

Weill Medical College of Cornell University
Class of 1981 25th Reunion

Personalized Medicine: Are We Ready?

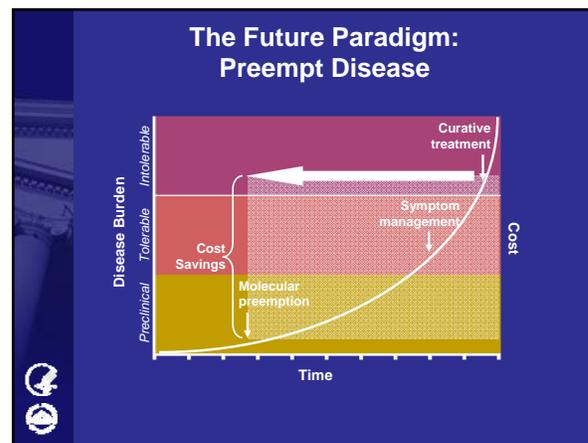
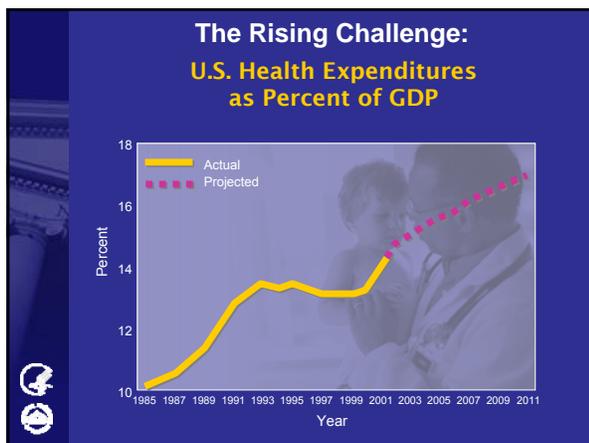
Elizabeth G. Nabel, M.D.
Director
National Heart, Lung, and Blood Institute
October 13, 2006



Evolving Public Health Challenges:



- Acute to Chronic Conditions
- Aging Population
- Health Disparities
- Emerging and Re-emerging Infectious Diseases
- Biodefense



Need to Transform Health and Medicine in the 21st Century

20 th Century	21 st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

Circa 2015

- Dan, a 50 something year XY, had his genome scanned 4 years ago by his physician and has 5 gene variants that increase his risk for heart disease 6-fold; he also has 3 genes that protect him from getting cancer.
- Recommendations for his diet and medications have been selected based on his profile for drug metabolizing enzyme variants.

Circa 2015

- He developed chest pain while jogging. A analysis of his serum based upon biomarkers for myocardial ischemia revealed no necrosis.
- Molecular imaging showed a 'hot' plaque in his right coronary artery.
- A *targeted* anti-inflammatory agent and *targeted* blood thinner were given to him and re-imaging showed quiescence of the 'hot' plaque.

The Future Paradigm: The 4 P's

Transform Medicine from Curative to Preemptive



Genomic Medicine

- **Prediction** of individual risk for various diseases
- **Preemption** of clinical disease through early detection
- **Personalized** treatments
- **Participation** in health maintenance

Predictive: End Stage Renal Disease



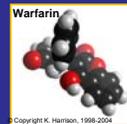
- End-stage Renal Disease:
 - \$22.8 billion in U.S. public and private spending (2001)
 - In the past decade, the absolute number of ESRD patients more than doubled and the incidence rate doubled
 - More than 85,000 new cases per year
- Apolipoprotein E (APOE)
 - Variation predicts kidney disease progression
 - Prediction independent of diabetes, race, lipid and non-lipid risk factors

Preemptive: HPV Vaccine



- Human Papillomavirus (HPV) infects over 80% of 15-50 year old women and can cause cervical cancer
- Prevent sexually transmitted HPV infection = prevent cervical cancer
- Anti-Viral Vaccines are among the most cost effective public health interventions (e.g., smallpox, polio, & measles)
- NIH has two vaccines currently in clinical trials

Personalized: New Discoveries and Cardiovascular Treatment



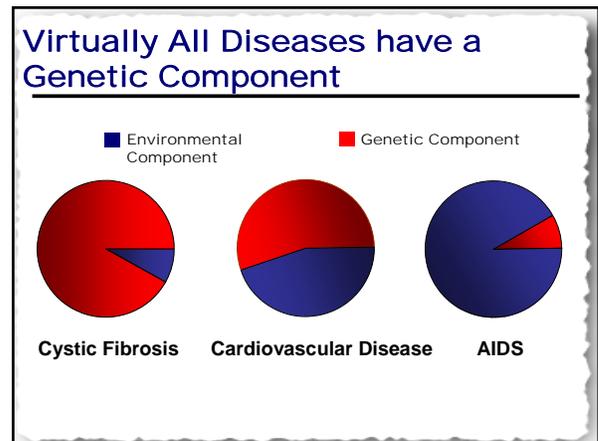
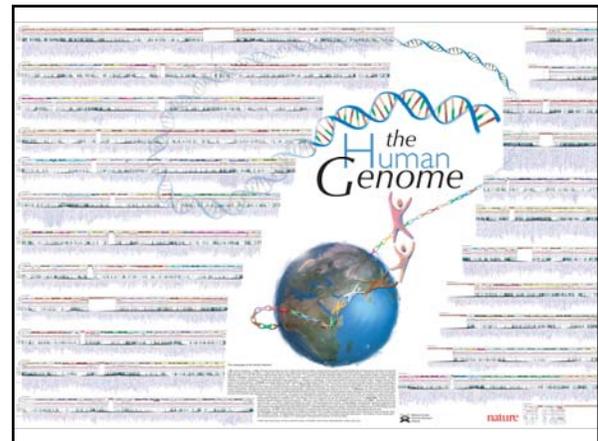
- **Warfarin:** Anticoagulant drug that reduces risk of clots causing strokes or heart attacks
 - Effective daily dose ranges from 0.5 mg to 60 mg
 - Too little: clots, stroke
 - Too much: bleeding/death
- Genomic experiments revealed: Can test for genetic variations that **predict** best dose for **individual patients**

Participatory: Community Involvement

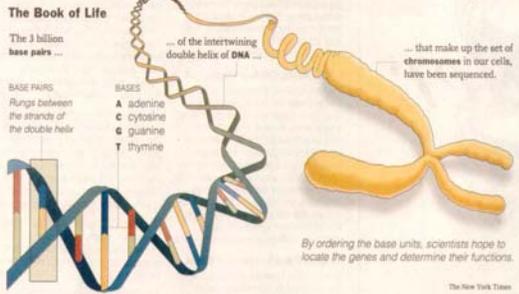


Jackson Heart Study

- Extension of ARIC
- Community participation
- Community education
 - Health awareness
 - Student outreach
 - Encourage involvement
- Identify minority risk factors for CVD



"The Book of Life" 3 billion chemical base pairs, when strung together as genes, determine how all the cells in the human body develop and function.



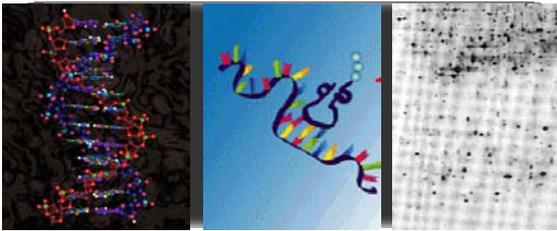
The 3 billion base pairs ... of the intertwining double helix of DNA ... that make up the set of chromosomes in our cells, have been sequenced.

BASE PAIRS: Rungs between the strands of the double helix

BASES:
 A adenine
 C cytosine
 G guanine
 T thymine

By ordering the base units, scientists hope to locate the genes and determine their functions.

- ### The Human Genome
- 3.1 billion bases of DNA sequence
 - ~97% of the genome contains coding regions
 - 30,000 genes
 - 100,000 proteins
 - Mutations causing disease have been identified in >1,000 genes



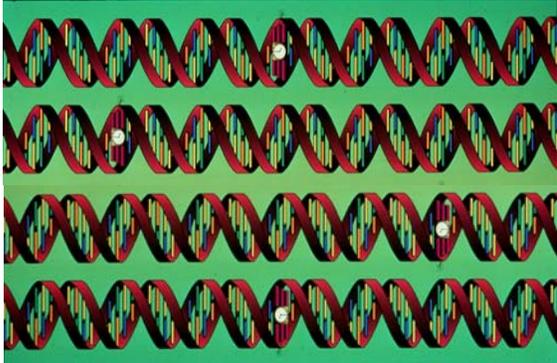
Genotype:
DNA sequences within a gene.

RNA expression:
Microarray

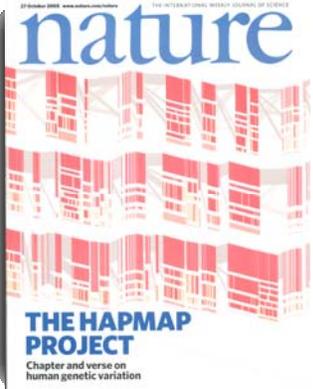
Proteomics:
Proteins.

What are the variants in a gene? Which genes are expressed? Which proteins are present?

Single Nucleotide Polymorphisms



Identification of all SNPs within neighborhoods or haplotypes on each chromosome from individuals in diverse populations.



THE HAPMAP PROJECT
Chapter and verse on human genetic variation

SNPs – markers of human genetic variation

- Single nucleotide polymorphisms are nucleotide substitutions that does not alter the encoded protein.

AUG GCC TAC GTT CGA CCC
Met Ala Tyr Val Arg Pro

AUG GAC TAC GTT CGA CCC
Met Ala Tyr Val Arg Pro

But in Practice, Only Two are Observed

```

...C...A...A...
...C...A...G...
...C...C...A...
...C...C...G...
...T...A...A...
...T...A...G...
...T...C...A...
...T...C...G...

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Variant A

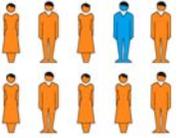


Diabetic



Unaffected

Variant B



Diabetic



Unaffected

Gene Chip

- Gene Chip technology can reveal 500,000 genetic sequences in a single DNA specimen and indicate which sequences are "variants".



The First HapMap Success Story: Age-Related Macular Degeneration

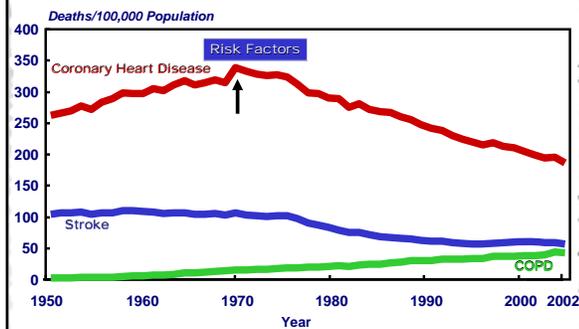
Complement Factor H Polymorphism in Age-Related Macular Degeneration

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,⁶ Shrikant M. Mane,⁶ Susan T. Mayne,⁷ Michael B. Bracken,⁷ Frederick L. Ferris,⁸ Jurg Ott,¹ Colin Barnstable,² Josephine Hoh⁹



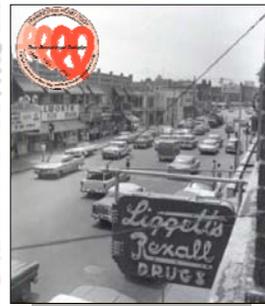
A Tyrosine to Histidine variant in codon 402 of the Complement Factor H gene accounts for approximately half of the attributable risk of AMD in older adults

Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950-2002



Framingham Heart Study

Downtown Framingham, MA (circa 1960)



Major Risk Factors for Heart Attack, Stroke, other Cardiovascular Diseases

- High blood pressure
- High cholesterol
- Cigarette smoking
- Diabetes mellitus
- Parental or sibling history
- Obesity

Important New Markers of Risk

- C-reactive protein & other biomarkers
- Metabolic syndrome
- Thick heart muscle on ultrasound
- Artery plaques on CT & MRI scans
- Genetic markers

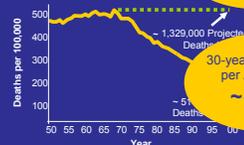
Coronary Heart Disease



- 63% decrease in Mortality
- ~ 1 million early deaths averted per year
- \$2.6 trillion in economic return
- New, effective treatments and prevention strategies
- New discoveries being developed with industry



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Average investment per American
~\$3.70 per year

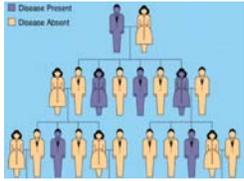
30-year investment per American:
~\$110 Total



Framingham SHARe

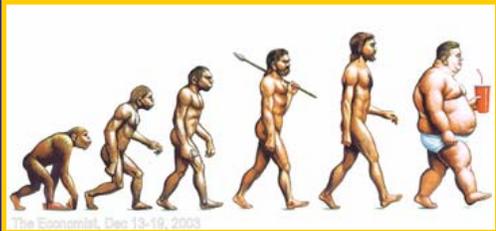


Three generations of families with >9000 participants

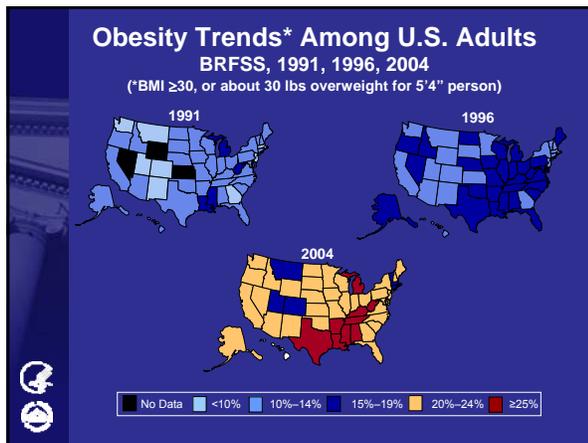


- Genotyping of the entire cohort using 500k SNP chips and genome-wide association.
- Phenotyping of three generations obtained at the same age within a family, and measurements have been made over several decades.
- Creation of a database, maintained by the NCBI, which will be available to approved users for biomedical research purposes.
- NHLBI oversight of data access and IP.

The Shape of Things to Come: Risk Factors, Present and Future



The Economist, Dec 11 & 18, 2005



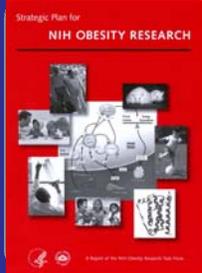
Strategic Plan for NIH Obesity Research

Goal:

- Maximize collaboration among 19 NIH Institutes and Centers
- Capitalize on their expertise and interest

Emphasizes research toward preventing and treating obesity:

- Lifestyle modification
- Pharmacologic, surgical, or other medical approaches
- Breaking the link between obesity and its associated health conditions
- Cross-cutting research topics, including health disparities




Ways to Enhance Children's Activity & Nutrition



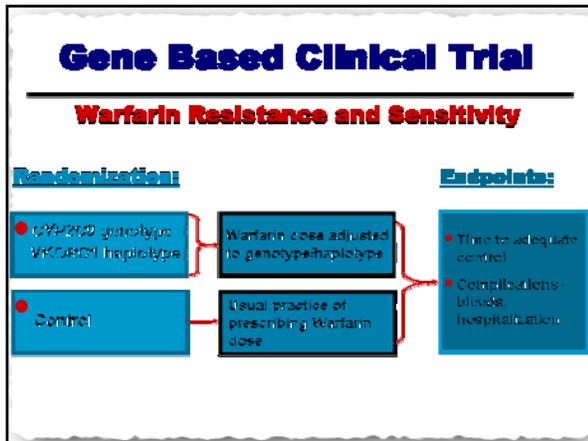
An NIH national education program targeting youth, ages 8-13, and their parents and caregivers in home and community settings to help prevent overweight and obesity.



It's Time for Genetics



"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."



Scientific Advances Lead to Profound Changes in Health

In the past 30 years:

- Life expectancy up by over 6 years
- 60% drop in mortality from acute stroke and heart disease
- Increased survival from Cancer
- 30% drop in disability rates for seniors
- Population is living longer and healthier but:
 - Age-related and chronic rather than acute diseases now main source of health burden
 - Health disparities remain
 - Emerging diseases (obesity, diabetes, mental health)
 - Re-emerging diseases (infectious causes)
 - Biodefense