Pharmacogenomics: Origins and Concepts

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Disclosure

Dr. Weinshilboum 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.**

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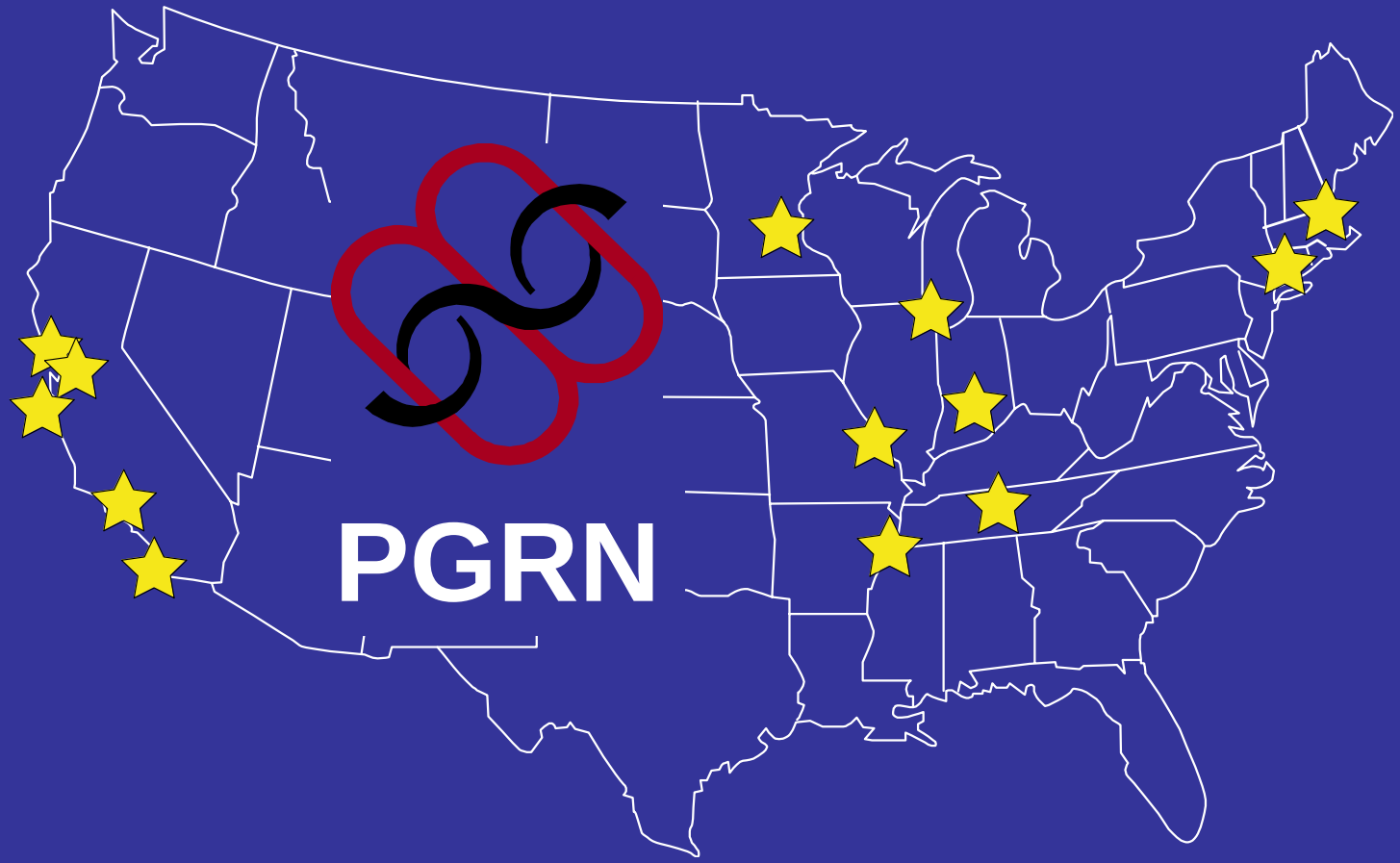

www.nigms.nih.gov/pharmacogenetics

www.pharmgkb.org

PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base

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Pharmacogenetics

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

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Pharmacogenetics-Pharmacogenomics

Two Revolutions

- The Therapeutic Revolution
- The Genomic Revolution

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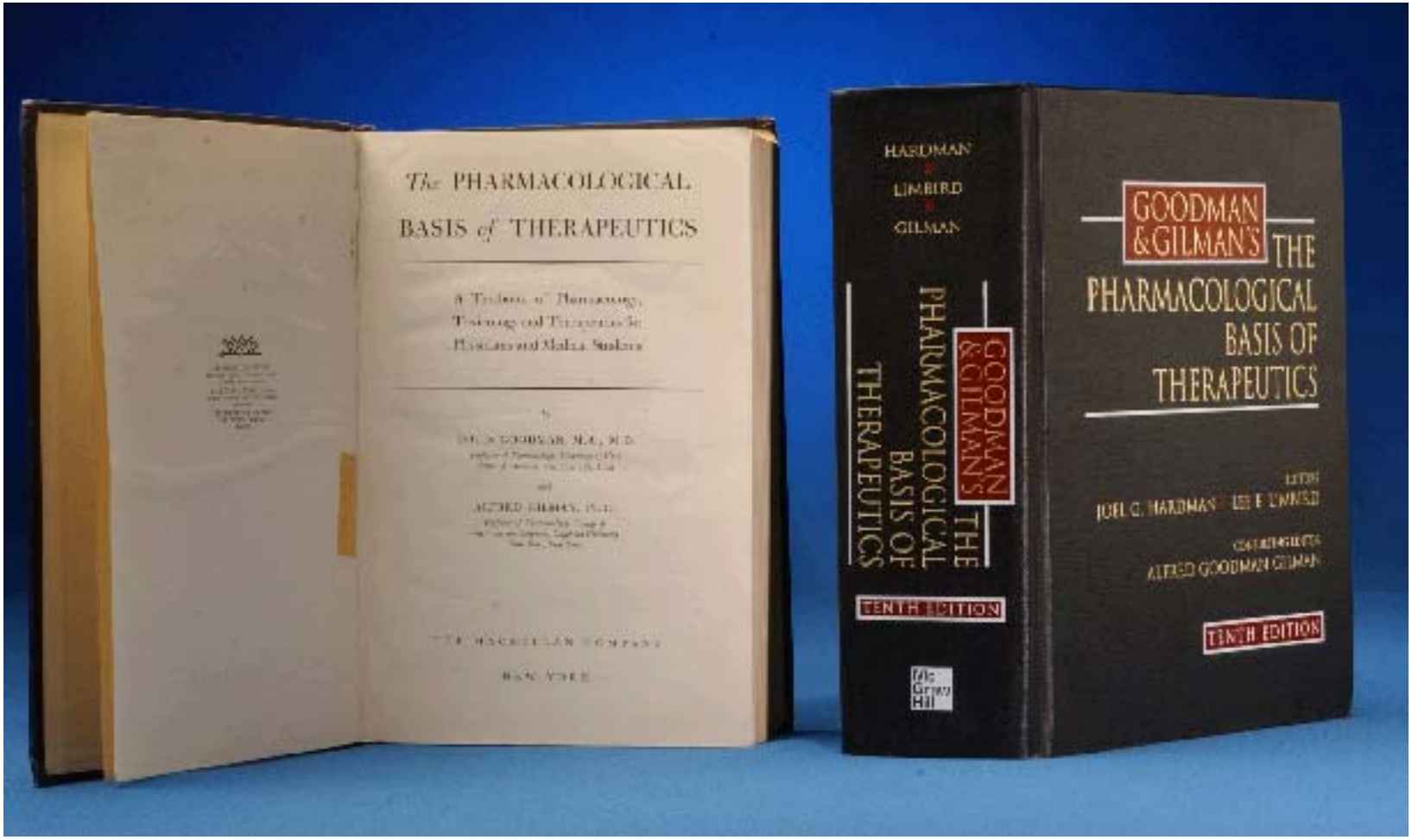
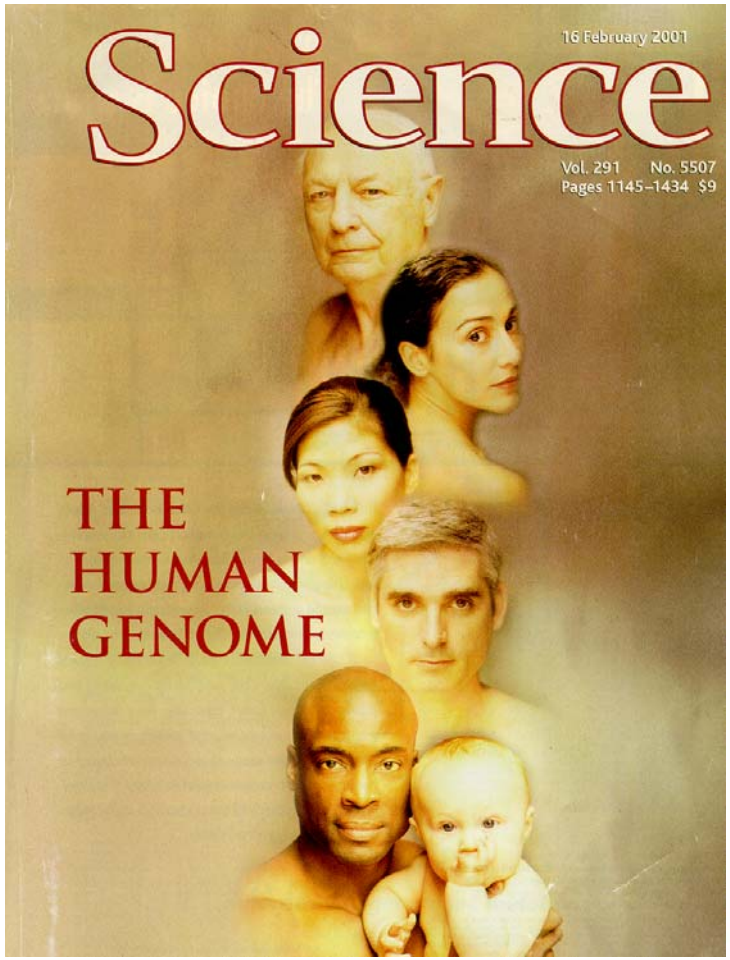
The Therapeutic Revolution



Goodman and Gilman's The Pharmacological Basis of Therapeutics

The Human Genome
February 2001



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Pharmacogenomics

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

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Pharmacogenetics-Pharmacogenomics

Clinical Goals

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

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Pharmacogenetics

Scientific Goal

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

Genotype-Phenotype Correlation

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Patient Factors and Drug Effect

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

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Pharmacogenomic Variation

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

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Pharmacogenetic-Pharmacogenomic Science

Scientific Evolution

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

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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).**

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2003 FDA "Draft Pharmacogenomic Guidance"

Valid Biomarkers

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

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Pharmacogenetics-Pharmacogenomics

TPMT Pharmacogenetics

A “prototypic” example

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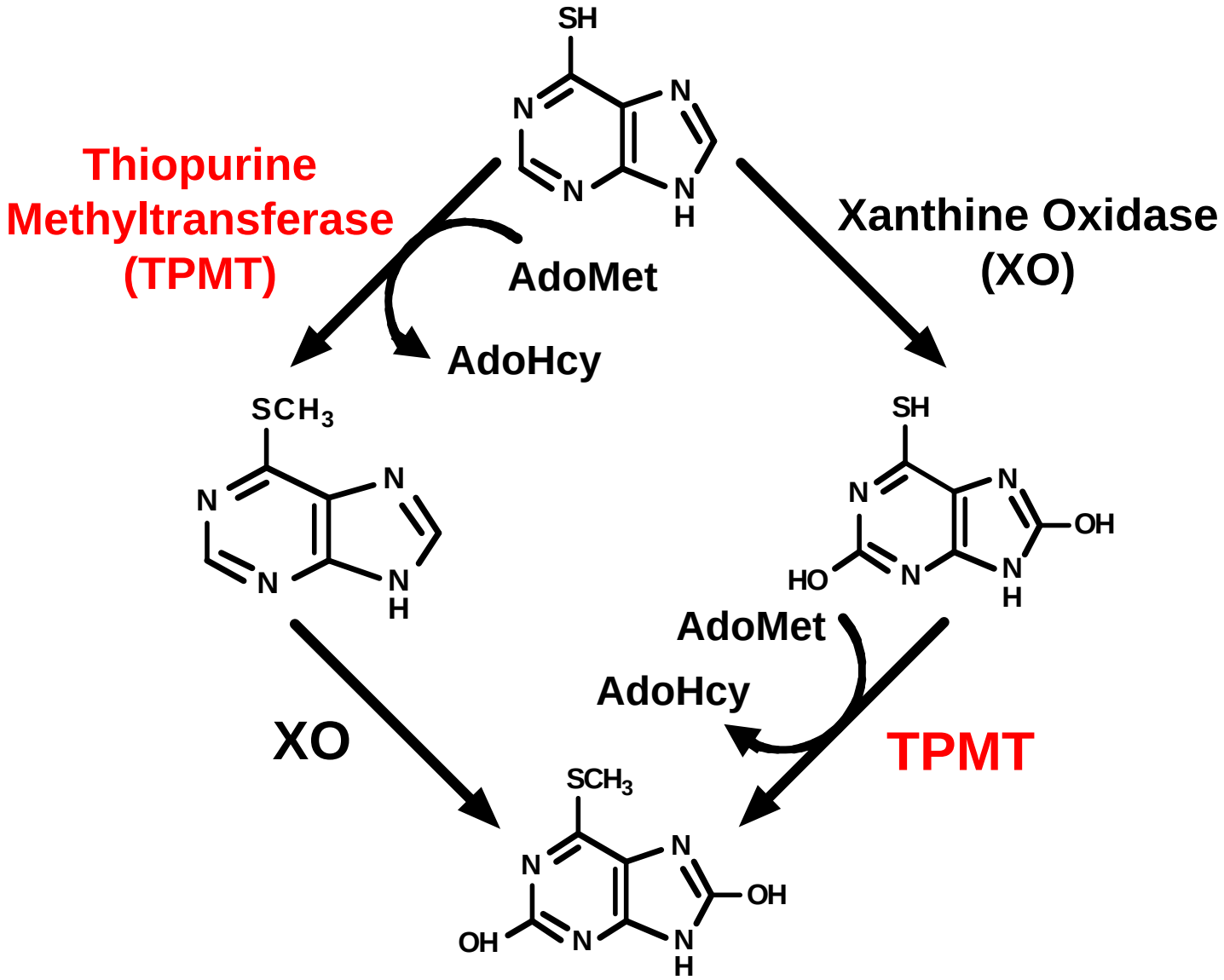
Metabolism of 6-Mercaptopurine



2,8-Dihydroxy-6-Methylmercaptopurine

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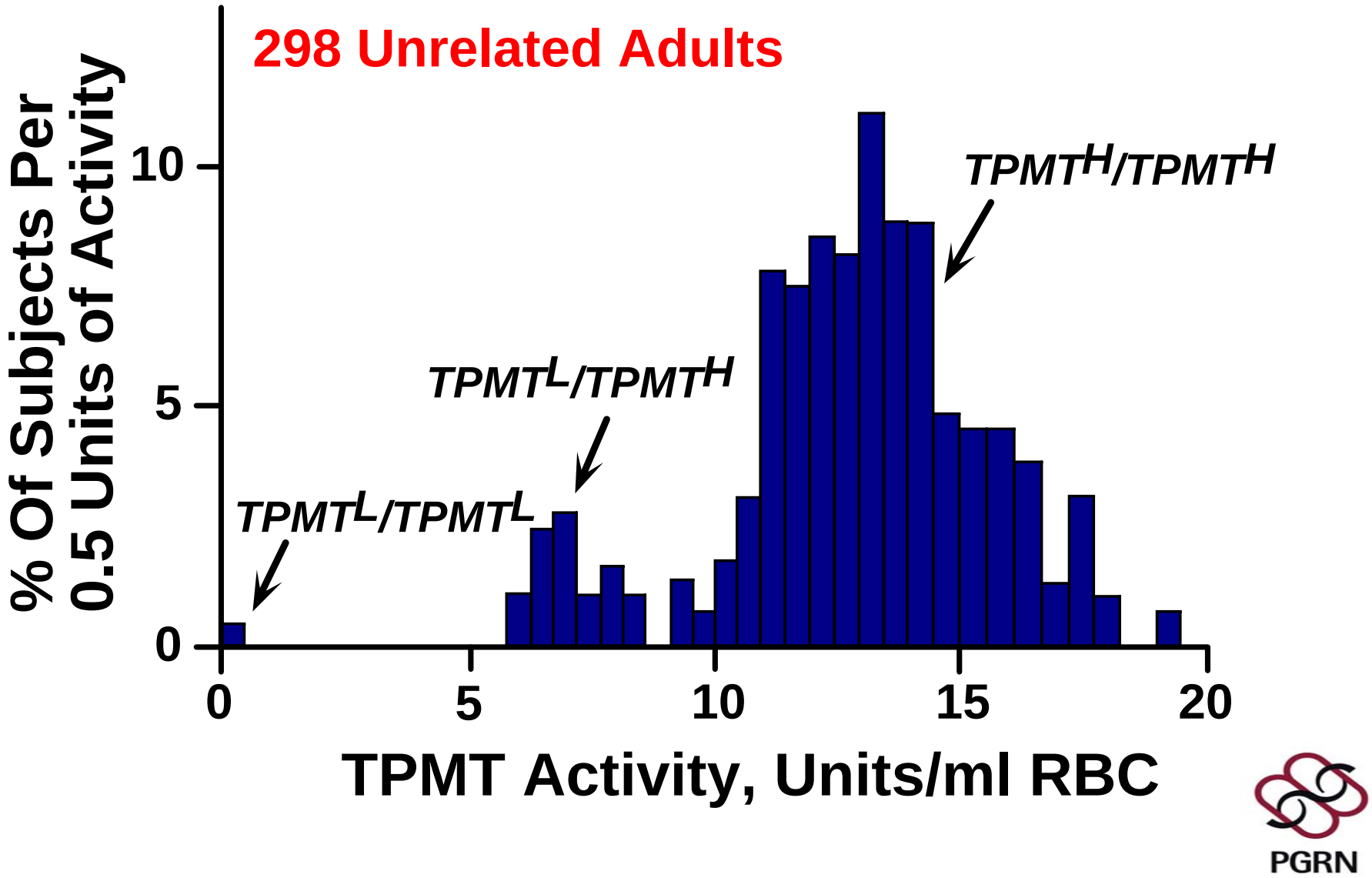
Human RBC TPMT



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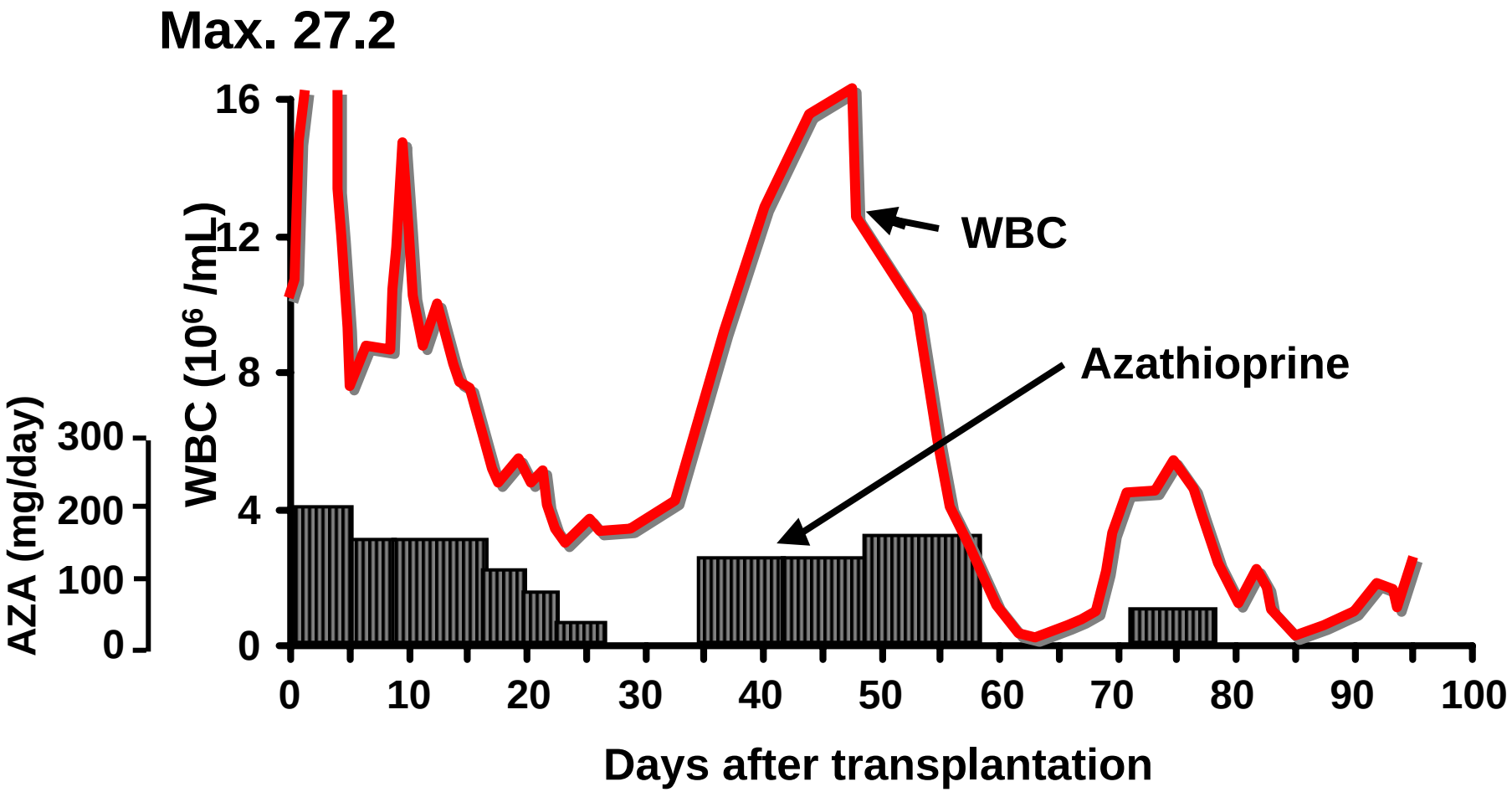

Peripheral blood leukocyte count (WBC) and azathioprine (AZA) dose in TPMT deficient heart transplant recipients

Lancet 341:436, Feb 13, 1993

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TPMT
Genetic Polymorphism
Clinical Consequences

- **Low TPMT**
  - Increased thiopurine toxicity
  - Increased risk for secondary neoplasm
- **High TPMT**
  - Decreased therapeutic effect

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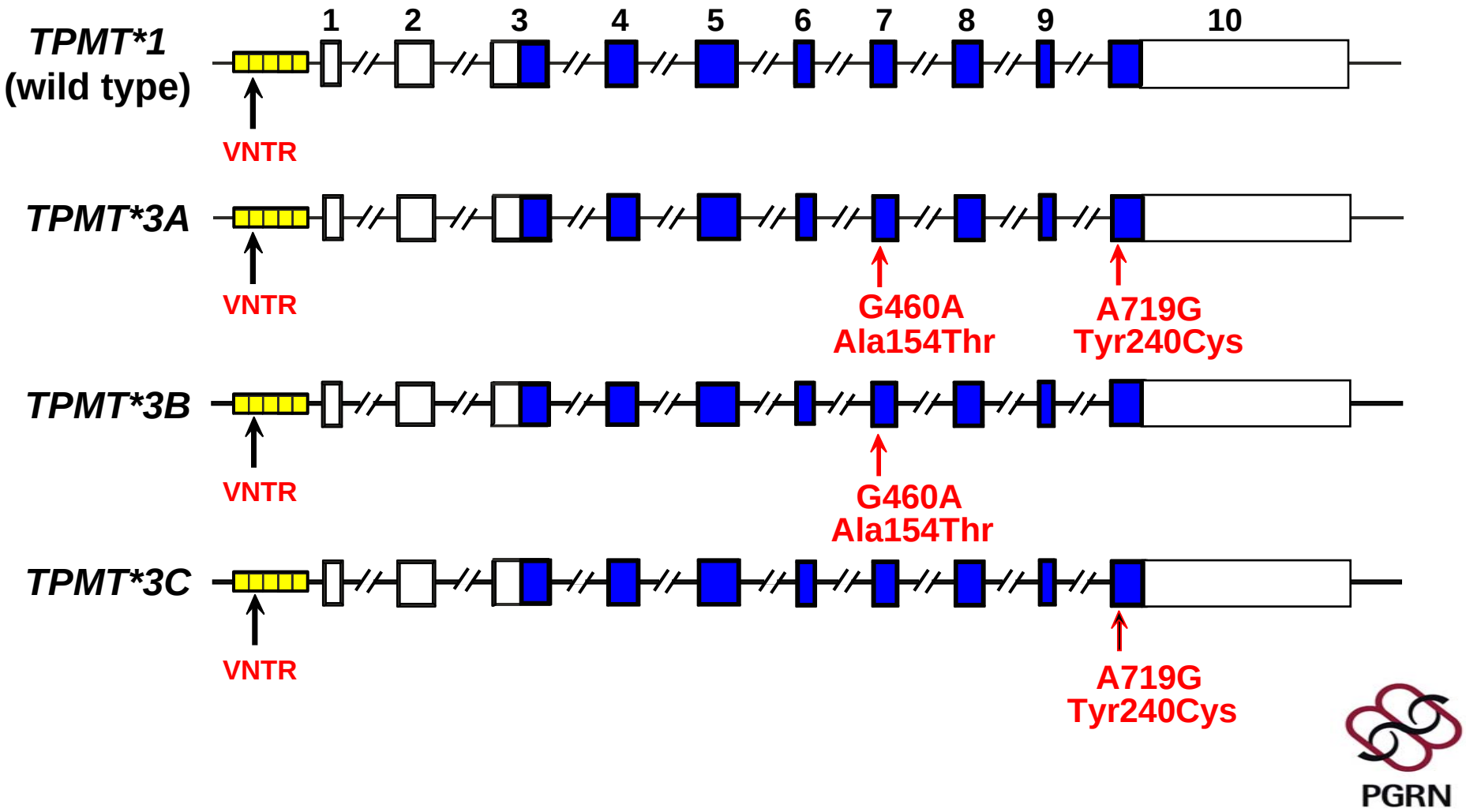
Selected Human TPMT Alleles



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TPMT Genetic Polymorphism

FDA

One of the first examples considered for possible inclusion in labeling

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Cytochrome P450 Genetic Polymorphisms

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

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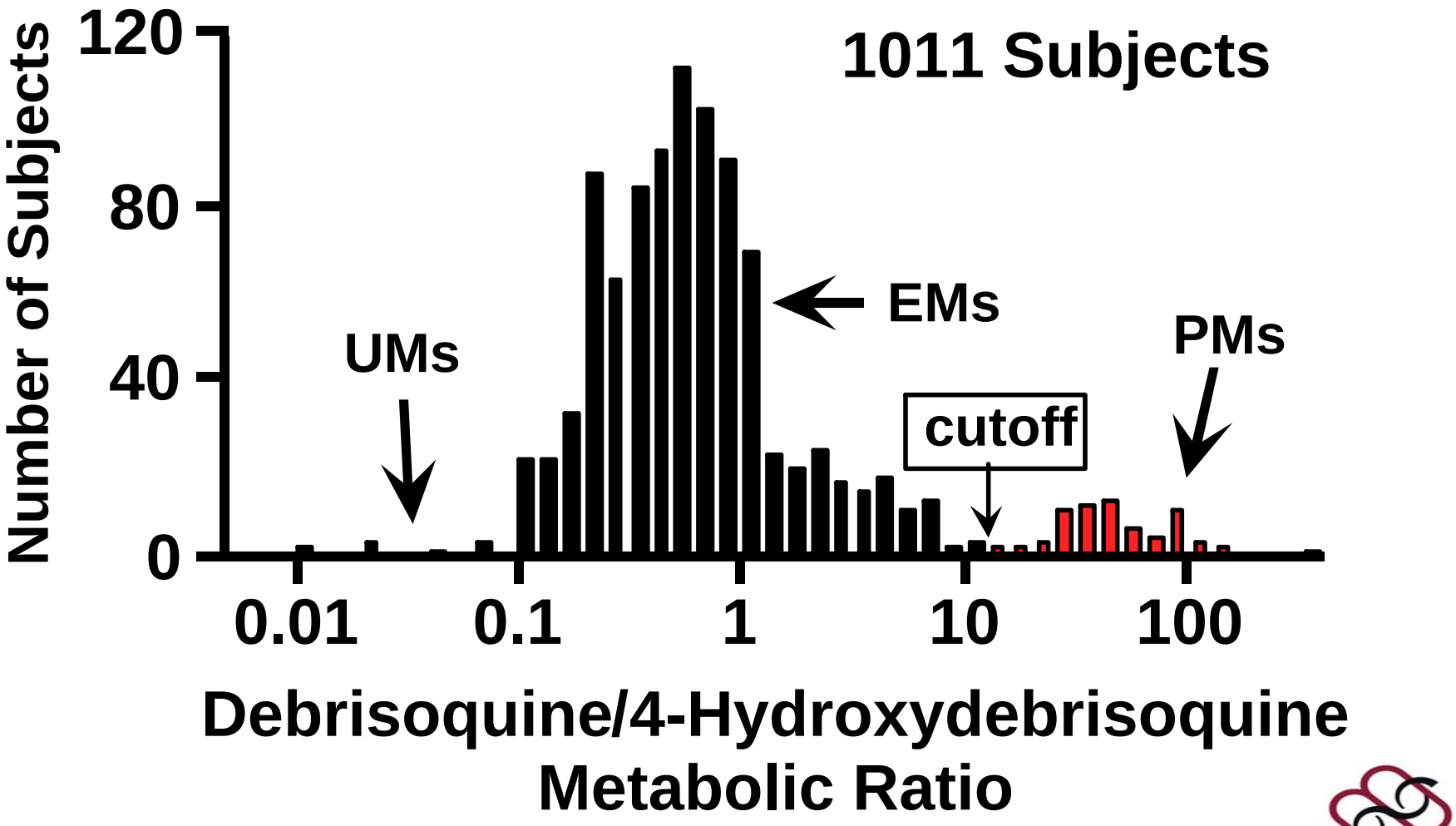
CYP2D6 Pharmacogenetics



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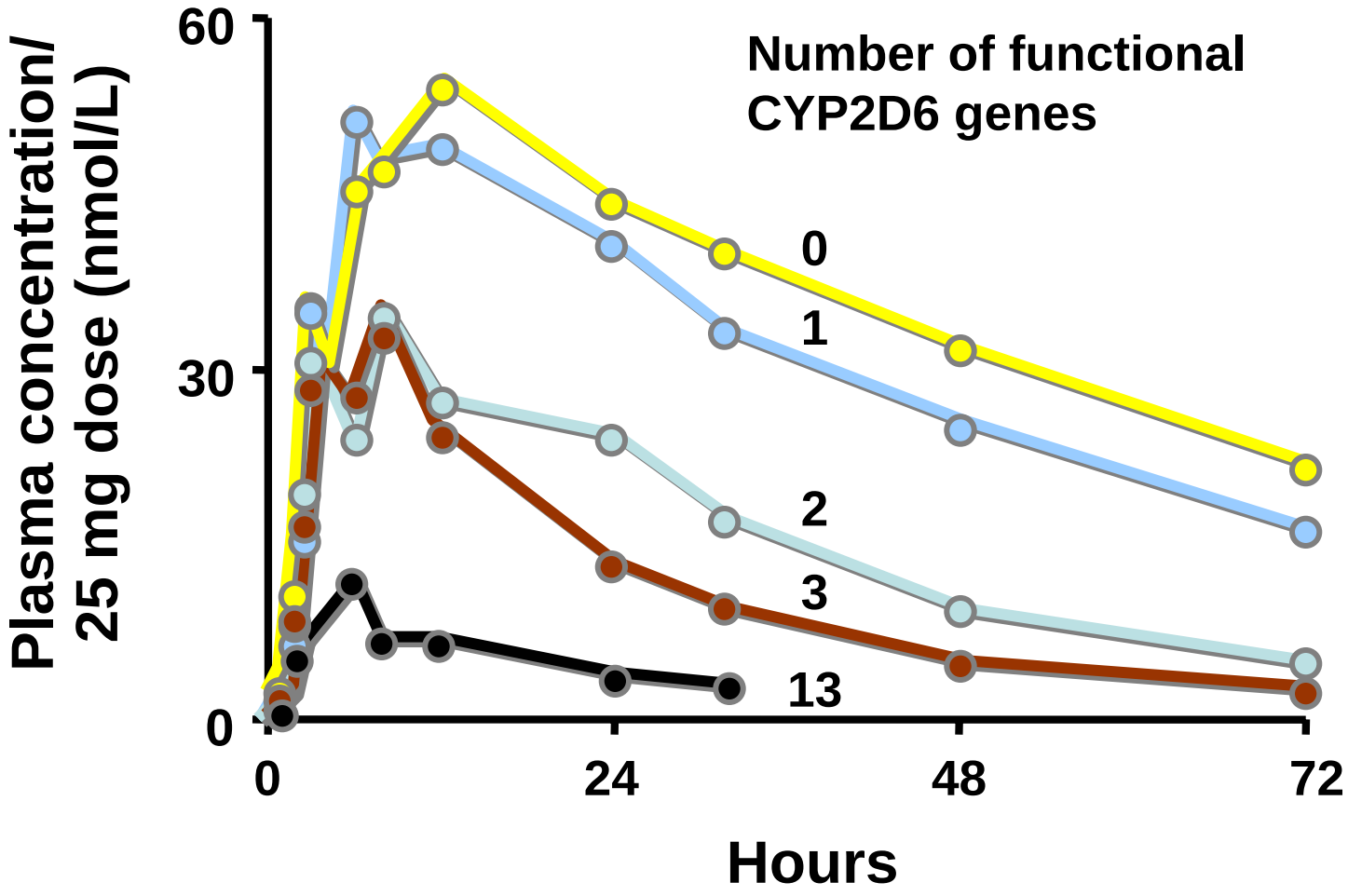
Nortriptyline Pharmacogenetics



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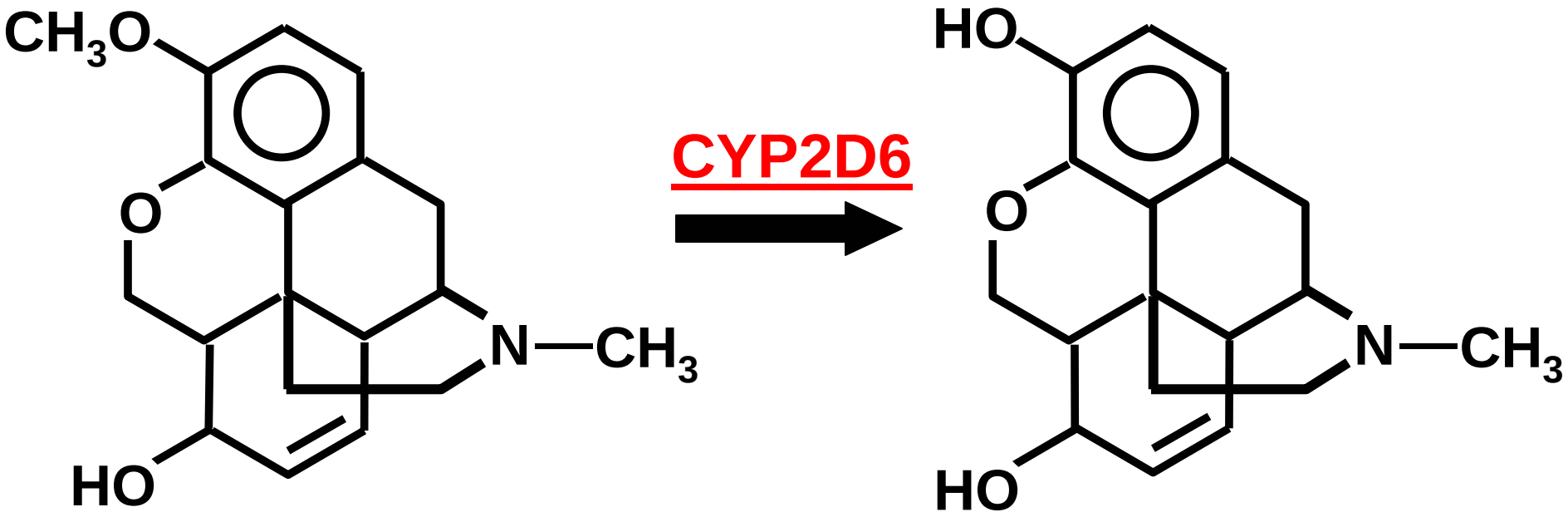
Codeine
Biotransformation to Morphine



Codeine **Morphine**

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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

2827 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. Tornóczky 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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R M WEINSHILBOUM MD 2737
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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

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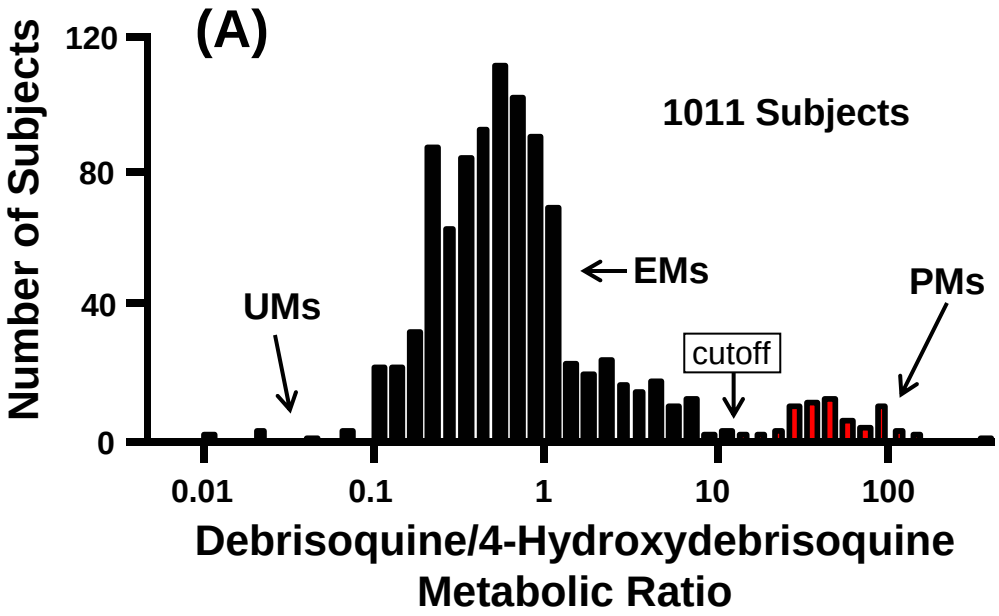
CYP2D6 Pharmacogenetics



AmpliChip CYP450 Array

(B)

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Karl Paul Link
Discoverer of Warfarin

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Cytochrome P450 Genetic Polymorphisms

- CYP2D6
- CYP2C9
- CYP2C19

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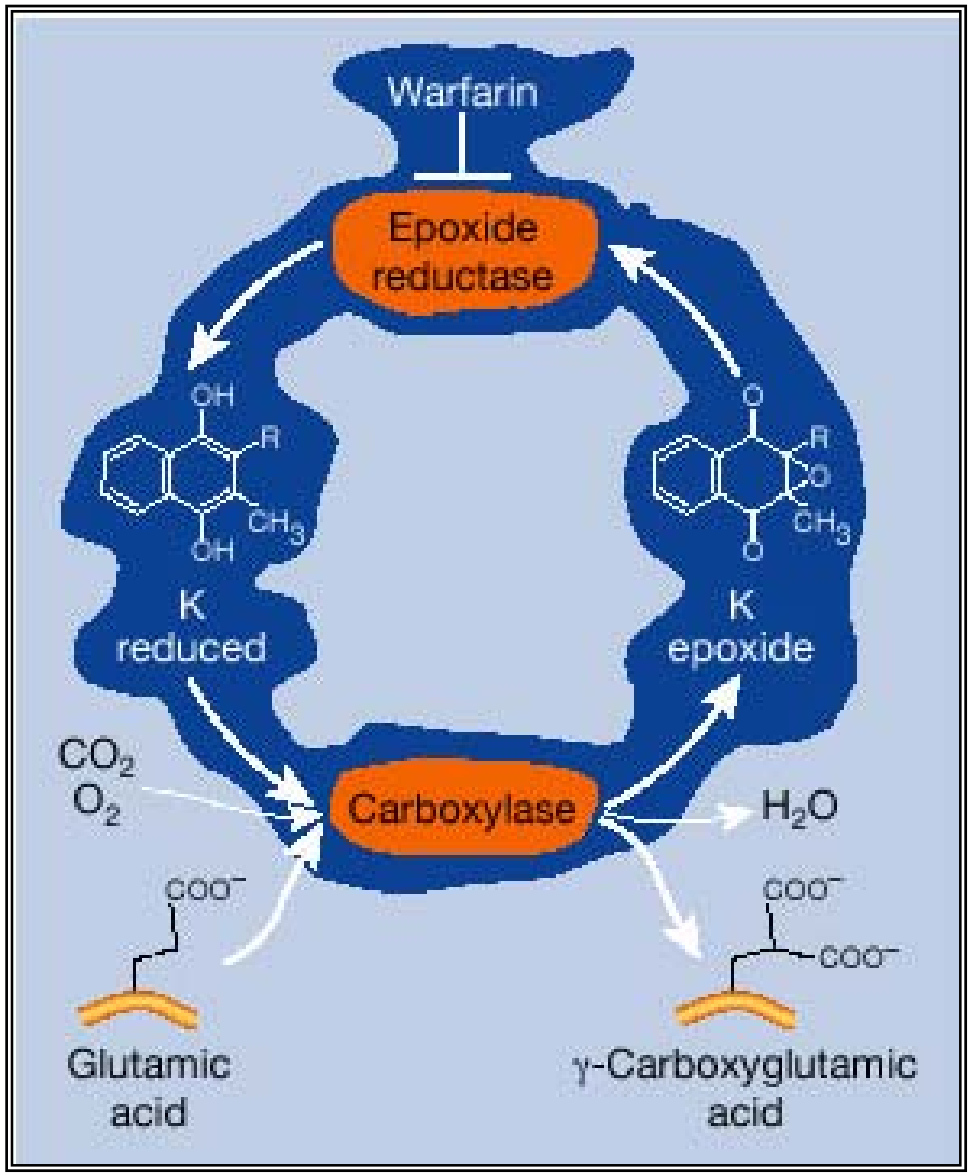
Vitamin K Cycle



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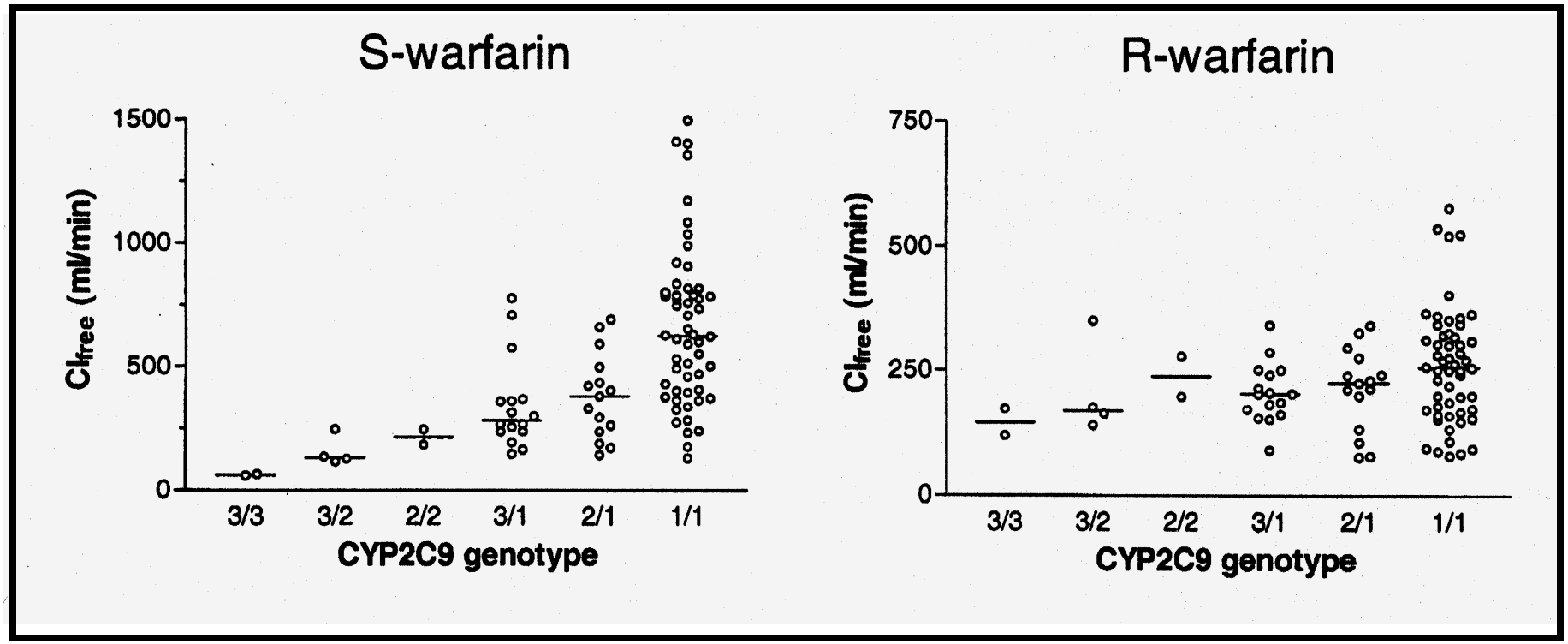
Warfarin Pharmacogenetics



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

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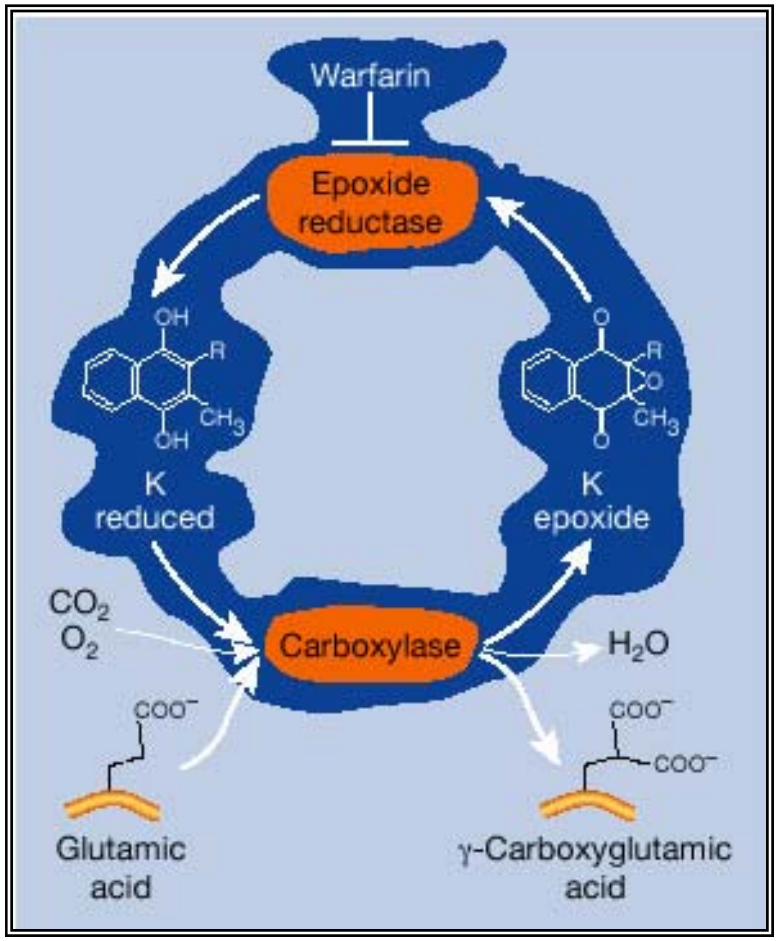
Vitamin K Cycle

February 5, 2004



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New England Journal of Medicine
June 2, 2005

Warfarin Pharmacogenetics

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2261 THIS WEEK IN THE JOURNAL

PERSPECTIVE
2263 Americans as Survivors R.J. Lifton
2266 Aging, Immunity, and the Varicella–Zoster Virus A. Arvin
2268 Type II Collagen and Avascular Necrosis of the Femoral Head D.J. Prockop

ORIGINAL ARTICLES
2271 A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults M.N. Oxman and Others
2285 Effect of *VKORC1* Haplotypes on Transcriptional Regulation and Warfarin Dose M.J. Rieder and Others
2294 Type II Collagen Gene Variants and Inherited Osteonecrosis of the Femoral Head Y.-F. Liu and Others
2302 Adjuvant Docetaxel for Node-Positive Breast Cancer M. Martin and Others

CLINICAL PRACTICE
2314 Atopic Dermatitis H.C. Williams

REVIEW ARTICLE
2325 Medical Progress: Brucellosis G. Pappas and Others

IMAGES IN CLINICAL MEDICINE
2337 A Medical Mystery — Bradycardia R. Rosenberg

CLINICAL PROBLEM-SOLVING
2338 Don't Know Much about History S. Dames and Others

EDITORIALS
2344 Varicella–Zoster Virus Vaccine — Grown-ups Need It, Too D.H. Gilden
2346 TAC — A New Standard in Adjuvant Therapy for Breast Cancer? E.A. Perez

2349 CORRESPONDENCE
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

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Pharmacogenetics-Pharmacogenomics

Clinical Goals

- Avoid adverse drug reactions
- Maximize drug efficacy
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Pharmacogenetics

Scientific Goal

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

Genotype-Phenotype Correlation

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Pharmacogenomics

The Vision

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

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