

Pharmacogenomics in the Practice of Medicine

Challenges and Opportunities

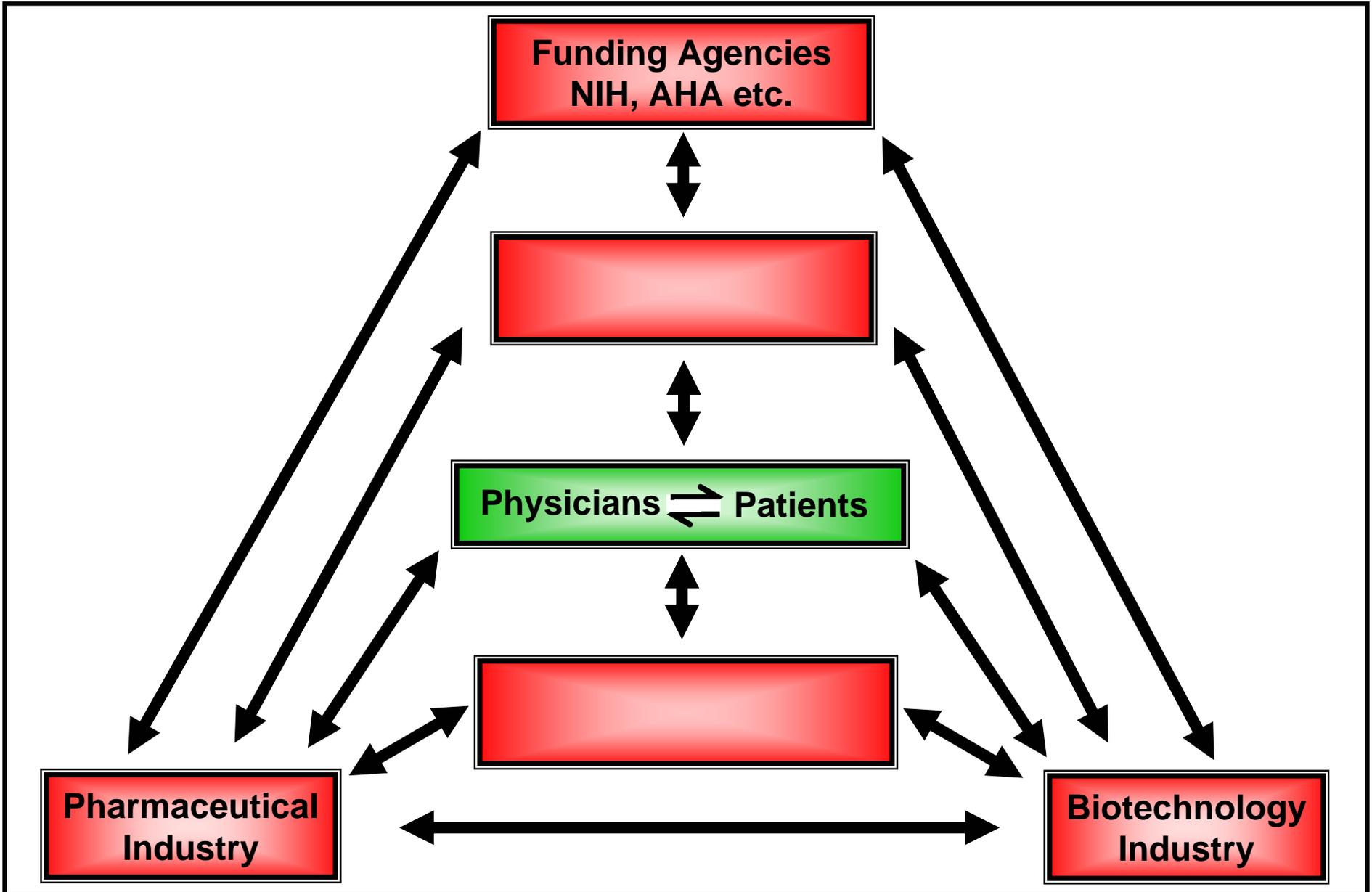
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Pharmacogenomics Challenges and Opportunities

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

Pharmacogenomics Discovery, Translation, Application

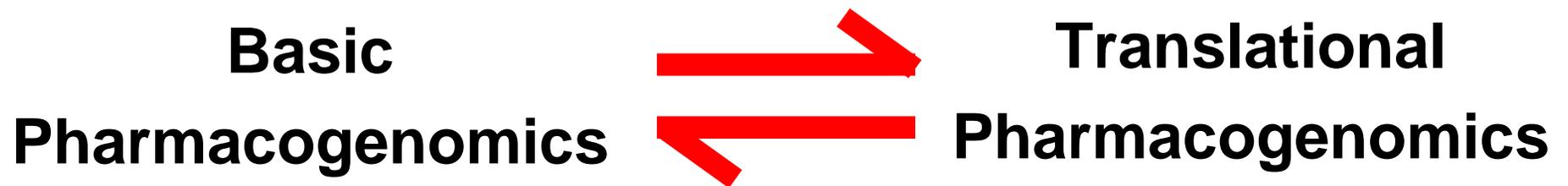


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Pharmacogenomics

Pharmacogenomic Research



Pharmacogenetics

Scientific Goal

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

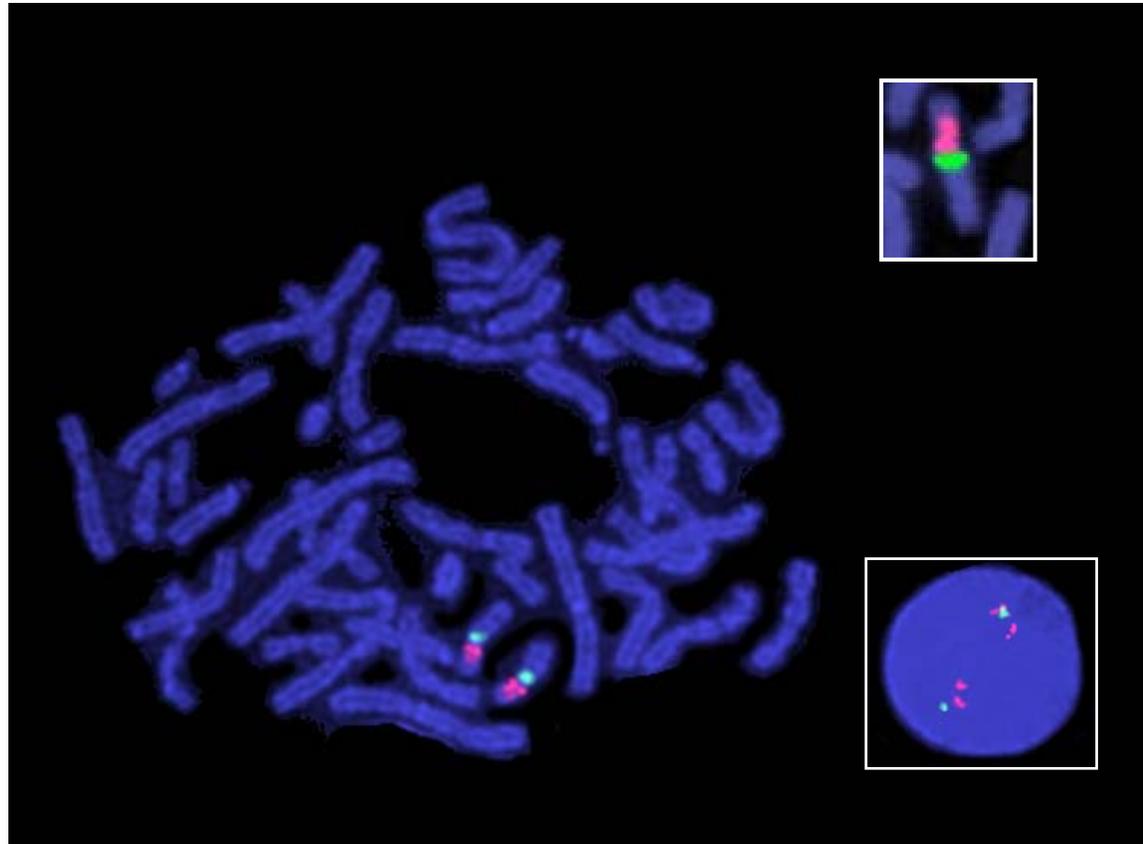
Genotype-Phenotype Correlation

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

Human *SULT1A3/1A4* FISH

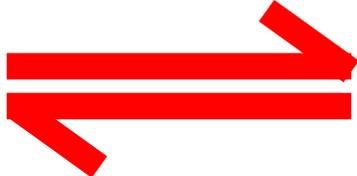


Biomedical Research

The NIH Roadmap

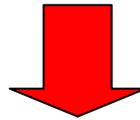
- New Pathways to Discovery – the need to understand complex biological systems.
- Research Teams of the Future – the need to explore new organizational models for team science.
- Reengineering the Clinical Research Enterprise – the need for multicenter, multigroup organization

Complementary Pharmacogenomic Research Strategies

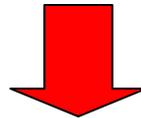
Phenotype  Genotype

Genotype-to-Phenotype Strategy

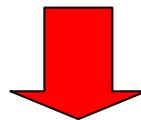
Gene sequence



Variation in gene sequence



Functionally significant
Variation in gene sequence

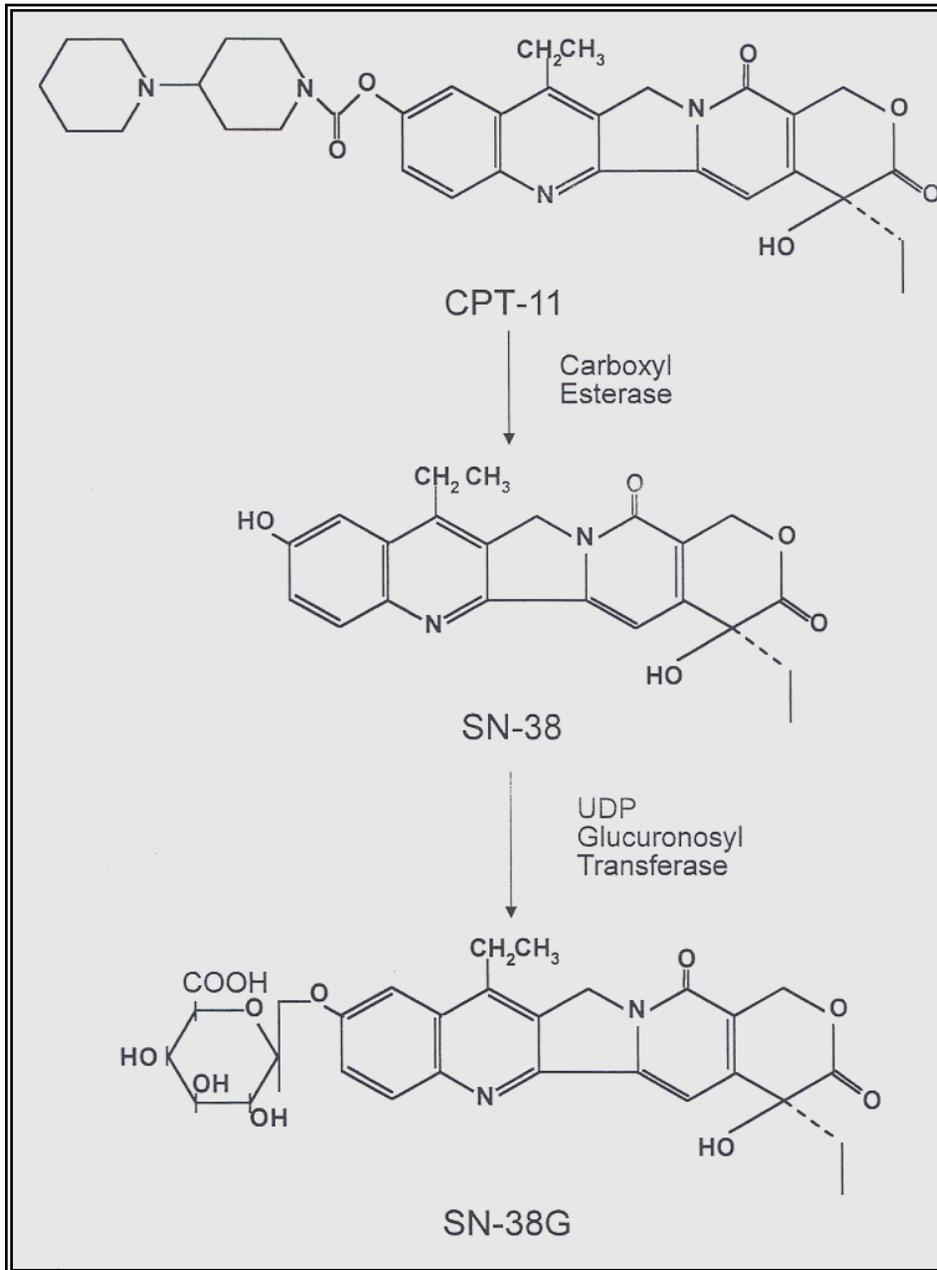


Clinical important functionally
Significant variation in gene sequence

Irinotecan Pharmacogenetics

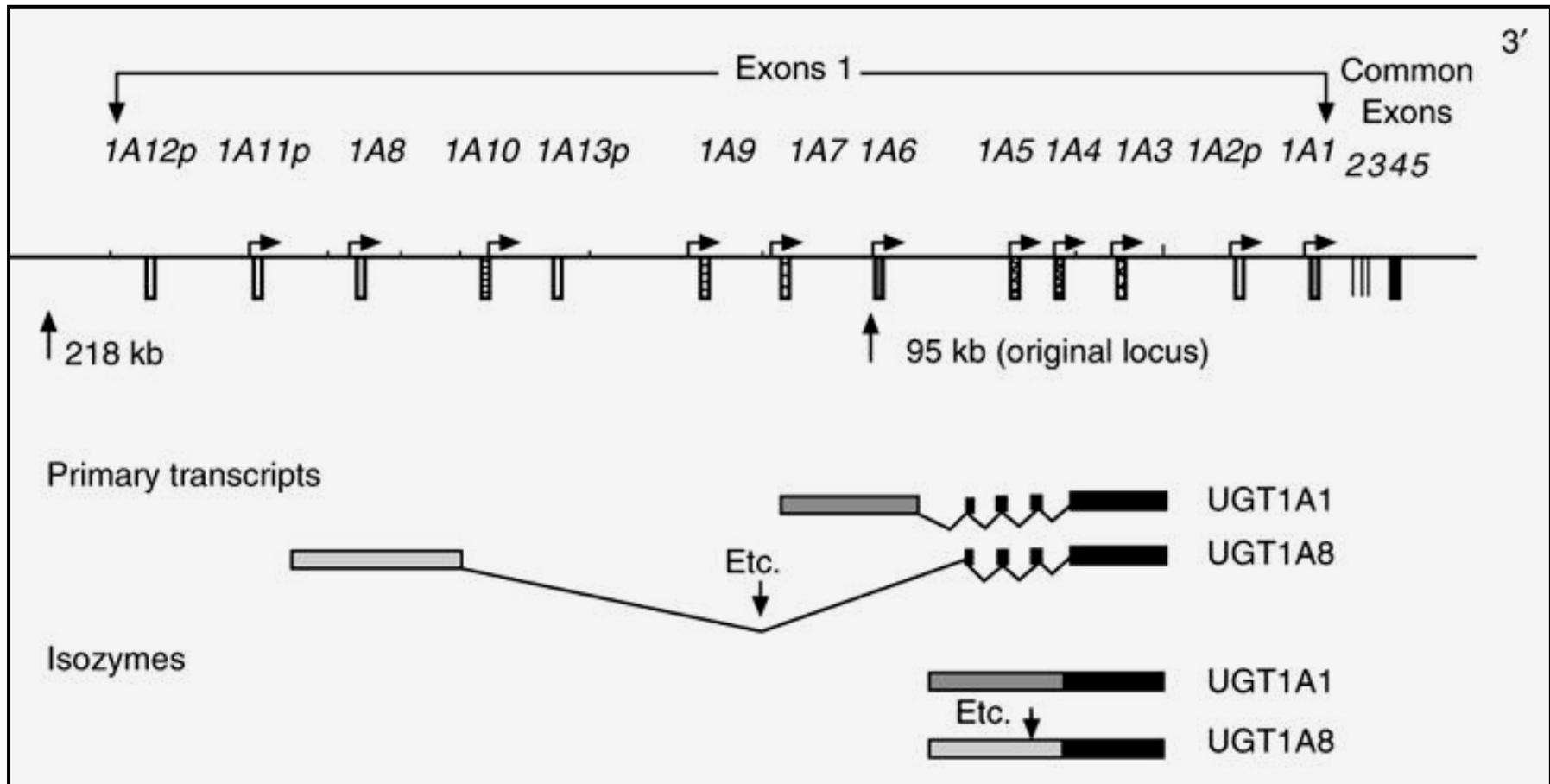
Irinotecan

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

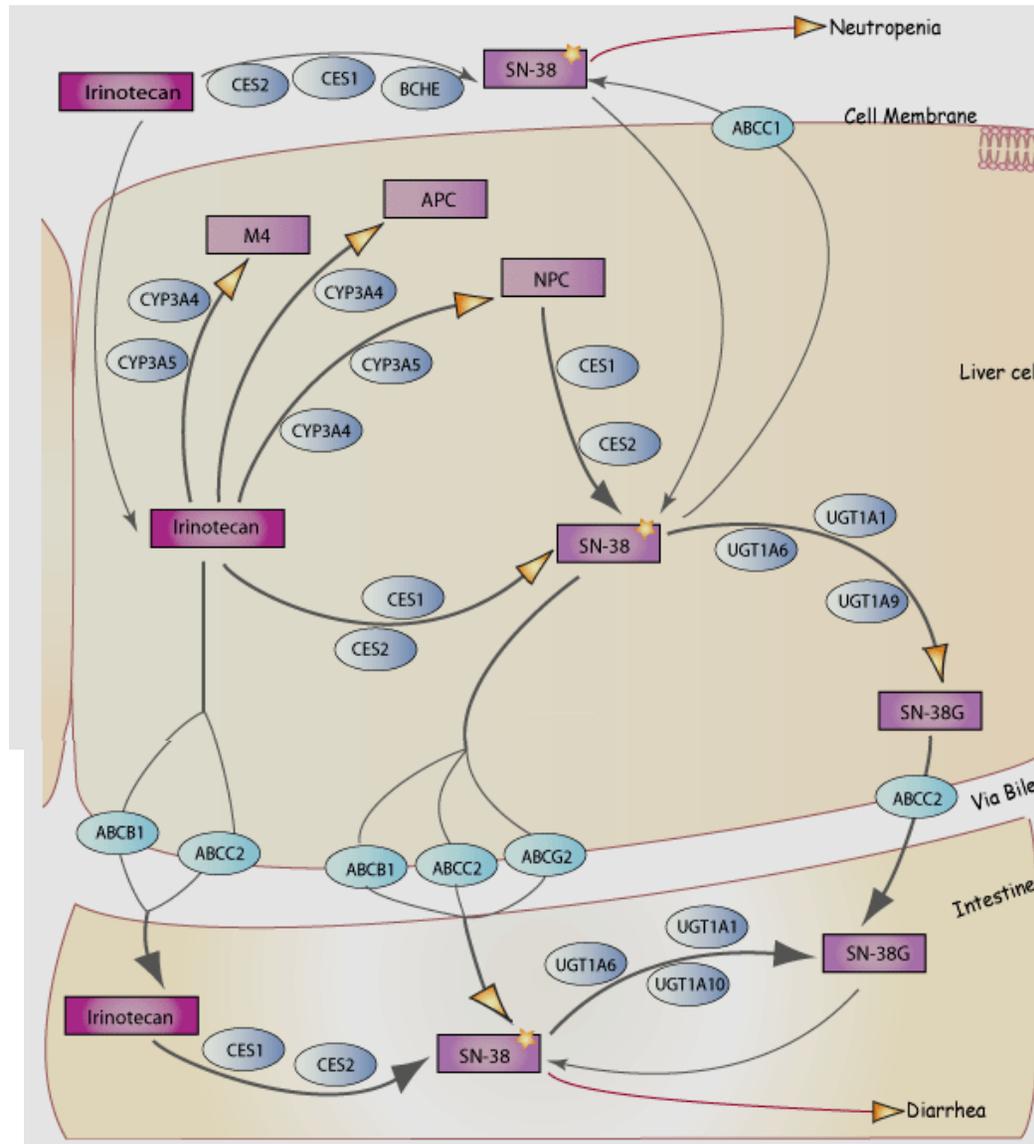


Irinotecan Biotransformation

Human UGT1A Locus



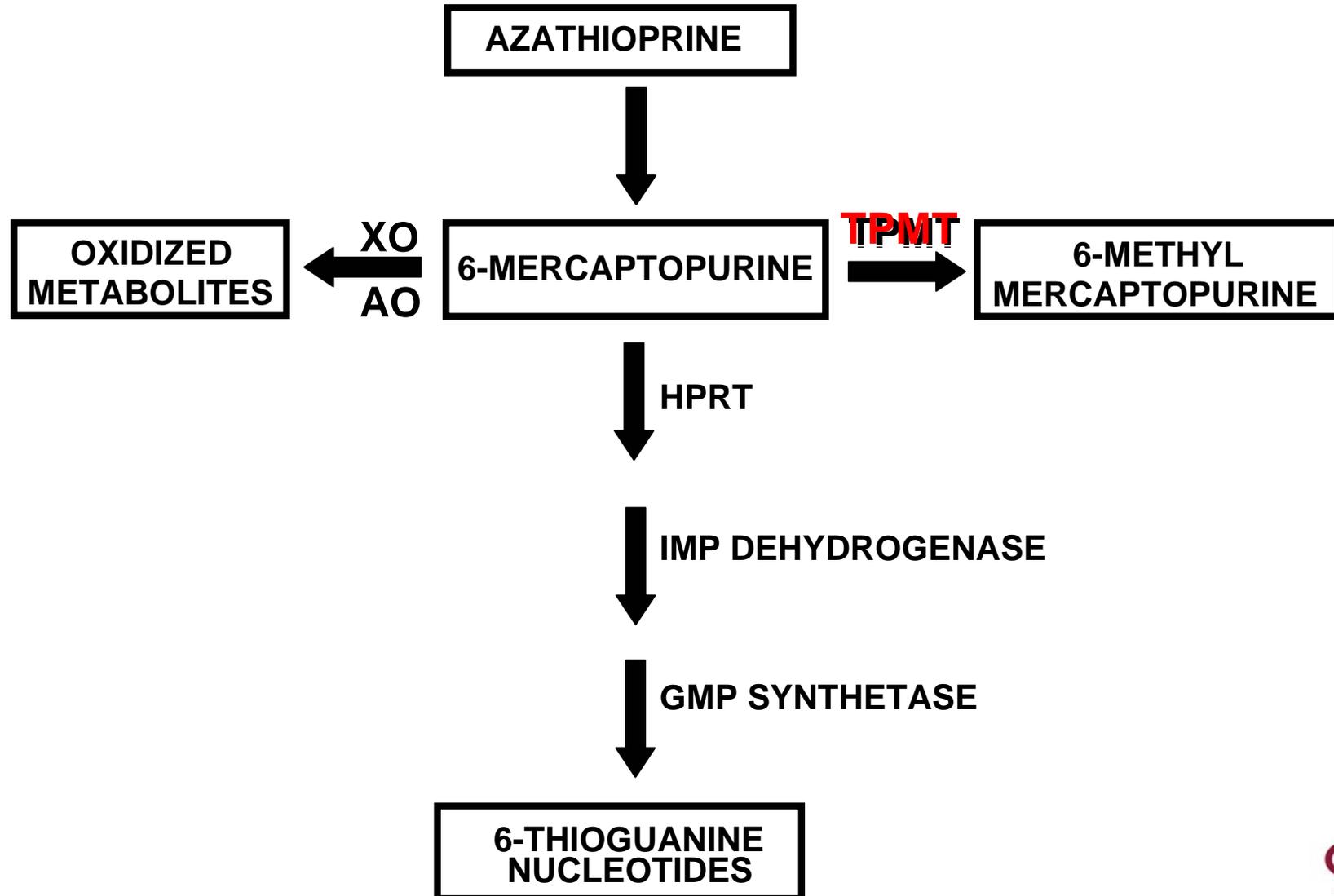
PharmGKB Irinotecan Pathway



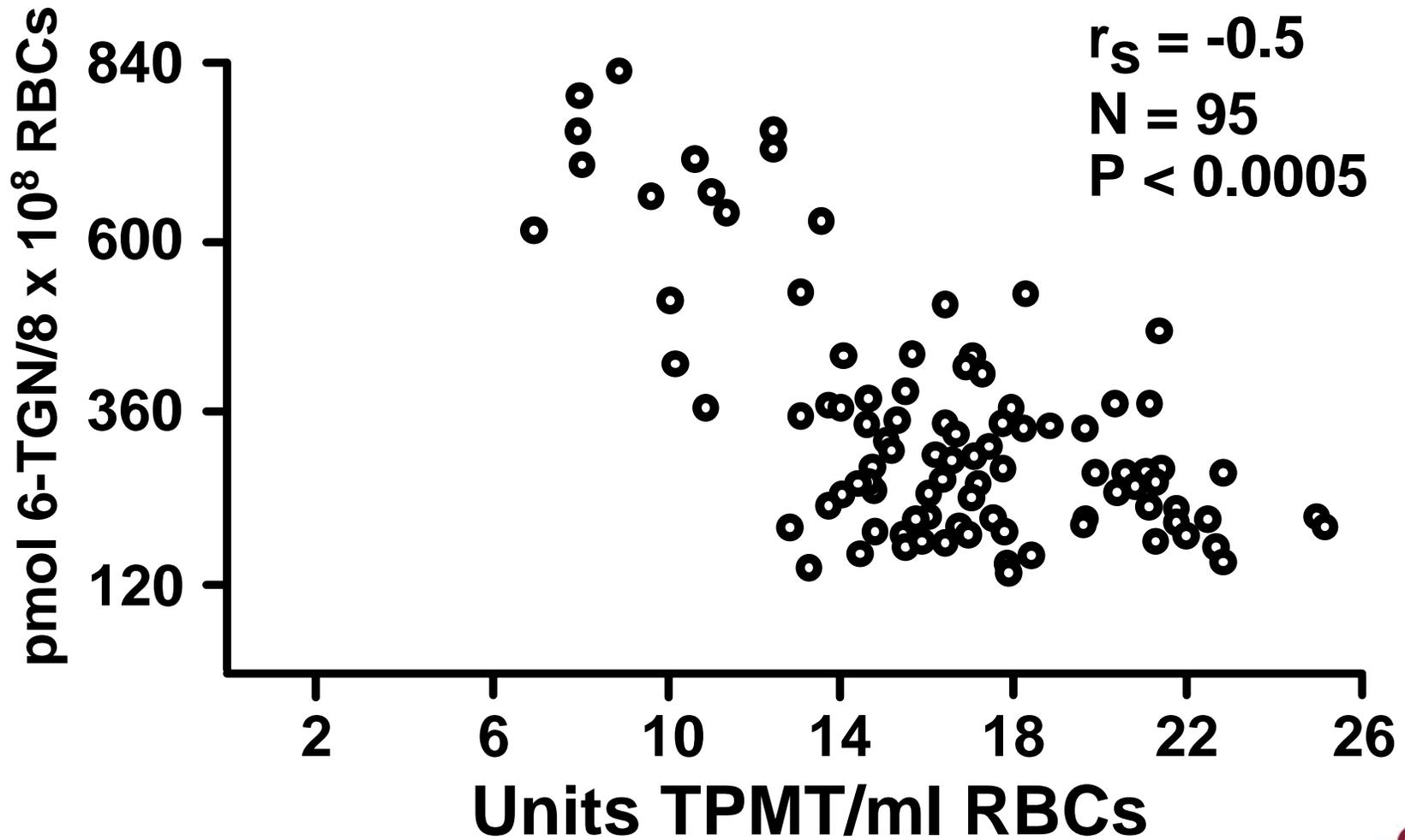
Pharmacogenetics-Pharmacogenomics

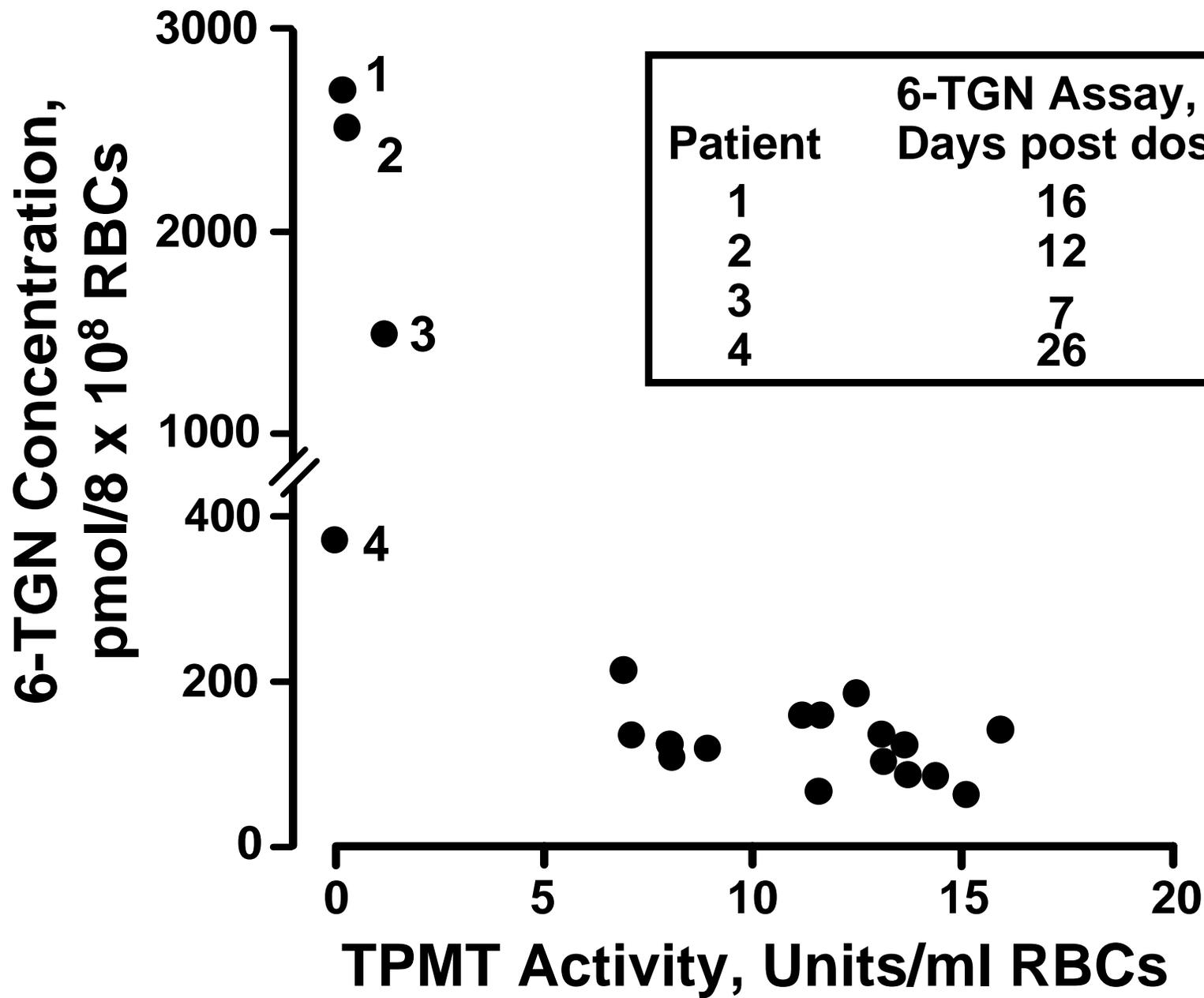
Thiopurine Metabolism and Metabolic Activation Pathway

Thiopurine Metabolism



TPMT in ALL





TPMT Pharmacogenetics

Translational Lessons

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

Modified “Central Dogma”

Genome (Genomics)



Transcriptome (Transcriptomics)



Proteome (Proteomics)



Metabolome (Metabolomics)

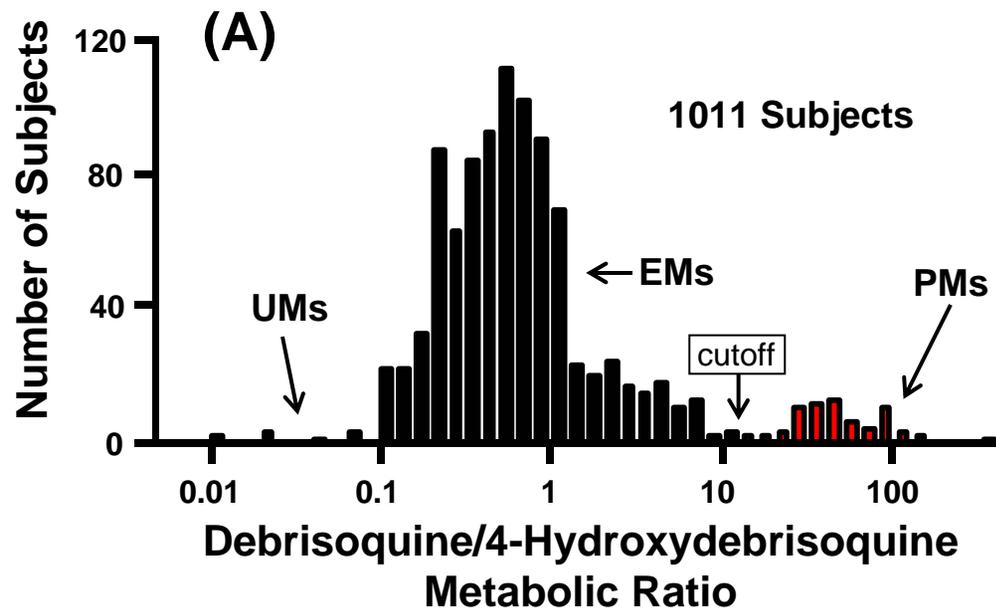


Pharmacogenomics Challenges and Opportunities

Clinical Assays

- **Phenotypes -- clinical and “intermediate”**
- **Genotypes and haplotypes**
- **Development and validation**

CYP2D6 Pharmacogenetics



AmpliChip CYP450 Array

(B)



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

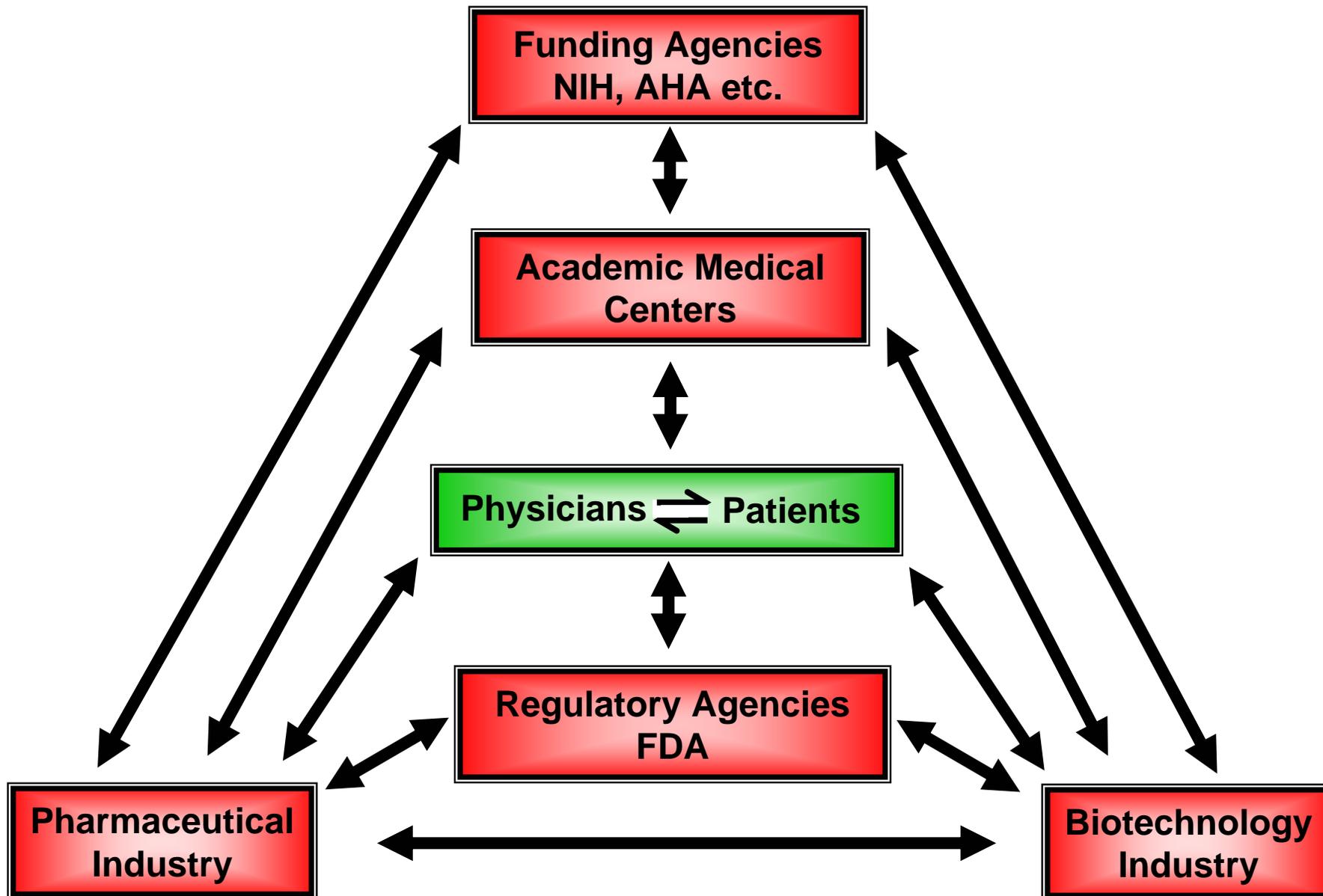
Lack of Pharmaceutical Industry Incentives

“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.



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

Ethical Challenges

- Confidentiality
- Insurance
- Therapeutic “activism”

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



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.**

New England Journal of Medicine

March 20, 2003

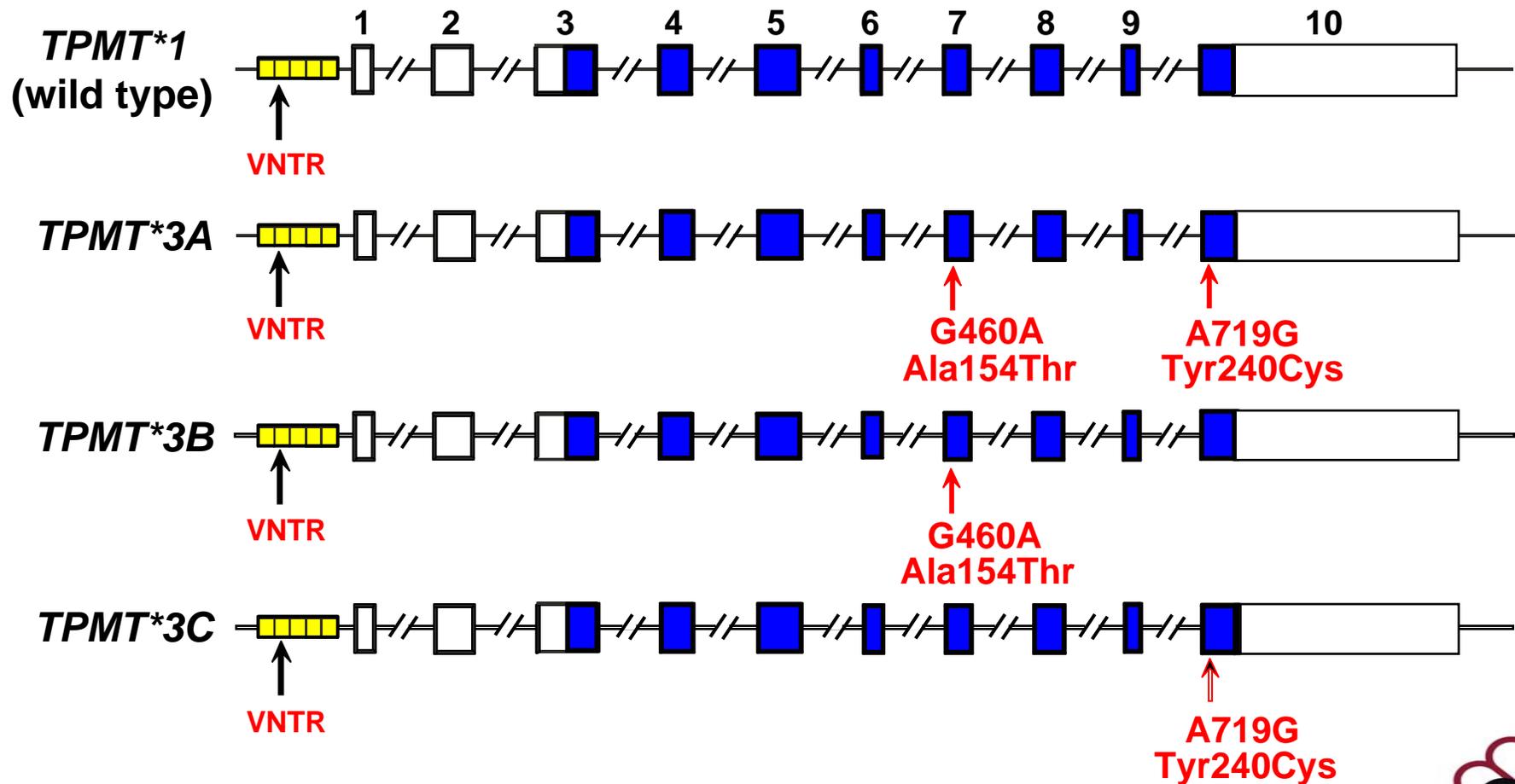
“Sounding Board”

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

“Perspective”

- **Medicine and the racial divide.**

Selected Human TPMT Alleles



Pharmacogenomics

Education

- Healthcare Professionals
- Patients

Patient Factors and Drug Effect

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

Pharmacogenomics

Clinical Goals

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

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

Pharmacogenomics

The Future

The Vision

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