“Digitally Revealing the Dynamics of Your Superorganism Body”

IEEE International Conference on
Healthcare Informatics 2013
Philadelphia, PA
September 10, 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

Abstract

For over a decade, Calit2 has had a driving vision that healthcare is being transformed into “digitally enabled genomic medicine.” To put a more personal face on the "patient of the future," I have been increasingly quantifying my own body. In addition to external markers I also currently track over 100 blood and stool biomarkers every few months. Calit2 uses advanced interactive visualization techniques to visually explore my organs. Using my saliva 23andme.com obtained 1 million single nucleotide polymorphisms (SNPs) in my human DNA. My gut microbiome has been metagenomically sequenced by the J. Craig Venter Institute, yielding 25 billion DNA bases. I will show how one can use this Big Data approach to decipher the complex dynamic interactions between the various components of my immune system and the human and microbial DNA present in my “superorganism” body. Doing so in my case led to the unexpected diagnosis of a chronic incurable disease. My hope is that by "living in the future" I can provide some early insights into the digital transformations of wellness and health care

Calit2 Has Been Had a Vision of "the Digital Transformation of Health" for a Decade

- Next Step—Putting You On-Line!
  - Wireless Internet Transmission
  - Key Metabolic and Physical Variables
  - Model -- Dozens of Processors and 60 Sensors / Actuators Inside of our Cars

www.bodymedia.com



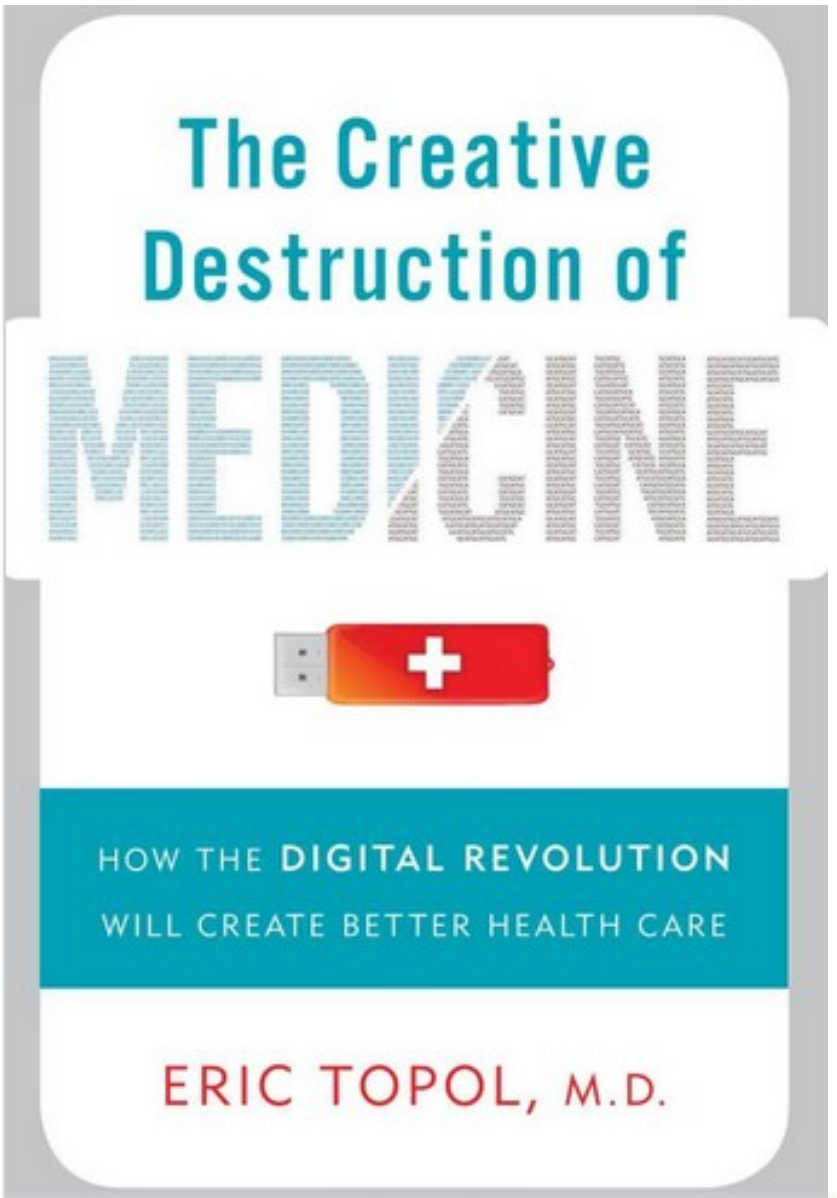
- Post-Genomic Individualized Medicine
  - Combine
    - Genetic Code
    - Body Data Flow
  - Use Powerful AI Data Mining Techniques

The Content of This Slide from 2001 Larry Smarr Calit2 Talk on Digitally Enabled Genomic Medicine

The Calit2 Vision of Digitally Enabled Genomic Medicine is an Emerging Reality



July/August 2011



February 2012

Where I Believe We are Headed: Predictive, Personalized, Preventive, & Participatory Medicine

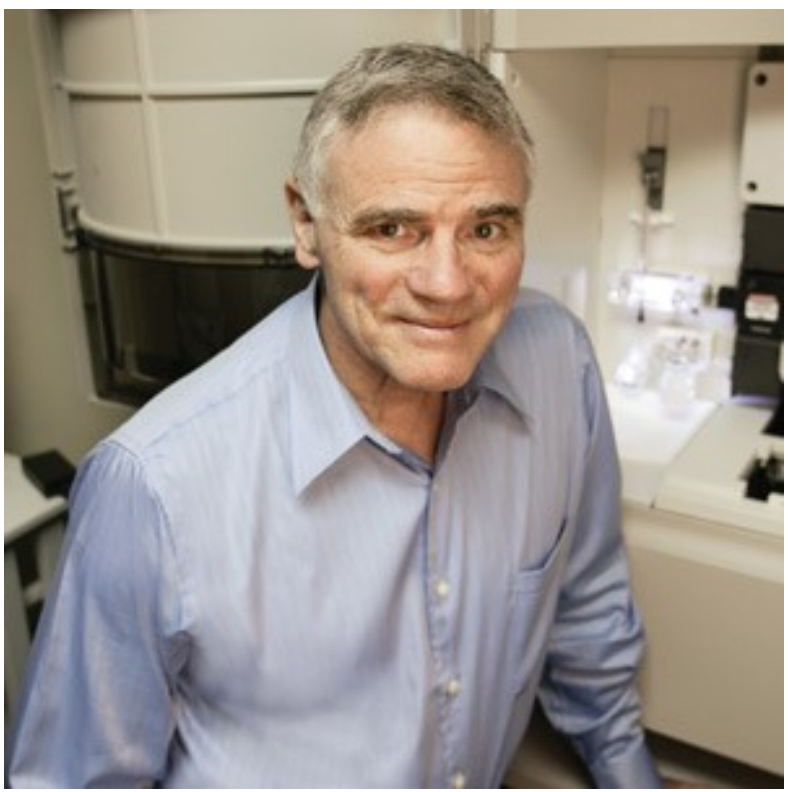
Newsweek

I am Leroy Hood's Lab Rat!

A Doctor's Vision of the Future of Medicine

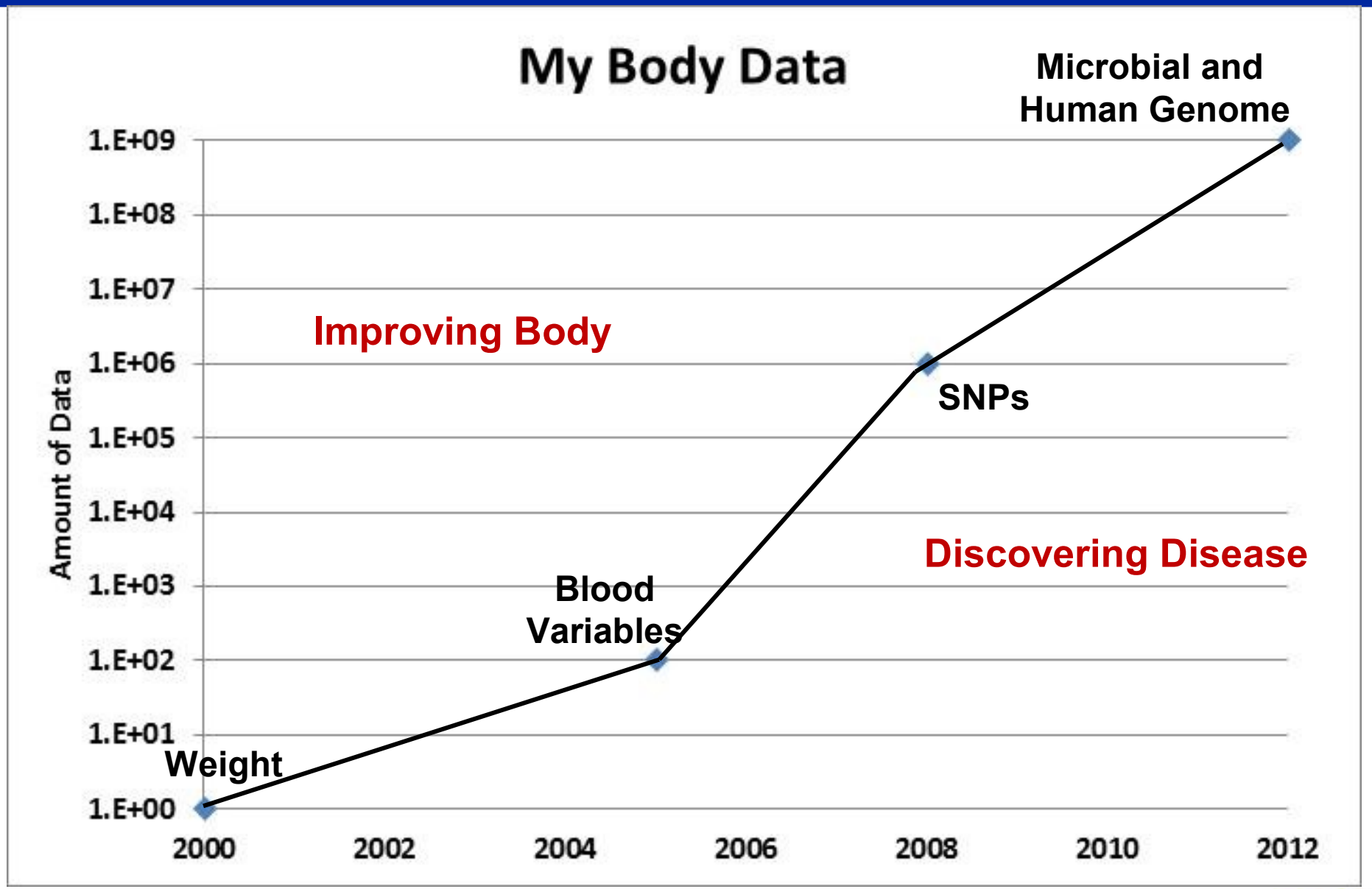
Leroy Hood
NEWSWEEK

From the magazine issue dated Jul 13, 2009



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

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



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



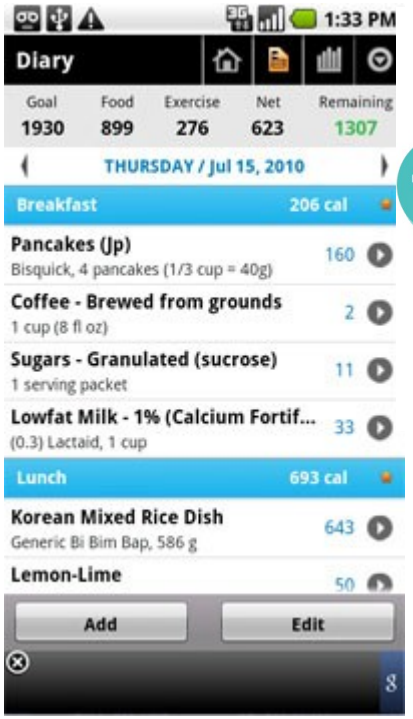
Age 61



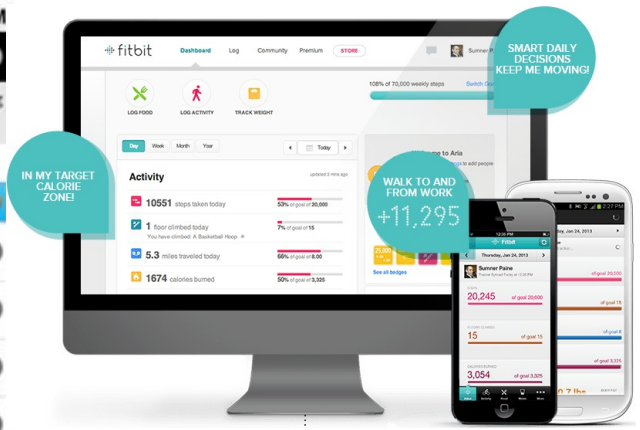
I Reversed My Body's Decline By Quantifying and Altering Nutrition and Exercise

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

Challenge-Develop Standards to Enable MashUps of Personal Sensor Data Across Private Clouds



MyFitnessPal-Calories Ingested



FitBit - Daily Steps & Calories Burned



Withing/iPhone-Blood Pressure





EM Wave PC-Stress



Azumio-Heart Rate



Zeo-Sleep

From Measuring Macro-Variables to Measuring Your Internal Variables



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

Invited Paper for Focus Issue of Biotechnology Journal, Edited by Profs. Leroy Hood and Charles Auffray.

Perspective

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

Larry Smarr

University of California, San Diego, CA, USA

Download Pdfs from my Portal:

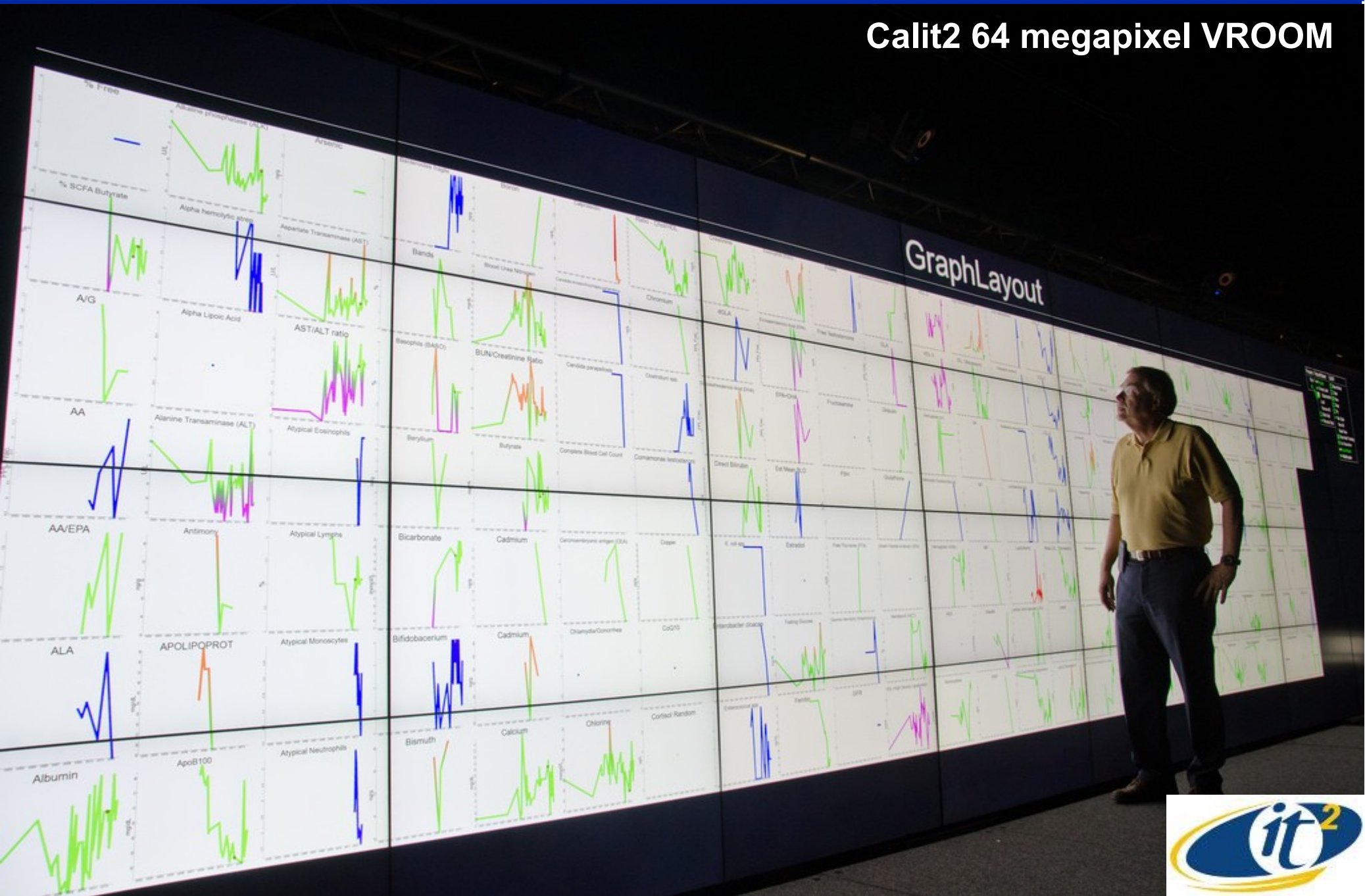
http://lsmarr.calit2.net/repository/Biotech_J._LS_published_article.pdf

http://lsmarr.calit2.net/repository/Biotech_J._Supporting_Info_published.pdf

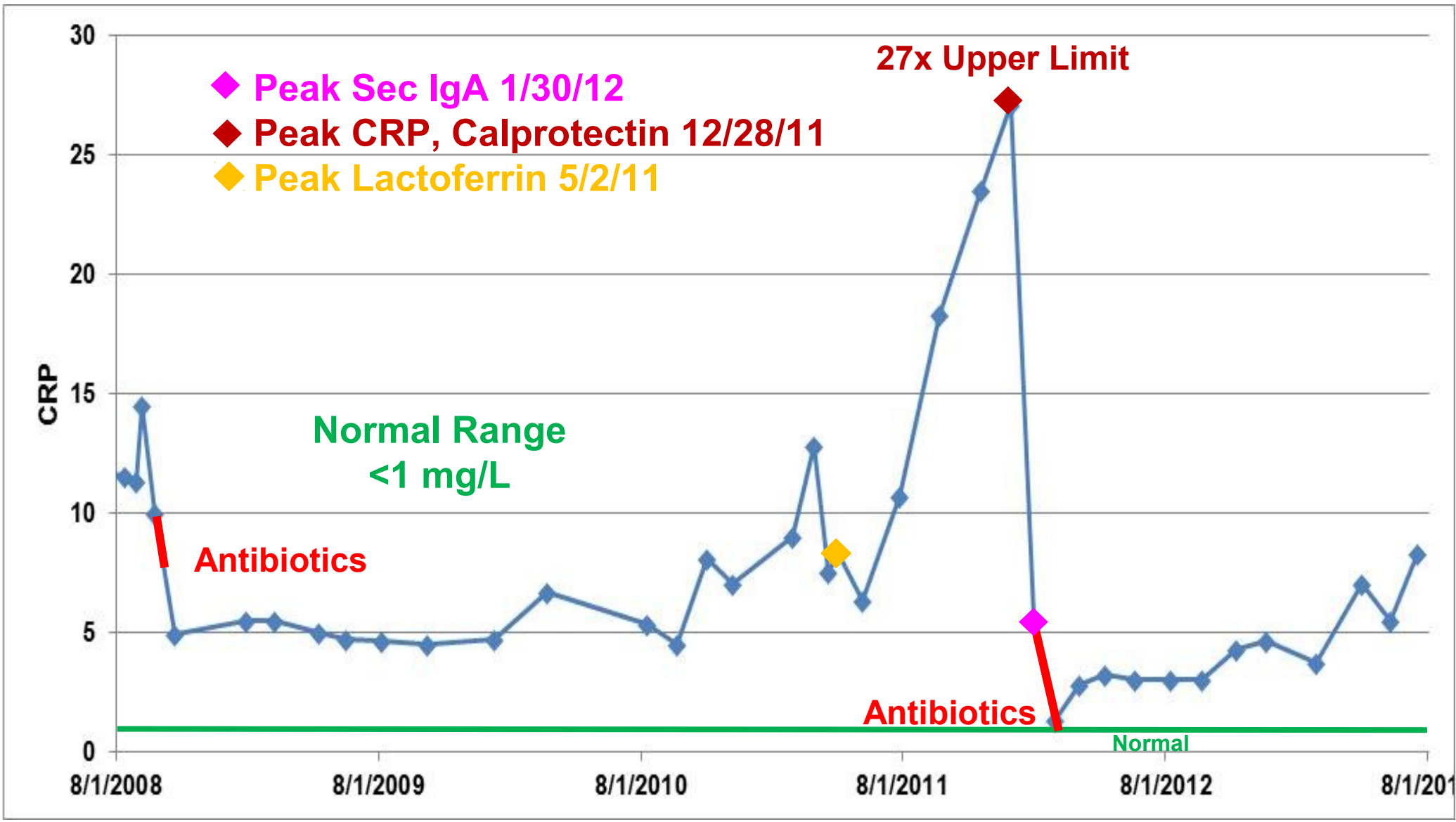
Biotechnol. J. 2012, 7, 980–991



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

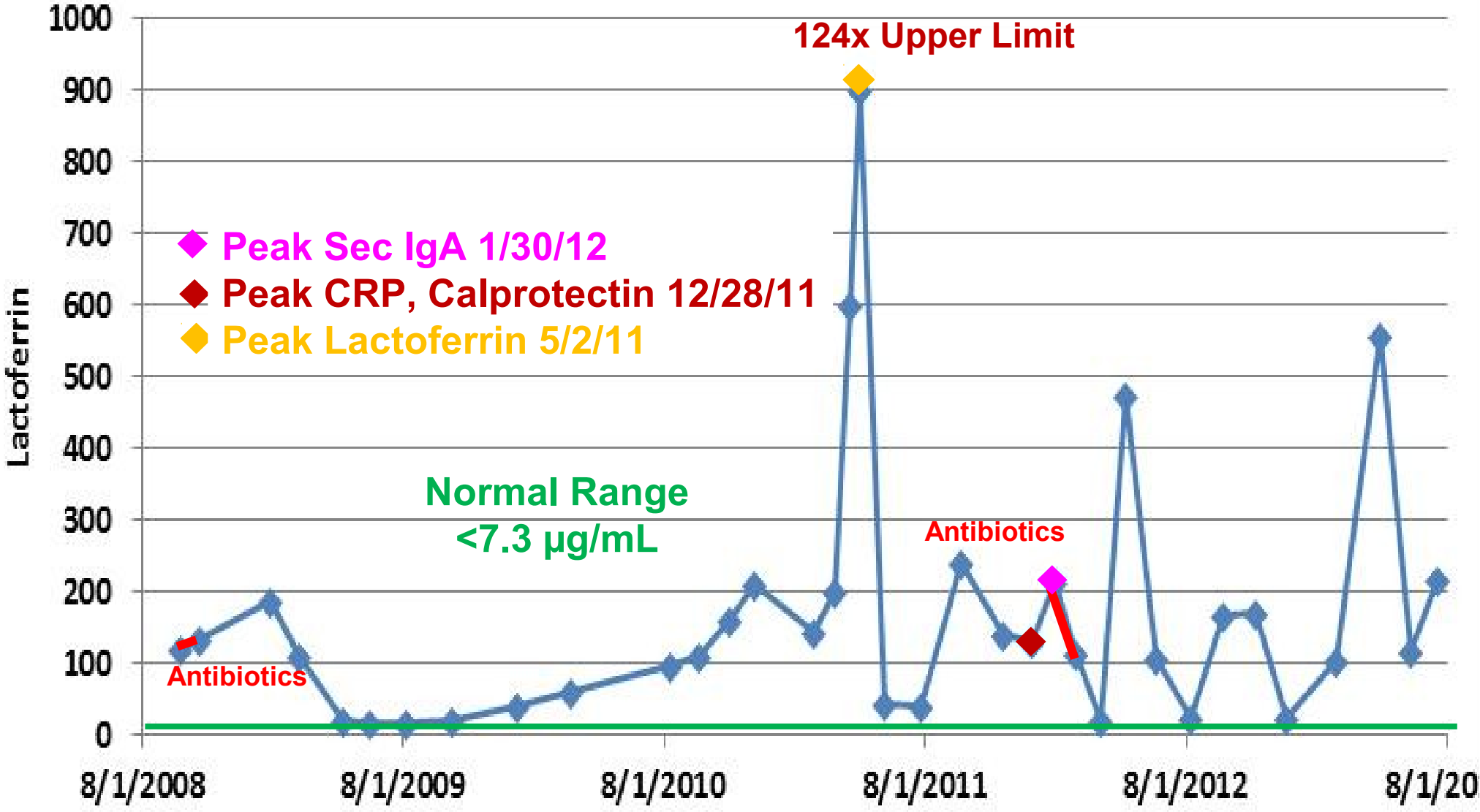


Complex Reactive Protein From Blood Samples



CRP is a Generic Measure of Inflammation in the Blood

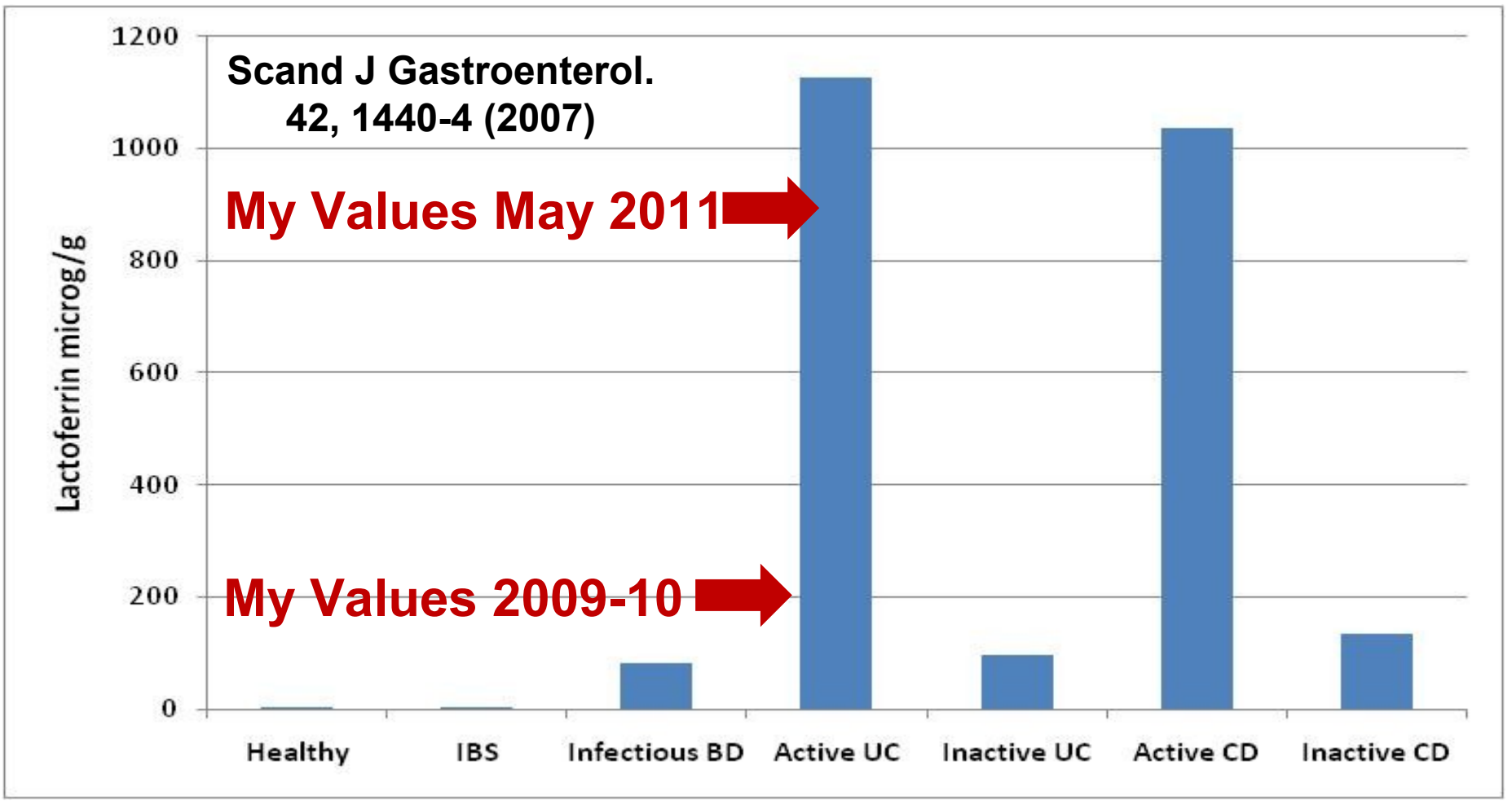
Lactoferrin is Shed from Neutrophils Into Stool Sample



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

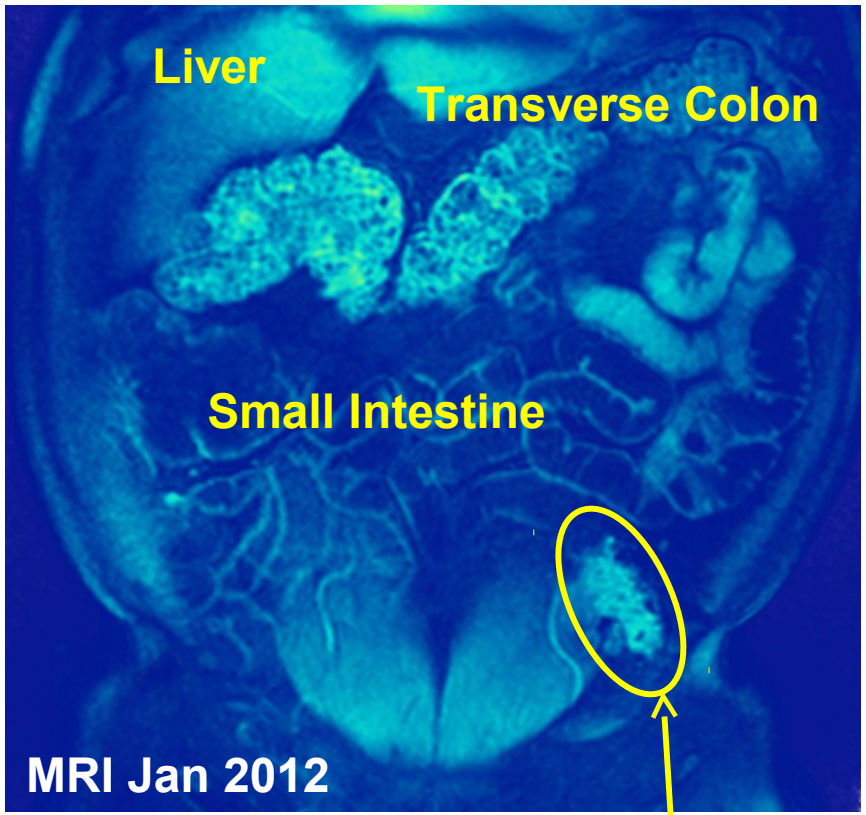
High Lactoferrin Biomarker Led Me to Hypothesis I Had Inflammatory Bowel Disease (IBD)

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



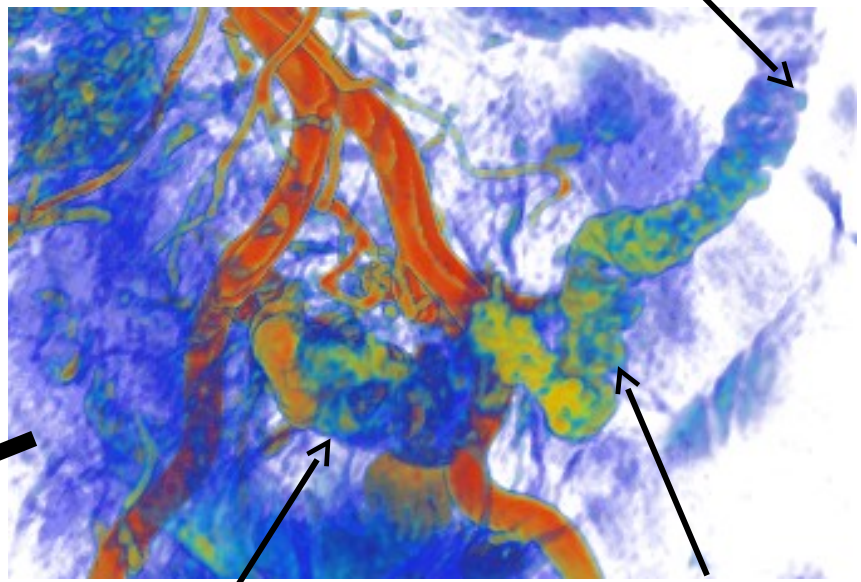
High Level of Calprotectin Confirmed Hypothesis

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

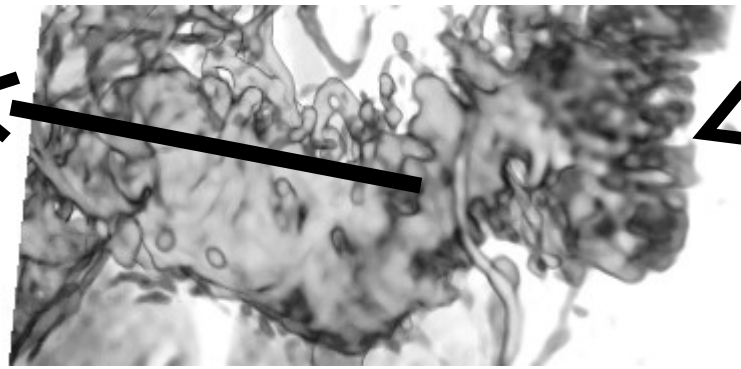
Descending Colon



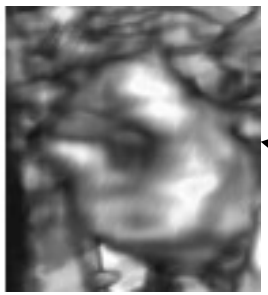
Major Kink

Sigmoid Colon Threading Iliac Arteries

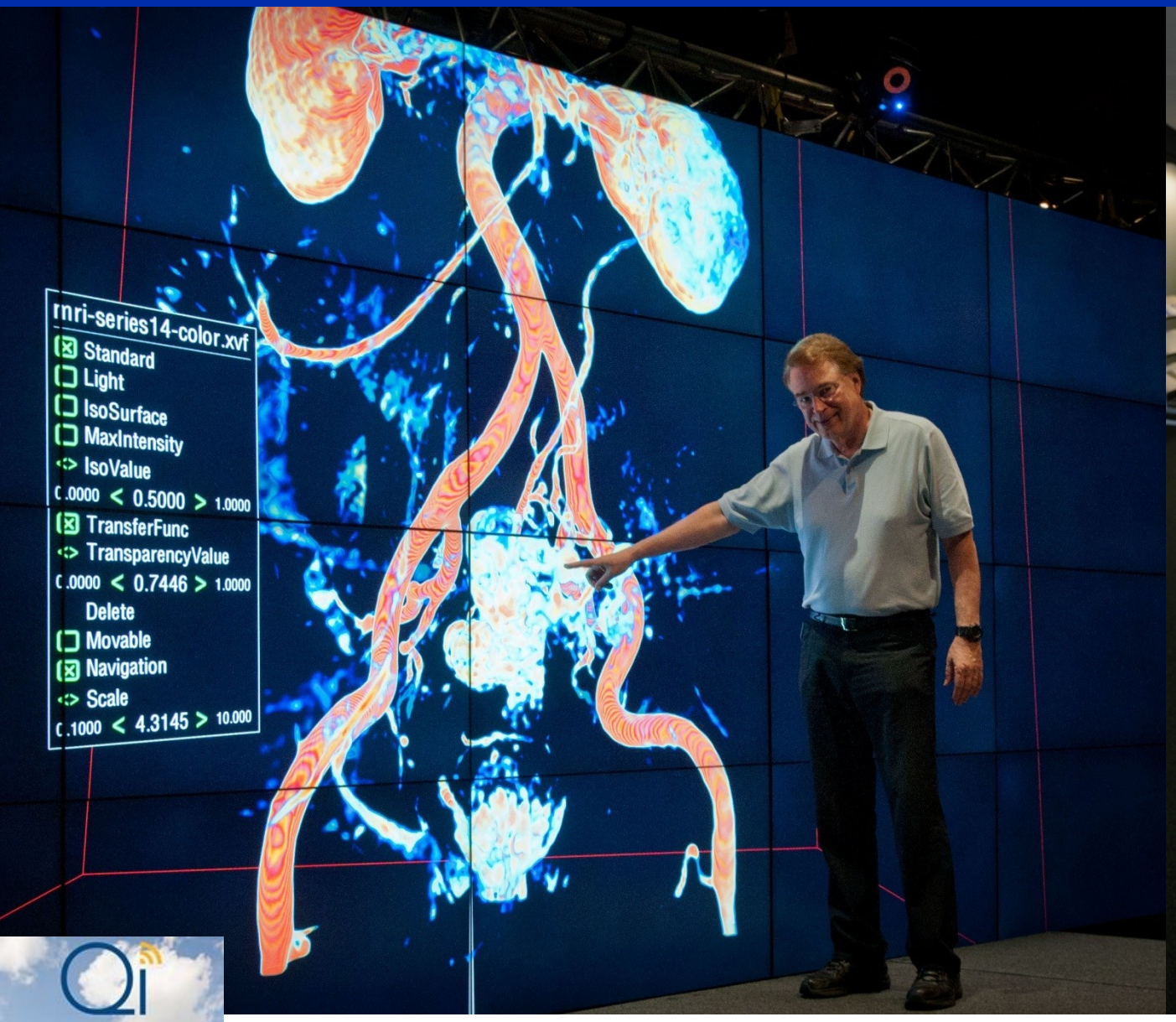
Diseased Sigmoid Colon



Cross Section



Converting MRI Slices Into 3D Interactive Virtual Reality AND 3-D Printing







Research: Calit2 FutureHealth Team

Why Did I Have an Autoimmune Disease like IBD?

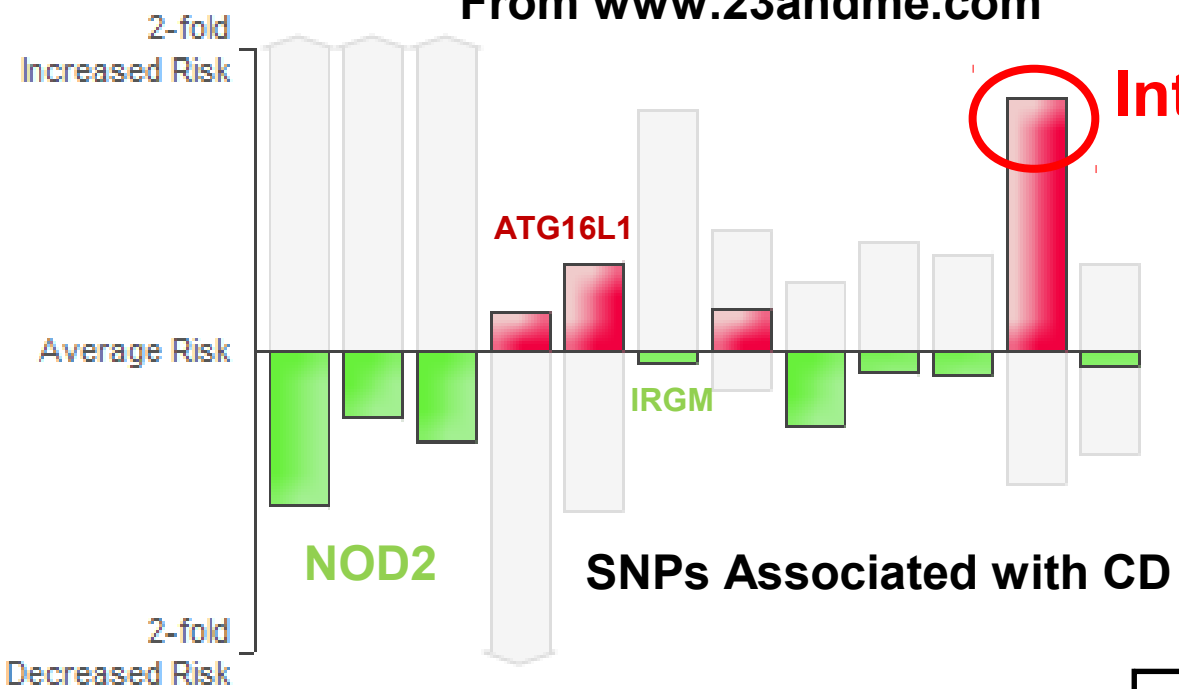
Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.
--*The Role of Microbes in Crohn's Disease*

So I Set Out to Quantify All Three!

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

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]

I Had My Full Human Genome Sequenced in 2012 - 1 Million/Year by 2015

Next Step: Compare Full Genome With IBD SNPs



PGP Used Complete Genomics, Inc. to Sequence my Human DNA

My Anonymized Human Genome is Available for Download

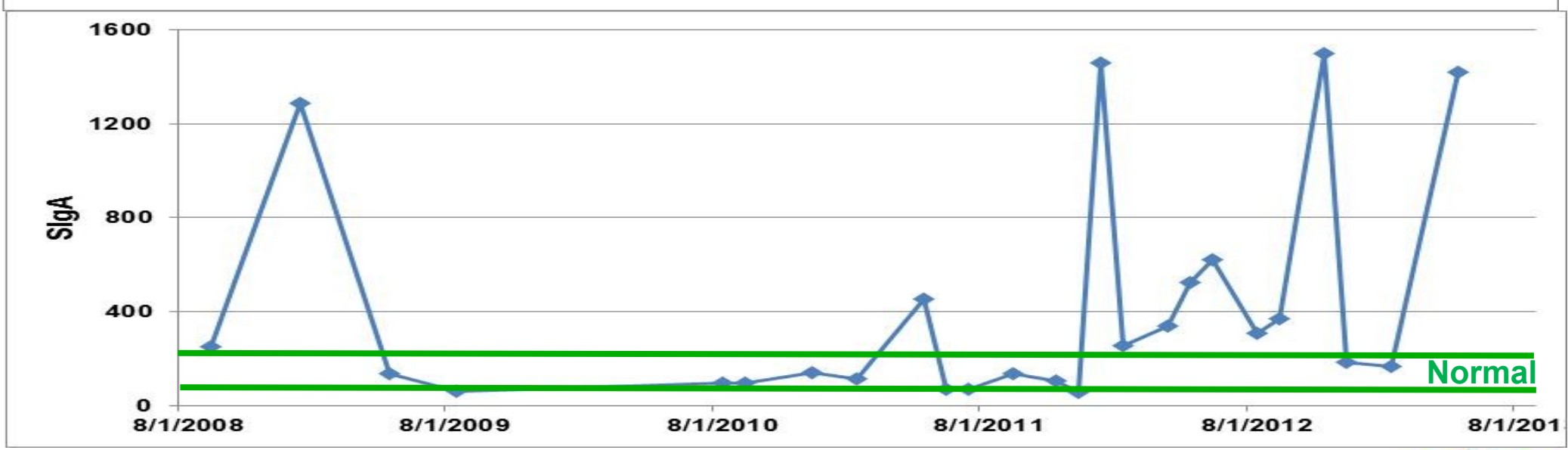
Personal Genome Project



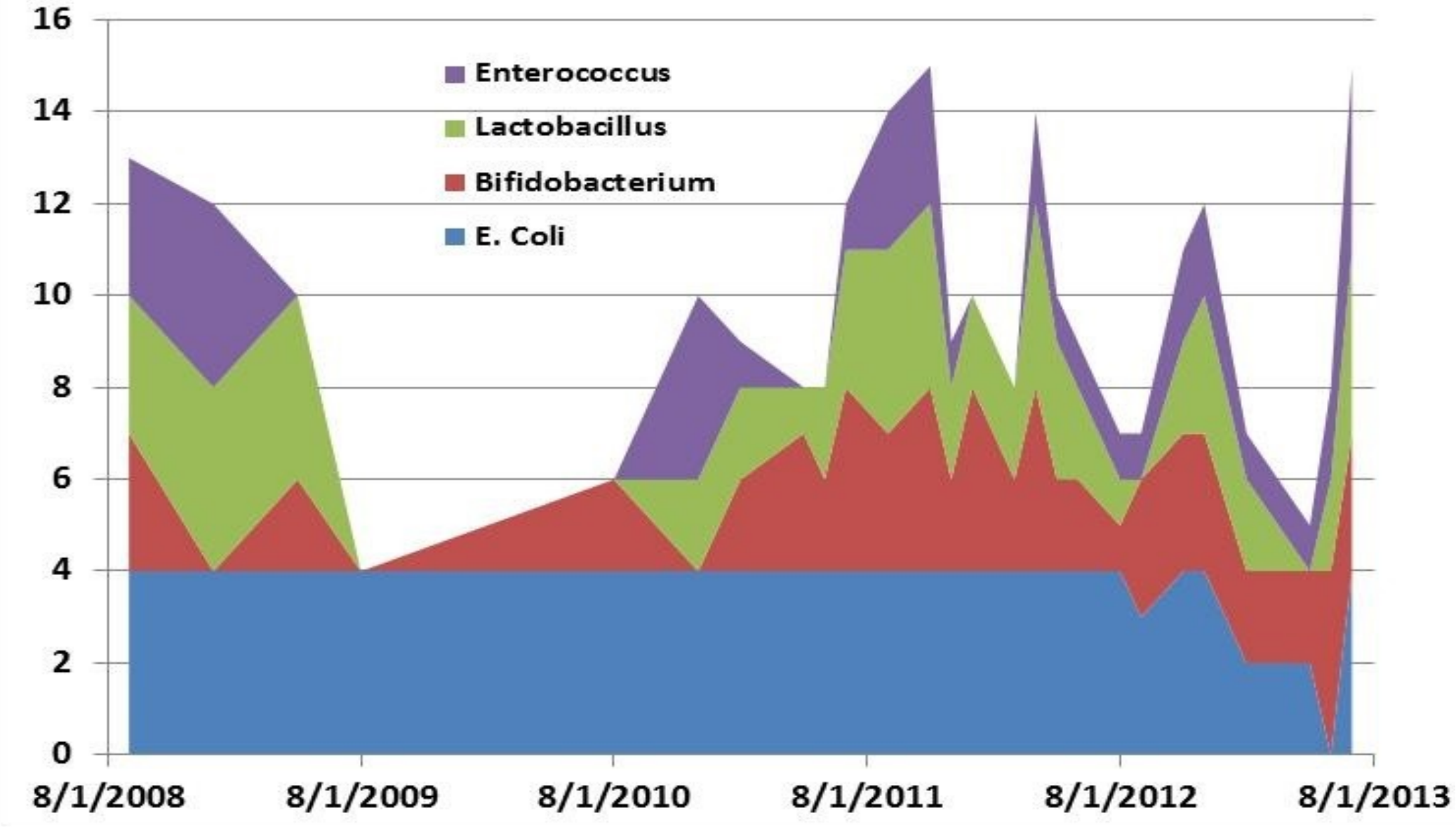
www.personalgenomes.org

Fine Time-Resolution Sampling Reveals Dynamics of Innate/Adaptive Immune System Dysfunction



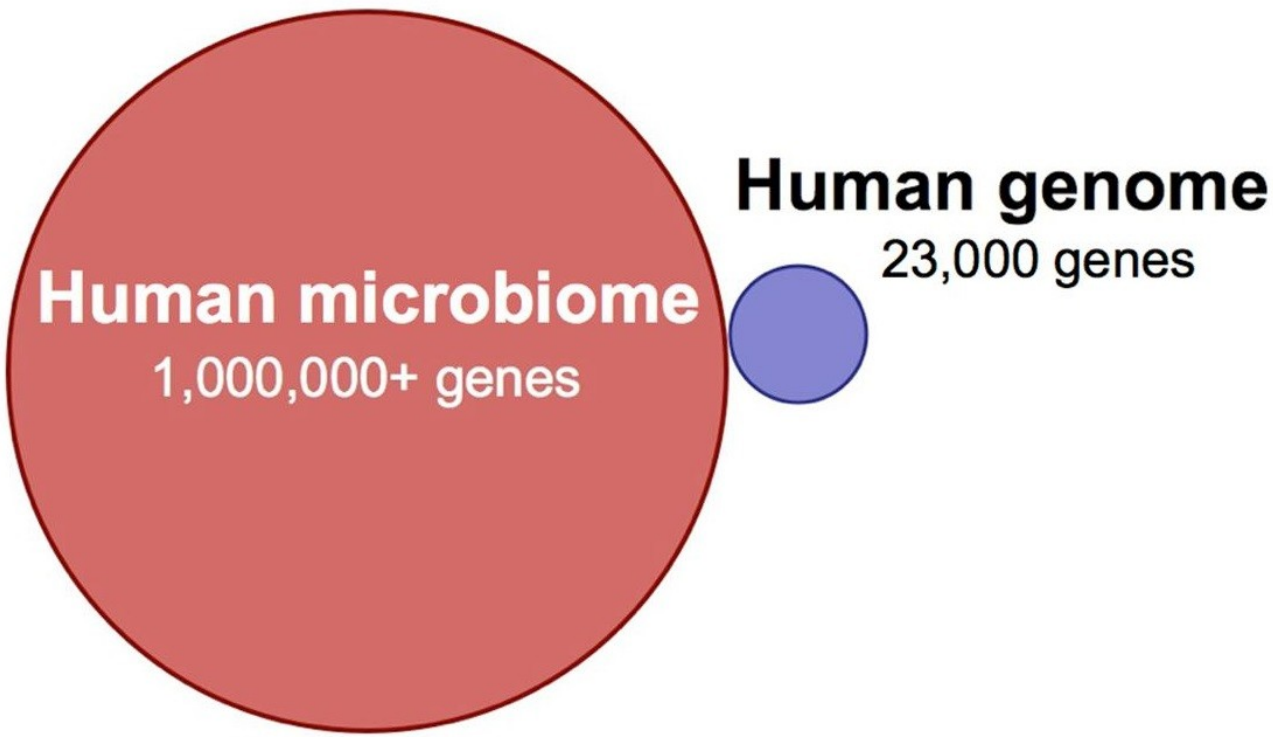


LS Cultured Bacterial Abundance Reveals Dynamic Microbiome Dysfunction



Next: Analyze the Dynamics of My Microbiome Ecology- 85% of the Species Can Not Be Cultured

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



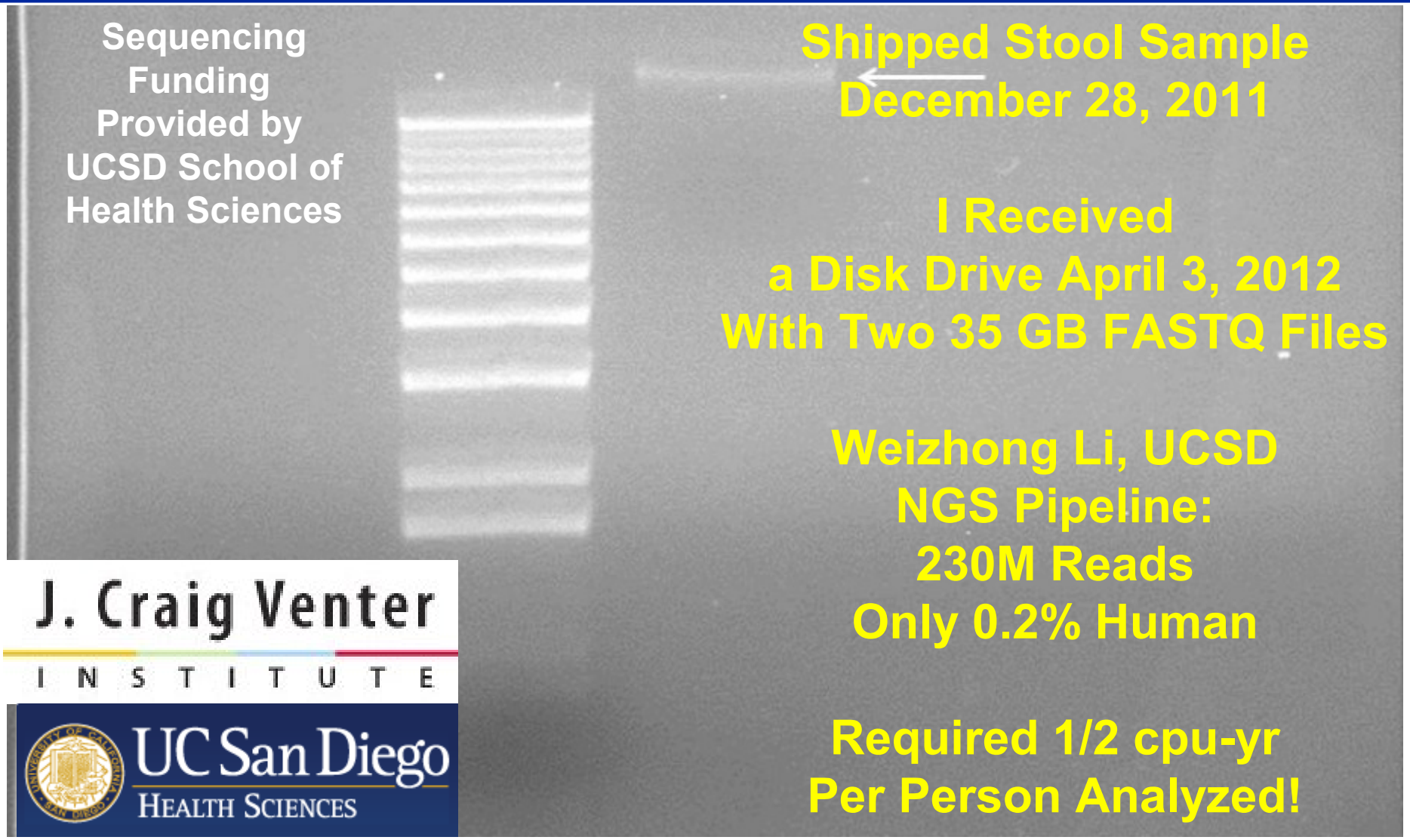
99% of Your DNA Genes Are in Microbe Cells Not Human Cells

Inclusion of the Microbiome Will Radically Change Medicine

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To Map My Gut Microbes, I Sent a Stool Sample to the Venter Institute for Metagenomic Sequencing

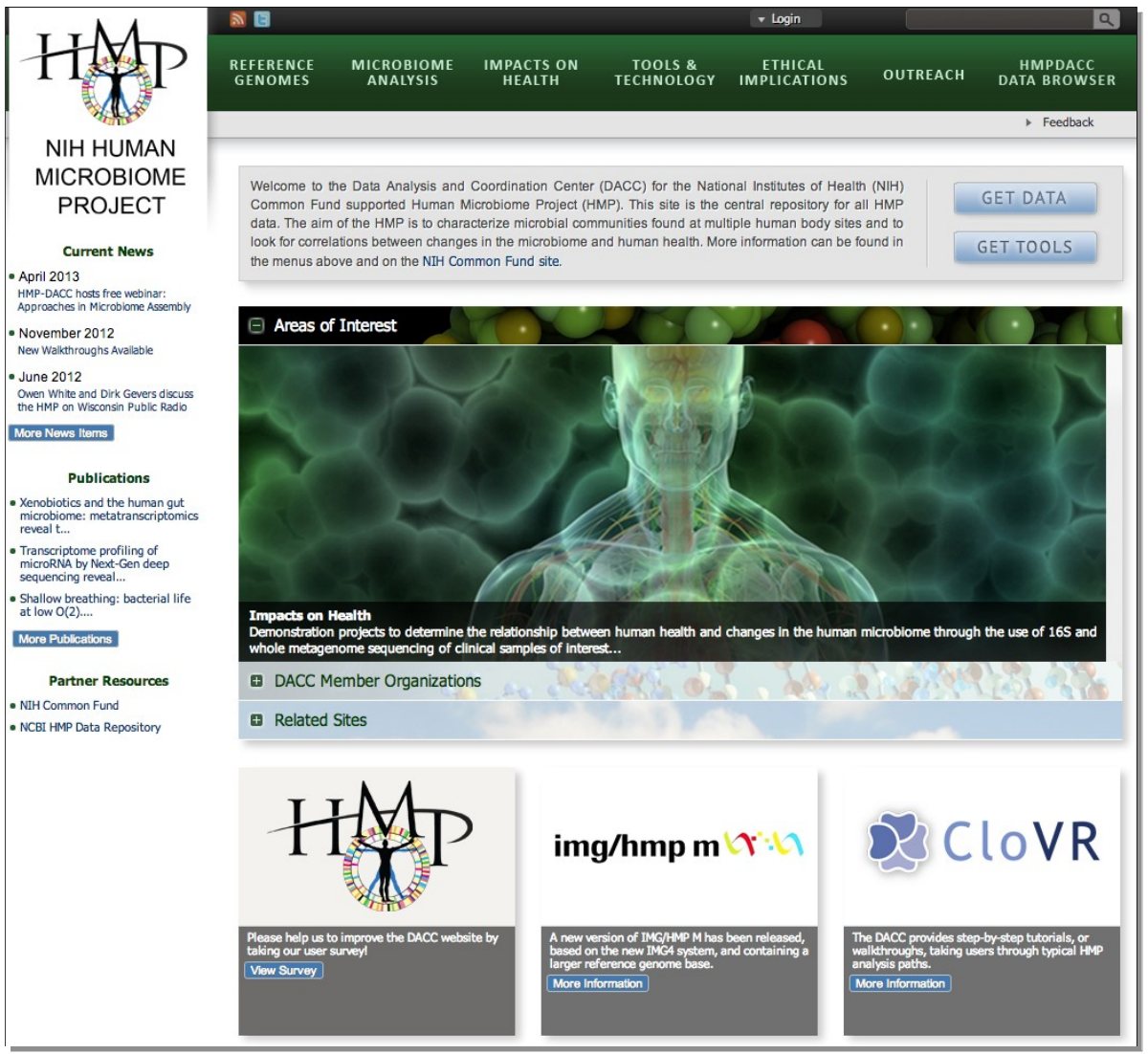


Gel Image of Extract from Smarr Sample-Next is Library Construction

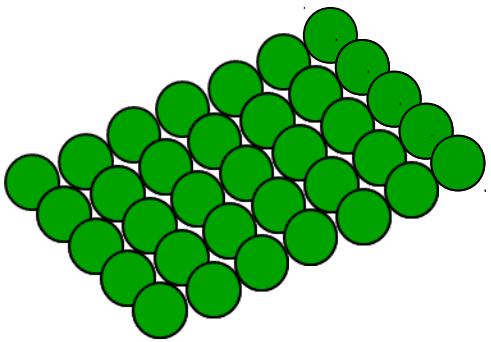
Manny Torralba, Project Lead - Human Genomic Medicine
J Craig Venter Institute

January 25, 2012

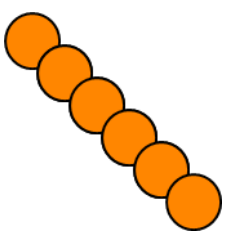
Additional Phenotypes Added from NIH HMP For Comparative Analysis



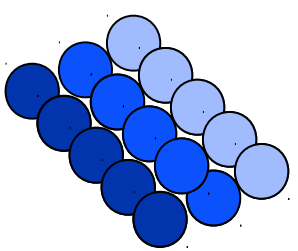
35 "Healthy" Individuals
1 Point in Time



6 Ulcerative Colitis, 1 Point in Time



5 Ileal Crohn's, 3 Points in Time



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Gut Microbiome Metagenomic Datasets

Sample Group	Samples	Average PE reads per sample	Total PE reads	Selected samples	Average filtered high quality PE reads per selected sample
LS	3	151,401,139	454,203,418	3	119,694,209
CD	15	91,477,052	1,372,155,785	15	57,624,823
UC	11	14,330,989	157,640,888	6	2,905,681
HE	154	68,609,164	10,565,811,331	34	39,692,865
Total	183	68,578,204	12,549,811,422	58	44,662,870

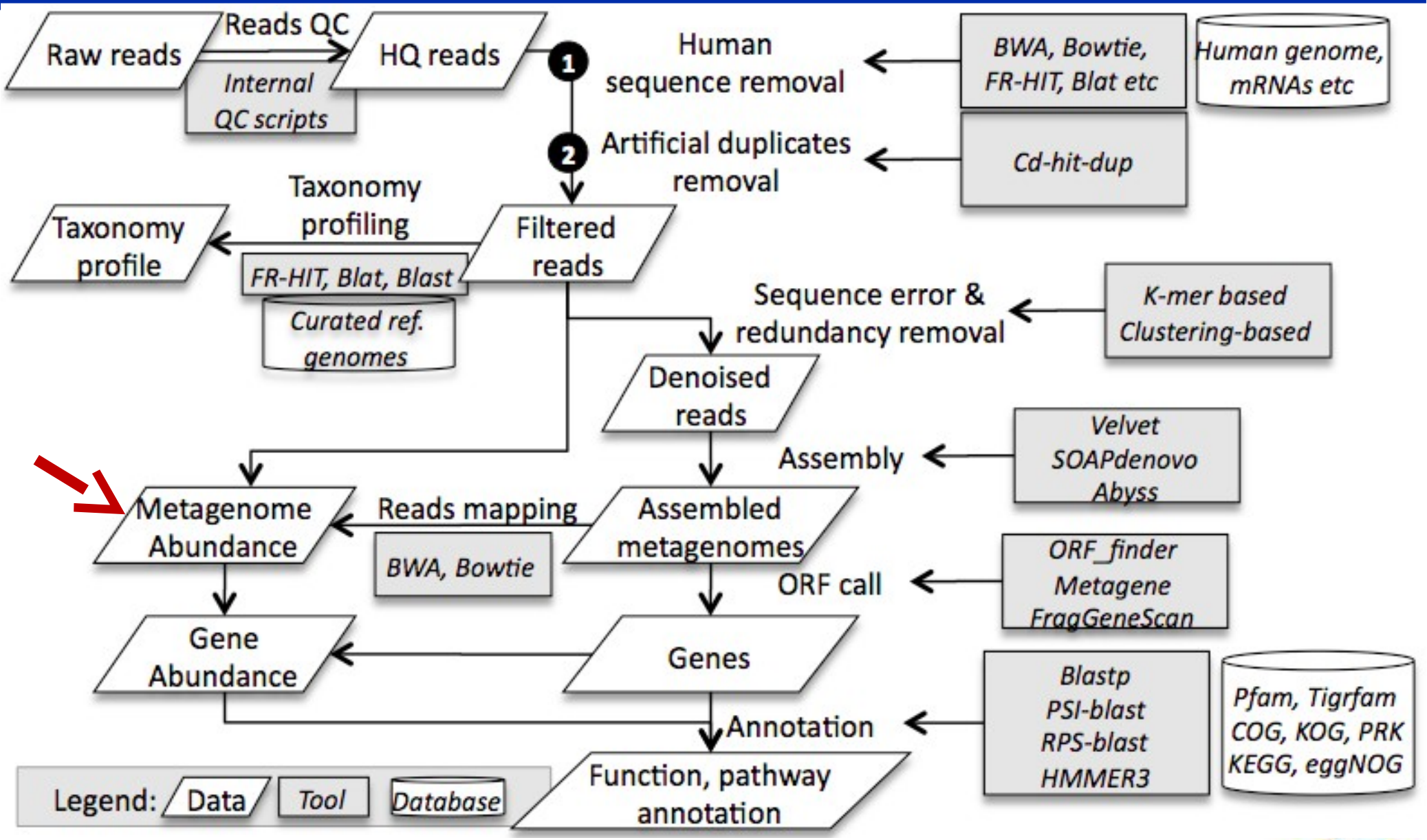
One "Read" = 100 DNA Bases
Total of 1.2 Trillion Bases!

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Source: Weizhong Li, CRBS, UCSD

it²

Computational NextGen Sequencing Pipeline: From "Big Equations" to "Big Data" Computing



National Human Genome Research Institute

HMP

PI: (Weizhong Li, CRBS, UCSD):
NIH R01HG005978 (2010-2013, $1.1M)

CRBS

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We Used SDSC's Gordon Data-Intensive Supercomputer to Analyze a Wide Range of Gut Microbiomes

- ~180,000 Core-Hrs on Gordon
  - KEGG function annotation: 90,000 hrs
  - Mapping: 36,000 hrs
    - Used 16 Cores/Node and up to 50 nodes
  - Duplicates removal: 18,000 hrs
  - Assembly: 18,000 hrs
  - Other: 18,000 hrs
- Gordon RAM Required
  - 64GB RAM for Reference DB
  - 192GB RAM for Assembly
- Gordon Disk Required
  - Ultra-Fast Disk Holds Ref DB for All Nodes
  - 8TB for All Subjects



SDSC

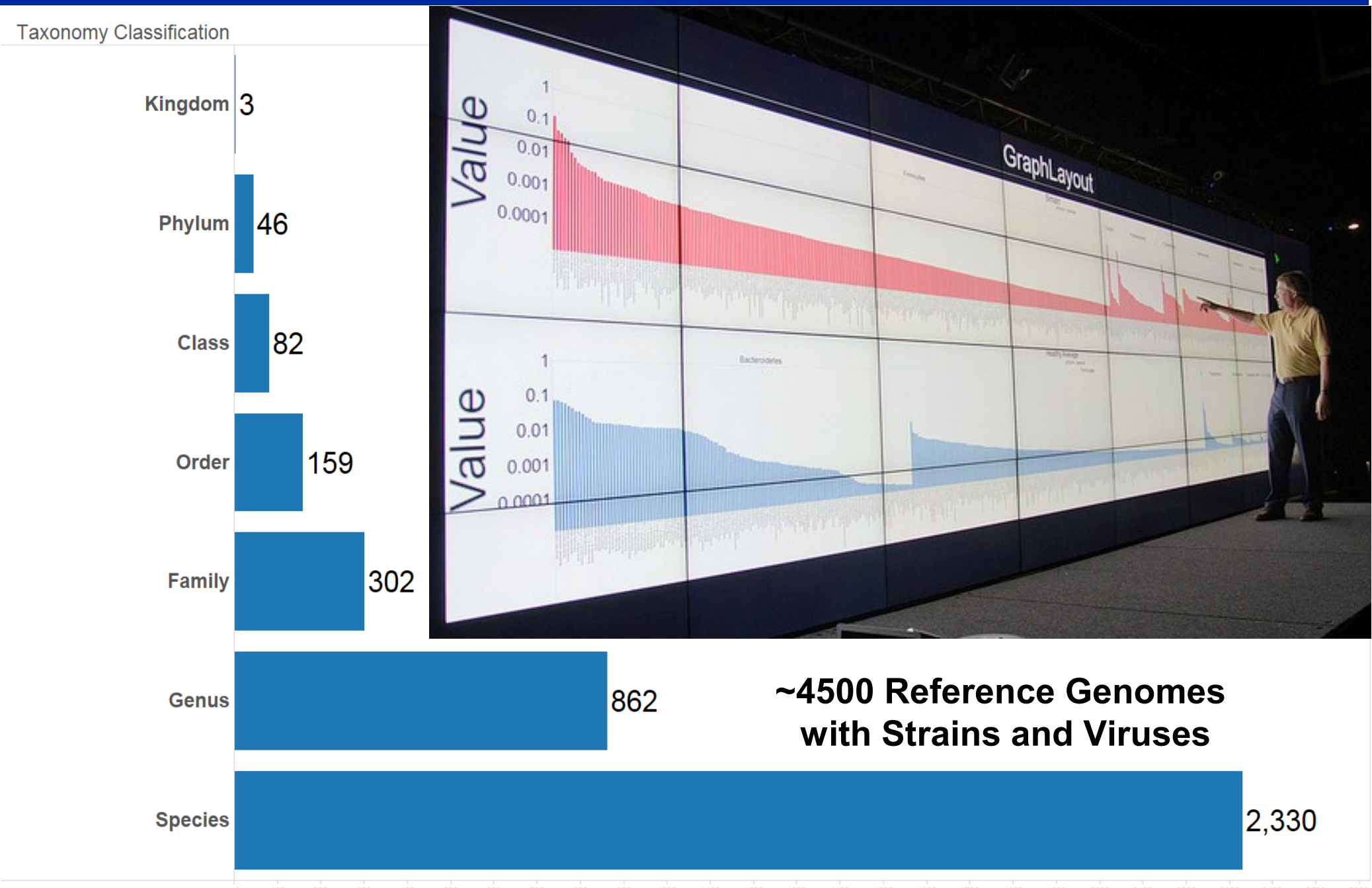
Enabled by
a Grant of Time
on Gordon from SDSC
Director Mike Norman

NSF NIH HMP

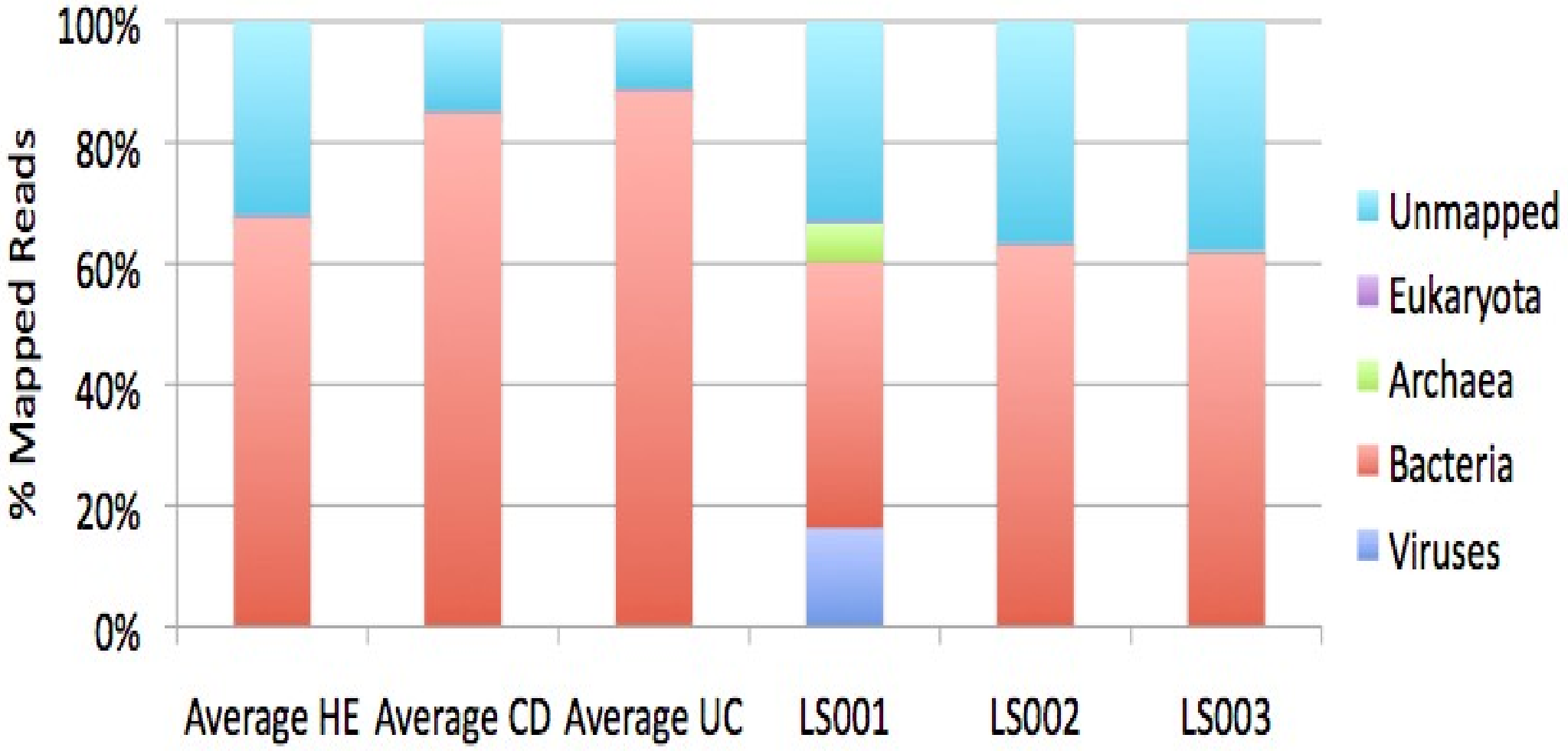
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CRBS it²

We Computationally Align 230M Illumina Short Reads With a Reference Genome Set & Then Visually Analyze



We Still Don't Know a Significant Fraction of the Gut Genomes



Illumina Short Reads Aligned Against >5000 Complete or Draft Genomes

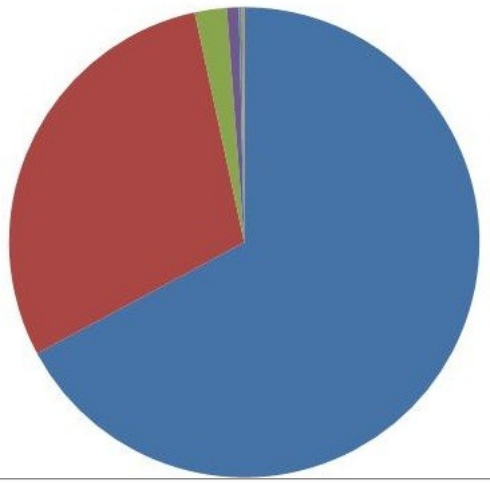
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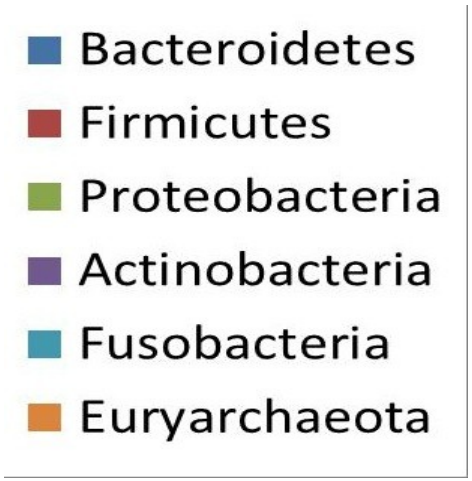
Source: Weizhong Li, CRBS, UCSD

We Find Major Shifts in Microbial Ecology Between Healthy and Two Forms of IBD

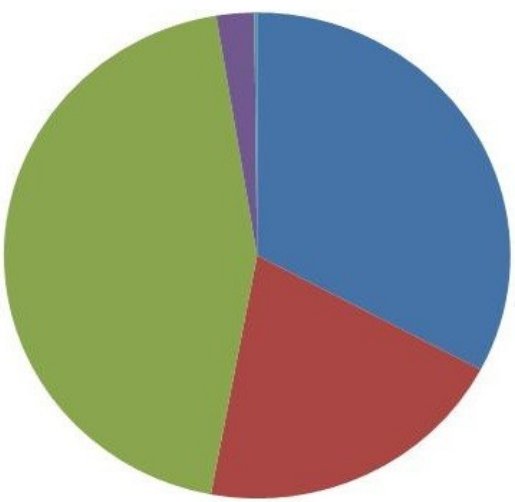
Microbiome "Dysbiosis" or "Mass Extinction"?

Ave. Healthy

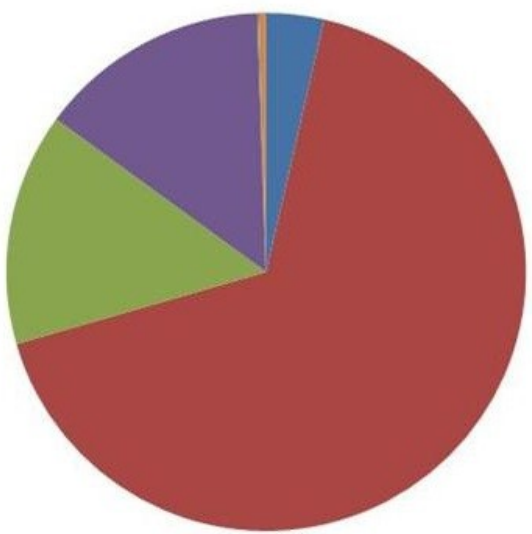




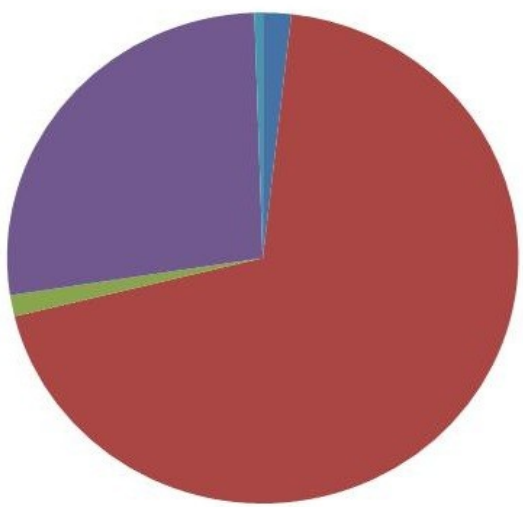
Ave. Ulcerative Colitis



LS Apr 2012



Ave. Crohn's



Explosion of Proteobacteria

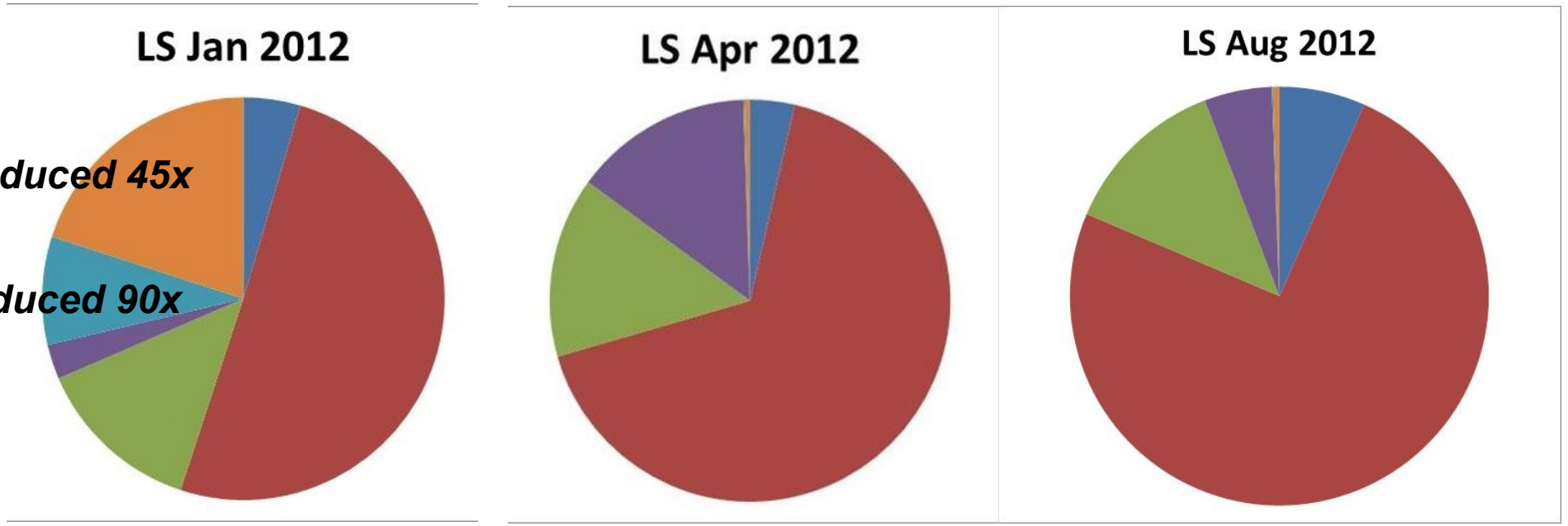
On the IBD Spectrum

Collapse of Bacteroidetes

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Major Changes in LS Microbiome Before and After 1 Month Antibiotic & 2 Month Prednisone Therapy



Therapy Greatly Reduced Two Phyla, But Massive Reduction in Bacteroidetes And Large % Proteobacteria Remain

Small Changes With No Therapy

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

How Does One Get Back to a "Healthy" Gut Microbiome?

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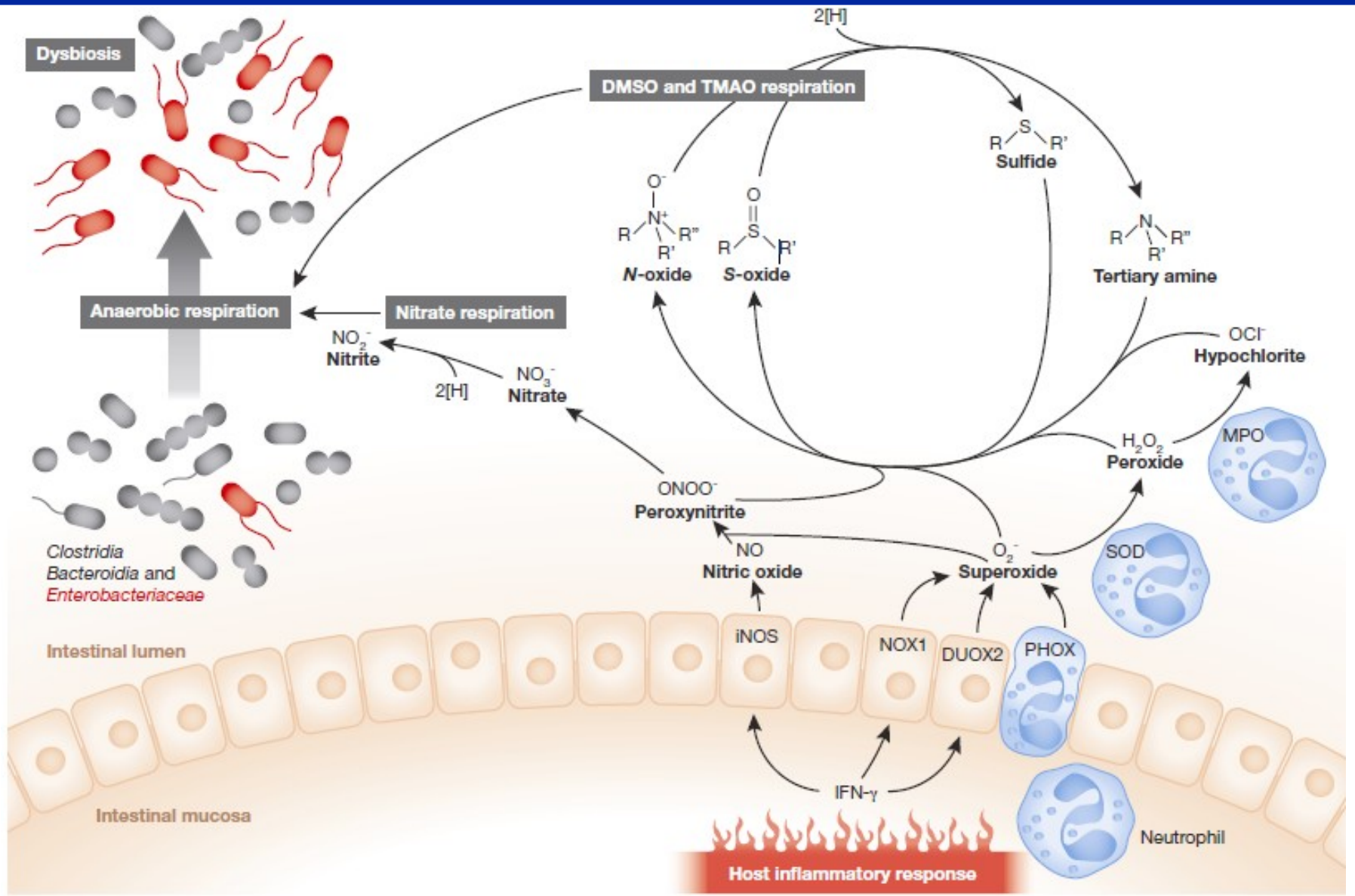
What Can We Learn About Early Disease Onset As We Sequence the Microbiome More Deeply?

Does the Gut Microbiome Intermediate Between Inflammation & the Development of Colorectal Cancer?

- **Colon Cancer is the most common cancer among Inflammatory Bowel Disease (IBD) patients**
- **IBD is one of the three leading high-risk factors for Colon Cancer**

The root cause of CRC is unclear,
but inflammation is a well-recognized risk factor
(Wu et al. 2009; McLean et al. 2011)

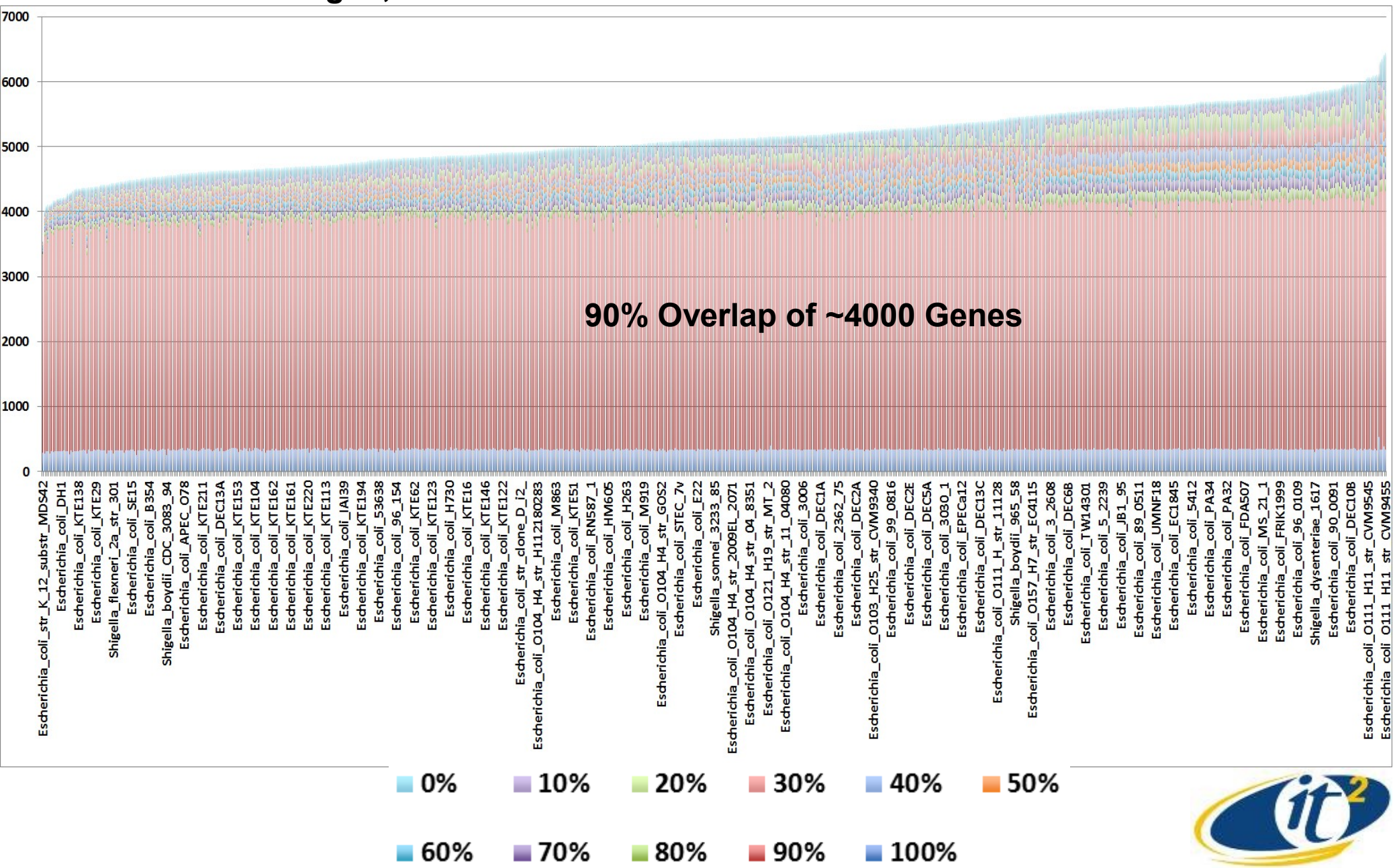
Inflammation Enables Anaerobic Respiration Which Leads to Phylum-Level Shifts in the Gut Microbiome



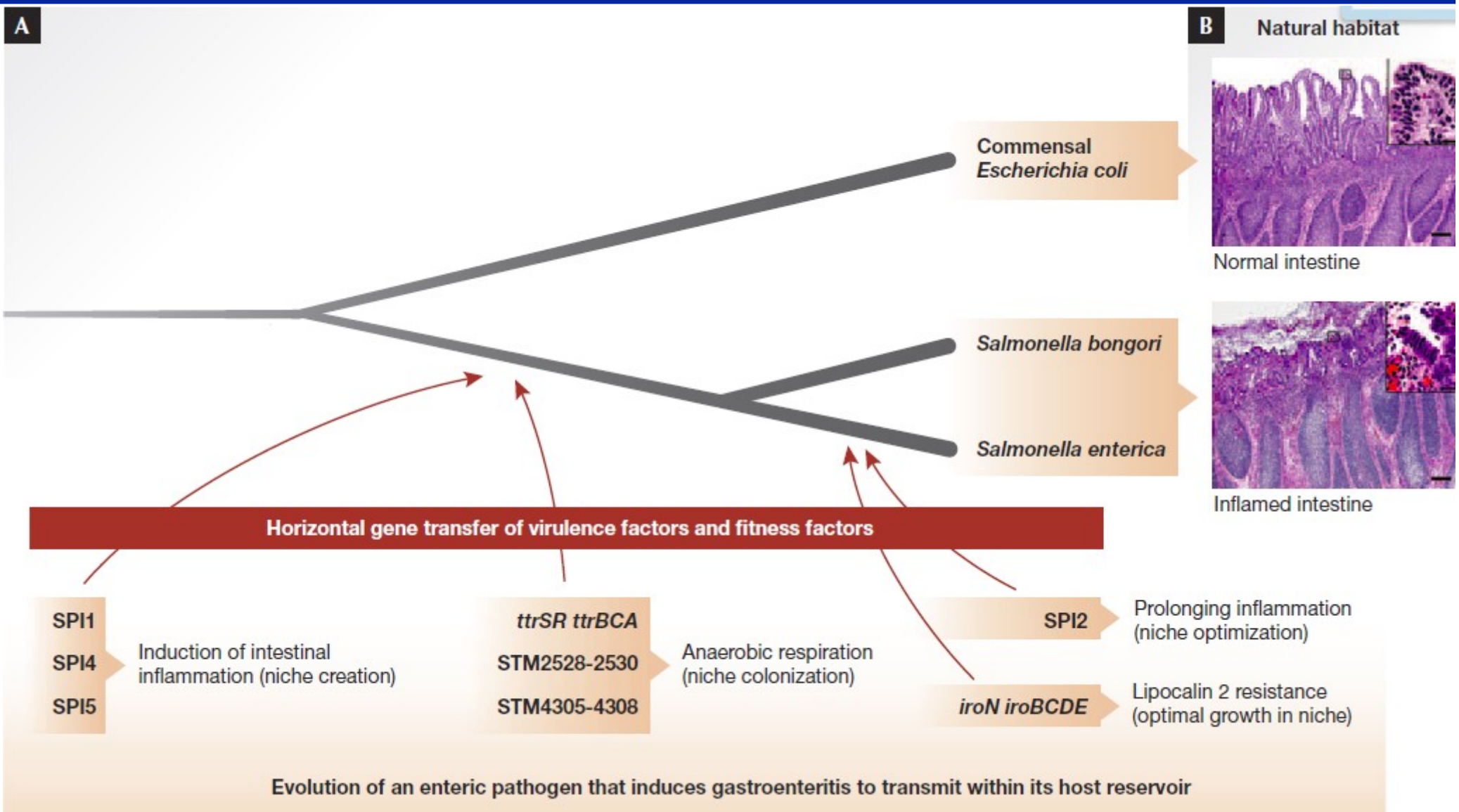
Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler, EMBO reports VOL 14, p. 319-327 (2013)

We Computed the Genes Which Define 761 E. coli Strains

Source: Weizhong Li, UCSD



Horizontal Gene Transfer Provides Pathogenic Strains: Additional Fitness Factors Leading to Growth Advantage

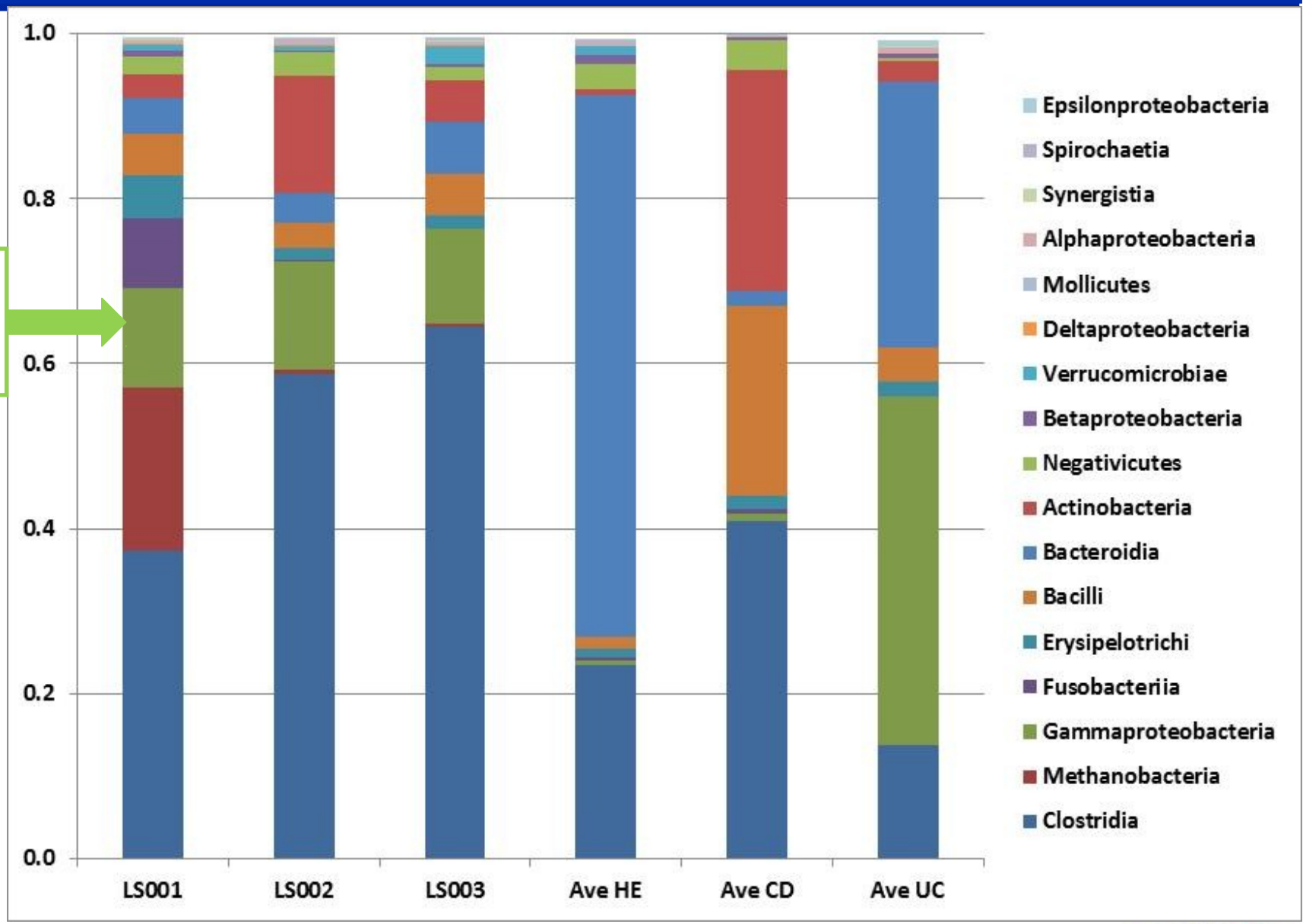


Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler, EMBO reports VOL 14, p. 319-327 (2013)

Image from Zhang S., et al. Infect Immun 71: 1–12 (2003)

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

Class Gamma-proteobacteria

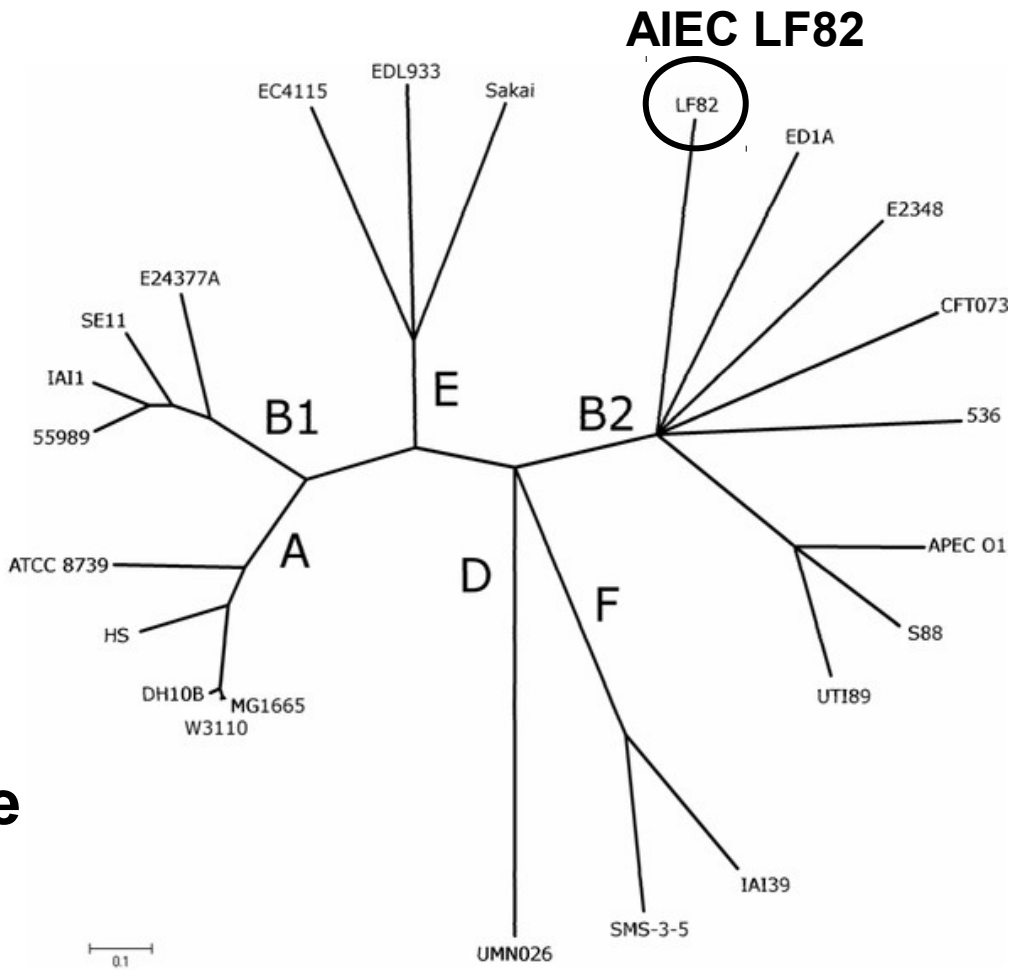


Does Intestinal Inflammation Select for Pathogenic Strains That Can Induce Further Damage?

"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 AIEC— thereby exacerbating inflammation and interfering with its resolution."

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)

*Family Containing E. coli

Intestinal Inflammation Targets Cancer-Inducing Activity of the Microbiota

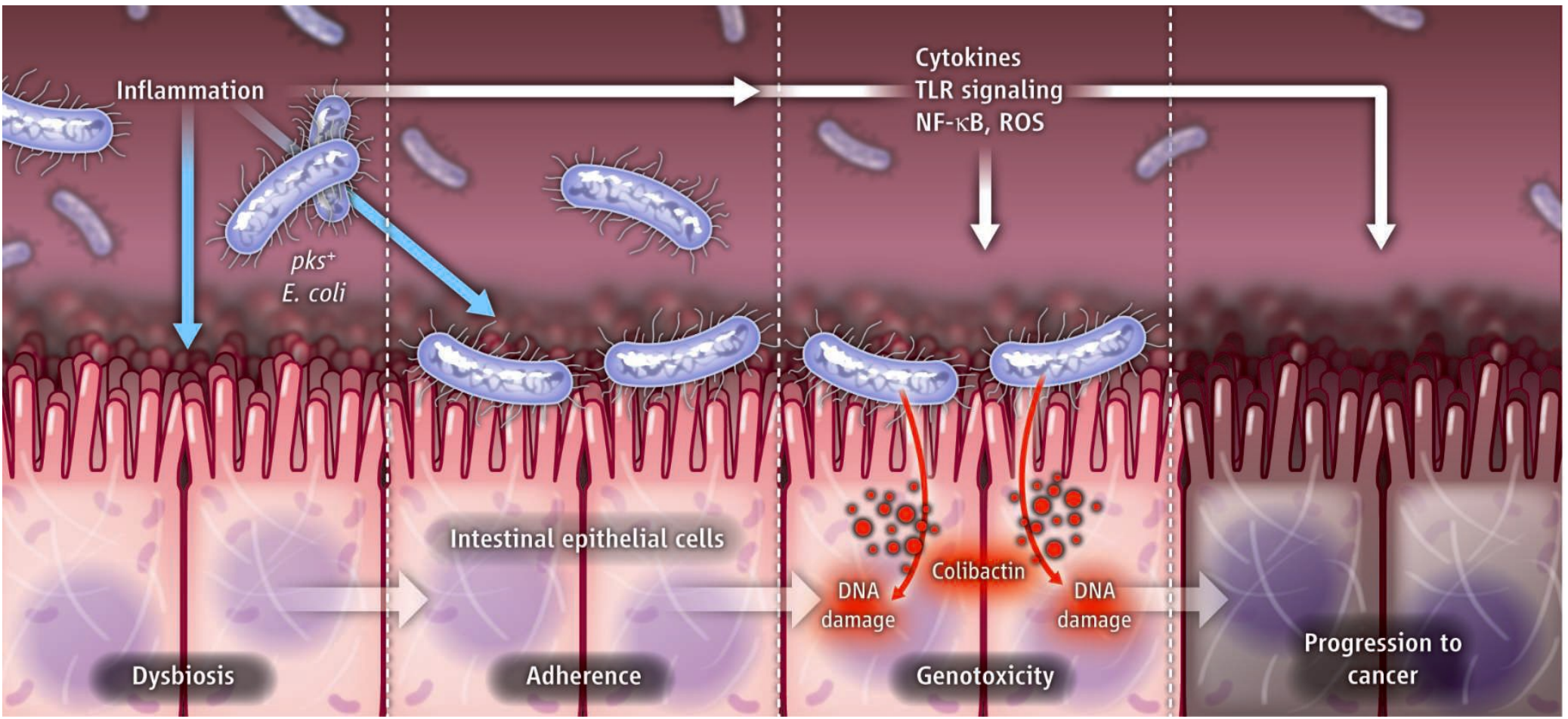


"Mucosa-associated pks+ E. coli [e.g. NC101] were found in a significantly high percentage of inflammatory bowel disease and CRC patients.

This suggests that in mice, colitis can promote tumorigenesis by altering microbial composition and inducing the expansion of microorganisms with genotoxic capabilities."

Janelle C. Arthur *et al.*
Science **338**, 120 (2012)

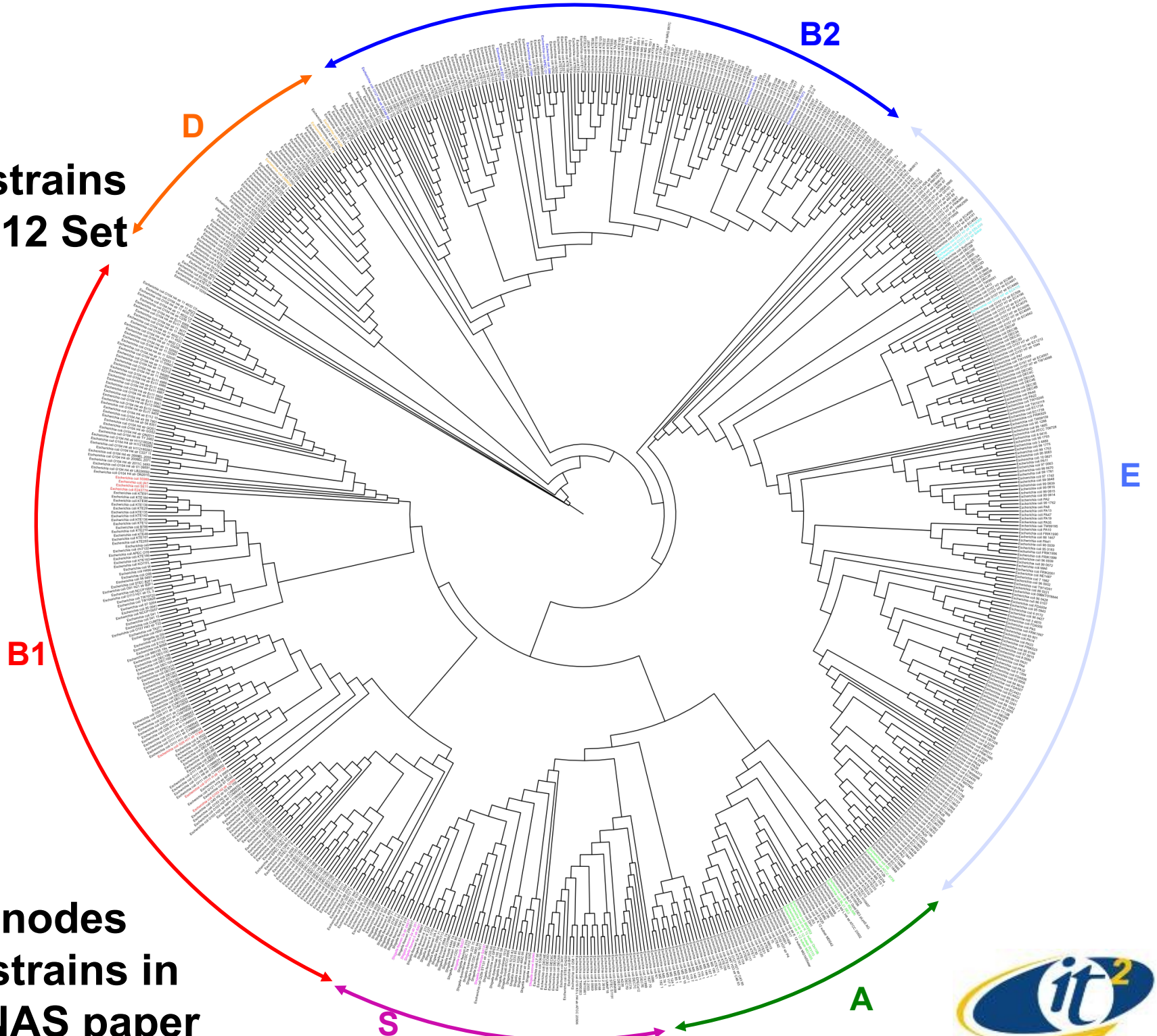
Chronic Inflammation Can Accumulate Cancer-Causing Bacteria in the Human Gut



Science
AAAS

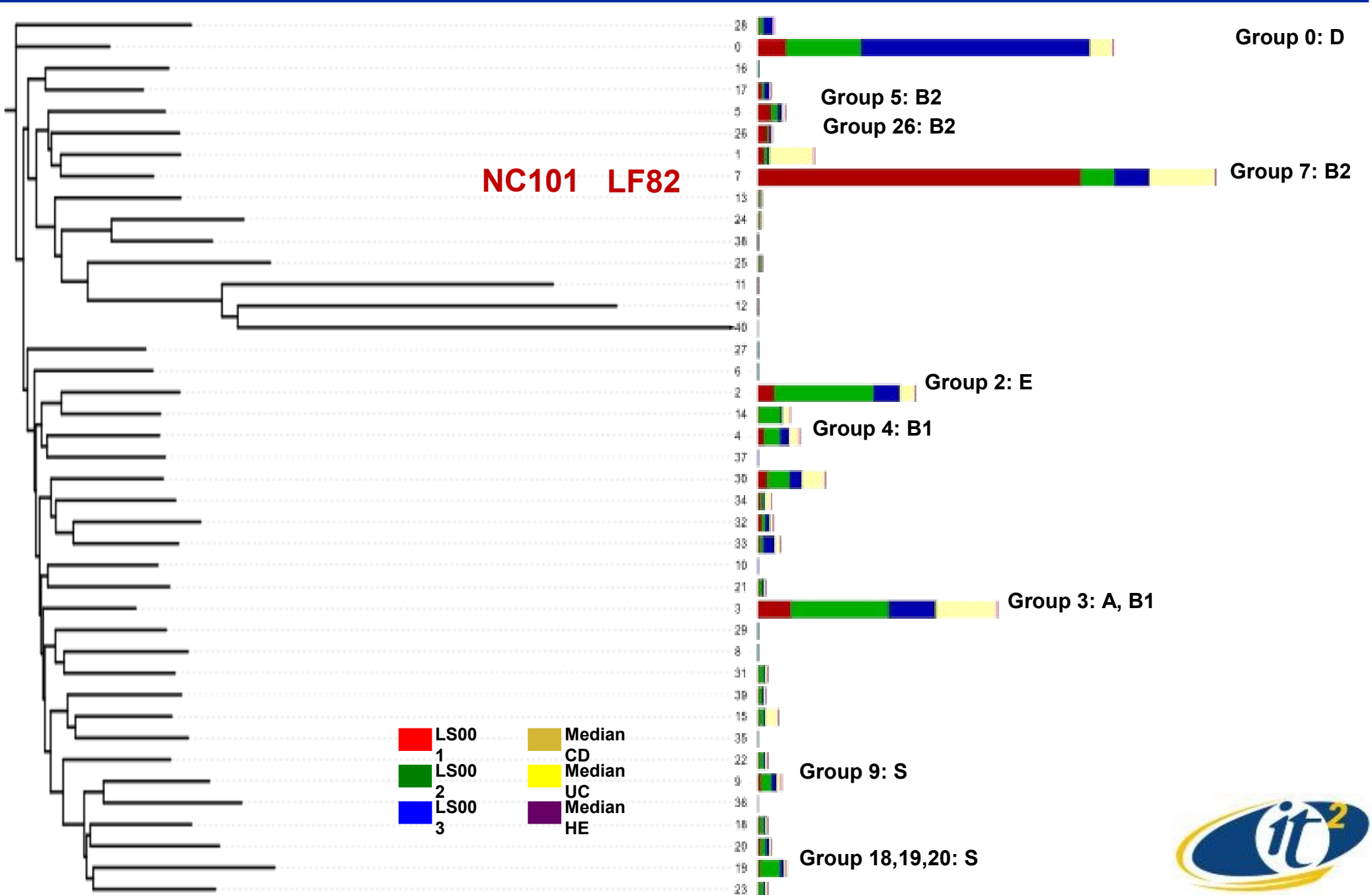
Bacteria Deliver a Genotoxic Hit
Robert F. Schwabe and Timothy C. Wang
Science **338**, 52 (2012);
DOI: 10.1126/science.1229905

761 Ecoli strains
=6x our 2012 Set

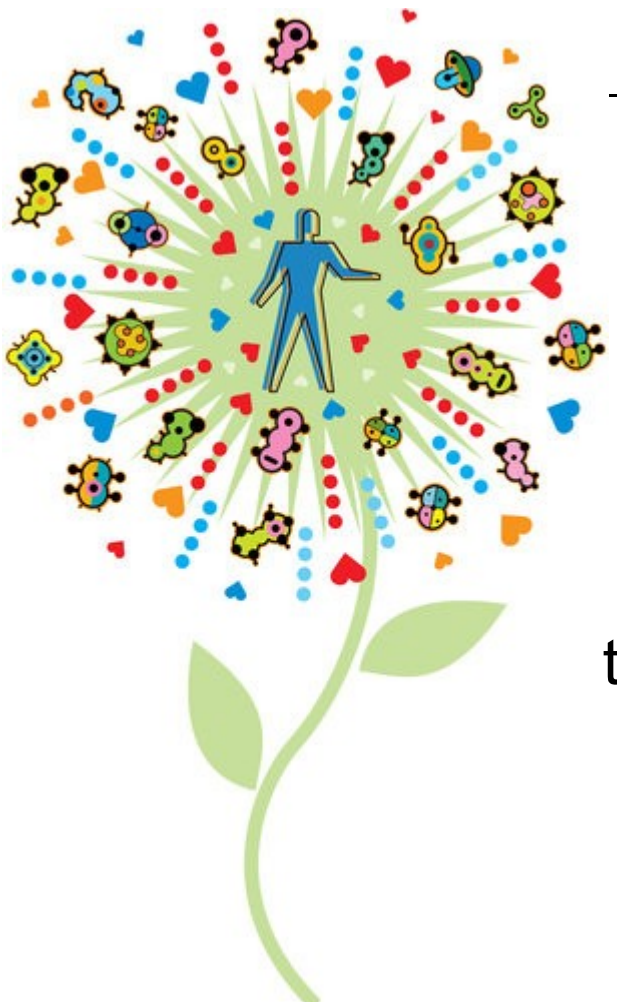


Colored nodes
are the 38 strains in
the 2011 PNAS paper

We Divided the 761 E. coli Strains into 40 Groups, Each of Which Had 80% Identical Genes



From War to Gardening: New Therapeutical Tools for Managing the Microbiome



The New York Times

Science

Tending the Body's Microbial Garden

By CARL ZIMMER
Published: June 18, 2012

"I would like to lose the language of warfare," said Julie Segre, a senior investigator at the National Human Genome Research Institute. "It does a disservice to all the bacteria that have co-evolved with us and are maintaining the health of our bodies."

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*†

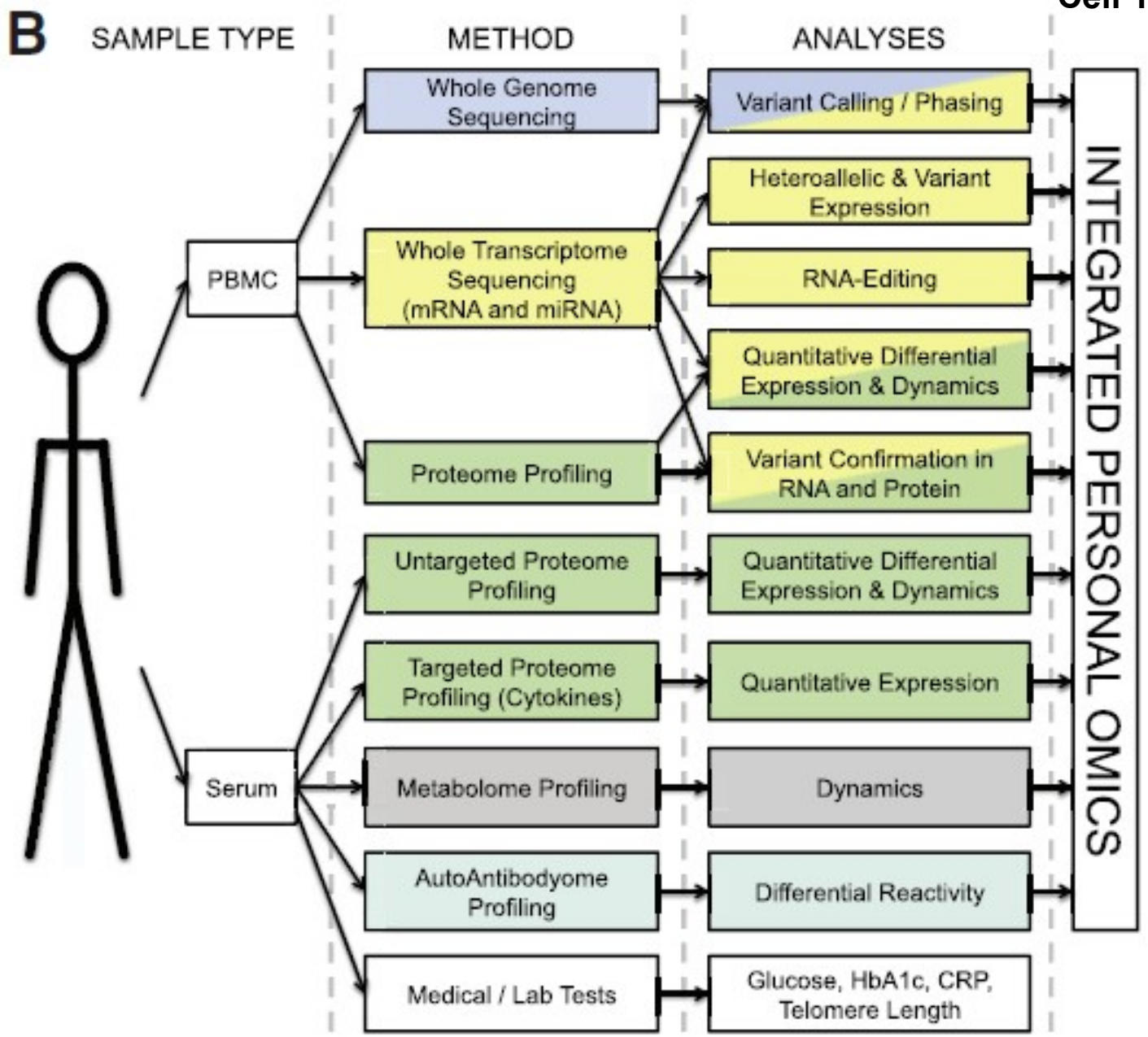
**Virginia Bioinformatics Institute*

†Department of Computer Science

Virginia Tech, Blacksburg VA 24061

Integrative Personal Omics Profiling Using 100x My Quantifying Biomarkers

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**

The Data-Enabled Life Sciences Alliance (DELSA Global)

DELSA Mission

Accelerate the impact of data-enabled life sciences research on the pressing needs of our global society.

DELSA Vision

Through interdisciplinary research and transdisciplinary engagement, the life science community will move from "one scientist—one project" to collective innovation in data-enabled science.



Website: www.delsaglobal.org
Twitter: @DELSAglobal
Email: info@delsaglobal.org

Source: Eugene Kolker

The DELSA Quantified Human Initiative

- **The Quantified Human Initiative** is an effort to combine our natural curiosity about self with new research paradigms. **Rich datasets of two individuals, Drs. Smarr and Snyder**, serve as 21st century personal data prototypes.

- **A true picture** requires multi-disciplinary analysis (genomic, proteomic, metabolomic, microbiomic, phenotypic, and clinical data).

- **The DELSA community** will use these data to build coherent datasets for studying the "normal condition" and work toward an understanding of genotype-to-phenotype, biological variability, environment as an influence, and clinical outcomes.

- **The Quantified Human Initiative** is working to enable each individual to make more informed and effective decisions in their everyday lives.

Source: Eugene Kolker

DELSA

Data e-Platform to Leverage Multilevel Personal Health Information (DELPHI)

- Integrate heterogeneous data into a "single" uniform database
- Approach this integration within a geospatial context
- Implement a machine learning analytics layer on top
- Open the data and analytics up to third party developers of apps and services

Enable Personalized Population Health Through the Creation of a "Whole Health Information" Platform that Takes into Account Everything from the Genome to the Exposome

UCSDCSE

UCSD

QUALCOMM INSTITUTE

QUALCOMM

SAN DIEGO BEACON eHEALTH COMMUNITY

COUNTY OF SAN DIEGO HHSA HEALTH AND HUMAN SERVICES AGENCY

CW PHS CENTER FOR WIRELESS & POPULATION HEALTH SYSTEMS

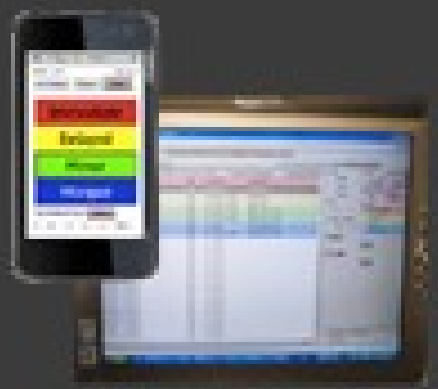
SANDAG

CONNECT

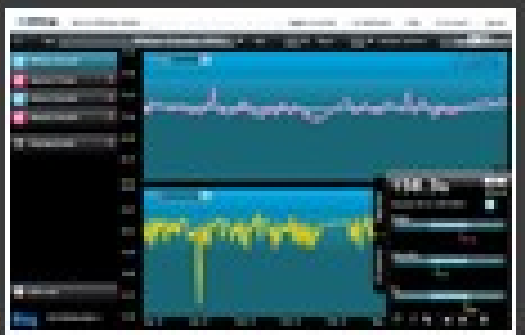
it²

Source: Kevin Patrick, MD UCSD

DELPHI Integrates Multiple Sources of Health-Relevant Data



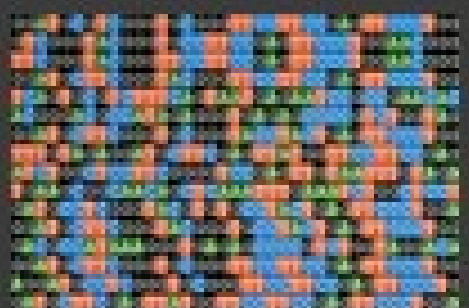
Medical Records



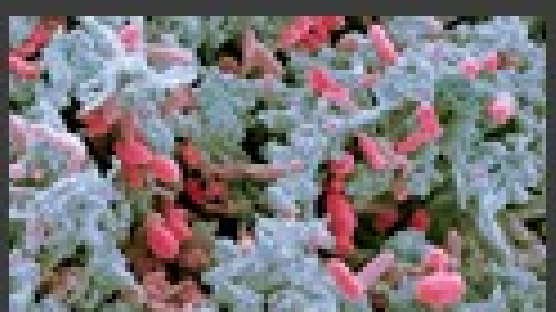
Personal Health Data
(weigh-ins, run info, ...)



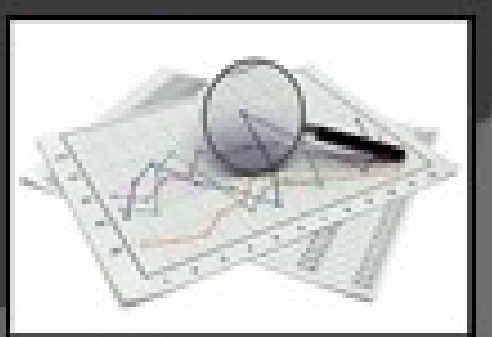
Environmental Data
(e.g. pollution, noise, greenspace)



Genomic Data



Microbiome Data



Public Health Data

Source: Kevin Patrick, MD UCSD

Gaining Insight from Patient and Person-Generated Real World/Real Time Data



Explore whether individual and population health can be improved by promoting research on the patient and person-generated data that are increasingly captured via consumer electronic devices, mobile apps and the telecommunications industry

Kevin Patrick, Jerry Sheehan, Matthew Bietz, Judith Gregory, Michael Claffey, Scout Calvert, Lori Melichar, Steve Downs

6-month Planning Grant (Commenced 5/1/13)
Calit2.net/hdexplore

Personal Data for the Public Good

Source: Kevin Patrick, MD UCSD

Robert Wood Johnson Foundation