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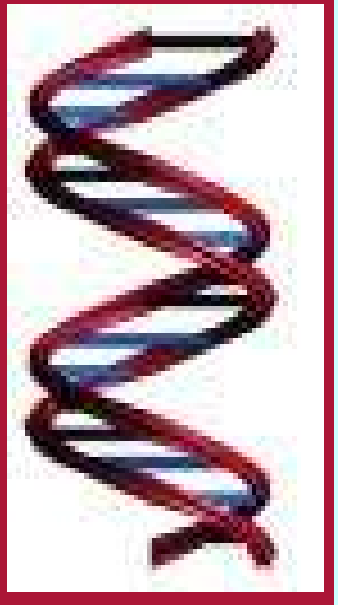


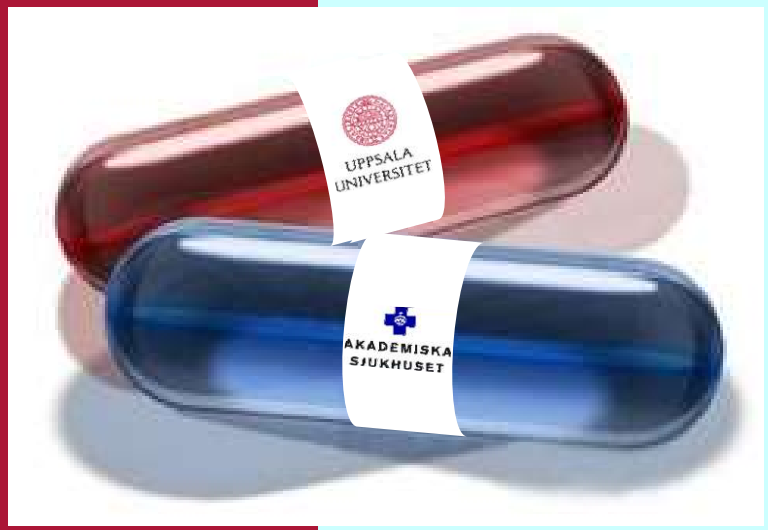
Precisionsmedicin nya gränser: användning av genotypning i klinisk praxis för att individualisera behandlingen

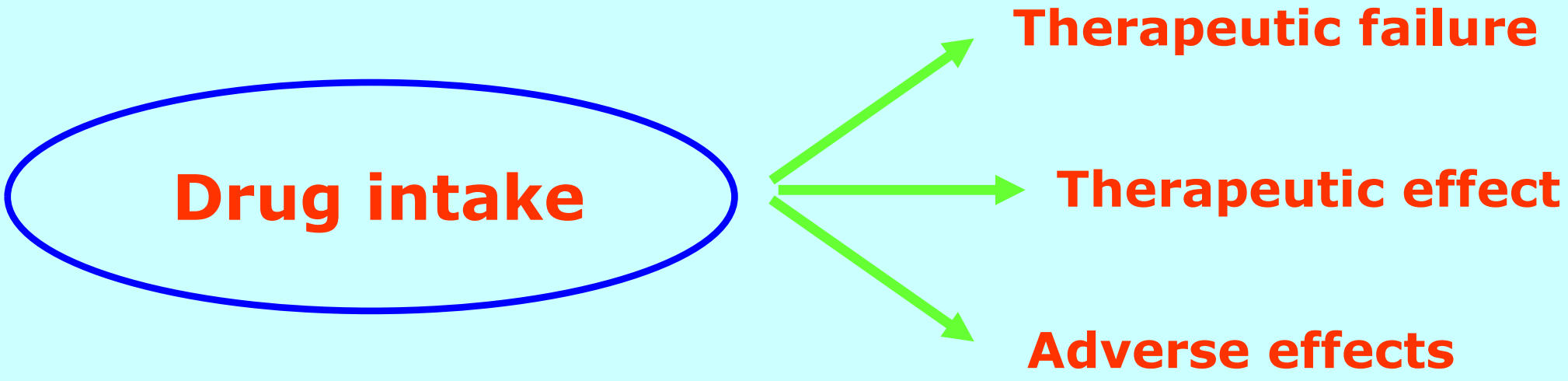
2025.12.02

Gabriella Scordo, MD, PhD

Överläkare Klinisk Farmakologi

Uppsala Akademiska Sjukhuset

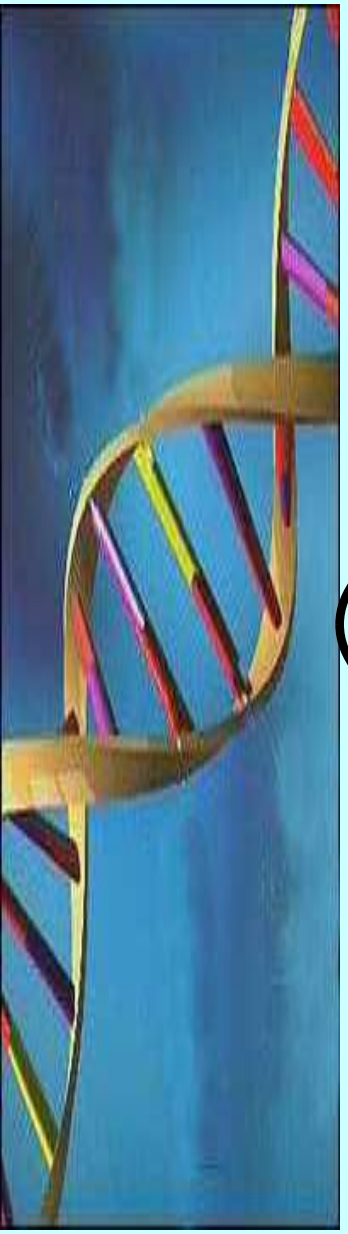



Drug intake
Therapeutic failure
Therapeutic effect
Adverse effects

One dose does NOT fit all

Variabilitet i läkemedelsrespons

- **Farmakokinetisk variabilitet**
  - skillnader i läkemedels omsättning, distribution och transport
- **Farmakodynamisk variabilitet**
  - skillnader i läkemedels effekt, t ex receptorkänslighet eller target variabilitet
  - "sjukdomens" patofysiologisk variabilitet
- **Psykologisk variabilitet**
  - placebo-effekt
  - förväntningar, tidigare erfarenheter
  - compliance
  - följsamhet till ordination



Interindividual variability in clinical efficacy

GENETIC FACTORS

Age/ Gender

Renal/liver function

Drug intake

PHARMACOKINETICS

PHARMACODYNAMICS

RESPONSE

Diseases

Interactions

Diet

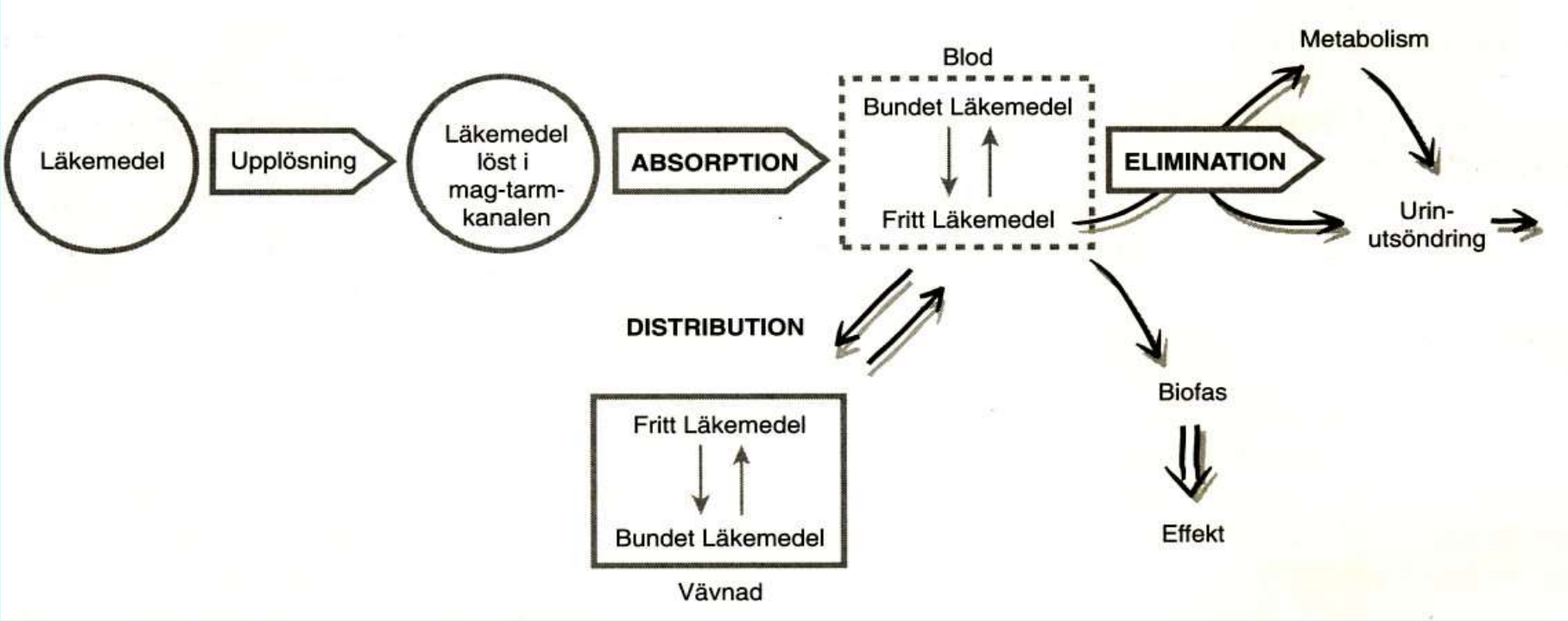
Drug plasma levels

Läkemedlets väg genom kroppen

Absorption (upptag)

Distribution (fördelning)

Elimination (metabolism/nedbrytning/utsöndring)



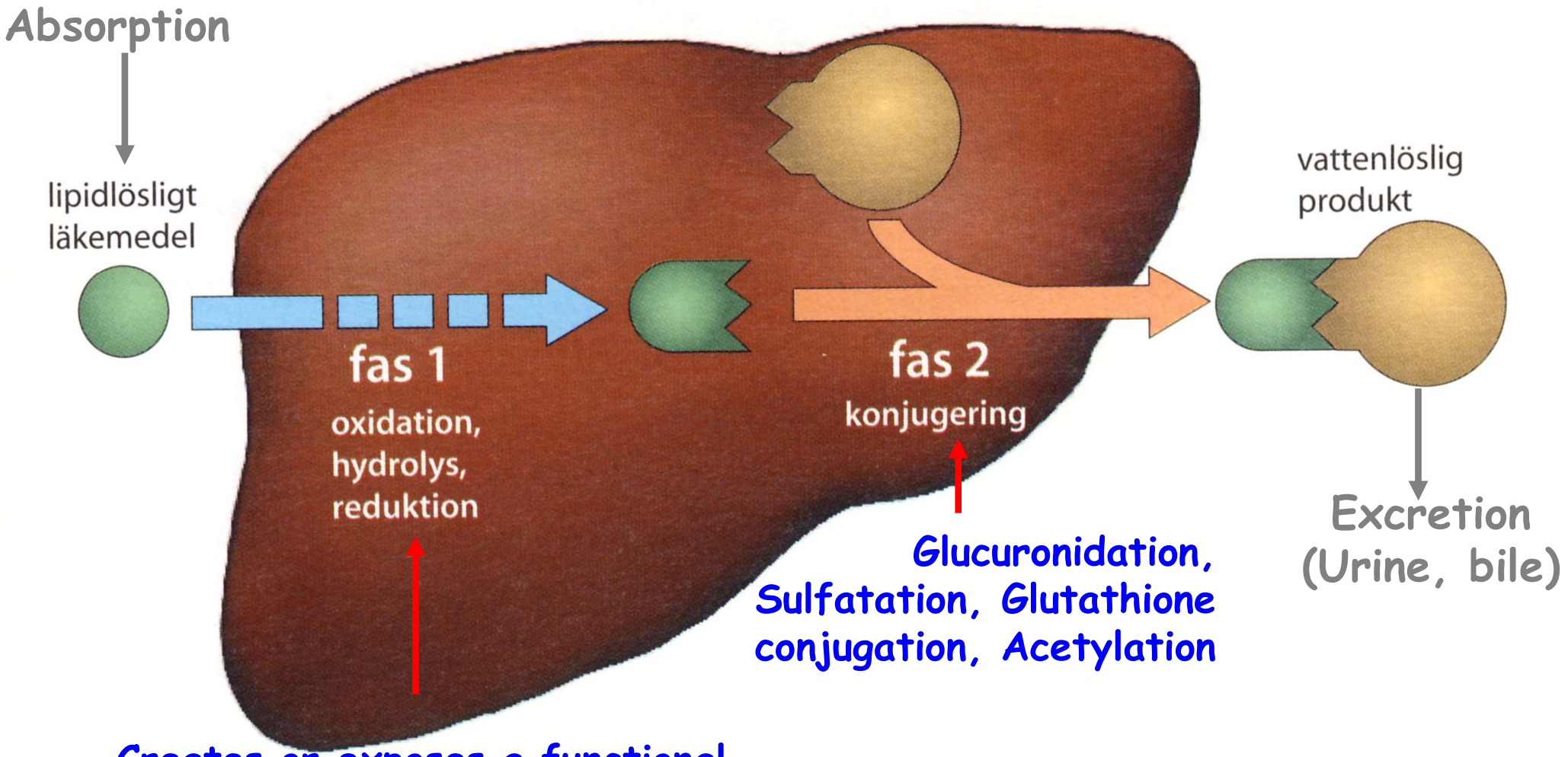
Varför metabolism?

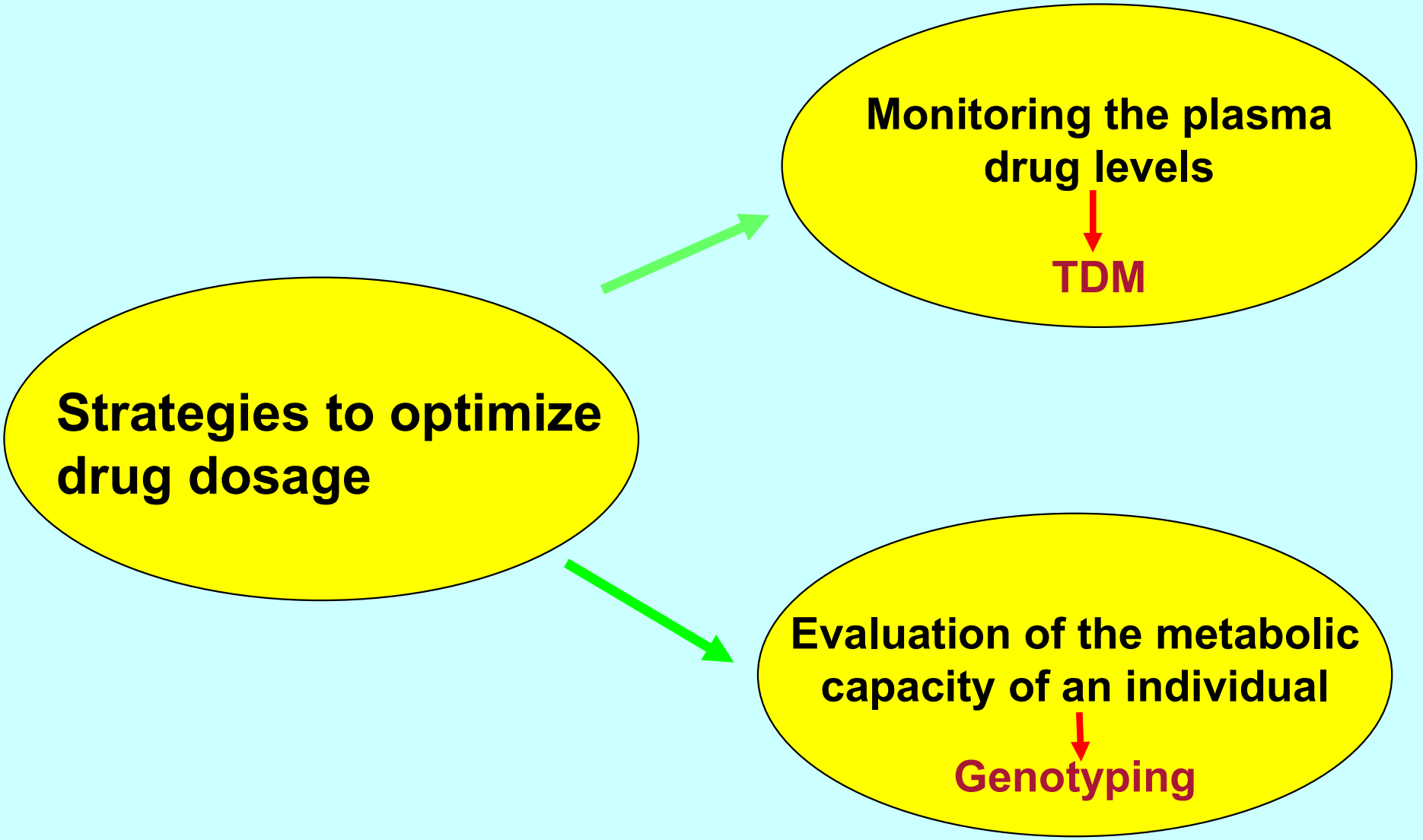
många läkemedel så fettlösliga att de efter primär utsöndring i njurarna absorberas tillbaka till blodet

genom metabolism omvandlas läkemedlet till mer vattenlösliga substanser som lättare kan utsöndras i urinen

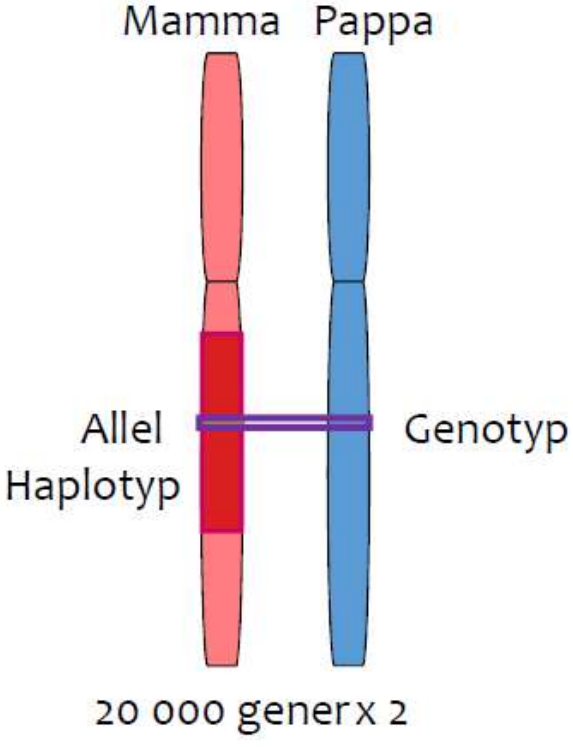
metabolismen sker huvudsakligen i tarmvägg och lever men även i andra vävnader såsom njure, lungor…..

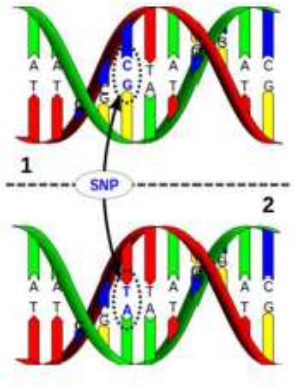
metabolismen utförs till största delen av katalysatorer i form av **enzym** som finns i levern, tarmvägg osv, och som gör läkemedel mer vattenlösliga.


Absorption
lipidlösligt läkemedel
fas 1
oxidation, hydrolys, reduktion
fas 2
konjugering
vattenlöslig produkt
Excretion (Urine, bile)
Glucuronidation, Sulfatation, Glutathione conjugation, Acetylation
Creates or exposes a functional group (OH, NH2, COOH)


Strategies to optimize drug dosage
Monitoring the plasma drug levels
TDM
Evaluation of the metabolic capacity of an individual
Genotyping

Genetisk variation





A C G T: Vi ärver 3 miljarder baser från vardera förälder

Var tusende bas varierar mellan 2 personer

Genetisk variation

Kodande och icke-kodande DNA

TATATATATATATAACGCGATGCCAACCACGGAAATAAAATCATGAATTAA

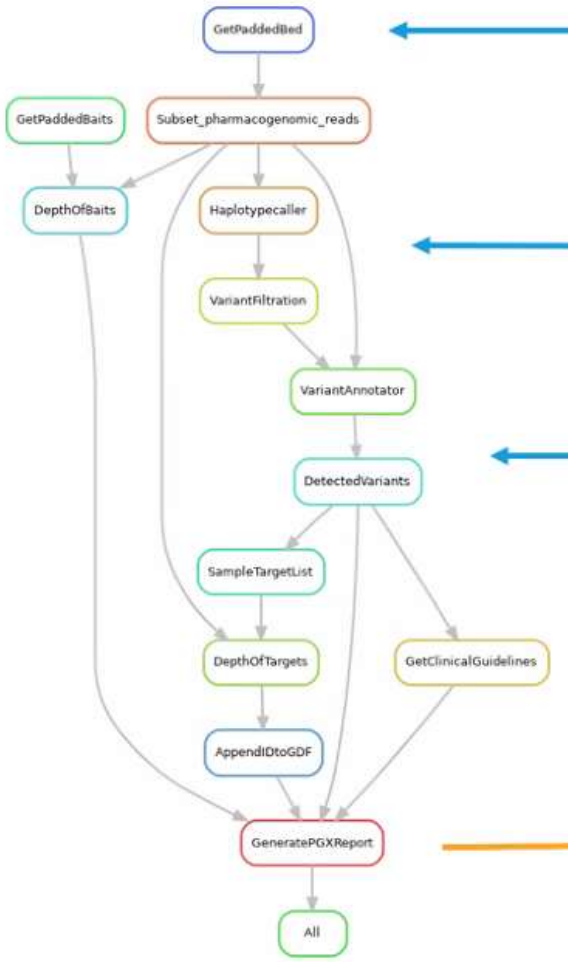
Basparsutbyte

- Single nucelotide polymorphism (SNP)

Variation i antal baser

- Insertion/deletion
- Copy number variation (CNV)

Farmakogenomiskt analysflöde



DNA sekvens

Detektion av ärftliga varianter

Kända funktionella varianter

Kliniska rekommendationer

Provsvar med rekommendationer

Pharmacogenetics methods in vivo

Genotyping

- **Analysis of variations (eg SNPs) in the gene of interest that will lead to the prediction of phenotype**
- **Prior knowledge of the SNPs effect on the enzyme activity**
- **Advantages: no need for (probe) drug intake, the sample can be obtained at any time**
- **Disadvantages: rough classification of the population in few groups, ev. interethnic differences, phenocopy**

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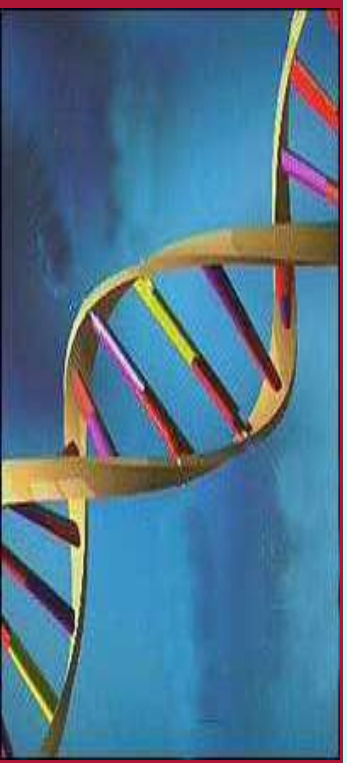
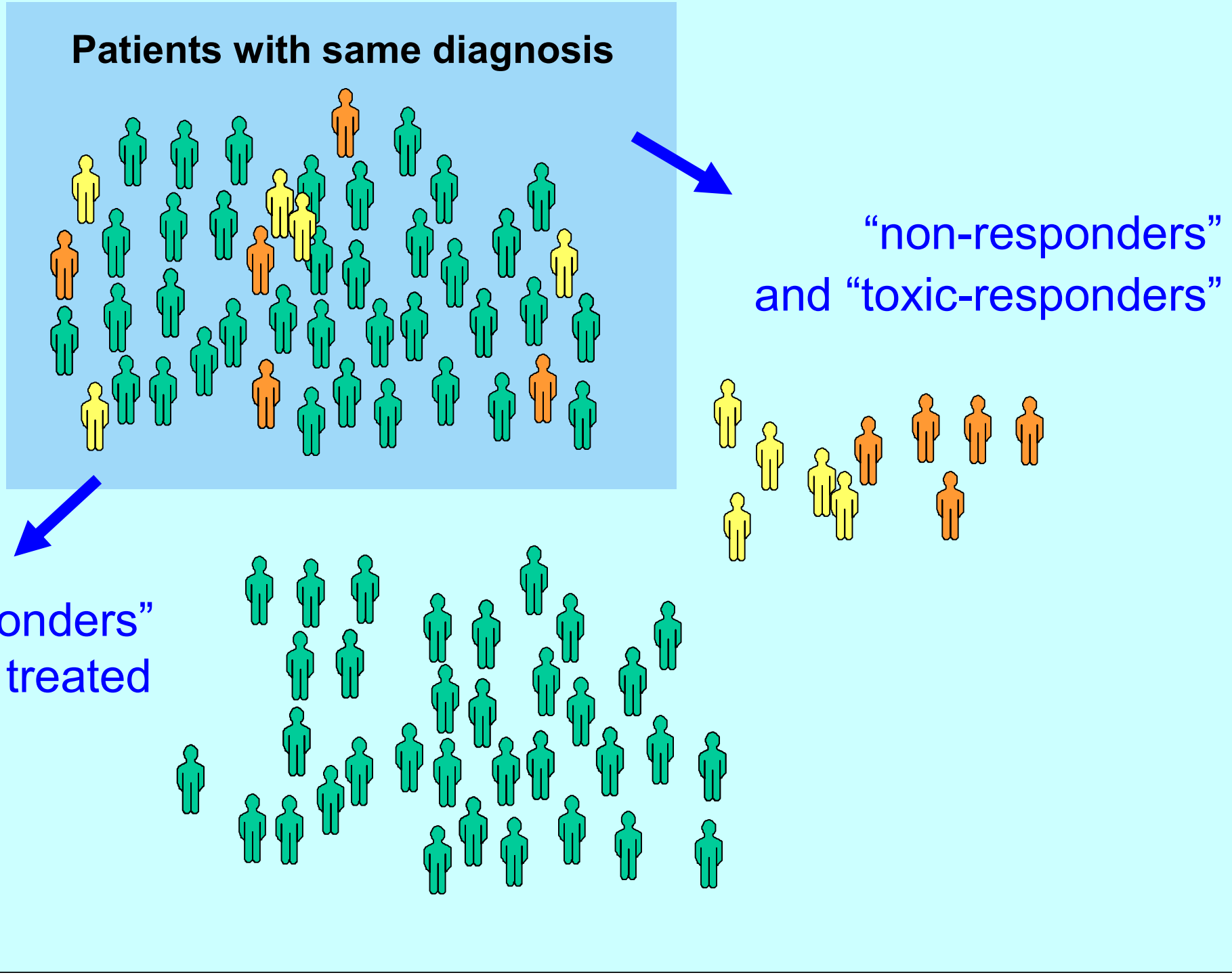


Indications for genotyping

- lack of optimal drug response/therapeutic failure
- side-effects
- patient characterisation before starting therapy


Patients with same diagnosis
"non-responders"
and "toxic-responders"
"responders"
to be treated

Kinetic and clinical consequences of genetic polmorphisms

Poor metabolisers

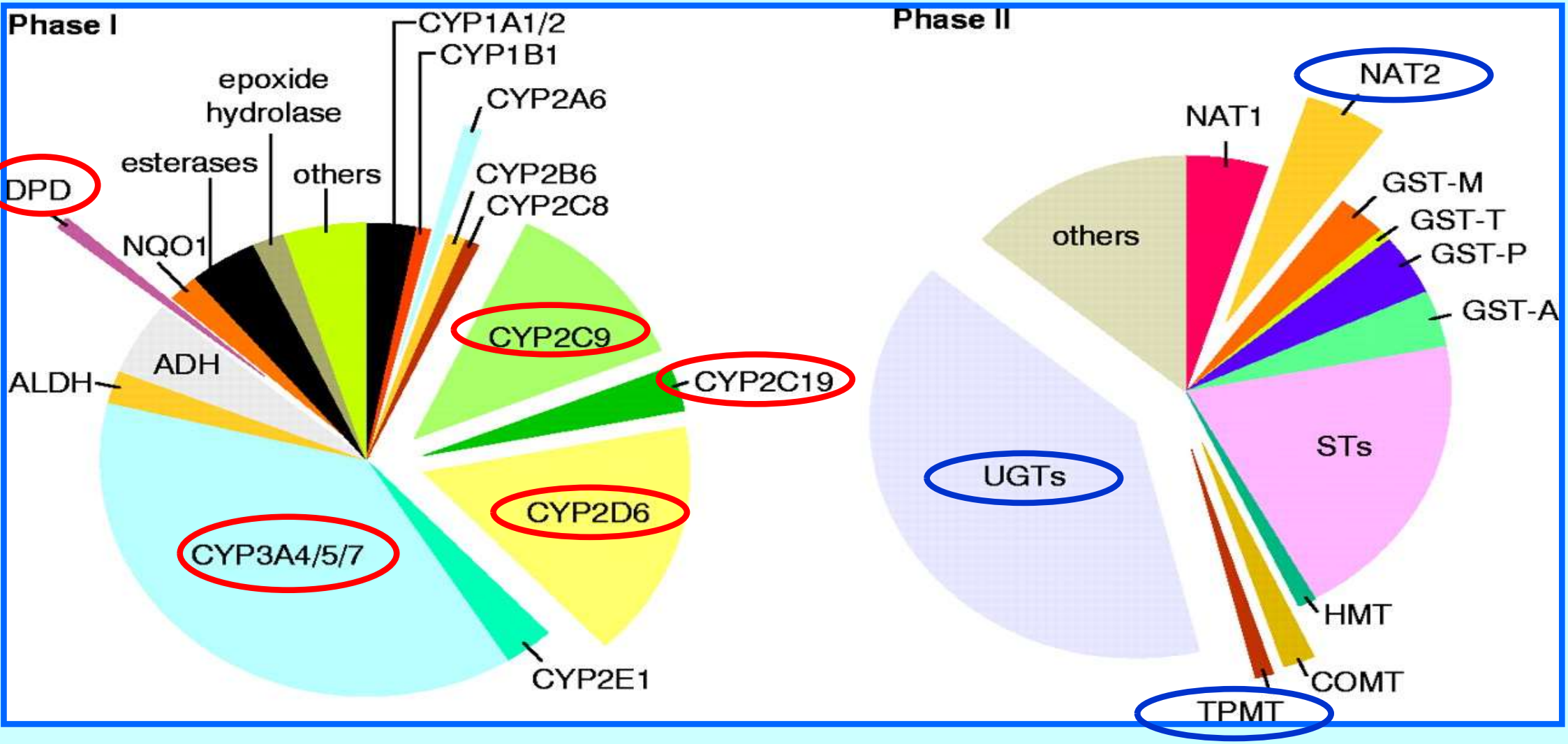
Reduced inactivation → **toxicity**

Reduced production of active metabolites → **therapeutic failure**

Ultrarapid metabolisers

Enhanced inactivation → **therapeutic failure**

Enhanced production of active metabolites → **toxicity**



Evans and Relling, Science 286:487-491, 1999

Hur bör man jobba med genotypningsanalyser?

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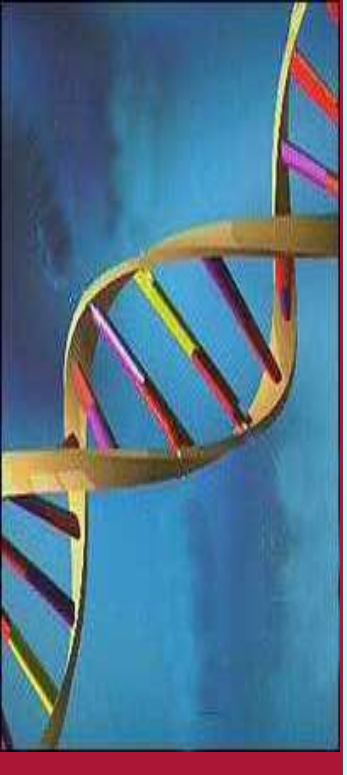

Preanalytisk bedömning

En preanalytisk granskning bör göras, för att minska onödiga beställningar. Vid oklarheter bör beställaren kontaktas för att diskutera och nå koncensus om vilka genotyper som ska analyseras. I bedömningen väger man in vilka analyser som är beställda, patientens läkemedel och indikation för genotypning.

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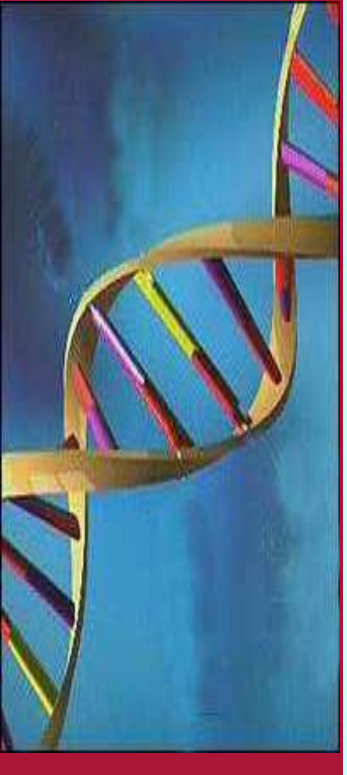

Stämmer allt?????

Behandlas patienten med läkemedel som är kända substraten av polymorfa enzymer?
Är alla beställda analyserna betydelsefulla i det aktuellt fall?
Har någon analys av betydelse inte beställts?

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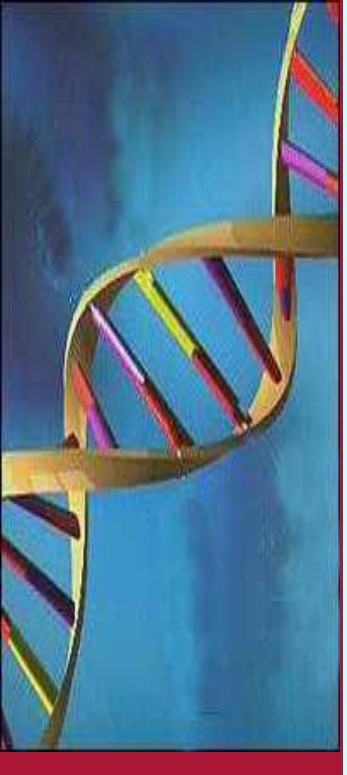

Viktiga källor

1. https://www.pharmgkb.org/

Hanteras av Stanford University

https://www.pharmgkb.org/

PharmGKB annotates PGx-based drug dosing guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), and other professional societies including the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and the French National Network of Pharmacogenetics (RNPGx). PharmGKB annotations present a brief summary of the genotype-based dosing recommendations and links to the source publications/documents.

Annotation of CPIC Guideline for clopidogrel and CYP2C19

Alternate Drug | Pediatric

Summary

The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy for CYP2C19 poor or intermediate metabolizers (cardiovascular indications: prasugrel or ticagrelor if no contraindication; neurovascular indications: alternative P2Y12 inhibitor if clinically indicated and no contraindication.)

Specify a genotype for specific annotations

Pick alleles for CYP2C19

*2 | *2

Alleles not present in the above pull-down menus have no guideline recommendation.

Alternate Drug

Submitted Genotype

CYP2C19: *2/*2

Matched Phenotype

CYP2C19: Poor Metabolizer

Implications

CYP2C19: Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events

Recommendation

Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication.

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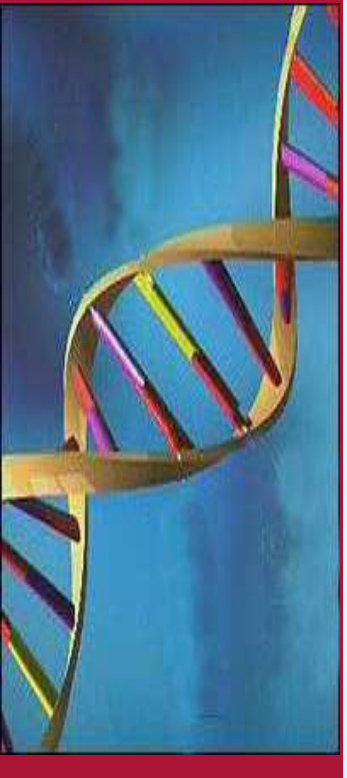

Viktiga källor

1. https://www.pharmgkb.org/
2. https://www.pharmvar.org/genes

Pharmacogene Variation Consortium
https://www.pharmvar.org/genes

The Pharmacogene Variation (PharmVar) Consortium is the new home for PGx gene nomenclature serving as a centralized 'Next-Generation' Pharmacogene Variation data repository. The major focus of PharmVar is to catalogue allelic variation of genes impacting drug metabolism, disposition and response and provide a unifying designation system (nomenclature) for the global pharmacogenetic/genomic community.
PharmVar has developed a rating system (0-100 points) to prioritize genes for PharmVar consideration.

PharmVar Gene	Points	Priority level
CYP2C19	100	high
CYP2C9	100	high
CYP2D6	100	high
CYP3A5	100	high
SLCO1B1	100	high
CYP2B6	95	high
CYP4F2	90	high
DPYD	85	high
NUDT15	85	high
NAT2	65	medium
CYP3A4	62	medium
CYP2C8	52	medium
CYP2A6	55	medium
CYP2A13	30	low
CYP1A2	5	low

Updated August 2024

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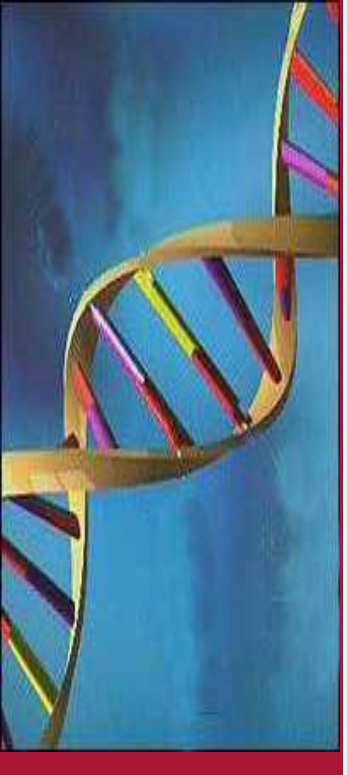
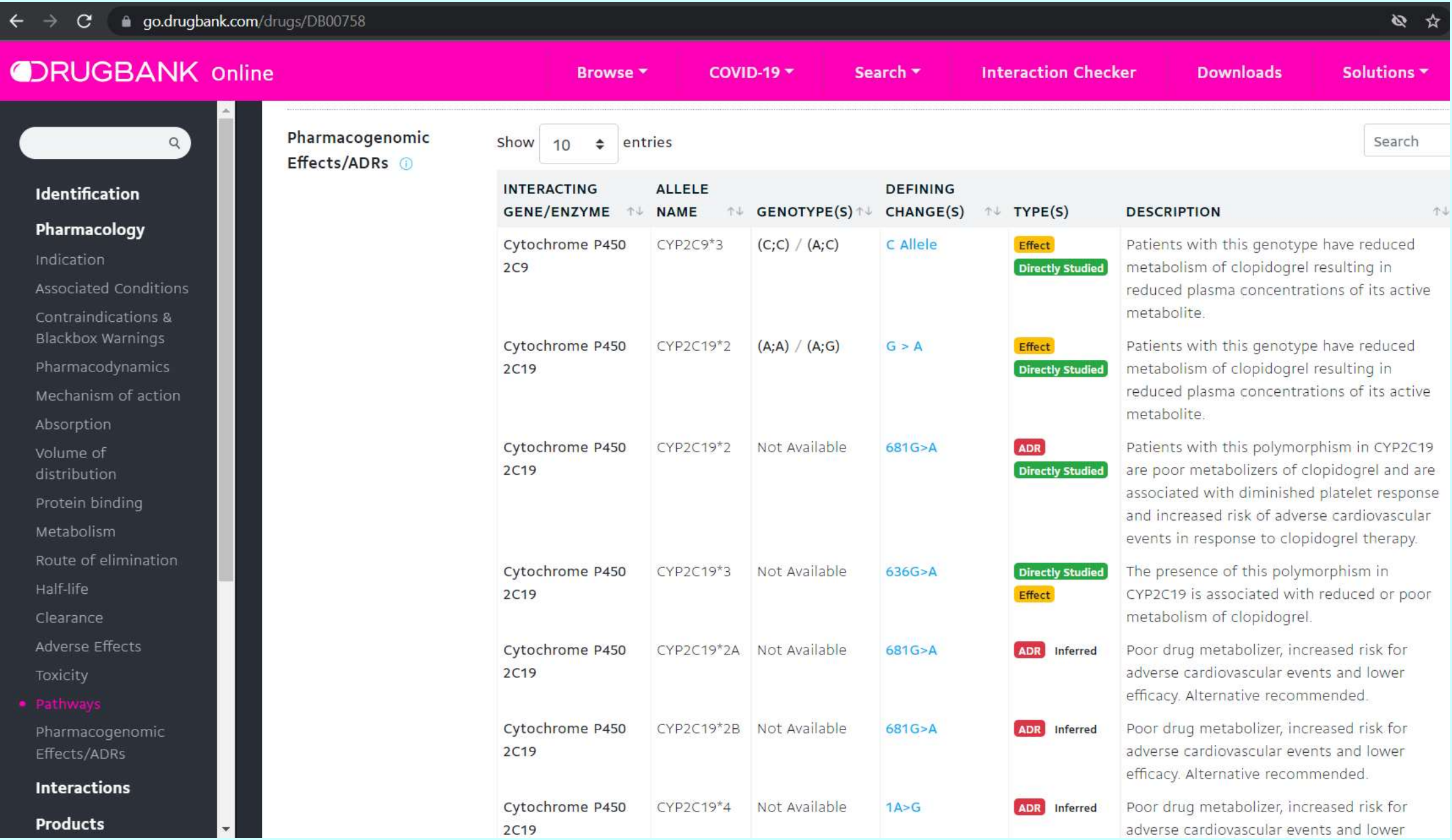


Viktiga källor

1. https://www.pharmgkb.org/
2. https://www.pharmvar.org/genes
3. go.drugbank.com

go.drugbank.com



INTERACTING GENE/ENZYME	ALLELE NAME	GENOTYPE(S)	DEFINING CHANGE(S)	TYPE(S)	DESCRIPTION
Cytochrome P450 2C9	CYP2C9*3	(C;C) / (A;C)	C Allele	Effect, Directly Studied	Patients with this genotype have reduced metabolism of clopidogrel resulting in reduced plasma concentrations of its active metabolite.
Cytochrome P450 2C19	CYP2C19*2	(A;A) / (A;G)	G > A	Effect, Directly Studied	Patients with this genotype have reduced metabolism of clopidogrel resulting in reduced plasma concentrations of its active metabolite.
Cytochrome P450 2C19	CYP2C19*2	Not Available	681G>A	ADR, Directly Studied	Patients with this polymorphism in CYP2C19 are poor metabolizers of clopidogrel and are associated with diminished platelet response and increased risk of adverse cardiovascular events in response to clopidogrel therapy.
Cytochrome P450 2C19	CYP2C19*3	Not Available	636G>A	Directly Studied, Effect	The presence of this polymorphism in CYP2C19 is associated with reduced or poor metabolism of clopidogrel.
Cytochrome P450 2C19	CYP2C19*2A	Not Available	681G>A	ADR Inferred	Poor drug metabolizer, increased risk for adverse cardiovascular events and lower efficacy. Alternative recommended.
Cytochrome P450 2C19	CYP2C19*2B	Not Available	681G>A	ADR Inferred	Poor drug metabolizer, increased risk for adverse cardiovascular events and lower efficacy. Alternative recommended.
Cytochrome P450 2C19	CYP2C19*4	Not Available	1A>G	ADR Inferred	Poor drug metabolizer, increased risk for adverse cardiovascular events and lower

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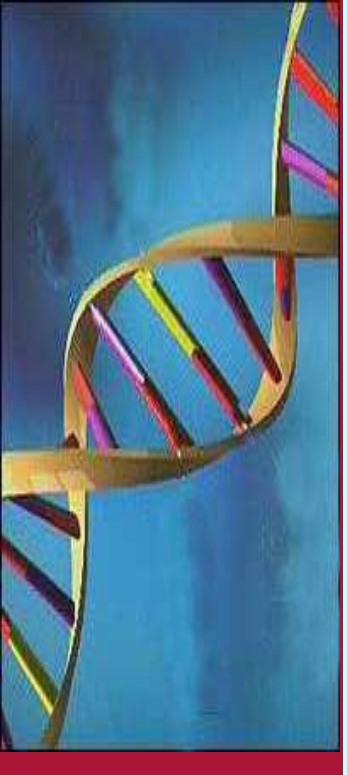


Viktiga källor

1. https://www.pharmgkb.org/
2. https://www.pharmvar.org/genes
3. go.drugbank.com
4. **Flockhart Table ™**

https://drug-interactions.medicine.iu.edu/MainTable.aspx

Hanteras av Dept of Medicine, Clinical Pharmacology,
at Indiana University

Flockhart Table ™

https://drug-interactions.medicine.iu.edu/MainTable.aspx

What do the pages contain?

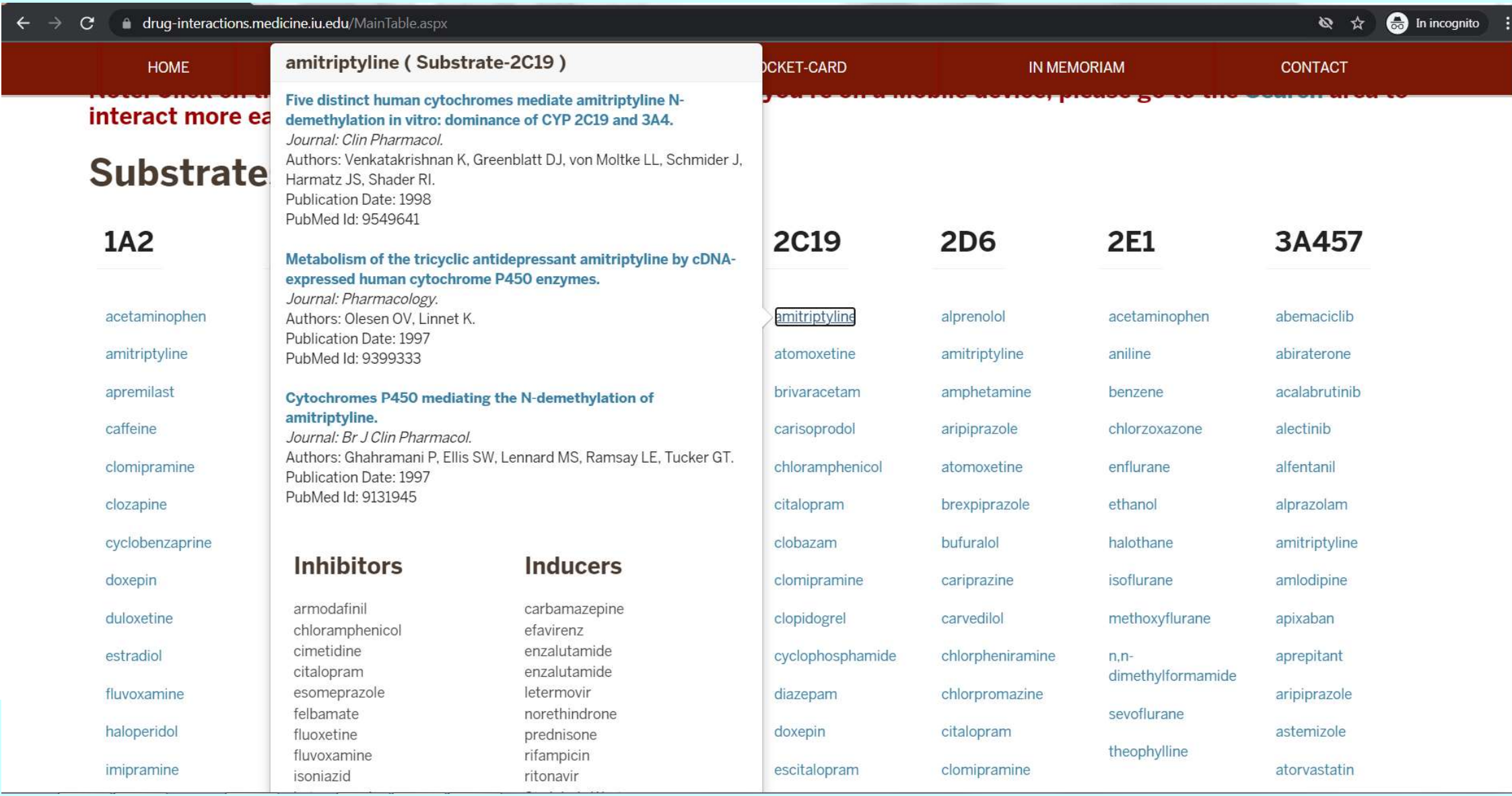
The P450 Drug Interactions Site contains a table with eight (8) columns, one for each of the P450 isoform groups: CYP1A2, etc. In each column you will find:

Substrates: drugs that are metabolized as substrates by the enzyme

Inhibitors: drugs that prevent the enzyme from metabolizing the substrates

Activators: drugs that increase the enzyme's ability to metabolize the substrates

Clicking on the drug name further information will pop up.



Viktiga källor

1. https://www.pharmgkb.org/
2. https://www.pharmvar.org/genes
3. go.drugbank.com
4. Flockhart Table ™
   https://drug-interactions.medicine.iu.edu/MainTable.aspx
5. https://www.micromedexsolutions.com/micromedex2/librarian
6. https://www.uptodate.com/contents/search
7. https://www.fass.se/LIF/startpage?userType=0
8. https://pubmed.ncbi.nlm.nih.gov/

….and if you are desperate: https://www.google.com/

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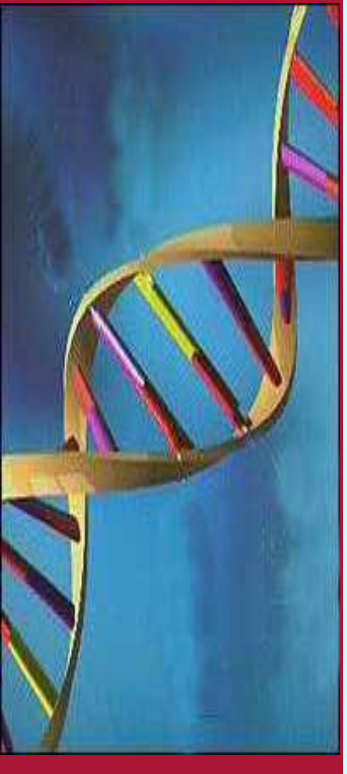
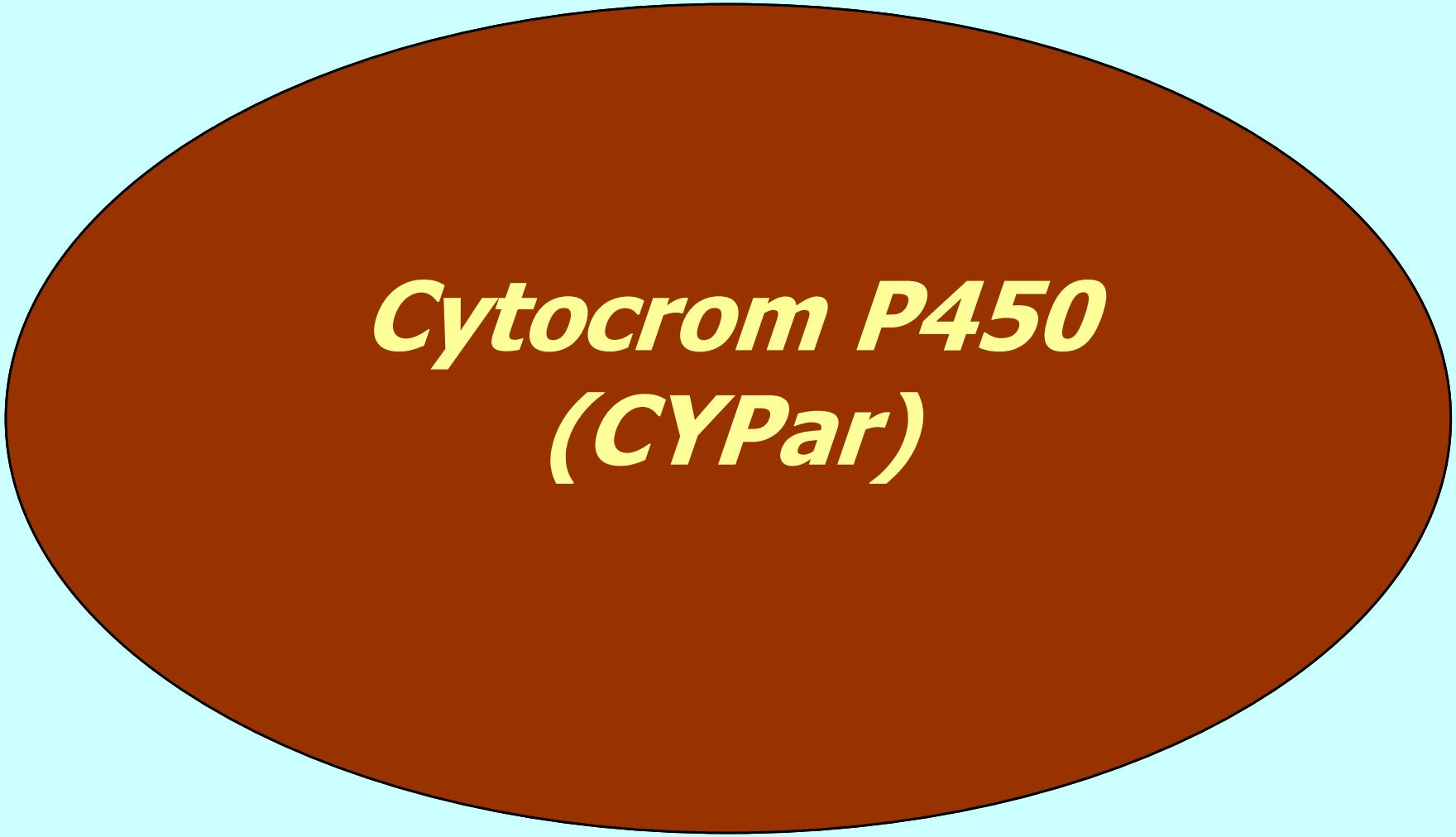
Genotypning bedömning



För de flesta genotypningarna kan en automatisk fast kommentar skickas ut.

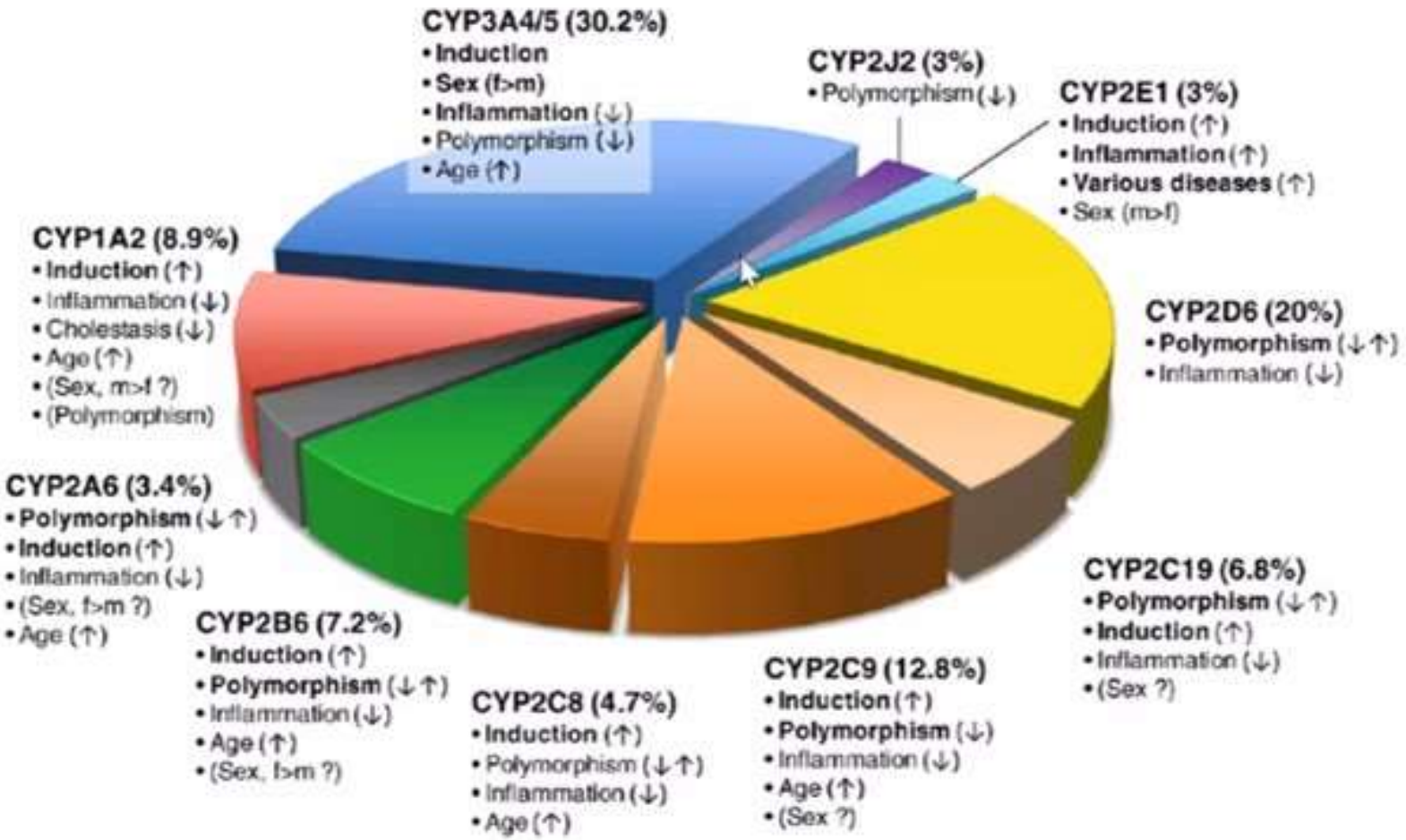
För de flesta CYPar bör dock den automatiska kommentaren kompletteras. I bedömningen väger man in vilka analyser som är beställda, patientens övriga läkemedel och indikation för genotypning.


Cytocrom P450
(CYPar)

Cytokrom P450 (CYP)

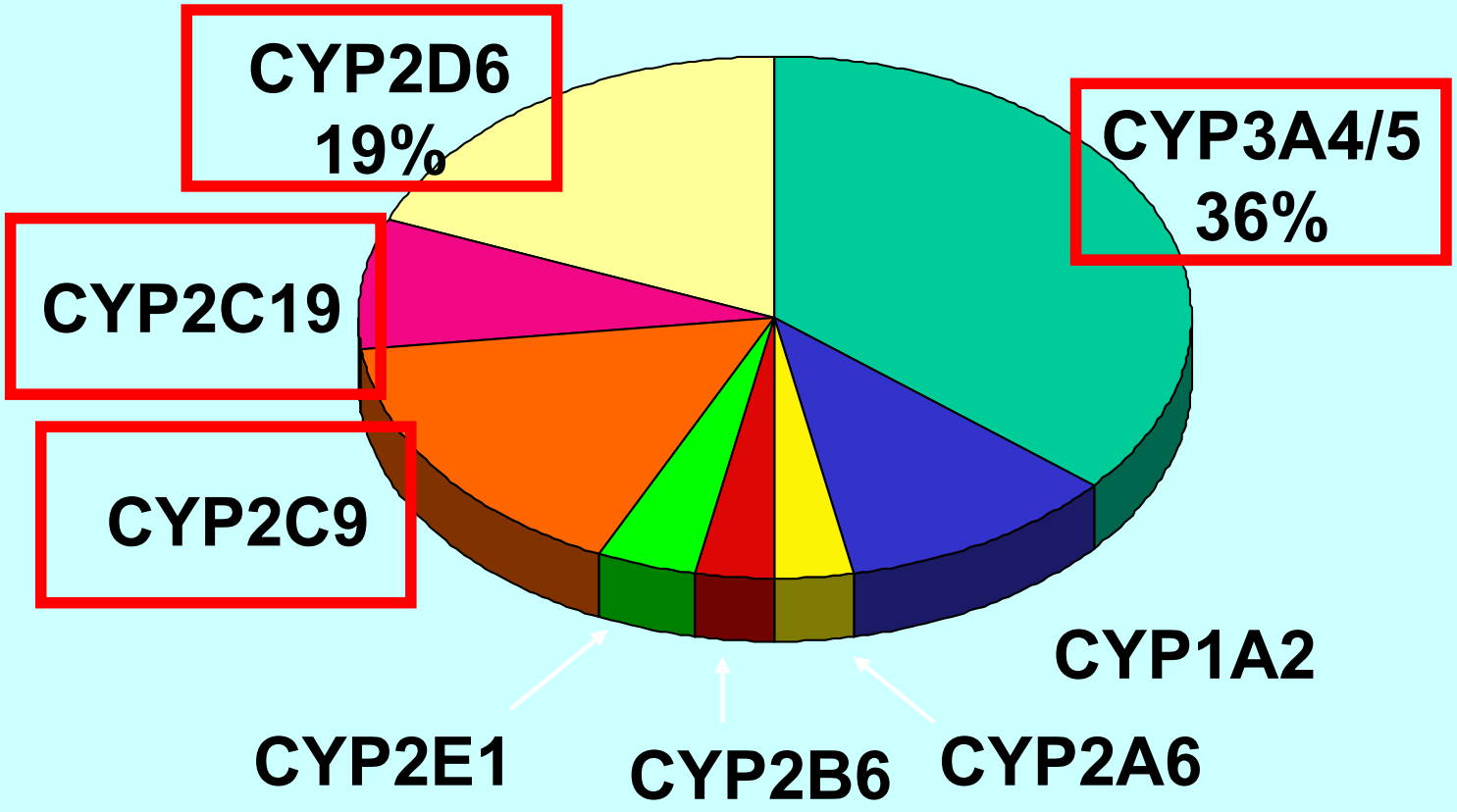
- Finns i samtliga av kroppens alla celler förutom
  – Erytrocyter
  – Muskelceller
- Stort antal isoezymer
- Stor genetisk och omgivningsinducerad variation

CYP450



Zanger & Schwab. Pharmacology & Theraputics 2013

Proportion of drugs metabolised by the different CYPs



Examples of polimorphic drug metabolism

CYP2D6

Substrates
amitriptyline, clomipramine, imipramine, desipramine, nortriptyline, trazodone, fluoxetine, paroxetine, fluvoxamine, citalopram, venlafaxine, mianserin, mirtazapine thioridazine, perphenazine, zuclopenthixol, haloperidol, risperidone, clozapine, olanzapine, sertindole, codeine, destromethorphan, tramadol, alprenolol, bufuralol, metoprolol, propanolol, timolol, pindolol, encainide, flecainide, propafenone, debrisoquine, sparteine, phenformin, **tamoxifen**

CYP2C9

Substrates
diclofenac, ibuprofen, naproxen, piroxicam, phenytoin, phenobarbital, valproic acid, ***S*-warfarin**, phenytoin, tolbutamide, losartan, torasemide
Siponimod (Mayzent)

CYP2C19

Substrates
amitriptyline, clomipramine, imipramine, citalopram, moclobemide phenytoin, diazepam, omeprazole, propranolol, proguanil, *S*-mephenytoin, *R*-warfarin
Mavacamten (Camzyos)

CYP2D6 GENETIC POLYMORPHISM

Enzyme	**CYP2D6**
Gene locus	**Chromosome 22**
Inheritance	**Autosomal recessive**
Phenotyping	**Probe drugs:** **- debrisoquine** **- sparteine** **- dextromethorphan**

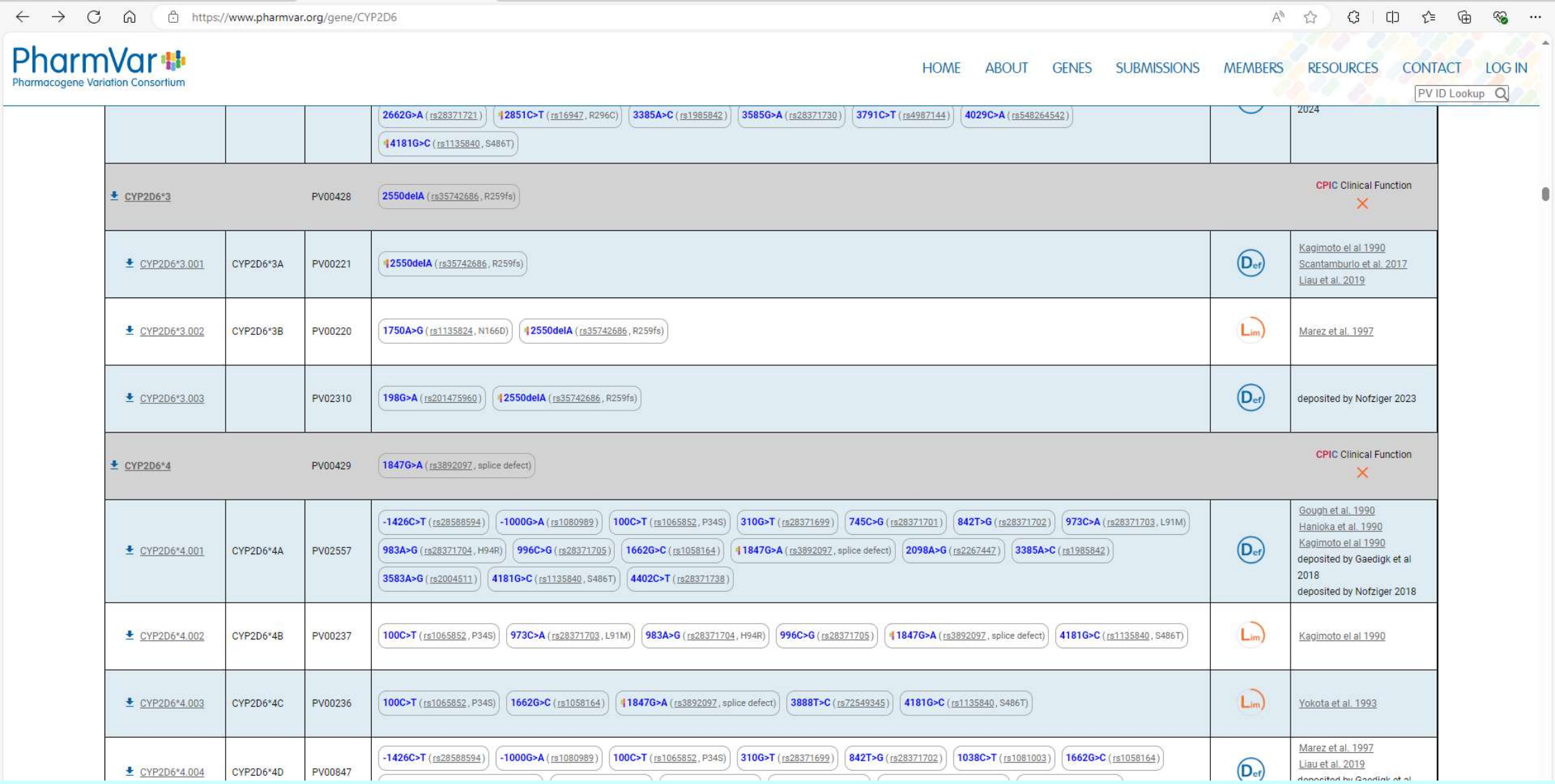
Interethinic differences

	% PM	% UM
Sweden	**7**	**1-2**
Italy	**5**	**10**
Orientals	**<1**	**0.5-2.5**
Blacks (Ethiopia)	**4-7**	**29**

Major *CYP2D6* allelic variants

Mutated alleles	Mutation	Consequences	Frequencies
*CYP2D6*3*	Frame-shift	Inactive enzyme	1-2%
*CYP2D6*4*	Defective splicing	Inactive enzyme	12-21 %
*CYP2D6*5*	Gene deletion	No enzyme	2-7%
*CYP2D6*6*	Frame-shift generating stop codon	Inactive enzyme	1-2%
*CYP2D6*2xN*	Gene duplication	Increased enzyme activity	2-10%
*CYP2D6*10*	Pro34Ser, Ser486Thr	Unstable enzyme	1-2% Caucasians 51% Asians
*CYP2D6*17*	Thr107Ile, Arg296Cys, Ser486Thr	Reduced affinity for substrates	0% Caucasians 34% Africans
*CYP2D6*41*	Splicing defect	Decreased activity	14% Caucasians

https://www.pharmvar.org/



https://www.pharmvar.org/gene/CYP2D6

PharmVar
Pharmacogene Variation Consortium

HOME ABOUT GENES SUBMISSIONS MEMBERS RESOURCES CONTACT LOG IN

PV ID Lookup

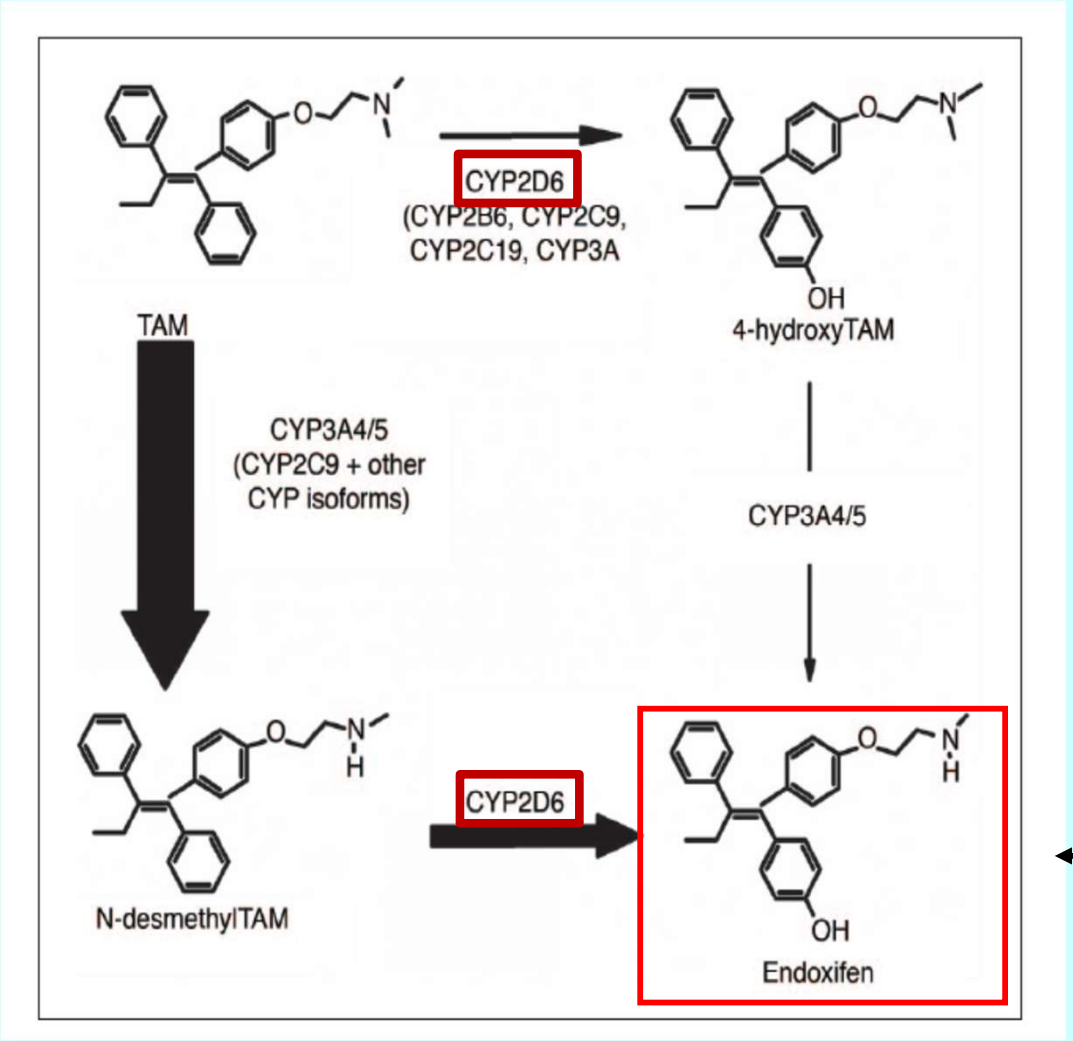
			2662G>A (rs28371721) 2851C>T (rs16947, R296C) 3385A>C (rs1985842) 3585G>A (rs28371730) 3791C>T (rs4987144) 4029C>A (rs548264542) 4181G>C (rs1135840, S486T)		2024
CYP2D6*3		PV00428	2550delA (rs35742686, R259fs)		CPIC Clinical Function ✕
CYP2D6*3.001	CYP2D6*3A	PV00221	2550delA (rs35742686, R259fs)	Def	Kagimoto et al 1990 Scantamburlo et al. 2017 Liau et al. 2019
CYP2D6*3.002	CYP2D6*3B	PV00220	1750A>G (rs1135824, N166D) 2550delA (rs35742686, R259fs)	Lim	Marez et al. 1997
CYP2D6*3.003		PV02310	198G>A (rs201475960) 2550delA (rs35742686, R259fs)	Def	deposited by Nofziger 2023
CYP2D6*4		PV00429	1847G>A (rs3892097, splice defect)		CPIC Clinical Function ✕
CYP2D6*4.001	CYP2D6*4A	PV02557	-1426C>T (rs28588594) -1000G>A (rs1080989) 100C>T (rs1065852, P34S) 310G>T (rs28371699) 745C>G (rs28371701) 842T>G (rs28371702) 973C>A (rs28371703, L91M) 983A>G (rs28371704, H94R) 996C>G (rs28371705) 1662G>C (rs1058164) 1847G>A (rs3892097, splice defect) 2098A>G (rs2267447) 3385A>C (rs1985842) 3583A>G (rs2004511) 4181G>C (rs1135840, S486T) 4402C>T (rs28371738)	Def	Gough et al. 1990 Hanioka et al. 1990 Kagimoto et al 1990 deposited by Gaedigk et al 2018 deposited by Nofziger 2018
CYP2D6*4.002	CYP2D6*4B	PV00237	100C>T (rs1065852, P34S) 973C>A (rs28371703, L91M) 983A>G (rs28371704, H94R) 996C>G (rs28371705) 1847G>A (rs3892097, splice defect) 4181G>C (rs1135840, S486T)	Lim	Kagimoto et al 1990
CYP2D6*4.003	CYP2D6*4C	PV00236	100C>T (rs1065852, P34S) 1662G>C (rs1058164) 1847G>A (rs3892097, splice defect) 3888T>C (rs72549345) 4181G>C (rs1135840, S486T)	Lim	Yokota et al. 1993
CYP2D6*4.004	CYP2D6*4D	PV00847	-1426C>T (rs28588594) -1000G>A (rs1080989) 100C>T (rs1065852, P34S) 310G>T (rs28371699) 842T>G (rs28371702) 1038C>T (rs1081003) 1662G>C (rs1058164)	Def	Marez et al. 1997 Liau et al. 2019

Last checked Dec 2nd, 2025: CYP2D6*184

Clinical consequences of *CYP2D6* poor metabolism

Tamoxifen	lack of antitumoral efficacy
Flecainide	ventricular tachiarhytmias
Propafenone	CNS toxicity, broncoconstriction
Metoprolol	loss of cardioselectivity
Nortriptyline	hypotension, confusion
Venlafaxine	Cardiovascular toxicity
Classical neuroleptics	EPS, sedation, QT-prolongation
Codein	lack of antidolorific effect

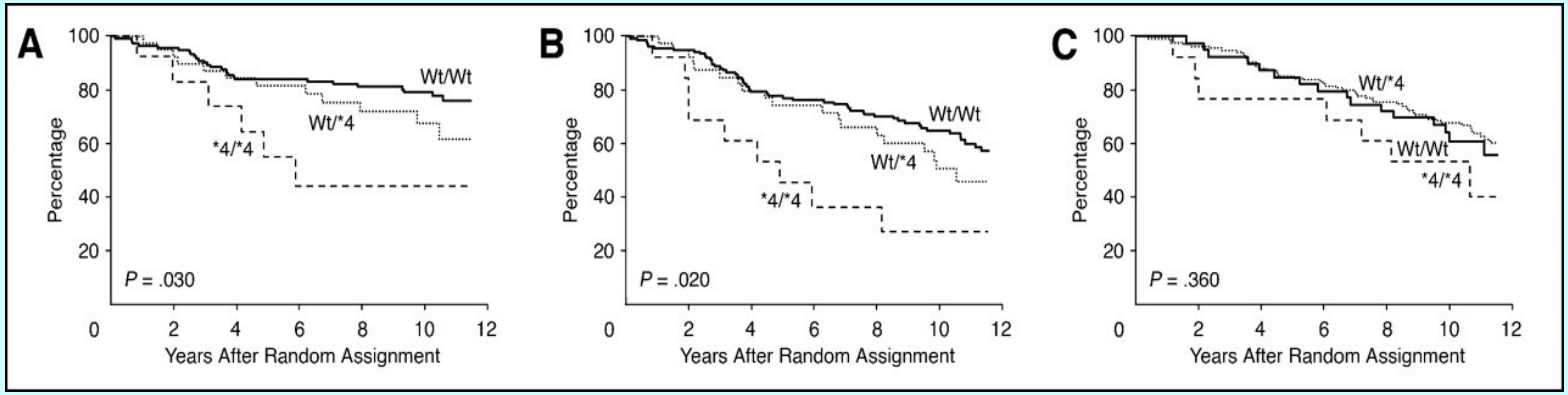
Tamoxifen: läkemedel vid bröstcancer



← Metaboliten ger effekten!

From Goetz et al, J Clin Oncol 2005; 23

Tamoxifen effekt och *CYP2D6* genotyp



Goetz M P et al. JCO 2005;23:9312-9318

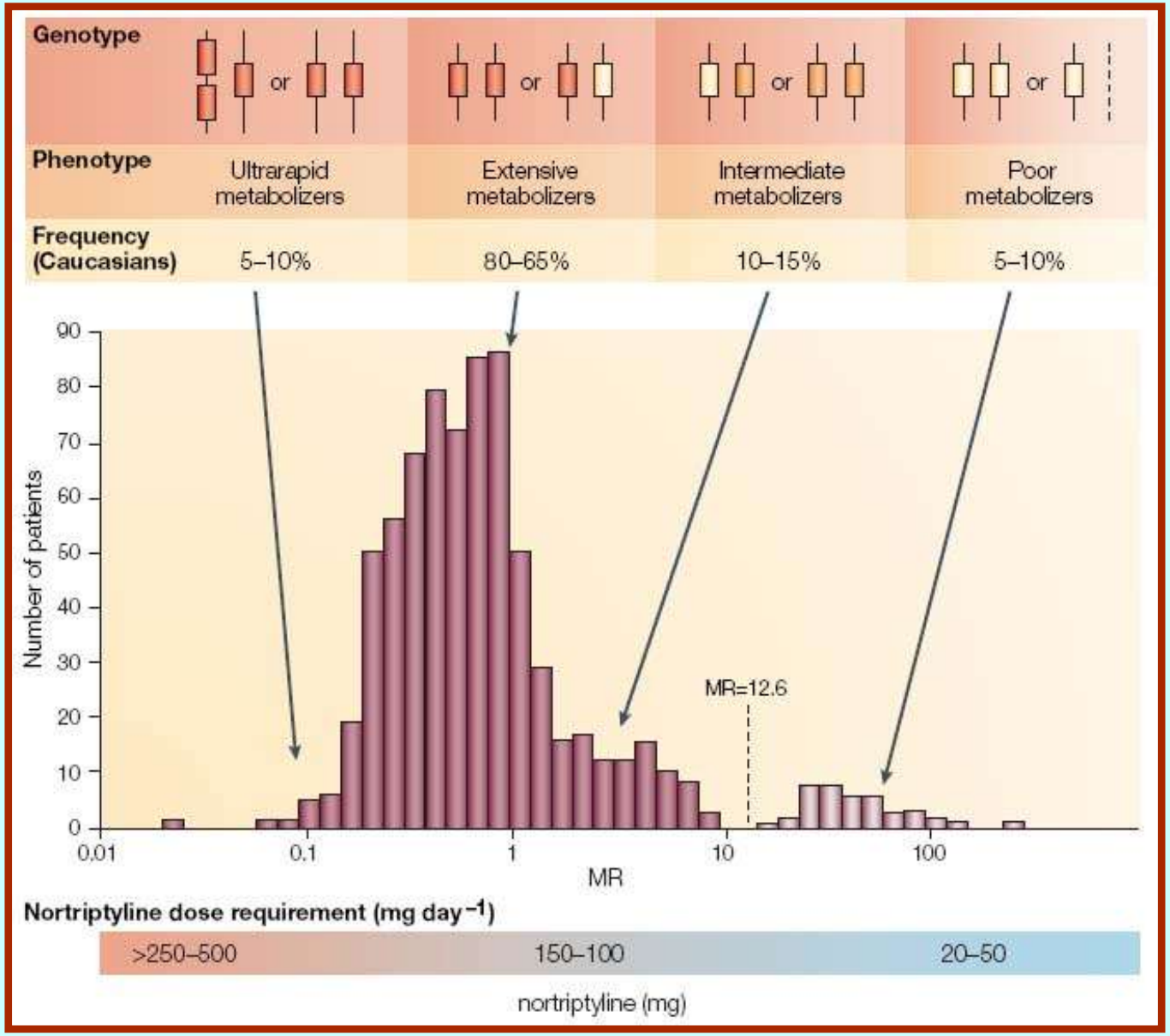
A) relapse-free time

B) disease-free survival

C) overall survival

About 200 postmenopausal women with resected ER-positive breast cancer

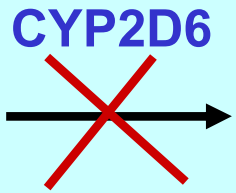
CYP2D6 genotype and nortriptyline dose requirement



Meyer, 2004

Opioids and CYP2D6

Reduced/lack of analgesic effect of codeine in patients PM for CYP2D6 due to the reduced production of morphine

Codein 

Morphine

Increased risk for morphine intoxication in patients UM for CYP2D6 due to the increased production of morphine

N Engl J Med 2004; 351:2827-2831 (life-threatening opioid intoxication)

Lancet 2006; 368: 704 (morphine poisoning in a breastfed neonate)

CYP2C9 GENETIC POLYMORPHISM

Enzyme	**CYP2C9**
Gene locus	**Chromosome 10**
% PM	**2-6%**
Inheritance	**Autosomal recessive**
Phenotyping	**Probe drugs:** **- S-warfarin** **- losartan**
Genotyping	**Major allelic variants:** ***CYP2C9*2*** **(8-10% Caucasians 0% Orientals)** ***CYP2C9*3*** **(6-10% Caucasians 2-3% Orientals)**

Clinical consequences of *CYP2C9* poor metabolism

Warfarin	→	**Bleeding**
Tolbutamide	→	**Hypoglycemia**
Phenytoin	→	**Ataxia**
Siponimod	→	**Toxicity (**bradycardia, risk of infection, elevated liver enzymes)

CYP2C19 GENETIC POLYMORPHISM

Enzyme	**CYP2C19**
Gene locus	**Chromosome 10**
% PM	**2- 4% Caucasians** **15-20% Orientals**
Inheritance	**Autosomal recessive**
Phenotyping	**Probe drugs:** **- omeprazole**
Genotyping	***CYP2C19*2*** **(10-15% Caucasians** **25-30% Orientals)** ***CYP2C19*3*** **(0-1% Caucasians** **5-10% Orientals)** ***CYP2C19*4*** **(0.5-1% Caucasians)** ***CYP2C19*17*** **(10-20%)**

Clinical consequences of *CYP2C19* poor metabolism

Clopidogrel	→	Lack of efficacy
Escitalopram	→	Risk for ADRs
Mavacamten	→	Risk for cardiotoxicity

Clinical consequences of *CYP2C19* increased metabolism

Escitalopram	→	Lack of efficacy

CYP3A4/3A5 GENETIC POLYMORPHISM

Enzyme	**CYP3A4/3A5**
Gene locus	**Chromosome 7**
Phenotyping	**Erithromycin**
Genotyping	**Major allelic variants:**

-*CYP3A4*1B* (4.5% Caucasians)	**decreased activity**
-*CYP3A5*3* (85-90% Caucasians)	**no activity**
-*CYP3A5*6* (0.5-1% Orientals)	**no activity**

Substrates

amitriptyline, clomipramine, imipramine, trazodone, sertraline, nefazodone, mirtazapine
haloperidol, clozapine, risperidone, quetiapine, ziprasidone, sertindole
alprazolam, midazolam, triazolam
diltiazem, felodipine, nifedipine, verapamil, cyclosporin, tacrolimus
cisapride, terfenadine, astemizole, carbamazepine, erythromocyn, clarytromycin,
tamoxifen, amiodarone, quinidine, methadone, ethynilestradiol, levonorgestrel, statins

CYP-related drug labels recommendations

Drug		*Biomarker*	*Odd effect*
Clopidogrel	**Actionable PGx**	**CYP2C19**	**Therapy failure**
Mavacamten	**Test Required**	**CYP2C19**	**Toxicity**

Långsam CYP2C19-metaboliserare kan ha ökad mavakamtenexponering (upp till 3 gånger), vilket kan leda till ökad risk för systolisk dysfunktion. Den rekommenderade startdosen är 2,5 mg peroralt en gång dagligen. Den maximala dosen är 5 mg en gång dagligen.

Nortriptyline	**Actionable PGx**	**CYP2D6**	**Toxicity**
Perphenazine	**Actionable PGx**	**CYP2D6**	**Toxicity**
Siponimod	**Test Required**	**CYP2C9**	**Toxicity**

Kontraindicedat för patienter homozygota för CYP2C9*3 (*CYP2C9*3/*3*).
Patienter med genotyp *CYP2C9*1/*3* eller *2/*3: rekommenderade underhållsdosen 1 mg/dygn

Warfarin	**Actionable PGx**	**CYP2C9 - VKORC1**	**Bleeding**

https://www.pharmgkb.org/
https://www.FASS.se

CYP2D6, CYP2C19 och *CYP2C9* analyser vid KKF

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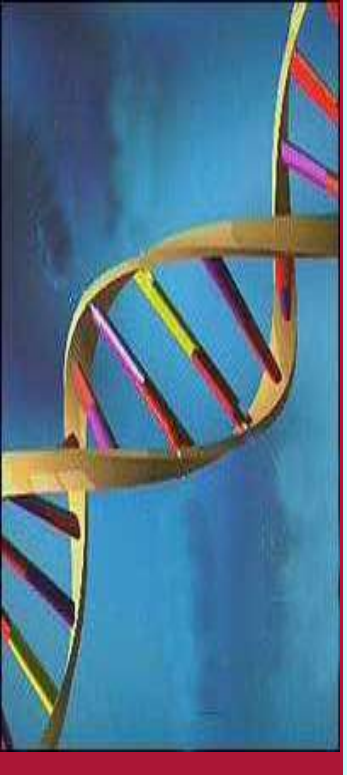

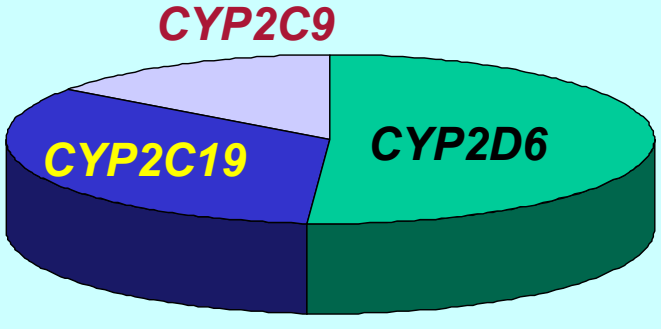

CYP2D6*3, *4, *5, *6, *10, *17, *41, *2xn

CYP2C19*2, *3, *4, *17

CYP2C9*2, *3

(depending on the ethnic background of the patients)

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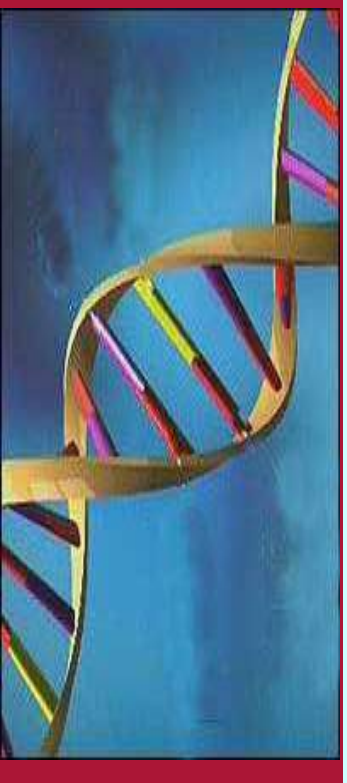

Indications for genotyping

- 50% lack of optimal drug response/therapeutic failure
- 35% side-effects
- 15% patient characterisation before starting therapy

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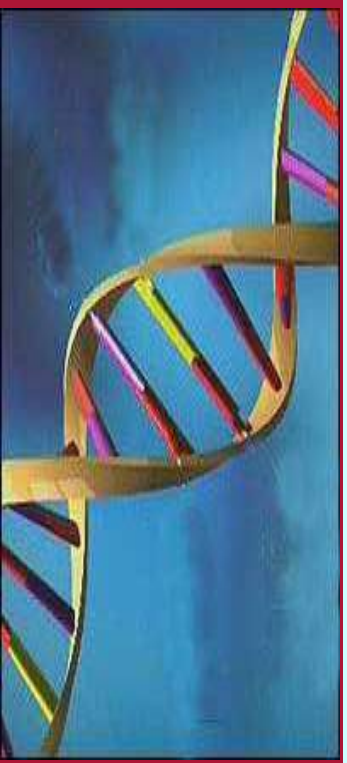

Drugs

- **70% neuropsychoactive drugs**
  - Antipsychotics, antidepressants, anticonvulsants, opioids
- **15% cardiovascular drugs**
  - Metoprolol, propafenon, warfarin, clopidogrel, mavacamten
- **Others**
  - Tamoxifen, NSAIDs, PPIs, siponimod

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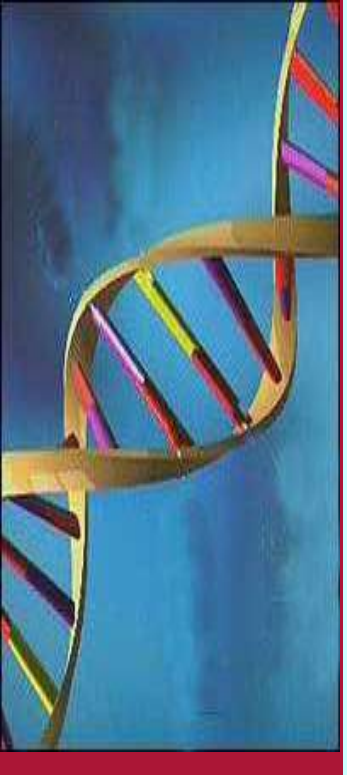


Results

Subjects experiencing therapeutic failure

☞5-10% UMs

Subjects experiencing side-effects

☞~ 15% PMs and ~40% heterozygous EMs

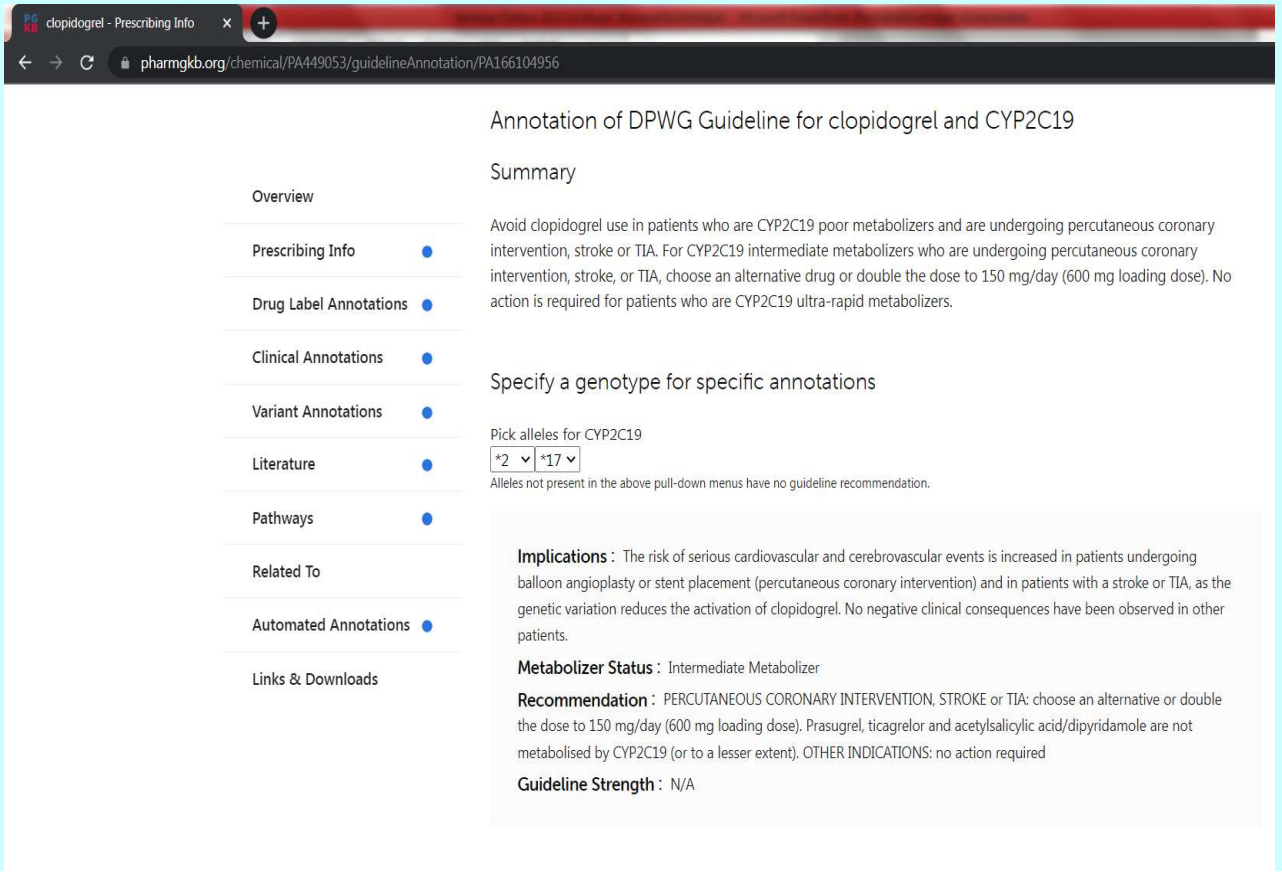
☞~ 5-10% assuming interacting drugs
(t.ex. Bupropion, Fluoxetin or Paroxetin)

CYP2C19 genotyp bedömnig

CYP2C19, genotyp: *2/*17. Denna genotyp är förenad med risk för nedsatt effekt av **klopidogrel**. Annat behandlingsalternativ kan övervägas. Undersökta alleler: *2, *4 och *17.

För utförlig lista över läkemedel som metaboliseras via CYP2C19, vg se: <http://medicine.iupui.edu/clinpharm/ddis/main-table/>

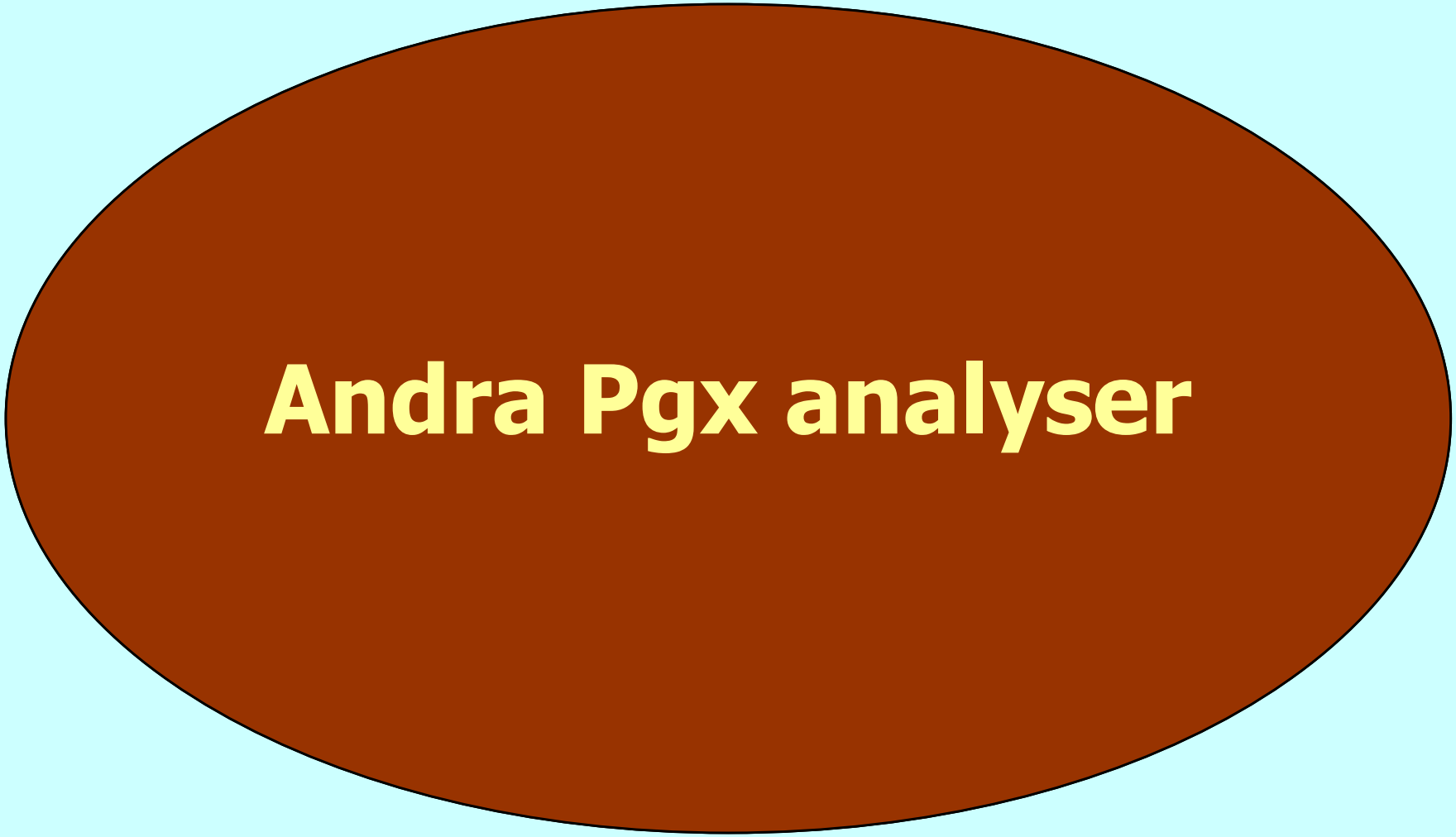
För ytterligare information om analysen se: www.labhandbok.se och www.genotypning.se



Cytocrom P450 i framtid

Cytocrom P450 i framtid

- **Full genome scanning**
- **Broader panel of genes of interest: *CYP2B6*, *CYP2C9*, *CYP2C29*, *CYP2D6*, *CYP3A4/5*…*CYP1A2*??**
- **Evaluation of all the variations according to the guidelines/informations published in www.pharmgkb.org**
- **National genomic network consensus on the clinical evaluations**


Andra Pgx analyser

FDA Drug labels

Drug		*Biomarker*	*Odd effect*
Abacavir	Test Required	HLA-B*5701	Hypersensitivity
Azathioprine	Test recommended	TMPT, NUDT15	Leukopenia
Carbamazepine	Test Required	HLA-B*5701	Hypersensitivity
Imatinib	Test Required	Ph Chromosome	
Irinotecan	Actionable PGx	UGT1A1	Toxicity
Isoniazid	Informative PGx	NAT2	
Mercaptopurine	Test recommended	TMPT, NUDT 15	Leukopenia

https://www.pharmgkb.org/

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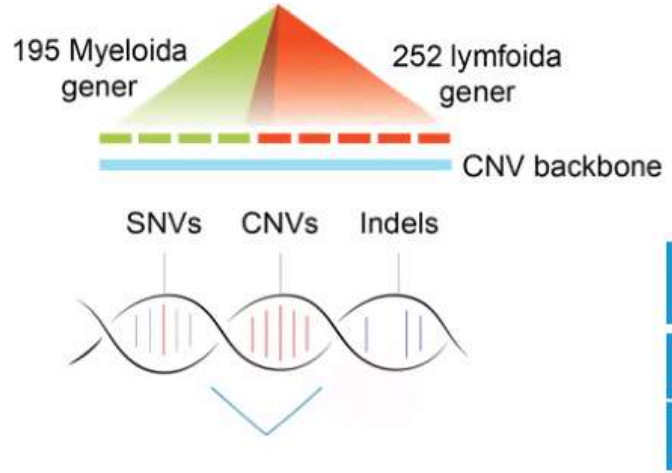
Hematologi

Nationell hematologipanel



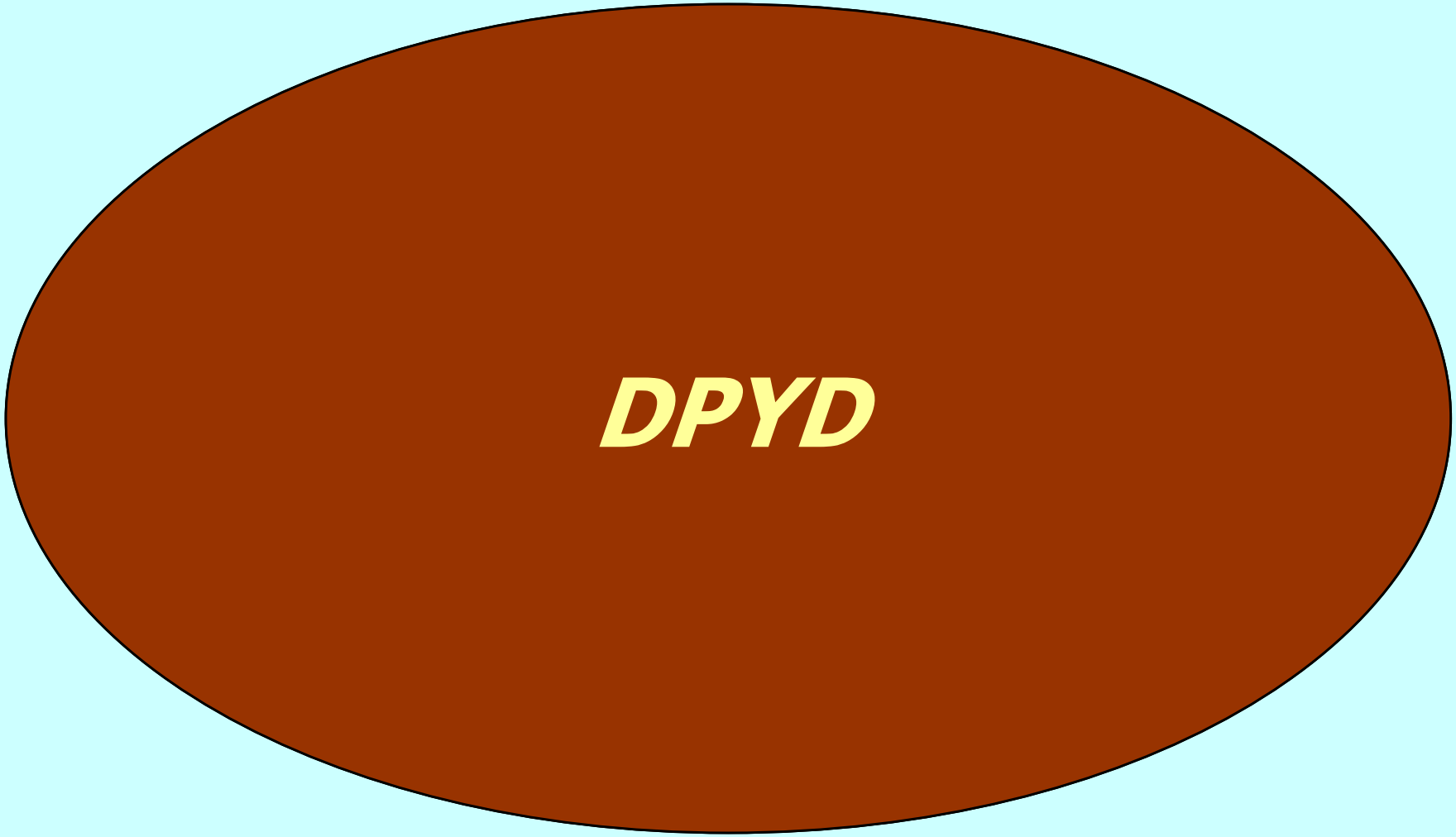
AML MDS MPN CLL Lymfom

I panelerna ingår utvalda farmakogener som

- påverkar viktiga läkemedel
- har kliniska rekommendationer

Farmakogener	Läkemedel
TPMT & NUDT15	merkaptopurin, azatioprin, tioguanin
DPYD	fluorouracil, kapecitabin
UGT1A1	irinotekan
CYP2D6	kodein, oxykodon, tramadol, tamoxifen, ondansetron
CYP2D6 & CYP2C19	SSRI och tricykliska antidepressiva

gms


DPYD

DPYD GENETIC POLYMORPHISM

Enzyme **DPD (Dihydropyrimidine dehydrogenase)**
Substrates: 5-fluorouracil, capecitabine, tegafur

Gene locus **Chromosome 1**

Genotyping **Allelic variants:**

DPYD*2A	(rs3918290 c.1905+1G>A)	No activity (1.0-1.2%)
DPYD*13	(rs55886062 c.1679T>G)	No activity (0.1%)
DPYDc.2846	(rs67376798 c.2846A>T)	Reduced (0.8-1.4%)
DPYDc.1129-5923	(rs75017182 1129-5923C>G)	Reduced (4.1-4.8%)

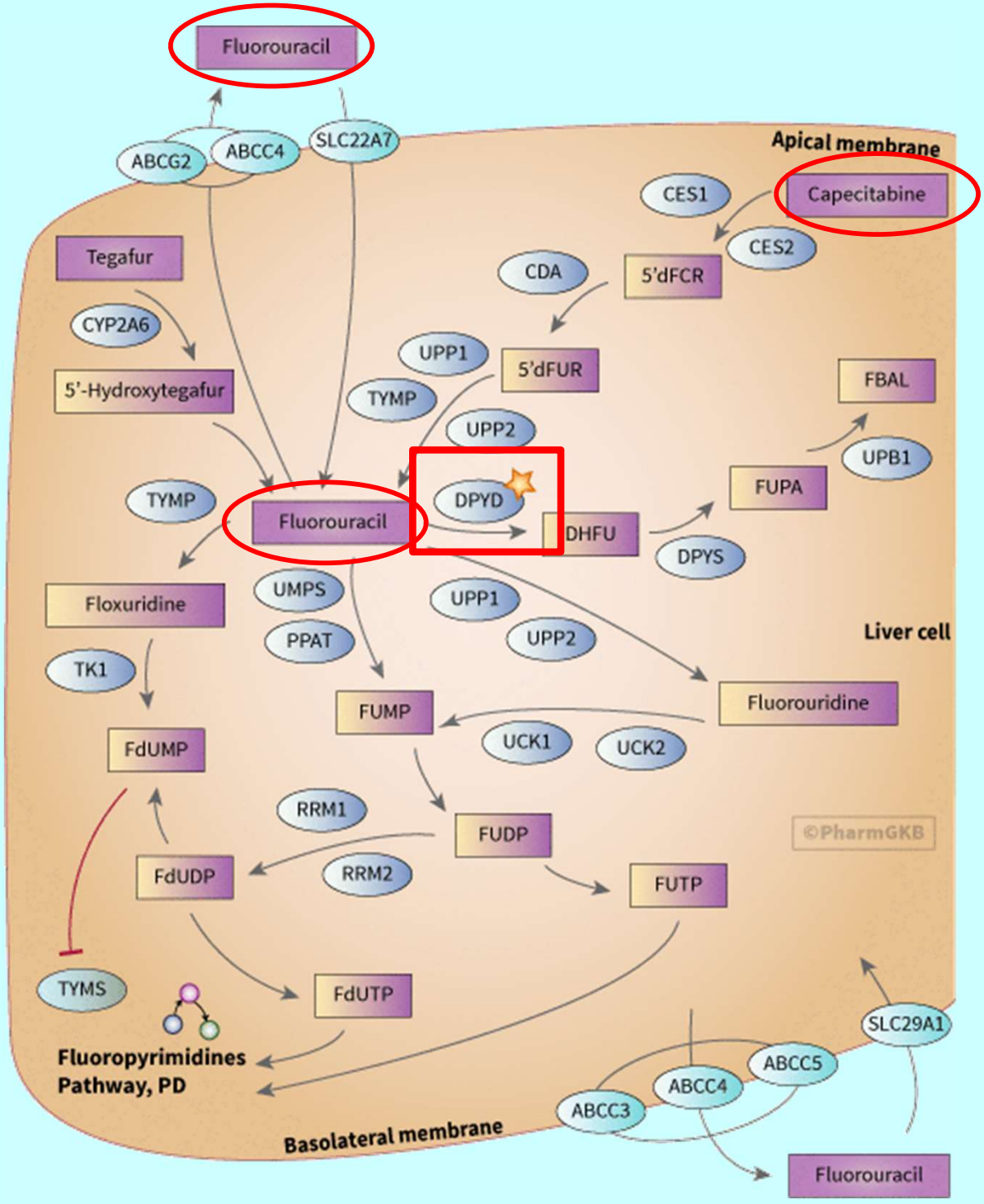
Ca 6% of Europeans have a reduced metabolic activity

INDIKATION: Riskbedömning inför planerad behandling med 5-fluorouracil, kapecitabin eller tegafur. Utredning av biverkningar hos patient behandlad med 5-fluorouracil, kapecitabin eller tegafur.

I Sverige säljs för närvarande följande läkemedel som påverkas av variation i DPYD: 5-fluorouracil (Fluorouracil®) och kapecitabin (Capecitabin®, Capecitabine®, Ecansya® och Xeloda®) samt tegafur (ingår som en av tre aktiva substanser i Teysuno®). Patienter som är bärare av DPYD-varianterna rekommenderas sänkt dos av dessa läkemedel eller att ta ett alternativt läkemedel.

FDA varnar för ökad risk för svår eller dödlig toxicitet om personer med sänkt aktivitet av dihydropyrimidindehydrogenas behandlas med 5-fluorouracil eller kapecitabin i normal dos. Den europeiska läkemedelsmyndigheten (EMA) rekommenderar sedan 2020 screening av dihydropyrimidindehydrogenas före behandling med fluoropyrimidiner. DPYD genotypning rekommenderas inför behandling med 5-fluorouracil, kapecitabin och tegafur enligt Fass

Metod: Realtids-PCR


Fluorouracil
ABCG2
ABCC4
SLC22A7
Apical membrane
CES1
Capecitabine
CES2
Tegafur
CDA
5'dFCR
CYP2A6
UPP1
5'dFUR
5'-Hydroxytegafur
TYMP
FBAL
UPP2
UPB1
TYMP
Fluorouracil
DPYD
FUPA
DHFU
DPYS
Floxuridine
UMPS
UPP1
PPAT
UPP2
Liver cell
TK1
Fluorouridine
FUMP
FdUMP
UCK1
UCK2
RRM1
FUDP
©PharmGKB
FdUDP
RRM2
FUTP
TYMS
FdUTP
SLC29A1
Fluoropyrimidines
Pathway, PD
ABCC5
ABCC4
ABCC3
Basolateral membrane
Fluorouracil

DPYD-varianter; screening inför fluoropyrimidinbehandling

Lämplig startdos?

SNP	Allel	Genotyp	Fe
rs3918290	DPYD*2A	c.1905+1G>A	Ing
rs55886062	DPYD*13	c.1679T>G	Ing
rs67376798	DPYDc.2846	c.2846A>T	Re
rs75017182	Haplotyp B3	c.1129-5923C>G	Re

Fenotyp	Aktivitets poäng	Genotyp
Normal metaboliserare	2	*1/*1
Intermediär metaboliserare	1,5	*1/ c.1129-5923 G HapB3 *1/c.2846 T
Intermediär metaboliserare	1,0	*1/*2A *1/*13 c.1129-5923 G/c.2846 T c.1129-5923 G/ c.1129- 5923 G c.2846 T/ c.2846 T
Långsam metaboliserare	0,5	*2A/ c.1129-5923 G *2A/c.2846 T *13/c.1129-5923 G *13/c.2846 T
Mycket långsam metaboliserare	0	*2A/*2A *13/*13 *2A/*13

Ger råd om **startdos** baserat på funktionaliteten av enzymet inte metabola förmågan via DPD för patienten!

Tar ej hänsyn till skillnader i DPD-mängd.

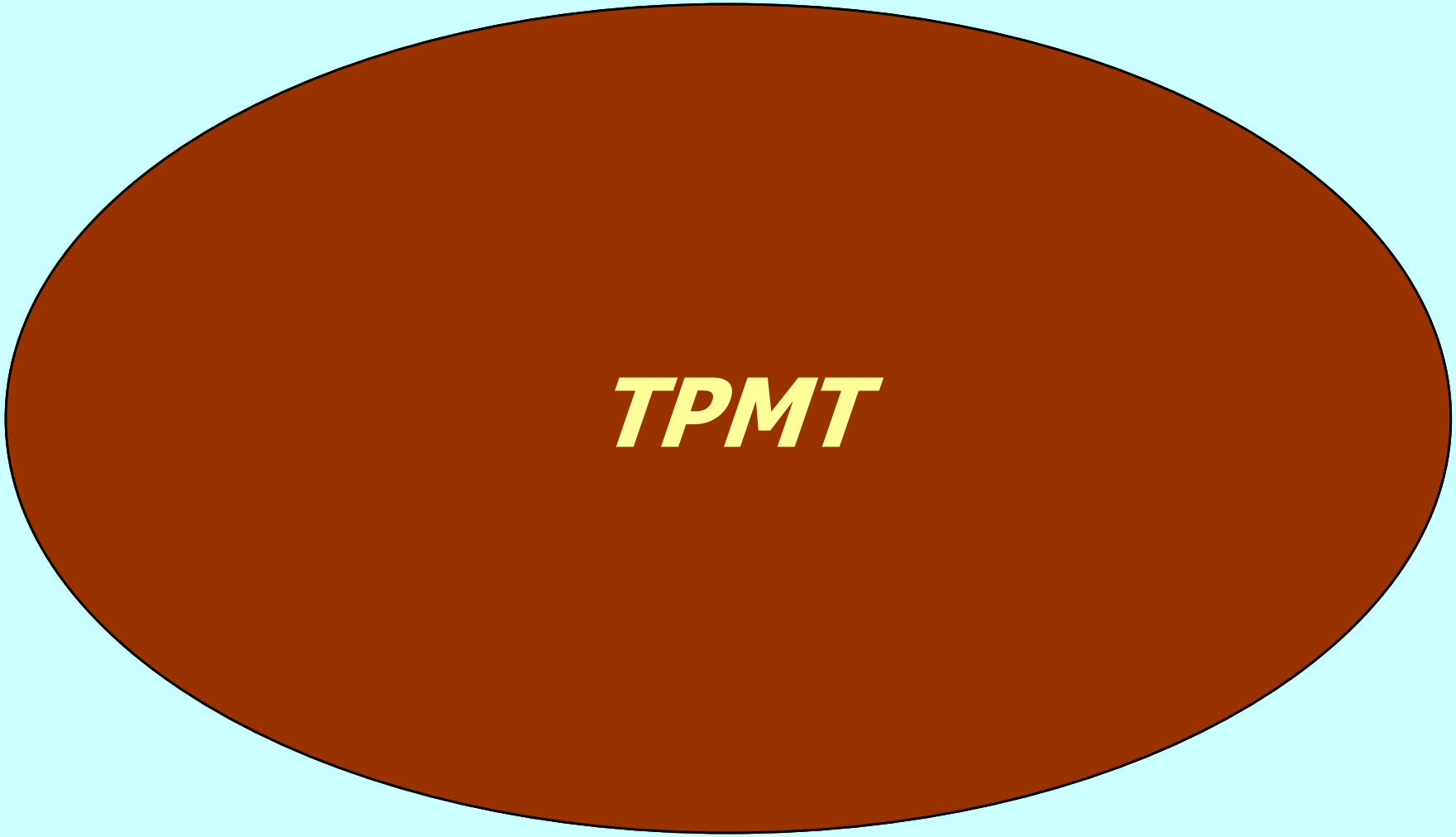
https://www.pharmgkb.org/guidelineAnnotations

DYPD genotyp bedömnig

DPYD, genotyp: *1/*1: Normal genotyp.
Vid behandling med kapecitabin eller 5-fluorouracil rekommenderas normal startdos. Koncentrationsbestämning av 5-fluorouracil kan övervägas.
Undersökta alleler *2A, *13, c.1129-5923 C>G HapB3 och c.2846 A>T.

DPYD, genotyp: *1/*2A. Nedsatt enzymaktivitet förväntas.
Vid behandling med kapecitabin eller 5-fluorouracil rekommenderas 50% av normal startdos. Koncentrationsbestämning av 5-fluorouracil bör övervägas.
Undersökta alleler *2A, *13, c.1129-5923 C>G HapB3 och c.2846 A>T.

DPYD, genotyp: *1//c.1129-5923 G HapB3. Lätt nedsatt enzymaktivitet förväntas.
Vid behandling med kapecitabin eller 5-fluorouracil rekommenderas 50-75% av normal startdos.
Koncentrationsbestämning av 5-fluorouracil bör övervägas.
Undersökta alleler *2A, *13, c.1129-5923 C>G HapB3och c.2846 A>T.


TPMT

TPMT GENETIC POLYMORPHISM

Enzyme

Thiopurine methyltransferase
Substrates: azathioprine, 6-mercaptopurine

Gene locus

Chromosome 6

Genotyping

Major allelic variants:

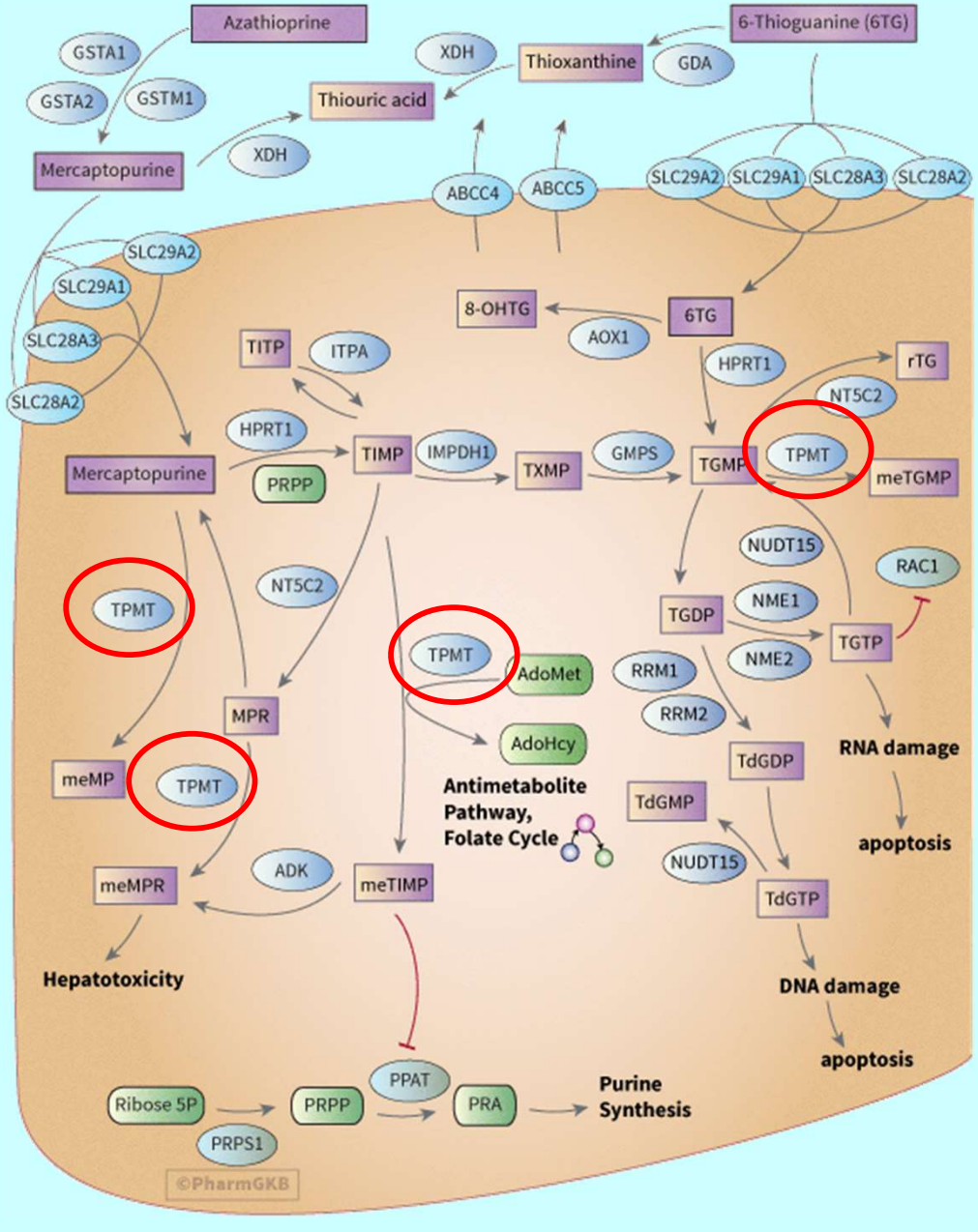
***1** (wild type)
***1S** (c.474 A>G, rs2842934)
***2** (G238C, rs1800462 → Ala80Pro)
***3A** (G460A/A719G → Ala154Thr/ Try240Thr)
***3B** (G460A, rs1800460 → Ala154Thr)
***3C** (A719G, rs1142345 → Try240Thr)

Ca 10% of Caucasians have a reduced metabolic activity

INDIKATION: Riskbedömning inför planerad behandling med azatioprin, 6-merkaptopurin eller tioguanin. Utredning av biverkningar hos patient behandlad med azatioprin, 6-merkaptopurin eller tioguanin.

I Sverige säljs för närvarande tiopurinerna azatioprin (Imurel®, Immunoprin, Azathioprin Orifarm, Azathioprin Actavis, Azatioprin Mylan), 6-merkaptopurin (Puri-nethol®, Xaluprine) samt 6-tioguanin (Lanvis®). Patienter som är bärare av genvarianterna rekommenderas sänkt dos av dessa läkemedel eller att ta ett alternativt läkemedel

Metod: Realtids-PCR

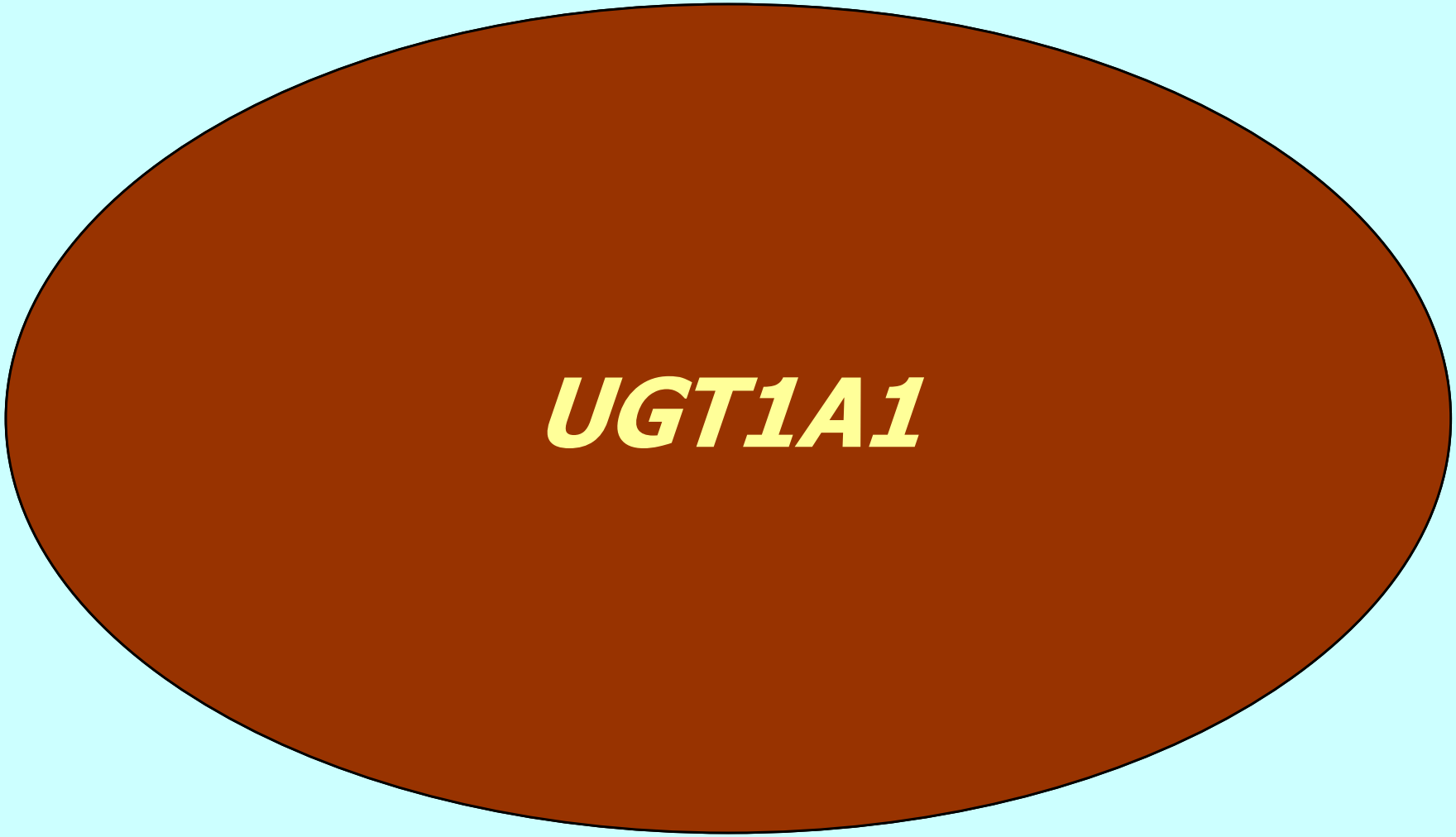

Azathioprine
GSTA1
GSTA2
GSTM1
Mercaptopurine
XDH
Thiouric acid
XDH
Thioxanthine
6-Thioguanine (6TG)
GDA
ABCC4
ABCC5
SLC29A2
SLC29A1
SLC28A3
SLC28A2
SLC29A2
SLC29A1
SLC28A3
SLC28A2
8-OHTG
AOX1
6TG
HPRT1
rTG
NT5C2
TITP
ITPA
HPRT1
TIMP
IMPDH1
TXMP
GMPS
TGMP
TPMT
meTGMP
Mercaptopurine
PRPP
NUDT15
RAC1
TPMT
NT5C2
TGDP
NME1
TGTP
TPMT
AdoMet
RRM1
NME2
MPR
RRM2
AdoHcy
RNA damage
meMP
TPMT
Antimetabolite
Pathway,
Folate Cycle
TdGDP
TdGMP
apoptosis
ADK
meTIMP
NUDT15
meMPR
TdGTP
Hepatotoxicity
DNA damage
apoptosis
PPAT
Ribose 5P
PRPP
PRA
Purine
Synthesis
PRPS1
©PharmGKB

TPMT genotyp bedömnig

TPMT, genotyp: *1/*1, dvs två funktionella alleler. Normal enzymaktivitet kan förväntas. Undersökta alleler: *2, *3B och *3C.
Vid behandling med merkaptopurin, azatioprin eller tioguanin rekommenderas normal startdos.

TPMT, genotyp: *1/*2, dvs heterozygot med en funktionell allel och en icke-funktionell allel. Sänkt enzymaktivitet kan förväntas. Undersökta alleler: *2, *3B och *3C
Vid behandling med merkaptopurin, azatioprin eller tioguanin rekommenderas reducerad startdos (ca 50% av normaldos) eller reducerad startdos enligt gällande behandlingsprotokoll. Koncentrationsbestämning av metaboliter bör övervägas.

TPMT, genotyp: *3A/*3A, dvs två icke-funktionella alleler. Mycket låg eller ingen enzymaktivitet kan förväntas. Undersökta alleler: *2, *3B och *3C
Vid behandling med merkaptopurin, azatioprin eller tioguanin rekommenderas kraftigt reducerad startdos (5-10 % av normaldos) eller reducerad startdos enligt gällande behandlingsprotokoll. Koncentrationsbestämning av metaboliter rekommenderas. Alternativ läkemedelsbehandling bör övervägas.


UGT1A1

UGT1A1 GENETIC POLYMORPHISM

Enzyme — **UDP-Glucuronosyltransferase Family 1 member A1**
the sole enzyme responsible for the metabolism of bilirubin in the liver

Gene locus — **Chromosome 2**

Inheritance — **Autosomal recessive**

Genotyping — **Major allelic variants:**
1 **TA(6) (wild type)**
****28*** **TA (7) dvs 2-bp insertion in the TATA box promoter region → decreased (70%) transcription**
frequencies: 26-31% Caucasians
42-56% African-Americans
9-16% Asian populations

Substrater

Irinotecan

Östrogen

Statiner (simvastatin)

Buprenorfin

****37*** **TA (8) further decreased activity**
****36*** **TA (5) increased promoter activity**

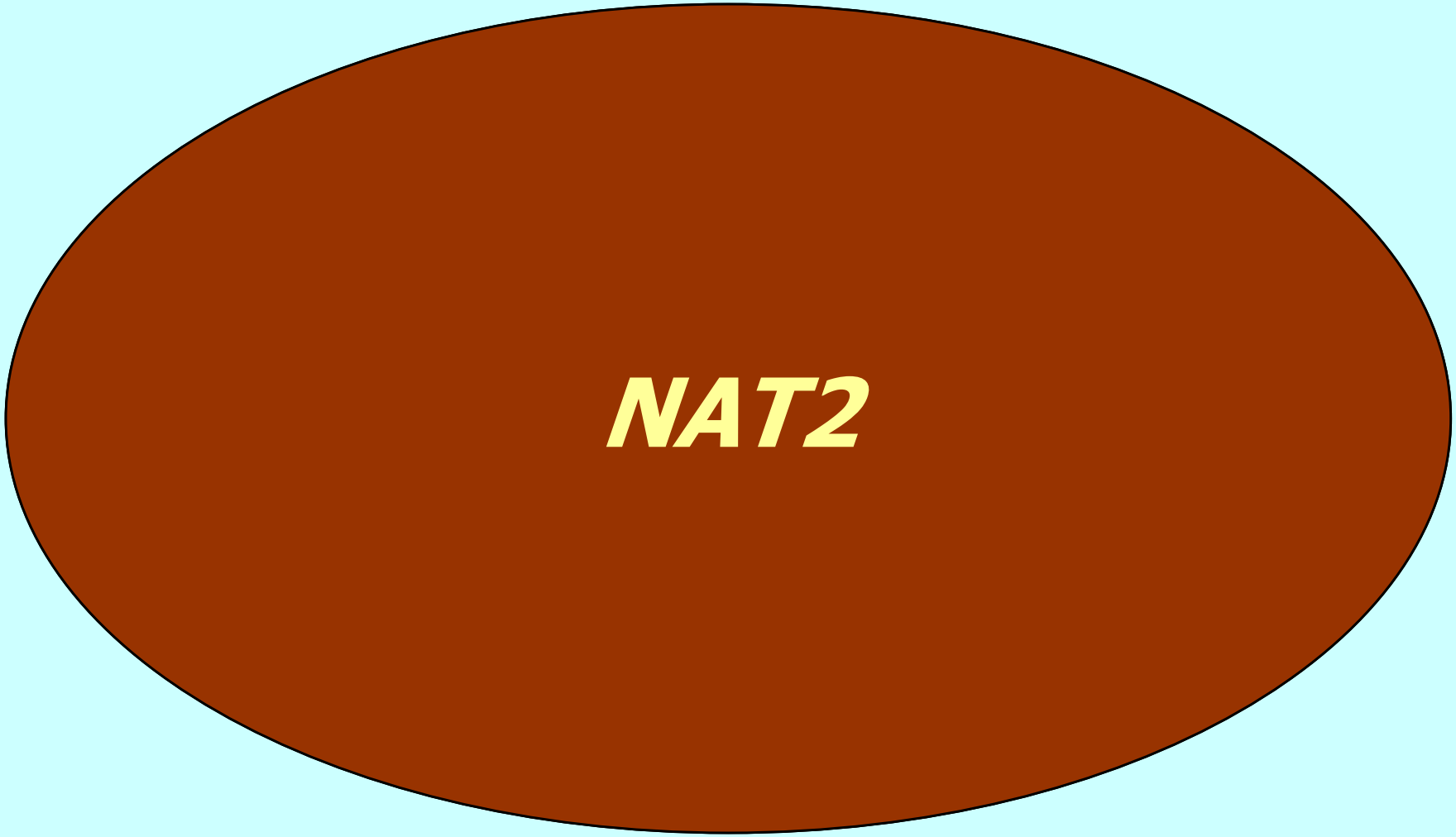
UGT1A1 genotyp bedömnig

UGT1A1 28, genotyp: *1/*1, dvs (TA)6/(TA)6. Undersökt allel *28, dvs (TA)n. Enligt genotypning har patienten inte anlag för Gilberts syndrom.

UGT1A1 28, genotyp: *1/*28, dvs (TA)6/(TA)7. Undersökt allel *28, dvs (TA)n. Enligt genotypning har patienten endast ett anlag (heterozygoti) för Gilberts syndrom och har därför sannolikt inte Gilberts syndrom.
För att få Gilberts syndrom krävs att båda UGT1A1-generna är muterade.

UGT1A1 28, genotyp: *28/*28, dvs (TA)7/(TA)7. Undersökt allel *28, dvs (TA)n. Enligt genotypning har patienten dubbelt anlag (homozygoti) för Gilberts syndrom och har därför sannolikt Gilberts syndrom.
Gilberts syndrom förekommer hos ca 10 % av svensk befolkning. Dessa personer kan få intermittent bilirubinstegring t ex vid behandling med läkemedel som glukoronideras av UGT1A1: irinotekan, östrogen, statiner, buprenorfin m.fl.

Ca 5-10% of Europeans have Gilbert syndrome and their ability to metabolize drugs can be affected


NAT2

NAT2 GENETIC POLYMORPHISM

Enzyme	**N-acetyltransferase 2 (NAT2)**
Gene locus	**Chromosome 8**
Genotype frequency	**60% slow acetylators** **(up to 80% among Scandinavians)** **40% fast acetylators**
Inheritance	**Autosomal recessive**
Genotyping	**Allelic variants:** ***1* (wild type)** ***5* *T>C*** ***6* G>A** ***7* G>A** ***14* *G>A*** ***321***

Läkemedel

- **isoniazid**
- **psykofarmaka**
  - **Nitrazepam, klonazepam**
- **sulfapreparat**

NAT2 genotyp bedömnig

NAT2, genotyp: *1/*1. Undersökta alleler *1, *5A, *5B, *5C, *6, *7, *14, 341.
Enligt genotypning är patienten homozygot snabb metaboliserare via NAT2.
Bland svenskar är ca 40% snabba metaboliserare, resten är långsamma.
Patienten förväntas ha en relativt snabb metabolism av psykofarmaka såsom klonazepam

NAT2, genotyp: *5B/*6.
Undersökta alleler *1, *5A, *5B, *5C, *6, *7, *14, 341.
Enligt genotypning är patienten långsam metaboliserare via NAT2.
Långsam metabolism anses förenat med ökad risk för biverkningar av höga doser **isoniazid**. Om återinsättning blir aktuell rekommenderas långsamma acetylerare relativt låg dos av isoniazid (Tibinide) pga risk för biverkningar. Samtidig behandling med rifampicin ökar risken för leverskada.

*HLA-B*57:01* analys vid Klinisk immunologi och transfusionsmedicin

*HLA-B*57:01* GENETIC POLYMORPHISM

Protein

HLA-B (major histocompatibility complex, class I, B) antigen B57.

The *HLA-B*5701* variant is associated with drug-induced inflammatory disease of the skin. Carriers of the variant are highly sensitive to **Abacavir**.

Gene locus

Chromosome 6

Frequencies: 6% Caucasians
2-3% African-Americans