"Dynamics of the Interaction Between the Human Gut Microbiome and Immune System"

Discussion

Janssen La Jolla Research and Development

La Jolla, CA

February 22, 2013

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

UCSD UCIrvine

From Measuring Macro-Variables to Measuring Your Internal Variables

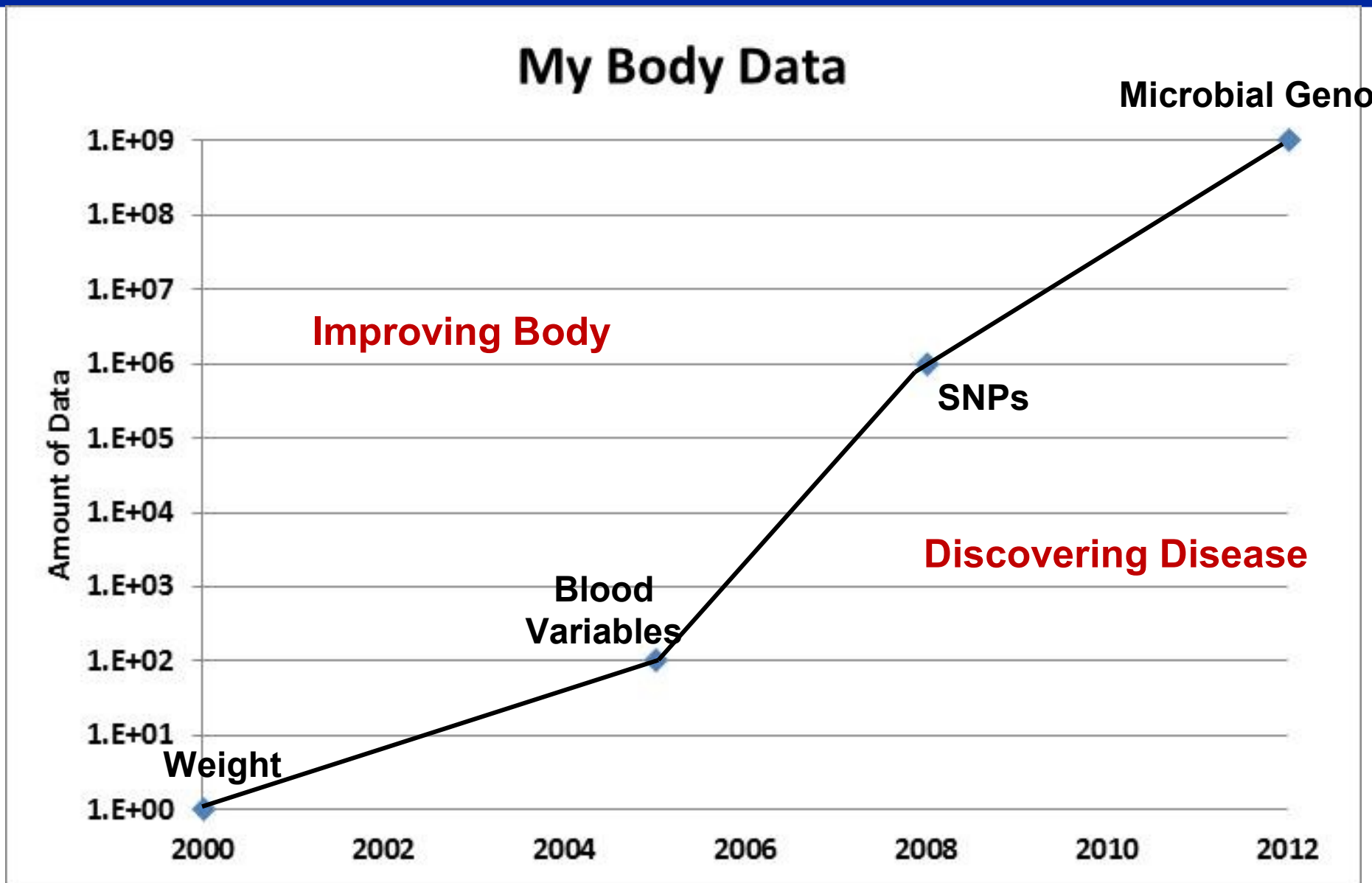


www.technologyreview.com/biomedicine/39636

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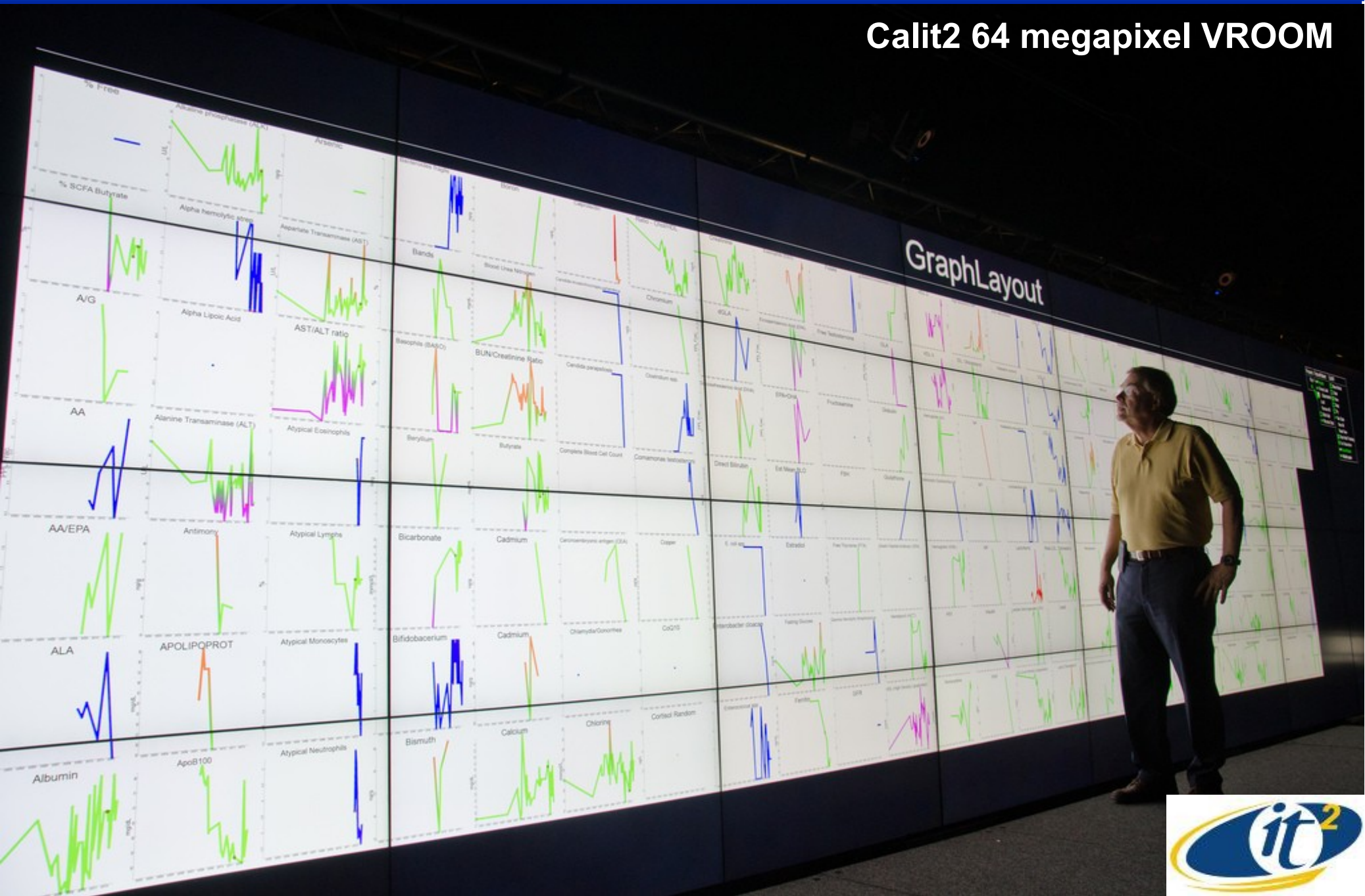
it²

From One to a Billion Data Points Defining Me: The Exponential Rise in Body Data in Just One Decade!

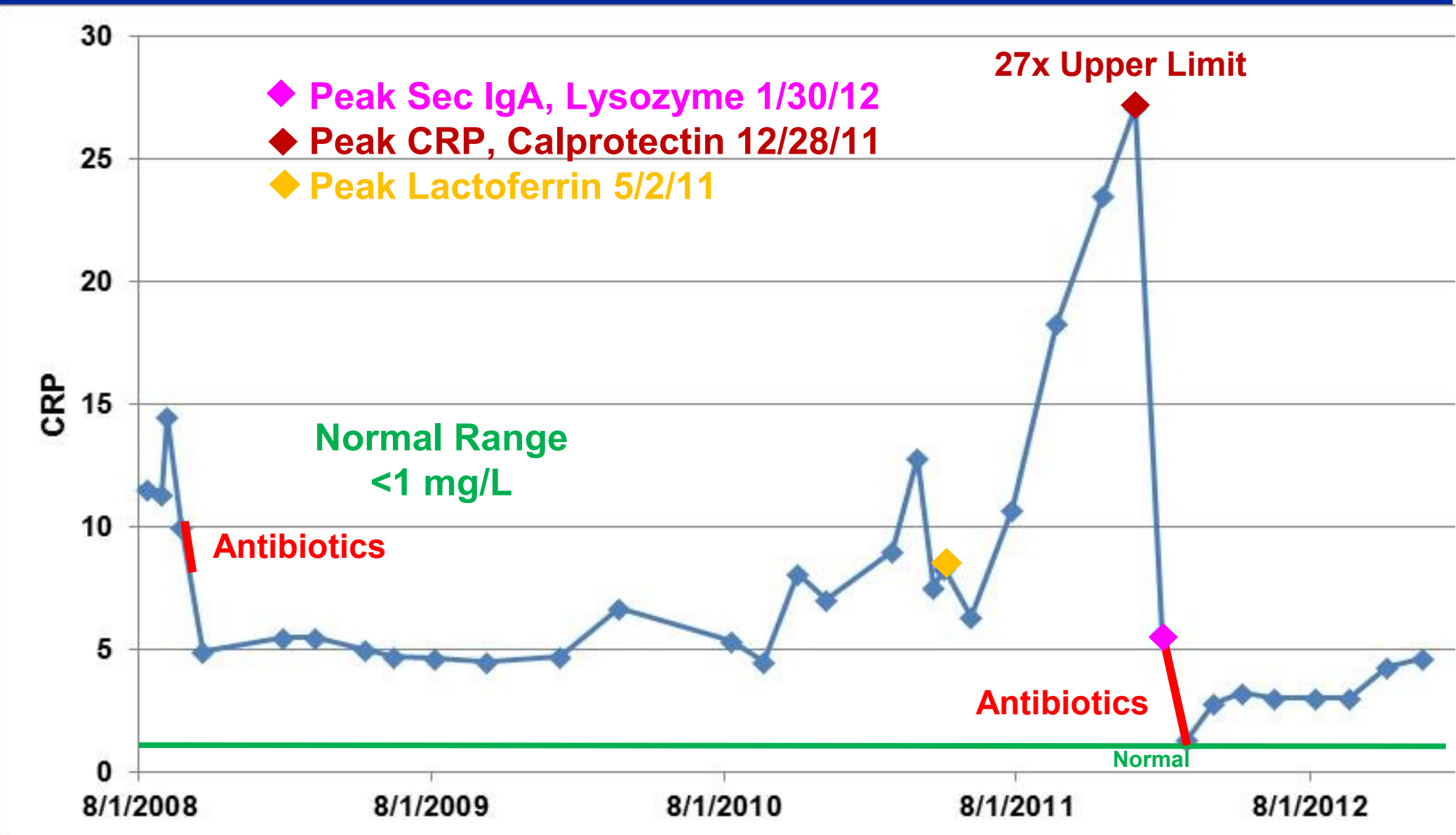


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Visualizing Time Series of 150 LS Blood and Stool Variables, Each Over 5 Years

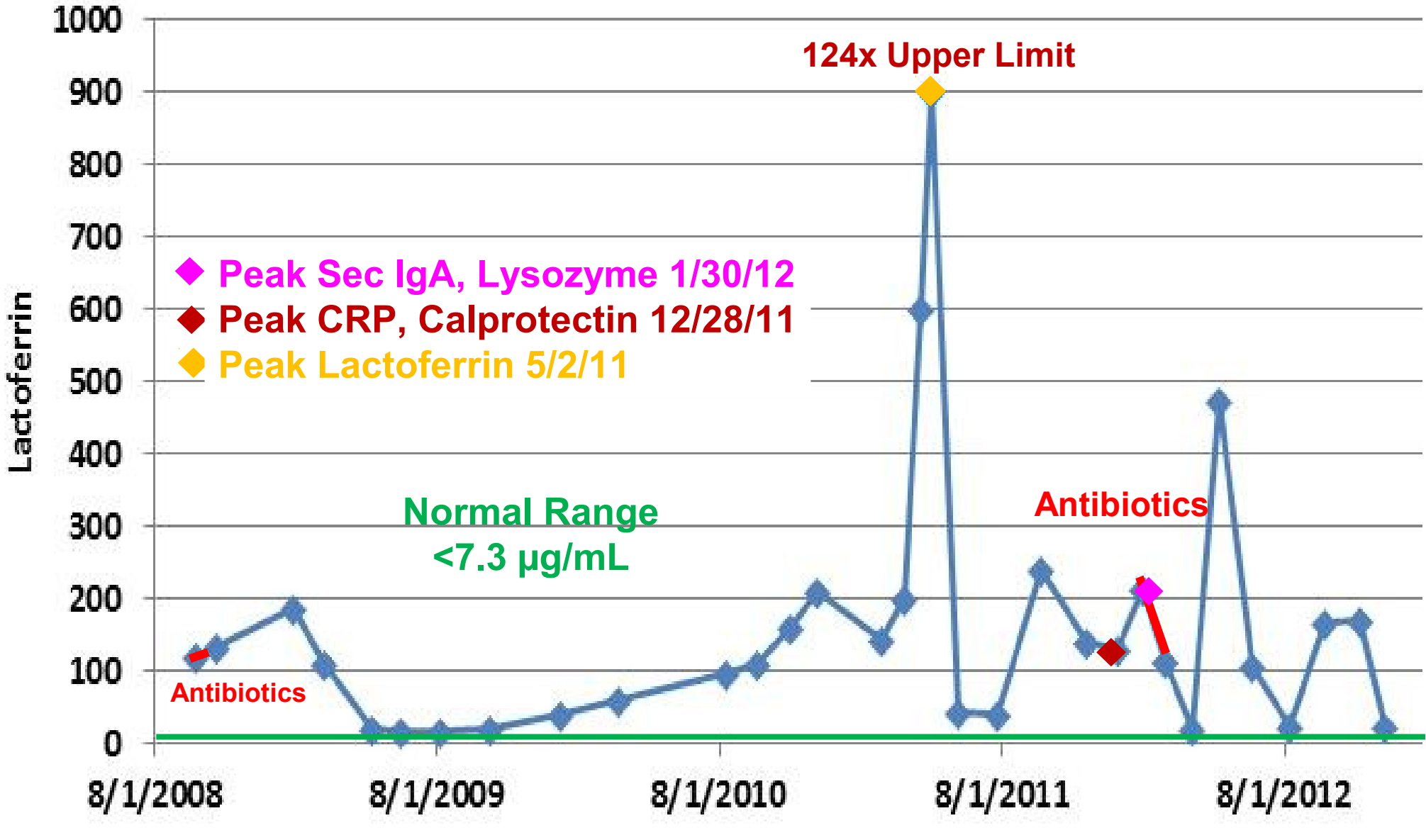


Complex Reactive Protein From Blood Sample



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Lactoferrin
From Stool Sample

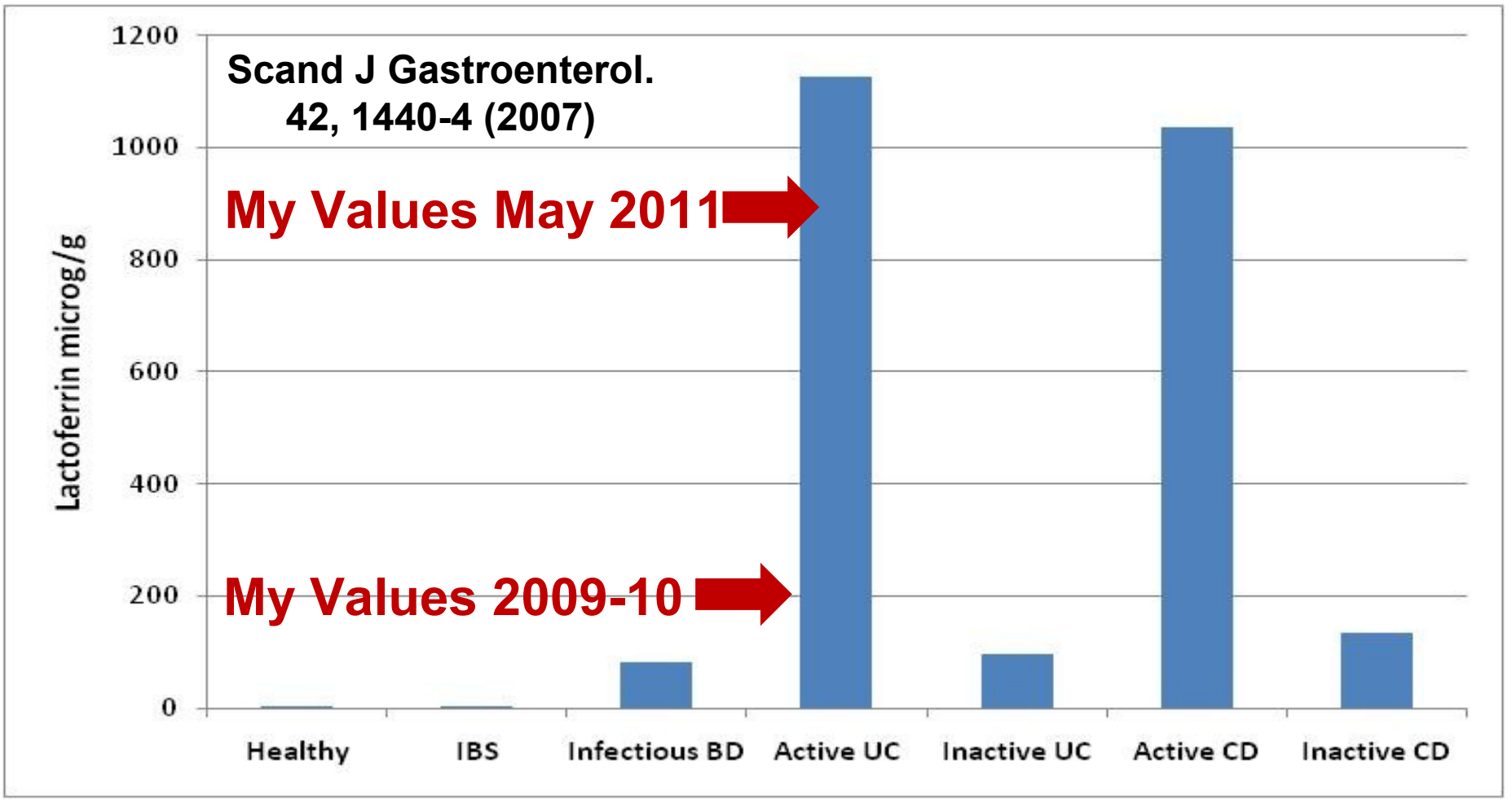


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High Lactoferrin Biomarker Led Me to Hypothesis I Had Inflammatory Bowel Disease (IBD)

IBD is an Autoimmune Disease Which Comes in Two Subtypes: Crohn's and Ulcerative Colitis



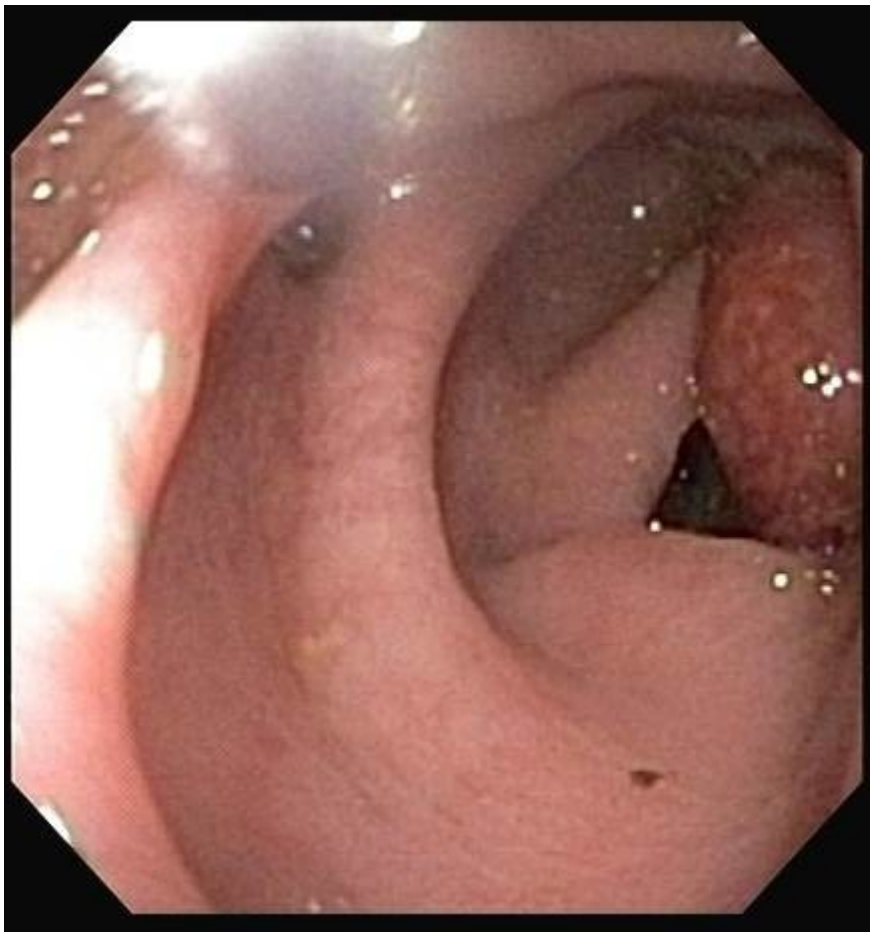
High Level of Calprotectin Confirmed Hypothesis

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Colonoscopy Images Show Sigmoid Colon Inflammation



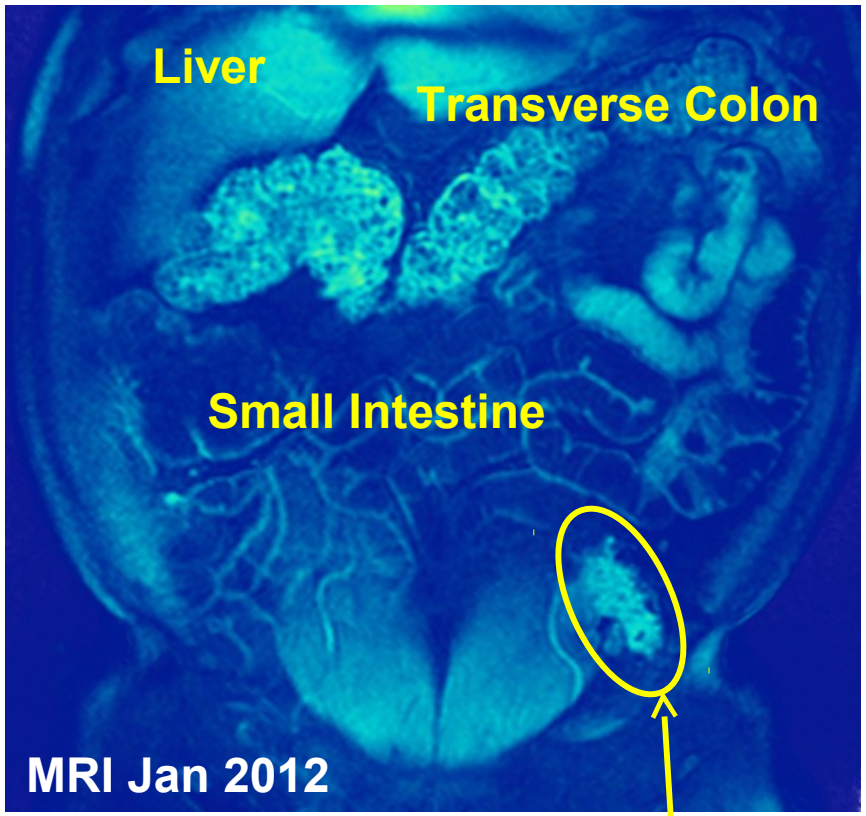
Dec 2010



May 2011

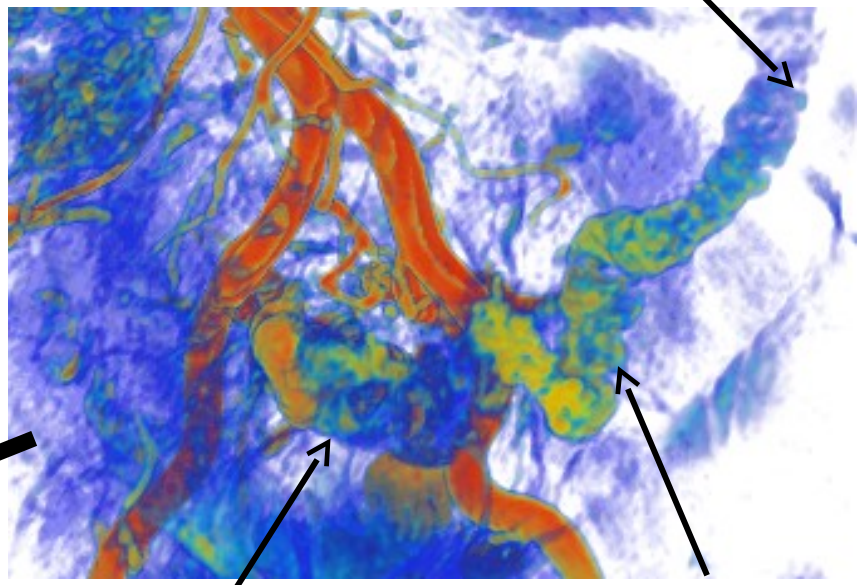
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Confirming the IBD (Crohn's) Hypothesis: Finding the "Smoking Gun" with MRI Imaging



I Obtained the MRI Slices From UCSD Medical Services and Converted to Interactive 3D Working With Calit2 Staff & DeskVOX Software

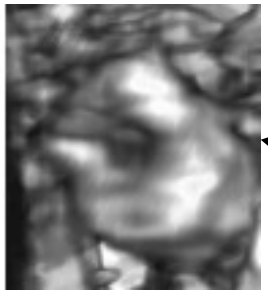
Descending Colon



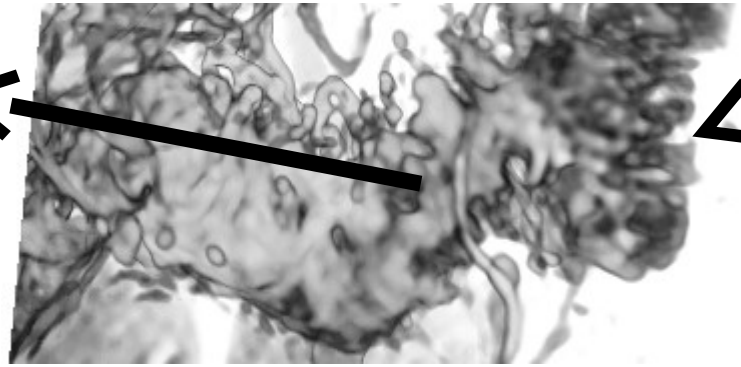
Major Kink

Sigmoid Colon
Threading Iliac Arteries

Cross Section



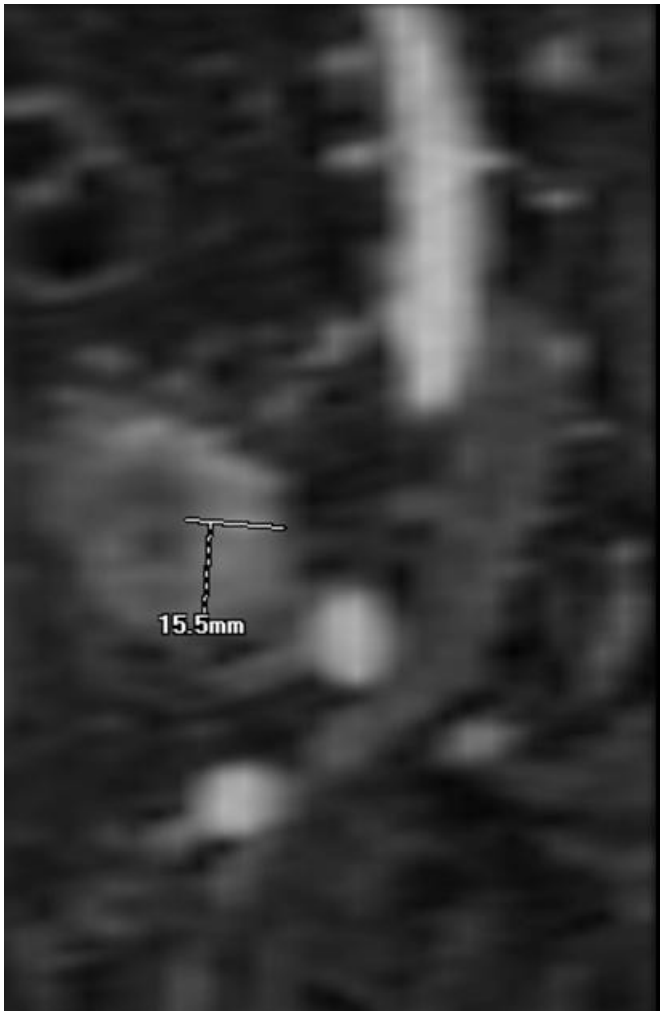
Diseased Sigmoid Colon

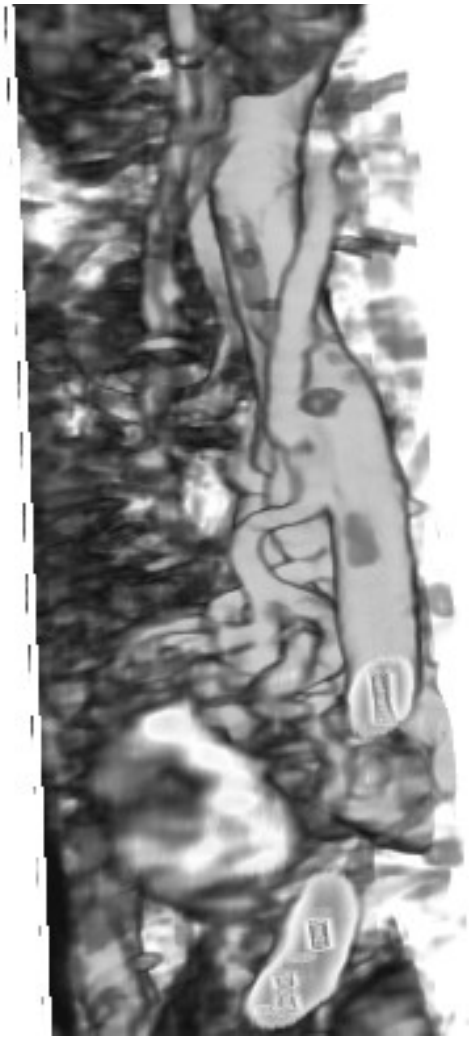


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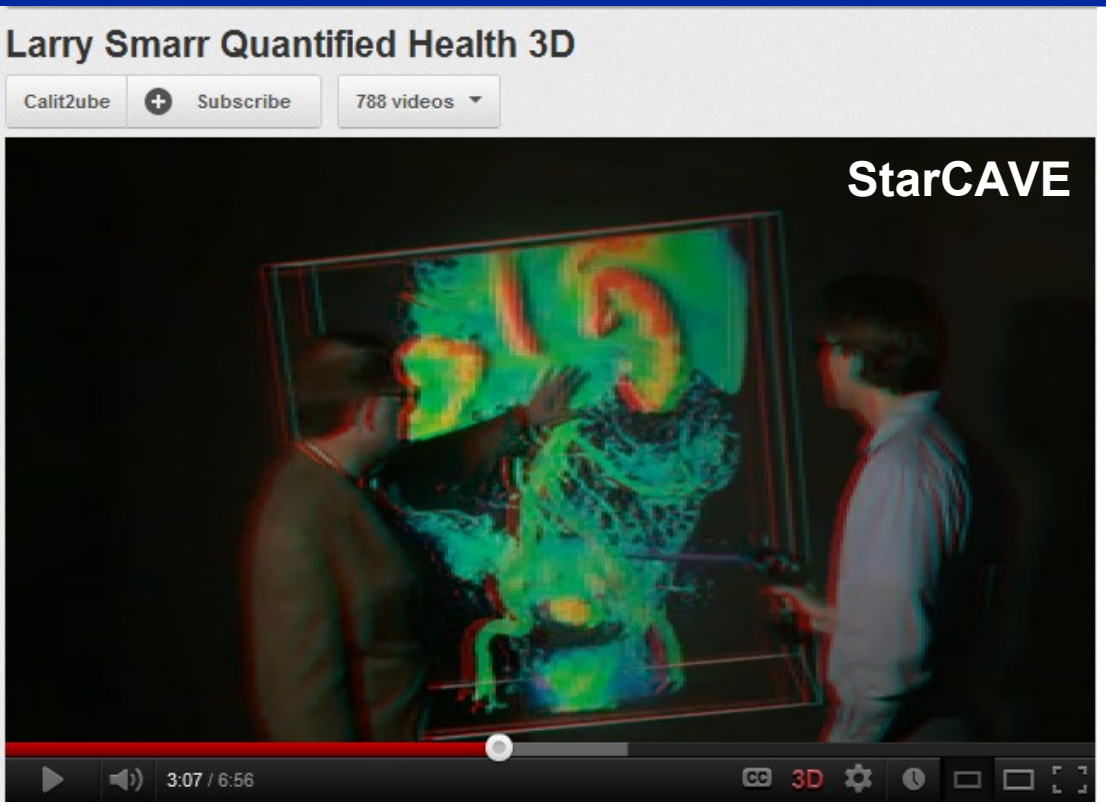
Comparison of DeskVOX with Clinical MRI Slice Program





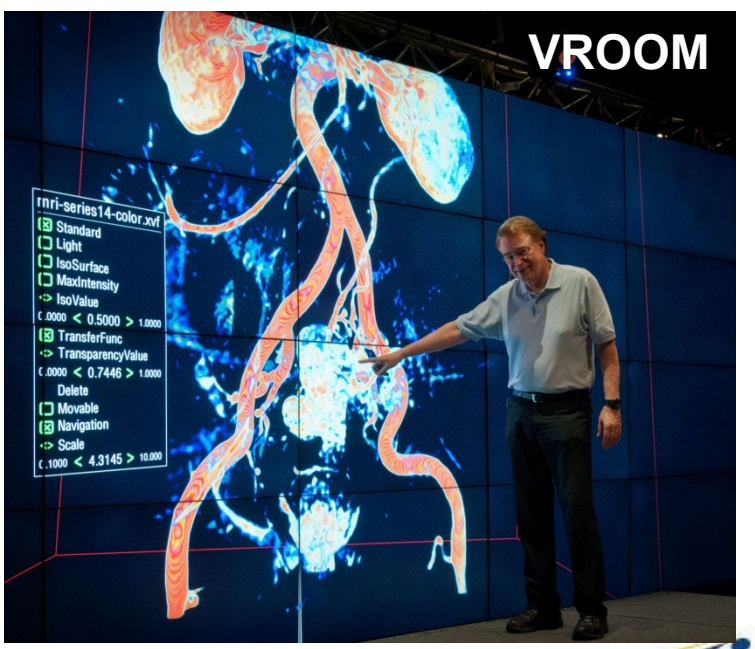
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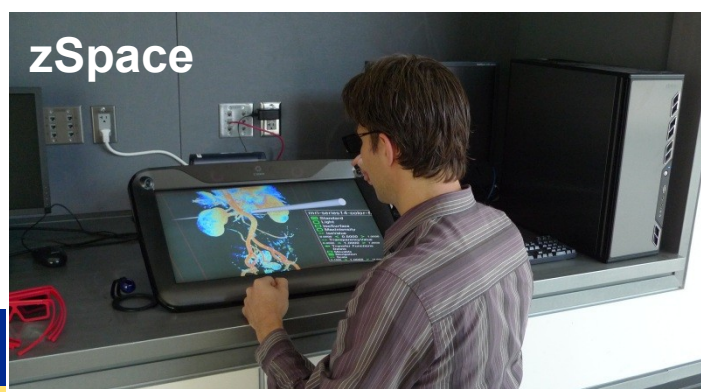
Interactively Exploring My Body With Calit2 Virtual Reality Facilities



www.youtube.com/watch?v=9c4DtJ_L_Ps







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Photo & CalVR software Courtesy of Jurgen Schulze, Calit2

Connecting Colonoscopy "Inside View" With MRI "Outside View"



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LS Colon Images and Colonoscopy Video On Calit2 Director's Colony OptIPortable Wall

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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!

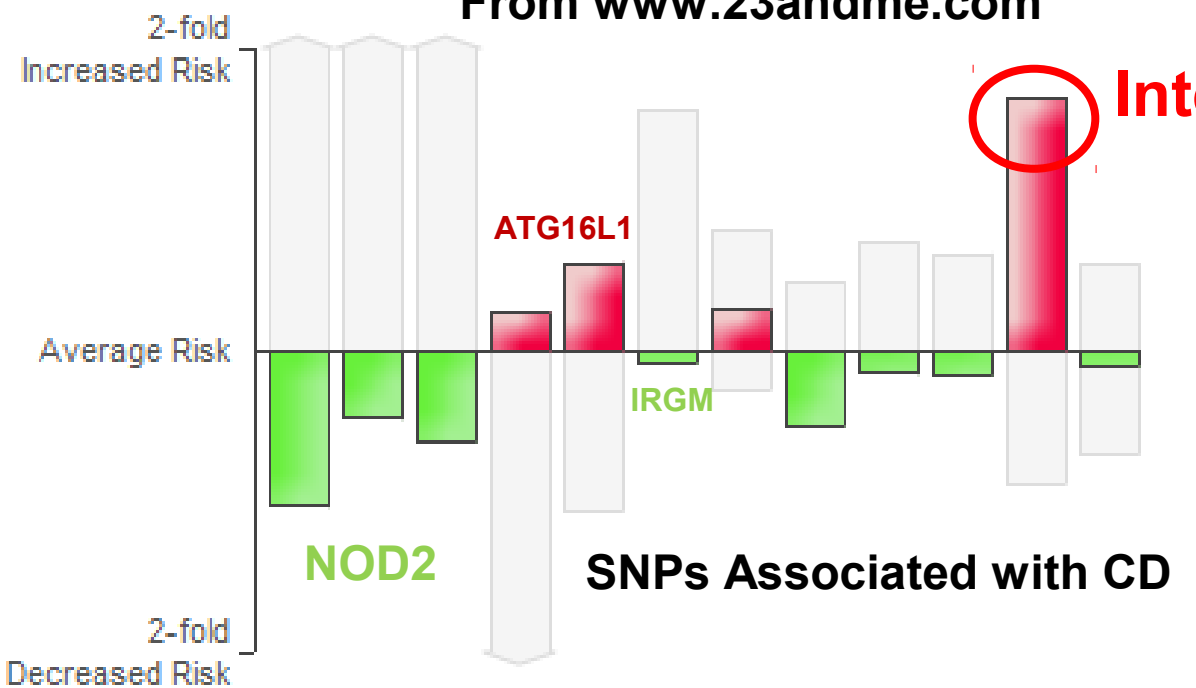
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Paul B. Eckburg & David A. Relman
Clin Infect Dis. 44:256-262 (2007)

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I Wondered if Crohn's is an Autoimmune Disease, Did I Have a Personal Genomic Polymorphism?

From www.23andme.com



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

Now Comparing 163 Known IBD SNPs with 23andme SNP Chip

News and Views

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

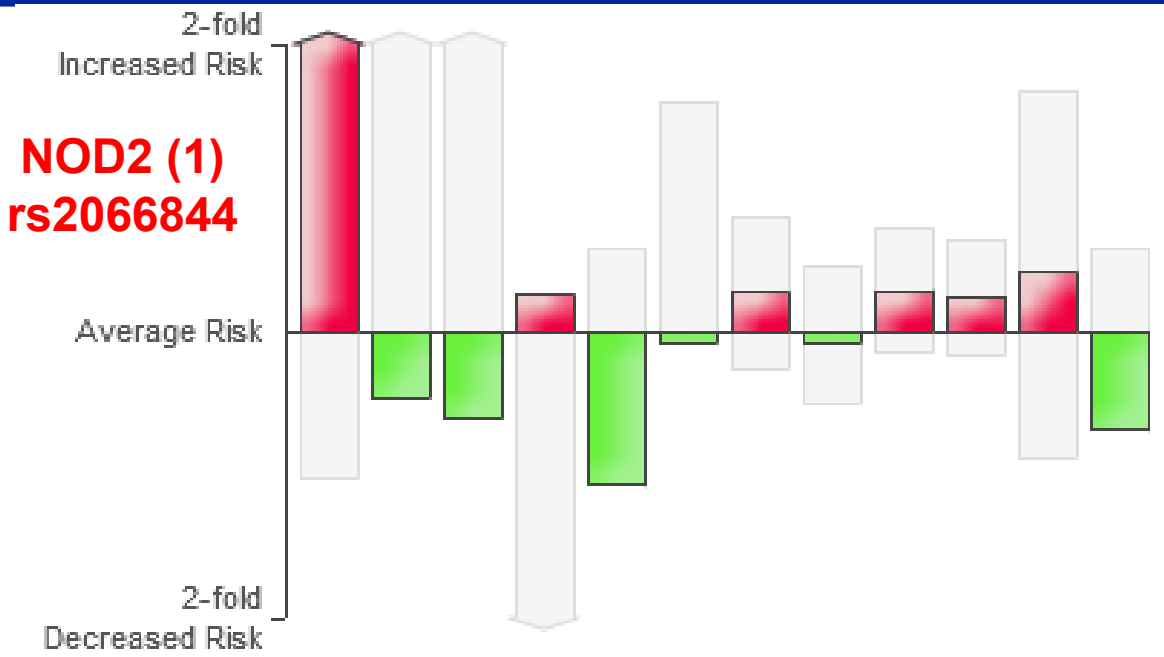
IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

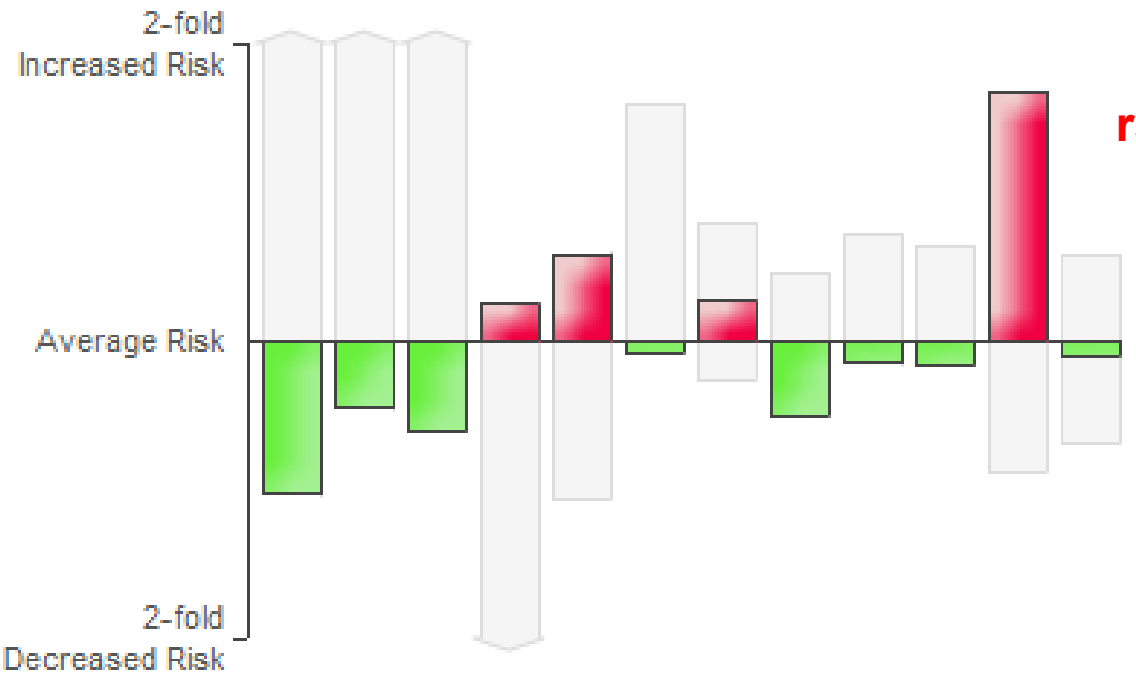
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Crohn's May be a Related Set of Diseases Driven by Different SNPs



Female
CD Onset
At 20-Years Old

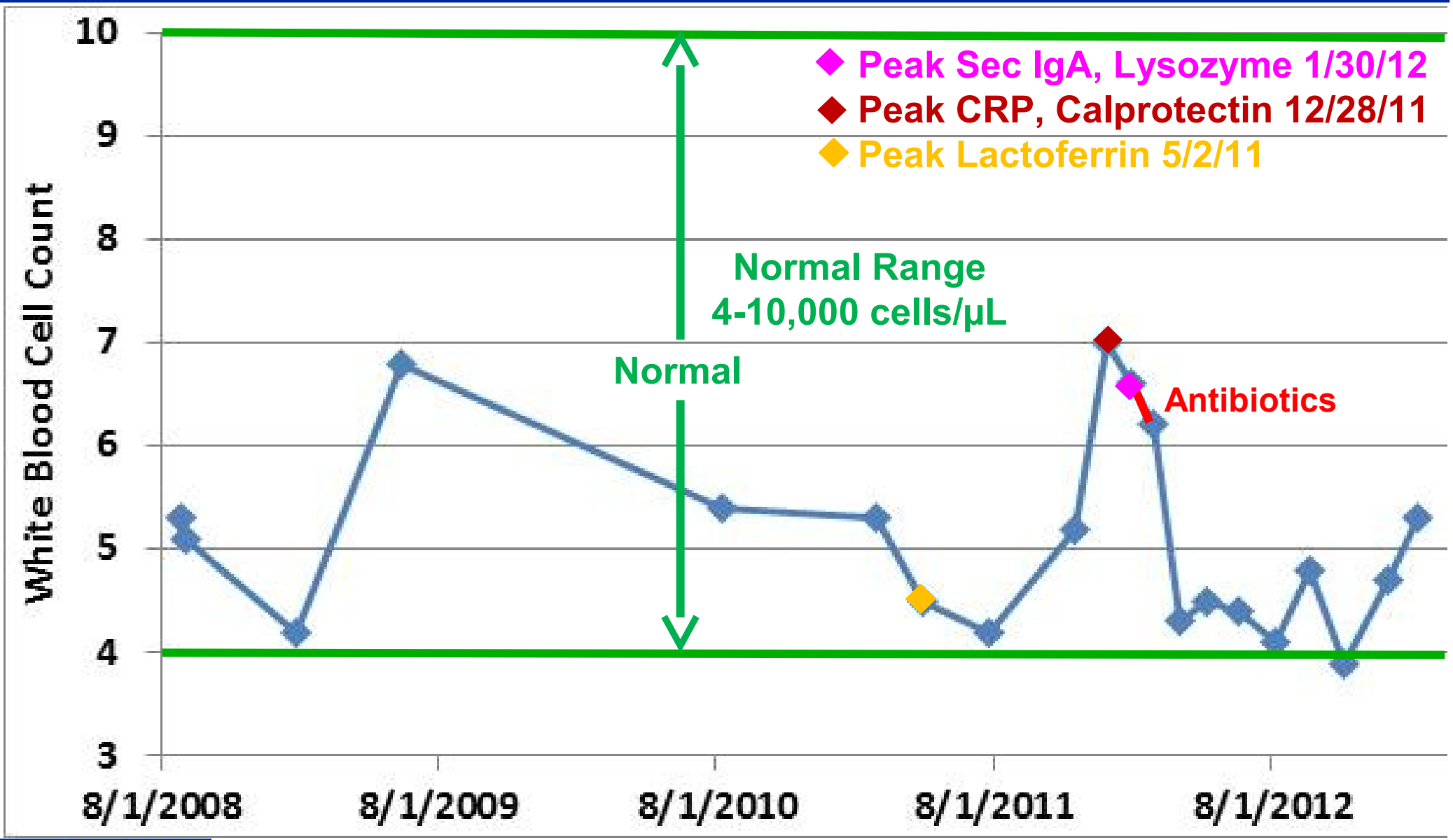


Il-23R
rs1004819

Me-Male
CD Onset
At 60-Years Old

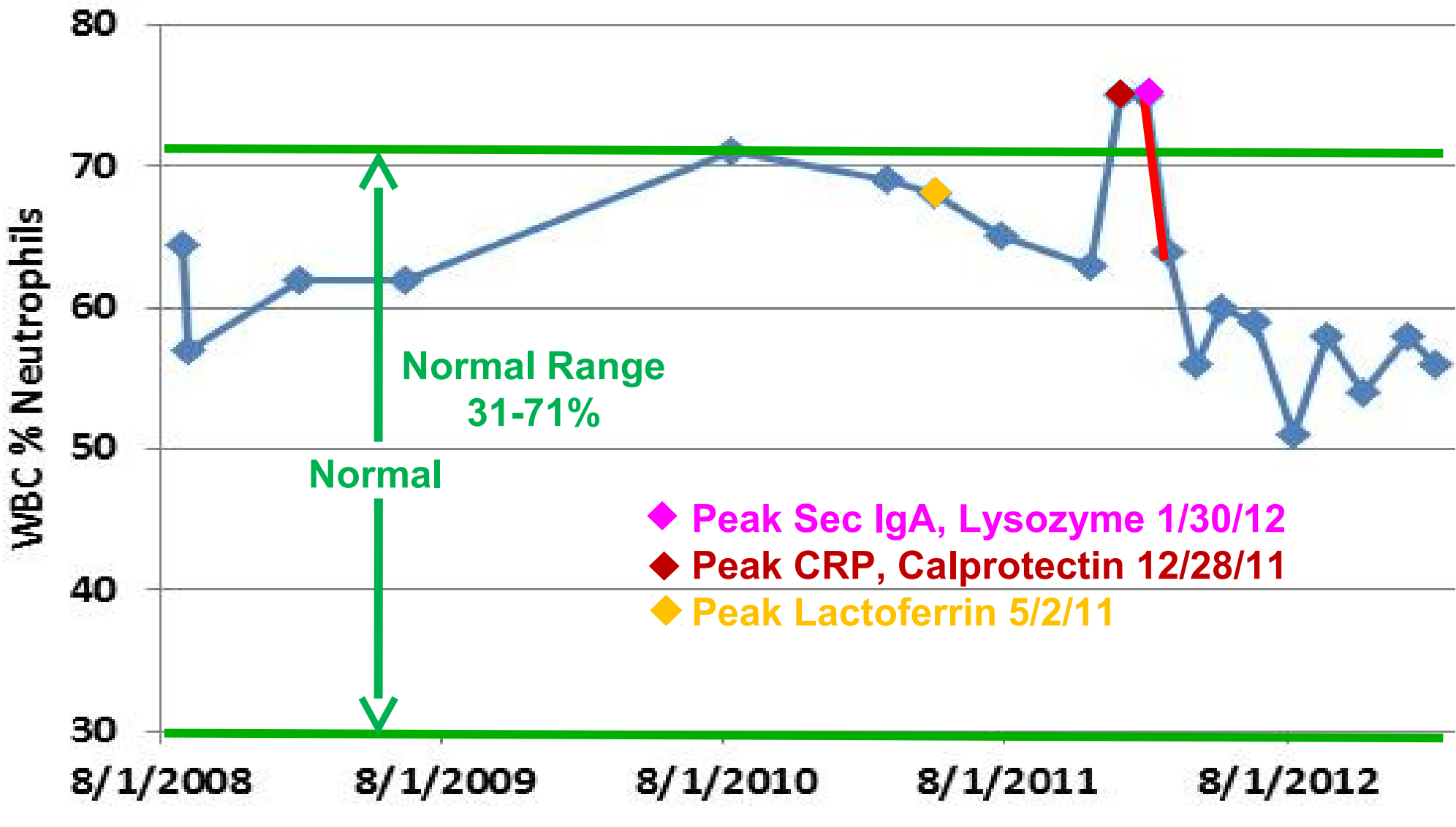
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White Blood Cell Count From Blood Sample



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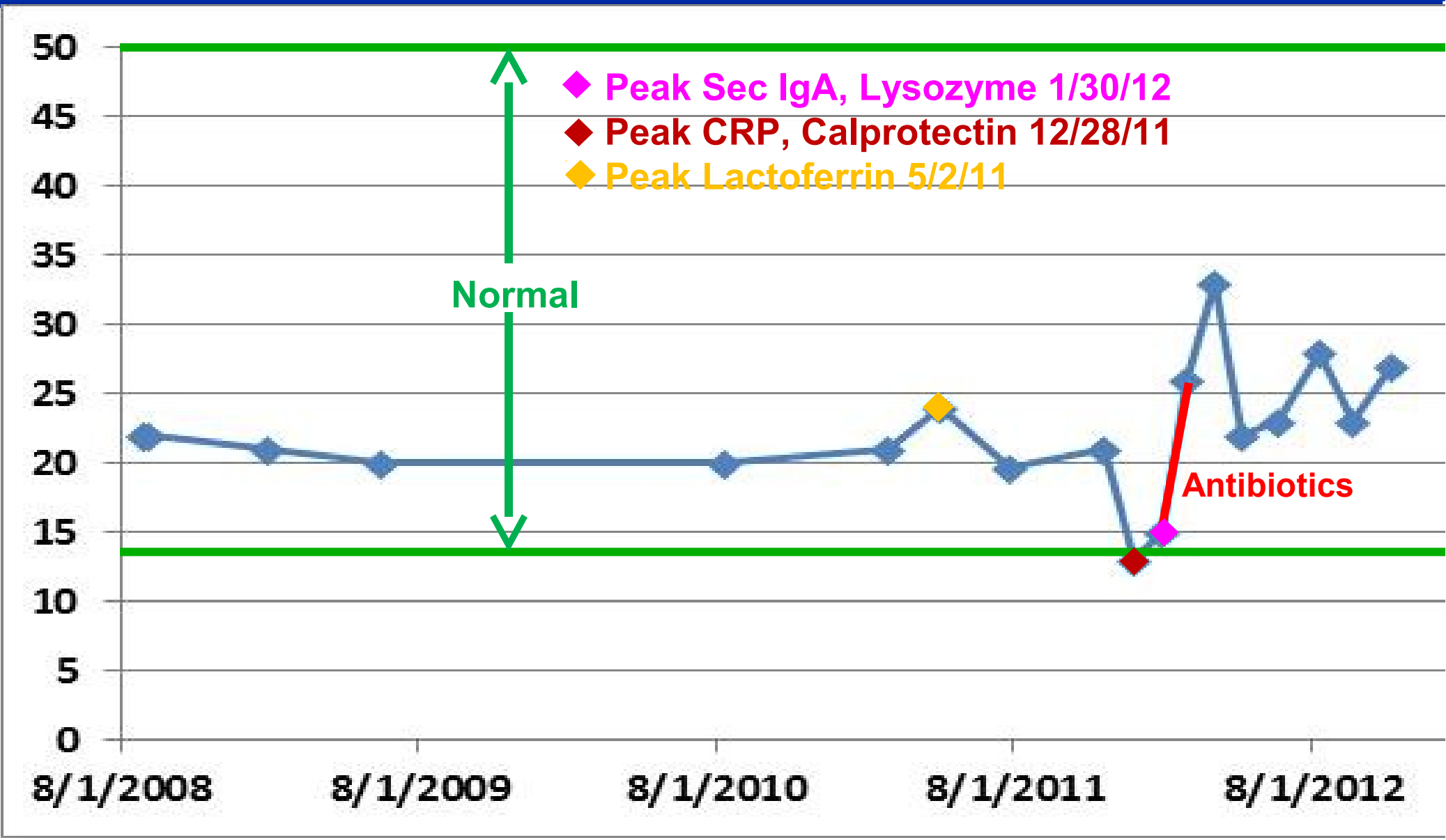
Neutrophils as % of WBCs From Blood Sample



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Lymphocytes as % of WBCs From Blood Sample

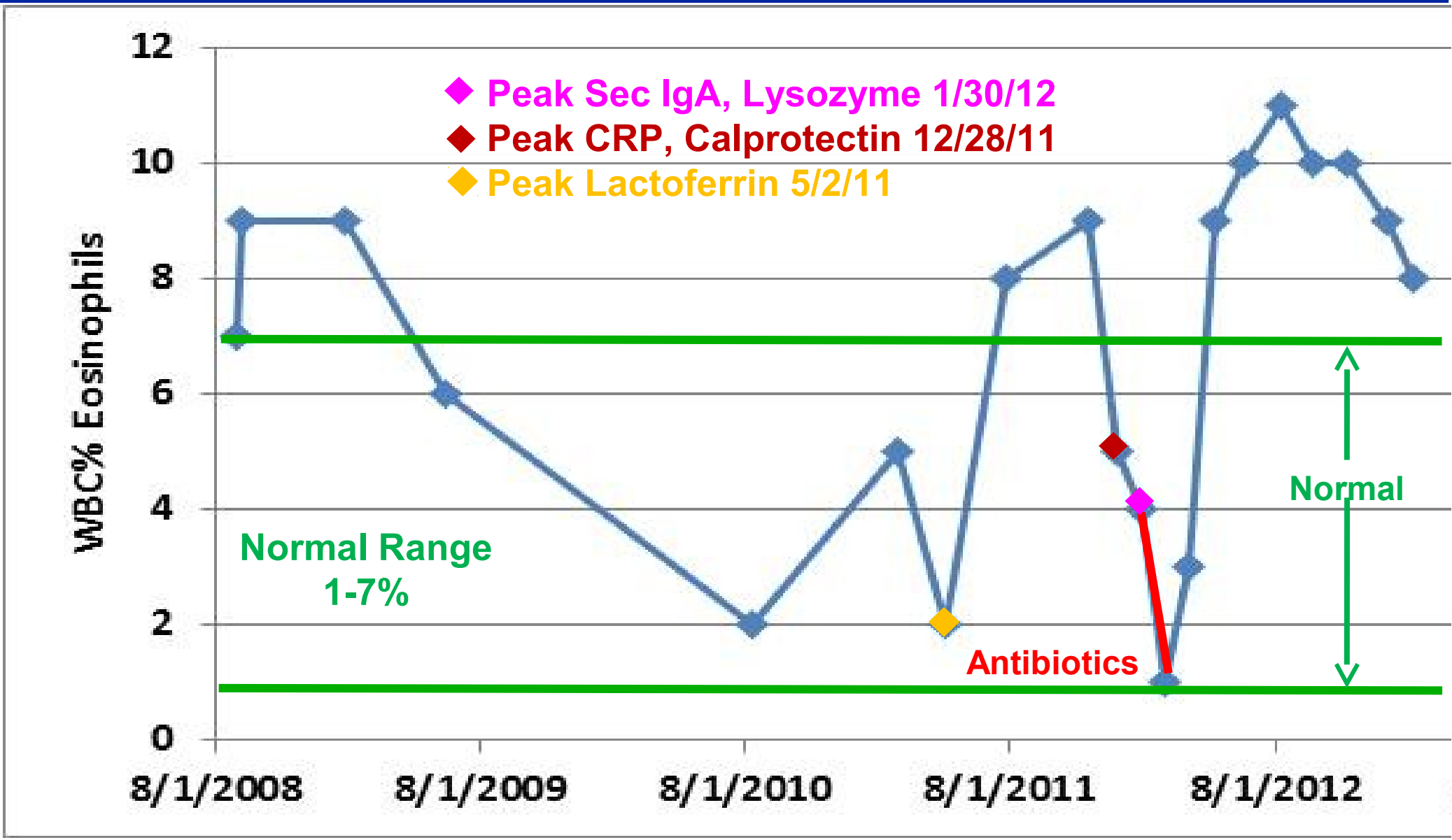


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Lymphocytes Include B Cells, T cells, and Natural Killer Cells

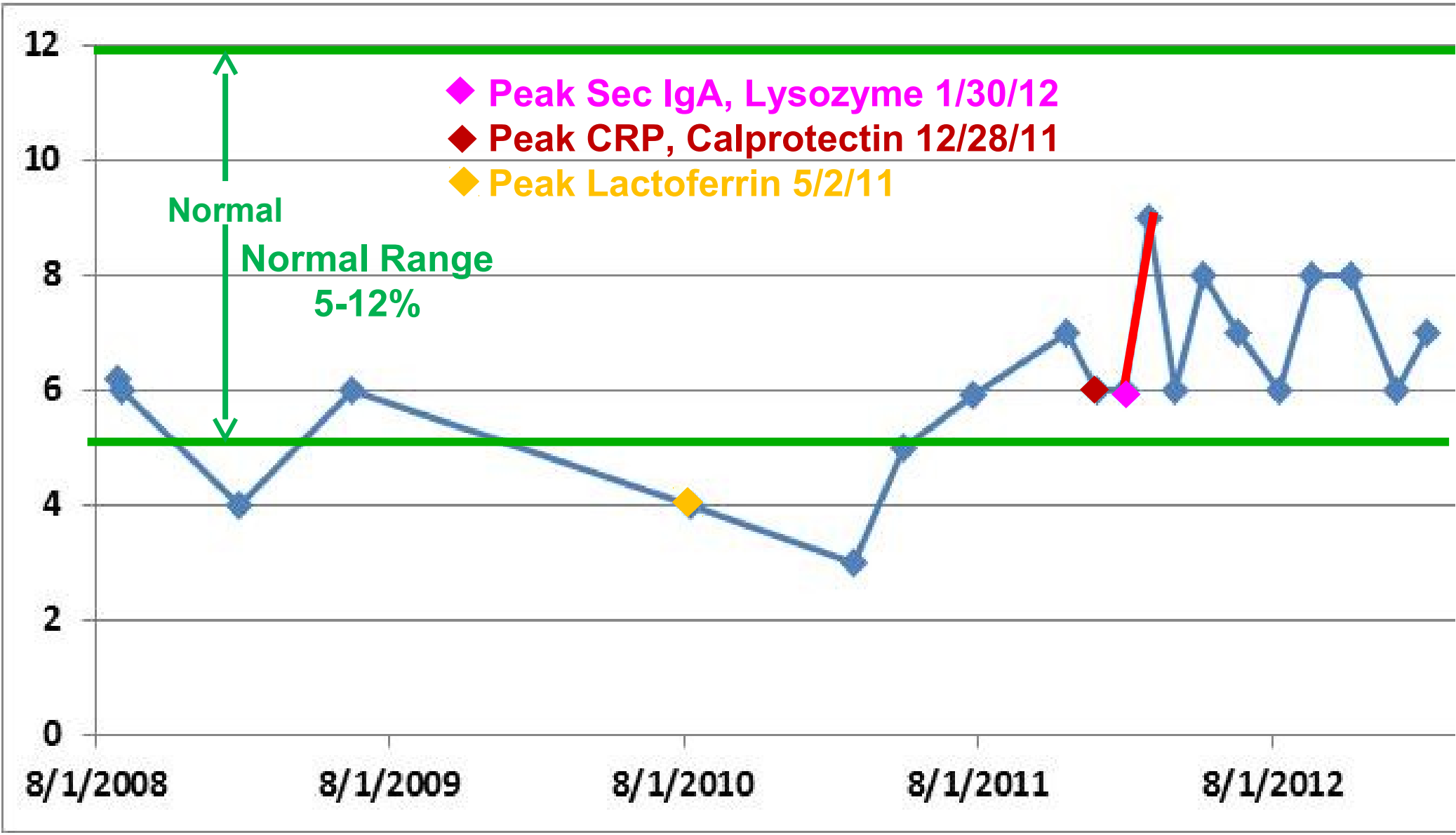
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Eosinophils as % of WBCs From Blood



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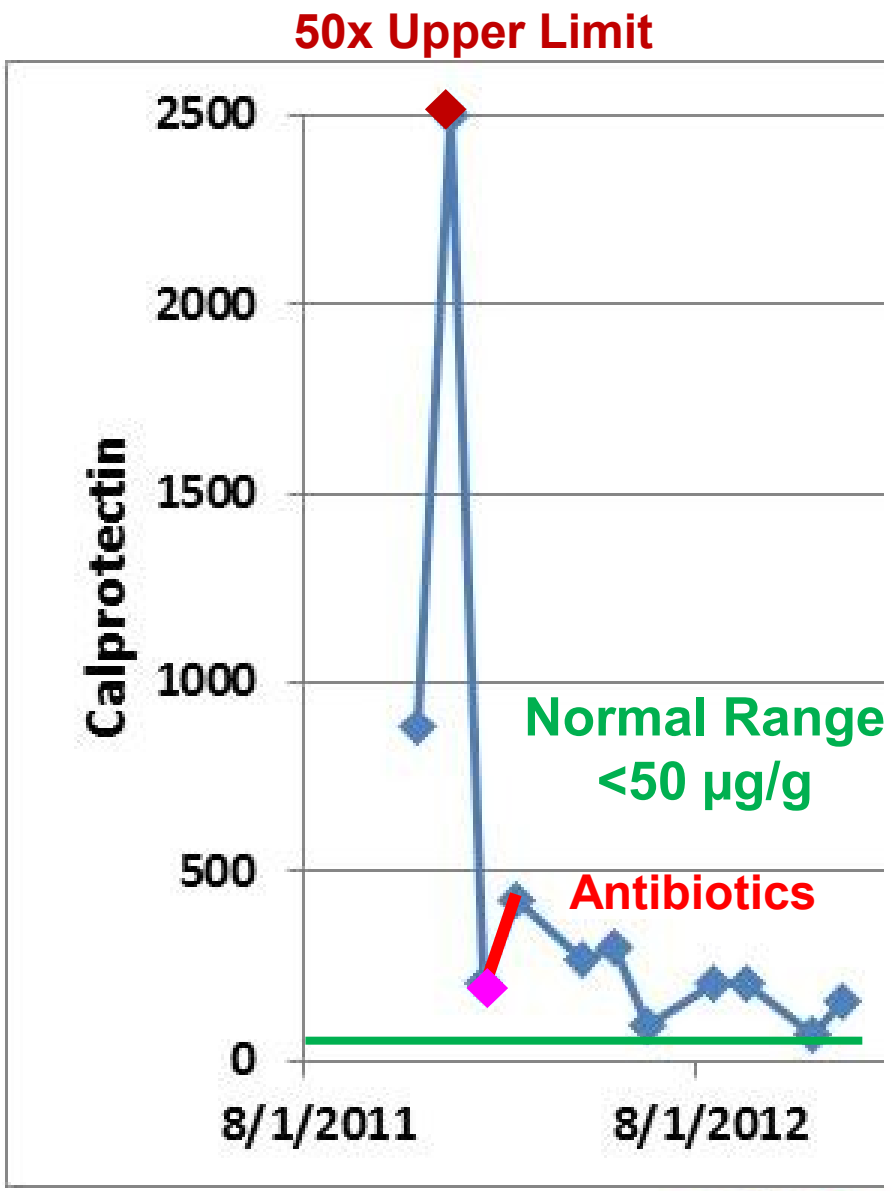
Monocytes as % of WBCs From Blood



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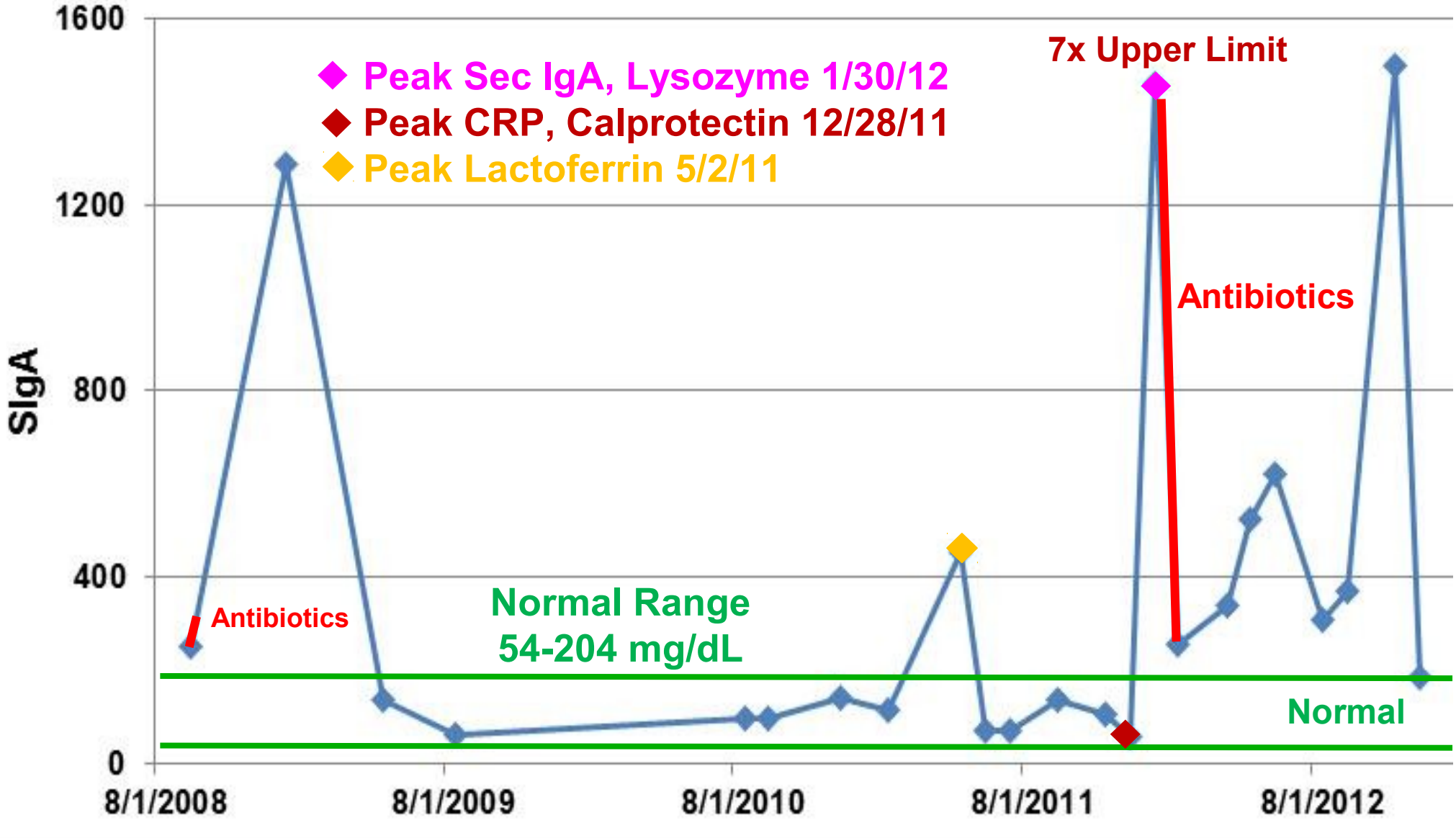
Calprotectin
From Stool Sample

- Peak Sec IgA, Lysozyme 1/30/12
- Peak CRP, Calprotectin 12/28/11
- Peak Lactoferrin 5/2/11



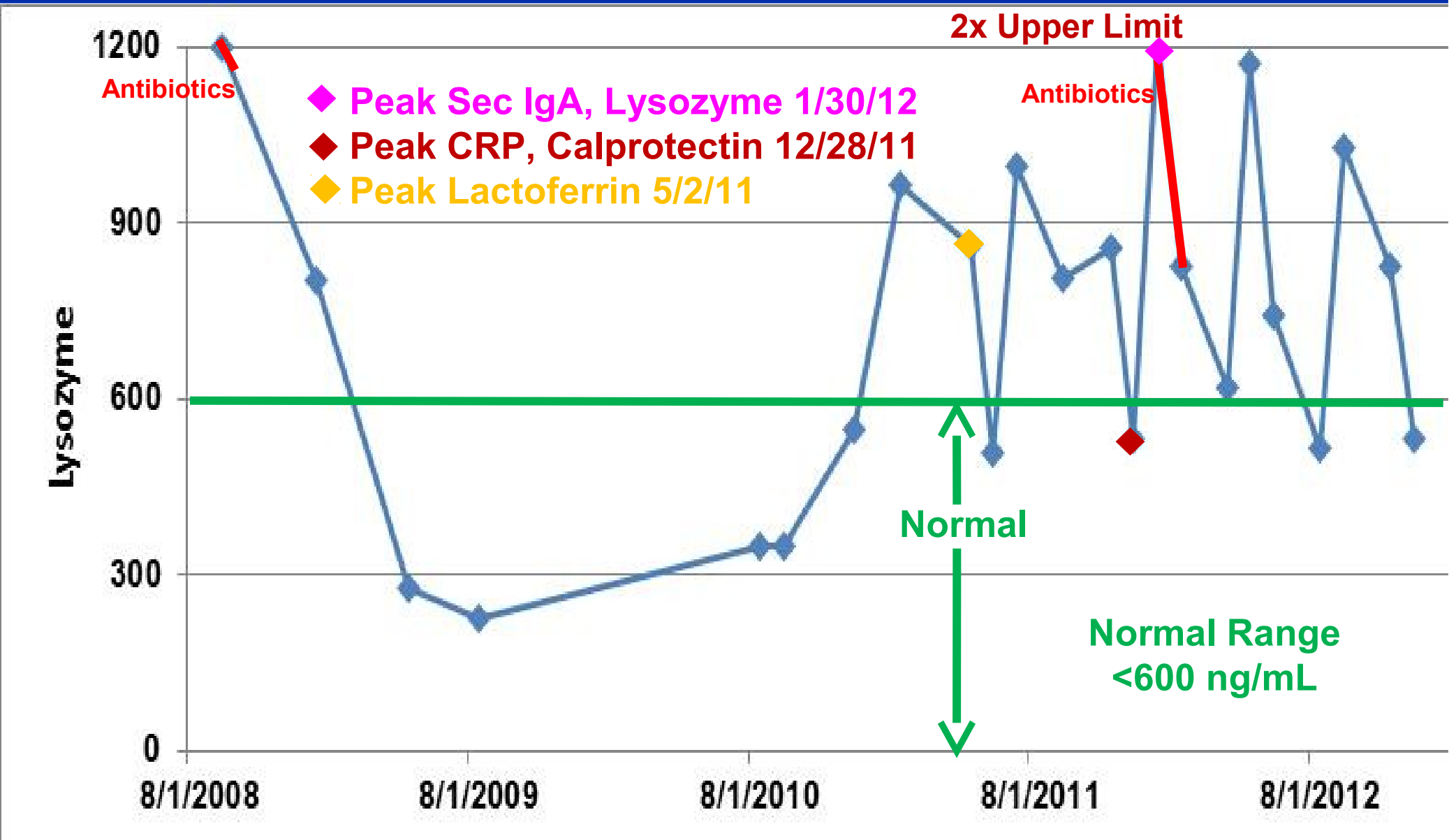
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Secretory IgA
From Stool Sample



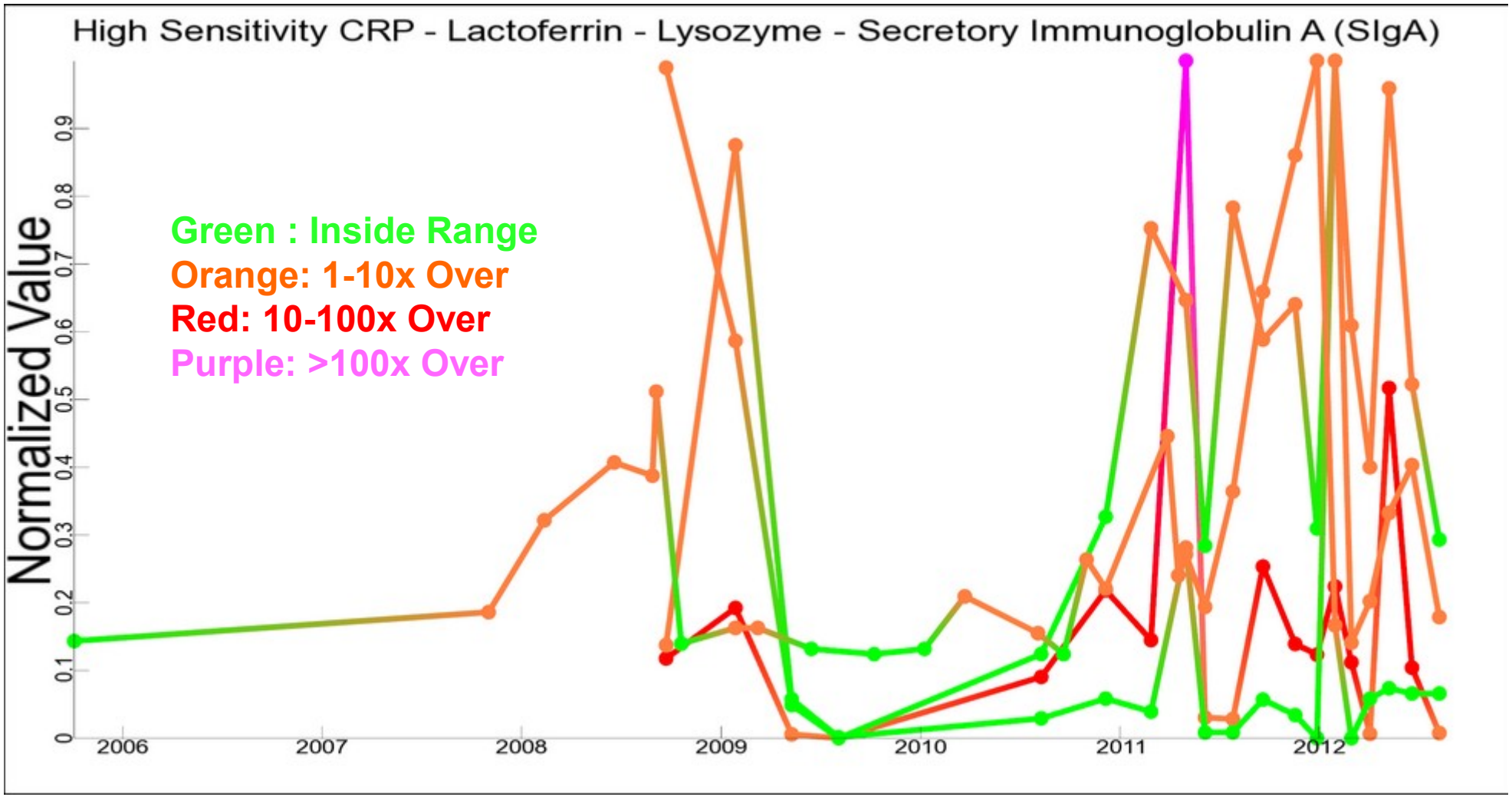
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Lysozyme
From Stool Sample



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Putting Multiple Immunological Biomarker Time Series Together, Reveals Major Immune Dysfunction



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Source: Calit2 Future Health Expedition Team

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Four Immune Biomarkers Over Time Compared with Four Signs/Symptoms



Here Immune biomarkers are normalized 0 to 1, with 1 being the highest value in five years

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Source: Photo of Calit2 64-megapixel VROOM

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Microbes are 90% of Your Cells-So I Set Out to Determine My Gut Microbes & Their Time Variation



Shipped Stool Sample
December 28, 2011

I Received
a Disk Drive April 3, 2012
With 35 GB FASTQ Files

Weizhong Li, UCSD
NGS Pipeline:
230M Reads
Only 0.2% Human

Required 1/2 cpu-yr at SDSC
Per Person Analyzed!

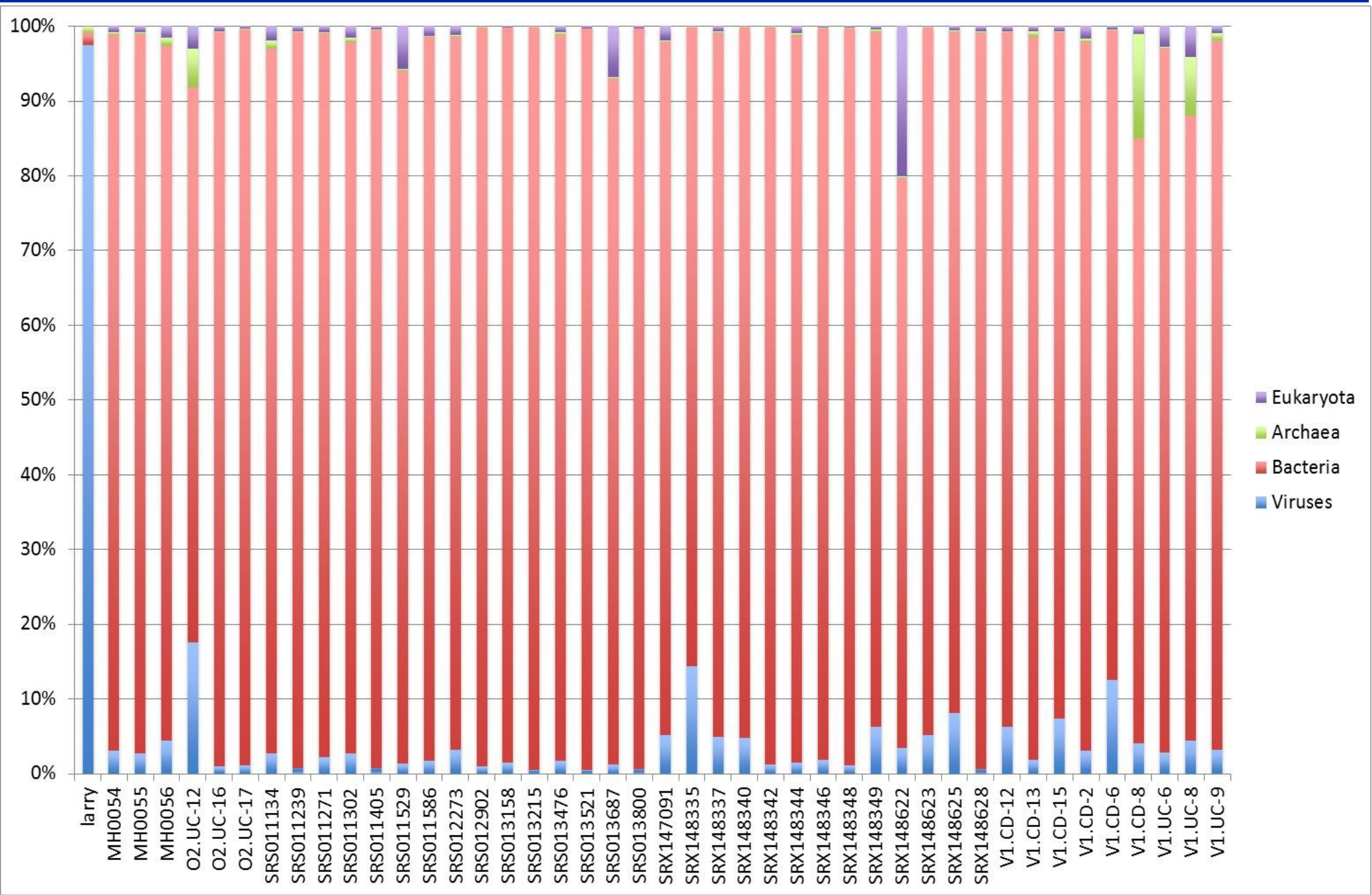
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UC San Diego
HEALTH SCIENCES

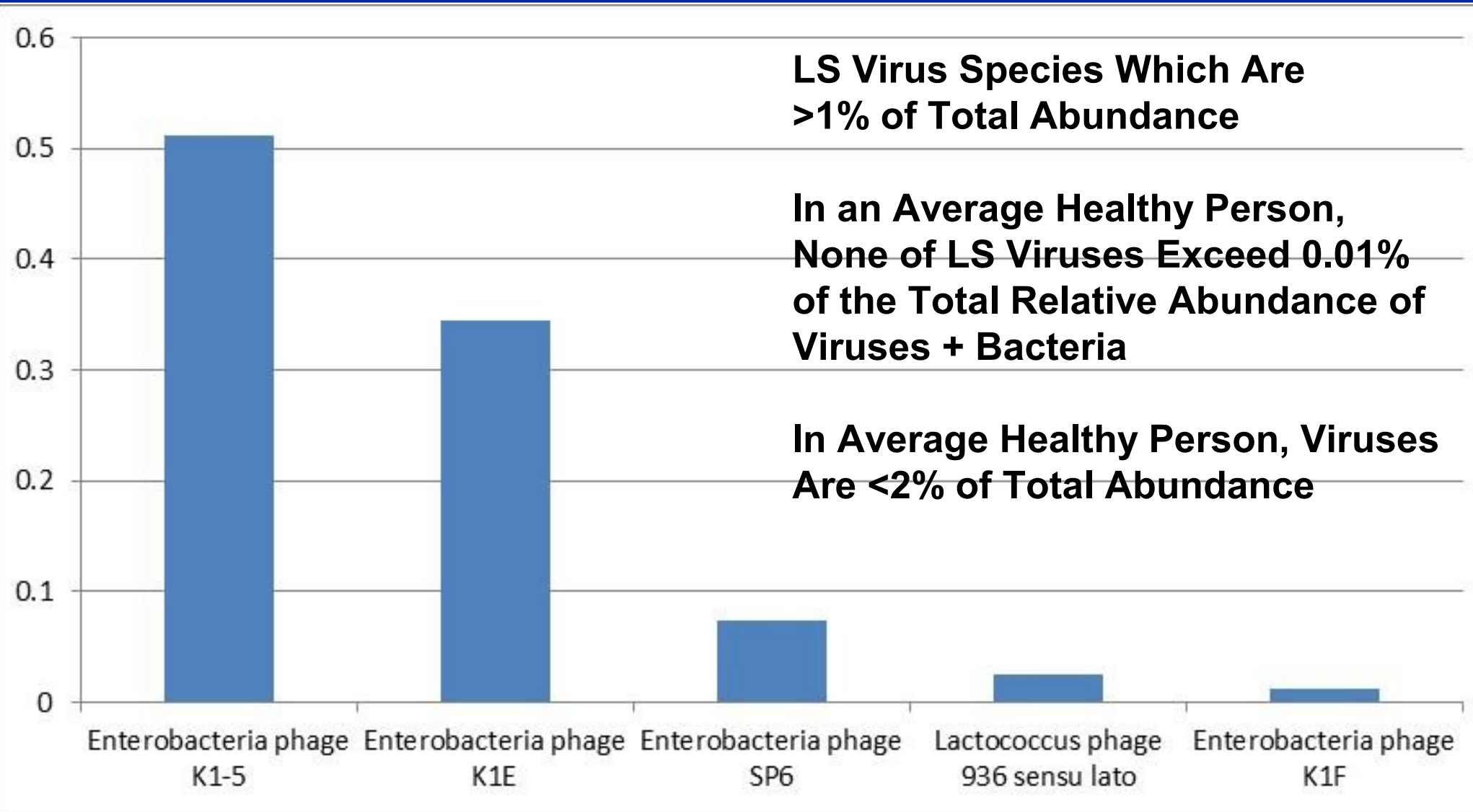
J. Craig Venter
INSTITUTE

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First Surprise:
Almost All My DNA Abundances are *Viral*!



LS Viral Species Comprise >97% Relative Abundance of Virus + Bacteria + Archaea



LS Virus Species Which Are >1% of Total Abundance

In an Average Healthy Person, None of LS Viruses Exceed 0.01% of the Total Relative Abundance of Viruses + Bacteria

In Average Healthy Person, Viruses Are <2% of Total Abundance

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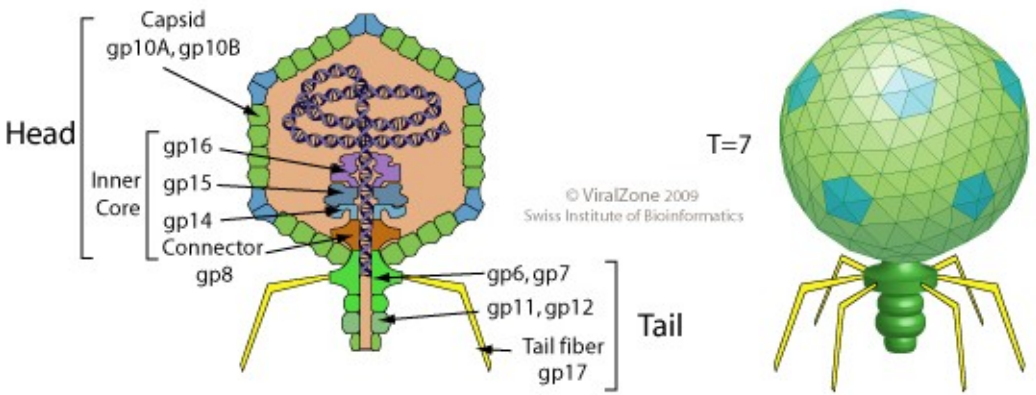
My Viral Load is Mainly SP-6 Like

search virus

SP6-like viruses

Molecular biology

VIRION



Nonenveloped, head-tail structure. Head is about 60-65 nm in diameter. The tail is non-contractile, has 6 prominent tail spikes.

GENOME

Linear, dsDNA genome of about 43 kb encoding for 52 genes.

GENE EXPRESSION

REPLICATION

CYTOPLASMIC

DB LINKS

Nucleotide DB: NCBI

Protein DB: UniProtKB

TAXONOMY

Group I: dsDNA viruses

Order: Caudovirales

Family: Podoviridae

Subfamily: Autographivirinae

Genus: **SP6-like viruses**

SPECIES

Type: Enterobacteria phage SP6

Main: Enterobacteria phage K1E Enterobacteria phage K1-5 Enterobacteria phage K5 Erwinia amylovora phage Era103

REFERENCE STRAINS

Enterobacteria phage SP6

Sequence | Genome | Proteome

HOST

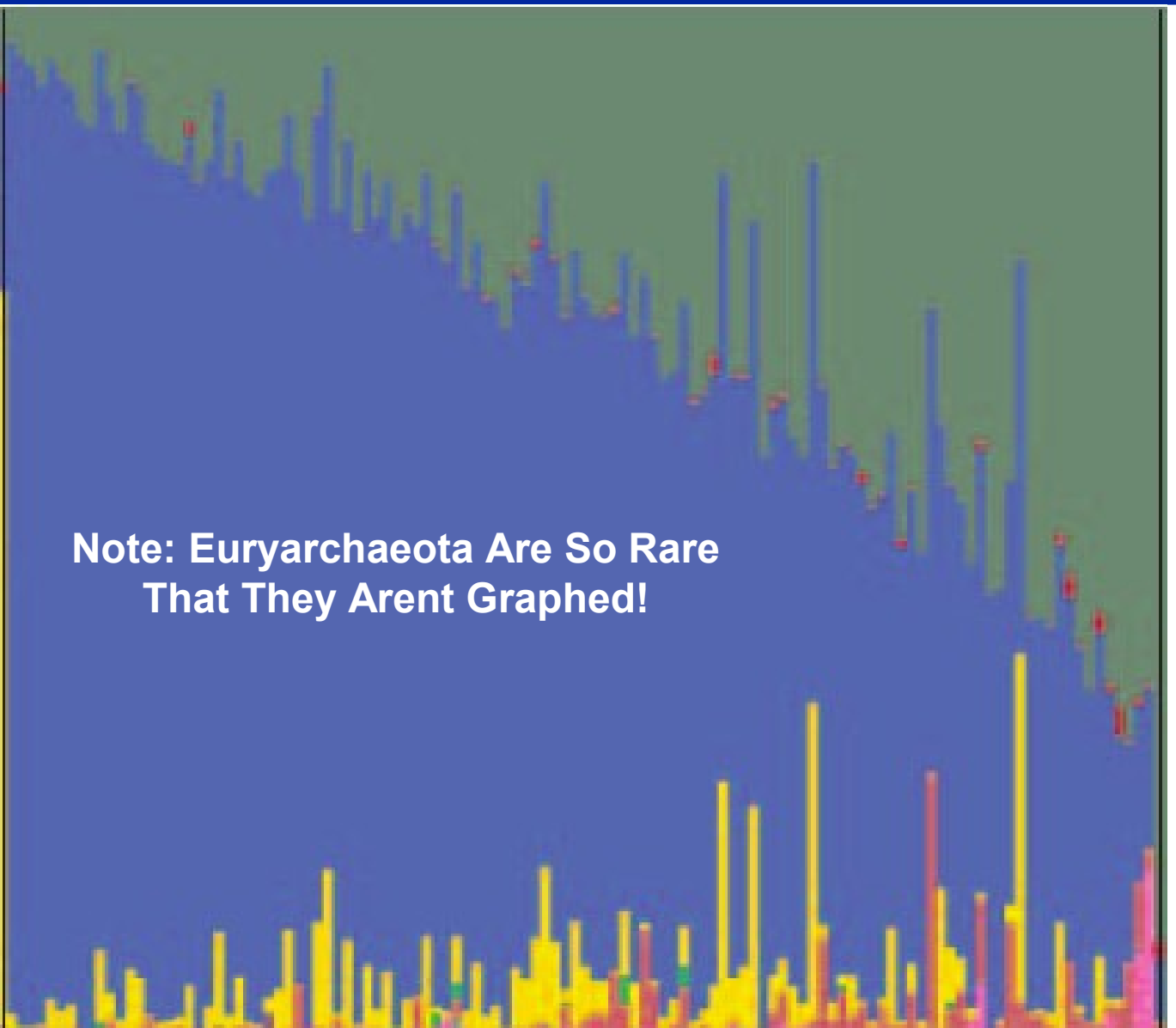
Bacteria

Epidemiology

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What is a "Healthy" Gut Microbiome? Considerable Phyla Variation Found in HMP



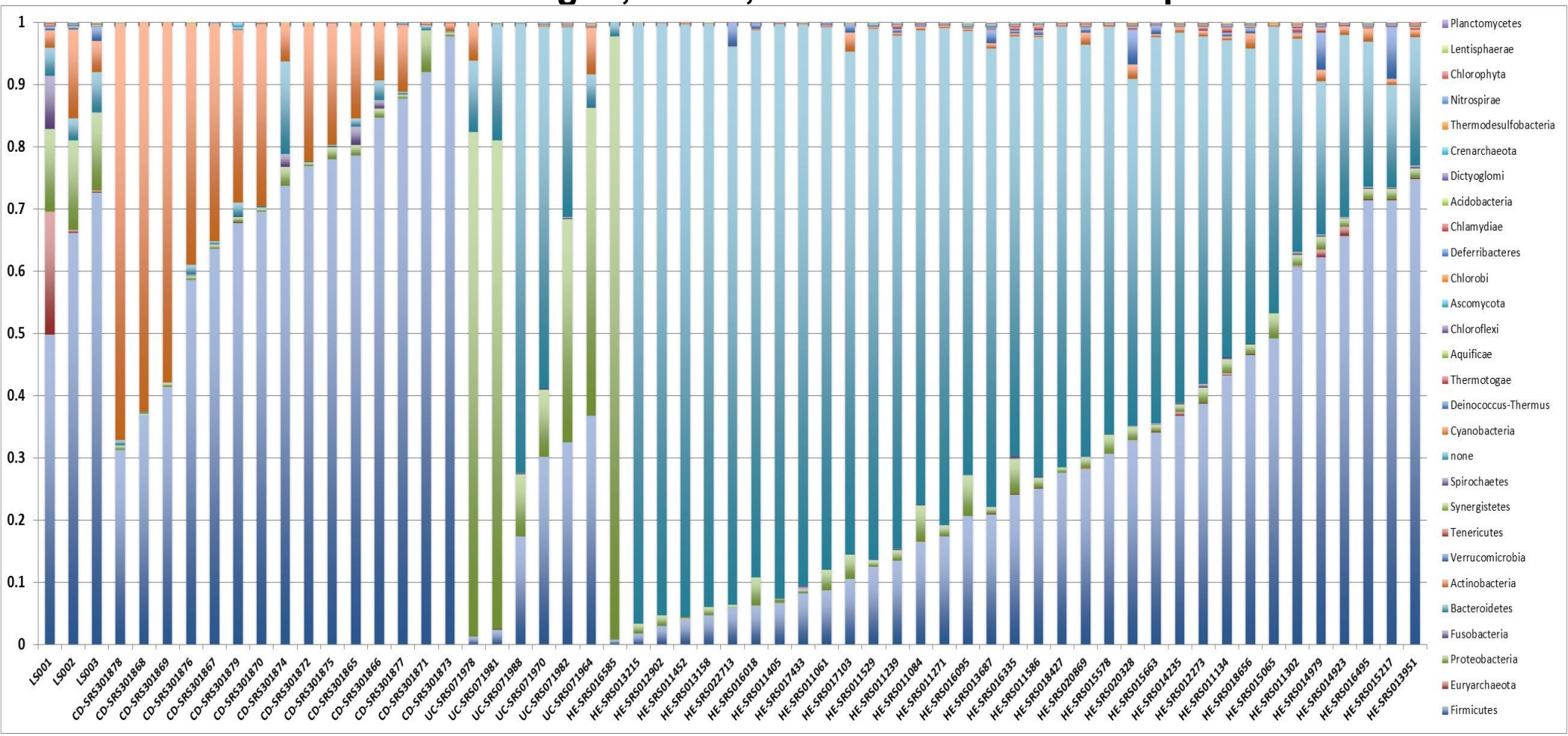
- Firmicutes
- Actinobacteria
- Bacteroidetes
- Proteobacteria
- Fusobacteria
- Tenericutes
- Spirochaetes
- Cyanobacteria
- Verrucomicrobia
- TM7

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Source: "Structure, function and diversity of the healthy human microbiome," HMP Consortium, Nature, 486, 207-212 (2012)

Phyla Gut Microbial Abundance Without Viruses: LS, Crohn's, UC, and Healthy Subjects

Source: Weizhong Li, UCSD; Calit2 FuturePatient Expedition



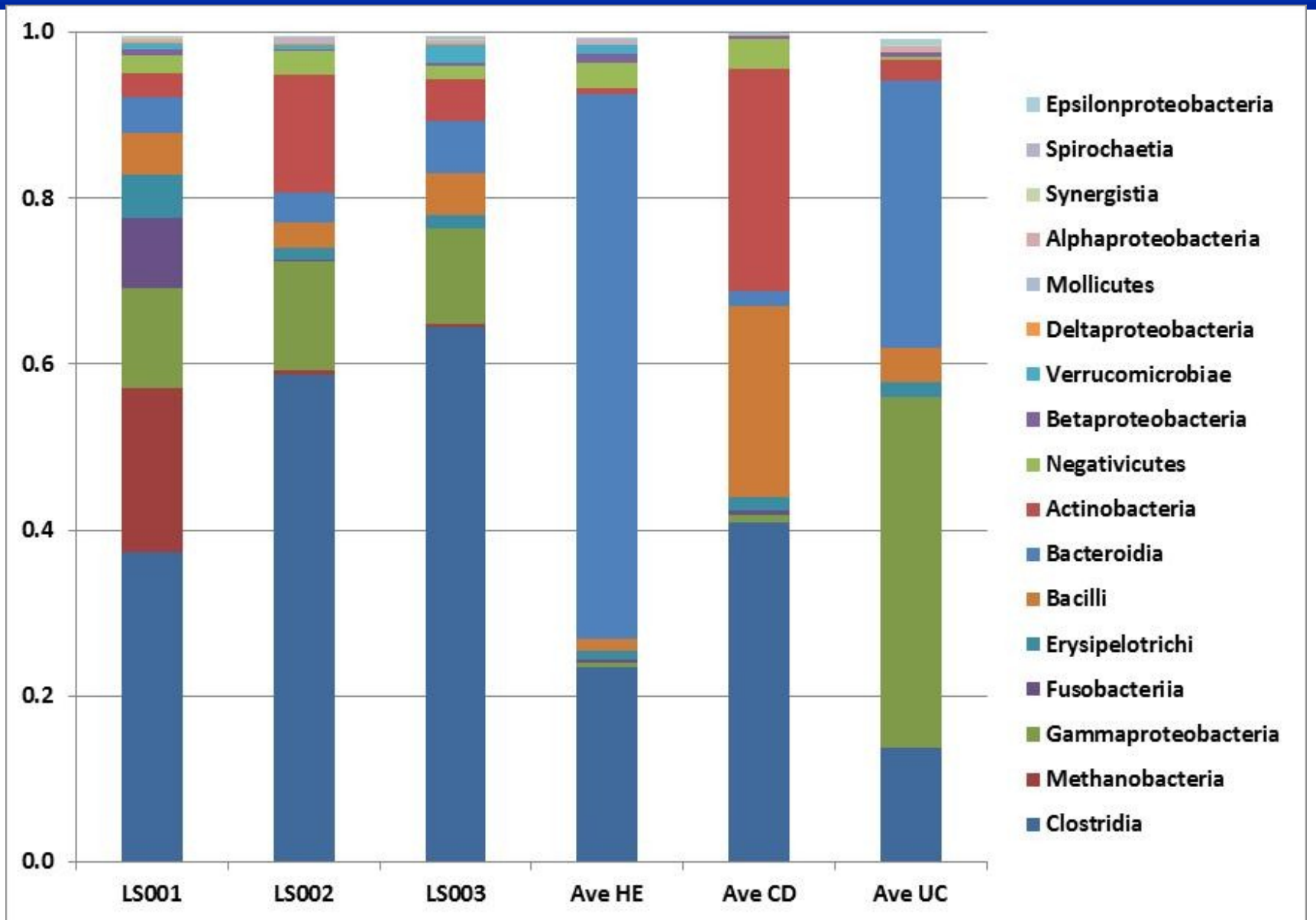
LS **Crohn's** **Ulcerative Colitis** **Healthy**

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Toward Noninvasive Microbial Ecology Diagnostics

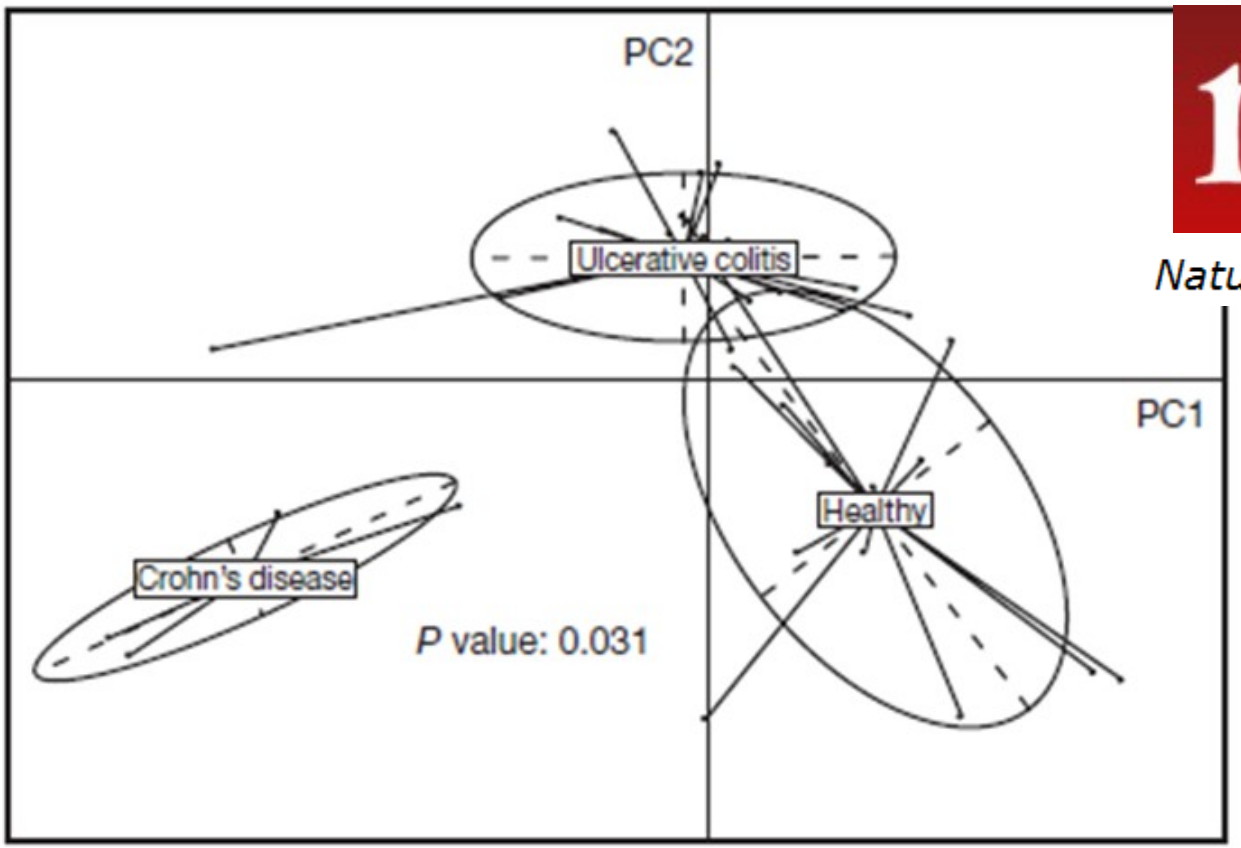
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LS Time Series Gut Microbiome Classes vs. Healthy, Crohn's, Ulcerative Colitis



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Microbial Metagenomics Can Diagnose Disease States Using Principal Component Analysis



nature

Nature **464**, 59-65 (4 March 2010)

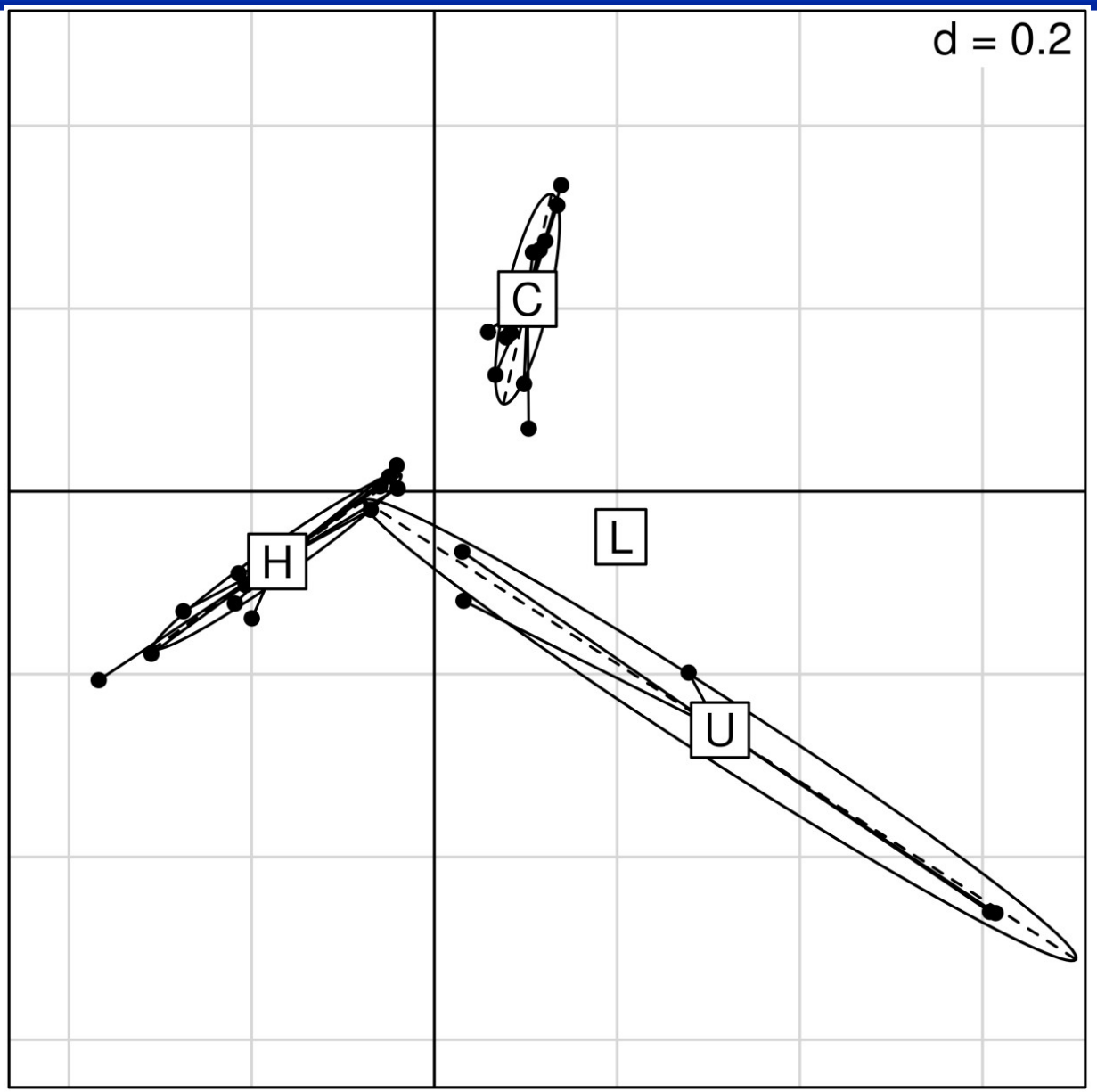
IBD Patients Harbored, on Average, *25% Fewer Microbial Genes* than the Individuals Not Suffering from IBD.

Figure 4 | Bacterial species abundance differentiates IBD patients and healthy individuals. Principal component analysis with health status as

A human gut microbial gene catalogue established by metagenomic sequencing

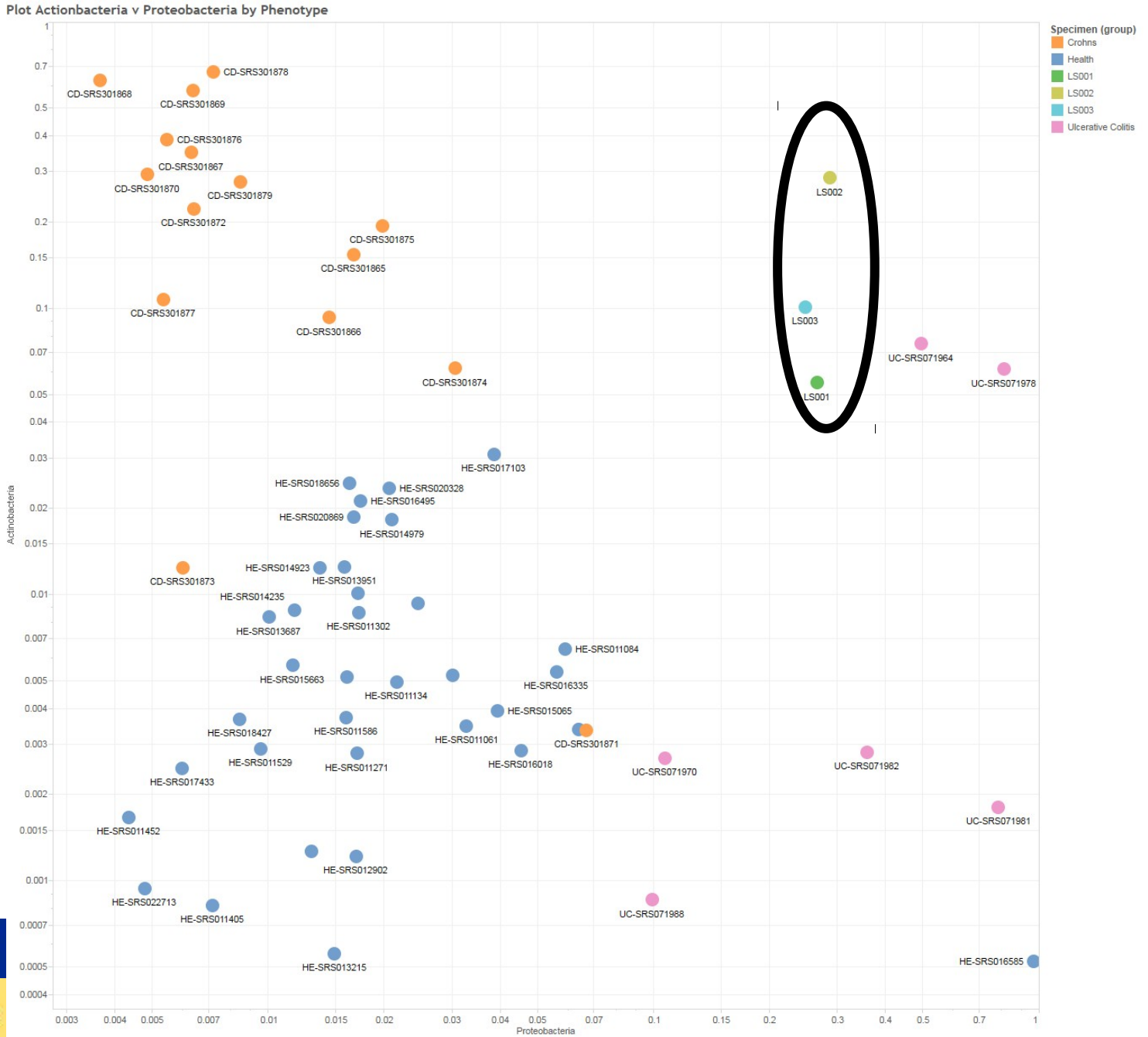
Junjie Qin[1]*, Ruiqiang Li[1]*, Jeroen Raes[2,3], Manimozhiyan Arumugam[2], Kristoffer Solvsten Burgdorf[4],

Principal Component Analysis On Microbial Species Abundance



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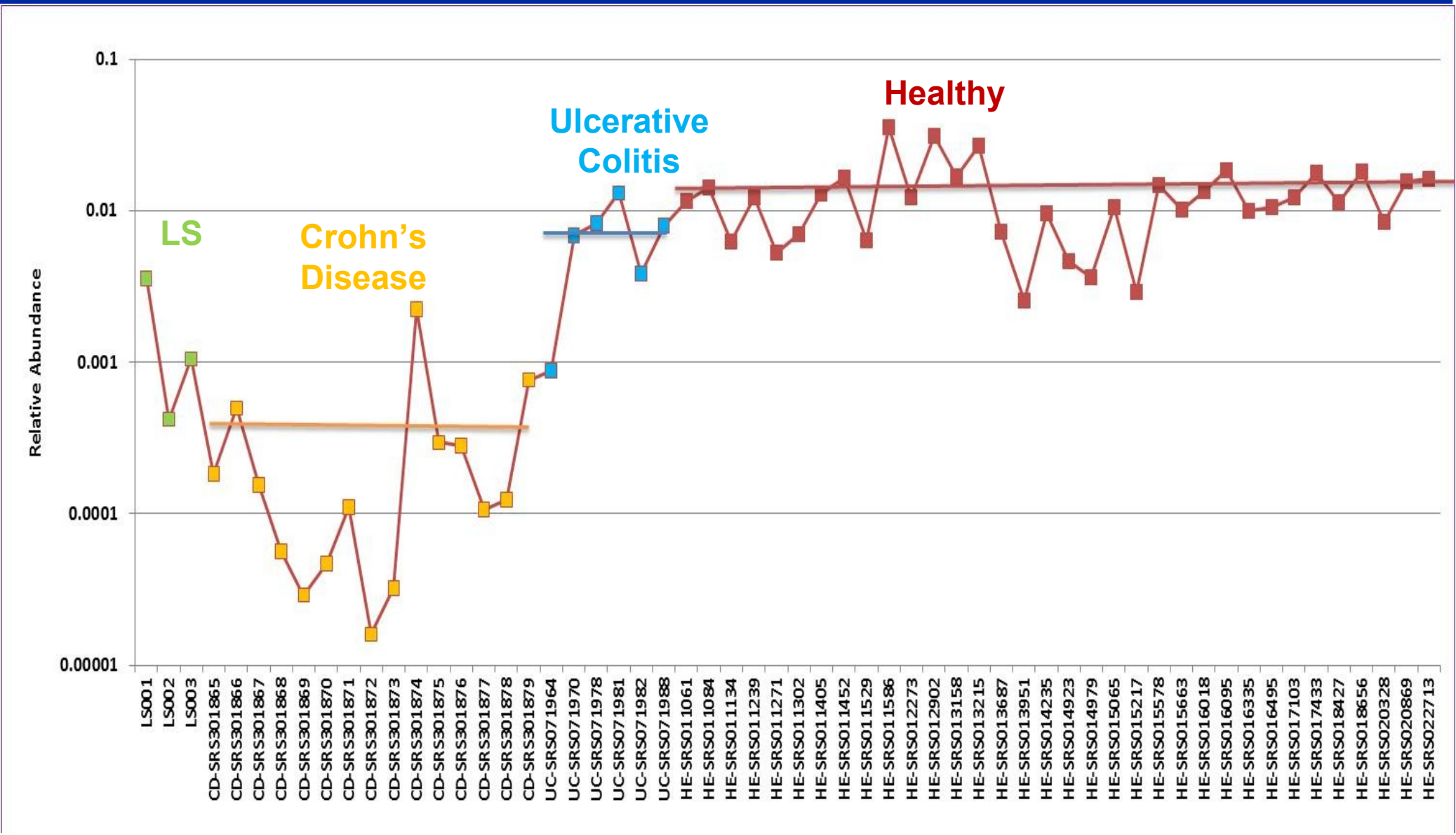
Healthy, CD, UC and LS
Relative Abundance of Proteobacteria to Actinobacteria



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Bacteroides fragilis Levels Different For Healthy and IBD Human Gut-Differentiates CD and UC

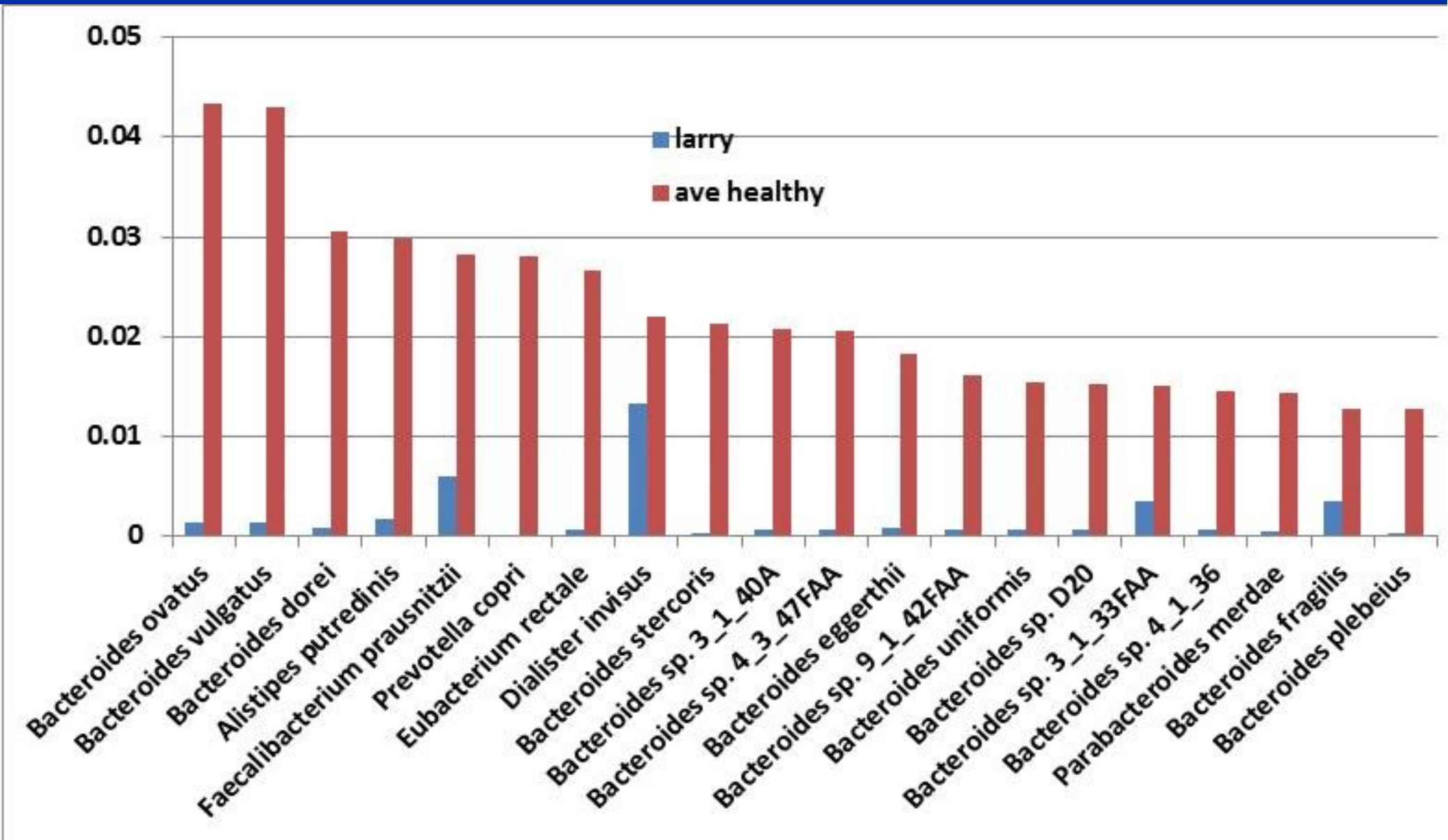


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Source: Analysis by LS working on Weizhong Li Data

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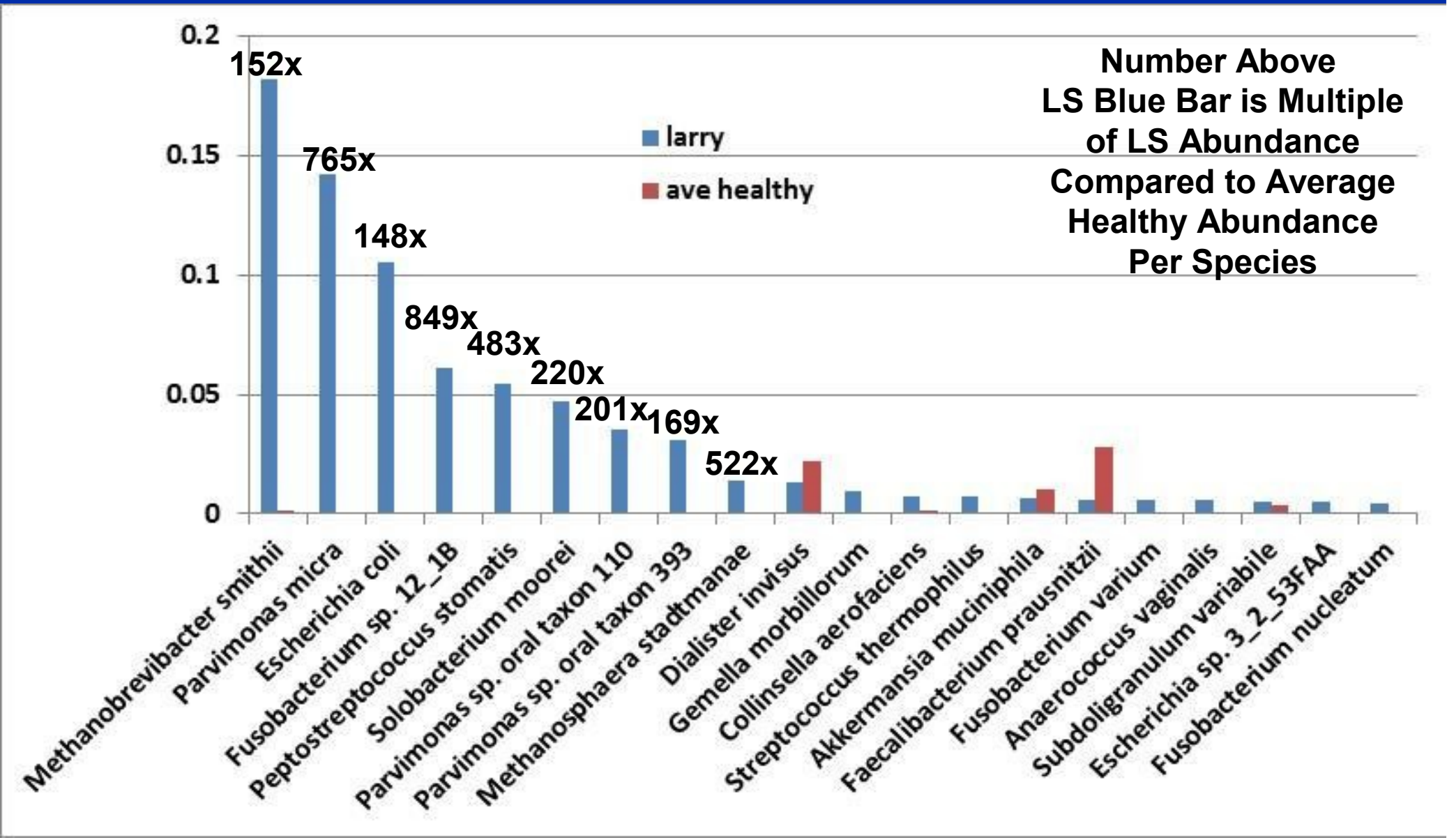
Almost All Abundant Species (≥1%) in Healthy Subjects Are *Severely Depleted* in LS Gut



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Top 20 Most Abundant Microbial Species In LS vs. Average Healthy Subject

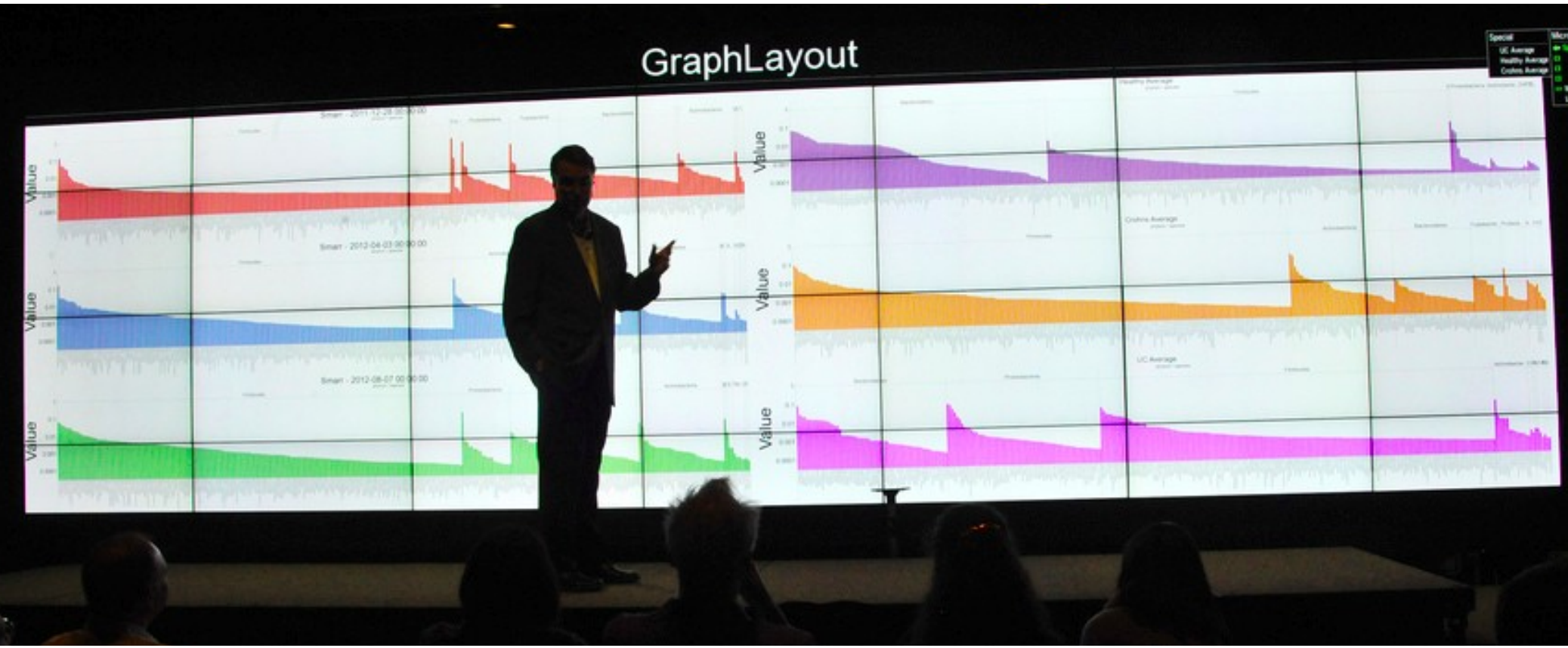


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Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

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Comparing 3 LS Time Snapshots (Left) with Healthy, Crohn's, UC (Right Top to Bottom)



LS Gut Microbe Species 12/28/11 (red) compared to Average of 35 Healthy Subjects (blue)



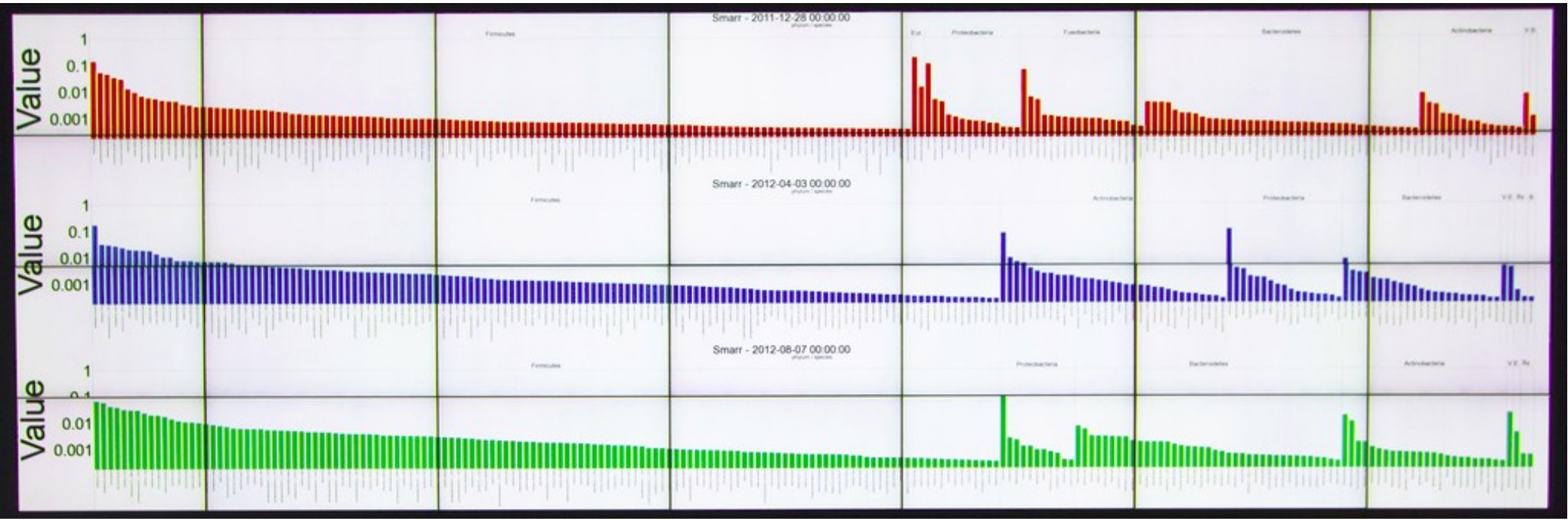
Derived from metagenomic sequencing of LS stool sample.
Each species is a bar,
height is logarithmic abundance,
species are divided into microbial phyla

Source: Photo of Calit2 64-megapixel VROOM

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200 LS Gut Microbe Species at 3 Times 12/28/11, 4/3/12, 8/7/12



Red is at Highest Value of CRP
Blue is the Day After End of Antibiotic/Prednisone Therapy
Green is Four Months Later

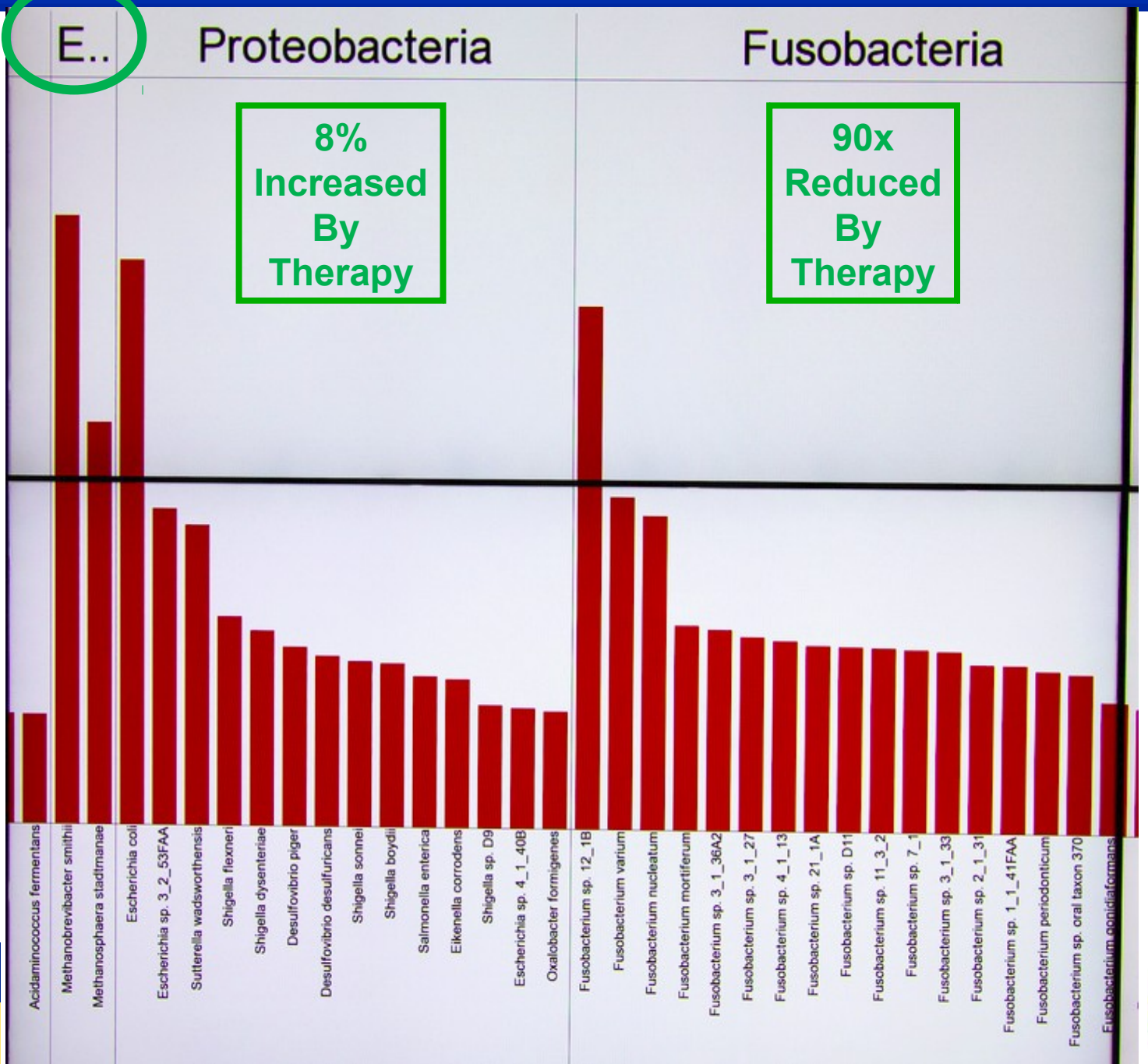
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Source: Photo of Calit2 64-megapixel VROOM

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Closeup of Uncommon LS Microbes 12/28/11 Stool Sample

45x Reduced By Therapy

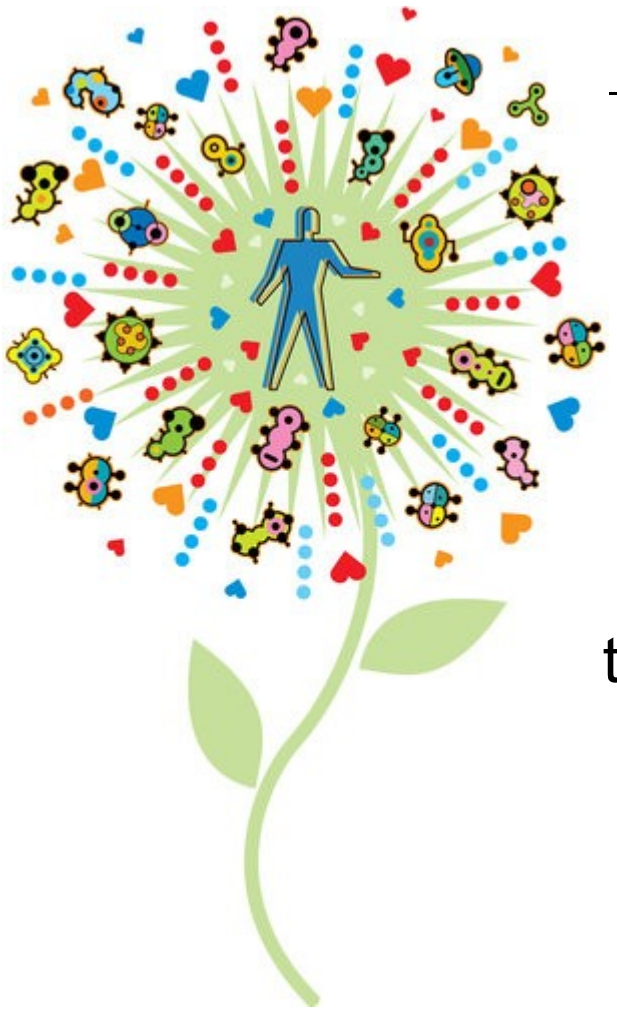


Two separate research teams have found strikingly high concentrations of *Fusobacterium* in tumor samples collected from colorectal cancer patients.
October 18, 2011

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From War to Gardening



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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Larry Smarr

University of California, San Diego, CA, USA

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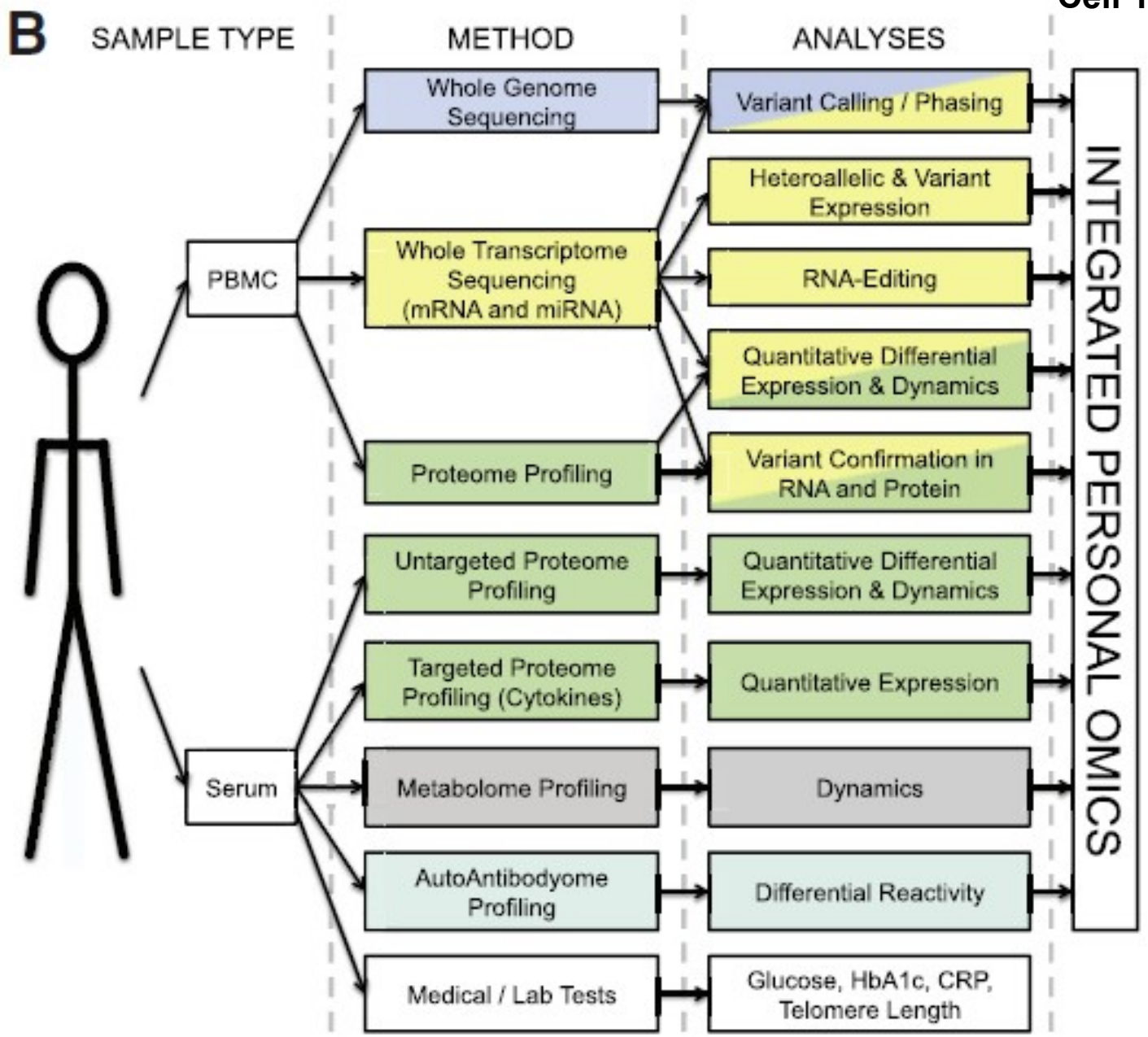
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Biotechnol. J. 2012, 7, 980–991

it²

Integrative Personal Omics Profiling Reveals Details of Clinical Onset of Viruses and Diabetes

Cell 148, 1293–1307, March 16, 2012



- **Michael Snyder, Chair of Genomics Stanford Univ.**
- **Genome 140x Coverage**
- **Blood Tests 20 Times in 14 Months**
  - **tracked nearly 20,000 distinct transcripts coding for 12,000 genes**
  - **measured the relative levels of more than 6,000 proteins and 1,000 metabolites in Snyder's blood**