Towards Digitally Enabled Genomic Medicine: with a Personal Illustration of Clinical Discovery

Invited Talk
Grand Rounds, UCSD School of Medicine Pediatrics Division
Rady Children's Hospital
San Diego, CA
September 9, 2011

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 on Twitter: lsmarr

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

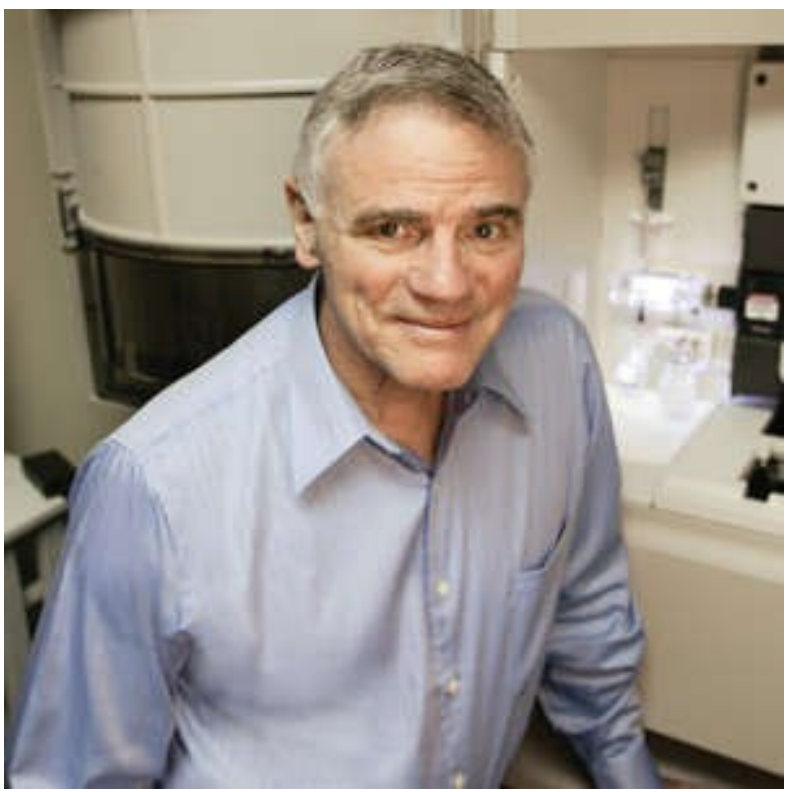
Newsweek

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



Quantify ~2500 Blood Proteins,
50 Each from 50 Organs or Cell Types
from a Single Drop of Blood
To Create a Time Series

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

it²

Calit2 is Engaged with UCSD/UCI Schools of Medicine in Prototyping the Digital Transformation of Health

- **Explosion of Individual's Biomedical Data**
  - **Time Series of Key Markers Become Routine**
  - **Greatly Lowered Cost of Testing via Nanotechnology**
  - **Wireless Social Networking Technologies will Enable More Effective Wellness Interventions**
  - **Population-Wide Individual Genetic Sequencing**
- **System Biology Approach to Understanding Disease**
- **Shift from "Sickness" to a "Wellness" Paradigm**
  - **Individuals Take Responsibility for Staying Healthy**
  - **Redirection Of Resources to the Promotion of Children's Health as a Foundation for Lifetime Health**

I am Using Myself as a Ongoing Experiment in Probing this Emerging Paradigm

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

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

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I am the Future Digital Health Consumer: Measuring the State of Your Body and "Tuning" It

I Arrived in La Jolla in 2000 After 20 Years in the Midwest and Decided to Move Against the Obesity Trend

Age 51





Age 61

HEALTH IT, PEOPLE, WIRELESS

How Internet Pioneer Larry Smarr Lost 20 Pounds by Becoming a "Quantified Self"

Luke Timmerman 5/12/10

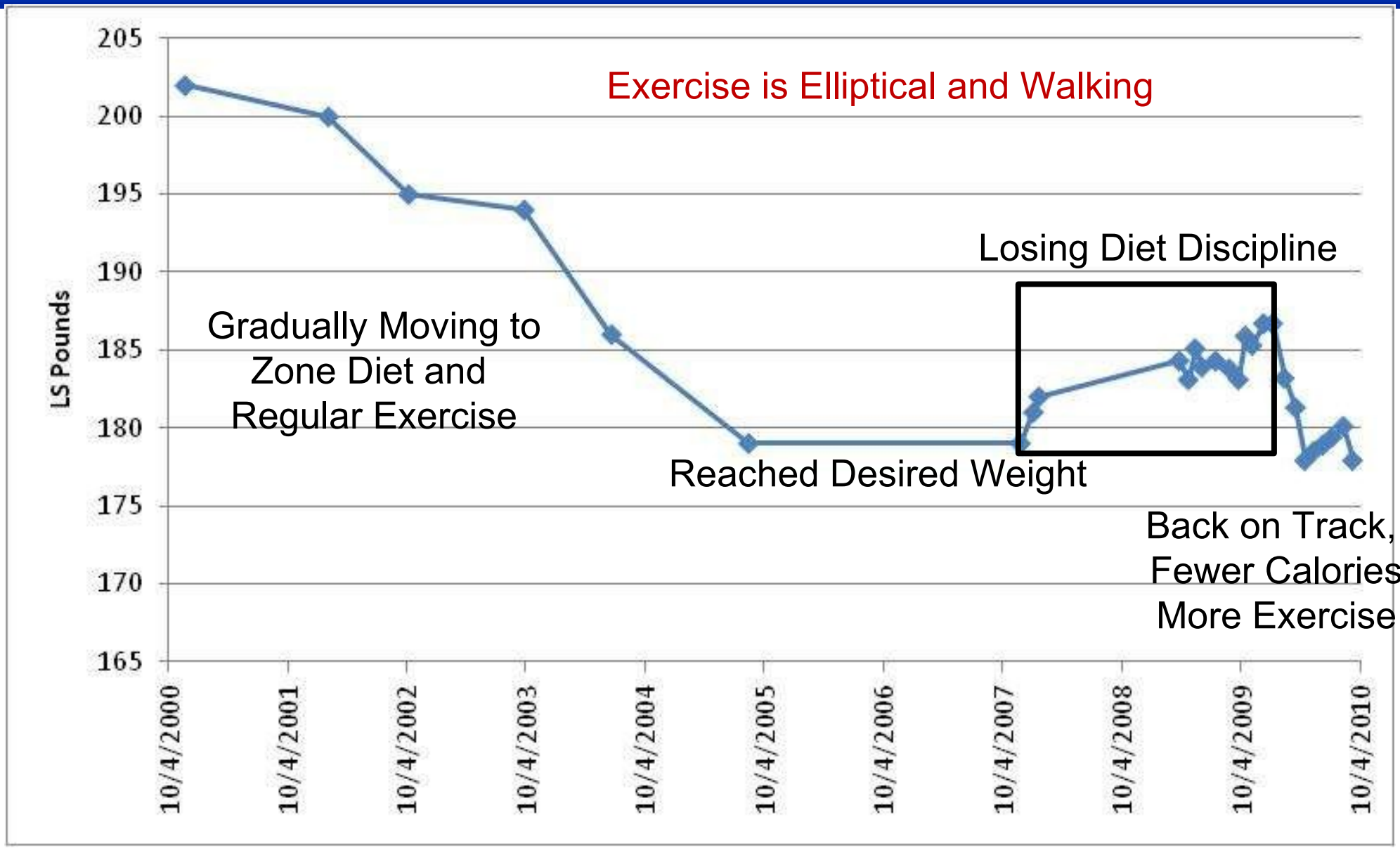
Now the Top Listed Article By Google for "Larry Smarr"

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www.xconomy.com/san-diego/2010/05/12/how-internet-pioneer-larry-smarr-lost-20-pounds-by-becoming-a-quantified-self/

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Goal: Lose Weight by Changing What &How Much I Eat, While Increasing Aerobic Exercise



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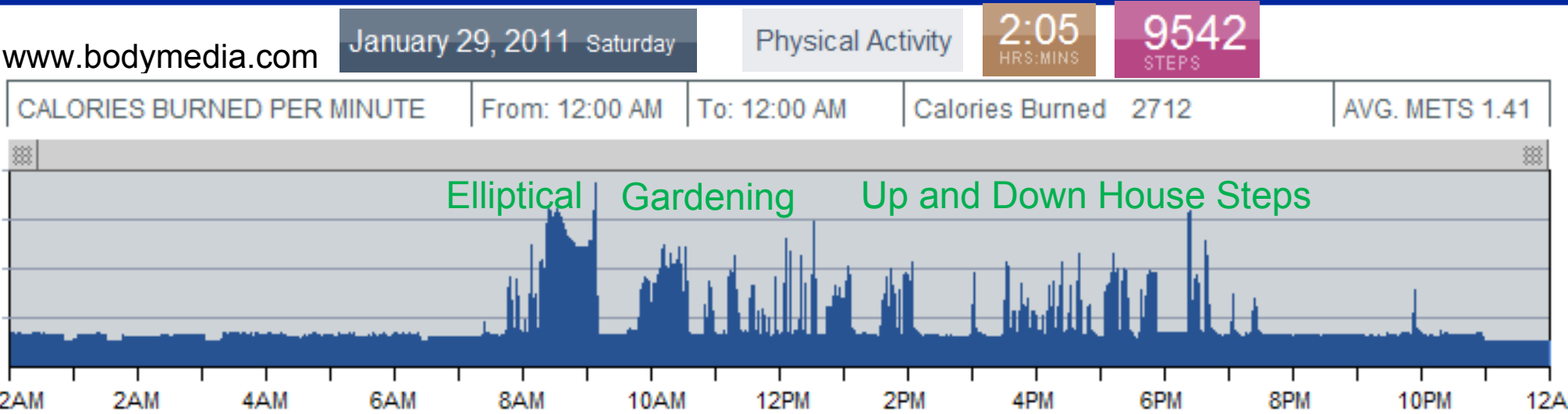
Blood Pressure 134/73 Pulse 55
Resting Pulse Lowered to 45

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Consumer Devices Allow For Recording My Metabolic Self

BODYMEDIA® Know your Body. Change your life

www.bodymedia.com



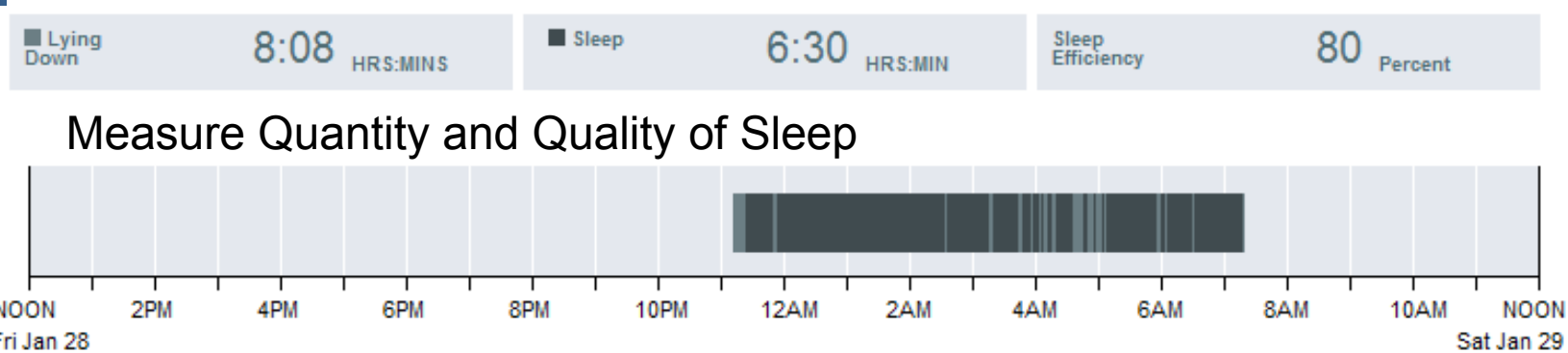


25 Week Average:

2473 Calories Burned/Day

1:19 hr Physical Activity/Day (>3 METs)

6887 Steps/Day (~3.4 Miles)

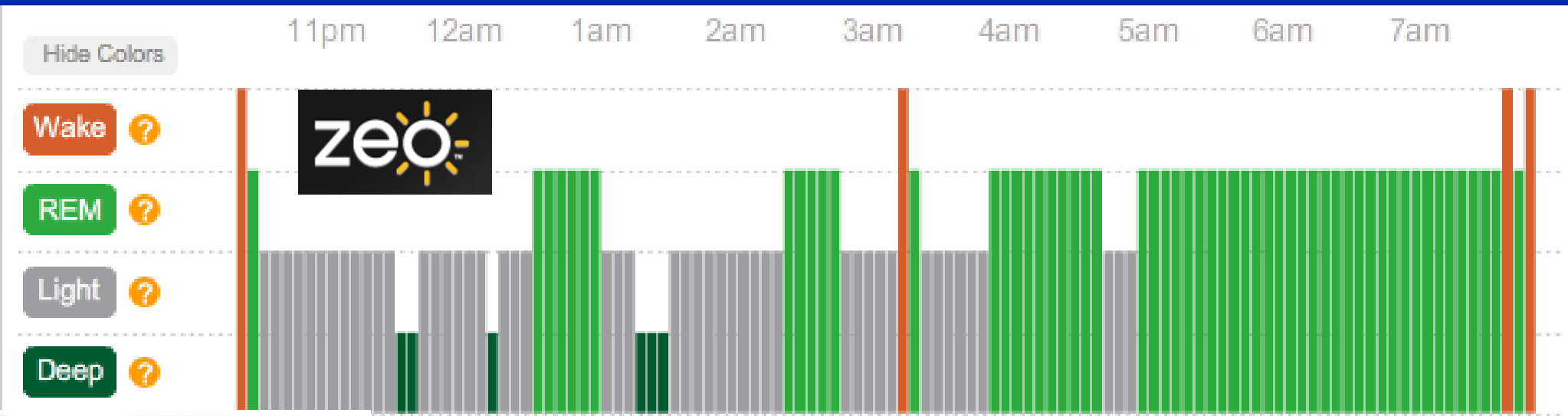


25 Week Ave: 6:51 hrs with 81% Efficiency

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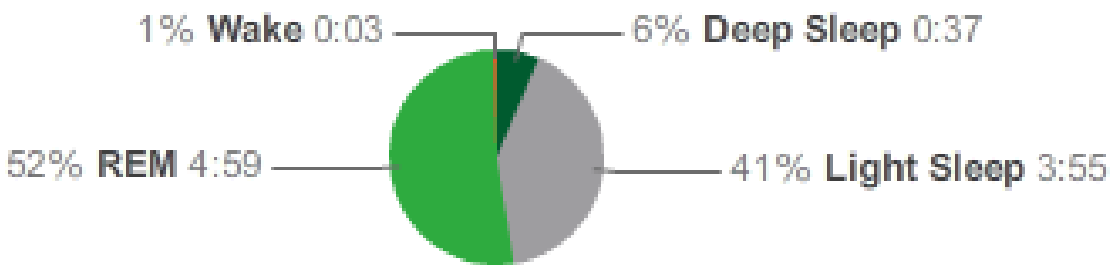
Quantifying My Sleep Pattern Using Zeo - Surprisingly About Half My Sleep is REM!





Total Z: 9 hr 31 min

Time to Z: 0 hr 2 min



Why are these numbers different from the sleep graph above?

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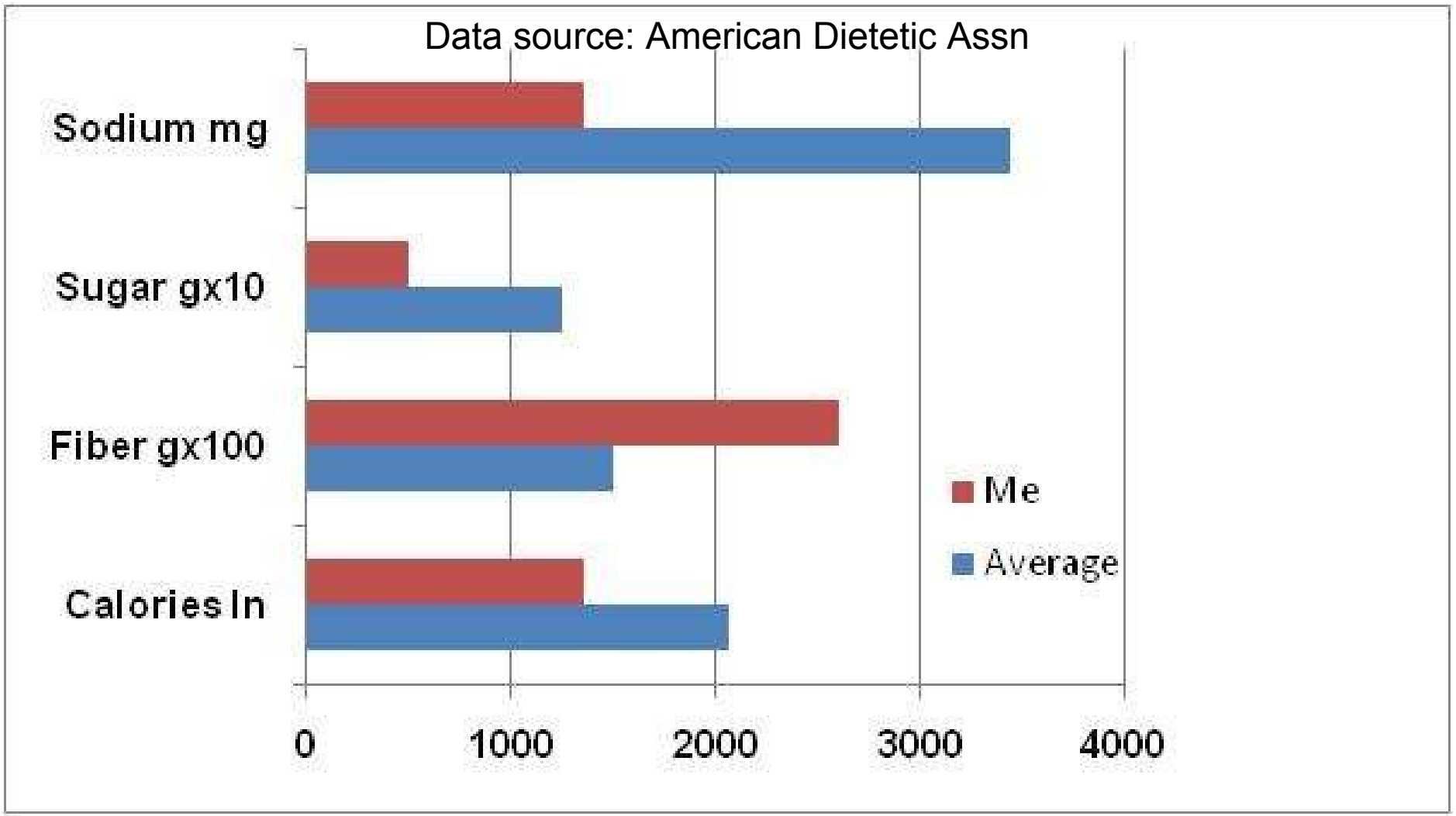
REM is Normally 20% of Sleep
Mine is Between 45-65% of Sleep

An Infant Typically
Has 50% REM

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Goals: Reduce Calories, Sugar, and Sodium Intake, While Increasing Fiber

Also, Average American Drinks 526 12-oz Sodas per Year--Me Zero



Me Compared to Average American Male Over 60

Goal: Quantify Your Food Intake So You Can "Tune" Your Glucose/Insulin System and Lower Inflammation

Computed Average Over 12 Days When at Home for Maximum Accuracy
Measure All Food and Drink Components,
Then Use USDA Lookup to Compute Each Item

calories	fat	carb	protein		fiber	sugar	sodium
kcal	g	g	g		g	g	mg
1441	46	122	80	0	26	53	1358

Still Need to Lower Sugar &
Increase Protein and Decrease Fat by 15%

- **Quality of Food**
  - **All Organic and Mostly Locally Grown**
  - **Carbs are Low Glycemic Index**
    - **No Added Sugar or Refined Flour – Mostly Fruits and Vegetables**
  - **Proteins are Lean**
    - **Meat is Grass Fed – No Corn or Antibiotics**
    - **Fish is Wild, Often Locally Caught**
  - **Fats are Omega-3 Rich**
    - **Supplemented by 7g Daily Pharmaceutically Purified Fish Oil Pills**

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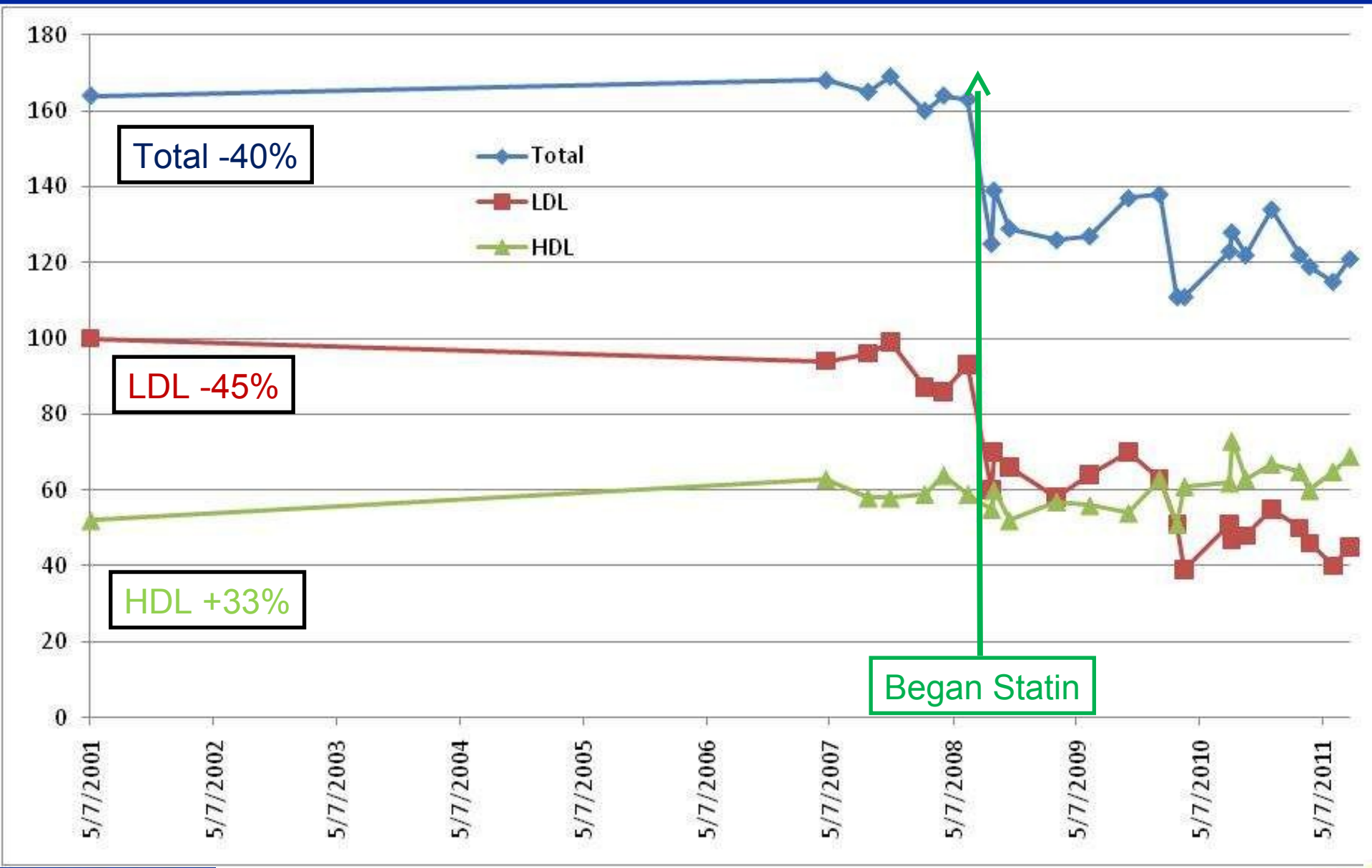
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Blood Tests I Do Quarterly to Annually In Addition to hsCRP, Lipids, Minerals, & Omegas

- **Electrolytes**
  - Sodium, Potassium, Chlorine, CO_2
- **Blood Sugar Cycle**
  - Glucose, Insulin, A1C Hemoglobin
- **Bones**
  - Alkaline Phosphatase
- **Kidneys**
  - Bun, Creatinine, Uric Acid
- **Protein**
  - Total Protein, Albumin, Globulin
- **Liver**
  - GGTP, SGOT, SGPT, LDH, Total and Direct Bilirubin
- **Thyroid**
  - T3 Uptake, T4, Free Thyroxine Index, FT4, 2nd Gen TSH
- **Heart**
  - Homocysteine
- **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.
- **Others**
  - Ferritin
  - Progesterone
  - Testosterone, Total and Free
  - FSH
  - Estradiol

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Goal: Change Your Cholesterol Levels to Lower LDL, Raise HDL, While Lowering Total

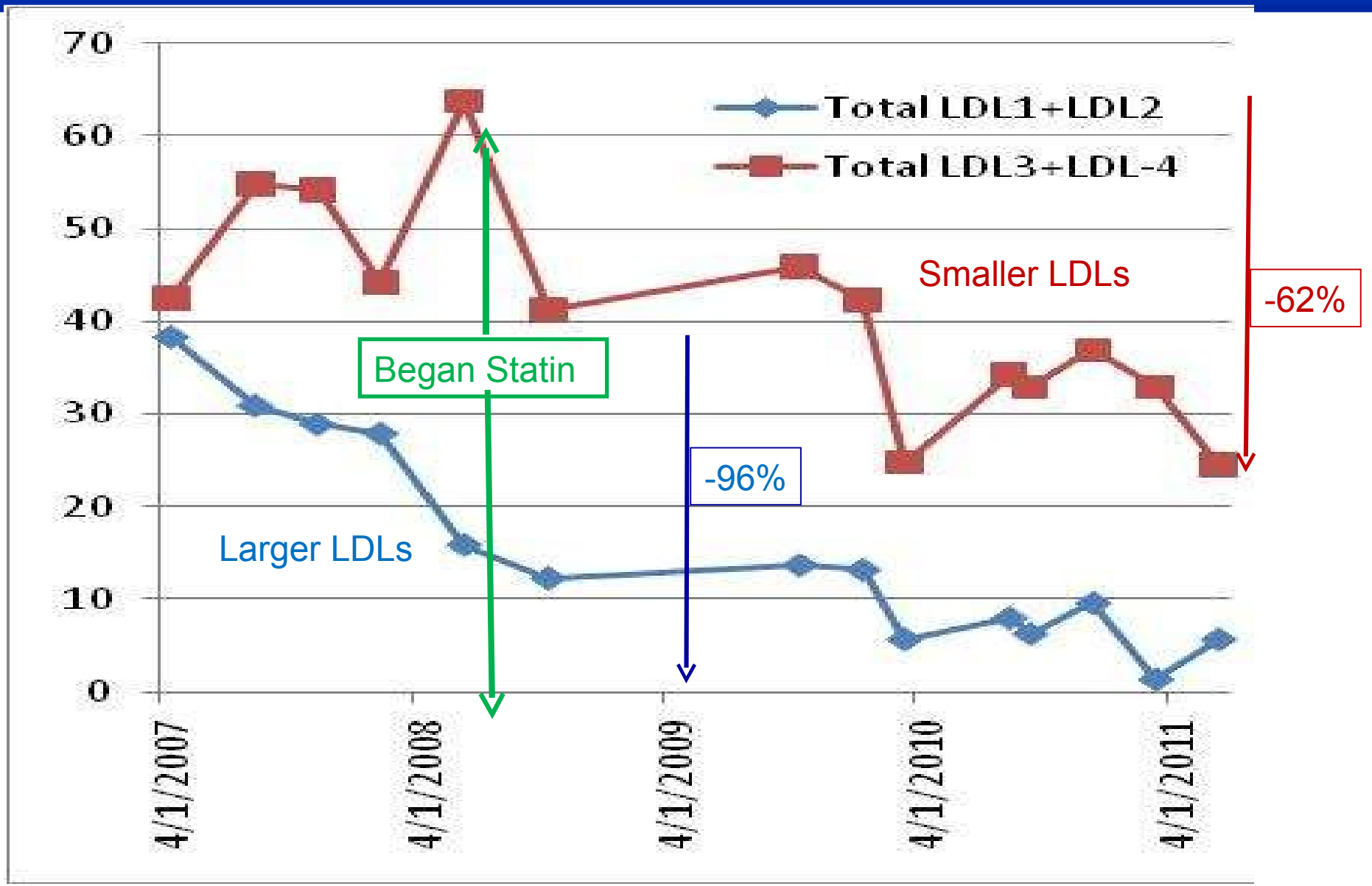


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Raising “Good” HDL Seems Most Difficult

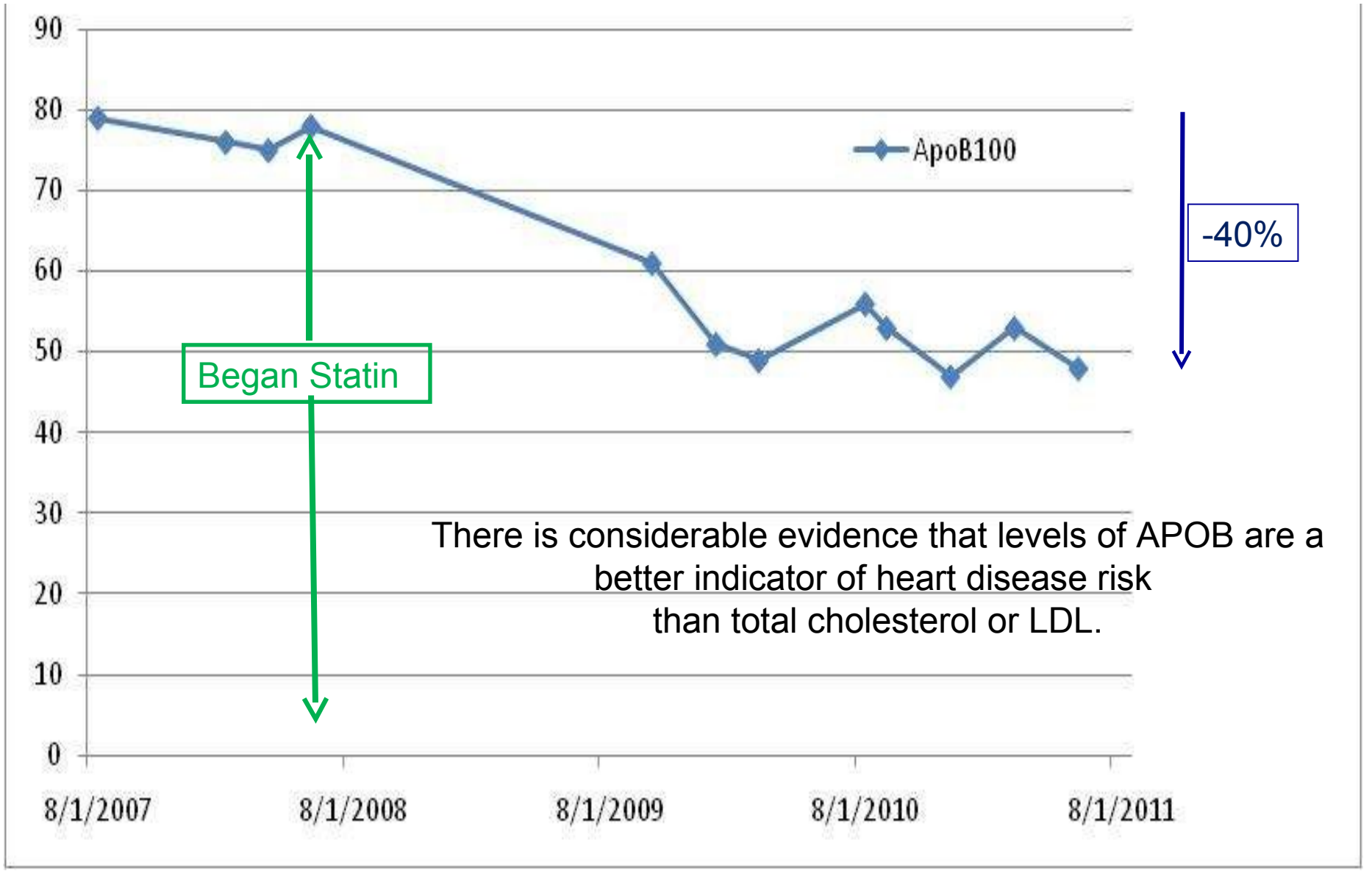
it²

Goal: Major Reductions in LDL Subfractions to Avoid Future Plaque Deposits, Particularly Smaller LDLs



Data Source: Scripps Clinic of Integrative Medicine

Lowered ApoB100 After Taking Statin—High Levels of APOB can Lead to Plaques that Cause Vascular Disease



There is considerable evidence that levels of APOB are a better indicator of heart disease risk than total cholesterol or LDL.

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Apolipoprotein B

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Goal: Lower Triglycerides and Cholesterol Ratios to Reduce Future Risk of Diabetes and Heart Disease

- **TG**
  - **High Risk 200-500**
  - **Best <150**
  - **My TG ~35**
- **TG/HDL**
  - **Ratio>4 Are Pre-Diabetic or Have Type 2 Diabetes**
  - **Average American Has a Ratio of ~3.3**
  - **My Ratio 0.5**

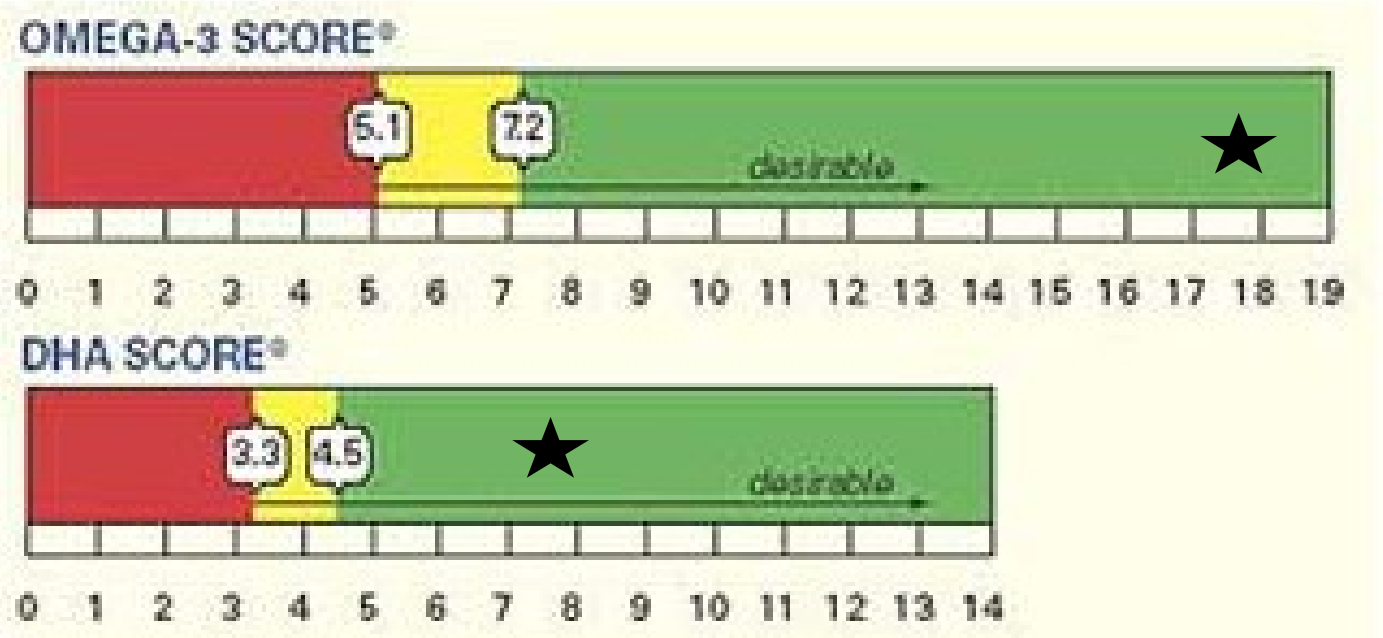
"The Ratio of Triglycerides to HDL Cholesterol (TG/HDL-C) is the Single Most Powerful Lipid Predictor of Extensive Coronary Disease."
[Clinics 2008; v.64: 427-432]

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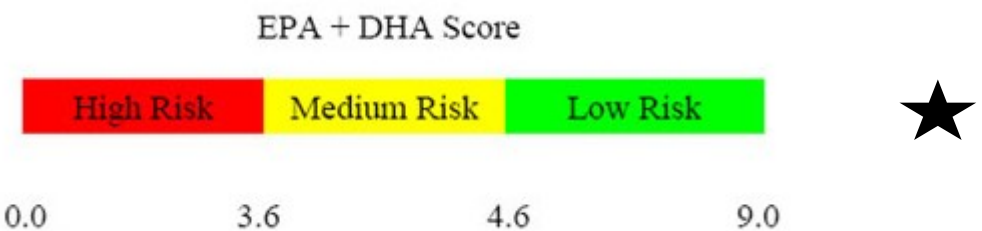
Goal: Improve My Omega-3 ScoresTo Reduce Inflammation & Protect Against Future Heart Disease

Graphics from www.anne-marie.ca/ratiokits/

If your Omega-3 Score is at least 7.2 and your DHA Score is at least 4.5, you are 32% less likely to develop heart disease



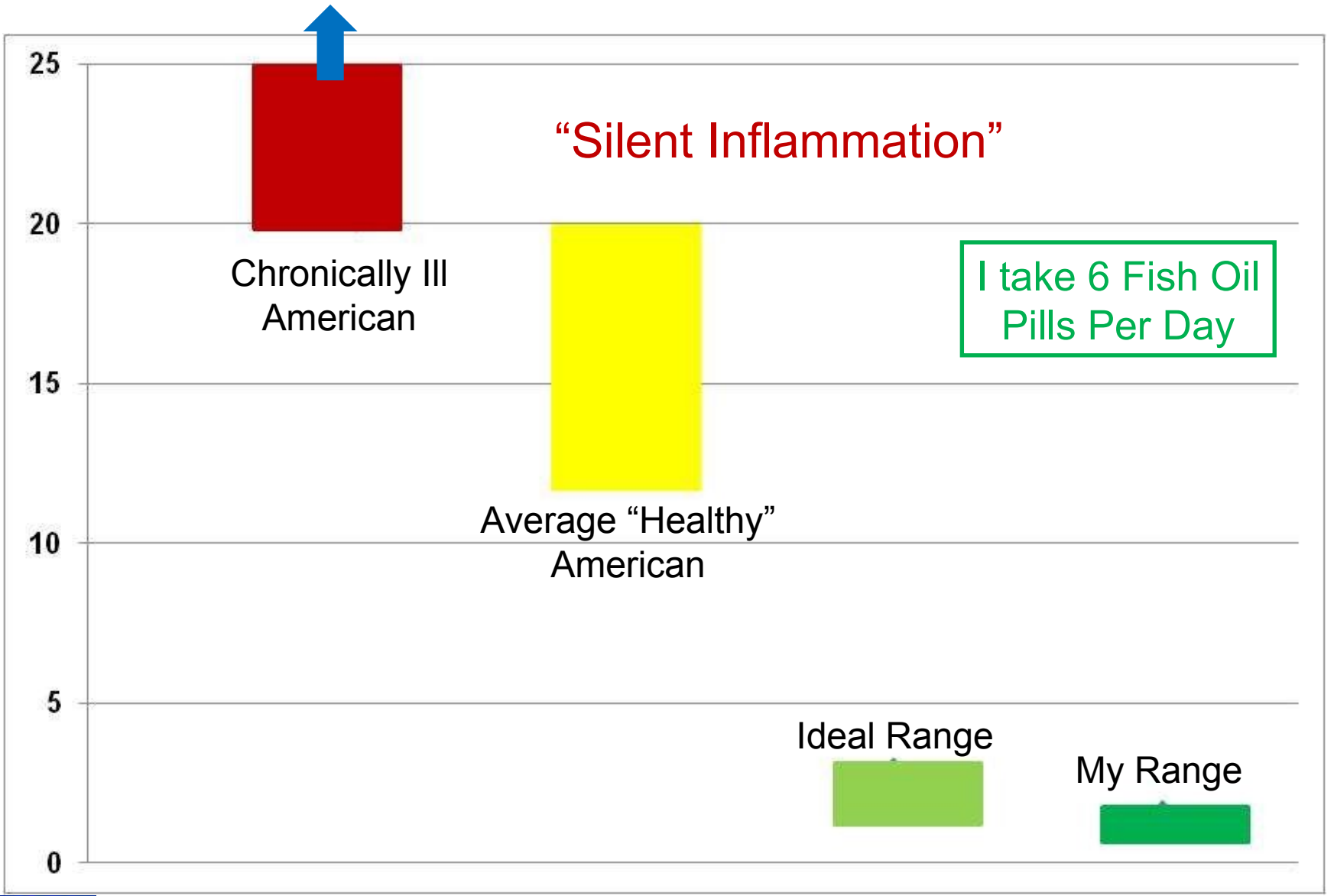
If your EPA+DHA Score is at least 4.6, you are 70% less likely of dying from a heart attack.



★ = My Values Tested by yourfuturehealth.com

Ref: Based on Lemaitre et al., n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am. J. Clin. Nutr. 77:319-325 (2003).

Goal: Lower Ratio of Arachidonic Acid to EPA to Reduce Pro-Inflammatory Potential of Your Cells

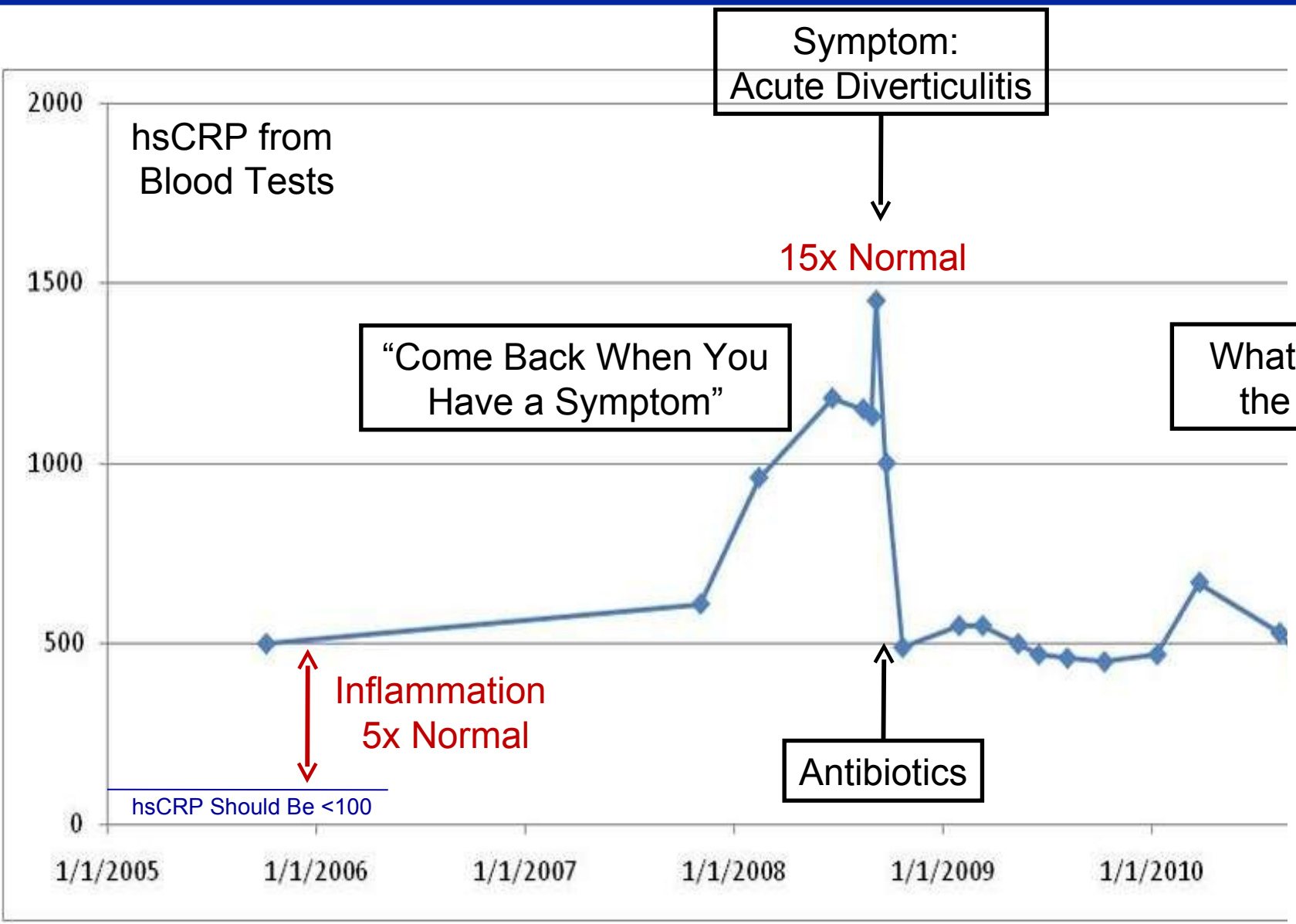


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Range Source: Barry Sears
My Tests by www.yourfuturehealth.com

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But, In Spite of My High Levels of Omega-3s, Blood Measurements Show Chronic Inflammation



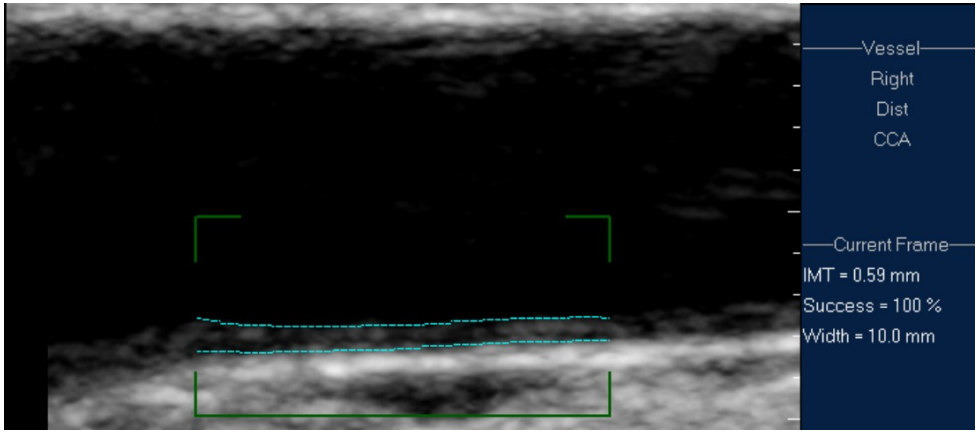
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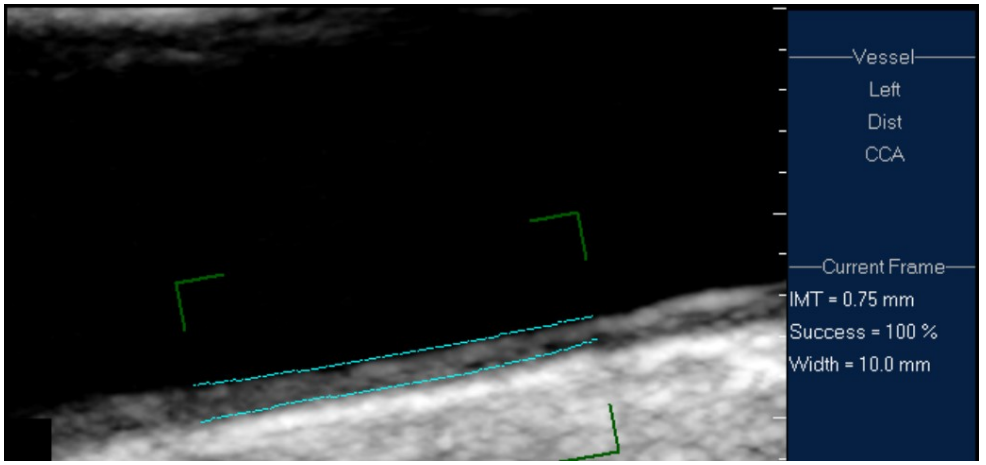
This Non-Dietary Chronic Inflammation is Driving Plaque Formation in My Blood Vessels

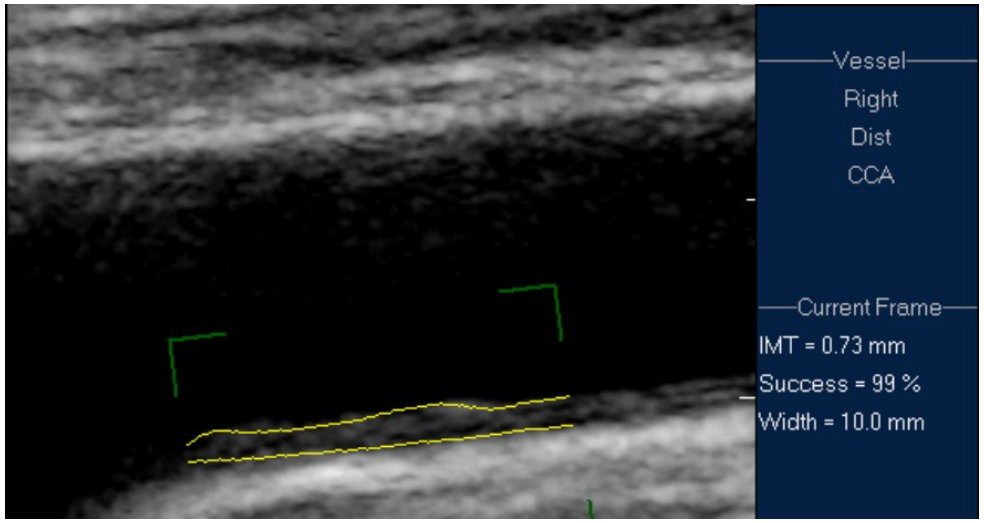
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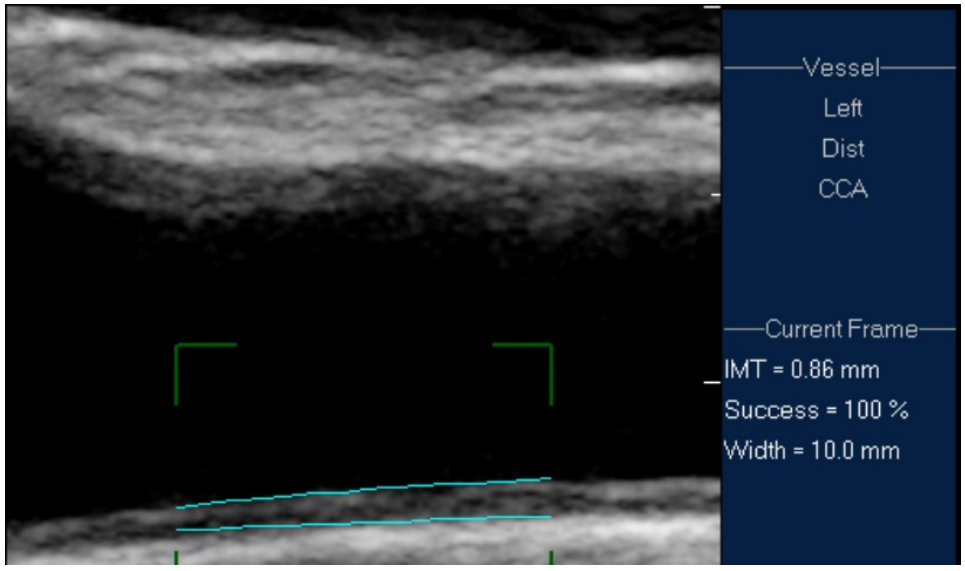
Carotid Artery Ultrasound Reveals Plaque Thickness Significantly Increasing In Just Two Years

Oct 31 2008









October 14, 2010

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Right 0.59 to 0.73mm
24% Thicker Plaque

Left 0.75 to 0.84 mm
12% Thicker Plaque

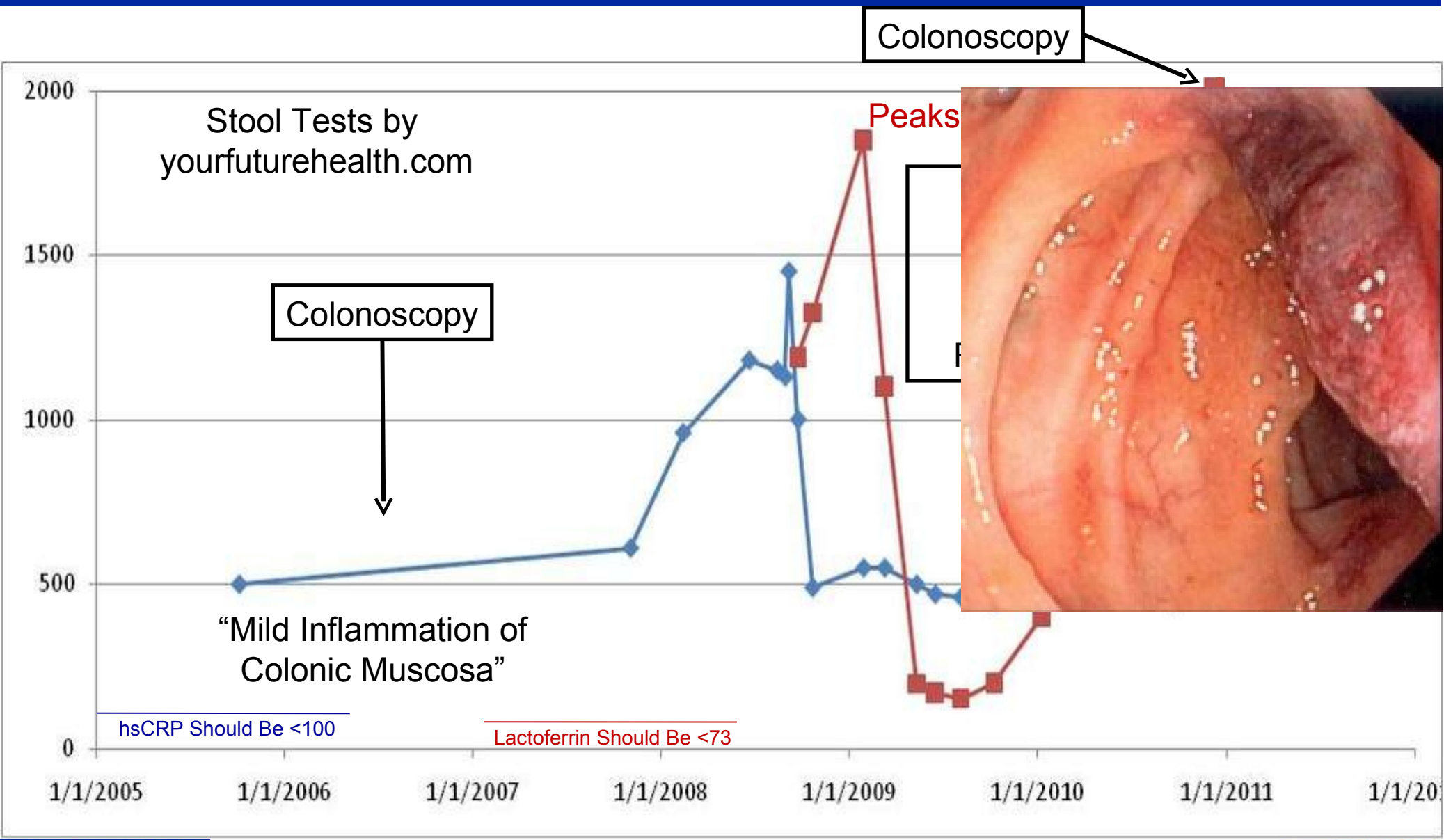
it²

Paradox- Anti-Inflammatory Diet, Plus Low LDL, Yet Chronic Inflammation & Plaque Increases

- **What Could be the Source of the Chronic Inflammation?**
- **Started Taking Stool Samples as Well as Blood Samples**

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Measuring Stool Revealed Episodic Peaks of Lactoferrin



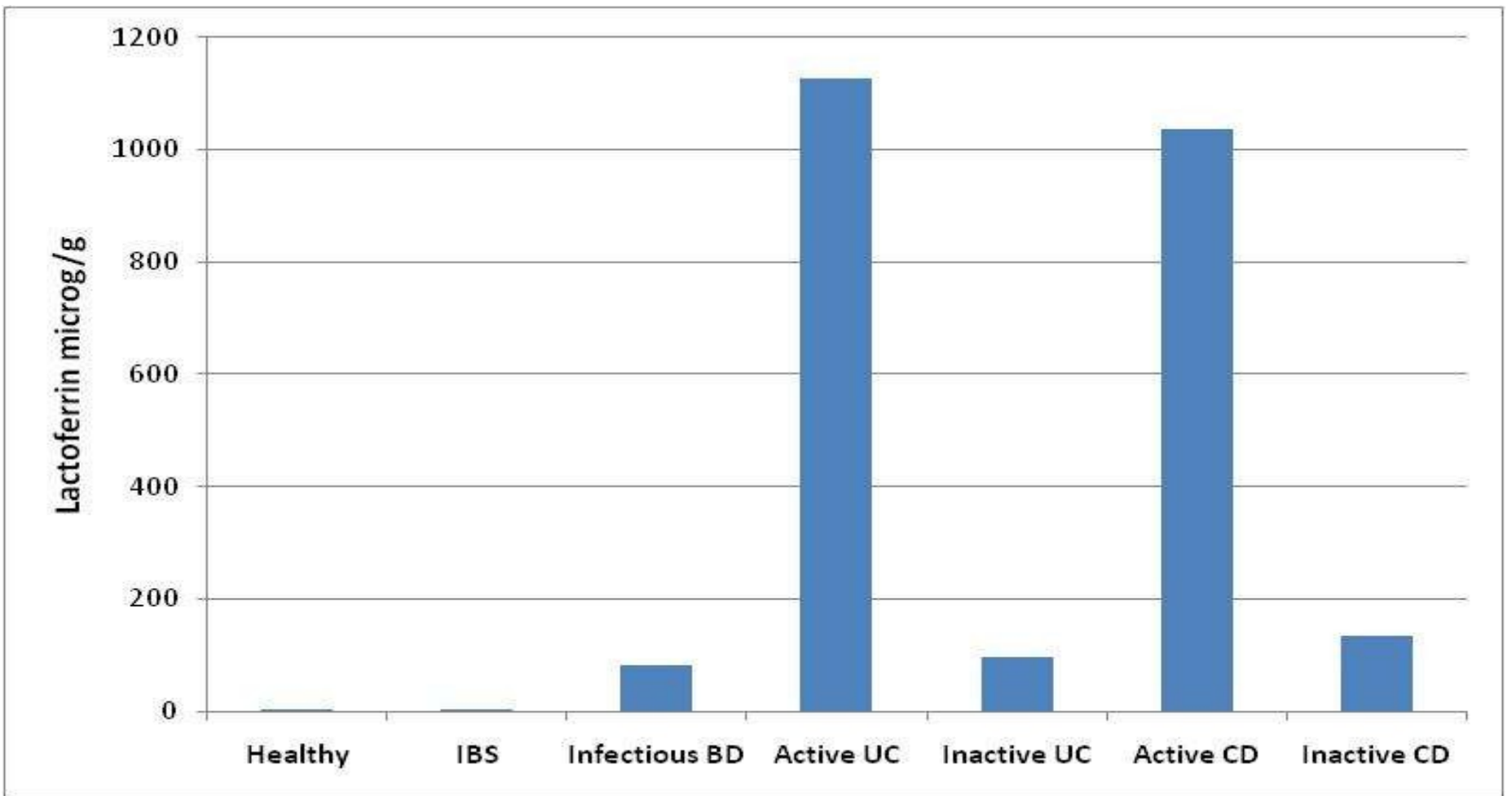
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Chronic Inflammation with Episodic Lactoferrin Flares

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Lactoferrin is a Specific and Sensitive Marker For Differentiating IBD from Other Bowel Diseases

Lactoferrin is Glycoprotein Expressed on the Surface of Neutrophil Leukocytes



"Relationship between fecal lactoferrin and inflammatory bowel disease," J. Dai, WZ Liu, YP Zhao, YB Hu, ZZ Ge, Scand J Gastroenterol. 2007 Dec;42(12):1440-4.

"Serial Fecal Lactoferrin Measurements are Useful in the Interval Assessment of Patients with Active & Inactive Inflammatory Bowel Disease"

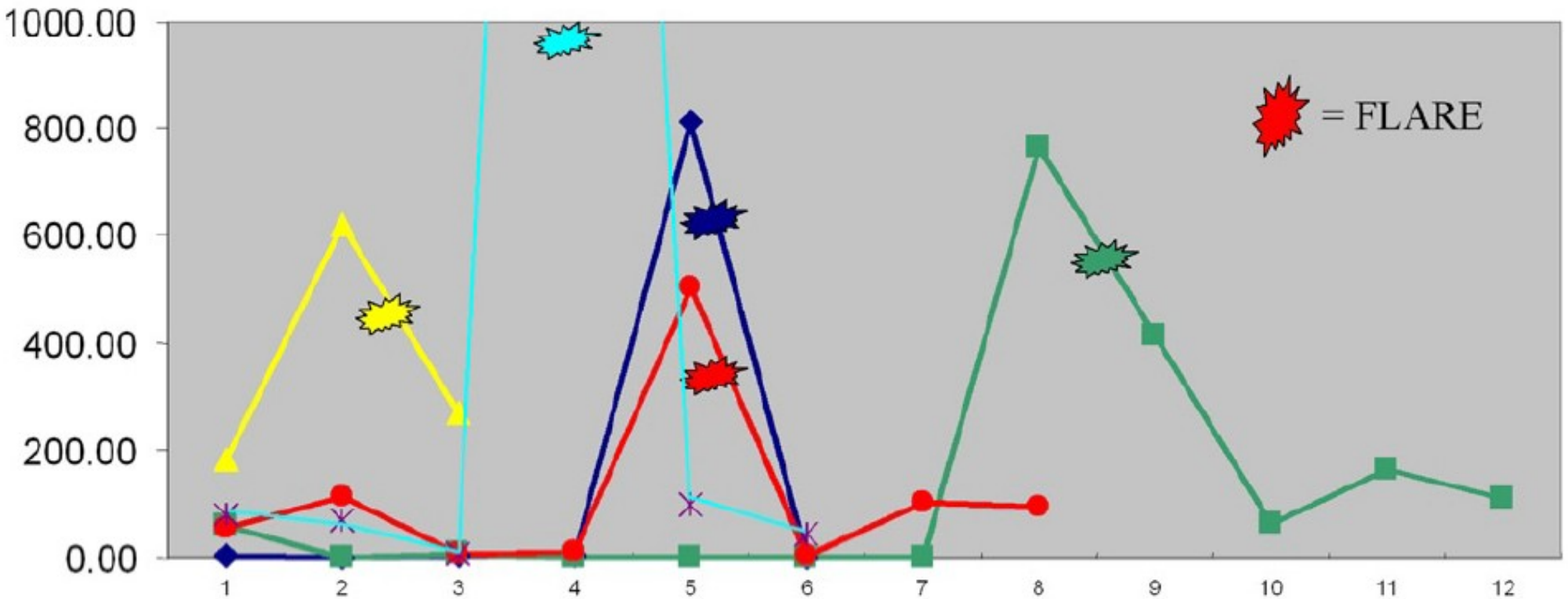


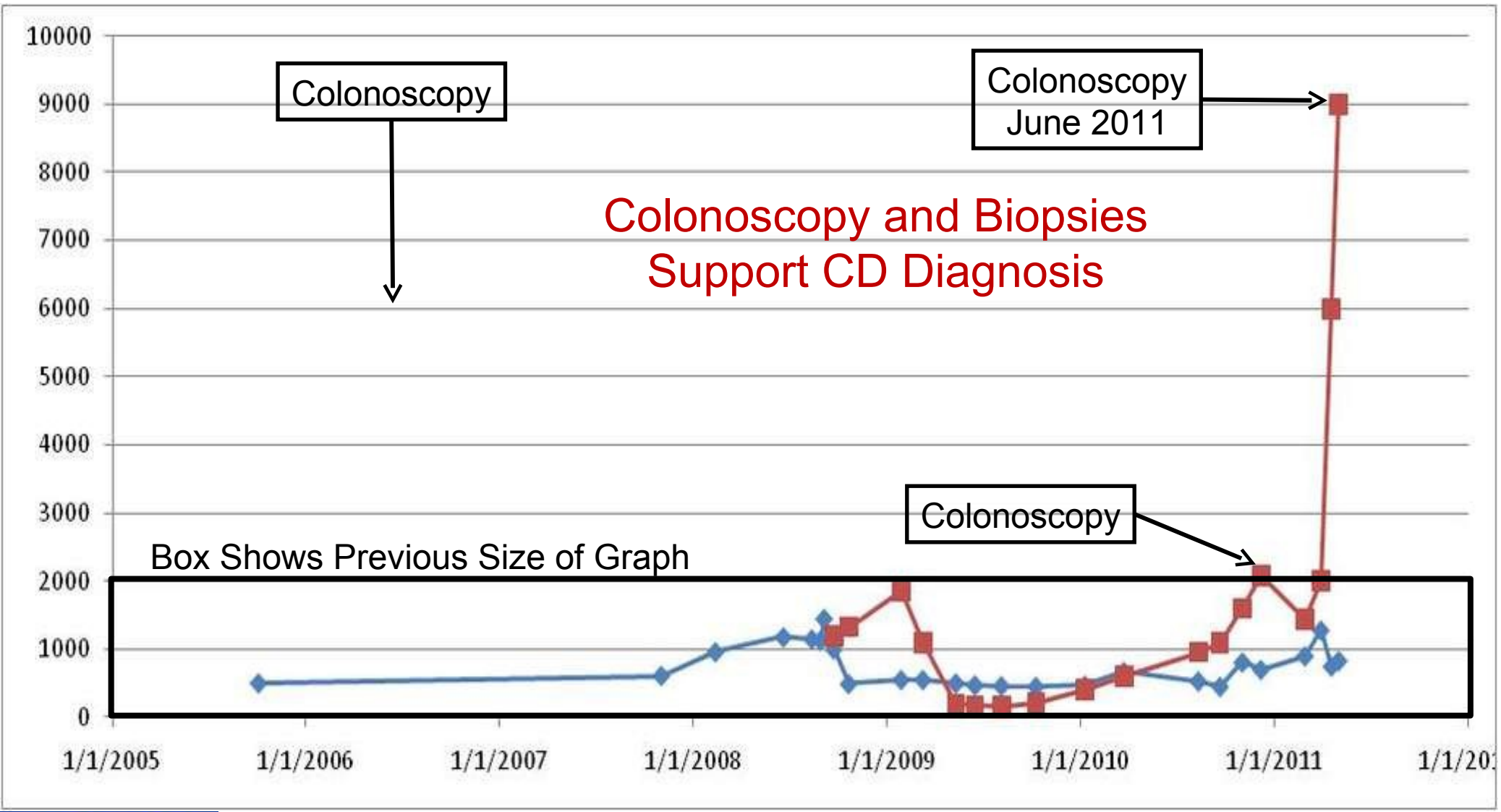
Figure 3: Elevated FLA can predict subsequent clinical flares

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T. R. Walker, M. L. Land, T. M. Cook, W. Sandborn, T. Johnson, J. Boone, D. Lyerly, P. A. Rufo, J., DDW 2004, New Orleans, LA

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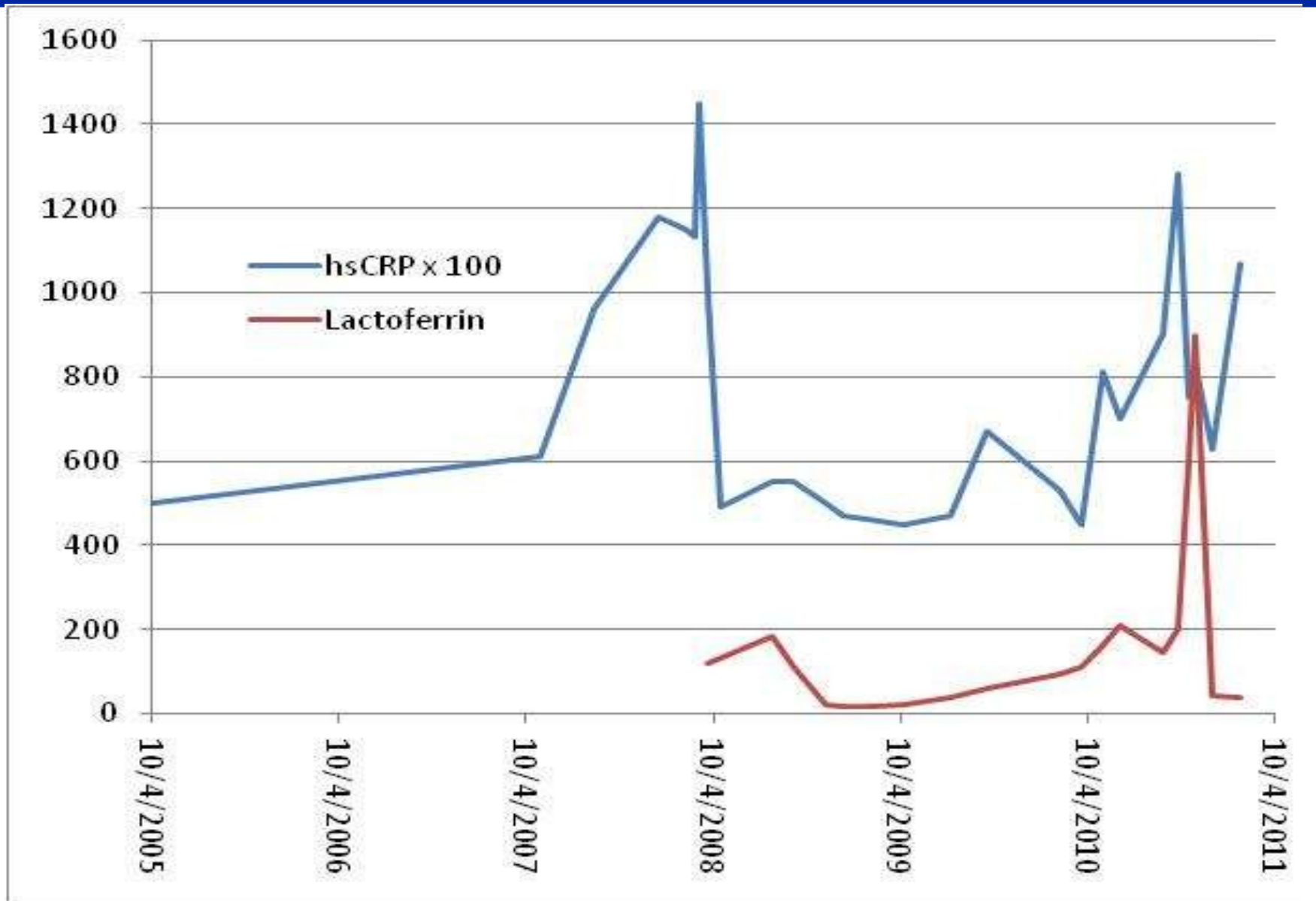
Latest Data Point Reveals Lactoferrin Spike to Active Crohn's Disease (CD) Level



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Strong Correlation Between Blood Inflammation (hsCRP) and Stool Inflammation (Lactoferrin)



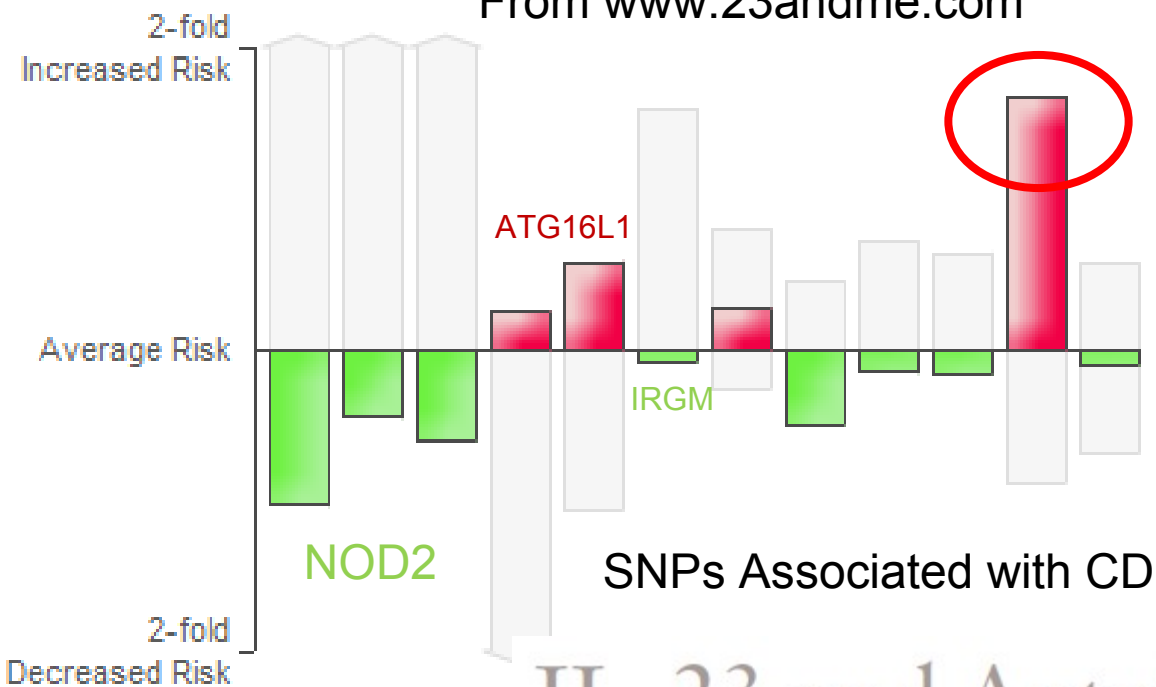
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hsCRP Measurements from Scripps Clinic and Your Future Health
Lactoferrin Measurements from Your Future Health

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

From www.23andme.com



SNPs Associated with CD

Mutation 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]

Pro-inflammatory Cytokine Interleukin (IL)-23

IL-23 and Autoimmunity: New Insights into the Pathogenesis of Inflammatory Bowel Disease

Clara Abraham[1] and Judy H. Cho[1,2]

Section of Digestive Diseases, Departments of [1]Medicine and [2]Genetics, Yale University,

2009

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

Anti-IL-12/23: The Next Big Thing in IBD?

Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008;135:1130–1141.

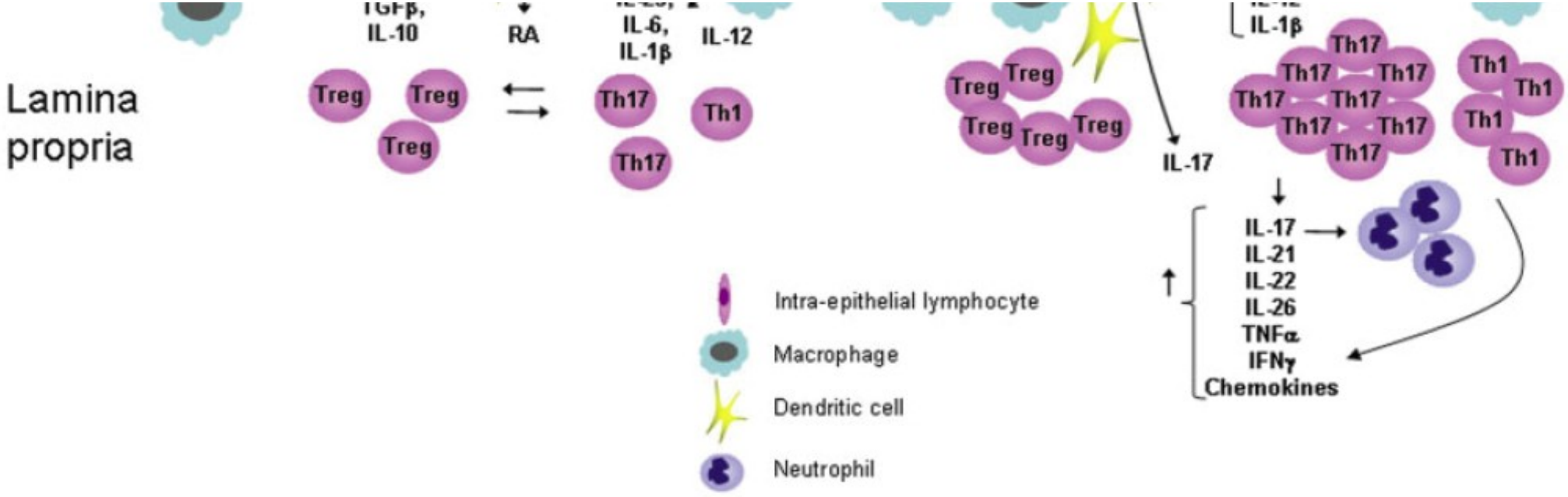


FIGURE 1. Dysregulation of intestinal immune homeostasis in CD. Under intestinal homeostatic conditions there is a balance between proinflammatory cytokines from innate cell populations (e.g., IL1β, IL-6, IL-12, IL-23) and effector T cell populations (e.g., Th1 and Th17 cells), relative to regulatory T cell populations that are influenced by factors such as IL-10, TGFβ, and retinoic acid (RA) in the environment. During CD there is dysregulation of this balance with an increased proportion of innate and effector T cell populations along with the cytokines they produce.

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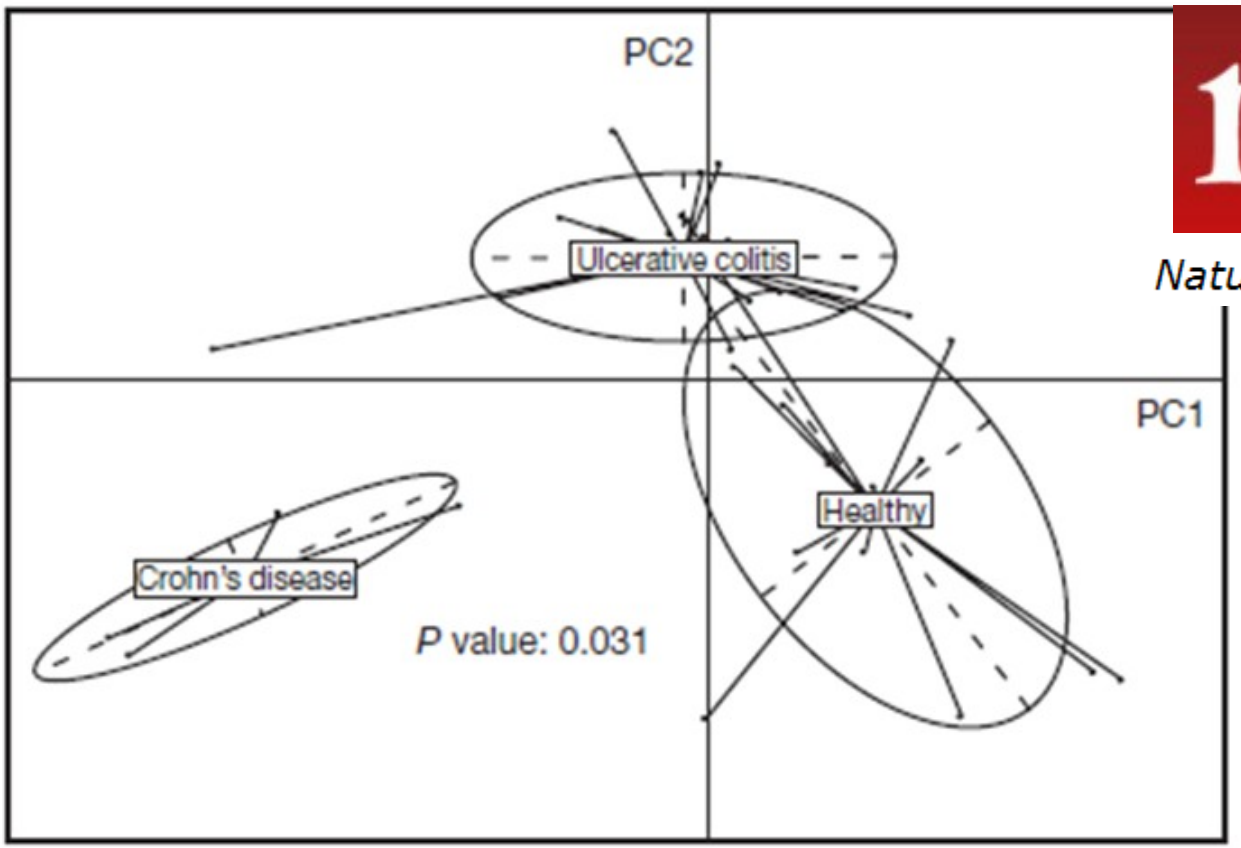
Interleukin-23/Th17 Pathways and Inflammatory Bowel Disease

Clara Abraham, MD, and Judy Cho, MD

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

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Crohn's is an Autoimmune Disease, Correlated with SNPs and Microbiome Metagenomics



nature

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

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],

"Crohn's pathogenesis may involve a complex interplay between host genetics, immune dysfunction, and microbial or environmental factors"

The role of microbes in Crohn's disease.
Eckburg PB, Relman DA.
Clin Infect Dis. 2007; 44 (2): 256-62

"We review how microbes
may participate in
the pathogenesis of CD
and how they may inappropriately
activate
the mucosal immune system
in genetically predisposed
individuals."

Can Increasing Use of Antibiotics and Western Diet Be Causing Increase in IBD?

The gut microbiota shapes intestinal immune responses during health and disease

Nature Reviews Immunology **9**, 313-323 (May 2009)

June L. Round[1] & Sarkis K. Mazmanian[1]

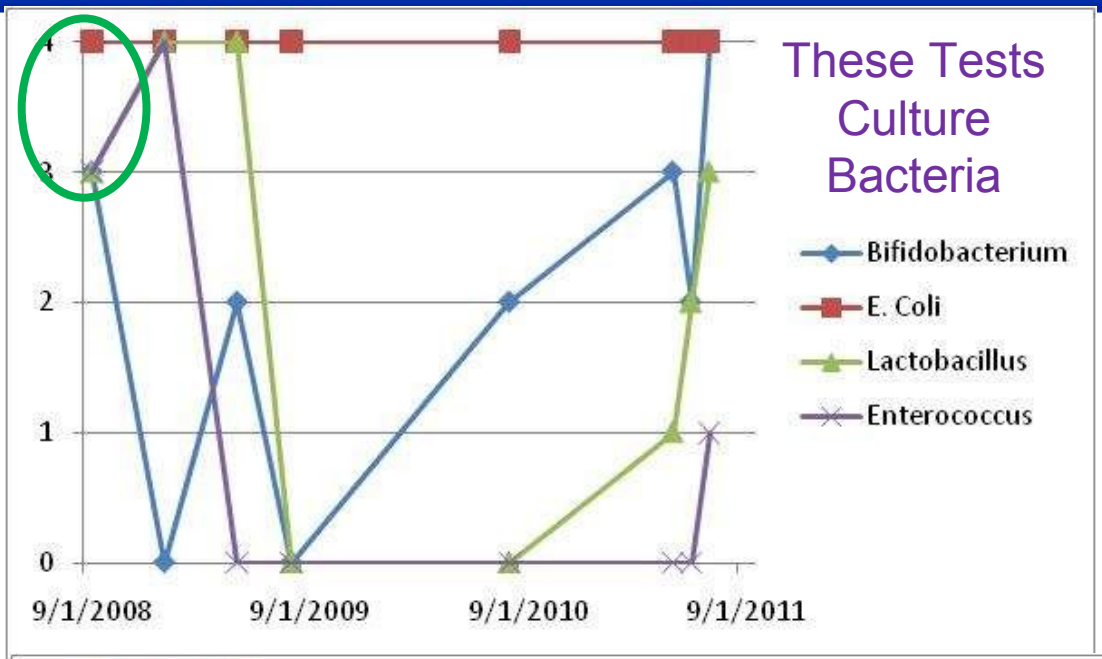
- **"Host-microbial interactions in the intestinal environment can down-regulate inflammatory responses"**
- **"Importantly, changes in diet, use of antibiotics, and intestinal colonization (eg, eradication of intestinal helminthes), have likely modified intestinal microbial communities and contributed to the increased prevalence of IBD during the past century."**

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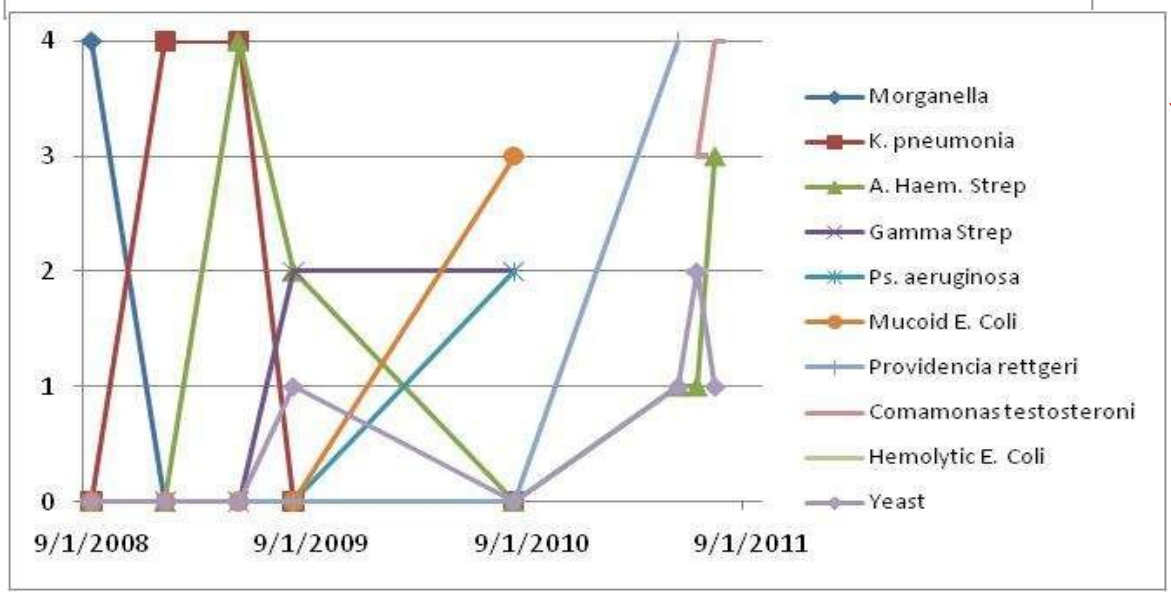
Antibiotics Are Highly Disruptive of Colon Microbiome--Takes 3-4 Years to Recover

All 3+ or 4+ Three Weeks Before Taking Antibiotics



"Good" Microbes

Three Years After 10 Days of Antibiotics Levaquin & Metronidaloze



Next Step Get DNA Microbe Metagenomics, Parasite, Yeast Test

"Bad" Microbes

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To Understand Causes of IBD, One Needs to Look at Interplay of Genes and Colonic Microbes

Associations between IBD and genes that regulate microbial recognition and innate immune pathways, such as *nucleotide oligomerization domain 2 (Nod2), genes that control autophagy* (eg, *ATG16L1, IRGM), and genes in the interleukin-*23–T helper cell 17 pathway indicate the important roles of host-microbe interactions in regulating intestinal immune homeostasis. There is increasing evidence that intestinal microbes influence host immune development, immune responses, and susceptibility to human diseases such as IBD, diabetes mellitus, and obesity.

Interactions Between the Host Innate Immune System and Microbes in Inflammatory Bowel Disease

GASTROENTEROLOGY 2011;140:1729–1737



Clara Abraham*



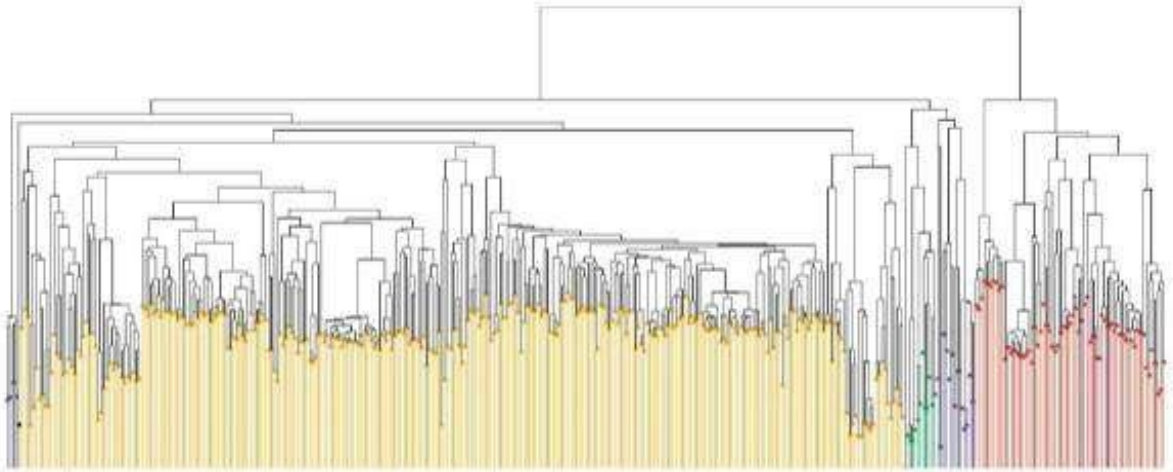
Ruslan Medzhitov[†,§]

*Department of Medicine and [†]Department of Immunobiology, [§]Howard Hughes Medical Institute, Yale University, New Haven, Connecticut

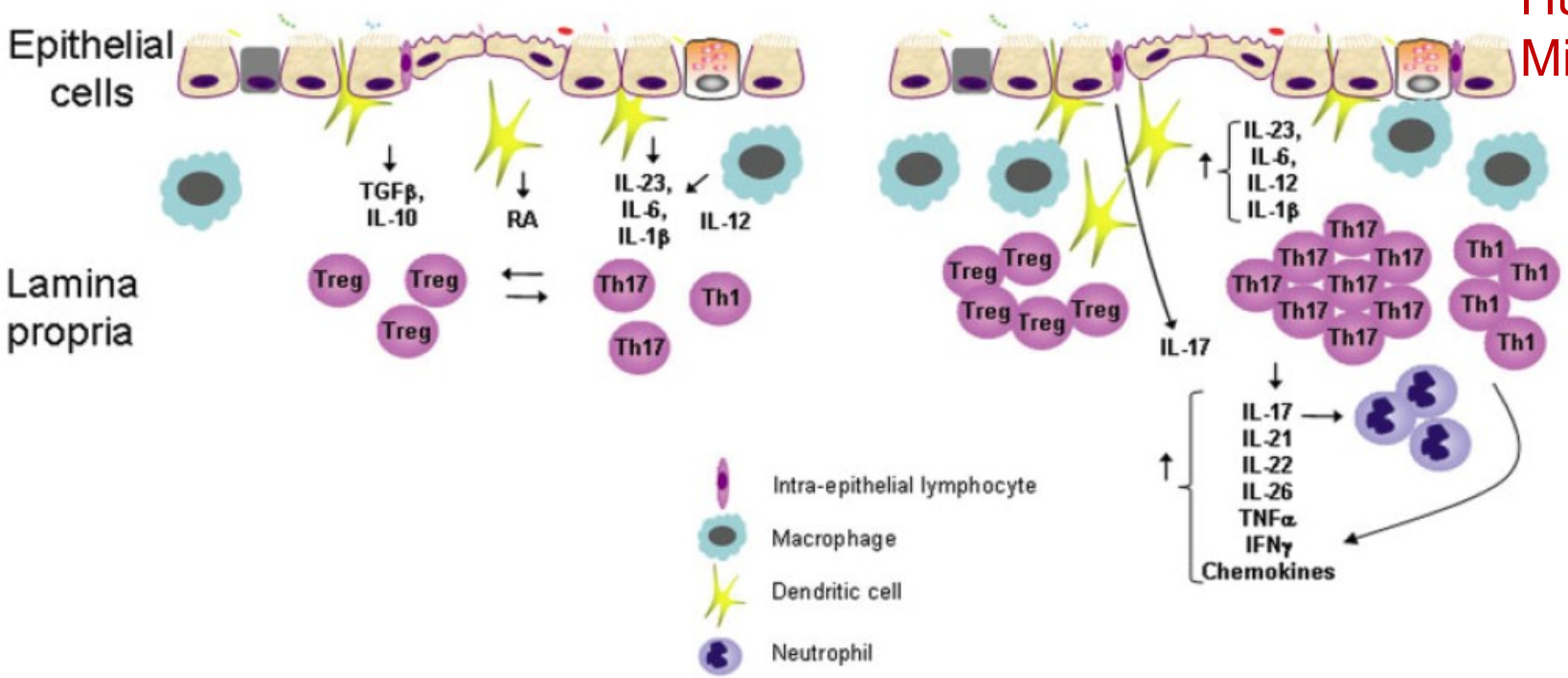
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Understanding of IBD Will Require Complete Genomes, Microbial Metagenomics, & Metabolomics Over Populations



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

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The Cost for Full Human Genome Sequencing is Exponentially Decreasing

Forbes

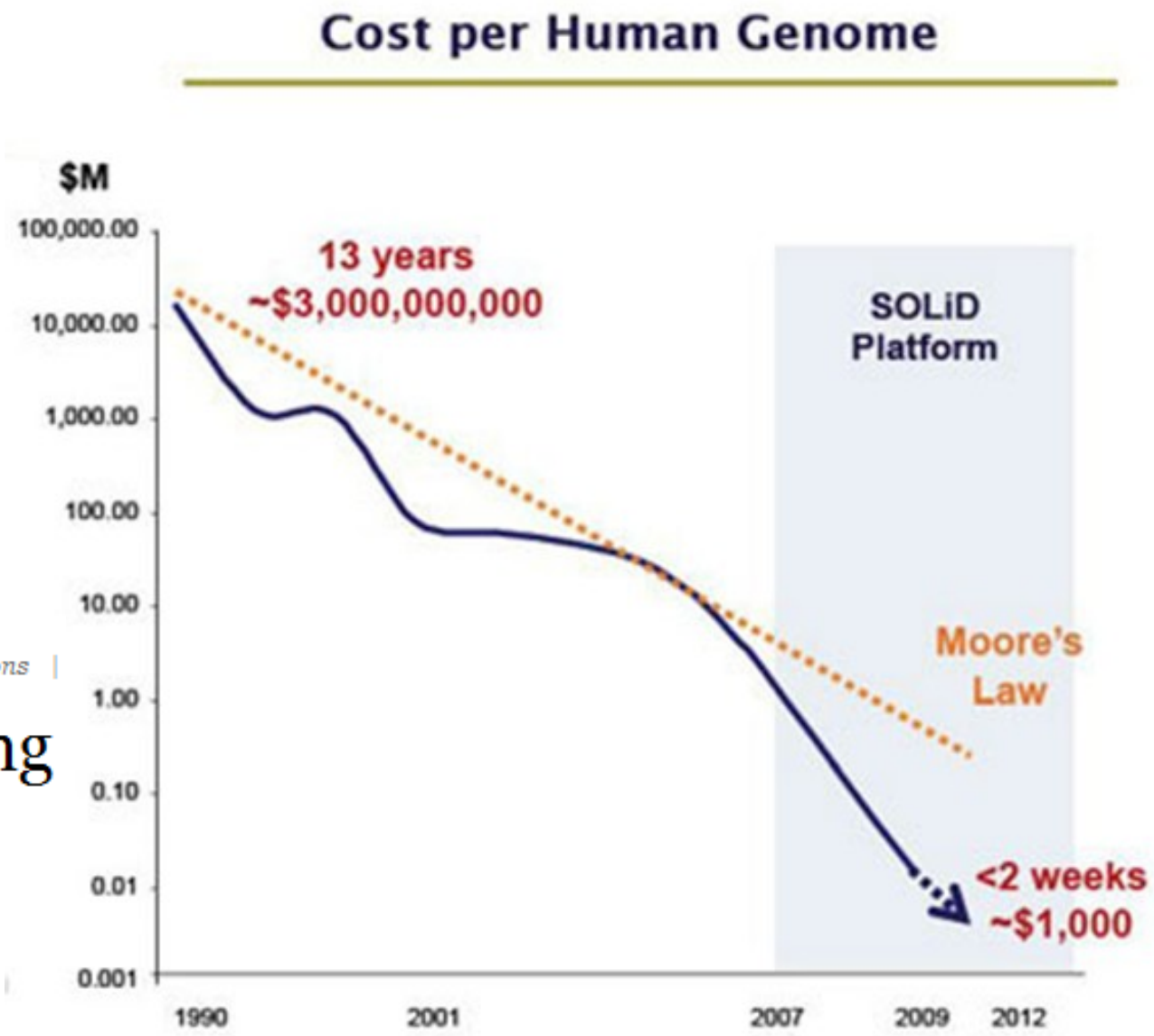


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Your Genome Is Coming

posted by **MATTHEW HERPER**



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http://blogs.forbes.com/sciencebiz/2010/06/03/your-genome-is-coming/

it²

What Does This Case Have to Do with Pediatrics?

- **Early Detection of Anomalies in Trends Can Lead to Prevention of Full Disease State**
- **Child Obesity is a Fast-Growing Threat to Health**
- **Most Crohn's is a Youth-Onset Disease**
- **Genetic Markers Can be Determined at Birth-Potential of Gene Therapy or Chemical Intervention**
- **Hood Shows Comparing Complete Genome of Child with Both Parents and Sibling Raises Signal-to-Noise for Detecting Mutations**