# “The Emerging Personalized Medicine Paradigm of Time-Series Tracking of Mind, Body, and Microbiome”

**Invited Zoom Remote Lecture**

**For Sara Gottfried, MD Personalized Medicine for Mental Health Course**

**Integrative Psychiatry Institute**

**Recorded June 28, 2022**

**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.calit2.net**

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# Learning Objectives

1. How Time Series Can Reveal Time Changes in the Body and its Microbiome
2. How a Million-Fold Reduction in Sequencing Costs Has Enabled a New View Into the Body's Gut Microbiome
3. An Introduction to the Gut Microbiome Ecology, its Time Evolution, and its Coupling to the Mind and Body
4. How Routine Medical Interventions Can Induce Microbiome Changes Which Alter the Human Host
5. Food and Diet Can Make Positive or Negative Impacts on the Host Through Altering the Microbiome Ecology
6. Emerging Medical Practices That Use Food as Medicine by Altering the Microbiome
7. Why Changes in the Microbiome Ecology Can Directly Impact Mental Health
8. How Medicine Will Gradually Change to a Sub-Field of Ecological Dynamics
9. The Emergence of Predictive, Personalized, Preventive, & Participatory (P4) Medicine
10. A Glimpse into the Future of Medicine and Healthcare Using Personal High-Time Frequency Wearables

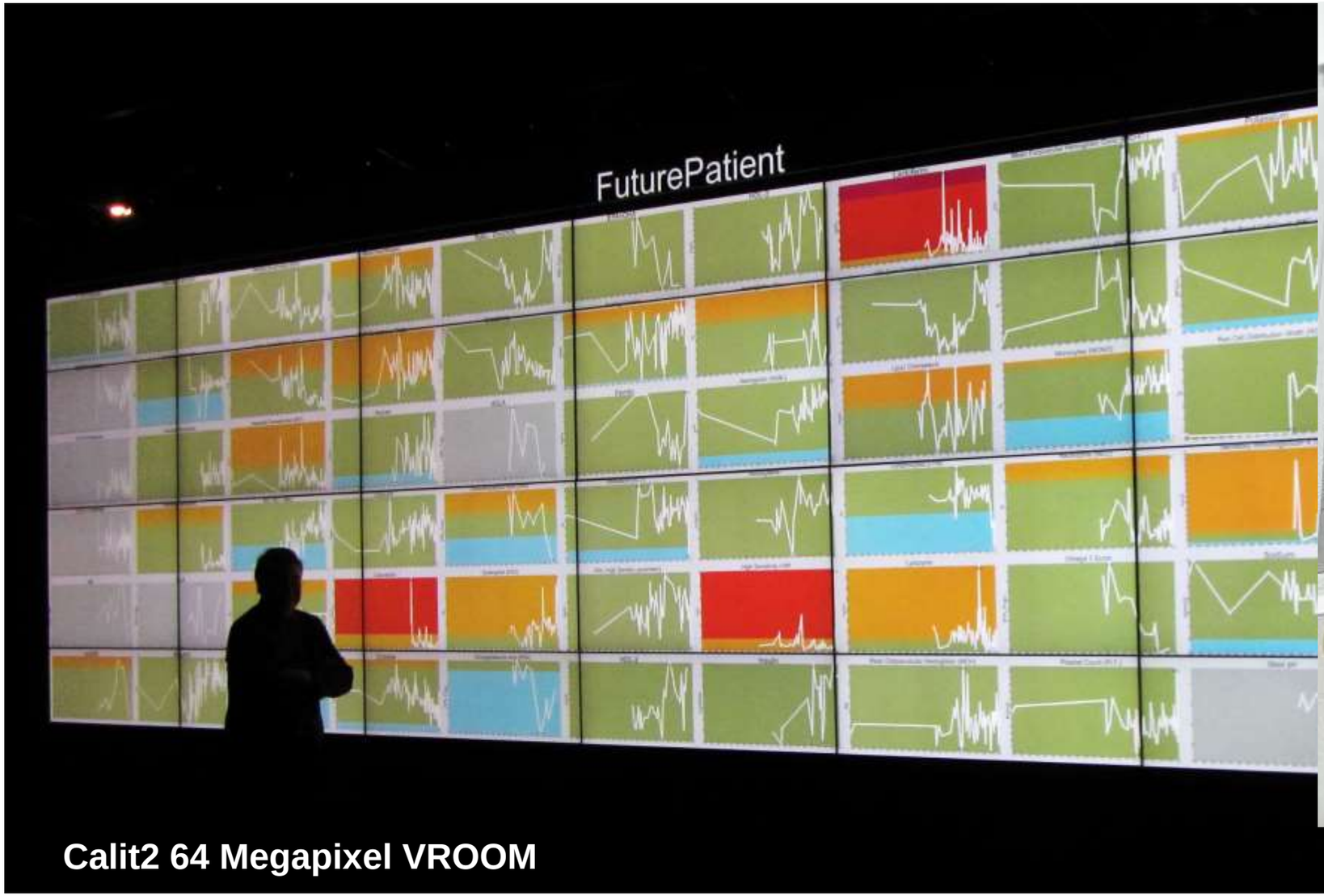
# “Know Thyself”
# From the Temple of Apollo to the Quantified Self




**From the Reichert-Haus in Ludwigshafen, Germany**

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



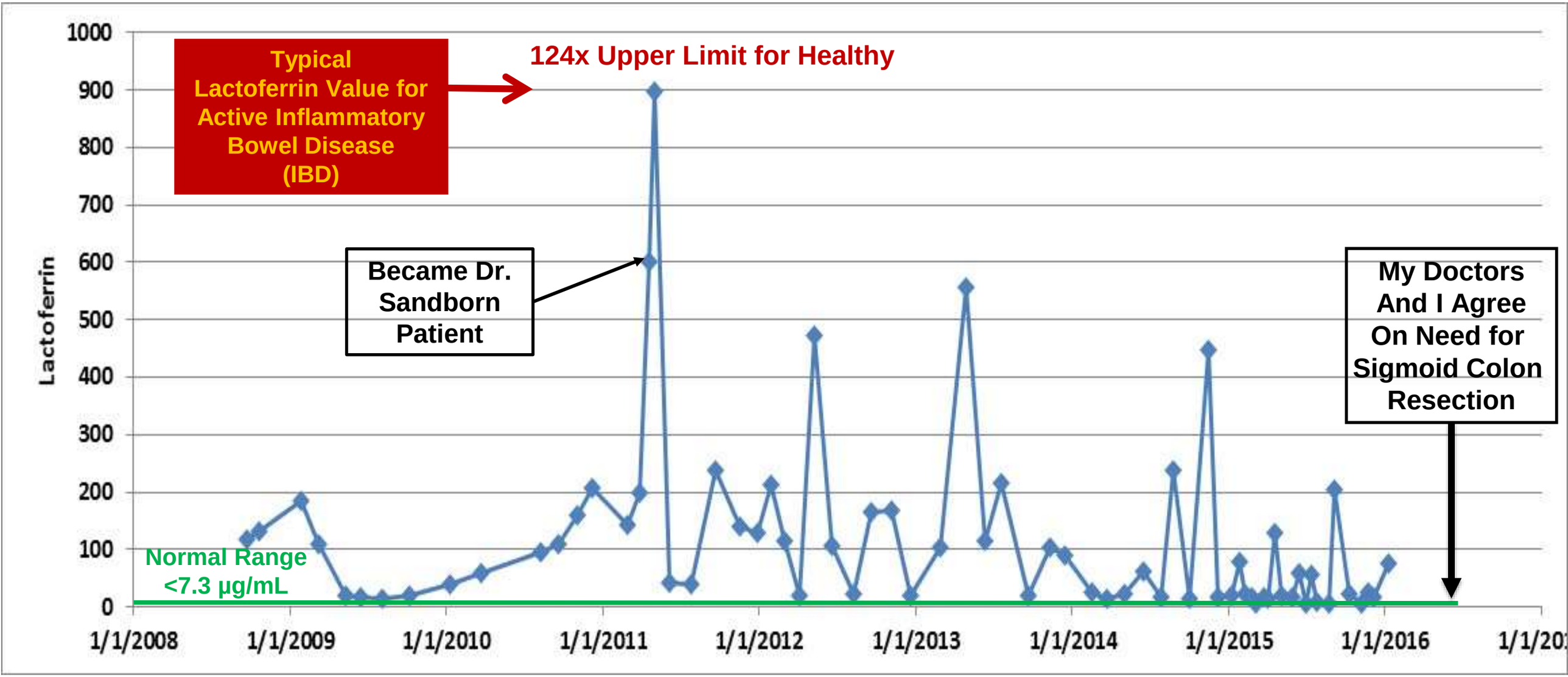

Calit2 64 Megapixel VROOM



My Latest Blood Draw

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# Stool Test Time Series Revealed Large Excursions in My Colon's Immune System: Inflammatory Bowel Disease (IBD)

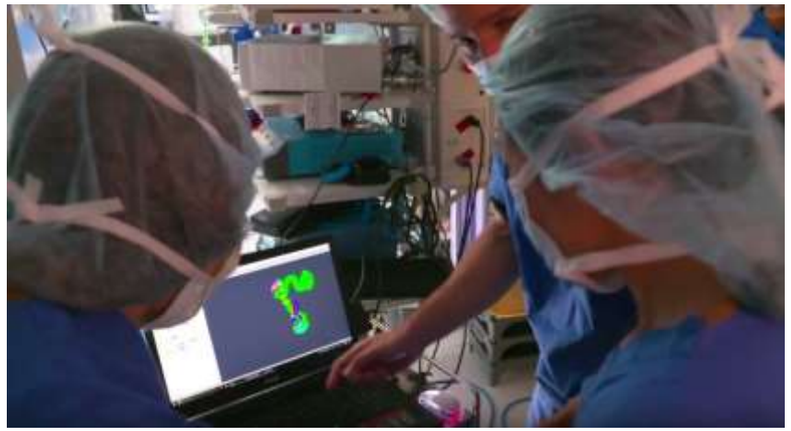



**Lactoferrin is a Protein Shed from Neutrophils - An Antibacterial that Sequesters Iron**

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# 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**



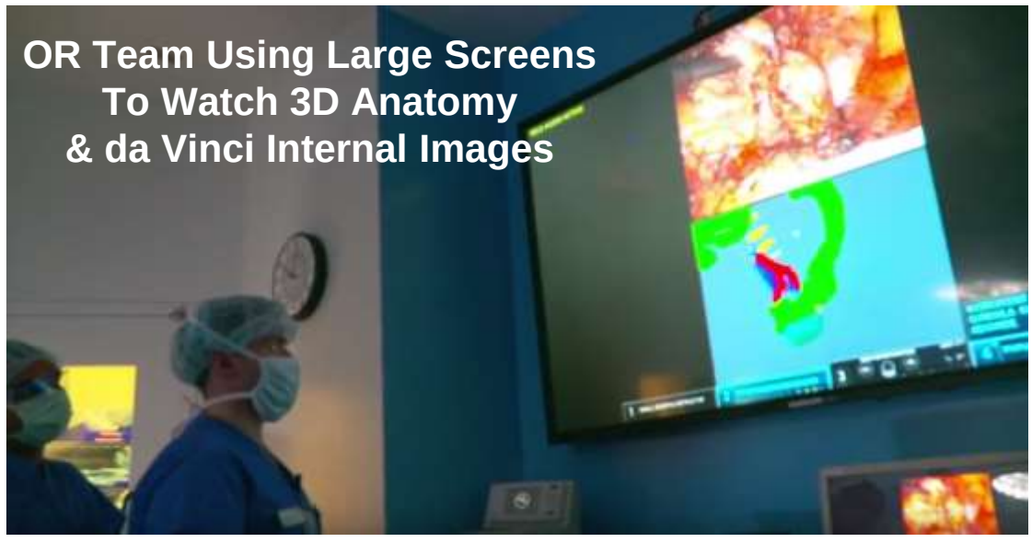


**Patient Smarr With da Vinci Robot Arms Inside Him**





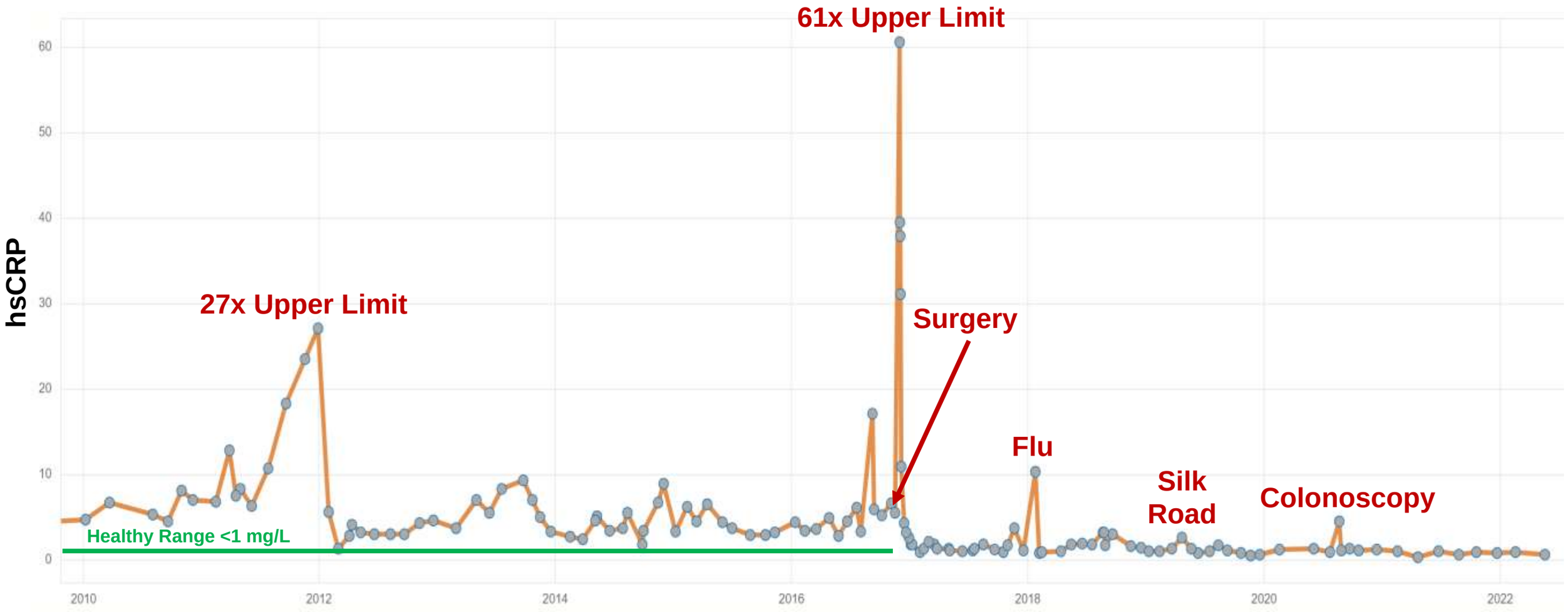

**Dr. Ramamoorthy Operating da Vinci Xi Robot During Surgery**



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

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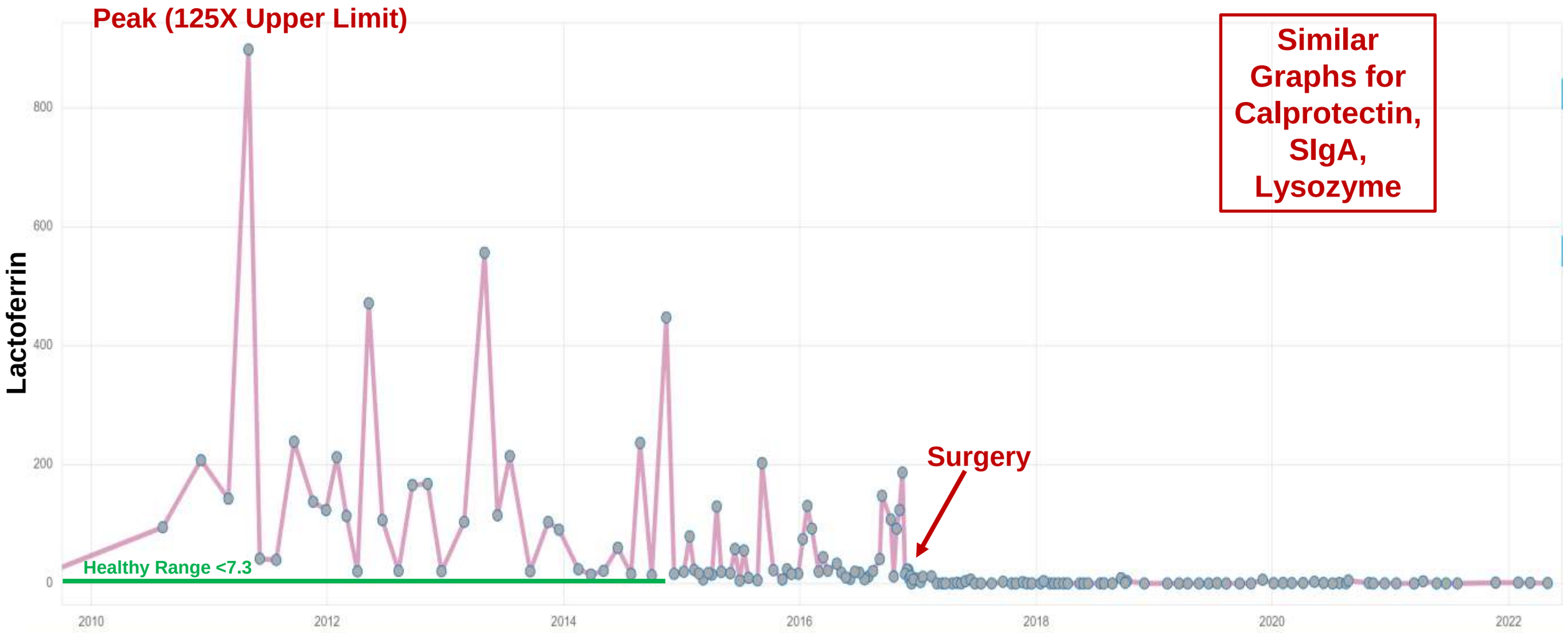
# My Blood hsCRP Had Been Consistently High, Indicating Episodic Chronic Inflammation – But After Surgery It Reverted to Normal




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

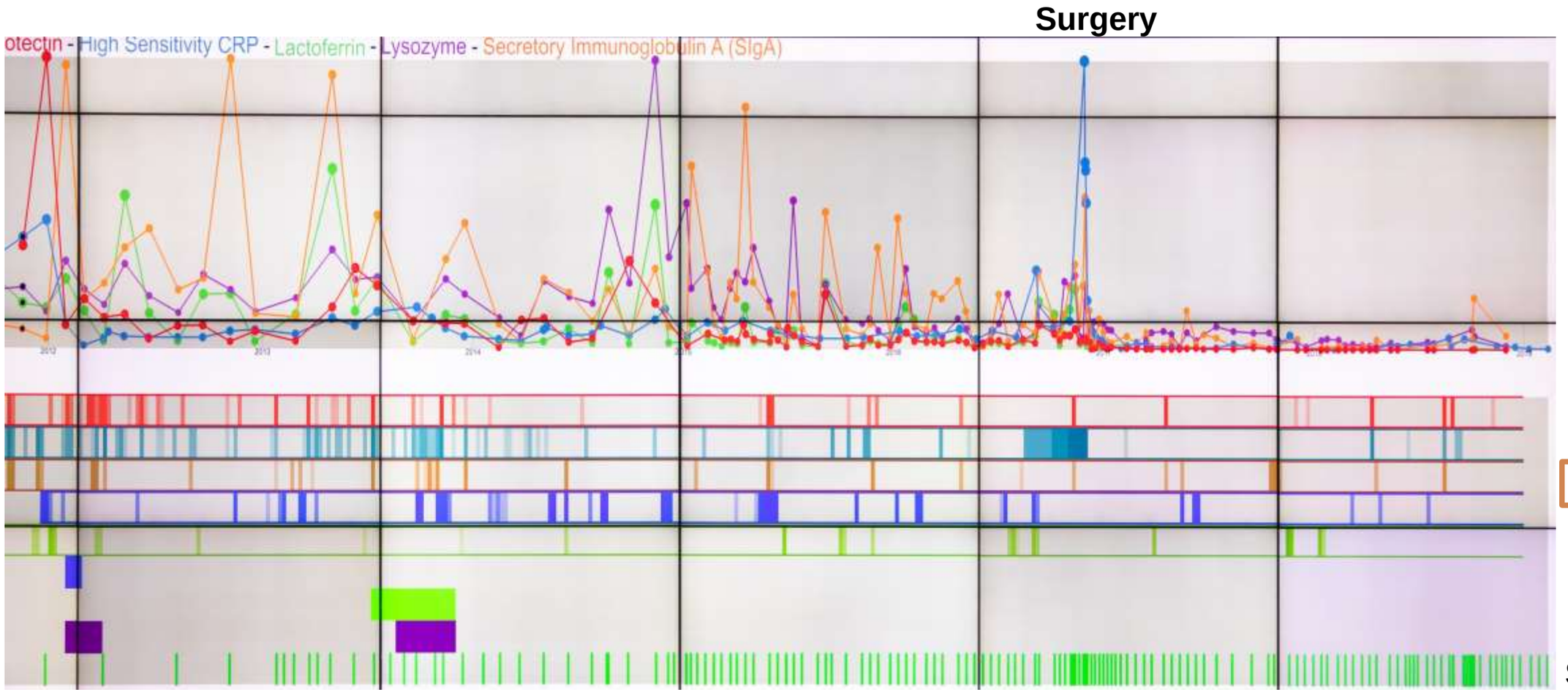
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# My Stool Lactoferrin Time Series Indicated Episodic Colonic Inflammation: Abrupt Shift to Healthy Following Surgical Resection




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




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

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# What Impact Do Medical Interventions Have on the Human Gut Microbiome?

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

**Your Microbiome is**
**Your "Near-Body" Environment**
**and its Cells**
**Contain 1000x as Many DNA Genes**
**As Your Human DNA-Bearing Cells**

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

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# When We Think About Biological Diversity
# We Typically Think of the Wide Range of Animals






## But All These Animals Are in One SubPhylum Vertebrata of the Chordata Phylum

All images from Wikimedia Commons.
Photos are public domain or by Trisha Shears & Richard Bartz

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# Think of These Phyla of Animals When You Consider the Biodiversity of Microbes Inside You



**Phylum Chordata**



**Phylum Cnidaria**



**Phylum Echinodermata**



**Phylum Annelida**



**Phylum Mollusca**



**Phylum Arthropoda**

**Microbiome Phyla**

- Bacteroidetes
- Firmicutes
- Proteobacteria
- Verrucomicrobia
- Actinobacteria
- Fusobacteria
- Euryarchaeota

WIKIMEDIA COMMONS

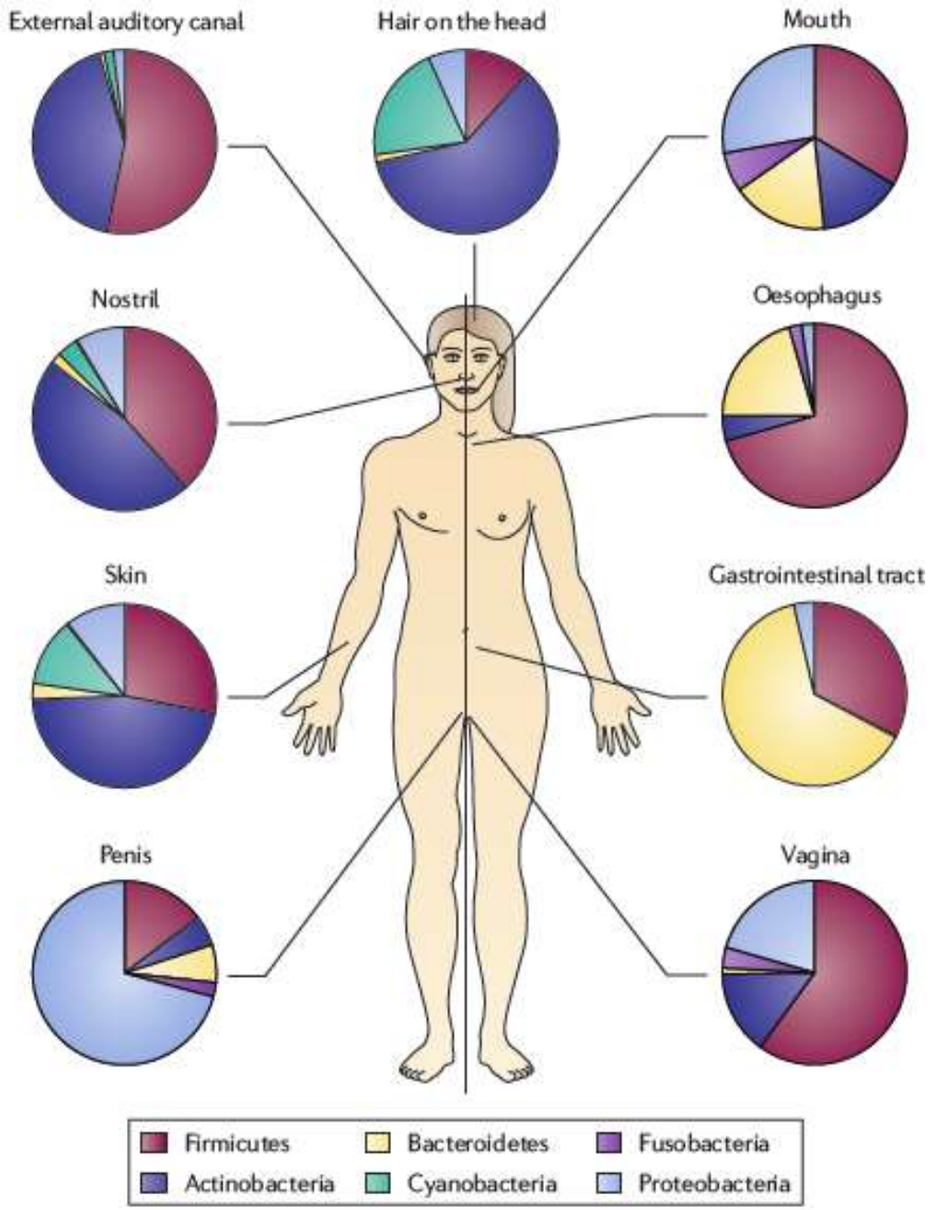
**All images from WikiMedia Commons.**
**Photos are public domain or by Dan Hershman, Michael Linnenbach, Manuae, B_cool**

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# Medicine Should be Treating the Entire Human Superorganism: Your Body is an Ecology!

Human Microbiome Project

The NIH Common Fund
WE ACCELERATE DISCOVERY.




**Nature Reviews Microbiology**
**v.9, p. 279 (2011)**

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# Analysis of My Personal Microbiome Ecology Dynamics is Done in Rob Knight's UCSD Center for Microbiome Innovation

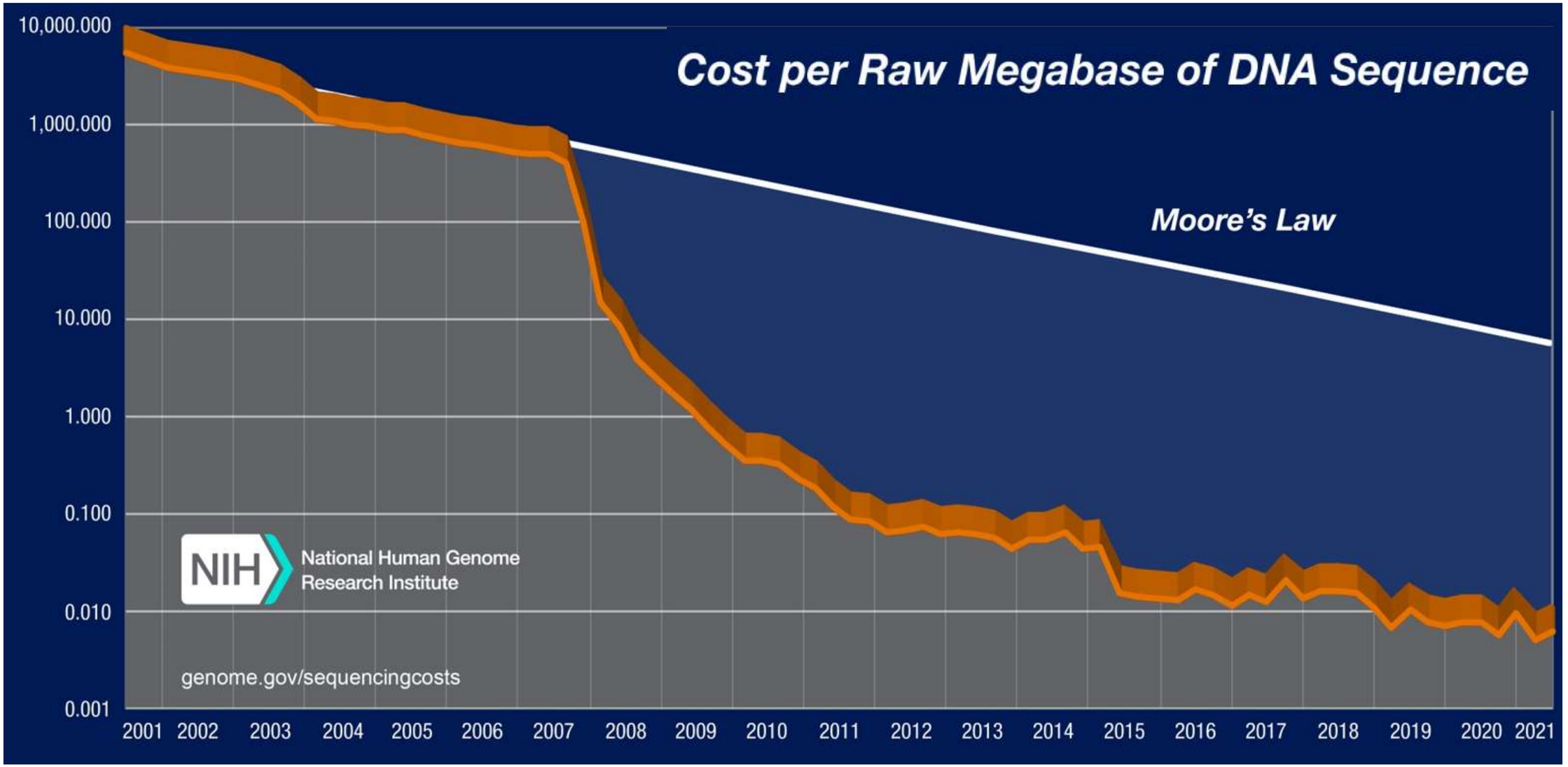



The power of industry
The expertise of a university
The revolution of the microbiome

CENTER FOR microbiome INNOVATION

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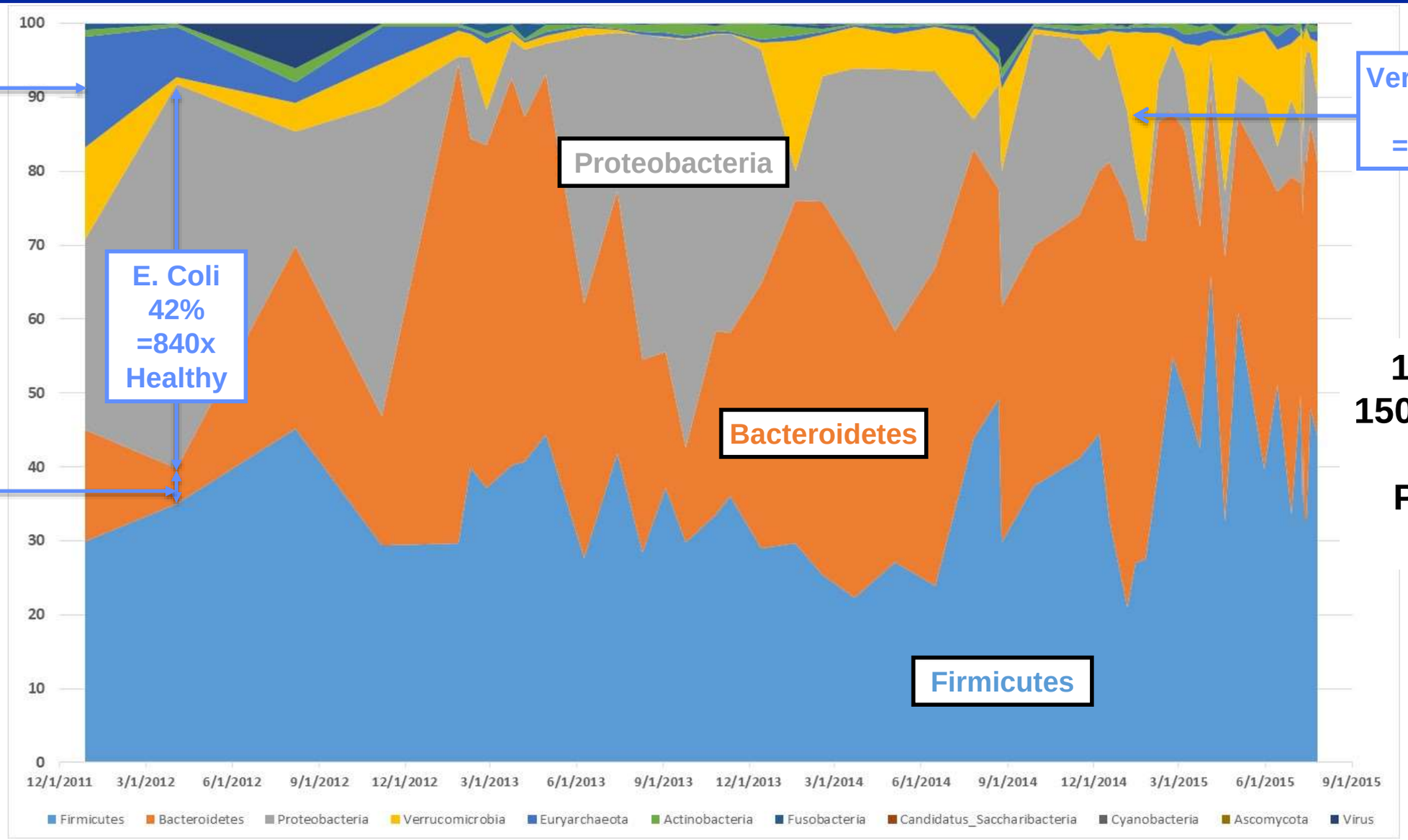
# Analysis of the Gut Microbiome Became Possible Because The Cost of Sequencing DNA Has Fallen Over 1,000,000x in the Last Twenty Years




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

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# We Created a Time Series by Sequencing 50 of My Stool Samples Over 2.5 Years: Revealing a Patient's Gut Microbiome Ecology Dynamics During Disease

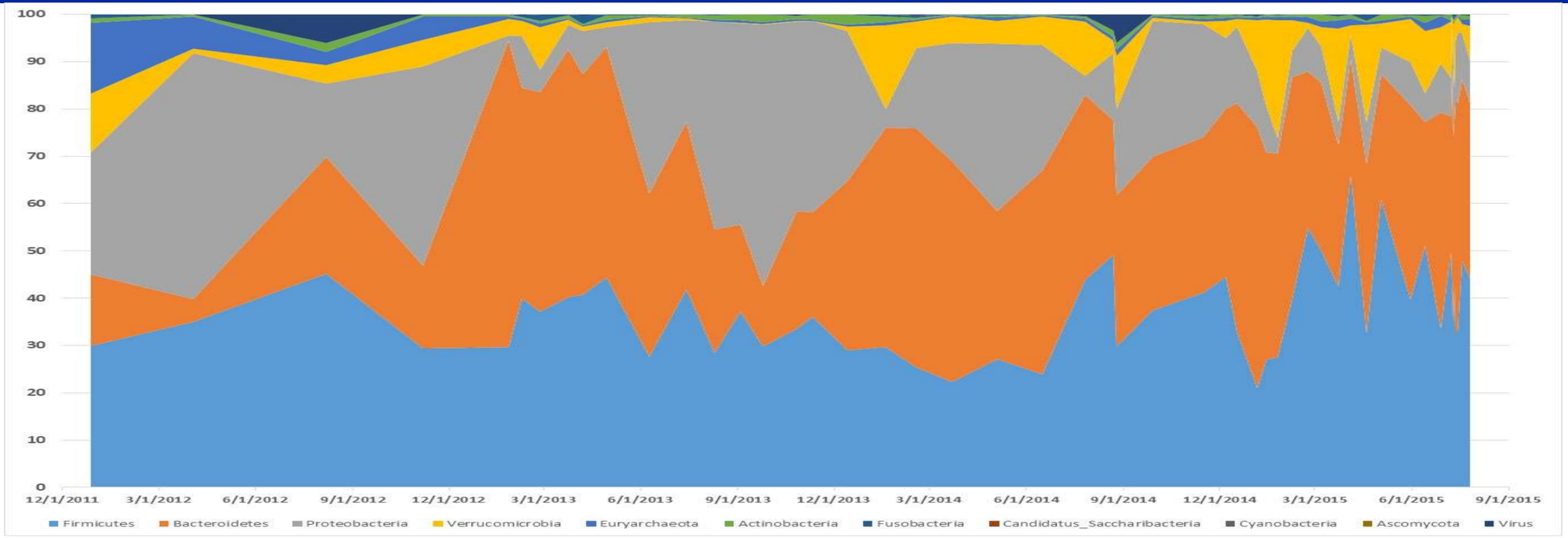


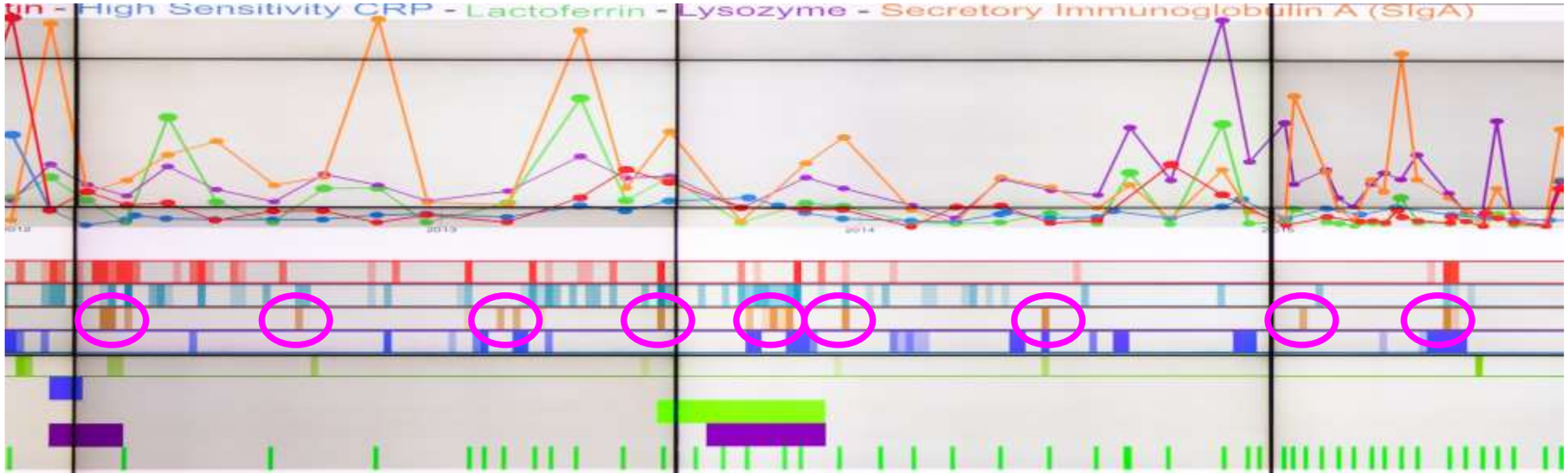

**1st 50 of 150 Samples at Phylum Level**

**Sequencing Rob Knight Lab; Analysis Xin Fang, UCSD**

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# An Early Experiment in Aligning in an Individual the Time Series of Microbiome Ecology with Inflammation and Immune Biomarkers, Pharma, Moods, and Symptoms

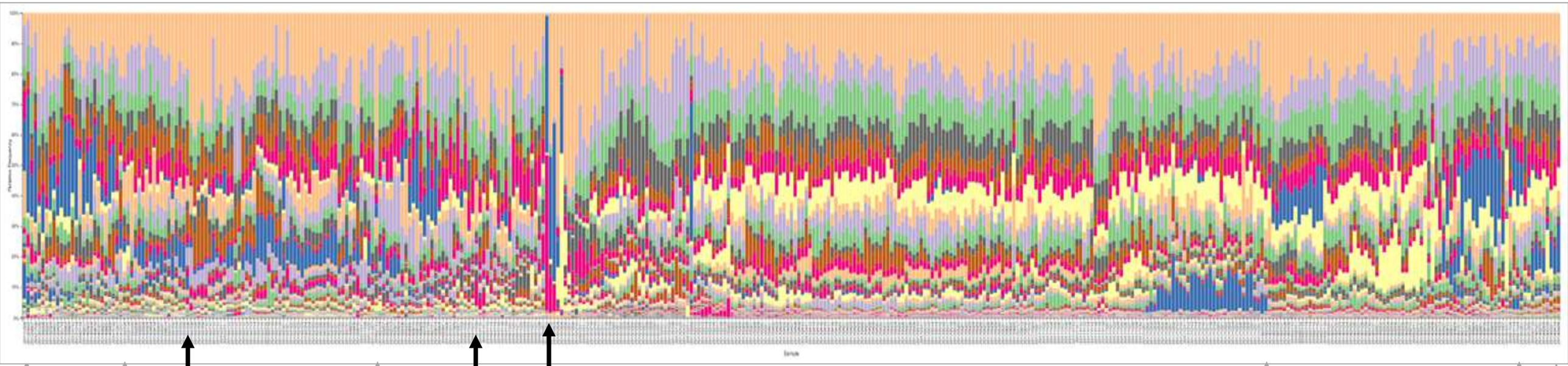



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# Gut Microbiome Ecological Dynamics Revealed by 16S Genomic Sequencing of ~400 Smarr Daily Stool Samples Over 8 Years

## 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

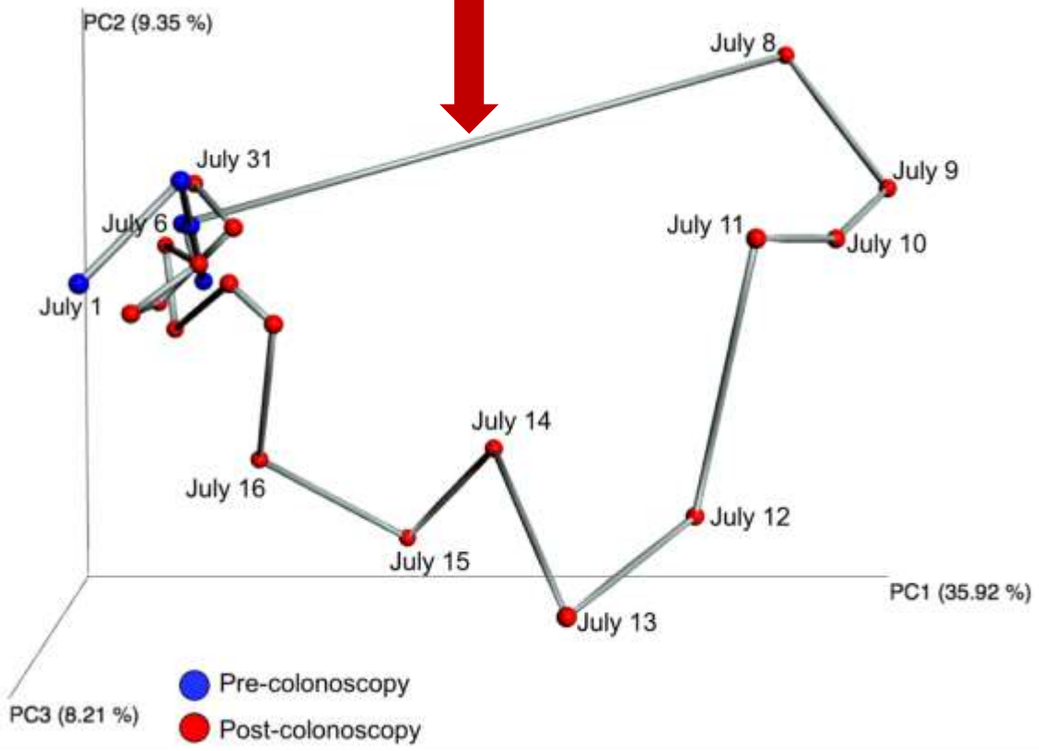
April 28, 2019

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

**July 2015 Colonoscopy**

**Shift Induced By Bowel Cleanse**




## 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



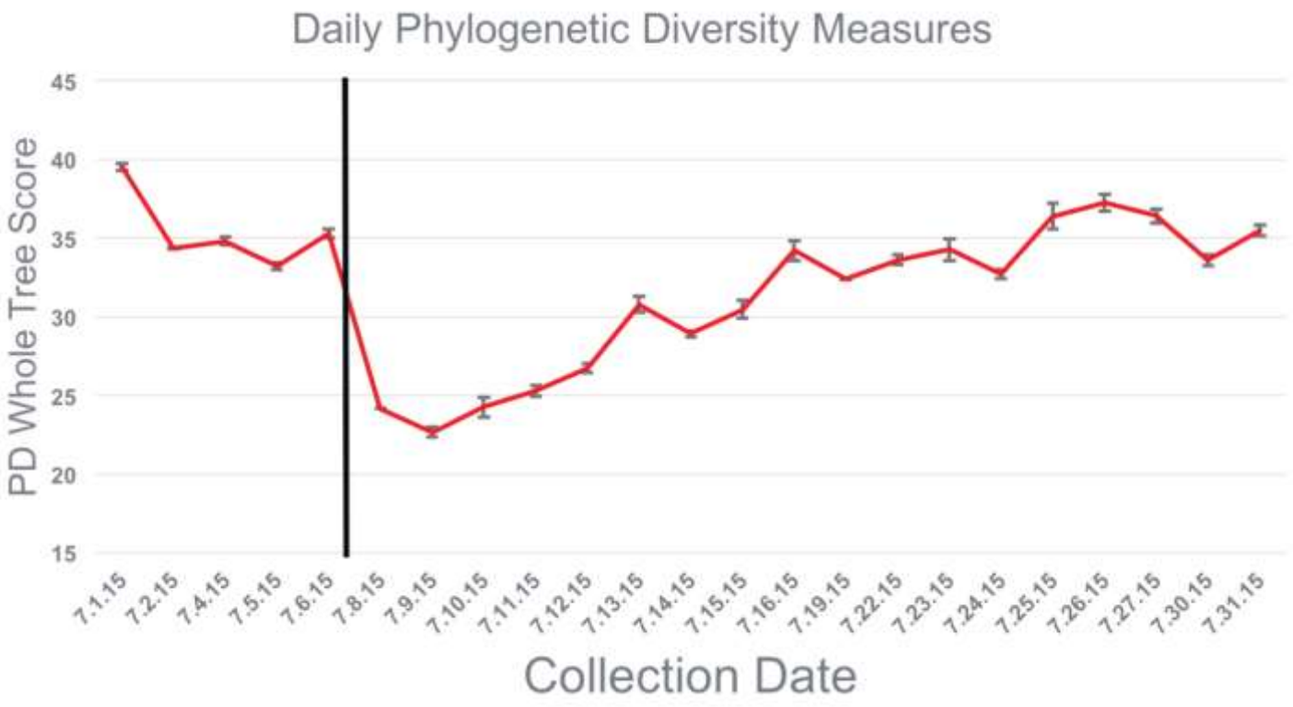
Methods Inf Med. 56, 442-447 (2017)

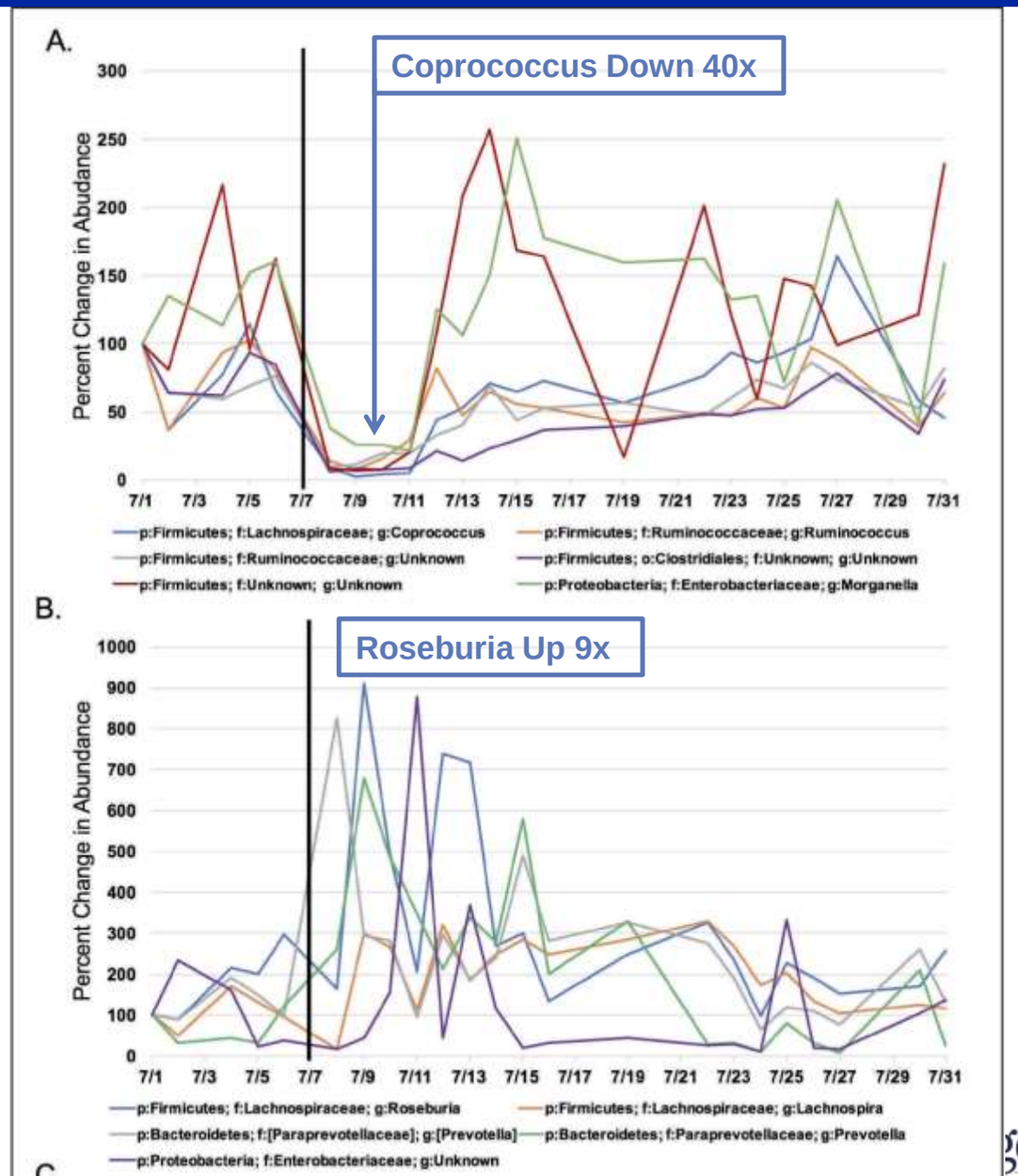

**Principal Component Analysis: Each Dot is a Single Day with a Full Gut Microbiome Ecology Consisting of 50 Genus, Each with a Relative Abundance**

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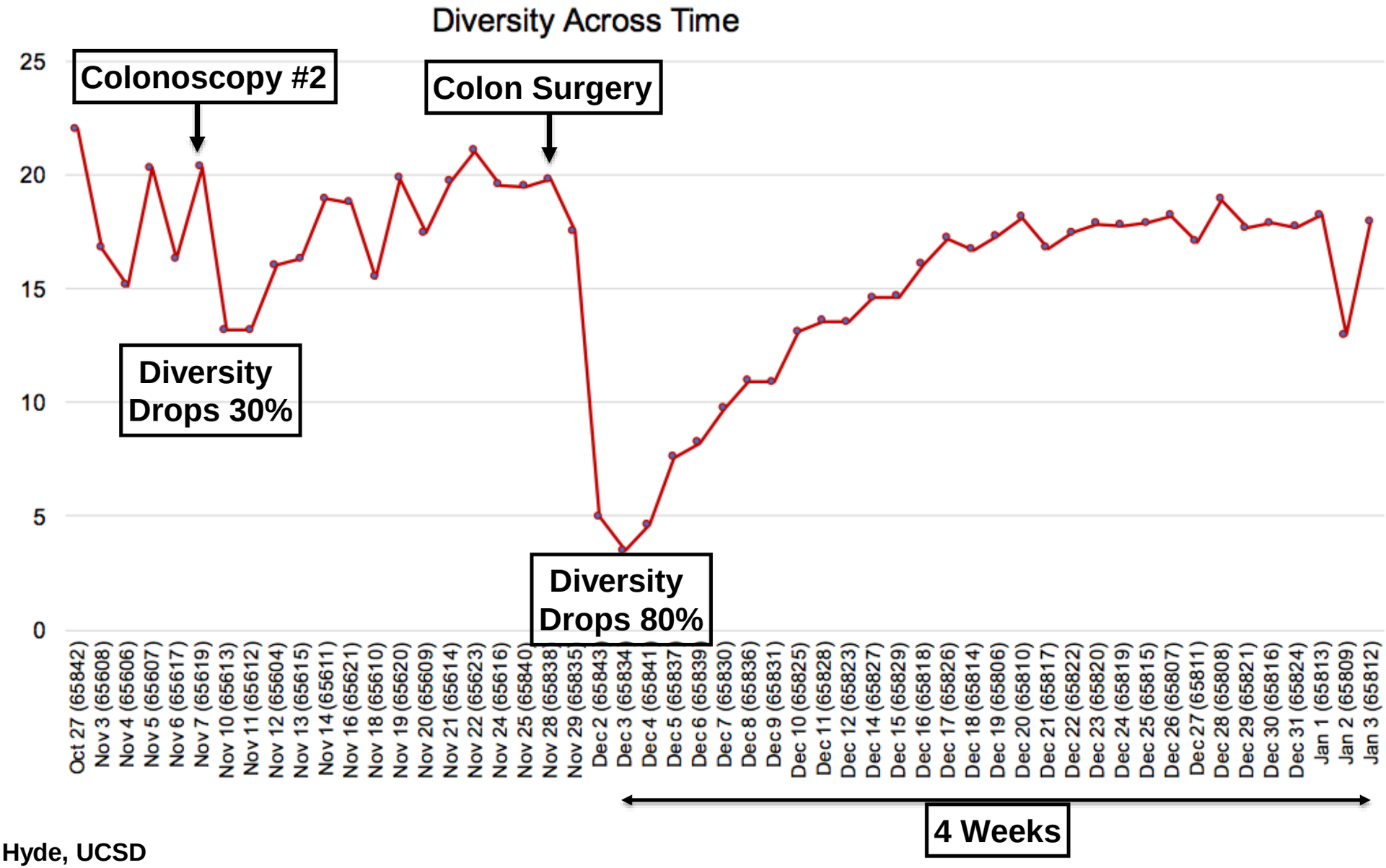
# Days Following Colon Cleanse There is a Drop in Ecological Diversity and Major Changes in Microbial Genus Relative Abundance

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



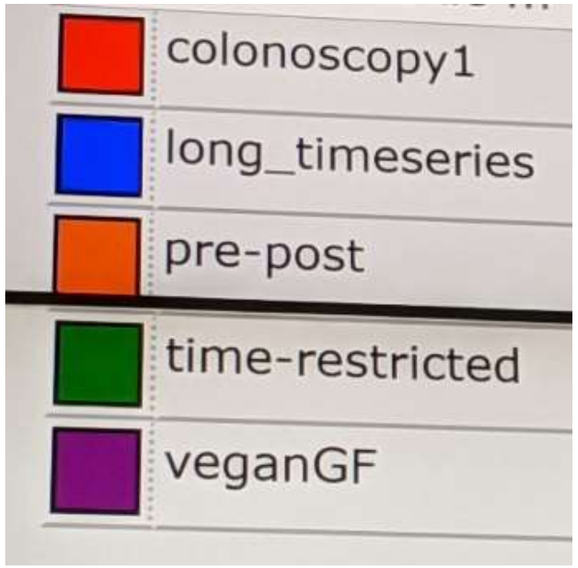
# Sigmoid Colon Resection Surgery Wiped Out My Gut Microbiome Ecological Diversity: It Slowly Recovered Over a Month, But To a New State

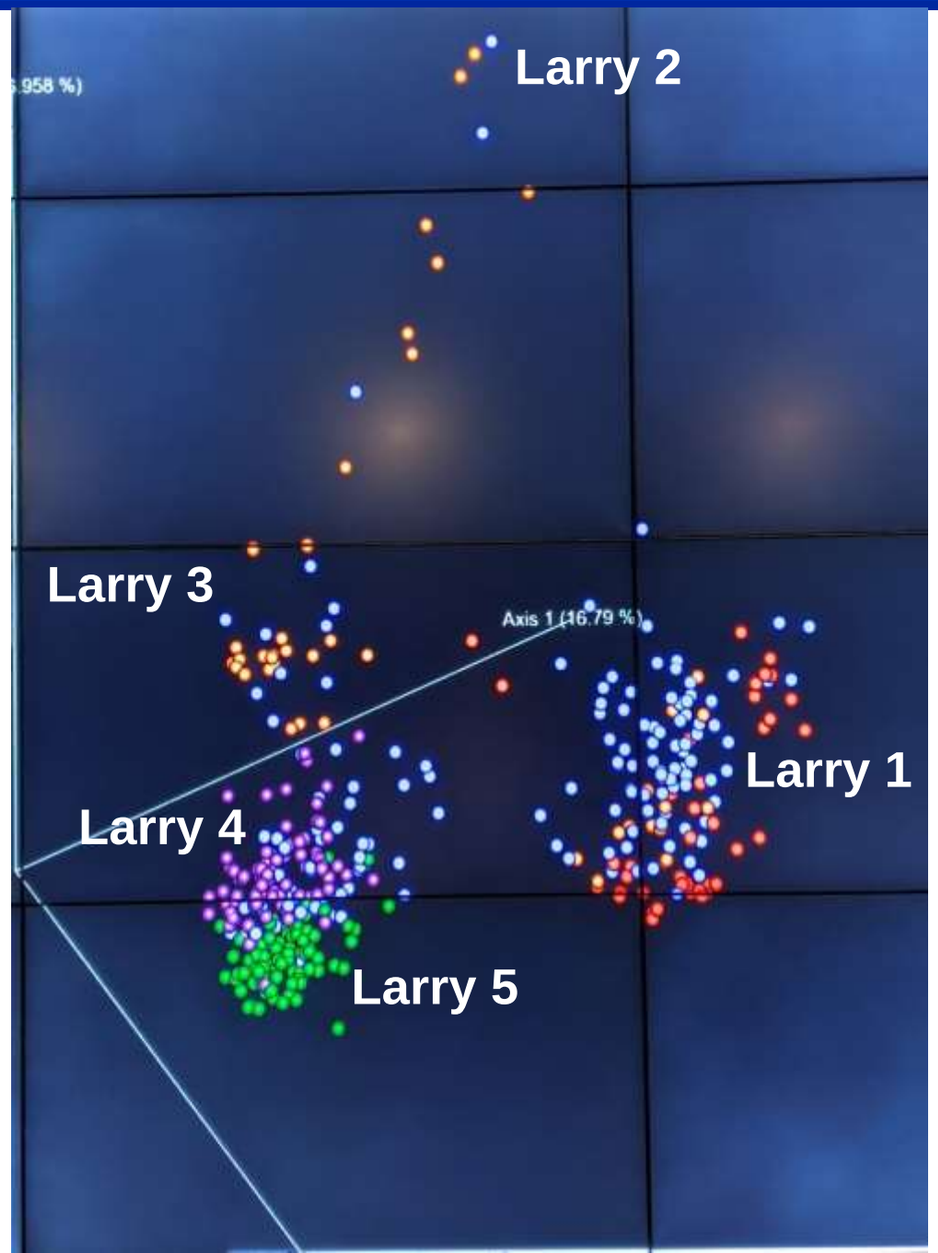



Source: Embriette Hyde, UCSD

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# I Became Five Different People Over 8 Years:
# First Three Were IBD Pre- and Post Surgery, Last Two From Dietary Changes

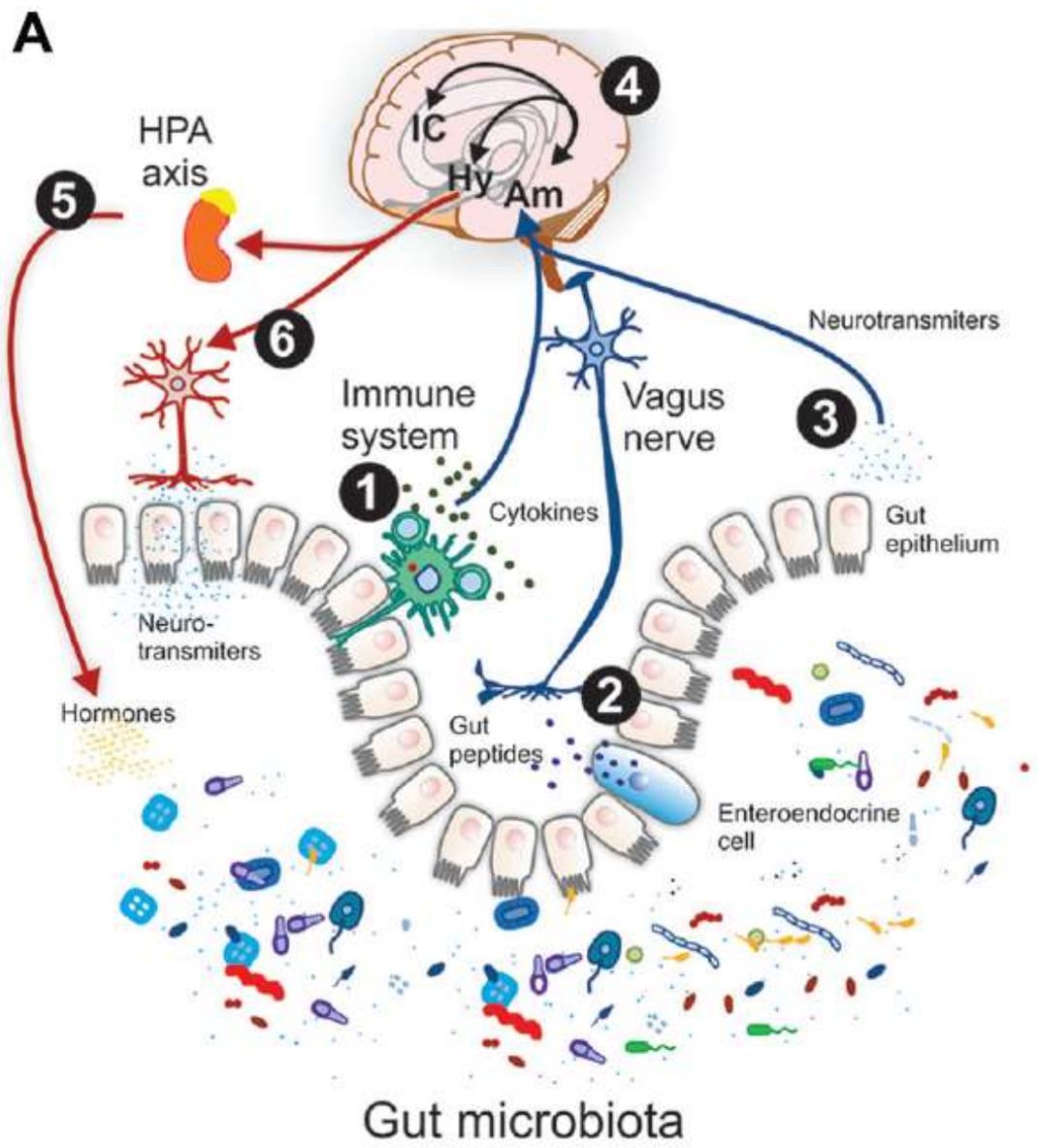


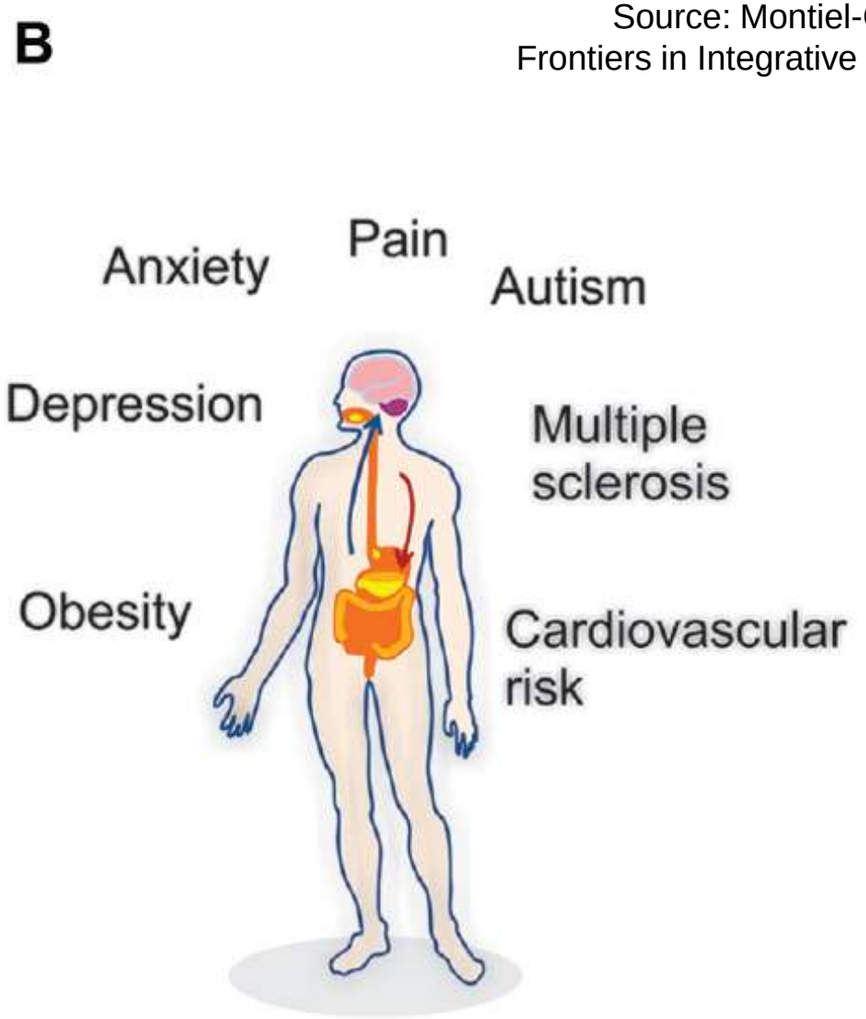






# The Individual's Gut Microbiome Time Evolution *Must* Lead to Time Shifts in Behavior and Disease via the Microbiome–Gut–Brain Axis

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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# Many New Research Studies are Demonstrating Deep Relationships Between the Gut Microbiome and Behavioral Disorders

Symposium

*The Journal of Neuroscience* 12 November 2014, 34(46): 15490-15496;

## Gut Microbes and the Brain: Paradigm Shift in Neuroscience

Emeran A. Mayer[1], Rob Knight[2], Sarkis K. Mazmanian[3], John F. Cryan[4], and Kirsten Tillisch[1,5]

Review

Trends in Neurosciences Volume 36, Issue 5, p305–312, May 2013

## Gut–brain axis: how the microbiome influences anxiety and depression

Jane A. Foster✉, Karen-Anne McVey Neufeld

frontiers in Cellular Neuroscience September 2013 | Volume 7 | Article 153

## Alzheimer's disease and the microbiome

***Surjyadipta Bhattacharjee and Walter J. Lukiw****

January 2013, 15:337 CURRENT PSYCHIATRY REPORTS

Date: 10 Jan 2013

## The Gut Microbiome: A New Frontier in Autism Research

Jennifer G. Mulle, William G. Sharp, Joseph F. Cubells

Molecular Psychiatry (2014) 19, 1252–1257

PERSPECTIVE

## Genomics of schizophrenia: time to consider the gut microbiome?

TG Dinan[1,2], YE Borre[1] and JF Cryan[1,3]

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

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

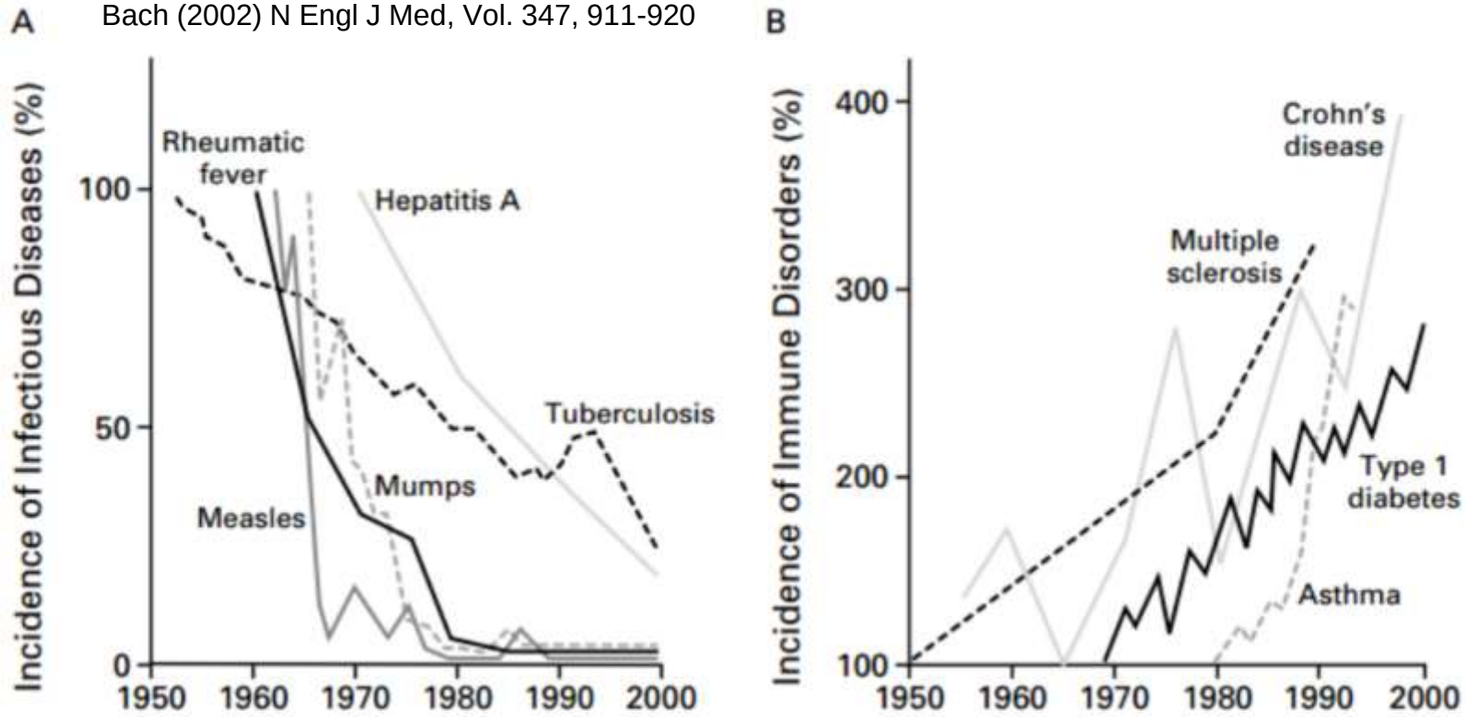
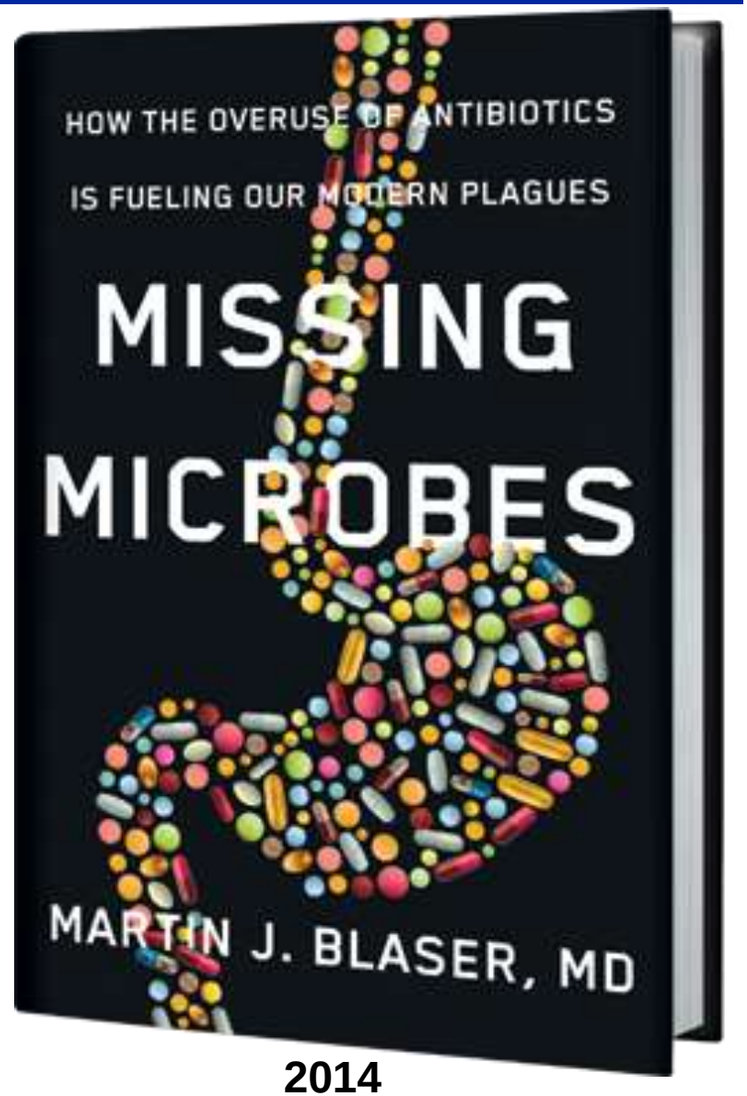



**Figure 1.** Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

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]



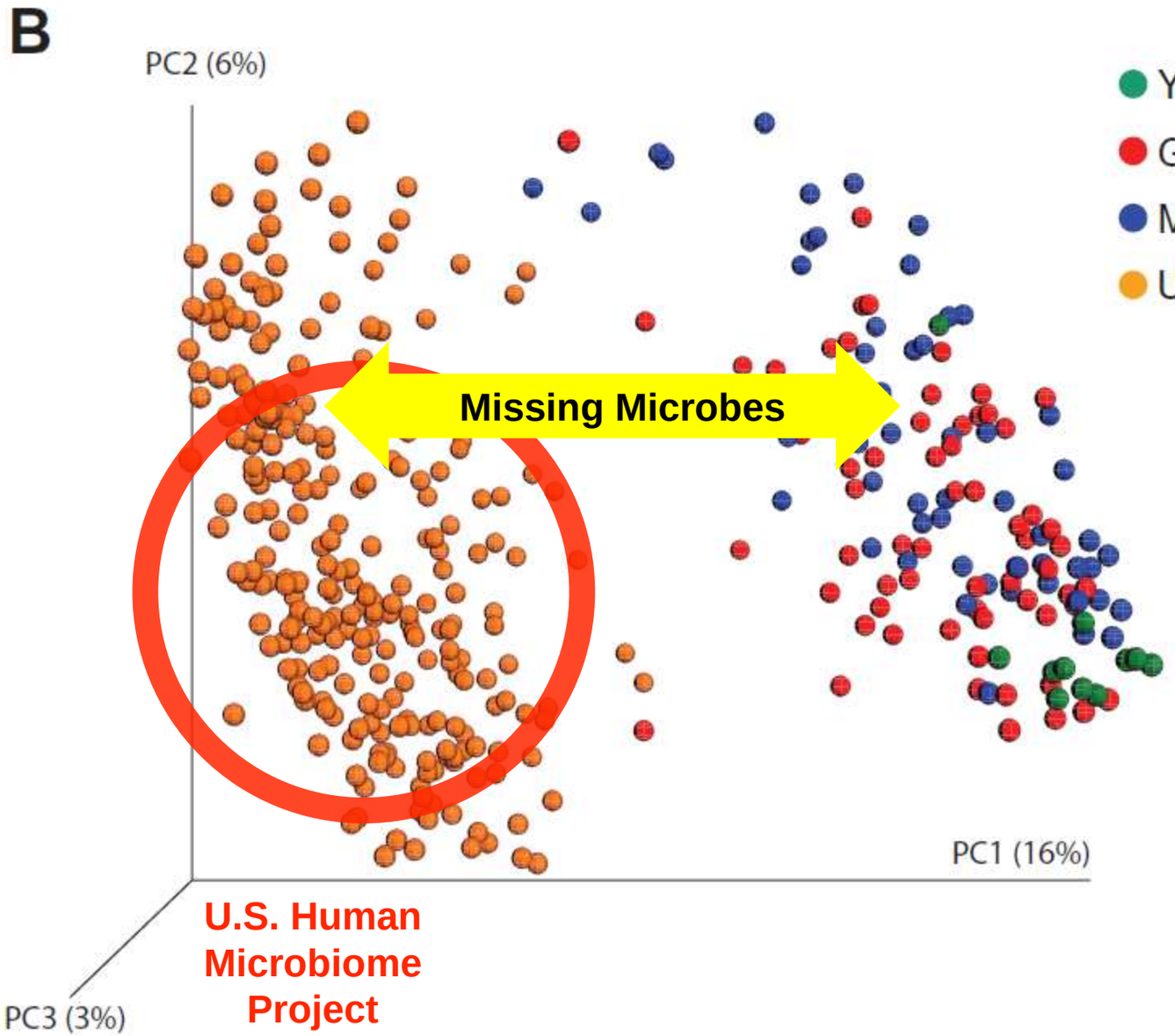

2014

**The Rise in the Use of Oral Antibiotics in the 1960s Has Had Multi-Decadal Harmful Impacts on Health**

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

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# 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).

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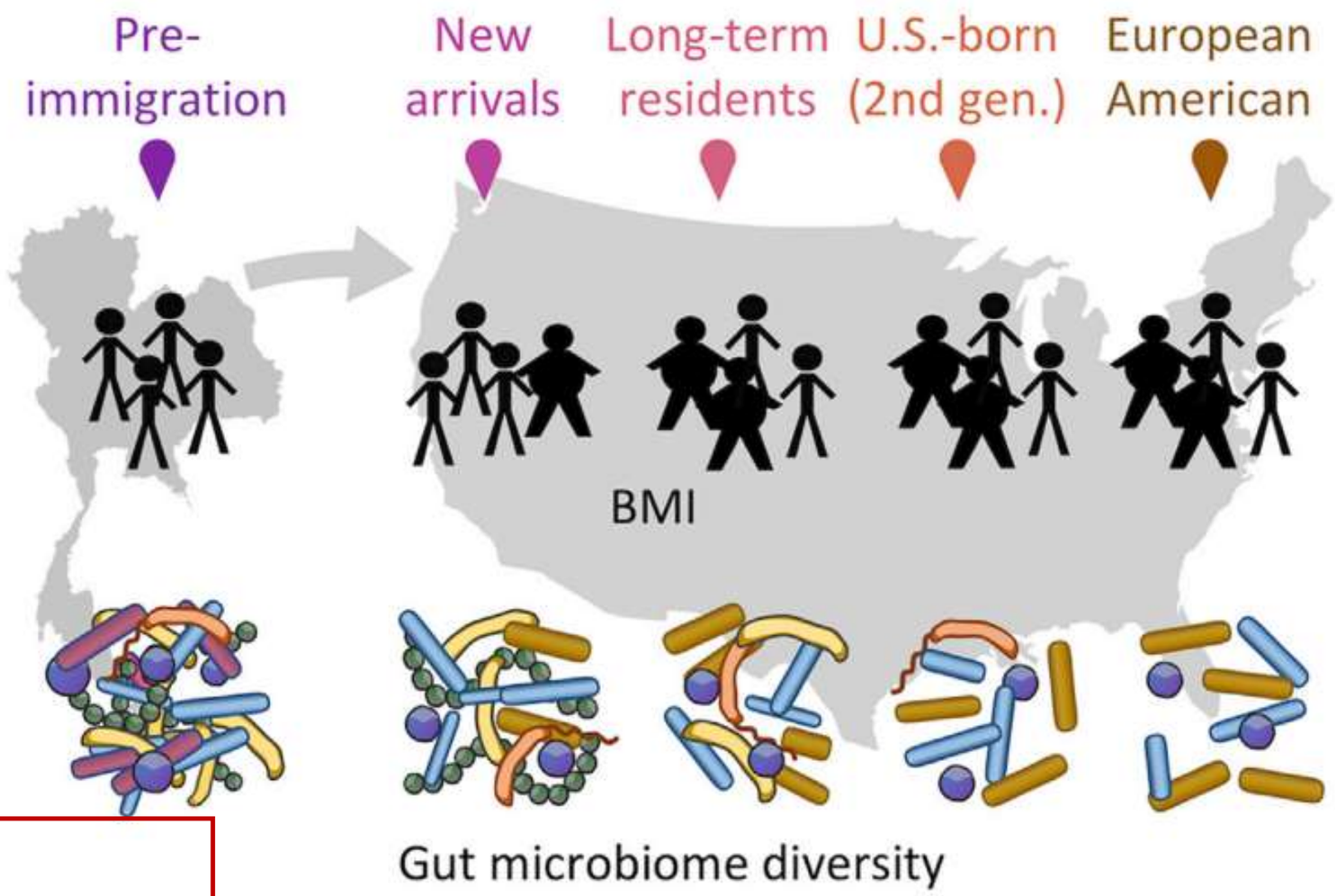
# The "Western Diet" Seems to Increase Obesity and Reduce the Gut Microbiome Ecological Diversity

Cell

## US Immigration Westernizes the Human Gut Microbiome

Pajau Vangay, …, Dan Knights

Cell *175*, 962–972, November 1, 2018

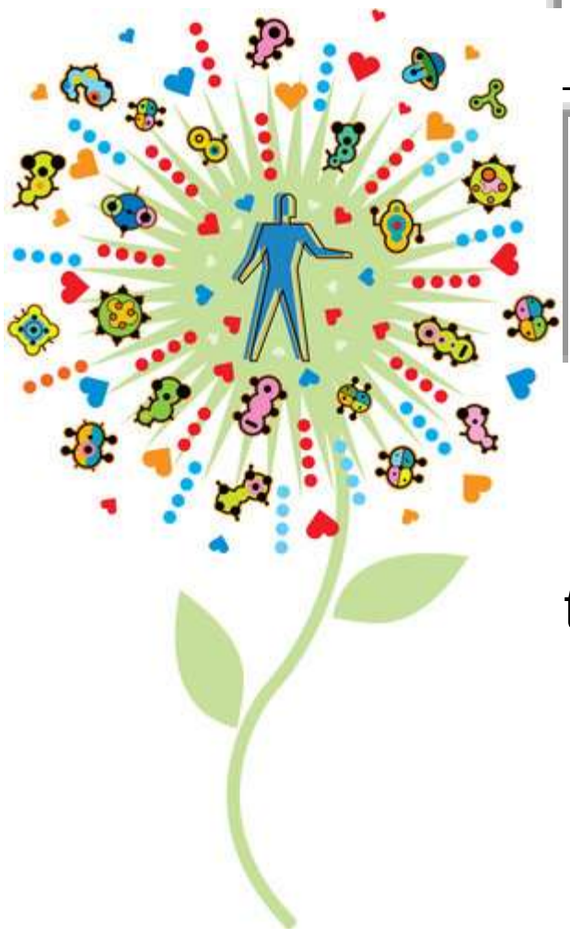



**Highlights:**

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

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# Can We “Garden” Our Gut Microbiome Back to Health? I Set Out to Find Out



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.”

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



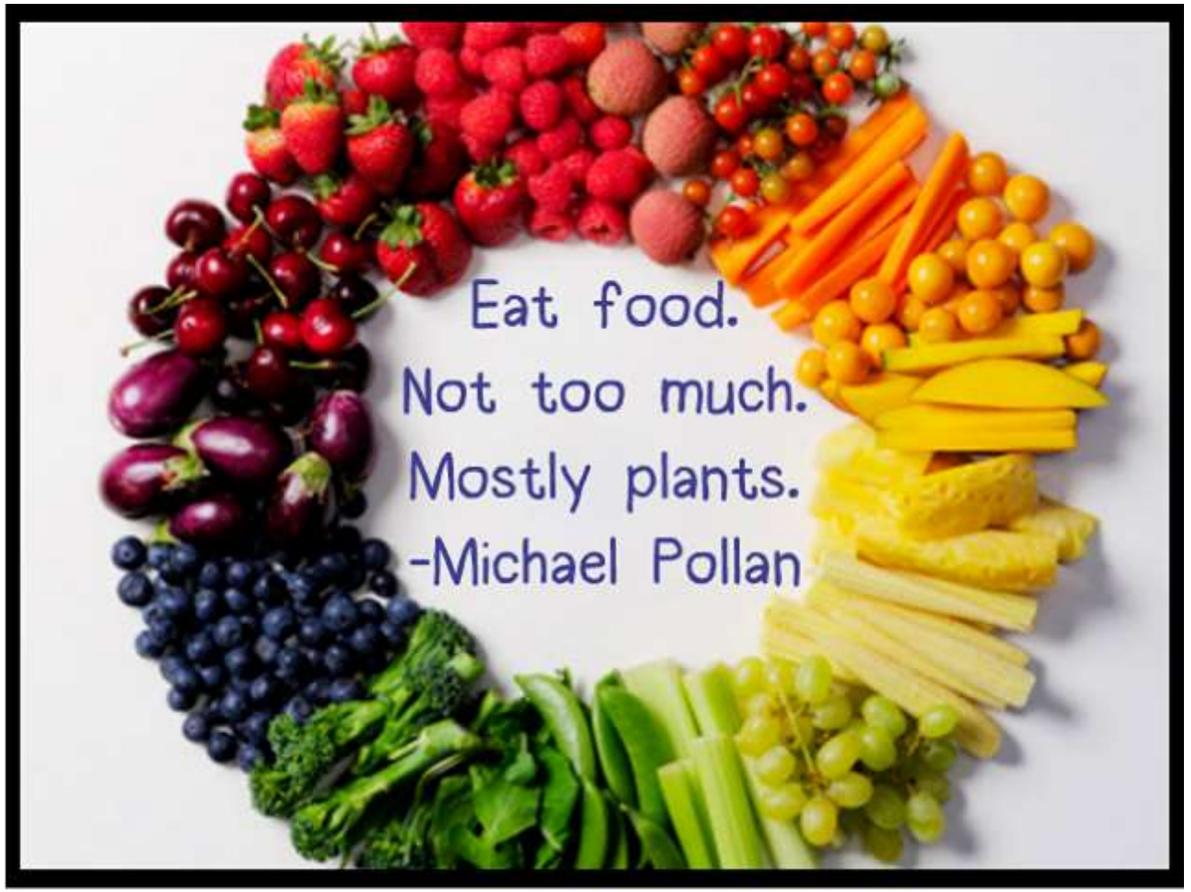
©Thomas Jefferson Foundation at Monticello. Photo by Robert Llewellyn

# 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/

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# 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

May 15, 2018

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# Can I Increase My Microbiome Diversity By Consuming ~60 Plant Species Per Day in a Green Smoothie?









**Real Food, Mostly Plants**

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# Aligning Your Eating Pattern With Your Body's Circadian Rhythm: When You Eat 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

**Not Too Much**

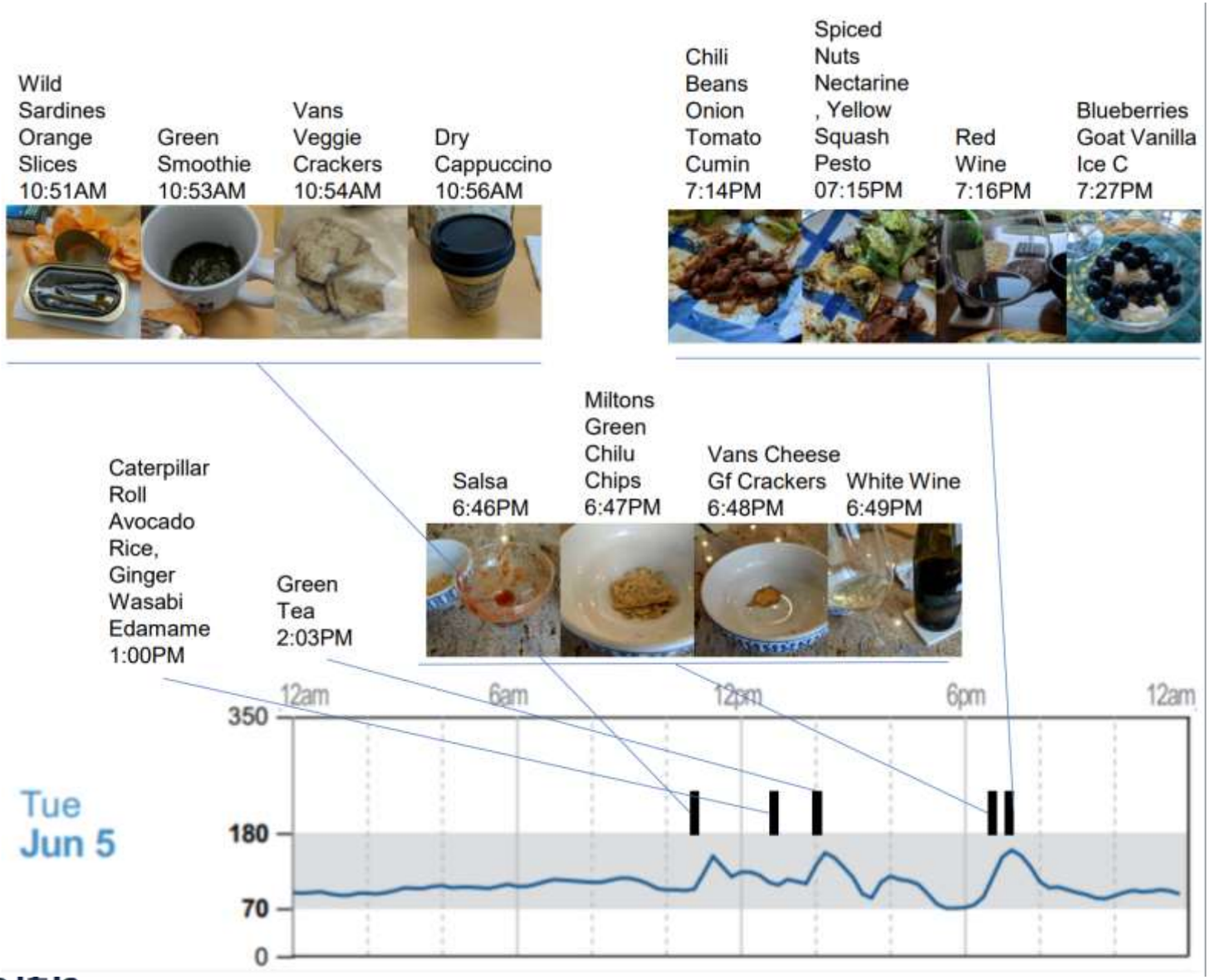
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# I Volunteered to Become a Patient in the UCSD/Salk Pilot Study of Time-Restricted Eating (TRE) in Metabolic Syndrome

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

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








**Pam Taub, MD**
**Cardiology**



**Satchin Panda, PhD**
**Circadian Biology**

**Emily Manoogian, Panda Lab, Salk Institute**

# A Decade of Daily Weight Measurements Created a Time Series to Track Reduction in Metabolic Syndrome

**Similar Weight Reductions Seen in Other TRE Trial Patients**




Vegan

Started TRE

Afib

Start
190 lb
5/6/12

180 lb
11/22/13

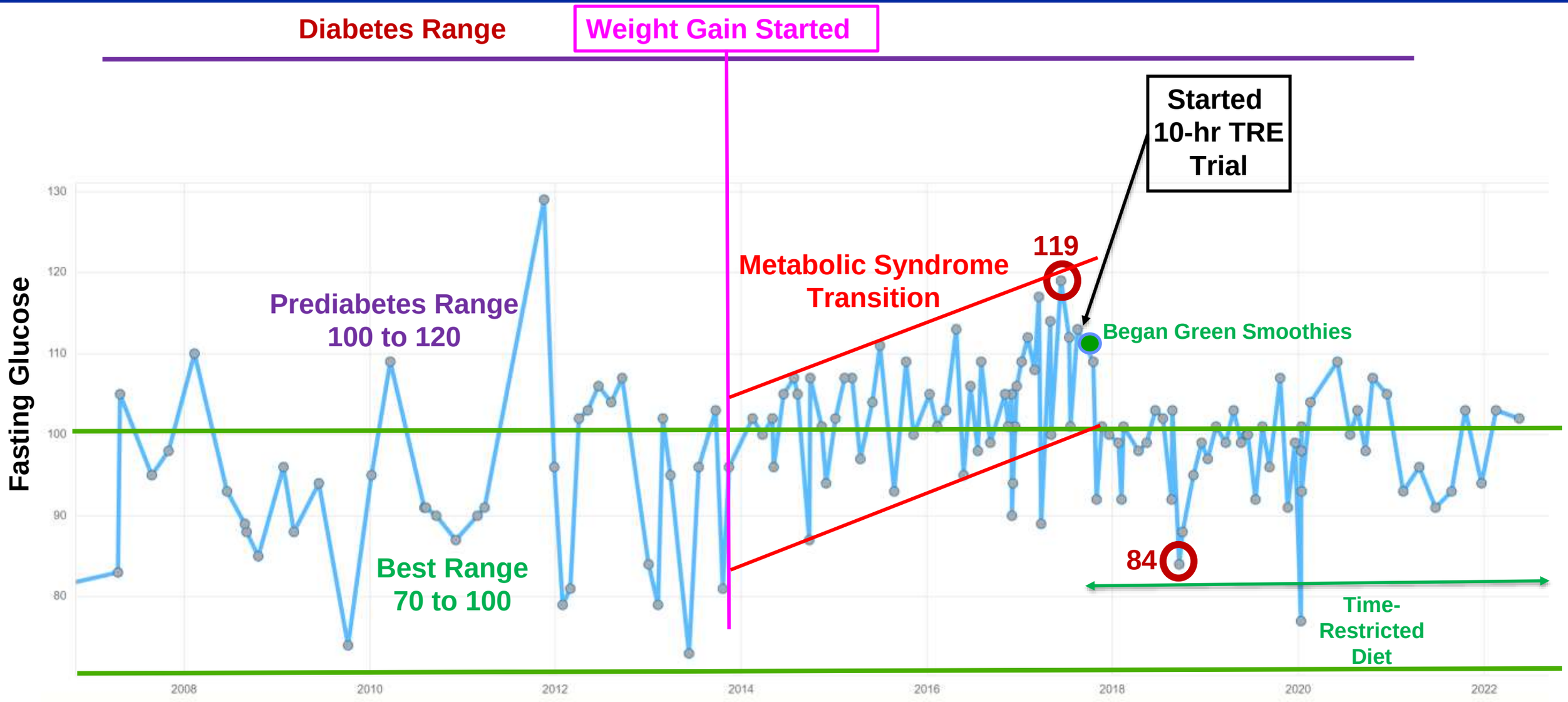
35 lbs

Low
165 lb
6/23/22

Home Withings WiFi Scale

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# 15 Years of Blood Draws Created a Fasting Glucose Time Series Which Revealed An Abrupt Drop After Start of Green Smoothies and Time-Restricted Diet

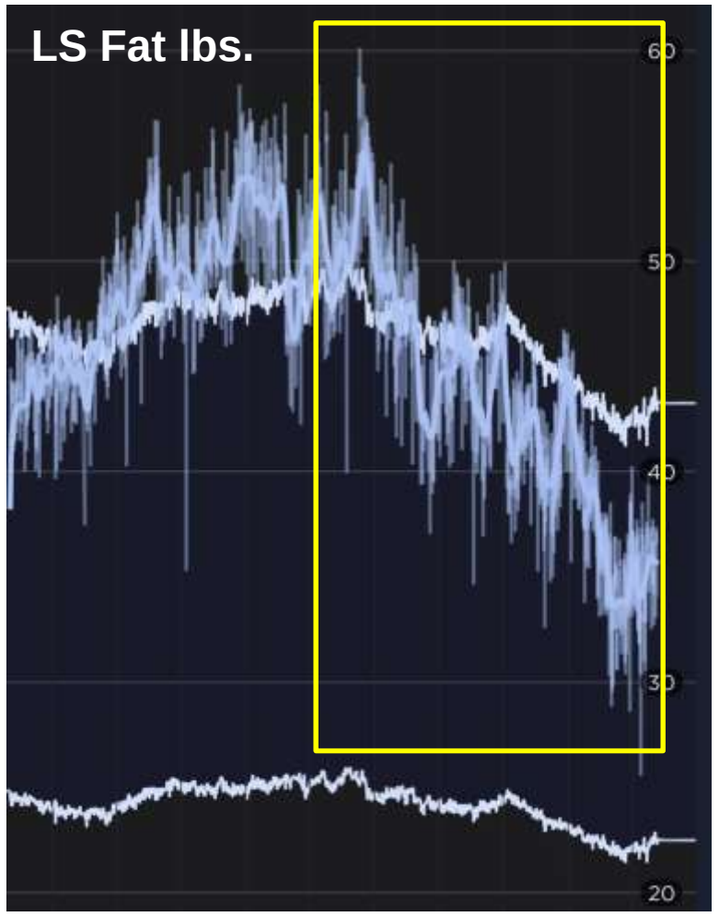



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# My Body Fat and Visceral Fat Were Also Dramatically Reduced Since 2017

**Peak**
**60 lbs**
**10/8/17**

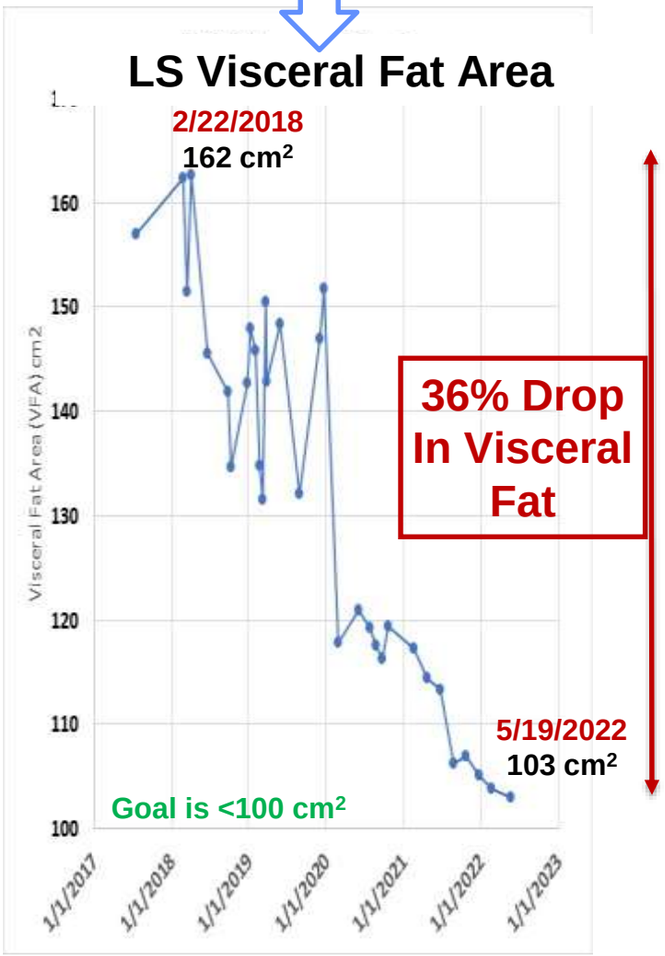
**Same Time Scale**



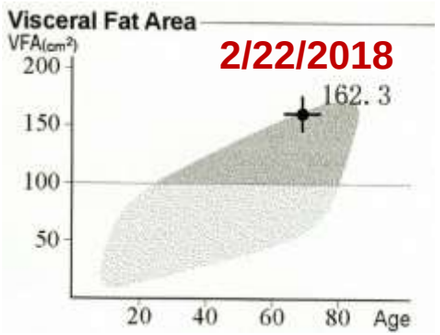

**Start**
**45 lbs**
**5/6/22**

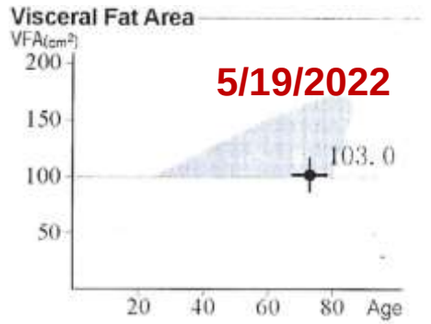
**Now**
**35 lbs**
**6/5/22**

**42% Drop In Total Fat**




**36% Drop In Visceral Fat**




**$17,000 InBody 770 Scale**

**$100 Home Withings WiFi Scale**

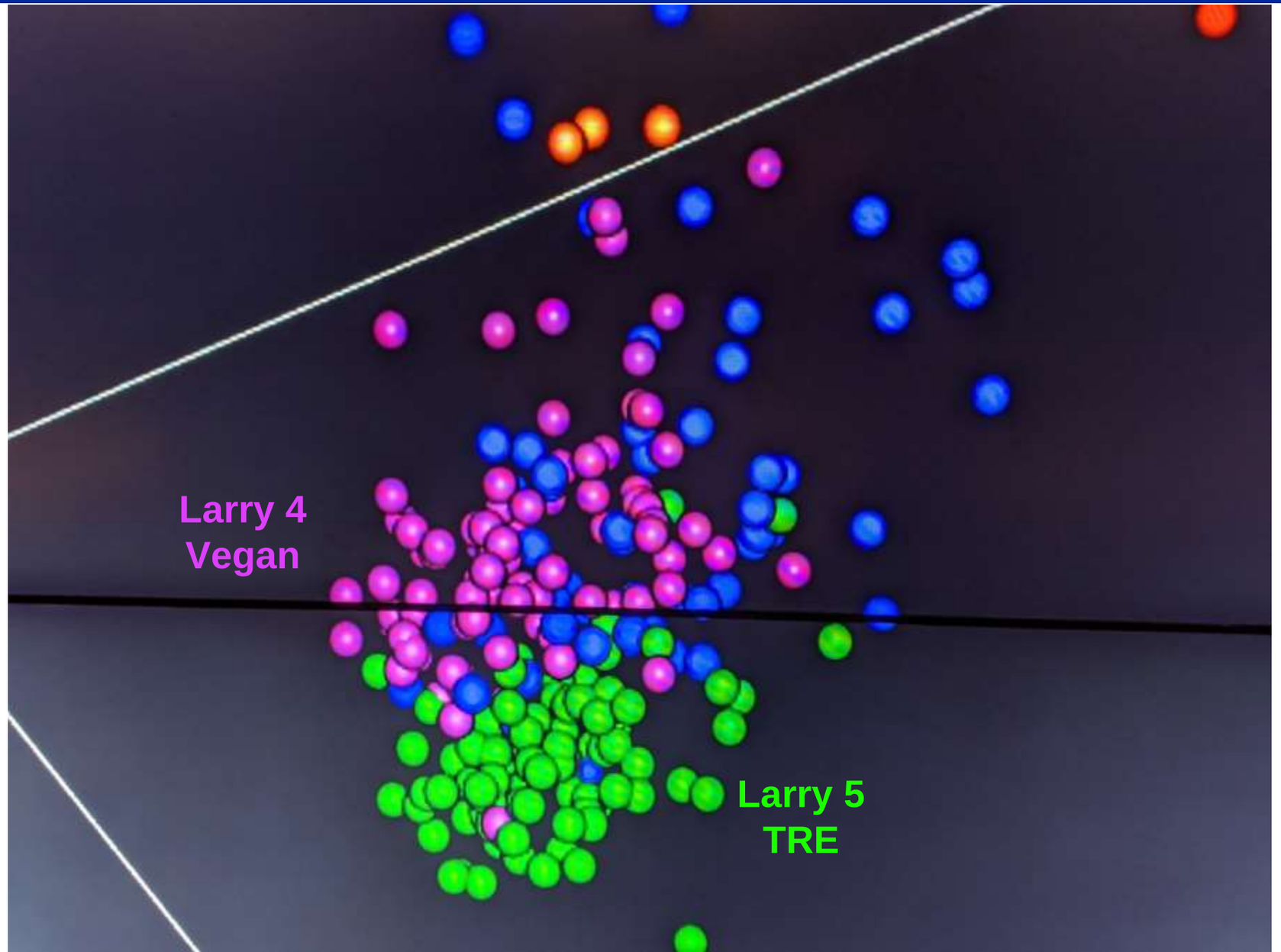
**Visceral Fat Area** is based on the estimated amount of fat surrounding abdominal internal organ. It's recommended <100 cm² for

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# Closeup of 16S Gut Microbiome Ecology PCA Time Series
# Switch to Vegan (Larry 4) and Then Time Restricted Eating with Green Smoothies (Larry 5)

**Using PCA Dimensional Reduction Reveals Distinct Clusters Indicating Microbiome Ecological Shifts With Dietary Interventions.**

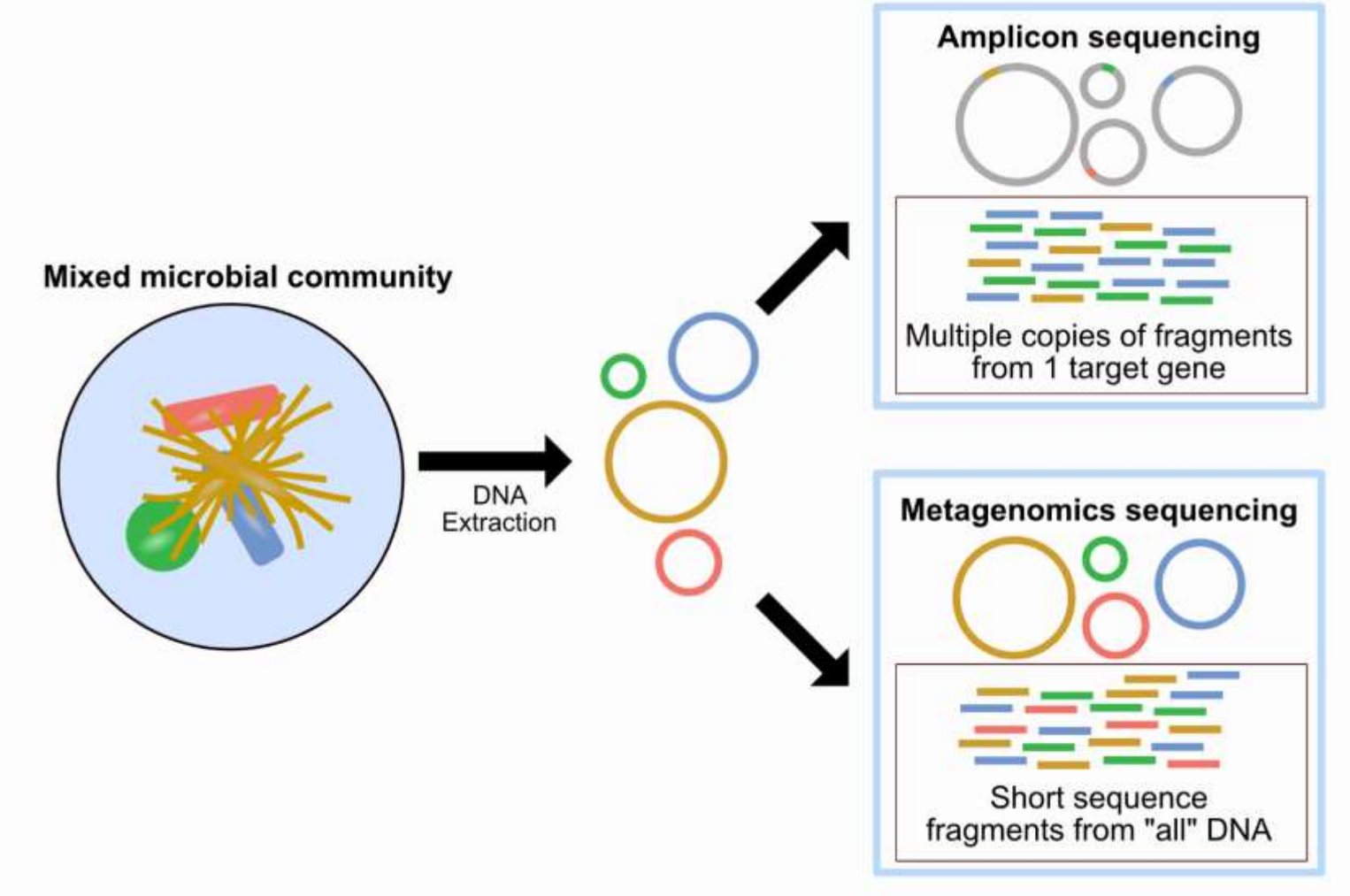
**Next, We Need to Find Out What the Microbiome Ecology Shifts Were in Detail.**




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# Next Step: UCSD Knight Lab Will Metagenomically Sequence 25,000x Deeper My Decade of ~500 Daily Stool Samples

https://astrobiomike.github.io/misc/amplicon_and_metagen



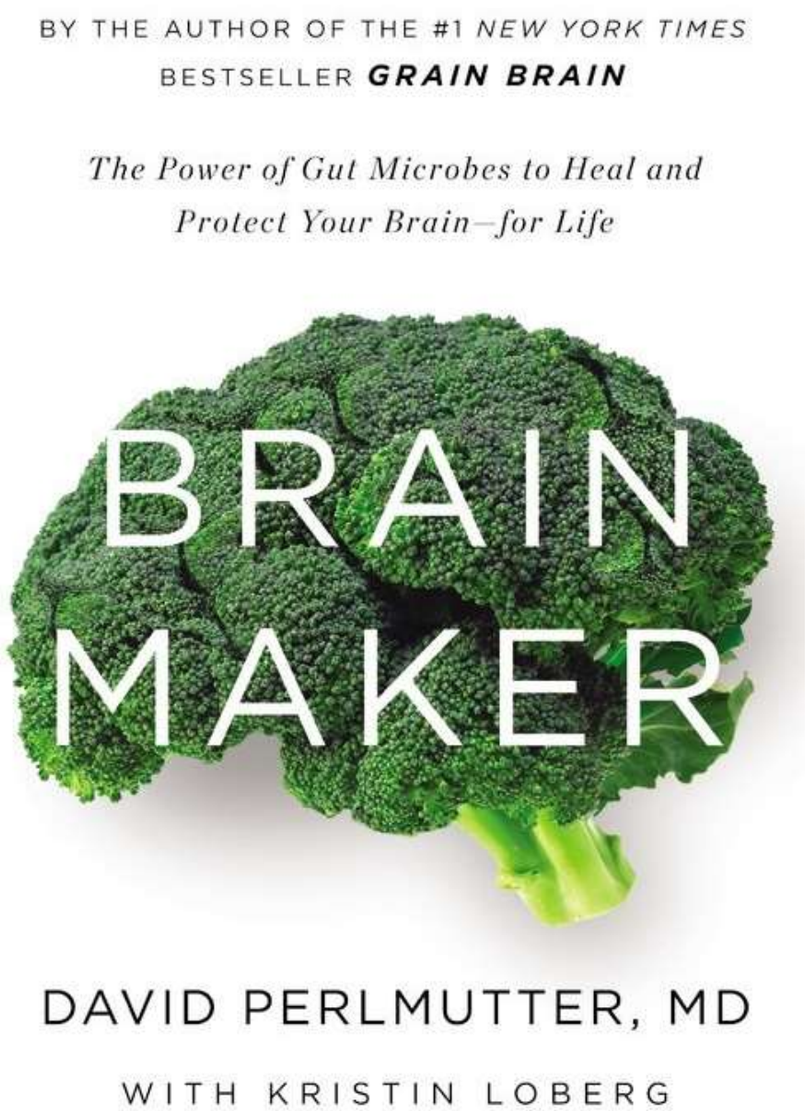

**16S:**
**~20,000**
**Illumina Short Reads**
**per Sample:**
**Resolves Taxonomy**
**to Genus Level**

**Metagenomics:**
**~50,000,000**
**Illumina Short Reads**
**per Sample:**
**Resolves Taxonomy**
**to Species or Strain Level**

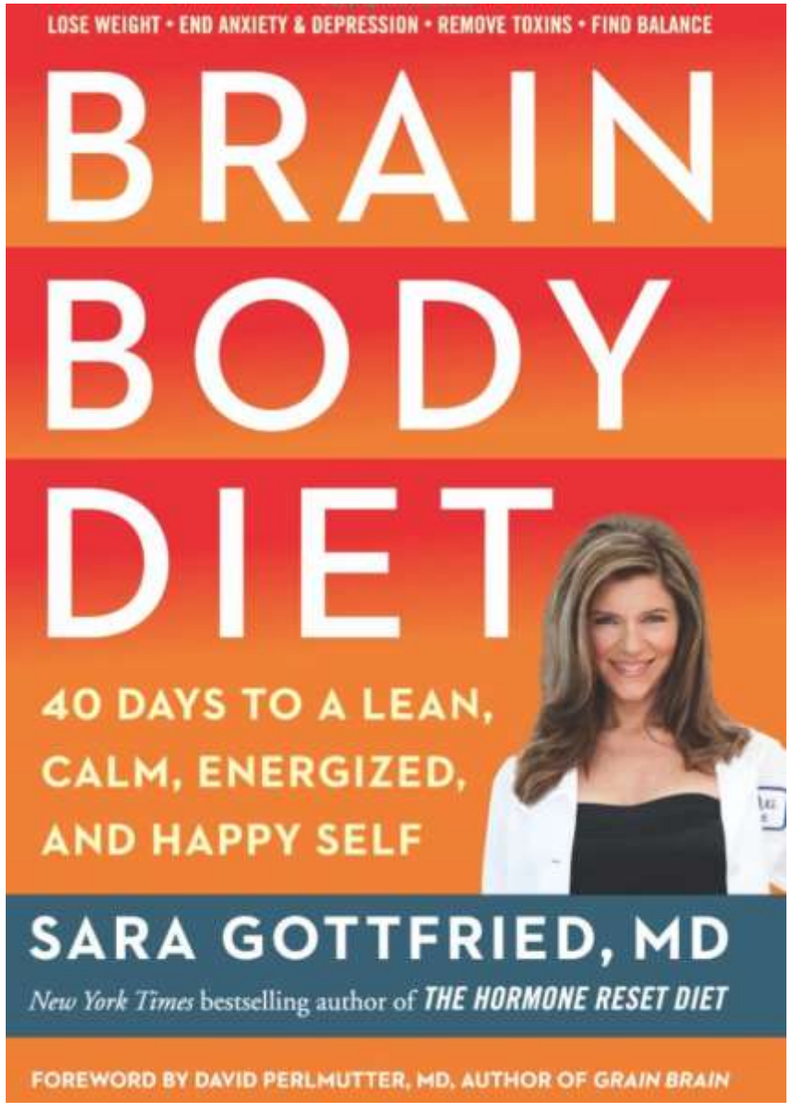
**One Illumina Short Reads is ~100 Bases**

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# Popular Books Are Translating the New Science of Neural, Hormonal, Immune, Food, and Microbiome Systems Coupling




2015




2019

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

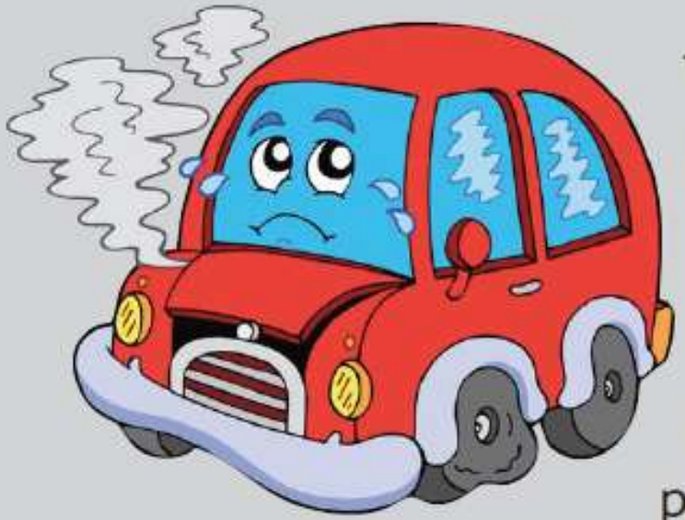
Perspective

## 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

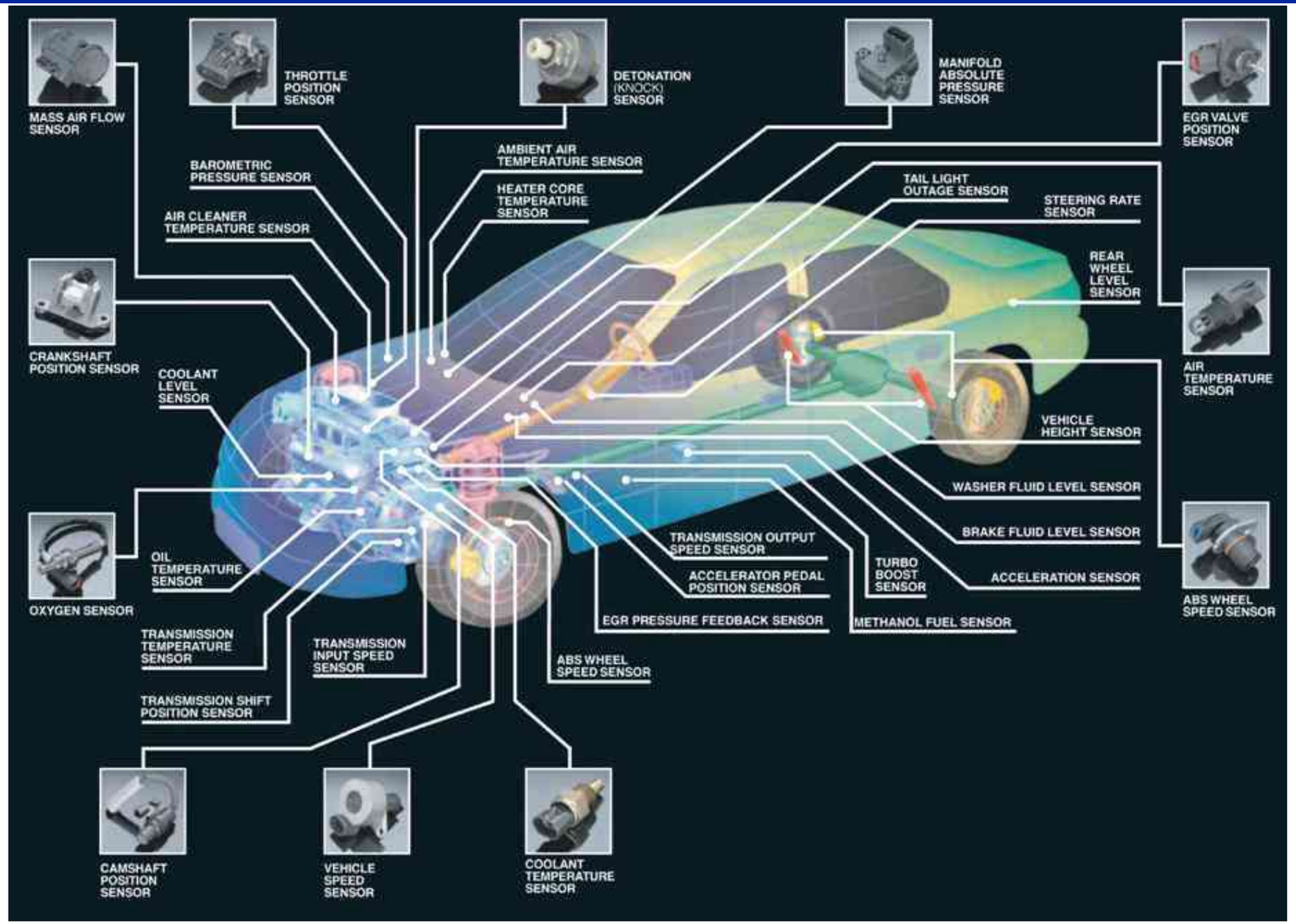
http://onlinelibrary.wiley.com/doi/10.1002/biot.201100495/abstract

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# 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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# Over the Last Decade, I Have Used a Variety of Personal Sensors To Quantify My Body & Drive Behavioral Change




**MyFitnessPal- Calories Ingested**




**Withings WiFi Scale - Daily Weight**




**FitBit - Daily Steps & Calories Burned**



**Withings/iPhone- Blood Pressure**






**Oura Ring - Sleep, HRV, Temperature, Respiratory Rate**




**Apple Watch- Health Metrics Integration**



**Wellue Ring: Continuous SpO2**

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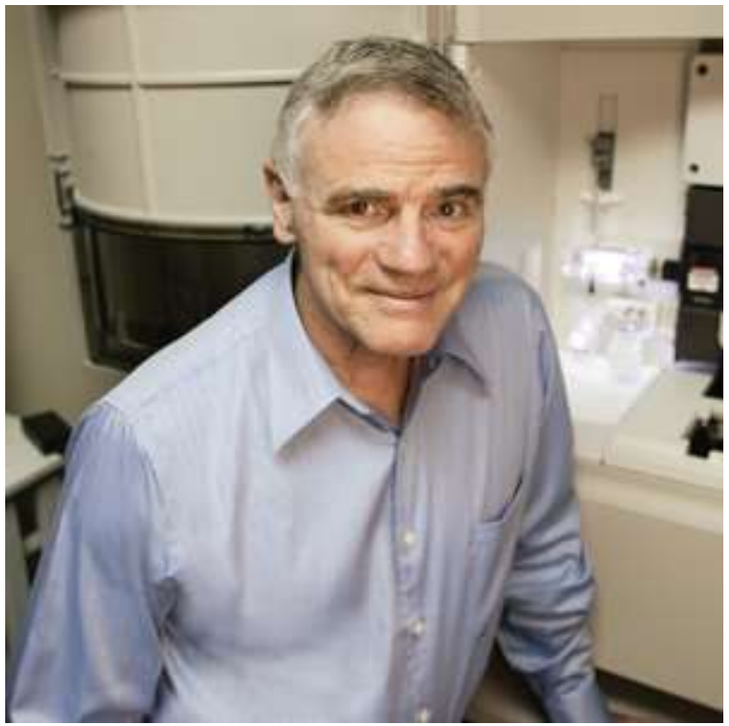
# The Near Future Transition
# to Predictive, Personalized, Preventive, & Participatory (P4) Medicine

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

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

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# In the Next Few Years, Wearables Will Add Continuous Glucose, ECG, Blood Pressure, Temperature Monitoring

03-11-22

## Rockley Photonics is developing a wearable to track blood sugar

DIGITAL HEALTH

## Apple plans to add blood pressure monitoring, thermometer to smartwatch: report

By **Heather Landi** • Sep 1, 2021 10:19am

MEDTECH

## AHA: Fitbit shows it can track down atrial fibrillation in 450,000-strong heart study

By **Conor Hale** • Nov 15, 2021 08:20am

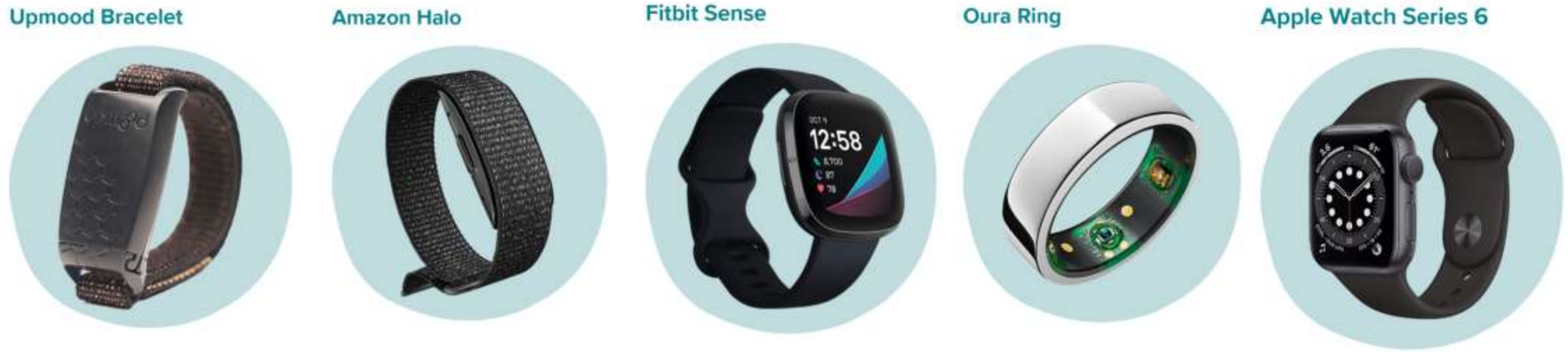
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# Emotional State Tracking is The Newest Wearable Feature

healthline

Medically reviewed by Tiffany Taft, PsyD — Written by Sam Lauron on February 18, 2021

## 5 Best Mood Trackers to Help You in Your Wellness Journey




## Global Emotion Detection & Recognition Market to Grow at a CAGR of 32.7% During 2018-2023 - ResearchAndMarkets.com

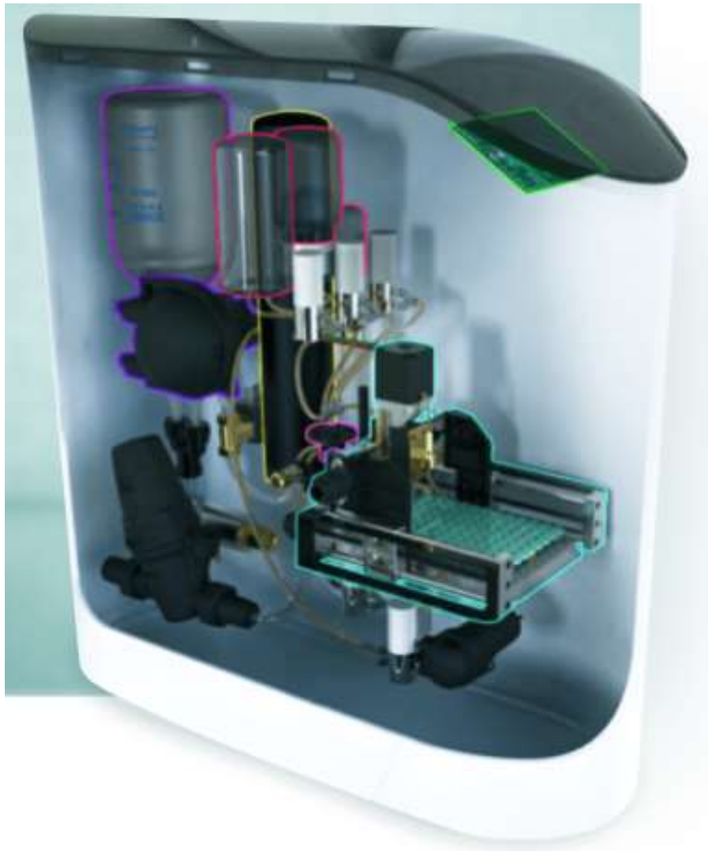
May 16, 2018 05:49 AM Eastern Daylight Time

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# Extending Continuous Personalized Monitoring to Your Gut Microbiome

BIOMESENSE

Continuous microbiome analysis



## The Future of Medical Treatment is in Your Toilet

Posted on July 12, 2019

"We're making wearables for your toilet," Gilbert said.



CO-FOUNDER
Dr. Jack Gilbert

**Co-Founder**
**the American Gut Project**
**Earth Microbiome Project**
**UCSD Professor in Pediatrics**

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# Can a Planetary Supercomputer with Artificial Intelligence Transform Our Sickcare System to a Healthcare System?

**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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