



Leiden University  
Medical Center

# *Empowering Personalized Medicine through Diagnostics*

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Leiden University Medical Center

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*Innovation for Health*

*Rotterdam, 13 February 2020*

# Three patients at the GP/pharmacy

Three patients A, B, C

Identical:

- Symptoms
- Diagnostic procedures
- Diagnosis X
- Treatment: Drug Rx at a dose  $x$  mg/day



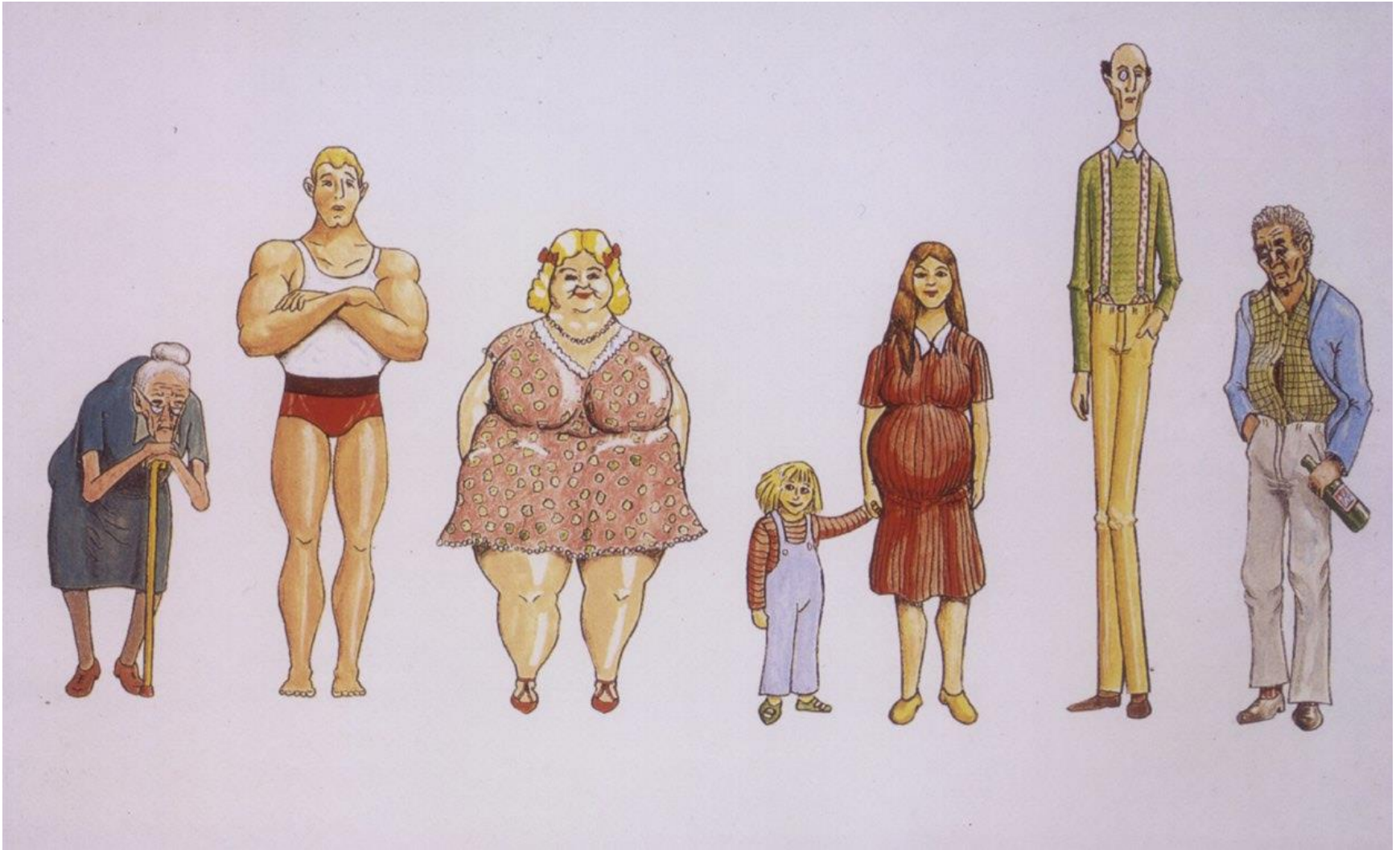
After 3 weeks

- Pat A: still symptoms, no effect of drug
- Pat B: symptoms resolved
- Pat C: still symptoms, side effects



**➔ Why respond individuals differently?**

# Variability in humans



# May 1975: Debrisoquine





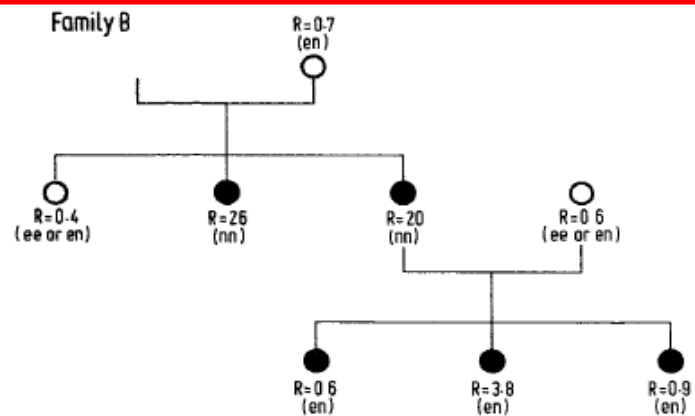
# Debrisoquine – 4-hydroxydebrisoquine

## POLYMORPHIC HYDROXYLATION OF DEBRISOQUINE IN MAN

A. MAHGOUB                      J. R. IDLE  
L. G. DRING                      R. LANCASTER  
R. L. SMITH

*Department of Biochemical and Experimental Pharmacology  
and Department of Clinical Pharmacology, St. Mary's  
Hospital Medical School, London W2 1PG*

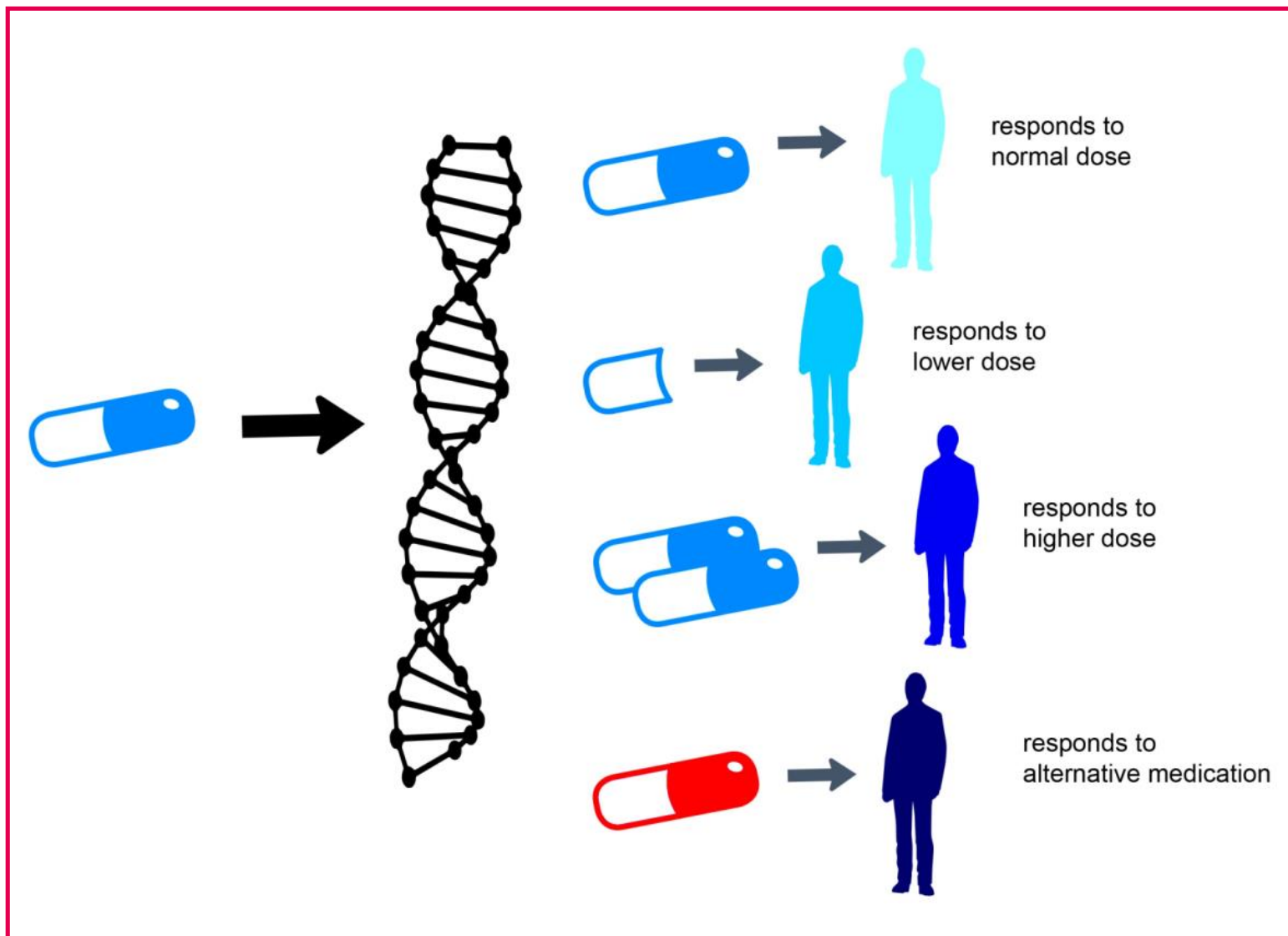
**Summary** Debrisoquine and its primary metabolite, 4-hydroxydebrisoquine, were measured in the urine of 94 volunteers after a single oral dose of 10 mg debrisoquine. The ratio between excreted debrisoquine and its metabolite was bimorphically distributed in the study population. Family studies supported the view that alicyclic 4-hydroxylation of debrisoquine is



## METABOLIC RATIOS (DUPLICATE VALUES)\* IN 6 EXTENSIVE METABOLISERS AND THE 3 NON-METABOLISERS

Subject no.	% Dose excreted in 8 h as		Metabolic ratio
	Debrisoquine	4-Hydroxydebrisoquine	
<i>Extensive metabolisers:</i>			
1	15.7	25.8	0.6
	41.3	55.8	0.7
2	16.6	30.5	0.5
	32.3	45.0	0.7
3	28.9	29.5	1.0
	20.0	23.8	0.8
4	45.1	45.4	1.0
	33.4	46.3	0.7
5	28.6	18.7	1.5
	10.4	8.1	1.3
6	24.8	48.2	0.5
	11.2	22.4	0.5
<i>Non-metabolisers:</i>			
7	42.7	2.0	21.4
	39.6	2.0	19.8
8	18.1	0.8	22.6
	59.7	3.1	19.3
9	36.7	1.6	22.9
	18.0	0.9	20.0
	56.4	2.7	20.9

# Drug response is a heritable trait



# Once upon a time there was a patient....

21-year old woman

recently started 20 mg tioguanine per day; M. Crohn

After 3 weeks: does not feel well, fatigue, tinnitus,  
headache, short of breath

Lab: pancytopenia

TPMT-genotyping:

Heterozygous TPMT \*3C/\*2

**bijwerkingen**  
**centrum**lareb



**diagnostic - reactive**



12 members multidisciplinary (DPWG):  
(clinical) pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologist, toxicologist, primary care physician



## Aim:

- To develop pharmacogenetic (dosing) guidelines based upon systematic review of literature
- To integrate these guidelines in electronic prescription systems and medication surveillance systems

**47 actionable interactions**

**2020: PGx guidelines for 103 gene-drug pairs**



Pon Geboren 02-09-1947 M  
Patiëntnummer 3760 63j  
alle klinische medicatie  
Poliklinische medicatie Klinische medicatie

	Geneesmiddel	Toedieningsweg	ZN	Dosering	Dag...	E...	Start...	St...	Stopdatum	S...	Motivatie	Motivatie in VCMO	VC...
	PANTOPRAZOL TABLET MSR 40MG	ORAAL		1 x per dag 40 milligram	40...	M...	04-05-2011	13:15	--				
	PARACETAMOL TABLET 500MG	ORAAL		3 x per dag 500 milligram	150...	M...	04-05-2011	13:14	--				

**A**

Pon Geboren 02-09-1947 M  
Patiëntnummer 3760 63j  
NORTRIPTYLINE TABLET 25MG (ORAAL), 1 x per dag 100 milligram

**Let op:** er zijn afgeleide contra-indicaties. [details](#)

**Medicatie opdracht**

Geneesmiddel: NORTRIPTYLINE TABLET 25MG (R) Aanvraager: A00148  
 Toedieningsweg: ORAAL Afdeling: J10-Q (lang verblijf)  
 Geneesmiddel yrietekst: Reg-type:  
 Periode: 04-05-2011 13:15 tot: - - - - -  
 Aantal: 0 STUK Chronisch

**Doseerschema**

Doseering	Eenheid	Duur	Interv	Motie	Tijd	Dosis	ZN
1d100	MG				08:00	100	<input type="checkbox"/>

+ Schema toevoegen [INS]

Vaste tijden

**Geneesmiddel waarschuwingen**  alleen relevante  alle waarschuwingen

**Contra-indicatie:** NORTRIPTYLINE TABLET 25MG - CYP2D6 POOR METABOLIZER

**Teksten**

Kan het reactievermogen verminderen  
Pas op met alcohol

Bewaar als VMO  TNQ gestopt  Eigen beheer

Zoeken Herstel Detail OK OK+Nieuw Annuleren

**B**

Tonen: Z-index Controle op contra-indicatie aard [00006564]

Contra-indicatie aard [00006564/00226157/CYP2D6 POOR METABOLIZER]

1 - Algemeen 2 - Teksten

Voorschrifttekst

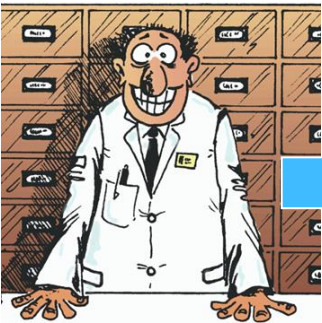
Het genetisch polymorfisme leidt tot een verlaagde metabole capaciteit van CYP2D6 waardoor de plasmaconcentratie van nortriptyline kan stijgen. Advies: Verlaag de dosering tot 40% van de normale dosering en monitor de plasmaconcentratie van nortriptyline voor het instellen van de onderhoudsdosering.

Alle details Sluiten

# DPYD @ LUMC



Oncologist considers DPYD testing 'standard of care'



Pharmacist alerts physician if FU/CAP is prescribed with no DPYD testing

pre-therapeutic - screening

Upfront Genotyping of *DPYD*\*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis

Maarten J. Daenen, Didier Meulendijks, Annemieke Cats, Marjolain K. Sechterberger, Johan L. Severens, Henk Boot, Paul H. Smits, Hilde Rosing, Caroline M.P.W. Mandigers, Marcel Soesan, Jos H. Beijnen, and Jan H.M. Schellens

See accompanying editorial on page 205

Prospective \*2A screening (n=2,038)  
50% dose reduction in patients with *DPYD*\*2A

(literature)

with  
*DPYD*\*2A variant  
(heterozygous)

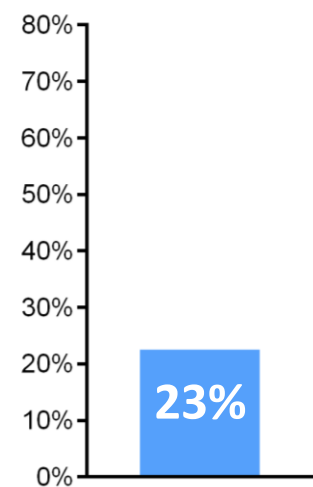
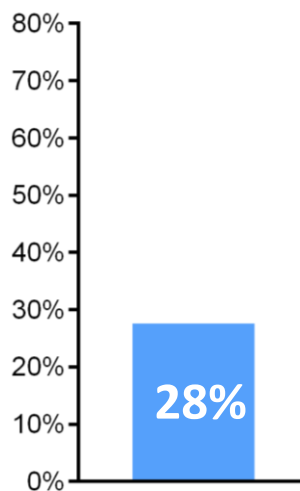
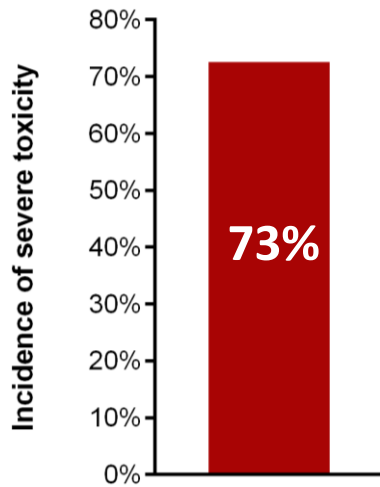
with  
*DPYD*\*2A variant  
(heterozygous)

no *DPYD*\*2A variant

normal dose

50% dose reduction

normal dose

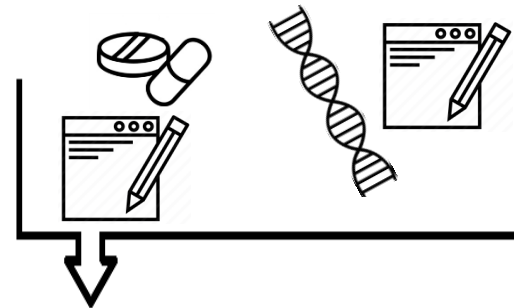


# DPYD screening @ LUMC

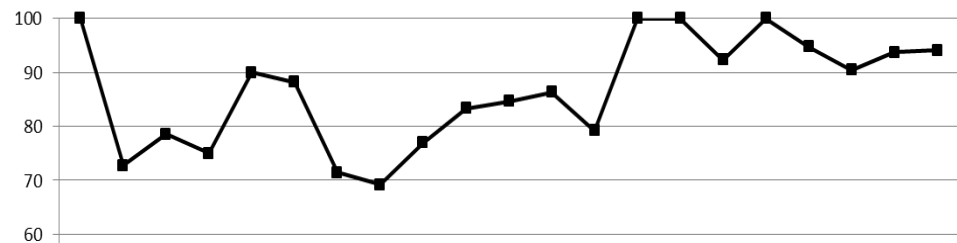
Routine pre-therapeutic DPYD  
screening LUMC (per april 2013)



Retrospective analysis: 314 patients  
(18 maanden)



Screening:  
mean: 87%  
final: 90-100%



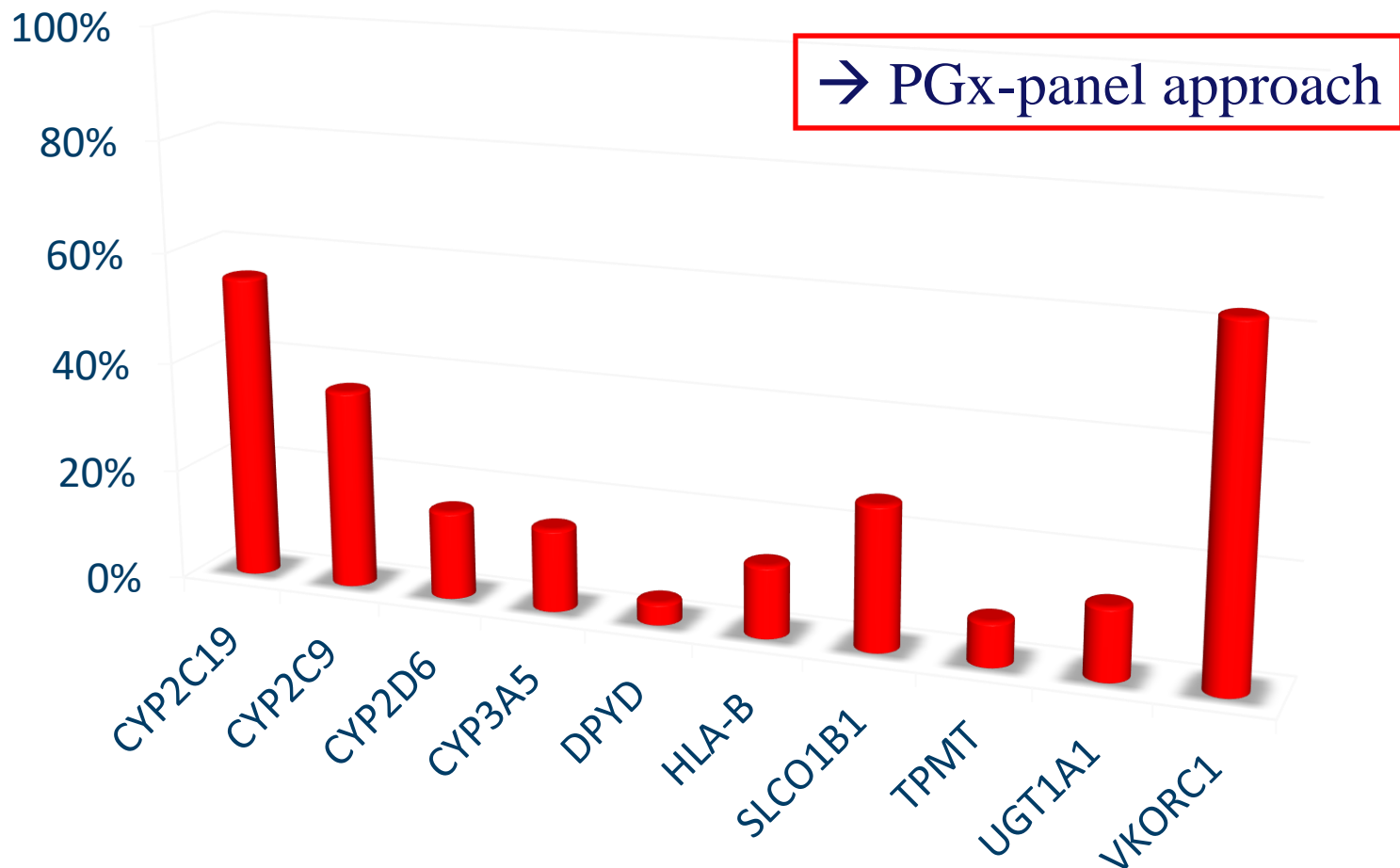
**No grade 3-4 toxicity in patients with initial dose reduction**

# Number needed to genotype

- How many patients do I have to screen/test to prevent one from having a Adverse Drug Reaction (grade 3-4 toxicity, death, etc.)?



# 'Actionable' genotypes



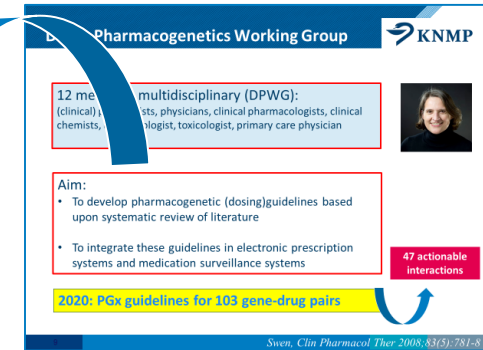
95% of patients have at least 1 'actionable' genotype

# Pharmacogenetics-passport

ARTICLE

## Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing

Cathelijne H. van der Wouden<sup>1,2</sup>, Mandy H. van Rhenen<sup>1</sup>, Wafa O.M. Jama<sup>1</sup>, Magnus Ingelman-Sundberg<sup>4</sup>, Volker M. Lauschke<sup>4</sup>, Lidija Konta<sup>5</sup>, Matthias Schwab<sup>6,7</sup>, Jesse J. Swen<sup>1,2</sup> and Henk-Jan Guchelaar<sup>1,2\*</sup>



All actionable gene-drug interactions  
 DPWG  
 14 pharmacogenes  
 58 genetic variants

 Name: Jane Doe Date of birth: 01.02.1934	
<i>The Medication Safety Code initiative</i>	
<b>Gene, status</b>	<b>Critical drug substances (modification recommended!)</b>
CYP2C19	Clopidogrel, Sertraline
Poor metabolizer	
CYP2D6	Amitriptyline, Aripiprazole, Clomipramine, Codeine, Doxepin, Haloperidol, Imipramine, Metoprolol, Nortriptyline, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine
Ultrarapid metabolizer	
TPMT	Azathioprine, Mercaptopurine, Thioguanine
Poor metabolizer	
<b>Other genes</b>	ABCB1, ADRB1, BRCA1, COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP3A4, CYP3A5, DPYD, G6PD, HMGR, P2RY12, SULT1A1, UGT1A1, VKORC1
Not actionable	
Date printed: 10.12.2015 <span style="float: right;">Card number: 0000001</span>	



# Impact Netherlands 2016



N = 3.221.696 (Unique pat.)	First Rx* (4.138.909)	Gene	Phenotype	Actionable#	Dose- adj. /switch**
PPI's	1.026.441	CYP2C19	UM	41058	871
Coumarines	62.558	VKORC1	TT	10634	10634
Clopidogrel	98.709	CYP2C19	PM + IM	24677	24677
Statines	305.999	SLCO-1B1	Lage act.	78029	
Thiopurines	11.424	TPMT	IM + PM		
Tramadol	357.389	CYP2D6			8934
Codeine	519.722	CYP2D6	IM + PM		12993
TCM		CYP2D6		60068	60068
V...	26.603		IM + PM	12503	11838
Flecainide	13.605	CYP2D6	IM + PM + UM	6394	680
Paroxetine	27.018	CYP2D6	IM + PM + UM	12698	675
Tamoxifen	10.807	CYP2D6	IM + PM	4809	4809
....	**based on prevalence from IP3		# based on DPWG guidelines		

**1 : 19 First prescriptions need dose adjustment or switch  
= 5,3% of first prescriptions**



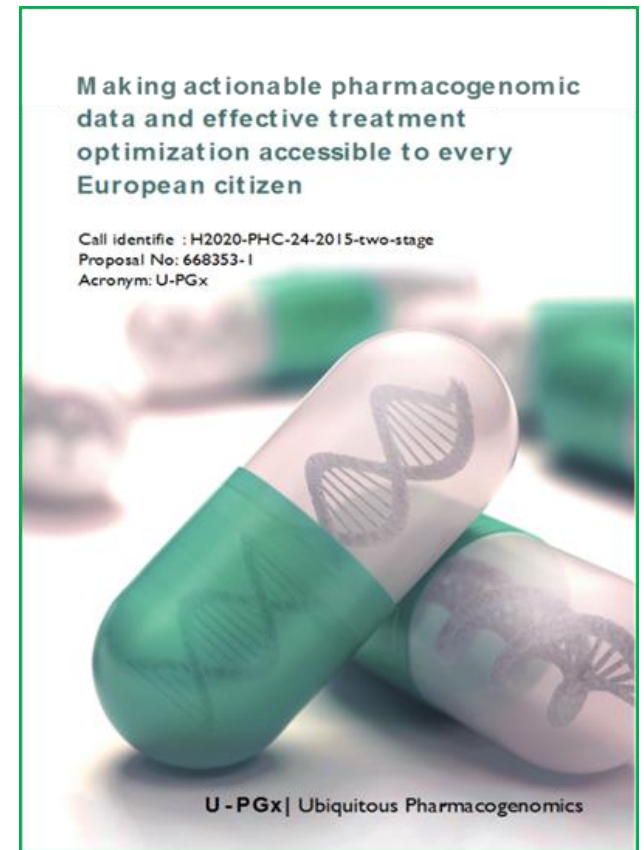
Overall aim U-PGx:

*“Making actionable pharmacogenomic data and effective treatment optimization accessible to every European citizen”*



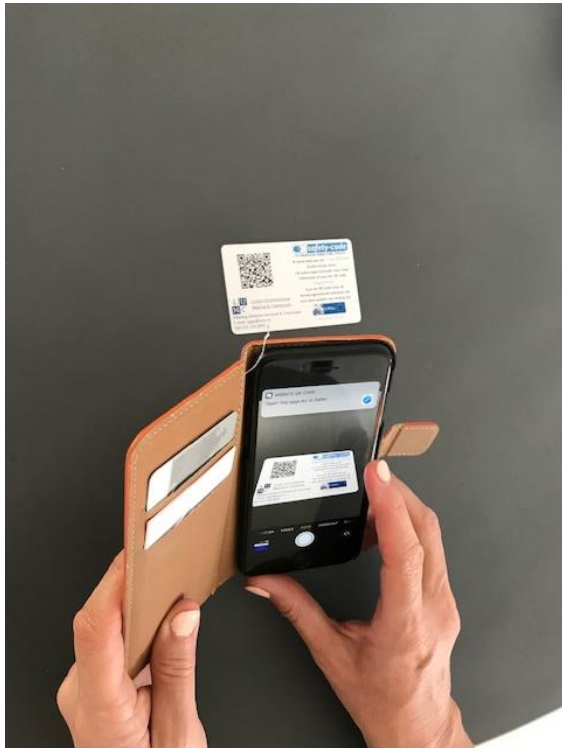
- €15 million, H2020, 10 EU countries
- Started 1 Jan 2016, 5 yr
- **Reduction severe ADR: 30%**
  - **8,100 patients**

[www.upgx.eu](http://www.upgx.eu)





# U-PGx | Ubiquitous Pharmacogenomics



Scan QR code

Vodafone NL Wi-Fi 11:11 39%

Gereed my.upgx.eu

**Farmacogenetisch testrapport**

**Geneesmiddelen met adviezen (in alfabetische volgorde)**

- [Fenytoïne](#)
- [WARFARIN](#)

**Farmacogenomische varianten die de geneesmiddel respons beïnvloeden (zie hieronder voor gedetailleerde resultaten)**

Gen	Fenotype / status
CYP2C9	CYP2C9 *1/*3

**AANBEVELINGEN (in alfabetische volgorde)**

- ▶ Fenytoïne
- ▶ WARFARIN

▶ Gedetailleerde resultaten genotype / fenotype

▶ Overzicht van geneesmiddelen, relevante fenotypen en beschikbaarheid van aanbevelingen

▶ Disclaimer

▶ Geteste varianten

actionable gene-drug interactions

Vodafone NL Wi-Fi 11:13 38%

Gereed my.upgx.eu

Gen	Fenotype / status
CYP2C9	CYP2C9 *1/*3

**AANBEVELINGEN (in alfabetische volgorde)**

▼ Fenytoïne

Fenotype / Variant: CYP2C9 \*1/\*3

De genetische variatie verlaagt de omzetting van fenytoïne in inactieve metabolieten. Hierdoor is het risico op bijwerkingen verhoogd. Met name bij Aziaten kan de levensbedreigende cutane bijwerking Stevens-johnsonsyndroom/toxische epidermale necrolyse optreden.

Advies:

1. een oplaaddosering hoeft niet te worden aangepast
2. gebruik voor de overige doseringen 75% van de normale dosis en beoordeel de dosering op geleide van effect en serumspiegel na 7-10 dagen
3. adviseer de patiënt om contact op te nemen wanneer bijwerkingen (zoals ataxie, nystagmus, spraakstoornis, sedatie of, met name bij patiënten van Aziatische afkomst, huiduitslag) optreden

▶ WARFARIN

▶ Gedetailleerde resultaten genotype / fenotype

▶ Overzicht van geneesmiddelen, relevante fenotypen en beschikbaarheid van aanbevelingen

▶ Disclaimer

▶ Geteste varianten

DPGW guideline

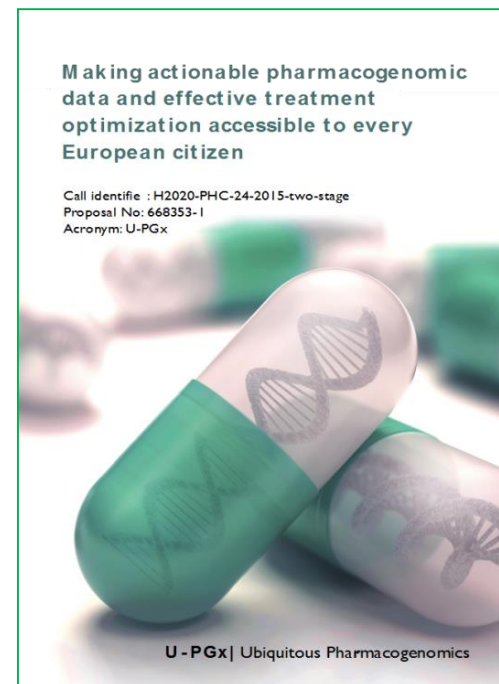
## Take home messages

- **Implementation of PGx in clinical practice is feasible and effective**
- **PGx testing has moved from a reactive to a pre-therapeutic and preemptive panel approach**
- **Personalizing therapy based upon PGx will improve patient outcome**

# Thank you for your attention!



U-PGx meeting Uppsala 26-27 June, 2019



[www.upgx.eu](http://www.upgx.eu)

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