Pharmacogenetics

and its potential contribution to personalized management of neurological disease

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A customer says
to the pharmacist:

"Why does my medication have 40 side effects?"

The pharmacist replies:

“Because that's all we've documented so far."

What is pharmacogenetics (PGx)?

= Pharmacology + Genetics

Genetic predisposition to drug effects

Individualized pharmacotherapy

Revolutionize medicine

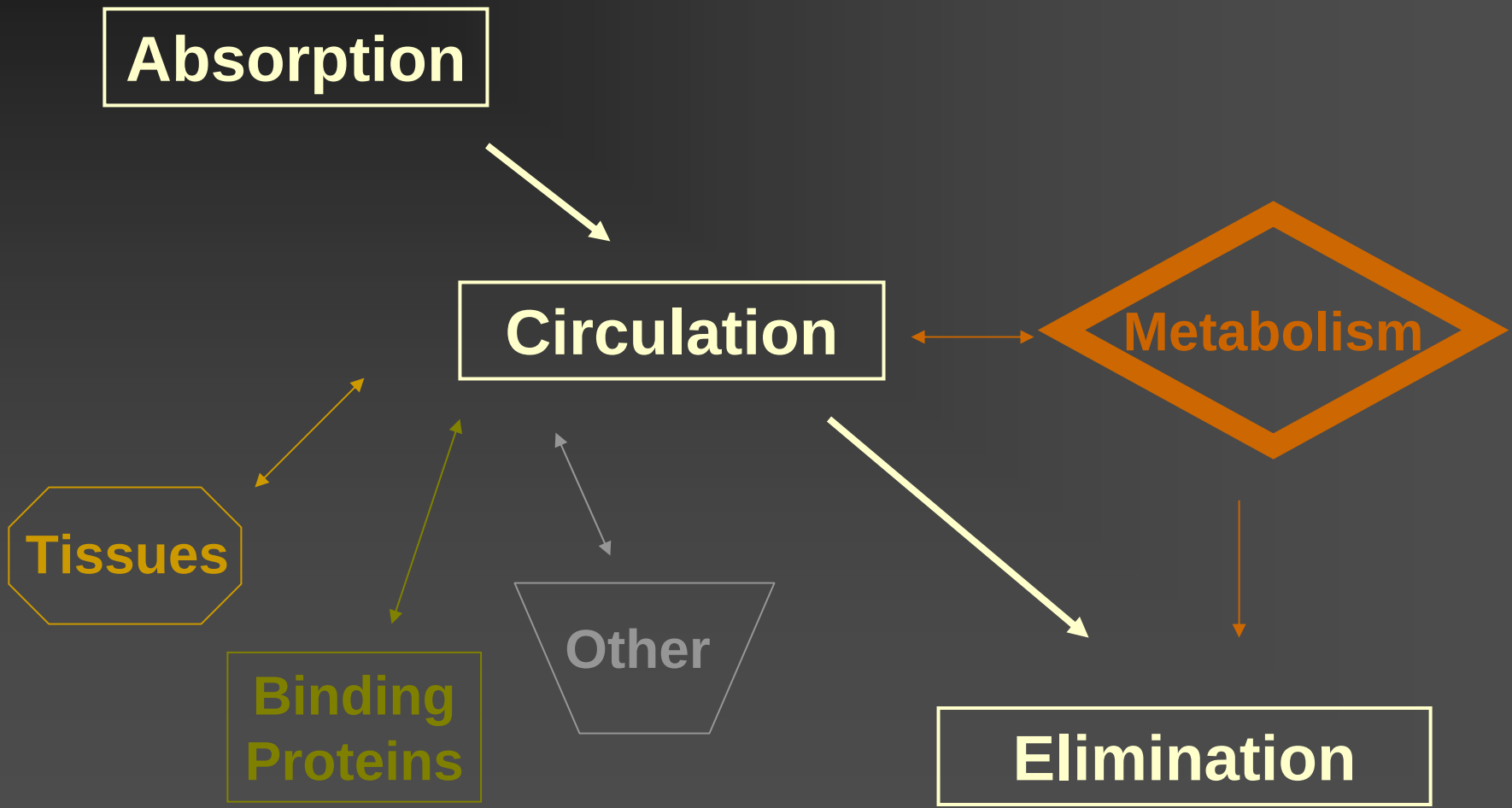
The right drug at the right dose,
the first time

Silent phenotypes

PGx contribution to therapeutics

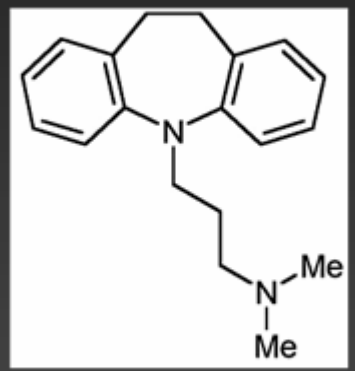
- Pre-therapeutic
  - Drug discovery
  - Drug development
  - Drug and dose selection
- Post-therapeutic
  - ADRs
  - Drug and dose selection

Drug handling = PGx targets



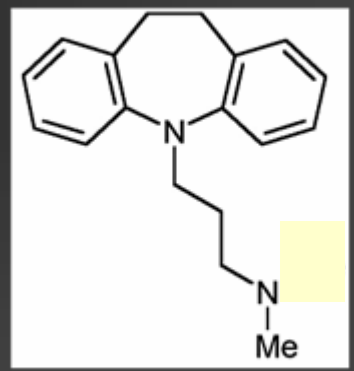
Metabolism of imipramine

imipramine



CYP3A4

desipramine



CYP2D6

inactive metabolites

CYP2D6

inactive metabolites

conjugation and/or elimination

Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy

"Impaired metabolism due to a genetically determined 'slow metabolizer' phenotype of CYP2D6… is suggested as a possible mechanism for…fatal accumulation of these TCAs"

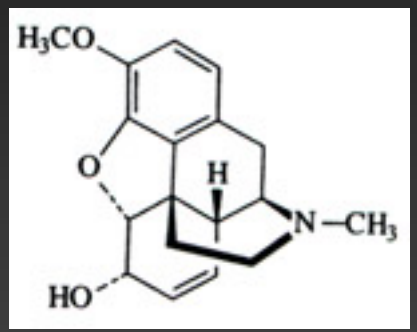
Swanson et al.

J Forensic Sci, 1997

42(2):335-9

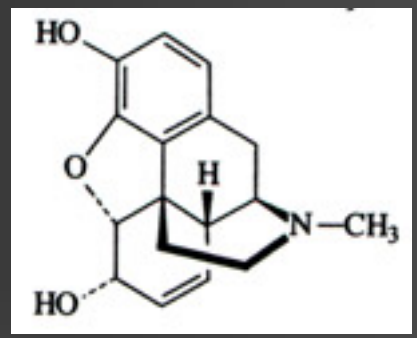
Metabolism of codeine

codeine



CYP2D6

morphine



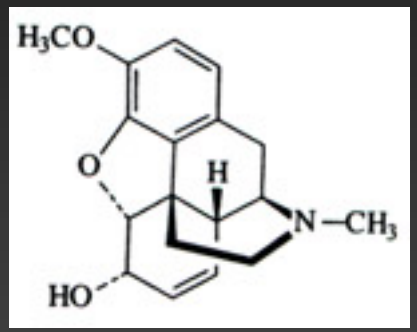
CYP3A4

norcodeine

conjugation
and/or
elimination

Metabolism of codeine

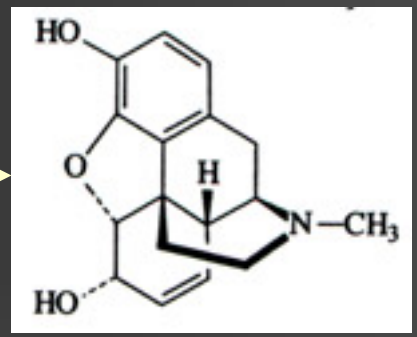
codeine



CYP2D6
CYP2D6
CYP2D6

CYP2D6

morphine



CYP3A4

norcodeine

conjugation
and/or
elimination

Codeine intoxication associated with ultrarapid CYP2D6 metabolism

"Life-threatening opioid intoxication development in a patient after he was given small doses of codeine for the treatment of a cough…"

Gasche Y et al.

N Engl J Med, 2004

351:2827-31

Clinical need for PGx

- Drug resistance, failure
- ADRs
- Polypharmacy
- Multiple clinical needs
- Drug dependency

www.rxlist.com/top200.htm

	# prescriptions filled in 2004 (USA)	rank
Hydrocodone	92,719,975	# 1
Alprazolam	32,404,743	12
Zoloft	29,877,707	14
Ambien	24,494,669	19
Lexapro	22,597,383	23
Celebrex	21,916,220	27
Fluoxetine	21,752,487	28
Lorazepam	18,873,635	33
Effexor XR	18,574,507	36
Clonazepam	15,968,529	43
Neurontin	15,476,692	44
Amitriptyline	15,086,803	46
Trazodone	14,450,339	48

Criteria for clinically useful PGx

- Good phenotype-genotype correlation
- Consequences of variant genotypes are severe and preventable by testing
- Frequency of variants high enough to justify testing

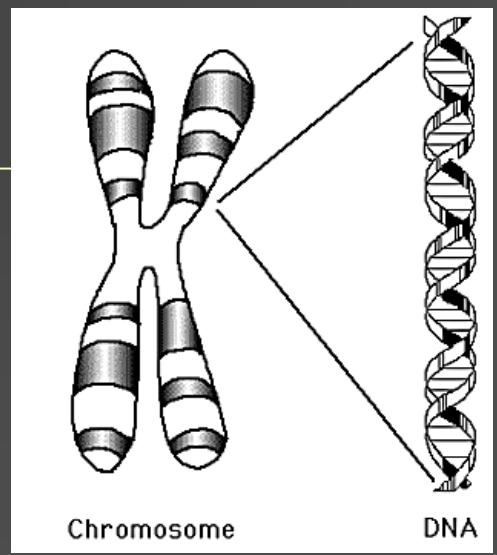
Approaches to PGx testing

I. Phenotyping tests
   such as TPMT, CYP2D6, G6PD, PChE

II. Monogenic tests
   such as *CYP2D6, TPMT, HER2, ABL, EGFR*

III. Polygenic panels
   such as several *CYPs*

IV. Polygenic panels
   based on applications
   and/or drug labeling



PGx for neurological disease

- What we can do NOW

CYPs

- What we may be doing in the future

Panels

Cytochrome P450s (CYPs)

Genetic variants are associated with altered drug levels, but not with disease

- CYP2D6: *25% of drugs*
- CYP2C9: *5%*
- CYP2C19: *15%*
- CYP3A4: *50%*

CYP phenotypes

Poor Metabolizer (PM): gene absent or produces nonfunctional protein

Intermediate Metabolizer (IM)

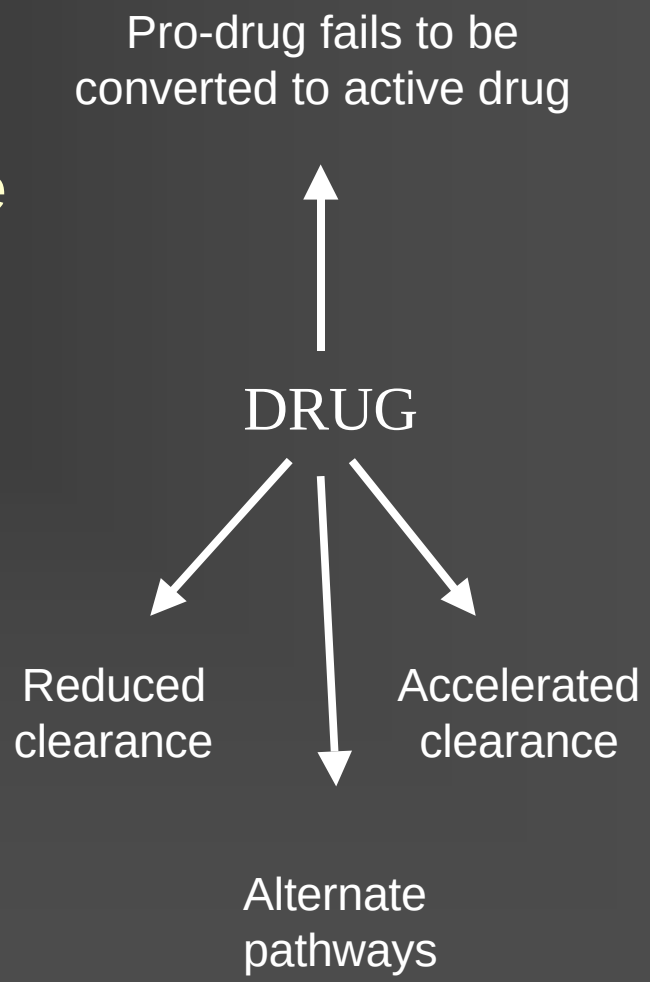
Extensive (normal) Metabolizer (EM)

Ultra-rapid Metabolizer (UM):
multiple copies of functional genes

Consequences of variant CYPs

- Inappropriate drug and metabolite concentrations
- Unanticipated metabolites
- Drug-drug interactions

- Non-compliance
- No or limited response
- ADRs



Alleles of **CYP2D6**

- More than 80 known
  - SNPs
  - INDELs
  - Complete gene deletion
  - More than 2 copies
- Clinical significance of most unclear

see http://www.imm.ki.se/CYPalleles

Frequency of variant CYPs

Gene	Allele	Enzyme activity	Caucasians		Asians		SouthEast Asian	African American		Midle East	
CYP2C9	*2	deficient	8-13%	17%			0.50%	1-4%			5%
	*3	deficient	6-10%	7%	1.7-5%	7.5%	10%	0.5-1.5%	5%		5%
CYP2C19	*2	deficient	13%	16%	32%	32.5%	20%	17%	15%		20%
	*3	deficient			6-10%	10%	5%				
CYP2D6	*3	deficient	2%	0.5%				2%			
	*4	deficient	12-21%	19.5%				1-9%	5%	3.5%	20%
	*5	deficient	4-6%	2%	5-13%	5%	10%	4-6%	5%	1%	0%
	*10	decreased	3%	1.5%	35-50%	48%	50%	6-10%	5%	3%	15%
	*17	decreased						34%	35%	3%	5%
	Dup	incresed	1-4%	1.5%	1-2%	1.6%		0.13	5%		5%

CYP allele detection methods

- PCR-RFLP
- Allele-specific PCR
- FRET probes
- Microsphere arrays
- Solid surface arrays
- Pyrosequencing
- Electrophoretic sequencing
- Nanoparticles

Using CYP genotypes

- Assign phenotype
- Extremes (PM, UM)
  - Avoid drugs that require that CYP
  - Adjust dose based on published guidelines
- IM and heterozygotes: interpretation is very specific to the patient and the drugs
  - Non-genetic factors
  - Clinical status
  - Penetrance

Drug levels important!

PGx and AEDs

- Metabolism
  - CYP2C9, CYP2C19, CYP3A4, UGTs
  - Risk of adverse effects
  - Drug-drug interactions
    - PB, PRM, PHT, CBZ induce CYPs
    - VPA inhibits many CYPs
    - Saturable or non-linear kinetics: PHT, CBZ, VPA
- Response, new drug targets
  - KCNQ2, KCNQ3
  - SCN1A, SCN1B, SCN2A
  - GABRB2

Example 1: phenytoin

- PGx targets: CYP2C9, CYP2C19, SCN1
- Consequence of variants:
  - More active drug, lower dose requirements
  - Nystagmus, ataxia, lethargy, seizures, coma, respiratory depression, paresthesia, arrhythmias, etc.
- Challenges to PGx interpretation
  - Inducer of CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6
  - Binds loosely to CYPs and to circulating proteins
  - Saturable kinetics

Example 1: phenytoin (cont.)

Genotype-based Dose Guidance:

2C9	2C19	Suggested dose
*1/*1	*1/*1	5.5 - 7 mg/kg/d
*1/*1	*1/*2 or *3	5 - 7
*1/*1	*2/*2 or *3	5 – 6
*1/*3	*1/*2 or *3	3 – 4
*1/*3	*2/*2 or *3	2 – 3

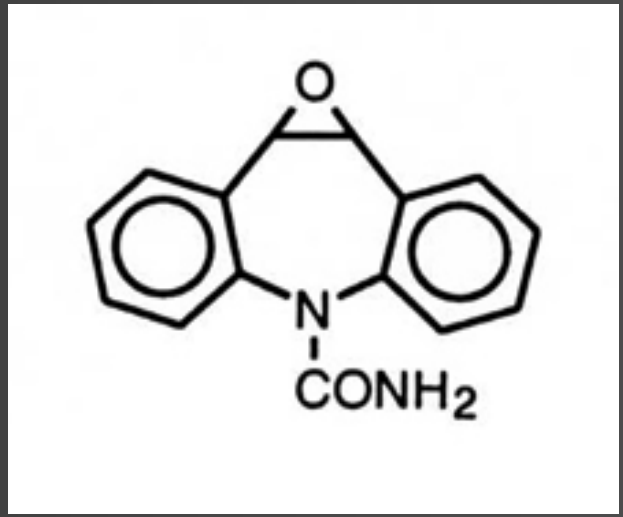
Hung C et al. *Ther Drug Monit* 2004, 26(5):534-40

Example 1: phenytoin (cont.)

CYP2C9		SCN1A IVS5-91G>A		Both
*1/*1	354 mg/d	AA	373	377
*1/*3	309	GA	340	297
*3/*3	250	GG	326	250

Tate SK et al. *PNAS* 2005, 102(15):5507-12

Example 2: carbamazepine



- Metabolism
  - 10,11-epoxide
    - Formation via CYPs
    - Innactivation via epoxide hydrolase
  - 9-hydroxymethyl-10-carbamoylacridan
  - Hydroxylation of aromatic rings

Example 2: carbamazepine (cont.)

- PGx target(s): CYP3A4, CYP2C9, EPHX1, SCN1A
- Consequences of variants:
  - CYPs: variants could produce less epoxide
  - EPHX1: Correlated with diol/epoxide ratios and activity

    Y113H (227T>C): reduced ratio, less (59%) catalytic activity

    H138R (416A>G, IVS3-114G>C, 1071C>T): more (123%) activity

    Nakajima Y et al. *Eur J Clin Pharmacol* 2005, 61:25-34
  - SCN1A: Correlated with maximum dose tolerated

    AA: 1313 mg/d

    GG: 1084 mg/d

Tate SK et al. *PNAS* 2005, 102(15):5507-12

PGx and antidepressants

- Metabolism
  - CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2, UDGTP
  - Risk of adverse effects
  - Drug-drug interactions
- Response, new drug targets
  - 5-HTT, 5-HTTPR, 5-HT2A
  - DRD2, DRD4
  - MAOA
  - TPH

Example 3: amitriptyline

- PGx target(s): CYP2C19 *and* CYP2D6
- Consequence of variants:
  - PM: more active drug
  - UM: less active drug
- Dose Adjustment (change from standard dose):
  - 2C19 2D6
    - PM: 53-92% 52-73%
    - IM: 81-98% 74-92%
    - EM: 98-109% 111-124%

Kirchheiner J et al. *Mol Psych* 2004;9:442-73

Example 4: nortriptyline

- PGx target(s): CYP2D6
- Consequence of variants:
  - PM: more active drug
  - UM: less active drug
- Dose Adjustment (change from standard dose):
  - PM: 42-59%
  - IM: 50-96%
  - EM: 119-149%
  - UM: 254%

Kirchheiner J et al. *Mol Psych* 2004;9:442-73

Example 5: fluoxetine

- PGx target(s): CYP2C19 *and* CYP2D6
- Consequence of variants:
  - PM: more active drug
- Dose Adjustment (change from standard dose):
  - 2C19 2D6
    - PM: 39-100% 56-84%
    - IM: 72-100% 87-96%
    - EM: 100-113% 107-119%

Kirchheiner J et al. *Mol Psych* 2004;9:442-73

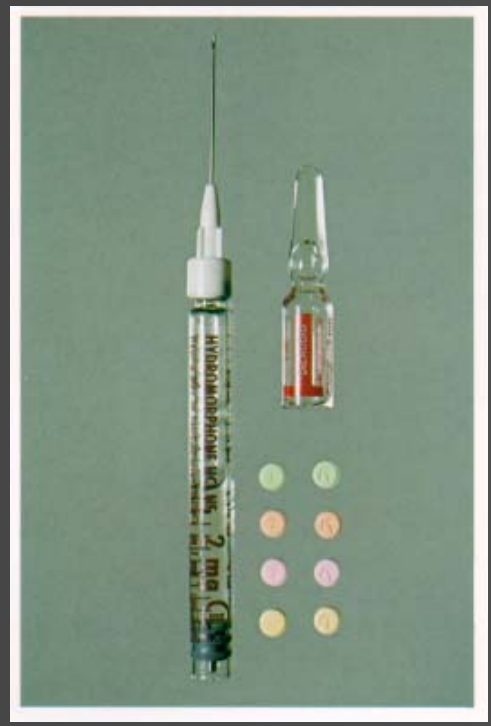
Example 6: citalopram

- PGx target(s): CYP2C19
- Consequence of variants:
  - PM: more active drug
- Dose Adjustment (change from standard dose):
  - PM: 61% 98%
  - IM: 84% 100%
  - EM: 108% 101%

Kirchheiner J et al. *Mol Psych* 2004;9:442-73

PGx and analgesics

- Metabolism
  - CYP2D6, CYP3A4, CYP2C9, UGT2B7
  - Risk of adverse effects
  - Risk of drug dependency
  - Drug-drug interactions
- Drug transporters
  - MDR1, MRP1-3, OAT1-3 for narcotics
- Response, new drug targets
  - OPRM1, OPRD1
  - 5-HTT, NMDA



Example 7: codeine

- PGx target(s): CYP2D6
- Consequence of variants:
  - PM: no active drug
  - IM: less active drug - approximately 20% lower concentrations of morphine than in EM
  - UM: more active drug - up to 800% higher concentrations of morphine than in EM
- Dose Adjustment (change from standard dose):
  - PM: Select a different drug
  - IM: Modest decrease - 100%
  - EM: 100 %
  - UM: Dramatic decrease in dose or a different

CYP2D6 PMs and other narcotics

- Hydrocodone, Oxycodone, Dihydrocodeine, Tramadol - potentialy decreased analgesia due to less conversion to active metabolites
- Morphine, Oxymorphone, Hydromorphone, Buprenorpine, Fentanyl - not metabolized by CYP2D6 - UGTs and/or CYP3A4 may be important
- Methadone - potential toxic due to less metabolic inactivation

Lotsch J et al, *Clin Pharmacokinet* 2004; 43(14): 983-1013
Armstrong SC and Cozza KL *Psychosomatics* 2003; 44:167-71

Future of PGx testing

- More clinical data
- Outcome studies
- Labeling changes
- Testing driven by products
- Wider availability of testing
- Personalized management “teams”
- Application-based panels

Is CYP genotyping cost-effective?

- Genotype-based dose selection reduces costs by reducing costs associated with ADRs
  - Clin Chem 2004 50(9):1623-33
  - Thromb Haemost. 2004 Sep;92(3):590-7
- Identify individuals at high-risk for ADRs; give less expensive drugs to low-risk individuals
  - Clin Chem 2005 51(2):376-85

Thank-you for your attention

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