19e Groninger Symposium Systeemziekten
“Medicatie en Systemische Auto-Immuunziekten”
Vrijdag 3 februari 2023

FARMACOGENETICA EN IMMUNOSUPPRESSIEVE GENEESMIDDELEN

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Inwendige Geneeskunde
Nefrologie & Transplantatie

Disclosures

Consulting fees

Astellas Pharma, Chiesi Pharma, Glaxo Smith Kline, Medincell, Novartis Pharma, Sangamo Therapeutics

Grant support

Astellas Pharma, Bristol-Myers Squibb, Chiesi Pharma

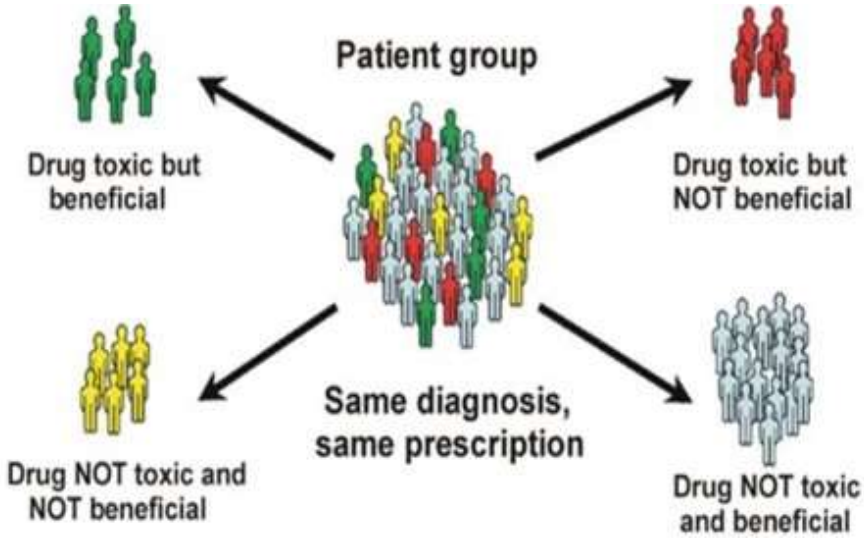
Lecture fees

Astellas Pharma, Chiesi Pharma, Fresenius Medical Care, Hikma Pharma, MSD, Novartis Pharma, Roche, Vifor Pharma

Disclosures

Farmacotherapie

- **Een patiënt met een diagnose**
- **Start farmacotherapie**
- **Standaard dosering, “one size fits all”**
- **Verschillende respons!**
- **“Trial and error”**



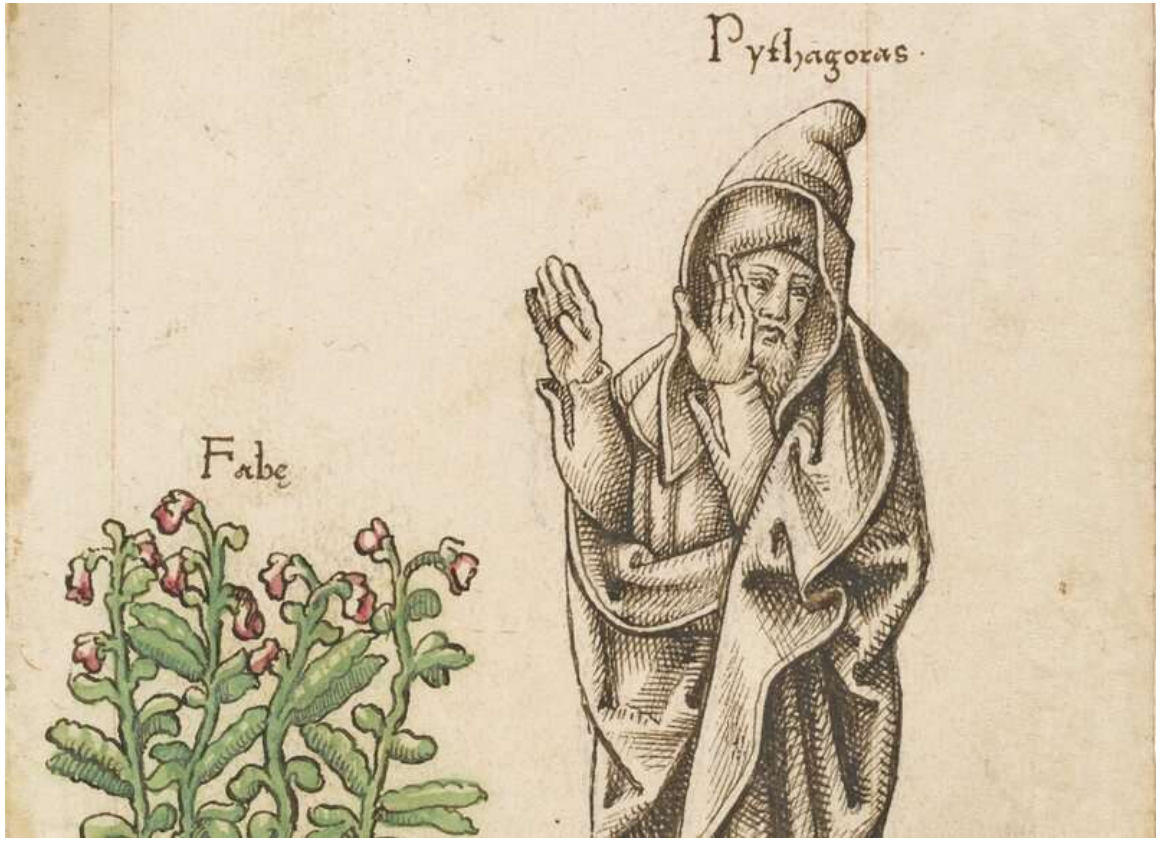
Personalized medicine

- **Het beste geneesmiddel voor een patiënt met een bepaalde diagnose**
- **De optimale (start)dosis**
- **Identificatie van patiënten met een risico op bijwerkingen vóór start therapie**

Farmacogenetica

- **De rol van erfelijkheid / genetische variatie in de individuele reactie op een geneesmiddel**
- **Genetische variatie in metaboliserende enzymen, drug transporters, receptoren / targets**

G6PD-deficiëntie



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pharmacogenetics

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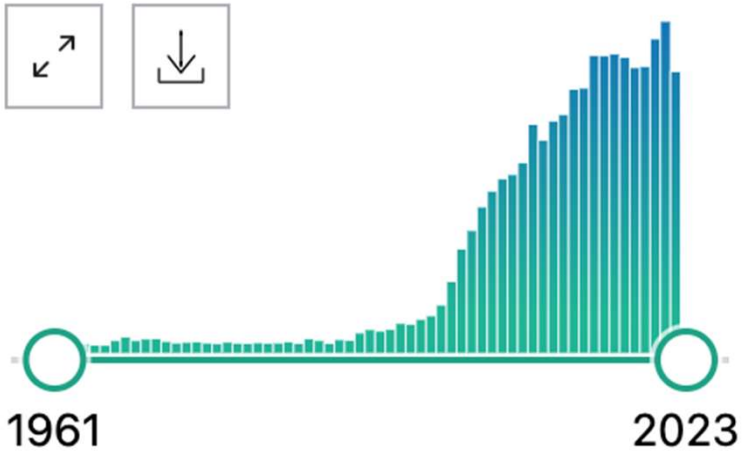


Werkgroepen & Consortia

- **Clinical Pharmacogenetics Implementation Consortium (CPIC®)**
- **Pharmacogenomics Knowledge Database (PharmGKB)**
- **Dutch Pharmacogenetics Working Group (DPWG)**
- **Ubiquitous Pharmacogenomics Consortium**

- **https://cpicpgx.org**
- **https://www.pharmgkb.org**
- **https://upgx.eu**

PharmGKB

CPIC® Clinical Pharmacogenetics Implementation Consortium

U-PGx | Ubiquitous Pharmacogenomics

Erasmus MC University Medical Center Rotterdam Transplant Institute

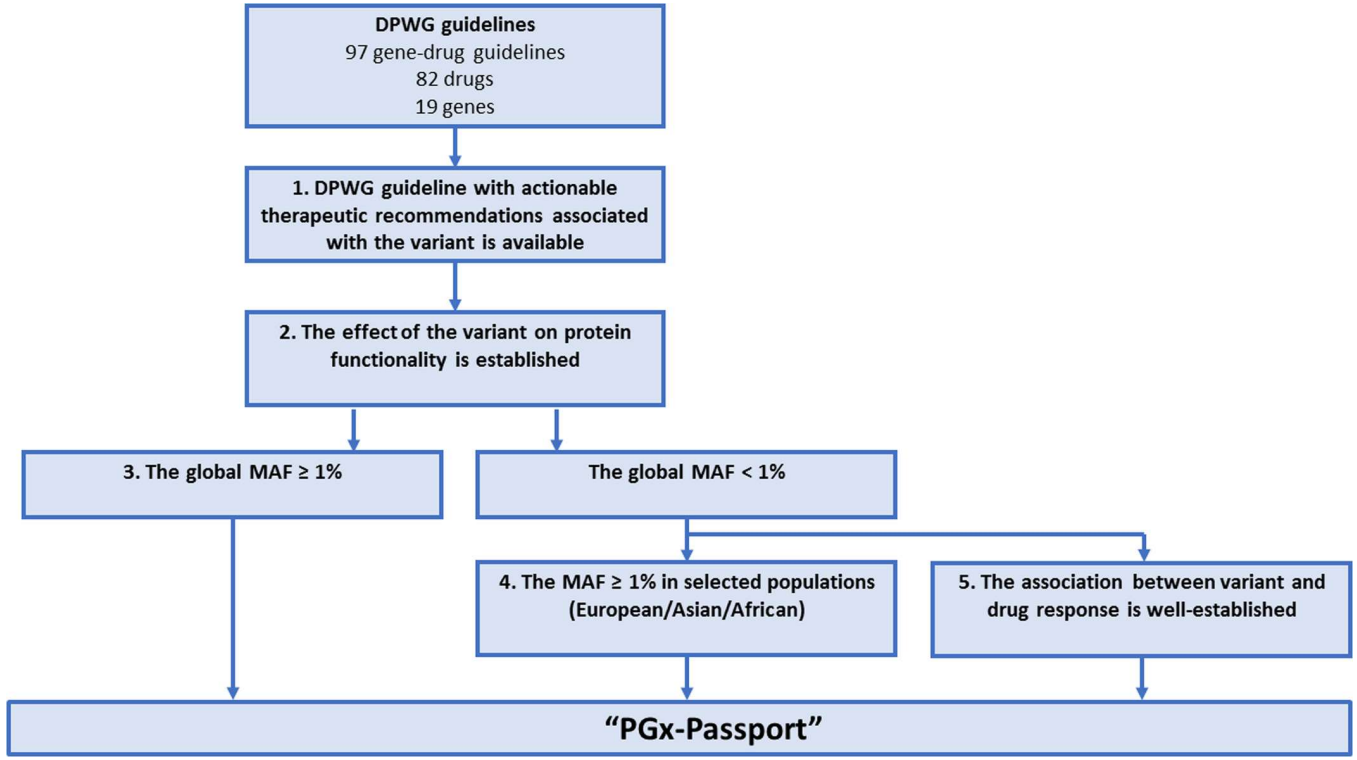
Richtlijnen

Table 1 Systematically selected clinically relevant variant alleles that reflect the complete set of actionable DPWG guidelines (58 variant alleles located in 14 pharmacogenes)

Genes	Variant allele	Allele functional status	Drug for which actionable DPWG guideline is available
CYP2B6	*6	Decreased function or no function	Efavirenz
	*9	Decreased function or no function	
	*4	Decreased function or no function	
	*16	Decreased function or no function	
	*18	Decreased function or no function	
	*5	Decreased function or full function	
CYP2C9	*2	Decreased function	Phenytoin Warfarin
	*3	Decreased function	
	*5	Decreased function	
	*11	Decreased function	
CYP2C19	*2	No function	Clopidogrel Citalopram Escitalopram Sertraline
	*3	No function	
	*4A/B	No function	

van der Wouden et al., Clin Pharmacol Ther 2019;106:866-72

Farmacogenetisch paspoort



van der Wouden et al., Clin Pharmacol Ther 2019;106:866-72

Farmacogenetisch paspoort

- **“Actionable genotypes”**
- **58 variant allelen in 14 farmacogenen**
- **49 veel voorgeschreven geneesmiddelen**
- ***CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5***
- ***DPYD*, *F5*, *HLA-A*, *HLA-B*, *NUDT15*, *SLCO1B1***
- ***TPMT*, *UGT1A1*, *VKORC1***

van der Wouden et al., Clin Pharmacol Ther 2019;106:866-72

PGx paspoort Erasmus MC

- **ISO 15189 gecertificeerd lab**
- **€ 674,-**
- **Turn around time 1 week**
- **Vergoed door zorgverzekeraar**

Farmacogenetica & immunosuppressiva

Table 1 Systematically selected clinically relevant variant alleles that reflect the complete set of actionable DPWG guidelines (58 variant alleles located in 14 pharmacogenes)

Genes	Variant allele	Allele functional status	Drug for which actionable DPWG guideline is available
CYP3A5	*3	No function	Tacrolimus
	*6	No function	
	*7	No function	
NUDT15	*2	Decreased function	6-Mercaptopurine Azathioprine Thioguanine
	*3	Decreased function	
	*6	Decreased function	
	*9	Decreased function	
TPMT	*2	No function	6-Mercaptopurine Azathioprine Thioguanine
	*3A	No function	
	*3B	No function	
	*3C	No function	

van der Wouden et al., Clin Pharmacol Ther 2019;106:866-72

PGx en overige immunosuppressiva

Received: 17 September 2017 | Revised and accepted: 24 November 2017
DOI: 10.1111/cge.13186

WILEY CLINICAL GENETICS

INVITED REVIEW

Pharmacogenetics: A strategy for personalized medicine for autoimmune diseases

S. Tavakolpour[1,2] | M. Darvishi[3] | M. Ghasemiadl[2]

Review > Pharmacogenomics J. 2020 Dec;20(6):749-759. doi: 10.1038/s41397-020-0176-z. Epub 2020 Jul 18.

Gene variants and treatment outcomes in antineutrophil cytoplasmic antibody-associated vasculitis

Arno C Hessels [1], Jan Stephan F Sanders [2], Abraham Rutgers [3], Coen A Stegeman [2]

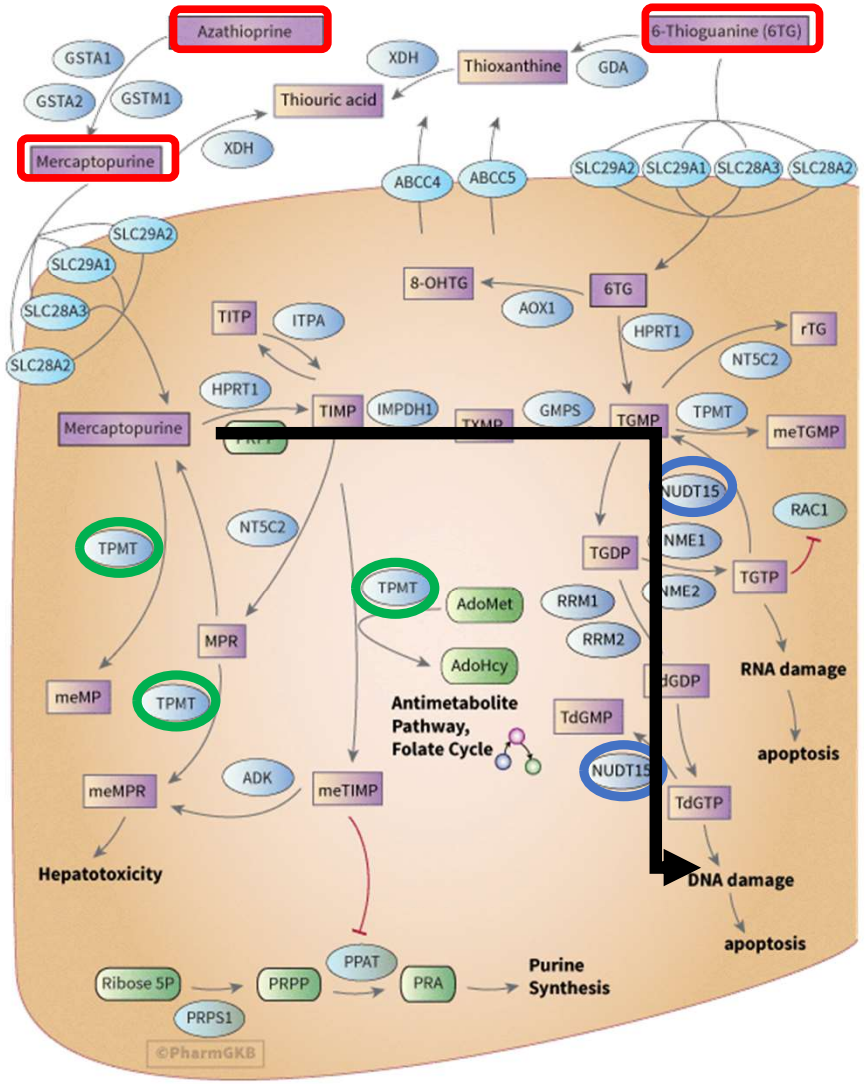
Affiliations + expand

Tavakolpour et al., Clin Genet 2018;93:481-97; Hessels et al., Pharmacogenomics J 2020;20:749-59

Thiopurines

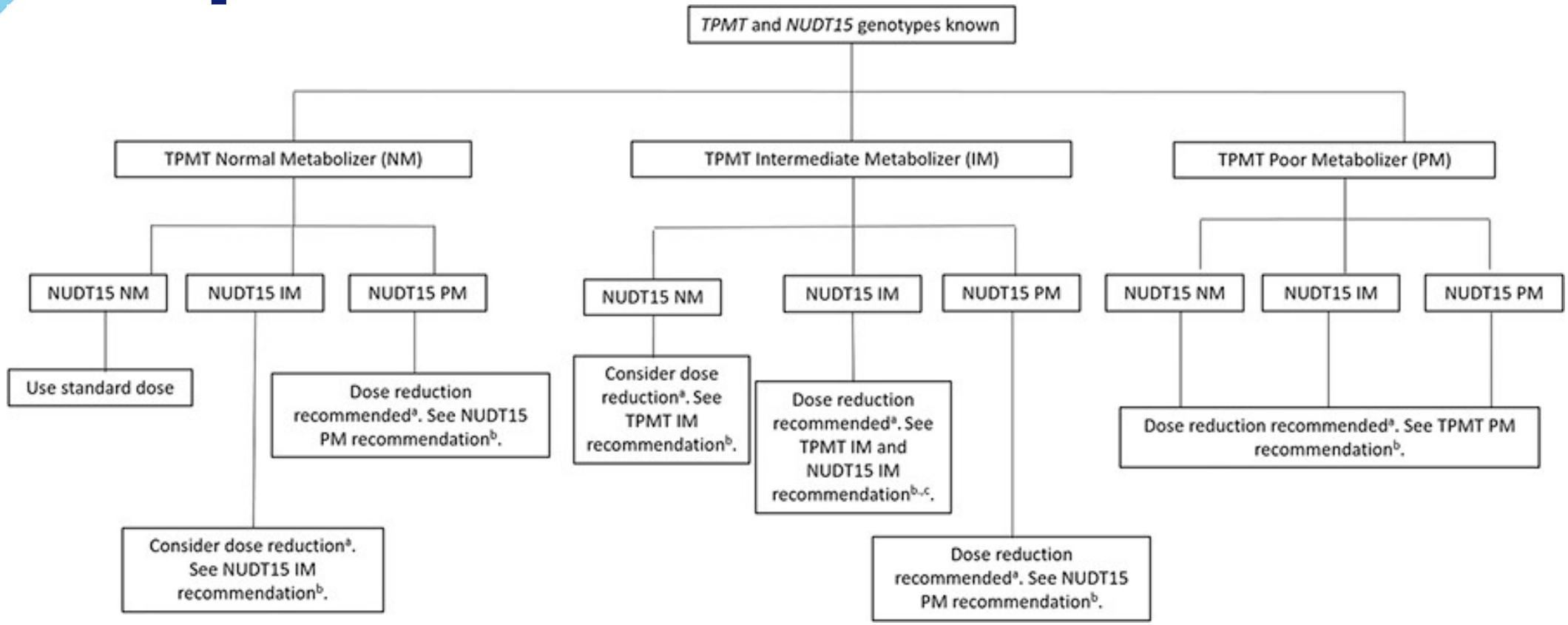
- **Azathioprine, mercaptopurine en thioguanine**
- **Detoxificatie via:**
  - **Thiopurine S-methyltransferase (*TPMT*)**
  - **Nudix hydrolase 15 (*NUDT15*)**

Relling et al., Clin Pharmacol Ther 2019;105:1095-1105; Pratt et al., J Mol Diagn 2022;24:1051-63



Relling et al., Clin Pharmacol Ther 2019;105:1095-1105

Thiopurines



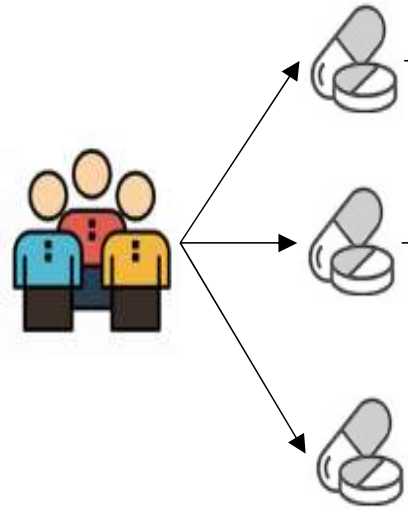
Relling et al., Clin Pharmacol Ther 2019;105:1095-1105; Pratt et al., J Mol Diagn 2022;24:1051-63

Tacrolimus

- **Hoeksteen van de immunosuppressieve therapie na transplantatie**
- **Startdosering i.h.a. op geleide van lichaamsgewicht**
- **Nadien dosisaanpassing op geleide van volbloedconcentraties**
- **Therapeutic Drug Monitoring**

Brunet et al., Ther Drug Monit 2019;41:261-307

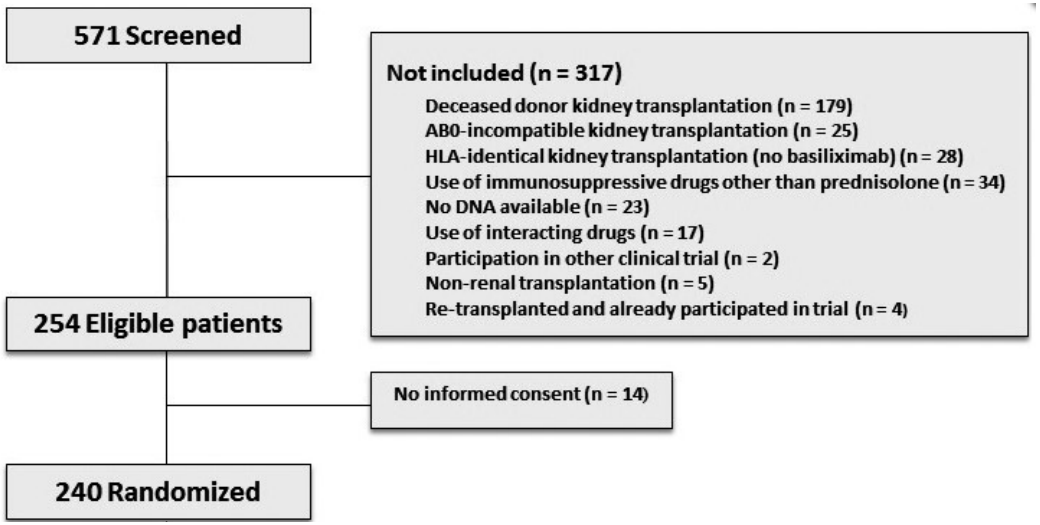
TDM



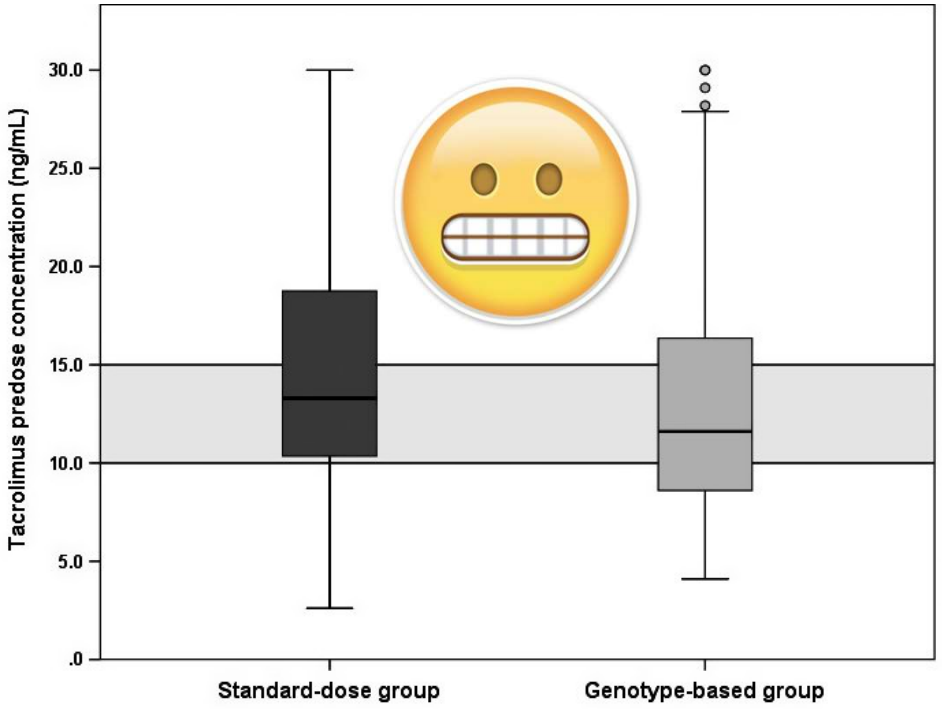
Farmacogenetica van Tacrolimus

- **CYP3A5 expressers hebben ~50% meer tacrolimus nodig**
- **Diverse RCTs verricht naar het nut van *CYP3A5*-geleid doseren**

Brunet et al., Ther Drug Monit 2019;41:261-307; Hesselink et al., Clin Pharmacokinet 2014;53:123-39

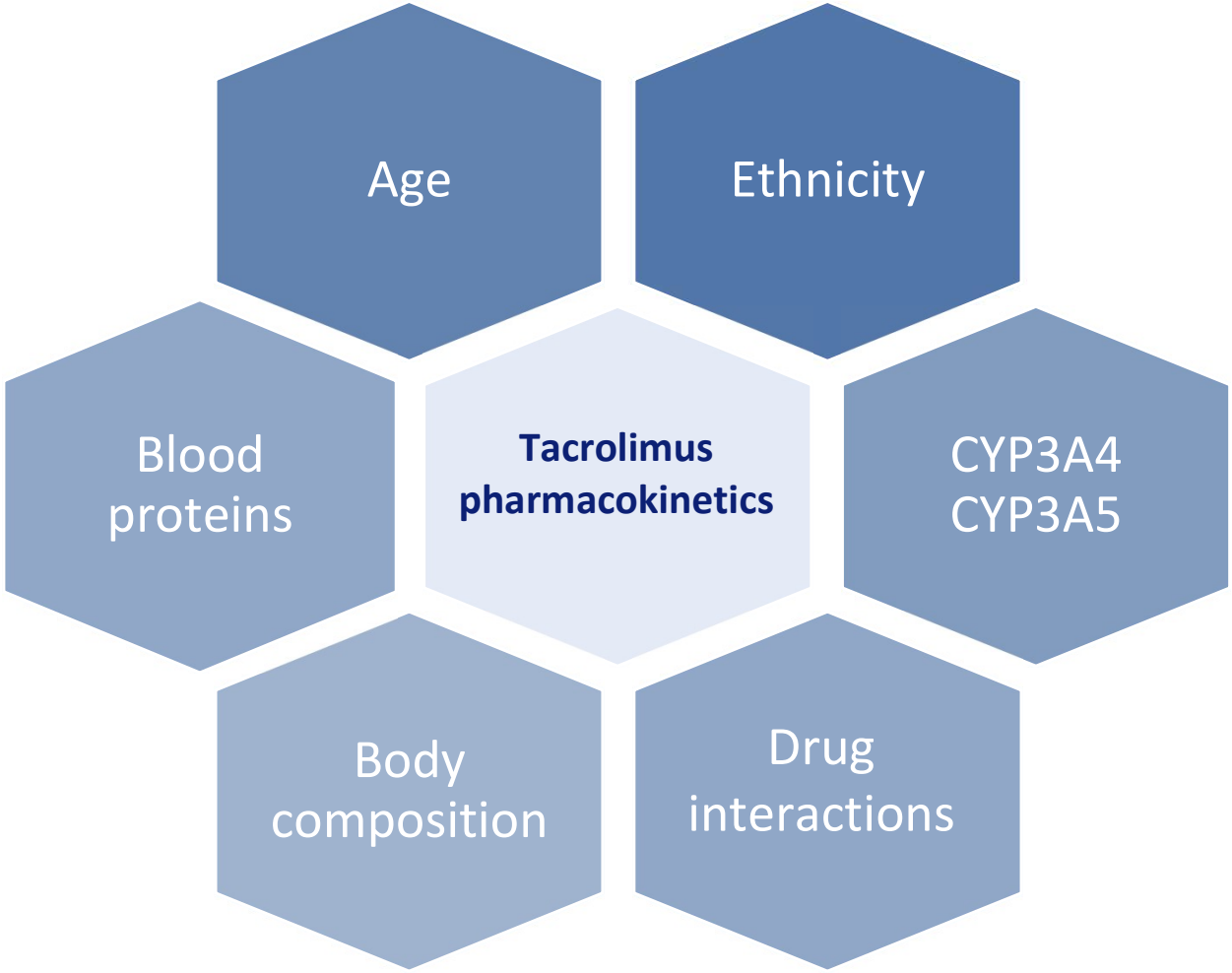


Shuker et al., Am J Transplant 2016;16:2085-96



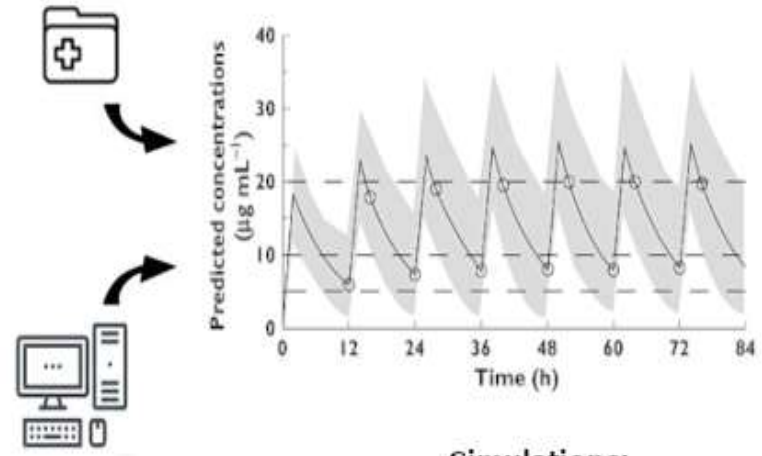
	Standard-dose group	Genotype-based group	*p*
	n = 99	n = 104	
Supra-therapeutic concentration	39 (39.4%)	31 (29.8%)	0.20
Therapeutic concentration	37 (37.4%)	37 (35.6%)	0.79
Sub-therapeutic concentration	23 (23.2%)	36 (34.6%)	0.10

Shuker et al., Am J Transplant 2016;16:2085-96


Age
Ethnicity
Blood proteins
Tacrolimus pharmacokinetics
CYP3A4 CYP3A5
Body composition
Drug interactions

Model-informed precision dosing

Patient data:
weight, renal function, gender,.... **Farmacogenetica**



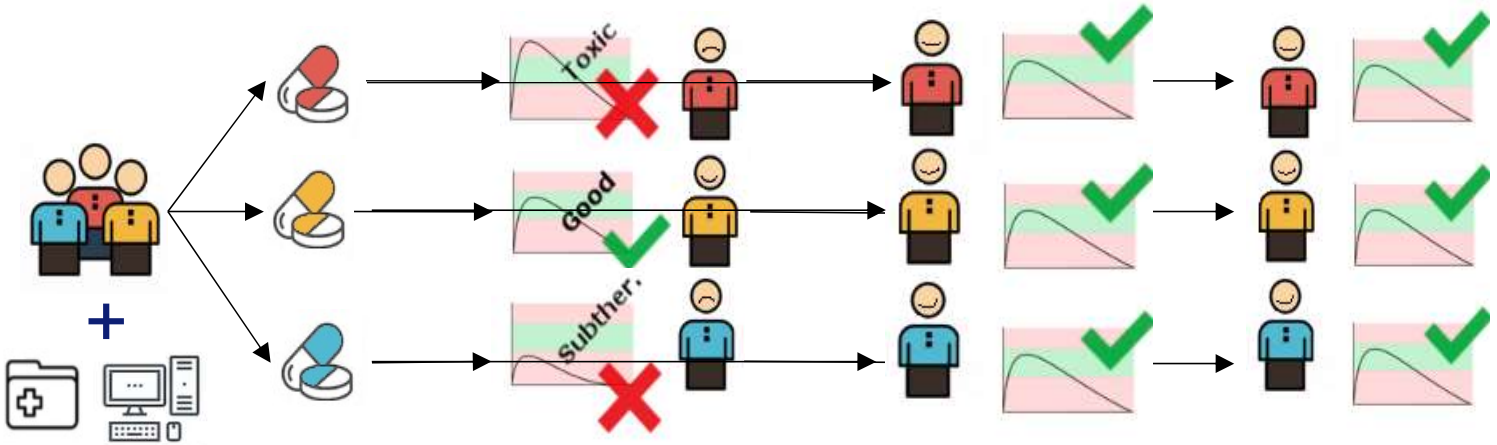
PK models:
Validated mathematical prediction models (NONMEM).

Simulations:
Run iterative simulations of PK model with input of individual patient characteristics

GUI:
Simple recommendation for starting dose for target concentrations (with confidence interval)

Andrews et al., Br J Clin Pharmacol 2019;85:601-15; Francke et al., Clin Pharmacol Ther 2021;110:169-78

Model-informed precision dosing

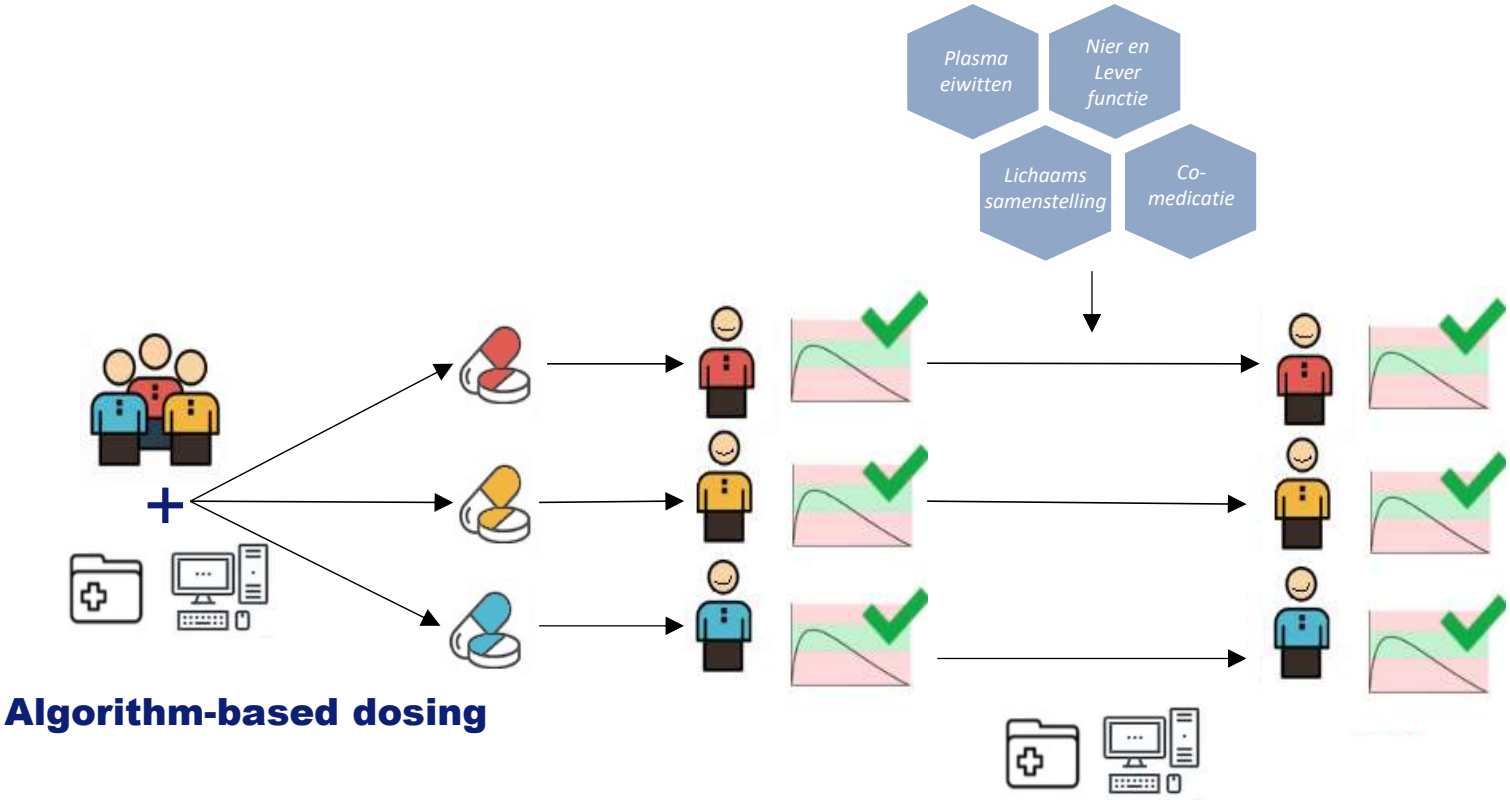


Standard body weight based dosing

Algorithm based dosing

Therapeutic Drug Monitoring

Andrews et al., Br J Clin Pharmacol 2019;85:601-15; Francke et al., Clin Pharmacol Ther 2021;110:169-78



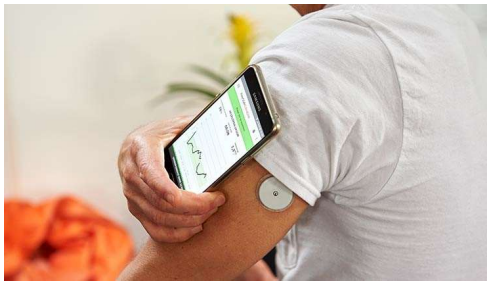
Algorithm-based dosing

Computerized follow-up dosing

Andrews et al., Br J Clin Pharmacol 2019;85:601-15; Francke et al., Clin Pharmacol Ther 2021;110:169-78

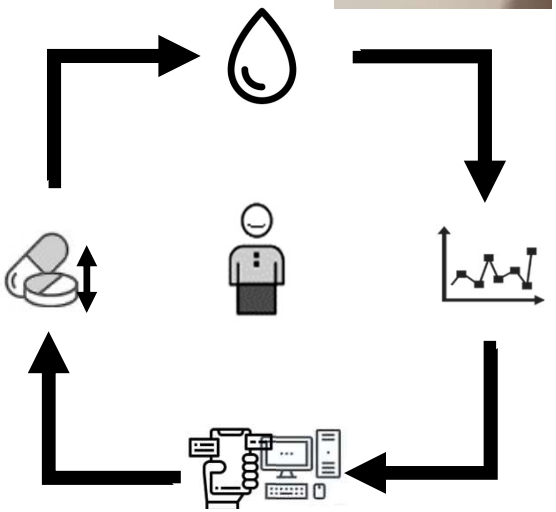
Closing the loop

Tacrolimus sensor

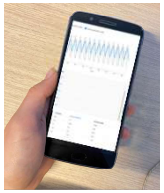


Thuis sampling met dried blood spot

Dosis aanpassing op geleide van algoritme



Lab bepalingen



Self-monitoring: Patient voert data in app / web-based interface

Conclusies

- **Farmacogenetica is here to stay**
- **Implementatie in klinische praktijk**
- **Impact voor immunosuppressie is vooralsnog beperkt (thiopurines en tacrolimus)**
- **Model-informed precision dosing met farmacogenetica**
- **Patiënt empowerment**

Merci!

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