Leiden University
Medical Center

Empowering Personalized Medicine through Diagnostics

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Innovation for Health
Rotterdam, 13 February 2020

Three patients at the GP/pharmacy

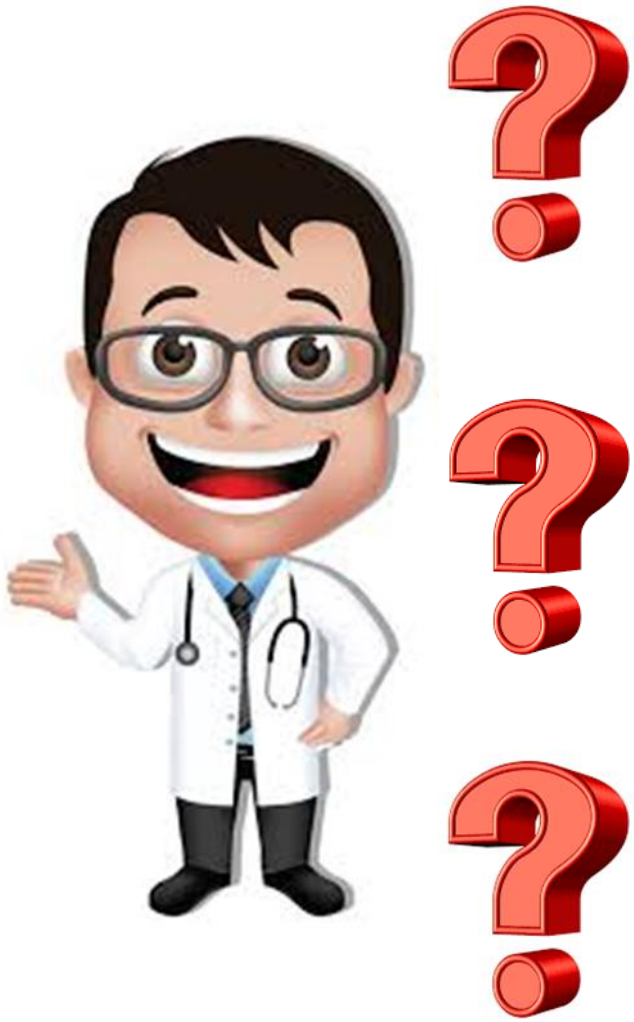
Three patients A, B, C

Identical:

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

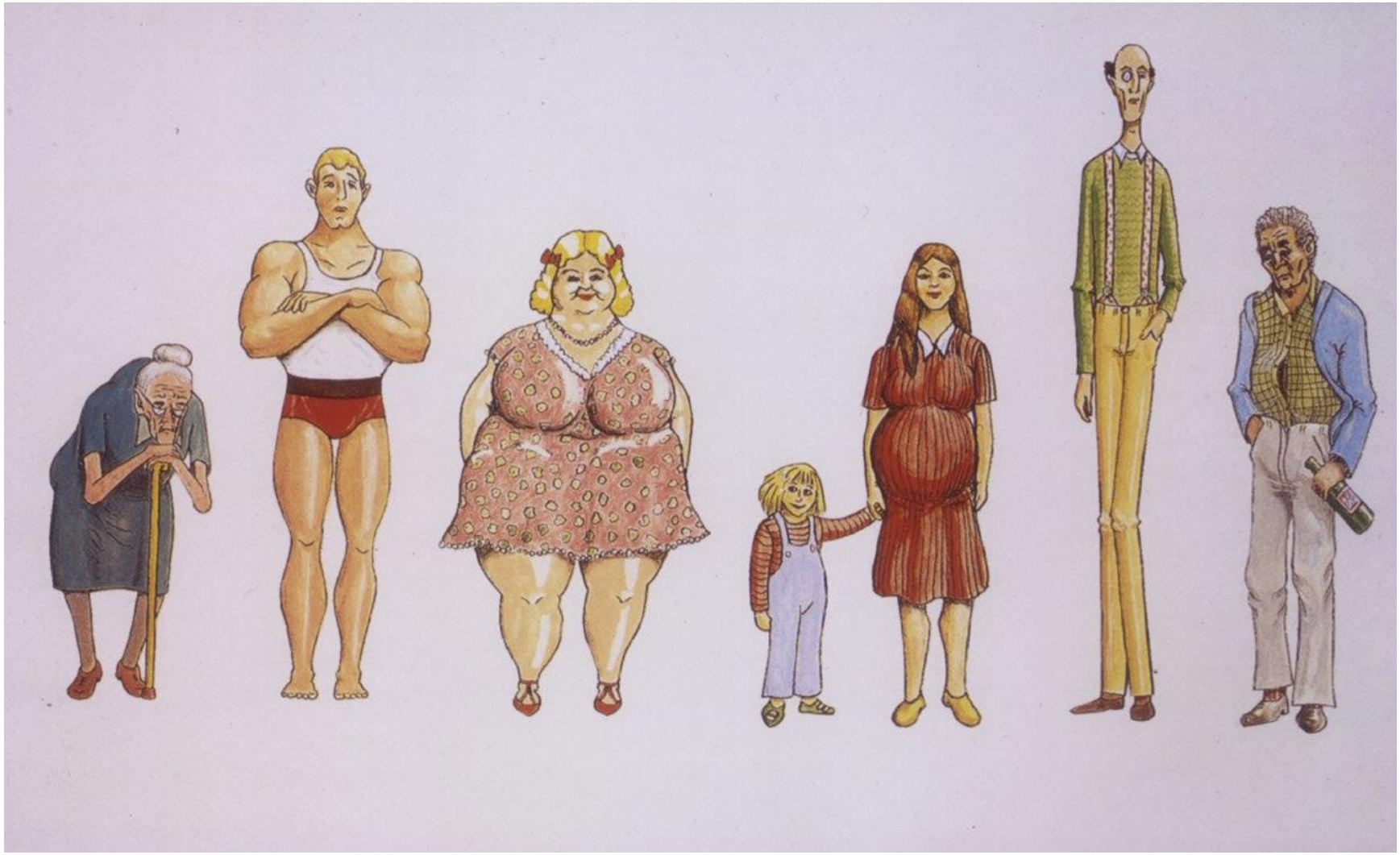
After 3 weeks

- **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

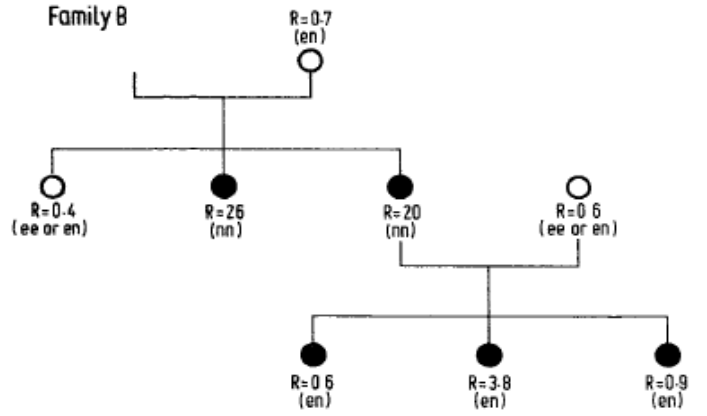
Debrisoquine – 4-hydroxydebrisoquine

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

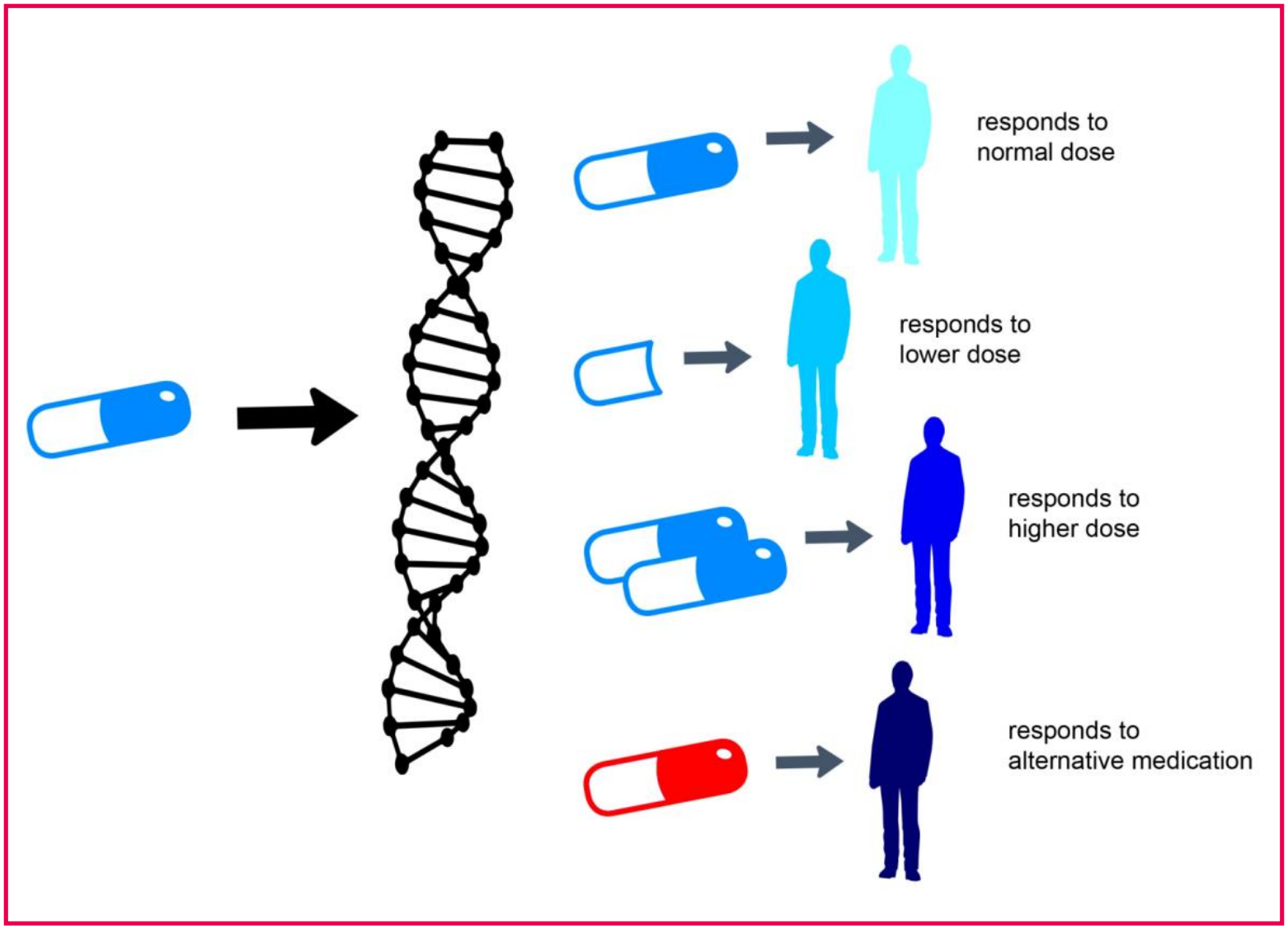
Summary Debrisoquine and its primary metabolite, 4-hydroxydebrisoquine, were measured in the urine of 94 volunteers after a single oral dose of 10 mg debrisoquine. The ratio between excreted debrisoquine and its metabolite was bimorphically distributed in the study population. Family studies supported 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 Debrisoquine	% Dose excreted in 8 h as 4-Hydroxydebrisoquine	Metabolic ratio
Extensive metabolisers:			
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
Non-metabolisers:			
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 centrumlareb

diagnostic - reactive

Dutch Pharmacogenetics Working Group

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

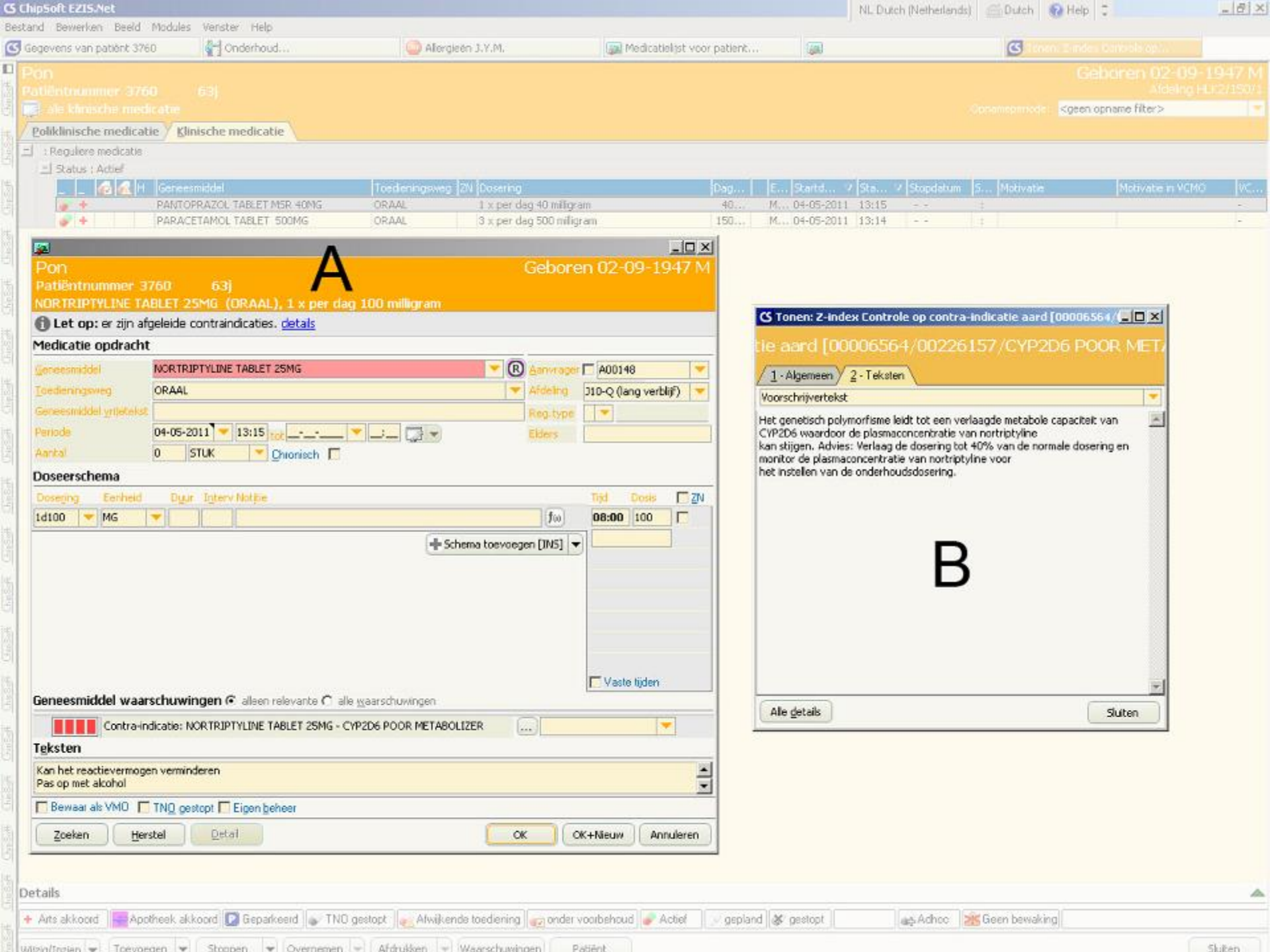
Aim:

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

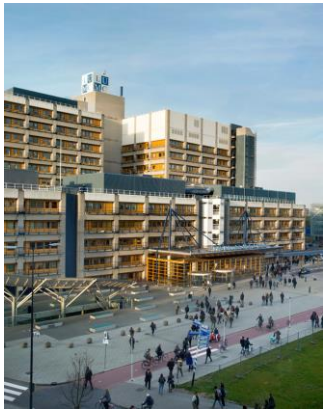
47 actionable interactions

2020: PGx guidelines for 103 gene-drug pairs

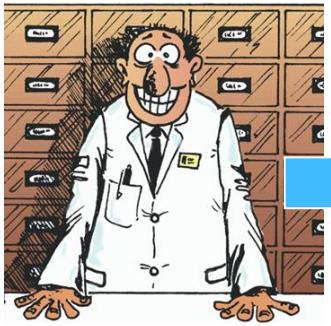
Swen, Clin Pharmacol Ther 2008;83(5):781-8


ChipSoft EZIS.Net
Pon
Patiëntnummer 3760 63j
Geboren 02-09-1947 M
Poliklinische medicatie
Klinische medicatie
PANTOPRAZOL TABLET MSR 40MG ORAAL 1 x per dag 40 milligram
PARACETAMOL TABLET 500MG ORAAL 3 x per dag 500 milligram
A
Pon
Patiëntnummer 3760 63j
Geboren 02-09-1947 M
NORTRIPTYLINE TABLET 25MG (ORAAL), 1 x per dag 100 milligram
Let op: er zijn afgeleide contraindicaties. details
Medicatie opdracht
Geneesmiddel NORTRIPTYLINE TABLET 25MG
Toedieningsweg ORAAL
Periode 04-05-2011 13:15
Aantal 0 STUK
Chronisch
Doseerschema
Dosering Eenheid Duur Interv Notitie Tijd Dosis ZN
1d100 MG 08:00 100
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 TNO gestopt Eigen beheer
Zoeken Herstel Detail OK OK+Nieuw Annuleren
B
Tonen: Z-index Controle op contra-indicatie aard [00006564/00226157/CYP2D6 POOR METABOLIZER]
1 - Algemeen 2 - Teksten
Voorschrijvertekst
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
Details

DPYD @ LUMC



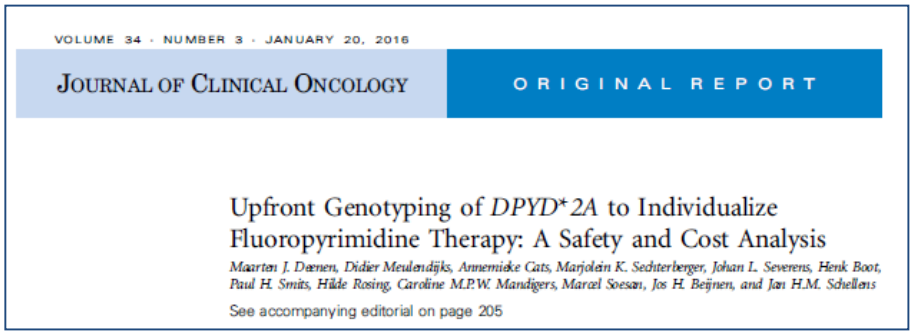
Oncologist considers DPYD testing ‘standard of care’



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

pre-therapeutic - screening

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


VOLUME 34 · NUMBER 3 · JANUARY 20, 2016
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

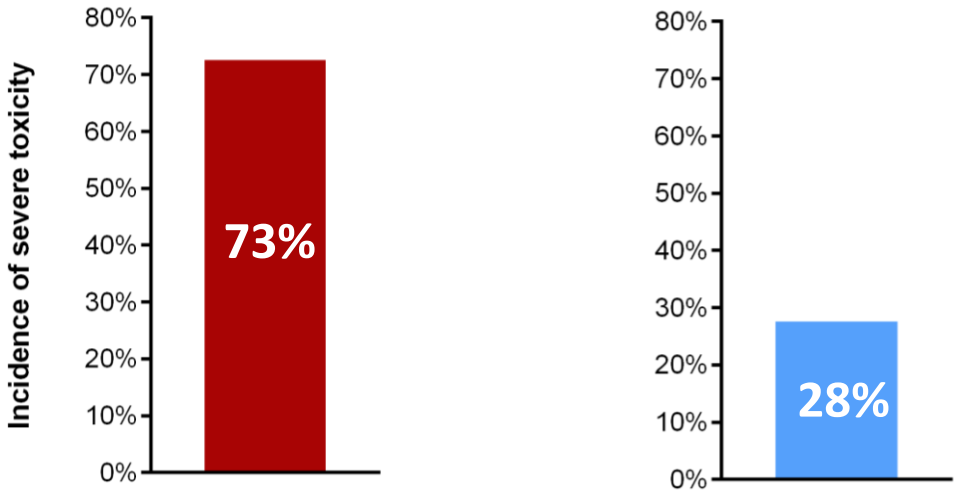
Upfront Genotyping of *DPYD*2A* to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis

Maarten J. Deenen, Didier Meulendijks, Annemieke Cats, Marjolein 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

(literature)

with *DPYD*2A variant (heterozygous)	with *DPYD*2A variant (heterozygous)	no *DPYD*2A variant
normal dose	50% dose reduction	normal dose

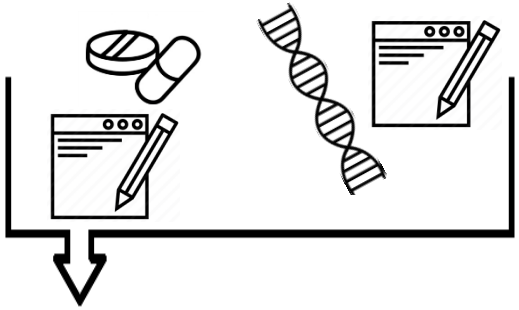


Deenen, J Clin Oncol 2016:227-34

DPYD screening @ LUMC

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

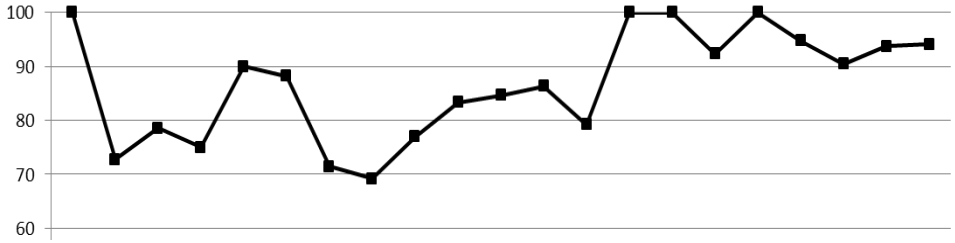
Retrospective analysis: 314 patients (18 maanden)



Screening:

mean: 87%

final: 90-100%

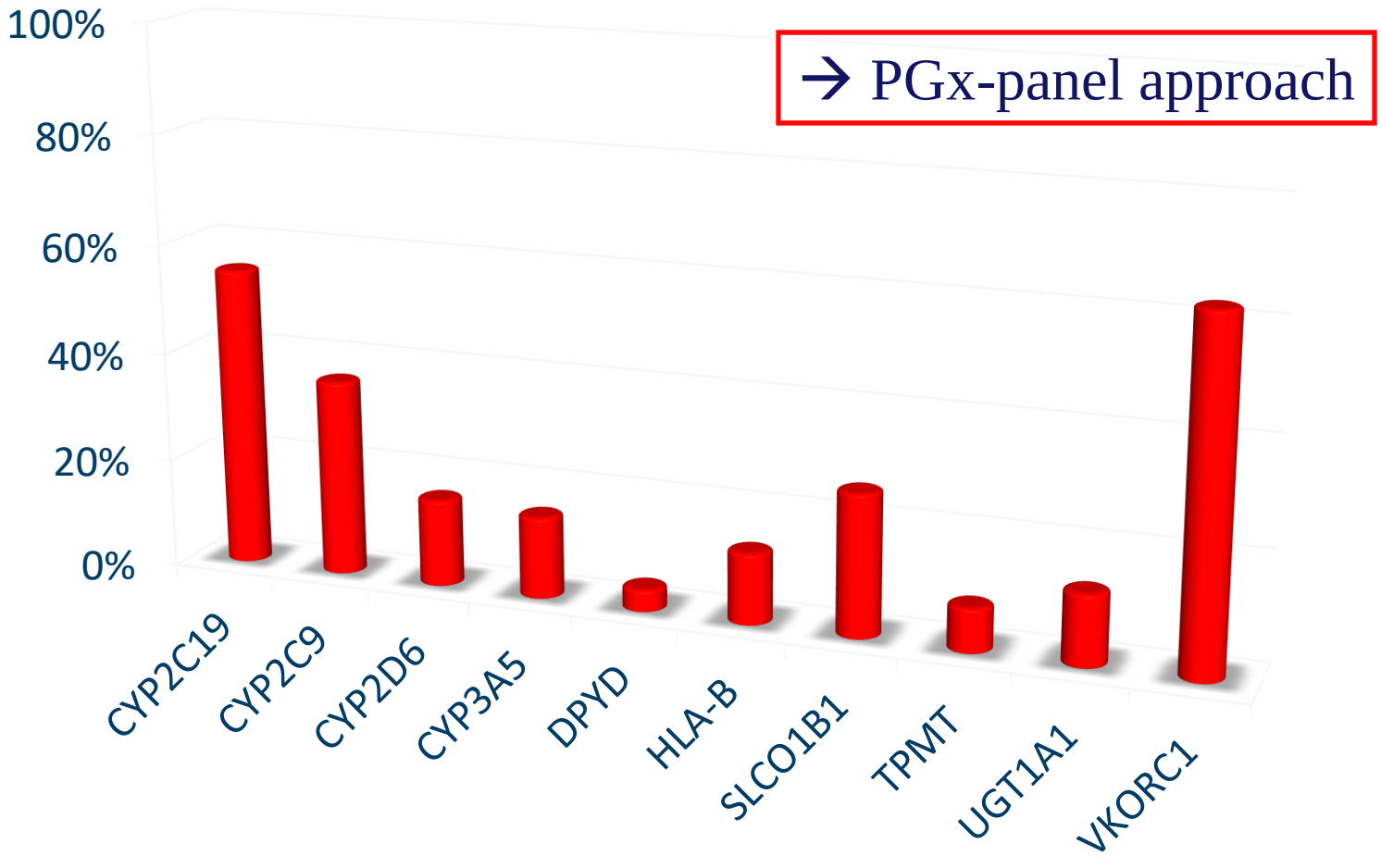


No grade 3-4 toxicity in patients with initial dose reduction

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



→ PGx-panel approach

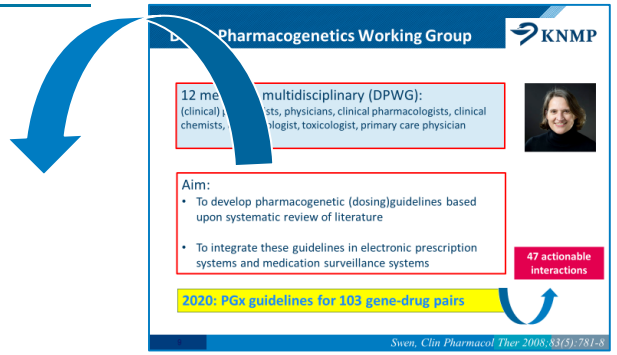
95% of patients have at least 1 *‘actionable’* genotype

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[1,2], Mandy H. van Rhenen[3], Wafa O.M. Jama[3], Magnus Ingelman-Sundberg[4], Volker M. Lauschke[4], Lidija Konta[5], Matthias Schwab[6,7], Jesse J. Swen[1,2] and Henk-Jan Guchelaar[1,2,*]



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

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	519.7				12993
T				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

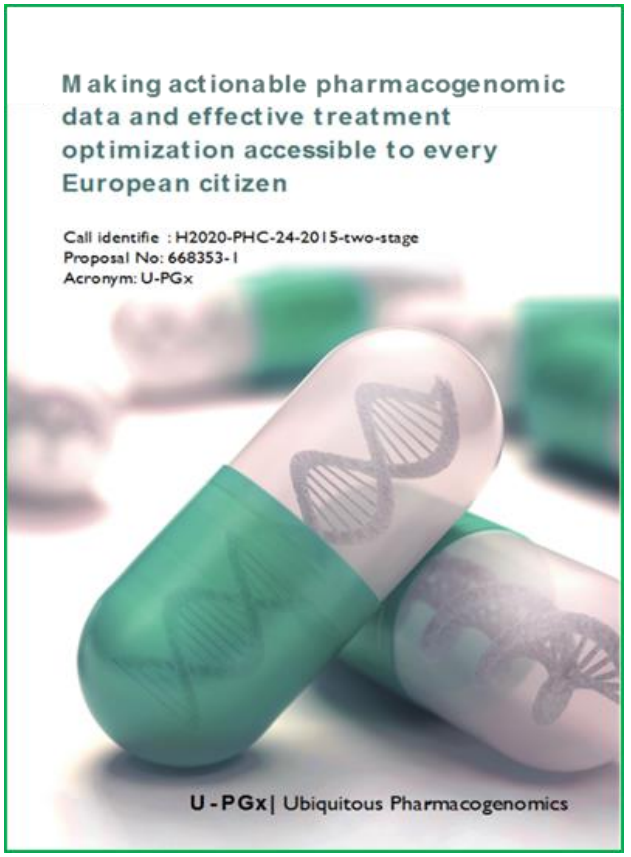
= 5,3% of first prescriptions

U-PGx | Ubiquitous Pharmacogenomics

Overall aim U-PGx:

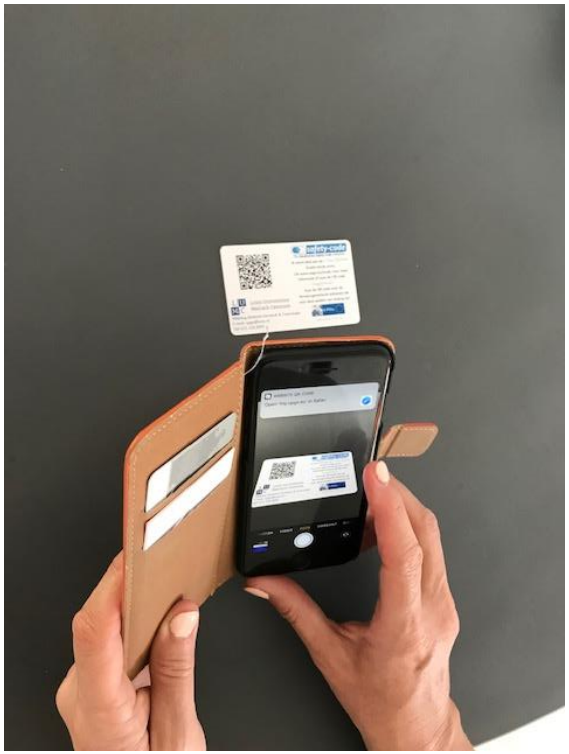
"Making actionable pharmacogenomic data and effective treatment optimization accessible to every European citizen"

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

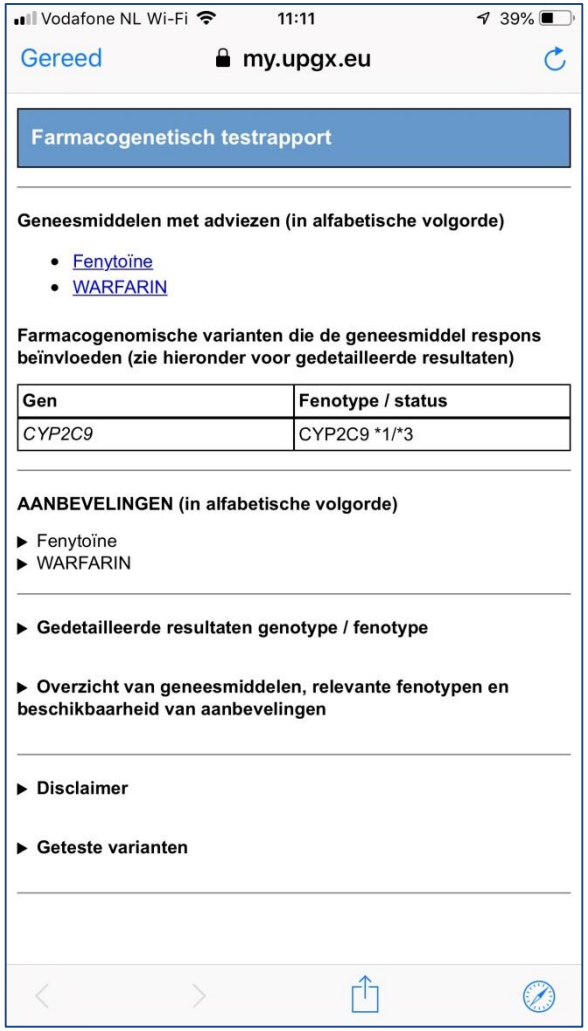


www.upgx.eu

U-PGx | Ubiquitous Pharmacogenomics



Scan QR code



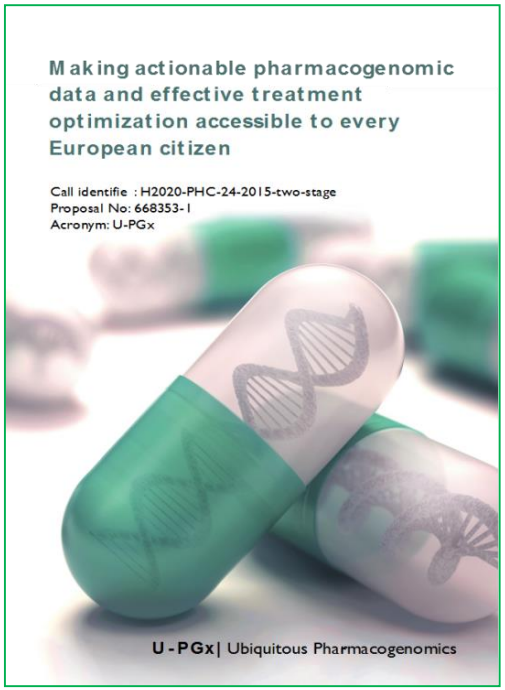
actionable gene-drug interactions

DPGW guideline

Take home messages

- **Implementation of PGx in clinical practice is feasible and effective**
- **PGx testing has moved form 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

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This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 668353