GENOMIC MEDICINE

Alan E. Guttmacher, M.D.
National Human Genome Research Institute

National Institutes of Health

March 29, 2007

Genetic Medicine

- Is based on understanding the impact of single genes on disease…

WEEKLY WORLD NEWS

June 1, 1993 85¢/95¢ CANADA

CREATURE CAPTURED ALIVE — IN VERMONT!

BAT WITH A HUMAN FACE!

He's smart as a whip, says stunned scientist

Genomic Medicine

- Is based on understanding the impact of our *entire genome* *and* environmental factors on disease *and* health …

Genomic Medicine

- 1. Heart disease (28.5% of deaths in ‘02)
- 2. Cancer (22.8%)
- 3. Cerebrovascular diseases (6.7%)
- 4. Chronic lower respiratory dis. (5.1%)
- ? 5. Injury (4.4%)
- 6. Diabetes (3.0%)
- 7. Pneumonia/Influenza (2.7%)
- 8. Alzheimer disease (2.4%)
- 9. Kidney disease (1.7%)
- 10. Septicemia (1.4%)

Genomic Medicine

- Is built on the foundation of the Human Genome Project…

The Human Genome Project

- An international government project that ended ahead of schedule!
- And under budget!!
- And from its start earmarked funds for consideration of its ethical, legal, and social implications (ELSI) - the greatest funding ever devoted to bioethics

HGP Fun Fact: Number of Genes - How Do We Humans Measure Up?

• H. flu	1,700
• E. coli	4,300
• Fruit fly	13,600
• Worm	18,400
• **You**	~22,000
• Arabidopsis	25,500

But, Why Should a Busy PA Care about Exactly How Many Genes Humans Have?

- That's ~22,000 potential drug targets!

Another Fun Fact: Between Them, How Many Human Genes Do All Current Drugs Target?

- ~500
- ~1,000
- ~5,000
- ~10,000
- ~20,000
- ~22,000

Another Fun Fact: Between Them, How Many Human Genes Do <u>All</u> Current Drugs Target?

- **~500**
- ~1,000
- ~5,000
- ~10,000
- ~20,000
- ~22,000

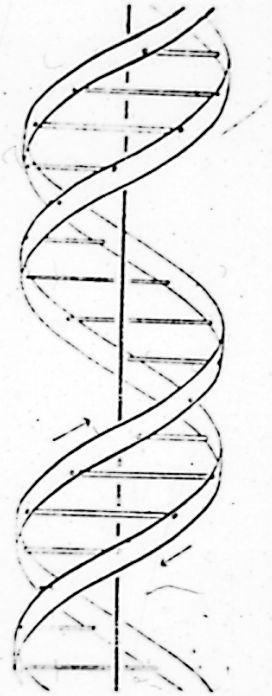
The Human Genome Project

FINISHED over three years ago, on APRIL 14, 2003…

No. 4356 April 25, 1953 NATURE

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

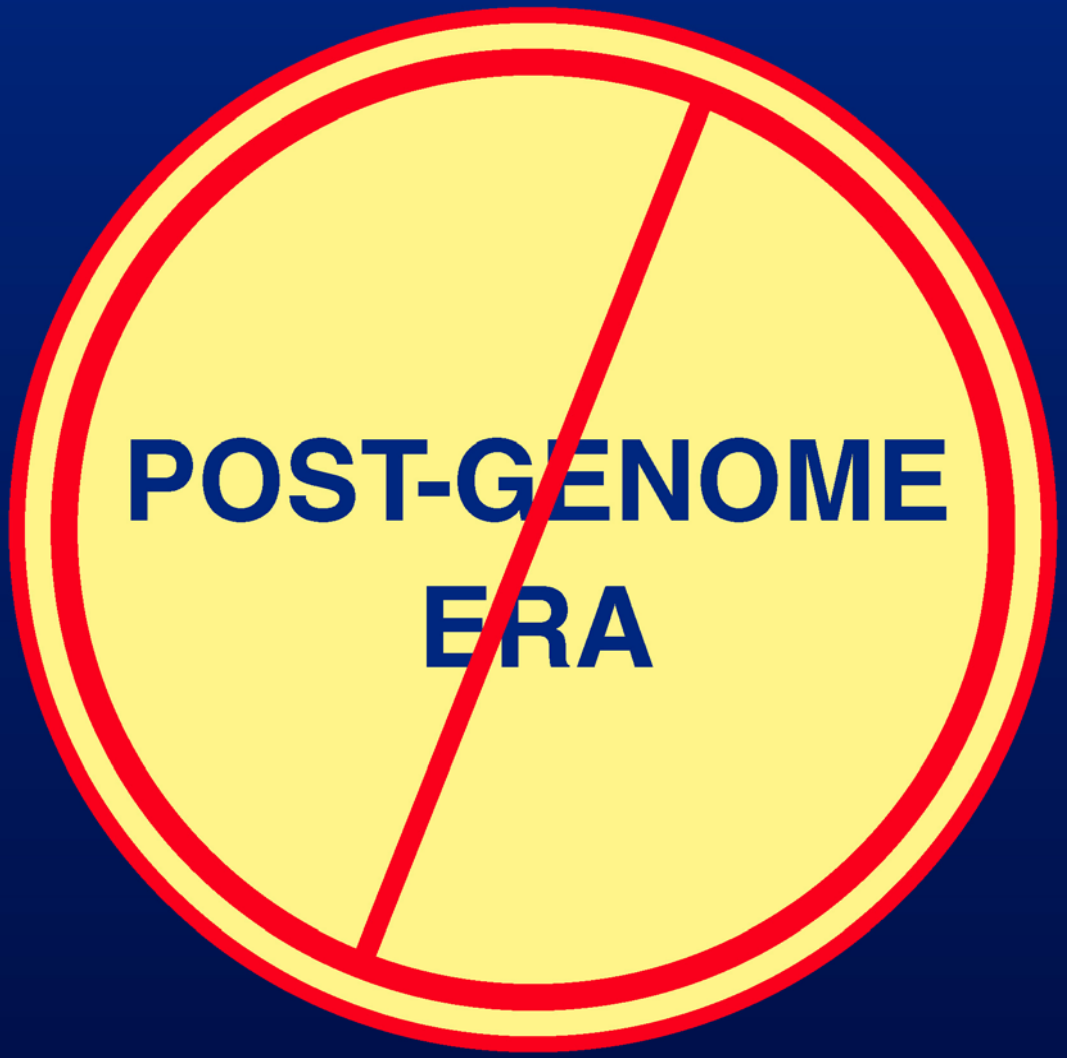
A Structure for Deoxyribose Nucleic Acid



J. D. Watson
F. H. C. Crick

Medical Research Council Unit for the
Study of the Molecular Structure of
Biological Systems,
Cavendish Laboratory, Cambridge.

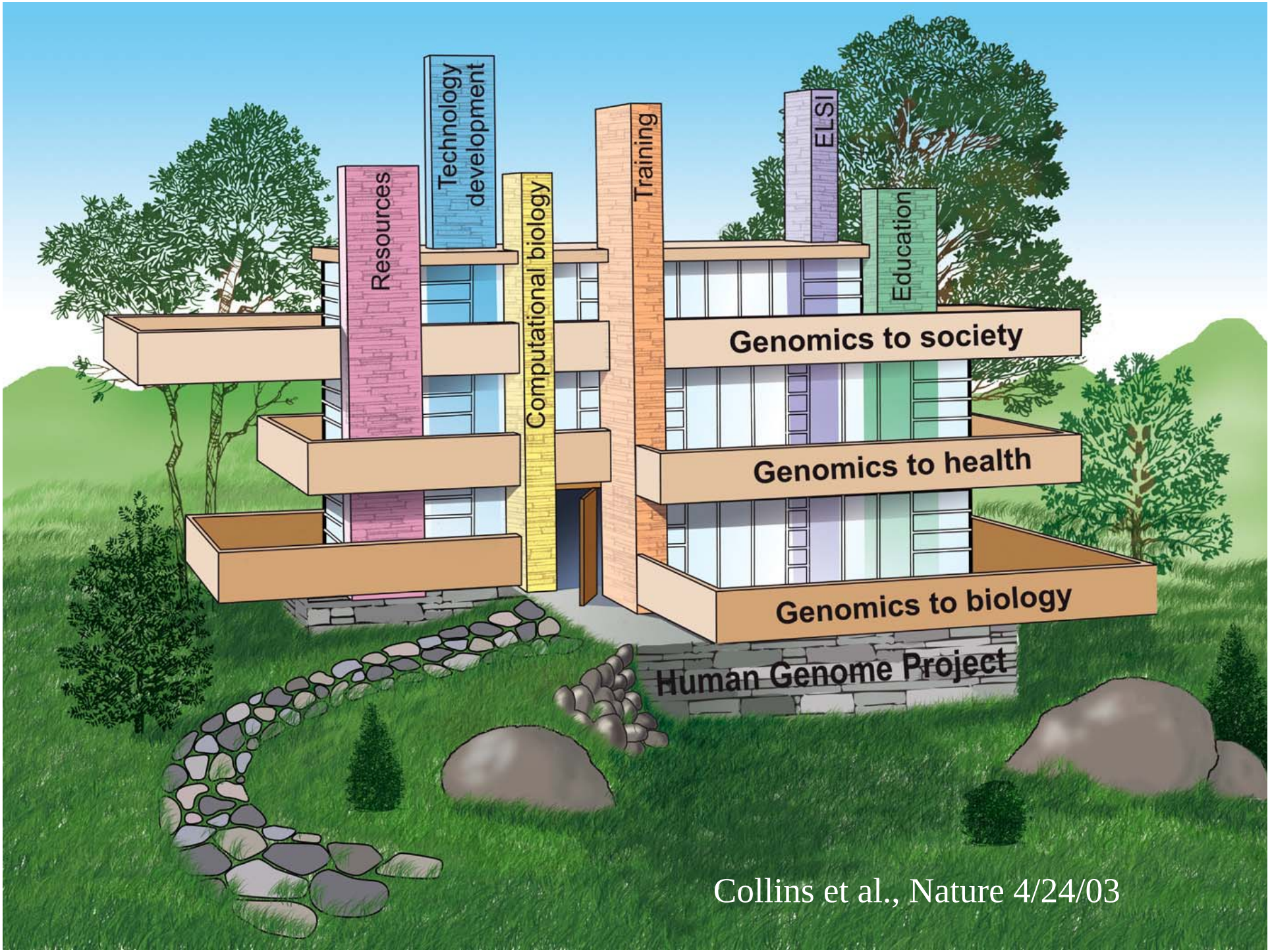
April 2.



WELCOME TO THE GENOME ERA

All of the original goals of the human genome project have been accomplished

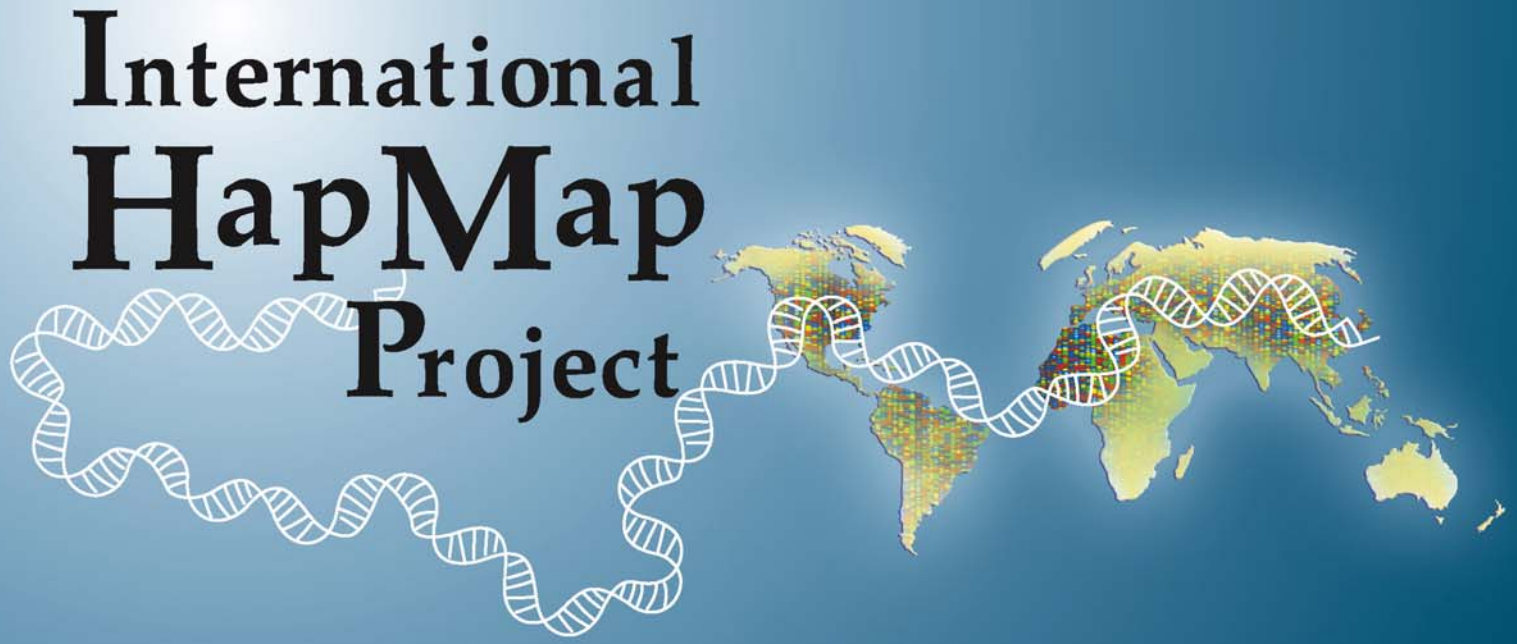
- So, what's next?


Resources
Technology development
Computational biology
Training
ELSI
Education
Genomics to society
Genomics to health
Genomics to biology
Human Genome Project
Collins et al., Nature 4/24/03

Genomics to Biology

Genomics to Biology: Elucidating the Structure and Function of Genomes

- Comprehensively identify the structural & functional components encoded in the human genome
- Elucidate the organization of genetic networks & protein pathways
- Develop a detailed understanding of the heritable variation in the human genome
- Understand evolutionary variation across species & the mechanisms underlying it
- Develop policy options that facilitate the widespread use of genome information in both research & clinical settings



www.hapmap.org

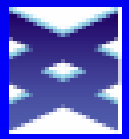
Current research: Analyzing genetic variation between individuals and populations

National Human Genome Research Institute

But, Why Does Variation in the Genome Matter to a Busy PA?

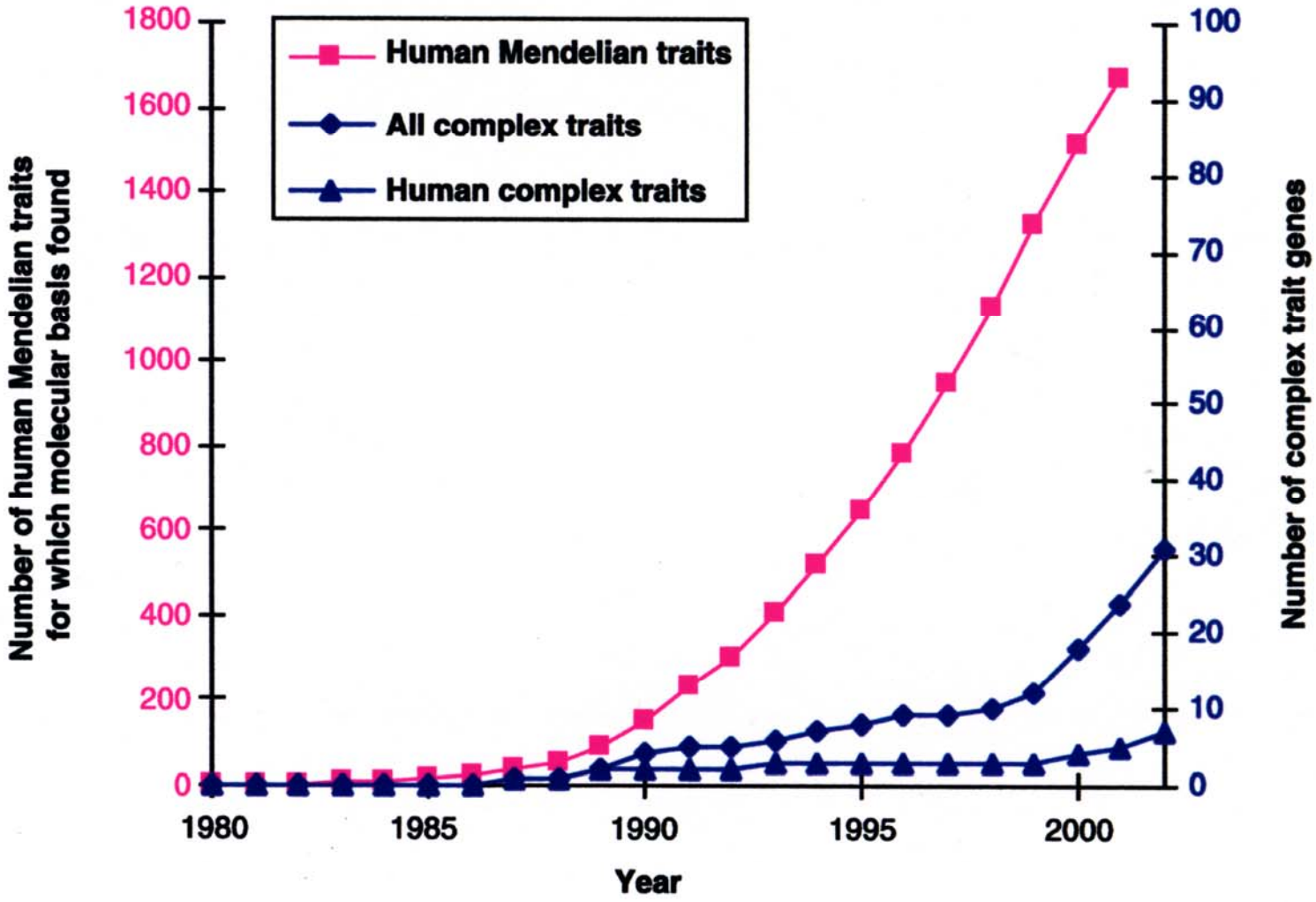
- We have always treated our patients as representatives of some category of humanity, e.g., “57 yo white male”
- However, none of us has actually ever seen a category of humanity in clinic
- All patients are individuals
- Genomic Medicine provides the tools to treat each patient as the individual he or she actually is
- This will markedly improve patient care

Genomics to Health



Genomics to Health: Translating Genome-Based Knowledge Into Health Benefits

- Develop robust strategies to identify genetic contributions to disease and drug response
- Develop strategies to identify gene variants that contribute to good health & disease resistance
- Develop genome-based approaches to prediction of disease susceptibility & drug response, early detection of disease, & molecular taxonomy of disease states
- Use new understanding of genes & pathways to develop powerful new therapeutic approaches
- Explore how genetic risk information is conveyed in clinical settings to improve health outcomes and reduce costs
- Develop genomics-based tools that improve the health of all



Glazier et al., Science 298:2345-9, 2002

Whole Genome Association Approach to Common Disease: The 2002 View

- Identify all 10 million common SNPs
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to 20 billion genotypes
- At 50 cents a genotype, that's **$10 billion** for each disease

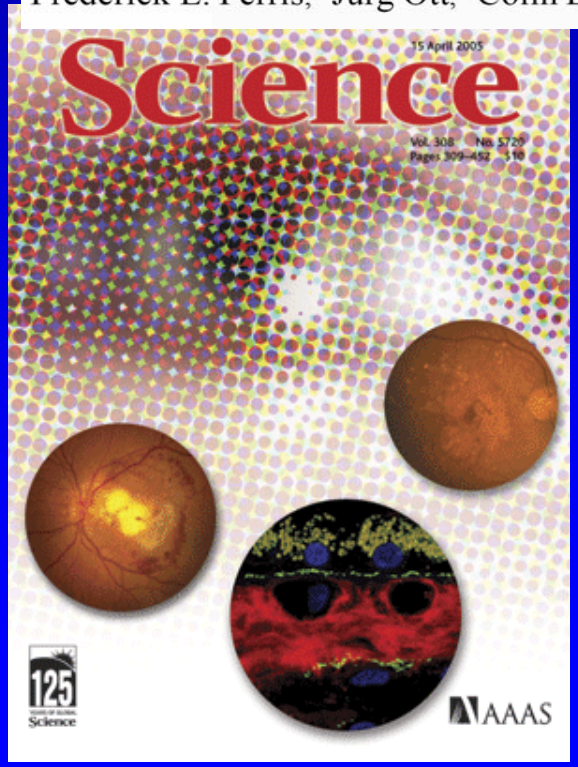
Whole Genome Association Approach to Common Disease: The 2007 View (The HapMap Era)

- Identify optimum set of ~500,000 (or more) variants
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to ~~20~~ **1** billion genotypes
- And, a genotype now costs ~~50 cents~~ 1/12 of a penny, so that's about ~~$10 billion~~ **$800,000** for each disease

The First HapMap Success Story: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]



A Tyrosine to Histidine variant in codon 402 of the Complement Factor H gene accounts for approximately half of the attributable risk of AMD in older adults

The First HapMap Success Story: Age-Related Macular Degeneration

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Three genes appear to account for approximately **74%** of the attributable risk of AMD in older adults – and we did not even view this as a particularly “genetic” disorder…

But, Before We Get Too Carried Away with All This New, Sexy Stuff…

- Let's makes sure we utilize properly the tools we already have…
- Family History!

In the Genome Era, Why Is Family History Important to a Busy PA?

- Bruce will tell you more this afternoon…, but…

Family History Changes Population Screening Guidelines

- Visual Impairment
- Hearing Impairment
- Thyroid Disease
- Thromboembolism
- Hypertension
- Diabetes
- Coronary Artery Disease
- Dyslipidemia
- Breast Cancer
- Colon Cancer
- Prostate Cancer
- Liver Cancer
- Hip Dysplasia
- Iron Def Anemia
- Osteoporosis
- Cardiomyopathy

Family History Changes Management of Common Disease

- Coronary Heart Disease
- Hypertension
- Heart Failure
- Emphysema & COPD
- Syncope
- Pancreatitis
- Diabetes
- Thromboembolism
- Thyroid Cancer
- Breast Cancer
- Colon Cancer
- Urticaria
- Developmental Delay
- Pancreatitis

U.S. Surgeon General's Family History Initiative

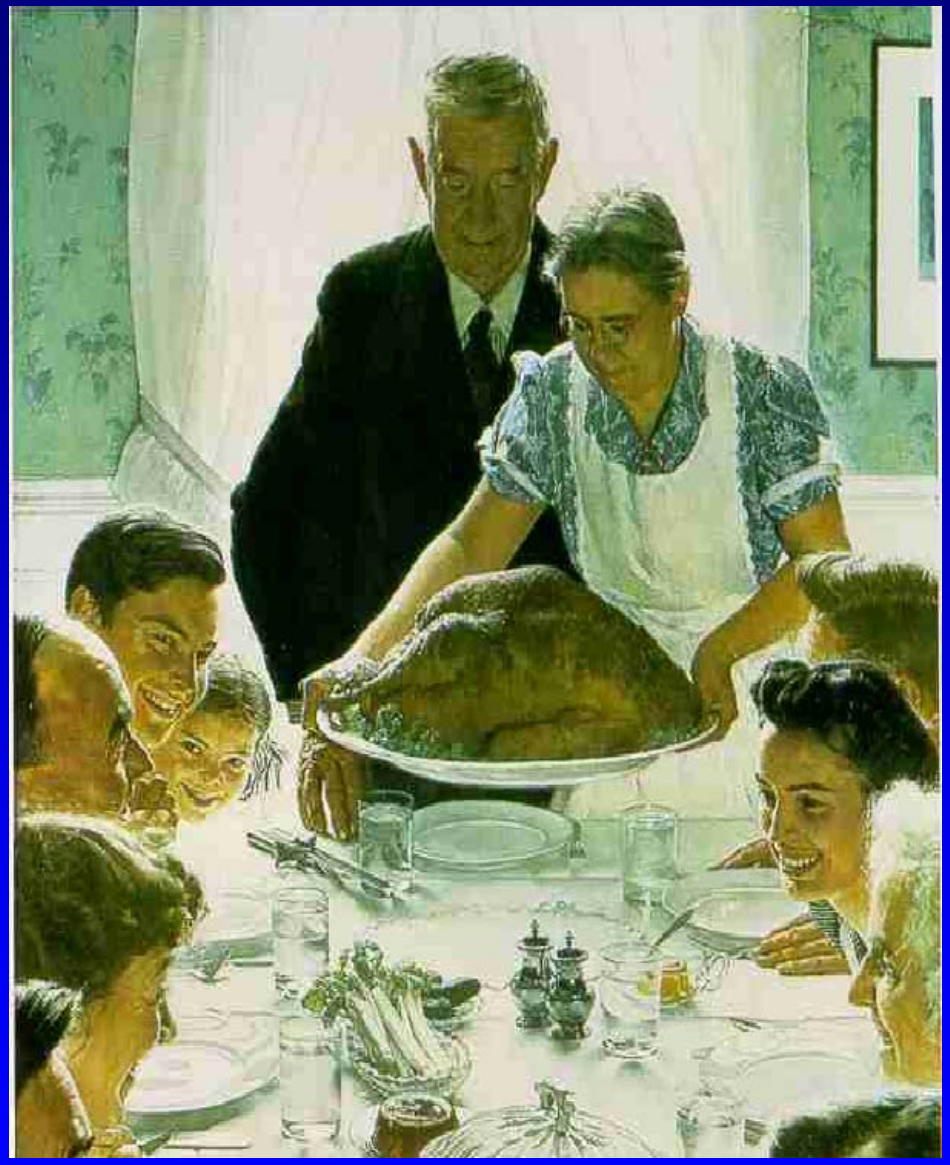
Web-Based Family History Tool Available in English and Spanish

My Family Health Portrait

A tool from the U.S. Surgeon General

URL: familyhistory.hhs.gov

THANKSGIVING IS THE ANNUAL NATIONAL FAMILY HISTORY DAY



Once we finish the family history, let’s eat!

Genomic Medicine/Health Care

Genomic Medicine

- Will change medicine by...
  - Creating a fundamental understanding of the biology of many diseases, even many "non-genetic" ones
  - Leading to defining disorders by biology of causation, rather than by symptoms

Genomic Medicine

- Will change medicine by...
  - providing knowledge of individual genetic predispositions via microarray and other technologies

Genomic Medicine

- Knowledge of individual genetic predispositions will allow:
  - Individualized screening

Genomic Medicine

- Knowledge of individual genetic predispositions will allow:
  - Individualized screening
  - Individualized behavior changes, e.g., informed dietary and lifestyle choices

Genomic Medicine

- Knowledge of individual genetic predispositions will allow:
  - Individualized screening
  - Individualized behavior changes
  - Presymptomatic medical therapies, e.g., antihypertensive agents before hypertension develops, anti-schizophrenia agents before schizophrenia develops

Genomic Medicine

- Will change medicine by…
  - Creating pharmacogenomics, including:
  - The right drug, at the right dosage, at the right time
  - New drug targets

Genomics to Society

Genomics to Society: Promoting the Use of Genomics to Maximize Benefits and Minin Harms

- Develop policy options regarding the uses of genomics in medical & non-medical settings
- Understand the relationship between genomics, race and ethnicity, and the consequences of uncovering these relationships
- Understand the consequences of uncovering the genomic contribution to human traits and behaviors
- Assess how to define the ethical boundaries for uses of genomics

Why is the Relationship between Genes and Race and Ethnicity Important to a Busy PA?

- Vence will tell you this afternoon, but…

The San Diego Union-Tribune.

June 4, 2003

No trace of race; Genome Sequencing Project proves nothing biological separates peoples

The New York Times

October 1, 2002

For Sale: A DNA Test To Measure Racial Mix

A company in Sarasota, Fla., is offering a DNA test that it says will measure customers' racial ancestry and their ancestral proportions if they are of a mixed race.

110th

~~109th~~ ~~108TH~~ CONGRESS
1ST SESSION

~~S. 1053~~ ~~S.306~~ ~~H.R.1227~~ S.358 H.R.493

AN ACT

To prohibit discrimination on the basis of genetic information with respect to health insurance and employment.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Genetic Information Nondiscrimination Act of ~~2003~~ 2007".

But, Why Should a Busy PA Care about GINA?

Betty's Story in 2017 (Betty is an 8-year old you will see in your office at 2:30 on Monday)

- Betty completes the Surgeon General's family history tool at age 18, learns of uncles with early heart disease
- She consults her Physician Assistant, who suggests complete genome sequencing for $1000
- She inquires about the risk of genetic discrimination, but federal legislation has outlawed this

Betty's Story in 2017

- She is found to have three gene variants that well validated studies have conclusively shown to increase risk of early heart attack 5-fold
- She and her PA design a program of prevention based on diet, exercise, and medication precisely targeted to her genetic situation

Betty's Story Continues…

- Betty does well until age 75
- She develops left arm pain that she assumes is due to gardening, but her PA knows her higher risk and diagnoses an acute MI
- Referring to her genome sequence, the drugs that will work best to treat her are chosen
- She survives and is alive and well in the 22nd century

Personalized Medicine: Could the Dream Become a Nightmare?

Betty's Story Gone Wrong

- The Surgeon General's Family History Initiative never really takes off and her pediatrician is too busy to ask about family history, so Betty never learns about her family history
- Betty is offered genome sequencing, but after seeing her brother lose his health insurance from this information, she declines
- Betty eats an unhealthy diet, gains weight, and develops hypertension

Betty's Story Gone Wrong

- While tests to predict which drug would be most effective for Betty have been proposed, they have never been validated, and are not reimbursed
- Betty's hypertension is treated with a drug that causes a hypersensitivity reaction, so she stops treatment
- After 10 years of uncontrolled hypertension, Betty develops left arm pain at age 45

Betty's Story Gone Wrong

- Her PA, unaware of her high risk, assumes this is musculoskeletal and prescribes rest
- Betty returns to the ER the next day in cardiogenic shock
- The absence of her genome sequence information prevents optimal choice of therapy
- Betty dies in the ER

Executive Summary

- Will all this genomic medicine stuff really make any difference?

Executive Summary

"Our age may be known to history as the age of genetic health care, a time when many of the most feared illnesses were overcome."

- President Bush
April 10, 2002

Executive Summary

"It is now conceivable that our children's children will know the term cancer only as a constellation of stars."

- President Clinton

June 26, 2000