“Reading Out the State of the Body and How it Changes Under Therapy”

Guest Lecture

Pharmacy Informatics 2013

University of California San Diego

June 7, 2013

Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

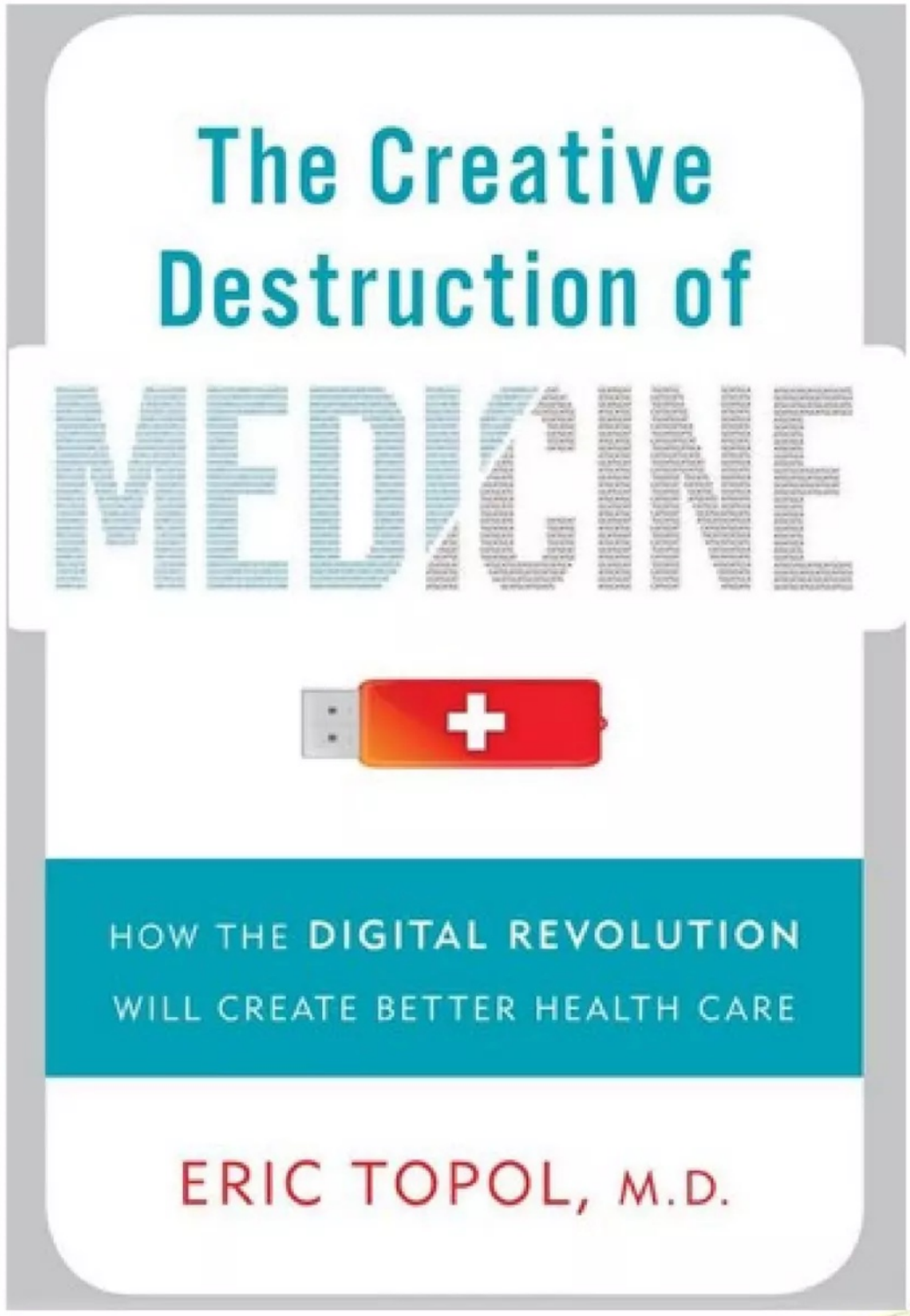
Dept. of Computer Science and Engineering

Jacobs School of Engineering, UCSD

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

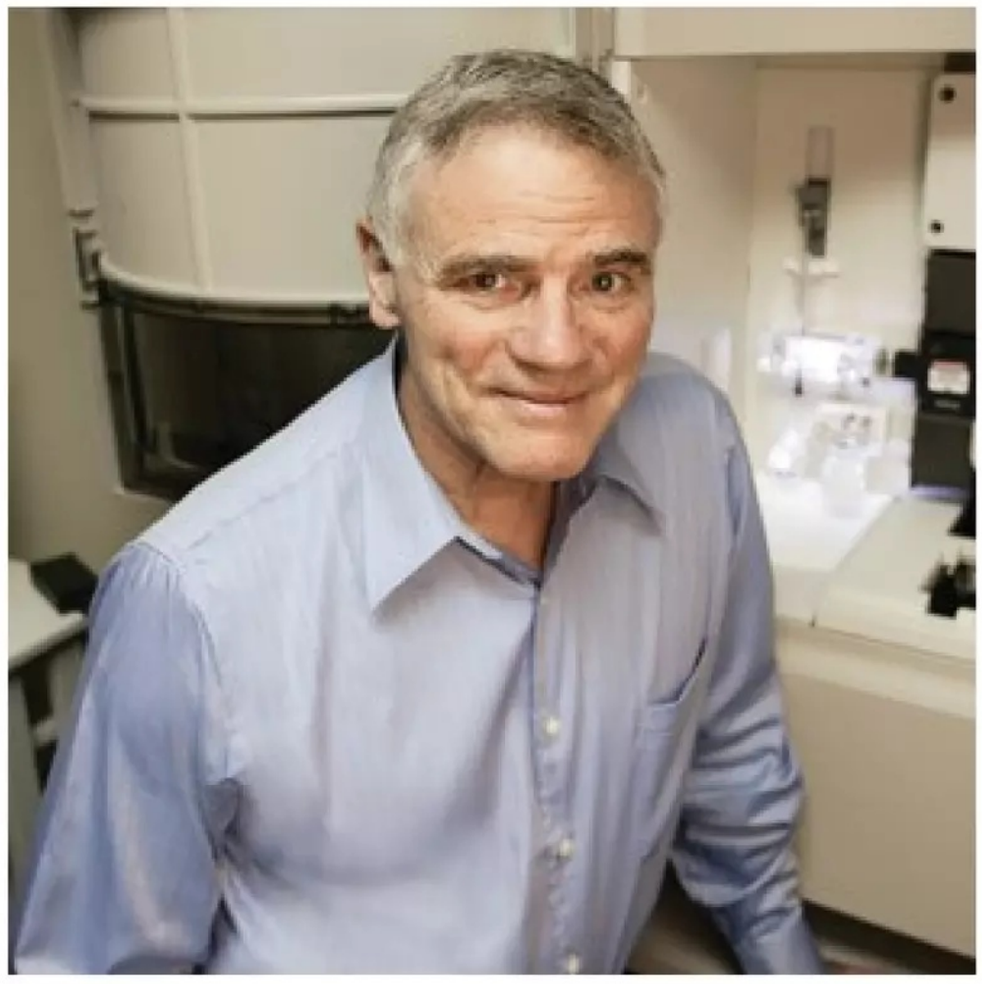
Newsweek

I am Lee 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

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



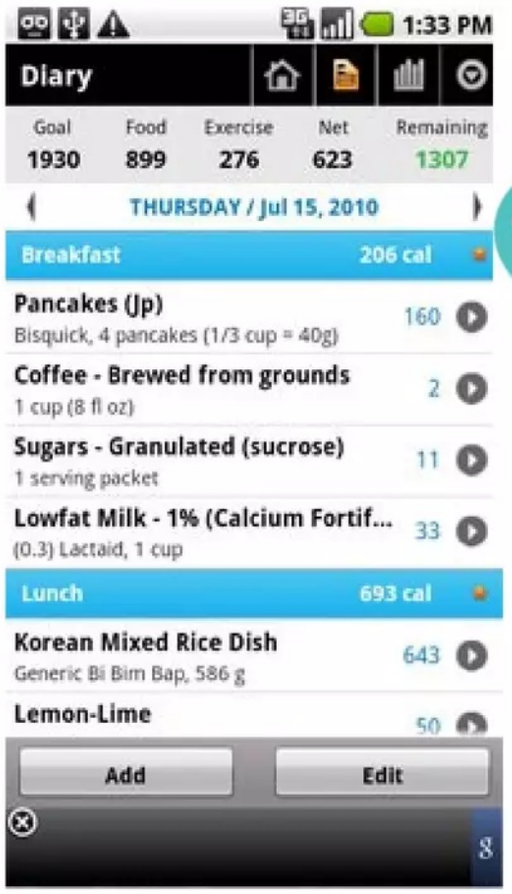
Age 61



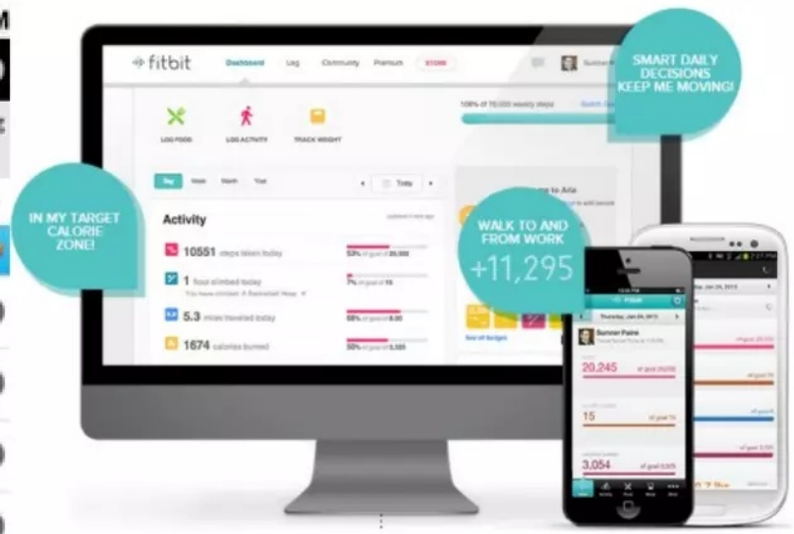
I Reversed My Body's Decline By Quantifying and Altering Nutrition and Exercise

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



Zeo-Sleep



Azumio-Heart Rate

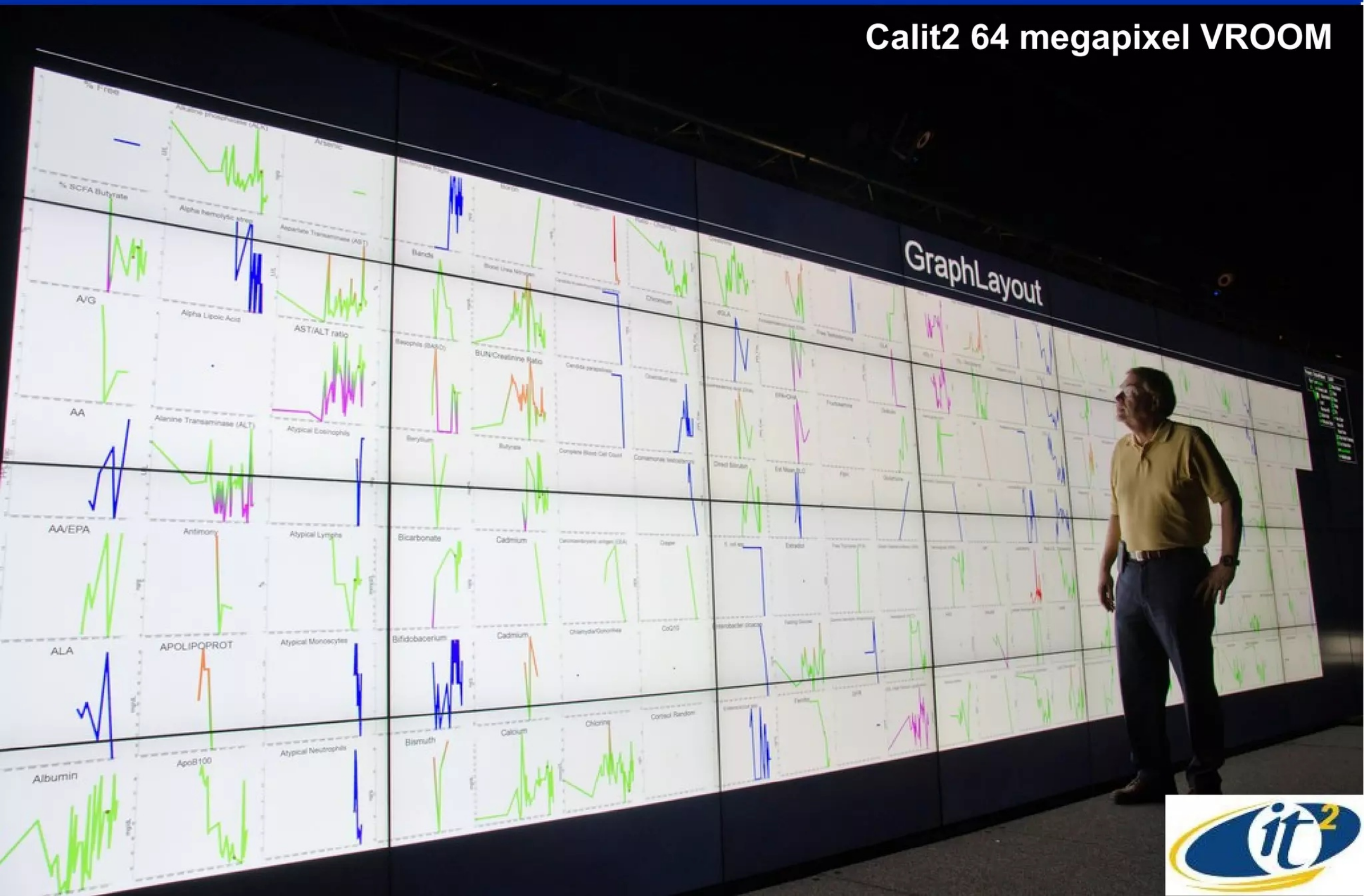
From Measuring Macro-Variables to Measuring Your Internal Variables



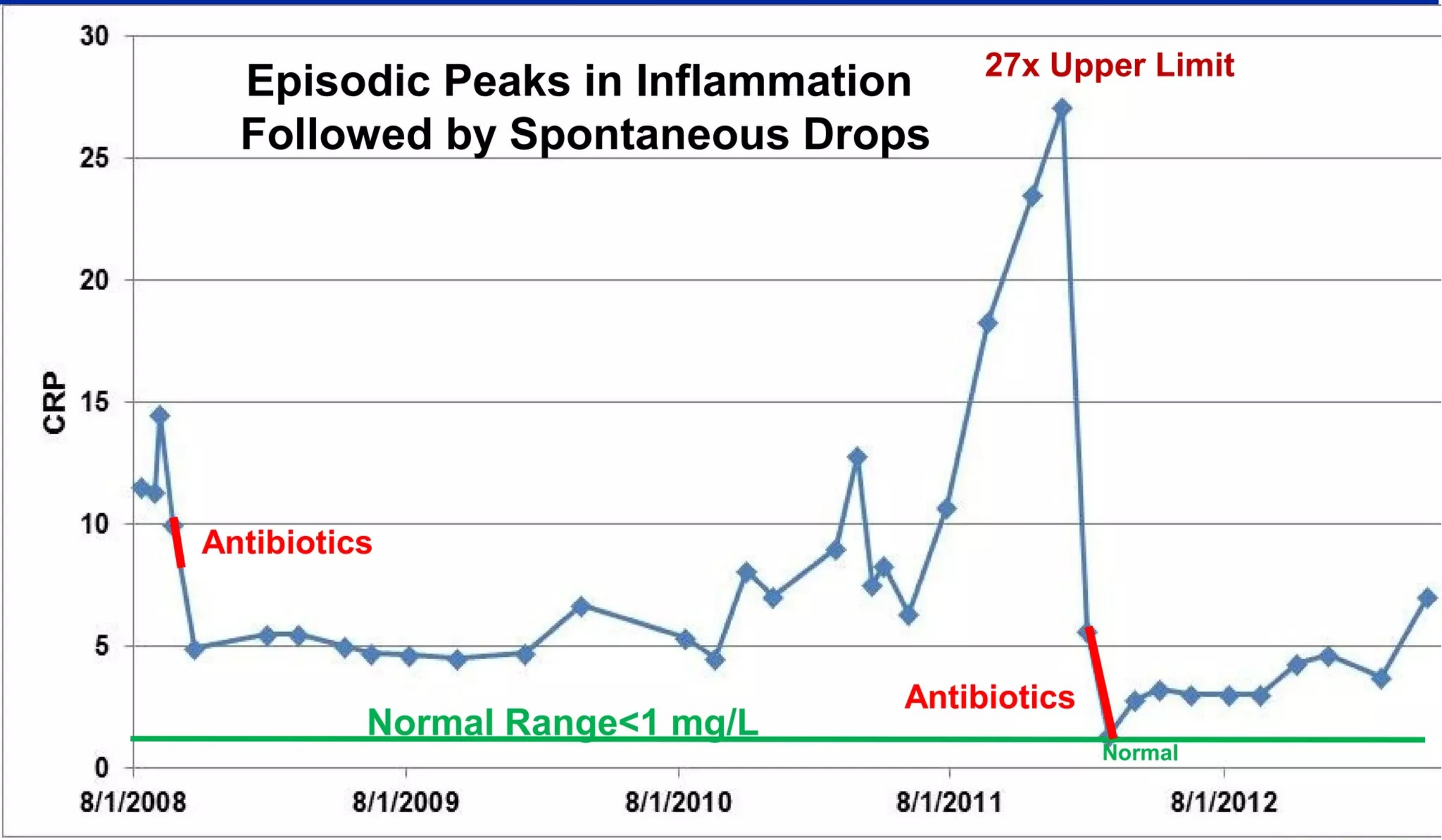
www.technologyreview.com/biomedicine/39636

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

Calit2 64 megapixel VROOM

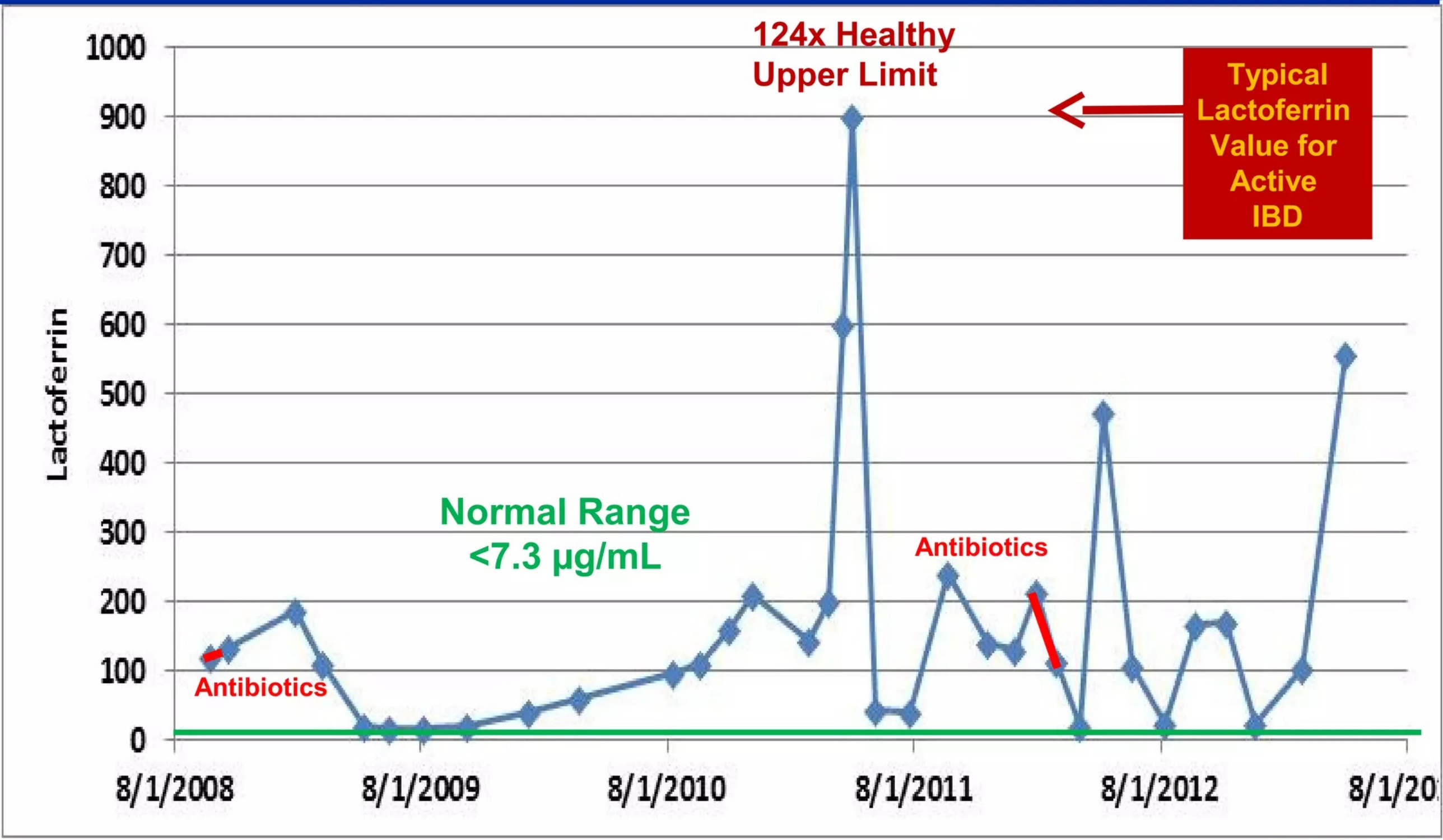


Only One of My Blood Measurements Was Far Out of Range--Indicating Chronic Inflammation



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

Stool Samples Revealed Episodic Autoimmune Response

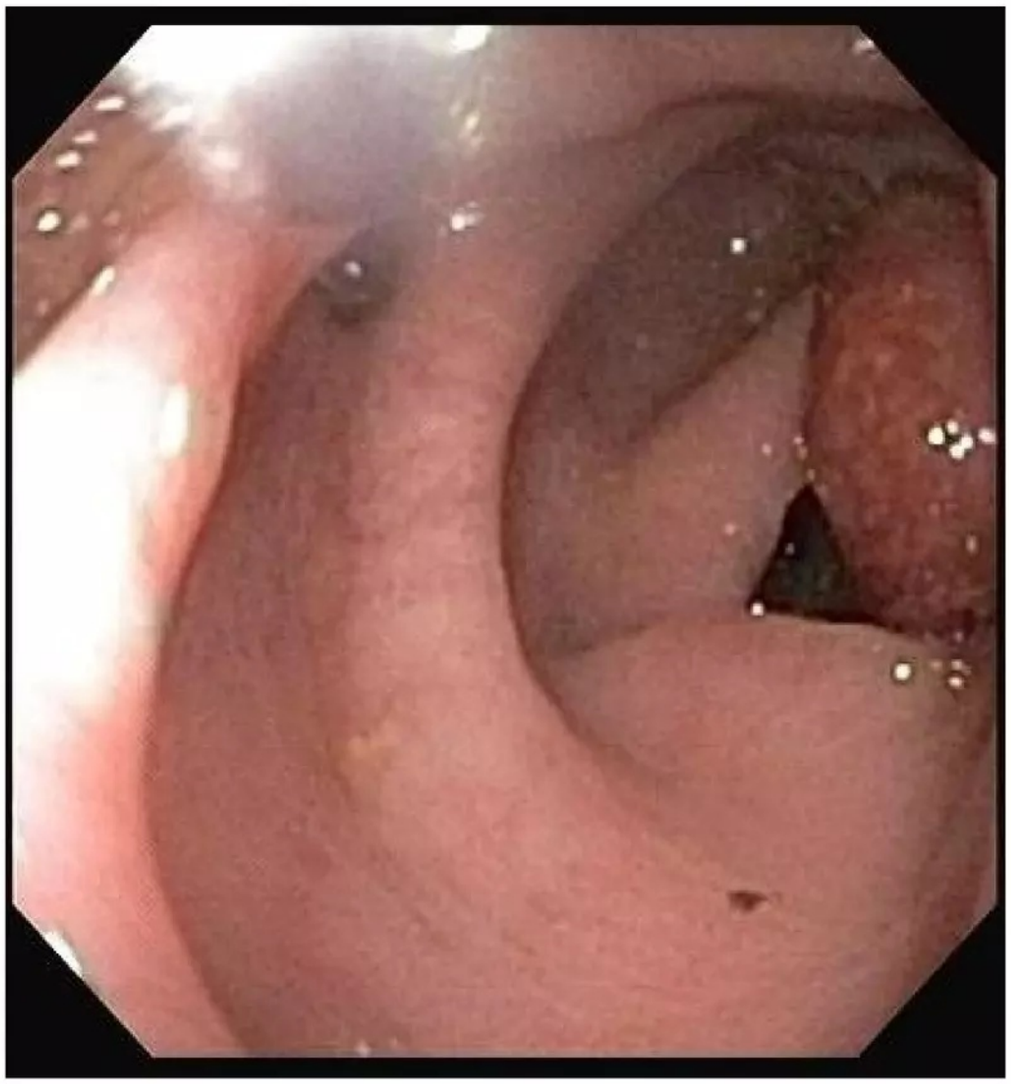


Lactoferrin is an Antibacteria Glycoprotein Shed from Attacking WBC Neutrophils

Colonoscopy Images Show Inflamed Pseudopolyps in 6 inches of Sigmoid Colon

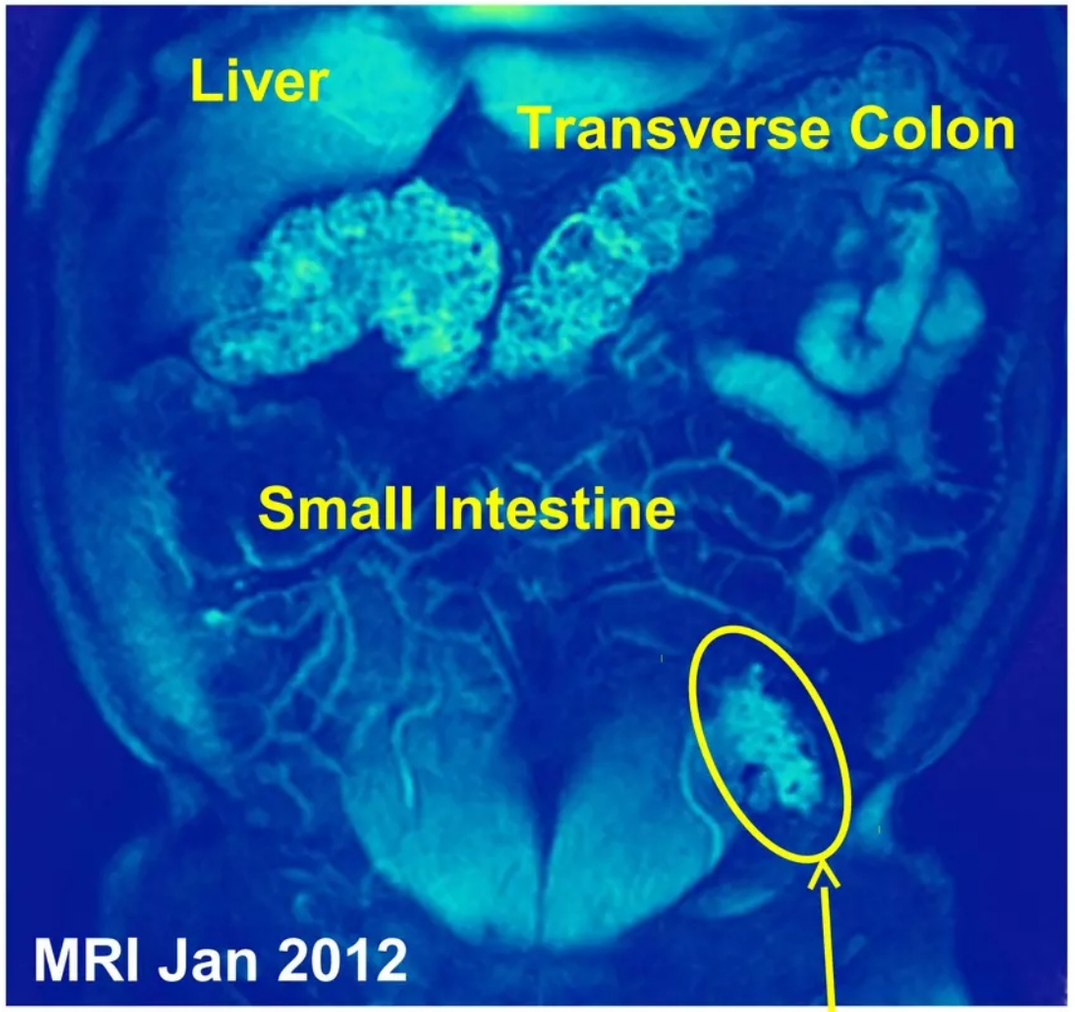


Dec 2010



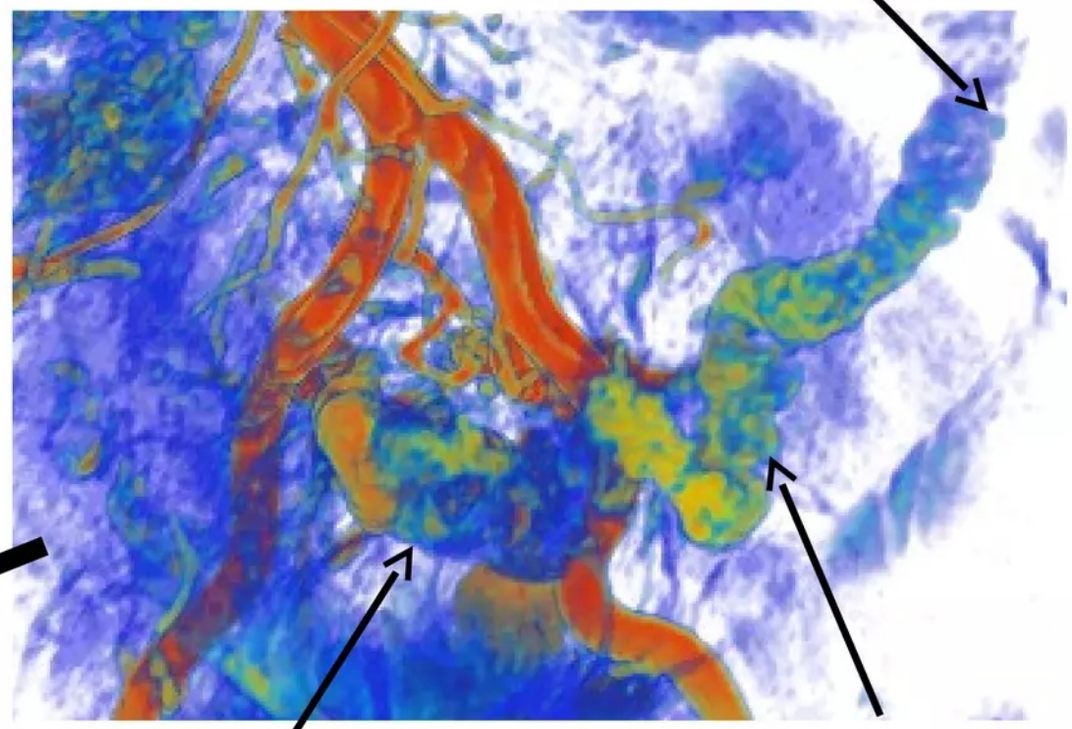
May 2011

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

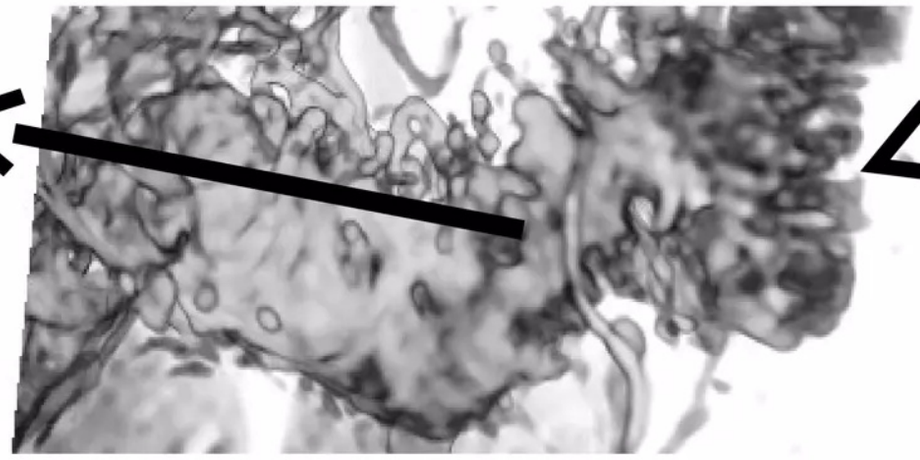
Descending Colon



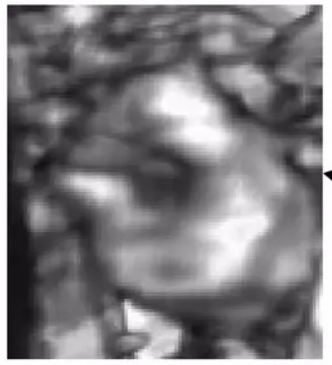
Major Kink

Sigmoid Colon Threading Iliac Arteries

Diseased Sigmoid Colon



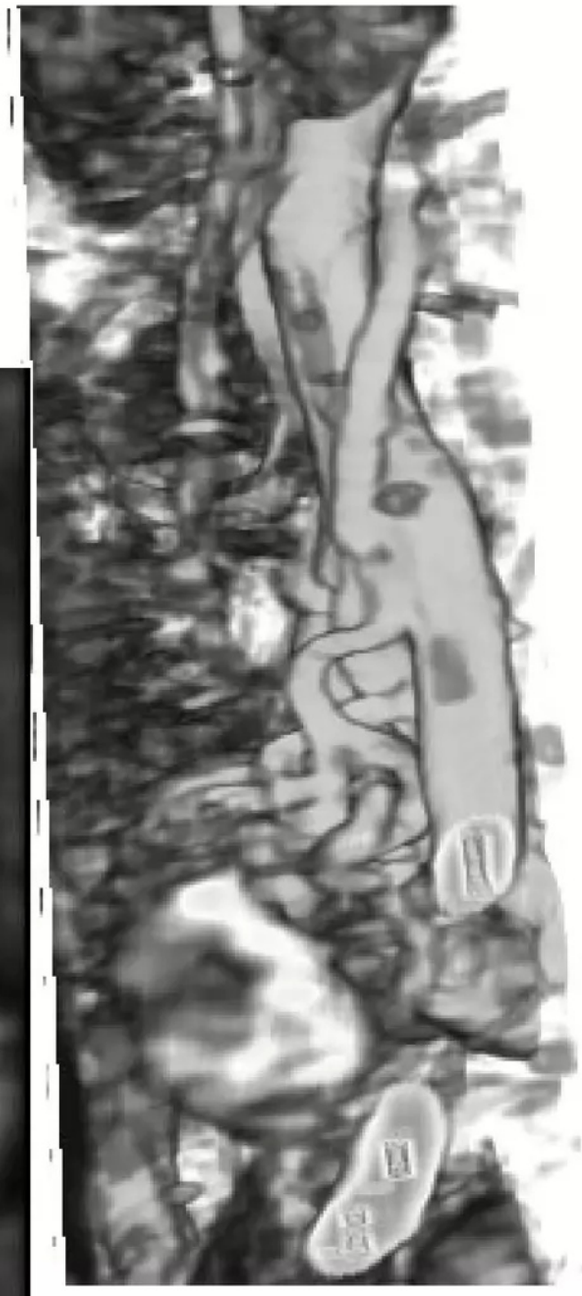
Cross Section

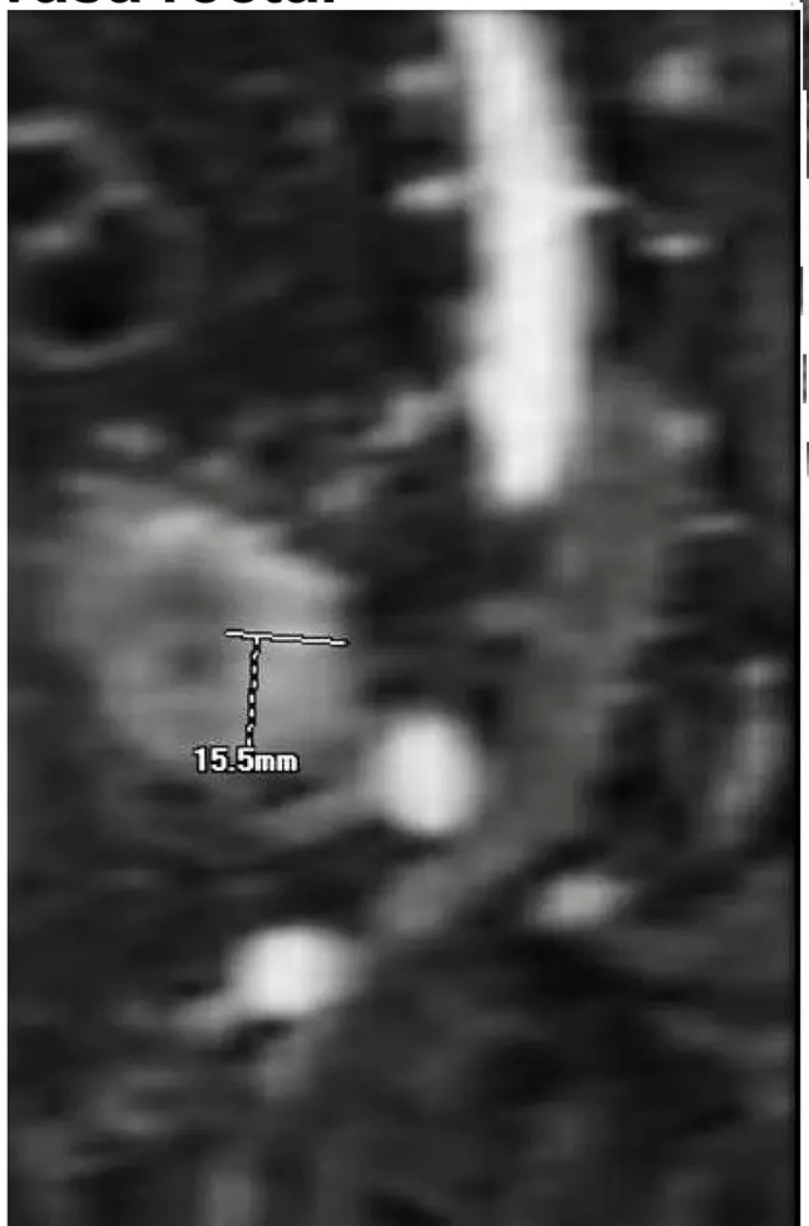


MRE Reveals Inflammation in 6 Inches of Sigmoid Colon
Thickness 15cm – 5x Normal Thickness

**"Long segment wall thickening
in the proximal and mid portions of the sigmoid colon,
extending over a segment of approximately 16 cm,
with suggestion of intramural sinus tracts.
Edema in the sigmoid mesentery
and engorgement of the regional vasa recta."
– MRI report**

DeskVOX 3D Image





MAYO CLINIC

**Crohn's disease
affects the thickness
of the intestinal wall.**

**Having Crohn's disease
that affects your colon
increases your risk
of colon cancer.**

**Clinical MRI
Slice Program**

it²

Why Did I Have an Autoimmune Disease like IBD?

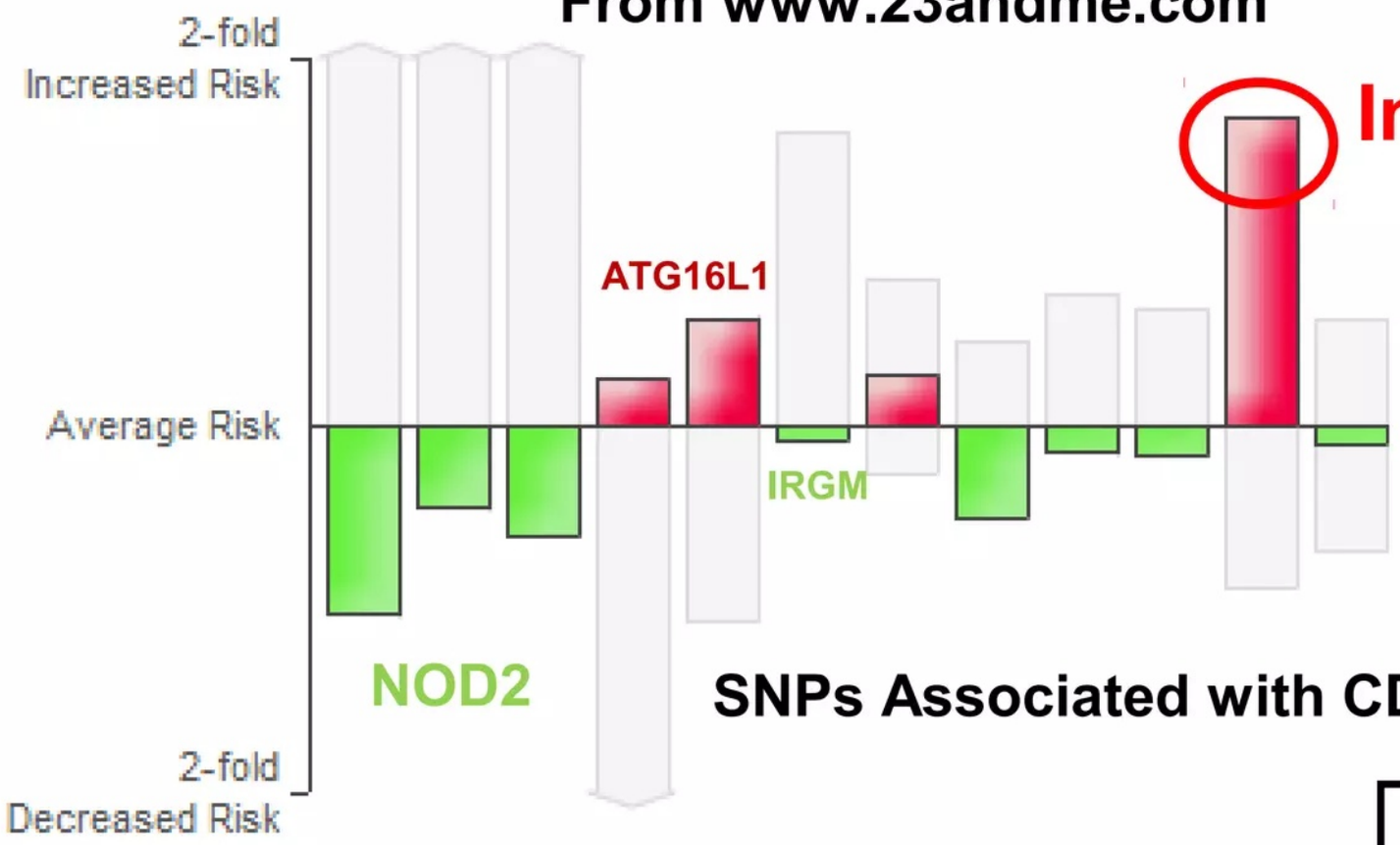
Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.
--The Role of Microbes in Crohn's Disease

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



SNPs Associated with CD

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

I am Now an Advisor on the 23andme IBD Project

News and Views

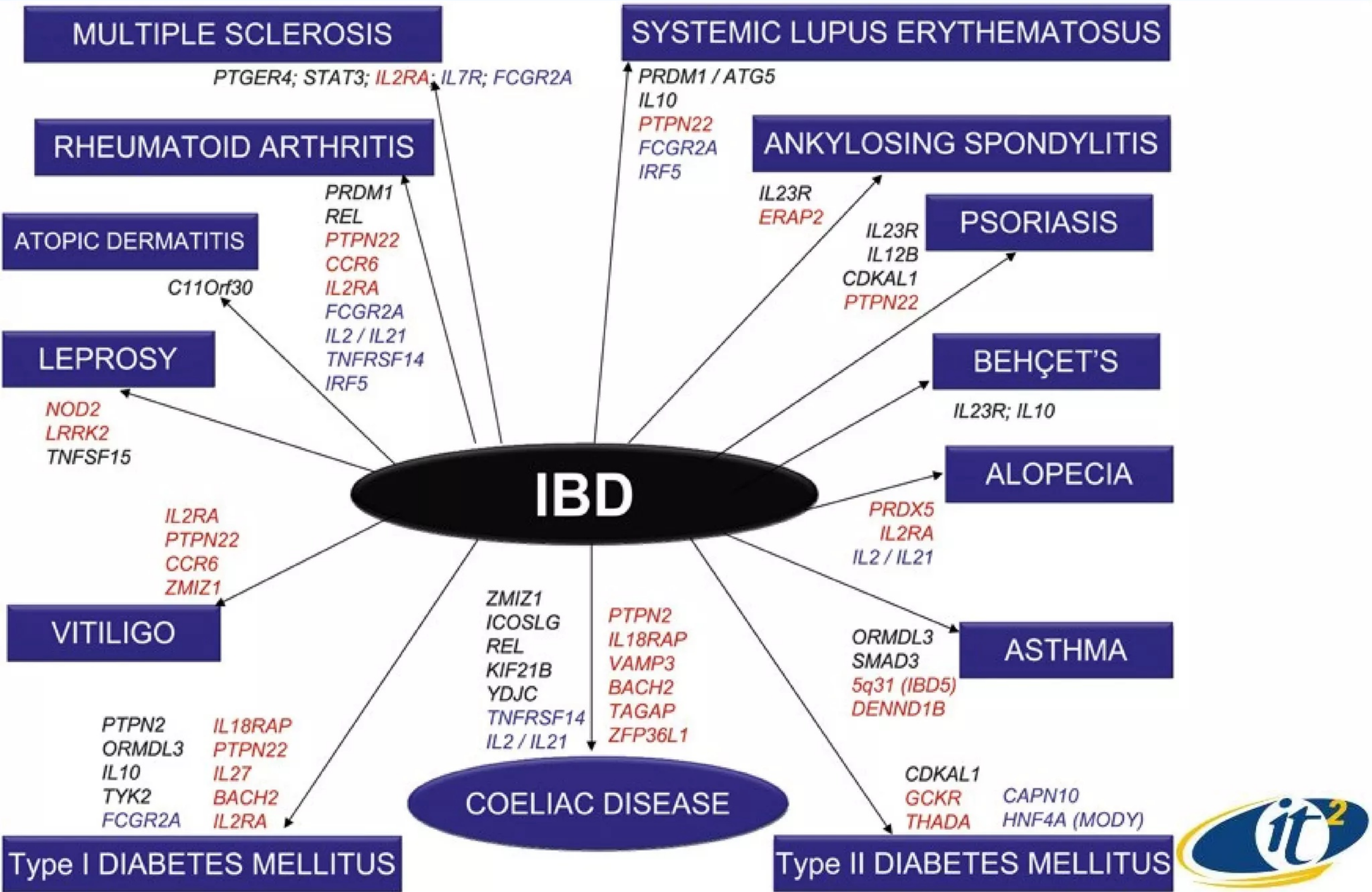
Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

Autoimmune Disease Overlap from SNP GWAS

Gut Lees, et al. 60:1739-1753 (2011)

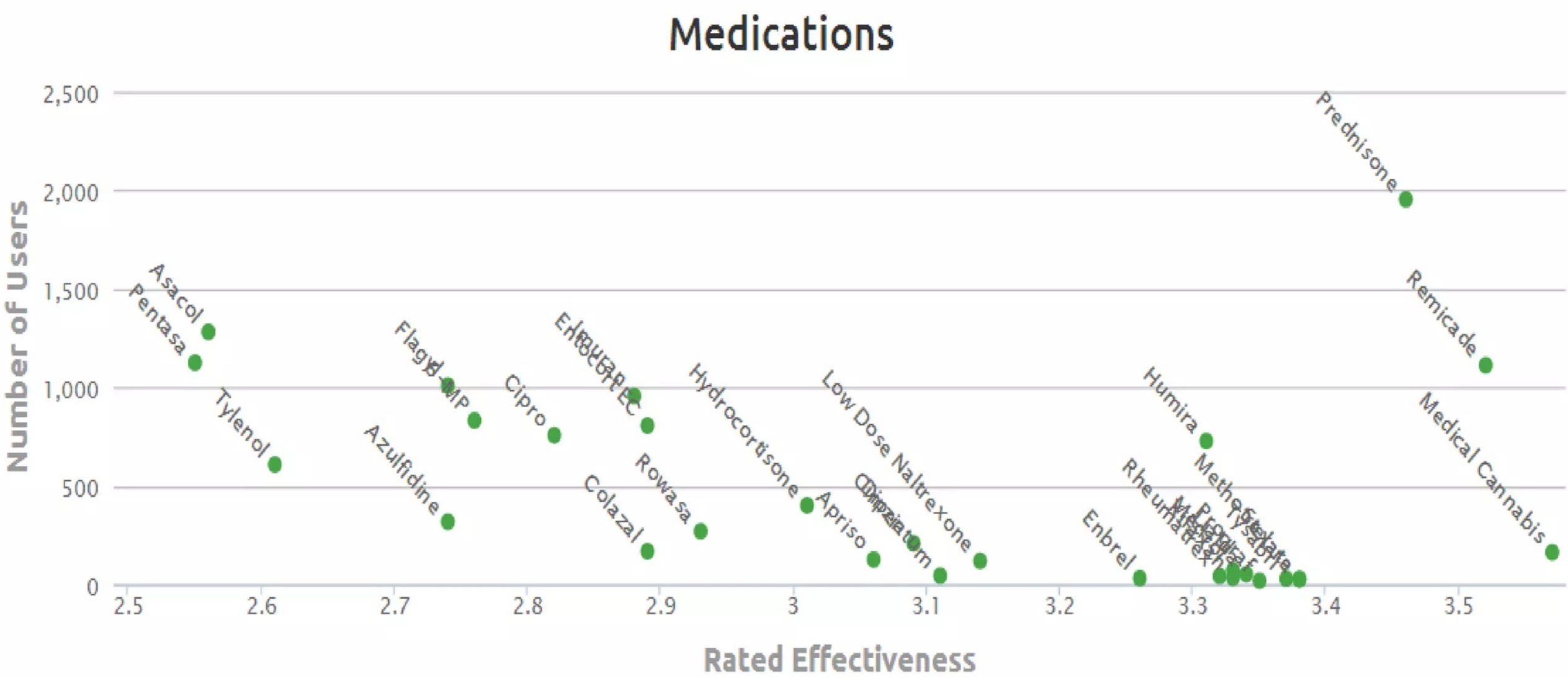


Imagine Crowdsourcing 23andme SNPs For Even a Small Portion of Crohnology!



www.crohnology.com

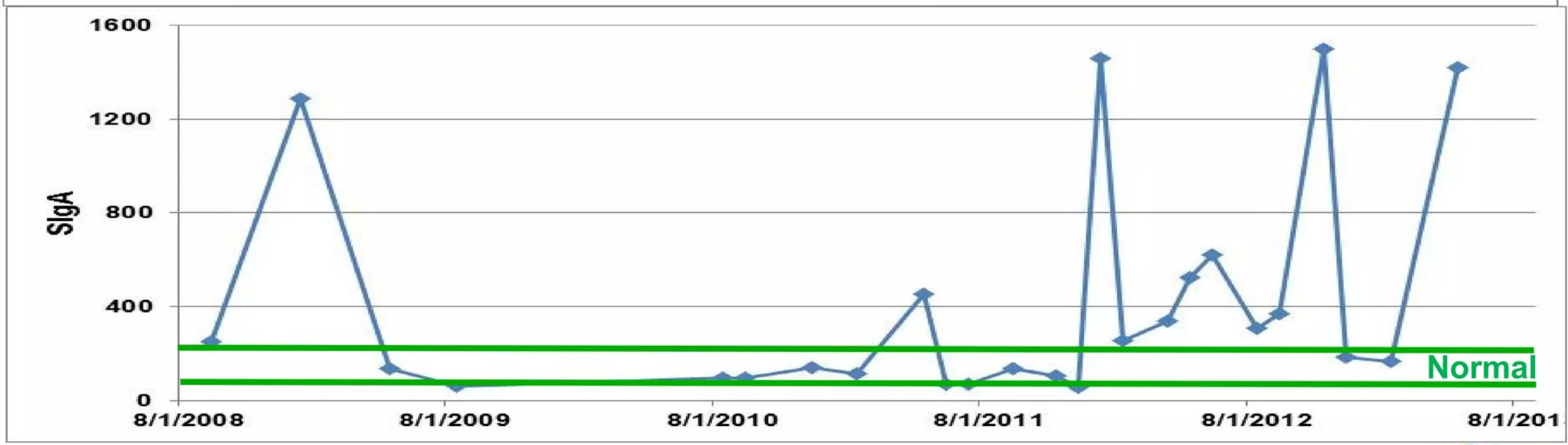
Crowd-Sourcing the Effectiveness of Pharmaceutical Medications for Crohn's Disease



www.crohnology.com

Fine Time Resolution Sampling Reveals Distinct Dynamics of Innate and Adaptive Immune System





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



J. Craig Venter INSTITUTE

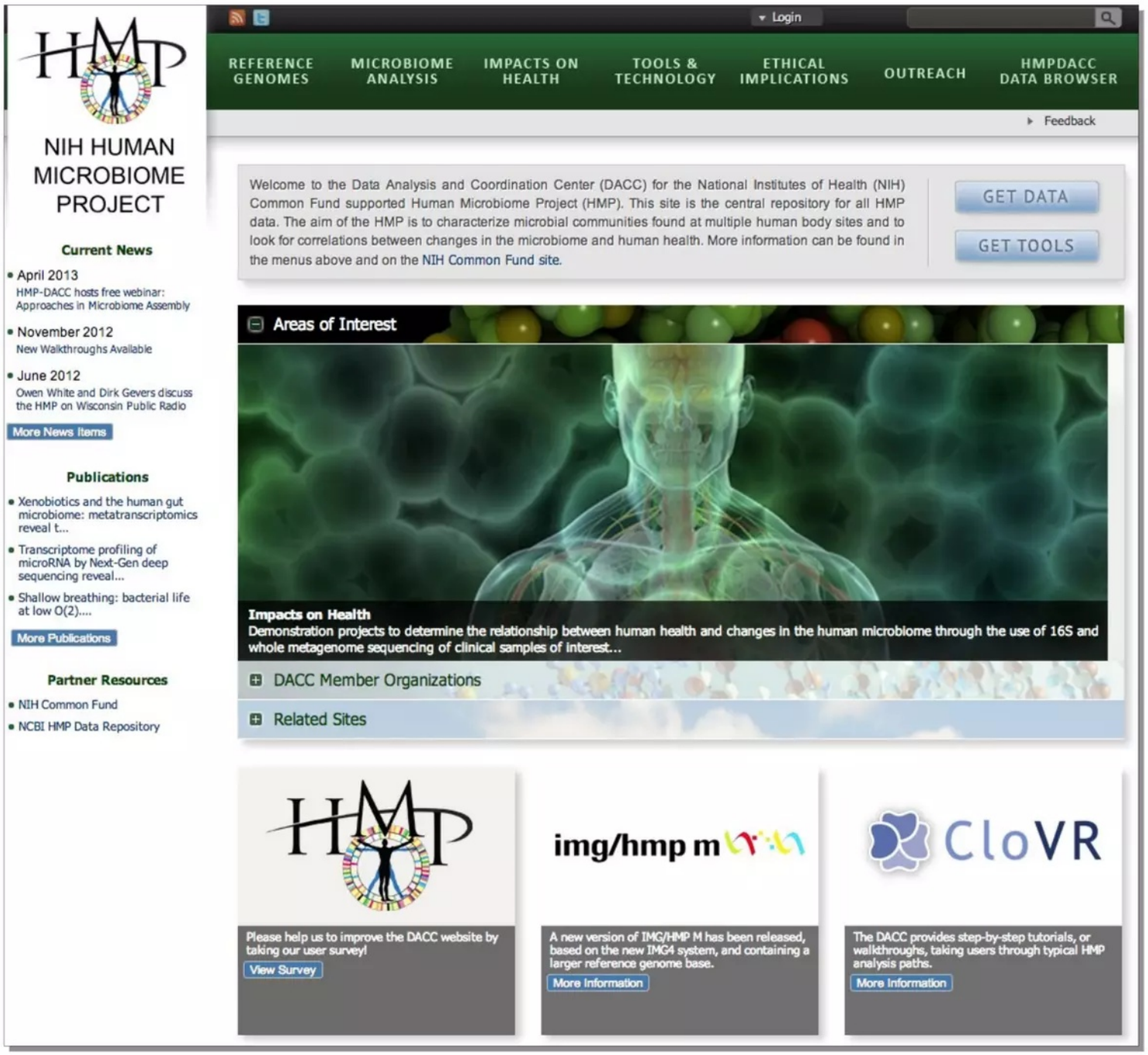
UC San Diego HEALTH SCIENCES

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

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

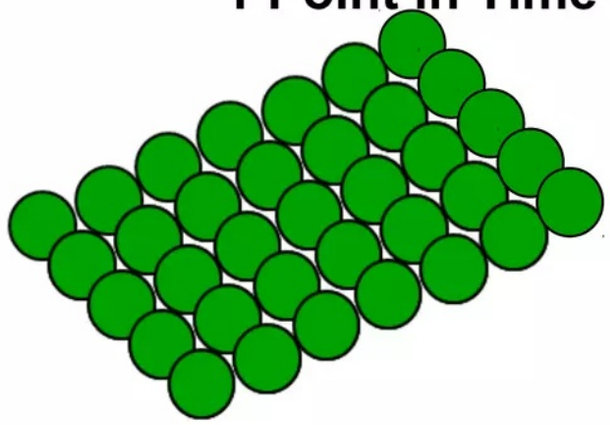
January 25, 2012

Additional Phenotypes Added from NIH HMP For Comparative Analysis

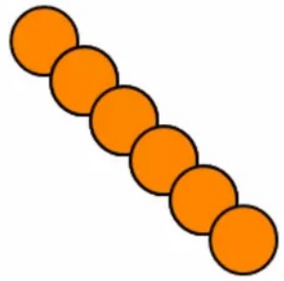


Download Raw Reads ~100M Per Person

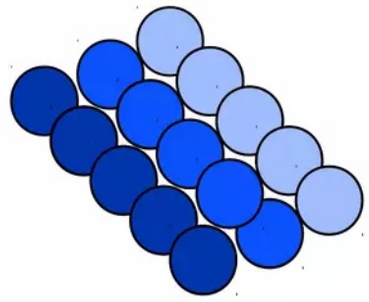
35 "Healthy" Individuals 1 Point in Time



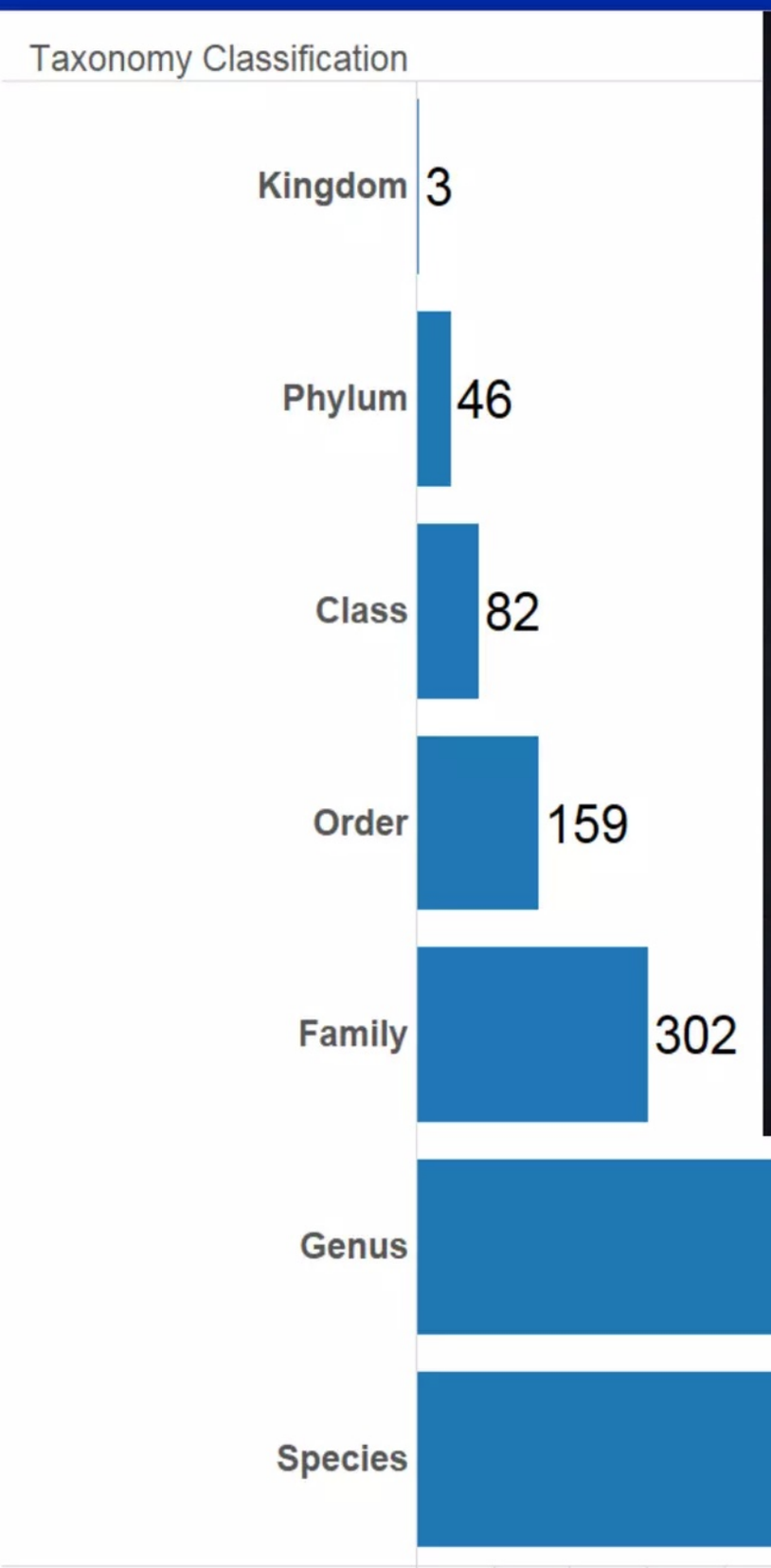
6 Ulcerative Colitis, 1 Point in Time

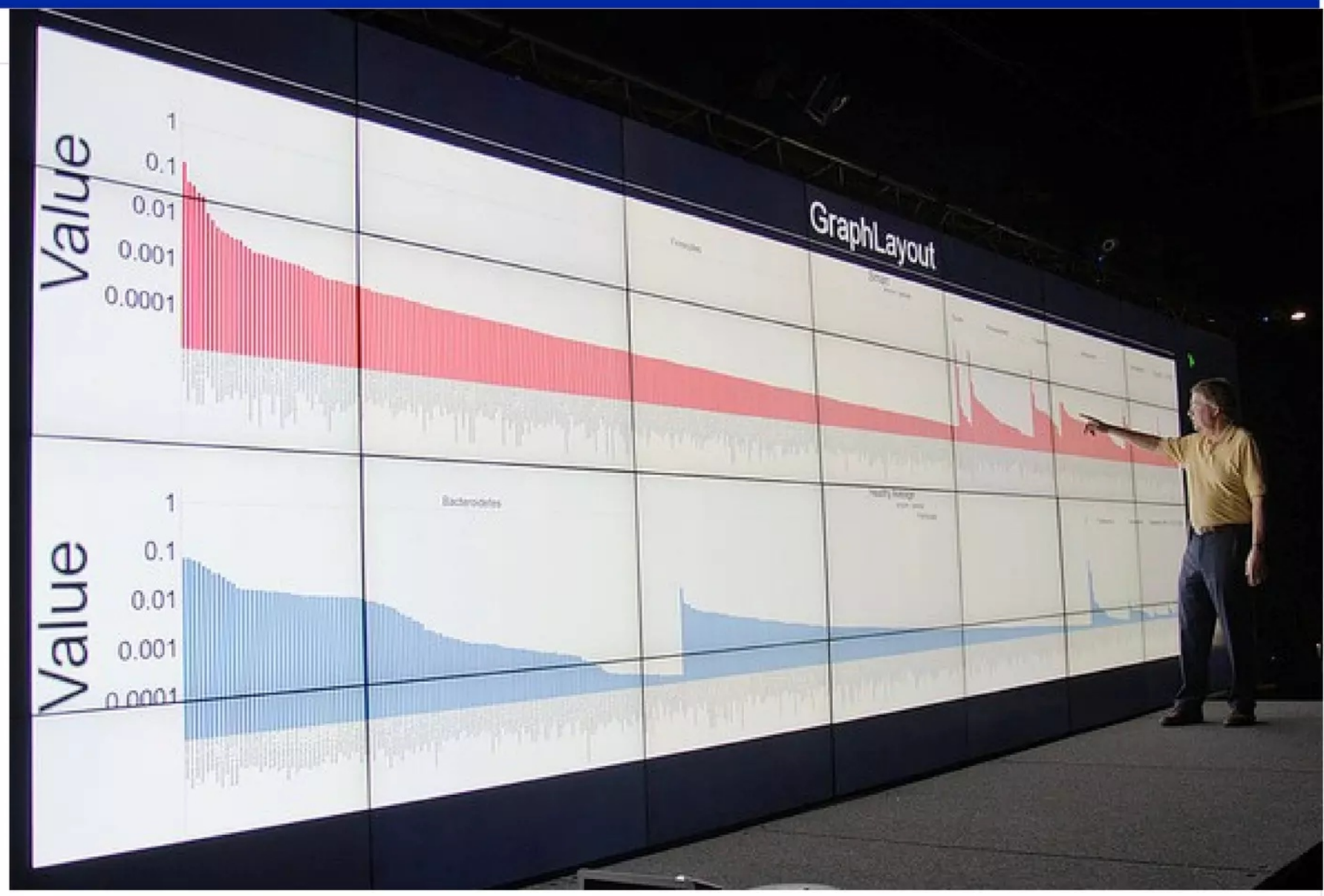


5 Ileal Crohn's, 3 Points in Time



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

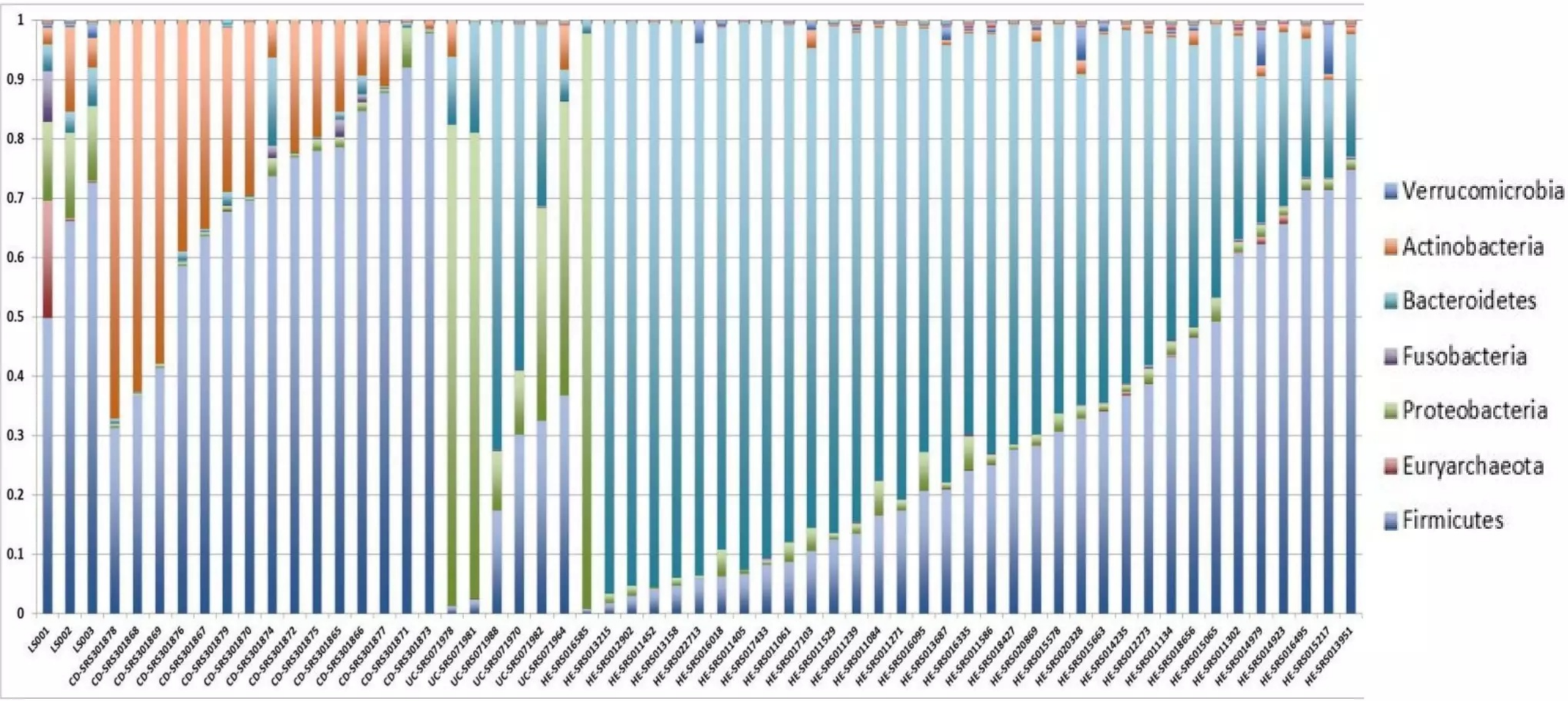




~4500 Reference Genomes with Strains and Viruses

Major Shifts in Microbial Ecology in Health and Disease

Source: Weizhong Li, UCSD; Calit2 FuturePatient Expedition

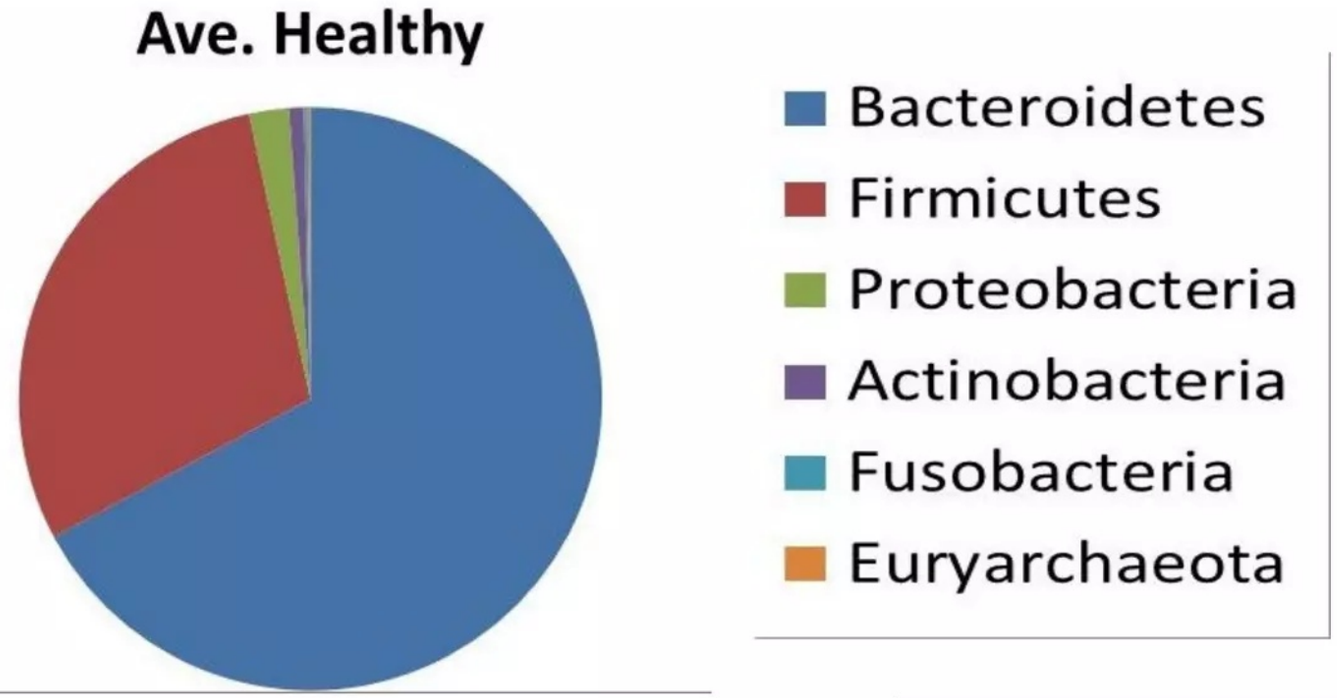


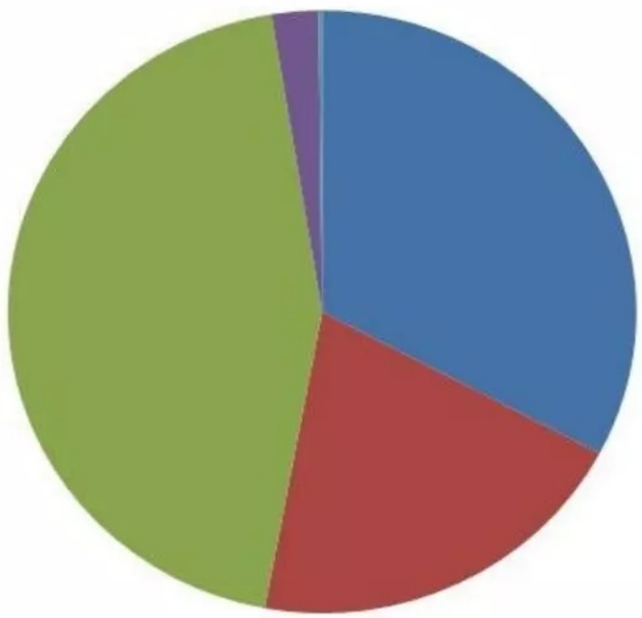
LS **Crohn's** **Ulcerative Colitis** **Healthy**

Toward Noninvasive Microbial Ecology Diagnostics

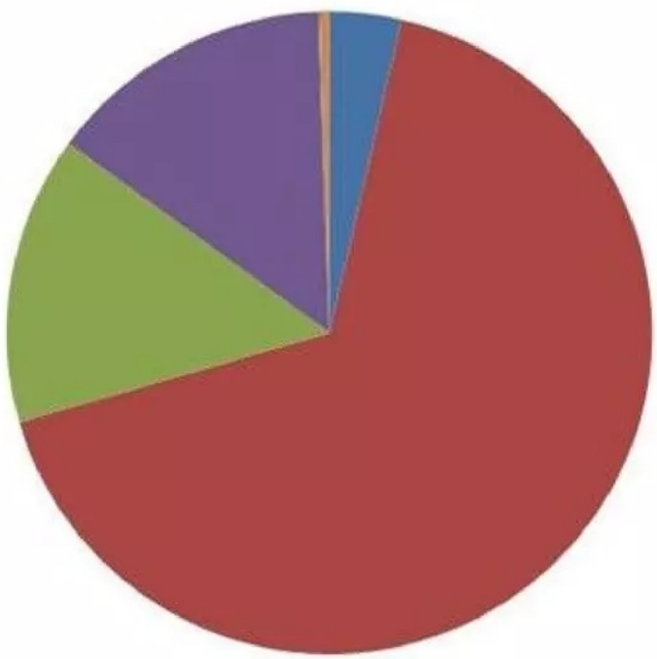
We Can Measure the Changes in Microbial Ecology Between Healthy and Two Forms of IBD

Microbiome "Dysbiosis" or "Mass Extinction"?

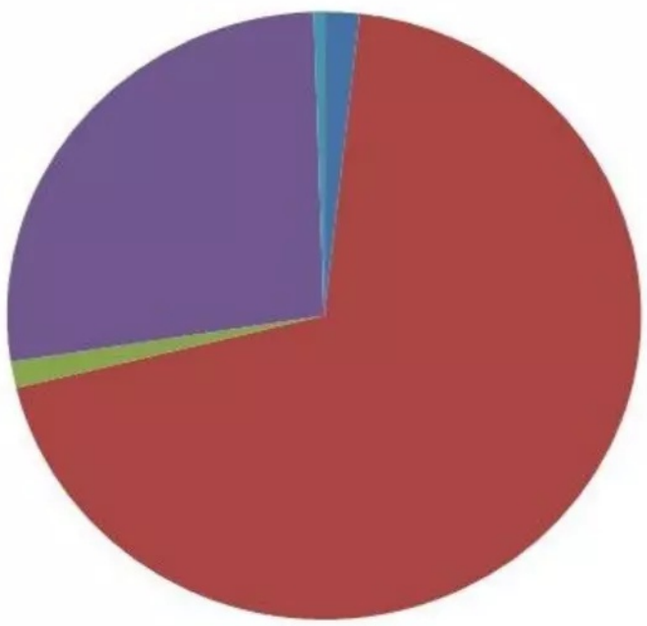




Explosion of Proteobacteria

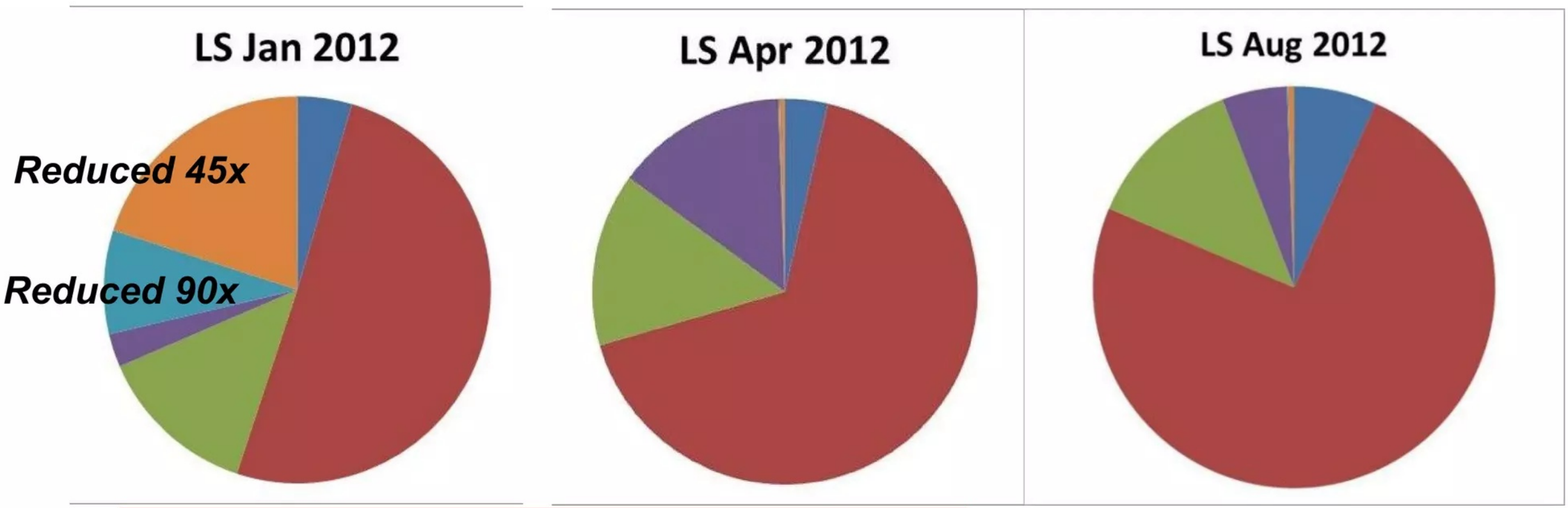


On the IBD Spectrum



Collapse of Bacteroidetes

Tracking How 1 Month Antibiotic, 2 Months Prednisone Therapy Alters the Gut Microbial Ecology



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

Small Changes With No Therapy

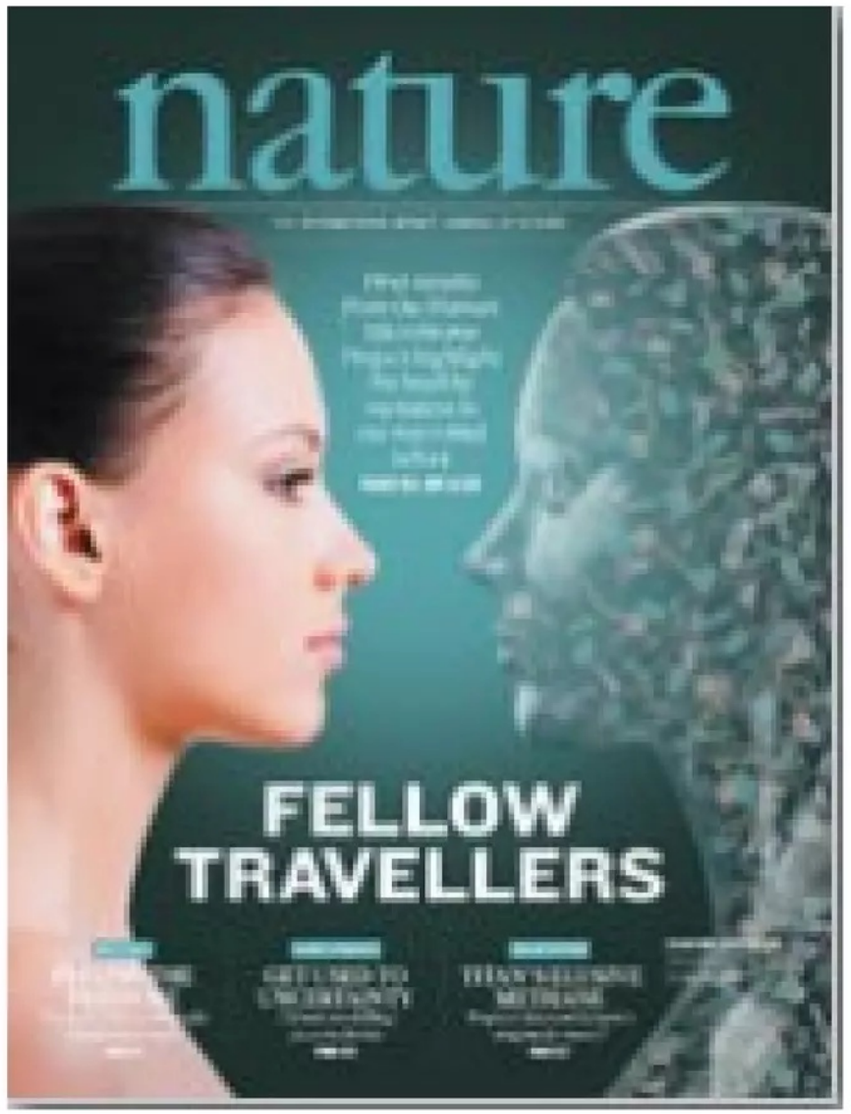
- Bacteroidetes
- Firmicutes
- Proteobacteria
- Actinobacteria
- Fusobacteria
- Euryarchaeota

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

Intense Scientific Research is Underway on Understanding the Human Microbiome



June 8, 2012



June 14, 2012

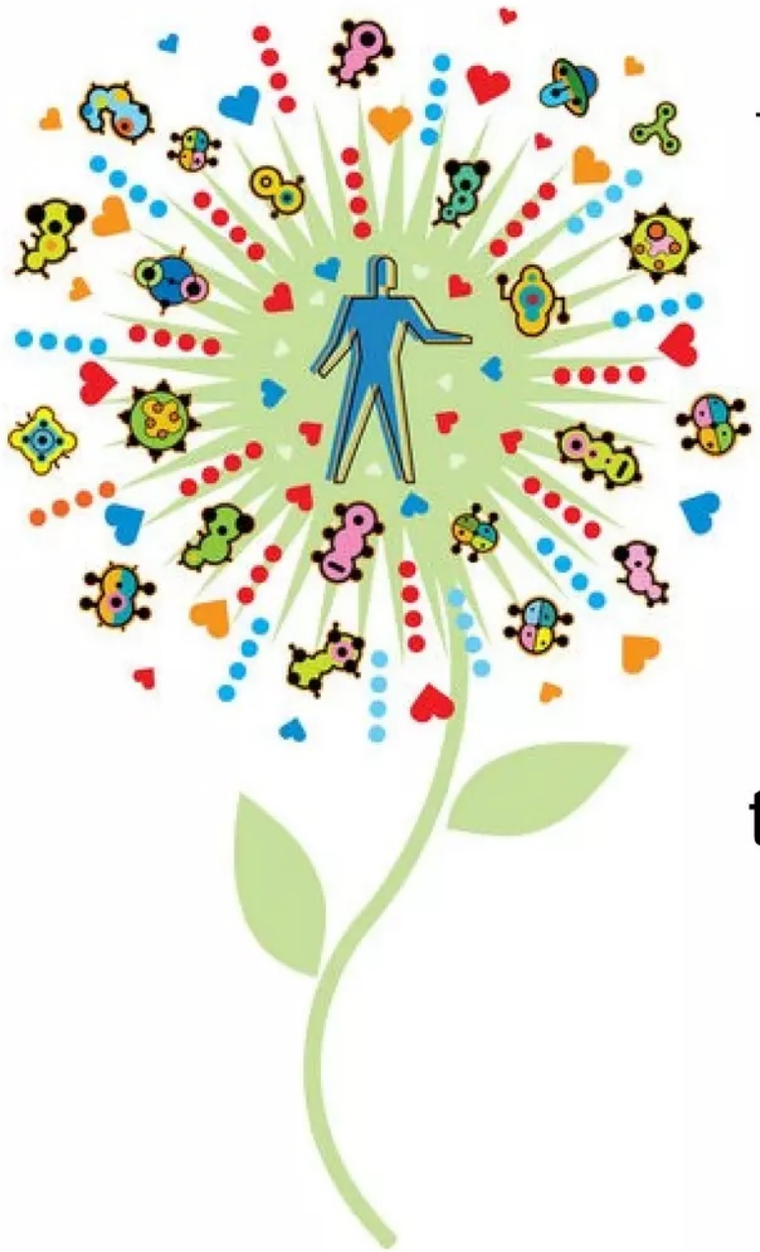
From Culturing Bacteria to Sequencing Them

2012 Was the Year
the Human Microbiome Entered the Public's Mind





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."

Evidence for the Efficacy of Probiotics is IBD is Mixed - More Clinical Research Needed

VSL#3 Probiotic-Mixture Induces Remission in Patients with Active Ulcerative Colitis Am J Gastroenterol 2005;100:1–8

Probiotics for Inflammatory Bowel Disease: A Critical Appraisal Dig Dis 2009;27(suppl 1):111–114

"...there is virtually no evidence of probiotic efficacy in Crohn's disease."

Journal of Medical Microbiology

Editorial

Butyric acid-producing anaerobic bacteria as a novel probiotic treatment approach for inflammatory bowel disease

J Med Microbiol **February 2010**
vol. 59 no. 2 **141–143**

I Take a Probiotic "Cocktail" to Enhance Microbial Diversity-48 Species of Bacteria

Jarro	Jarro	VSL#3	HLC	Flora V	Prescript	Keefer
Dophilus	Dophilus		Intensive		Assist	
EPS	FOS					

- **Genera Covered:**
  - **Azospirillum**
  - **Azotobacter**
  - **Bacillus**
  - **Bacteriodes**
  - **Bifidobacteria**
  - **Brevibacterium**
  - **Kurtha**
  - **Lactobacillus**

- **Genera Covered:**
  - **Lactococcus**
  - **Leuconostoc**
  - **Myrothecium**
  - **Pediococcus**
  - **Phanerochaete**
  - **Pseudomonas**
  - **Streptococcus**
  - **Streptomyces**

From the Single "Bad" Microbe Medical Target to the Microbiome Ecology Paradigm

REVIEW Sci Transl Med 4, 137rv5 (2012);

MICROBIOLOGY

Microbiota-Targeted Therapies: An Ecological Perspective

Katherine P. Lemon,[1,2]* Gary C. Armitage,[3] David A. Relman,[4,5,6] Michael A. Fischbach[7,8]*

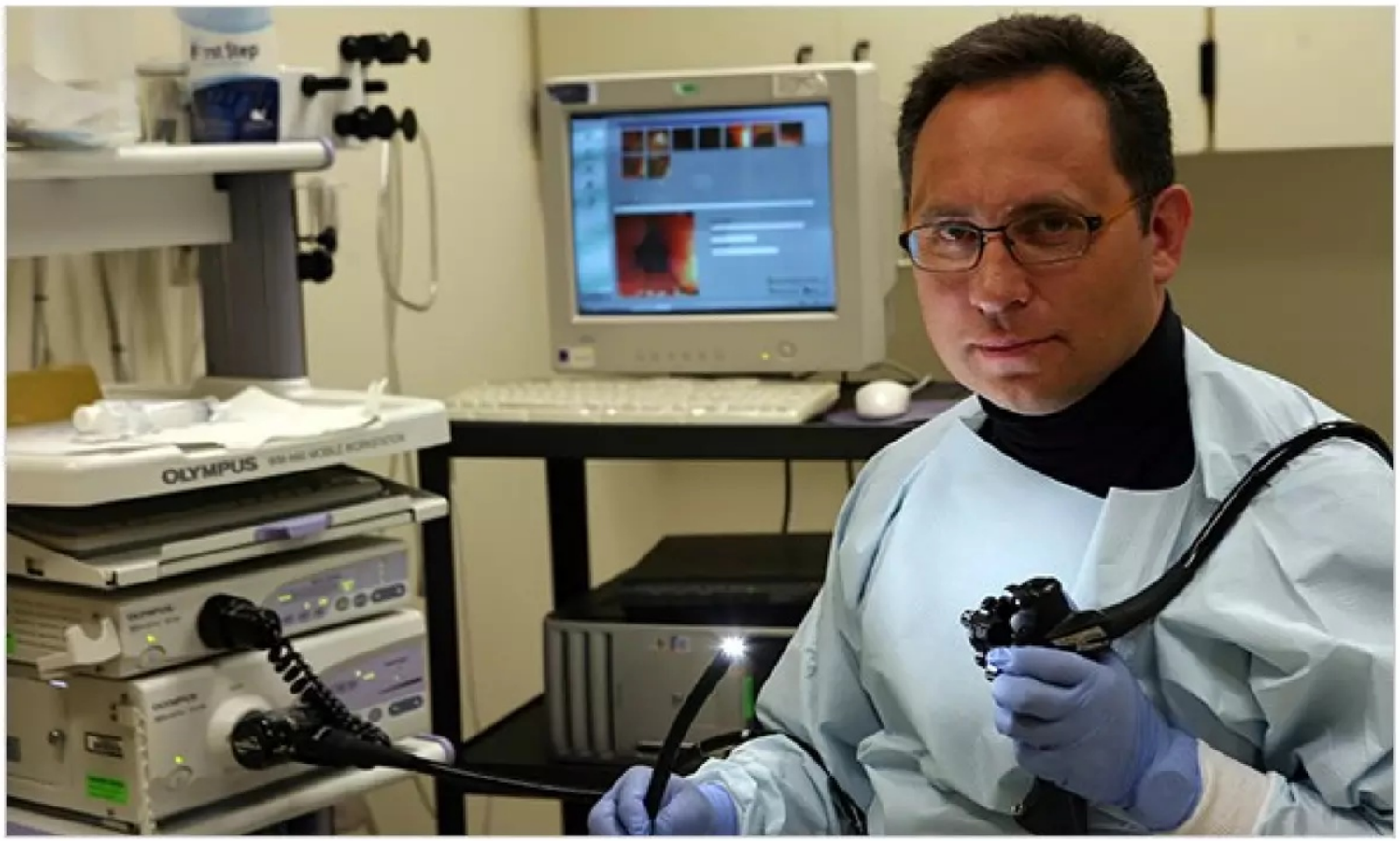
The Application of Ecological Theory Toward an Understanding of the Human Microbiome

Elizabeth K. Costello[1], Keaton Stagaman[2], Les Dethlefsen[1,3], Brendan J. M. Bohannan[2], David A. Relman[1,3,4,*]

Science 336, 1255 (2012)

Problem of Alternative Stable States In Ecological System Dynamics

Microbiome Transfer
May Be a Radical New Treatment for IBD



Dr. Alexander Khoruts, NY Times
www.nytimes.com/2010/07/13/science/13micro.html

Procedures Starting With Natural Microbiome

Next Steps:
Create Synthetic Microbiomes Tuned to the Patient
See *Microbiome* 1:3 (2013)

Not FDA Approved Yet;
Increasing Number of Doctors Performing Procedure;
Clinical Trials Under Way;
Encouraging Results…

www.gihealthfoundation.org/reuters/articles.cfm?article=20111102drgd011

Next Decade Will See New Microbiome "Gardening Tools"

Could Bacteria-Fighting Viruses Replace Overused Antibiotics? [Preview]

SCIENTIFIC AMERICAN™

August 7, 2012

Long ignored by mainstream researchers, the viruses that infect bacteria have a role to play in modern medicine, Vincent Fischetti says

By Brendan Borrell

Review Article

Immunocompatibility of Bacteriophages as Nanomedicines

Journal of Nanotechnology (2012)

Treating the Human Superorganism:
Your Body Has Ten Microbes for Every Human Cell!

Human Microbiome Project

The NIH Common Fund
WE ACCELERATE DISCOVERY.

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

