



# **Investing in Discovery**

## **The Impact of Basic Research and the Role of the National Institute of General Medical Sciences**

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National Institutes of Health**





# Themes

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- The importance and impact of basic research
  - Biology is deeply unified at the molecular and cellular levels
  - Fundamental processes underlie our understanding of health and disease and lay the foundation for medical advances
- The key roles of research training and early stage investigators





## Two Stories

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- The discovery of telomerase, recognized by 2009 Nobel Prize in physiology or medicine
- The rapidly developing field of pharmacogenomics, illustrated by studies of the blood-thinner warfarin





## DNA

### Genetic Information Storage Common to All Organisms

- A double helix with strands running in opposite directions
- Genetic information is stored in the sequence of bases (A,C,G,T)
- Strands are complementary, with A paired with T and G paired with C
- Genetic code relating DNA sequence to protein sequence is common to all organisms
- DNA structure suggested a mechanism for DNA replication





# The “End Replication” Problem

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- The mechanism of DNA replication was investigated and elucidated
- By this mechanism, linear DNA molecules were predicted to become slightly shorter every time they are copied
- How is this **potential disaster** avoided?
  - Bacterial chromosomes are circular (they do not have any ends)
  - Higher organisms (including humans) have linear chromosomes, requiring a special mechanism





## Telomeres: Repetitive Sequences at Chromosome Ends

- Human cells contain 46 chromosomes (92 ends)
- *Tetrahymena thermophila*, a ciliated protozoan, contains approximately 5,000 minichromosomes (~10,000 ends)
- Elizabeth Blackburn (then a postdoctoral fellow in the lab of Joe Gall) determined that *Tetrahymena* chromosomes end in --TTGGGG**TTGGGG**TTGGGG-- (1978) suggesting special sequences are added
- Human chromosomes end in --TTAGGG**TTAGGG**TTAGGG-- (1988)

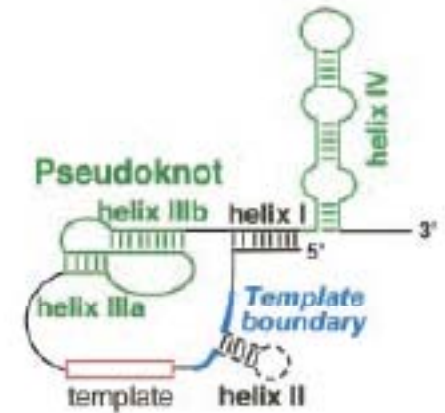




# Telomerase:

## Adding Telomeres to the Ends of Chromosomes

- Carol Greider (then a graduate student in the lab of Elizabeth Blackburn) sought and discovered an enzyme that adds telomere sequences to the ends of Tetrahymena chromosomes in 1984
- Telomerase includes both a protein component (called **T**elomerase **R**everse **T**ranscriptase or TERT) and a specialized RNA molecule
- The RNA acts as a **template** that determines the telomere sequence





# Carol Greider's License Plate as a Young Scientist at Cold Spring Harbor Laboratory

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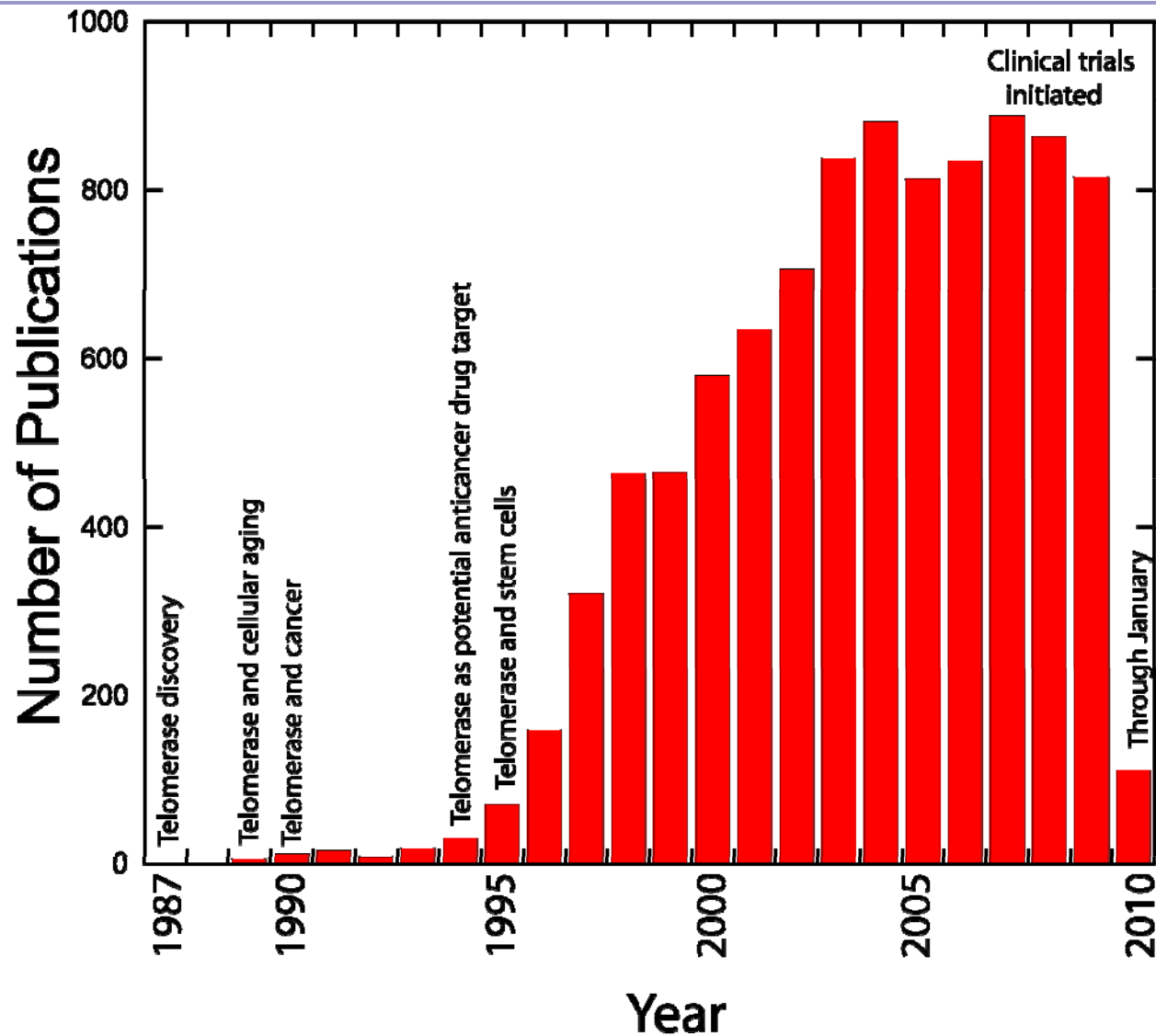






# Telomerase:

## Connections with Human Health and Disease





# Nobel Prize Ceremony-December 2009

Prize in Physiology or Medicine to  
Elizabeth Blackburn, Carol Greider, and Jack Szostak

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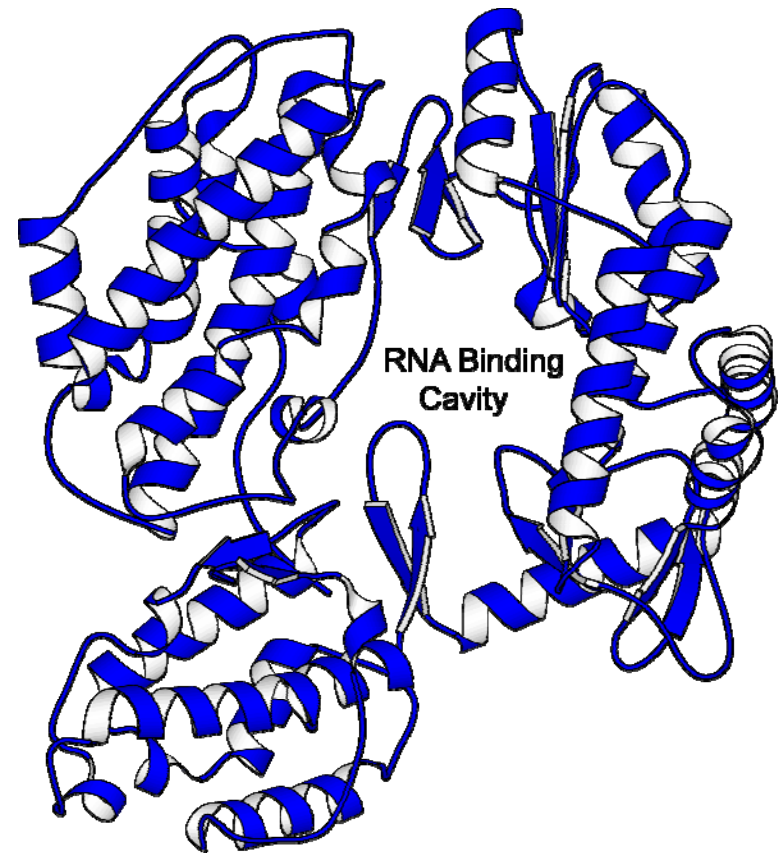


# The Three-Dimensional Structure of TERT

- Structure determined for TERT from *Tribolium castaneum* by Emmanuel Skordalakes



- Human TERT certain to have similar structure (based on sequence similarity)
- Structure similar to HIV reverse transcriptase, a well-explored drug target





# Anti-Cancer Drugs Directed Against Protein Kinases

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- Enzymes termed protein kinases were discovered in basic studies of energy utilization by muscle
  - Nobel Prize in physiology or medicine, 1992
- Protein kinases found to control cell division
  - Nobel Prize in physiology or medicine, 2001
- More than 10 drugs directed against protein kinases have been approved by the FDA for treatment of various cancers
  - Gleevec (leukemia)
  - Tarceva (lung, pancreatic cancer)
  - Herceptin (breast cancer)





# Pharmacogenomics

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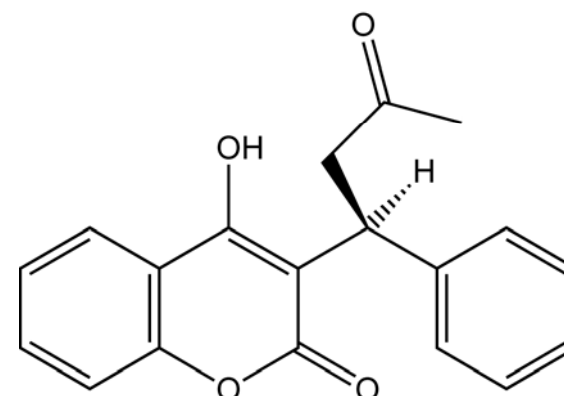
- Responses to specific medicines can vary significantly from one individual to another
  - Increased sensitivity
  - Lack of response
  - Adverse reactions
- Part of this variation is due to genetic differences
- The field of pharmacogenomics (also referred to as pharmacogenetics) is the study of how genes affect the way people respond to medicines





## Warfarin (Coumadin)

- Widely used (>20 million prescriptions per year in U.S.) anticoagulant (to prevent stroke, heart attack)
- Dose must be carefully controlled--too little can fail to prevent stroke and heart attack, too much can lead to adverse events related to bleeding
- Dose is adjusted repeatedly until effective anticoagulation is achieved
- Adjusted doses can vary over 20-fold between individuals!





# Genome-Wide Association Studies

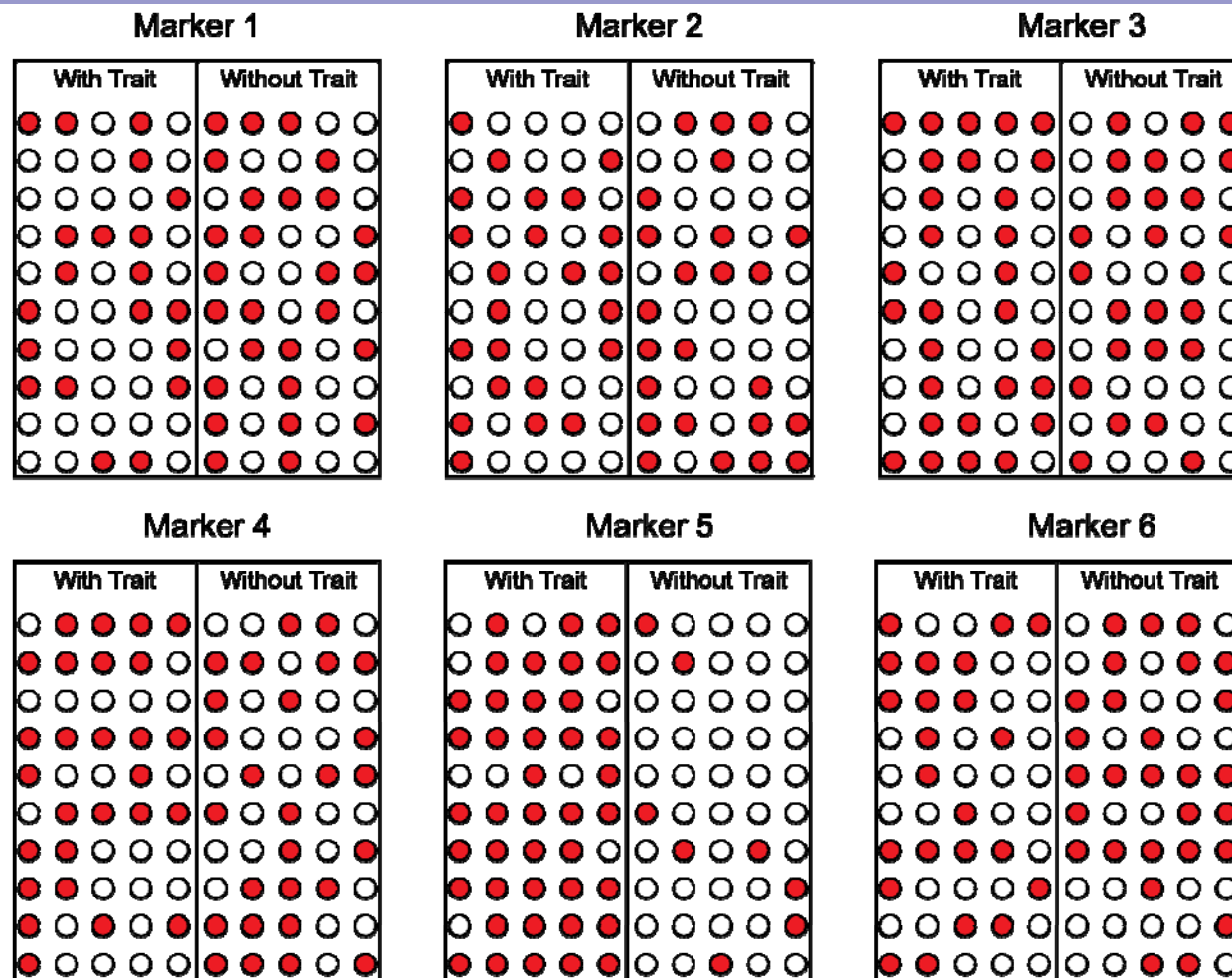
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- Identify a trait (such as the requirement for a high dose of warfarin for effective anticoagulation) for which information is available from a large population of diverse individuals
- Test genetic markers from across the human genome to look for specific markers that vary between individuals with the same pattern as the trait
- Identify genes that are adjacent to the genetic markers as candidates for contributing to the variation in the trait





# Genome-Wide Association Studies

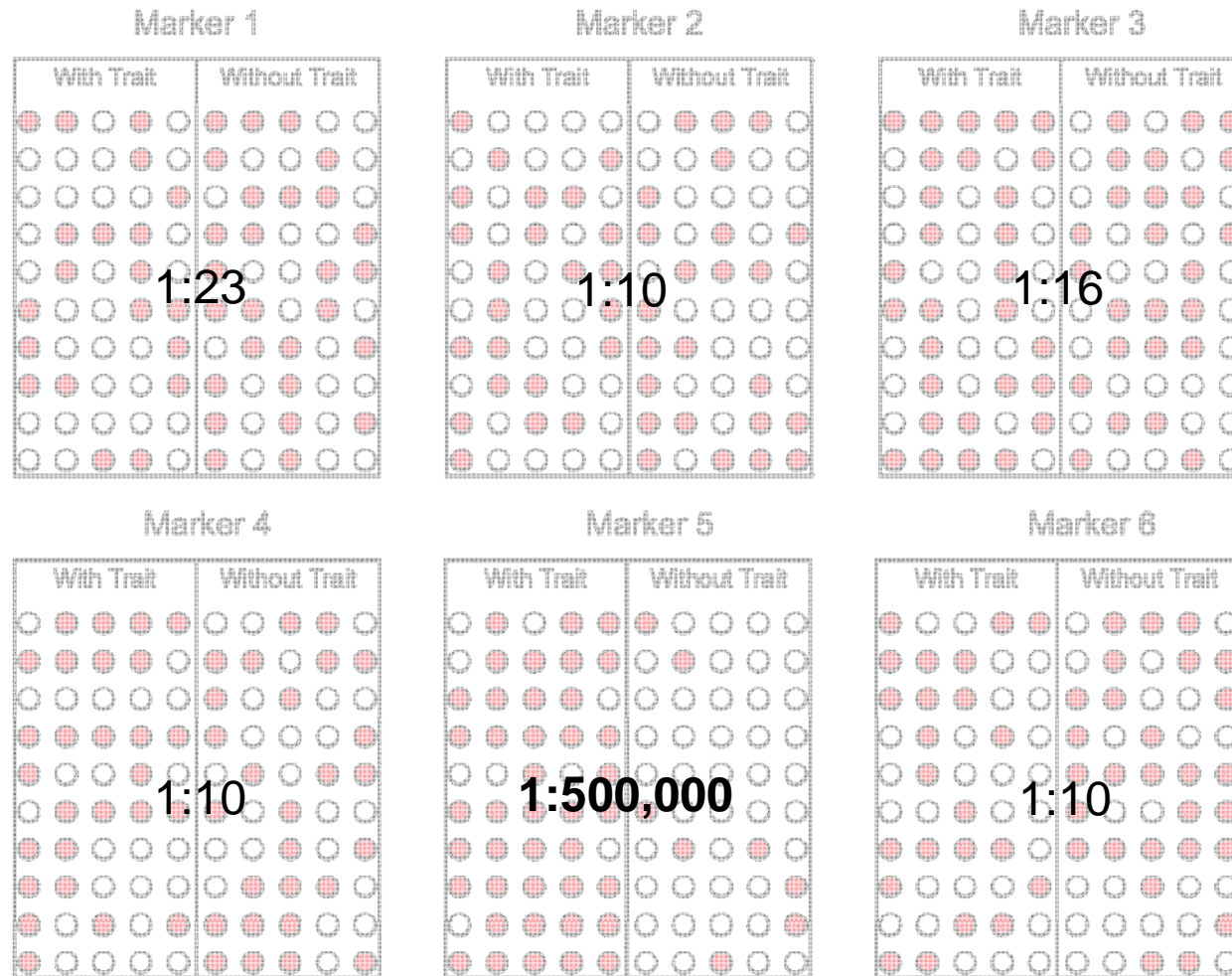


What are the odds of these patterns occurring by chance?





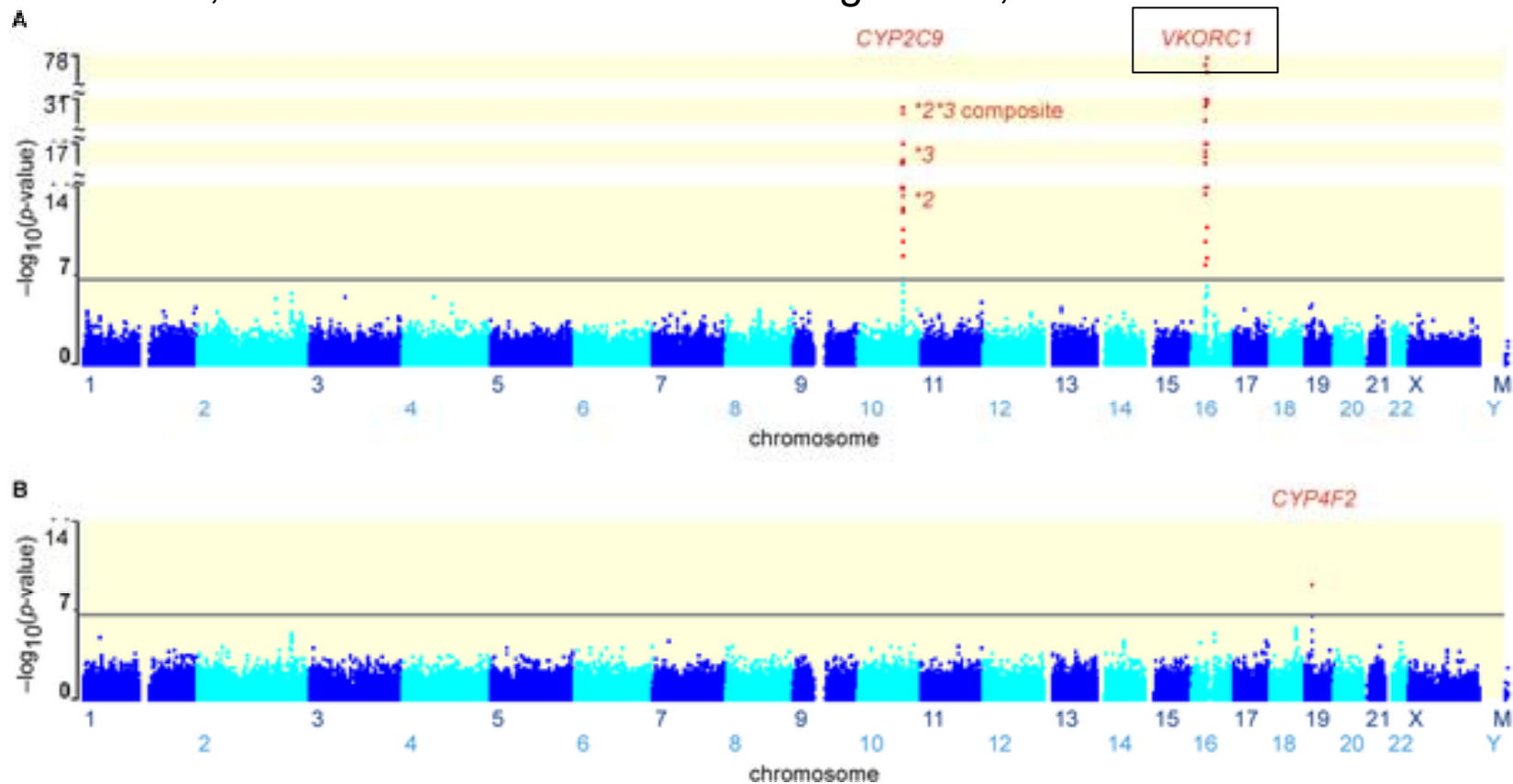
# Genome-Wide Association Studies





# Genome-Wide Association Study for Warfarin Dose Requirement

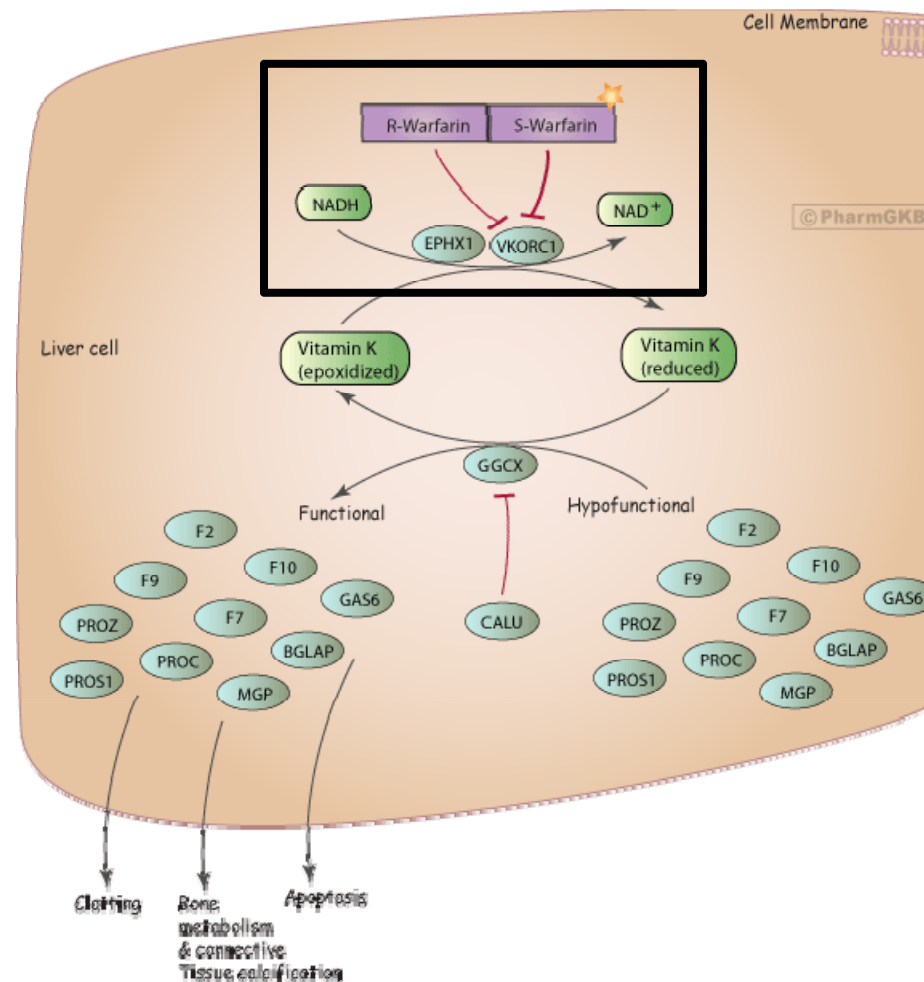
>300,000 markers across the human genome, >1000 individuals





# VKORC1-The Target of Warfarin Action

From PharmGKB





## Discovery of the VKORC1 Gene

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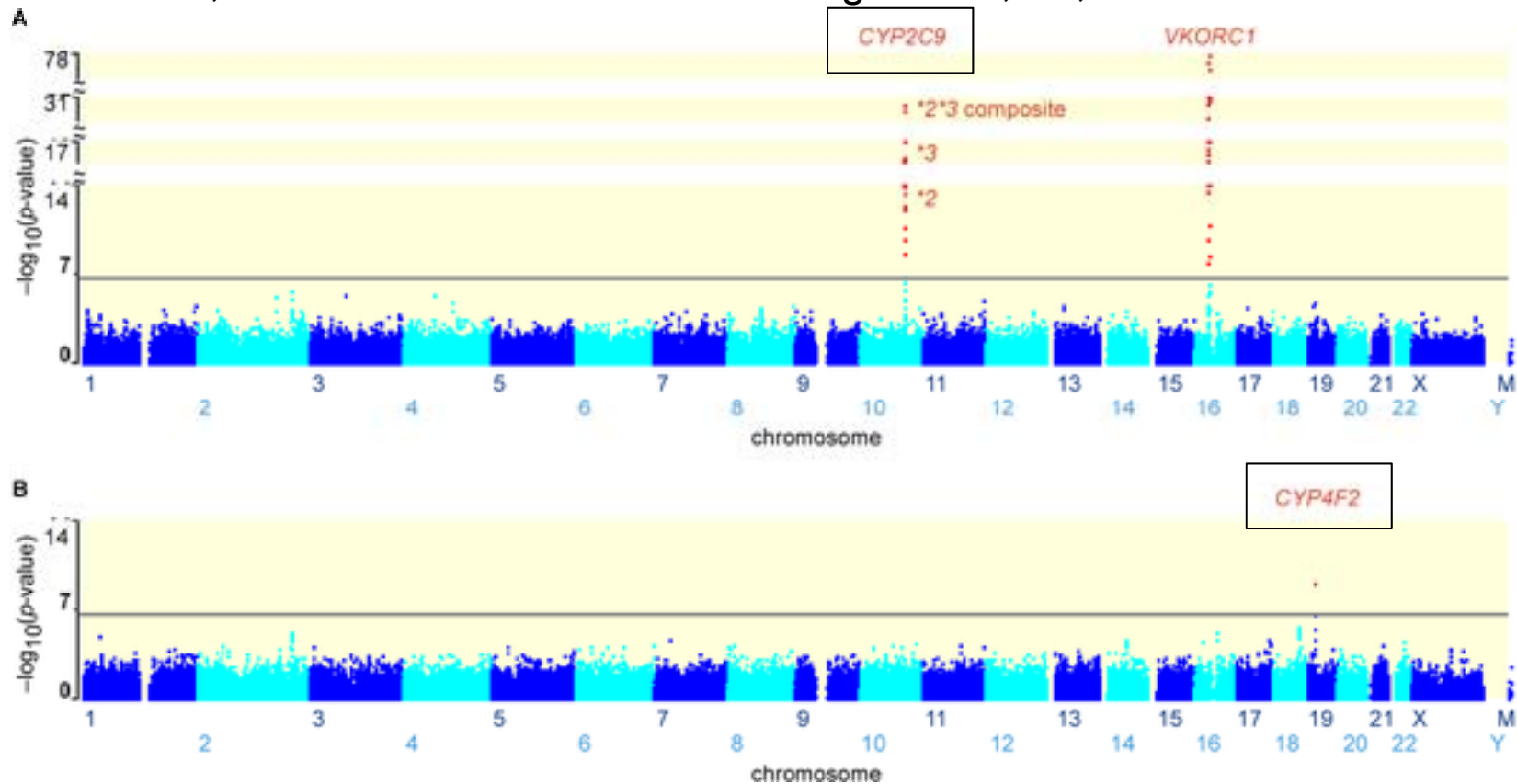
- Target of warfarin identified as Vitamin K epoxide reductase (VKORC1) in 1974
- Gene for VKORC1 localized to human chromosome 16 (based on localization of homologous gene to rat chromosome 1)
- 190 potential genes in this region reduced to 13 candidates by biochemical considerations
- 13 genes tested by RNA interference methods (discovered in 1998 by NIGMS grantees Fire and Mello, Nobel Prize in physiology or medicine, 2006) to identify VKORC1 gene in 2004





# Genome-Wide Association Study for Warfarin Dose Requirement

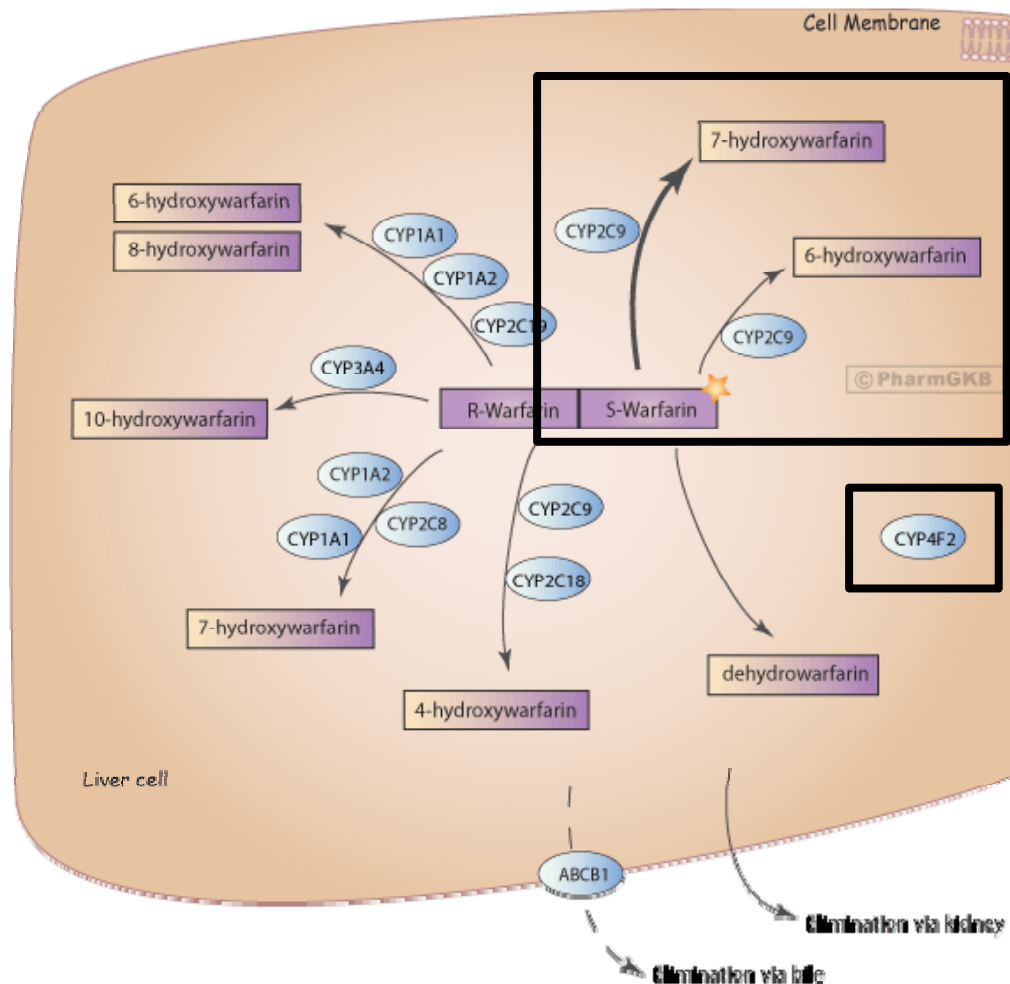
>300,000 markers across the human genome, >1,000 individuals





# CYP2C9-The Major Enzyme Metabolizing the More Active Form of Warfarin

From PharmGKB





# The Cytochrome P450 Enzymes

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- Discovered by Julius Axelrod in 1955 in one of his first independent studies as a basic pharmacologist in the intramural program at NIH
- The human genome encodes 57 cytochrome P450 enzymes, of which 29 are known to be involved in the metabolism of foreign compounds
- Cytochrome P450 2C9 is involved in metabolizing over 100 different drugs including the active form of warfarin
- Cytochrome P450 4F2 was not previously known to be involved in warfarin metabolism





# Can Genomic Information be Used to Predict the Appropriate Warfarin Dose?

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- International Warfarin Pharmacogenetics Consortium (21 research groups from 9 countries) combined data on over 5000 individuals with known final warfarin doses and genotype information
- Algorithms to predict the appropriate warfarin dose were developed based on only clinical information or clinical and genomics information
- Predicted doses compared with actual doses

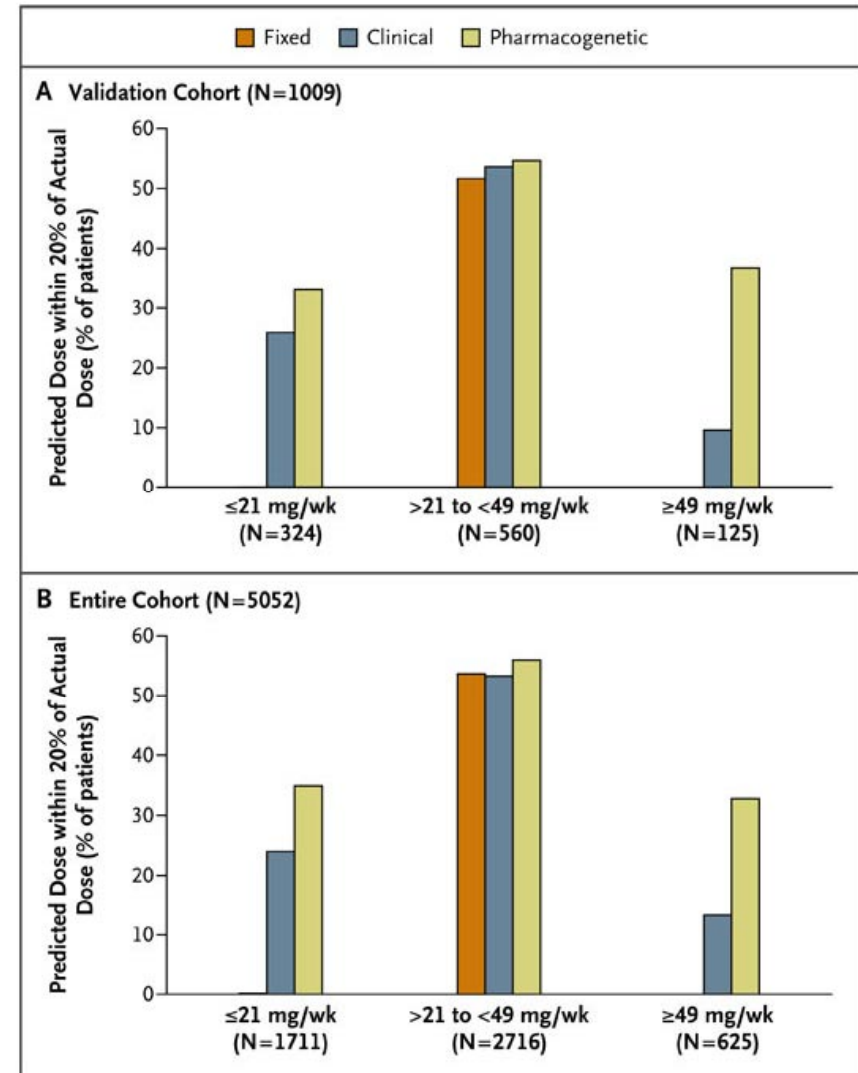






# Can Genomic Information be Used to Predict the Appropriate Warfarin Dose?

- The inclusion of genomic information substantially increased the accuracy of the predicted dose (particularly for individuals requiring high or low doses)
- A clinical trial under way to test if the inclusion of genomic information improves outcomes, decreases costs



## Cardiovascular

### **Pharmacogenomic Evaluation of the Antihypertensive Response (PEAR)**

Julie A. Johnson, Pharm.D., University of Florida

### **Pharmacogenomics and Risk of Cardiovascular Disease (PARC)**

Ronald M. Krauss, M.D., Children's Hospital Oakland Research Institute

### **Pharmacogenomics of Arrhythmia Therapy (PAT)**

Dan M. Roden, M.D., Vanderbilt University

### **Amish Pharmacogenomics of Antiplatelet Intervention Study (PAPI)**

Alan R. Shuldiner, M.D., University of Maryland

## Pulmonary

### **Pharmacogenetics of Asthma Treatment (PHAT)**

Scott T. Weiss, M.D., Brigham and Women's Hospital

## Addiction

### **Pharmacogenetics of Nicotine Addiction and Treatment (PNAT)**

Neal L. Benowitz, M.D., University of California at San Francisco  
Huijun Ring, Ph.D., SRI International

## Cancer

### **Consortium on Breast Cancer Pharmacogenomics (COBRA)**

David A. Flockhart, M.D., Ph.D., Indiana University

### **Comprehensive Research on Expressed Alleles in Therapeutic Intervention (CREATE)**

Howard L. McLeod, Pharm.D., Washington University

### **Pharmacogenetics of Anticancer Agents Research Group (PAAR)**

Mark J. Ratain, M.D., University of Chicago  
Mary V. Relling, Pharm.D., St. Jude Children's Hospital

## Metabolism/Transport

### **Pharmacogenetics of Membrane Transporters (PMT)**

Kathleen M. Giacomini, Ph.D., University of California, San Francisco

### **Pharmacogenetics of Phase II Drug Metabolizing Enzymes (PPII)**

Richard M. Weinshilboum, M.D., Mayo Clinic

## Informatics

### **PharmGKB: Catalyzing Research in Pharmacogenetics**

Russ B. Altman, M.D., Ph.D., Stanford University



# Part of the Pharmacogenetics Research Network Team

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## **PharmGKB**

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) is an integrated knowledge base for pharmacogenetics, linking phenotypes and genotypes.

**Features:**

- A web-based format for pharmacogenetics knowledge
- Curated, linked genotypes and phenotypes
- Genomic, molecular and cellular, and clinical datasets
- Annotated, interactive, consensus drug pathways
- Automated methods for identifying relationships
- Community-based literature submissions
- Access to the entire research community

**[www.pharmgkb.org](http://www.pharmgkb.org)**



# Potential Impact of Pharmacogenomics

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- Personalized medicine
  - Selecting and dosing medicines based on individual genomic characteristics
- Improvements in the drug development process
  - Understanding the bases for variations in response and adverse drug reactions





# Authorization for the National Institute of General Medical Sciences

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The general purpose of the National Institute of General Medical Sciences is the conduct and support of research, training, and as appropriate, health information dissemination, and other programs with respect to **general or basic medical sciences and related natural or behavioral sciences** which have **significance for two or more national research institutes** or are **outside the general area of responsibility of any other national research institute**.







# National Institute of General Medical Sciences

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- Promote cutting-edge basic research
  - Supported research of 73 Nobel laureates
- Support innovative approaches to research training
  - Supports approximately 50% of Ph.D. research training positions at NIH including the Medical Scientist Training (M.D.-Ph.D) program
  - Leading efforts to promote inclusive, diverse biomedical workforce
- Lay the foundation for advances impacting the health of the nation
  - Supported research leading to cross-cutting concepts and tools and to the development of the biotechnology industry





## Ruth Kirschstein, M.D.

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- Long-time Director, NIGMS
- Acting Director, NIH (Twice)
- Principal Deputy Director, NIH

