Geographic Variations in Response and Toxicity of Anticancer Agents

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Japan-SWOG “Common Arm Analysis” of Paclitaxel/Carboplatin Therapy in Advanced NSCLC: A Model for Prospective Comparison of Cooperative Group Trials

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SWOG 0003: Phase III Trial of Paclitaxel/Carboplatin +/- Tirapazamine in Advanced NSCLC

→ Paclitaxel/Carboplatin

→ Paclitaxel/Carboplatin + Tirapazamine

Paclitaxel: 225 mg/m2 & Carboplatin: AUC = 6

Tirapazamine: 260 (1st cycle) → 330 mg/m2

Four Arm Cooperative Study (FACS) in Advanced NSCLC

→ Irinotecan/Cisplatin

→ Paclitaxel/Carboplatin

→ Gemcitabine/Cisplatin

→ Vinorelbine/Cisplatin

Paclitaxel : 200 mg/m2 & Carboplatin : AUC = 6

Toxicity Analysis

	FACS (N=145)	S0003 (N=186)	p value
Neutropenia (gr 4)	**102 (69%)**	**48 (26%)**	**<0.0001**
Febrile Neutropenia (gr 3-4)	**26 (18%)**	**6 (3%)**	**<0.0001**
Anemia (gr 3-4)	**22 (15%)**	**12 (6.5%)**	**0.010**
Platelets (gr 3-4)	16 (11%)	14 (8%)	0.270
Myalgias (gr 3-4)	3 (2%)	11 (6%)	0.084
Neuropathy (gr 3-4)	5 (3%)	30 (16%)	0.001

Treatment Delivery

	FACS	S0003	p value
Cycles delivered (median)	3	4	NA
% receiving > 3 cycles	**35 (24%)**	**100 (54%)**	**<0.0001**
% receiving 6 cycles	**16 (11%)**	**68 (36.5%)**	**<0.0001**
% patients dose reduced	pending	26%	--

Efficacy

	FACS (N=145)	S0003 (N=182)	p value
Complete Response (CR)	1 (0.7%)	3 (1.6%)	0.27
Partial Response (PR)	46 (31.7%)	59 (32.4%)	0.89
CR + PR	47 (32%)	62 (34%)	0.75
MST (months)	**12**	**9**	**NA**
1 year survival	**51%**	**37%**	**0.009**

CONCLUSION

- Variable results are not due to study design or conduct

- Variable results may be due to biologic and/or environmental differences

Pharmacogenetics

- Inherited variations in genes encoding:
  - Drug targets
  - Transport proteins
  - Metabolic enzymes
- And their contribution to the toxicity and/or efficacy of therapeutic agents.

Human Genetic Variation

- Each human person carries millions of normal variations in our DNA
  - Germline = inherited
  - Common variations = polymorphism
  - Stable in person during lifetime
    - except in reproductive organs and with errors in cell division (e.g. cancer)
  - Each parent passes ½ of their variations to their children

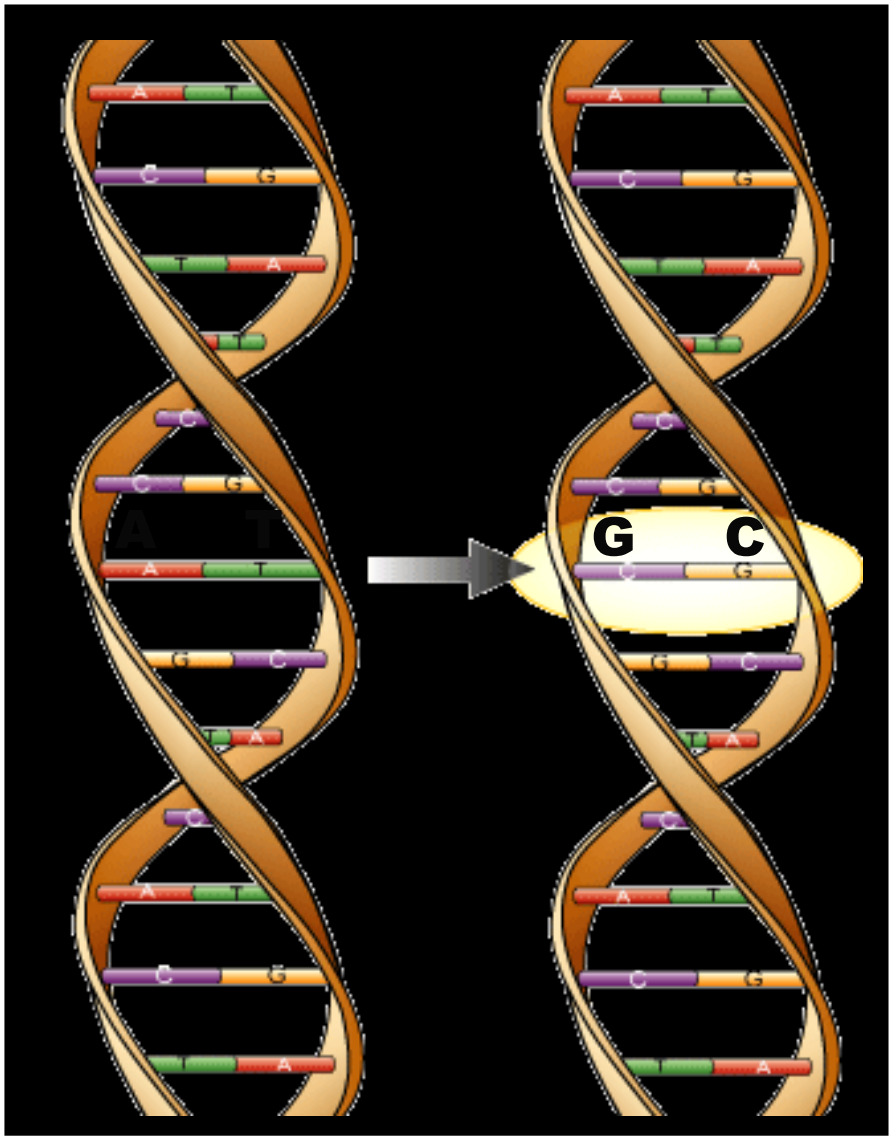
Human Genetic Variation

- 1 SNP in every 500-1000 nucleotides
- Homo sapiens 99.6-99.8% identical
- Human variation ~0.2 – 0.4% (3 billion nucleotides) gives ~10 million DNA variants
- 10% variation between population groups gives 1 million DNA variants

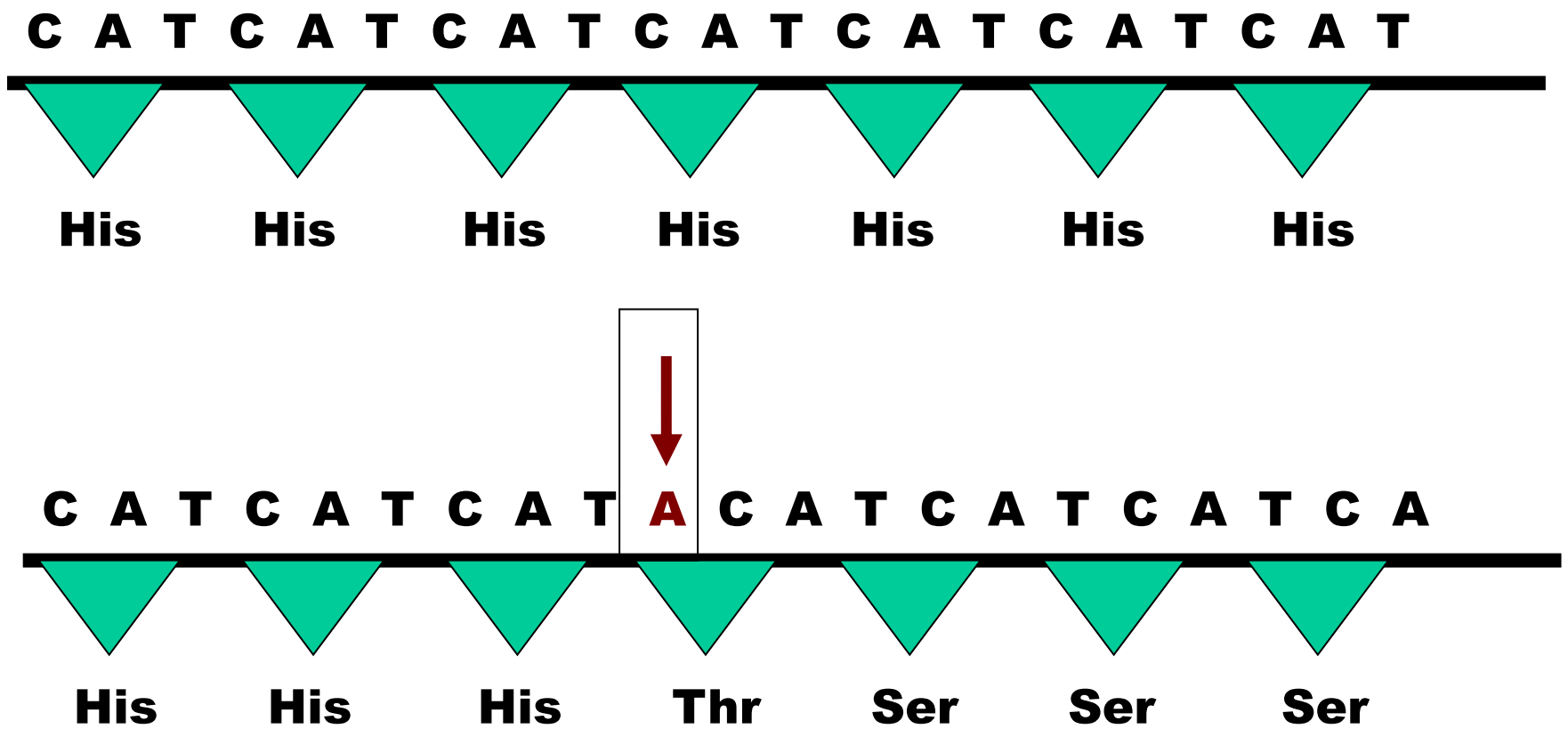
Single Nucleotide Polymorphisms

- A Single substitution in the DNA sequence

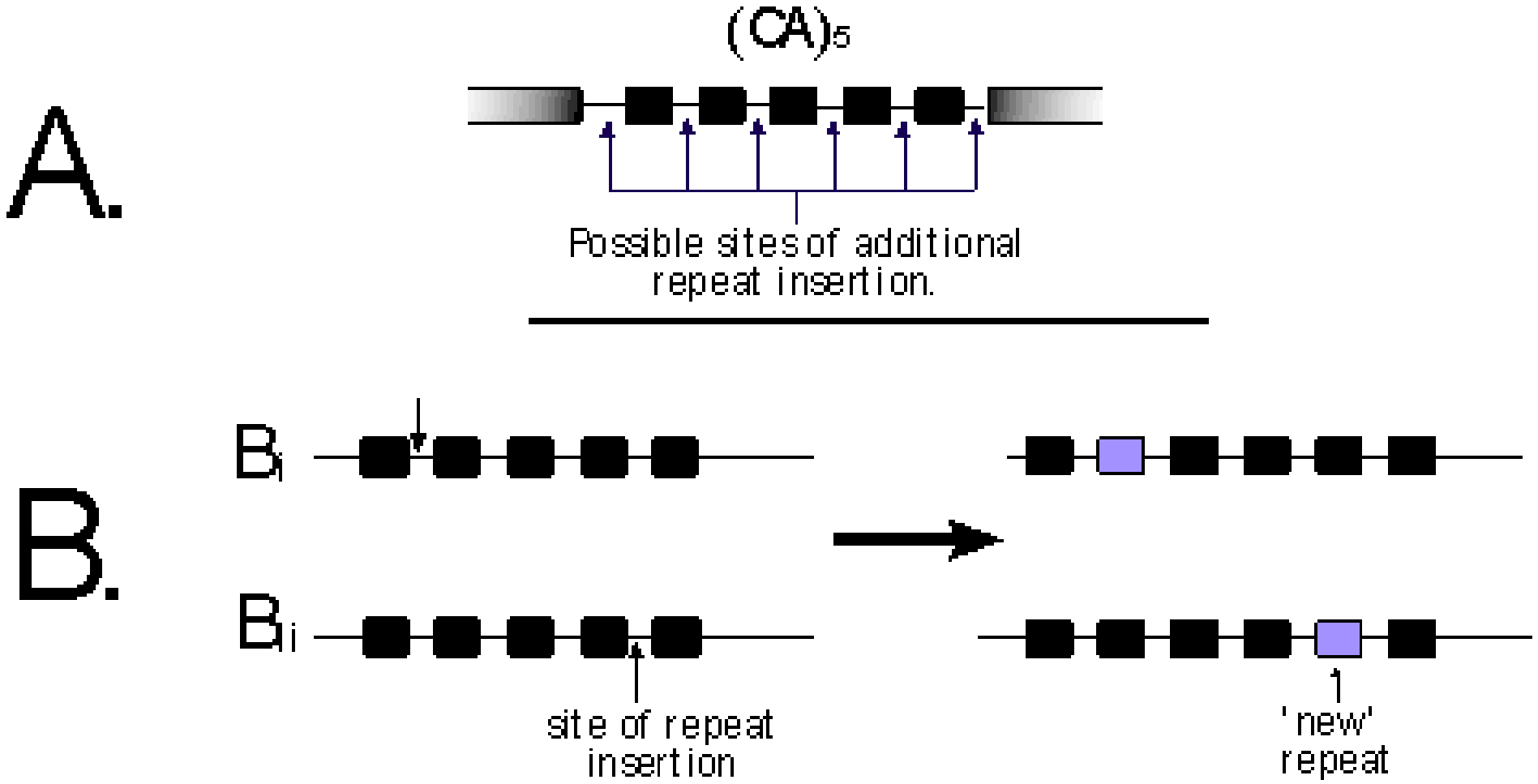
- A → C
- A → T
- A → G



Insertion (Deletion)



VNTR (Variable Number Tandem Repeats) Microsatellite



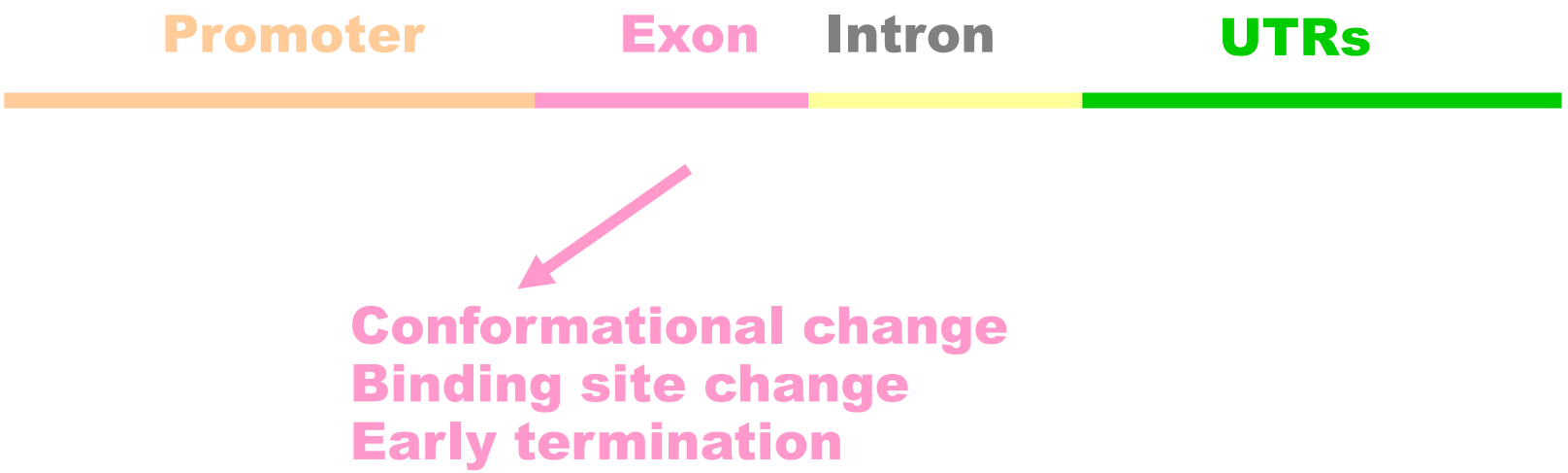
Copy Number Variants

- A duplication or deletion involving > 1kb of DNA

- If > 1% in reference population, Copy Number Polymorphism

- Non-homologous end joining
- Non allelic homologous recombination
- Can affect expression levels, function

Polymorphisms can alter function through multiple mechanisms



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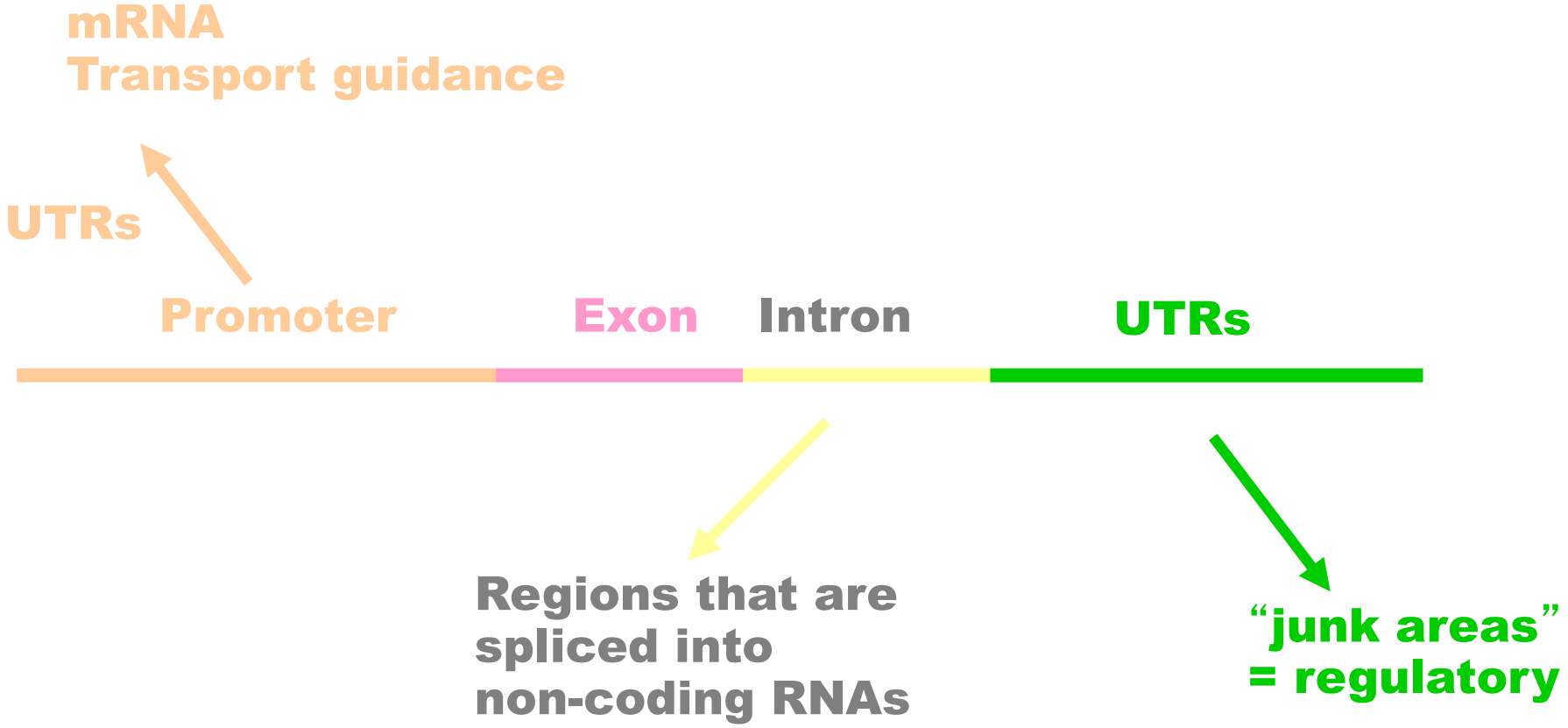


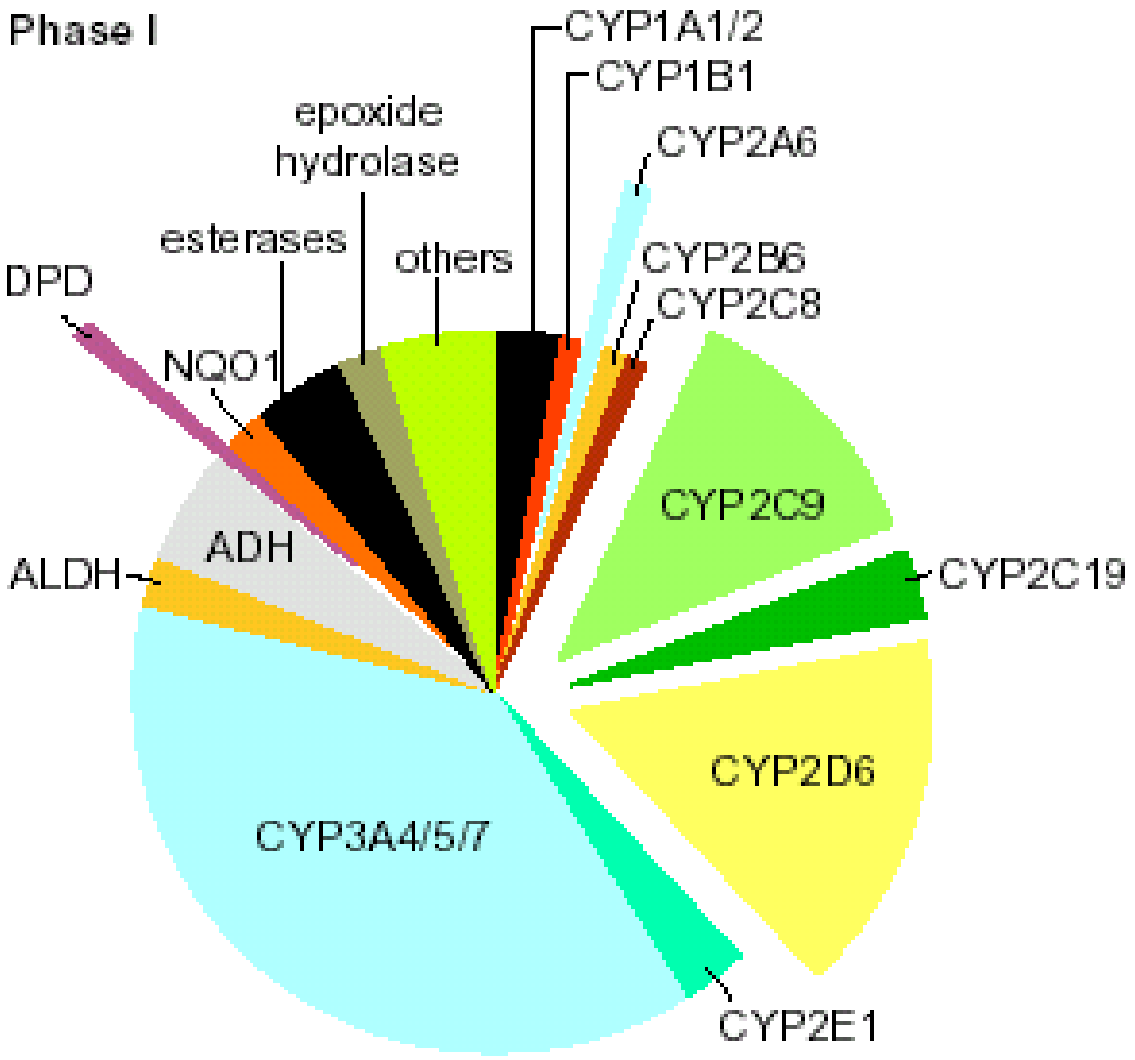
Pharmacogenetics and FDA

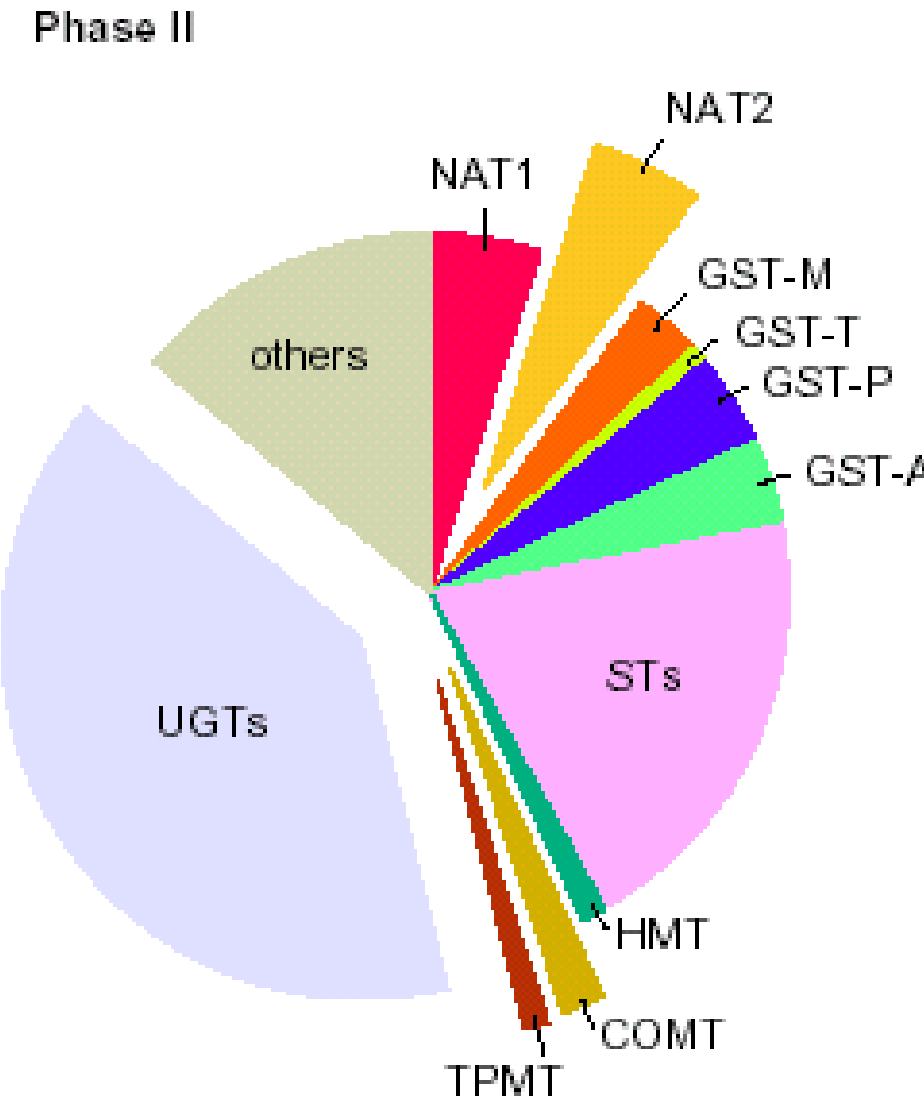
Hematology/OncologyDrugs with FDA label modifications

Drug	*Genetic Variation*	*Involved in:*	*Outcome*
6MP and AZA	*TPMT*	PK	Toxicity
Irinotecan	*UGT1A1*	PK	Toxicity
Coumadin	*CYP2C9 & VKORC1*	PK and PD	Toxicity
Tamoxifen	*CYP2D6*	PK	Efficacy

Modification

Conjugation





Tamoxifen

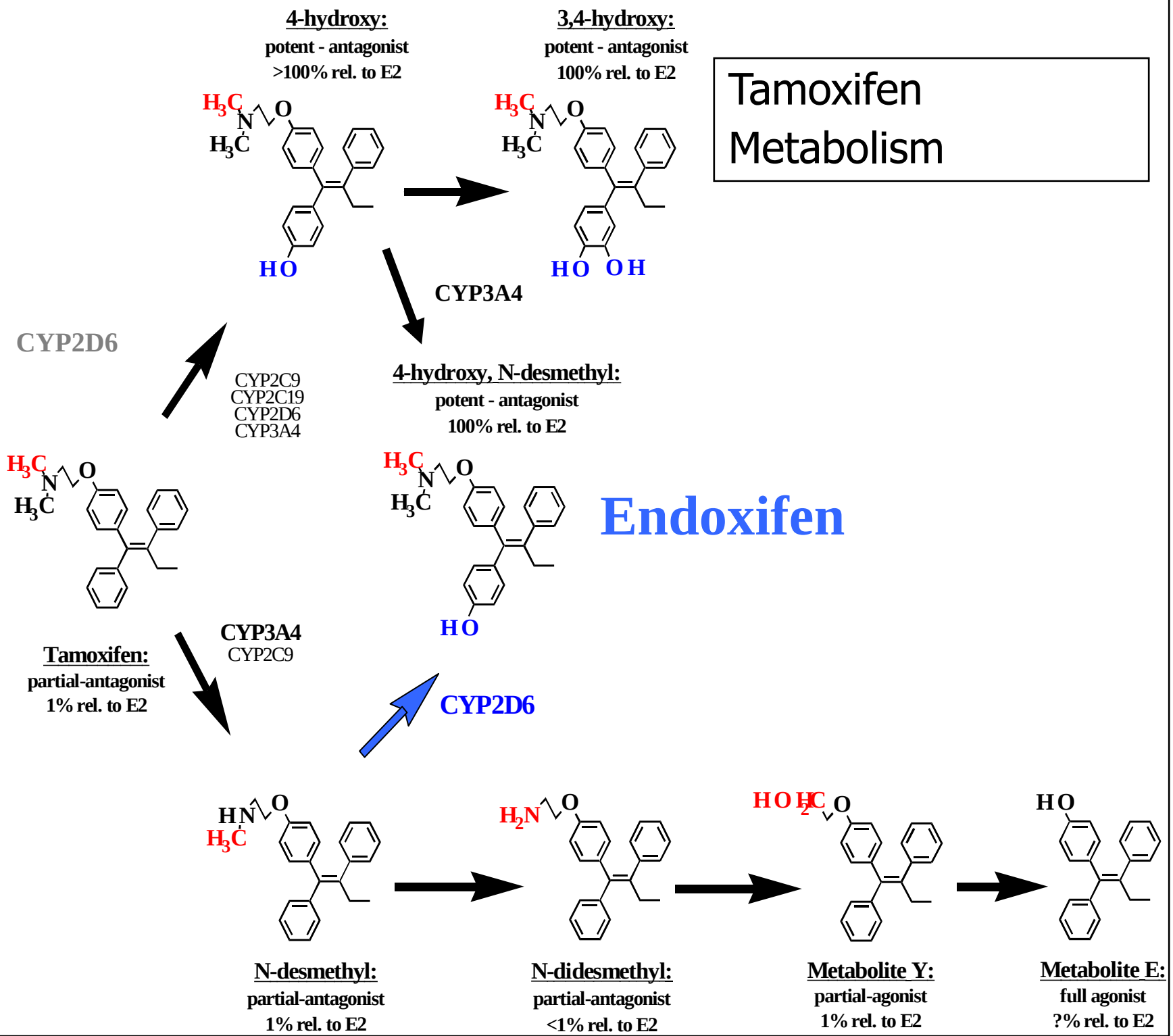
Approved since 1970s

Used widely in breast cancers
- metastatic, adjuvant, prevention

Complex metabolic pathway

Difficult to directly measure drug effects

Tamoxifen Metabolism



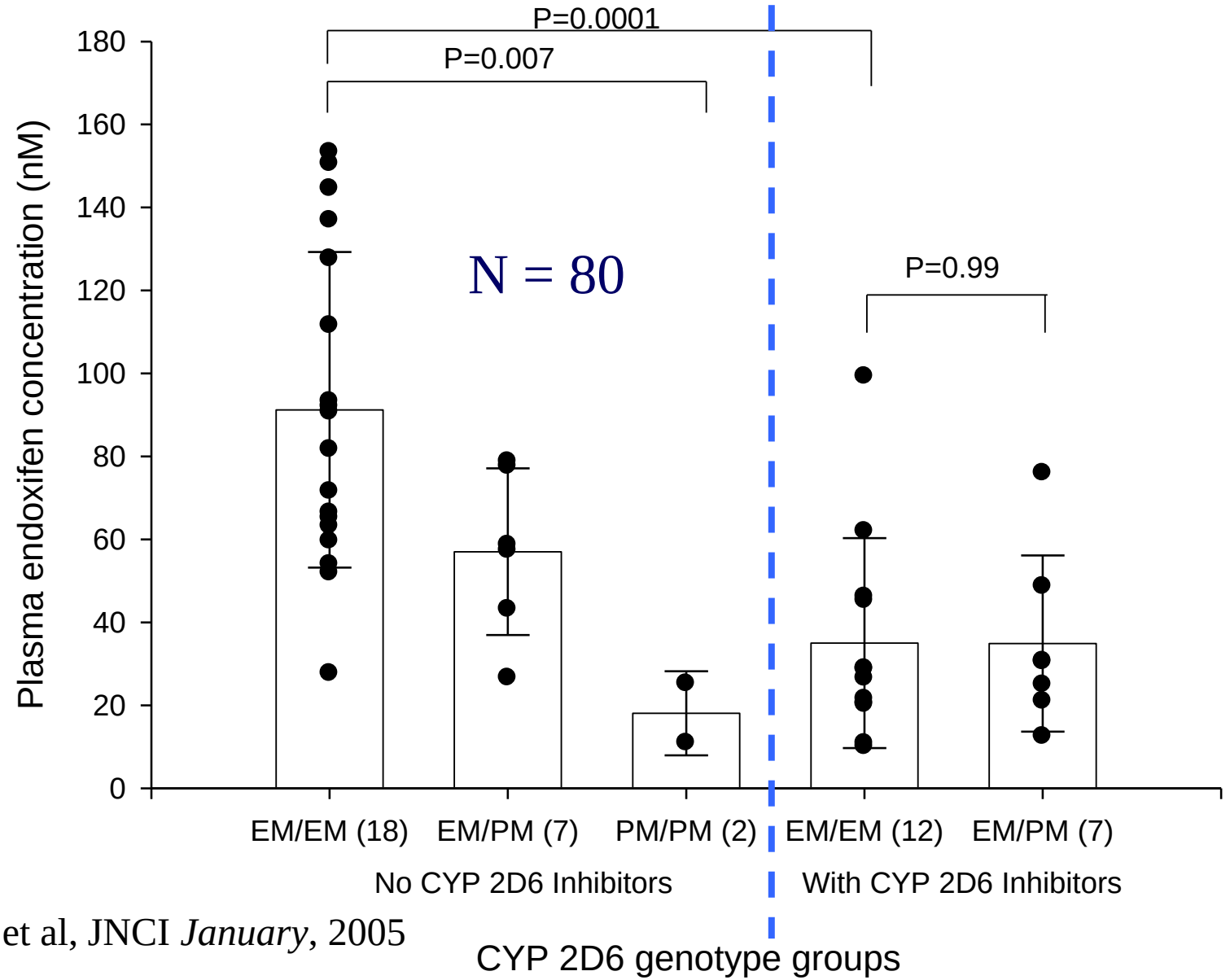
Distribution of *CYP2D6* alleles in different populations

Population	n	*4	*10	*17	Duplication
European Caucasians	589	0.207	0.015	--	0.021
American Caucasians	464	0.181	0.040	--	--
Turkish	404	0.113	0.061	0.001	0.008
Chinese	127	0.012	0.700	--	--
Japanese	206	--	0.386	--	0.01
Malays	107	0.028	0.495	0.005	--
Koreans	212	--	0.463	--	0.01
Ethiopians	122	0.012	0.086	0.09	0.136
Tanzanians	106	0.009	0.038	0.17	0.042
Zimbabwean	80	0.025	0.056	0.34	0.025

Bradford et al. Pharmacogenomics 2002, 3: 229-43
Lim et al. J Clin Oncol 2007, 25: 3837-45

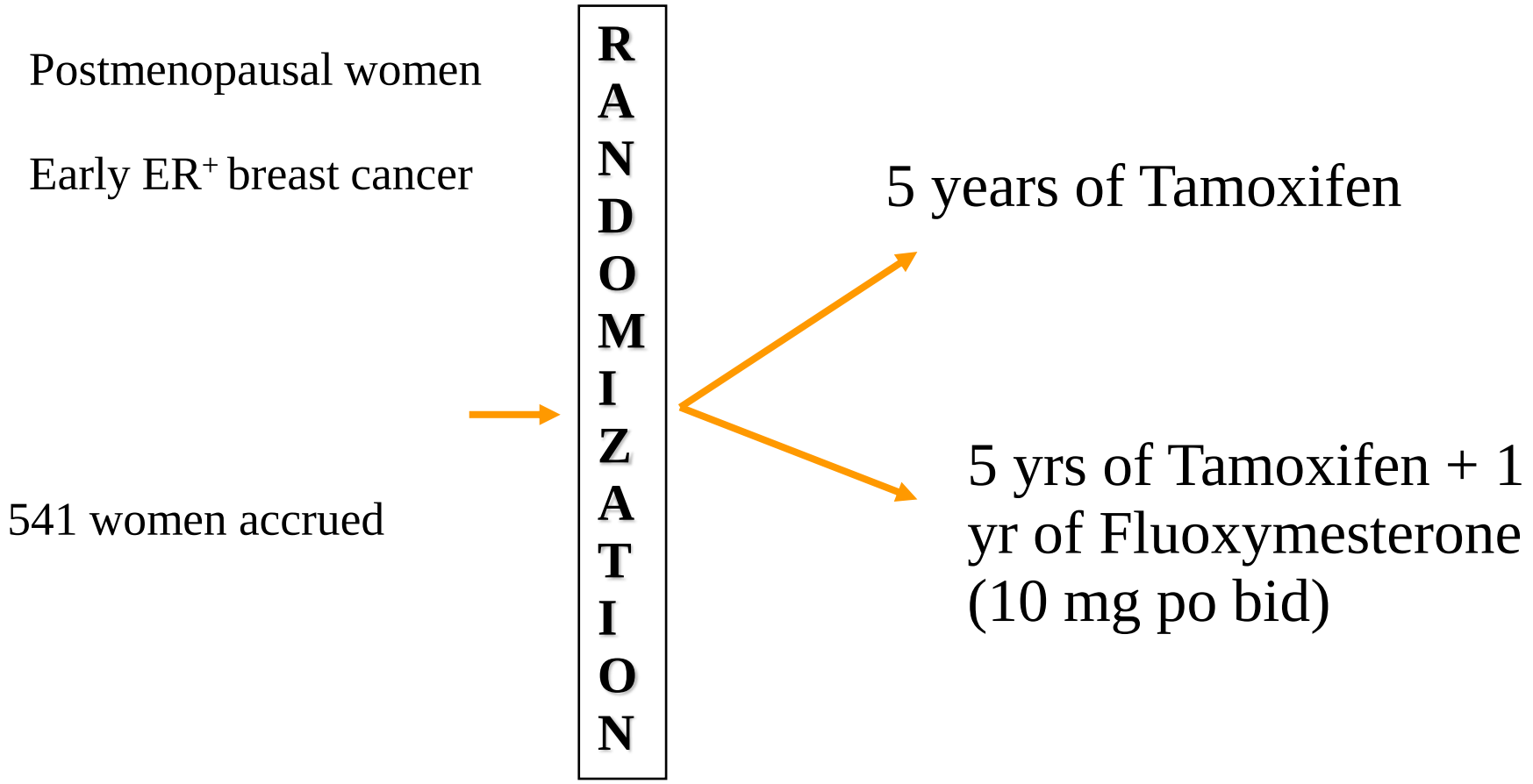
CYP2D6 variant genotype and CYP2D6 inhibitors lower Endoxifen levels

Figure 3

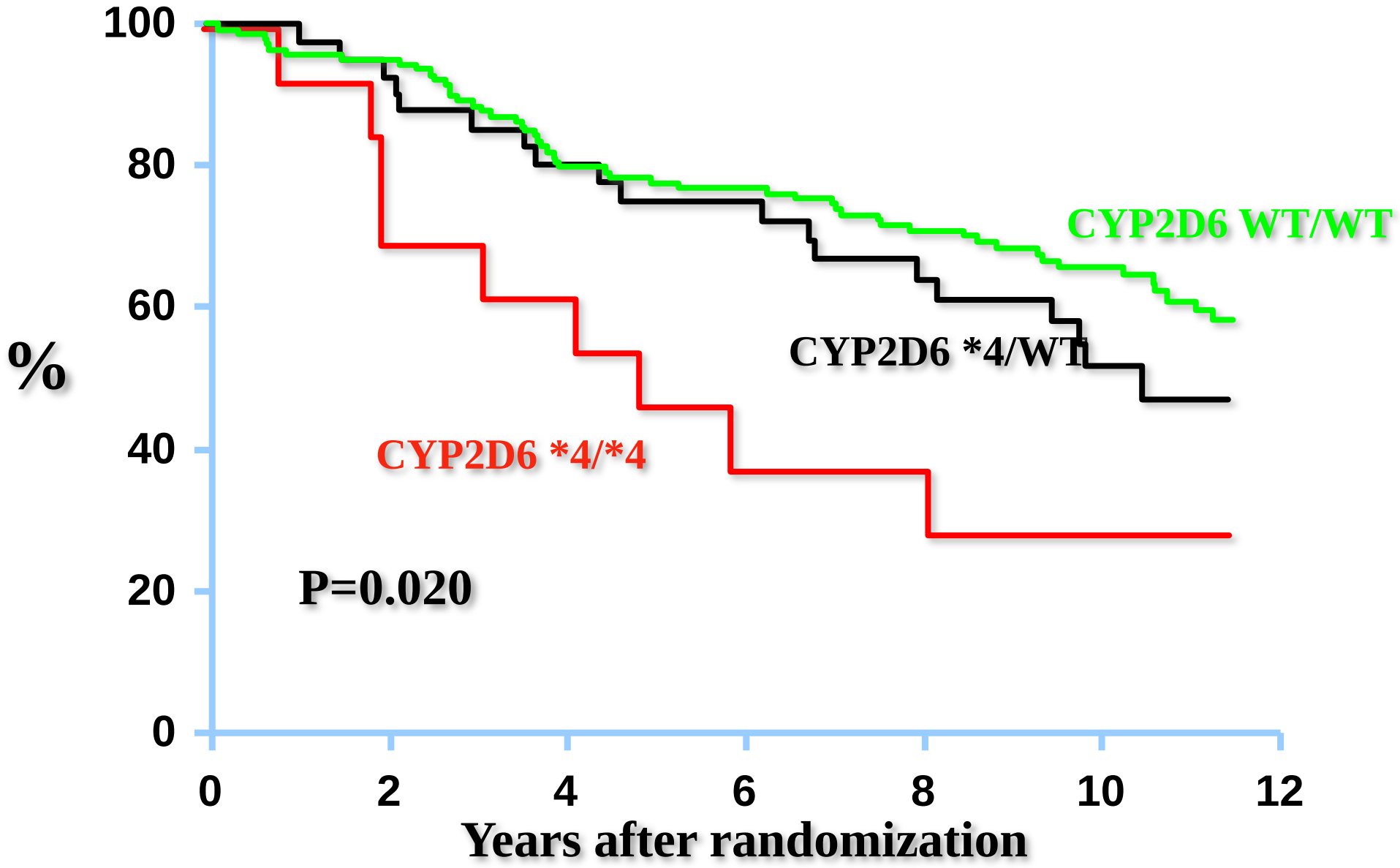


Jin Y, Desta Z, et al, JNCI *January*, 2005

A Trial where Tamoxifen Outcomes and Germline DNA were collected: NCCTG 89-30-52



Relapse-free Survival



Goetz et al J Clin Oncol. 2005;23(36):9312-8.

CYP2D6 and tamoxifen

Convincing association between *CYP2D6* genotype/phenotype with tamoxifen-related outcome

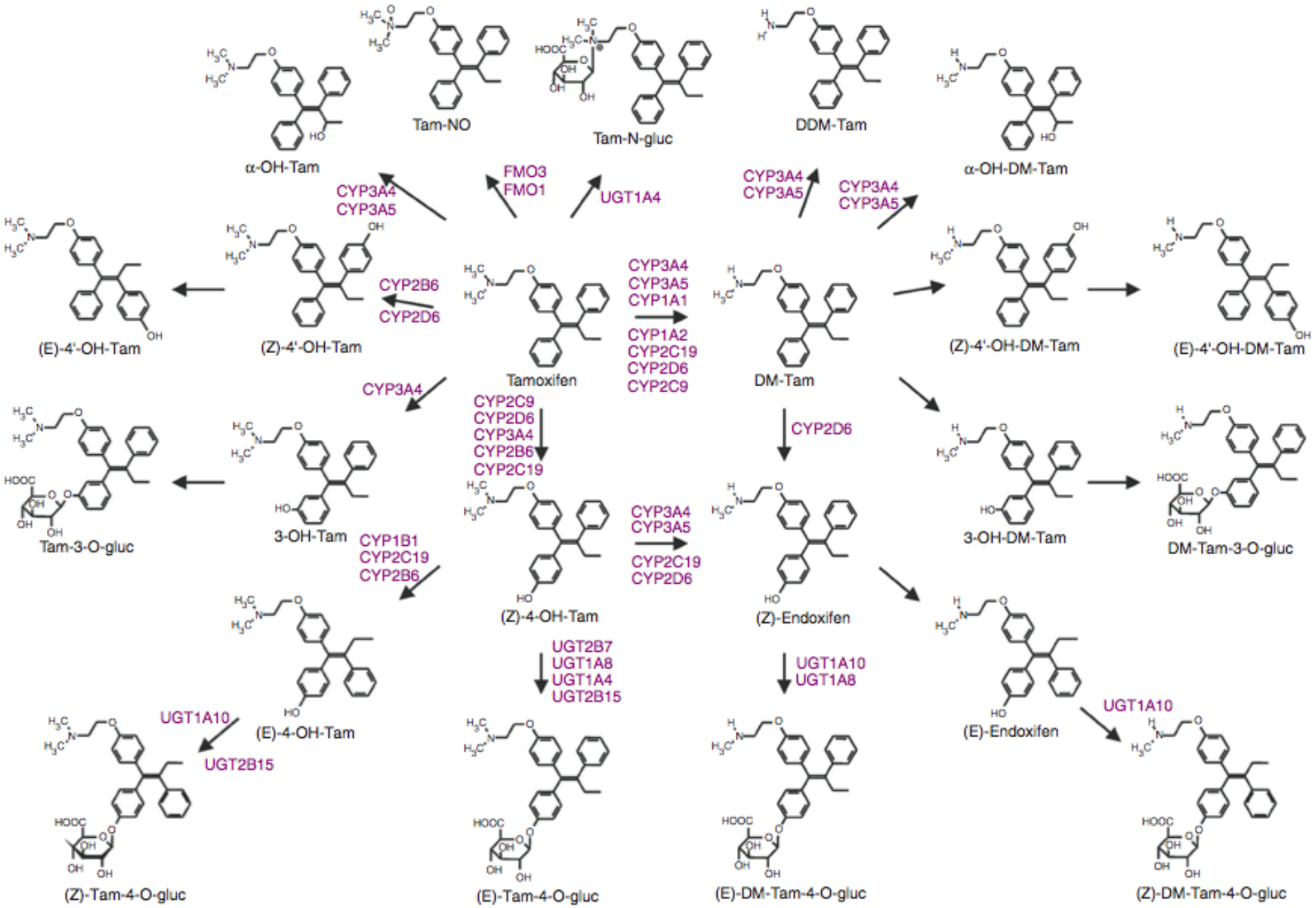
CYP2D6 testing commercially available

Proposal to update tamoxifen label to incorporate *CYP2D6* testing

No clinical guidelines or algorithm on management of patients with intermediate or poor metabolizer phenotypes

- *Increase dose?*
- *Use alternative agent (eg aromatase inhibitor)?*

Metabolism of Tamoxifen



Bridging studies

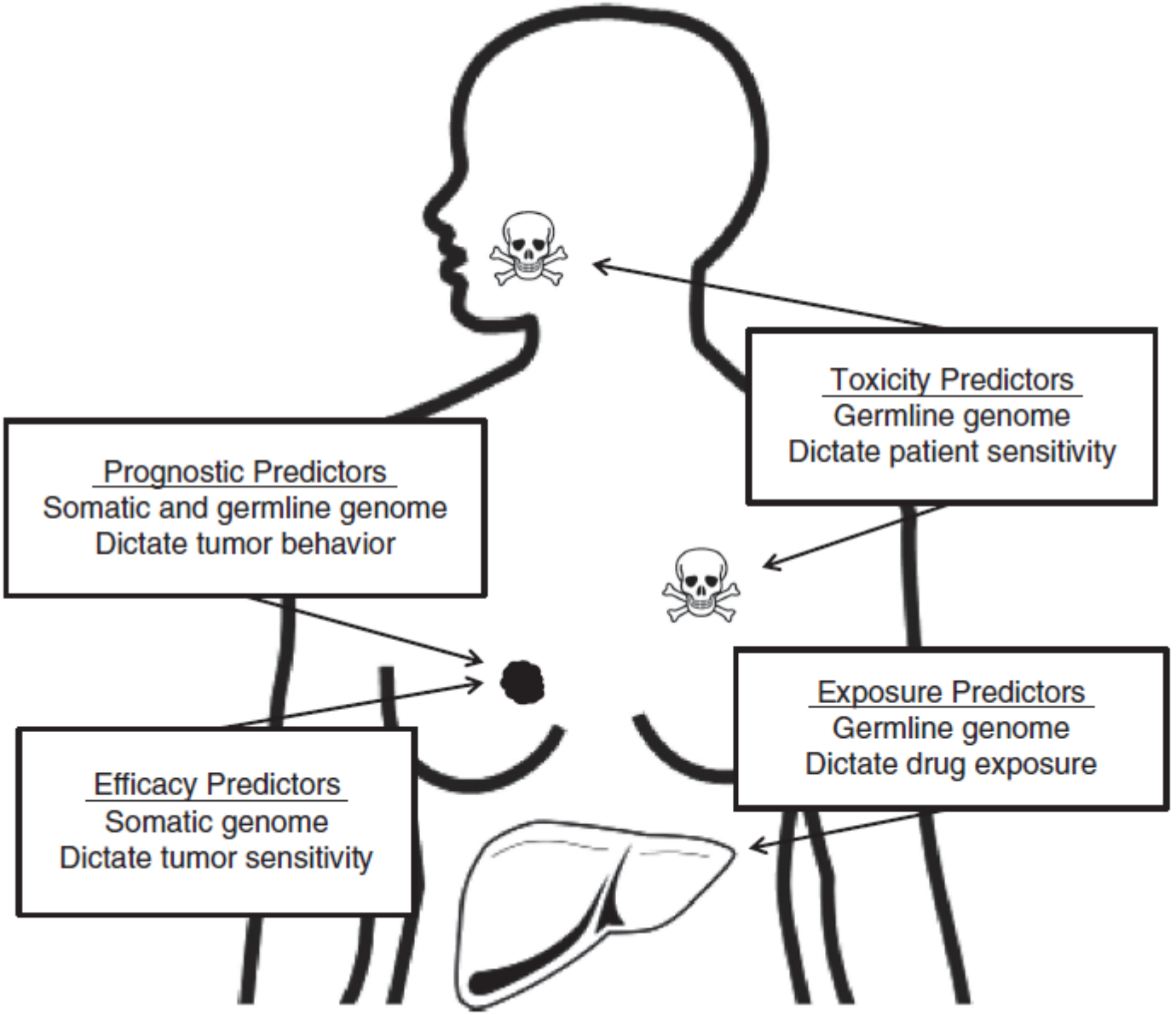
- Supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region

- Additional pharmacokinetic information may be included

Pharmacogenomics

The convergence of advances in pharmacogenetics and human genomics

Incorporating Pharmacogenomics into Clinical Care



Ethnic sensitivity (FDA E5)

- Nonlinear pharmacokinetics
- Steep dose-response curve for efficacy and safety
- Narrow therapeutic window
- Highly metabolized, especially through a single pathway(drug-drug interaction)
- Metabolism by enzymes known to show genetic polymorphism
- Prodrug, with the potential for ethnically variable enzymatic conversion
- High intersubject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple co-medications
- High likelihood for inappropriate use e.g.,analgesics and tranquilizers

Issues in using race/ethnicity to study drug response

- Social, cultural and political classification
- Correlation with geographical location
- Correlation with population genetic structure (ancestry)
- Issues of self reporting
- Population admixture
- Do genetic factors affect ethnic/racial groups similarly?