Pharmacogenomics in the Practice of Medicine

Challenges and Opportunities

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Pharmacogenomics Challenges and Opportunities

- Basic and translational science
- Drug development and regulatory science
- Ethical, legal and social science

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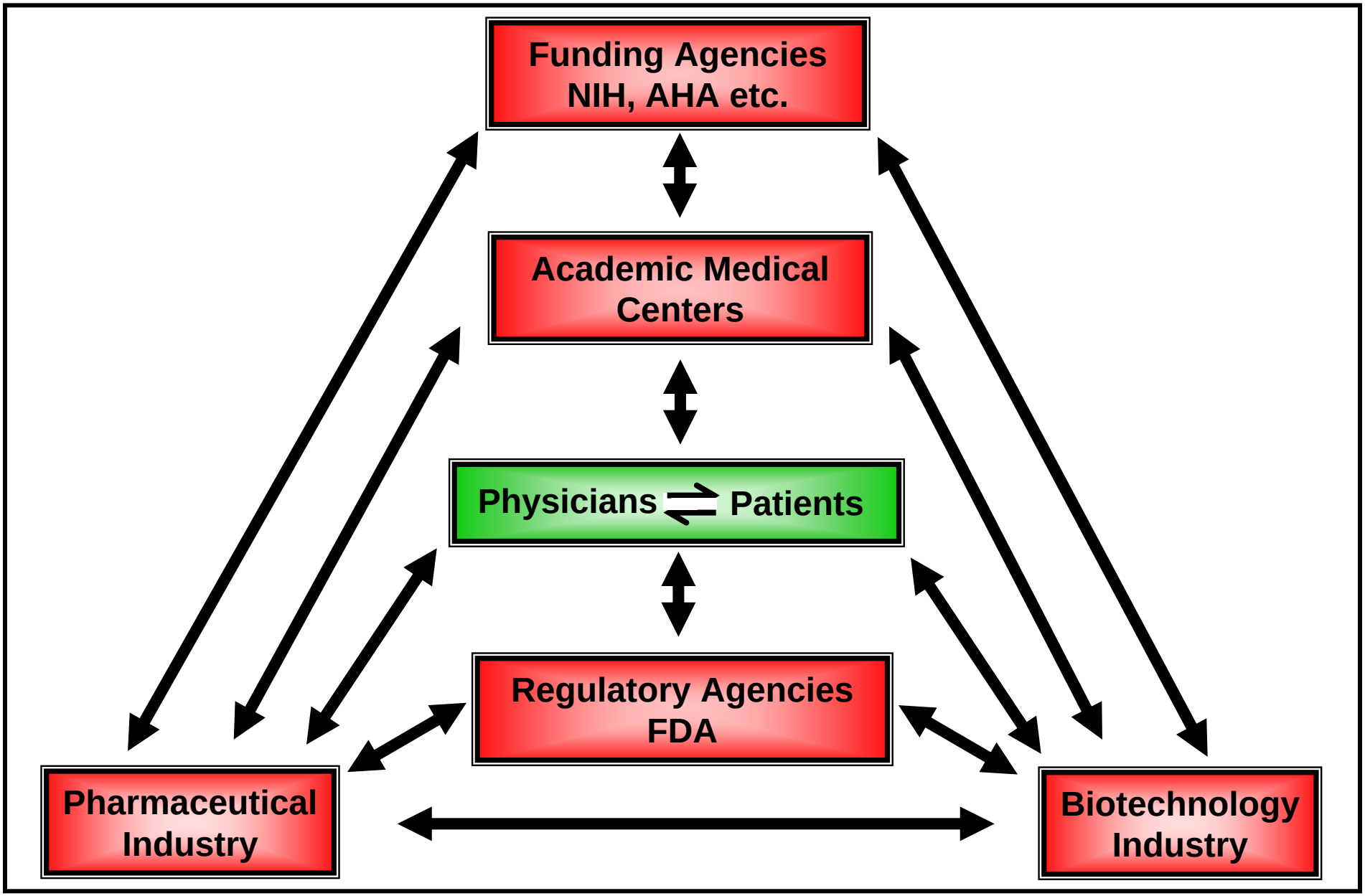
Pharmacogenomics
Discovery, Translation, Application



Pharmacogenomics Challenges and Opportunities

- **Basic and translational science**
- **Drug development and regulatory science**
- **Ethical, legal and social science**

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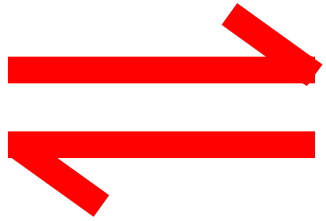
Pharmacogenomics

Pharmacogenomic Research

Basic Pharmacogenomics  **Translational Pharmacogenomics**

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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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Pharmacogenetics-Pharmacogenomics

Genomic Variation

- Single nucleotide polymorphisms (SNPs)
- Insertion-deletions (Indels)
- Variable number of tandem repeats (VNTRs)
- Gene deletion and/or duplication
- Large segmental duplications
- Gene sequence variation resulting in alternative splicing
- Epigenetic variation

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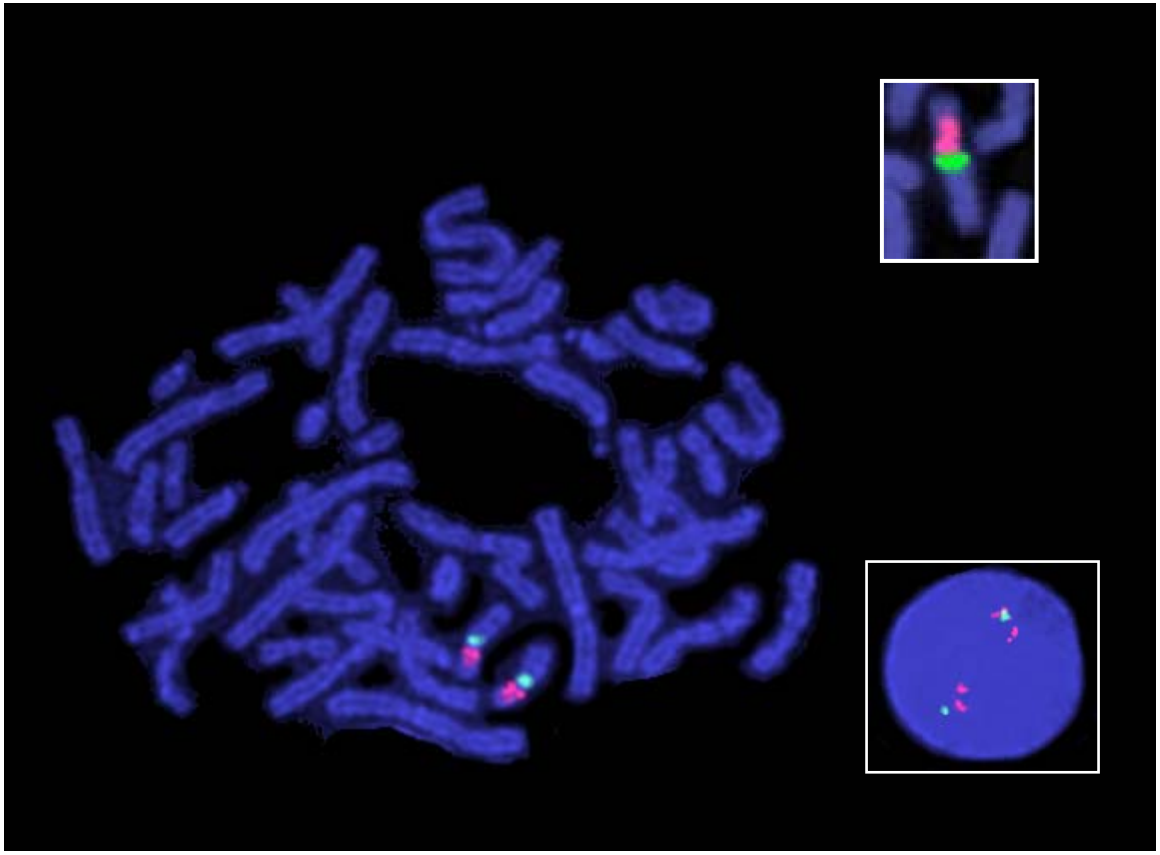
Human *SULT1A3/1A4* FISH



Biomedical Research

The NIH Roadmap

- **New Pathways to Discovery – the need to understand complex biological systems.**
- **Research Teams of the Future – the need to explore new organizational models for team science.**
- **Reengineering the Clinical Research Enterprise – the need for multicenter, multigroup organization**

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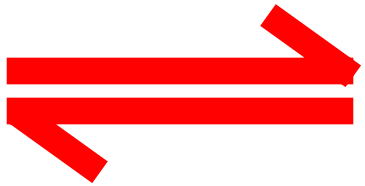
Complementary Pharmacogenomic Research Strategies

Phenotype  **Genotype**

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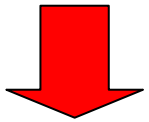
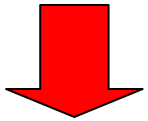
Genotype-to-Phenotype Strategy

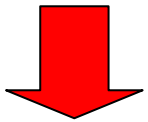
Gene sequence



Variation in gene sequence



Functionally significant Variation in gene sequence



Clinical important functionally Significant variation in gene sequence

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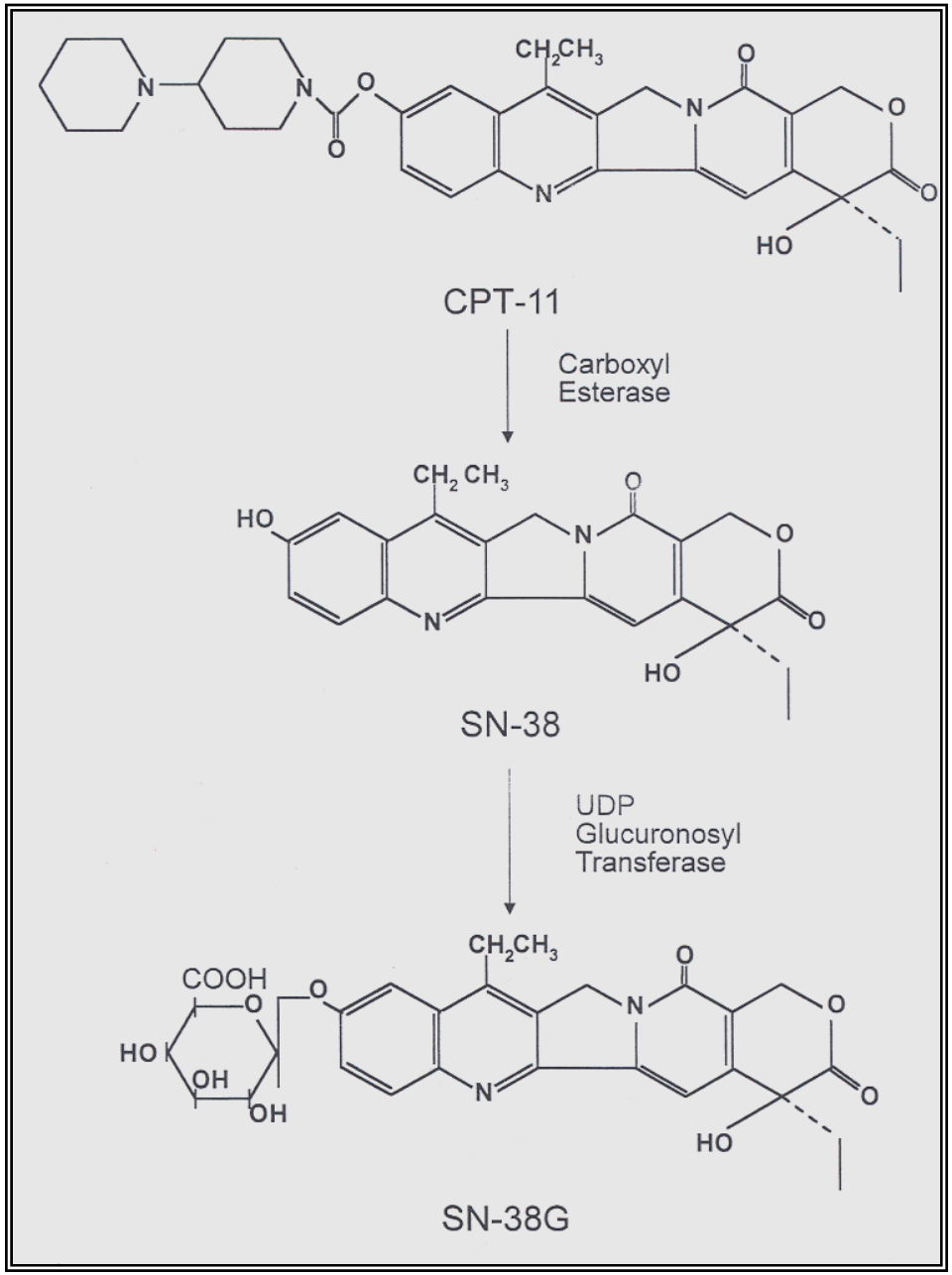
Irinotecan Pharmacogenetics

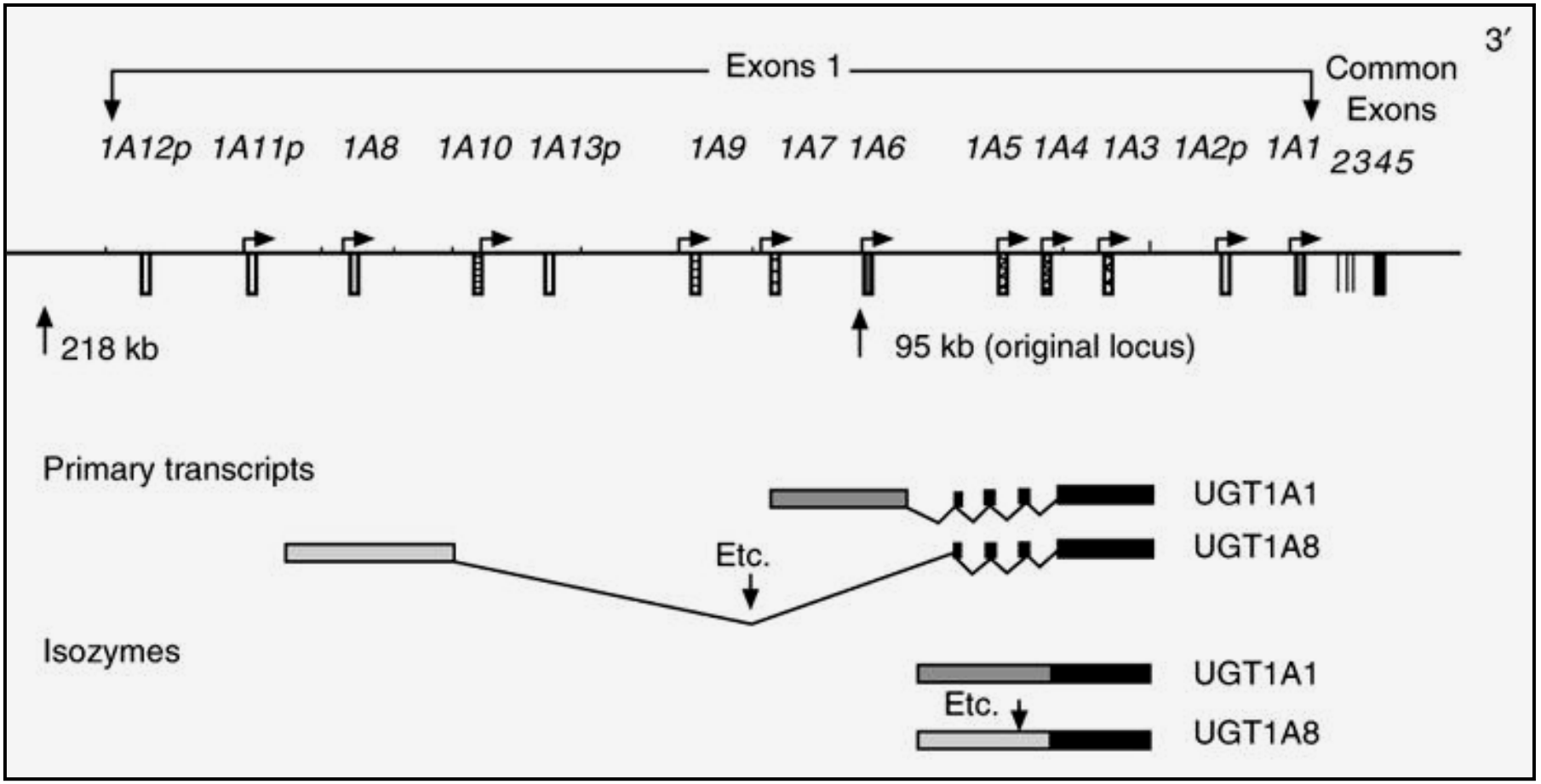
Irinotecan

- Camptothecin derivative
- Inhibits topoisomerase I
- Toxicity
  - Diarrhea
  - Myelosuppression

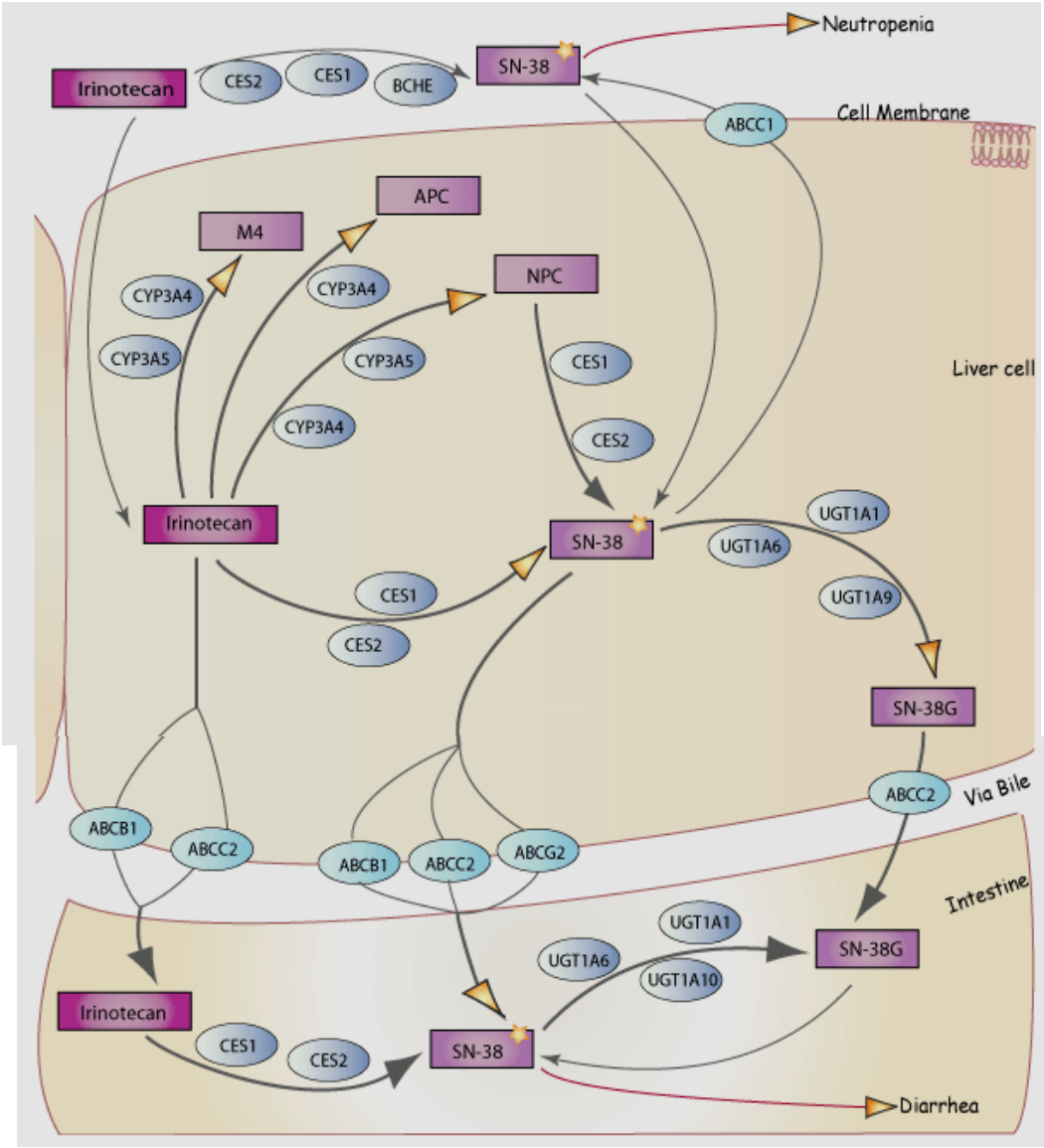


Irinotecan Biotransformation

Human UGT1A Locus



PharmGKB
Irinotecan Pathway



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PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base
Search PharmGKB:
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Resources
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Contributors
My PharmGKB
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Welcome | Overview | Events | Projects | Policies | Team | Register
The PharmGKB is an integrated resource about how variation in human genes leads to variation in our response to drugs. more ...
Browse:
Genes with PharmGKB Primary Data
Genes with Genotype Data
Genes with Phenotype Data
Drugs with PharmGKB Primary Data
Diseases with PharmGKB Primary Data
All Pathways
more ...
Search PharmGKB:
Go
e.g. a gene ("TPMT"), drug ("codeine") or disease ("leukemia")
Genomic data, molecular and cellular phenotype data, and clinical phenotype data are accepted from the scientific community at large. These data are then organized and the relationships between genes and drugs are then categorized into the following categories:
Phenotype
CO Clinical Outcome
PD Pharmacodynamics & Drug Responses
PK Pharmacokinetics
FA Molecular & Cellular Functional Assays
News
New XML Schema
New XML Validator
Templates
PGRN RFA
NIH RFA for PGRN Renewal
PharmGKB Renewal
PharmGKB Pathways
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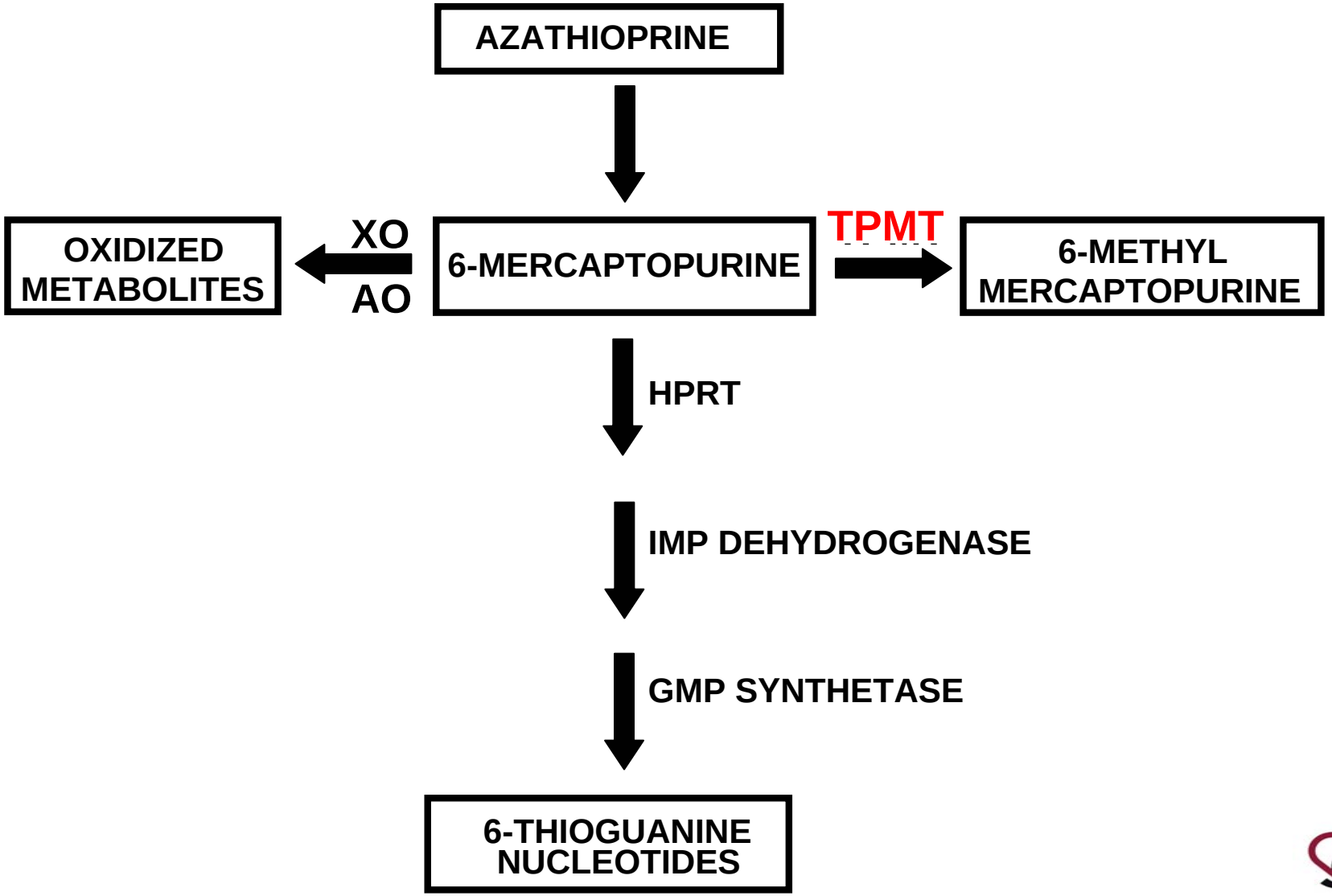
Pharmacogenetics-Pharmacogenomics

Thiopurine Metabolism and Metabolic Activation Pathway

Thiopurine Metabolism



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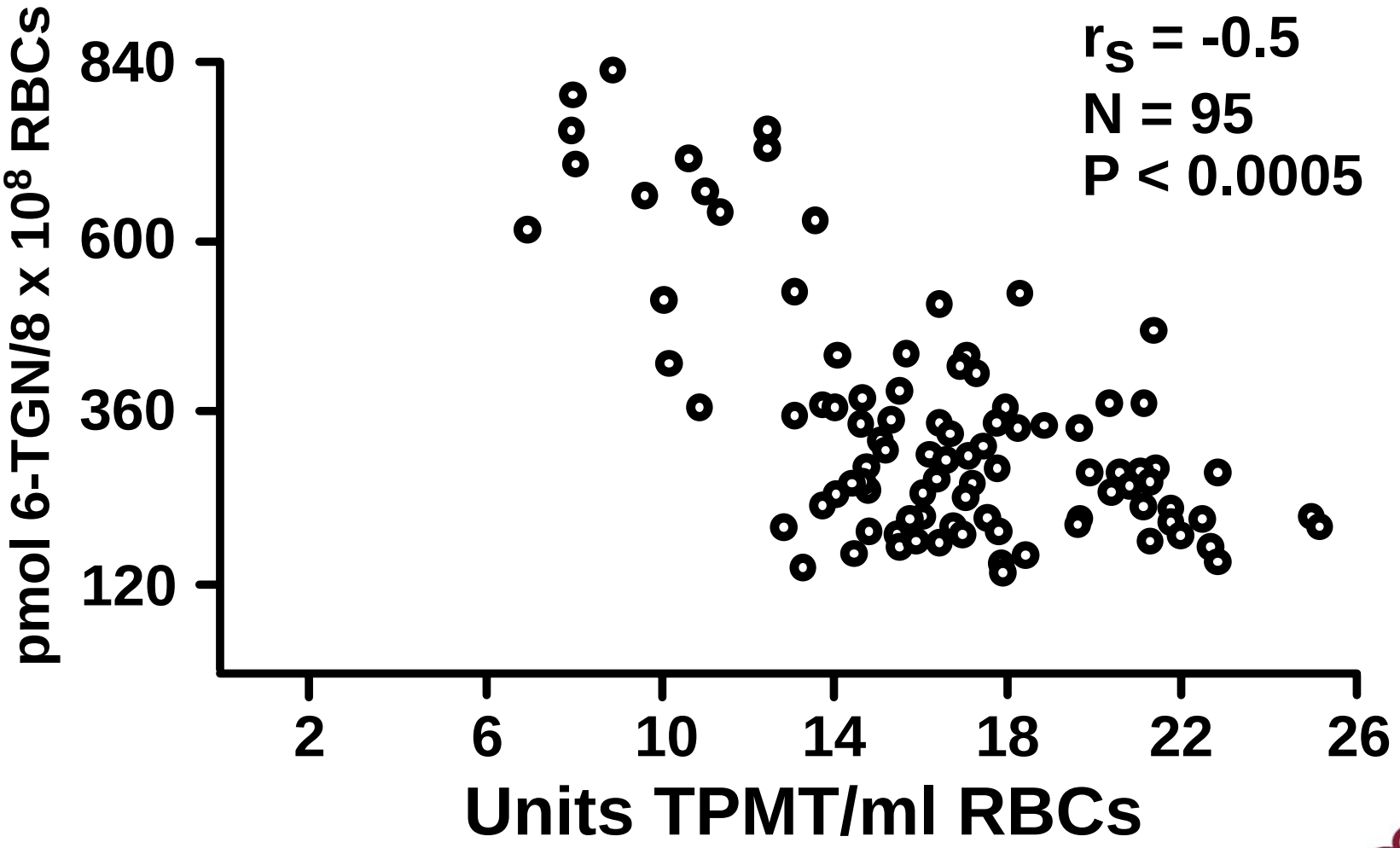
TPMT in ALL



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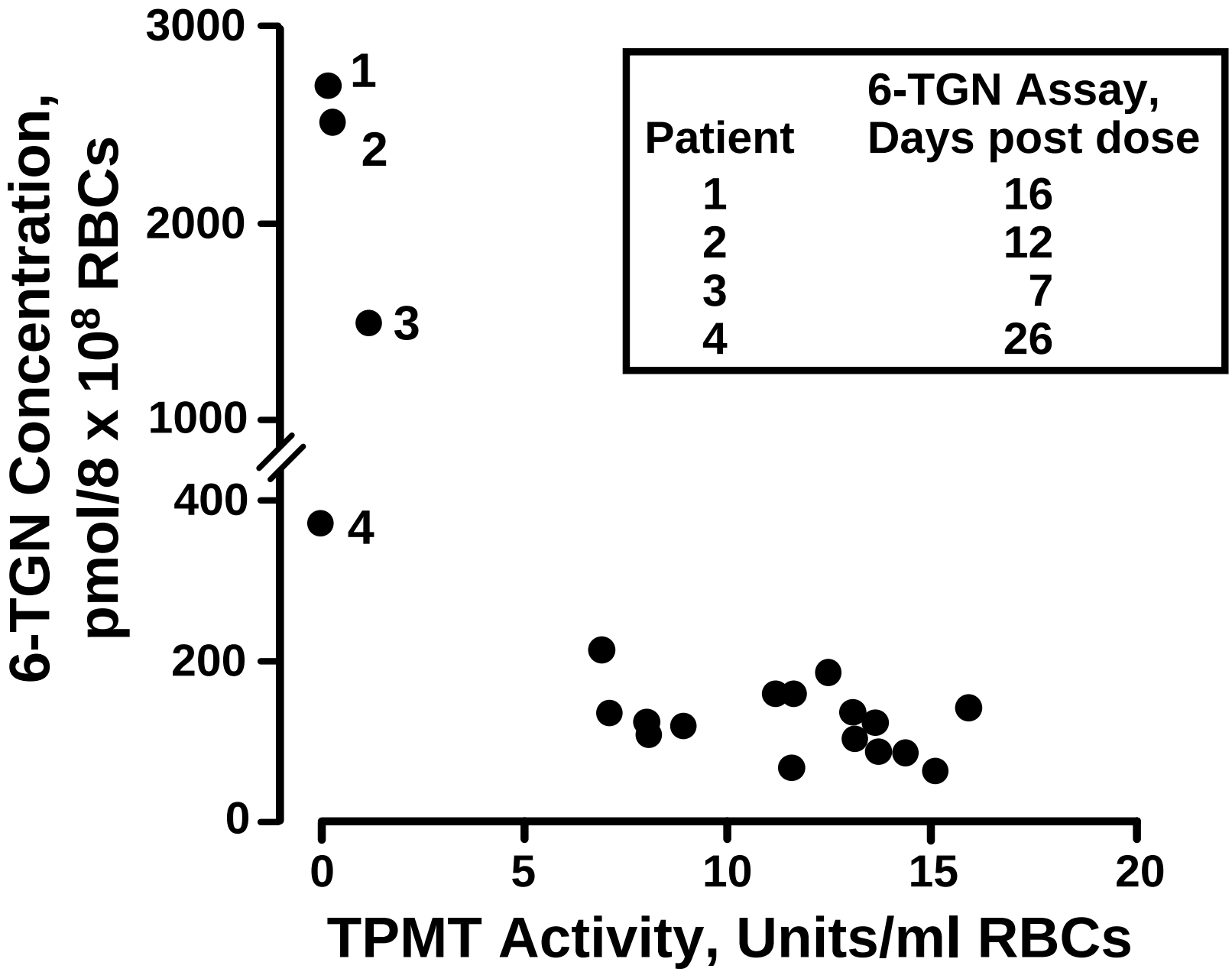
6-TGN Concentration, pmol/8 x 10^8 RBCs
3000
2000
1000
400
200
0
1
2
3
4
0
5
10
15
20
TPMT Activity, Units/ml RBCs
Patient
6-TGN Assay, Days post dose
1 16
2 12
3 7
4 26

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TPMT Pharmacogenetics

Translational Lessons

- Importance of “intermediate phenotypes” (6-TGNs)
- Difficulty of pathway analysis

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Modified “Central Dogma”

Genome (Genomics)

Transcriptome (Transcriptomics)

Proteosome (Proteomics)

Metabalome (Metabolomics)

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Pharmacogenomics Challenges and Opportunities

Clinical Assays

- Phenotypes -- clinical and "intermediate"
- Genotypes and haplotypes
- Development and validation

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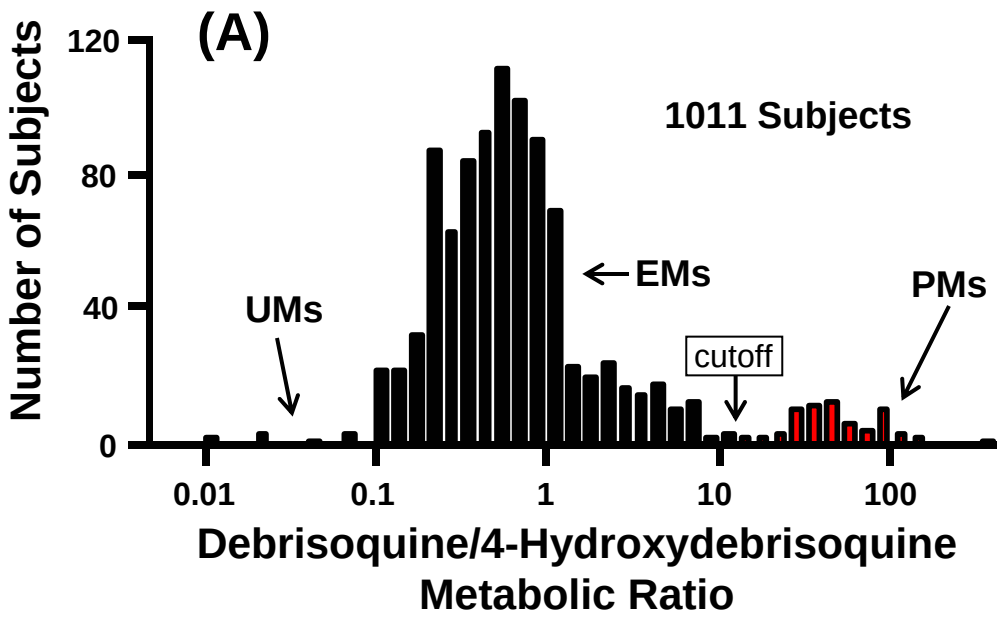
CYP2D6 Pharmacogenetics



AmpliChip CYP450 Array

(B)

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Pharmacogenomics

Scientific Evolution

- Phenotype-to-genotype → genotype-to-phenotype
- Monogenic traits → polygenic traits
- Single genes/proteins → pathways
- Single polymorphisms → haplotypes → genomewide screens
- "Mom and pop stores" approach → high throughput platforms

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Pharmacogenomics Challenges and Opportunities

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Pharmacogenomics

Lack of Pharmaceutical Industry Incentives

"Another strategy……, known as pharmacogenomics, is to tailor drugs more precisely to the genetic profile of patients…. It's been slow to get off the ground. ……Business managers have been skeptical of an approach that limits the market to a subset of patients".

R.F. Service, "Surviving the Blockbuster Syndrome". Science 303:1796-1799, 2004.

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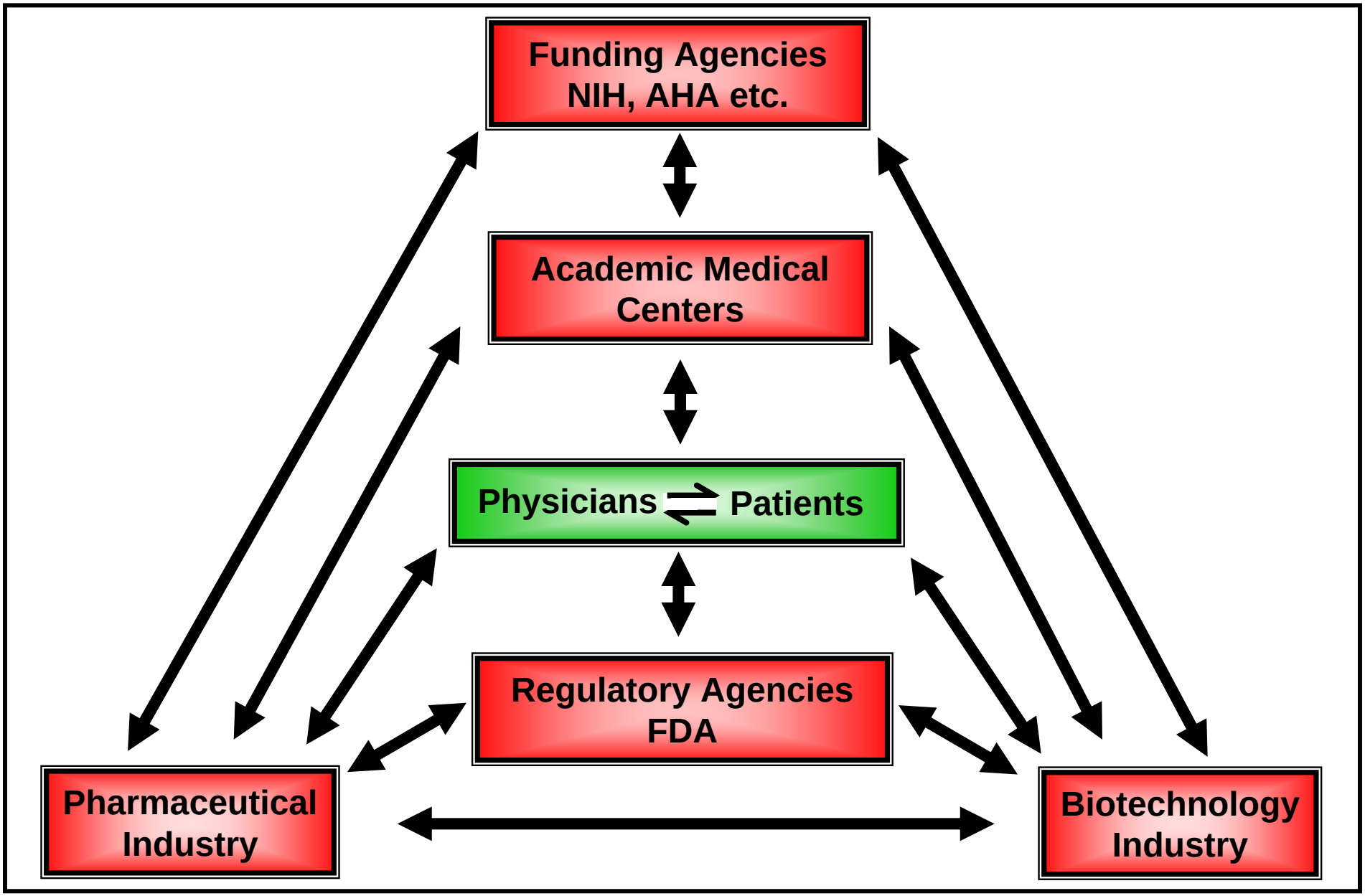
Pharmacogenomics
Discovery, Translation, Application



PERSPECTIVES

OPINION

Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective

Lawrence J. Lesko and Janet Woodcock

Abstract | Pharmacogenomics and pharmacogenetics provide methodologies that can lead to DNA-based tests to improve

MAPS, HAPLOTYPE MARKERS and alterations in gene expression or inactivation that might be correlated with pharmacological function and ther-

Administration regarding the value and challenges of integrating PGx and PGt into the continuum of drug research and development and regulatory decision making; second, the major, structured approach that the FDA has undertaken to encourage the use of PGx and PGt both in drug development and clinical practice; and third, selected examples of how PGx and PGt have been used both in new drug development and in updating the labels of approved drugs. Within the context of these three areas, we will point out various challenges that drug developers, regulatory agencies, health-care providers and others will have to address in order to attain the benefits of PGx and PGt more fully.

Pharmacogenomics Challenges and Opportunities

Translational Science

- Drug development process
- Clinical trials -- public, private
- Public-private partnerships

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Pharmacogenomics Challenges and Opportunities

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- Ethical, legal and social science

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Pharmacogenomics

Ethical Challenges

- Confidentiality
- Insurance
- Therapeutic “activism”

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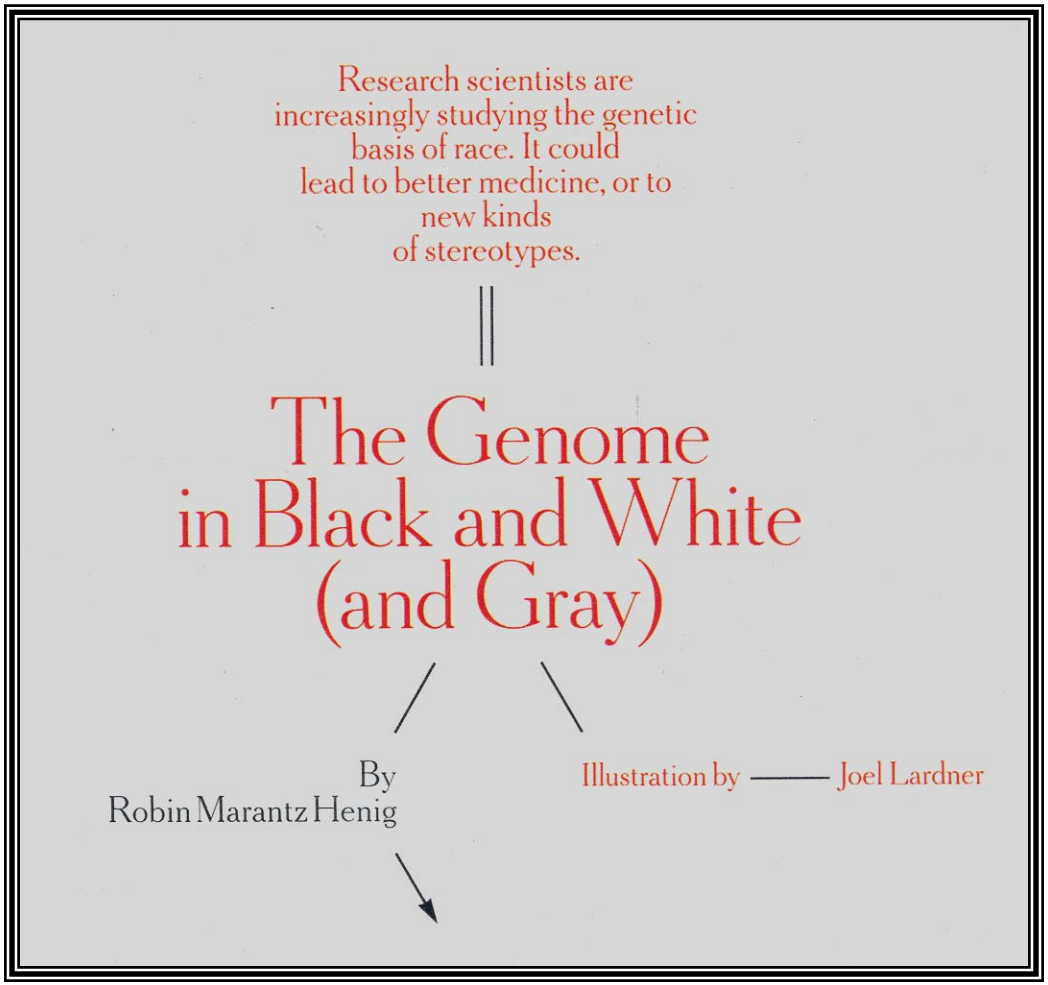
Genomics and Race
New York Times Magazine
October 10, 2004



Research scientists are increasingly studying the genetic basis of race. It could lead to better medicine, or to new kinds of stereotypes.

The Genome in Black and White (and Gray)

By Robin Marantz Henig

Illustration by — Joel Lardner

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New England Journal of Medicine
May 3, 2001

"Original Articles"

- **Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction.**
- **Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure.**

"Editorials"

- **Racial profiling in medical research.**
- **Racial differences in response to drugs -- pointers to genetic differences.**

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New England Journal of Medicine
March 20, 2003

"Sounding Board"

- **Race and genomics.**
- **The importance of race and ethnic background in biomedical research and clinical practice.**

"Perspective"

- **Medicine and the racial divide.**

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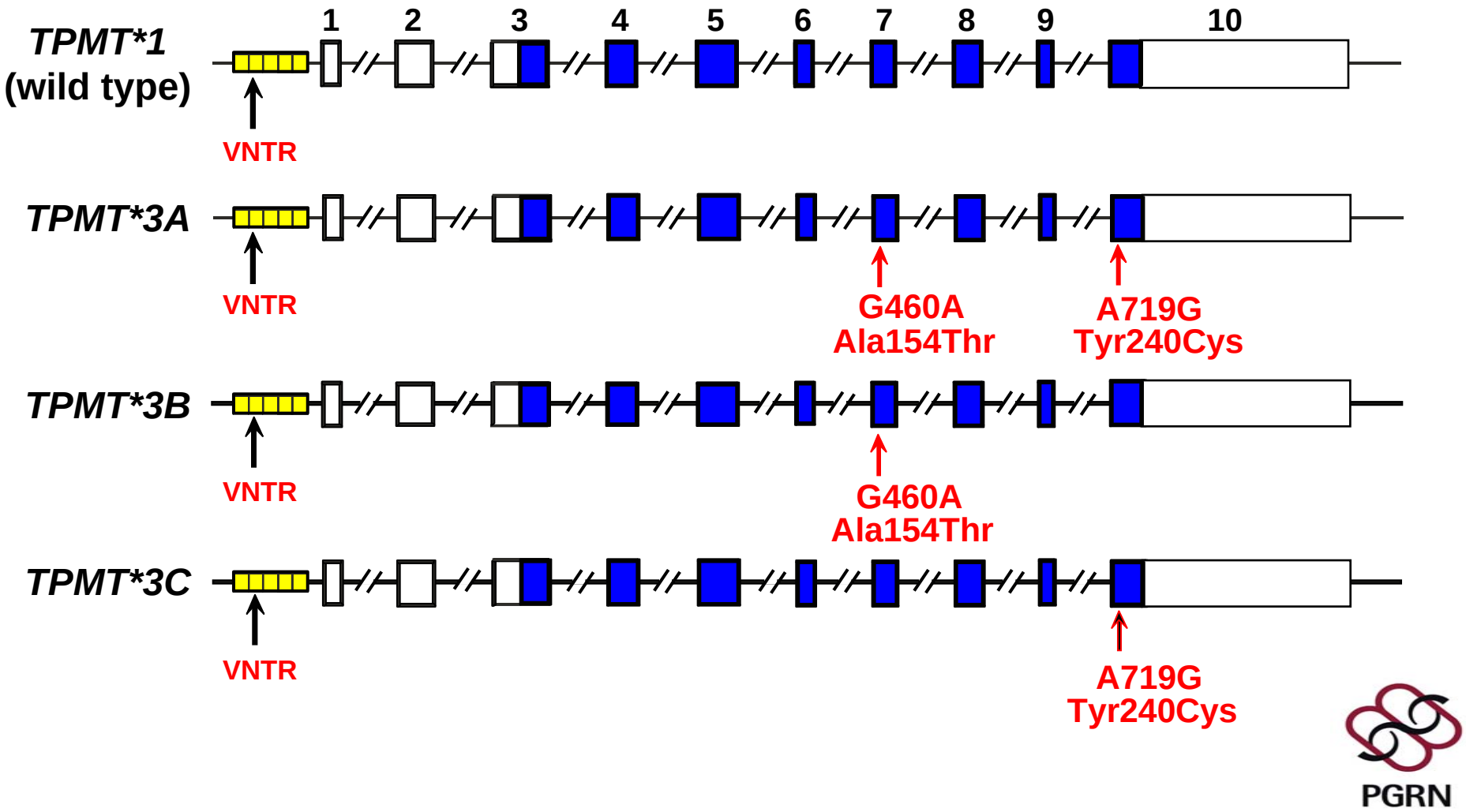
Selected Human TPMT Alleles



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Pharmacogenomics

Education

- Healthcare Professionals
- Patients

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Patient Factors and Drug Effect

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

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Pharmacogenomics

Clinical Goals

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

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Pharmacogenomics

Genetic inheritance is only one factor in the drug response phenotype

but

understanding is increasing rapidly and the promise for enhanced drug safety and efficacy is real

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Pharmacogenomics
The Future

The Vision

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

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