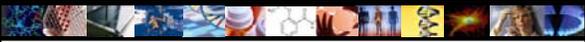
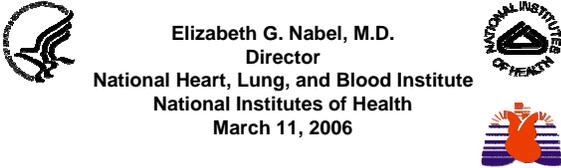
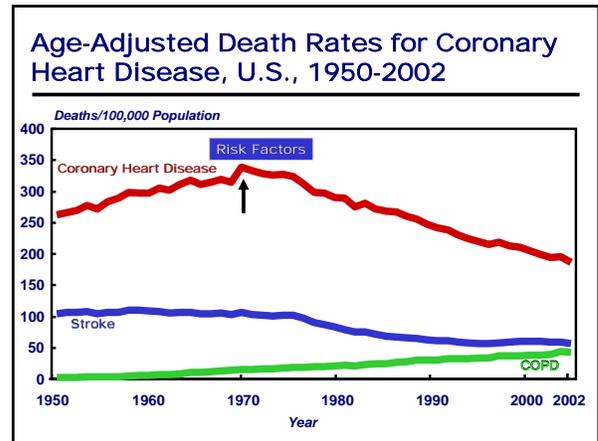


The Simon Dack Lecture  
American College of Cardiology

## Genomic Medicine and Cardiovascular Disease



Elizabeth G. Nabel, M.D.  
Director  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
March 11, 2006

### Framingham Heart Study

Downtown Framingham, MA (circa 1960)



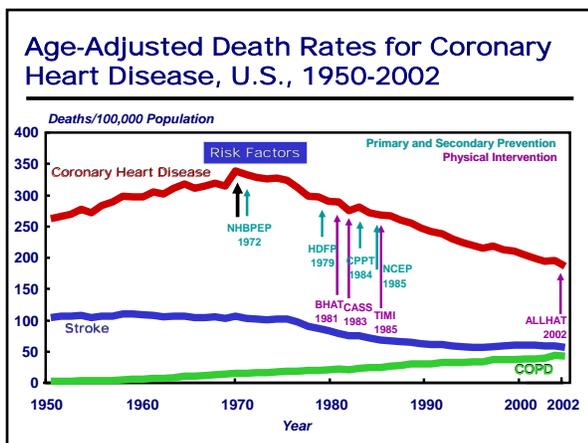

### "Factors of Risk" for CVD

**Annals of Internal Medicine**  
Established in 1937 by the American College of Physicians

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

W. Kannel et al.  
November 1961  
Vol. 55, No. 1

- High Blood Pressure
- Increased Cholesterol
- Smoking
- Diabetes
- Family History
- Male Gender



### Eisenhower's Billion-Dollar Heart Attack — 50 Years Later

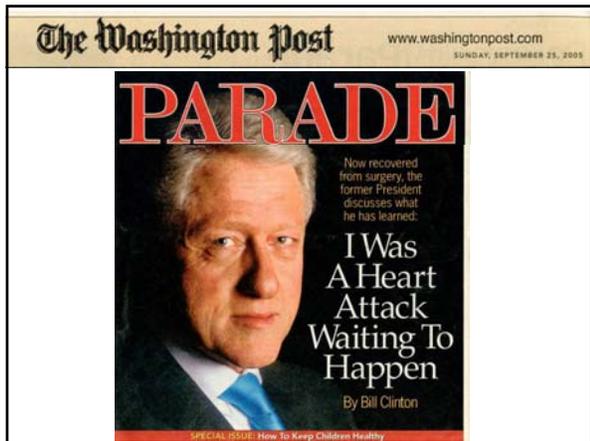
Franz H. Messerli, M.D., Adrian W. Messerli, M.D., and Thomas F. Lüscher, M.D.  
N. ENGL. J. MED. 353:12 WWW.NEJM.ORG SEPTEMBER 22, 2005

The NEW ENGLAND JOURNAL of MEDICINE  
4 ENGL. MED. 353:12 WWW.NEJM.ORG SEPTEMBER 22, 2005

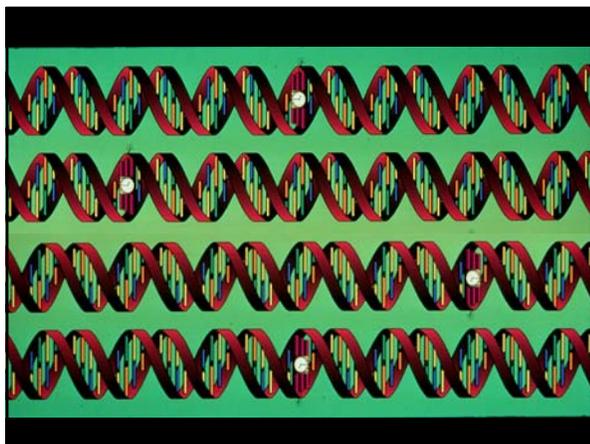
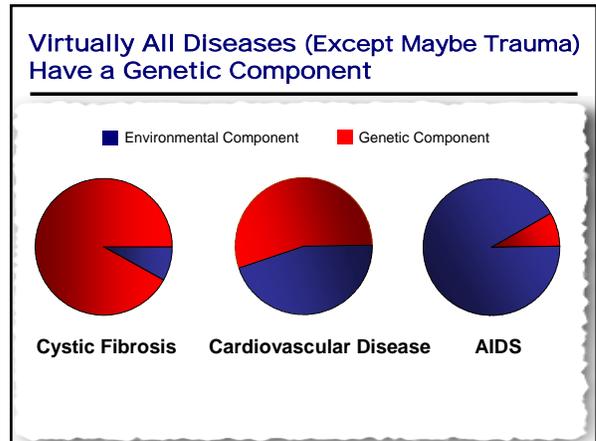
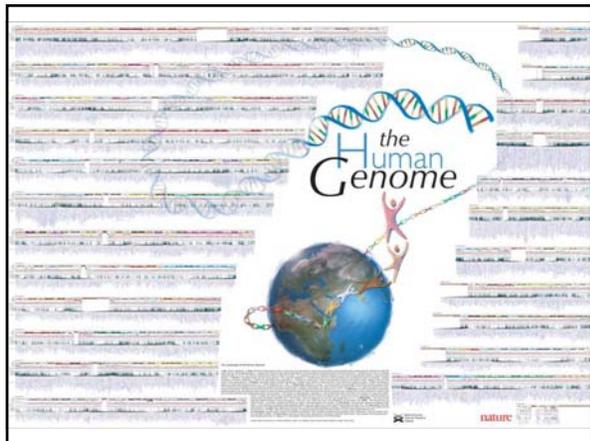
Eisenhower's Billion-Dollar Heart Attack — 50 Years Later



**"Wall Street panicked, the DOW Jones had dropped by 6 percent – a paper loss of \$14 billion, the largest decline since the crash of 1929"**



We look to a future in which medicine will be predictive, preemptive and personalized.



## The First HapMap Success Story: Age-Related Macular Degeneration

### Complement Factor H Polymorphism in Age-Related Macular Degeneration

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



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

## Discovery of Hereditary Factors in Common Disease Will Allow

### “Predictive, preemptive, personalized medicine”

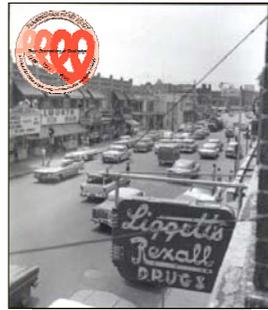
- New ways to predict individual risk for common diseases
- New and individualized ways to prevent common diseases
- New and individualized ways to treat common diseases

## NHLBI Genetics and Genomics Studies

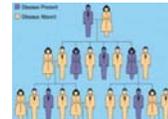
- FHS Genetic Research Study
- Genome-Wide Association Studies
- Women’s Health Initiative Genomic Studies
- Large-Scale Genotyping of NHLBI Cohorts
- Genetic Association Identification Network (GAIN)
- Genes and Environment Initiative (GEI)

## Framingham Heart Study

Downtown Framingham, MA (circa 1960)



Three Generations of Families



- Women and men
- Multiple phenotypic markers
  - Obtained at the same age within a family
  - Measurements over decades
- DNA samples in 9000 participants



## Framingham Heart Study: The Genomic Era

Framingham Heart Genetic Research Study 2006-2007



- GWAS of all 9000 participants
- Database with genotypes and phenotypes, maintained by NCBI
- Public resource
- Informed Consent & Ethics Oversight
- Rapid Conduct of Genetic Research
- Stimulate gene discovery and generation of new hypotheses
- Translation to novel diagnostics and therapeutics

## Women’s Health Initiative

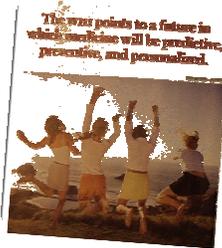


- Initiated in 1992 to collect clinical trial data in the critical health issues affecting women
- 161,000 healthy post-menopausal women, ages 50-79
- 3 intervention trials
  - Hormone Therapy → CV outcomes
  - Dietary Modification → 1’ Breast, Colorectal Cancer Risk, 2’ CV Risk
  - Calcium/Vitamin D → Bone density and fractures, colorectal cancer
- Results have overturned dogma!

## The Best is Yet to Come!

### ■ The Greatest Potential

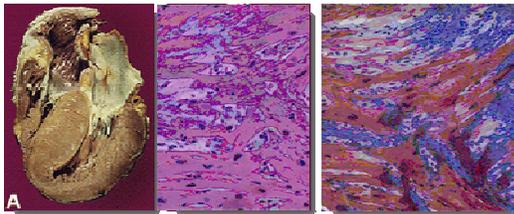
- Genotyping studies to determine risk for stroke, blood clots (HT); breast cancer (DM); bone fractures (Ca. Vit. D)



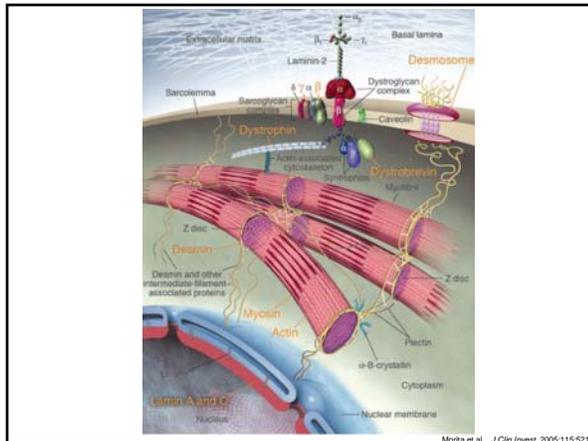
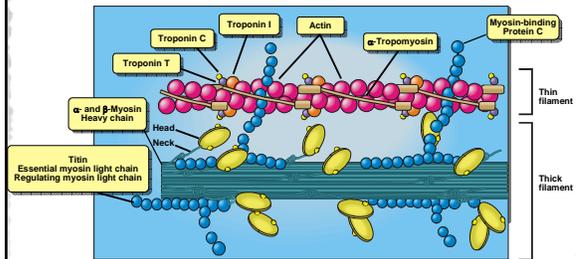
## Familial Hypertrophic Cardiomyopathy

- Most common heritable cardiac disorder.
- Most frequent cause of sudden cardiac death in children and adolescents.
- 300 cardiac deaths a year in high school and college athletes in the USA; one-third of these deaths are caused by FHC.
- Sarcomeric mutations account for 75% of diagnoses in familial hypertrophy and 20% of diagnoses in elderly onset hypertrophy

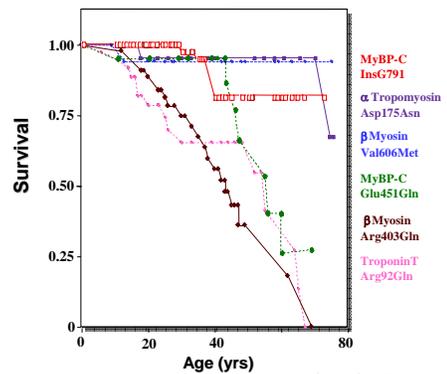
## Cardiomyopathies Patterns of Cardiac Remodeling

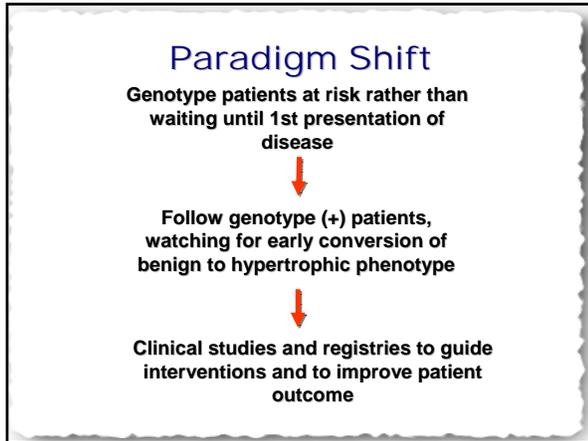


## HCM Caused by Gene Mutations in Sarcomere Proteins

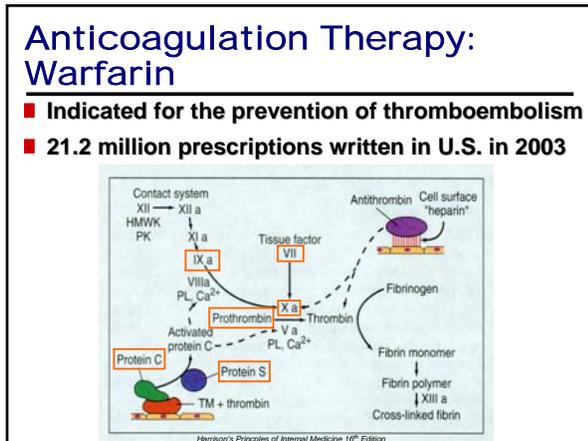


## Influence of HCM Genotype on Survival





- ### Translating Basic Knowledge to Clinical Practice in HCM
- **Identify genetic mutations**
    - Only one CLIA-certified lab in the US
    - Insurance coverage
  - **Collect systematic clinical information**
    - Registry of patients with HCM
    - Registry of sudden cardiac death
    - Registry of athletes
  - **Initiate intervention trials based upon genotype**



- ### Warfarin dose is influenced by:
- Dietary stores of vitamin K
  - Liver function
  - Co-existing medical conditions
  - Concurrent medications
  - Cytochrome P450 2C9 gene mutations
  - VKORC1 haplotypes (vitamin K epoxide reductase complex 1)
- 

The Journal of the American Medical Association

#### Association Between CYP2 C9 Genetic Variants and Anticoagulations-Related Outcomes During Warfarin Therapy

M. Higashi, et al.

April 3, 2002  
Vol. 287, No. 13

#### Patients with *CYP2C9*\*2 and \*3 allelic variants:

- Require lower maintenance doses
- Have longer times to dose stabilization
- Present a higher risk for serious, life-threatening bleeding
- Mechanism: *CYP2C9* is responsible for the metabolic clearance of the more pharmacologically potent S-enantiomer of warfarin.

The New England Journal of Medicine  
Volume 352, No. 22, June 2, 2005

### Effect of *VKORC1* Haplotypes on Transcriptional Regulation and Warfarin Dose

M. J. Rieder, et al.

June 2, 2005  
Vol. 352, No. 22

#### VKORC1 Haplotypes are Associated with Warfarin Dose

VKORC1 explains ~25% of warfarin dose variance

## Gene Based Clinical Trial

### Warfarin Resistance and Sensitivity

#### Randomization:

- CYP2C9 genotype
- VKORC1 haplotype

Warfarin dose adjusted to genotype/haplotype

- Control

Usual practice of prescribing Warfarin dose

#### Endpoints:

- Time to adequate control
- Complications – bleeds, hospitalization



*"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."*

Sir Winston Churchill,  
November, 1942