Quantifying My Body: The Role of the Human and Microbiome DNA

Invited Talk

Systems Biology and the Microbiome

Institute for Systems Biology

Seattle, WA

April 16, 2012

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

Follow me at http://lsmarr.calit2.net

I am the Digitally-Enabled "Patient of the Future": Measuring the State of Your Body and "Tuning" It

Age 51





Age 61

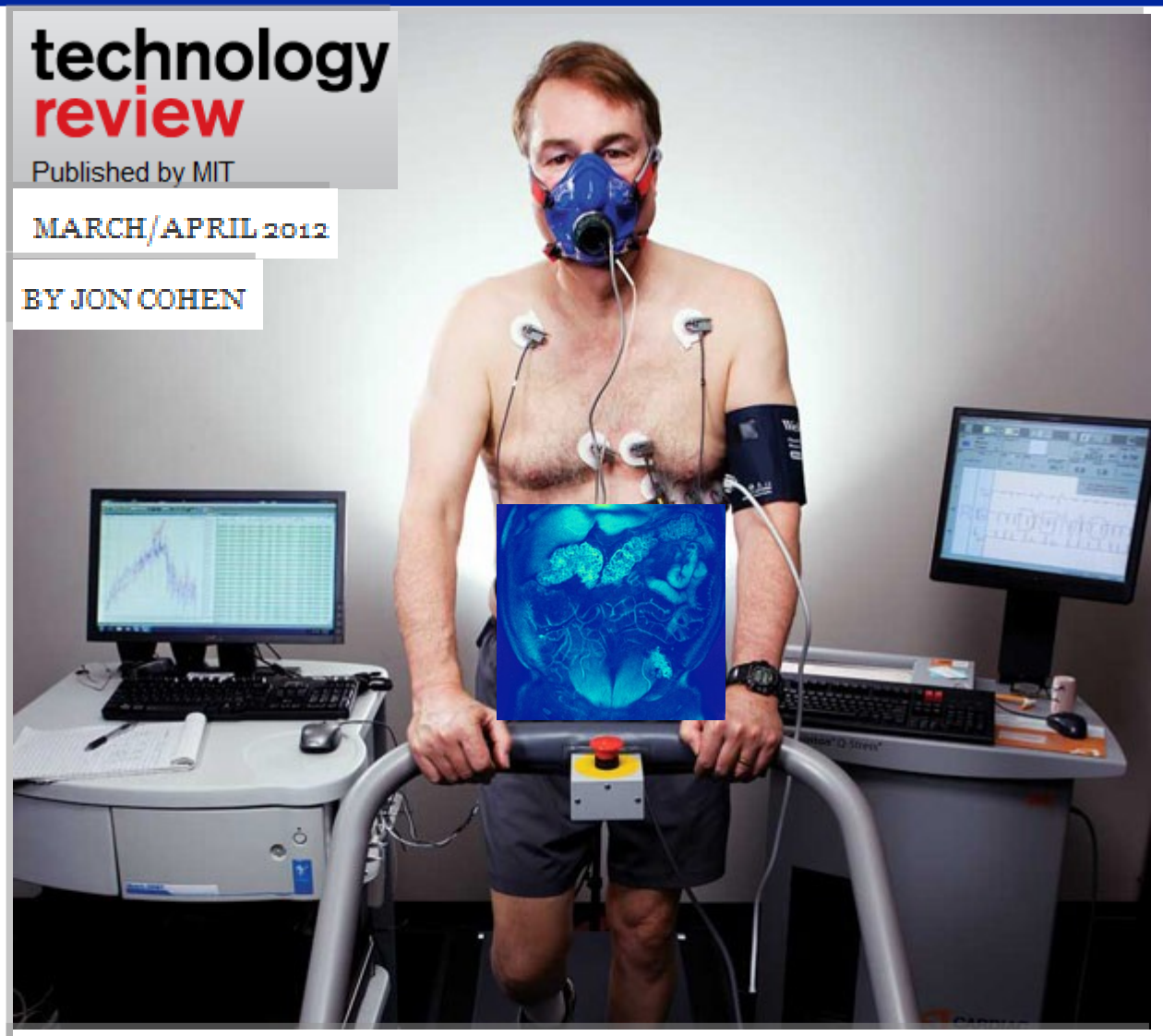
I Arrived in La Jolla in 2000 After 20 Years in the Midwest and Discovered I was Pre-Diabetic.

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

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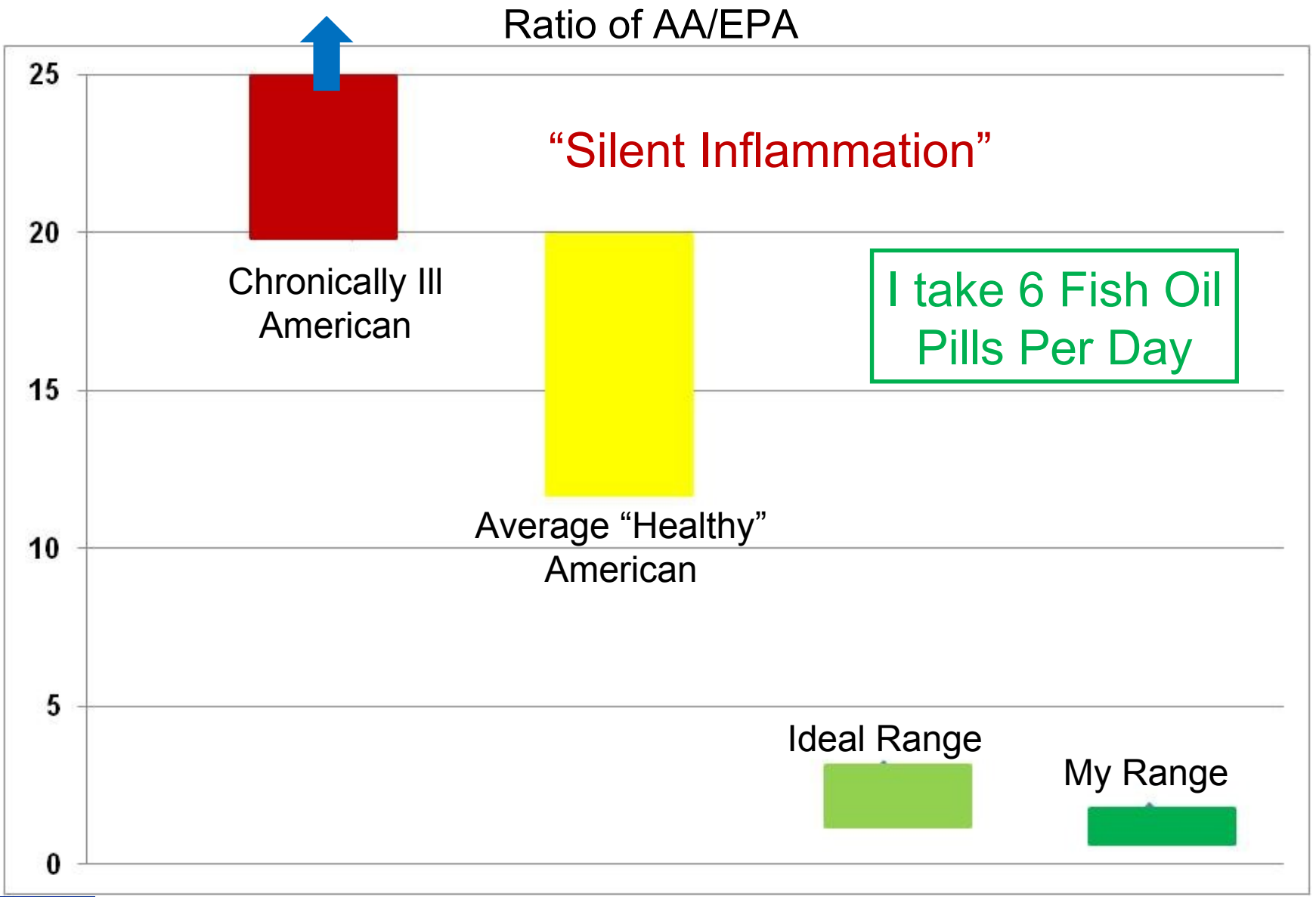
it²

From Measuring Macro-Variables to Measuring Your Internal Variables



www.technologyreview.com/biomedicine/39636

I Have Greatly Lowered My Body's Inflammation From Food By Increasing Omega-3s & Lowering Omega-6s



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Range Source: Barry Sears
My Tests by www.yourfuturehealth.com

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My Quarterly Blood Tests In Addition to Lipids: Only One Was Far Beyond Normal Limits

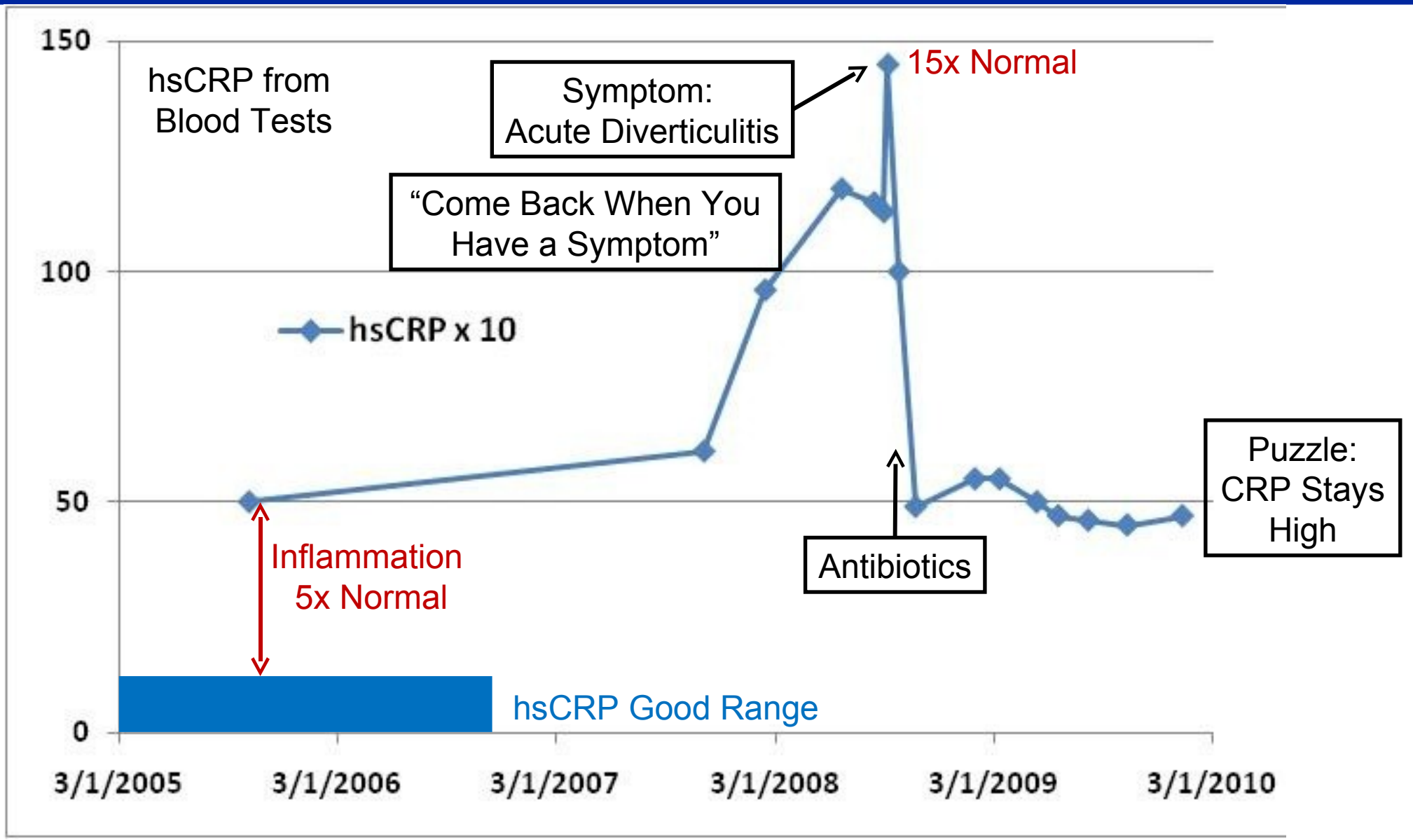
- **Electrolytes**
  - Sodium, Potassium, Calcium, Magnesium, Phosphorus, Boron, Chlorine, CO_2
- **Micronutrients**
  - Arsenic, Chromium, Cobalt, Copper, Iron, Manganese, Molybdenum, Selenium, Zinc
- **Blood Sugar Cycle**
  - Glucose, Insulin, A1C Hemoglobin
- **Cardio Risk**
  - Complex Reactive Protein
  - Homocysteine
- **Kidneys**
  - Bun, Creatinine, Uric Acid
- **Protein**
  - Total Protein, Albumin, Globulin
- **Liver**
  - GGTP, SGOT, SGPT, LDH, Total Direct Bilirubin, Alkaline Phosphatase
- **Thyroid**
  - T3 Uptake, T4, Free Thyroxine Index, FT4, 2nd Gen TSH
- **Blood Cells**
  - Complete Blood Cell Count
  - Red Blood Cell Subtypes
  - White Blood Cell Subtypes
- **Cancer Screen**
  - CEA, Total PSA, % Free PSA
  - CA-19-9
- **Vitamins & Antioxidant Screen**
  - Vit D, E; Selenium, ALA, coQ10, Glutathione, Total Antioxidant Fn.

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I Track Over 100 Blood Variables Over Time

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In Spite of Very Low Food Induced Inflammation, Blood Measurements Show Chronic Inflammation

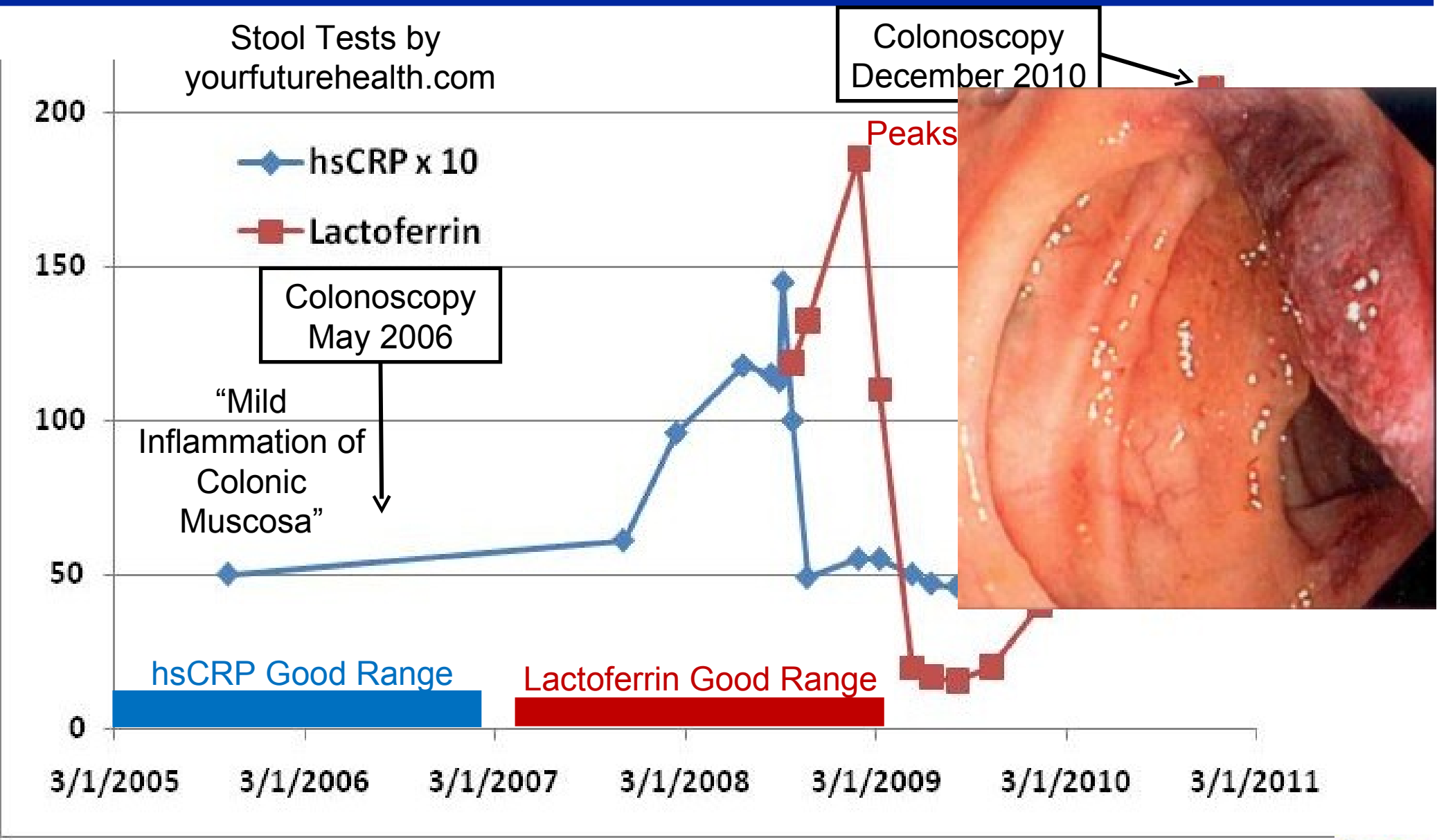


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CRP=Complex Reactive Protein

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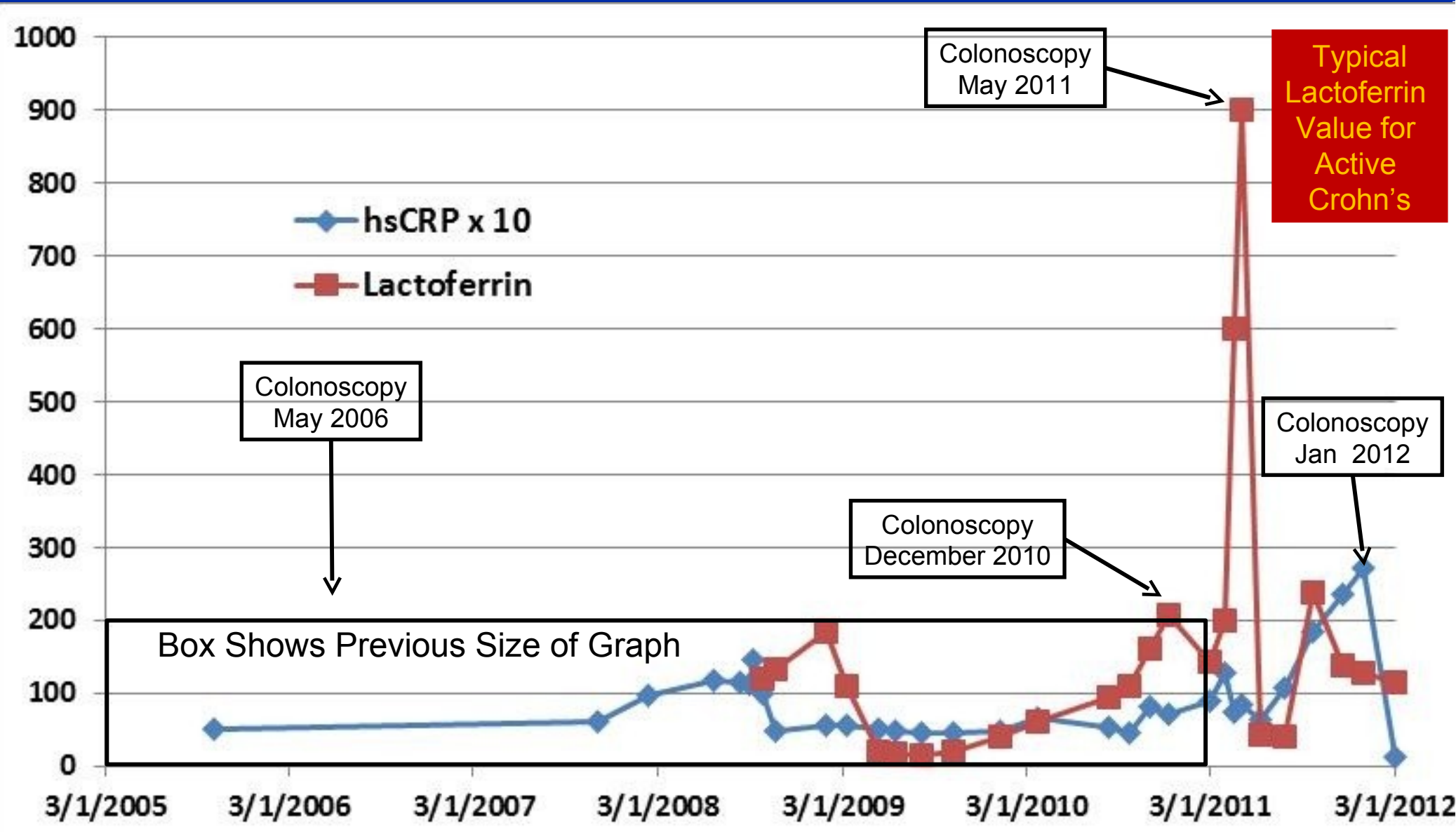
Measuring Blood and Markers Revealed Episodic Inflammation Peaks of CRP and Lactoferrin



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Frequent Stool Analysis Reveals Lactoferrin Spike to Active Crohn's Disease (CD) Level

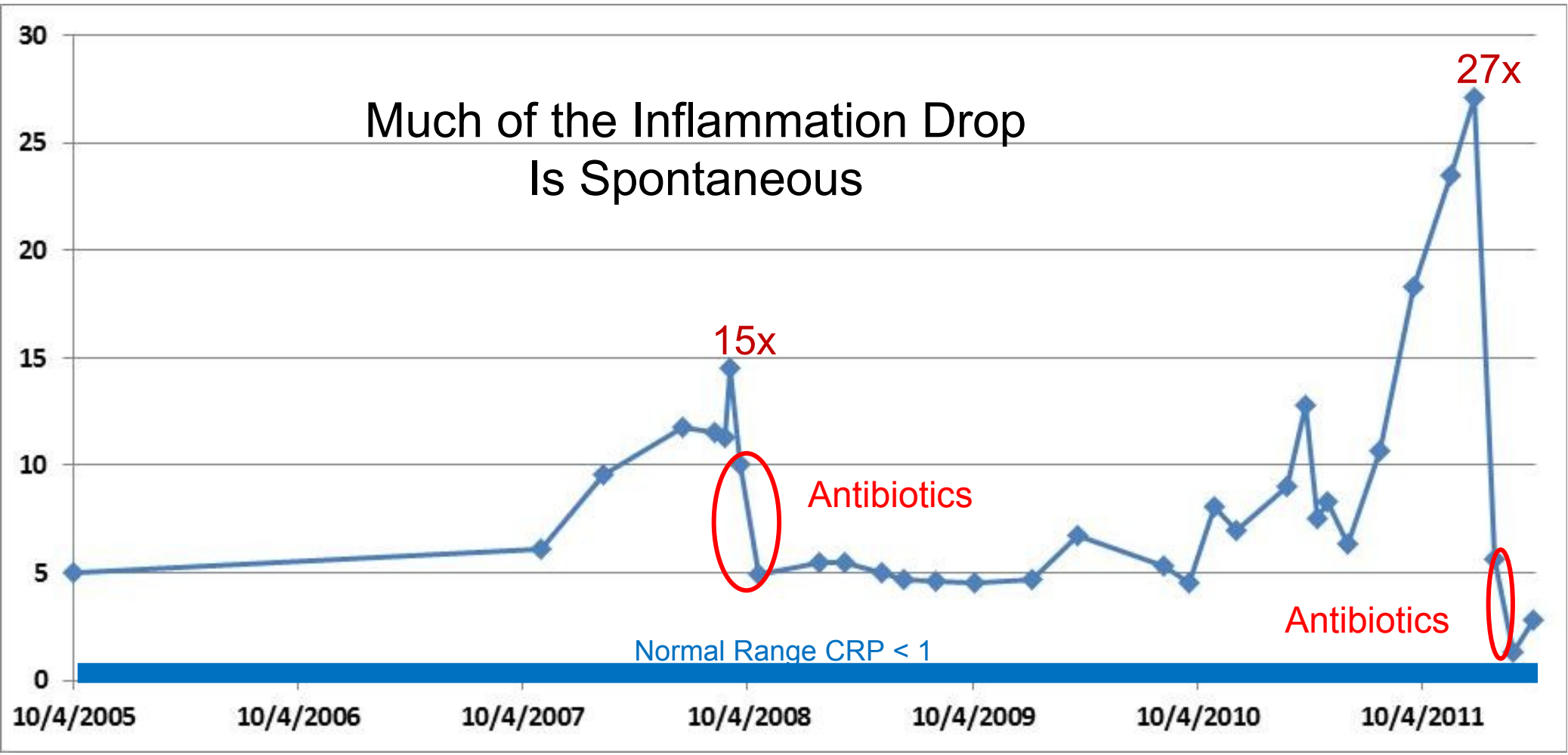


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Colonoscopy and Biopsies Support CD Diagnosis

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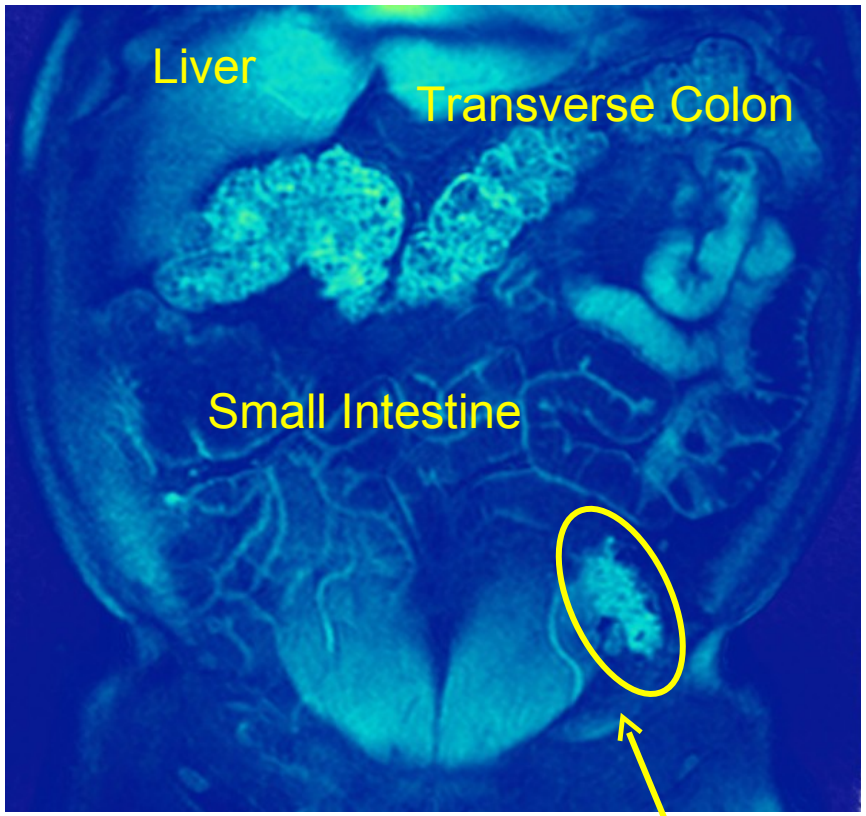
Natural Anti-Inflammation Can Be Much Larger Effect Than Antibiotic-Induced Inflammation Remission



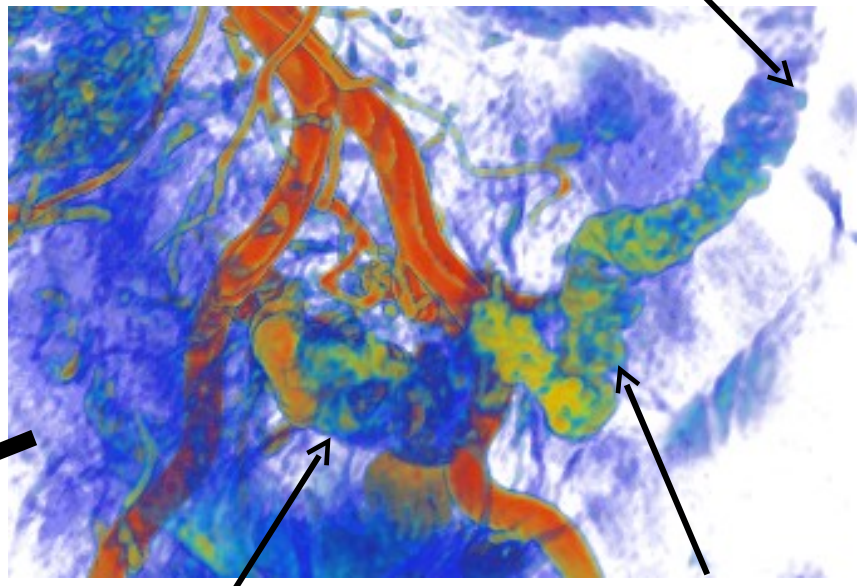
Demonstrates Value of Fine-Grained Time Series

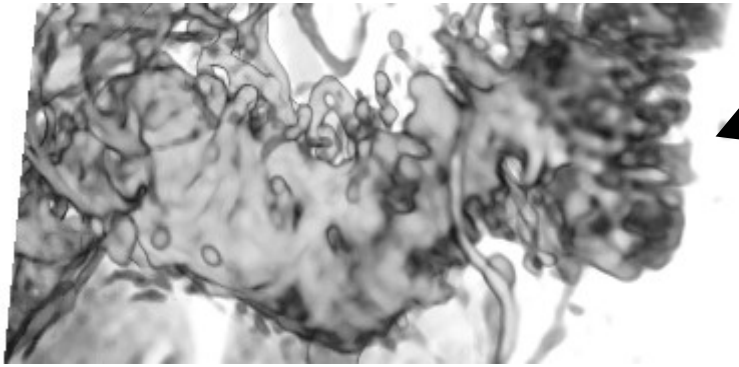
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Confirming the Crohn's Hypothesis: Finding the "Smoking Gun" with MRI Imaging



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





Sigmoid Colon
Threading Iliac Arteries

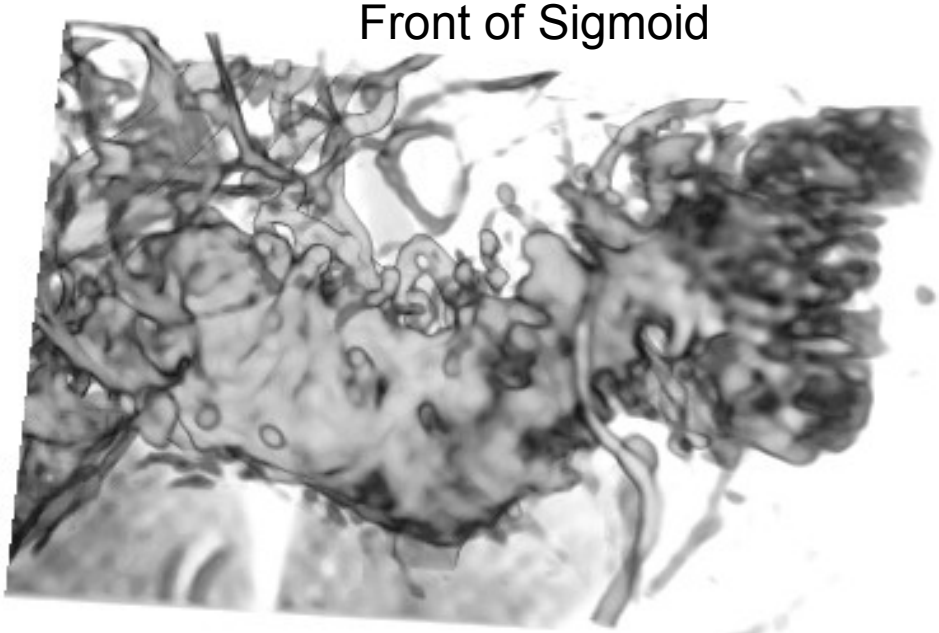
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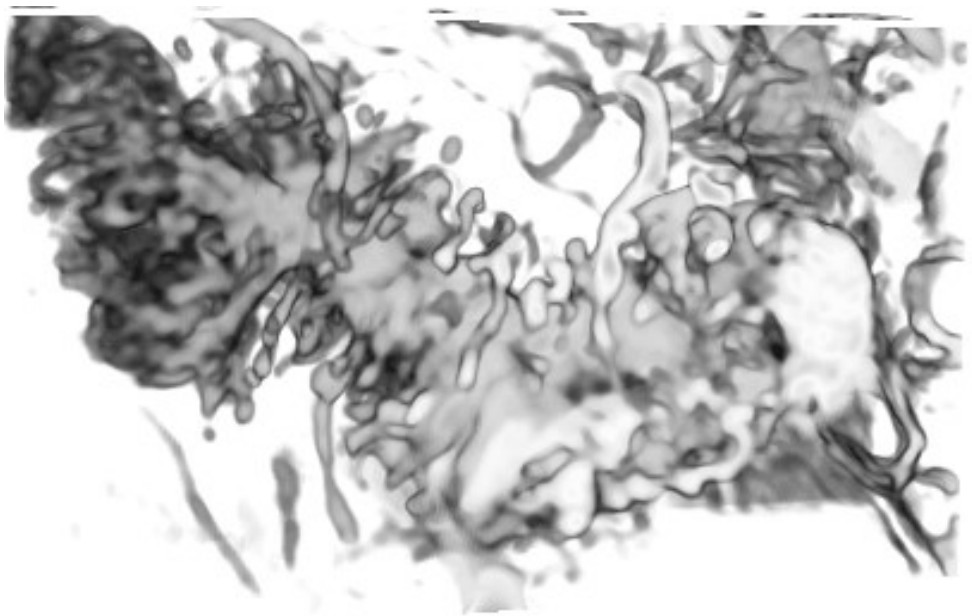
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Front and Back View of LS Diseased Sigmoid Colon

Jan 2012 MRI Enterography report: There are colonic diverticula. There is edema in the sigmoid mesentery, engorgement of the regional vasa recta, with numerous small mesenteric lymph nodes in this region."

Front of Sigmoid





Back of Sigmoid

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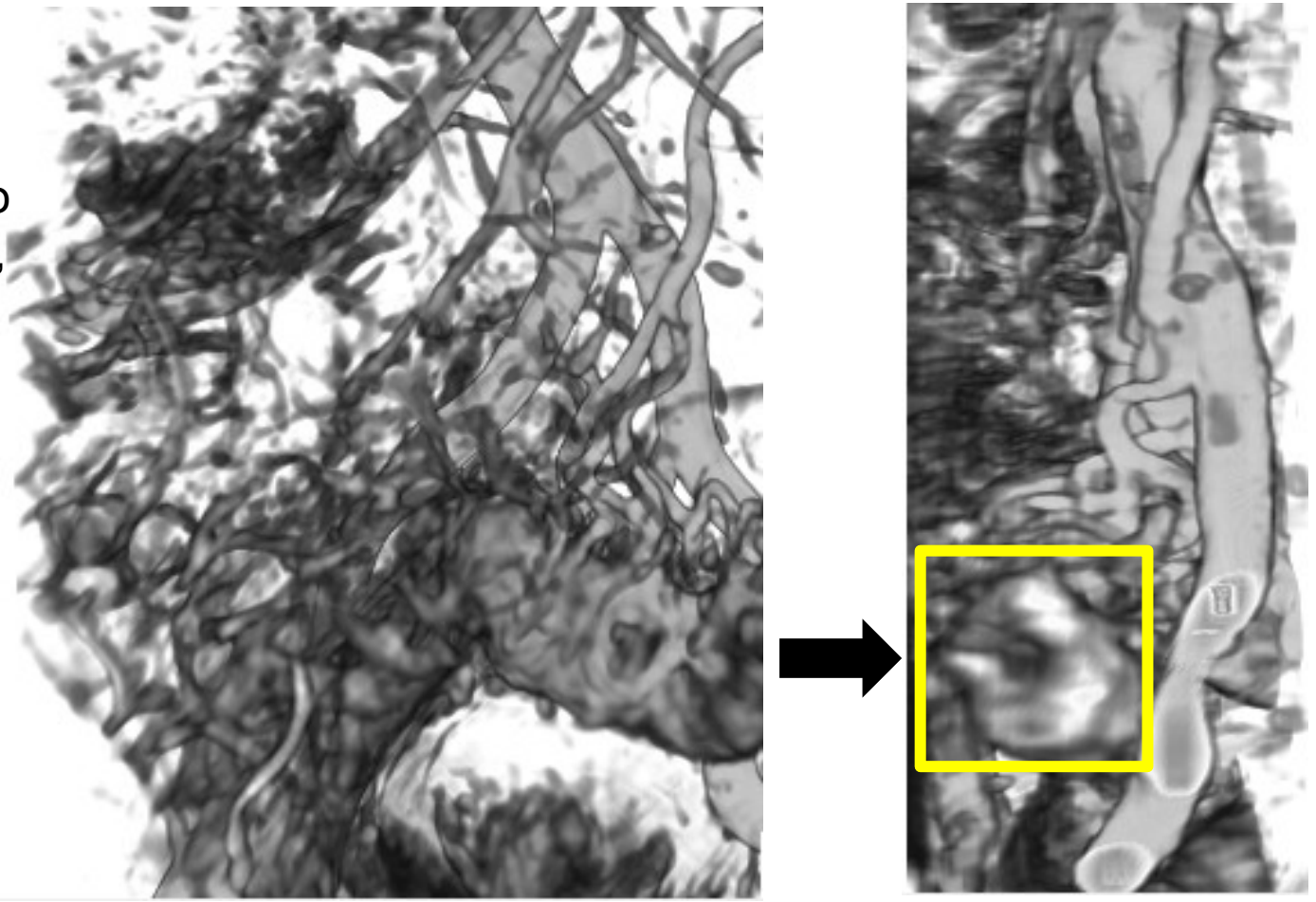
Source: L Smarr Using Calit2's Jurgen Schultz Software

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LS Sigmoid Colon Cross Sections Showing Inflamed Wall

Jan 2012 MRI Enterography report: “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.

Ulcerative Colitis is Restricted to the Mucosa, while Crohn's Disease Affects the Whole Bowel Wall



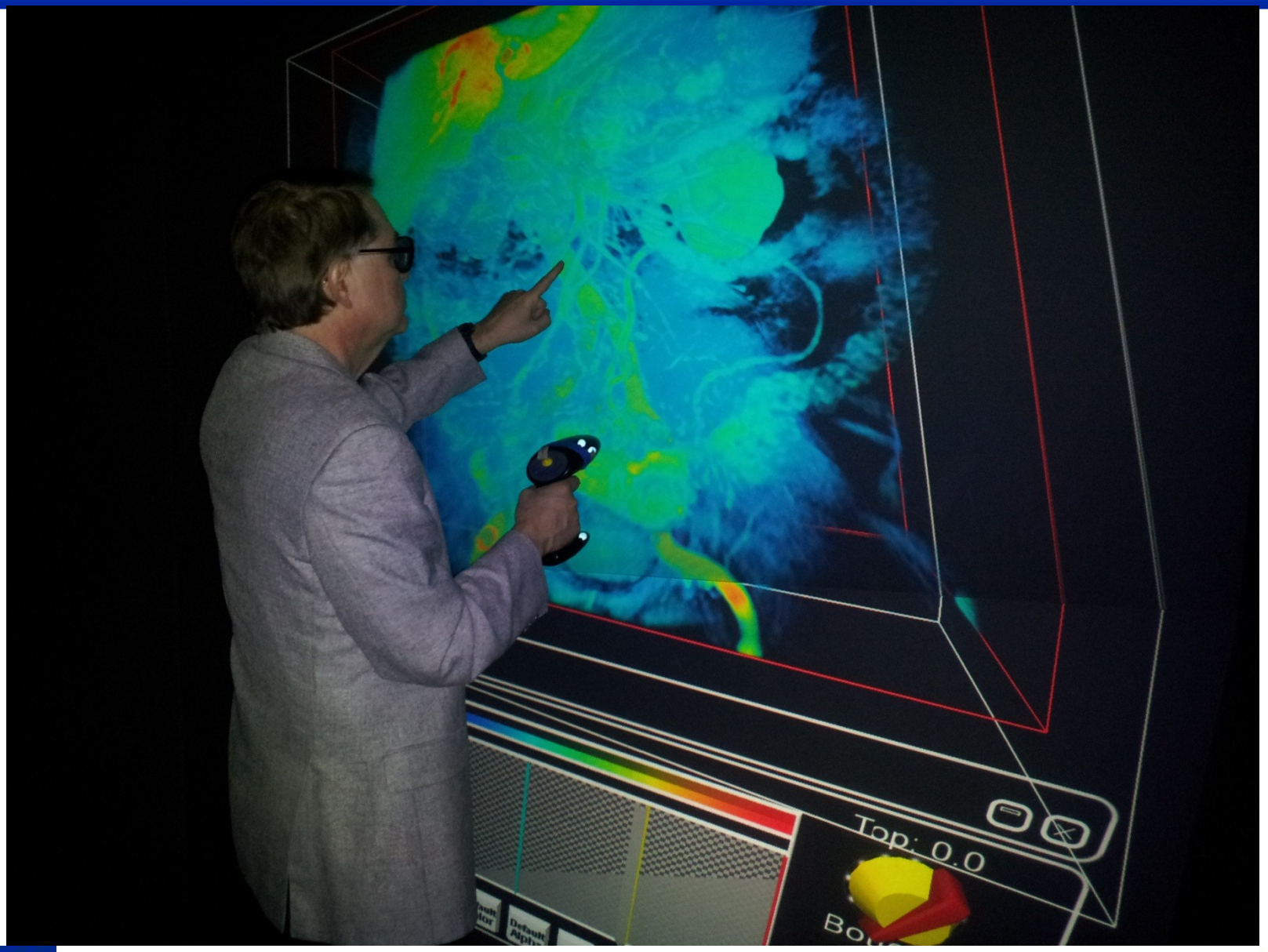
Note Thickness of Wall - Normal is 3mm (like a Balloon)

Source: L Smarr Using Calit2’s Jurgen Schultz Software

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Exploring My Internal Organs in the Calit2 Virtual Reality CAVE Using DeskVOX Software



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Photo & DeskVOX Software Courtesy of Jurgen Schulze, Calit2

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Autoimmune Diseases
Effect 5-8% of Americans

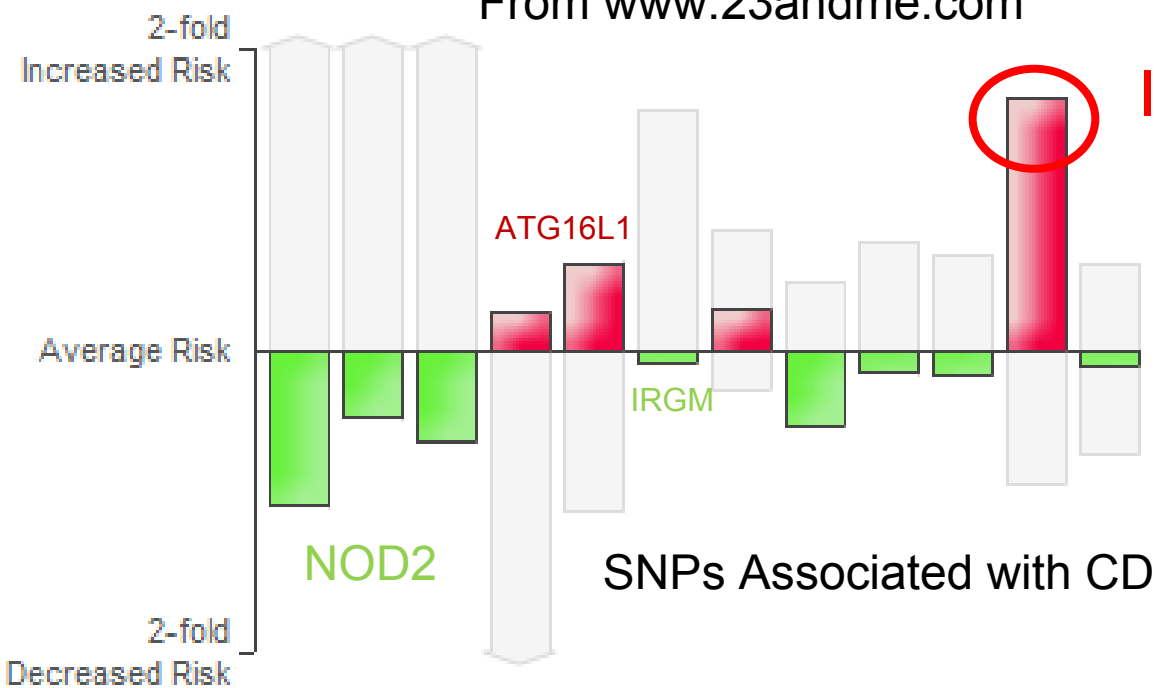
- **Crohn's Disease**
- **Ulcerative Colitis**
- **Rheumatoid Arthritis**
- **Multiple Sclerosis**
- **Psoriasis**
- **Type 1 Diabetes,**
- **Ankylosing Spondylitis**
- **Lupus Erythematosus**
- **Plus Over 70 Others**

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*
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

News and Views

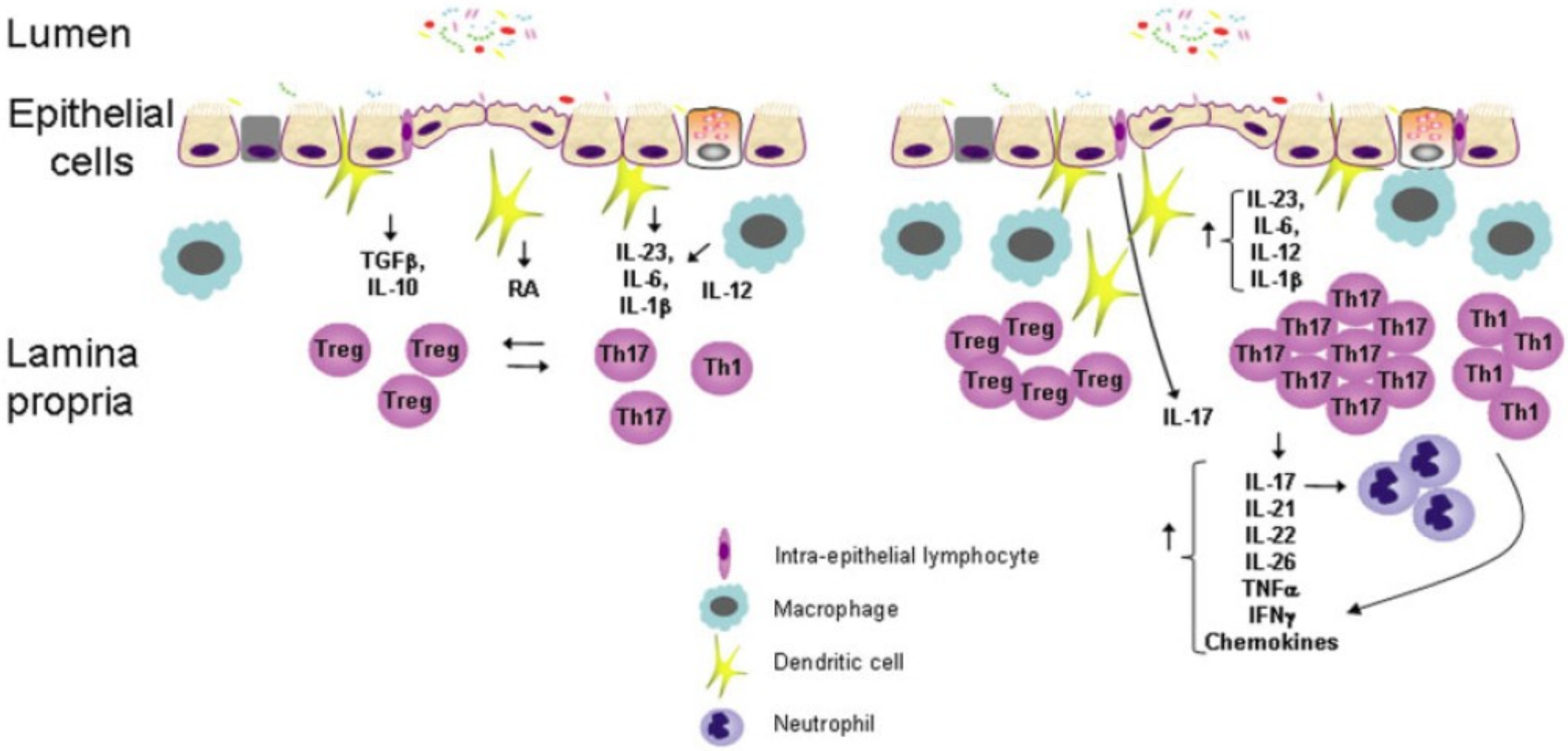
Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

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Genetic Mutation of IL-23 Leads to Pro-Inflammatory Excess



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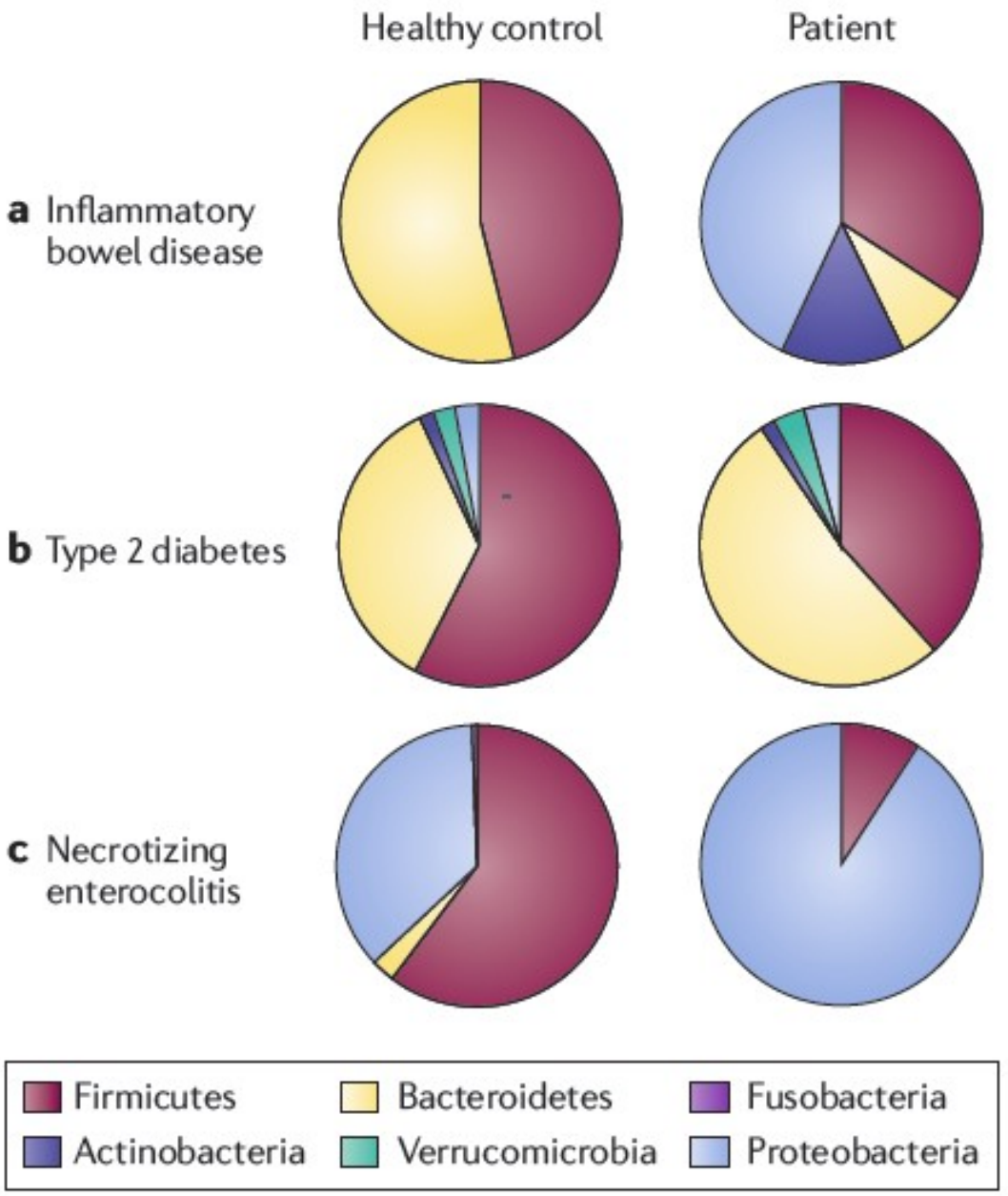
Interleukin-23/Th17 Pathways and Inflammatory Bowel Disease

Clara Abraham, MD, and Judy Cho, MD

Inflamm Bowel Dis • Volume 15, Number 7, July 2009

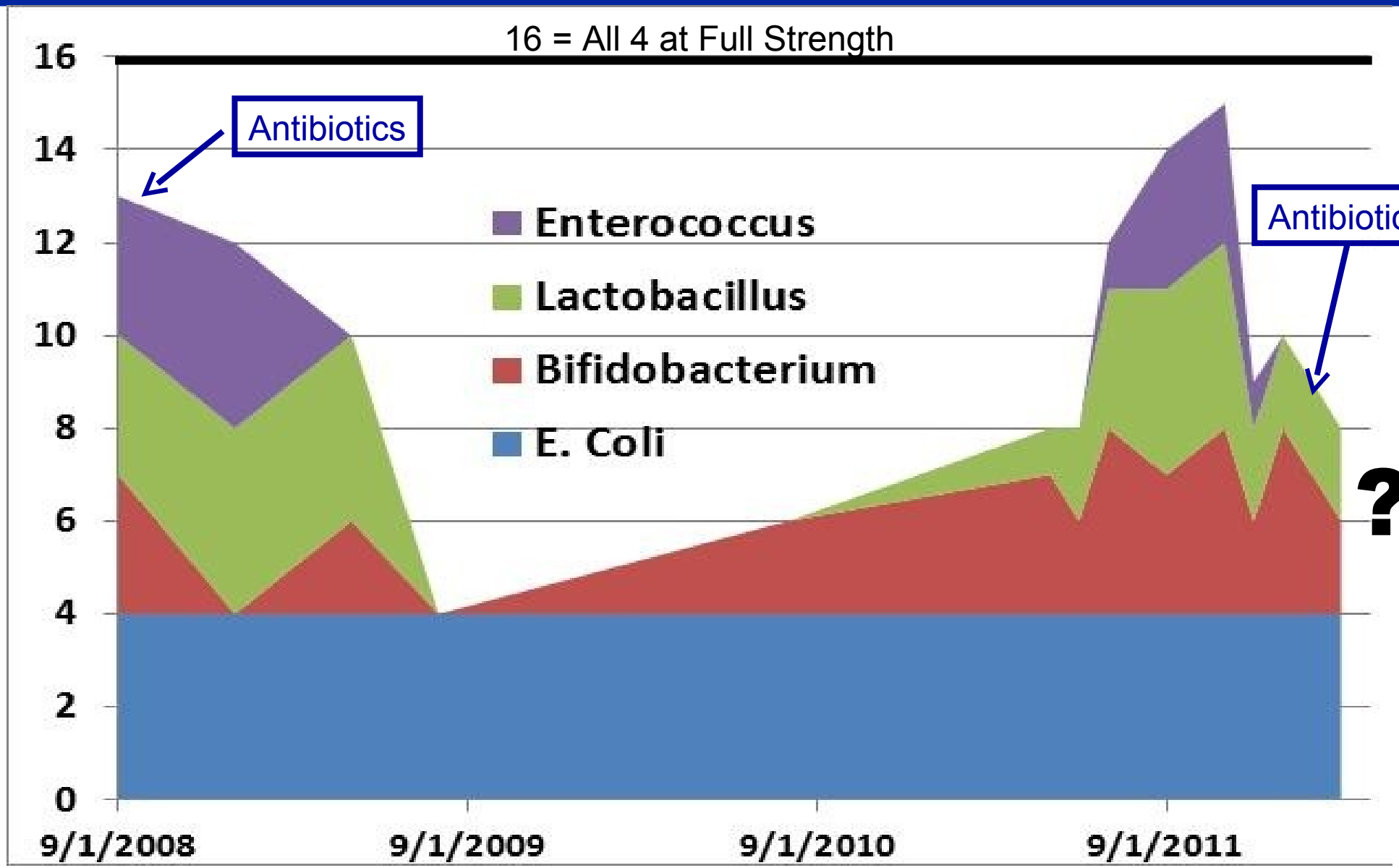
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Disease States are Associated With Major Shifts in Gut Microbiome Ecology



Nature Reviews Microbiology 9:279 (April 2011)

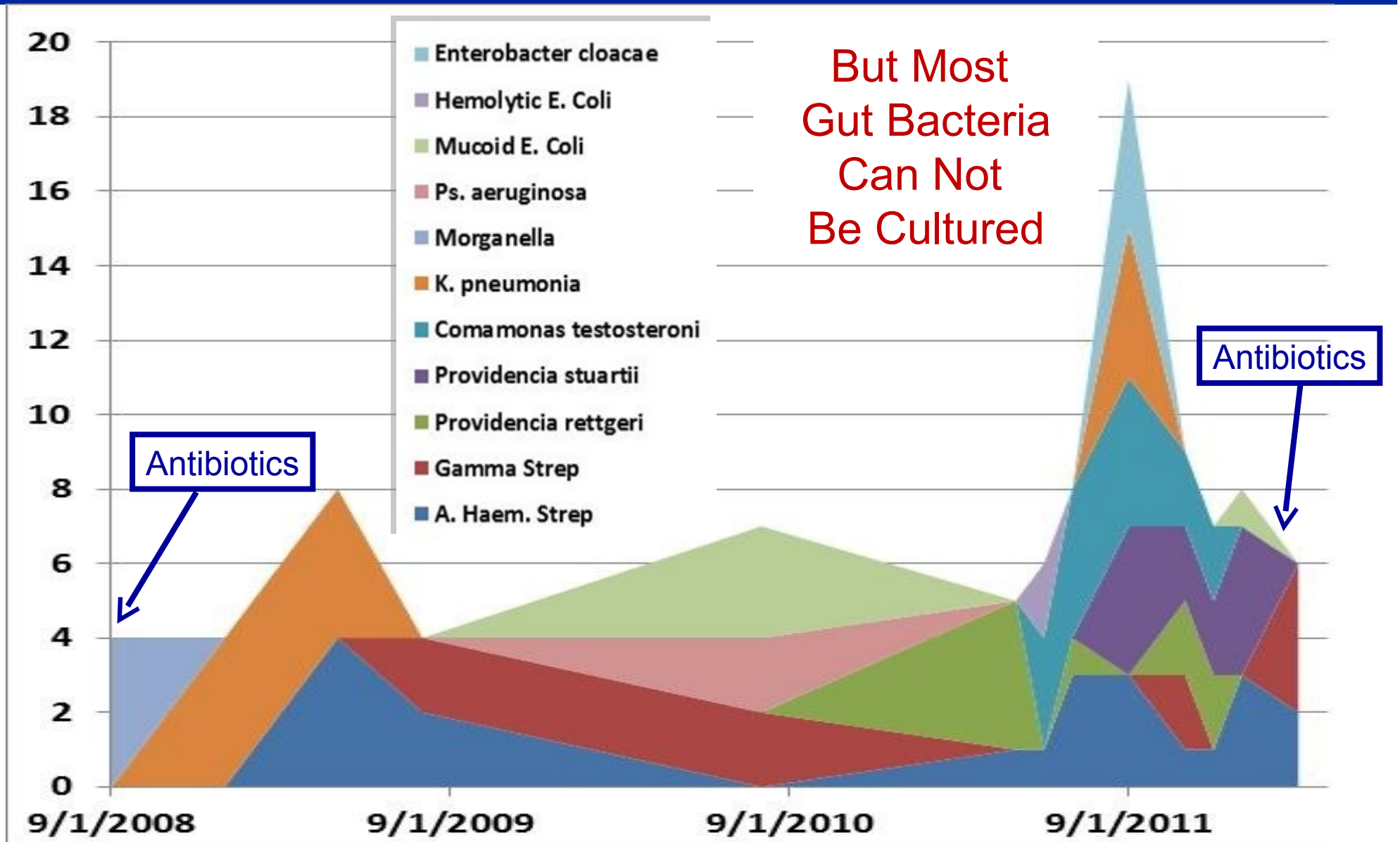
Except for E. Coli, My "Good" Cultured Gut Bacteria Collapsed After Antibiotics



Antibiotics: Levaquin & Metronidaloze

Values From www.yourfuturehealth.com stool test

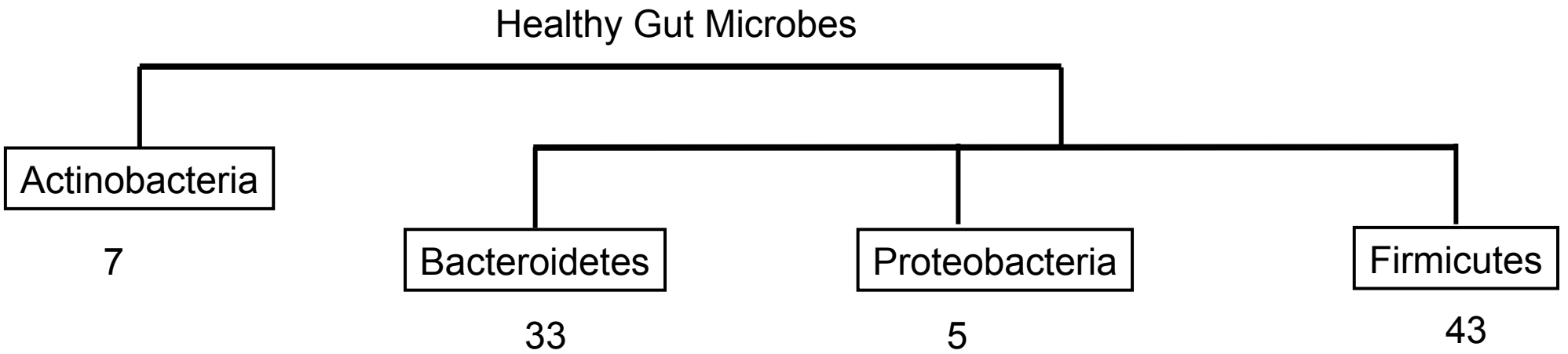
My Cultured "Bad" Dysbiotic Bacteria Have Been Flourishing

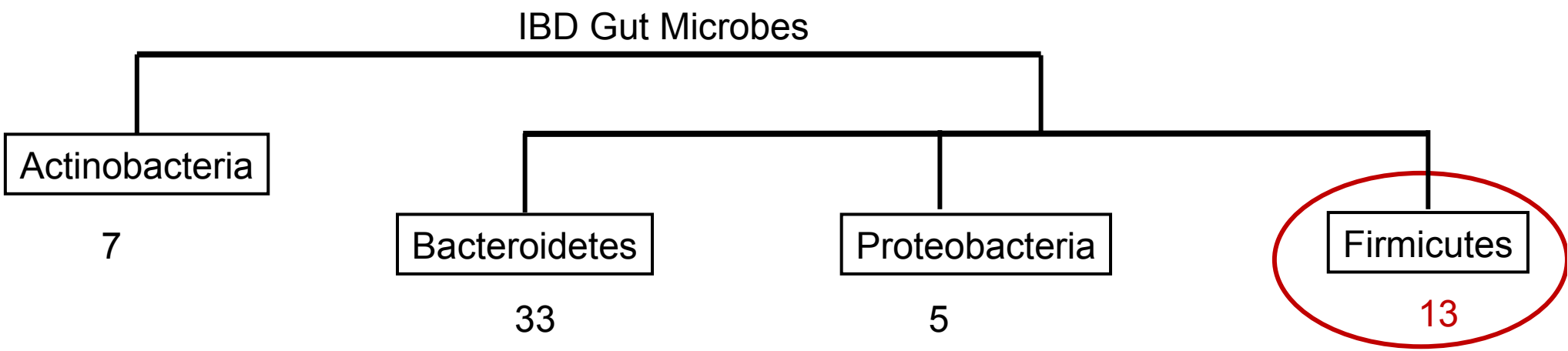


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Crohn's Disease Patients Have Number of Firmicute Gut Microbe Species Reduced by Over 2/3!





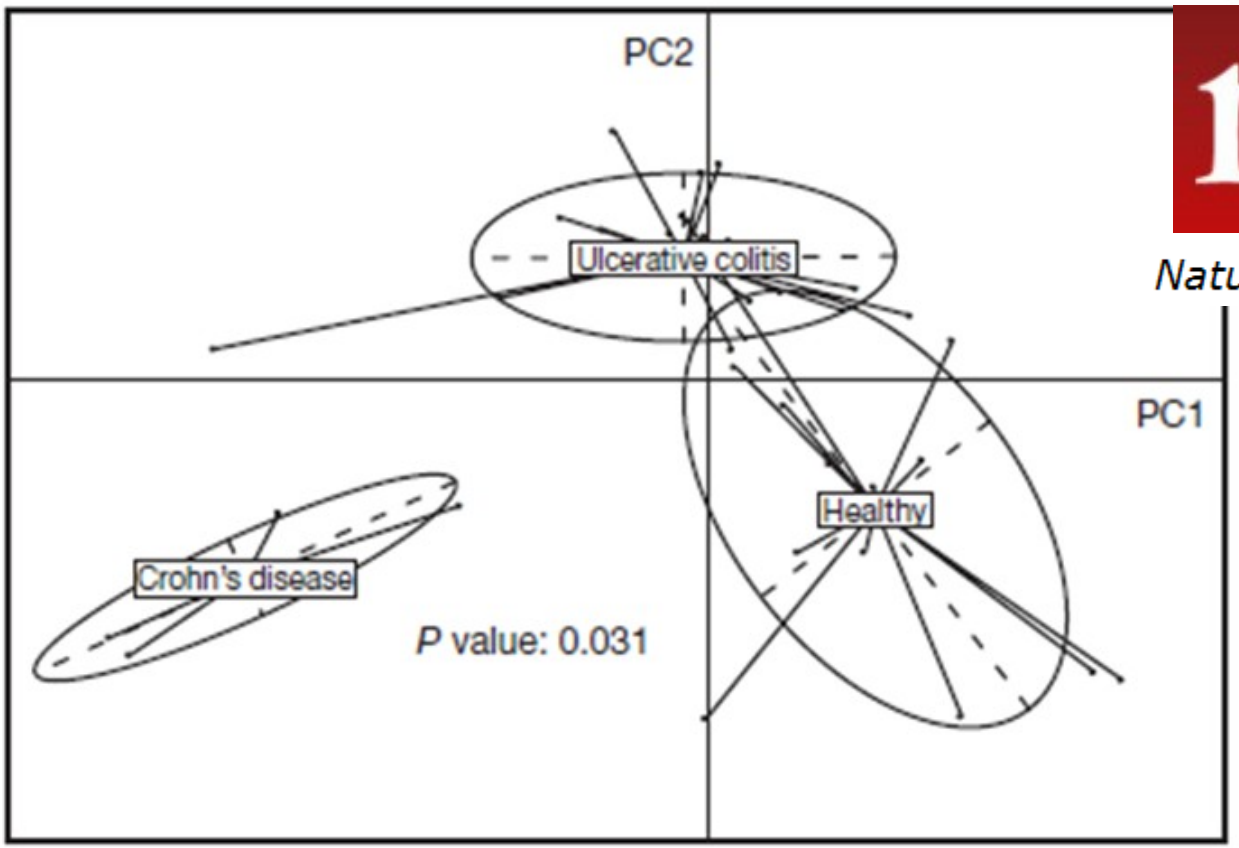
The Missing Firmicutes Inhibit Pro-Inflammation

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Manichanh, et al, *Gut* 2006;55:205–211

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Microbial Metagenomics Can Diagnose Disease States



nature

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

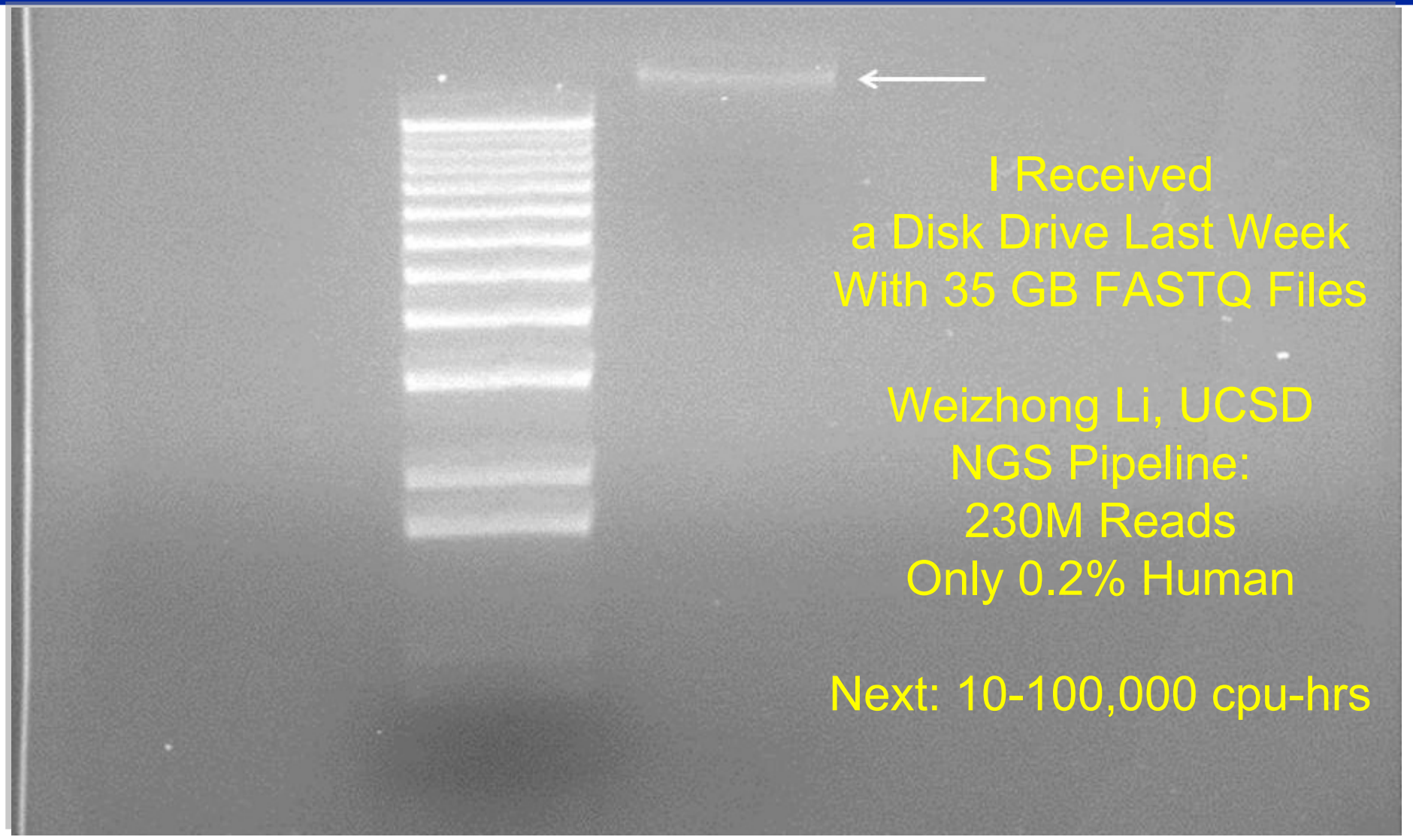
IBD Patients Harbored, on Average, *25% Fewer Microbial Genes* than the Individuals Not Suffering from IBD.

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],

First Stage of Metagenomic Sequencing of My Gut Microbiome at J. Craig Venter Institute



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

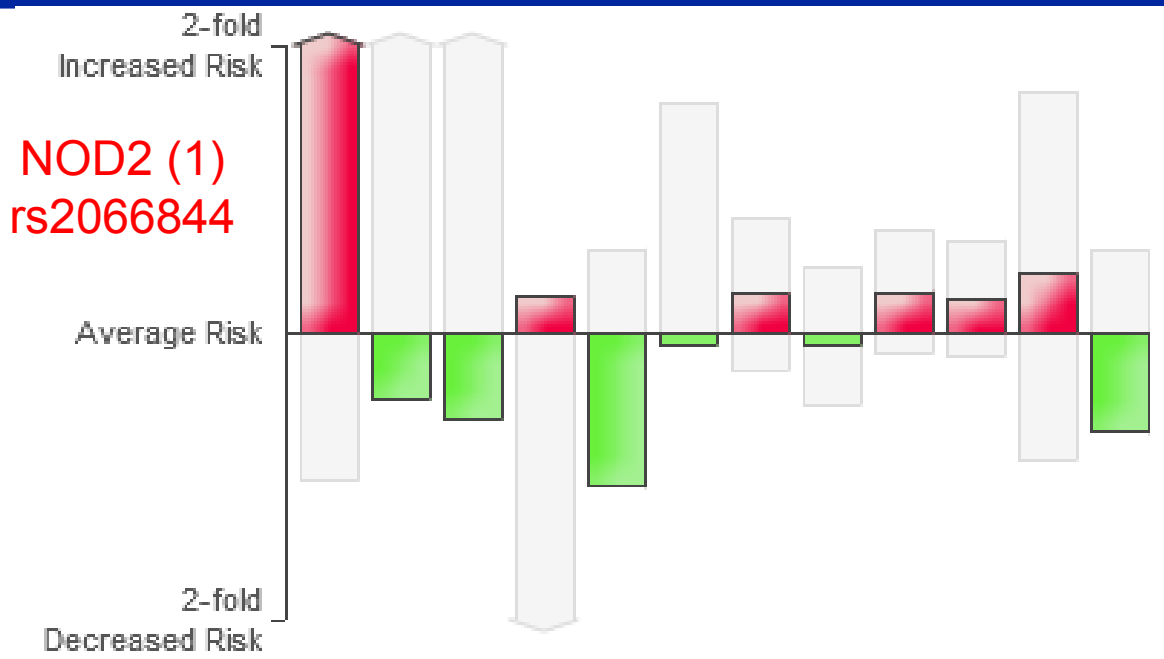
Manny Torralba, Project Lead - Human Genomic Medicine
J Craig Venter Institute

January 25, 2012

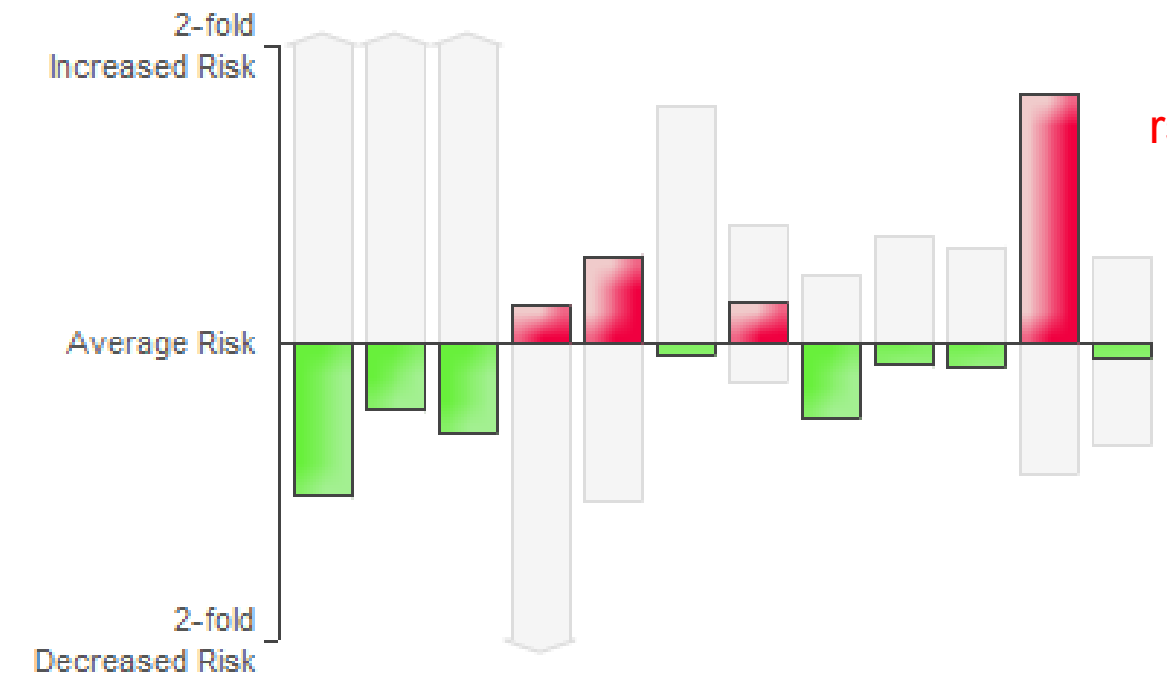
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Crohn's May be a Related Set of Diseases Driven by Different SNPs



Female
CD Onset
At 20-Years Old

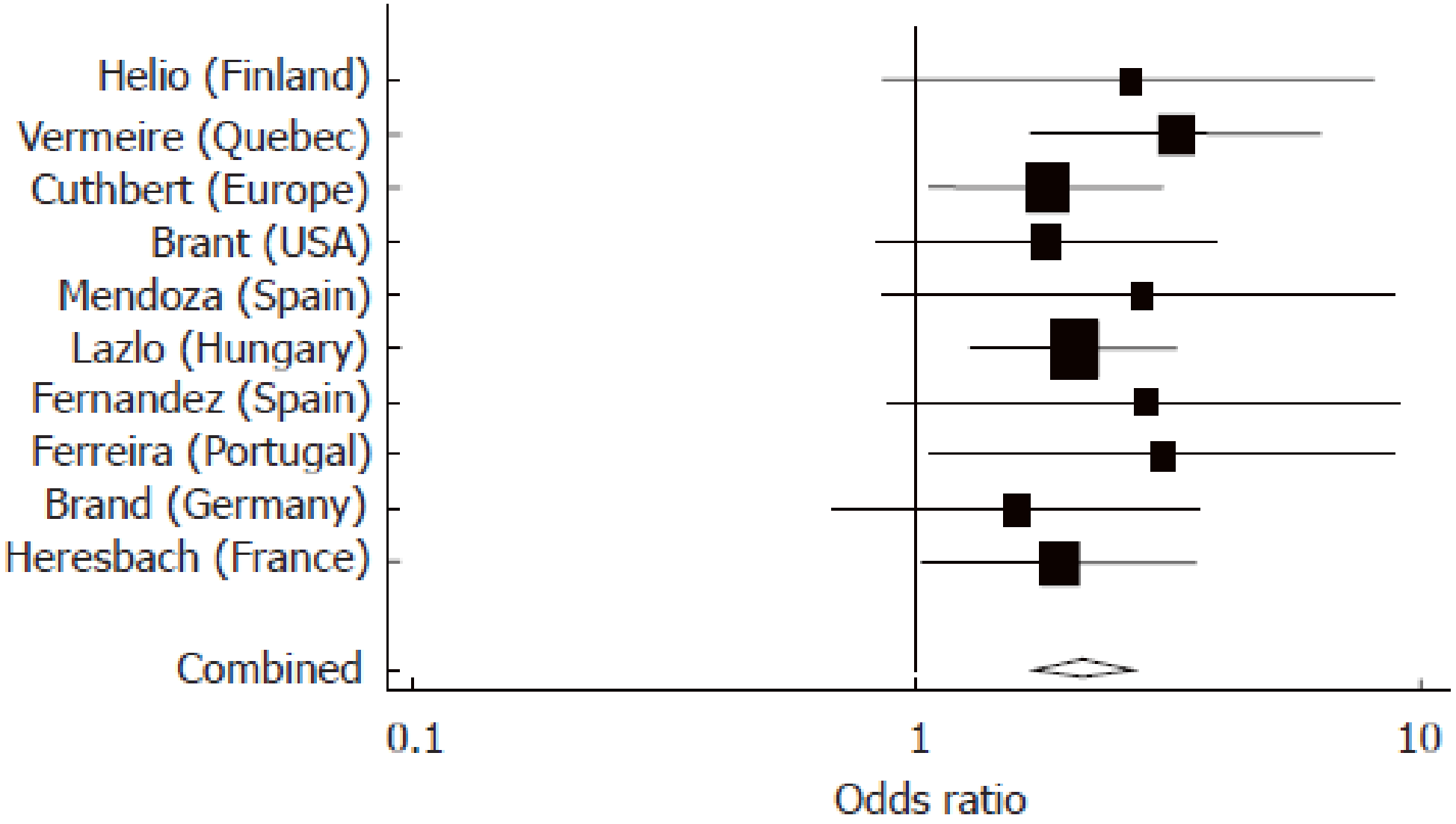


Il-23R
rs2066844

Me-Male
CD Onset
At 60-Years Old

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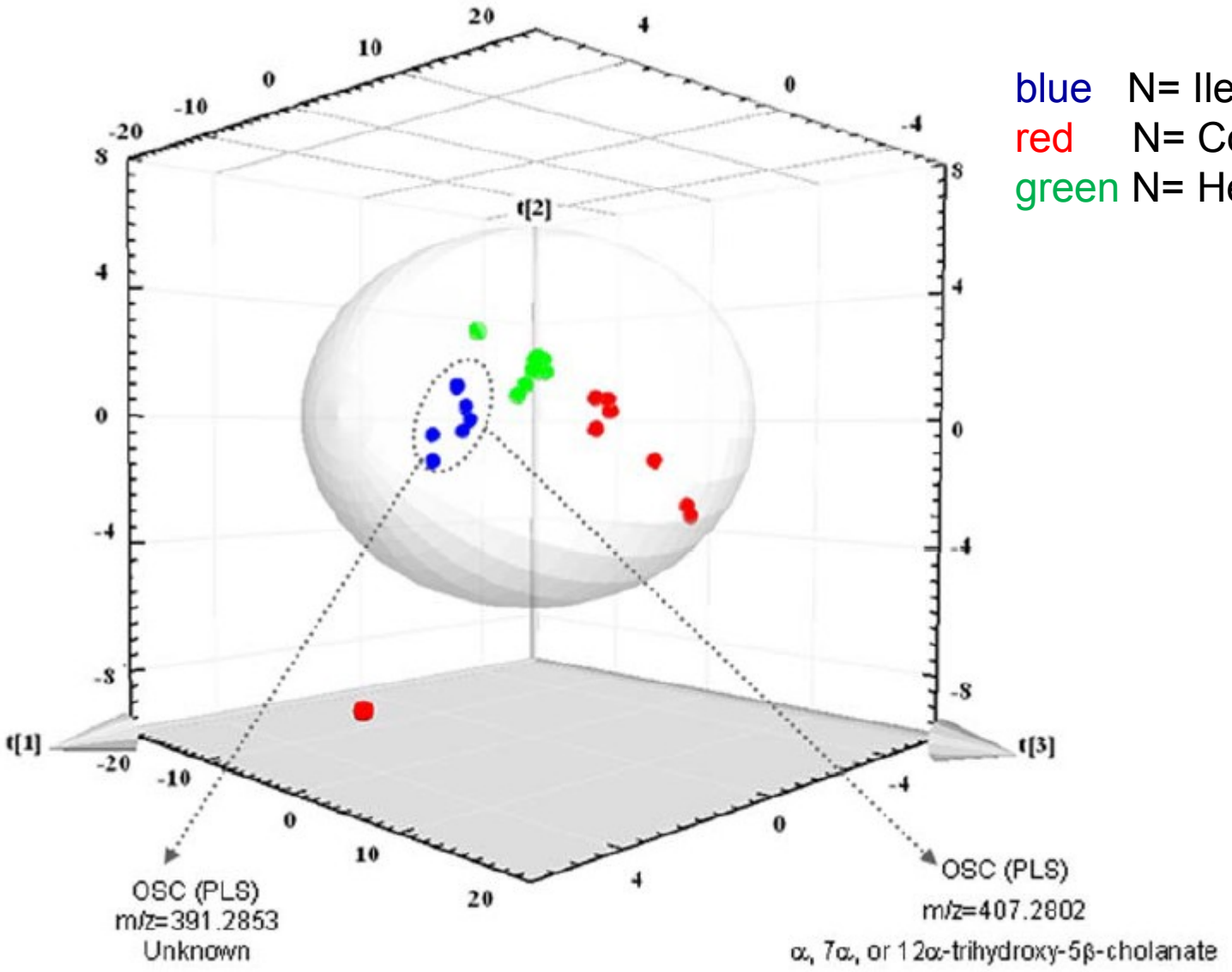
Meta-Study Shows NOD2 SNP is Correlated with Ileocolonic vs. Colonic CD



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Radford-Smith & Pandeva World J Gastroenterol 12: 7097 (2006)

Metabolomics Can Differentiate Ileum vs. Colon Inflammation in Crohn's Disease



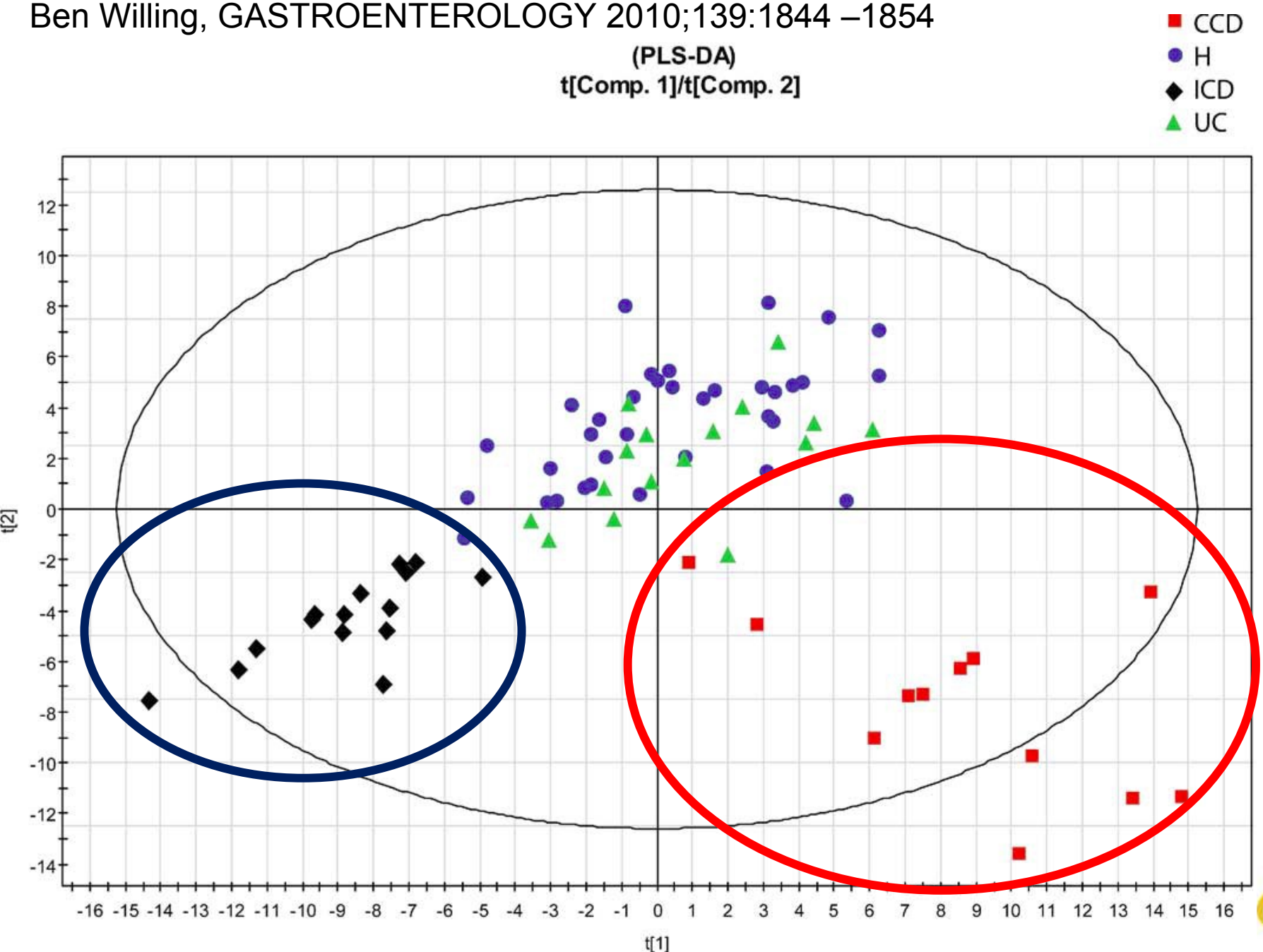
blue N= Ileum (ICD)
red N= Colon (CCD)
green N= Healthy

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Jansson, et al. PLOS ONE. July 2009 | Volume 4 | Issue 7 | e6386

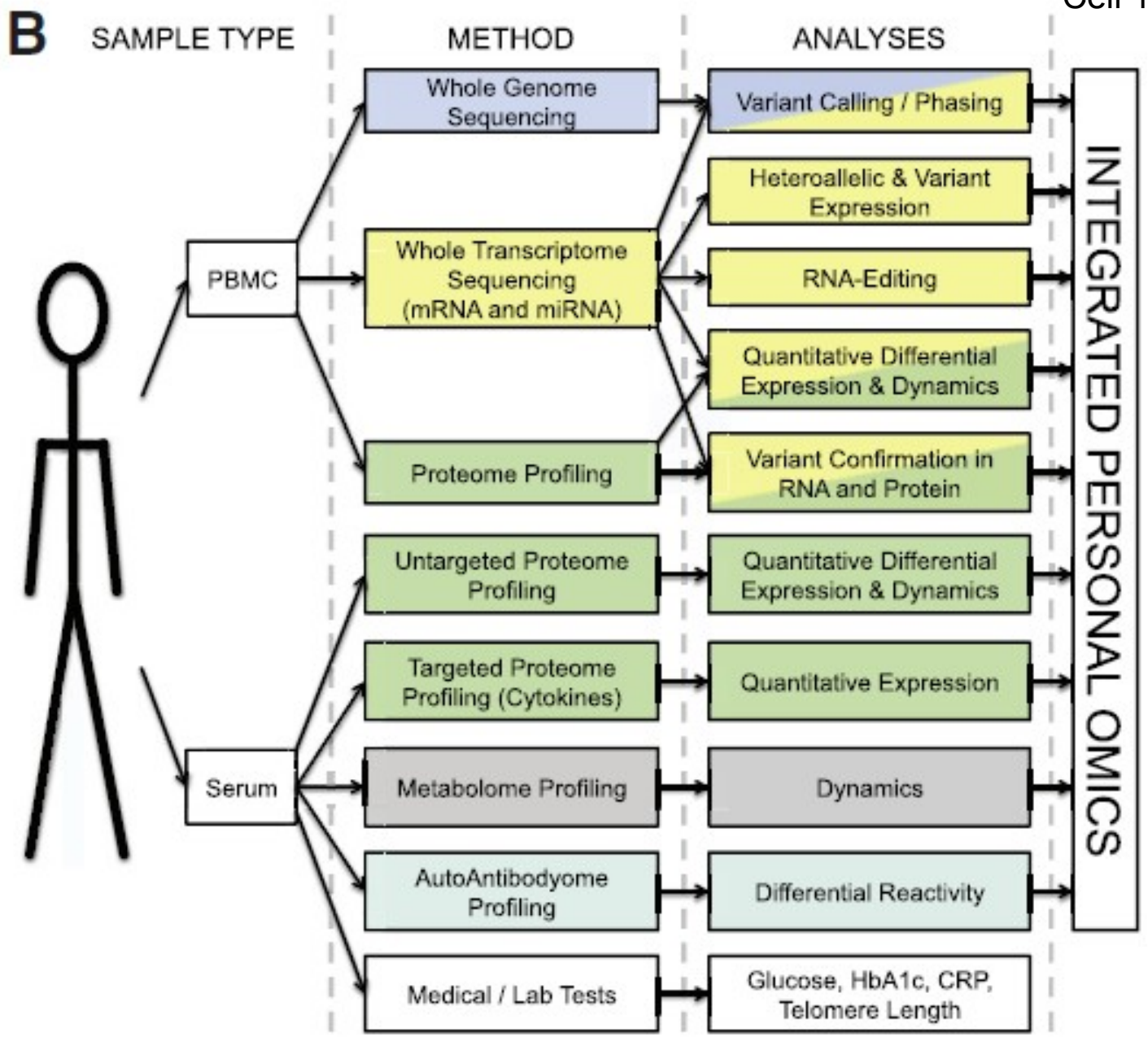
Discrimination of disease phenotypes based on microbial composition

Ben Willing, GASTROENTEROLOGY 2010;139:1844 –1854



Integrative Personal Omics Profiling: What I am Doing, But 1000 Times the Data!

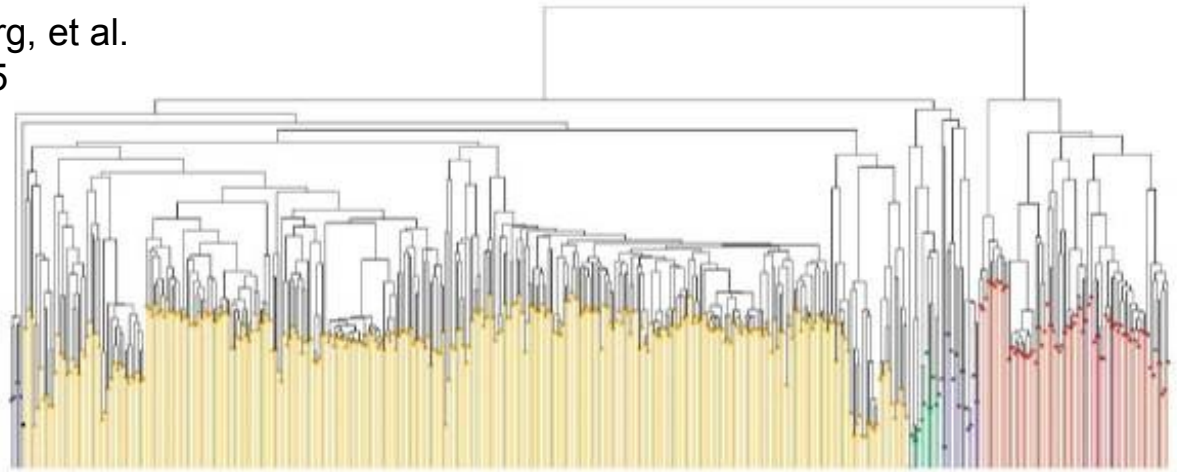
Cell 148, 1293–1307, March 16, 2012

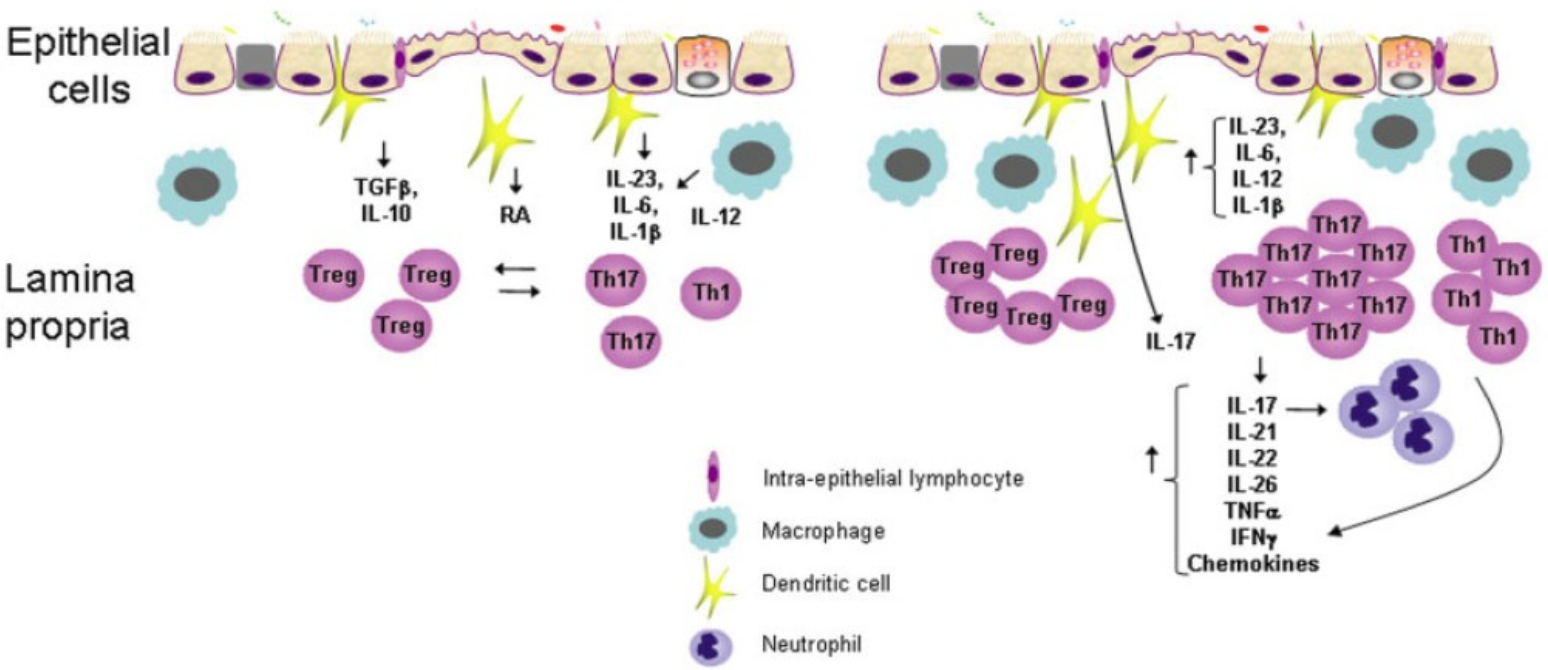


- **Michael Snyder, Chair of Genomics Stanford Univ.**
- **Genome 140x Coverage**
- **Blood Tests 20 Times in 14 Months**
  - **tracked nearly 20,000 distinct transcripts coding for 12,000 genes**
  - **measured the relative levels of more than 6,000 proteins and 1,000 metabolites in Snyder's blood**

Understanding Autoimmune Diseases Will Require Complete Genomes, Microbial Metagenomics Over Populations

From: Eckburg, et al.
Science 2005





Follow Molecular Interactions with Proteomics, Metabolomics, &Transcriptomics of Joint Genomic Production of Human DNA and Microbiome DNA

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~80% of Our Immune System is Based in our Gut