"Assay Lab Within Your Body: Biometrics and Biomes"

Invited Lecture

TSensors Summit

La Jolla, CA

November 12, 2014

Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

Dept. of Computer Science and Engineering

Jacobs School of Engineering, UCSD

http://lsmarr.calit2.net

Abstract

The human body contains 100 trillion microbial cells, each acting as sensors and actuators. This is ten times the number of cells as human cells. Furthermore, these microbes contain 100 times the number of DNA genes that our human DNA does. The microbial component of this "superorganism" is comprised of hundreds of species spread over many taxonomic phyla. To decode the details of my own gut microbial ecology required high resolution metagenomics sequencing at the Venter Institute, several CPU-decades of supercomputer time, and data analysis using scalable visualization systems. The human immune system is tightly coupled with this microbial ecology. I have been collecting massive amounts of biomarker time series data from inside my own body over the last six years. Analysis and graphing of this data demonstrates the episodic evolution of this coupled immune-microbial system. Can these microbes be thought of as one hundred trillion sensors, whose abundance can read out health or disease states in the host body?

Intense Scientific Research is Underway on Understanding the Human Microbiome



June 8, 2012



June 14, 2012

From Culturing Bacteria to Sequencing Them

J. Craig Venter™ INSTITUTE

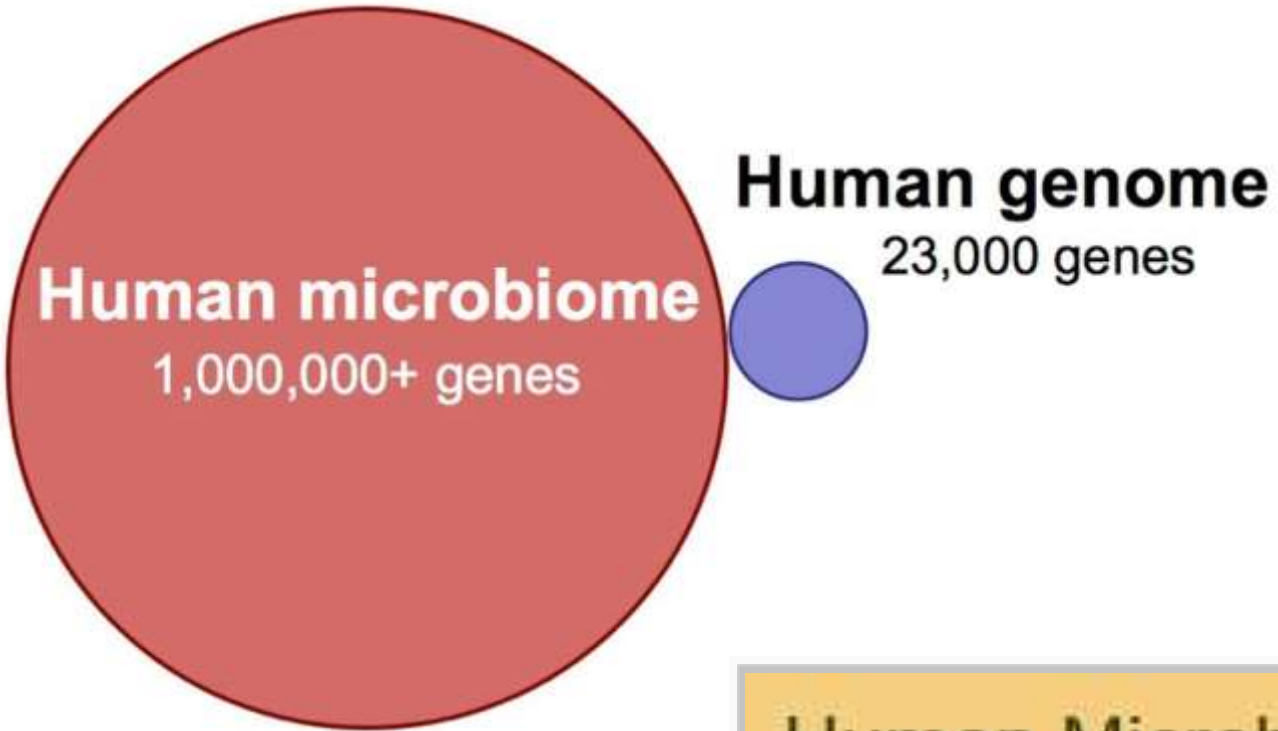
2012 Was the Year the Human Microbiome Went Public





Your Body Contains One Hundred Trillion Microbes, Each With Software Inside

Your Body Has 10 Times As Many Microbe Cells As Human Cells



99% of Your DNA Genes Are in Microbe Cells Not Human Cells

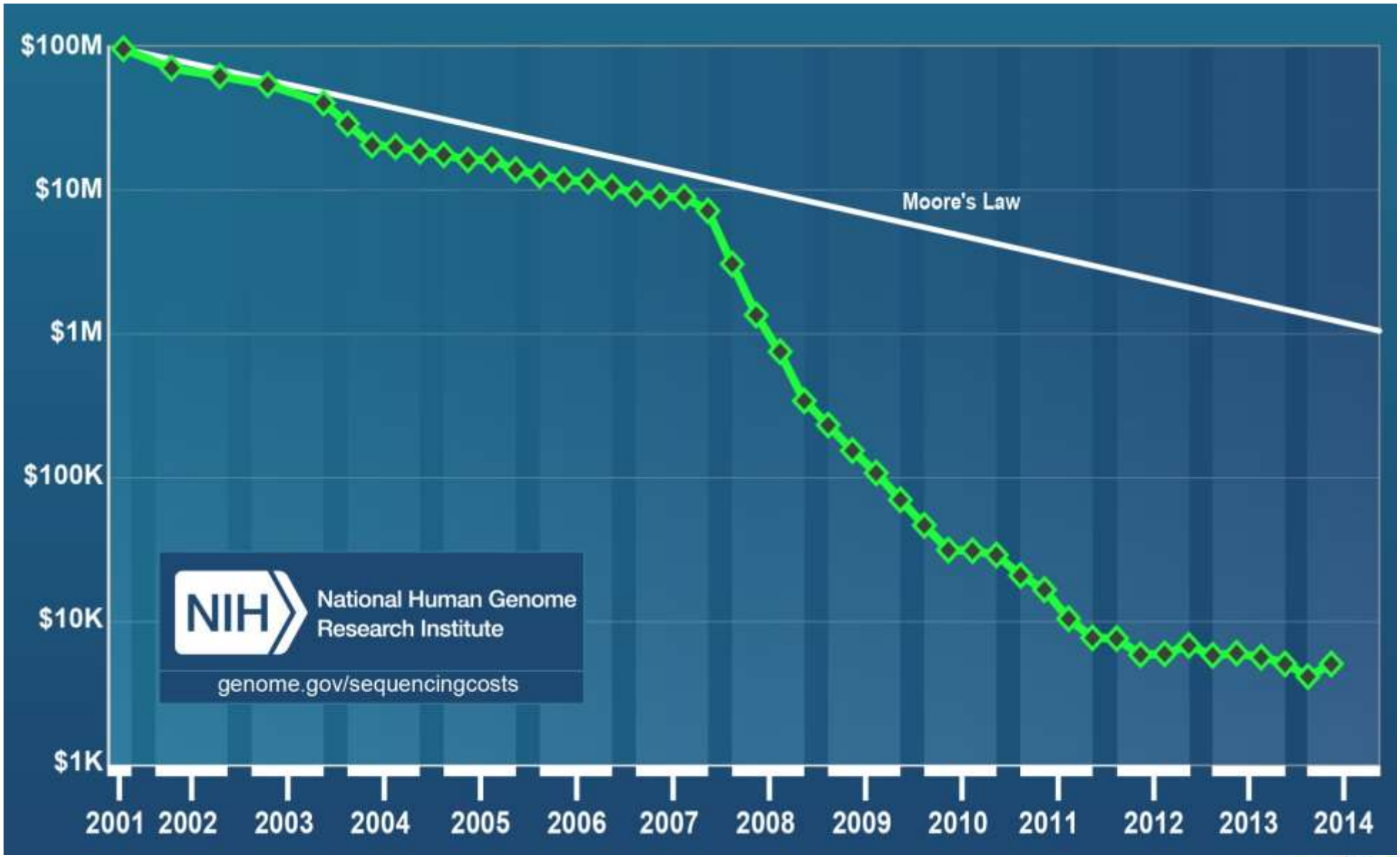
Human Microbiome Project

The NIH Common Fund
WE ACCELERATE DISCOVERY.

HMP

it²

We Can Now Sequence the Microbes Genomes Because of Exponential Decrease in Costs



Bacteria Are Programmable Sensors and Actuators Tightly Coupled to the Immune System

NATURE REVIEWS GENETICS 02 April 2014

MICROBIAL GENETICS

Bacterial sensors report on the gut

Programmable bacteria detect and record an environmental signal in the mammalian gut

Proceedings of the National Academy of Sciences March 17, 2014,

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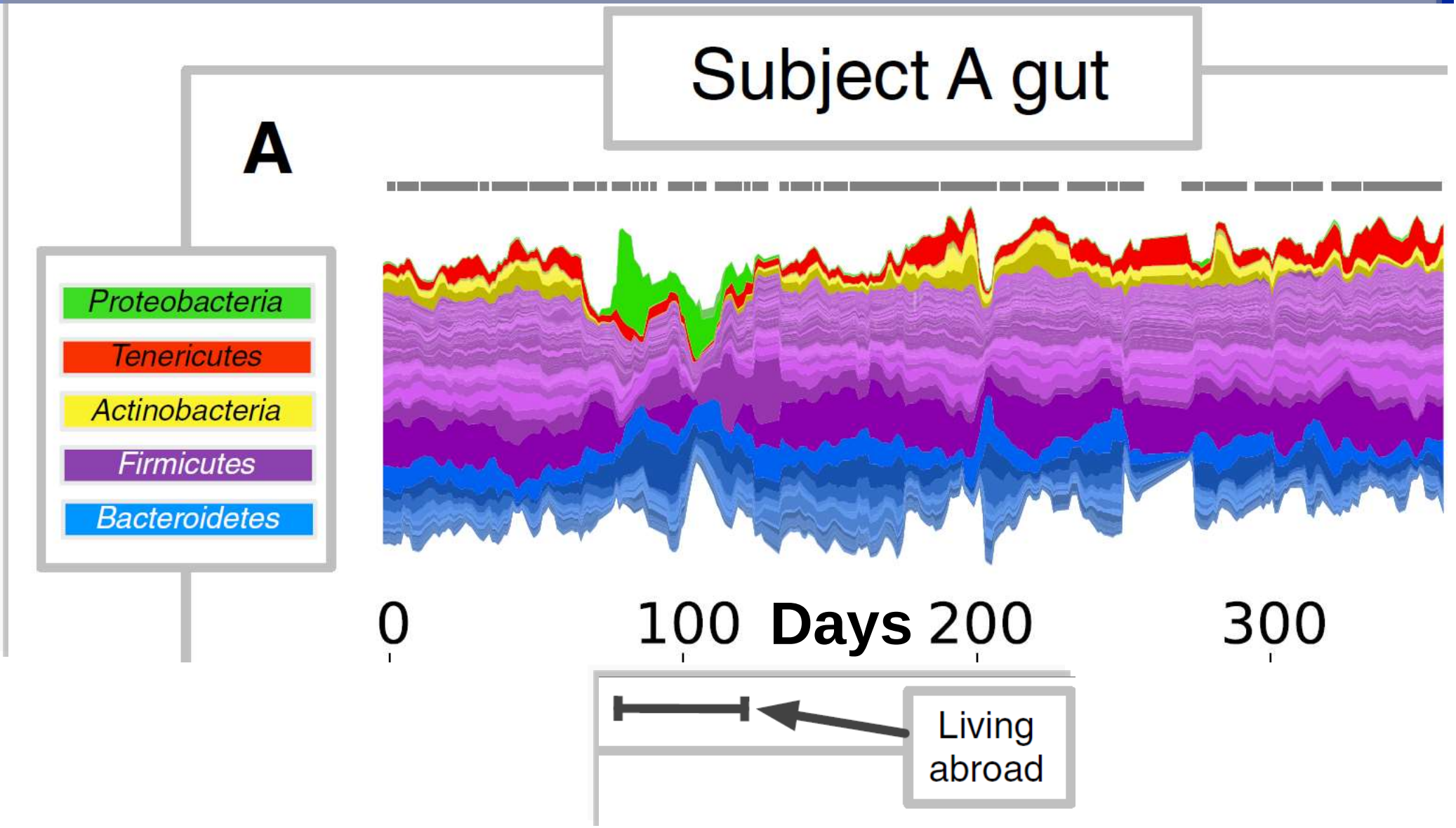
The gut microbiota shapes intestinal immune responses during health and disease

June L. Round & Sarkis K. Mazmanian May 2009

nature REVIEWS IMMUNOLOGY

Bacterial Abundance
As Indirect Sensors of Disease

A Year of Sequencing a Healthy Gut Microbiome Daily - Remarkable Stability with Abrupt Changes



Genome Biology (2014)
David, et al.

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

Example: Inflammatory Bowel Disease (IBD)

- **Metagenomic Sequencing**
  - JCVI Produced
    - ~150 Billion DNA Bases From Seven of LS Stool Samples Over 1.5 Years
  - We Downloaded ~3 Trillion DNA Bases From NIH Human Microbiome Program Data Base
    - 255 Healthy People, 21 with IBD
- **Supercomputing** (Weizhong Li, JCVI/HLI/UCSD):
  - ~20 CPU-Years on SDSC's Gordon
  - ~4 CPU-Years on Dell's HPC Cloud
- **Produced Relative Abundance of**
  - ~10,000 Bacteria, Archaea, Viruses in ~300 People
  - ~3Million Filled Spreadsheet Cells

Illumina HiSeq 2000 at JCVI



SDSC Gordon Data Supercomputer

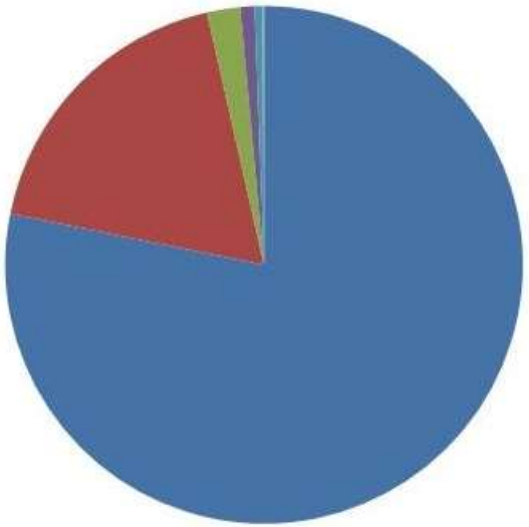


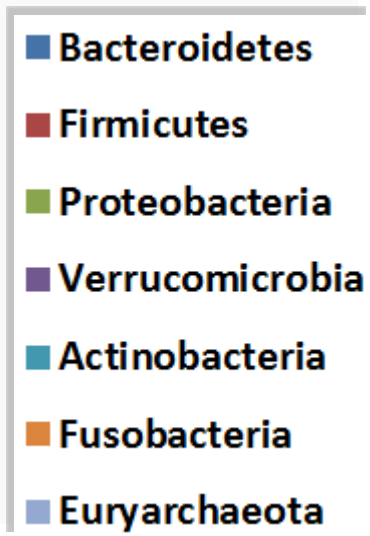
Dell Solutions Center
Industry Solutions Lab
SANGER DSU

J. Craig Venter INSTITUTE SDSC DELL NIH HMP CRBS it²

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

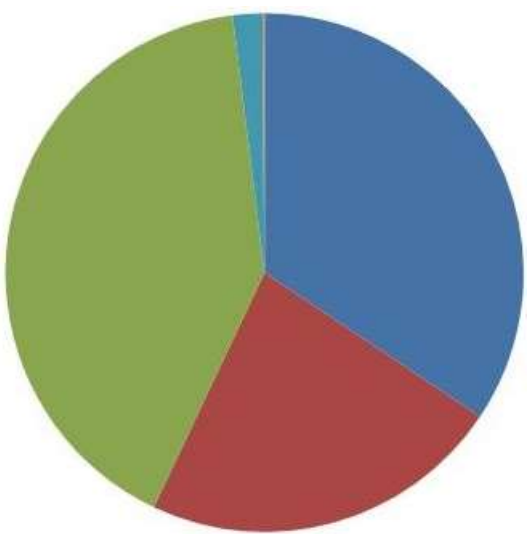
Average HE



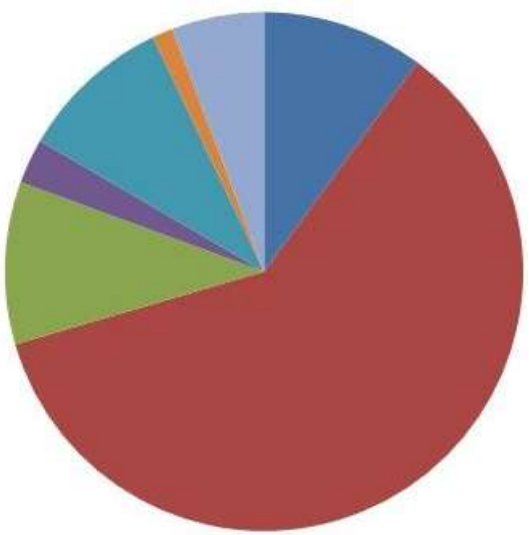


Most Common Microbial Phyla

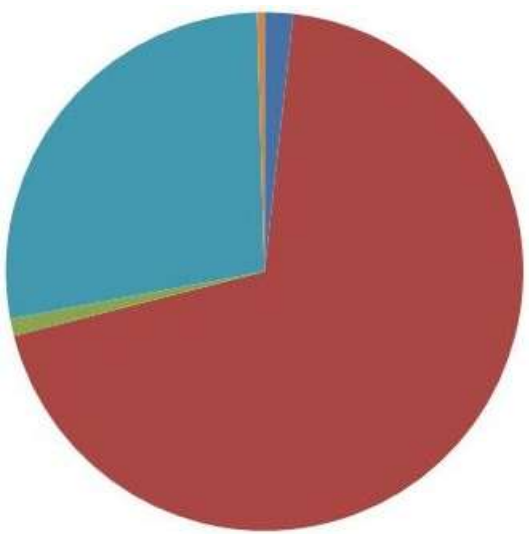
Average Ulcerative Colitis



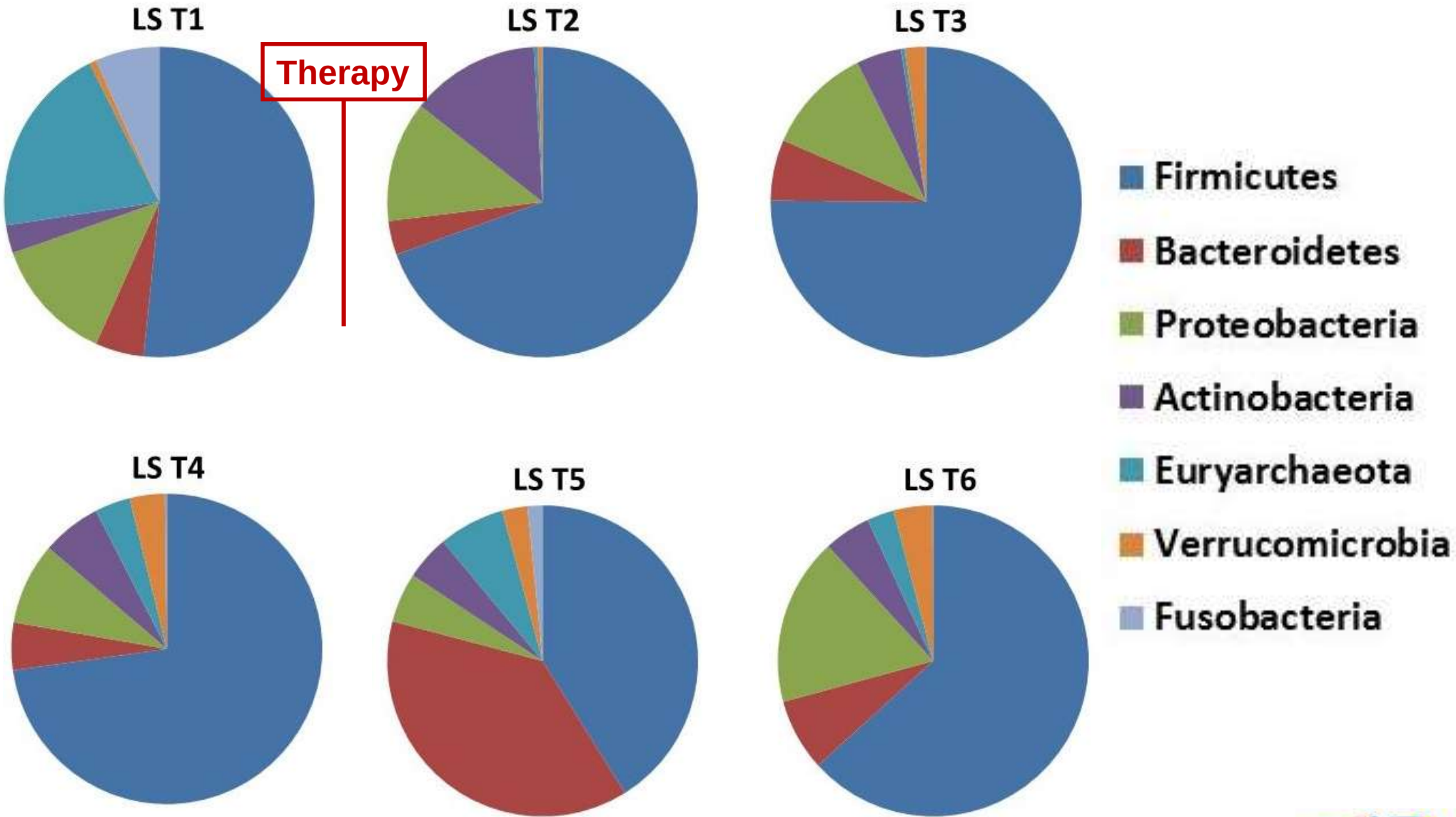
Average LS



Average Crohn's Disease

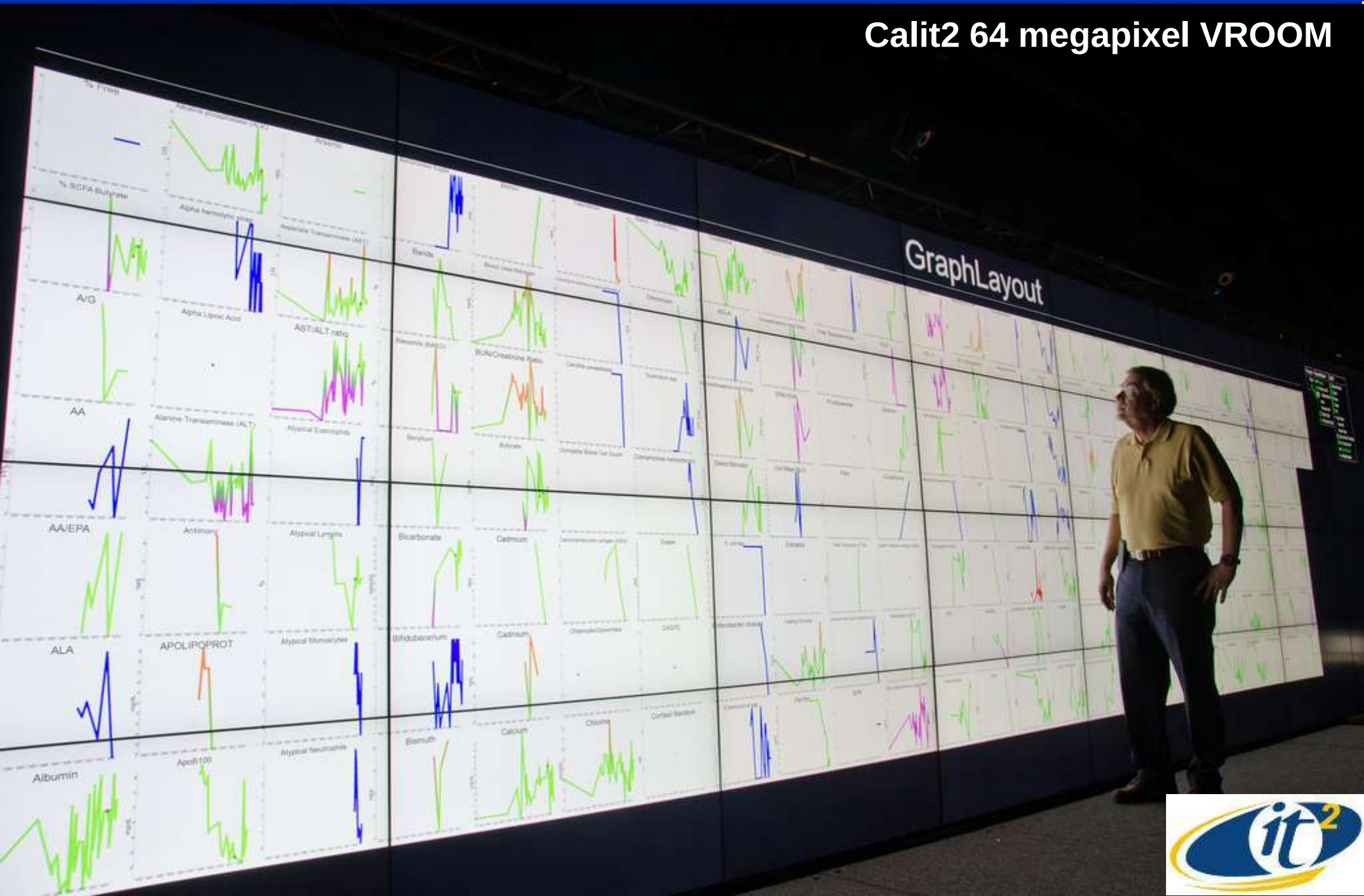


Time Series of My Gut Microbiome Reveals Autoimmune Dynamics by Phyla

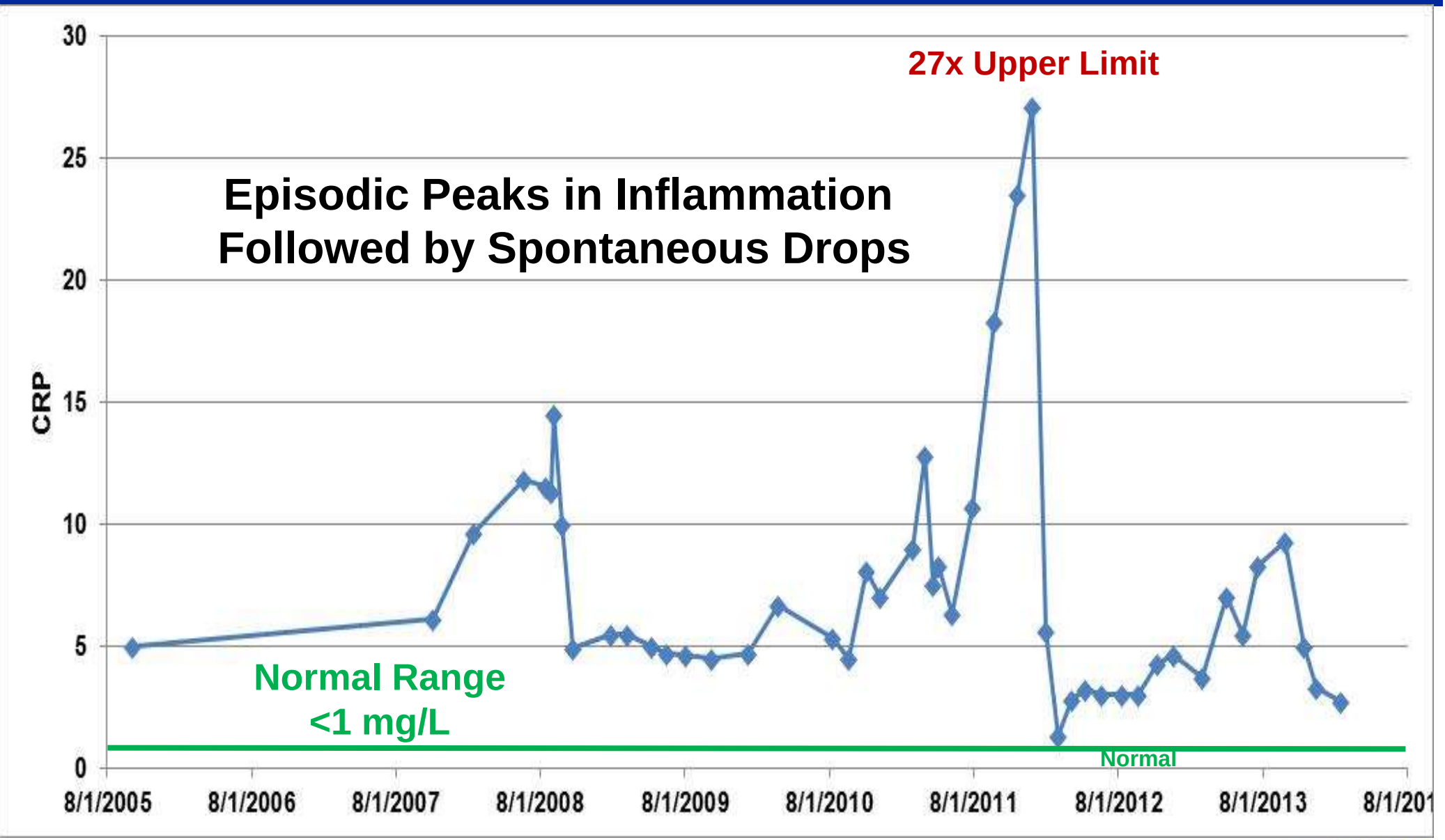


Six Metagenomic Time Samples Over 16 Months

Visualizing Time Series of 150 LS Blood and Stool Variables, Each Over 5-10 Years

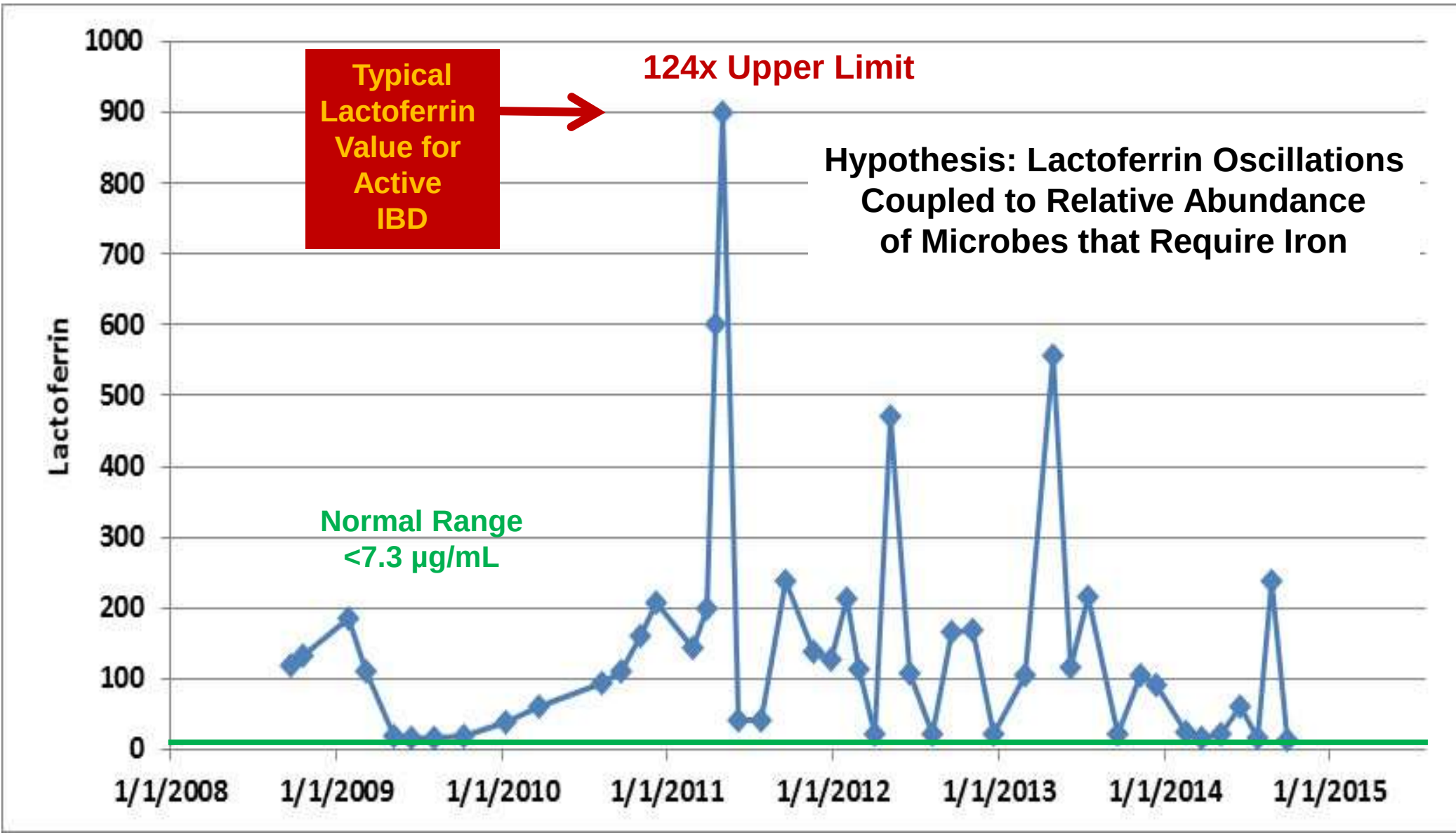


Only One of My Blood Measurements Was Far Out of Range--Indicating Chronic Inflammation



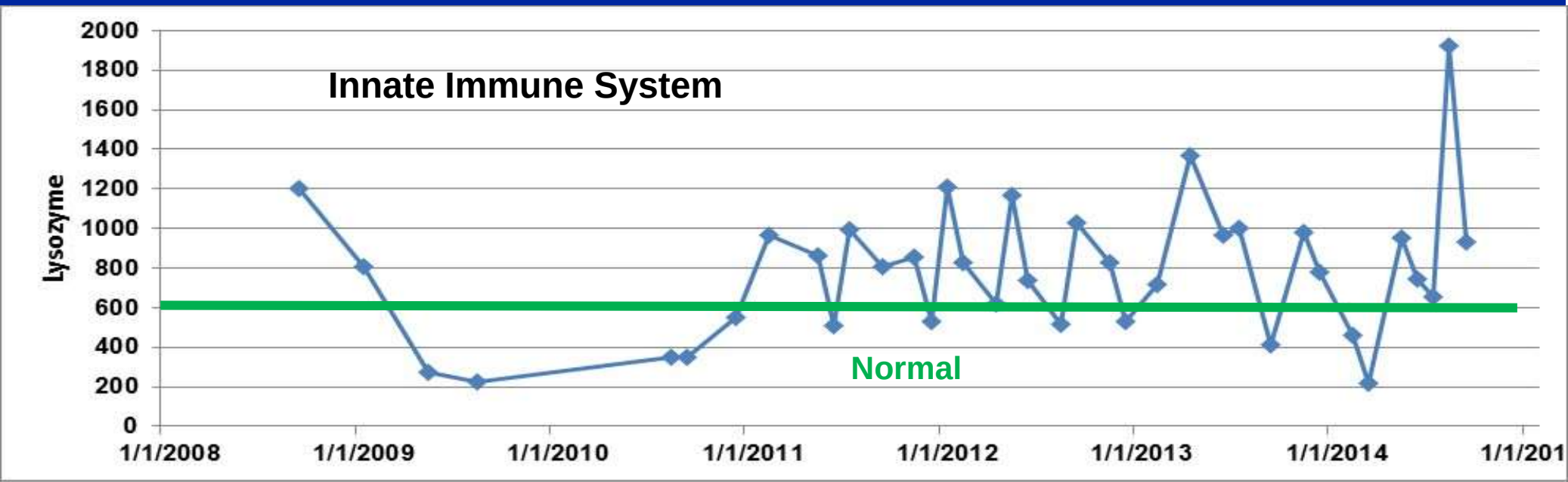
Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

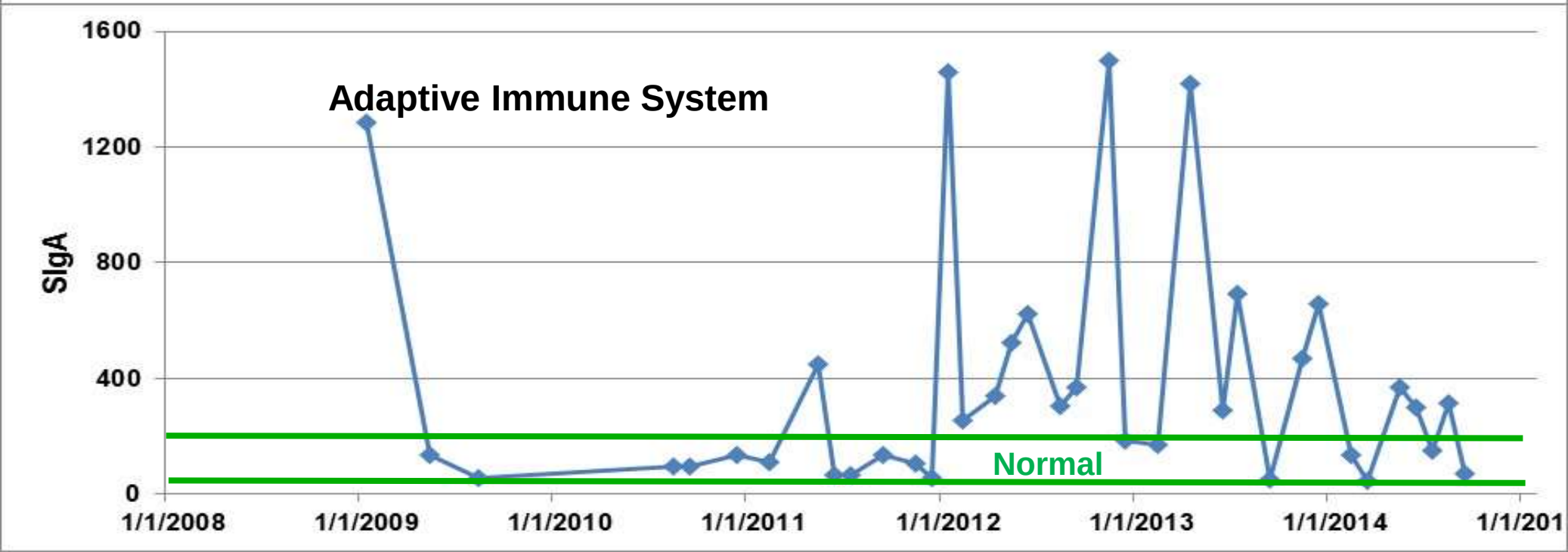
Adding Stool Tests Revealed Oscillatory Behavior in an Immune Variable



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

Fine Time-Resolution Sampling Also Reveals Dynamical Innate and Adaptive Immune Dysfunction





Early Attempts at Modeling the Systems Biology of the Gut Microbiome and the Human Immune System

Trends in Biotechnology June 2011, Vol. 29, No. 6

Prospects for systems biology and modeling of the gut microbiome

Fredrik H. Karlsson, Intawat Nookaew, Dina Petranovic and Jens Nielsen

Department of Chemical and Biological Engineering, Chalmers University of Technology, Kemivägen 10, SE-412 96 Göteborg, Sweden

2012 IEEE 26th International Parallel and Distributed Processing Symposium

High-Performance Interaction-Based Simulation of Gut Immunopathologies with ENteric Immunity SImulator (ENISI)

Keith Bisset*, Md. Maksudul Alam*, Josep Bassaganya-Riera*, Adria Carbo*, Stephen Eubank*, Raquel Hontecillas*, Stefan Hoops*, Yongguo Mei*, Katherine Wendelsdorf*, Dawen Xie*, Jae-Seung Yeom*†, and Madhav Marathe*†

**Virginia Bioinformatics Institute*

†Department of Computer Science

Virginia Tech, Blacksburg VA 24061

Next Step: Time Series of Metagenomic Gut Microbiomes and Immune Variables in an N=1000 Clinic Trial

Announced Last Friday!

Goal: Understand
"The Coupled Human Immune-Microbiome Dynamics In the Presence of Human Genetic Predispositions

Inflammatory Bowel Disease Biobank
For Healthy and Disease Patients

Already 120 Enrolled,
Goal is 1500

Drs. William J. Sandborn, John Chang, & Brigid Boland
UCSD School of Medicine, Division of Gastroenterology

Can We Learn to Program Gut Microbes to Become Direct Sensors of Disease?

Bacteria Have Been Designed as a Variety of Sensors

Bacteria Could Be Living Structural Sensors

December 26, 2013

SCIENTIFIC AMERICAN™

02/29/2012

Understanding Bacterial Sensors

Caltech

Bacterial redox sensors

Jeffrey Green & Mark S. Paget

nature REVIEWS MICROBIOLOGY

December 2004

it²

Microbial Biosensors Have Very Wide Applicability

"In recent years,
a large number of microbial biosensors
have been developed
for environmental, food, and biomedical applications."

Microbial biosensors: A review

Biosensors and Bioelectronics

Volume 26, Issue 5, 15 January 2011, Pages 1788–1799

Thanks to Our Great Team!

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