Leiden University
Medical Center

How to use pharmacogenetics to select patients for pharmaceutical care

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University of Leiden

PCNE Working Conference
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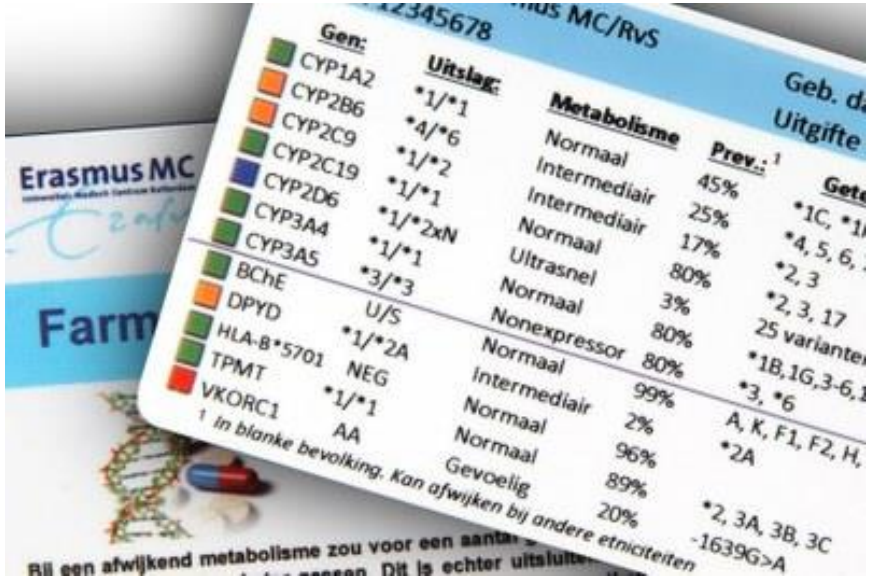
Pharmacogenetics-passport

safety-code
The Medication Safety Code initiative

Name: Jane Doe
Date of birth: 01.02.1934

Gene, status	*Critical drug substances (modification recommended!)*
CYP2C19 Poor metabolizer	Clopidogrel, Sertraline
CYP2D6 Ultrarapid metabolizer	Amitriptyline, Aripiprazole, Clomipramine, Codeine, Doxepin, Haloperidol, Imipramine, Metoprolol, Nortriptyline, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine
TPMT Poor metabolizer	Azathioprine, Mercaptopurine, Thioguanine
Other genes Not actionable	ABCB1, ADRB1, BRCA1, COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP3A4, CYP3A5, DPYD, G6PD, HMGCR, P2RY12, SULT1A1, UGT1A1, VKORC1

Date printed: 10.12.2015 Card number: 0000001



Three patients at the GP/pharmacy

Three patients A, B, C

Identical:

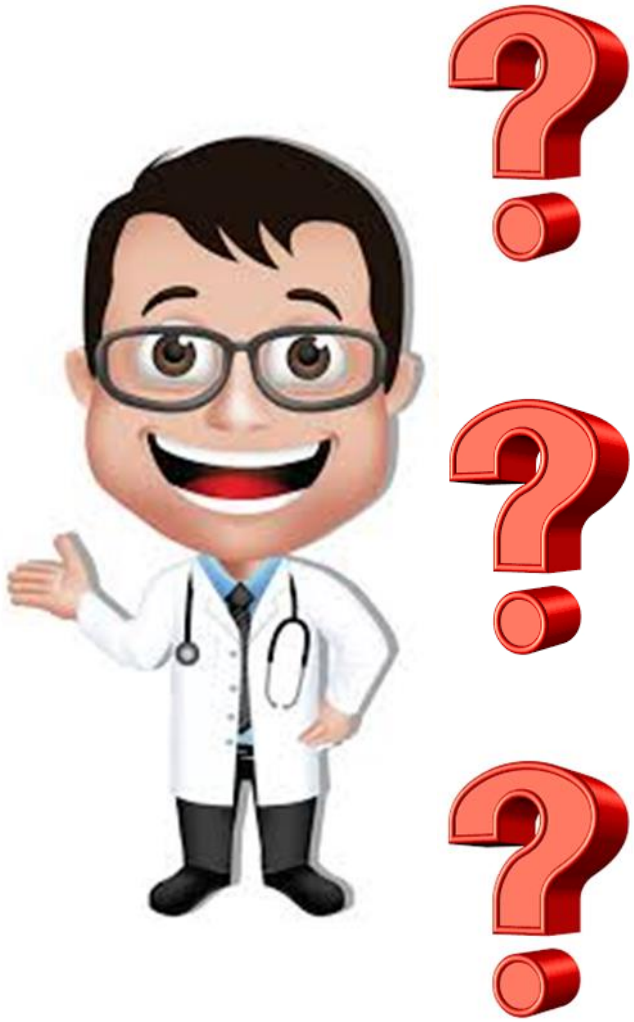
- Symptoms
- Diagnostic procedures
- Diagnosis X
- Treatment: Drug Rx at a dose x mg/day

Three patients at the GP/pharmacy

After 3 weeks

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

How is this possible?



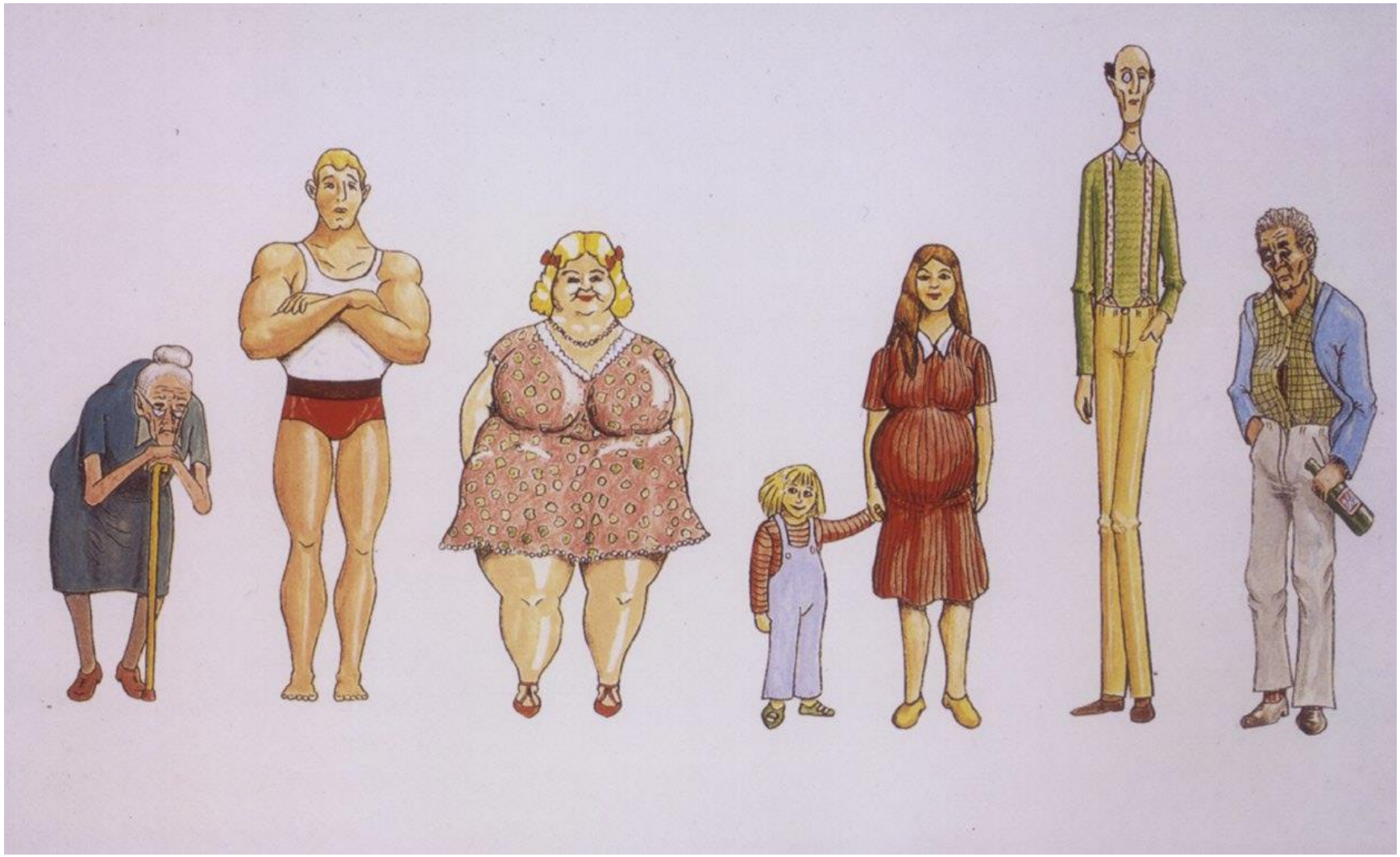
‘Most drugs don’t work’

Effective (%)…..

Alzheimer	30
Depression (SSRI)	62
Asthma	60
Diabetes mellitus	57
Incontinence	40
Migraine (acute)	52
Migraine (profyl.)	50
Cardiac dysrhythmia	60
Tumors	25
Schizophrenia	60
Rheumatoid arthritis	50
Reumat. art. (Cox-2)	80
Hepatitis C	47

Spear, Trends Mol Med 2001;7(5):201

Variability in humans



Holistic definition of 'disease'

= decreased glucose-tolerance

Table 1 Selected single nucleotide polymorphisms associated with type 2 diabetes mellitus

Gene	rs number	Chromosome	Risk allele	Year	Mechanism
NOTCH2	rs10923931	1	T	2008	Unknown
THADA	rs7578597	2	T	2008	Unknown
IGF2BP2	rs4402960	3	T	2007	β-cell dysfunction
PPARG	rs1801282	3	C	2000	Insulin sensitivity
ADAMTS9	rs4607103	3	C	2008	Unknown
WFS1	rs10010131	4	G	2007	Unknown
CDKAL1	rs7754840	6	C	2007	β-cell dysfunction
JAZF1	rs864745	7	A	2008	β-cell dysfunction
SLC30A8	rs13266634	8	C	2007	β-cell dysfunction
CDKN2A/CDKN2B	rs10811661	9	T	2007	β-cell dysfunction
	rs564398	9	A		
TCF7L2	rs7903146	10	T	2006	β-cell dysfunction
HHEX/IDE	rs1111875	10	G	2007	β-cell dysfunction
CDC123/CAMK1D	rs12779790	10	G	2008	Unknown
KCNJ11	rs5219	11	T	2003	β-cell dysfunction
KCNQ1	rs2237892	11	C	2008	β-cell dysfunction
MTNR1B	rs10830963	11	G	2009	Disturbance of circadian rhythm
TSPAN8/LGR5	rs7961581	12	C	2008	Unknown
FTO	rs8050136	16	A	2007	Obesity
HNF-1β (TCF2)	rs757210	17	A	2007	β-cell dysfunction

Prescribing drugs – Trial and Error

Dx

Rx

Guideline

Clinical studies

- **Dx**
- **Inclusion criteria**
  - **Age**
  - **Organ function**
  - **Severity of disease**

First choice Drug

- **'Normal' dose**
- **Individualize**
  - **Co-morbidity**
  - **Co-medication**
  - **Age, Organ function**

Monitor effect

- **Efficacy & Toxicity**
  - **Tumorsize, Biomarkers**
  - **Pain(score), Bloodpressure**
  - **Cholesterol levels**
  - **Liverfunction, Myalgia**

Drug dose

- **Increase/decrease**

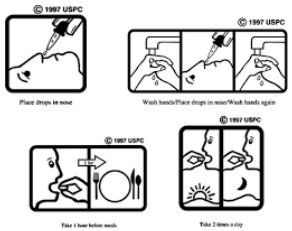
Switch drug

- **Second choice Drug**

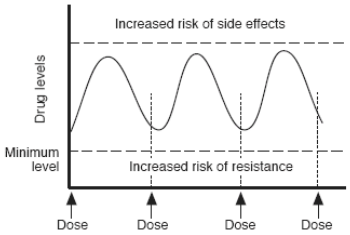
Individualizing drug treatment

organ function

drug use



drug levels

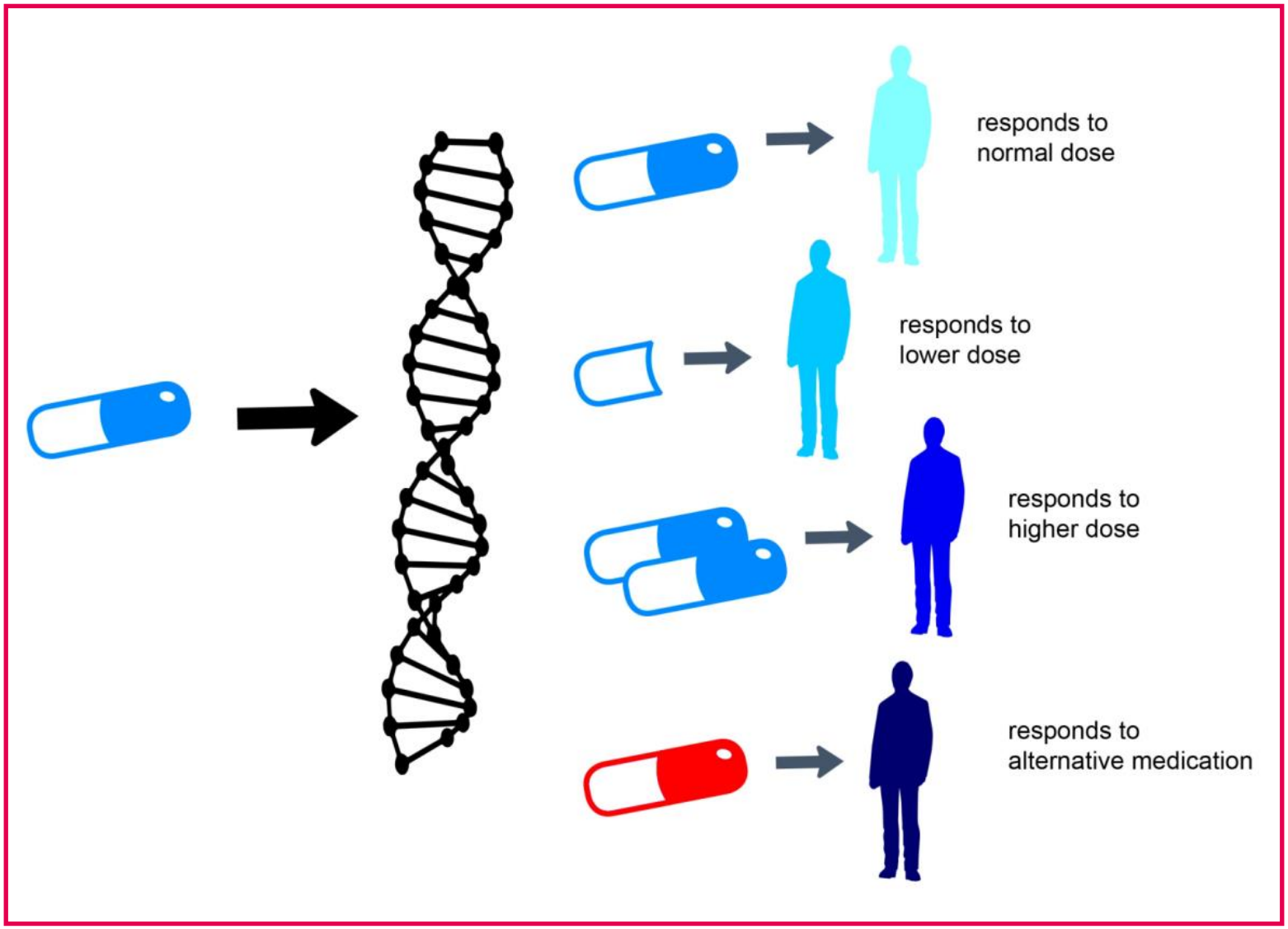


special populations

drug interactions

co-morbidity

Drug response is a heritable trait



Mei 1975: Debrisoquine

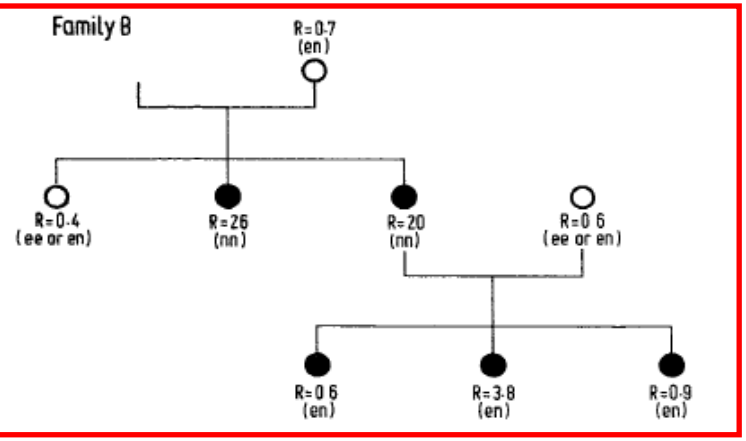
Debrisoquine – 4-hydroxydebrisoquine

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

Smith, Lancet 1977(2): 584-586

Would you vote for a (non-)believer?

Survey physicians and pharmacists

- 97.6% of physicians agreed that genetic variations may influence drug response (Stanek)
- 99.7% of pharmacists agreed that a patients' genetic profile may influence the response on a drug (Bank)
- Did you order or recommend a pharmacogenetic test in the recent 6 months (Guchelaar, Swen)?

Yes

4%

15%

~400 GP's

~667 pharmacists

High expectations

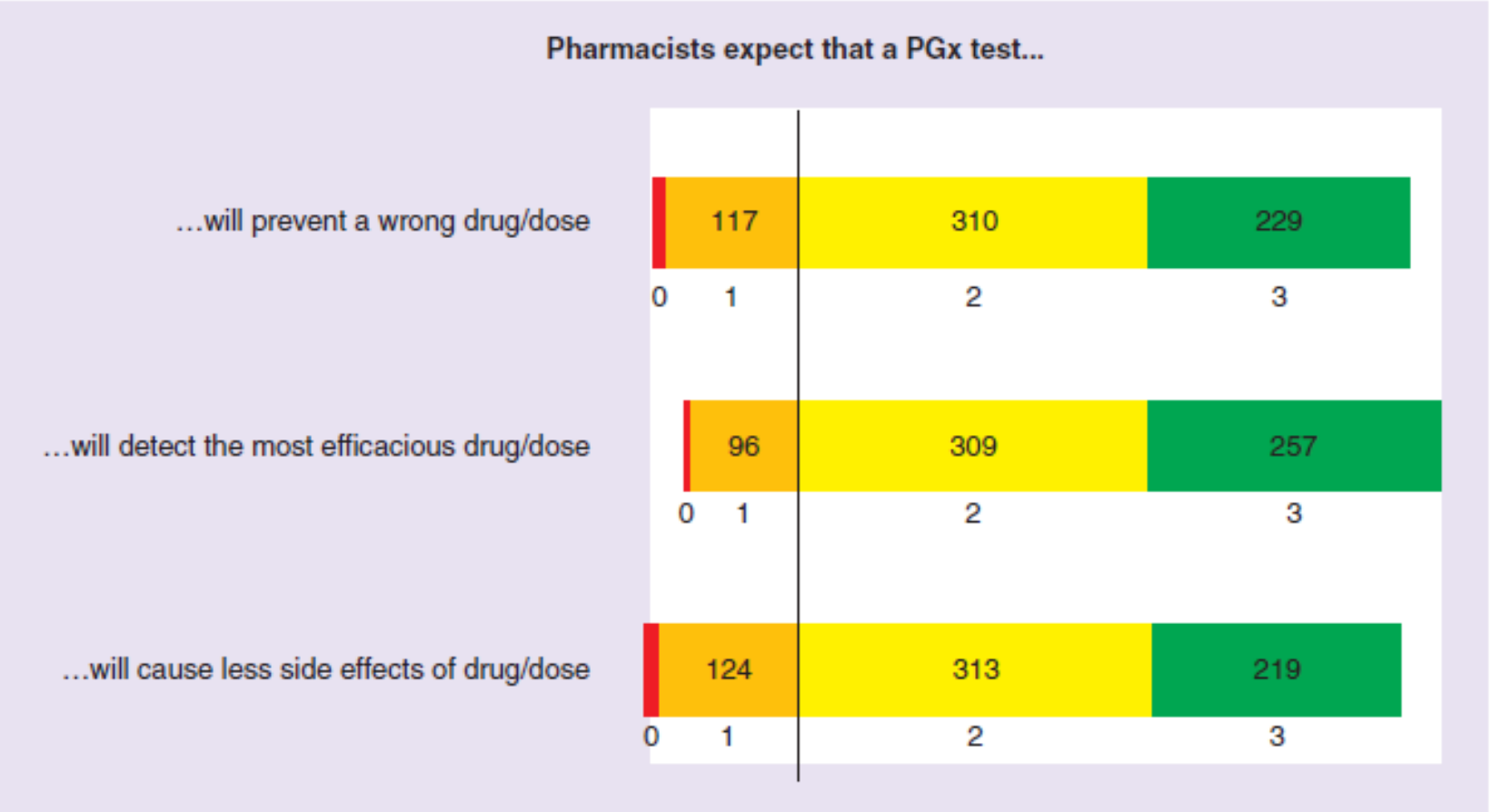
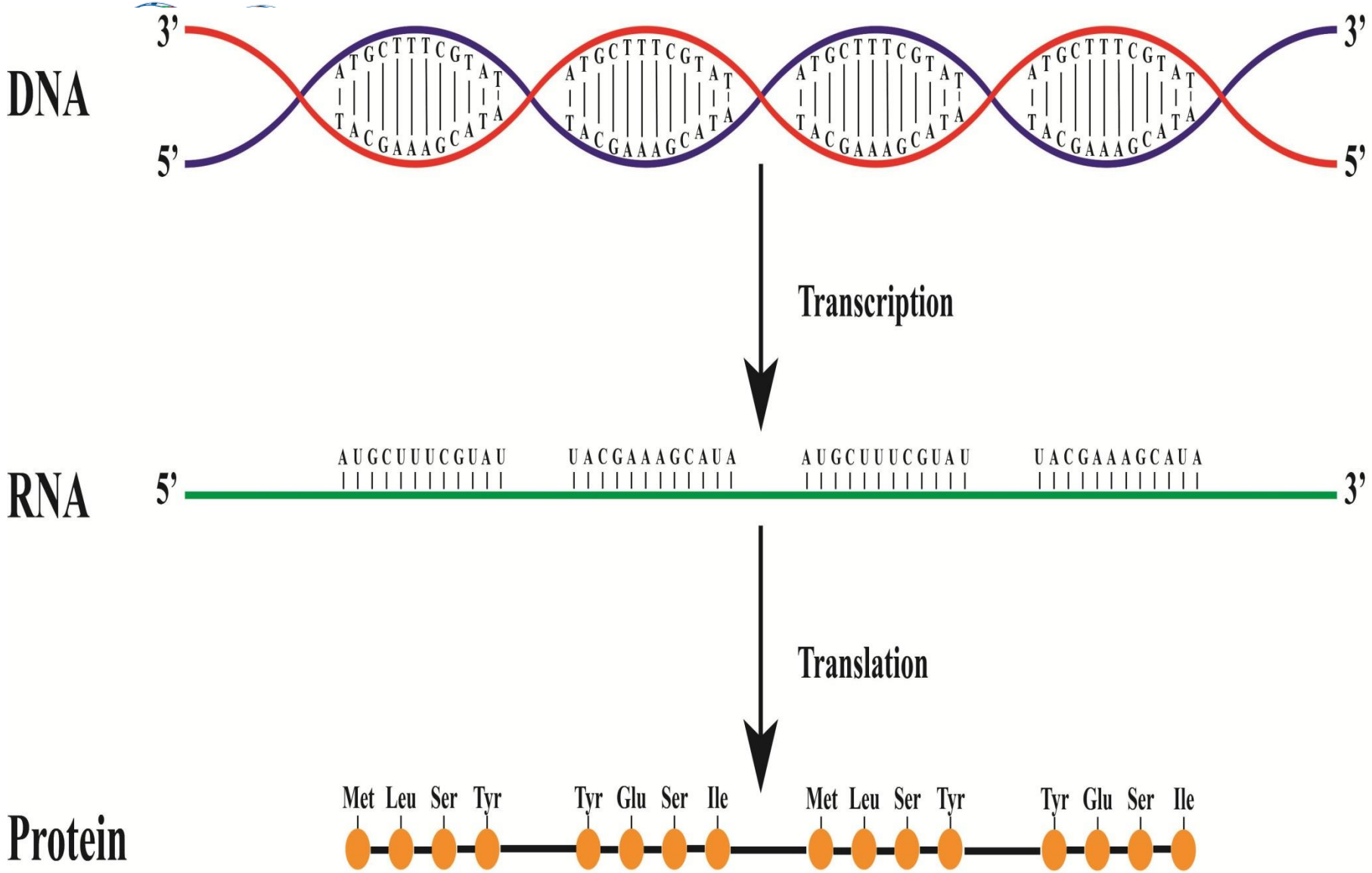
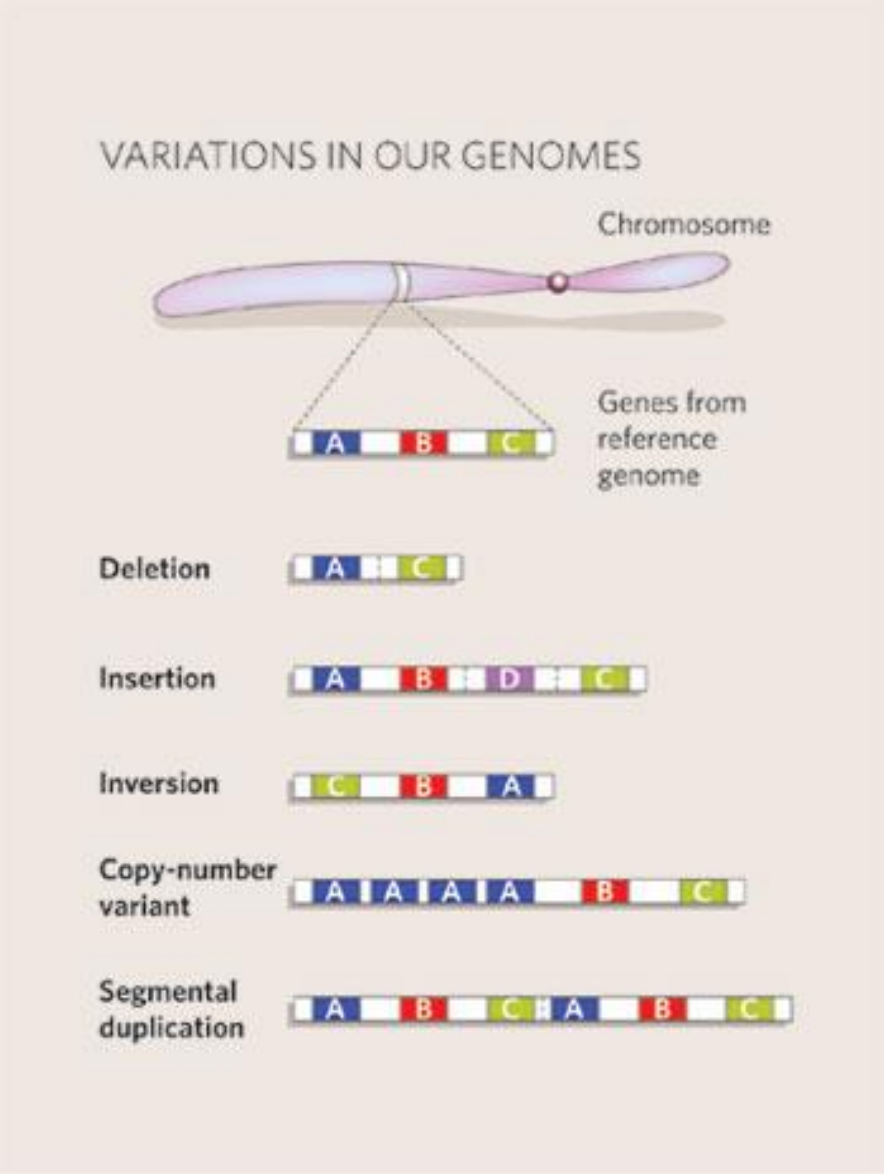


Figure 3. Expectations of pharmacists towards pharmacogenetic testing. Red = I have no expectations that a pharmacogenetic test... (0); orange = I have low expectations that a pharmacogenetic test... (1); yellow = I have high expectations that a pharmacogenetic test... (2); green = I have very high expectations that a pharmacogenetic test... (3).
The size of the bar is proportional to the number of responders.
PGx: Pharmacogenetic.

Pharmacist's refresher course in genetics



“Book of Life”



Complete sequence human genome is known

“the same for everyone”

Typografic errors:

Letter mis.ing

Letter too muuch

Interchnage

Tylo

Dupliplipliplicationsssss

Paragraphs doubledouble

Opposite noitcerid

Variability in DNA

2 not related individuals:

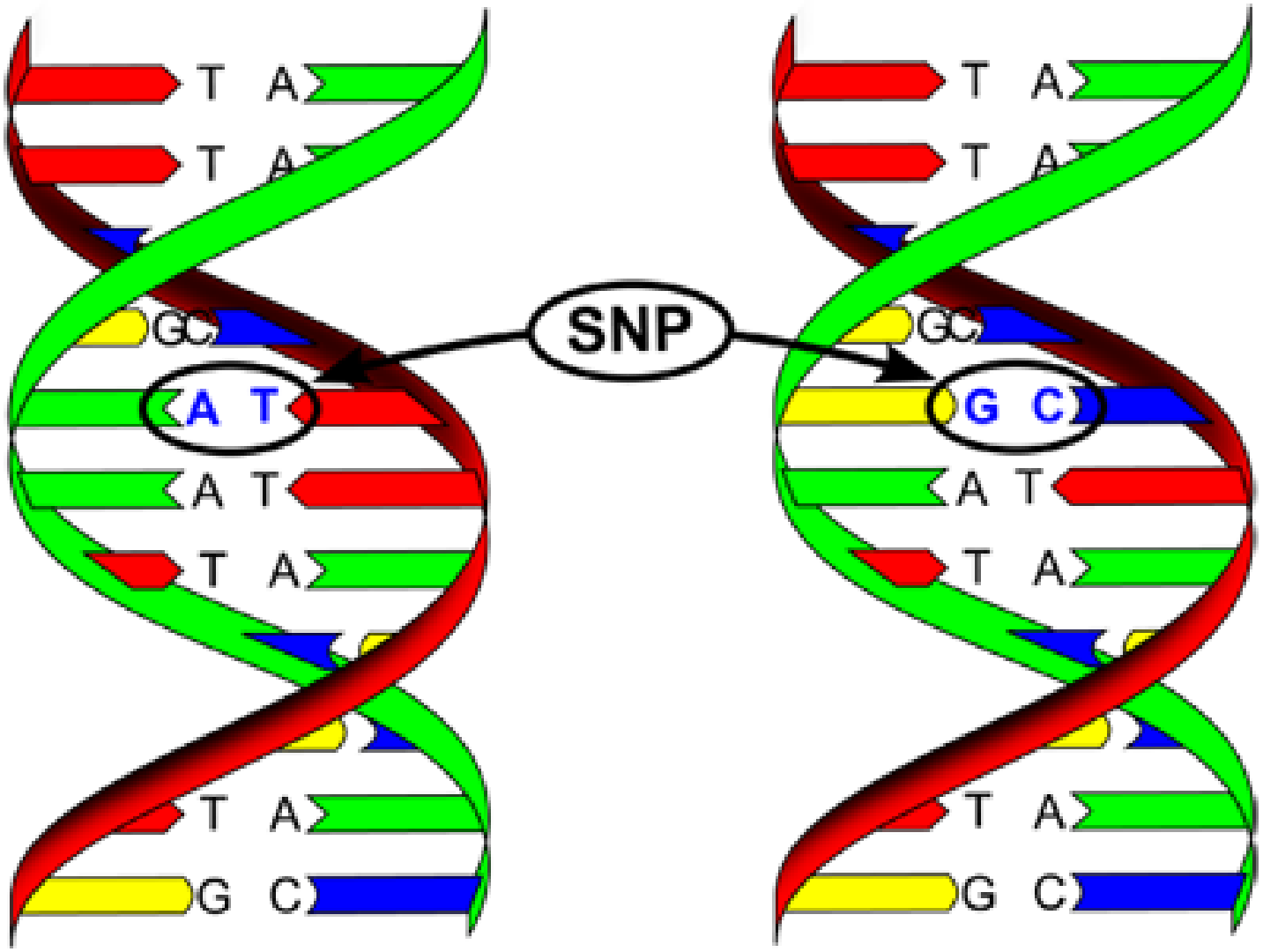
$3.200 * 10^6$ basepairs

1: 300-1000 basepairs are different

= $3\text{-}10 * 10^6$ basepairs are different

99,7-99,9% similarity

Single Nucleotide Polymorphism



DNA variants: small changes, large effects

Deletions

- DNA
- Protein

Wild type	Mutant
GAA AAG CCT GGT	GAA GCC TGG TGA
Glu Lys Pro Gly	Glu Ala Trp Stop

SNPs

- DNA
- Protein

ATG AAC CCG	ATG AAC TGG
Met Asn Arg	Met Asn Trp

From genotype to phenotype

Allele	1	2	3	4	5	6	7	8	9	10	11	14A	14B	15	17	19	20	25	26	29	30	31	35	36	40	41	1XN	2XN	4XN	10XN	17XN	35XN	41XN
1	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
2		E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
3			P	P	P	P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
4				P	P	P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
5									I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
6									I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
7									I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
8									I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
9									I	I	I	I	N	I	I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
10									I	I	I	I	N	I	I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
11											P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
14A												P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
14B													N	N	N	N	N	N	N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
15														P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
17															I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
19																P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
20																	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
25																		N	N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
26																			N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
29																				I	N	N	E	I	I	I	E	E	I	I	I	E	I
30																					N	N	E	N	N	N	N	N	N	N	N	N	N
31																						N	E	N	N	N	N	N	N	N	N	N	N
35																							E	E	E	E	U	U	E	E	E	U	E
36																								I	I	I	E	E	I	I	I	E	I
40																									P	I	E	E	P	I	I	E	I
41																										I	E	E	I	I	I	E	I

P

E	Extensive
I	Intermediate
P	Poor
U	Ultrarapid
N	Unknown

Roche, AmpliChip CYP450 Test, manual

CYP2D6 genotype

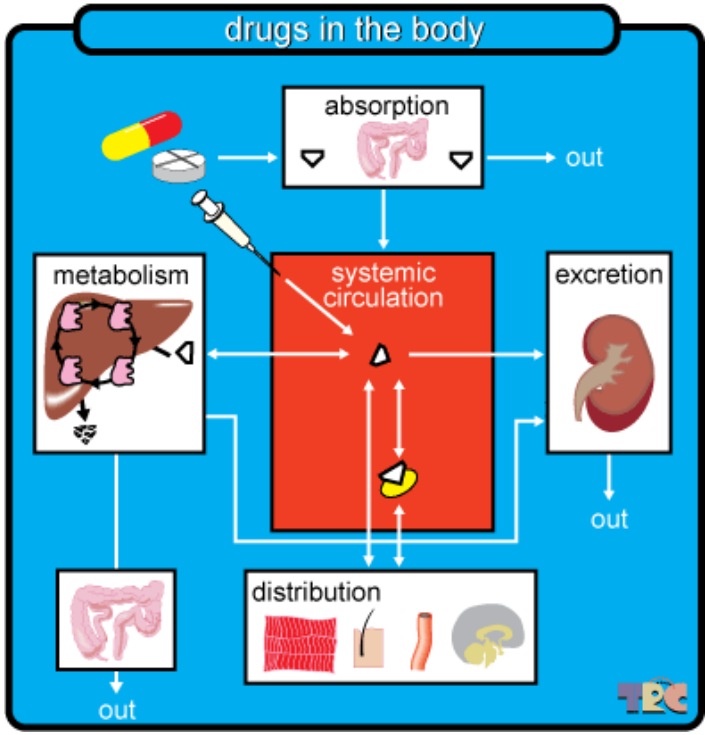
Allele	Enzyme activity	Genetic variant	Allele frequency (%)		
			Caucasians (Europe)	Japan	Tanzania
***1**	Normal	Wild-type	32.2-36.4	43	27.8
***2**	Normal	2850C>T, 4180G>C	28.5-32.4	12.3	40
***2x2**	High	duplication	1-1.3		
***3**	Absent	2549delA	1-2		0
***4**	Absent	1846G>A	17.2-20.7	.2	.9
***5**	Absent	CYP2D6 deletion	2-6.9	4.5	6.3
***6**	Absent	1707delT	.9-1.3		0
***9**	Reduced	2615_2617delAAG	1.8-2.7		
***10**	Reduced	100C>T	1.5-2	38.1	3.8
***17**	Reduced	1023C>T, 2850C>T			17
***41**	Reduced	2988G>A	8.4		

Phenotype : Poor Metabolizer (5-10%)

Intermediate Metabolizer (10-15%)

Not only liver enzymes

Compliance

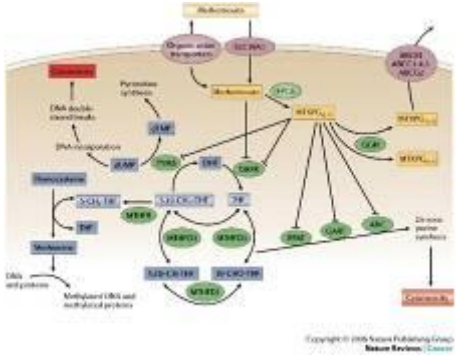


Absorption

Metabolism

Elimination

Target/Receptor



Signal transduction

February 2019: CYP2D6 genotyping

Allele	1	2	3	4	5	6	7	8	9	10	11	14A	14B	15	17	19	20	25	26	29	30	31	35	36	40	41	1XN	2XN	4XN	10XN	17XN	35XN	41XN
1	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
2		E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
3			P	P	P	P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
4				P	P	P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
5					P	P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
6						P	P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
7							P	P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
8								P	I	I	P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
9									I	I	I	I	N	I	I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
10										I	I	I	N	I	I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
11											P	P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
14A												P	N	P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
14B													N	N	N	N	N	N	N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
15														P	I	P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
17															I	I	I	N	N	I	N	N	E	I	I	I	E	E	I	I	I	E	I
19																P	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
20																	P	N	N	I	N	N	E	I	P	I	E	E	P	I	I	E	I
25																			N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
26																			N	N	N	N	E	N	N	N	N	N	N	N	N	N	N
29																				I	N	N	E	I	I	I	E	E	I	I	I	E	I
30																					N	N	E	N	N	N	N	N	N	N	N	N	N
31																						N	E	N	N	N	N	N	N	N	N	N	N
35																							E	E	E	E	U	U	E	E	E	U	E
36																								I	I	I	E	E	I	I	I	E	I
40																									P	I	E	E	P	I	I	E	I
41																										I	E	E	I	I	I	E	I

Pharmacogenetics

DNA Test

100% Dose

Drug A

50% Dose

Drug A

Drug B

The evidence

OPEN ACCESS Freely available online

PLoS MEDICINE

Research In Translation

Translating Pharmacogenomics: Challenges on the Road to the Clinic

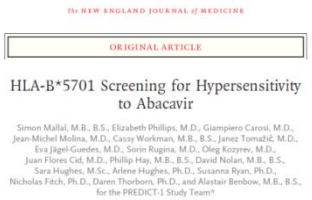
Jesse J. Swen, Tom W. Huizinga, Hans Gelderblom, Elisabeth G. E. de Vries, Willem J. J. Assendelft, Julia Kirchheiner, Henk-Jan Guchelaar*

- Providing evidence for improvement in patient care
- Providing information on cost-effectiveness/consequences
- Providing data on diagnostic test criteria
- Selecting clinically relevant PGx tests
- Developing guidelines directing clinical use of PGx testing
- Improving acceptance by patients & health care professionals

Swen, Plos Med 2007(4): e209

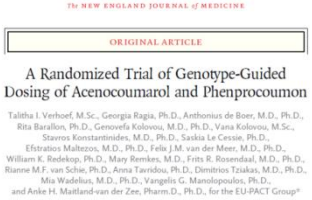
RCTs in Pharmacogenetics

Drug	Clinical Endpoint	Variant
Abacavir	hypersensitivity	HLA-B*5701
Acenocoumarol / Fenprocoumon	% time between therapeutic INR	VKORC1/CYP2C9
Warfarin	% time between therapeutic INR	VKORC1/CYP2C9
Warfarin	% time between therapeutic INR	VKORC1/CYP2C9
Mercaptopurine	leucopenia	TPMT
Warfarin	major bleeding, INR>4, venous thromboembolism	VKORC1/CYP2C9/CYP4F2


The NEW ENGLAND JOURNAL of MEDICINE

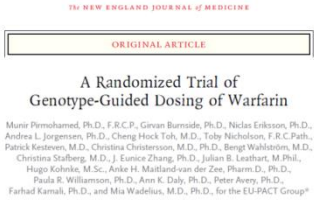
ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon


The NEW ENGLAND JOURNAL of MEDICINE

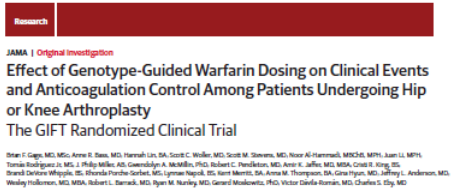
ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin


The NEW ENGLAND JOURNAL of MEDICINE

DECEMBER 12, 2013

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing


Research

JAMA | Original Investigation

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty

The GIFT Randomized Clinical Trial

TOPIC Trial

Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics

- 783 IBD patients; mercaptopurine or azathioprine
- 1:1 randomized to screening *vs* no screening TPMT*2, TPMT*3A, and TPMT*3C
- HET: 50% dose reduction, HOM 90% dose reduction
- Primairy en
- **"10-fold r**

treatmer

s in

tients will not be forthcoming. In truth, I believe we all know beyond reasonable doubt that TPMT testing before starting a thiopurine is the right thing to do for our patients. The time for debate is over: just do it.

JEREMY D. SANDERSON
Department of Gastroenterology
Guy's & St. Thomas' Hospitals NHS Foundation Trust
London, United Kingdom

			(95%CI)
Total (n)			
Hematological side effect	29 (7,2%)	29 (7,8%)	
TPMT variant	**1 / 39 (2,6%)**	**8 / 35 (22,9%)**	**0,11 (0,01-0,85)**
No TPMT variant	29 / 360 (8,1%)	22 / 335 (6,6%)	1,2 (0,72-2,09)

Coenen MJ, Gastroenterology. 2015 907-17

Number needed to genotype

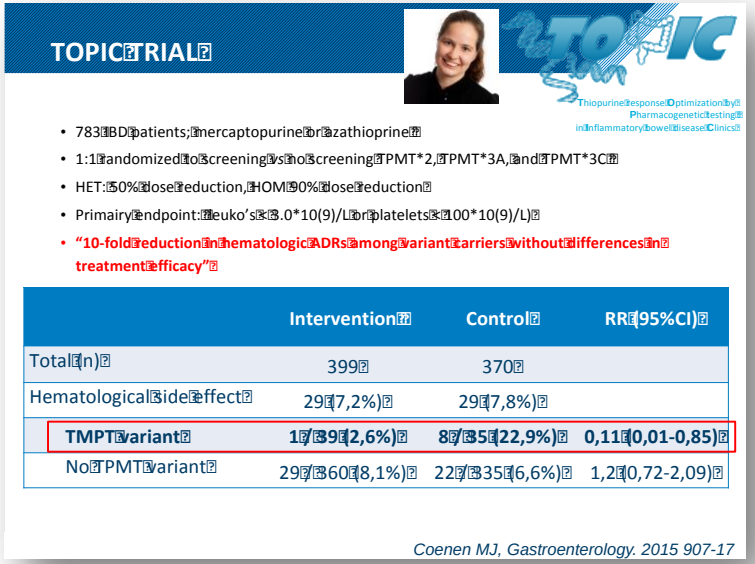
- How many patients do I have to screen/test to prevent one from having a Adverse Drug Reaction (grade 3-4 toxicity, death, etc.)?

NNG for TPMT testing in Topic

- Hematological ADR: leuko's < 3.0*10(9)/L or platelets < 100*10(9)/L)
  - NNG= 200
  - Risk: 7.4% versus 7.9%

- In TPMT variant carriers:
  - NNT= 5

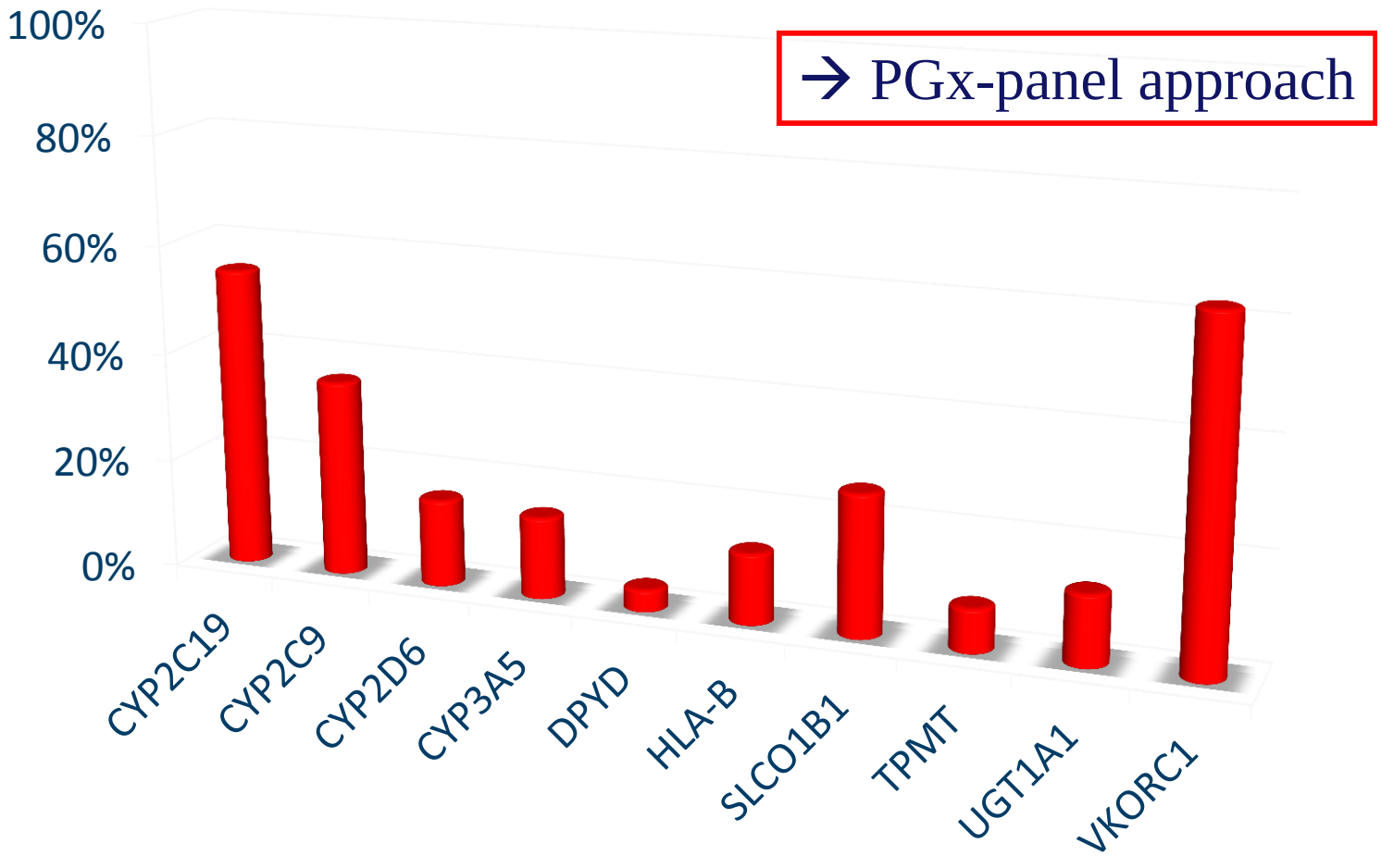
  Risk: 2.6% versus 22.9%



	Intervention	Control	RR (95%CI)
Total (n)	399	370	
Hematological side effect	29 (7,2%)	29 (7,8%)	
TMPT variant	**1/39 (2,6%)**	**8/35 (22,9%)**	**0,11 (0,01-0,85)**
No TPMT variant	29/360 (8,1%)	22/335 (6,6%)	1,2 (0,72-2,09)

Coenen MJ, Gastroenterology. 2015 907-17

‘Actionable’ genotypes



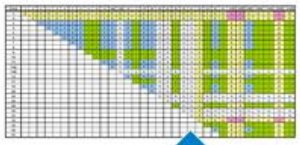
→ PGx-panel approach

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

What is a safe and effective dose for Bob?

Mei 1975: Debrisoquine

February 2019: CYP2D6 genotyping



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

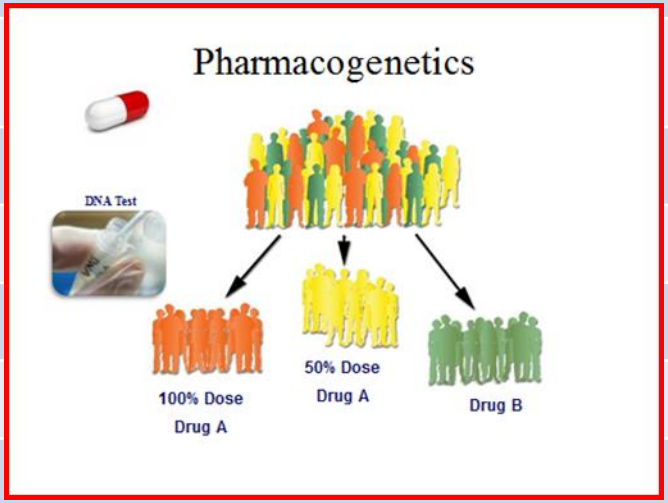
2018: guidelines for 94 gene-drug pairs

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

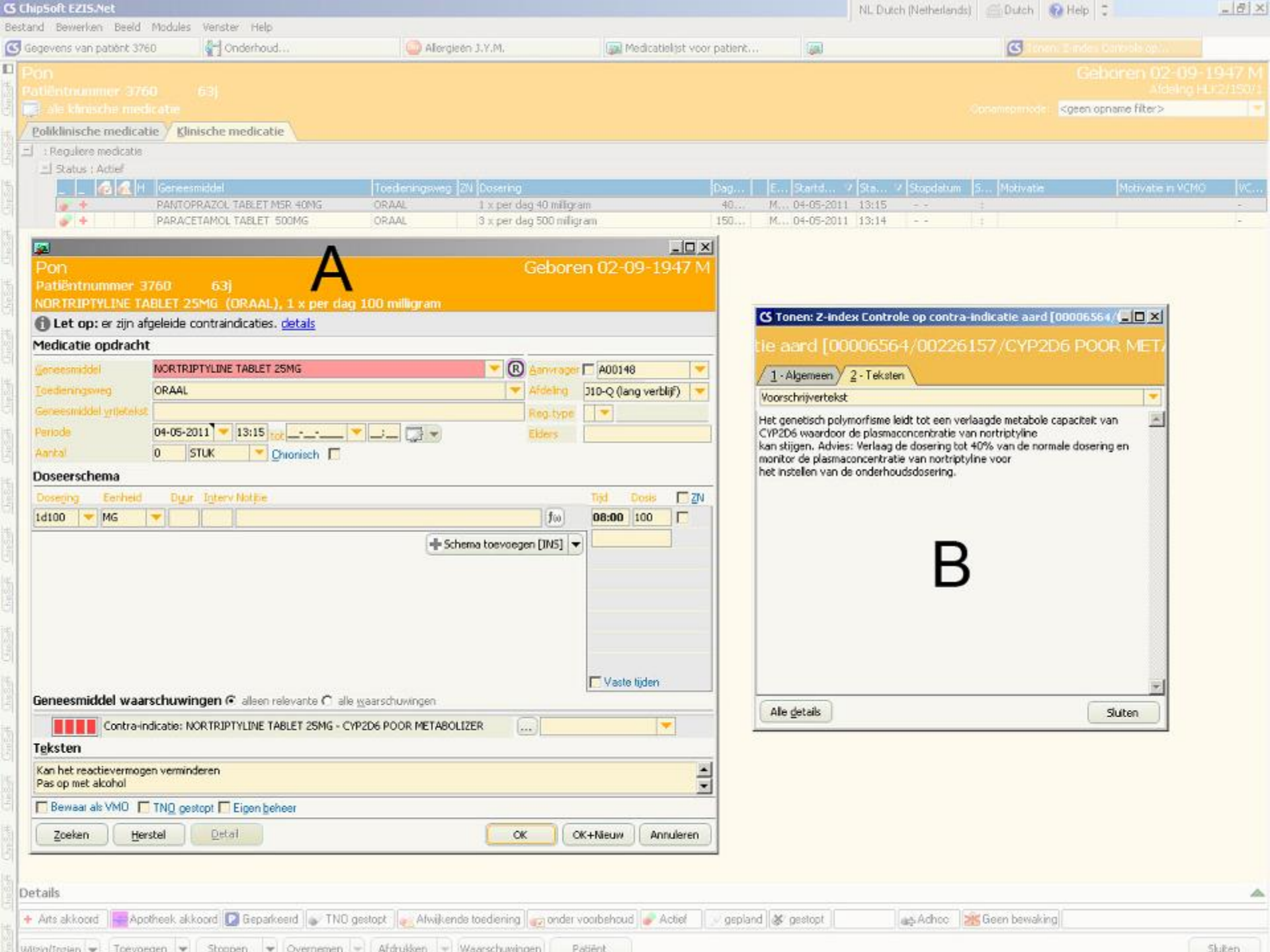
PGx: improving efficacy or preventing toxcity?

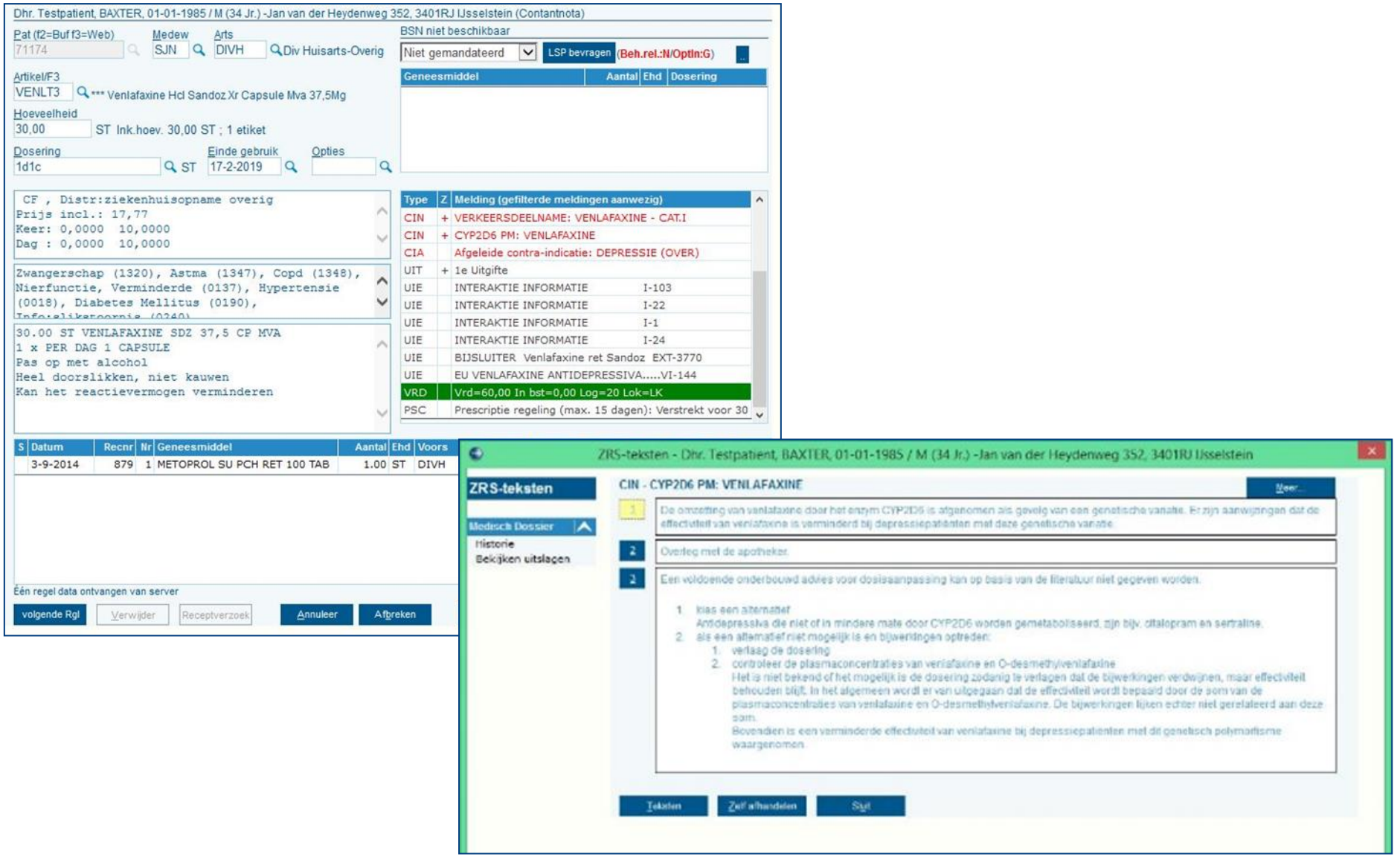
Actionable interactions

Preventing toxicity		Improving efficacy	
CYP2C9	phenytoin; warfarin; acenocoumarol, phenprocoumon		
CYP2C19	(es)citalopram; imipramine; sertraline; voriconazole	CYP2C19	clopidogrel; voriconazole; lansoprazole, omeprazole, pantoprazole
CYP2D6	amitriptyline; clomipramine; codeine (CI); doxepine; imipramine; nortriptyline, aripiprazole	CYP2D6	amitriptyline; clomipramine; codeine; doxepine; imipramine; nortriptyline; paroxetine, atomoxetine
CYP3A5		CYP3A5	tacrolimus
DPYD	capecitabine; fluorouracil; tegafur		
HLA-B	abacavir; carbamazepine, allopurinol, phenytoin, flucloxacillin		
SLCO1B1	simvastatin,atorvastatin		
TMPT	azathioprine; mercaptopurine; thioguanine		
VKORC1	warfarin, acenocoumarol, phenprocoumon		
UGT1A1	irinotecan		
CYP2B6	efavirenz		



Bank, Clin Pharmacol Ther. 2017;103(4):599-618


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


Dhr. Testpatient, BAXTER, 01-01-1985 / M (34 Jr.) -Jan van der Heydenweg 352, 3401RJ IJsselstein (Contantnota)
Pat (f2=Buf f3=Web)
71174
Medew
SJN
Arts
DIVH
Div Huisarts-Overig
BSN niet beschikbaar
Niet gemandateerd
LSP bevragen
(Beh.rel.:N/OptIn:G)
Artikel/F3
VENLT3
*** Venlafaxine Hcl Sandoz Xr Capsule Mva 37,5Mg
Hoeveelheid
30,00
ST Ink.hoev. 30,00 ST ; 1 etiket
Dosering
1d1c
ST
Einde gebruik
17-2-2019
Opties
Geneesmiddel
Aantal
Ehd
Dosering
CF , Distr:ziekenhuisopname overig
Prijs incl.: 17,77
Keer: 0,0000 10,0000
Dag : 0,0000 10,0000
Zwangerschap (1320), Astma (1347), Copd (1348), Nierfunctie, Verminderde (0137), Hypertensie (0018), Diabetes Mellitus (0190),
30.00 ST VENLAFAXINE SDZ 37,5 CP MVA
1 x PER DAG 1 CAPSULE
Pas op met alcohol
Heel doorslikken, niet kauwen
Kan het reactievermogen verminderen
Type
Z
Melding (gefilterde meldingen aanwezig)
CIN + VERKEERSDEELNAME: VENLAFAXINE - CAT.I
CIN + CYP2D6 PM: VENLAFAXINE
CIA Afgeleide contra-indicatie: DEPRESSIE (OVER)
UIT + 1e Uitgifte
UIE INTERAKTIE INFORMATIE I-103
UIE INTERAKTIE INFORMATIE I-22
UIE INTERAKTIE INFORMATIE I-1
UIE INTERAKTIE INFORMATIE I-24
UIE BIJSLUITER Venlafaxine ret Sandoz EXT-3770
UIE EU VENLAFAXINE ANTIDEPRESSIVA.....VI-144
VRD Vrd=60,00 In bst=0,00 Log=20 Lok=LK
PSC Prescriptie regeling (max. 15 dagen): Verstrekt voor 30
S
Datum
Recnr
Nr
Geneesmiddel
Aantal
Ehd
Voors
3-9-2014
879
1
METOPROL SU PCH RET 100 TAB
1.00
ST
DIVH
Één regel data ontvangen van server
volgende Rgl
Verwijder
Receptverzoek
Annuleer
Afbreken
ZRS-teksten - Dhr. Testpatient, BAXTER, 01-01-1985 / M (34 Jr.) -Jan van der Heydenweg 352, 3401RJ IJsselstein
ZRS-teksten
Medisch Dossier
Historie
Bekijken uitslagen
CIN - CYP2D6 PM: VENLAFAXINE
Meer...
1
De omzetting van venlafaxine door het enzym CYP2D6 is afgenomen als gevolg van een genetische variatie. Er zijn aanwijzingen dat de effectiviteit van venlafaxine is verminderd bij depressiepatiënten met deze genetische variatie.
2
Overleg met de apotheker.
3
Een voldoende onderbouwd advies voor dosisaanpassing kan op basis van de literatuur niet gegeven worden.
1. kies een alternatief
Antidepressiva die niet of in mindere mate door CYP2D6 worden gemetaboliseerd, zijn bijv. citalopram en sertraline.
2. als een alternatief niet mogelijk is en bijwerkingen optreden:
1. verlaag de dosering
2. controleer de plasmaconcentraties van venlafaxine en O-desmethylvenlafaxine
Het is niet bekend of het mogelijk is de dosering zodanig te verlagen dat de bijwerkingen verdwijnen, maar effectiviteit behouden blijft. In het algemeen wordt er van uitgegaan dat de effectiviteit wordt bepaald door de som van de plasmaconcentraties van venlafaxine en O-desmethylvenlafaxine. De bijwerkingen lijken echter niet gerelateerd aan deze som.
Bovendien is een verminderde effectiviteit van venlafaxine bij depressiepatiënten met dit genetisch polymorfisme waargenomen.
Teksten
Zelf afhandelen
Sluit

Endorsement DPWG guidelines

EACPT

eahp
european association
of hospital pharmacists

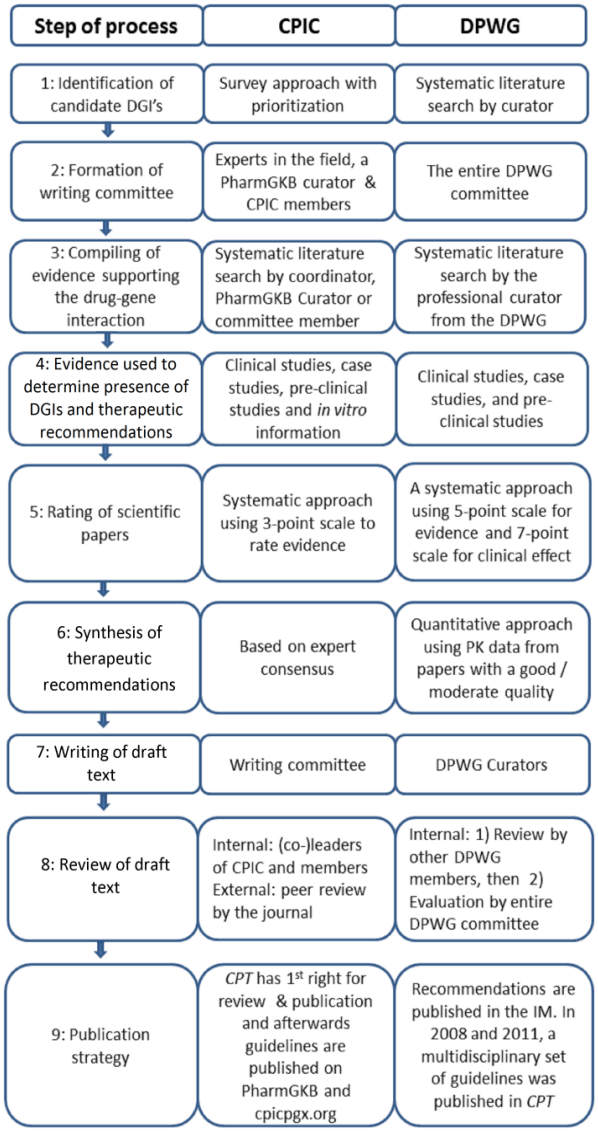
EGAN
Patients Network for Medical Research and Health

IRISH
PHARMACY
UNION
The voice of
community pharmacy

EUROPEAN PHARMACEUTICAL STUDENTS' ASSOCIATION
EPSA

VSOP

DPWG and CPIC



Step of process	CPIC	DPWG
1: Identification of candidate DGI's	Survey approach with prioritization	Systematic literature search by curator
2: Formation of writing committee	Experts in the field, a PharmGKB curator & CPIC members	The entire DPWG committee
3: Compiling of evidence supporting the drug-gene interaction	Systematic literature search by coordinator, PharmGKB Curator or committee member	Systematic literature search by the professional curator from the DPWG
4: Evidence used to determine presence of DGIs and therapeutic recommendations	Clinical studies, case studies, pre-clinical studies and *in vitro* information	Clinical studies, case studies, and pre-clinical studies
5: Rating of scientific papers	Systematic approach using 3-point scale to rate evidence	A systematic approach using 5-point scale for evidence and 7-point scale for clinical effect
6: Synthesis of therapeutic recommendations	Based on expert consensus	Quantitative approach using PK data from papers with a good / moderate quality
7: Writing of draft text	Writing committee	DPWG Curators
8: Review of draft text	Internal: (co-)leaders of CPIC and members External: peer review by the journal	Internal: 1) Review by other DPWG members, then 2) Evaluation by entire DPWG committee
9: Publication strategy	*CPT* has 1st right for review & publication and afterwards guidelines are published on PharmGKB and cpicpgx.org	Recommendations are published in the IM. In 2008 and 2011, a multidisciplinary set of guidelines was published in *CPT*

Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group

PCD Bank[1], KE Caudle[2], JJ Swen[1], RS Gammal[2,3], M Whirl-Carrillo[4], TE Klein[4], MV Relling[2] and H-J Guchelaar[1]

"CPIC and the DPWG guidelines are generally similar in terms of allele classification, genotype to phenotype translations and therapeutic recommendations for most gene-drug pairs."

Clin Pharmacol Ther. 2017;103(4):599-618

‘If genotype is known’

DPWG gen-drug interaction guidelines

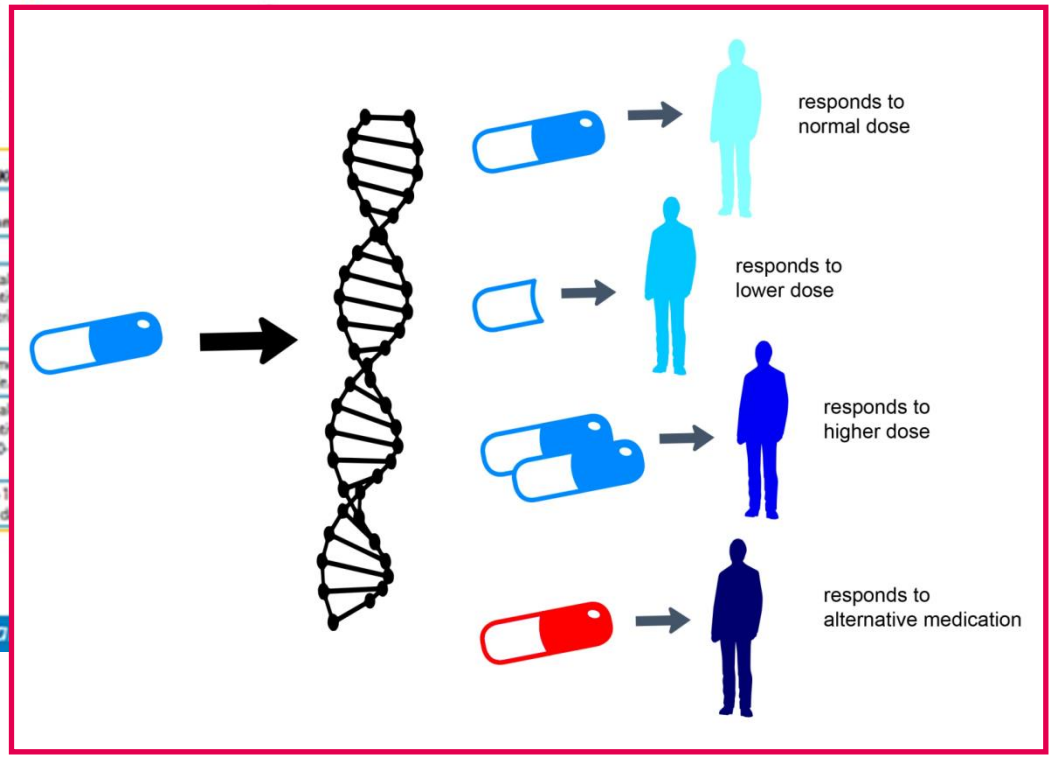
Pharmacogenetics: From Bench to Byte—An Update of Guidelines

JJ Swen[1], M Nijenhuis[2], A de Boer[3], L Grandia[2], AH Maitland-van der Zee[3], H Mulder[3,4], GAPJM Rongen[5,6,7], RHN van Schaik[8], T Schalekamp[9], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

Table 1 Results for *CYP2D6, CYP2C9, CYP2C19, UGT1A1, TPMT, HLA-B44, HLA-B*5701, CYP3A5, VK*

Drug	Subjects (N)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recom
CYP2D6						
Amitriptyline	459	PM	3	A	Yes	Insufficient data to allow ca adjustment. Select alternati sertraline) or monitor amitr plasma concentration
		IM	3	C	Yes	Reduce dose by 25% and m or select alternative drug (e.
		UM	3	C	Yes	Insufficient data to allow ca adjustment. Select alternati sertraline) or monitor (E-10- plasma concentration
Aripiprazole	124	PM	4	C	Yes	Reduce maximum dose to 1 maximum recommended d

Swen, Clin Pha



Clinical Implication Score

Pharmacogenetic Information in Clinical Guidelines: The European Perspective

Jesse J. Swen[1,2], Marga Nijenhuis[3], Mandy van Rhenen[3], Nienke J. de Boer-Veger[4], Anne-Marie Buunk[5], Elisa J.F. Houwink[6], Hans Mulder[7], Gerard A. Rongen[8,9], Ron H.N. van Schaik[10], Jan van der Weide[11], Bob Wilffert[12], Vera H.M. Deneer[13], Henk-Jan Guchelaar[1,2] and on behalf of the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacists Association (KNMP)

Table 1 Clinical Implication Score Criteria

	Possible score
Clinical effect associated with gene/drug interaction	
• CTCAE grade 3 or 4 ("Clinical effect score" D or E)	+
• CTCAE grade 5 ("Clinical effect score" F)	++
Level of evidence supporting the associated clinical effect	
• One study with "level of evidence score" 3	+
• At least two studies with "level of evidence score" 3	++
• Three or more studies with "level of evidence score" 3	+++
Number needed to genotype (NNG) in the Dutch population	
• $100 \leq NNG \leq 1000$	+
• $10 \leq NNG \leq 100$	++
• $NNG \leq 10$	+++
PGx information in the drug-label	
• Recommendation to genotype, a genotype mentioned as a contraindication (section 4.3), or a genotype mentioned in the special warnings and precautions for use (section 4.4)	++
• At least one genotype/phenotype mentioned in SPC	+
Total Score:	

Table 2 Available DPWG Clinical Implication Scores

Potentially beneficial	PGx testing for this gene/drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene/drug guideline.	0-2 +
Beneficial	PGx testing for this gene/drug pair is beneficial. It is advised to genotype the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection.	3-5 +
Essential	PGx testing for this gene/drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.	6-10 +

For the 47 actionable drug-gene interactions

Do our patients want genotyping?

Feasibility of pharmacogenetic screening for CYP2D6 and CYP2C19 in GP-practices

Polypharmacy patients; >60 years

Screening; no ADE

Consent: 58.1%

DNA extraction (Oragene®): 83.3%

Call rate:

- 93.3% CYP2D6
- 100% CYP2C19

Swen, Eur J Clin Pharmacol 2011, 8 Oct

Implementation study LUMC: IP3

Implementation of Pharmacogenetics in Primary care Project

- 200 patients included and pre-emptively genotyped
- Panel of genetic variants: CYP2C9; 2C19, 2D6, 3A5, DYPD, SLCO-1B1, TPMT and VKORC1; 40 alleles

KNMP

Zorg en Zekerheid

- 40 pharmacies (Leiden)
- 200 patients included
  - 89.5% ≥ 1 “actionable” genotype
  - 61.5 % ≥ 2
  - 28.5% ≥ 3
  - 9.5% ≥ 4
  - 2.0% ≥ 5
- 31.0 % of patients → therapeutic recommendation; dose adjustment or monitoring

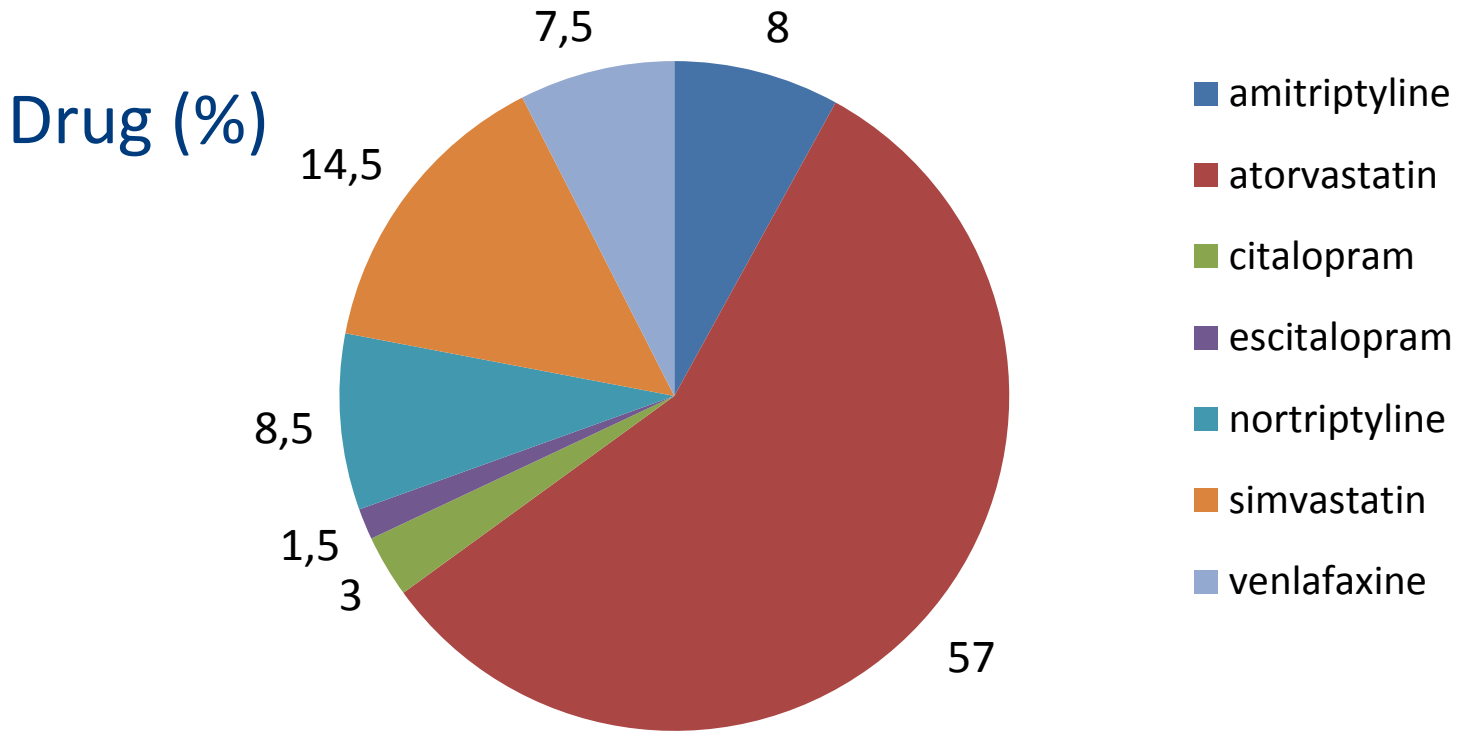
Implementation in Primary Care (IP3)

Pharmacist alerts, orders the PGx test and provides physician with a personalized recommendation

pre-emptive - pro-active & panel

Adherence PGx guidelines

- >85% of the recommendations accepted
- Follow-up data being collected: healthcare costs

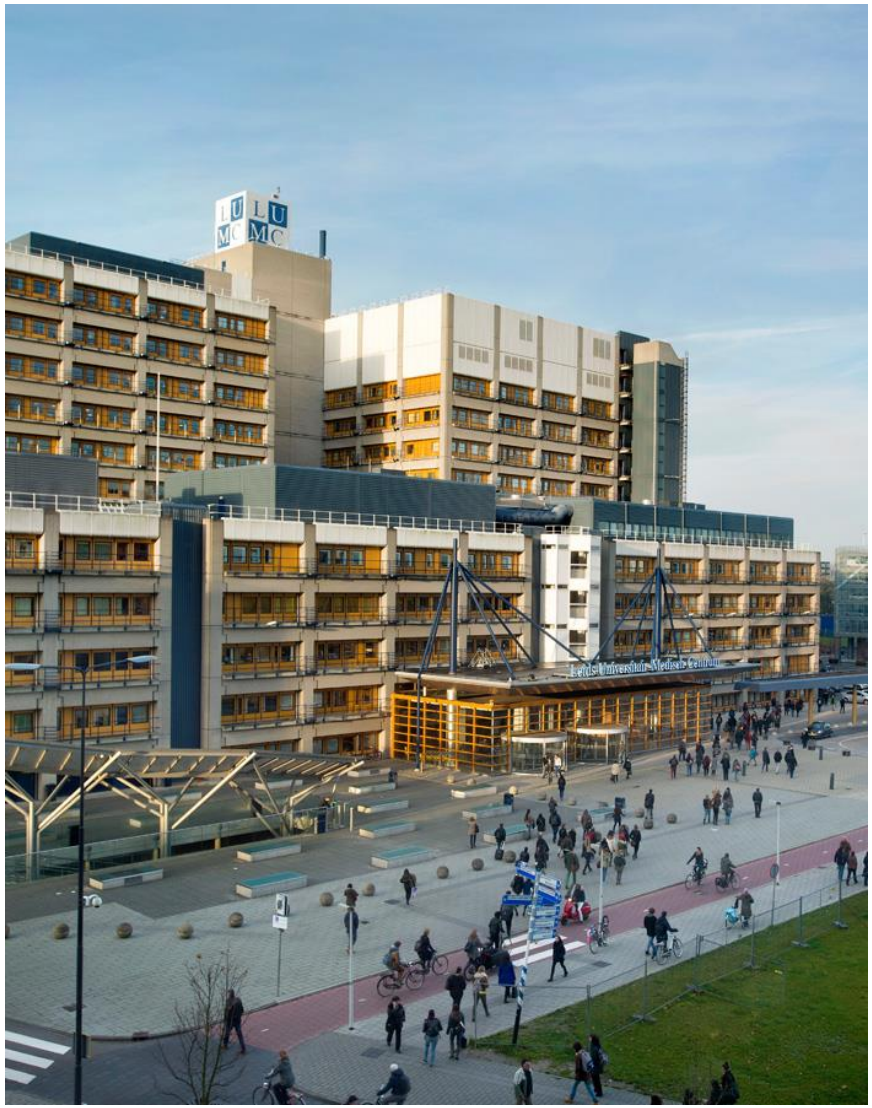


Impact Netherlands 2016

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		PM + UM	244272	12993
T		CYP2D6	IM + PM + UM	60068	60068
V	26.603	CYP2D6	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

Inpatient care

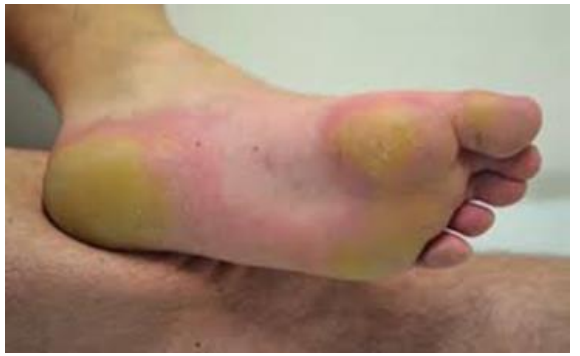


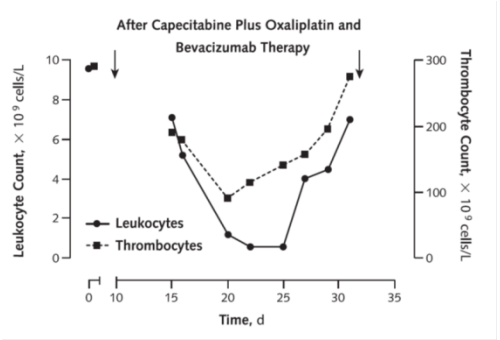
Leiden University
Medical Center

DPYD testing 5-Fluorouracil/capecitabine

- Colorectal cancer, head-neck cancer, breast cancer
- Grade 3 or higher toxicity: 15-30%
- Drug induced lethality: 0,5-1%

- 5FU → inactive metabolites
- Dihydropyrimidine dehydrogenase (DPD)
- *DPYD* gene





DPYD @ LUMC

Oncologist considers DPYD testing ‘standard of care’

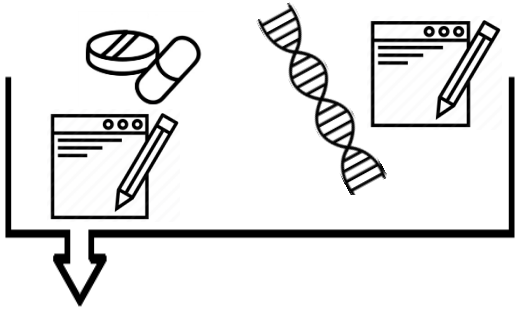
Pharmacist alerts physician if FU/CAP is prescribed with no DPYD testing.

pre-therapeutic - screening

DPYD screening @ LUMC

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

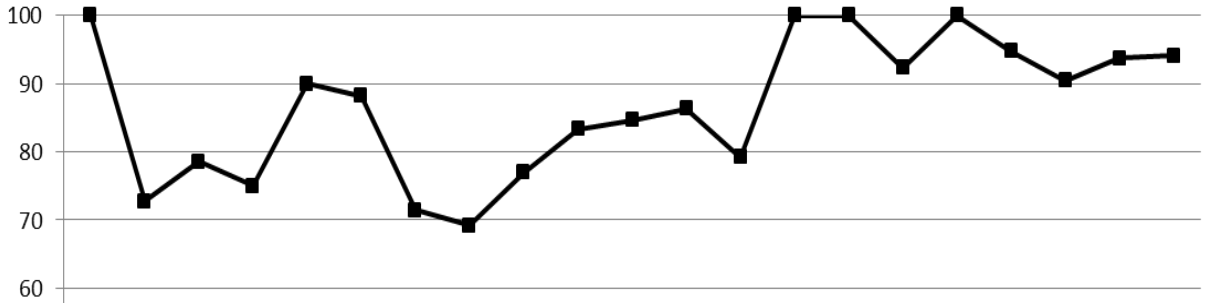
Retrospective analysis: 314 patients (18 maanden)



Screening:

mean: 87%

final: 90-100%



Implementation DYPD screening

- Pre-therapeutic screening was performed in 87% of patients, reaching 90-100% in the last 6 months of the project
- Acceptance of dose recommendation: 90%
  - Chemoradiaton

- **No grade 3-4 toxicity in patients with initial dose reduction**
- Grade 3-4 toxicity was only seen in DPYD variant carriers without a dose reduction or who received a dose increase in subsequent cycles
- Dose titrations possible, guided by toxicity (not too fast)

→ *DPYD* screening is feasible in clinical practice

Lunenburg et al. Pharmacogenomics 2015;17(7):721

Genetic counseling

- Pharmacogenetics clinic LUMC
  - Clinical pharmacist & clinical geneticist
  - PGx screened patients are offered genetic counseling

Example counseling patient

- **I am a CYP2D6 poor metabolizer**

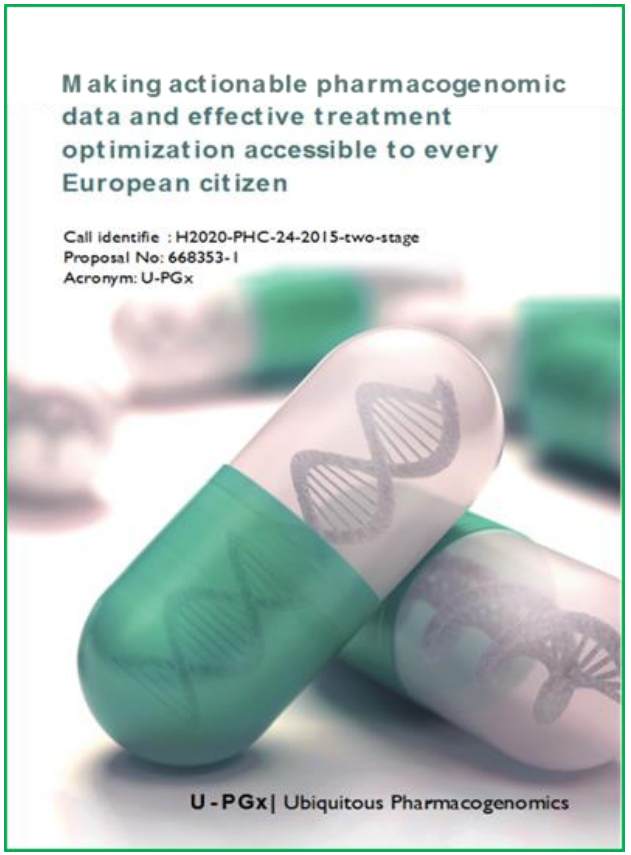
- For which drugs is this relevant?
- Is this relevant for certain food products?
- Is this relevant for my children?
- Can I take paracetamol safely?
- Should my parents be tested?
- Should I be re-tested in 5 or 10 years?

U-PGx | Ubiquitous Pharmacogenomics

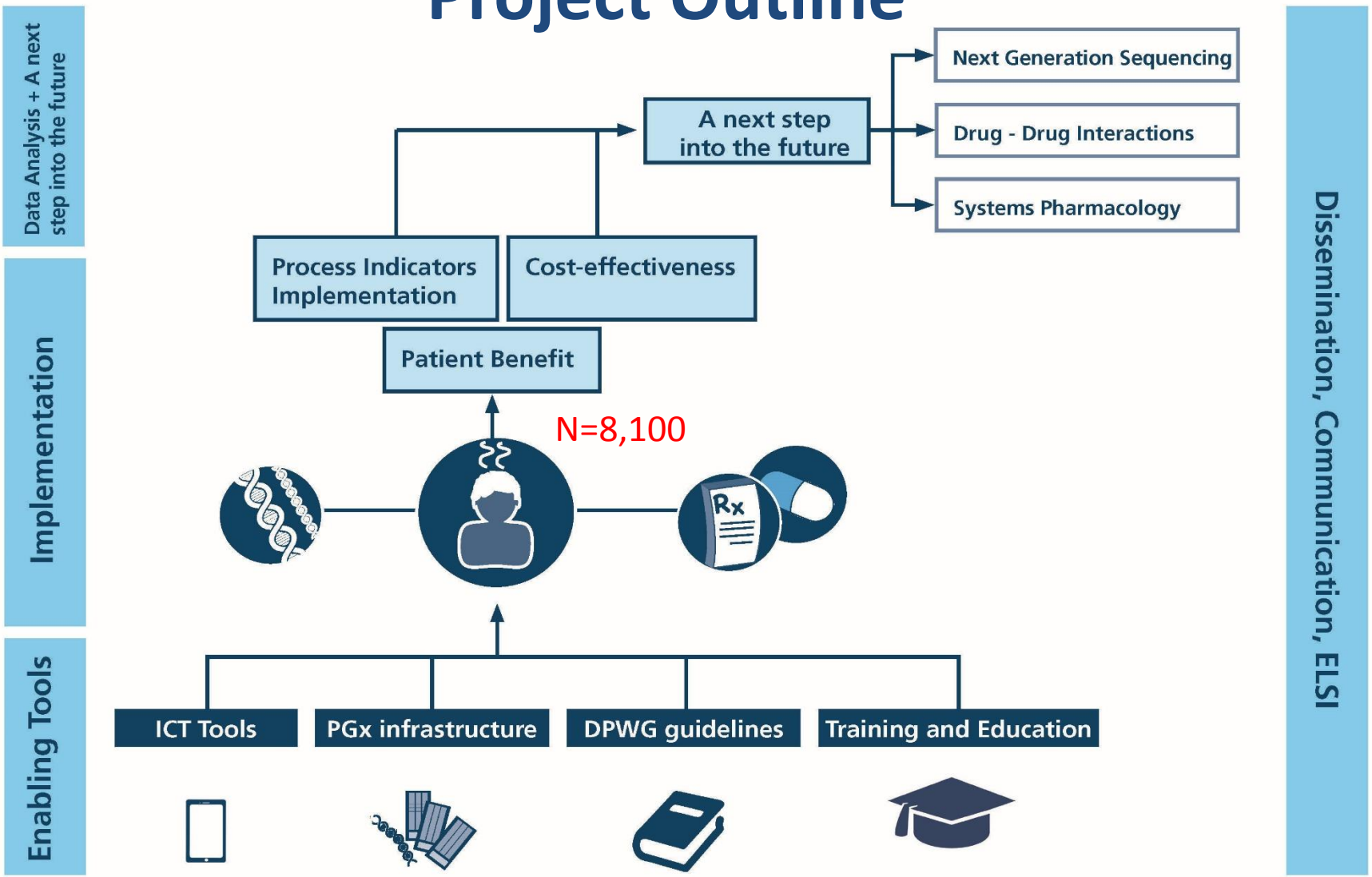
Overall aim U-PGx:

"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%

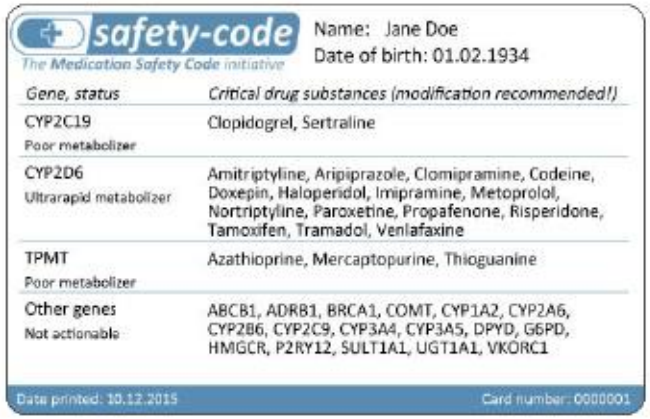


Project Outline



Development of powerful and barrier-free CDSS

Scan QR code



http://safety-code.org/

How to use pharmacogenetics to select patients for pharmaceutical care

A patient....

21-year old woman
recenty started with 20 mg tioguanine once daily;
M. Crohn;
3 weeks after start: fatigue, headache, short of breath
Lab: pancytopenia

bijwerkingen centrumlareb

TPMT-genotyping:
Heterozygous TPMT *3C/*2

Kies alternatief of verlaag de startdosering tot 6-7% van de normale dosering; evt. aanpassing op geleide van toxiciteit (monitoring van het bloedbeeld) en effectiviteit. De frequentie van monitoring dient te worden verhoogd. Adviseer de patiënt om contact op te nemen bij symptomen van beenmergdepressie (zoals erge keelpijn in combinatie met koorts, regelmatig een bloedneus en snel blauwe plekken) optreden.

diagnostic - reactive

Ekhart, Pharm Weekblad 2017: 35

diagnostic

Impact Netherlands 2016

SFK

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	518.7		IM + UM	244272	12993
T		CYP2D6	IM + PM + UM	60068	60068
V	26.603	CYP2D6	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

pre-therapeutic first Rx

Implementation in Primary Care (IP3)

Pharmacist alerts, orders the PGx test and provides physician with a personalized recommendation

pre-emptive - pro-active & panel

order test, provide recommendation

Genetic counseling

- Pharmacogenetics clinic LUMC
  - Clinical pharmacist & clinical geneticist
  - PGx screened patients are offered genetic counseling

counsel patients

Take home messages

- Implementation of PGx in clinical practice is feasible and effective
- Personalizing therapy based upon PGx will improve patient outcome
- Pharmacists are at the forefront of PGx