correlate With Human Inflammation/Immune Biomarkers

b







Amino Acid Transport & Metabolism

Protein Name and Genus

- Aspartyl aminopeptidase, *Anaerostipes*
- ABC-type dipeptide transport system, *Collinsella*
- Glycine cleavage system T protein, *Alistipes*
- Urea amidohydrolase (urease), *Clostridium*
- Saccharopine dehydrogenase, *Ruminococcus*
- Di- and tripeptidases, *Anaerostipes*
- Dihydrodipicolinate reductase, *Ruminococcus*
- ABC-type polar amino acid transporter, *Clostridium*
- Homoserine dehydrogenase, *Ruminococcus*
- ABC-type dipeptide transporter, *Clostridium*
- DAHP synthase, *Anaerostipes*
- Argininosuccinate synthase, *Ruminococcus*
- Acetylornithine deacetylase, *Anaerostipes*
- Diaminopimelate epimerase, *Anaerostipes*
- Cysteine sulfinate desulfinase, *Anaerostipes*
- Argininosuccinate synthase, *Ruminococcus*
- DAHP synthase, *Ruminococcus*
- Urea amidohydrolase (urease), *Ruminococcus*

Chaperones

Protein Name and Genus

- Molecular chaperone, *Unknown*
- Molecular chaperone, *Collinsella*
- Small heat shock protein, *Dorea*
- Molecular chaperone, HSP90 family, *Roseburia*
- ATP-dependent Zn proteases, *Eubacterium*
- Molecular chaperone, HSP90 family, *Blautia*
- ATP-dependent Zn proteases, *Fusicatenibacter*
- Small heat shock protein, *Anaerostipes*
- Molecular chaperone, *Coprococcus*
- Molecular chaperone, HSP90 family, *Blautia*
- Molecular chaperone, HSP90 family, *Blautia*
- ATP-dependent Zn proteases, *Blautia*
- ATP-dependent Zn proteases, *Bacteroides*
- Small heat shock protein, *Ruminococcus*
- ATP-dependent Zn proteases, *Ruminococcus*
- ATP-dependent Zn proteases, *Eubacterium*
- HSP90 family chaperone, *Ruminococcus*
- Rotamase - cyclophilin family, *Anaerostipes*
- Molecular chaperone, *Carnobacterium*
- Chaperonin GroEL, *Eggerthella*
- ATP-dependent Zn proteases, *Blautia*
- Chaperonin GroEL, *Collinsella*
- ATP-dependent protease Clp, *Roseburia*
- Chaperonin GroEL, *Coprococcus*
- ATP-dependent Zn proteases, *Blautia*
- Collagenase and relate proteases, *Blautia*
- ATP-dependent Zn proteases, *Blautia*

Gram Positive

Protein Name and Genus

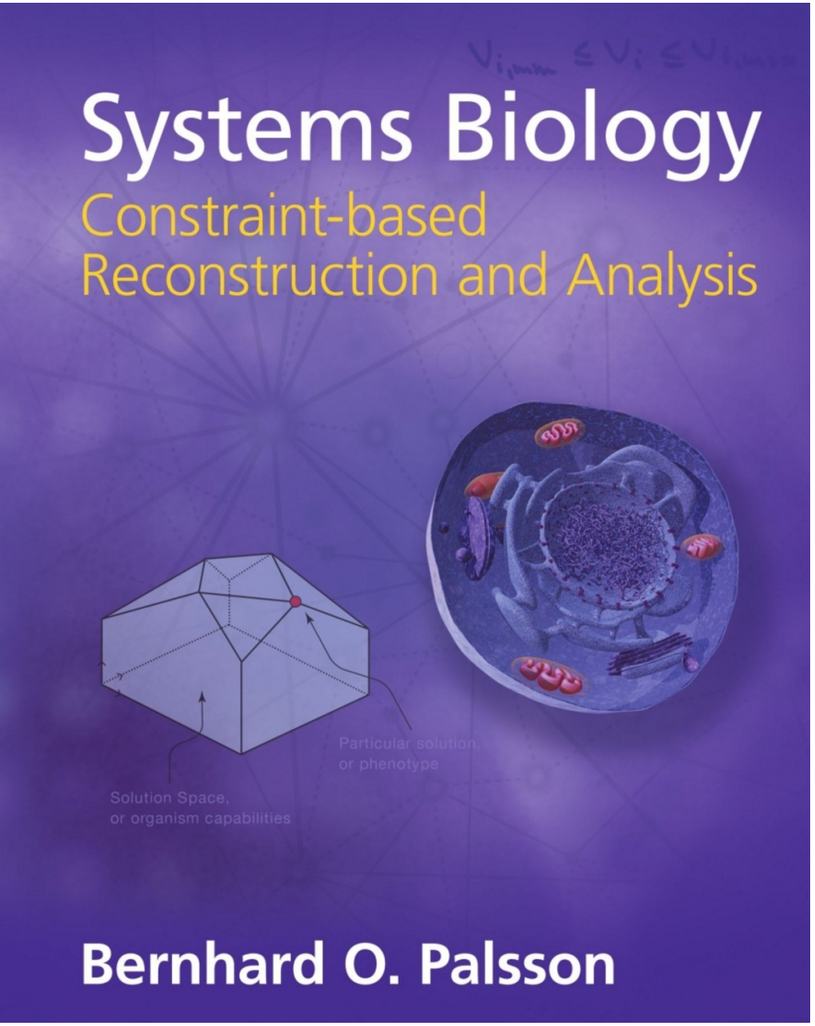
- Uncharacterized protein, *Faecalibacterium*
- FeS assembly ATPase SufC, *Faecalibacterium*
- Uncharacterized protein, *Butyrivibrio*
- ABC transporter, *Faecalibacterium*
- V-type ATP synthase beta chain, *Faecalibacterium*
- 3-hydroxybutyryl-CoA dehydrogenase, *Butyrivibrio*
- 30S ribosomal protein S13, *Butyrivibrio*
- 50S ribosomal protein L22, *Butyrivibrio*
- 30S ribosomal protein S9, *Butyrivibrio*
- Carbon starvation protein CstA, *Faecalibacterium*
- 30S ribosomal protein S12, *Faecalibacterium*
- Rubredoxin (Fragment), *Butyrivibrio*
- 50S ribosomal protein L2, *Faecalibacterium*
- Endoglucanase, *Butyrivibrio*
- 5'-nucleotidase, *Faecalibacterium*
- ATP synthase subunit a, *Faecalibacterium*
- Cysteine--tRNA ligase, *Faecalibacterium*
- Chaperone protein DnaK, *Faecalibacterium*
- 50S ribosomal protein L4, *Faecalibacterium*

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Discovering Gut Microbiome Metabolite Dynamics

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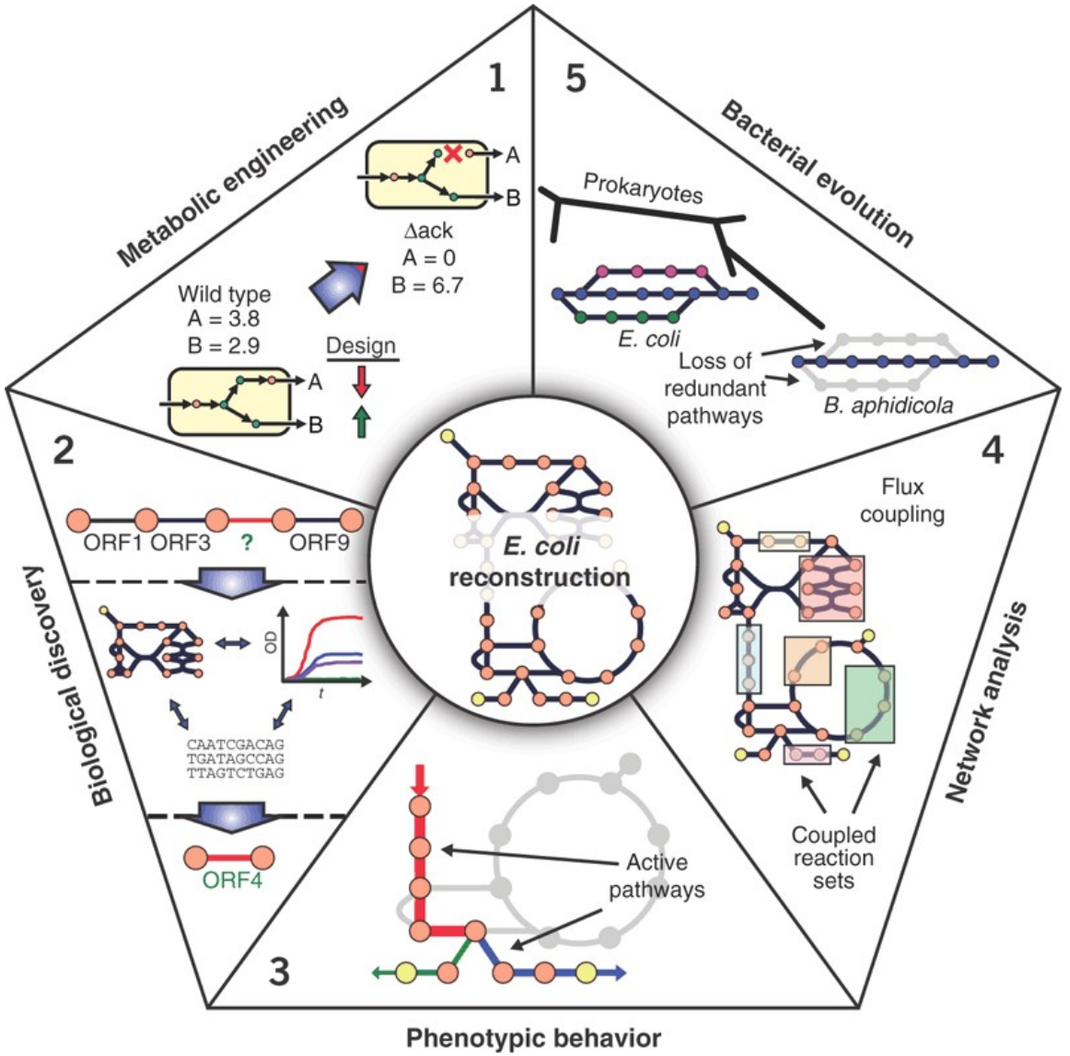
Genome-Scale Metabolic Models
Create Virtual Models of Living Microbes



January 2015

Large Computational Models of Metabolism Account for:

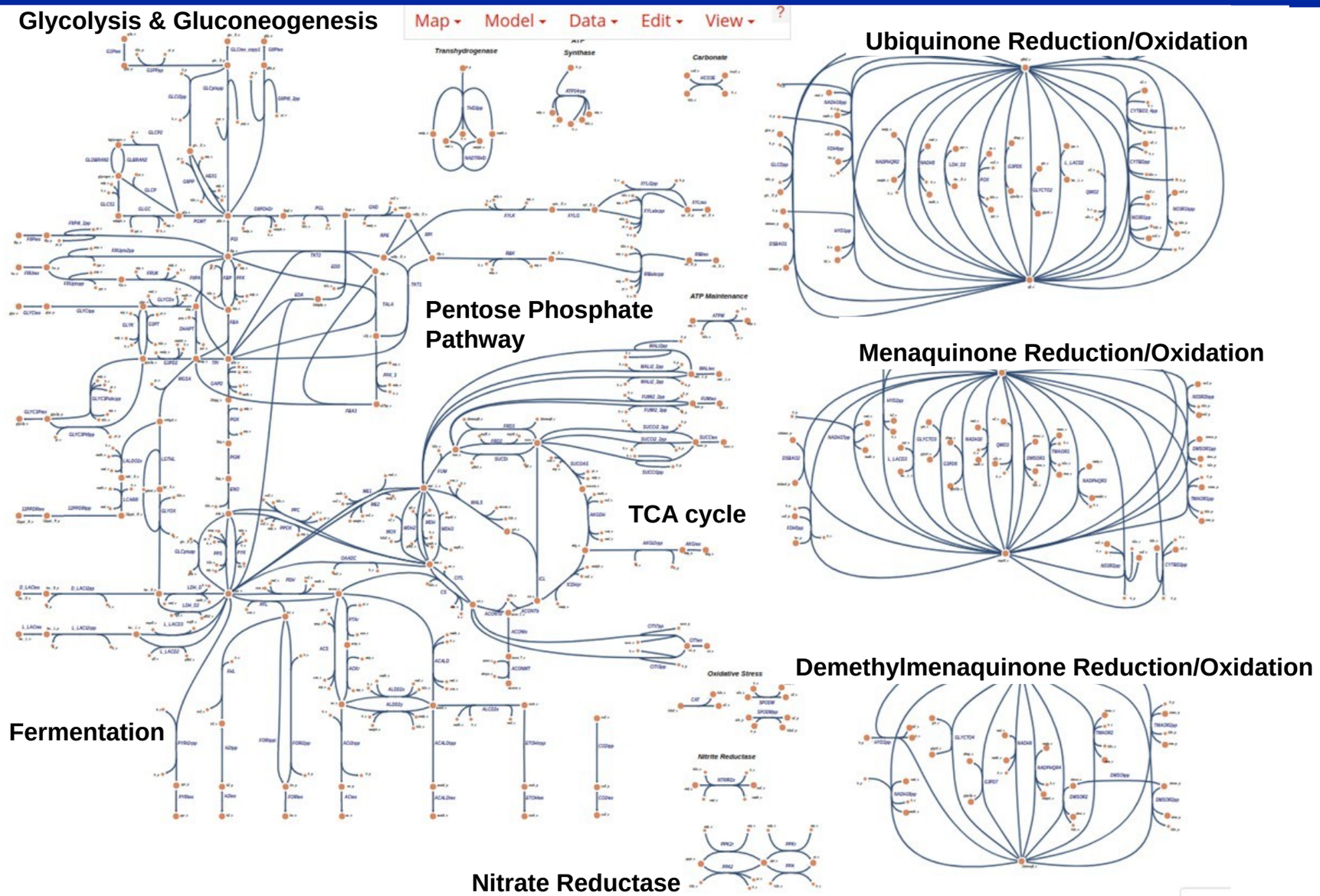
- **Thousands of Unique Metabolites**
- **> 2000 Unique Reactions**
- **Product of Thousands of Genes (>1/3 of Genome for Some Species)**



Feist & Palsson
Nature Biotechnology 26,
659 - 667 (2008)

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



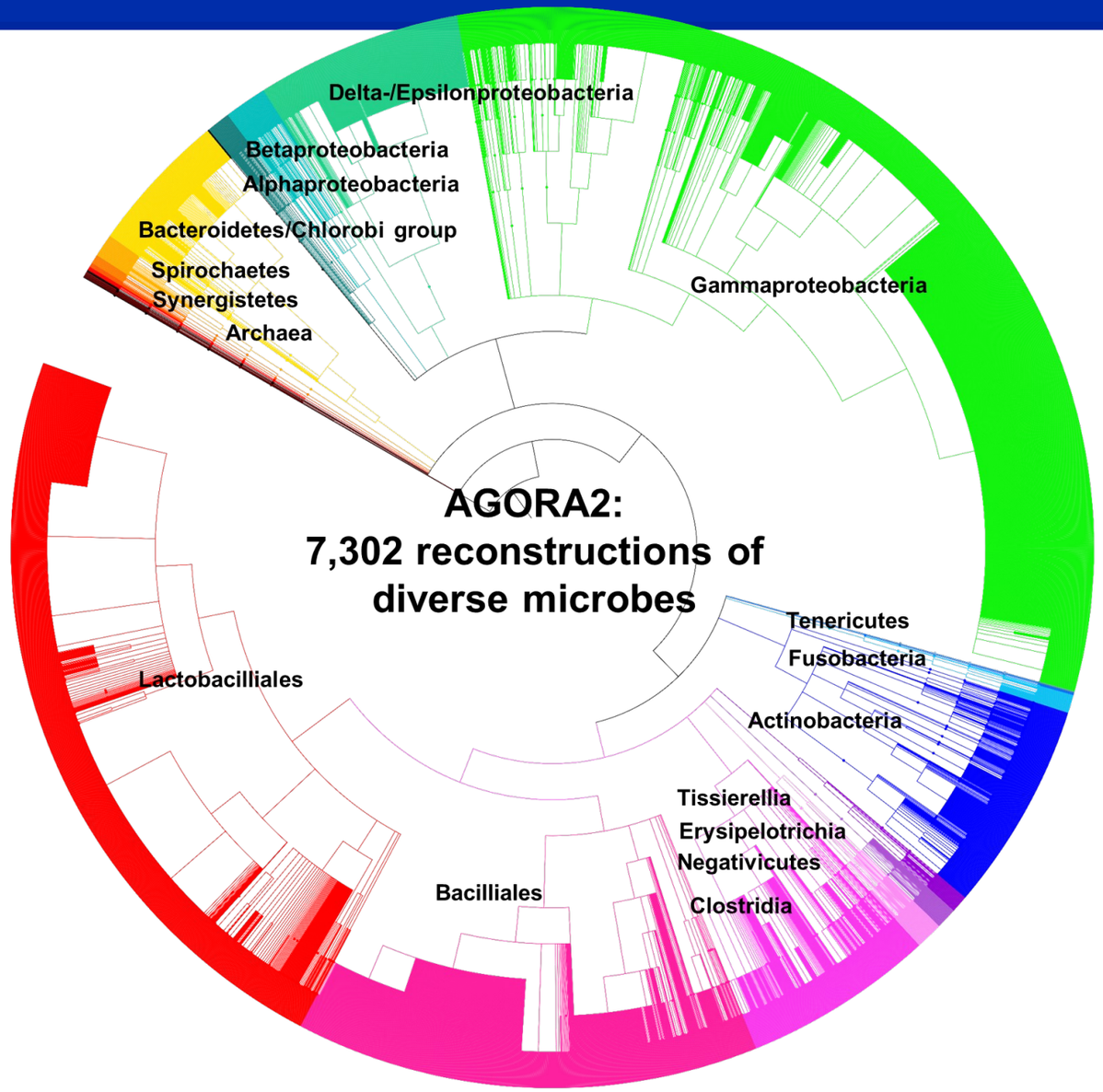
- Metabolic Network for Central Metabolism in *E.coli*
- Other Metabolic Pathways Not shown:
  - Amino Acid Metabolism
  - Fatty Acid Metabolism
  - Nucleotide Metabolism
  - ……
- Metabolic Network Varies For Different Strains

Bernhard Palsson Systems Biology Research Group-UC San Diego

UC San Diego

King et al. PLOS Computational Biology (2015)

AGORA2: Reconstruction Resource of Human Microbes Accounting for Drug Metabolism



- 7,302 strains
- 1,734 species
- 422 genera
- 24 phyla

Prof. Ines Thiele,
National University of Ireland, Galway
Earned PhD in Bioinformatics from UCSD in 2009 Under Prof. Bernhard Palsson

- **Biochemistry**: 732 papers and >8,000 pages of textbooks
- **Drug metabolite structures**: 73 papers and databases
- **Comparative genomic analyses** for up to 5,438 strains and 35 metabolic subsystems
- *Special focus:* drug metabolism for 25 genes, the subcellular localization, and 12 drug-transporter

Article | Open access | Published: 19 January 2023

Genome-scale metabolic reconstruction of 7,302 human microorganisms for personalized medicine

Almut Heinken, Johannes Hertel, Geeta Acharya, Dmitry A. Ravcheev, Malgorzata Nyga, Onyedika Emmanuel Okpala, Marcus Hogan, Stefanía Magnúsdóttir, Filippo Martinelli, Bram Nap, German Preciat, Janaka N. Edirisinghe, Christopher S. Henry, Ronan M. T. Fleming & Ines Thiele

Nature Biotechnology **41**, 1320–1331 (2023) | Cite this article

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Toward a “Digital Twin” Computational Model of the Human Host/Gut Microbiome System

Longitudinal flux balance analyses of a patient with episodic colonic inflammation reveals microbiome metabolic dynamics

Arianna Basile[a,b], Almut Heinken[b,c], Johannes Hertel[d], Larry Smarr[e], Weizhong Li[f], Laura Treu[a], Giorgio Valle[a], Stefano Campanaro[a§], and Ines Thiele[b,c,g,h§]

[a]Department of Biology, University of Padova, Padua, Italy; [b]School of Medicine, University of Galway, Galway, Ireland; [c]Ryan Institute, University of Galway, Galway, Ireland; [d]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany; [e]Department of Computer Science and Engineering, University of California, San Diego, La Jolla, CA, USA; [f]J. Craig Venter Institute, San Diego, La Jolla, CA, USA; [g]Discipline of Microbiology, University of Galway, Galway, Ireland; [h]APC Microbiome Ireland, University College Cork, Cork, Ireland

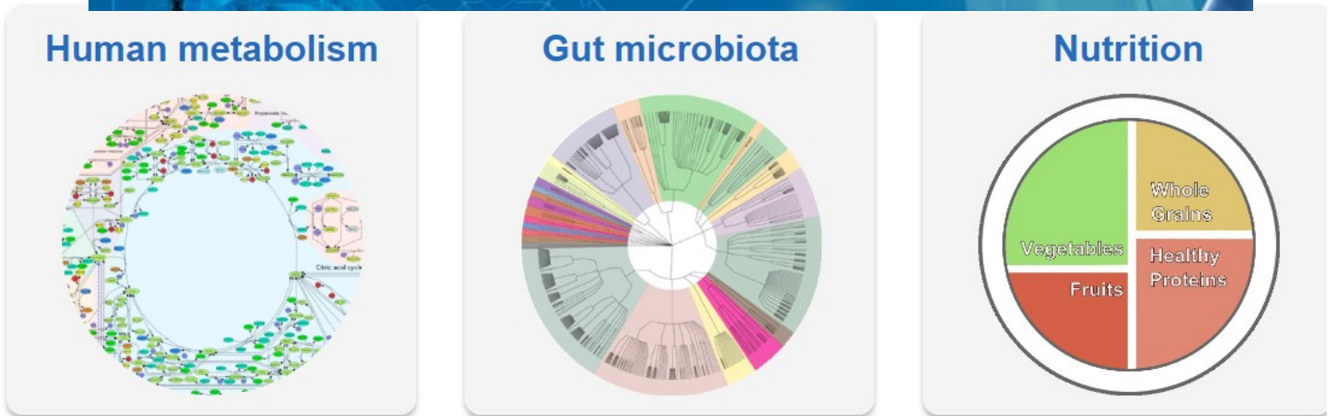
GUT MICROBES
2023, VOL. 15, NO. 1, 2226921
https://doi.org/10.1080/19490976.2023.2226921

OPEN ACCESS

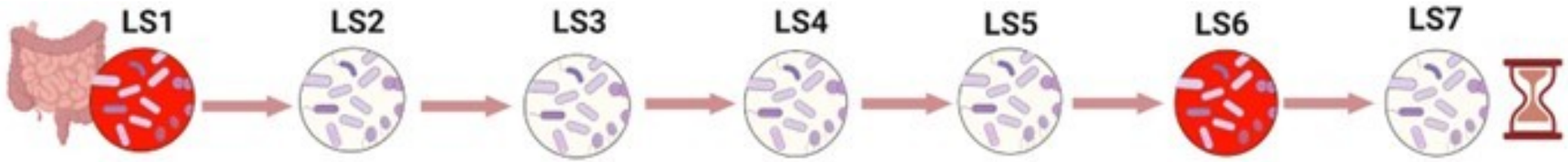
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My Initial Seven Gut Microbiome Metagenomic Sequenced Stool Samples Hav Been Analyzed by the Virtual Metabolic Human Team





Collaboration with
Professor Ines Thiele,
National University of Ireland, Galway
PI, Molecular Systems Physiology Group
www.thielelab.eu/



	LS1	LS2	LS3	LS4	LS5	LS6	LS7
Date	28/12/2011	03/04/2012	07/08/2012	06/11/2012	26/01/2013	08/02/2013	25/02/2013
Inflammation	Yes	No	No	No	No	Yes	No
Blood CRP (mg/dL)	27.1	2.8	3	4.3	3.2	26.3	3.7
Antibiotic treatment	None	Yes	None	None	None	None	None
Alpha diversity	74.86	77.86	76.85	77.11	74.50	80.18	77.46
Microbes	76	125	102	91	87	101	106
Reactions	142,358	253,294	185,468	140,923	115,612	173,610	141,914
Metabolites	126,065	222,120	164,170	126,108	104,972	154,198	129,276

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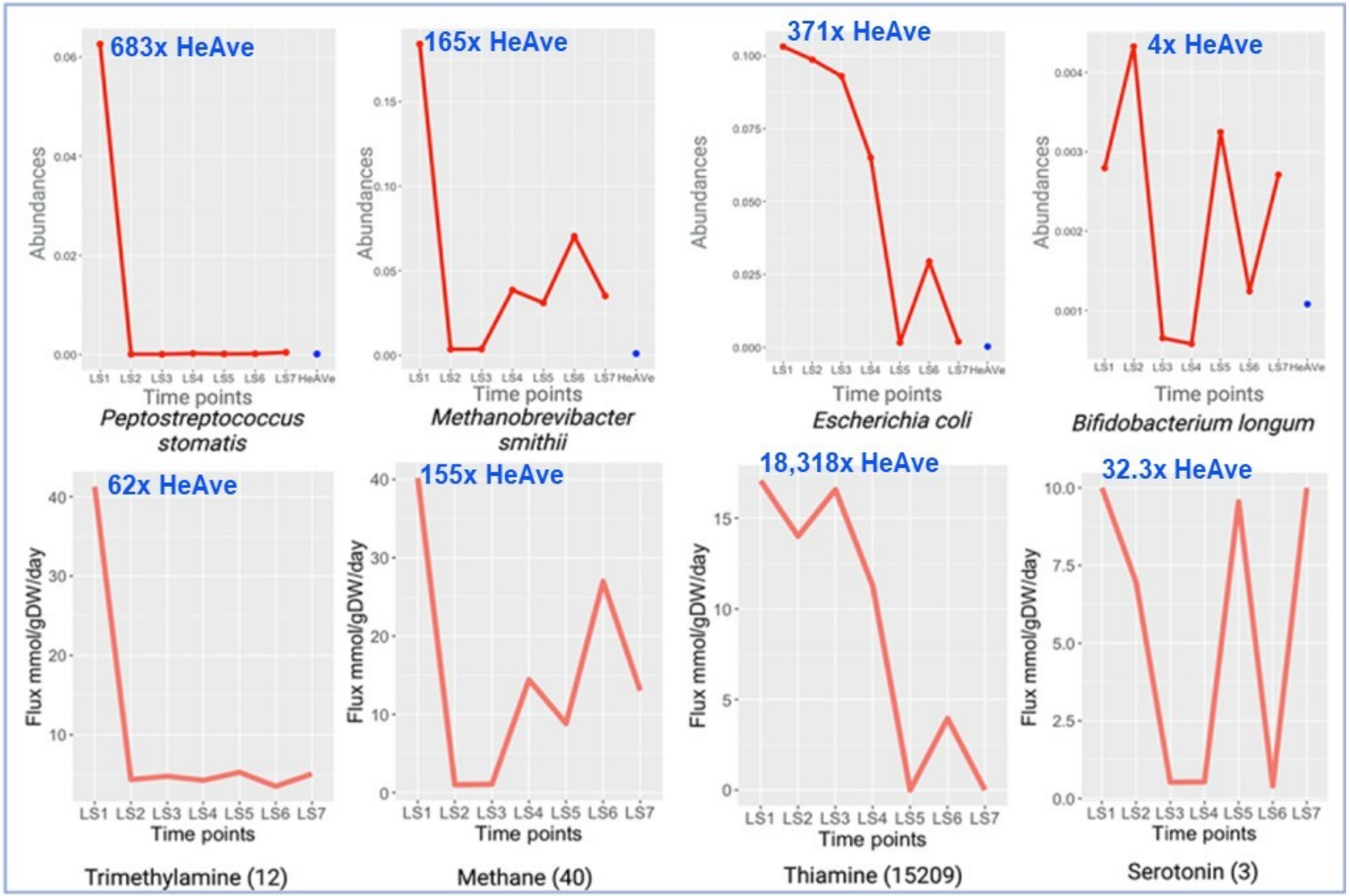
Surprising Result from the Thiele Lab Model on LS Metabolite Overproduction

We found that LS's major gut microbiome taxonomic shifts over time led to correspondingly large Flux Balance Analysis (FBA) metabolic shifts from the personalized microbial community models. Since we also computed the metabolite production from each of the 34 healthy controls' microbiome, **we could compare LS's metabolite production at each time point to the average value (HeAve) of the healthy controls.**

The results of our models showed that **several biologically important metabolites *were highly (10–10,000×) overproduced*, compared to HeAve**, at various time points in LS's samples, including oxygen, methane, thiamine, formaldehyde, trimethylamine N-oxide, folic acid, serotonin, histamine, and tryptamine.

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Time-Correlated Microbial Species and Metabolites Reveal (10–10,000×) Overproduction of Biologically Important Metabolites

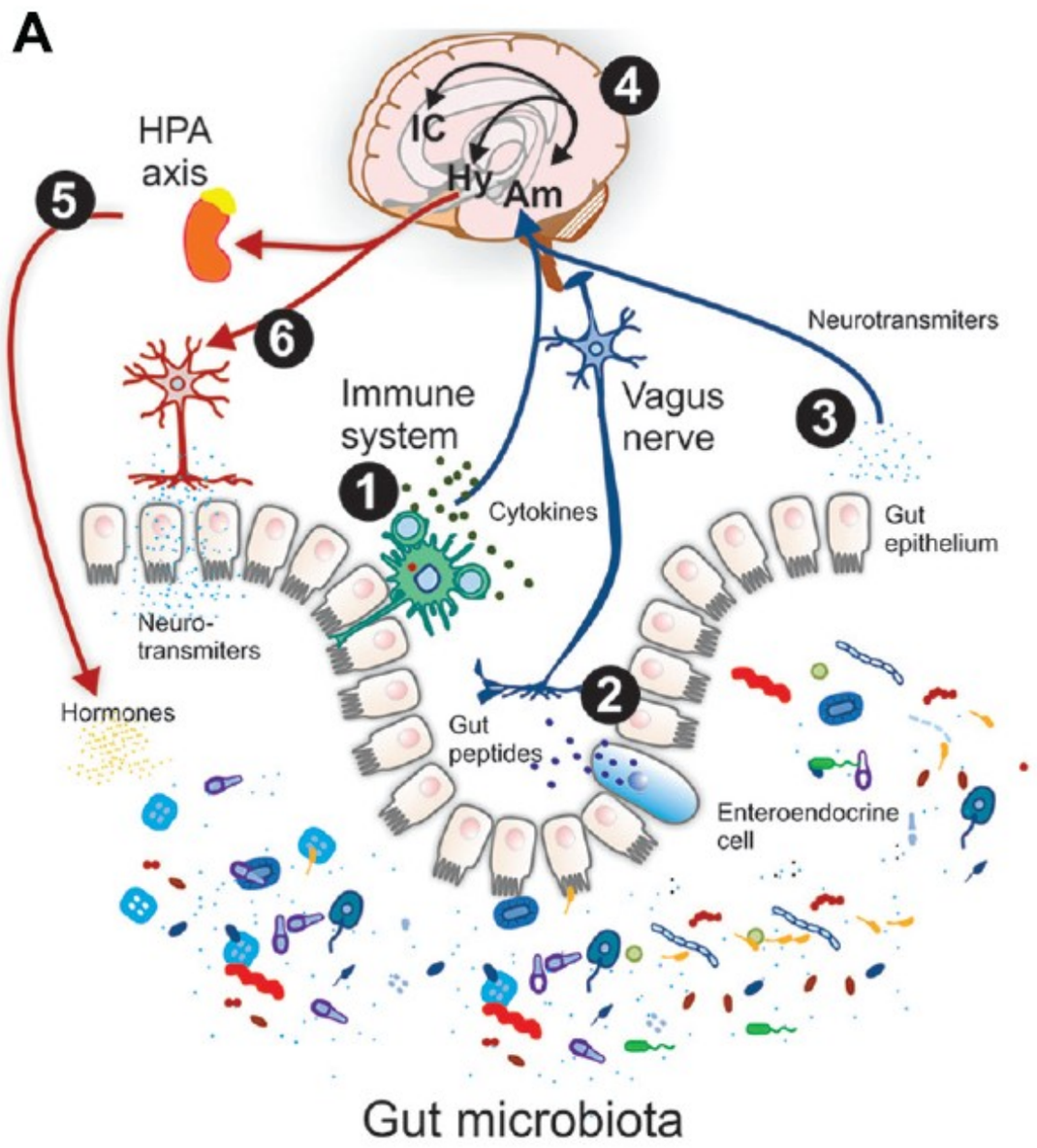


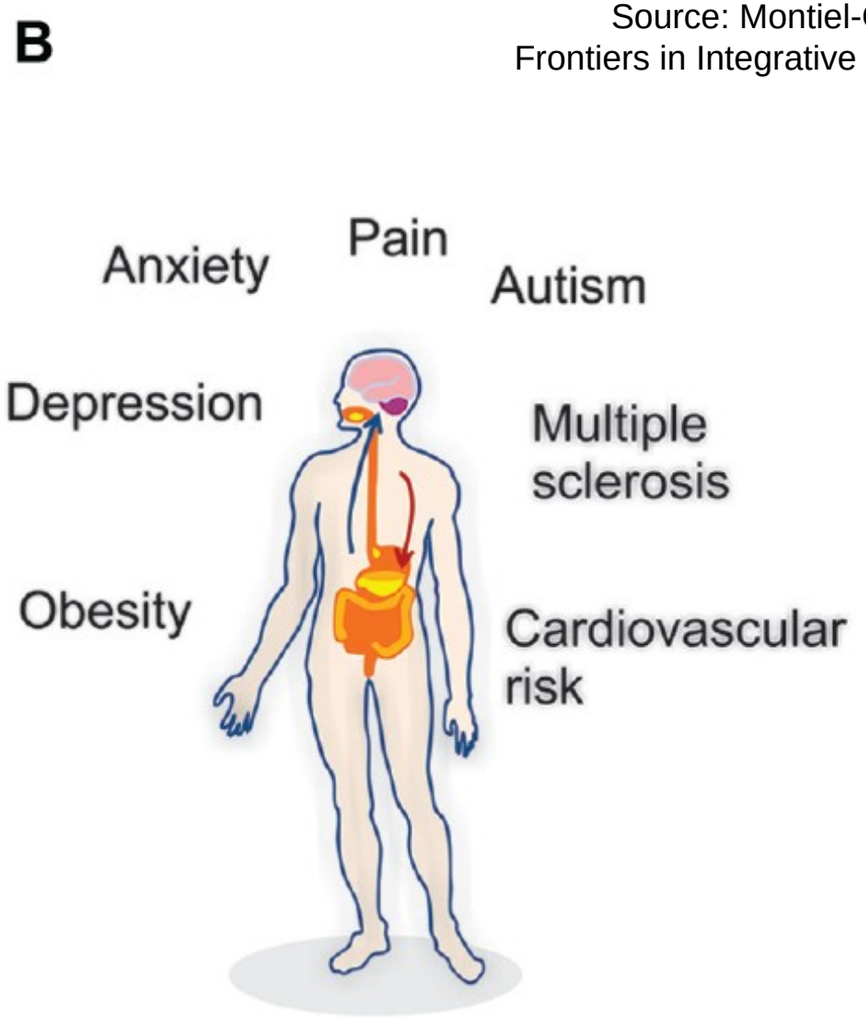
UC San Diego

Basile A et al., Gut Microbes, 2023

The Individual's Gut Microbiome Time Evolution *Must* Lead to Time Shifts in Behavior and Disease via the Microbiome–Gut–Brain Axis

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





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

frontiers in Cell and Developmental Biology

11 March 2021

Brain Neurotransmitter Modulation by Gut Microbiota in Anxiety and Depression

Fei Huang and Xiaojun Wu*

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,

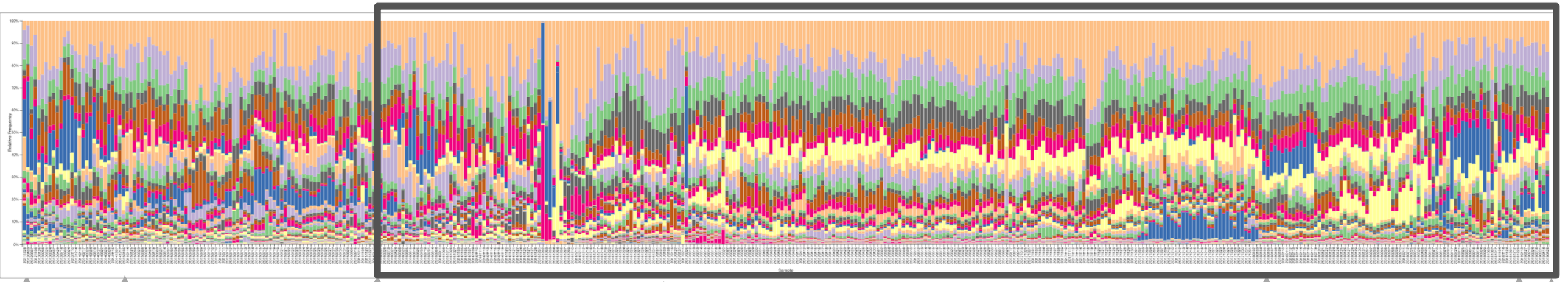
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Toward a Human Digital Twin Next Steps: Collaboration of Knight Lab, Thiele Lab, with Smarr Time Series

- **Step One is Done:**
  - **Seven Stool Samples Over 13 Months**
  - **Published in Gut Microbes July 2023**
- **Step Two is Underway:**
  - **51 Stool Samples Over 2.5 Years**
  - **Stool Sample Metagenomics From Knight Lab**
  - **Thiele AGORA2 Computations Are Done**
  - **Planning Comparison with Dorrestein Lab Metabolomics from LS Stool Samples**
- **Step Three Has Begun:**
  - **500 Stool Samples Over a Decade**
  - **Knight Lab Has Done 16S on Time Series**
  - **Starting on Long Read Metagenomics and Quantitative Cell Counts**
  - **Coupling That into AGORA2 Next Step**

Knight Lab Currently Applying PacBio Long-Read Metagenomics with Newly Developed Absolute Quantification to LS Stool Time Series

Omar Din is Initially Processing LS Samples in this Time-Range (Species and Strain Level Quantification!)



Bar Graph of 16S Taxonomy Relative Abundances

2015 | 2016 | 2017 | 2018

Resection Surgery

December 28, 2011

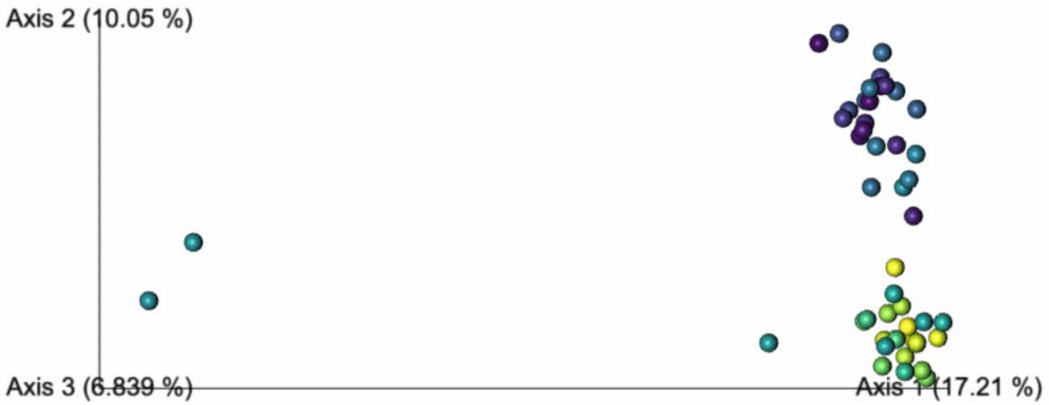
April 28, 2019

UC San Diego

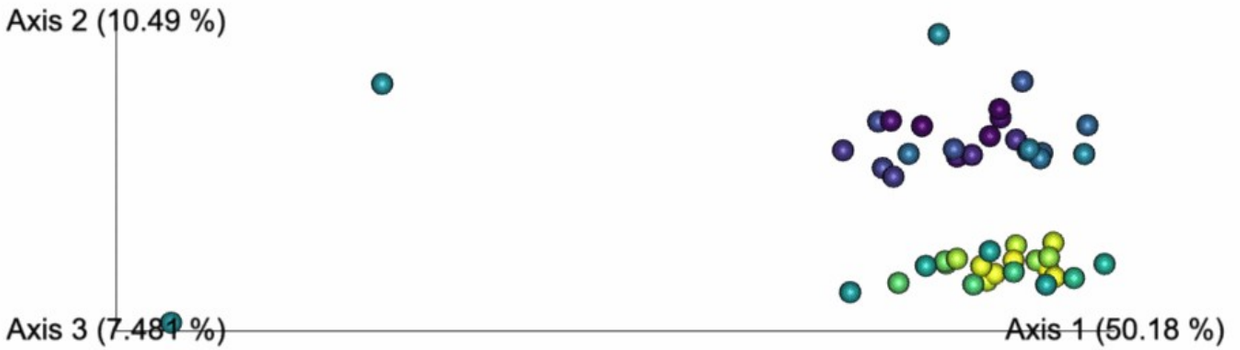
Research by Omar Din, UCSD Knight Lab

Verifying that PacBio Recaptures 16S Results for Dramatic Pre/Post Surgery Shift – PCoA Comparison

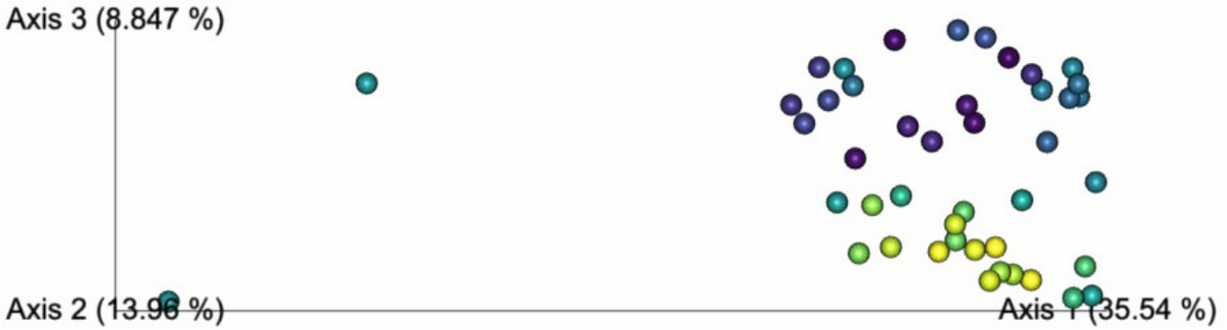
Research by Omar Din, UCSD Knight Lab



16S



PacBio (Long-Read Metagenomics)



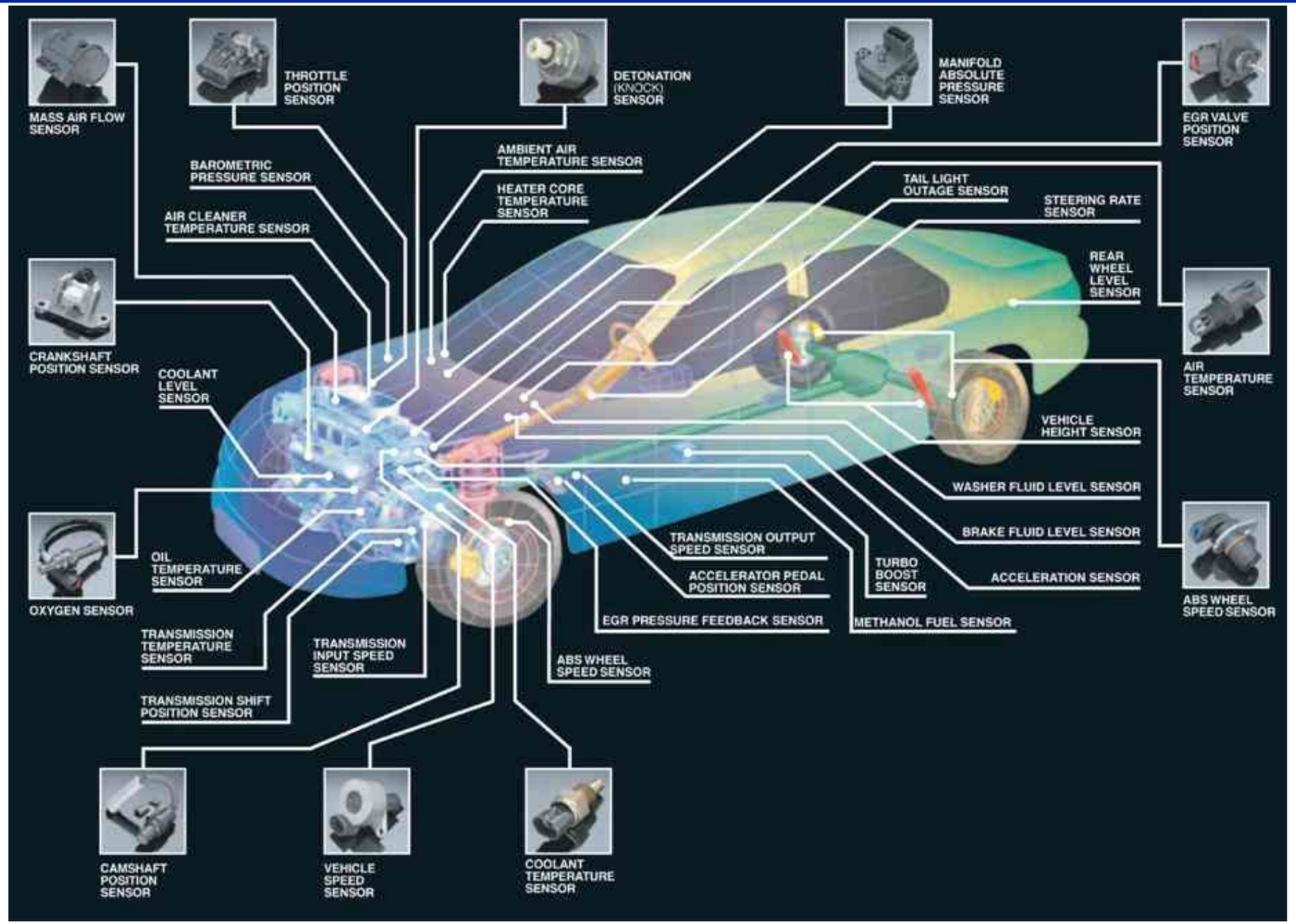
PacBio (Absolute Cell

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Modern Cars Have Massive Sensor Arrays Which Record Time Series Enabling Computer Diagnostics For Early Warning

Before the computer diagnostics technology, most car owners did not know something was wrong with the engine until something drastic happened, such as overheating or running out of gas.

www.thepeoplehistory.com/carelectronics.html



http://blog.asautoparts.com/5-common-symptoms-of-faulty-car-sensors/

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The Transformation in Automobile Healthcare Gives Us Insight into the Human Healthcare Shift to Come

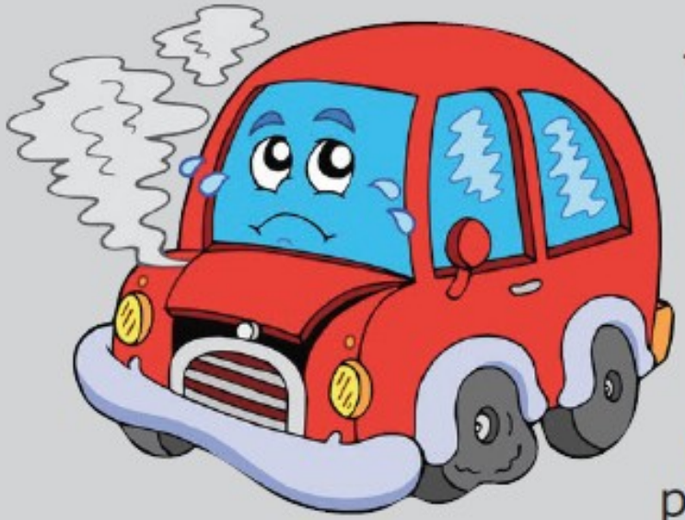
Perspective

Quantifying your body: A how-to guide from a systems biology perspective

Biotechnol. J. 2012, 7, 980–991

Larry Smarr

Box 1: The car analogy to personalized medicine.



The paradigm shift required to make the change from today's medical practices to the predictive personalized medical care is revolutionary, but by no means unprecedented. A metaphor for this is how radically automobile "healthcare" has been digitally transformed over the past five decades by

http://onlinelibrary.wiley.com/doi/10.1002/biot.201100495/abstract

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Coupling Human Digital Twins with Personal Digital Assistants: A Vision for Healthcare in the Coming Decades

Using this data, the planetary computer will be able to build a computational model of your body and compare your sensor stream with millions of others. Besides providing early detection of internal changes that could lead to disease, cloud-powered voice-recognition wellness coaches could provide continual personalized support on lifestyle choices, potentially staving off disease and making health care affordable for everyone.

ESSAY | The New York Times | Science

An Evolution Toward a Programmable Universe

By LARRY SMARR

Published: December 5, 2011

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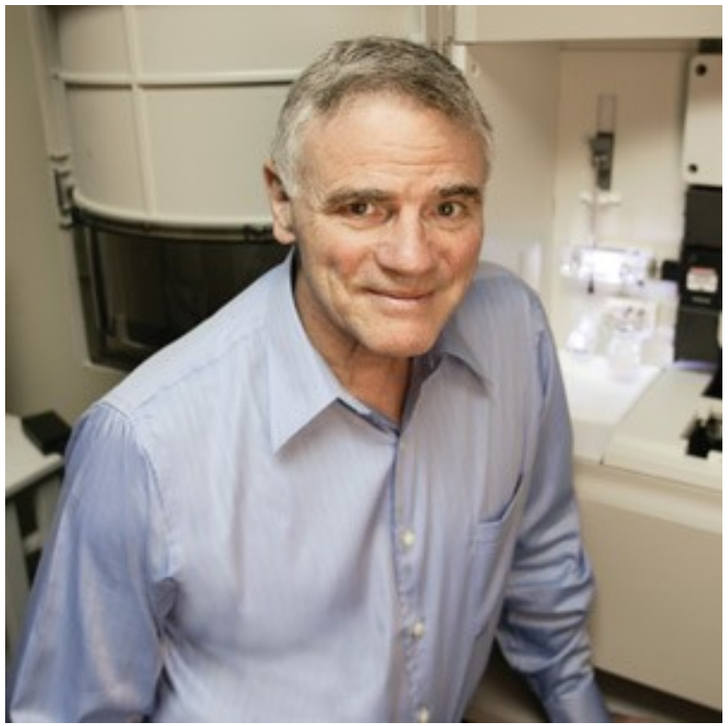
The Near Future Transition
to Predictive, Personalized, Preventive, & Participatory (P4) Medicine

Newsweek

A Doctor's Vision of the Future of Medicine

Leroy Hood
NEWSWEEK

From the magazine issue dated Jul 13, 2009



Dr. Lee Hood,
the CEO of Phenome Health,
a Nonprofit which Seeks
to Sequence
the Human and Microbial Genes,
As Well as Generating
the Longitudinal Phenomes
of 1 Million People
Over the Next 10 Years

Phenome HEALTH

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