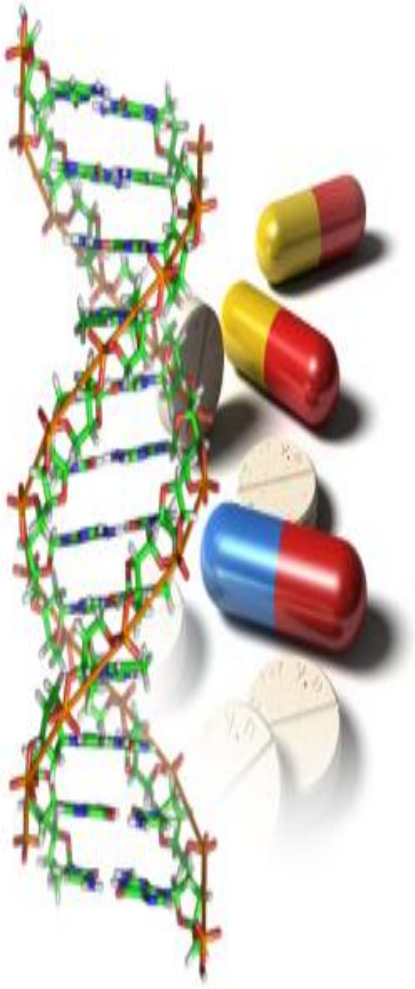


Farmakogenomika

prof.dr.sc. Nada Božina

Medicinski fakultet
Sveučilište u Zagrebu
Klinički bolnički centar Zagreb

Farmakogenomika

Ispituje ulogu gena koji određuju

učinkovitost i toksičnost-nuspojave lijekova

Spektar gena koji određuju ponašanje lijeka i osjetljivost na lijek

Istražuje čitav genom i procjenjuje multigensku determiniranost učinka lijeka

Nuspojave lijekova (NL)

Ranging from the fifth to seventh leading cause of death according to studies in the United States and Sweden

- *Lazarou J et al. Incidence of adverse drug reactions in hospitalized patients. J Am Med Assoc 1998.*

- *Wester K, Jonnson AK, Sigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population base study.*
  Br J Clin Pharmacol 2008.

Nuspojave lijekova (NL)

- **90% nastaje pri primjeni preporučenih doza lijeka**
- **Odgovorne za 7% hospitalizacija, a broj se penje i do > 30% u starijoj populaciji**
- **10% bolničkih pacijenata razvije nuspojavu**

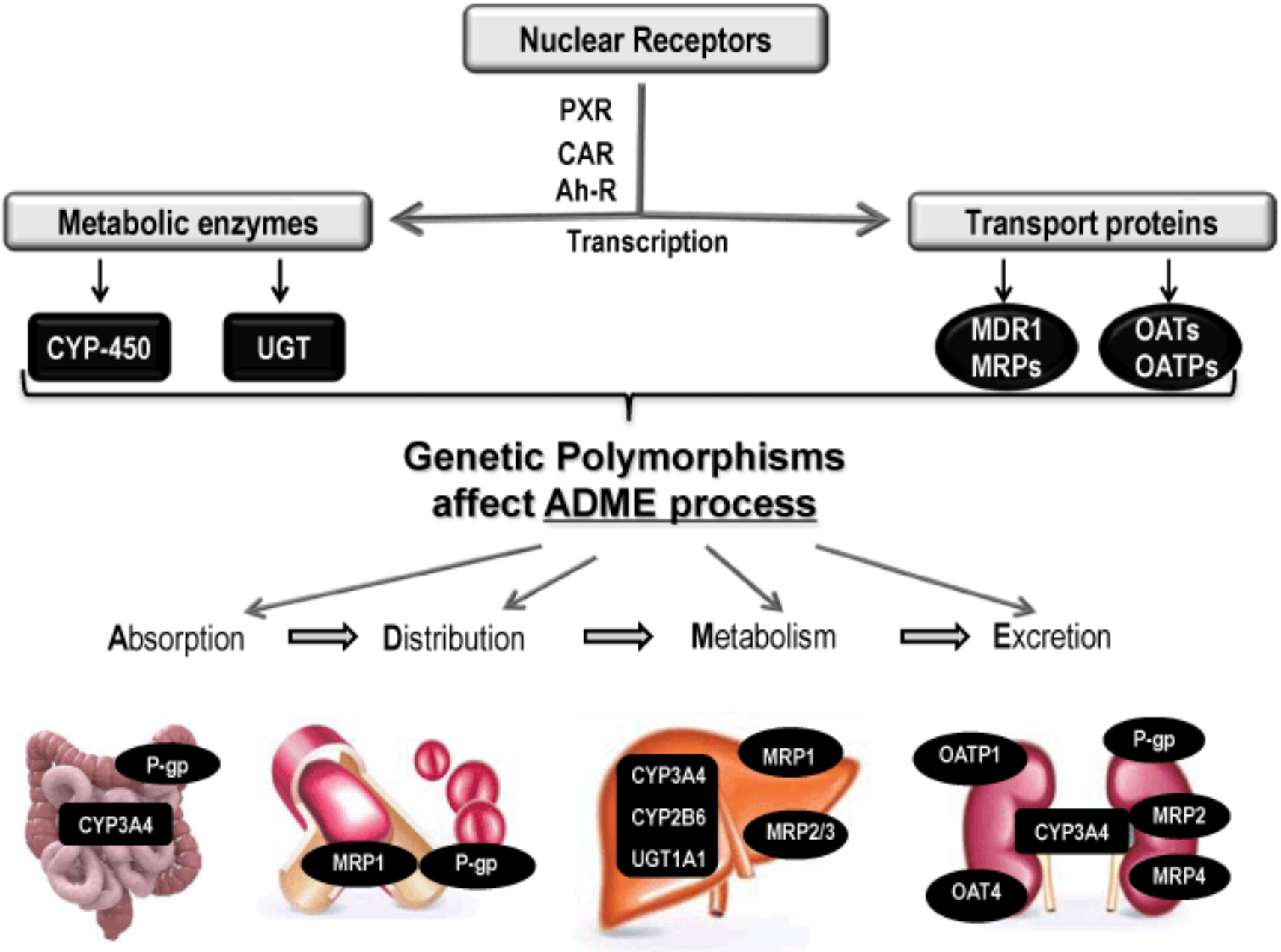
- *Davies EC et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS ONE 2009.*
- *Paul E et al.. Adverse drug reactions: a common cause of hospitalization of the elderly. A clinical retrospective study. Läkartidningen 2008.*
- *Eichelbaum M et al. Pharmacogenomics and individualized drug therapy. Annu Rev Med 2006.*

Nuspojave i interakcije lijekova

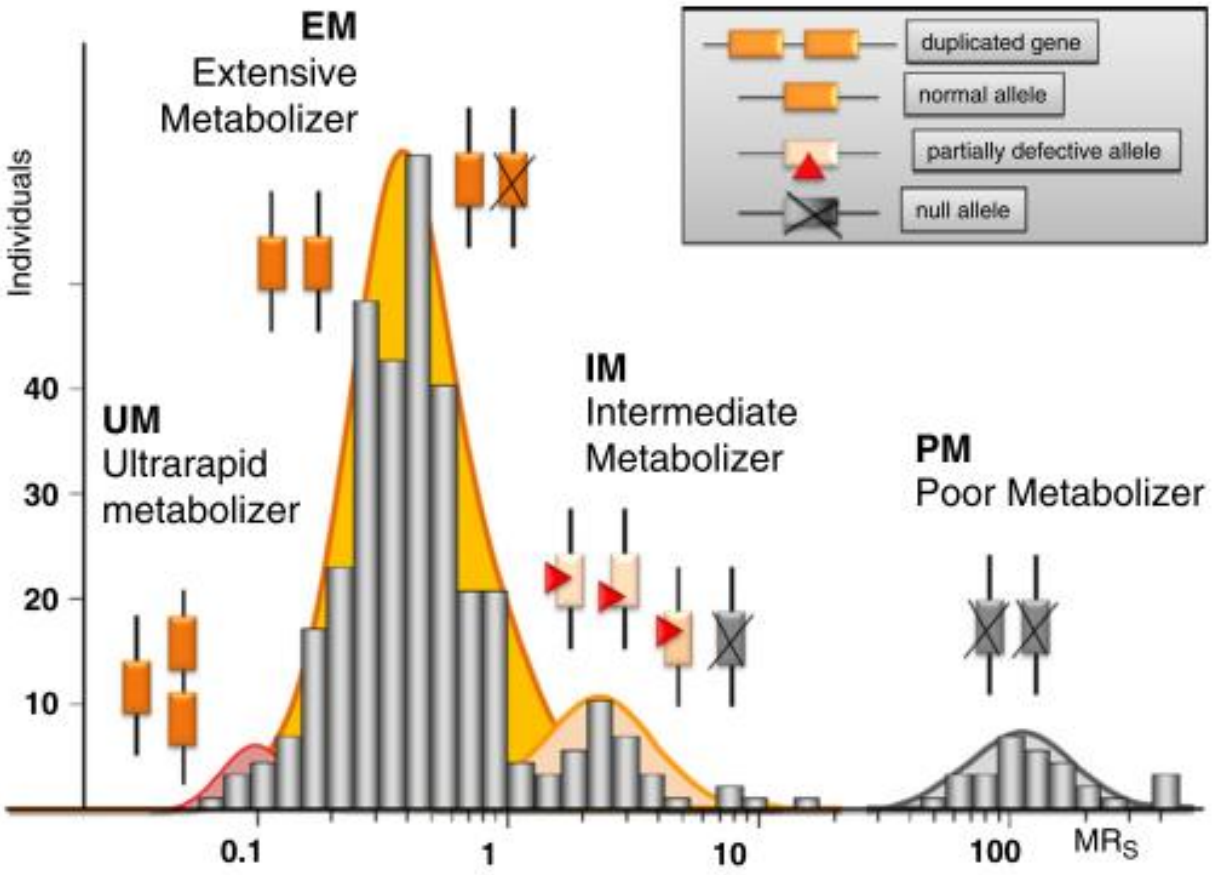
- Interakcije lijek-lijek
  (DDI, od engl. Drug – Drug Interactions)
  44% je uzrokovano Drug - Drug Interactions
  14% je uzrokovano Multi - Drug Interactions

- **Interakcije lijek-gen**
  (DGI, od engl. Drug – Gene Interactions)
  19% je uzrokovano Drug – Gene Interactions

- **Interakcije lijek-lijek-gen**
  (DDG, od engl. Drug Drug – Gene Interactions)
  23% je uzrokovano Drug Drug – Gene Interactions

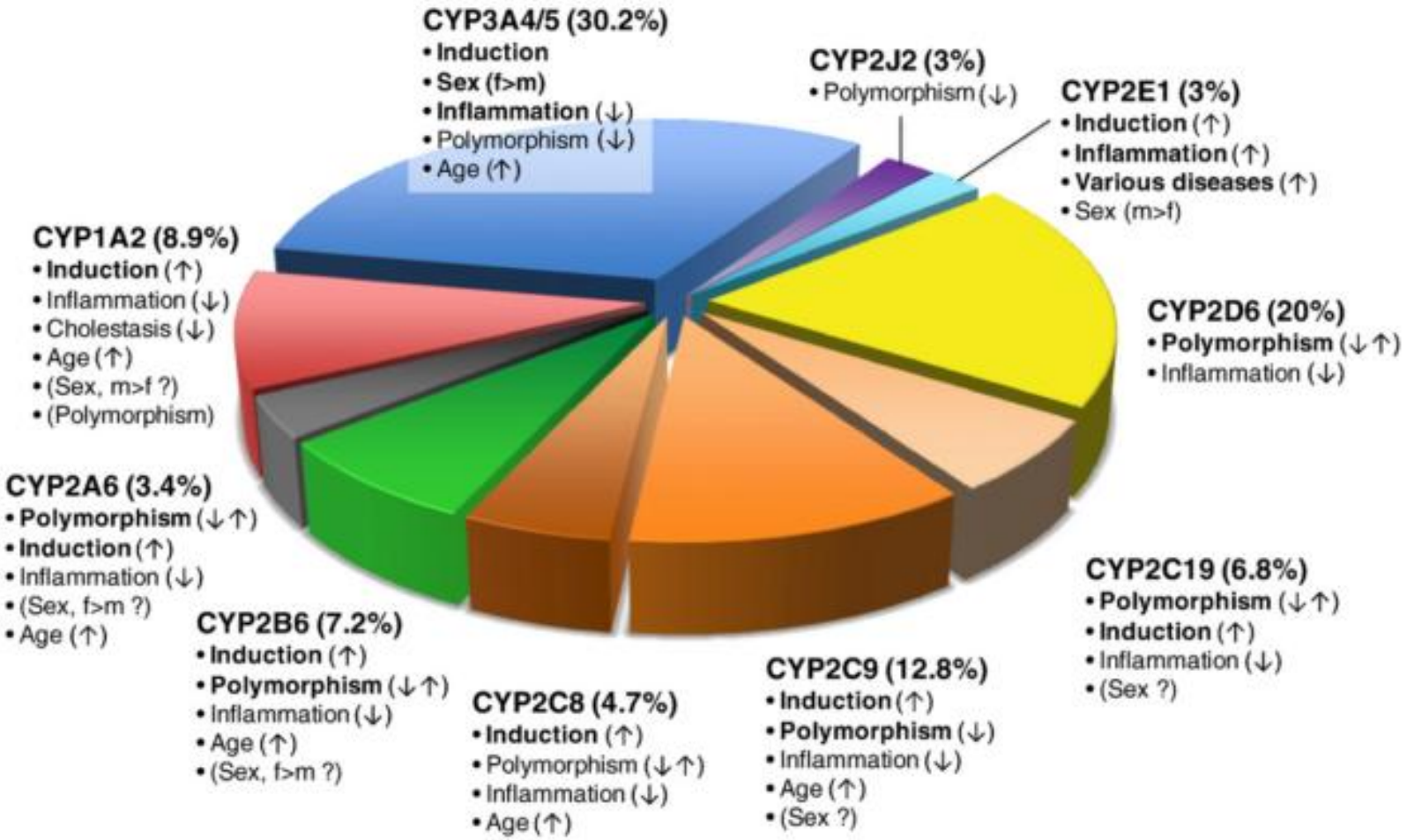

Nuclear Receptors
PXR
CAR
Ah-R
Transcription
Metabolic enzymes
Transport proteins
CYP-450
UGT
MDR1
MRPs
OATs
OATPs
Genetic Polymorphisms
affect ADME process
Absorption
Distribution
Metabolism
Excretion
P-gp
CYP3A4
MRP1
P-gp
CYP3A4
CYP2B6
UGT1A1
MRP1
MRP2/3
OATP1
P-gp
CYP3A4
MRP2
OAT4
MRP4

Genotip → Fenotip CYP2D6



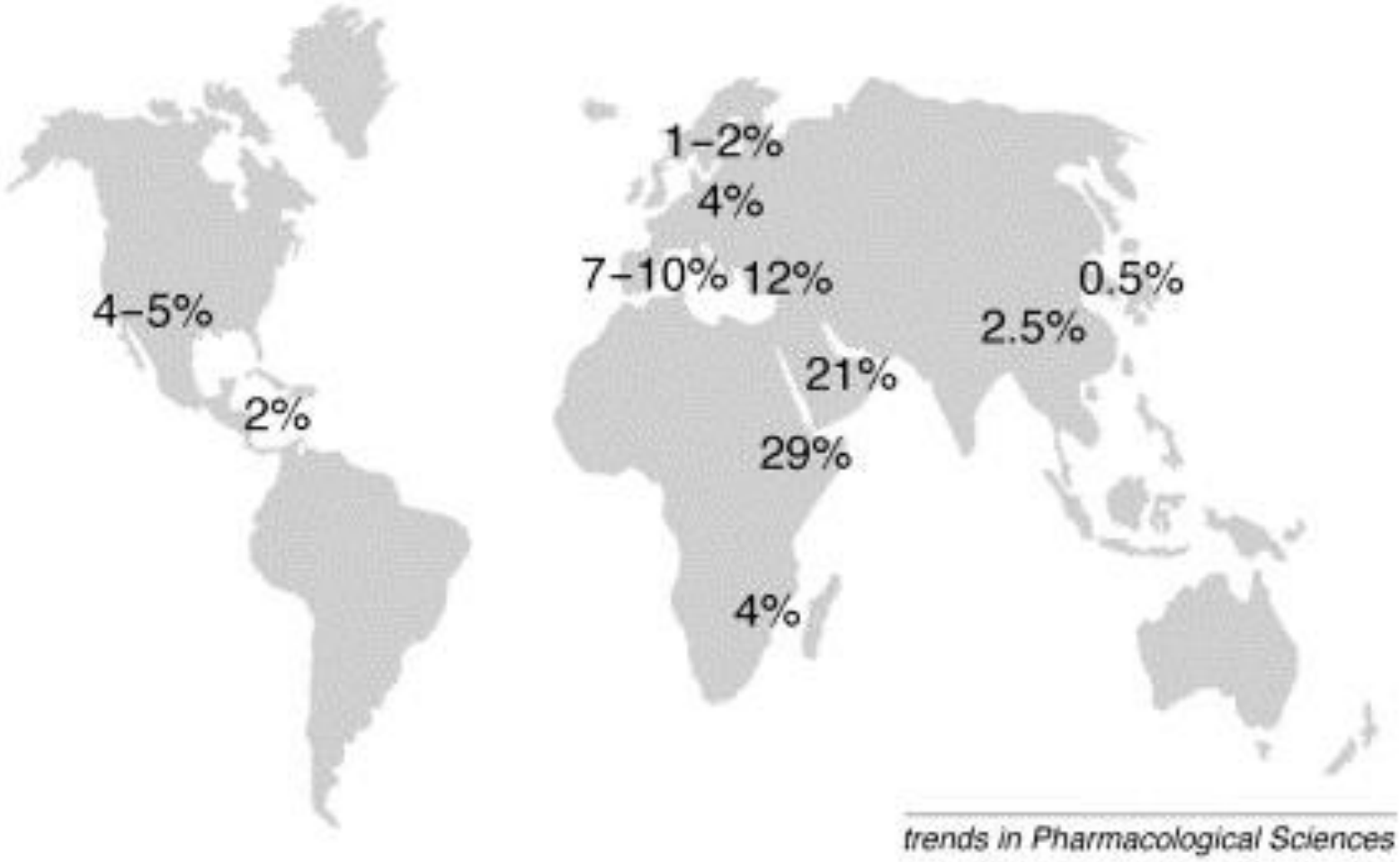
Zanger UM, Schwab M. Pharmacol Ther 2013

Enzimi P450 (CYP) i čimbenici koji utječu na varijabilnost farmakoterapije

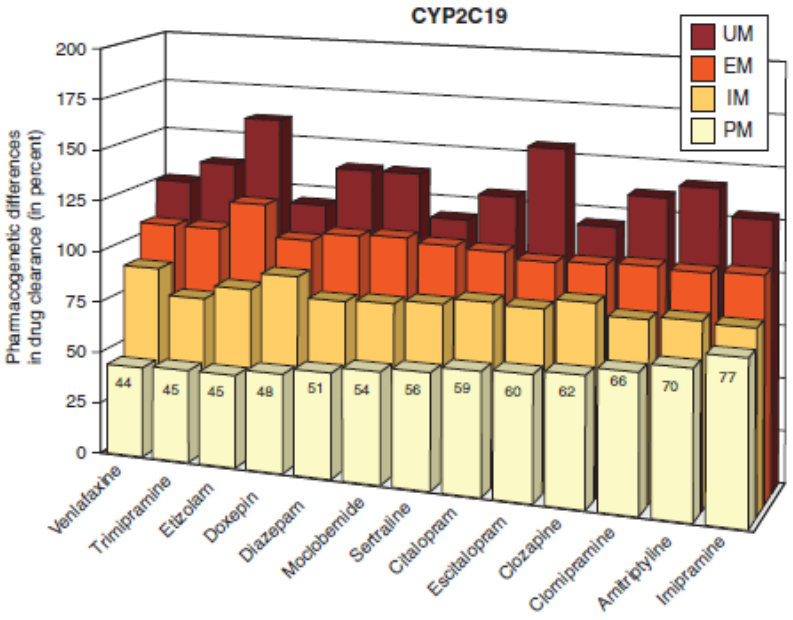


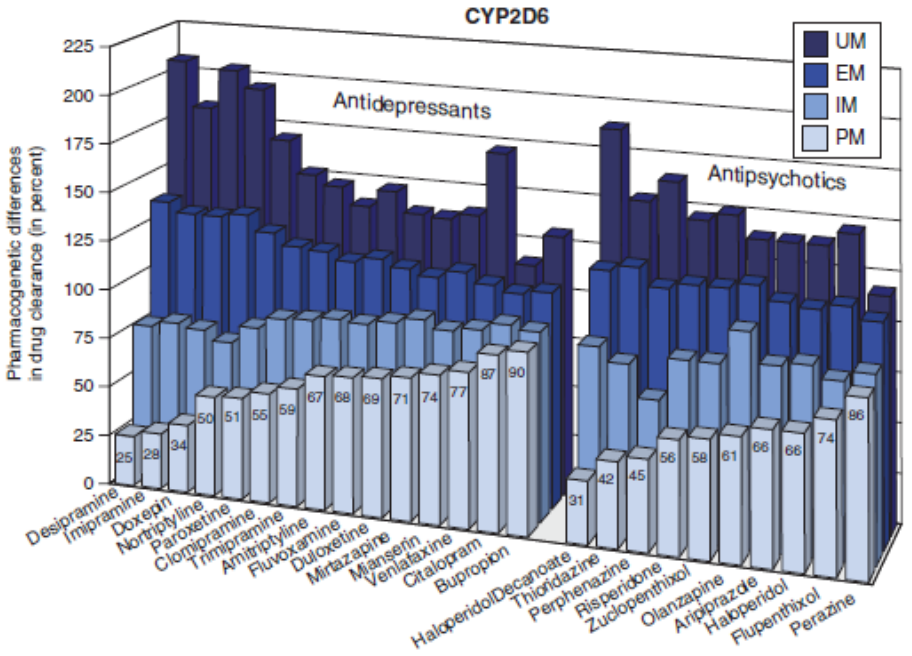
Zanger UM, Schwab M. Pharmacol Ther 2013

Učestalost genotipova UEM CYP2D6

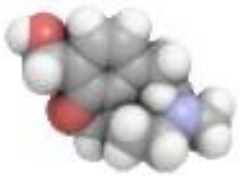


Prilagodba doze prema genotipu
CYP2C19 i CYP2D6





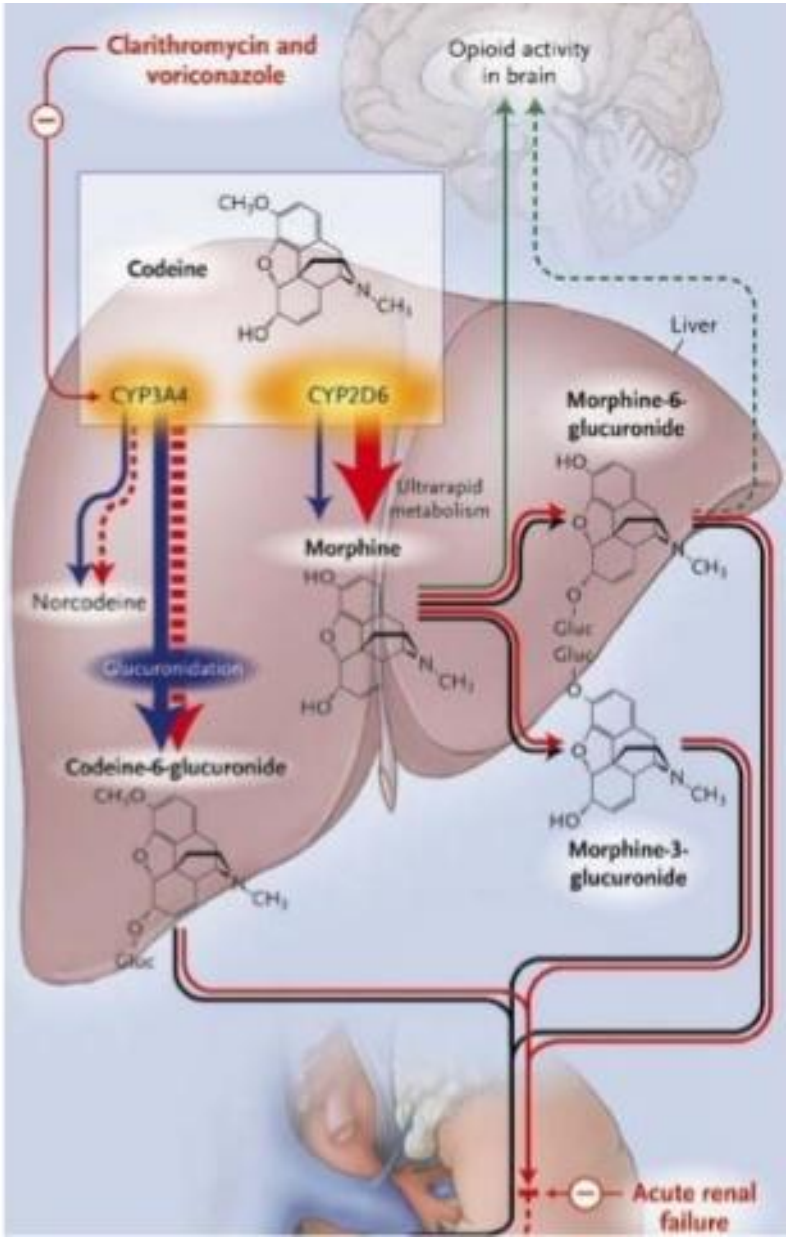
Stingl JC et al. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry. 2012*



Codeine Metabolism

- 80% codeine normally converted to glucuronide, eliminated by kidney.
- 5-10% codeine is metabolized into morphine by CYP2D6
- inhibition of CYP3A4 or rapid metabolic variants of CYP2D6 during renal failure would show toxicity
  - 7% of caucasians have a nonfunctional CYP2D6 variant
  - <2% are CYP2D6 ultrarapid metabolizers which may suffer from opioid intoxication

Gasche Y et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. NEJM 2004



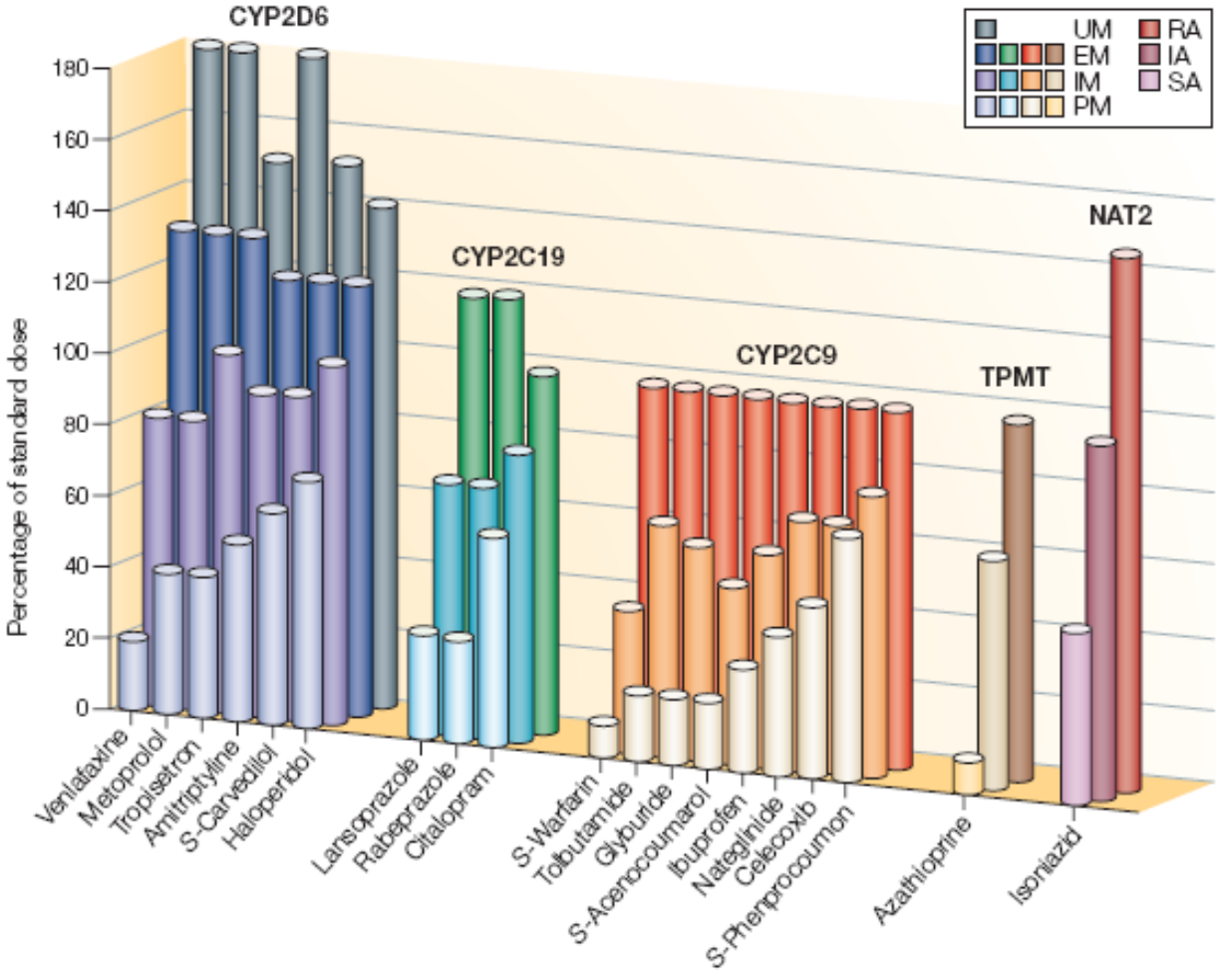
Preporuke za doziranje kodeina ovisno o genotipu/fenotipu CYP2D6
(*prema smjernicama Dutch Pharmacogenetics Working Group*

Lijek	CYP2D6 genotip / fenotip	Preporučeno doziranje
Kodein	EM	Analgezija: standardne doze
	IM	Analgezija: **odabrati alternativni lijek** (npr. acetaminofen, NSAIL, morfin – **isključiti tramadol i oksikodon**) ili pratiti simptome nedovoljnog analgetskog učinka
	PM	Analgezija: **odabrati alternativni lijek** (npr. acetaminofen, NSAIL, morfin – isključiti tramadol i oksikodon) ili pratiti simptome nedovoljnog analgetskog učinka
	UM	Analgezija: odabrati alternativni lijek (npr. acetaminofen, NSAIL, morfin – isključiti tramadol i oksikodon). **Posebno obratiti pažnju na moguće nuspojave zbog povećanja koncentracije morfina u krvi**

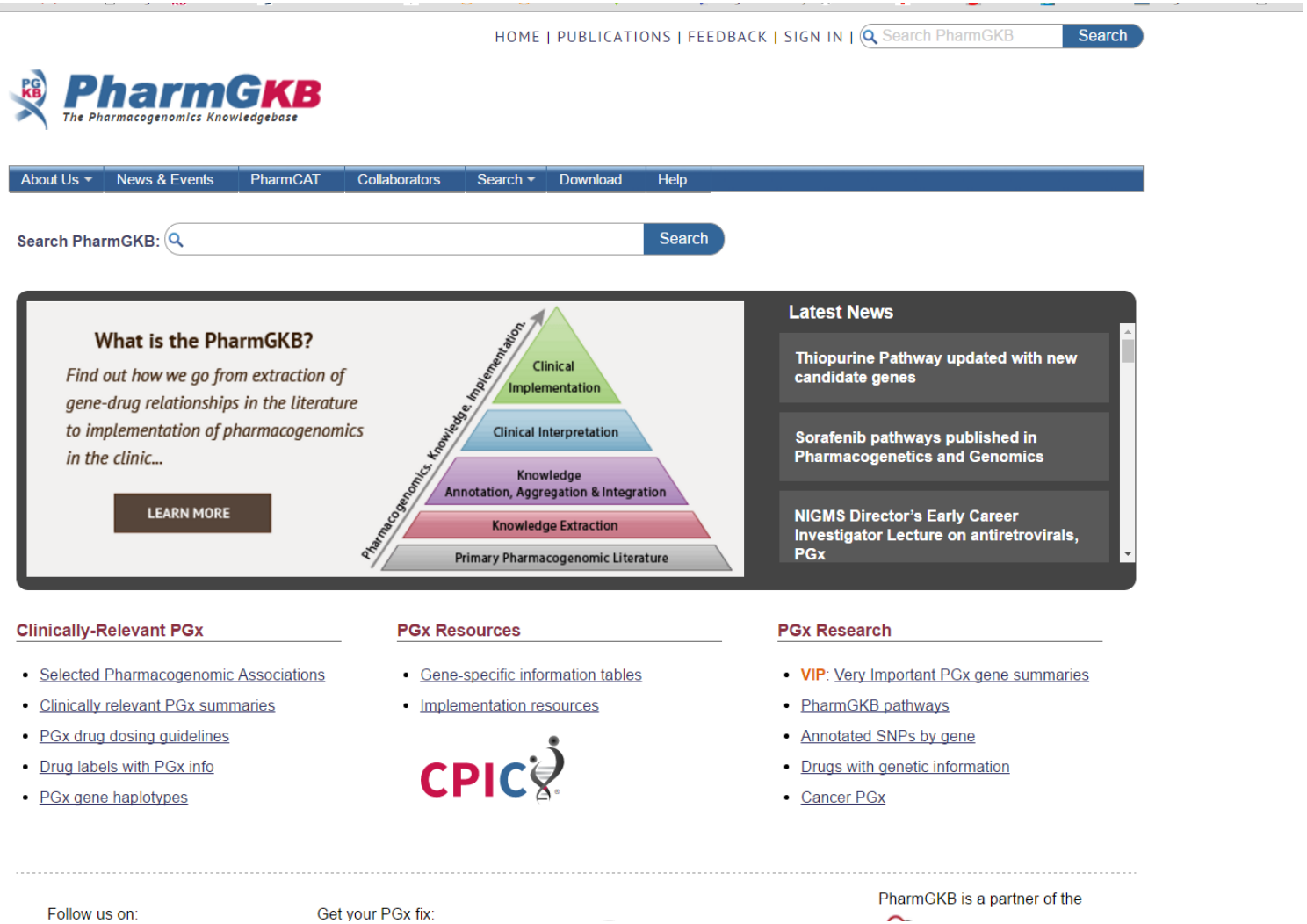
Preporučene dnevne doze varfarina (mg/dan) prema kombinaciji genotipova CYP2C9 i VKORC1 za postizanje terapijskog INR (iz uputa o lijeku, odobrenih od FDA, 2004)

Genotip VKORC1 -1639G>A	**Genotip *CYP2C9*2*3***					
	****1/*1***	****1/*2***	****1/*3***	****2/*2***	****2/*3***	****3/*3***
GG	5 – 7	5 – 7	3 – 4	3 – 4	3 – 4	**0,5 – 2**
GA	5 – 7	3 – 4	3 – 4	3 – 4	**0,5 – 2**	**0,5 – 2**
AA	3 – 4	3 – 4	**0,5 – 2**	**0,5 – 2**	**0,5 – 2**	**0,5 – 2**

Gen-doza

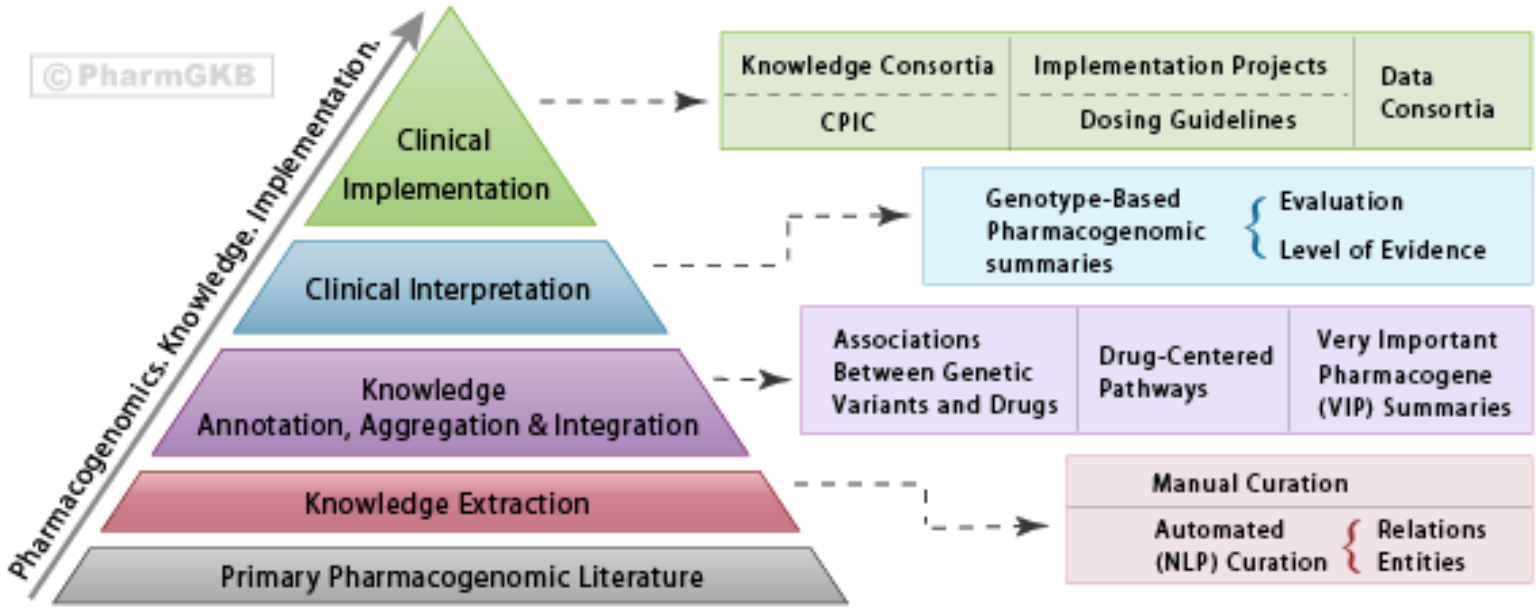

CYP2D6
CYP2C19
CYP2C9
TPMT
NAT2
UM
EM
IM
PM
RA
IA
SA
Percentage of standard dose
0
20
40
60
80
100
120
140
160
180
Venlafaxine
Metoprolol
Tropisetron
Amitriptyline
S-Carvedilol
Haloperidol
Lansoprazole
Rabeprazole
Citalopram
S-Warfarin
Tolbutamide
Glyburide
S-Acenocoumarol
Ibuprofen
Nateglinide
Celecoxib
S-Phenprocoumon
Azathioprine
Isoniazid

https://www.pharmgkb.org



The PharmGKB Knowledge Pyramid

Vizualizira različite tipove informacija dostupnih u PharmGKB bazi te kako se te informacije međusobno nadopunjuju i integriraju čineći implementaciju znanja o farmakogenomici u samu kliniku.



https://www.pharmgkb.org

Drug labels - PGx Level

Total of 251 drugs has drug labels containing pharmacogenetic information

- **Testing required**
- **Testing recommended**
- **Actionable PGx**
- **Informative PGx**

https://www.pharmgkb.org/search/knownPairs.action

Selected PGx Associations

PharmGKB
Pharmacogenomics. Knowledge. Implementation.

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Selected PGx Associations

The criteria for this list of Drug-Gene pairs is 1) each pair must be annotated in either a dosing guideline annotation or a drug label annotation and 2) each pair must be specified in more than 1 type of annotation (dosing guideline, drug label, clinical annotation, variant annotation, VIP, or pathway).

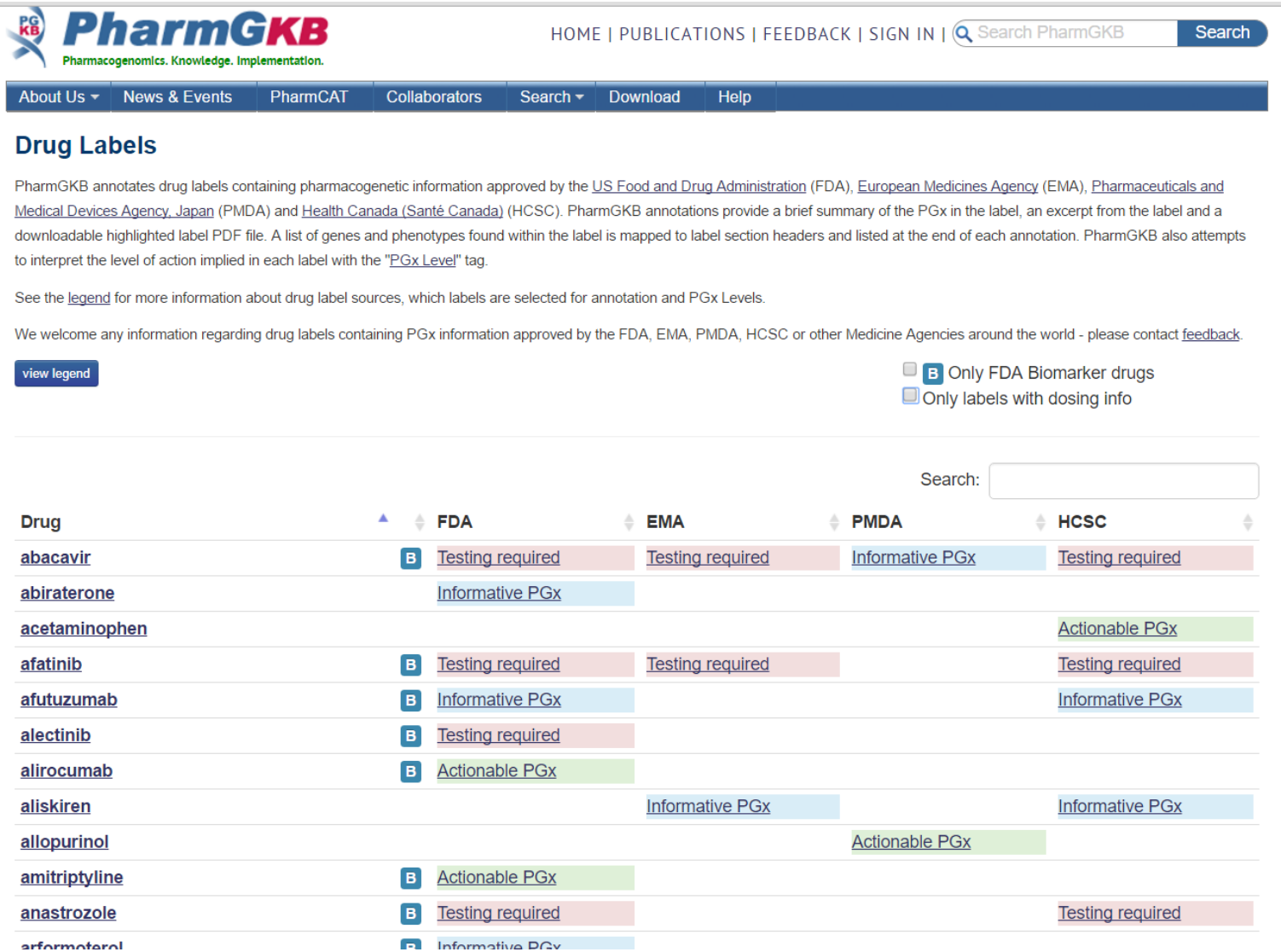
view legend

Drug	Gene	Types of data
abacavir	HLA-B	DG DL CA VA VIP
acenocoumarol	CYP2C9	DG CA VA
acenocoumarol	VKORC1	DG CA VA VIP
acetaminophen	CYP2D6	DL VA PW
afatinib	EGFR	DL VA VIP
allopurinol	HLA-B	DG CA VA VIP
amitriptyline	CYP2C19	DG CA VA VIP
amitriptyline	CYP2D6	DG DL CA VA VIP
anastrozole	ESR1	DL CA VA
anastrozole	ESR2	DL VA
anastrozole	PGR	DL VA
aripiprazole	CYP2D6	DG DL CA VA
aripiprazole	CYP3A4	DL VIP
atazanavir	UGT1A1	DG CA VA VIP
atomoxetine	CYP2D6	DG DL CA VA VIP
atorvastatin	CYP3A4	DL CA VA VIP PW
atorvastatin	HMGCR	DL CA VA VIP

DG Dosing Guideline information is available
DL Drug Label information is available
CA High-level Clinical Annotation is available
VA Variant Annotation is available
VIP VIP information is available
PW Pathway is available

https://www.pharmgkb.org/search/knownPairs.action

Drug labels with PGx info



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Drug Labels

PharmGKB annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency, Japan (PMDA) and Health Canada (Santé Canada) (HCSC). PharmGKB annotations provide a brief summary of the PGx in the label, an excerpt from the label and a downloadable highlighted label PDF file. A list of genes and phenotypes found within the label is mapped to label section headers and listed at the end of each annotation. PharmGKB also attempts to interpret the level of action implied in each label with the "PGx Level" tag.

See the legend for more information about drug label sources, which labels are selected for annotation and PGx Levels.

We welcome any information regarding drug labels containing PGx information approved by the FDA, EMA, PMDA, HCSC or other Medicine Agencies around the world - please contact feedback.

view legend

B Only FDA Biomarker drugs
Only labels with dosing info

Search:

Drug		FDA	EMA	PMDA	HCSC
abacavir	B	Testing required	Testing required	Informative PGx	Testing required
abiraterone		Informative PGx			
acetaminophen					Actionable PGx
afatinib	B	Testing required	Testing required		Testing required
afutuzumab	B	Informative PGx			Informative PGx
alectinib	B	Testing required			
alirocumab	B	Actionable PGx			
aliskiren			Informative PGx		Informative PGx
allopurinol				Actionable PGx	
amitriptyline	B	Actionable PGx			
anastrozole	B	Testing required			Testing required
arformoterol	B	Informative PGx			

https://www.pharmgkb.org/view/drug-labels.do

Dosing Guidelines - CPIC

These dosing guidelines take into consideration patient genotype and have been published by the Clinical Pharmacogenetics Implementation Consortium CPIC, the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group DPWG (manually curated by PharmGKB), or other professional society PRO (manually curated by PharmGKB).

Filter: CPIC

Drug	Guidelines	Updated
abacavir	CPIC CPIC Guideline for abacavir and HLA-B	09/30/2014
allopurinol	CPIC CPIC Guideline for allopurinol and HLA-B	06/12/2015
amitriptyline	CPIC CPIC Guideline for amitriptyline and CYP2C19,CYP2D6	02/07/2014
atazanavir	CPIC CPIC Guideline for atazanavir and UGT1A1	09/18/2015
azathioprine	CPIC CPIC Guideline for azathioprine and TPMT	02/07/2014
capecitabine	CPIC CPIC Guideline for capecitabine and DPYD	08/06/2014
carbamazepine	CPIC CPIC Guideline for carbamazepine and HLA-B	02/07/2014
citalopram	CPIC CPIC Guideline for citalopram,escitalopram and CYP2C19	05/11/2015
clomipramine	CPIC CPIC Guideline for clomipramine and CYP2C19,CYP2D6	02/07/2014
clopidogrel	CPIC CPIC Guideline for clopidogrel and CYP2C19	02/07/2014
codeine	CPIC CPIC Guideline for codeine and CYP2D6	05/05/2016

Implementation Resources for Pharmacogenomics

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
- Translational Pharmacogenetics Project (TPP)
- Dutch Pharmacogenetics Working Group
- DeBartolo Family Personalized Medicine Institute at Moffitt Cancer Center
- ICAPS - International Consortium for Antihypertensives Pharmacogenomics Studies
- European Pharmacogenetics Implementation Consortium

https://www.pharmgkb.org/page/pgxImplementationResources

https://cpicpgx.org

What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN). CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC's goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Background

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines. CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. The guidelines can center on genes (e.g. thiopurine methyltransferase and its implications for thiopurines) or around drugs (e.g. warfarin and CYP2C9 and VKORC1). Priority is given to genotyping tests that are already offered in CLIA-approved clinical settings.

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
abacavir	HLA-B	In individuals with the HLA-B*57:01 variant allele, abacavir is not recommended and should be considered only under exceptional circumstances.	CPIC
allopurinol	HLA-B	Allopurinol is contraindicated in individuals with the HLA-B*58:01 variant allele due to significantly increased risk of allopurinol-induced SCAR (severe cutaneous adverse reactions, which includes drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).	CPIC
carbamazepine	HLA-B	Carbamazepine is not recommended for carbamazepine-naive individuals who have at least one copy of the HLA-B*15:02 allele. The variant allele is associated with an increased risk of SJS and TEN in response to carbamazepine treatment.	CPIC

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
aripiprazole	CYP2D6	DPWG recommends reducing maximum dose of aripiprazole for patients carrying poor metabolizer alleles of CYP2D6.	DPWG
atomoxetine	CYP2D6	For CYP2D6 ultrarapid metabolizers, be alert to reduced efficacy of atomoxetine or select an alternative drug. Be alert to ADEs in CYP2D6 poor metabolizers.	DPWG
azathioprine	TPMT	Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30-70% of target dose for patients with intermediate enzyme activity.	CPIC
boceprevir, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, telaprevir	IFNL3	IFNL3 (IL28B) variation (rs12979860) is the strongest baseline predictor of response to PEG-interferon-alpha-containing regimens in HCV genotype 1 patients. Patients with the favorable response genotype (rs12979860 CC) have increased likelihood of response (higher SVR rate) to PEG-interferon-alpha-containing regimens as compared to patients with unfavorable response genotype (rs12979860 CT or TT). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.	CPIC

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
capecitabine, fluorouracil, tegafur	DPYD	Dosing Guidelines for fluoropyrimidines (i.e. 5-fluorouracil, capecitabine or tegafur) recommends an alternative drug for patients who are homozygous for DPYD non-functional variants (*2A rs3918290, *13 rs55886062, and rs67376798) as these patients are typically DPD deficient. Consider a 50% reduction in starting dose for heterozygous patients (intermediate activity).	CPIC
citalopram	CYP2C19	For CYP2C19 ultrarapid metabolizers, monitor citalopram plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse drug event, or select an alternative drug.	DPWG
escitalopram	CYP2C19	For CYP2C19 ultrarapid metabolizers, monitor escitalopram plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse drug event, or select alternative drug.	DPWG
clomipramine	CYP2C19,CYP2D6	Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including clomipramine, imipramine.	CPIC

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
hormonal contraceptives for systemic use	F5	In individuals who carry the Factor V Leiden allele and have a family history of thrombotic events, estrogen-containing oral contraceptives should be avoided and alternative forms of contraception used.	DPWG
irinotecan	UGT1A1	Reduce the starting dose of irinotecan for UGT1A1*28 homozygous patients receiving more than 250 mg/m^2.	DPWG
ivacaftor	CFTR	Ivacaftor treatment is recommended only in CF patients that are either homozygous or heterozygous for the G551D-CFTR variant (rs75527207 genotype AA or AG). In patients who are homozygous for F508del-CFTR (F508del/F508del, rs113993960 or rs199826652 genotype del/del) ivacaftor is not recommended. See full guideline for disclaimers, further details and supporting evidence. In the amended FDA-approved ivacaftor drug label, the indication has been changed to include additional CFTR variants. The clinical trial to support this data is not yet published.	CPIC
lansoprazole, omeprazole	CYP2C19	For CYP2C19 ultrarapid metabolizers, be extra alert to insufficient response and consider increasing the dose by 200%.	DPWG

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
pantoprazole	CYP2C19	For CYP2C19 ultrarapid metabolizers, be extra alert to insufficient response and consider increasing pantoprazole dose by 400%.	DPWG
metoprolol	CYP2D6	Select another drug or reduce dose of metoprolol for CYP2D6 poor and intermediate metabolizer patients. Use a dose titration of metoprolol for CYP2D6 ultra metabolizers or select an alternative drug.	DPWG
paroxetine	CYP2D6	Select an alternative drug rather than paroxetine for CYP2D6 ultra metabolizer patients.	DPWG
phenytoin	CYP2C9	Use the standard starting dose of phenytoin and reduce the maintenance dose based on CYP2C9 genotype; monitor response and serum concentrations and be aware of ADEs.	DPWG
risperidone	CYP2D6	Select an alternative drug or be extra alert to adverse drug events (ADR) for patients who are CYP2D6 poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers with risperidone. Adjust risperidone dose to clinical response.	DPWG

DRUG	GENE	RECOMMENDATION	GUIDELINES BY
sertraline	CYP2C19	Reduce sertraline dose by 50% for patients with CYP2C19 poor metabolizer genotypes, and be extra alert to adverse drug events in patients with CYP2C19 intermediate metabolizer genotypes .	DPWG
simvastatin	SLCO1B1	The FDA recommends against 80mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at lower simvastatin doses (40mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered. The association of rs4149056 with myopathy has been less compelling for other statins. Guideline is focused on simvastatin.	CPIC
tamoxifen	CYP2D6	For CYP2D6 poor and intermediate metabolizers, consider using aromatase inhibitors for postmenopausal women due to increased risk for relapse of breast cancer with tamoxifen. For intermediate metabolizers, avoid concomitant CYP2D6 inhibitor use.	DPWG

Lijekovima izazvano oštećenje jetara - *Drug-induced liver injury - DILI*

LIJEK	Razina dokaza	Genetičke determinante
acetaminofen	3	UGT1A, UGT1A9
amoksicilin-klavulanat	3	HLA-DQB1
antiretroviralni lijekovi	2a, 4	ABCB1, CYP2B6, GSTT1, GSTM1, HLA-B*35:01, HLA-DRB1*01:01:01
citarabin, fludarabin, idarubicin	3	CYP2E1, SLCO1B1
antiTB lijekovi	3	ABCB1, CYP2E1, NAT2, PXR, GSTM1,GSTT1
azatioprin	1a	TPMT, GSTM1
diklofenak	3	ABCC2, CYP2C9, UGT2B7
flukloksacilin	3	HLA-B*57:01:01, NR1I2, PXRTT
flupirtin	3	HLA-DRB1*16:01-HLA-DQB1-*05:02
gemtuzumab, ozogamicin	3	SLCO1B1
lapatinib	2b	HLA-DQA1
metotreksat	2a, 3	MTHFR, ABCC2, SLCO1B1, TYMS, AMPD1, DHFR, MDR1, RFC-1, GGH, GSTM1
pirazinamid	2a, 3	NAT2, TNF, GSTT1, STAT3
rifampicin	2a, 3	NAT2, TNF, NOS2, GSTM1, GSTT1, STAT3
takrolimus	3	CYP3A5
tiklopidin	3	HLA-B*44:03, HLA-A*3303

MEF Zagreb, KBC Zagreb i HALMED

Drug	Avers drug reaction	Pharmacogenetic marker
statins	myotoxicity, hepatotoxicity	CYP2C9, CYP2C19, CYP3A4, SLCO1B1, ABCB1, ABCG2
warfarin	bleeding	CYP2C9, VKORC1, MDR1
clopidogrel	bleeding, ineffectiveness	CYP2C19, CYP3A4, ABCB1
dabigatran, rivaroxaban	bleeding	CYP3A4, ABCB1

Drug	Avers drug reaction	Pharmacogenetic marker
antiepileptic drugs	hepatotoxicity, tremor, hair loss, headache, vertigo, hypersensitivity,	CYP2C9, CYP2C19, CYP3A4, UGT2B7, ABCC2
psychotropic drugs	acute extrapyramidal symptoms, parkinsonism, akathisia, aggression,	CYP2D6, CYP3A4, CYP1A2, SERT, D2R, 5HTR, COMT, DAT, MAO,
immuno-suppressants	gastrointestinal intolerance, bone marrow/ hepato/nephro-toxicity	CYP3A4/5, UGT1A9, ABCB1, ABCC2, ABCG2, SLCO1B3, TPMT, ITPA, XO

Drug	Avers drug reaction	Pharmacogenetic marker
5-FU, irinotecan	myelosuppression, diarrhea, death	DPYD, UGT1A1, SLCO1B1
tyrosine kinase inhibitors	pancreatitis, rhabdomyolysis, headache, rush, pruritus	CYP2D6, CYP2C9, CYP2C19, CYP3A4, ABCB1, ABCG2, SLCO1B1
NSAID	nausea, gastrointestinal intolerance, liver toxicity, bleeding	CYP2C9, CYP2C19, ABCC2,UGT2B7

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Prevalence of genetic polymorphisms of *CYP2C9* and *VKORC1* — Implications for warfarin management and outcome in Croatian patients with acute stroke ☆

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CYP2C9 and *ABCG2* polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case–control study

Aim: To investigate whether an association exists between fluvastatin-induced adverse drug reactions (ADRs) and polymorphisms in genes encoding the metabolizing enzyme CYP2C9 and the drug transporter ABCG2 in renal transplant recipients (RTRs). **Materials & methods:** Fifty-two RTRs that experienced fluvastatin ADRs and 52 controls matched for age, gender, dose of fluvastatin and immunosuppressive use were enrolled in the study. Genotyping for *CYP2C9*2, *3* and *ABCG2* 421C>A variants was performed by real-time PCR. **Results:** *CYP2C9* homozygous and heterozygous mutant allele (**2* or **3*) carriers had 2.5-times greater odds of developing adverse effects ($\chi^2 = 4.370$; degrees of freedom = 1; $p = 0.037$; $\varphi = 0.21$, odds ratio [OR]: 2.44; 95% CI: 1.05–5.71). Patients who were the carriers of at least one mutant *CYP2C9* allele (**2* or **3*) and who were receiving CYP2C9 inhibitors, had more than six-times greater odds of having adverse effects than those without the inhibitor included in their therapy ($p = 0.027$; OR: 6.59; 95% CI: 1.24–35.08). Patients with *ABCG2* 421CA or AA (taken together) had almost four-times greater odds of developing adverse effects than those with *ABCG2* 421CC genotype ($\chi^2 = 6.190$; degrees of freedom = 1; $p = 0.013$; $\varphi = 0.24$, OR: 3.81; 95% CI: 1.27–11.45). Patients with A allele had 2.75-times (95% CI: 1.02–7.40) greater odds of developing adverse effects than those with C allele. **Conclusion:** Our preliminary data demonstrate an association between fluvastatin-induced ADRs in RTRs and genetic variants in the *CYP2C9* and *ABCG2* genes.

preliminary data demonstrate an association between fluvastatin-induced ADRs in RTRs and genetic variants in the *CYP2C9* and *ABCG2* genes.

Mirošević Skvrce N, Božina N, Zibar L, Barišić I, Pejnović L, Macolić Šarinić V.
Pharmacogenomics 2013

Preliminary Communication

Pharmacogenomics

ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case–control study

Aim: To explore the association between dose-related adverse drug reactions (ADRs) of atorvastatin and polymorphisms of *ABCG2*, taking into account the influence of *CYP3A4* and *SLCO1B1* genes. **Materials & methods**: Sixty patients who experienced atorvastatin dose-related ADRs and 90 matched patients without ADRs were enrolled in the study. Genotyping for *ABCG2* 421C > A, *CYP3A4*22*, *SLCO1B1* 388A > G, *SLCO1B1* 521T > C variants was performed by real-time PCR. **Results**: Patients with *ABCG2* 421CA or AA genotypes had 2.9 times greater odds of developing atorvastatin dose-dependent ADRs (OR: 2.91; 95% CI: 1.22–6.95; p = 0.016) than those with *ABCG2* 421CC genotype. After adjustments for clinical and genetic risk factors, *ABCG2* remained a statistically significant predictor of adverse drug reactions (OR: 2.75; 95% CI: 1.1–6.87; p = 0.03;). Also, carriers of *SLCO1B1* 521 TC or CC genotypes had 2.3 greater odds (OR: 1.03–4.98; 95% CI: 1.03–4.98; p = 0.043) of experiencing ADRs caused by atorvastatin in comparison with carriers of *SLCO1B1* 521 TT genotype. **Conclusion**: Our study demonstrated an association between atorvastatin-induced ADRs and genetic variants in the *ABCG2* gene.

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PHARMACOKINETICS AND DISPOSITION

Steady-state pharmacokinetics of mycophenolic acid in renal transplant patients: exploratory analysis of the effects of cyclosporine, recipients' and donors' *ABCC2* gene variants, and their interactions

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Case Report

Pharmacogenomics

*CYP2D6 *6/*6* genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms

A 66-year-old male Caucasian, received 1 mg of haloperidol orally and rapidly developed severe iatrogenic extrapyramidal symptoms. Treatment was immediately discontinued, and the side effects resolved. Haloperidol is mainly metabolized by Phase I CYP2D6 and to the lesser extent by CYP3A4 and by Phase II UGT2B7 enzymes. Genotyping was performed revealing *CYP2D6*6/*6*, *CYP3A4*1/*1*, and *UGT2B7* -161 C/T genotypes, implicating poor, extensive and intermediate metabolism, respectively. Of the CYPs, haloperidol is metabolized by CYP2D6 and CYP3A4 primarily. It was the introduction of ciprofloxacin which was a trigger for the development of adverse drug reaction due to inhibition of CYP3A4, which was in presented patient main metabolic pathway for haloperidol since he was CYP2D6 poor metabolizer. Presented case report highlights the importance of genotyping. Pharmacogenetics testing should be considered when drug toxicity is suspected, polymorphic metabolic pathways used and drugs concomitantly applied.

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Fundamental & Clinical Pharmacology

CASE REPORT

Dapsone-induced agranulocytosis—possible involvement of low-activity *N*-acetyltransferase 2

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Keywords
adverse drug reactions, agranulocytosis, dapsone, glucose-6-phosphate dehydrogenase, NAT2 *5/*6

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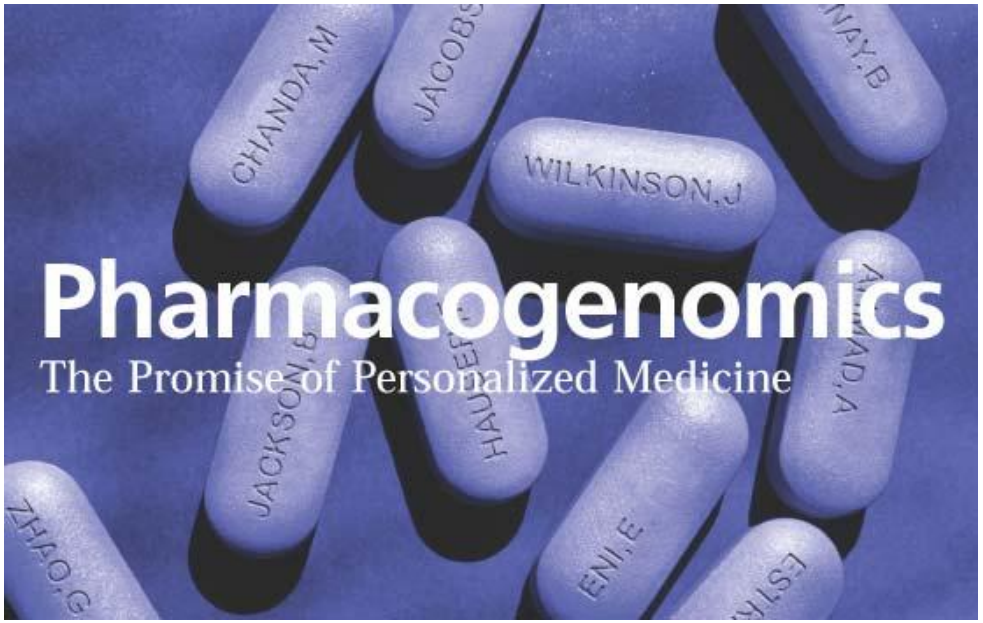
ABSTRACT

Dapsone-induced agranulocytosis is a rare but potentially fatal adverse drug reaction (ADR). A 45-year-old male Caucasian patient developed agranulocytosis caused by dapsone (diamino-diphenyl sulfone), which he was prescribed for leukocytoclastic vasculitis. Patient's treatment consisted of termination of dapsone, antibiotic therapy, and granulocyte colony-stimulating factor leading to prompt improvement of symptoms and normalization of laboratory blood values. Diagnostic evaluation revealed methemoglobinemia and excluded glucose-6-phosphate dehydrogenase deficiency. Pharmacogenetics testing showed that he was a carrier of *NAT2* *5/*6 genotype, predisposing to low activity of the *N*-acetyltransferase 2 enzyme. This was the first and only ADR to dapsone reported in Croatia. In total, there have been 73 ADR to dapsone recorded worldwide, including only four cases of agranulocytosis.

Budućnost farmakogenomike

- Personalizirani farmakogenetički profili analizom farmakogentičkih panela ili sekvenciranjem genoma



"Here's my sequence..."

New Yorker, 2000