Robert G. Petersdorf Lecture
2006 AAMC Annual Meeting

Frontiers in Personalized Medicine

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U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute

Evolving Public Health Challenges:


Acute to Chronic Conditions


Aging Population

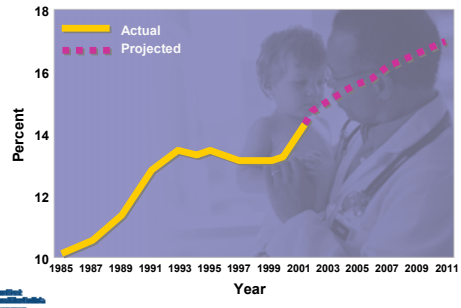

Health Disparities


Emerging and Re-emerging Infectious Diseases

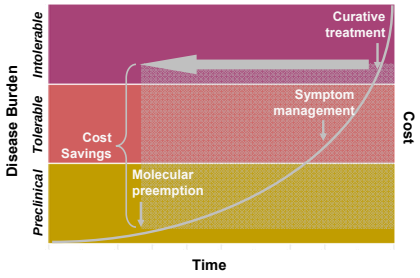

Biodefense

The Rising Challenge:

U.S. Health Expenditures as Percent of GDP



The Future Paradigm: Preempt Disease



Need to Transform Health and Medicine in the 21st Century

20th Century	21st 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

- Maria, a 50 something year XX, had her genome scanned 4 years ago by her physician and has 5 gene variants that increase her risk for heart disease 6-fold; she also has 3 genes that protect him from getting cancer.
- Recommendations for her diet and on her profile for variants of drug metabolizing enzymes in the liver.

Circa 2015

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

The Future Paradigm: The 4 P's

Transform Medicine from Curative to Preemptive


Predictive ↔ Personalized ↔ Preemptive

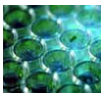
Participatory

Genomic Medicine

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

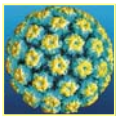
Predictive: End Stage Renal Disease





- 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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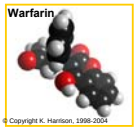
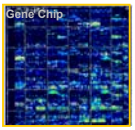
- Human papilloma virus (HPV) infects over 80% of 15-50 year old women and can cause cervical cancer
- Prevent sexually transmitted HPV infection = prevent cervical cancer
- Anti-viral vaccines are among the most cost effective public health interventions (e.g., smallpox, polio, & measles)
- NIH has 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 that tests for genetic variations can predict the best dose for individual patients

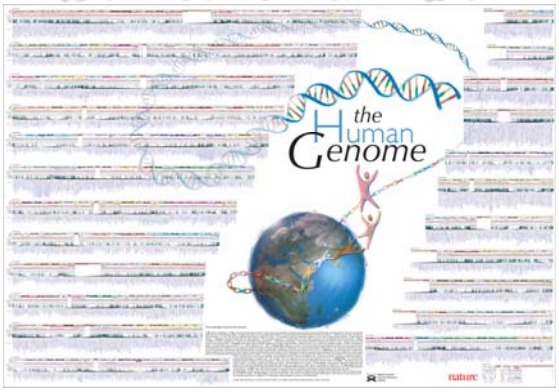
Participatory: Community Involvement

NHMHD

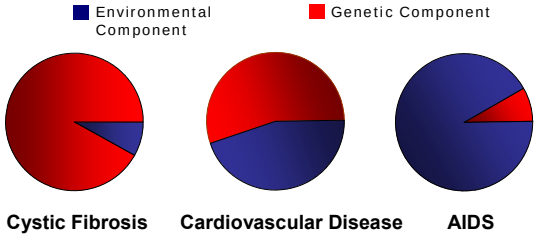
National Heart Lung and Blood Institute

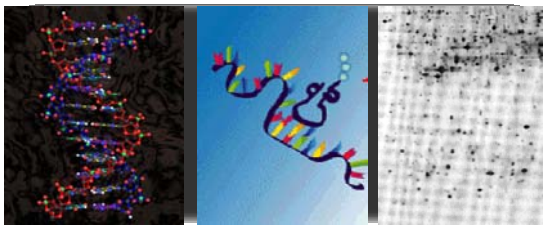
Jackson Heart Study

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



Virtually All Diseases have a Genetic Component



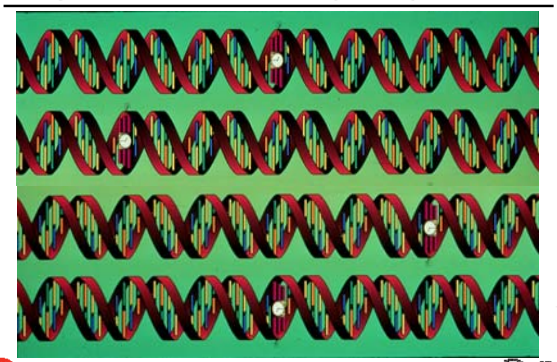


Genotype: DNA sequences within a gene — What are the variants in a gene?

RNA expression: Microarray — Which genes are expressed?

Proteomics: Proteins — Which proteins are present?

Single Nucleotide Polymorphisms



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

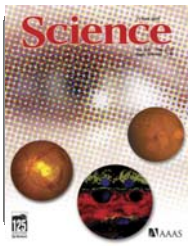
Gene Chip

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

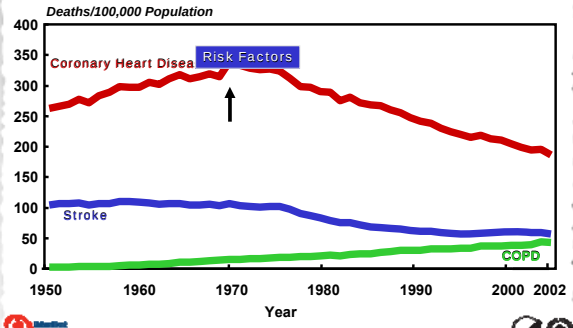
Complement Factor H Polymorphism in Age-Related Macular Degeneration

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,[3] 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†]



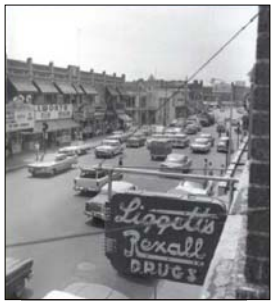
A Tyrosine to Histidine variant in codon 402 of the Complement Factor H gene accounts for approximately half of the attributable risk of AMD in older adults

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



Framingham Heart Study

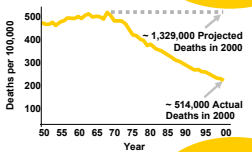
Downtown Framingham, MA (circa 1960)



- "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

Average investment per American ~$3.70 *per year*

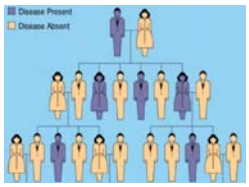


30-year investment per American: ~$110 *Total*

- 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

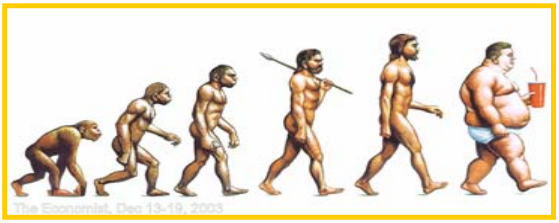
Framingham SHARe

Three generations of families with >9000 participants



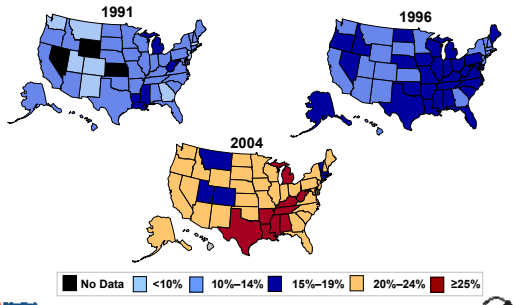
- Genotyping of the entire cohort using 500k SNP chips and genome-wide association.
- Phenotyping of three generations obtained at the same age within a family, and measurements have been made over several decades.
- Creation of a database, maintained by the NCBI, which will be available to approved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

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



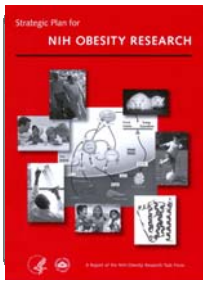
Obesity Trends* Among U.S. Adults
BRFSS, 1991, 1996, 2004

(*BMI ≥30, or about 30 lbs overweight for 5'4" person)



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



It's Time for Genetics

Gene Based Clinical Trial

Warfarin Resistance and Sensitivity

Randomization:

Endpoints:

CYP2C9 genotype
VKORC1 haplotype

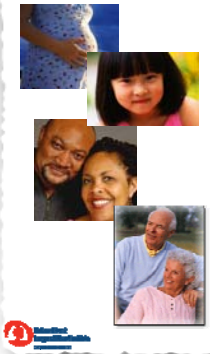
→ Warfarin dose adjusted to geneotype/haplotype

Control

→ Usual practice of prescribing Warfarin dose

- Time to adequate control
- Complications – bleeds, hospitalization

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

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