Genomics in Society: Genomics, Preventive Medicine, and Society

Guest Lecture to UCSD Medical and Pharmaceutical Students
Foundations of Human Biology--Lecture #41
UCSD
October 6, 2011

Dr. Larry Smarr
Director, California Institute for Telecommunications and Information Technology
Harry E. Gruber Professor,
Dept. of Computer Science and Engineering
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Required Reading

- **Quantified Self**
  - www.xconomy.com/san-diego/2010/05/12/how-internet-pionee
- **Future of Personalized Preventive Medicine**
  - www.newsweek.com/2009/06/26/a-doctor-s-vision-of-the-futu
- **Personalized Genomic Sequencing**
  - www.technologyreview.com/biomedicine/25218/
  - www.mercurynews.com/business/ci_15580695
  - http://blogs.forbes.com/sciencebiz/2010/06/03/your-genome-is-coming

Genetics and Society Learning Objectives

- **Explain the relationships between genetics, disease and society**
- **List and explain the major issues concerning genetic testing for predisposition to disease**
- **Explain how measurements of an individual¹s chemical states relate to genetic testing and how both contribute to preventive medicine**

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Genetics and Society Learning Objectives

- Explain the interactions between the genome, cellular networks, systems biology, and emergence of disease states
- Explain the difference between Single Nucleotide Polymorphism mapping and complete genomic maps and how each is used in medicine
- Present both sides of the debate over keeping a patient[1]s genetic information private versus sharing data openly
- Vocabulary: SNP, genome, cellular networks, system biology, genetic testing, genome sequencers

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Genetics, Disease, and Society: Inherited Genetics Plus Environmental Variables

Centers for Disease Control and Prevention
Your Online Source for Credible Health Information

Most human disease results from a combination of inherited genetic variations and environmental factors (such as lifestyle, social conditions, chemical exposures, and infections).

Thanks to the genome-based tools now available to public health researchers, we can study how and where disease occurs in populations and families using biological markers (e.g., genes) that can help identify exposures, susceptibilities, and effects.

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www.cdc.gov/genomics/population/

Genomics Plays a Role in 9 of the 10 Leading Causes of Death in the U.S., most Notably Cancer & Heart Disease

Number of deaths for leading causes of death:

- Heart disease: 616,067
- Cancer: 562,875
- Stroke (cerebrovascular diseases): 135,952
- Chronic lower respiratory diseases: 127,924
- Accidents (unintentional injuries): 123,706
- Alzheimer's disease: 74,632
- Diabetes: 71,382
- Influenza and Pneumonia: 52,717
- Nephritis, nephrotic syndrome, and nephrosis: 46,448
- Septicemia: 34,828

Source: Deaths: Final Data for 2007, tables B, D, 7, 30

The Cost for Full Human Genome Sequencing is Exponentially Decreasing

Forbes

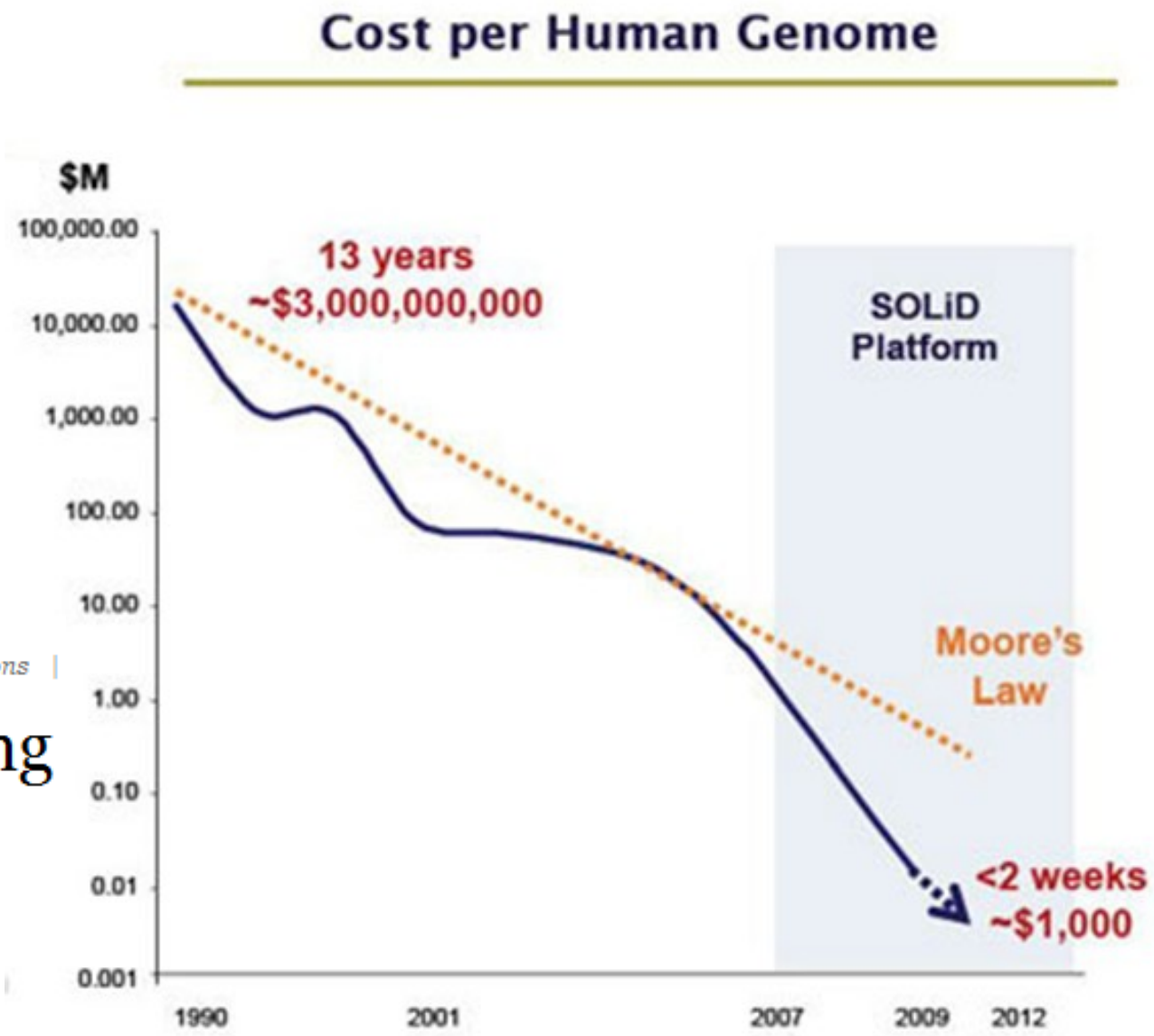


Science Business
RESEARCH, INNOVATION & POLICY
PROFILE | HEADLINE GRABS | RSS FEED

Jun. 3 2010 - 5:32 pm | *30 views* | *0 recommendations* |

Your Genome Is Coming

posted by **MATTHEW HERPER**

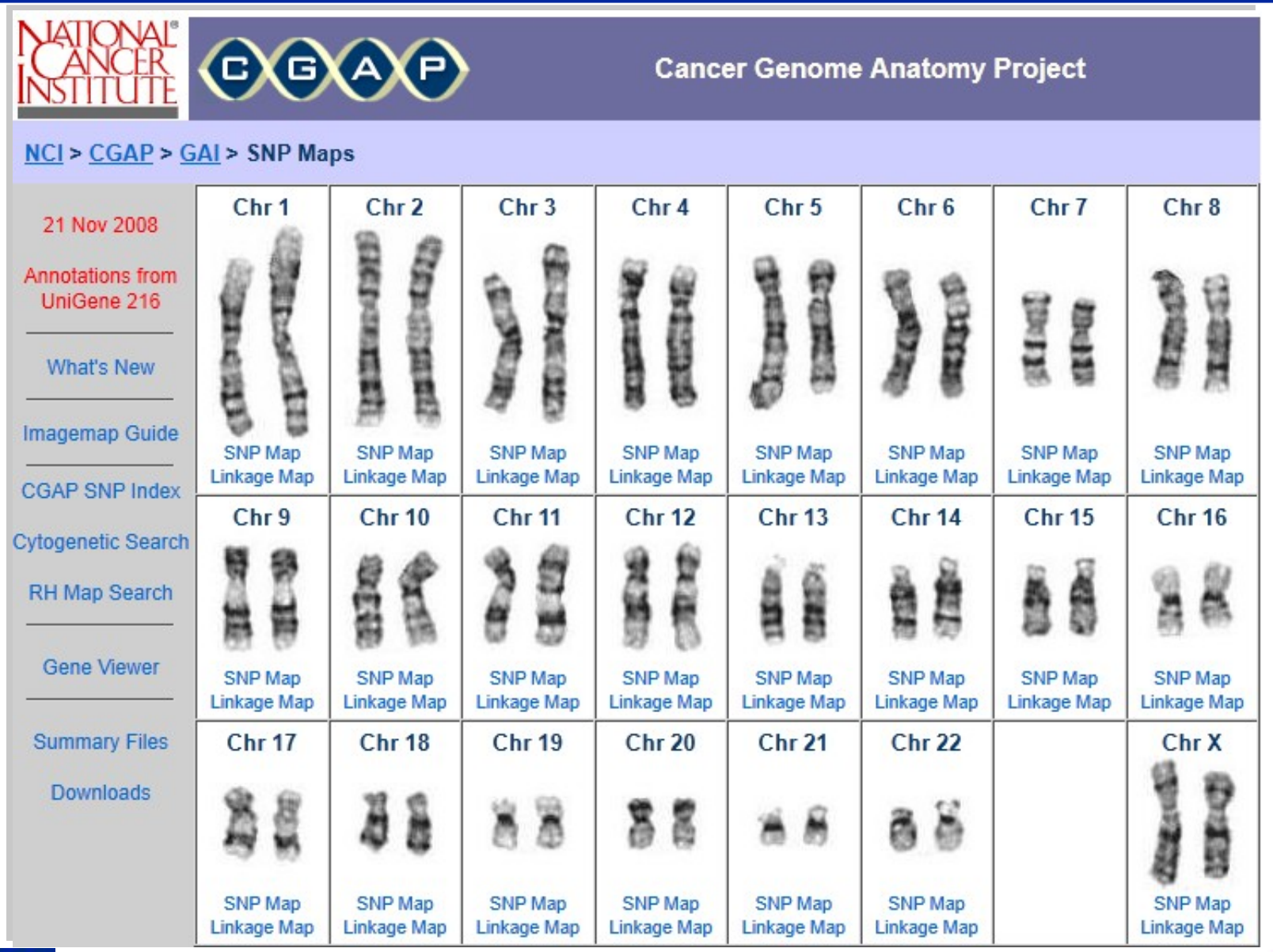


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http://blogs.forbes.com/sciencebiz/2010/06/03/your-genome-is-coming/

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Mapping the Human Genome Across the Chromosomes



http://gai.nci.nih.gov/html-snp/imagemaps.html

Single Nucleotide Polymophisms (SNPs)

www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml#snps

- **DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered**
  - **Example: DNA sequence AAGGCTAA to ATGGCTAA**
- **For a variation to be considered a SNP, it must occur in at least 1% of the population**
- **SNPs make up about 90% of all human genetic variation**
- **SNPs occur every 100 to 300 bases along the 3-billion-base human genome**
- **Many SNPs have no effect on cell function, but scientists believe others could predispose people to disease or influence their response to a drug**

Why We Study SNPs

99.9% of One's Individual DNA
Sequence will be Identical
to that of Another Person.
Of the 0.1% Difference,
Over 80% will be
Single Nucleotide Polymorphisms
(SNPs).

The Rise of Individual and Societal Genomic Testing- Promise and Concerns

Technology Review
PUBLISHED BY MIT

How Personal Genomics Could Change Health Care

The select few who have had their genomes sequenced learn to use that information for health care.

By Emily Singer

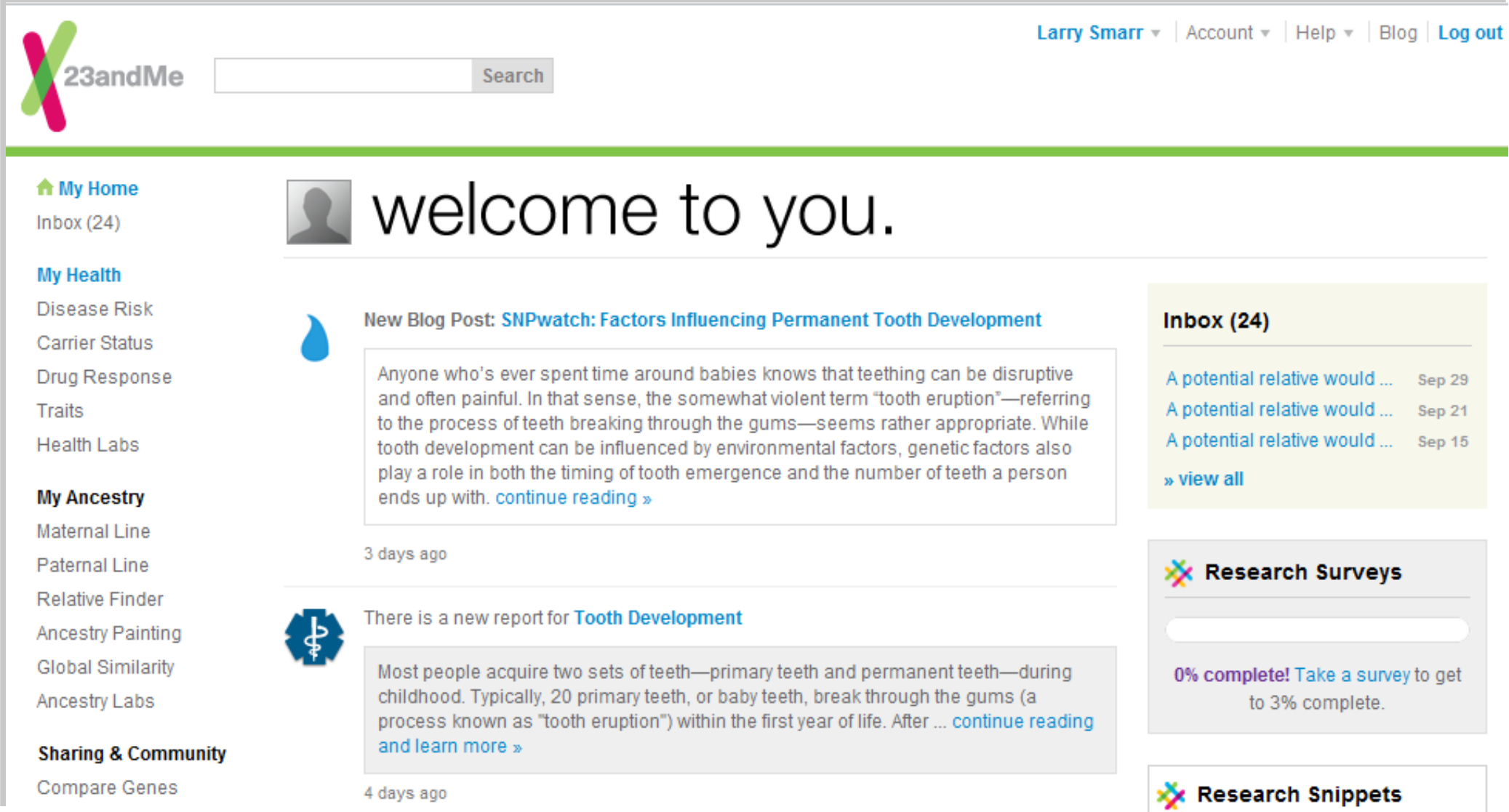
FRIDAY, APRIL 30, 2010

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www.technologyreview.com/biomedicine/25218/

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Consumer Companies Provide Your SNPs



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What Can SNPs Tell Us About Our Future Health?
Genome Wide Association Studies (GWAS)

Decreased Risk

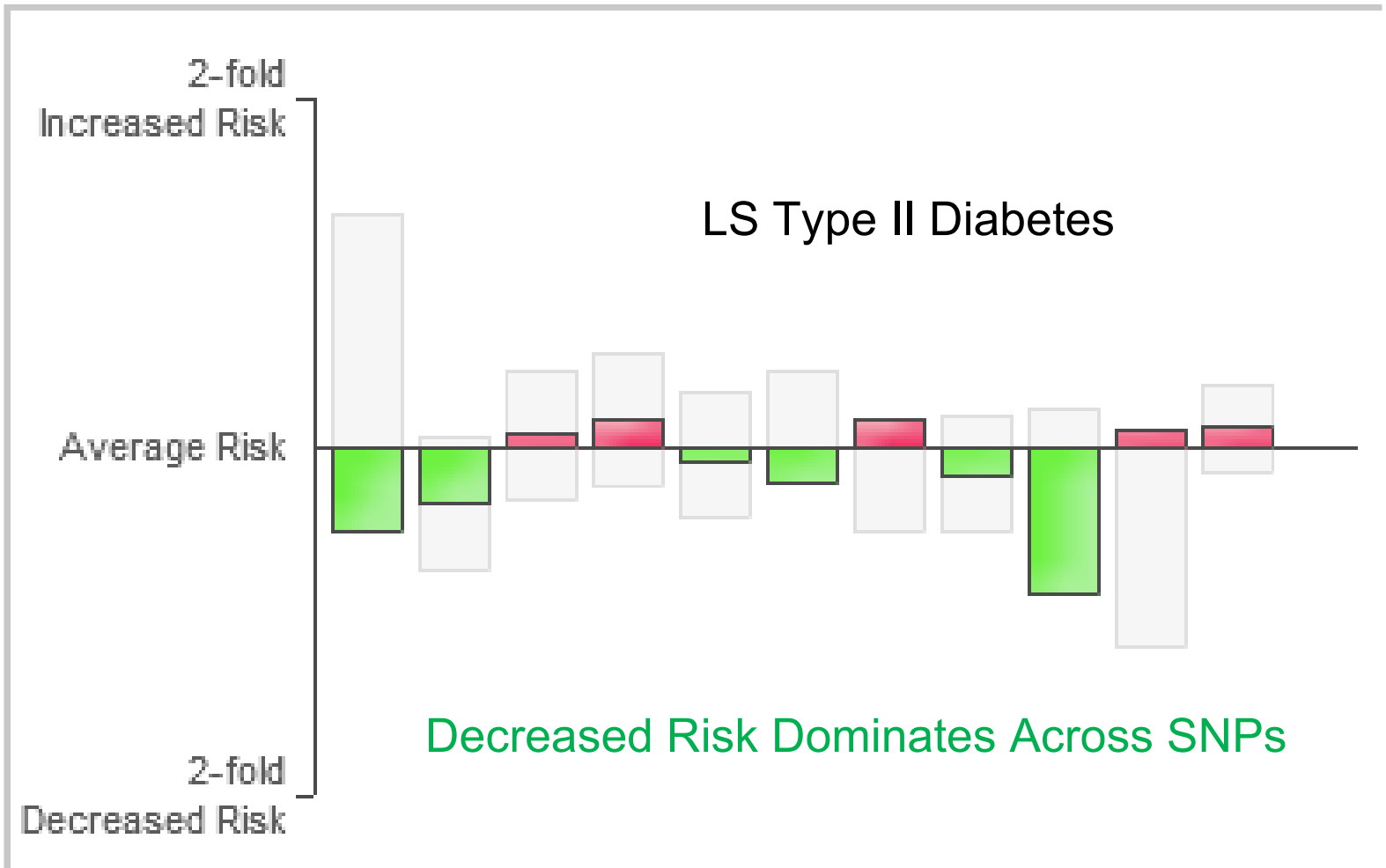
Name	Confidence	Your Risk	Avg. Risk	Compared to Average
Type 2 Diabetes	★★★★	17.1%	25.7%	0.66x
Prostate Cancer ♂	★★★★	12.2%	17.8%	0.69x
Melanoma	★★★★	2.2%	2.9%	0.75x
Rheumatoid Arthritis	★★★★	1.8%	2.4%	0.77x
Restless Legs Syndrome	★★★★	1.5%	2.0%	0.74x
Age-related Macular Degeneration	★★★★	1.2%	6.5%	0.18x

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Each Disease Has a Set of SNPs That GWAS Have Shown Are Potentially Linked



Name	Confidence	Your Risk	Avg. Risk	Compared to Average
Type 2 Diabetes	★★★★	17.1%	25.7%	0.66x

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Risk of Disease Results From SNPs Mainly Reveal Average Risks – Are They Consistent?

Navigenics®

0 - 1%	>1 - 10%	>10 - 25%	>25 - 50%	>50 - 100%
Graves' disease You: 0.93% Avg: 0.55%	Lung cancer You: 8% Avg: 8%	Prostate cancer You: 17% Avg: 17%	Osteoarthritis You: 44% Avg: 40%	You have no results in this range
Glaucoma You: 0.78% Avg: 1.1%	Colon cancer You: 6% Avg: 6%	Diabetes, type 2 You: 12% Avg: 25%	Heart attack You: 38% Avg: 42%	
Macular degeneration You: 0.74% Avg: 3.1%	Psoriasis You: 6% Avg: 4.0%		Obesity You: 32% Avg: 34%	

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You: 1.7%
Avg. 3.0%

You: 22.4%
Avg. 11.4%

You: 14.7%
Avg. 23.7%

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SNP Indications of Adverse Drug Side Effects May Be Quite Useful

Navigenics

23andMe

Side Effects

Drug	Your Risk	Side Effect	
Abacavir (Ziagen®) Used to treat HIV infection	High Risk	Severe allergic reaction, including fever, rash, and nausea	Increased Risk
Floxacillin (Floxapen®) Used to treat infections	High Risk	Severe liver toxicity, leading to liver damage	Greatly Increased Risk

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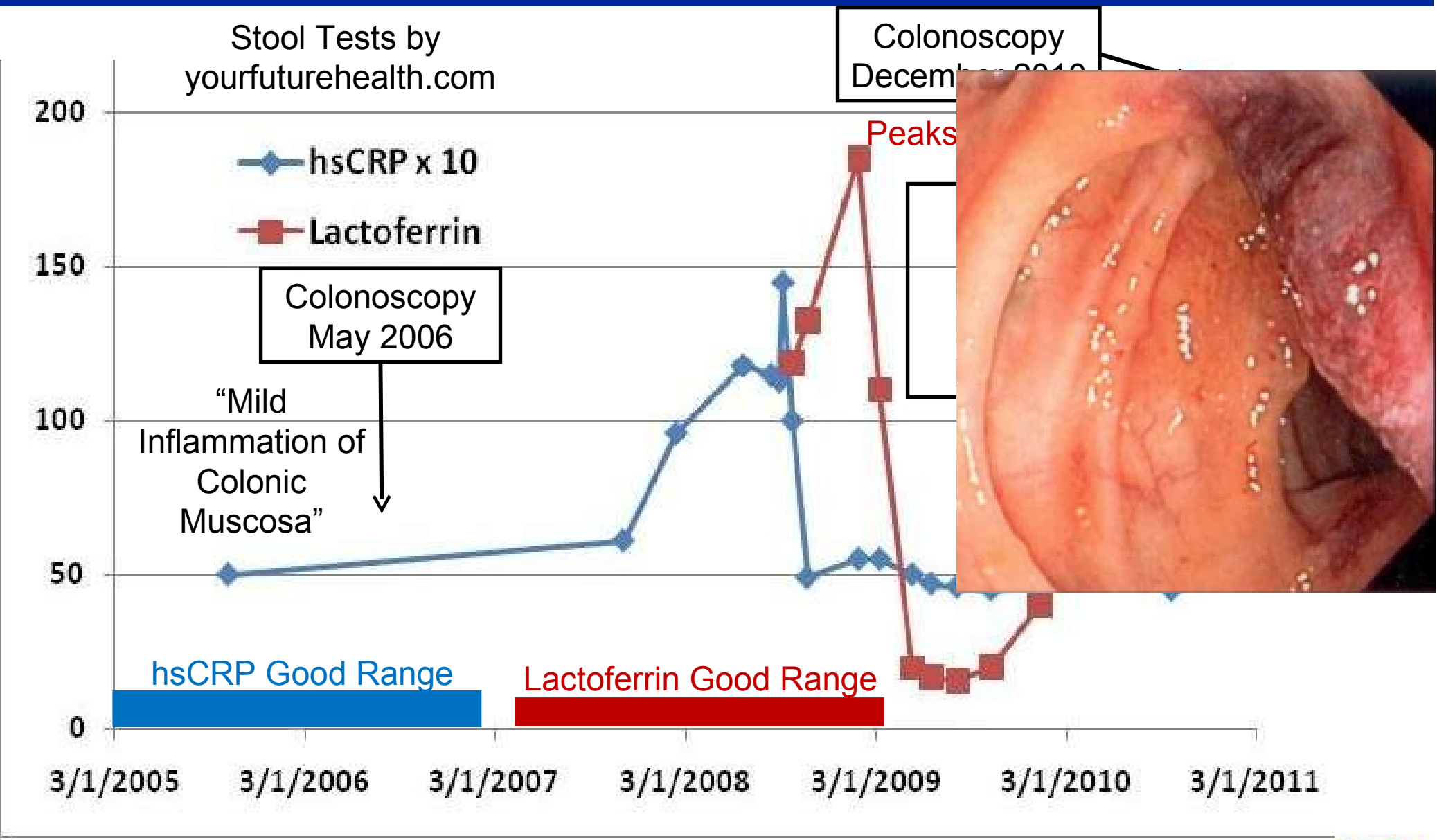
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How SNPs Can Help Clinical Medicine: A Worked Example of Crohn's Disease

- No Symptoms
- Molecular Markers
- Look at SNPs
- Diagnosis

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

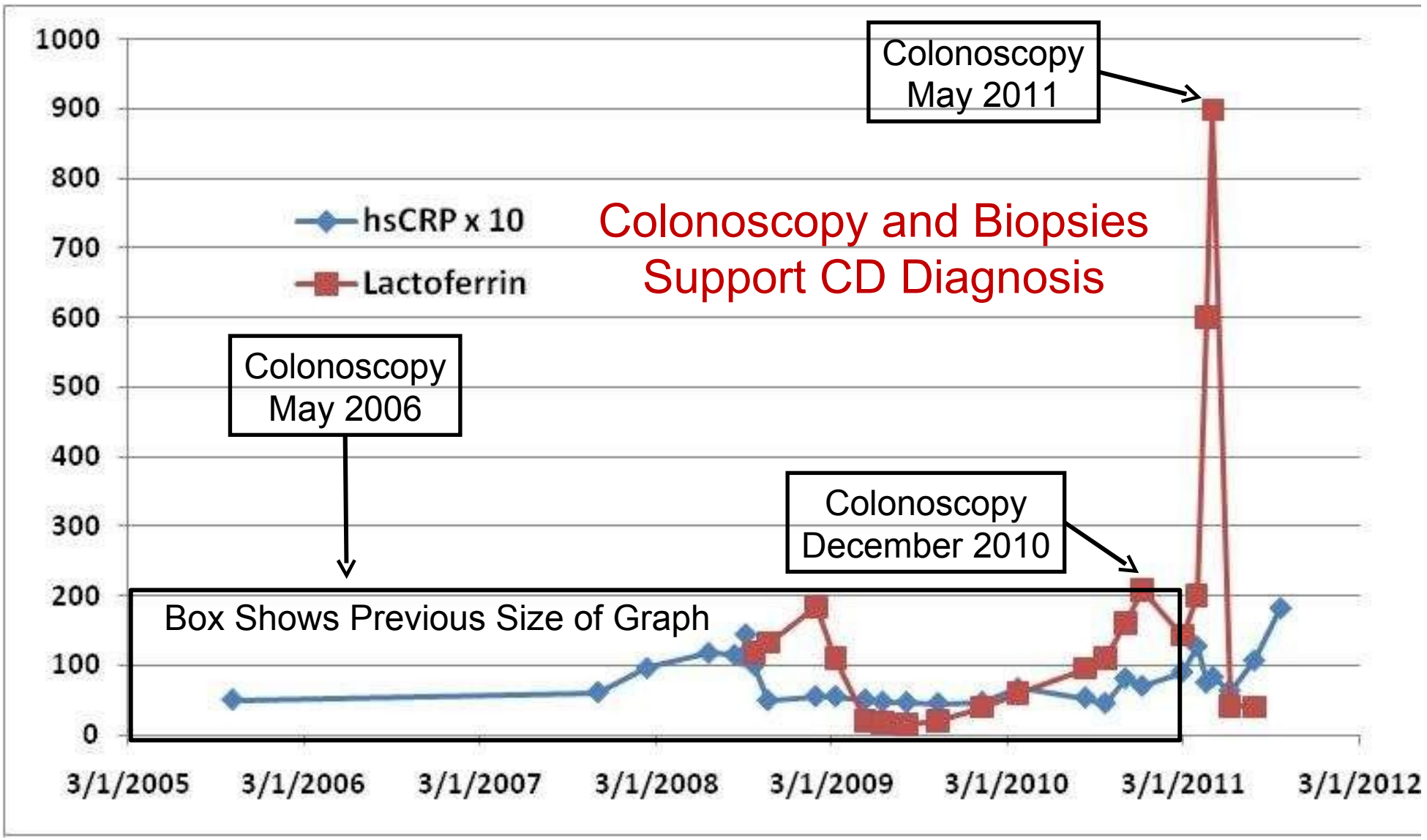


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Chronic Inflammation with Episodic Lactoferrin Flares

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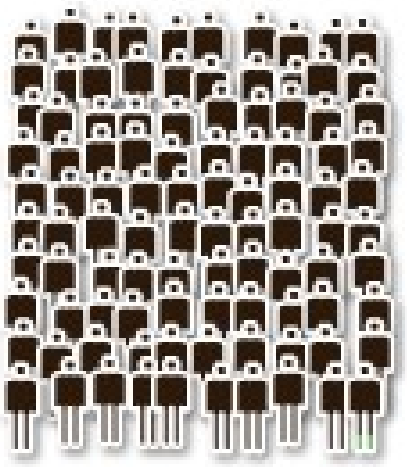
Latest Data Point Reveals Lactoferrin Spike to Active Crohn's Disease (CD) Level



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Averaging Across SNPs My Chances of Having Late-Onset Crohn's Are Very Low

Only 5% of Crohn's Patients are Diagnosed After Age 60

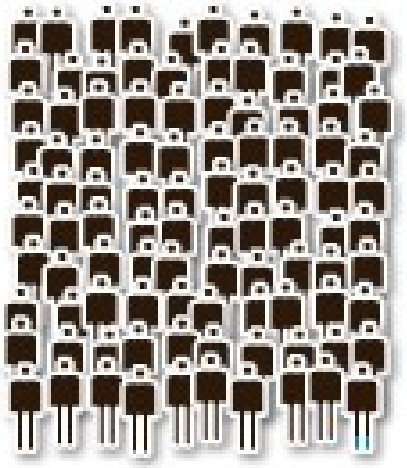


Larry Smarr

< 0.1 out of 100

men of European ethnicity who share Larry Smarr's genotype will develop Crohn's Disease between the ages of 60 and 69.

www.23andme.com



Average

< 0.1 out of 100

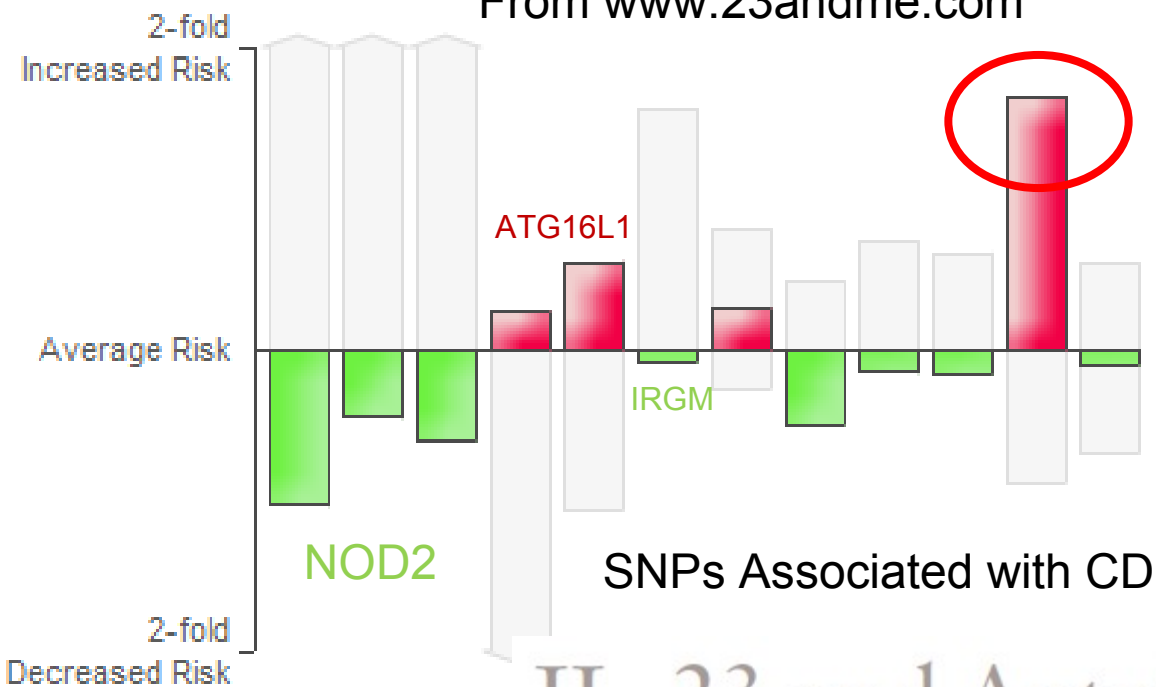
men of European ethnicity will develop Crohn's Disease between the ages of 60 and 69.

Odds are Less Than 1 in a Thousand

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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

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

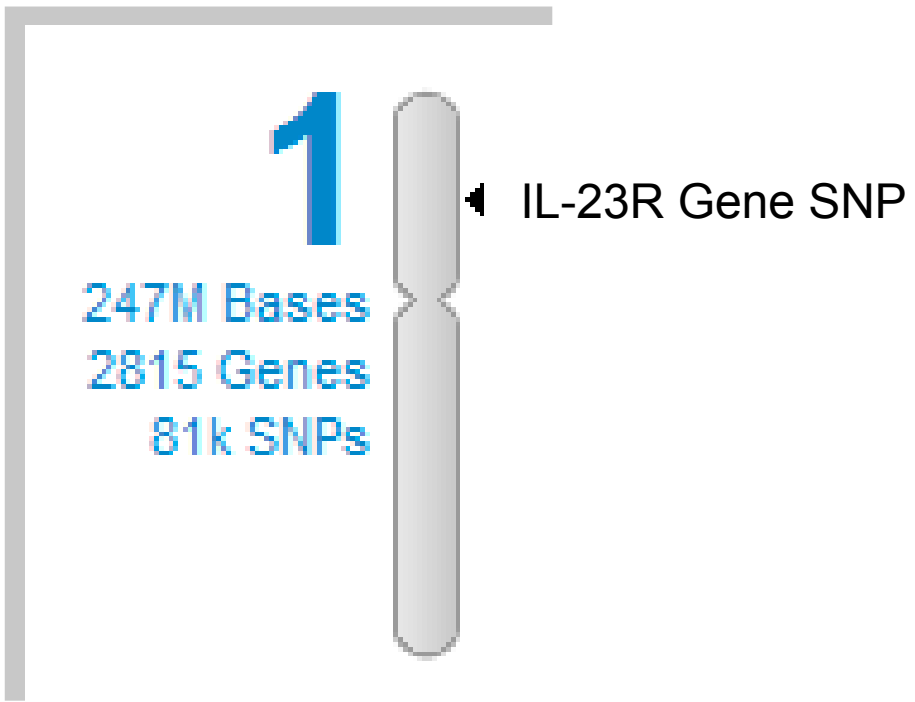
Clara Abraham[1] and Judy H. Cho[1,2] 2009

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

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My Pro-Inflammatory SNP is One of 44 SNPS on the IL-23R Gene



The IL23R Gene is Located From Base Pair 67,632,168 to Base Pair 67,725,661
—93,493 Bases Long

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The Interleukin-23 Receptor Gene Codes for Creation of the Interleukin-23 Receptor Protein

- **This Protein is Embedded in The Cell Membrane of Several Types of Immune System Cells**
  - **These Cells Identify Foreign Substances & Defend the Body Against Infection & Disease**
- **At the Cell Surface, the Interleukin 23 Receptor Interacts with a Protein Called Interleukin 23**
  - **These Two Proteins Fit Together Like a Lock & Its Key**
  - **Interleukin 23 is a Cytokine, a Type of Protein that Regulates the Activity of Immune System Cells**
- **When Interleukin 23 Binds To Its Receptor, it Triggers a Series of Chemical Signals Inside the Cell**
  - **These Signals Promote Inflammation**

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.

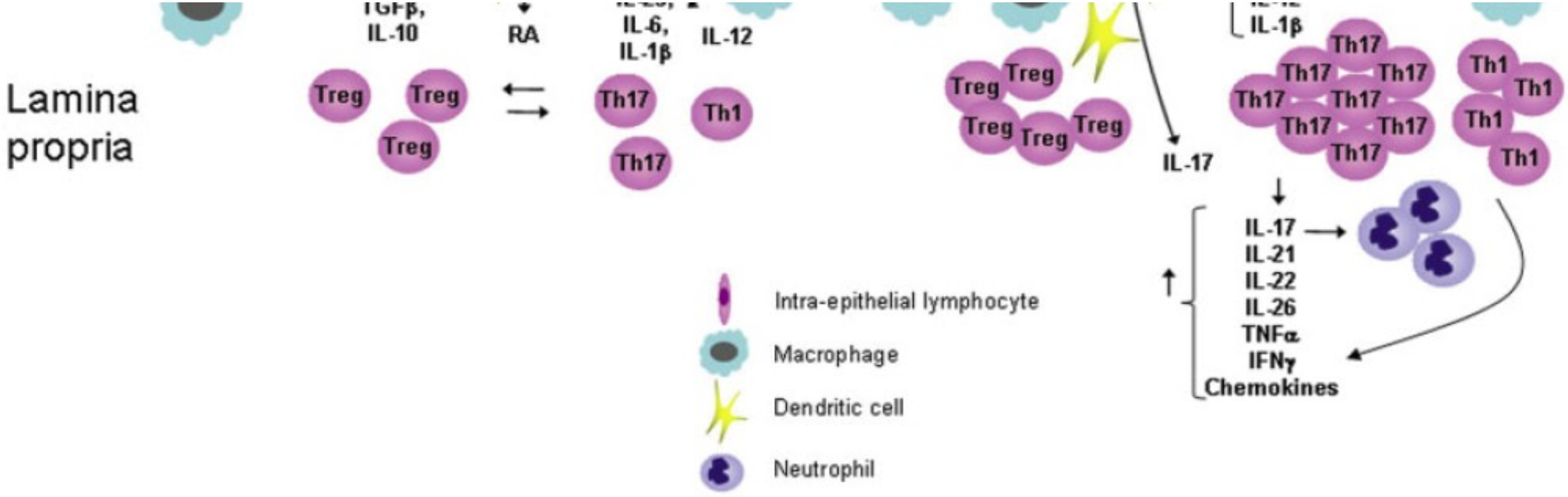


FIGURE 1. Dysregulation of intestinal immune homeostasis in CD. Under intestinal homeostatic conditions there is a balance between proinflammatory cytokines from innate cell populations (e.g., IL1β, IL-6, IL-12, IL-23) and effector T cell populations (e.g., Th1 and Th17 cells), relative to regulatory 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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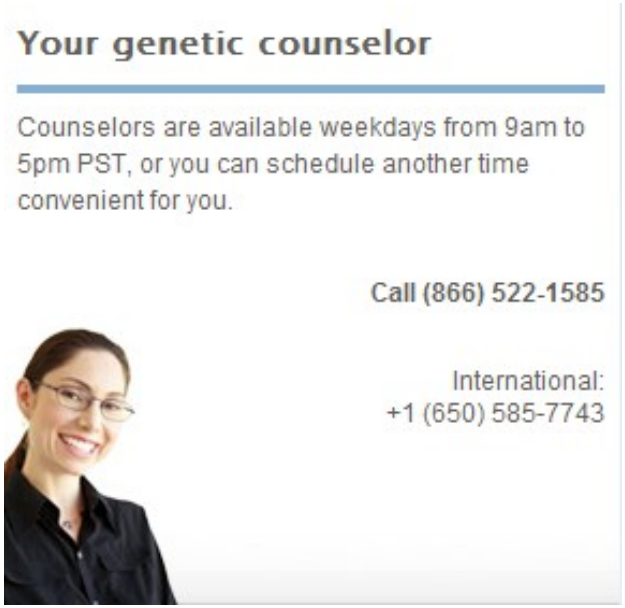
Interleukin-23/Th17 Pathways and Inflammatory Bowel Disease

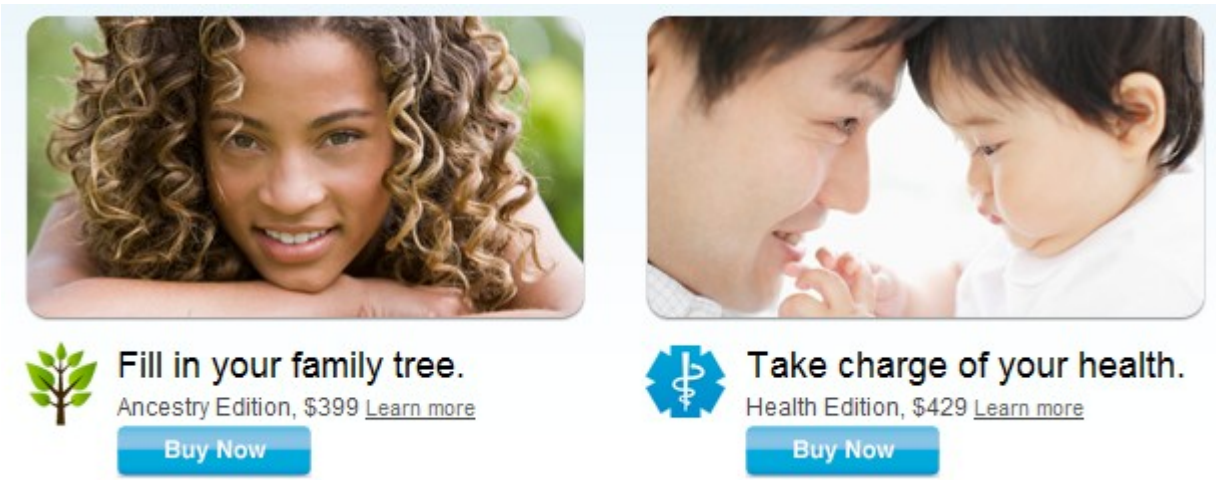
Clara Abraham, MD, and Judy Cho, MD

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

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The Promise and Controversy of Personal SNP Genomics





Navigenics, 23andMe slammed in government report

By Steve Johnson
sjohnson@mercurynews.com
Posted: 07/22/2010 09:18:19 PM PDT
Updated: 07/24/2010 04:06:35 AM PDT

Silicon Valley MercuryNews.com

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www.mercurynews.com/business/ci_15580695

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Should You Keep Your Health Data Private or Share to Gain the Most Knowledge?

U.S. Department of Health & Human Services
HHS.gov *Improving the health, safety, and well-being of America*

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Rules

trusera

Trusera is an online health network platform where you can find and share real-world experiences. Share your story and experience the Power of Been There™.

patientslikeme®

Share Your Health Profile

By openly sharing your health profile with the community, you can learn more about yourself while helping other patients like you.

Social Networks and Health NEXT

Medicine 2.0 #10 – Medicine and the Second Generation of Internet-based Services

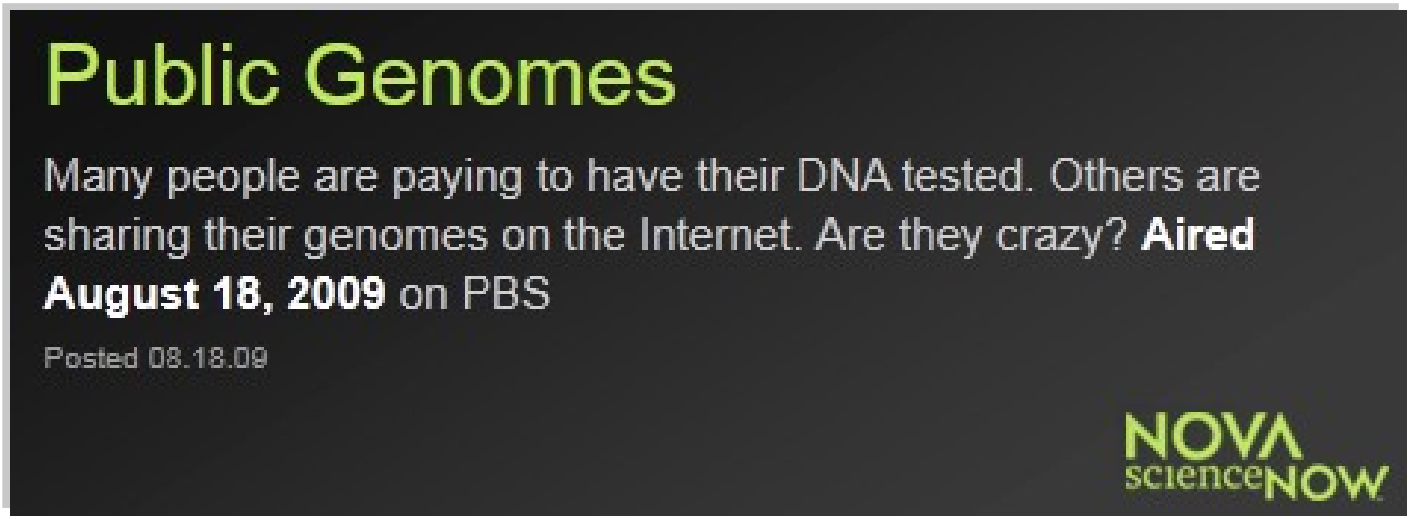
by Walter Jessen

Quantified Self
tools for knowing your own body and mind

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Publically Sharing Your Genome and Medical Records: Is it Crazy or the Future?



Personal Genome Project

Posted 06.01.08 | NOVA scienceNOW

The Personal Genome Project, spearheaded by George Church of Harvard's Center for Computational Genetics, aims to recruit 100,000 people willing to offer up their DNA and personal life histories. It's all in an effort to further knowledge of human genetics and why we get—or don't get—diseases.

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From 10,000 Human Genomes Sequenced in 2011 to 1 Million by 2015 Out of Less Than 5,000 sq. ft.!

Proprietary Sequencing Technology

Designed and Optimized for Whole Human Genome Sequencing **Quality**, **Cost** and **Scale**



Outsourced Business Model

A Turnkey Service Enabling Customers to **Outsource** WGS – Samples In, **Research Ready Data** Out



Complete genomics

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4 Million Newborns / Year in U.S.

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The Promise of Whole Genome Sequencing Combined with Family Testing

Science 30 April 2010:
Vol. 328. no. 5978, pp. 636 - 639
DOI: 10.1126/science.1186802

REPORTS

Analysis of Genetic Inheritance in a Family Quartet by Whole-Genome Sequencing

Jared C. Roach,[1,*] Gustavo Glusman,[1,*] Arian F. A. Smit,[1,*] Chad D. Huff,[1,2,*] Robert Hubley,[1] Paul T. Shannon,[1] Lee Rowen,[1] Krishna P. Pant,[3] Nathan Goodman,[1] Michael Bamshad,[4] Jay Shendure,[5] Radoje Drmanac,[3] Lynn B. Jorde,[2] Leroy Hood,[1,†] David J. Galas[1,†]

- **We analyzed the whole-genome sequences of a family of four, consisting of two siblings and their parents.**
- **Both offspring in this family have two recessive disorders: Miller syndrome, for which the gene was concurrently identified**
- **Family-based genome analysis enabled us to narrow the candidate genes for both of these Mendelian disorders to only four.**
- **Our results demonstrate the value of complete genome sequencing in families.**

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www.sciencemag.org/cgi/content/abstract/328/5978/636?rss=1

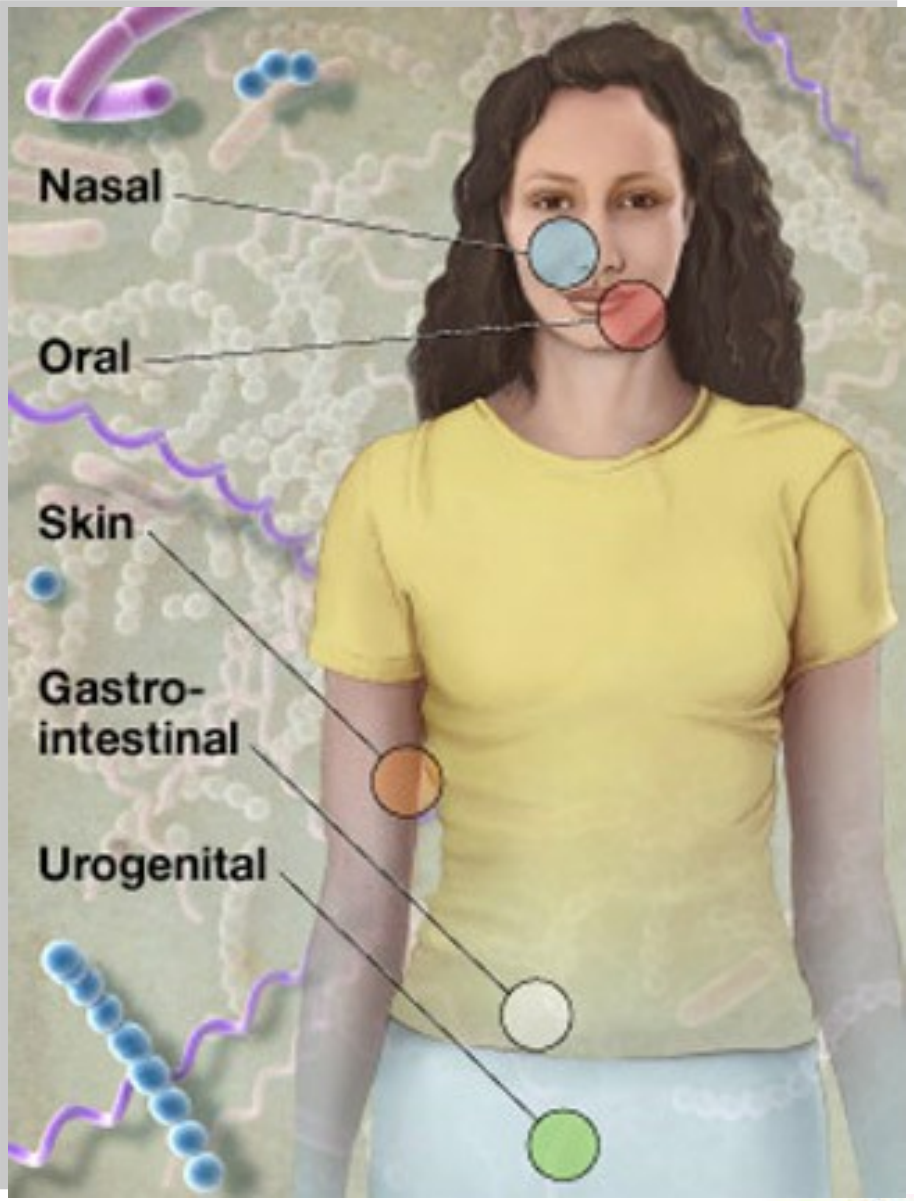
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But the Human Genome Contains Less Than 1% of the Bodies Genes

Human Microbiome Project

HMP

The Total Number of These Bacterial Cells
is 10 Times the Number
of Human Cells in Your Body



The NIH Common Fund
WE ACCELERATE DISCOVERY.

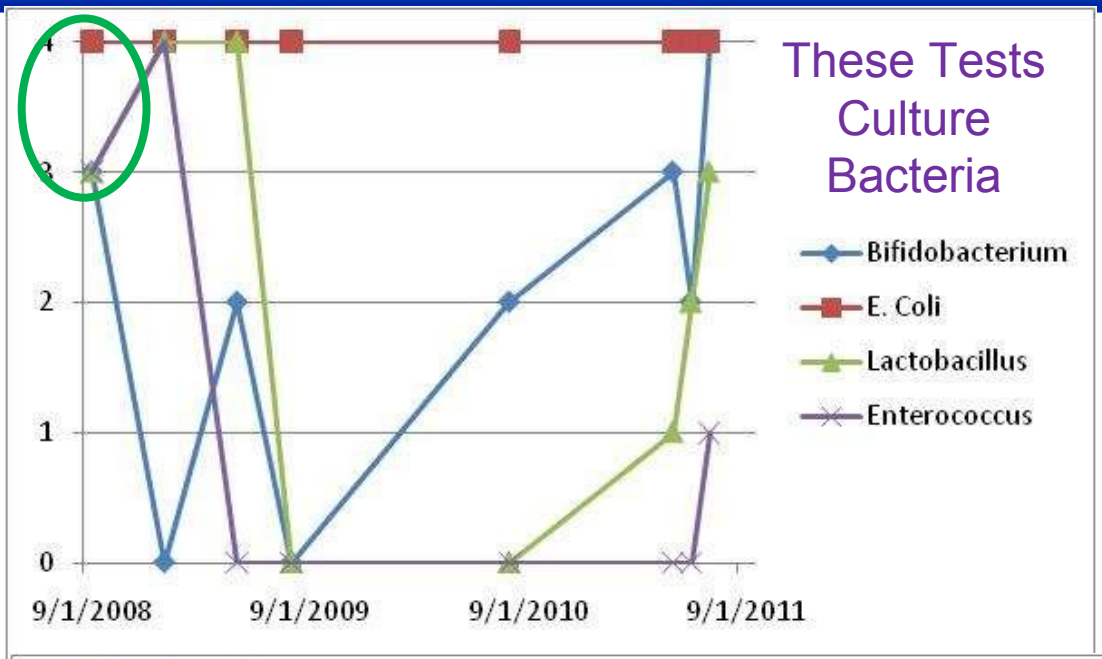
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http://commonfund.nih.gov/hmp/

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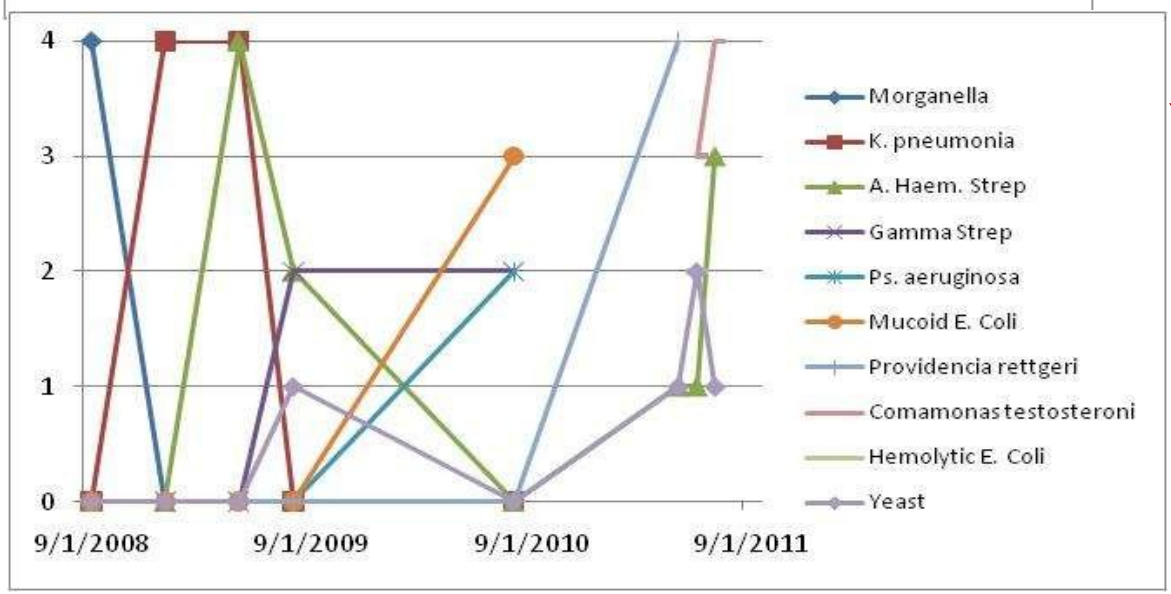
Antibiotics Are Highly Disruptive of Colon Microbiome--Takes 3-4 Years to Recover

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

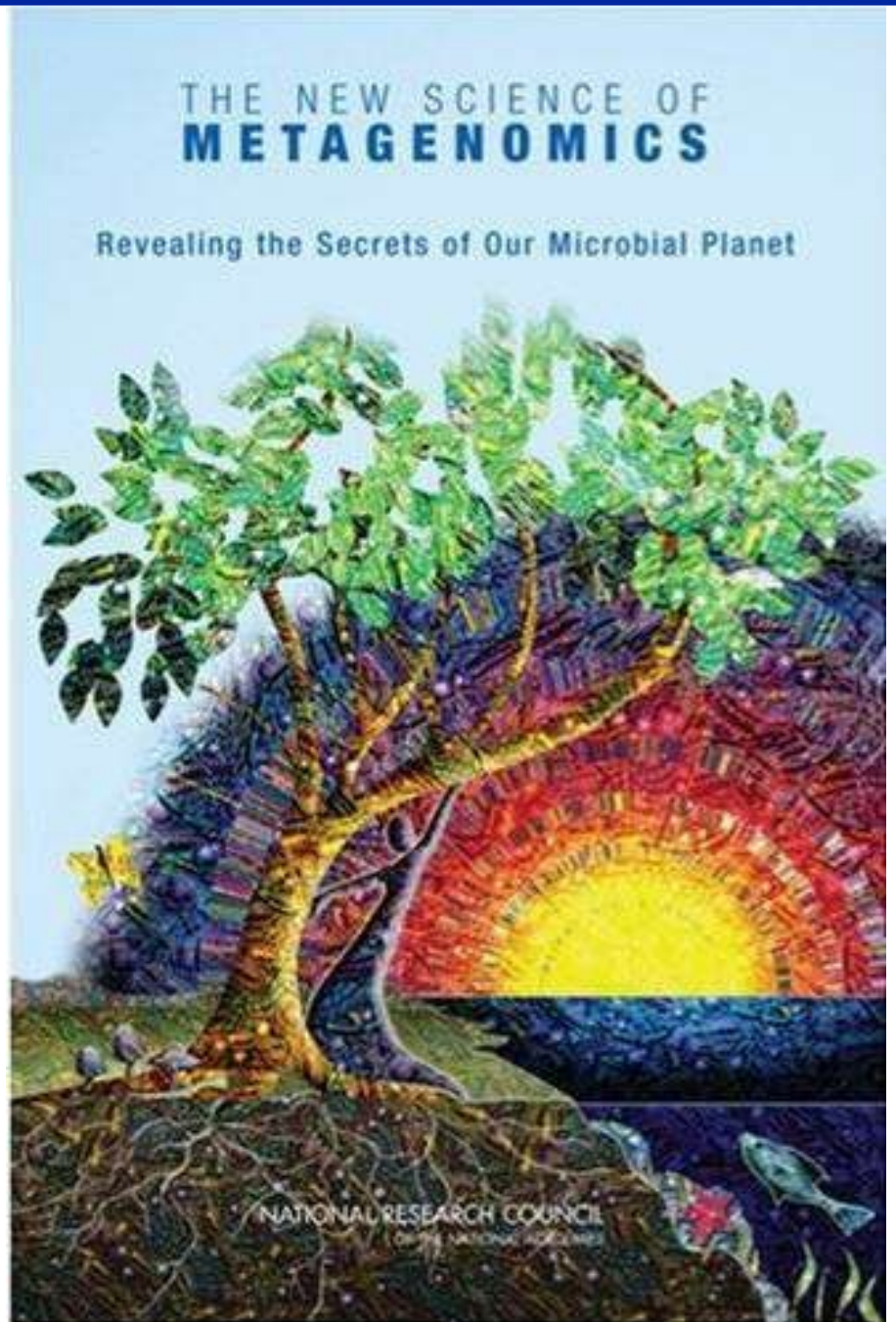
"Bad" Microbes

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The New Science of Metagenomics

NRC Report:

Metagenomic data should be made publicly available in international archives as rapidly as possible.



"The emerging field of metagenomics, where the DNA of entire communities of microbes is studied simultaneously, presents the greatest opportunity -- perhaps since the invention of the microscope – to revolutionize understanding of the microbial world." –

National Research Council
March 27, 2007

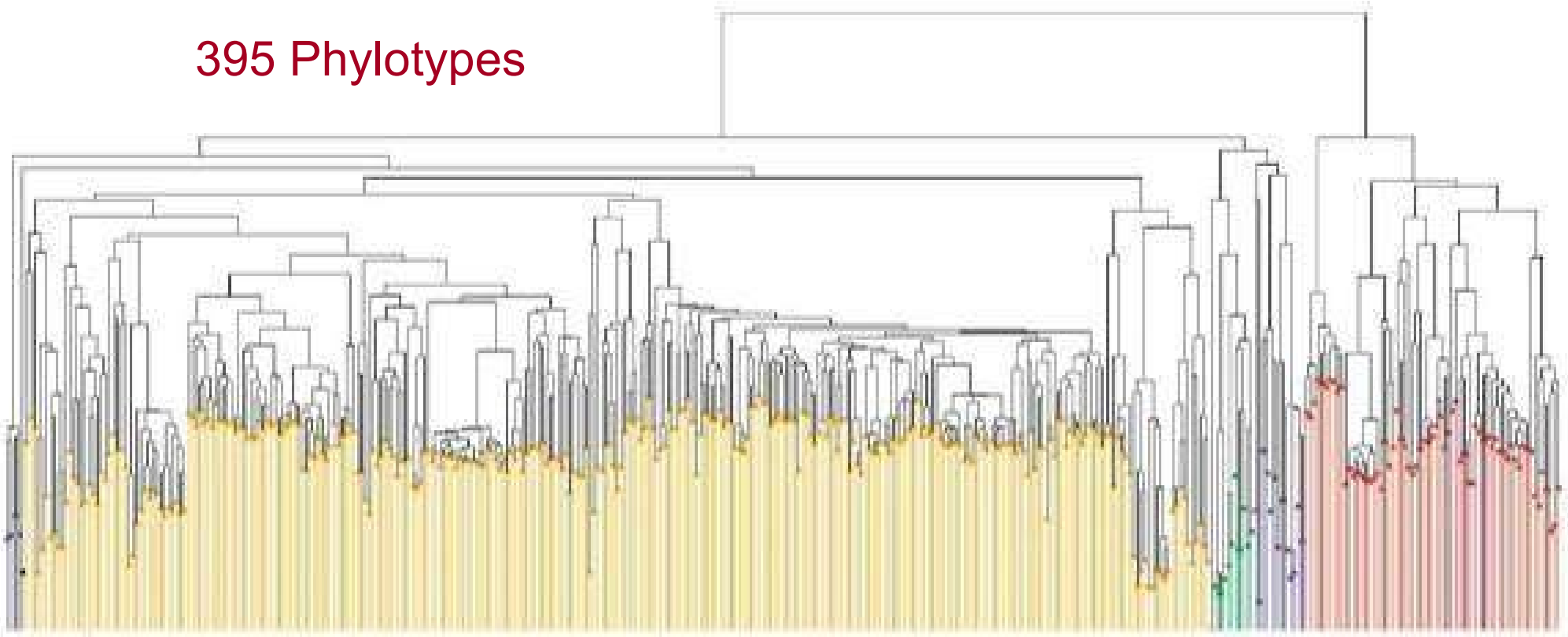
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The Human Microbiome is the Next Large NIH Drive to Understand Human Health and Disease

- **"A majority of the bacterial sequences corresponded to uncultivated species and novel microorganisms."**
- **"We discovered significant inter-subject variability."**
- **"Characterization of this immensely diverse ecosystem is the first step in elucidating its role in health and disease."**

395 Phylotypes

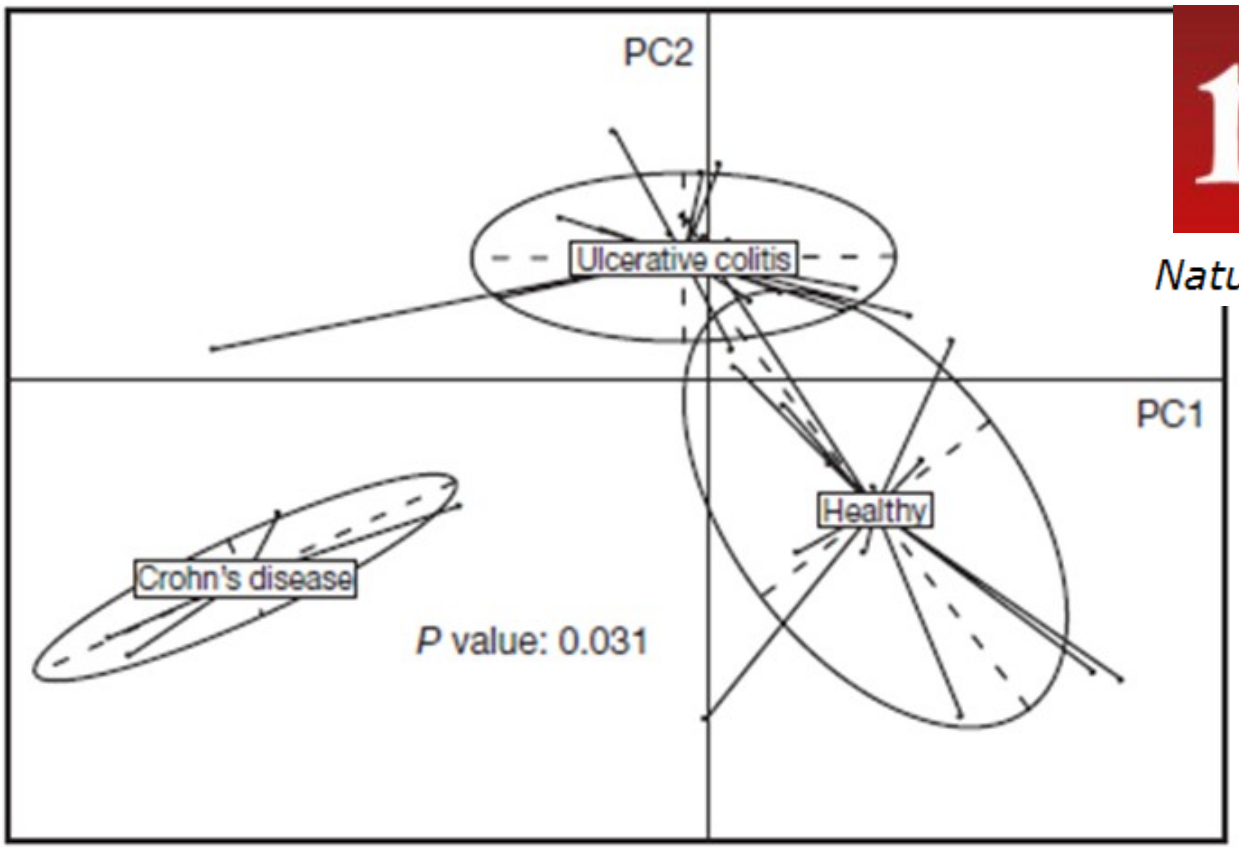


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"Diversity of the Human Intestinal Microbial Flora"
Paul B. Eckburg, et al *Science* (10 June 2005)

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



nature

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

The Microbial Gene Set is 150 Times Larger than the Human Gene Complement.

IBD Patients Harbored, on Average, 25% Fewer 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],

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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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*



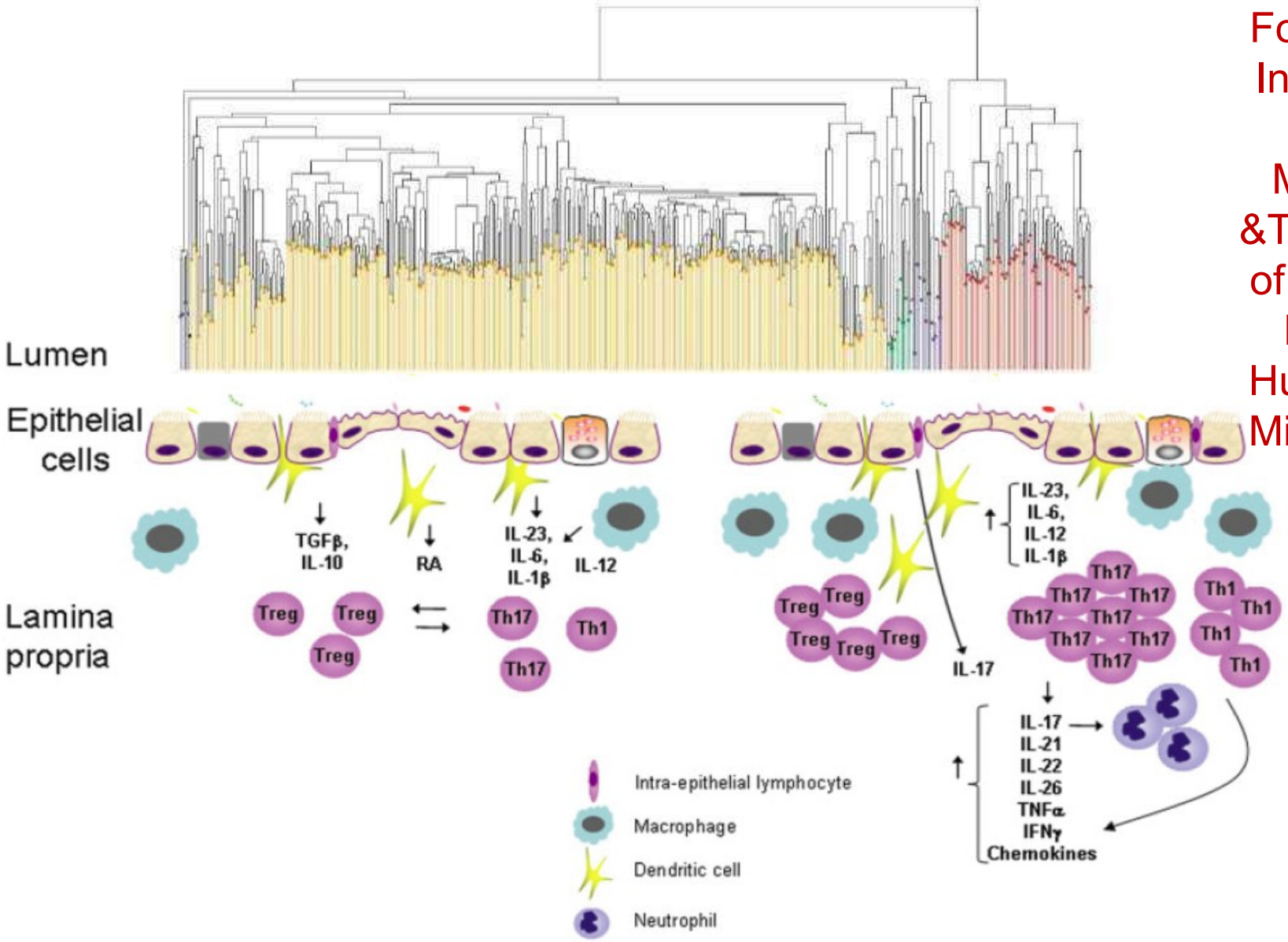
Ruslan Medzhitov[†,§]

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

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Understanding Autoimmune Diseases Will Require Complete Genomes, Microbial Metagenomics 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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