

Pharmacogenomics: Origins and Concepts

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Disclosure

Dr. Weinshilbom has either provided consulting services or presented seminars at:

- Abbott Laboratories**
- Bristol-Myers Squibb**
- Eli Lilly and Co.**
- Johnson & Johnson**
- Merck and Co.**
- F. Hoffmann-La Roche Ltd.**

All fees and honoraria were paid to Mayo Foundation to support its missions in research and education.

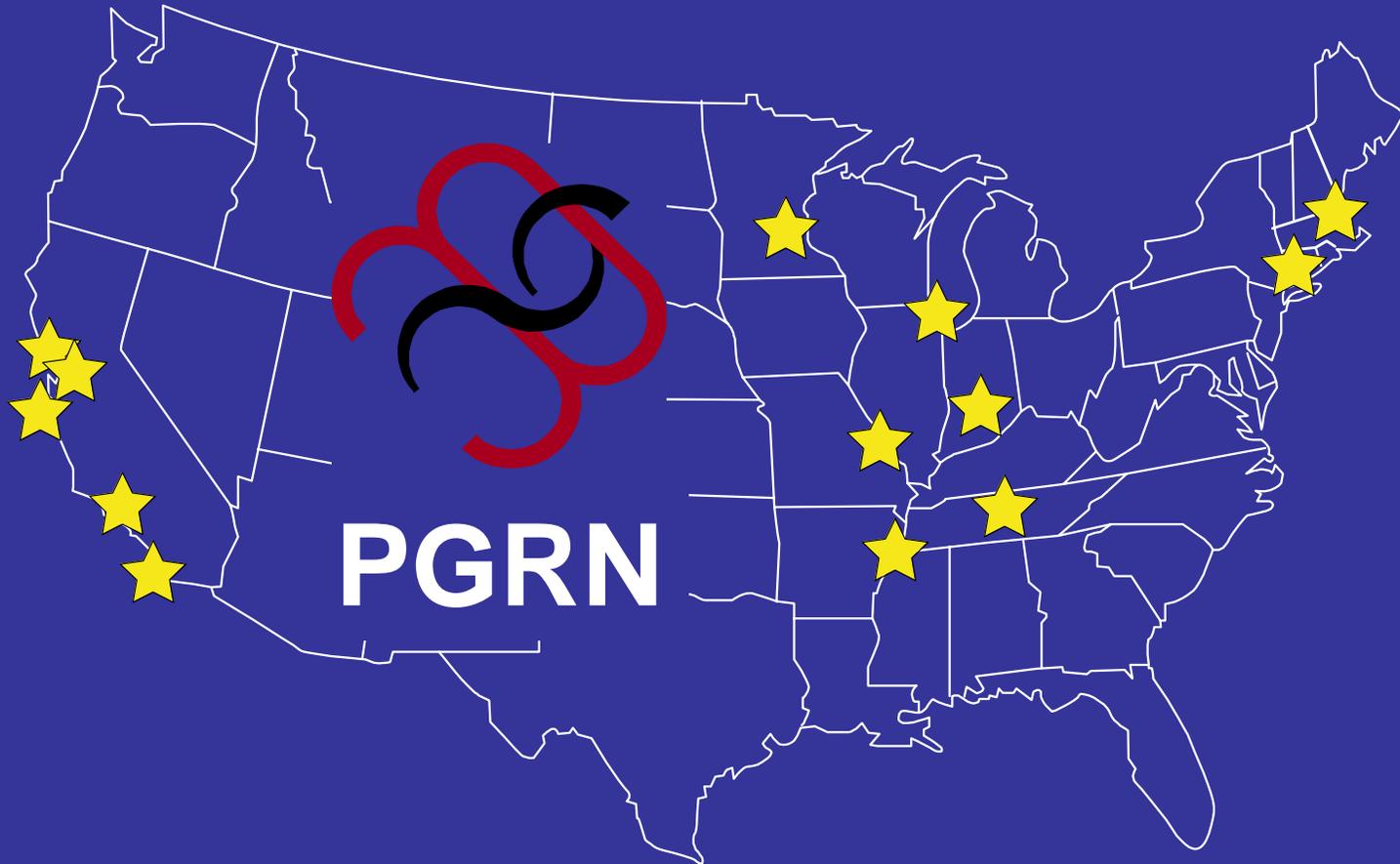
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NIH Pharmacogenetics Research Network



www.nigms.nih.gov/pharmacogenetics

www.pharmgkb.org



PharmGKB

The Pharmacogenetics and Pharmacogenomics Knowledge Base



Pharmacogenetics

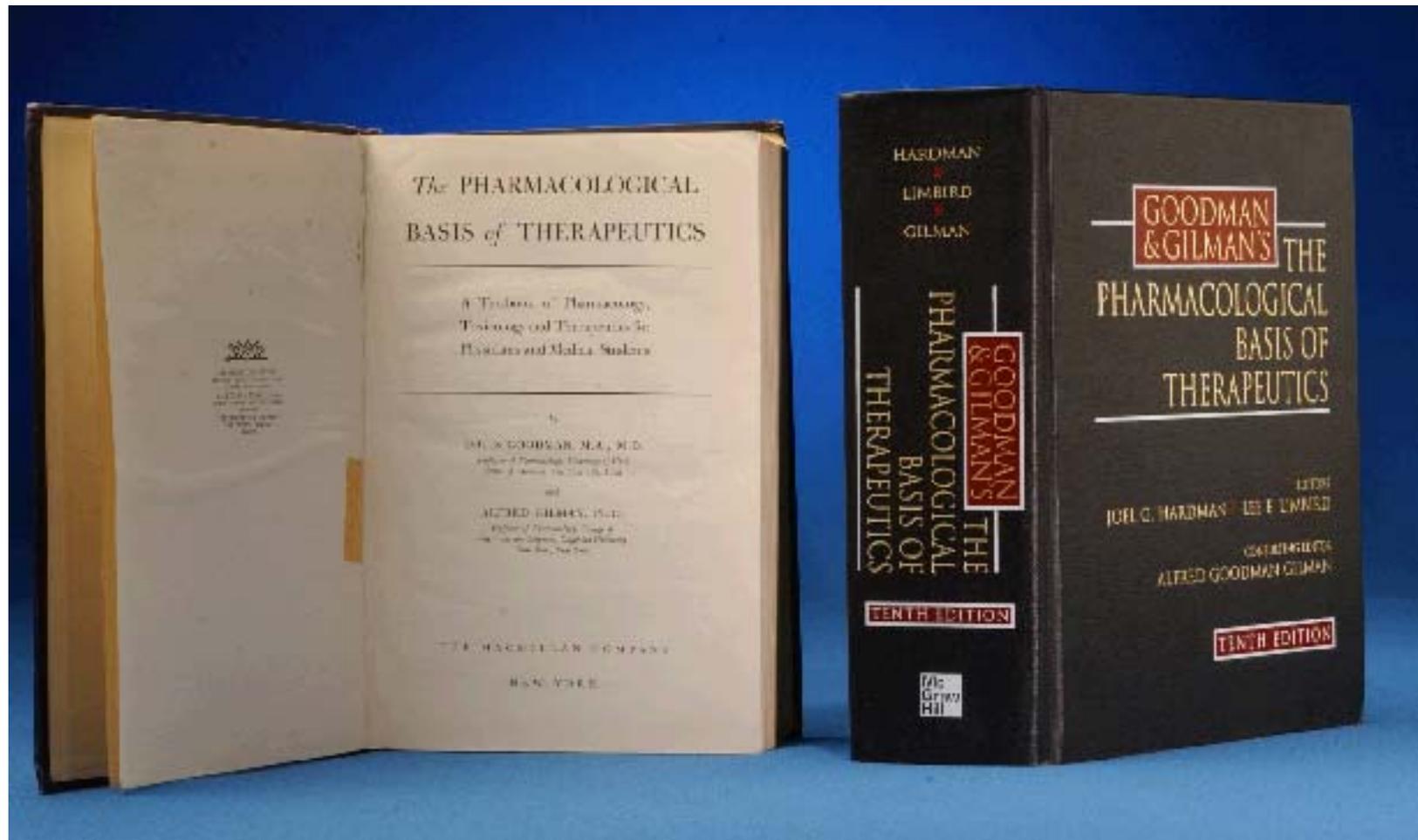
The study of the role of inheritance in individual variation in response to xenobiotics, including drugs.

Pharmacogenetics-Pharmacogenomics

Two Revolutions

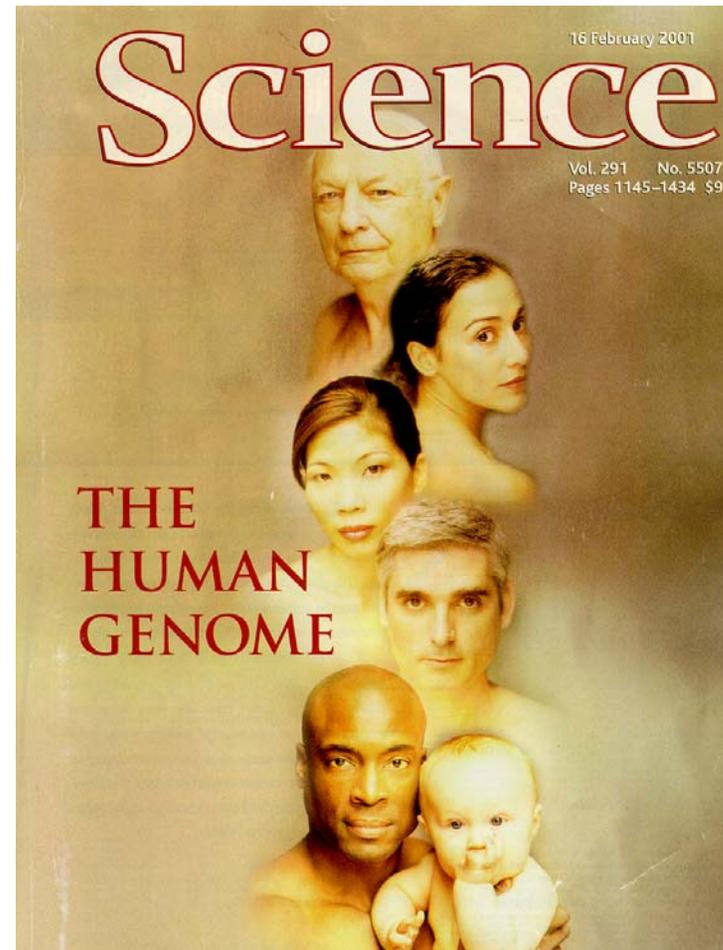
- **The Therapeutic Revolution**
- **The Genomic Revolution**

The Therapeutic Revolution



Goodman and Gilman's The Pharmacological Basis of Therapeutics

The Human Genome February 2001



Pharmacogenomics

The convergence of advances in pharmacogenetics with the striking progress that has occurred in human genomics

Pharmacogenetics-Pharmacogenomics

Clinical Goals

- **Avoid adverse drug reactions**
- **Maximize drug efficacy**
- **Select responsive patients**

Pharmacogenetics

Scientific Goal

Correlation of variation in DNA sequence and/or structure with variation in drug response phenotype.

Genotype-Phenotype Correlation

Patient Factors and Drug Effect

- **Genetics**
- **Age**
- **Gender**
- **Disease**
- **Drugs**

Pharmacogenomic Variation

- Drug absorption
- Drug distribution
- Drug-target interaction
- Drug metabolism
- Drug excretion

Pharmacogenetic-Pharmacogenomic Science

Scientific Evolution

- **Monogenic traits**
- **Pathways -- PK and PD**
- **Genomewide screens/scans**

Pharmacogenomics

PK-PD

- **Pharmacokinetics (PK)** -- factors that influence the final drug concentration at target(s).
- **Pharmacodynamics (PD)** -- factors that influence the response of target(s).

2003 FDA “Draft Pharmacogenomic Guidance”

Valid Biomarkers

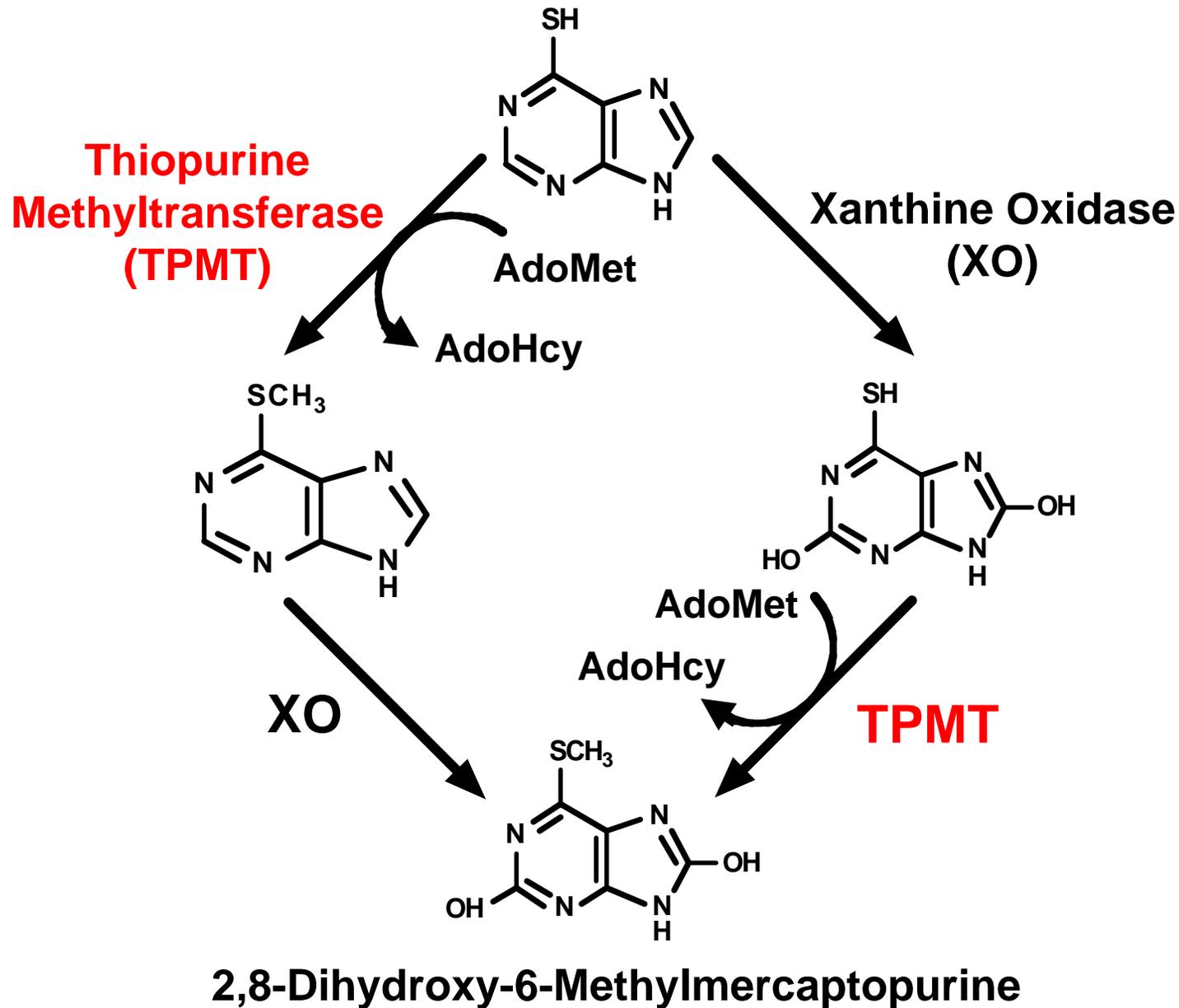
- Thiopurine S-methyltransferase (TPMT)
- Cytochrome P450 2D6 (CYP2D6)

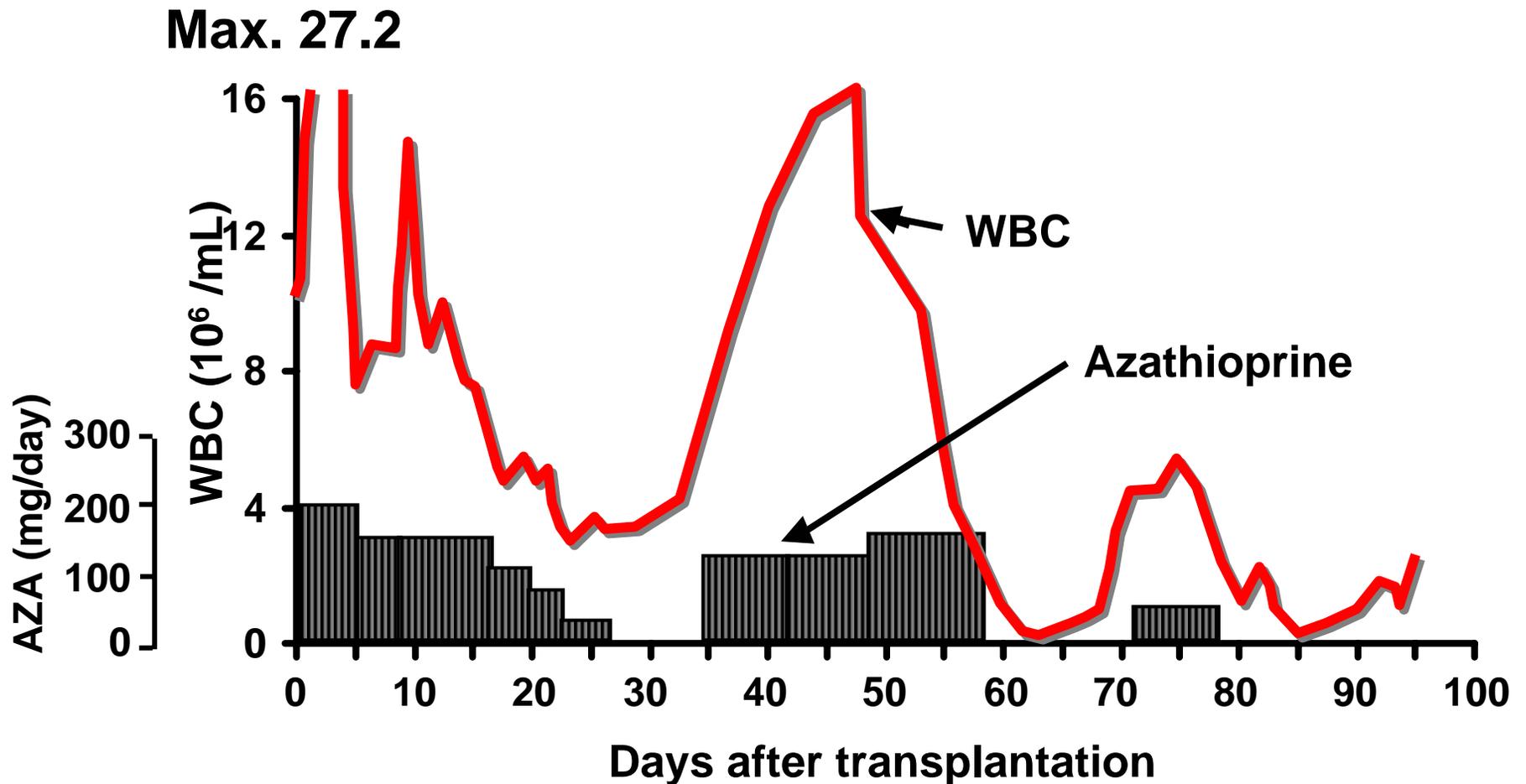
Pharmacogenetics-Pharmacogenomics

TPMT Pharmacogenetics

A “prototypic” example

Metabolism of 6-Mercaptopurine





Peripheral blood leukocyte count (WBC) and azathioprine (AZA) dose in TPMT deficient heart transplant recipients

Lancet 341:436, Feb 13, 1993



TPMT

Genetic Polymorphism

Clinical Consequences

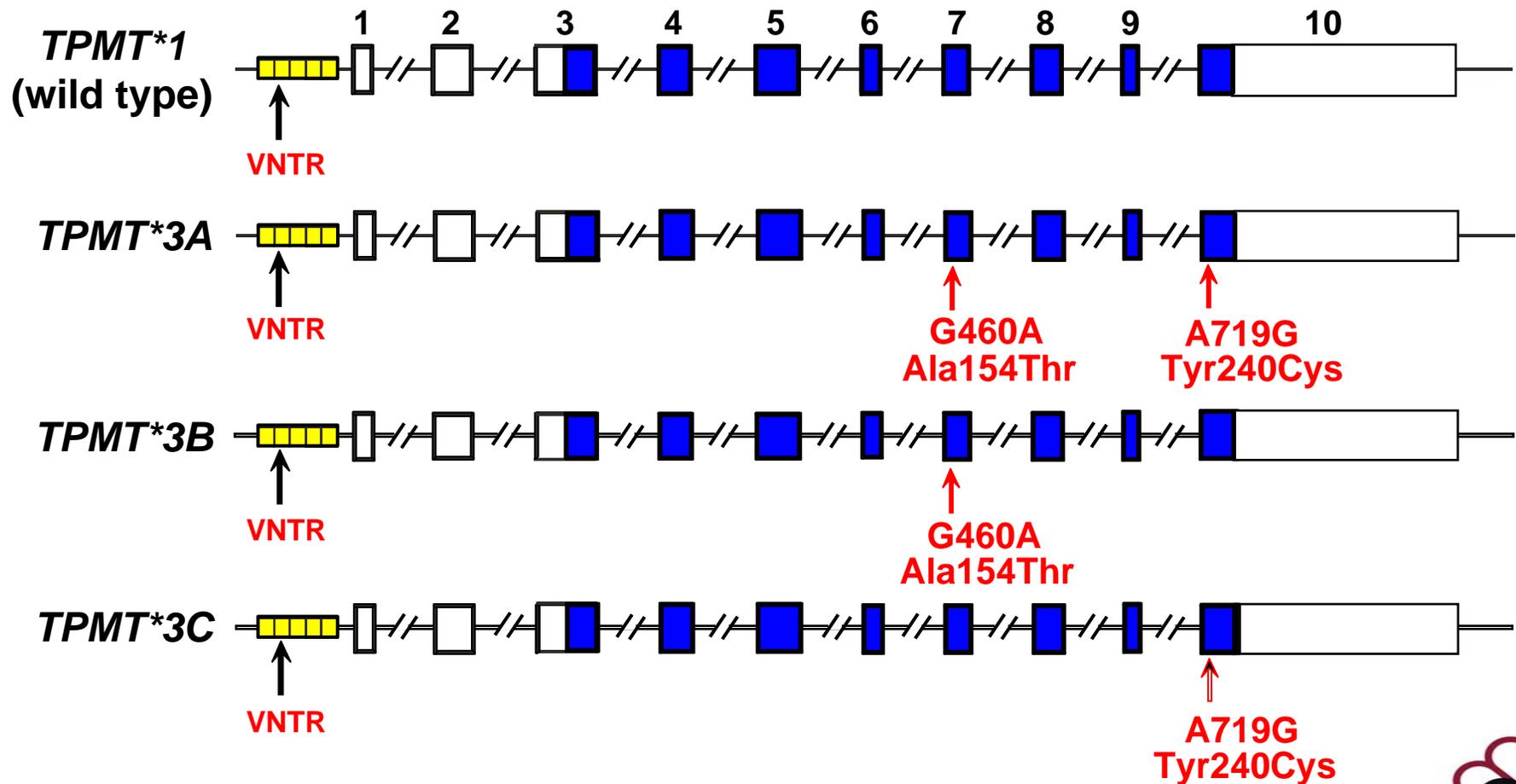
- **Low TPMT**

- Increased thiopurine toxicity
- Increased risk for secondary neoplasm

- **High TPMT**

- Decreased therapeutic effect

Selected Human TPMT Alleles



TPMT Genetic Polymorphism

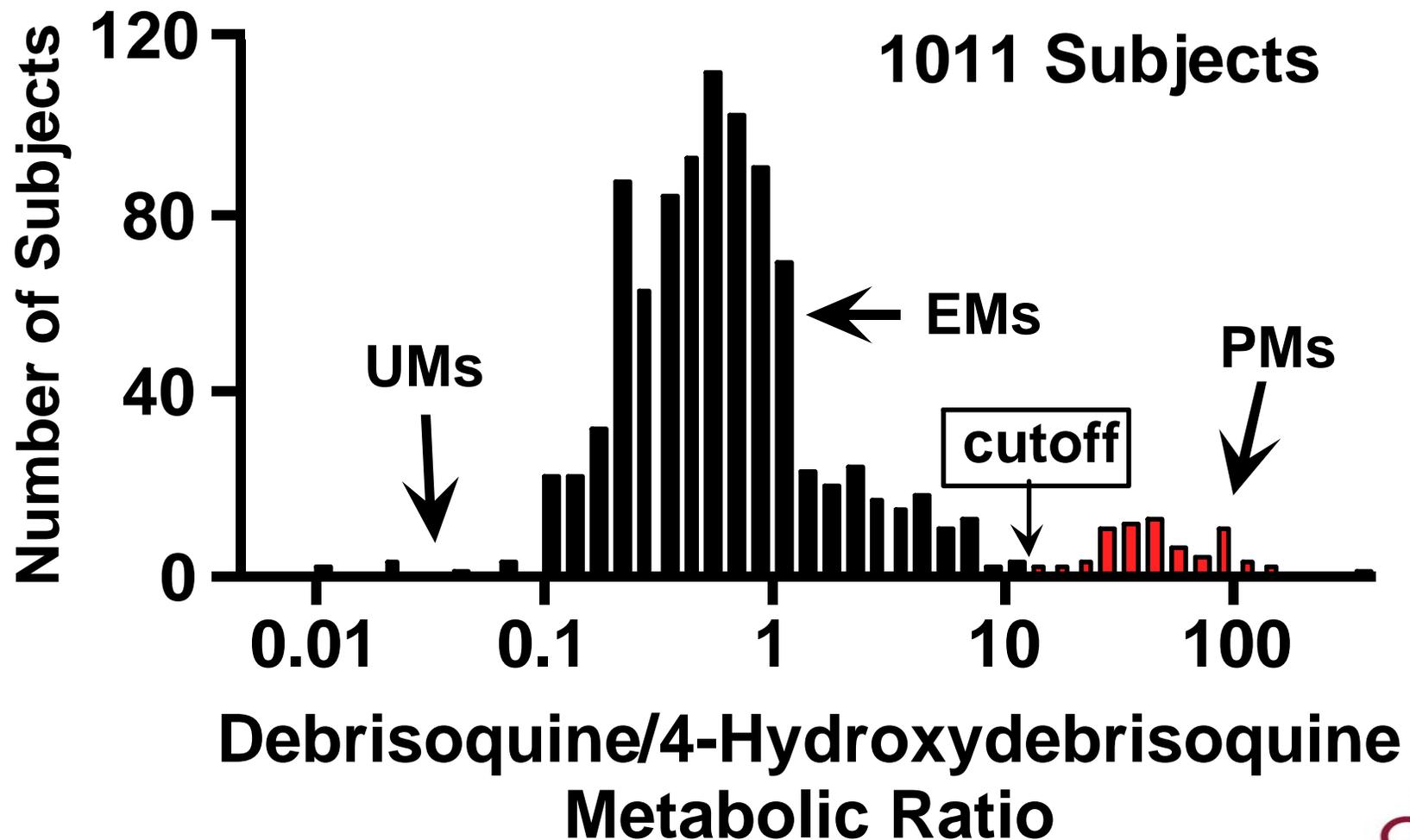
FDA

**One of the first examples
considered for possible
inclusion in labeling**

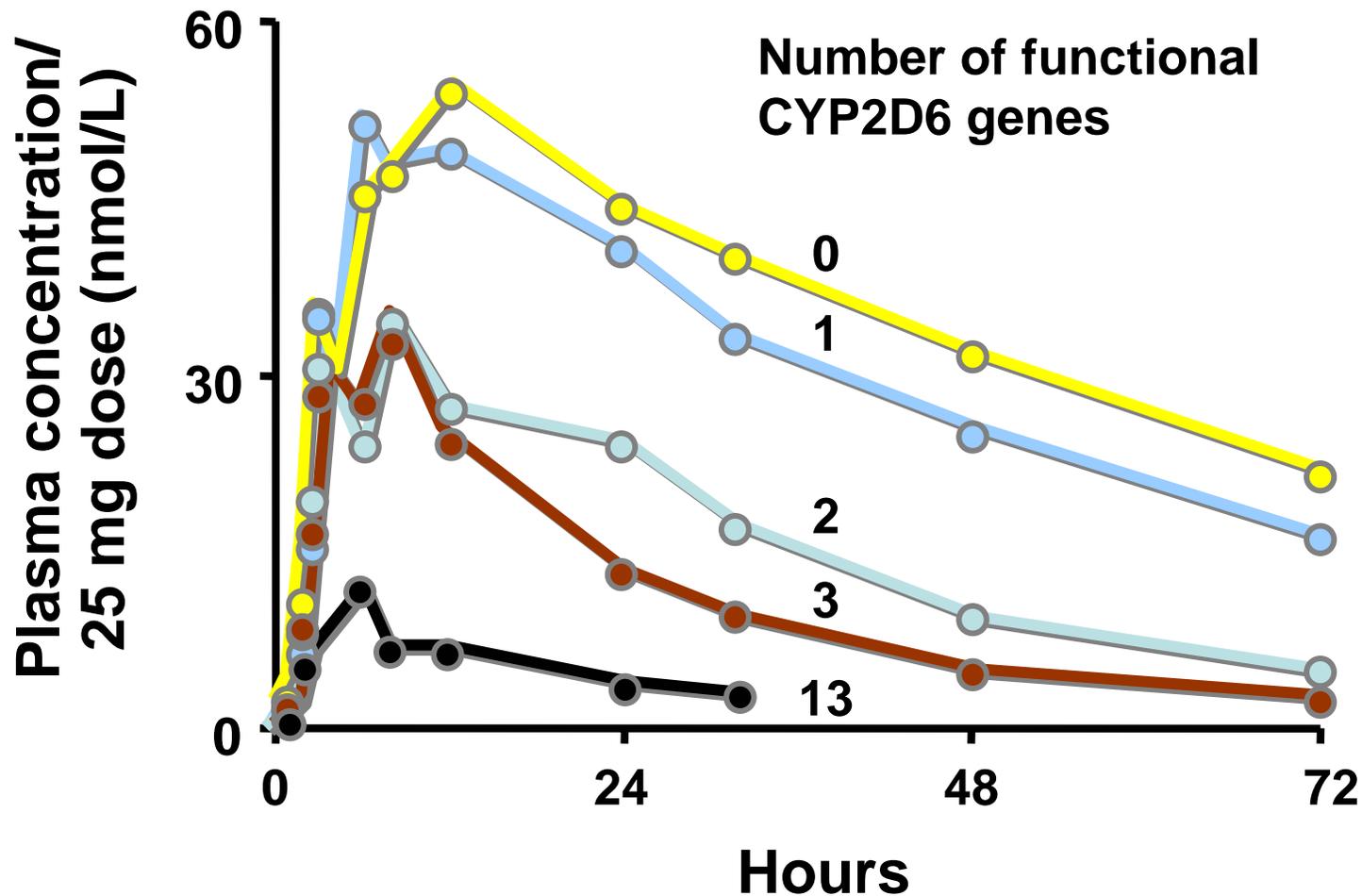
Cytochrome P450 Genetic Polymorphisms

- **CYP2D6**
- **CYP2C9**
- **CYP2C19**

CYP2D6 Pharmacogenetics

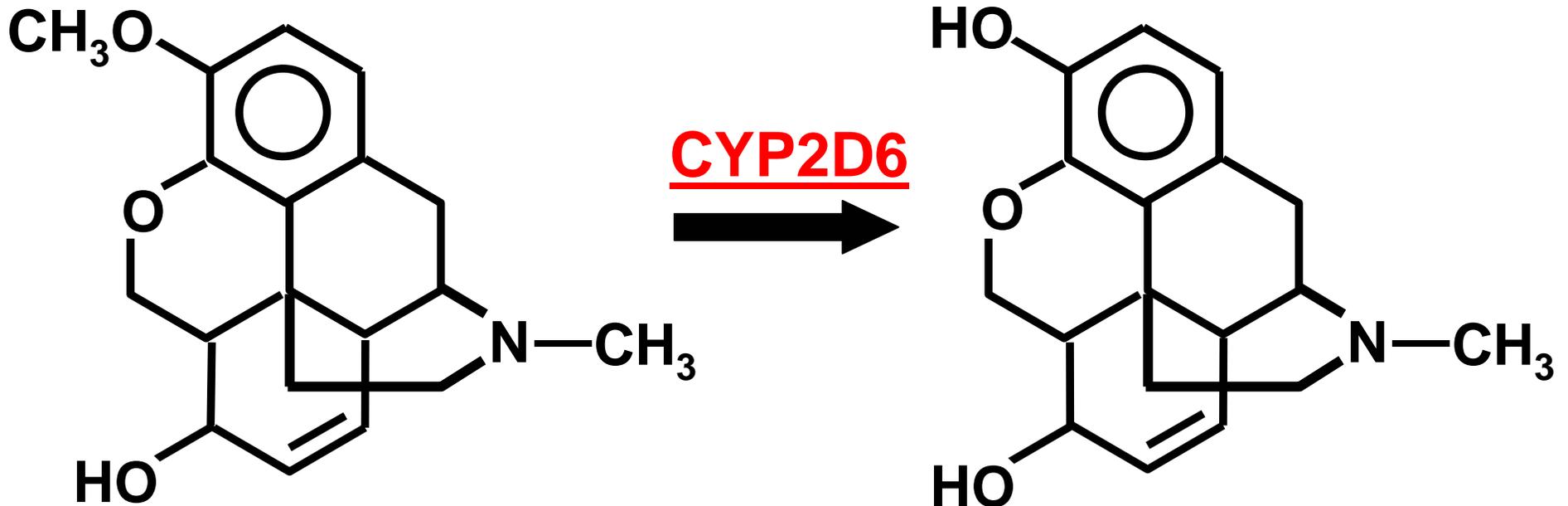


Nortriptyline Pharmacogenetics



Codeine

Biotransformation to Morphine



Codeine

Morphine

Codeine Toxicity Case Report NEJM December 30, 2004

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2785 THIS WEEK IN THE JOURNAL

PERSPECTIVE

2787 Human Cloning R. Jaenisch
2791 Altered Nuclear Transfer in Stem-Cell Research
D.A. Melton, G.Q. Daley, and C.G. Jennings
2792 Medical Discoveries and Scientific Priority H. Markel

ORIGINAL ARTICLES

2795 Coronary-Artery Revascularization before Elective
Major Vascular Surgery
E.O. McFalls and Others
2805 Pegaptanib for Neovascular Age-Related Macular
Degeneration
E.S. Gragoudas and Others
2817 Multigene Assay to Predict Recurrence of Tamoxifen-
Treated, Node-Negative Breast Cancer
S. Paik and Others
2822 Brief Report: Codeine Intoxication Associated
with Ultrarapid CYP2D6 Metabolism
Y. Gasche and Others

CLINICAL PRACTICE

2832 Prevention of Hepatitis B with the Hepatitis B Vaccine
G.A. Poland and R.M. Jacobson

REVIEW ARTICLE

2839 Mechanisms of Disease: Osteopetrosis
J. Tolar, S.L. Teitelbaum, and P.J. Orchard

IMAGES IN CLINICAL MEDICINE

2850 Lytic Lesions in Breast Cancer
D. Katz and D. Aharoni
e25 Fatal Free-Floating Left Atrial Thrombus
T. Tornóczy and Z. Ajtay

**CASE RECORDS OF THE MASSACHUSETTS
GENERAL HOSPITAL**

2851 A Woman with Long-Standing Hematuria
D.J.R. Steele and P.J. Michaels

EDITORIALS

2861 Coronary Revascularization before Noncardiac
Surgery
M. Moscucci and K.A. Eagle
2863 A New Treatment for Ocular Neovascularization
F.L. Ferris III
2865 Individualized Care for Patients with Cancer
R.C. Bast, Jr., and G.N. Hortobagyi
2867 Genes and the Response to Drugs
Y. Caraco

SOUNDING BOARD

2870 Potential Pitfalls of Disease-Specific Guidelines
for Patients with Multiple Conditions
M.E. Tinetti, S.T. Bogardus, Jr., and J.V. Agostini

2875 **CORRESPONDENCE**

Rofecoxib, Merck, and the FDA
Peginterferon and Lamivudine for Hepatitis B
Public Access to Biomedical Research
Undercover and Overlooked
Multiple-System Atrophy
Somatic Mutations of EGFR in Cancer

2884 **BOOK REVIEWS**
2888 **CORRECTIONS**
2888 **NOTICES**
2889 **CONTINUING MEDICAL EDUCATION**

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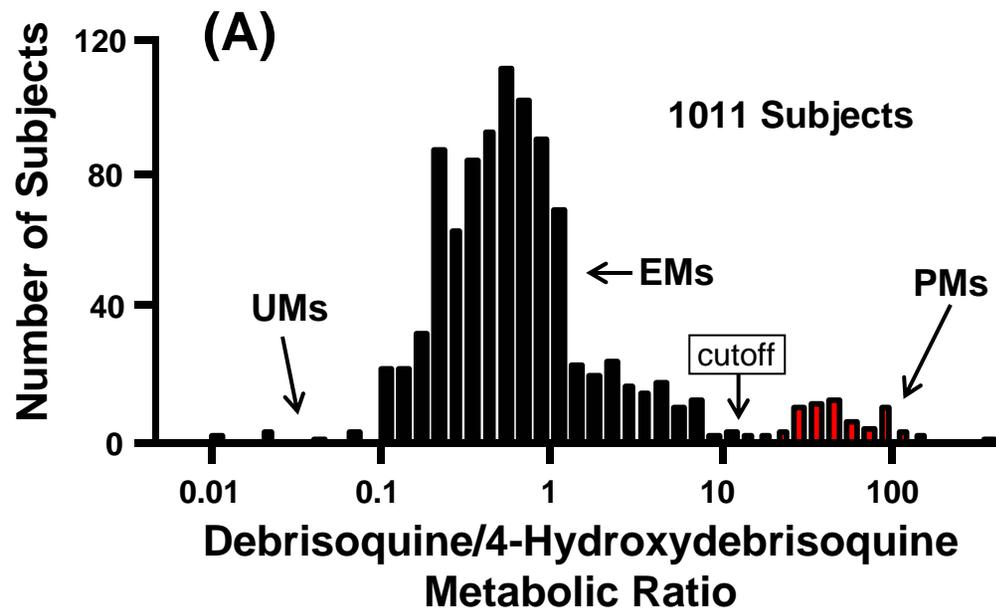
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- 62 year old man hospitalized for pneumonia
- Treated with “standard” doses of codeine as a cough suppressant
- Coma – morphine levels 20 times expected levels

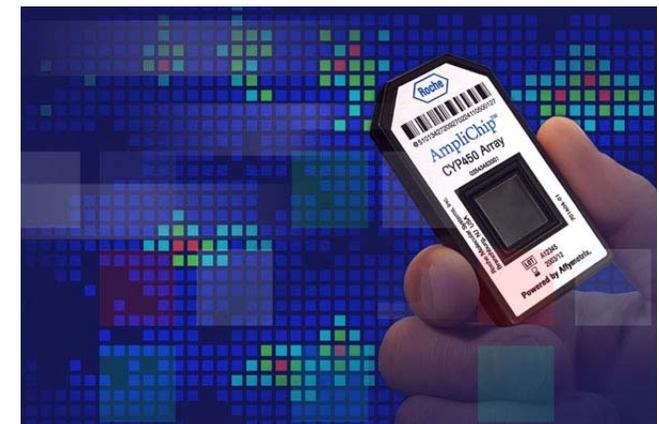


CYP2D6 Pharmacogenetics



AmpliChip CYP450 Array

(B)



Karl Paul Link

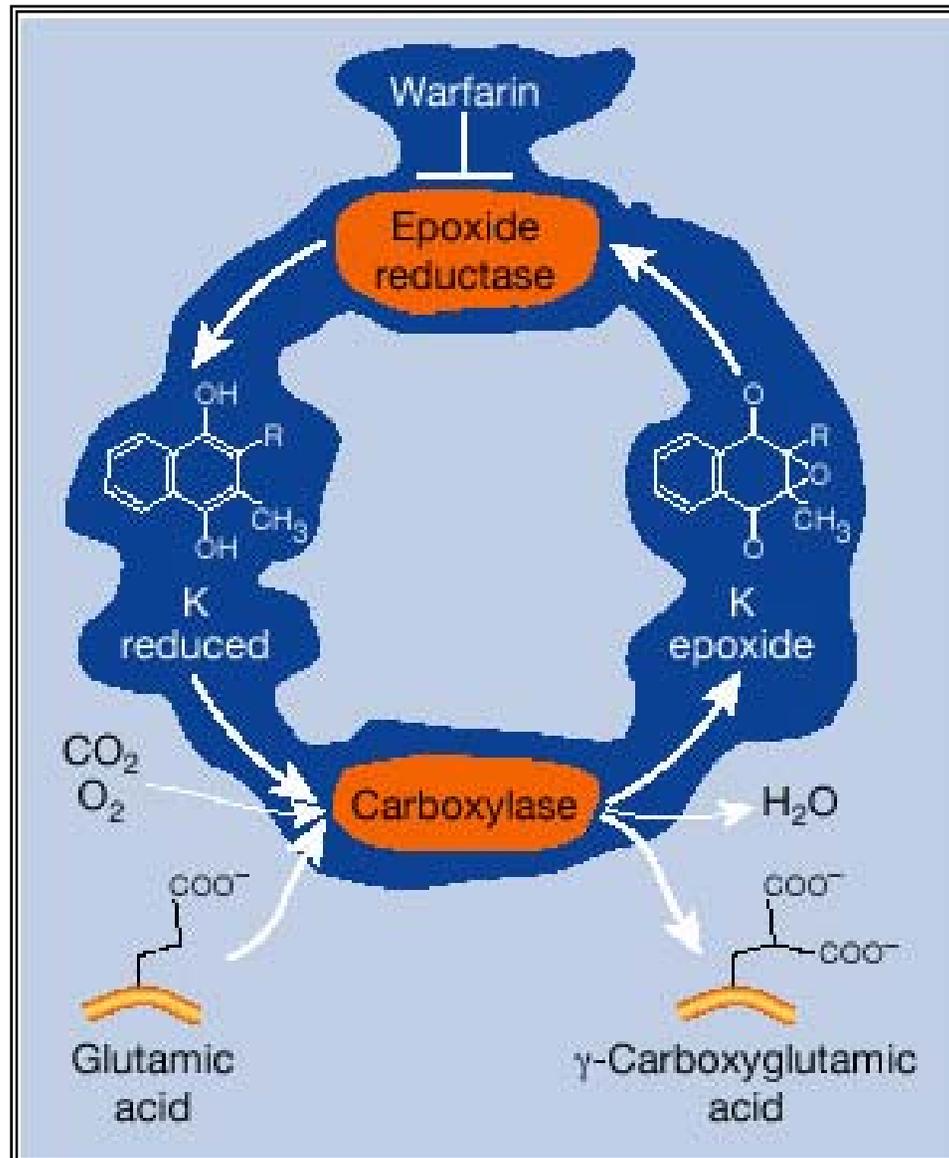
Discoverer of Warfarin



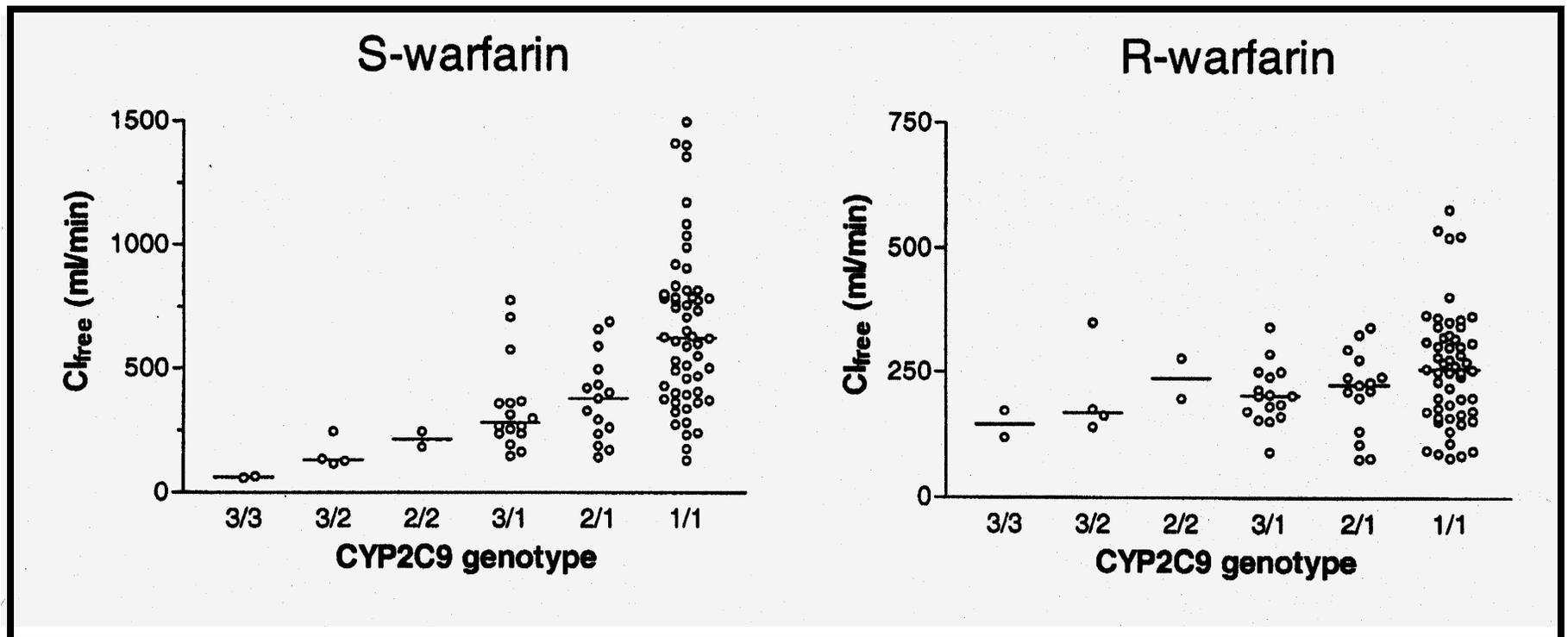
Cytochrome P450 Genetic Polymorphisms

- CYP2D6
- CYP2C9
- CYP2C19

Vitamin K Cycle

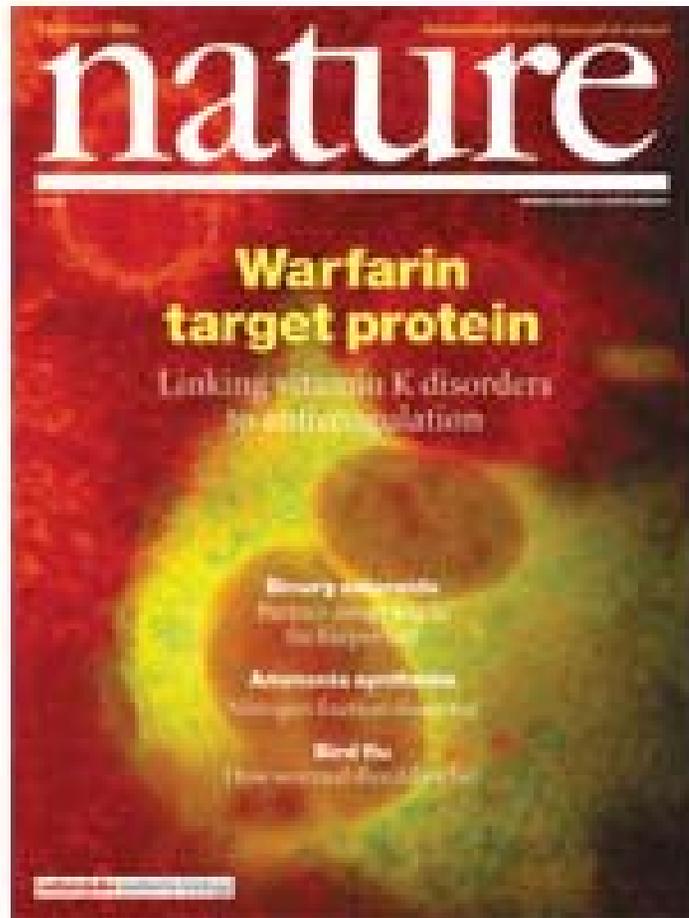


Warfarin Pharmacogenetics

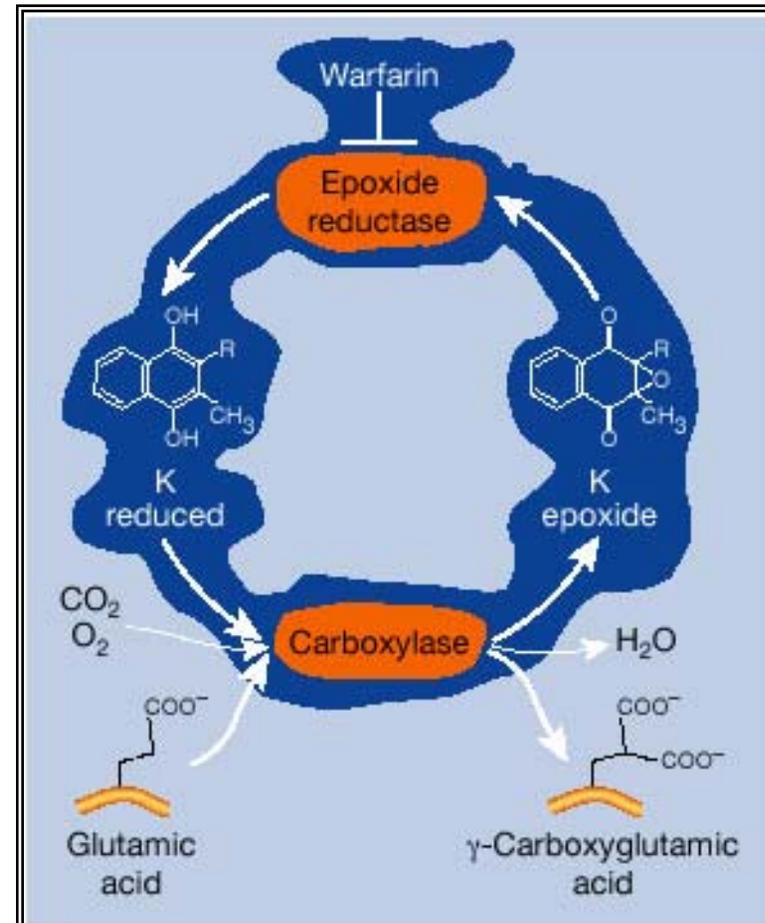


Scordo et al., CPT 72:702, 2003.

Vitamin K Cycle



February 5, 2004



New England Journal of Medicine

June 2, 2005

Warfarin Pharmacogenetics

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2261 THIS WEEK IN THE JOURNAL

PERSPECTIVE	REVIEW ARTICLE
2263 Americans as Survivors R.J. Lifton	2325 Medical Progress: Brucellosis G. Pappas and Others
2266 Aging, Immunity, and the Varicella-Zoster Virus A. Arvin	IMAGES IN CLINICAL MEDICINE
2268 Type II Collagen and Avascular Necrosis of the Femoral Head D.J. Prockop	2337 A Medical Mystery — Bradycardia R. Rosenberg
ORIGINAL ARTICLES	CLINICAL PROBLEM-SOLVING
2271 A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults M.N. Oxman and Others	2338 Don't Know Much about History S. Dames and Others
2285 Effect of <i>VKORC1</i> Haplotypes on Transcriptional Regulation and Warfarin Dose M.J. Rieder and Others	EDITORIALS
2294 Type II Collagen Gene Variants and Inherited Osteonecrosis of the Femoral Head Y.-F. Liu and Others	2344 Varicella-Zoster Virus Vaccine — Grown-ups Need It, Too D.H. Gilden
2302 Adjuvant Docetaxel for Node-Positive Breast Cancer M. Martin and Others	2346 TAC — A New Standard in Adjuvant Therapy for Breast Cancer? E.A. Perez
CLINICAL PRACTICE	2349 CORRESPONDENCE
2314 Atopic Dermatitis H.C. Williams	Electronic Alerts to Prevent Venous Thromboembolism Treatment of Brain Tumors Euthanasia in Severely Ill Newborns Medical Mystery — The Answer Transmission of Amyloidosis by Liver Transplantation Correction of Factor XI Deficiency by Liver Transplantation

- *VKORC1* gene resequenced
- 10 common SNPs and 5 common haplotypes
- Low-dose (A) and high-dose (B) haplotypes
- Mean maintenance dose 2.7 ± 0.2 mg/day for AA, 4.9 ± 0.2 for A/B and 6.2 ± 0.3 for BB ($P < 0.001$)

Pharmacogenetic-Pharmacogenomic Science

Scientific Evolution

- **Monogenic traits**
- **Pathways -- PK and PD**
- **Genomewide screens/scans**

Pharmacogenetics-Pharmacogenomics

Clinical Goals

- **Avoid adverse drug reactions**
- **Maximize drug efficacy**
- **Select responsive patients**

Pharmacogenetics

Scientific Goal

Correlation of variation in DNA sequence and/or structure with variation in drug response phenotype.

Genotype-Phenotype Correlation

Pharmacogenomics

The Vision

The **right** drug, at the **right**
dose for **every** patient.