MedNet
Vergroot je medische vakkennis

ON DEMAND
WEBCAST

Farmacogenetica

Heeft u uw DNA paspoort al?

Uitdagingen in de behandeling van SPMS

- Prof. Dr. Ron H.N. van Schaik

Inhoud

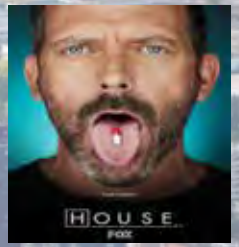
- Wat is Farmacogenetica?
- Klinische toepassingen
- Genotyperingen
- Een DNA uitslag: en wat nu?
- Take home message…

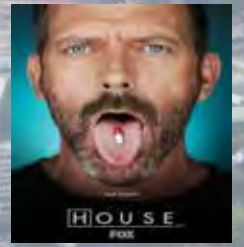
Pharmacogenetics

DNA analyse om te
verklaren/ voorspellen
hoe een patiënt reageert
op geneesmiddelen

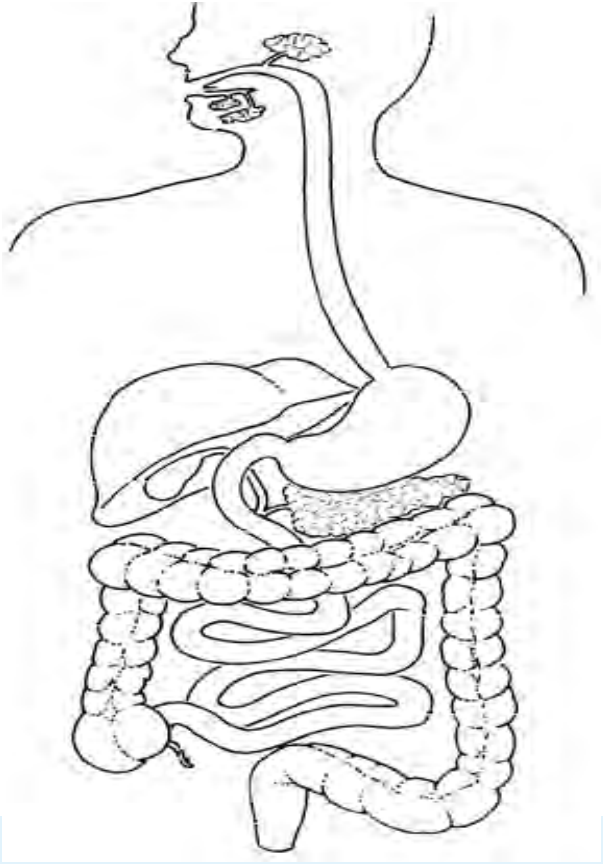
Personalized Medicine

Medical need…





Afbraak van geneesmiddelen…



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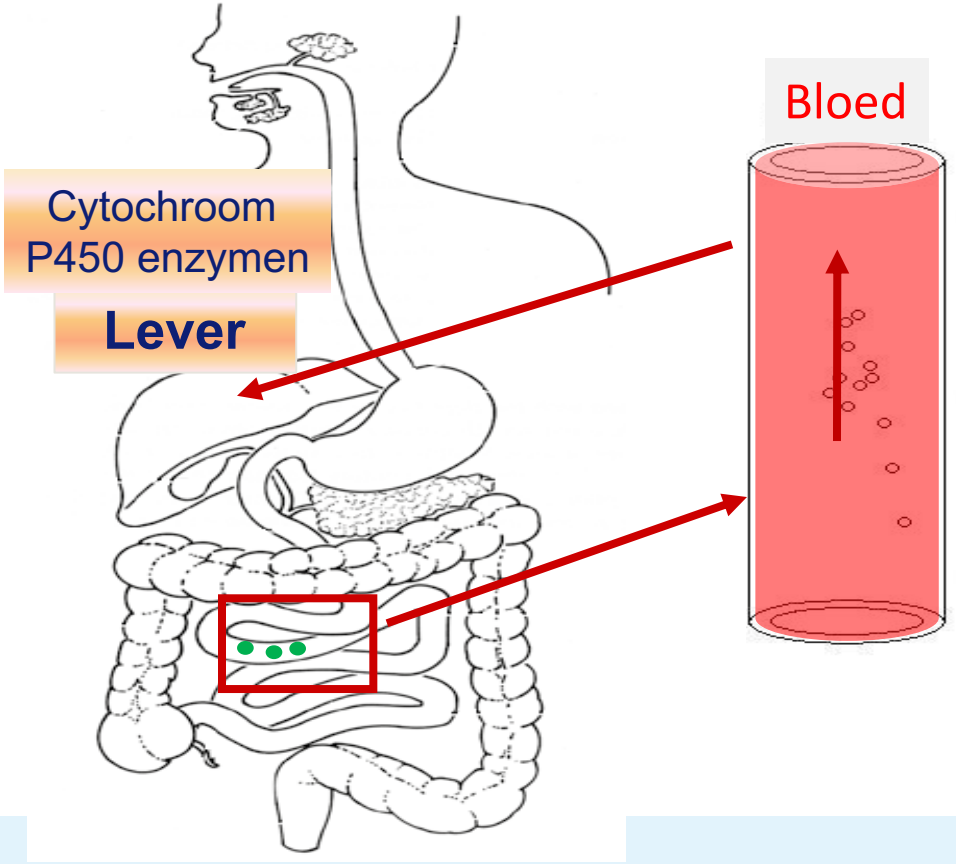

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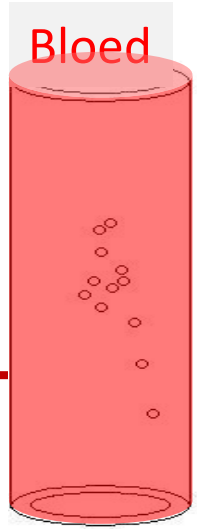
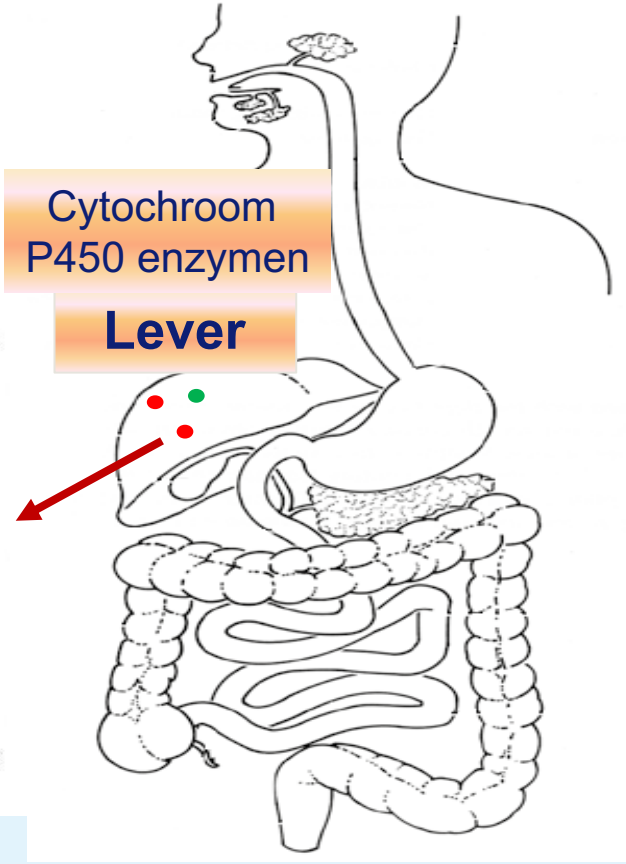
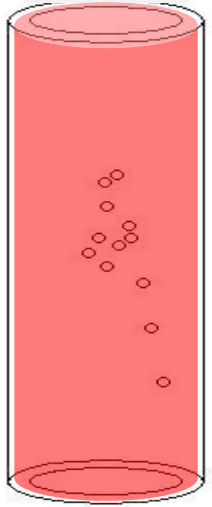






Afbraak van geneesmiddelen…

Dosis

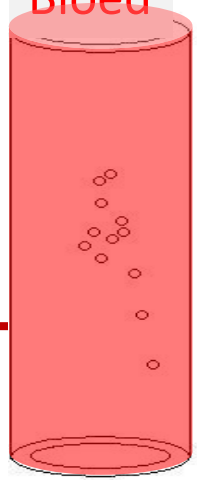
Nierfunctie

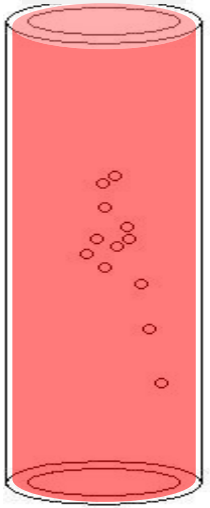
Afbraakvermogen van de lever

Cytochroom P450 enzymen

Lever

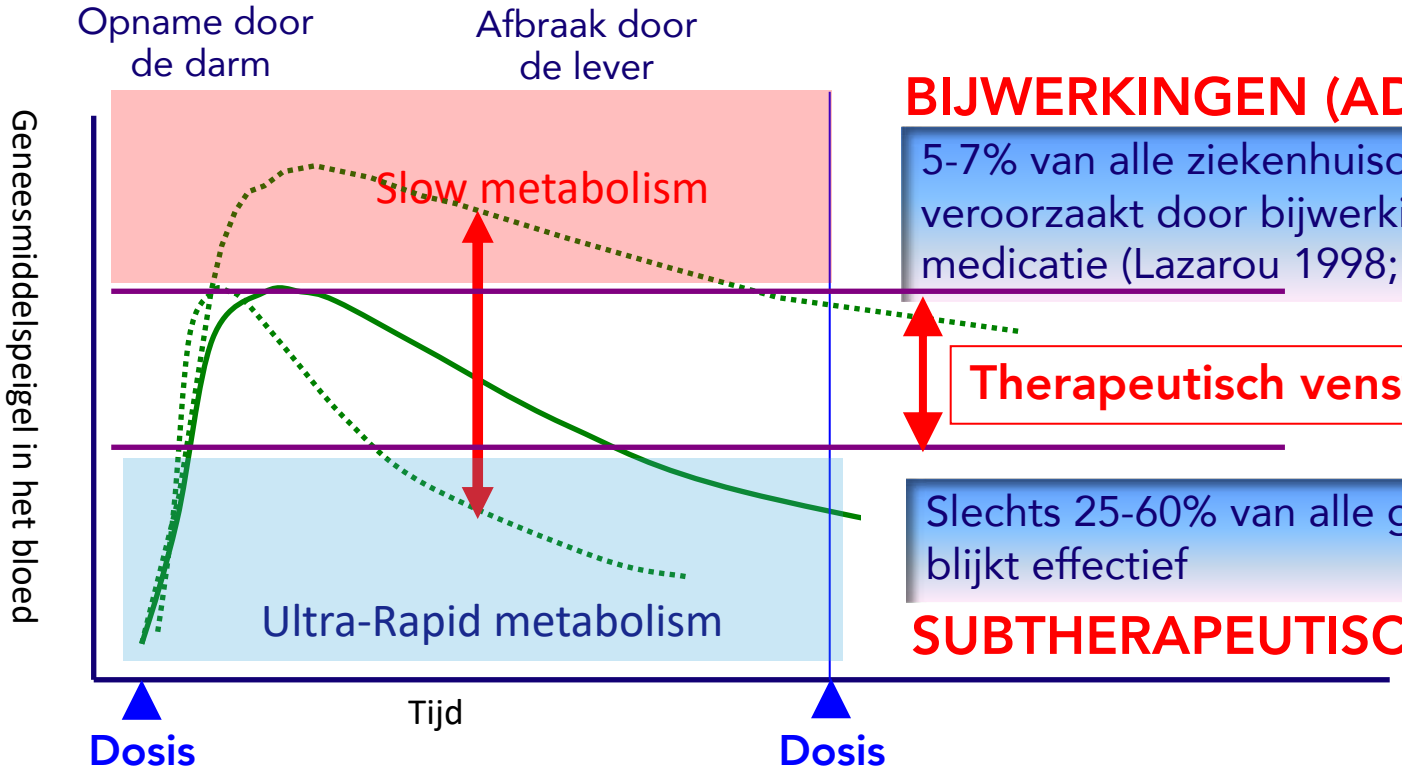
Bloed





Bloed

Afbraak van geneesmiddelen…



BIJWERKINGEN (ADRs)

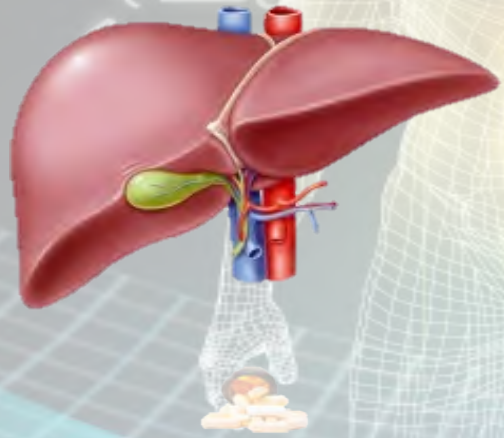
5-7% van alle ziekenhuisopnames worden veroorzaakt door bijwerkingen op medicatie (Lazarou 1998; HARM rapport).

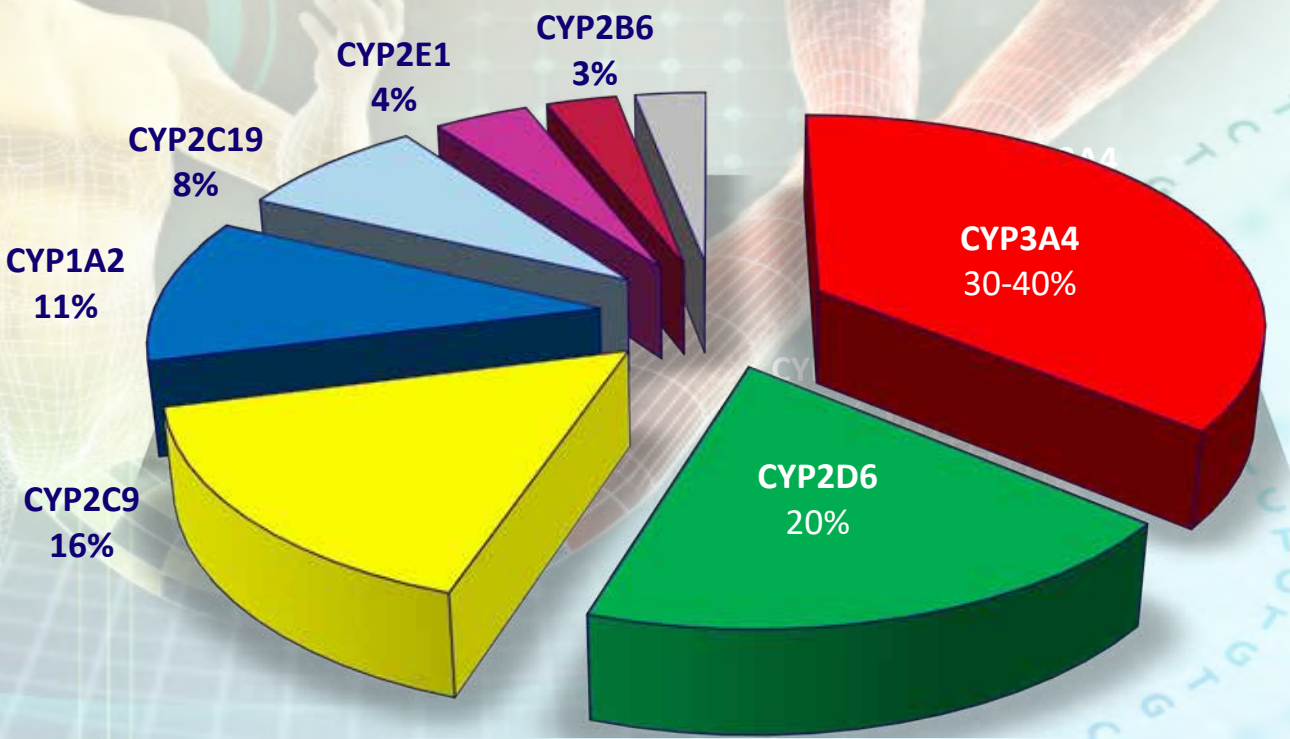
Therapeutisch venster

Slechts 25-60% van alle geneesmiddelen blijkt effectief

SUBTHERAPEUTISCH

Cytochroom P450: 80% van alle geneesmiddelen





Cytochroom P450: 80% van alle geneesmiddelen

Antidepressiva
Clopidogrel
Protonpompremmers

Efavirenz

CYP2B6
3%

CYP2E1
4%

CYP2C19
8%

CYP1A2
11%

CYP2C9
16%

Antistollingsmedicatie
(warfarine, acenocoumarol)

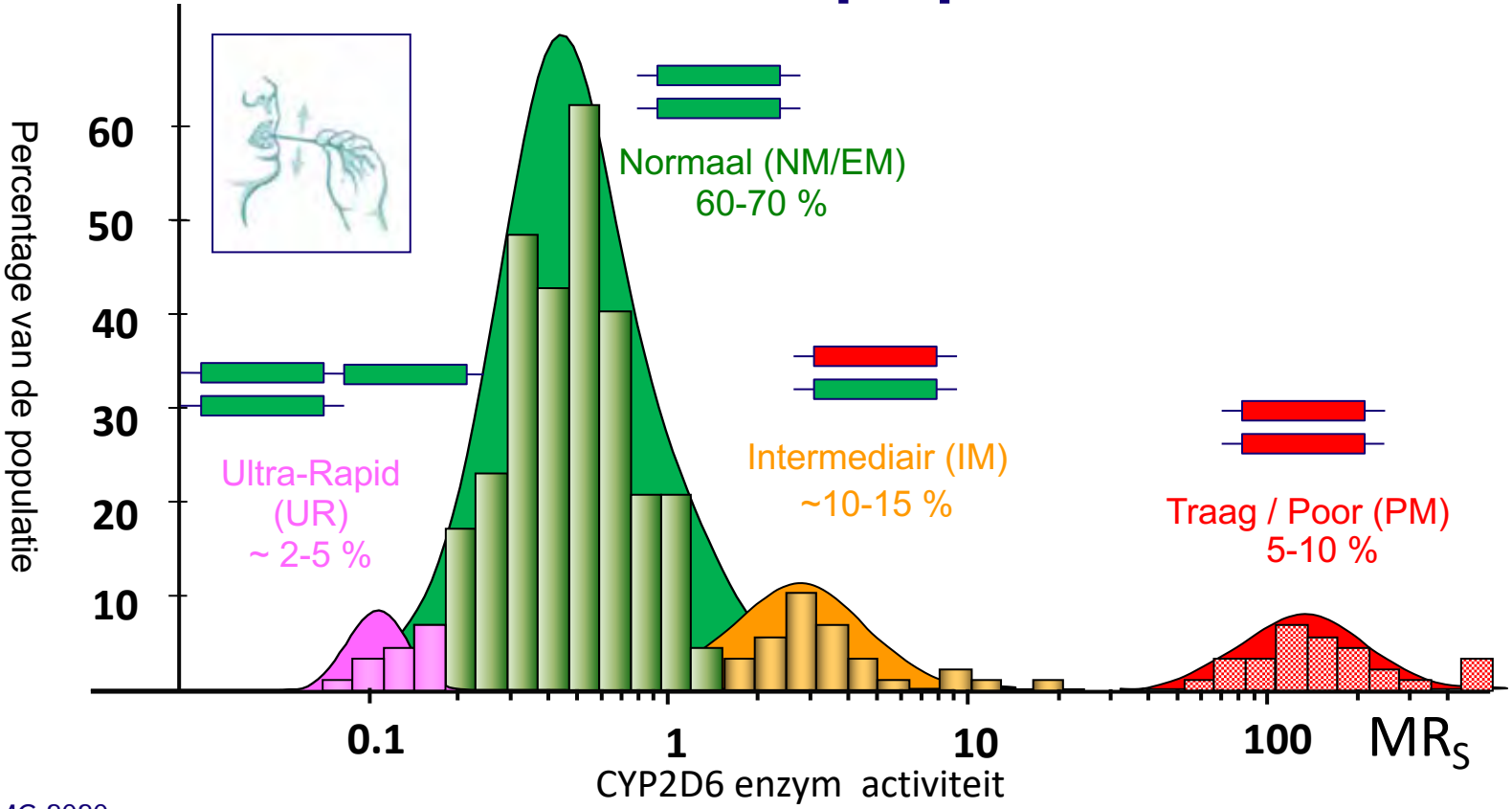
Oncolytica
Psychotrope medicatie
& heel veel andere
medicamenten

CYP3A4
30-40%

CYP2D6
20%

Antidepressiva
Antipsychotica
Bètablokkers
Tamoxifen
Opiaten

CYP2D6 activiteit in de populatie



Waar kan Farmacogenetica helpen?

Psychiatry:	Antidepressants, antipsychotics	CYP2D6, 2C19, 1A2, 3A4	40%
Cardiology:	Clopidogrel	CYPC19	15%
	Metoprolol	CYP2D6	40%
	Statins	SLCO1B1 (521T>C)	20%
	Acenocoumarol, Fenprocoumon	CYP2C9, VKORC1	20%
Oncology:	Tamoxifen (breast)	CYP2D6	10%
	Capecitabine / 5-FU	DPYD (*2A)	2-3%
	6-mercaptopurine (ALL)	TPMT	11%
	Irinotecan (colon)	UGT1A1	15%
Neurology	Carbamazepine	HLA-B*1502	5-8% (Asians)
	Clobazam	CYP2C19, CYP3A4	20%
	Clopidogrel	CYPC19	15%
	Lamotrigine	HLA-B*1502	5-8% (Asians)
	Phenytoin	CYP2C9, CYP2C19	20%
	Siponimod	CYP2C9	1%
	Valproate	CYP2C9, CYP2C19, POLG	30%
Dermatology	Azathioprine	TPMT	11%
Pain	Codeine, tramadol	CYP2D6	40%
Internal Med	Azathioprine (Crohns)	TPMT	11%
HIV	Efavirenz	CYP2B6	5%
	Abacavir	HLA-B*5701	4%

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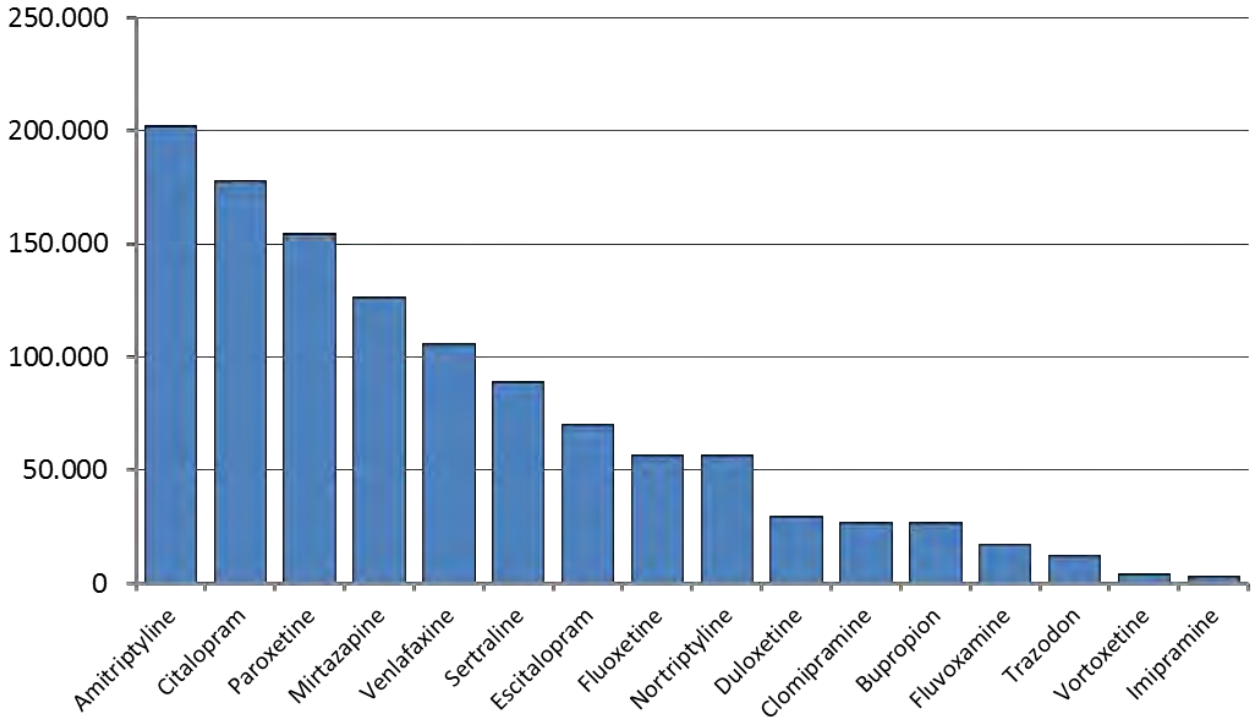
Antidepressiva

Zorginstituut Nederland

GIPdatabank.nl

Aantal gebruikers antidepressiva (2018; NL)
(totaal: 1.051.978 gebruikers, kosten: € 40.375.000)



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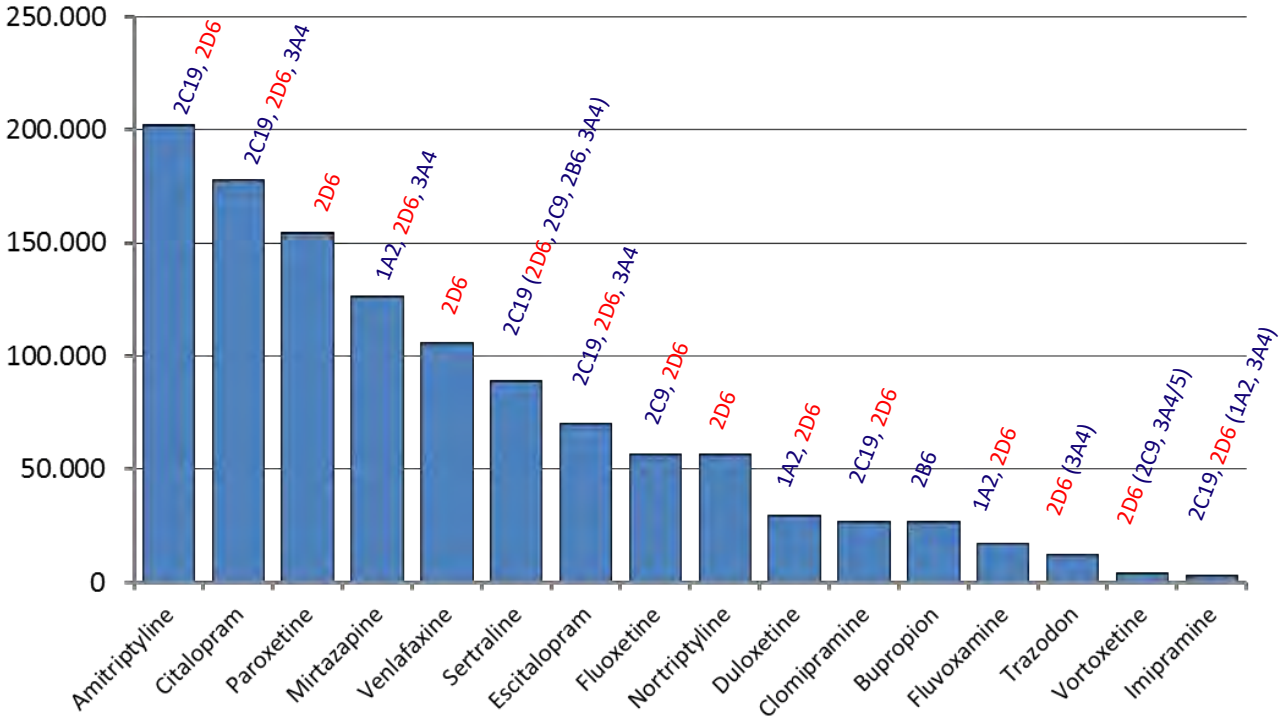
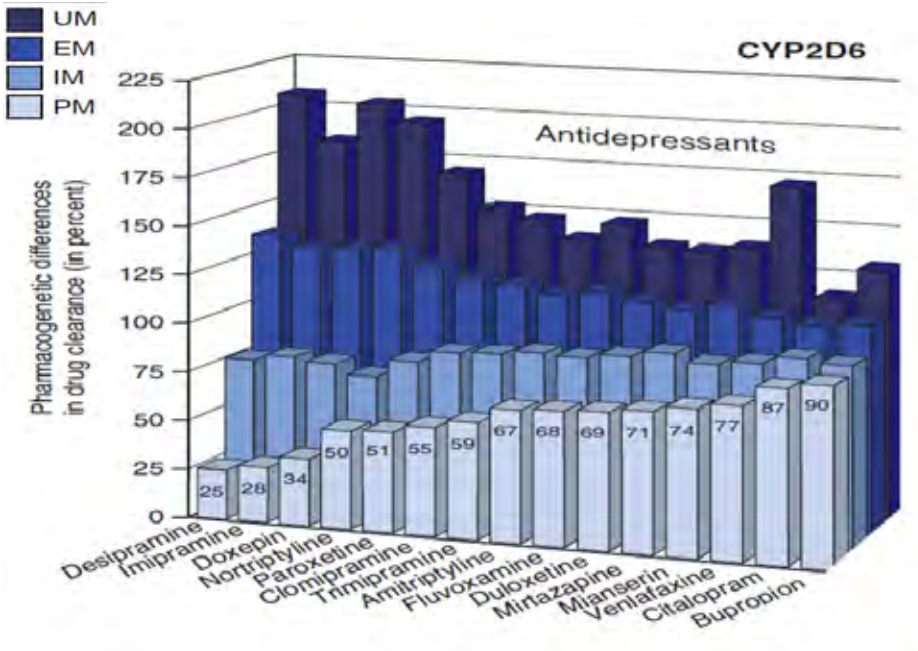
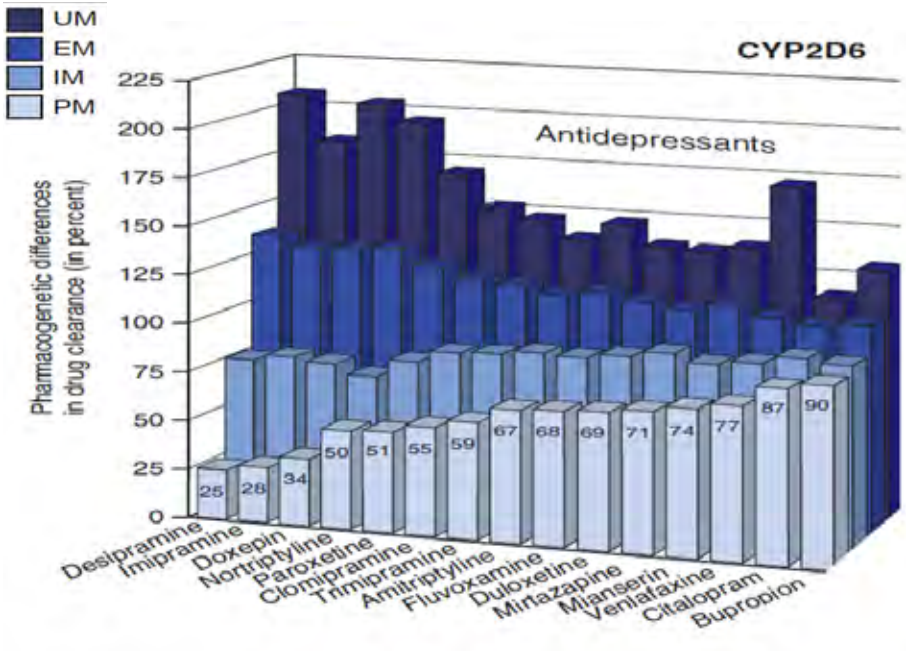


Dosering naar CYP2D6 genotype



Bron: Stingl et al (2013) Mol Psychiatry

Dosering naar CYP2D6 genotype



Amitriptyline

KNMP Kennisbank

De digitale informatiebron voor de apotheker en het apotheekteam

Farmacogenetica (Fg.)

Bij CYP2D6-genvariaties:

poor metabolizers: de plasmaconcentratie kan verhoogd zijn, dosisverlaging tot 70% van de standaarddosering met monitoring wordt aanbevolen.

intermediate metabolizers: de plasmaconcentratie kan verhoogd zijn, dosisverlaging tot 75% van de standaarddosering met monitoring wordt aanbevolen.

ultrarapid metabolizers: de plasmaconcentratie kan verlaagd zijn, dosisverhoging tot 1 ½ maal de standaarddosering met monitoring of een alternatief wordt aanbevolen.

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Azathioprine

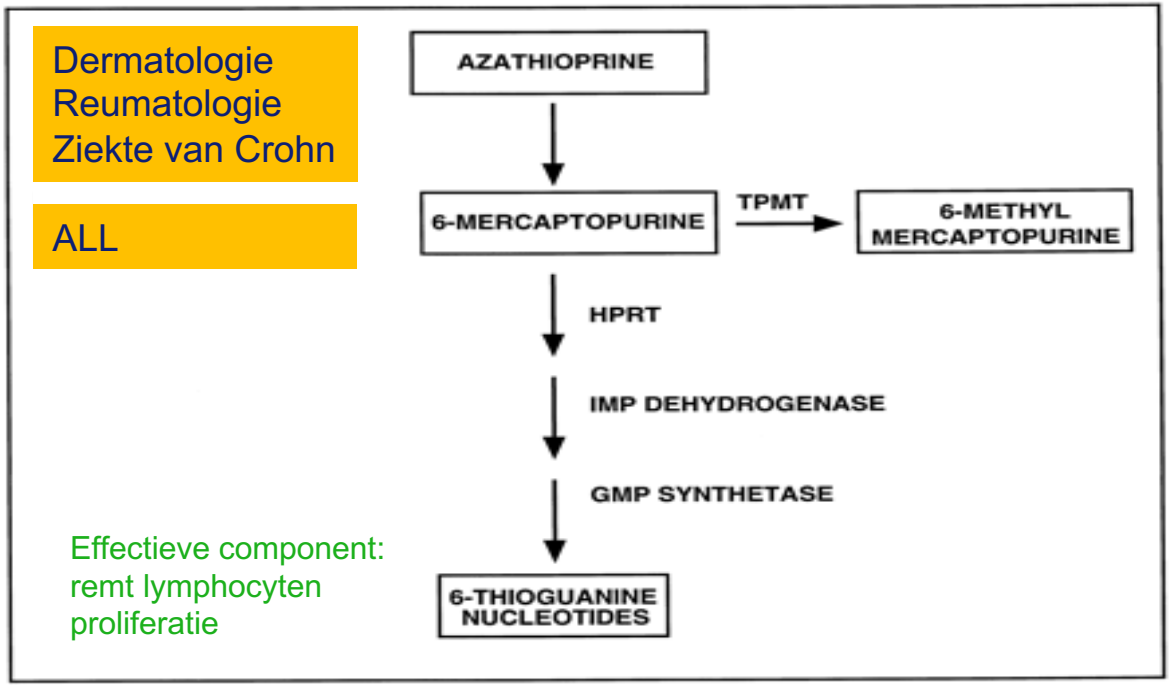
Deze webcast wordt mogelijk gemaakt door:

NOVARTIS | Reimagining Medicine

Azathioprine en TPMT

Dermatologie
Reumatologie
Ziekte van Crohn

ALL

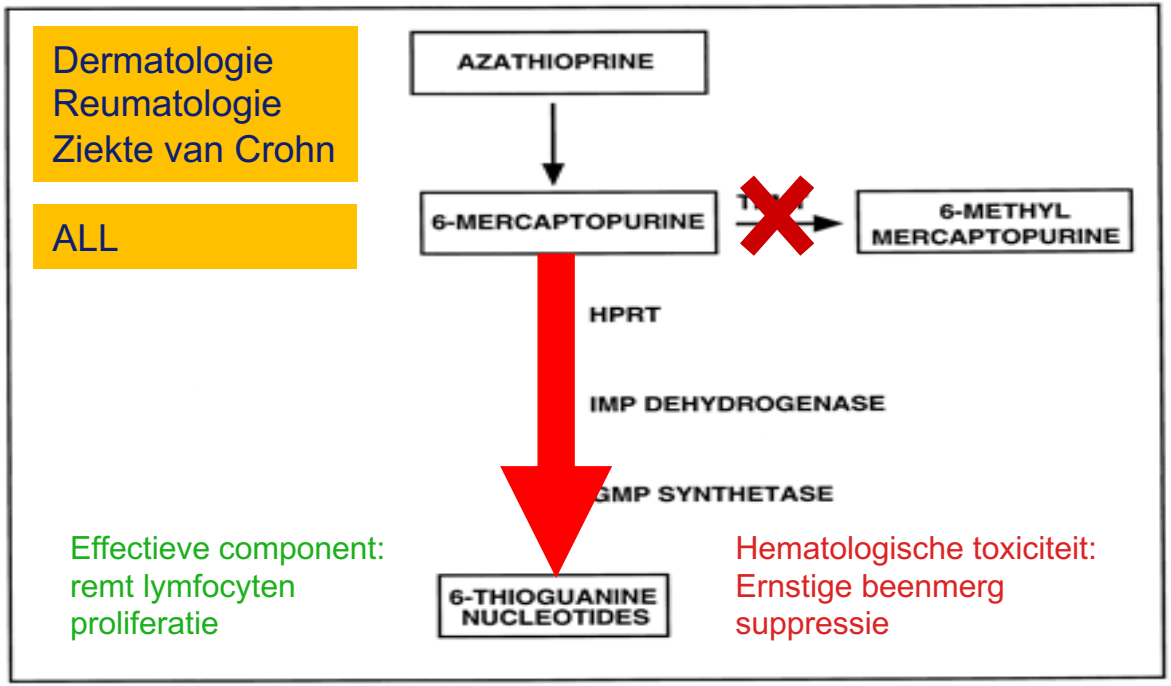


Effectieve component:
remt lymphocyten proliferatie

XO, xanthine oxidase; TPMT, thiopurine S-methyl transferase; HPRT, hypoxanthine phosphoribosyl transferase; IMP, inosine monophosphate; GMP, guanine monophosphate

Bron: Weinshilboum (2001) Drug Metab Dispos 29: 601-5

Azathioprine en TPMT



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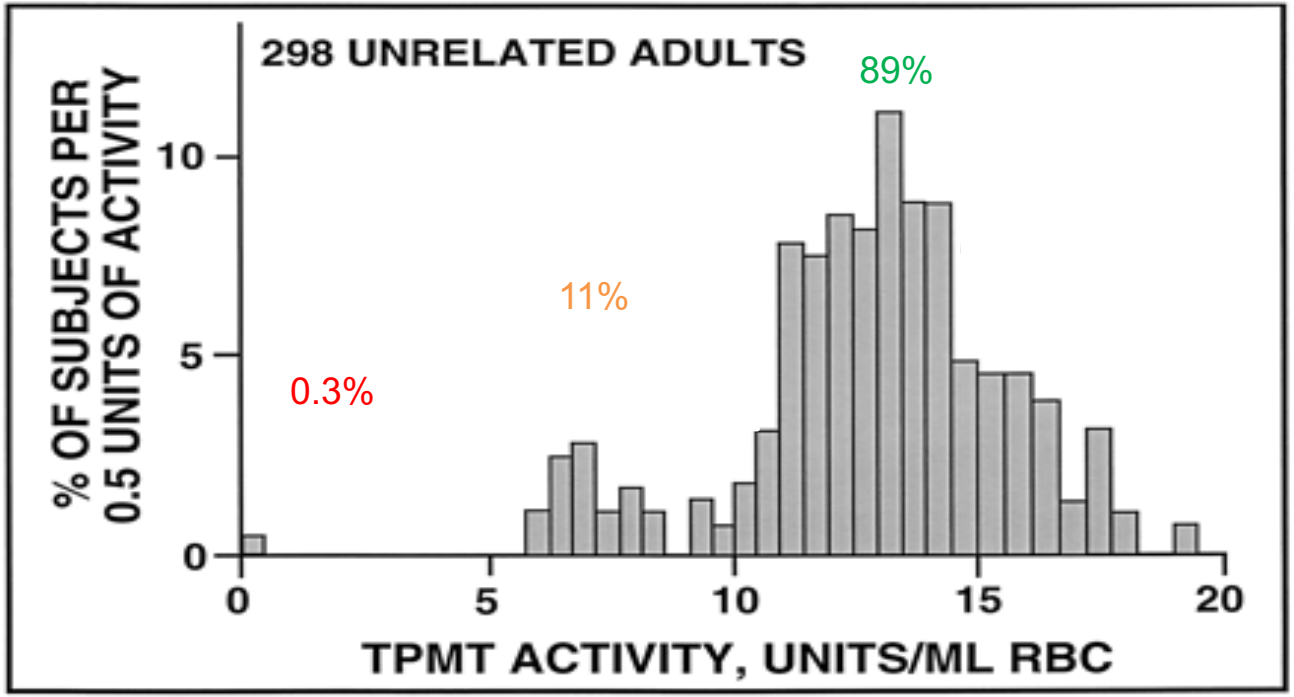

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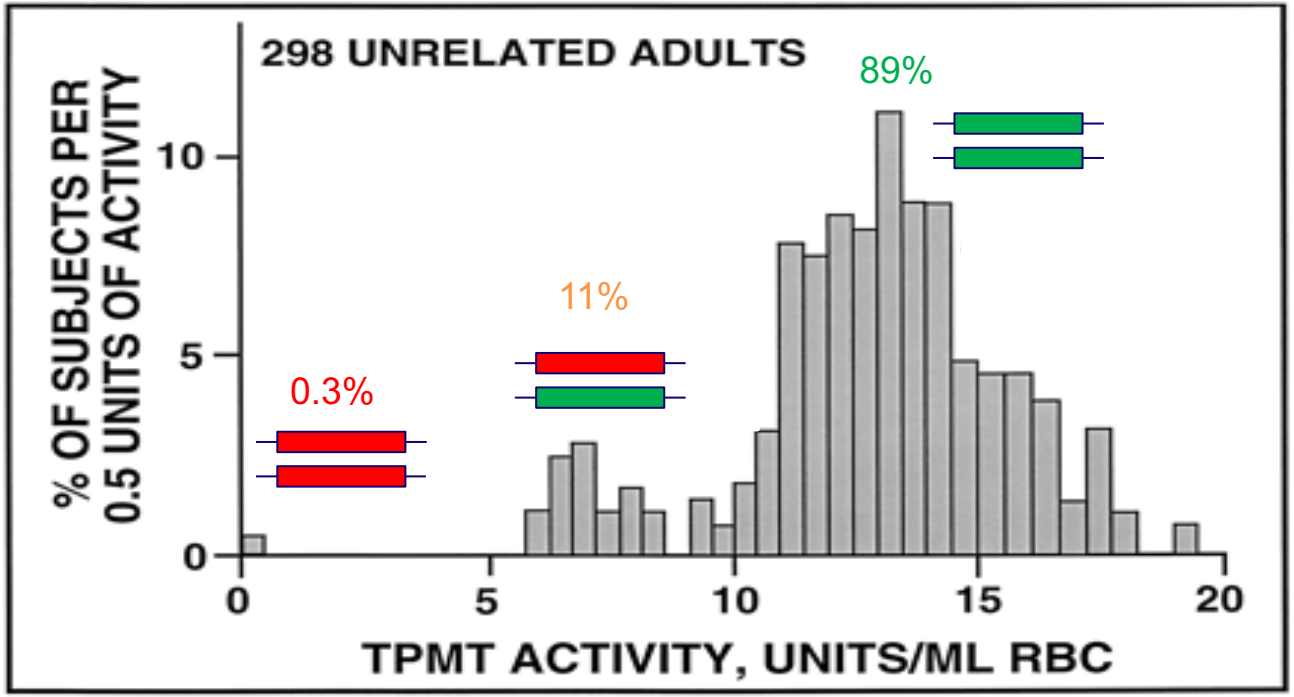
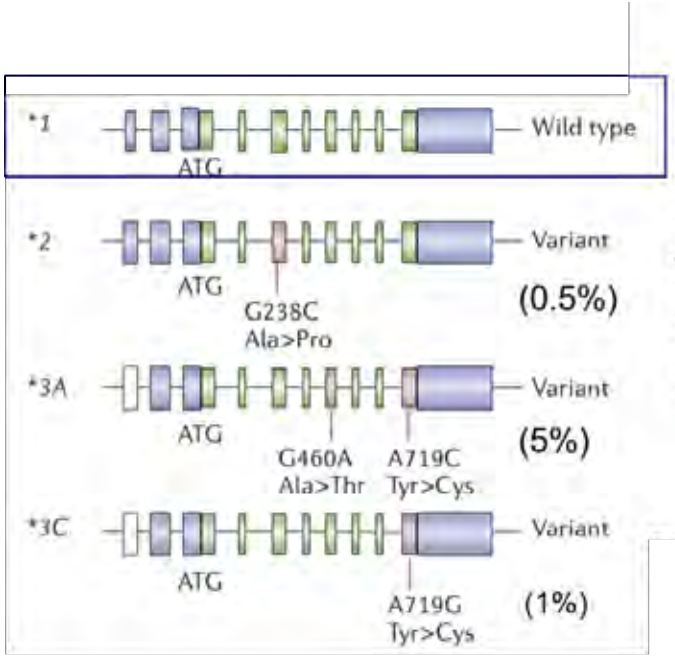
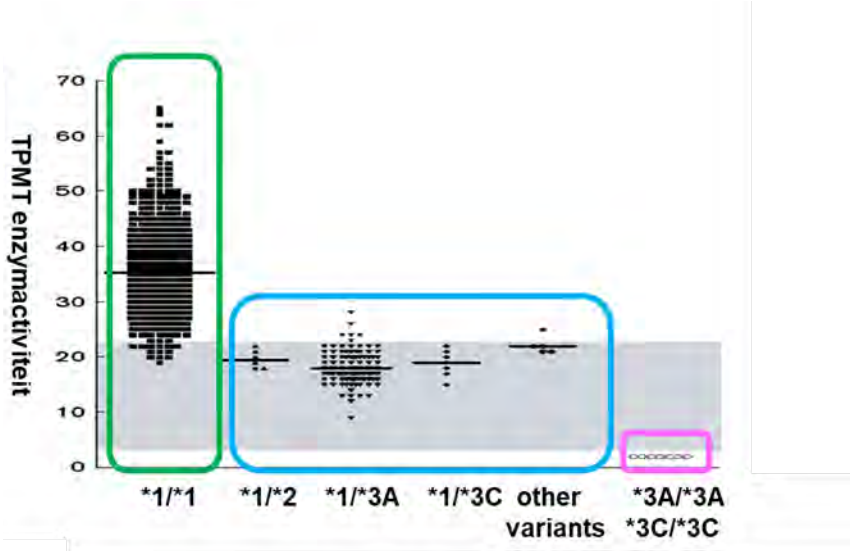
Azathioprine en TPMT



Bron: Weinshilboum (2001) Drug Metab Dispos 29: 601-5

TPMT: genotype en enzymactiviteit





95% predictivity of genotype for enzyme activity

Doseren op geleide van TPMT genotype

Identification of Patients With Variants in *TPMT* and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease

Marieke J. H. Coenen,[1,*] **Dirk J. de Jong**,[2,*] **Corine J. van Marrewijk**,[1,*] Luc J. J. Derijks,[3] Sita H. Vermeulen,[1,4] Dennis R. Wong,[5] Olaf H. Klungel,[6] Andre L. M. Verbeek,[4] Piet M. Hooymans,[5] Wilbert H. M. Peters,[2] Rene H. M. te Morsche,[2] William G. Newman,[7] Hans Scheffer,[8,9] Henk-Jan Guchelaar,[9,8] and Barbara Franke[8,10,9]

Set up: Patients in the control group and patients who did not carry a *TPMT* variant were treated according to standard IBD guidelines (2-2.5 mg/kg/day azathioprine or 1-1.5 mg/kg/day 6-mercaptopurine). Patients in the intervention group who carried a genetic variant received 50% (heterozygotes) or 0%-10% (homozygotes) of the standard thiopurine dose according to the evidence-based guidelines of the Dutch Pharmacogenetics Working Group.[16]

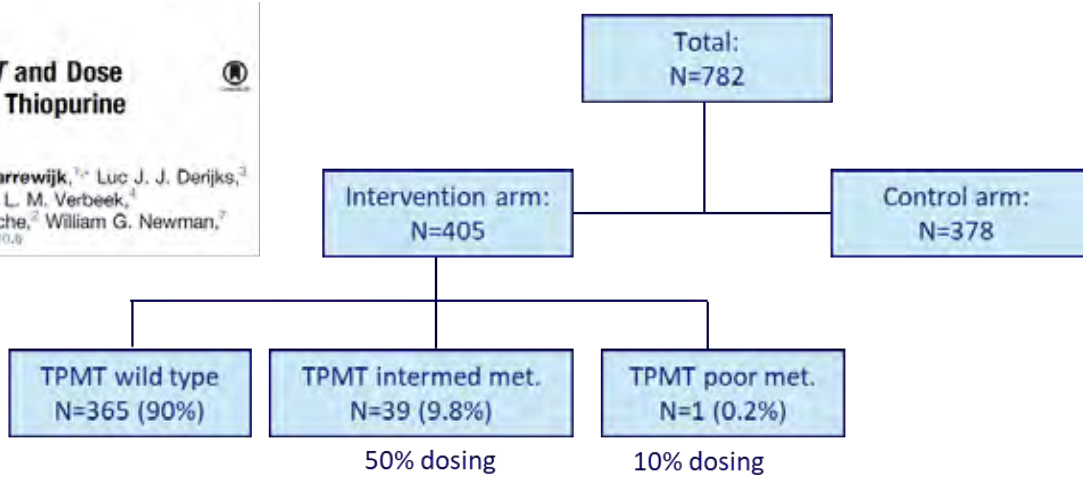


Table 3. Secondary Analysis: Hematologic ADR Occurrence in the Intervention and Control Groups

	Intervention	Control	RR (95% CI)
Total, n	399	370	
Hematologic ADR			
Total	29 (7.2%)	29 (7.8%)	
TPMT variant carriers	1 of 39 (2.6%)[a]	8 of 35 (22.9%)	0.11 (0.01–0.85)

Bron: Coenen et al (2015) Gastroenterology

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Coenen et al 2015 Gastroenterology:
TPMT Randomized controlled trial
in 782 Crohns disease patients

TPMT variant carriers will have a
10-fold increased risk on ADRs
when treated with normal dosages
compared to a genotype guided treatment

- TPMT wild type N=365 (90%)
- TPMT intermed met. N=39 (9.8%) — 50% dosing
- TPMT poor met. N=1 (0.2%) — 10% dosing

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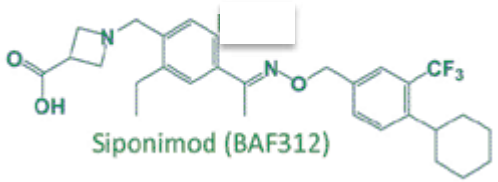
Siponimod

Deze webcast wordt mogelijk gemaakt door:

NOVARTIS | Reimagining Medicine

Siponimod

Metabolisme:

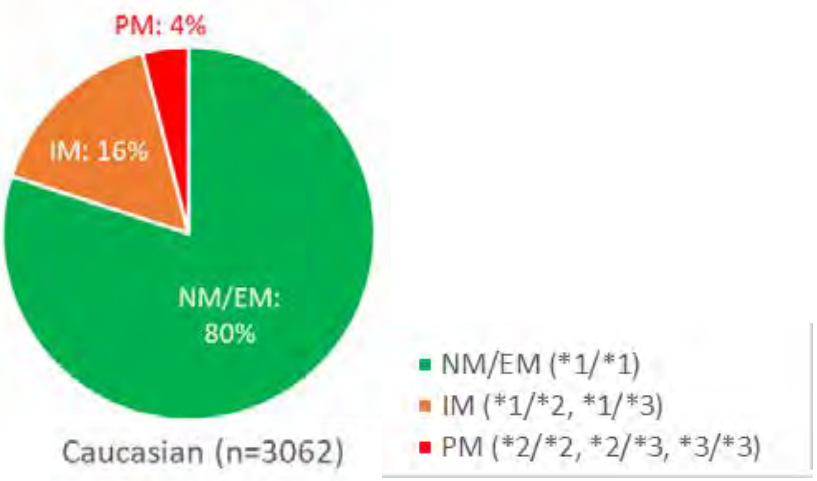


Siponimod (BAF312)

CYP2C9 (79%)

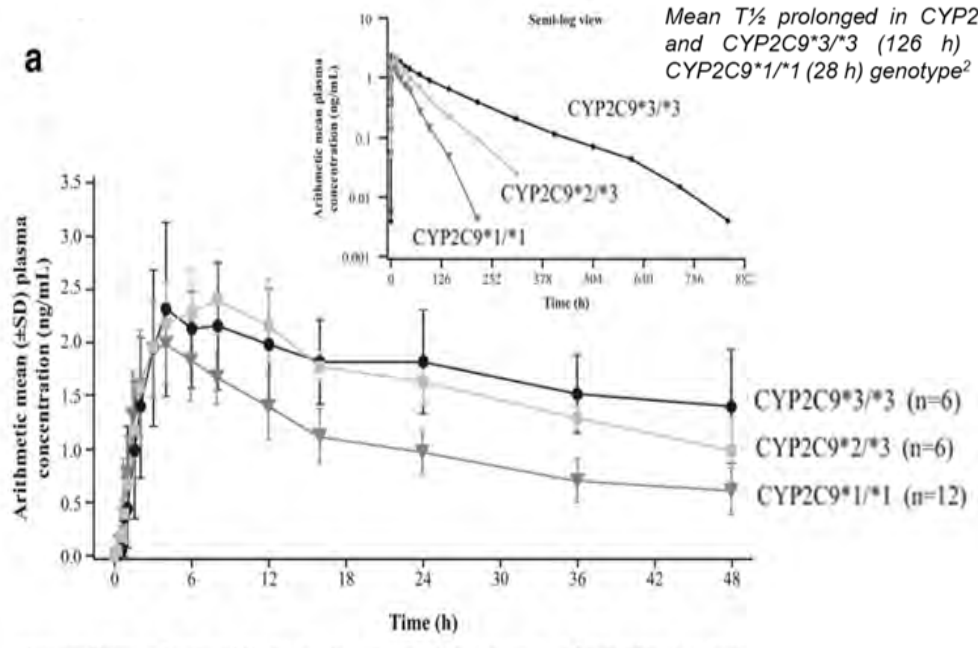
CYP3A4 (18%)

Inactieve metabolieten (M12, M17)



Farmacotherapeutisch Kompas > Geneesmiddelen >	
Metabolisering	door CYP2C9 (voor 79%) en in mindere mate (18,5%) door CYP3A4. CYP2C9 is polymorf en het genotype bepaalt de fractionele bijdrage van de twee oxidatieve metabolismeroutes tot aan eliminatie. Bij de genotypen met een verminderde metabole CYP2C9-activiteit verwacht men van de geneesmiddelen die ook door CYP3A4 worden omgezet een relatief groot effect van de CYP3A4-activiteit.

Siponimod en CYP2C9 genotype



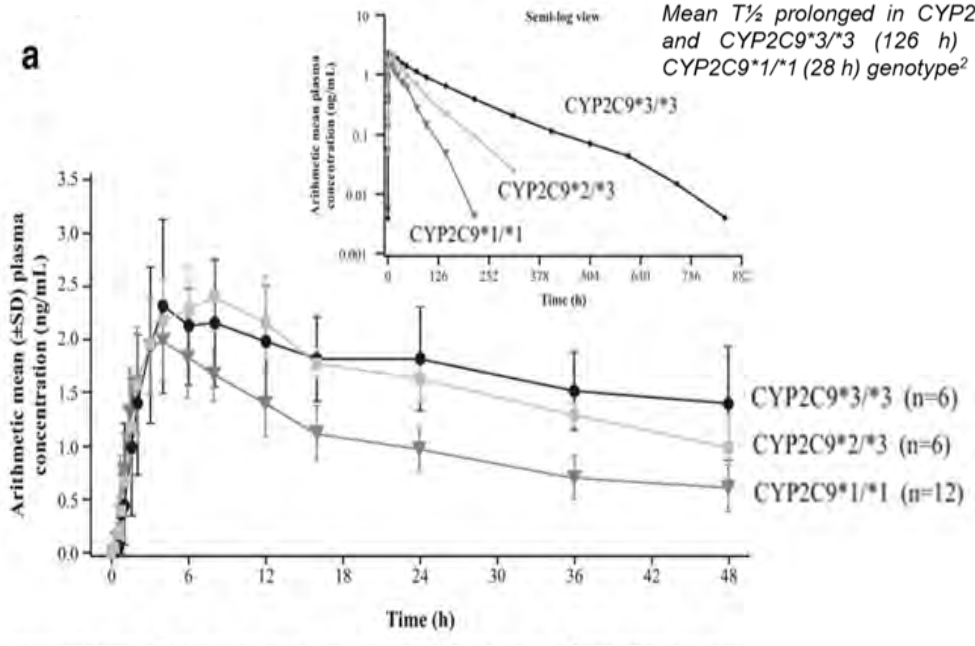
*Siponimod plasma concentration 2- to 4-fold increased in the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes vs. CYP2C9*1/*1 genotypephase of siponimod*[1]

*Mean T½ prolonged in CYP2C9*2/*3 (51 h) and CYP2C9*3/*3 (126 h) genotypes vs. CYP2C9*1/*1 (28 h) genotype*[2]

[1] Gardin A et al (2018) Clin Pharmacokin

[2] Jin Y et al (2018) Eur J Clin Pharmacol

Siponimod en CYP2C9 genotype



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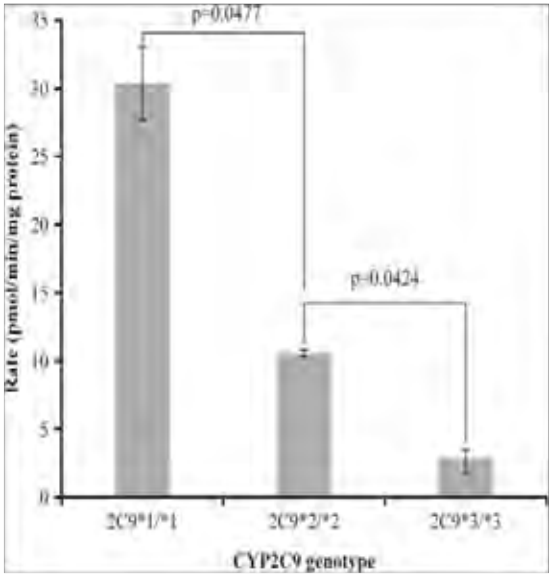

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Genotype-based dosing of Siponimod

CYP2C9 genotype	Extensive metabolizers	Intermediate metabolizers		Poor metabolizers		
						
Calculated dose[1]	2 mg	2 mg	1.24 mg	1.6 mg	1.04 mg	-
Recommended dose[2]						

- CYP2C9*3*3 subjects are contra-indicated for siponimod and have been excluded in Phase 3 trials due to expected significantly higher chronic exposure.[2]
- All subjects in the EXPAND trial received siponimod 2 mg maintenance dose irrespective of their genotypes[3]

RvS/Erasmus MC-2020; 1. Novartis Data on File (2.7.2 Siponimod Summary of Clinical Pharmacology Studies in multiple sclerosis; PopPK study); 2. SmPC Siponimod https://www.novartis.nl/medicijnen/mayzent; 3. Kappos L, et al. Lancet. 2018; 391:1263-73

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Genotype-based dosing of Siponimod

	87,5%			11%		0,4%
CYP2C9 genotype						
Calculated dose[1]	2 mg	2mg	1.6 mg	1.24 mg	1.04 mg	X
Recommended dose[2]	2 mg			1 mg		X

- CYP2C9*3*3 subjects are contra-indicated for siponimod and have been excluded in Phase 3 trials due to expected significantly higher chronic exposure.[2]
- All subjects in the EXPAND trial received siponimod 2 mg maintenance dose irrespective of their genotypes[3]

RvS/Erasmus MC-2020; 1. Novartis Data on File (2.7.2 Siponimod Summary of Clinical Pharmacology Studies in multiple sclerosis; PopPK study); 2. SmPC Siponimod https://www.novartis.nl/medicijnen/mayzent; 3. Kappos L, et al. Lancet. 2018; 391:1263–1273. Bron: CYP2C9 allel frequenties Erasmus MC 2019 (n=1,653)

MedNet
Vergroot je medische vakkennis

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WEBCAST

Een DNA-uitslag.....
En wat nu?

Deze webcast wordt mogelijk gemaakt door:

NOVARTIS | Reimagining Medicine

“Here is my sequence …”
(The New Yorker, 2000)

Dutch Pharmacy PGx working group:

KNMP

Evidence-based dosing guidelines per genotype for > 120 drugs

Rating evidence: 1 – 4 (RCT)
Rating Clinical effect: A – F (death)

MEDIQ
APOTHEEK

MEDIQ
APOTHEEK

Kom binnen voor advies

“Here is my sequence …”

(The New Yorker, 2000)

Did I make sure my patient can handle the drug I am prescribing?

Take home message…..

Website: farmacogenetica@erasmusmc.nl
Email: r.vanschaik@erasmusmc.nl

MedNet
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Bedankt voor uw aandacht

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