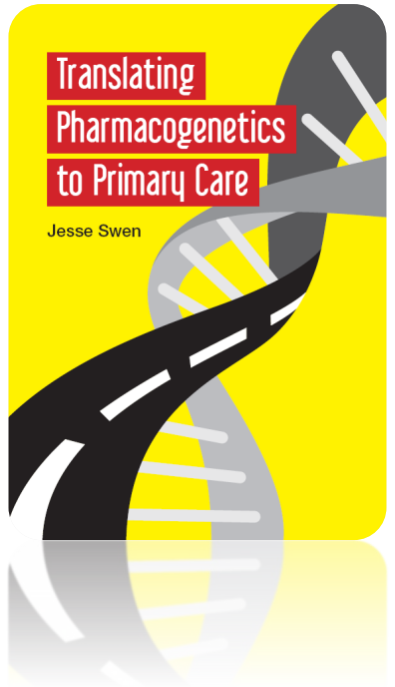
Leiden University Medical Center

LNPT Leiden Netwerk for Personalised Therapeutics

Farmacogenetica: *van onderzoek naar praktijk*

Personalized medicine in de intramurale zorg
09-02-2021



Dr. Jesse Swen, ziekenhuisapotheker-klinisch farmacoloog
Associate Professor of Pharmacogenetics
Sectiehoofd Klinisch Farmaceutisch laboratori
Klinische Farmacie & Toxicologie

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	

Vraag: Een patiënt meldt zich in met een DNA-paspoort en vraagt uw advies. De uitslag is CYP2D6 *1/*4. Wat doet u?

A. Ik geef voor de belangrijkste geneesmiddelen advies op maat

B. Ik duik de literatuur in (en vraag de patiënt om over 2 weken terug te komen)

C. Ik verwijs door naar een specialist

D. Ik leg de patiënt uit dat farmacogenetica een hype is (die wel overwaait)

Vraag: De kans dat je een *actionable* farmacogenetische variant hebt is vergelijkbaar met de kans dat:

A. Je de hoofdprijs in de lotto wint (1 op 49 miljoen)

B. Je komend jaar door de bliksem getroffen wordt (1 op 3 miljoen)

C. De trein vertraging heeft (1 op 10 tot 1 op 100)

D. Het kabinet Rutte IV (50:50)

E. Nederland wereldkampioen korfbal wordt (95%)

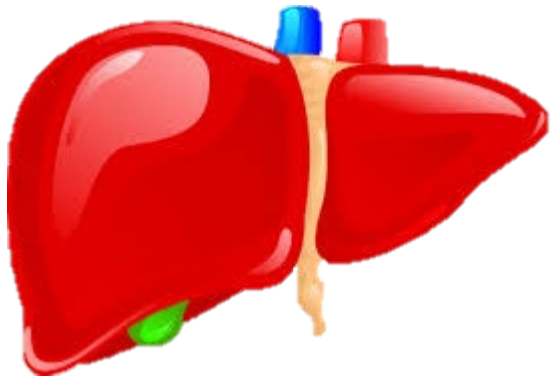
Doel van vandaag

- Uitleggen wat farmacogenetica is
- Belangrijke voorbeelden laten zien
- Laten zien wat er in de praktijk kan

Mei 1975; debrisoquine

Wat is er aan de hand?

Debrisoquine – 4-hydroxydebrisoquine

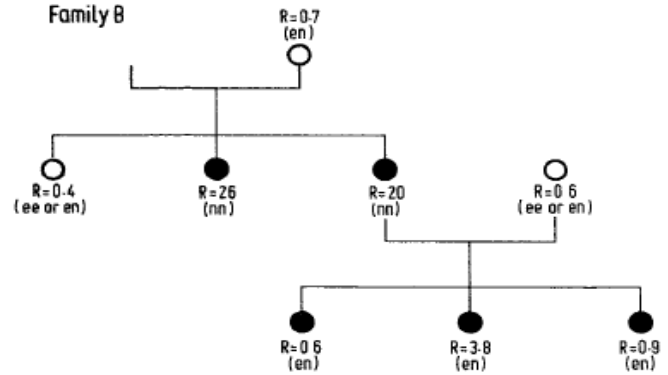


POLYMORPHIC HYDROXYLATION OF DEBRISOQUINE IN MAN

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



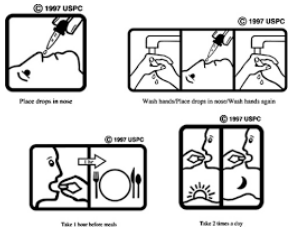
METABOLIC RATIOS (DUPLICATE VALUES)* IN 6 EXTENSIVE METABOLISERS AND THE 3 NON-METABOLISERS

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

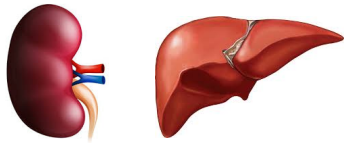
Smith, Lancet 1977(2): 584-586

Oorzaak verschillen reactie op geneesmiddel

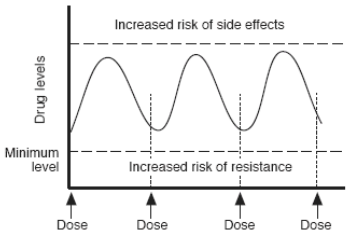
Incorrect use



Organ function



Drug levels



Special populations

Co-morbidity

Genetic Variation

Drug interactions

Farmacogenetica

DNA Test

100% dosis

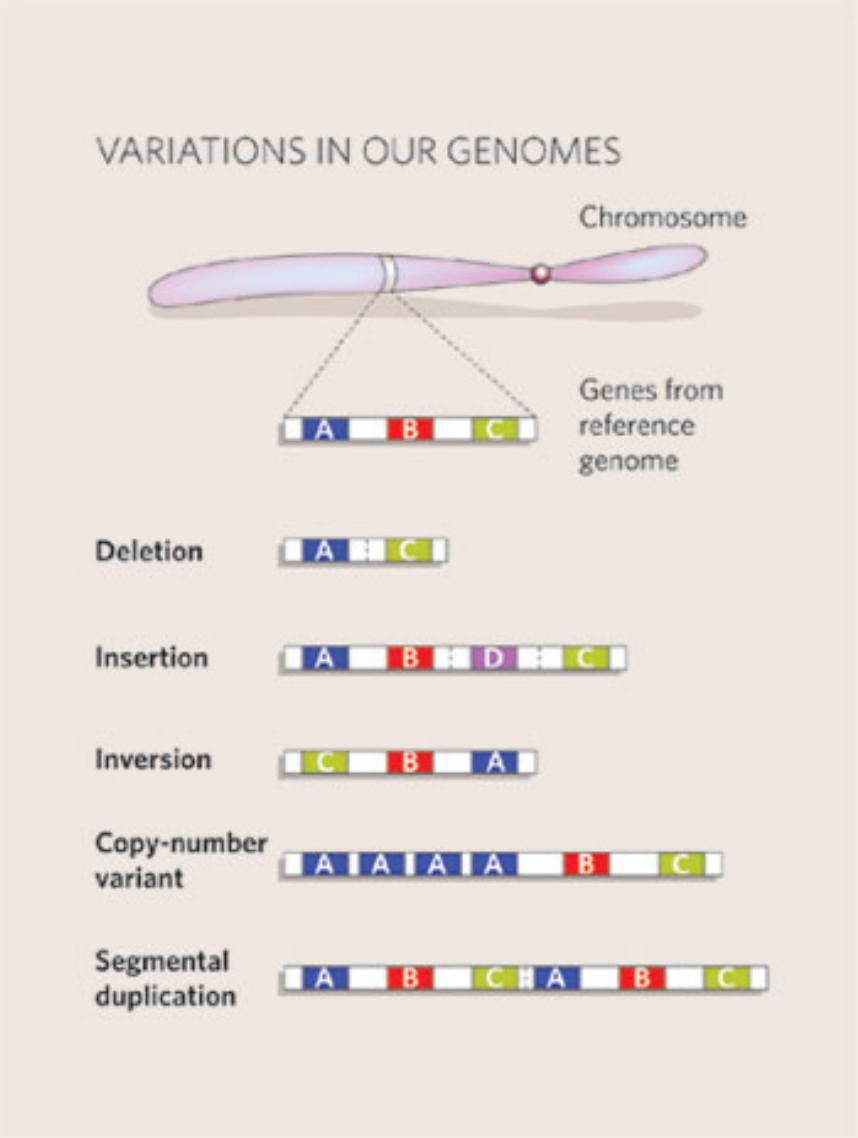
Geneesmiddel A

30% dosis

Geneesmiddel A

Geneesmiddel B

“Book of Life”



Check, Nature 2005:1084

Typografische fouten:

Letter mis.

Letter teveeel

Verwissleing

Typefouc

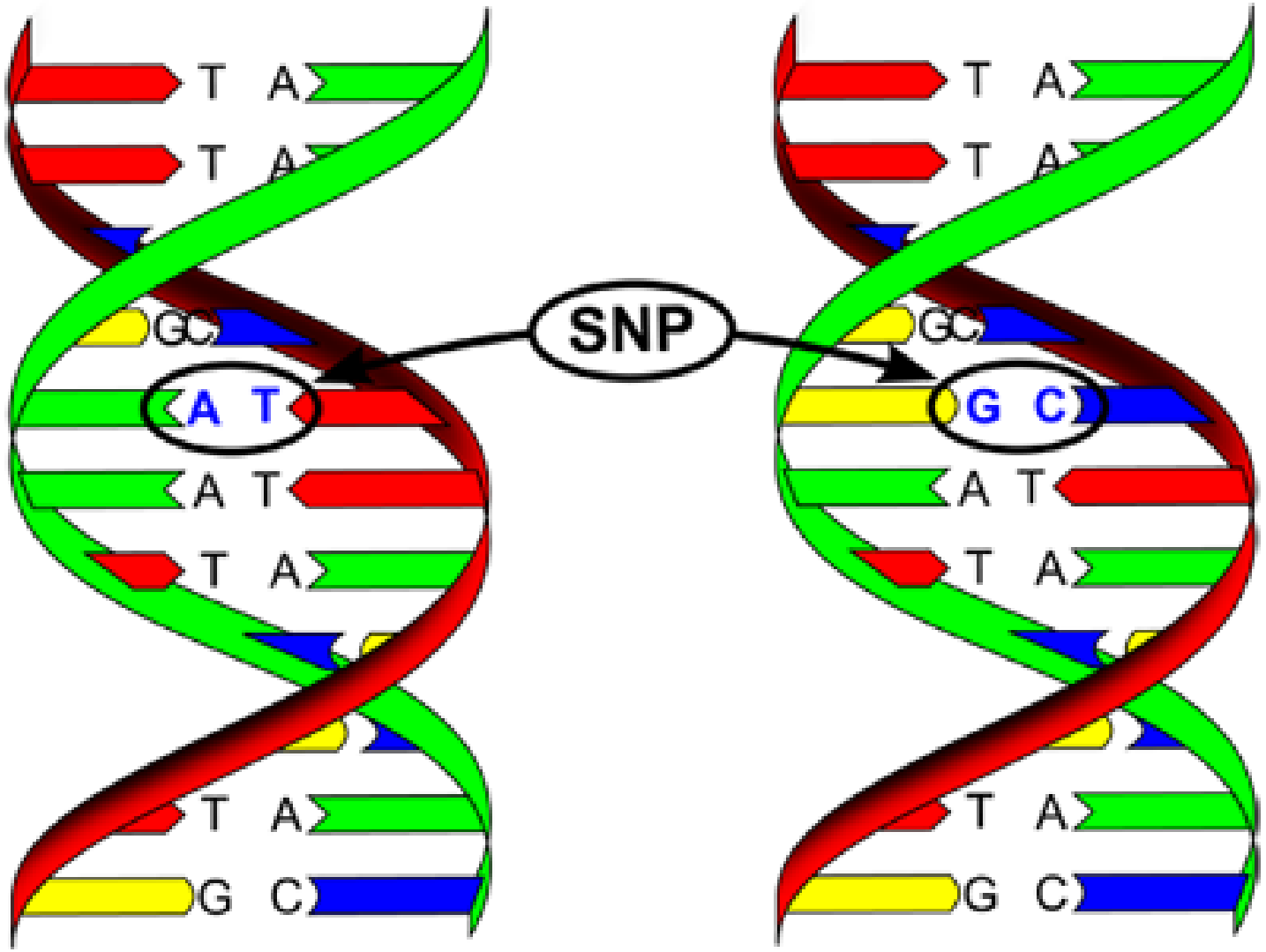
Dupliplipliplicatiesssss

Hele paragrafen dubbeldubbel

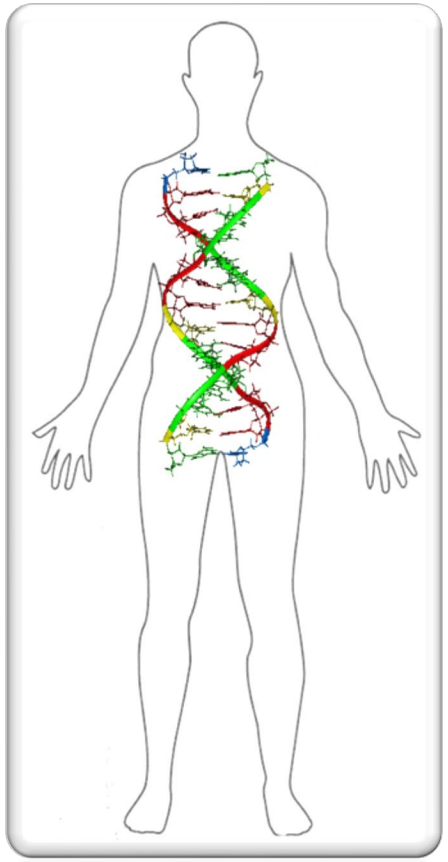
Passages missen

Dreekegmo

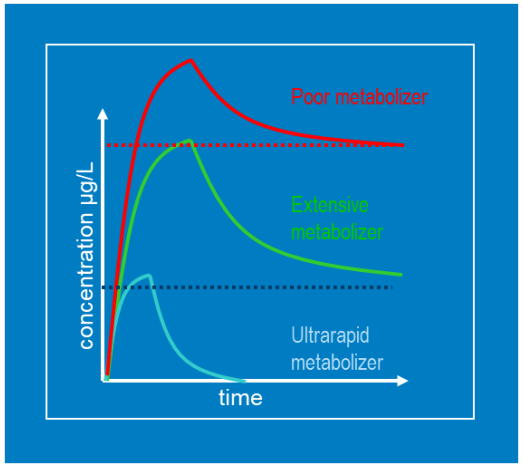
Single Nucleotide Polymorphism



Soorten gen-geneesmidel interacties

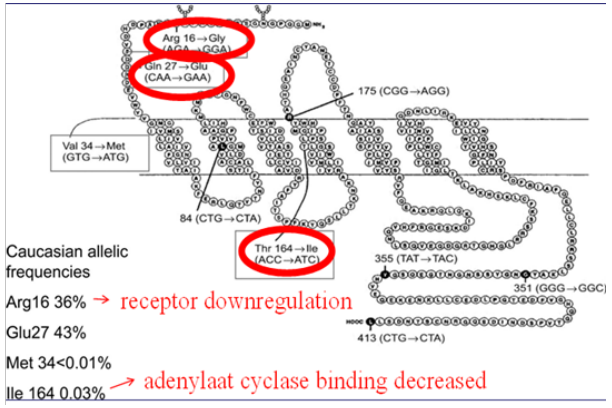


- Farmacokinetisch

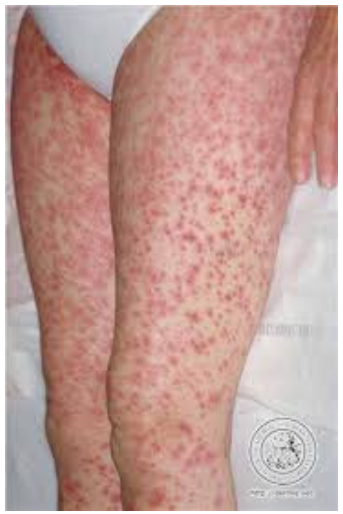


- Farmacodynamisch

PD

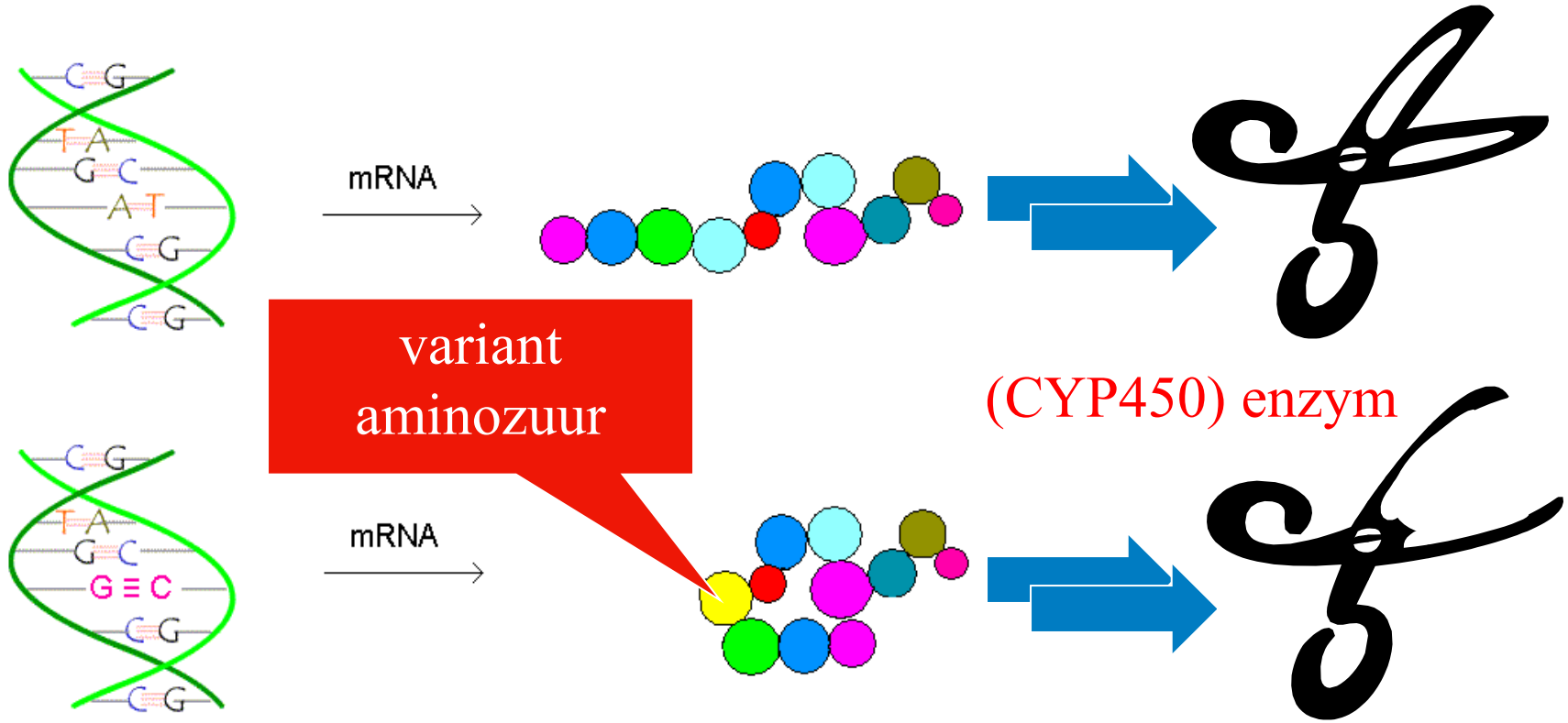


- Idiosyncratisch



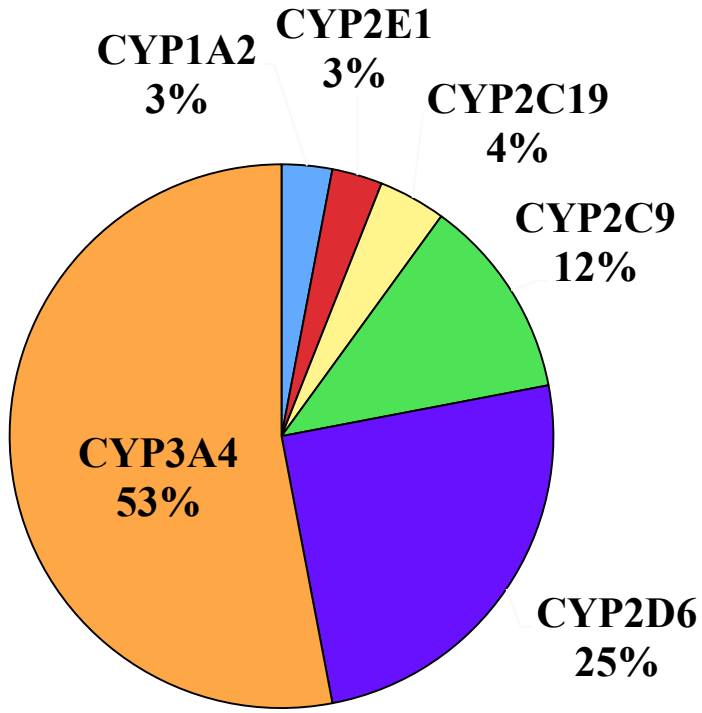
Effect op farmacokinetiek

Genetische variatie geeft ander eiwit en andere enzymactiviteit



Cytochroom (CYP) P450

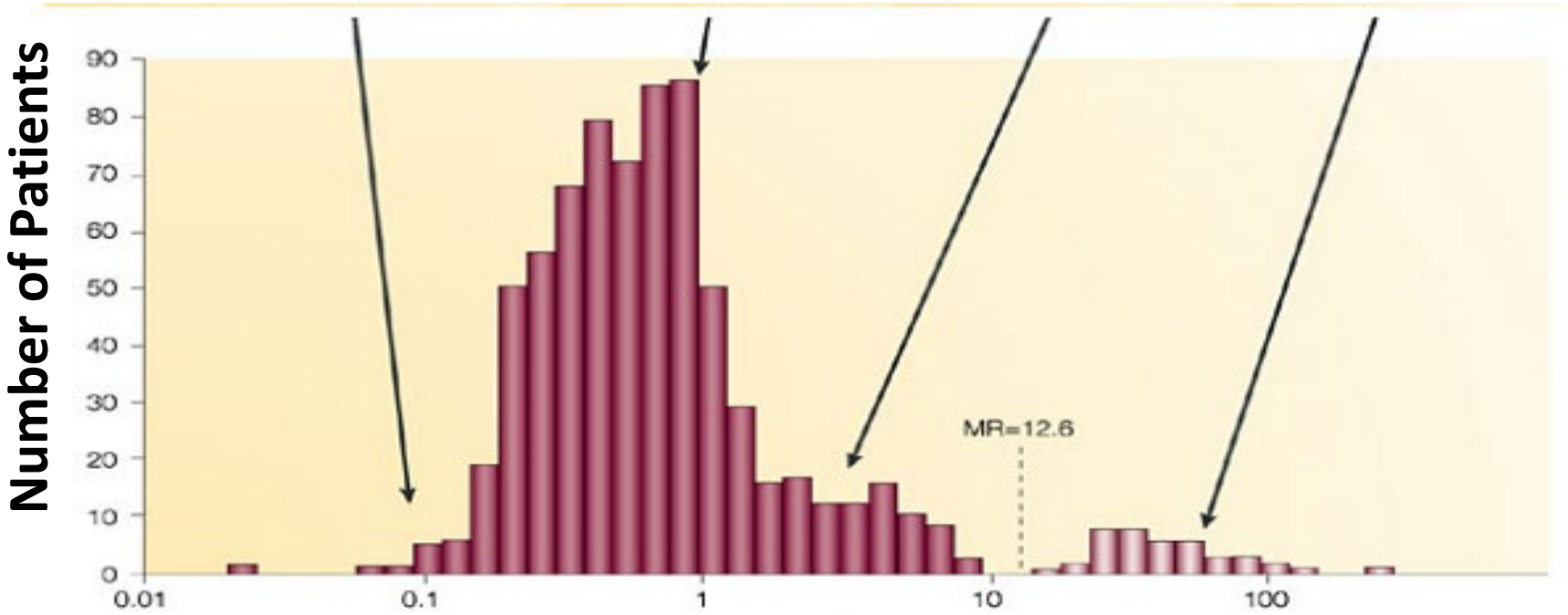
- Familie van > 200 enzymen in 12 families
- 57 verschillende actieve genen die coderen voor P450 enzymen
- Belangrijk voor geneesmiddelmetabolisme:
  - CYP1A2
  - CYP2E1
  - CYP2D6
  - CYP2C19
  - CYP2C9
  - CYP3A4



CYP2D6 fenotypen

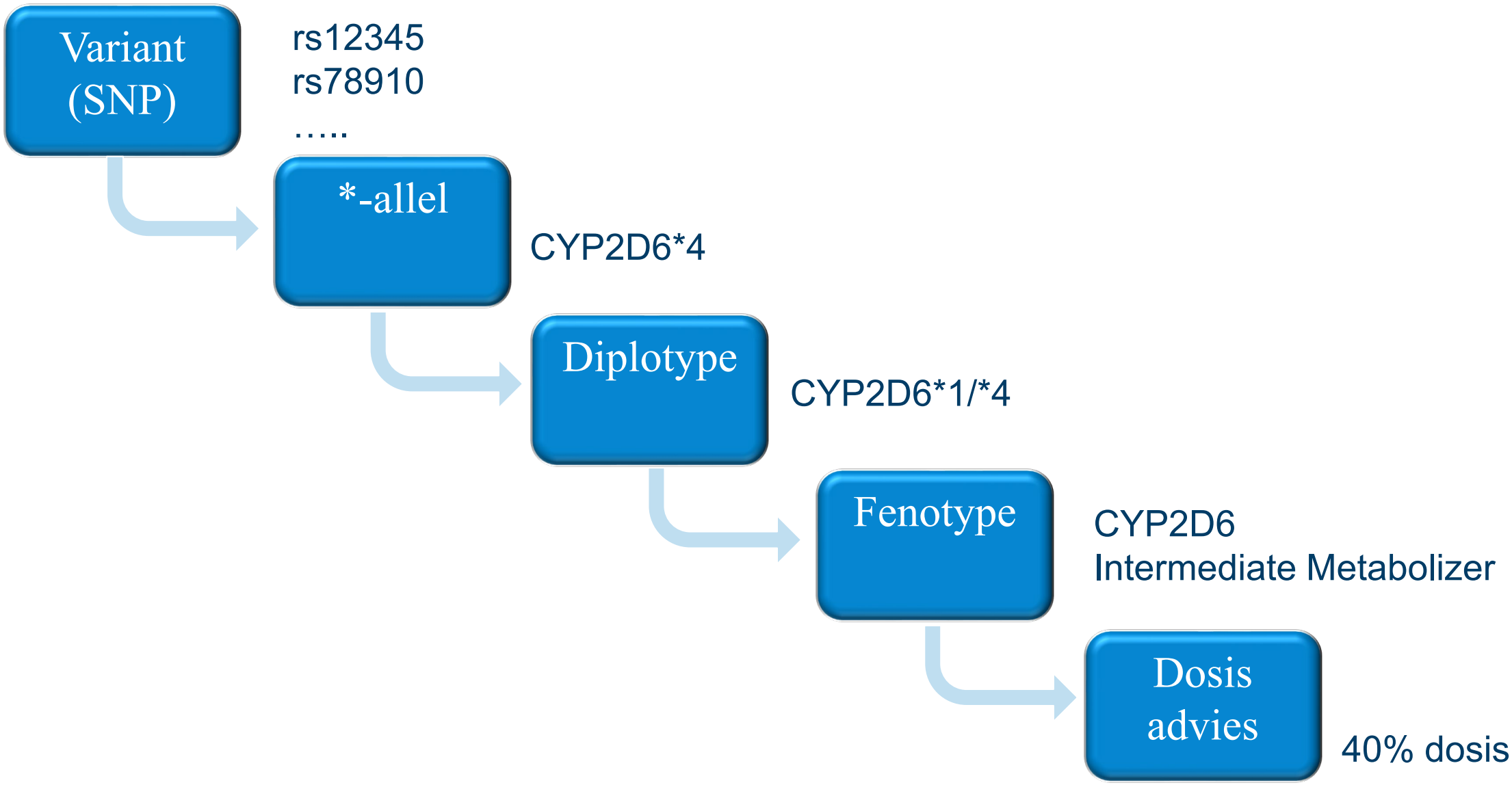
Debrisoquine —CYP2D6→ **4-hydroxy-debrisoquine**

Ultrarapid **Normal** **Intermediate** **Poor**

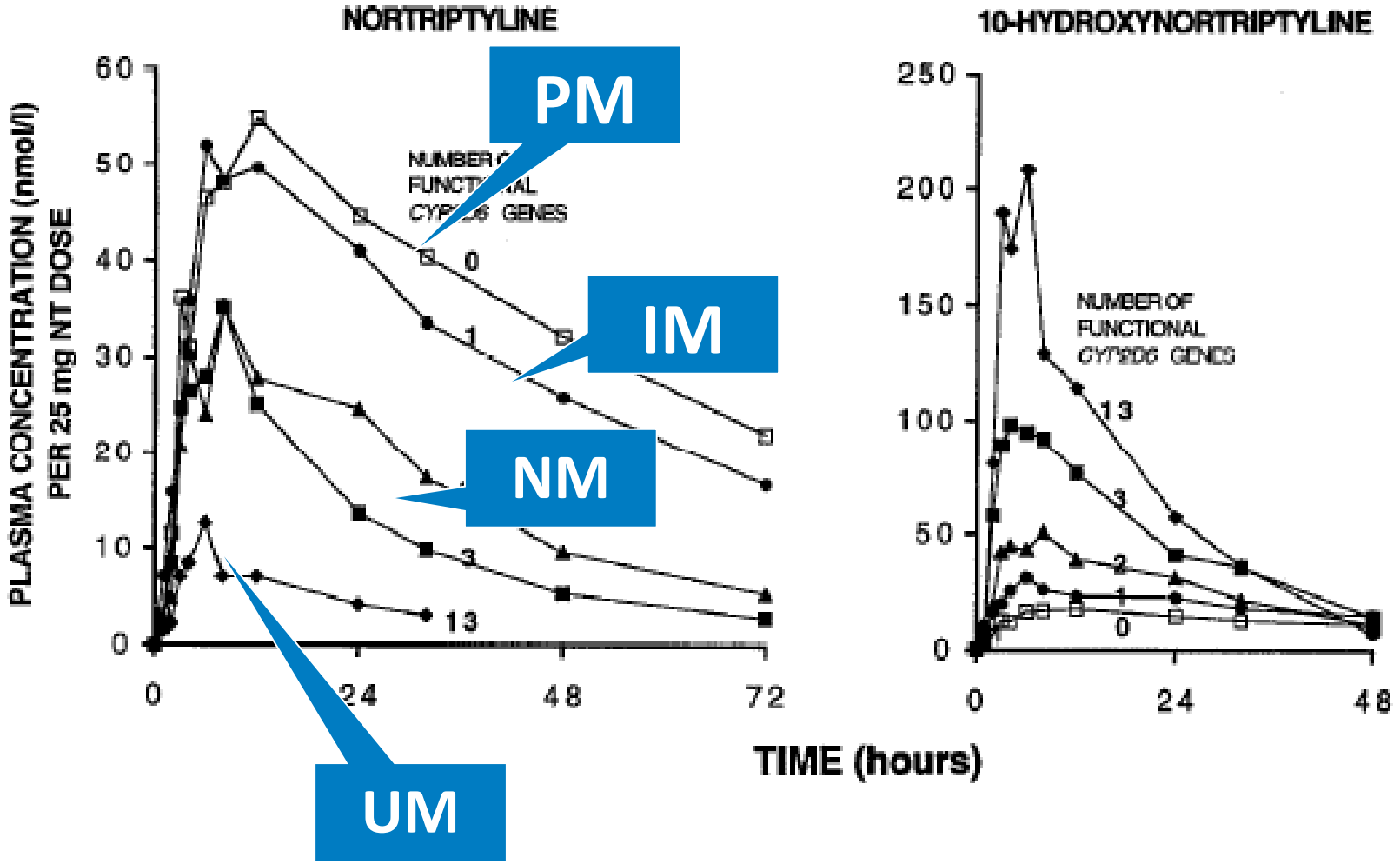


Meyer Nature reviews Genetics 2004 669-76

Van SNP naar Dosis

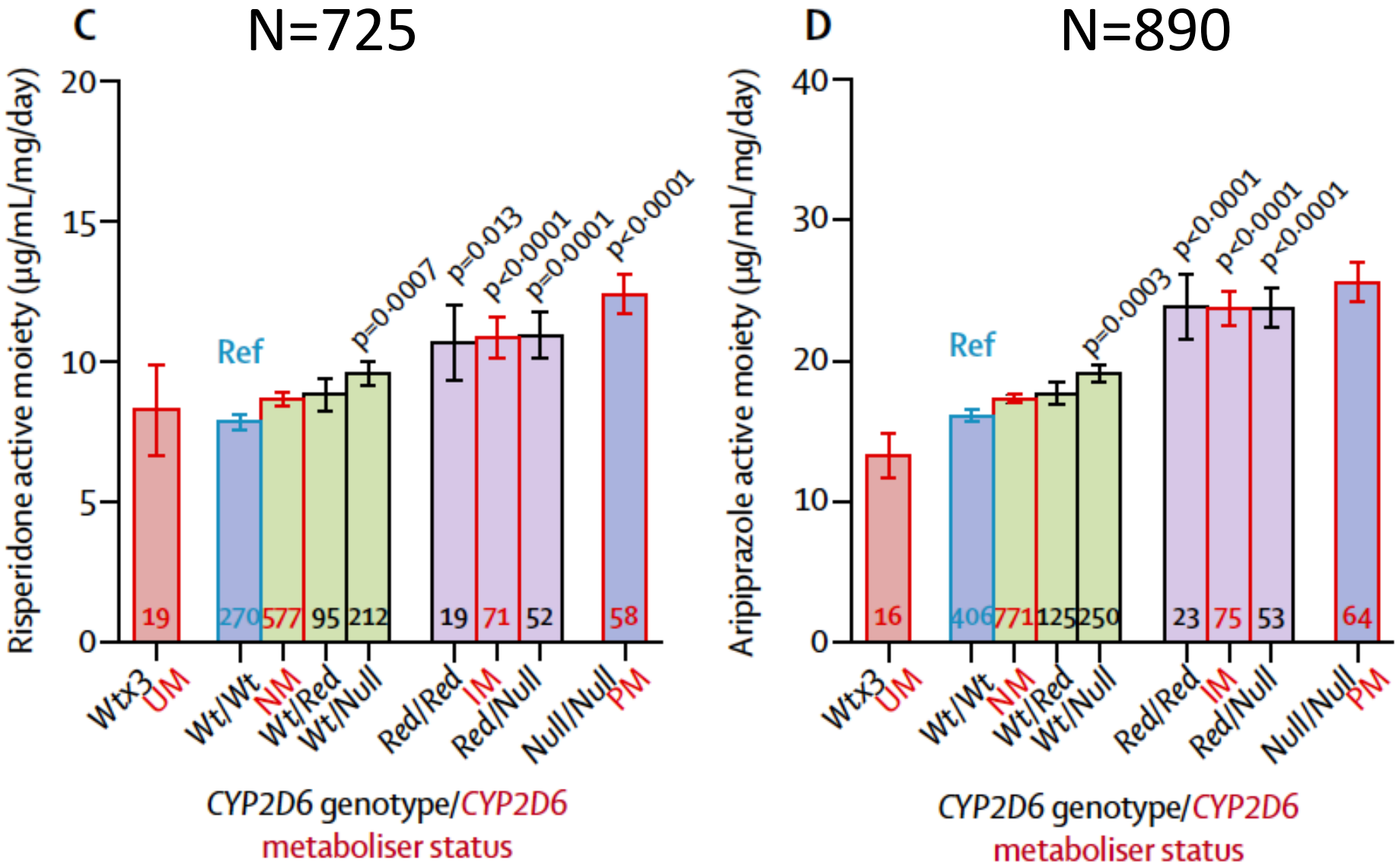


Effect op de farmacokinetiek van Nortriptyline



Dalen et al., 1998

Effect op farmacokinetiek Risperidon en Aripirazol



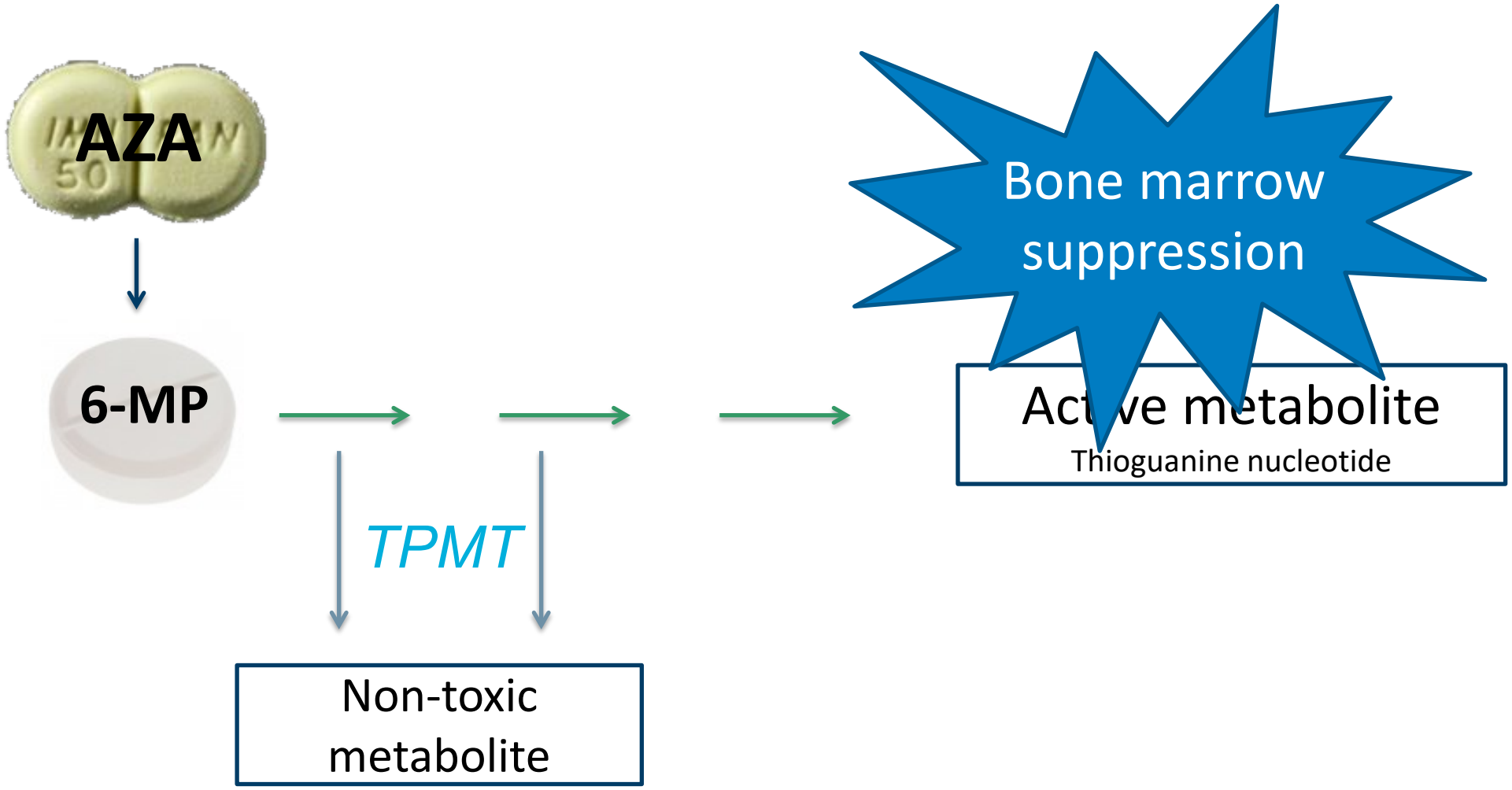
Jukic, Lancet Psychiatry 2019

Vraag: Wat is de meest waarschijnlijke oorzaak?

- Een jongetje van 10 (40 kg) met de ziekte van Crohn komt op de eerste hulp met koorts en overgeven
- Hij wordt behandeld met 1 dd 100mg azathioprine
- Er blijkt sprake van een pancytopenie

a. DPD poor metabolizer
b. Overdosering azathioprine
c. CYP2D6 poor metabolizer
d. TPMT poor metabolizer

Azathioprine metabolisme



TOPIC trial

TOPIC

Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics

- 783 patients
- 1:1 randomized : screening *vs* no screening TPMT*2, TPMT*3A, and TPMT*3C
- HET: 50% dose reduction, HOM 90% dose reduction
- Primary endpoint: leuco's < 3.0*10(9)/L of platletes < 100*10(9)/L)
- "10-fold reduction in hematologic ADRs among variant carriers without differences in treatment efficacy"

	Intervention	Control	RR (95%CI)
Total (n)	399	370	
Hematologic ADE	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

Vraag: een patient met slokdarmkanker wordt behandeld met fluorouracil. Ze overlijdt binnen 3 weken.

Welk testresultaat past hier bij?

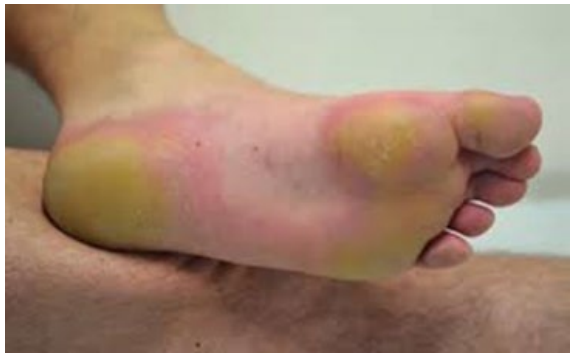
a. UGT1A1 poor metabolizer
b. DPD poor metabolizer
c. DPD ultrarapid metabolize
d. UGT1A1 ultrarapid metabol

www.change.org

Late December, I lost my mother in law **Janet North**. She had been diagnosed with the very early stages of *oesophageal cancer* but was killed by the chemotherapy drugs designed to save her life. Fighting fit and positive of the outcome, it took just **one month** from starting her cancer treatment to her premature death. Janet had a condition called ……, which could have been diagnosed with a medical test costing just £50 which we would paid without question.

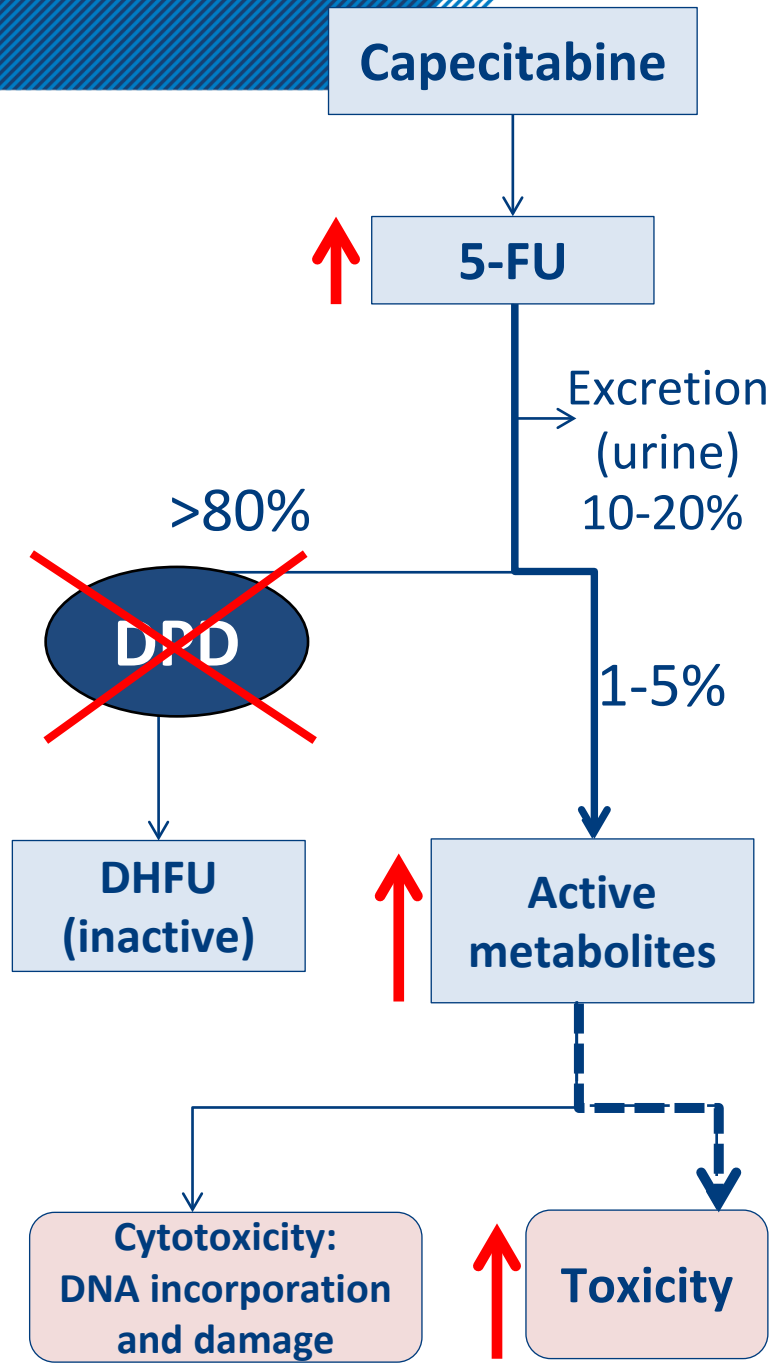
Fluoropyrimidines 5FU, Capecitabine

- Widely used anticancer drugs
- ~10-30% of patients develop severe (gr ≥3) tox
- This frequently results in hospital admission
- ~1% of patients develop fatal toxicity



Dihydropyrimidine dehydrogenase (DPD)

- Key role in fluoropyrimidine metabolism
- 3-5% of the population is deficient
- Deficiency is associated with substantially increased risk of severe / fatal toxicity
- Genetic variation



Prospective *2A screening (n=2,038)

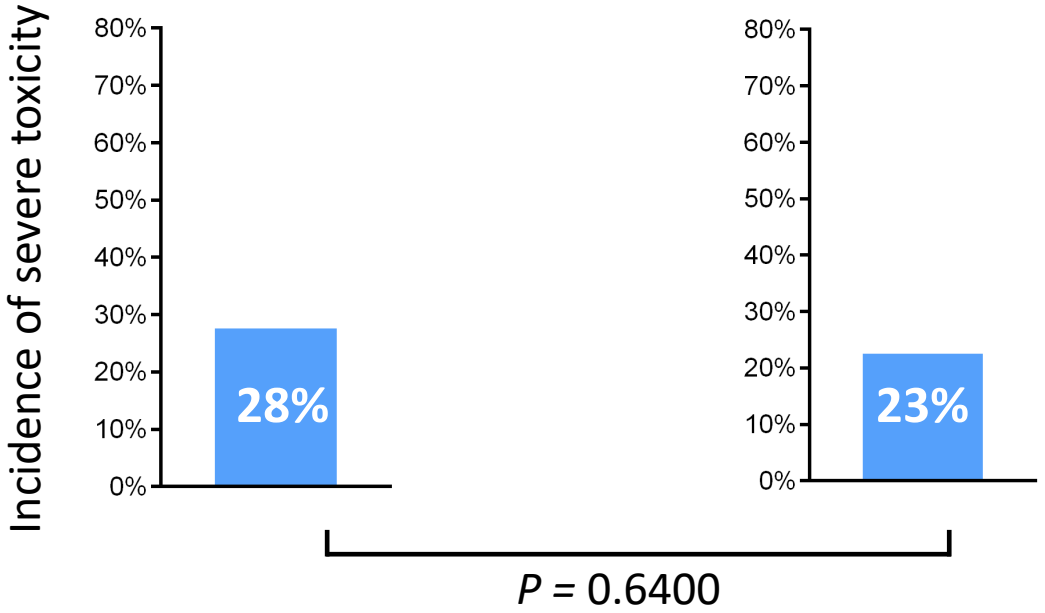
VOLUME 34 · NUMBER 3 · JANUARY 20, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

*DPYD**2A (heterozygous)	No variant
50% dose	normal dose



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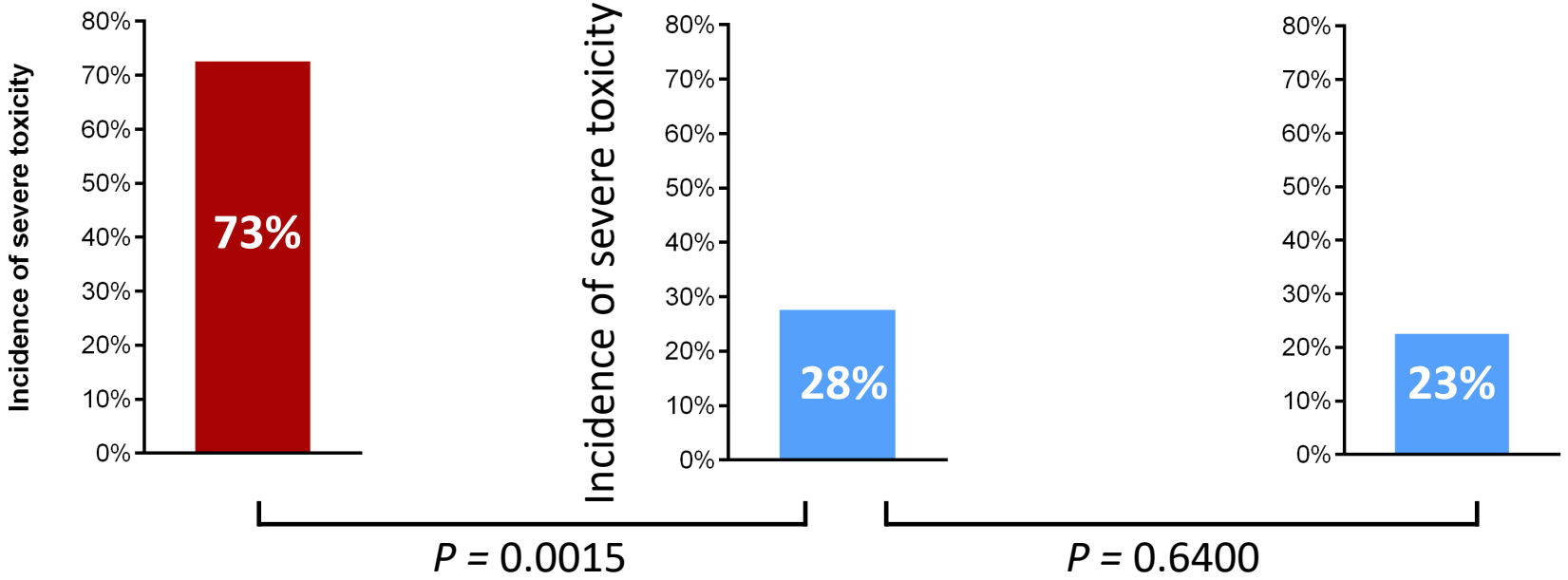
See accompanying editorial on page 205

(literature)

*DPYD**2A (heterozygous)	*DPYD**2A (heterozygous)	No variant
normal dose	50% dose	normal dose



Results of the ALPE DPYD study (n=1,181)

THE LANCET Oncology

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EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine

Share

Press release 30/04/2020

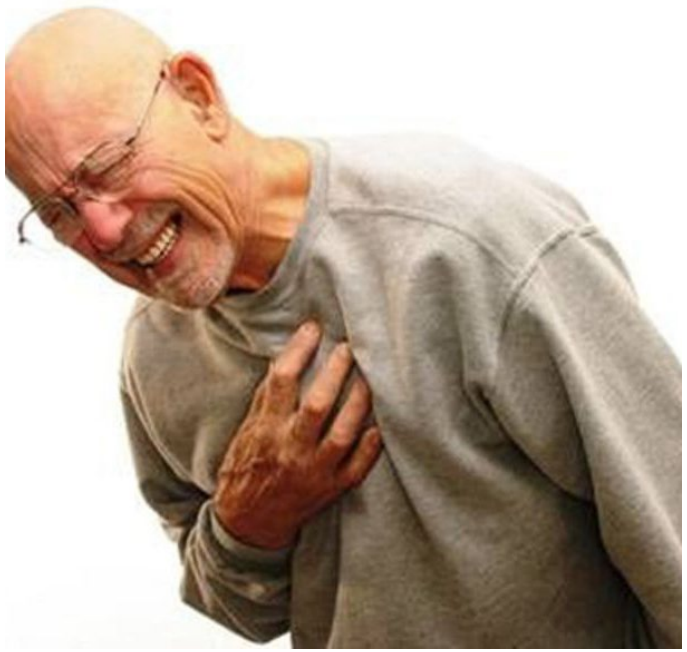
EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.

- No toxic deaths in patients with *DPYD* genotype-guided dosing
- *DPYD* genotyping strategy was cost-saving

Henricks LM et al Lancet Oncol. 2018 Oct 18

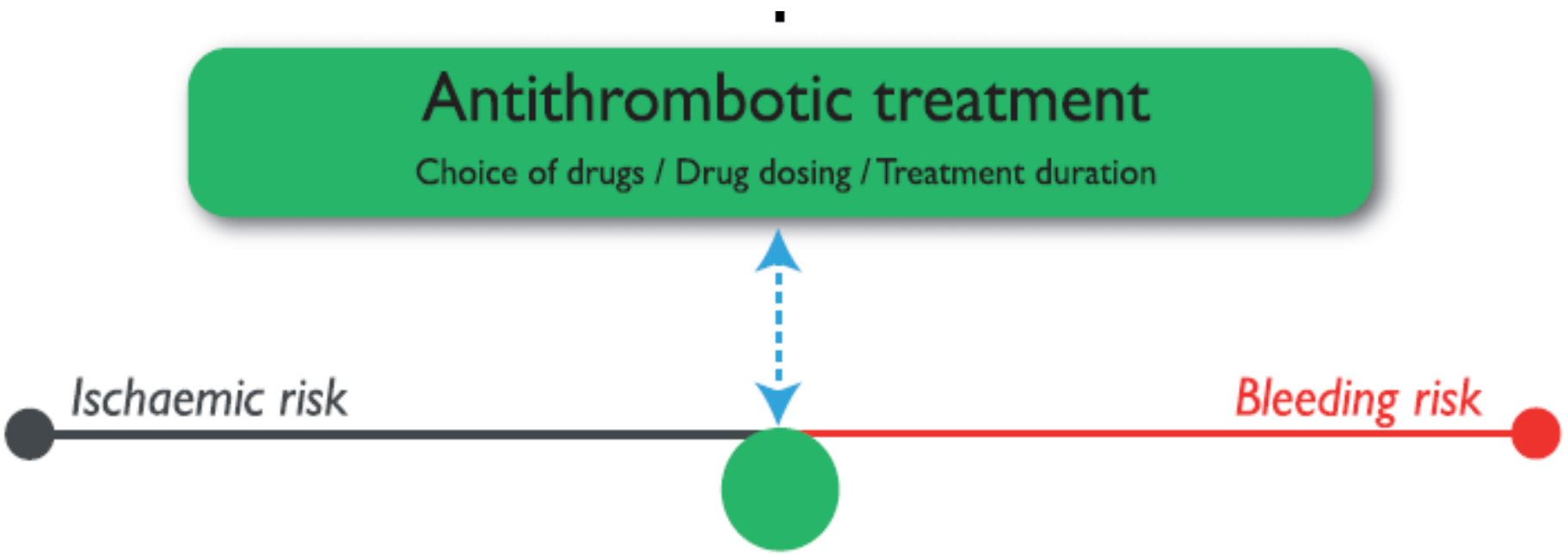
Vraag: een cardioloog vermoedt dat een patient clopidogrel resistentie heeft. Welk testresultaat past hier bij?

a. CYP2C9 poor metabolizer
b. CYP2C19 poor metabolizer
c. CYP2C9 ultrarapid metabolizer
d. CYP2C19 ultrarapid metabolizer

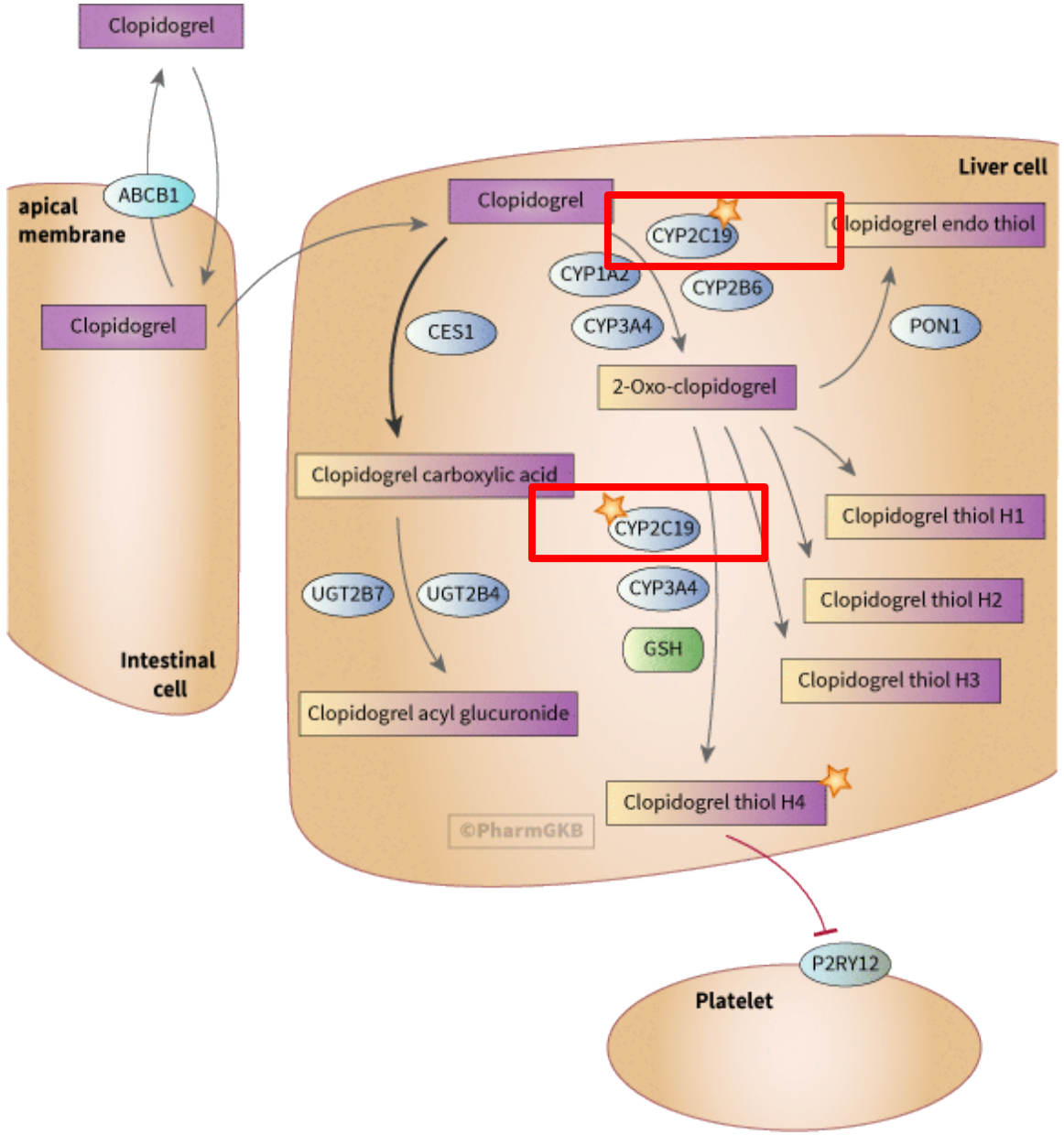


Huidige cardiovasculaire richtlijnen

- Prasugrel en Ticagrelor hebben de voorkeur boven Clopidogrel want ze zijn effectiever in het voorkomen van stolsel
- …..maar een nadeel is dat ze een hoger bloedingsrisico geven
- …..en duurder zijn (clopi: € 32,76/jaar, ticagrelor: € 906,36/jaar)



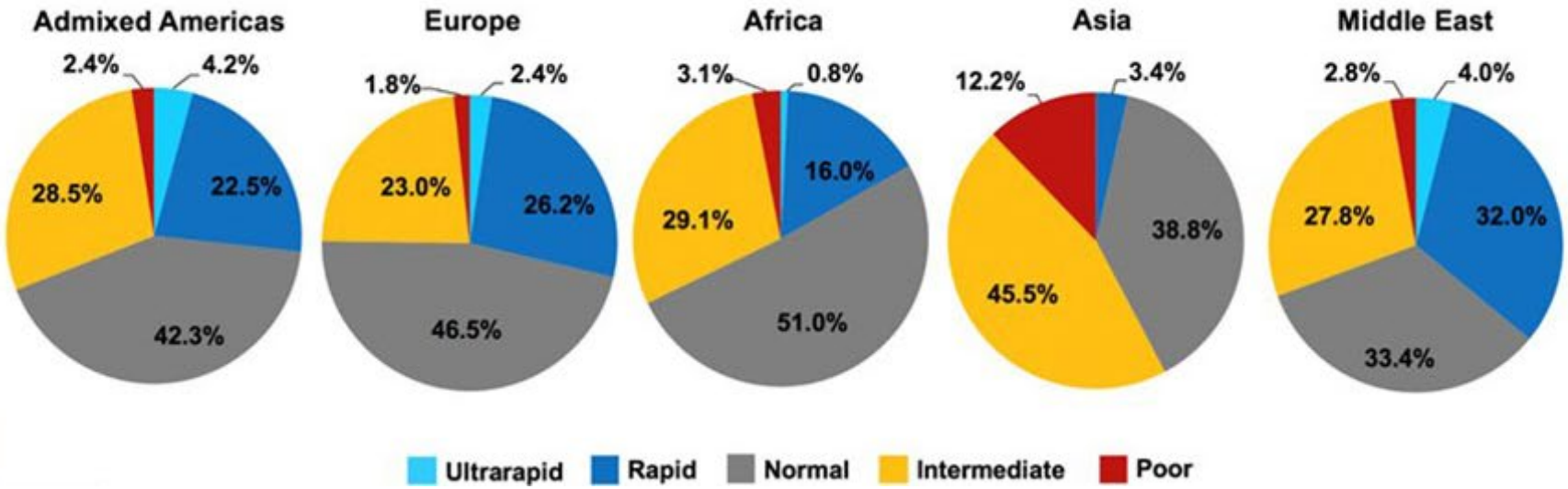
Clopidogrel Pathway



Activatie door CYP2C19

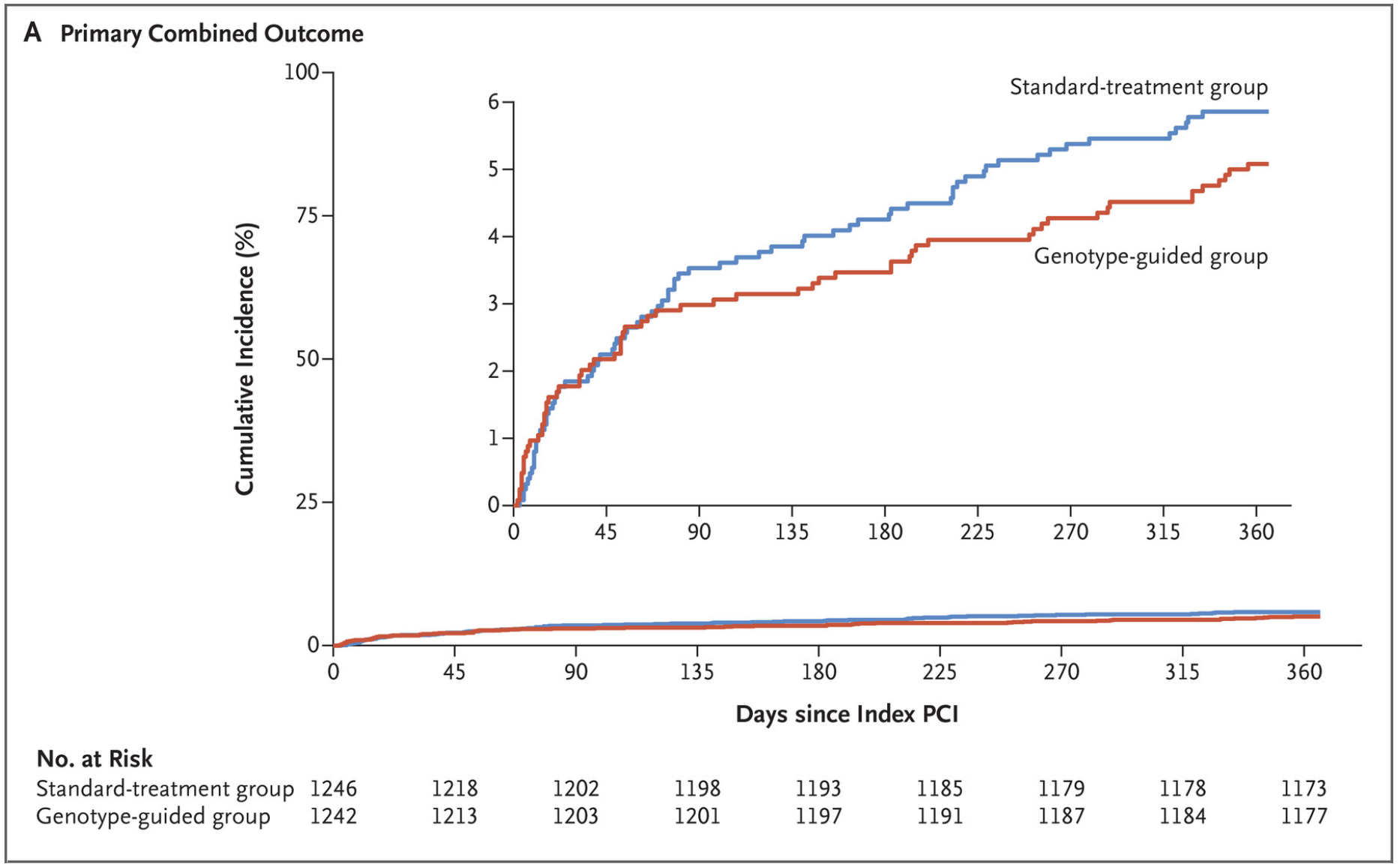
CYP2C19

Metabolizer Phenotype	Genotype	Frequency
Ultrarapid	*17/*17	1-5%
Normal	2 normal function alleles *1/*1	35-50%
Intermediate	1 LOF allele *1/*2, *2/*17	20-30%
Poor	2 LOF alleles *2/*2, *3/*3	1-5%



Klein. Arteriosclerosis, Thrombosis, and Vascular Biology. Volume: 39, Issue: 4, Pages: 647-652, DOI: (10.1161/ATVBAHA.118.311963)

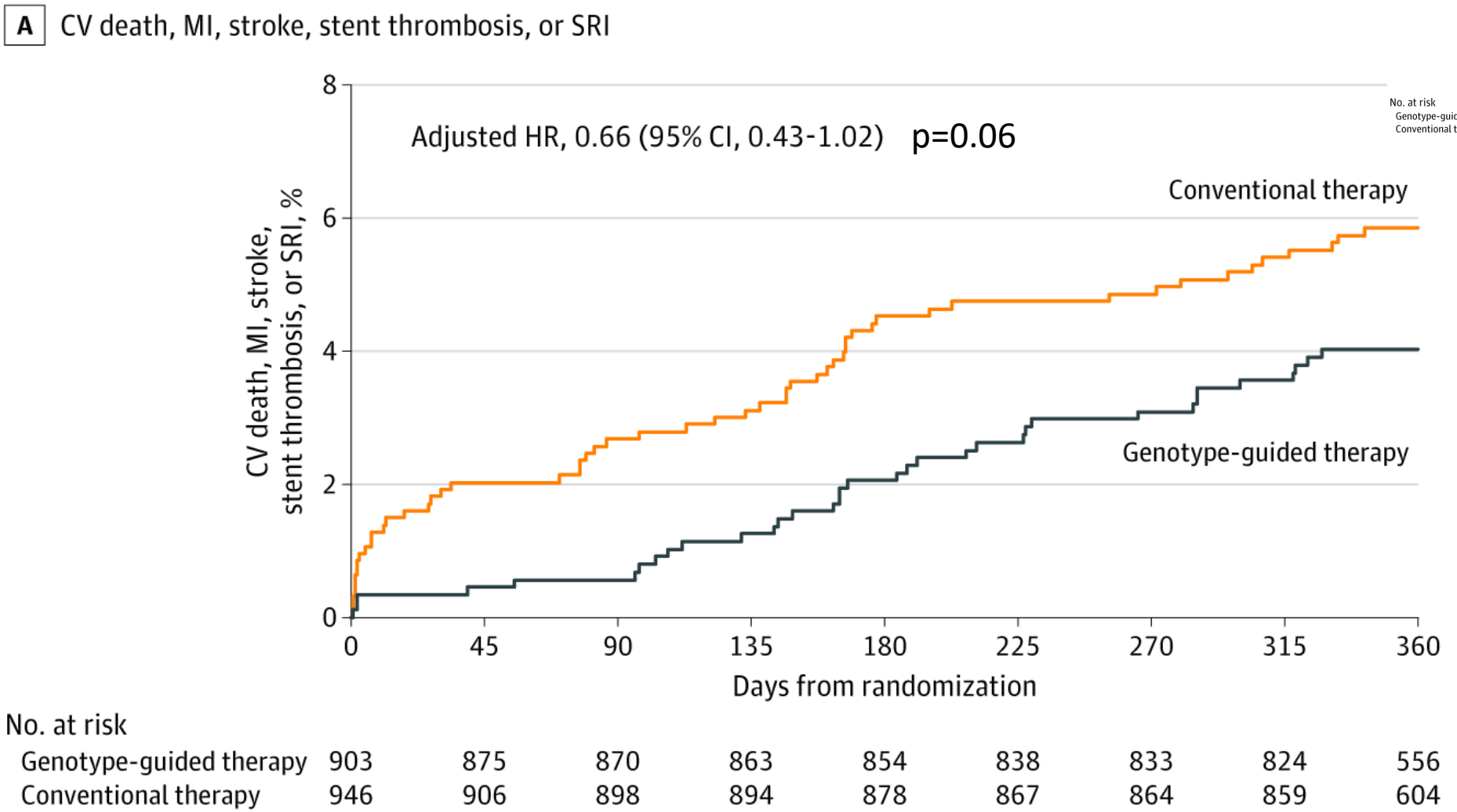
POPular Genetics Trial (n= 2.488)

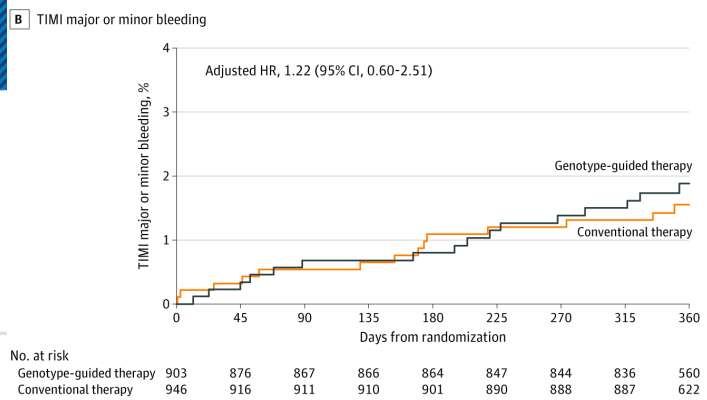


Conclusion:
CYP2C19 genotype–guided strategy for selection of oral P2Y12 inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding.

DM Claassens et al. N Engl J Med 2019;381:1621-1631.

TAILOR-PCI Randomized Clinical Trial (n=5,302)





JAMA. 2020;324(8):761-771. doi:10.1001/jama.2020.12443

Implementatiestudie met point-of-care test

- Leids Academisch Netwerk Apothekers
- 150 patienten prasugrel of ticagrelor
- Feasibility point of care test en interventie in de apotheek

Vraag: Wat is géén goed advies:

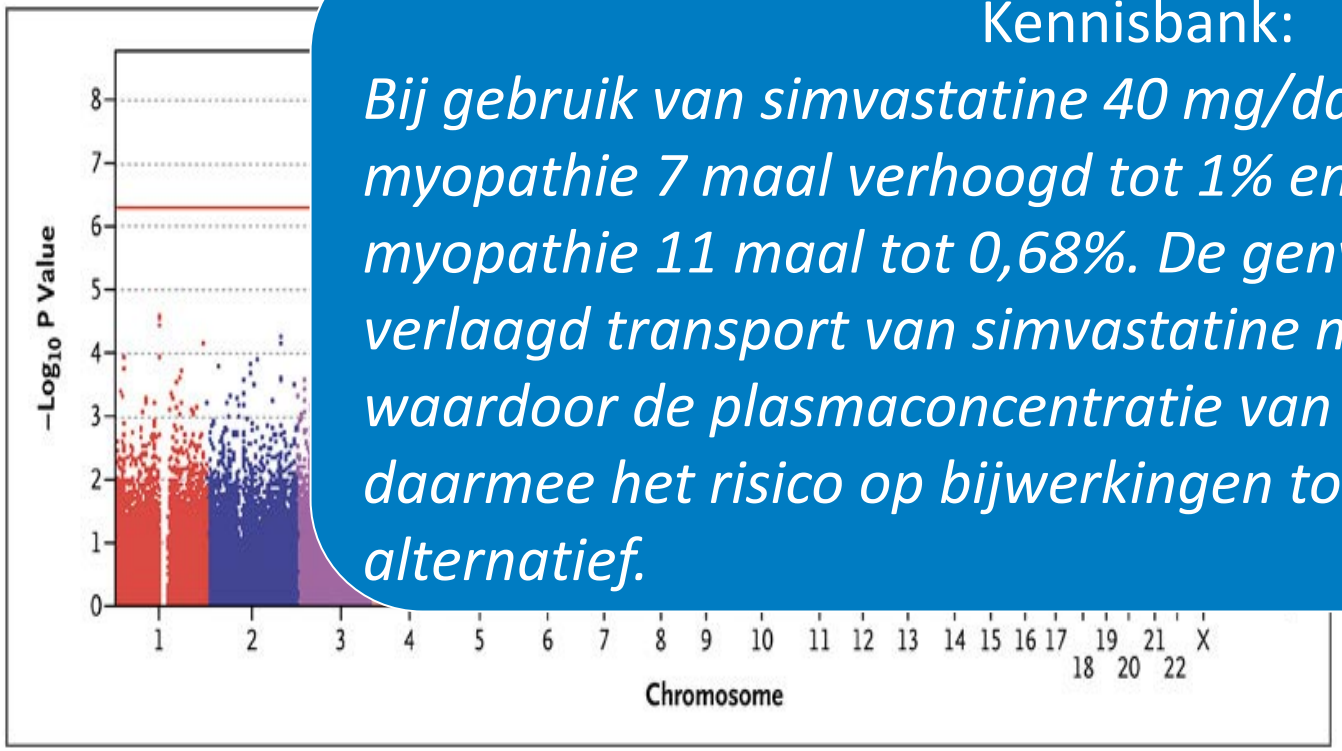
Een patient wordt behandeld met 40 mg simvastatine en ontwikkelt spierpijn.

Een test op SLCO1B1 toont het SLCO1B1 521CC genotype aan

a. Switch naar atorvastatine
b. Switch naar rosuvastatatine
c. Switch naar fluvastatine
d. Dosisverlaging naar 20 mg

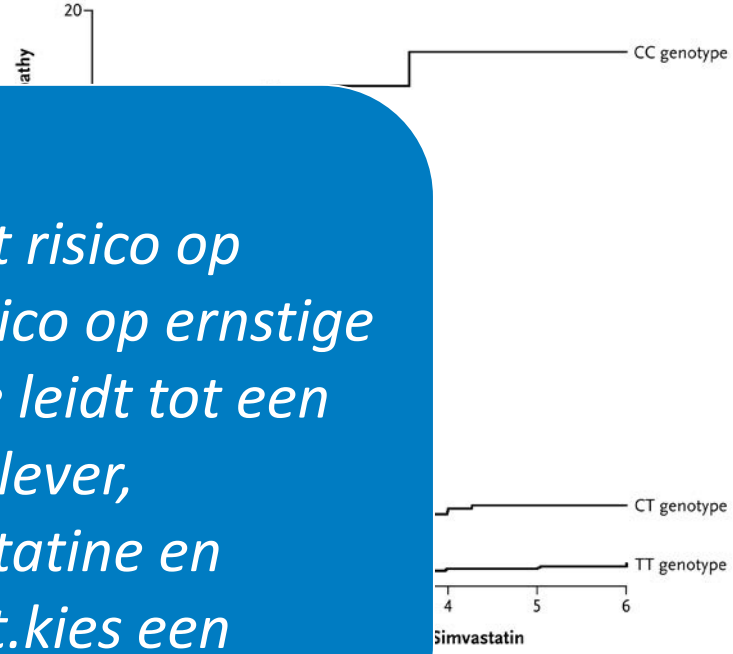
Simvastatin – SLCO1B1

- 85 “myopathy” cases (Caucasians)
- 90 controls matched for gender, age, GFR, amiodarone



Kennisbank:

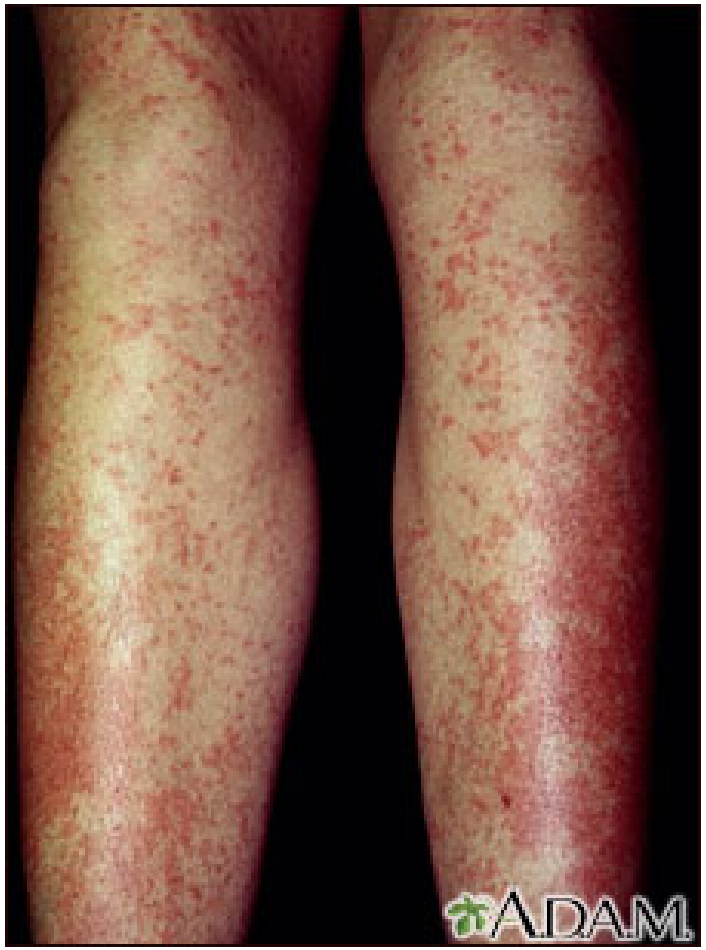
Bij gebruik van simvastatine 40 mg/dag is het risico op myopathie 7 maal verhoogd tot 1% en het risico op ernstige myopathie 11 maal tot 0,68%. De genvariatie leidt tot een verlaagd transport van simvastatine naar de lever, waardoor de plasmaconcentratie van simvastatine en daarmee het risico op bijwerkingen toeneemt.kies een alternatief.



- C-allel OR: 4.3
- CC OR: 17.4
- 60% myopathy-cases explained
- *SLCO1B1* encodes OATP1B1, liver uptake of statins

SEARCH, N Engl J Med 2008;359(8):789

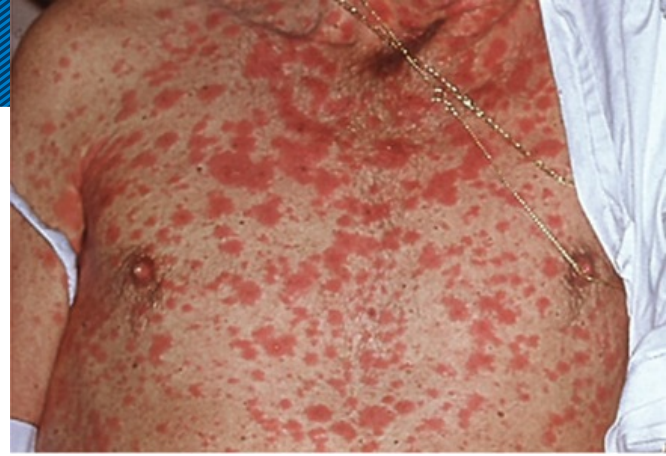
Vraag: huiduitslag 1 week na starten van carbamazepine



Welk testresultaat past hier bij?

a. HLA-A*3101
b. HLAB* 1502
c. HLA-B*1511
d. Kan alle drie, waarschijnlijkheid hangt af van achtergrond patiënt

Abacavir hypersensitivity, PREDICT-1



- 1,956 patients
- 1:1 randomized: screening *vs* no screening
- Prevalence HLA-B *5701= 5,6% (109 patients)
- *"Our results show that a PGx test can be used to prevent a specific toxic effect of a drug"*

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

NPV= 100%; PVV= 48%

SPC "Voor het starten van de behandeling met abacavir zou elke hiv-patiënt gescreend moeten worden op het drager zijn van het HLA-B*5701-allel, ongeacht het ras (zie rubriek 4.4). Abacavir moet niet worden gebruikt bij patiënten die drager zijn van het HLA-B*5701-allel.

Mallal, N Engl J Med 2008;358(6):568

Review: Bruikbaarheid HLA testen voor het voorspellen van geneesmiddelovergevoeligheid

Geneesmiddel	HLA variant	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	NNG	Incidence HSR (%)
Abacavir	HLA-B*5701	31-90 (clin.) 100 (im. conf.)	90-100	50	95-100 → 100	14-90 (Cauc) 200-400 (Black)	0.25-9.0
Allopurinol	HLA-B*5801	88-100	82-94	1-3	99.99-100	476-540	0.21
Flucloxacilline	HLA-B*5701	84.3	93.8	0.12	99.99	13.953	0.0085
Carbamazepine	HLA-B*1511	7-43	84-96	0.1-2.6	99.98	933-5.600	0.005-0.25
	HLA-A*3101	0-83	86-97	0-1.6	99.95-100	480-133.333	0.005-0.25
	HLA-B*1502	67-100	73-100	0.14-7.8	99.2-100	400-700 (Asians)	0.005-0.25
Oxcarbazepine	HLA-B*1502	70	88-92	0.7	99.97-100	1.211-1.715	0.0826
Fenytoine	HLA-B*1502	13-62	78-95	0.2-1.4	99.9	417-3.250	0.069-0.24
Lamotrigine	HLA-B*1502	0-33	81-100	0.1-1.4	99.9	3.000-4.400	0.1

Front Pharmacol. 2020 Sep 23;11:567048.

Nederlandse farmacogenetica werkgroep (n=103)

CYP2D6

- Amitriptyline
- Aripiprazol
- Atomoxetine
- Carvedilol
- Citalopram
- Clomipramine
- Clozapine
- Codeine
- Doxepine
- Flecainide
- Flupentixol
- Haloperidol
- Imipramine
- Metoprolol
- Mirtazapine
- Nortriptyline
- Olanzapine
- Oxycodone
- Paroxetine
- Propafenon
- Risperidone
- Tamoxifen
- Tramadol
- Venlafaxine
- Zuclopenthixol

DPYD

- Capecitabine / 5-FU

CYP2C9

- Acenocoumarol
- Fenprocoumon
- Phenytoin
- Glibenclamide
- Glicazide
- Glimepride
- Tolbutamide

UGT1A1

- Irinotecan

VKORC1

- Acenocoumarol
- Fenprocoumon

CYP3A5

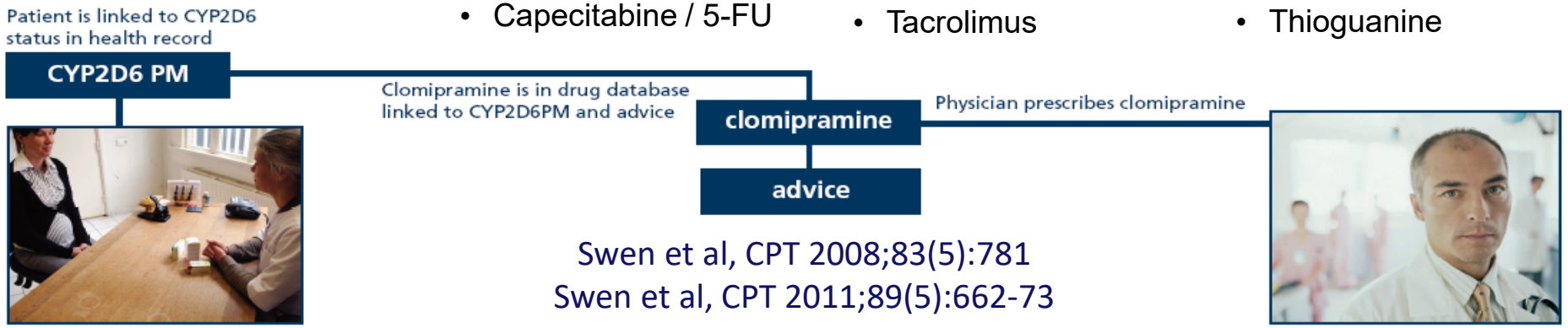
- Tacrolimus

CYP2C19

- Citalopram
- Clopidogrel
- Imipramine
- Lansoprazol
- Moclobemide
- (es)Omeprazol
- Pantoprazol
- Rabeprazol
- Sertraline
- Voriconazol

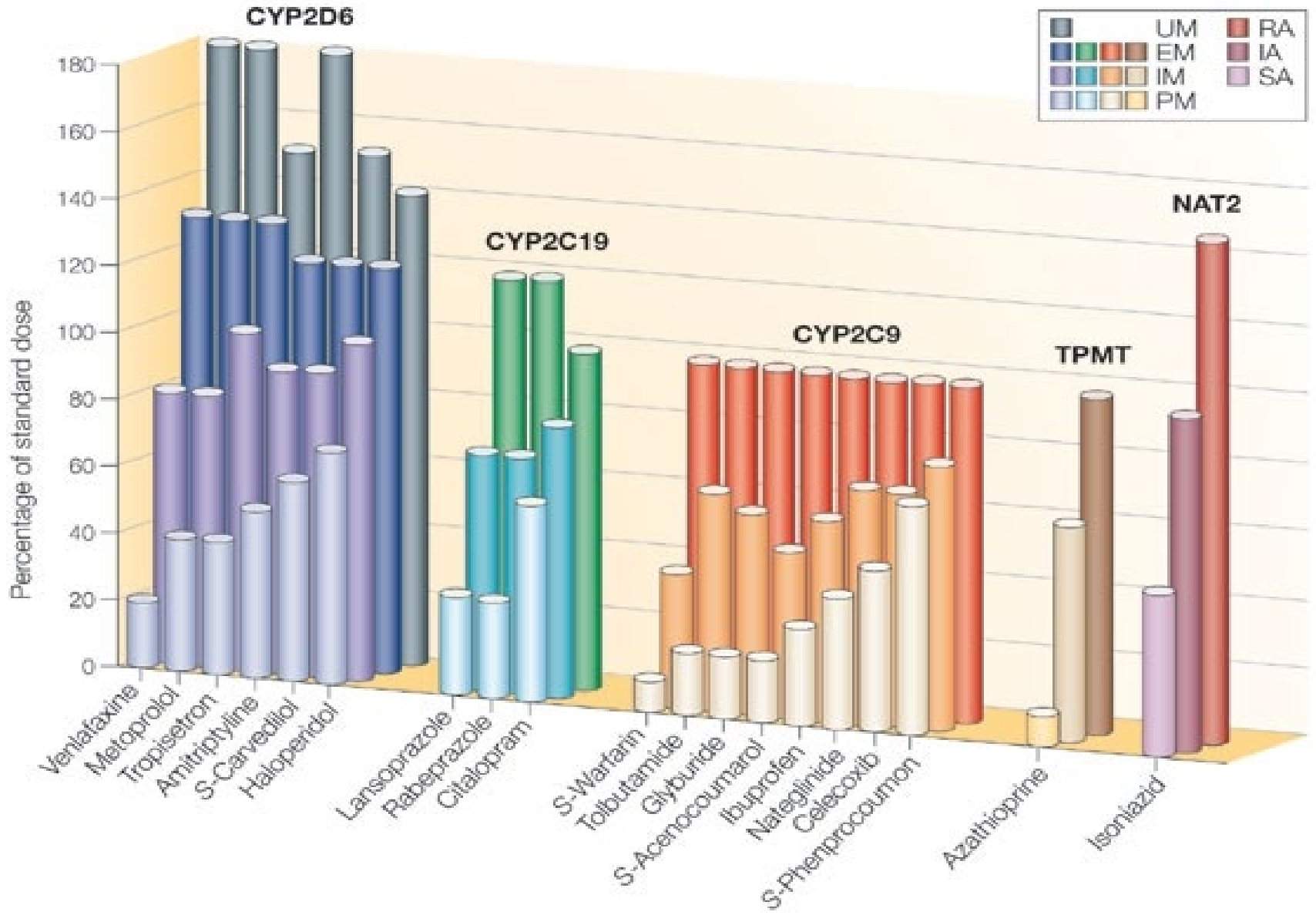
TPMT

- Azathioprine
- Mercaptopurine
- Thioguanine



Swen et al, CPT 2008;83(5):781
Swen et al, CPT 2011;89(5):662-73

Farmacokinetiek: dosisaanpassingen



DPWG advies: wanneer genotyperen?

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	Possible Score	Given Score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• 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 grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• 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 to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	++
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	8+
Corresponding Clinical Implication Score:		Essential

Table 1: Definitions of the available Clinical Implication Scores

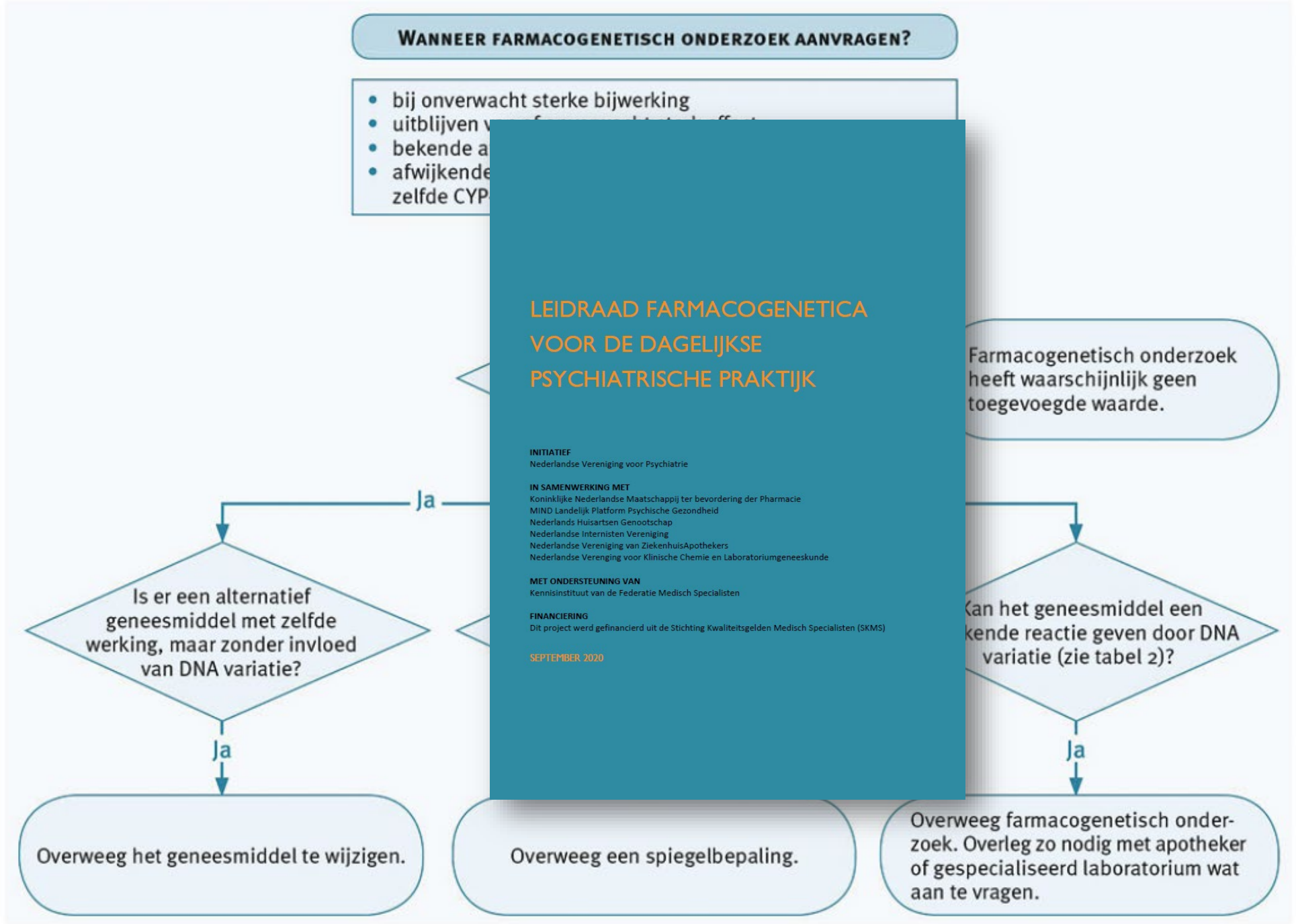
Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. 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 +

DPWG advies: wanneer genotyperen?

Genotypering	Advies	Geneesmiddel
Essentieel	Genotypeer voor start	5-FU, capecitabine, tegafur, irinotecan, clopidogrel (PTCA, beroerte en TIA), azathioprine, mercaptopurine, tioguanine, abacavir
Gunstig	Genotypeer voor (of direct na) start	Coumarines, codeine, fenytoine, lamotrigine, oxcarbazepine (aziaten)
Mogelijk gunstig	Overweeg genotypering voor start bij individuele patienten	(es)citalopram, TCAs, paroxetine, pimozide, sertraline, brexpiprazol, PPIs, tramadol, doxepine, cutaan 5-FU

Middelen met advies in NHG standpunt

Groep	Geneesmiddelen
Cardiale medicatie	Atorvastatine Simvastatine Clopidogrel Metoprolol
Maagzuurremmers	Lansoprazol Omeprazol Pantoprazol
Psychiatrische medicatie	Amitryptiline Clomipramine Nortriptyline Haloperidol Citalopram Paroxetine Sertraline Venlafaxine
Overige	Allopurinol Carbamazepine Flucloxacilline Tramadol


WANNEER FARMACOGENETISCH ONDERZOEK AANVRAGEN?
bij onverwacht sterke bijwerking
uitblijven v
bekende a
afwijkende
zelfde CYP
LEIDRAAD FARMACOGENETICA VOOR DE DAGELIJKSE PSYCHIATRISCHE PRAKTIJK
INITIATIEF
Nederlandse Vereniging voor Psychiatrie
IN SAMENWERKING MET
Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
MIND Landelijk Platform Psychische Gezondheid
Nederlands Huisartsen Genootschap
Nederlandse Internisten Vereniging
Nederlandse Vereniging van ZiekenhuisApothekers
Nederlandse Verenging voor Klinische Chemie en Laboratoriumgeneeskunde
MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten
FINANCIERING
Dit project werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS)
SEPTEMBER 2020
Farmacogenetisch onderzoek heeft waarschijnlijk geen toegevoegde waarde.
Ja
Is er een alternatief geneesmiddel met zelfde werking, maar zonder invloed van DNA variatie?
Ja
Overweeg het geneesmiddel te wijzigen.
Overweeg een spiegelbepaling.
Kan het geneesmiddel een kende reactie geven door DNA variatie (zie tabel 2)?
Ja
Overweeg farmacogenetisch onder-zoek. Overleg zo nodig met apotheker of gespecialiseerd laboratorium wat aan te vragen.

Vraag: heeft u in de afgelopen 6 maanden een PGx test geadviseerd?

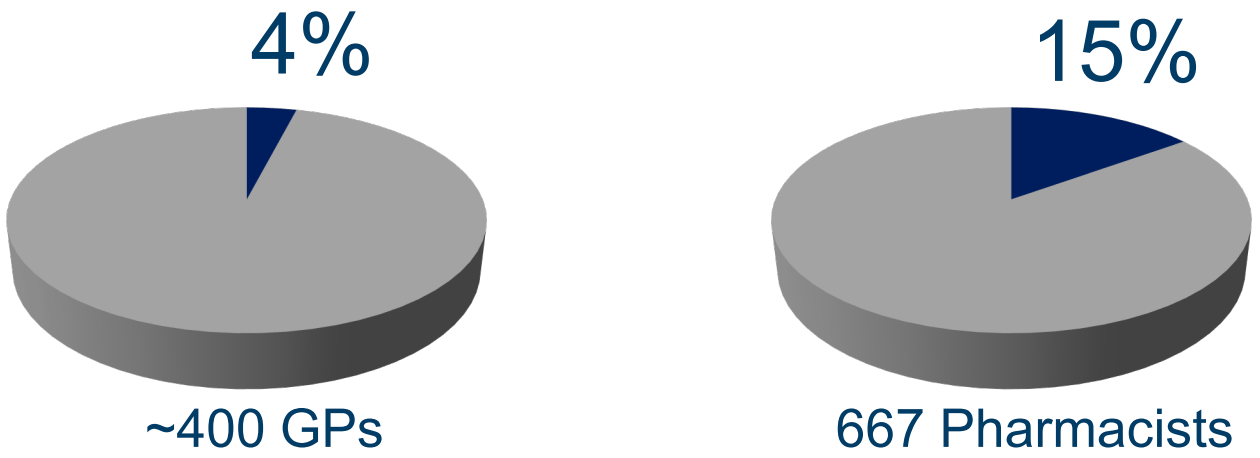
a. Ja

b. Nee

Survey Physicians and Pharmacists

- **97.6%** of physicians and **99.7%** of pharmacists agrees that genetic variations may influence drug response

- *Did you order or recommend a pharmacogenetic test in the preceding 6 months?*

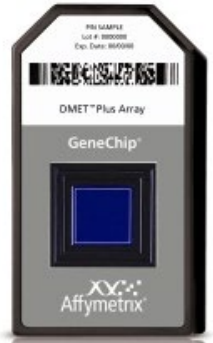


Stanek CPT 2012 450–458; Bank Pharmacogenomics 2017 215-225

Implementing PGx in Primary Care Project (IP^3)

- 200 patients
  - Primary care, vicinity Leiden
  - Experience PGx in own practice

- Focus on primary care drug with recommendation
  - *CYP2D6*: TCAs, atomoxetine, venlafaxine
  - *CYP2C9*: acenocoumarol, phenprocoumon
  - *CYP2C19*: (es)citalopram, imipramine,
  - *SLCO1B1*: simvastatine, atorvastatine

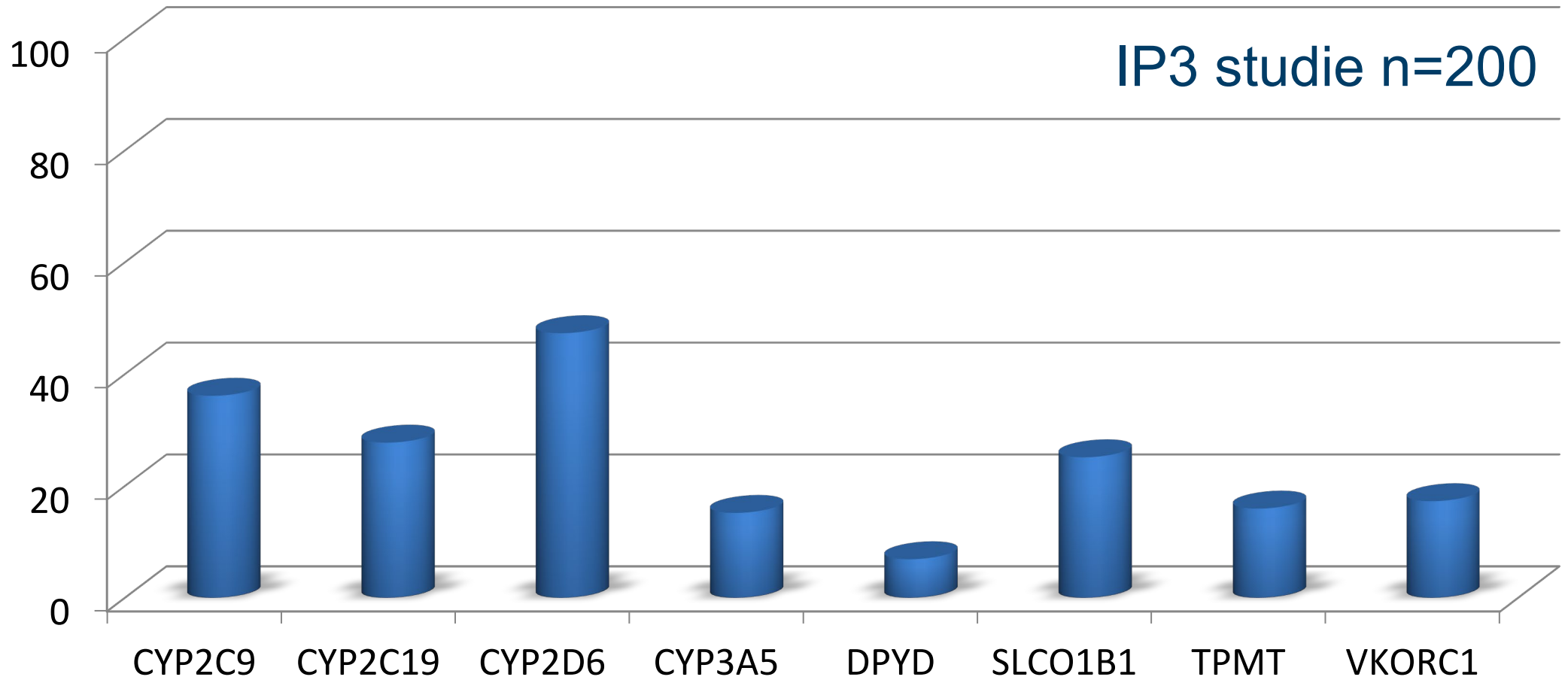


- Genotyping

  Panel of 8 genes: *CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, SLCO1B1, TPMT, VKORC1*

Zorg en Zekerheid Affymetrix® KNMP

Farmacogenetische variatie komt veel voor



~95% van de patiënten heeft ten minste 1 ***actionable*** genotype, 10% heeft er ≥4

Bank Eur J Hum Genet. 2019

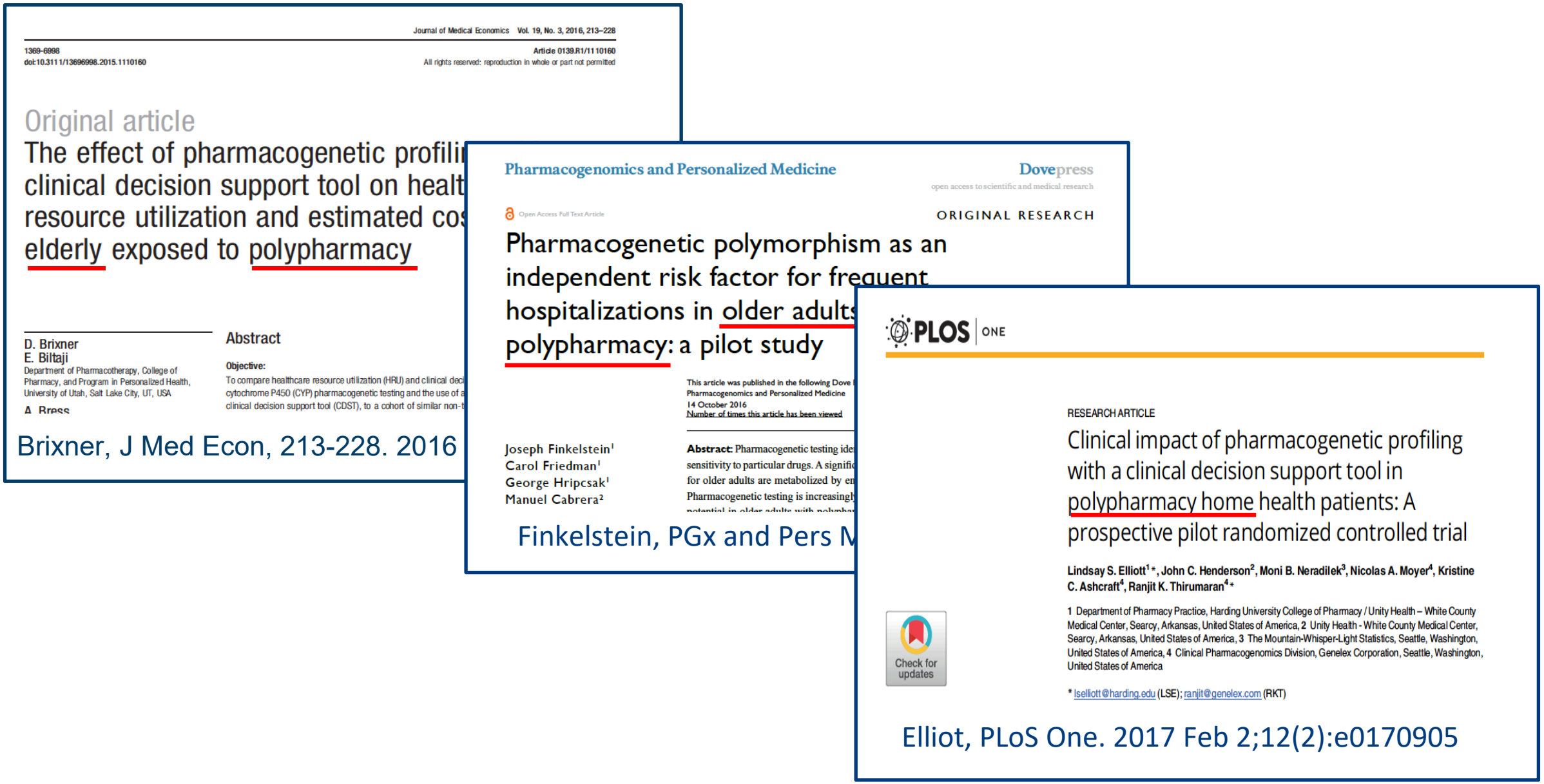
Het gaat om veel gebruikte medicatie

N = 3.221.696 (Unique pat.)	First Rx* (4.138.909)	Gene	Phenotype	Actionable#	Dose- adj. / switch**
PPI's	1.026.441	CYP2C19	UM	41.058	871
Coumarines	62.558	VKORC1	TT	10.634	4
Clopidogrel	98.709	CYP2C19	PM + IM	24.677	24.677
Statines	305.999	SLCO-1B1	Low act.		49.024
Thiopurines	11.424	TPMT	IM	1.828	1.828
Tramadol	357.389	CYP2	UM	167.972	8.934
Codeine	519.728		IM + PM + UM	244.272	12.993
TCA's		CYP2D6	IM + PM + UM	60.068	60.068
Venlafaxine	26.603	CYP2D6	IM + PM	12.503	11.838
Flecainide	13.605	CYP2D6	IM + PM + UM	6.394	680
Paroxetine	27.018	CYP2D6	IM + PM + UM	12.698	675
Tamoxifen	10.807	CYP2D6	IM + PM	4.809	4.809
….	**based on prevalence from IP3	# based on DPWG guidelines			

~192.000 1st prescriptions require dose adjustment or switch

Bank BMC Med 2019

Wat is het bewijs voor een PGx - panel?



Journal of Medical Economics Vol. 19, No. 3, 2016, 213–228

1369-6998
doi:10.3111/13696998.2015.1110160

Article 0139.R1/1110160

Original article

The effect of pharmacogenetic profili
clinical decision support tool on healt
resource utilization and estimated cos
elderly exposed to polypharmacy

D. Brixner
E. Biltaji
Department of Pharmacotherapy, College of Pharmacy, and Program in Personalized Health, University of Utah, Salt Lake City, UT, USA
A. Bress

Abstract

Objective:
To compare healthcare resource utilization (HRU) and clinical deci
cytochrome P450 (CYP) pharmacogenetic testing and the use of a
clinical decision support tool (CDST), to a cohort of similar non-t

Brixner, J Med Econ, 213-228. 2016

Pharmacogenomics and Personalized Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Pharmacogenetic polymorphism as an independent risk factor for frequent hospitalizations in older adults
polypharmacy: a pilot study

This article was published in the following Dove
Pharmacogenomics and Personalized Medicine
14 October 2016
Number of times this article has been viewed

Joseph Finkelstein[1]
Carol Friedman[1]
George Hripcsak[1]
Manuel Cabrera[2]

Abstract: Pharmacogenetic testing ide
sensitivity to particular drugs. A signifi
for older adults are metabolized by en
Pharmacogenetic testing is increasingl

Finkelstein, PGx and Pers M

PLOS ONE

RESEARCH ARTICLE

Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial

Lindsay S. Elliott[1]*, John C. Henderson[2], Moni B. Neradilek[3], Nicolas A. Moyer[4], Kristine C. Ashcraft[4], Ranjit K. Thirumaran[4]*

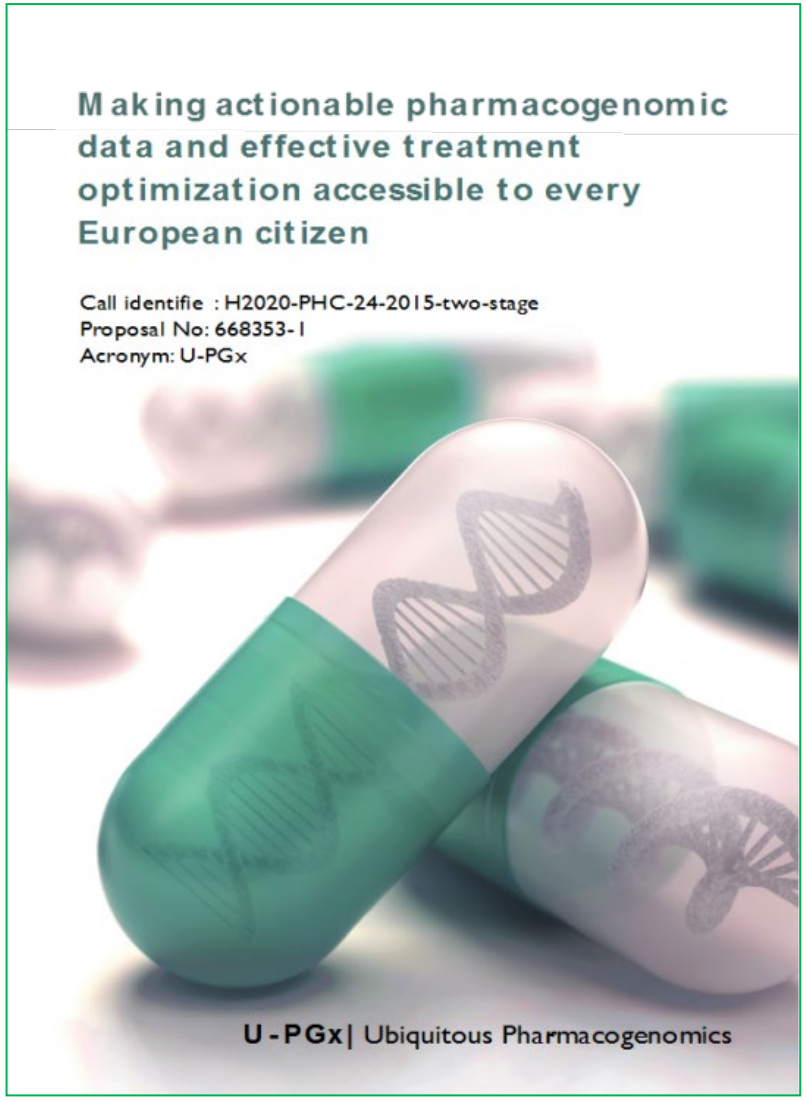
1 Department of Pharmacy Practice, Harding University College of Pharmacy / Unity Health – White County Medical Center, Searcy, Arkansas, United States of America, 2 Unity Health - White County Medical Center, Searcy, Arkansas, United States of America, 3 The Mountain-Whisper-Light Statistics, Seattle, Washington, United States of America, 4 Clinical Pharmacogenomics Division, Genelex Corporation, Seattle, Washington, United States of America

* lselliott@harding.edu (LSE); ranjit@genelex.com (RKT)

Check for updates

Elliot, PLoS One. 2017 Feb 2;12(2):e0170905

Ubiquitous Pharmacogenomics (www.upgx.eu)



- **Aim:** "*Make actionable PGx data and effective treatment optimization accessible to every European citizen*"
- **Funded by EU Horizon 2020, €15 million, 10 countries**
- **PREPARE study, n= 7.000**
- **Evaluate patient outcome and cost effectiveness of a pre-emptive PGx panel test**

Van der Wouden, Clin Pharmacol Ther. 2019 866-873

U-PGx | Ubiquitous Pharmacogenomics

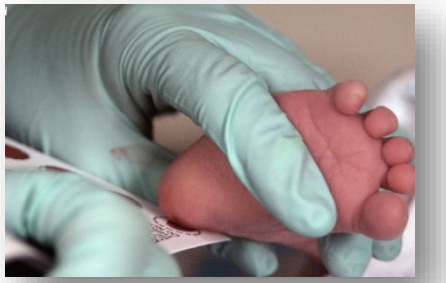
Waar staan we

Wanneer? **2021**

Reactief

Toxiciteit?

Recept?

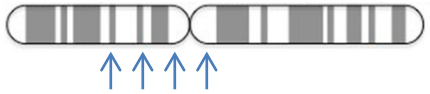


Hielprik?

Preemptive

Wat?

Single gene



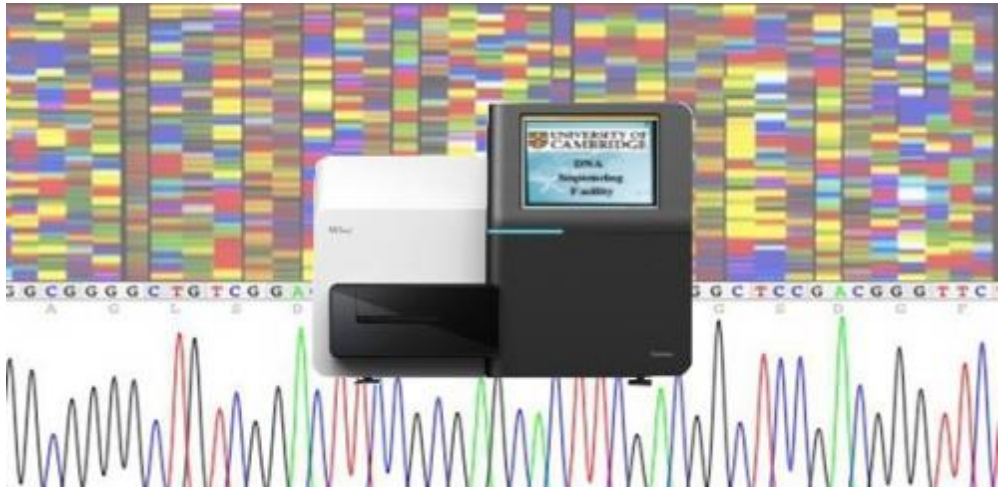
Panel

WES / WGS

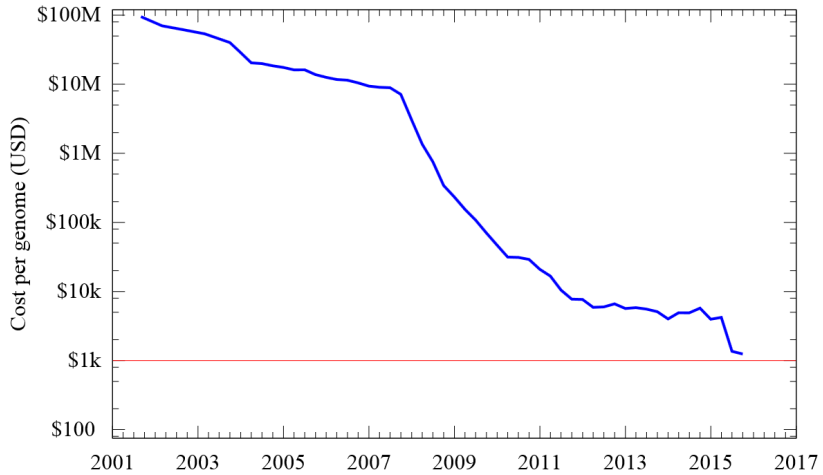
Hoe en waar een test aanvragen

- 16 geaccrediteerde labs
- http://www.pgx-net.nl/
- 4 ml EDTA bloed of speeksel
- 1 dag – 4 weken
- ~€75 per gen
- Vergoed bij ernstige bijwerkingen of onverwacht ineffectief

Netwerk Klinische Farmacogenetica Nederland PGx



Cost to sequence a human genome



For $999, Veritas Genetics Will Put Your Genome on a Smartphone App

Getting your entire genome decoded is now more affordable than ever. Will consumers buy it?

by Antonio Regalado March 4, 2016

MIT Technology Review

Price of sequencing your genome falls to $999

By Gary Robbins | 2:17 p.m. March 4, 2016

VeritasGenetics

Announced at Future of Genomic Medicine Conference
4 March 2016

UT San Diego

Common Medical Test/Scan/Med	Cost+
Head CT scan	$1,200
Abdominal CT scan	$1,420
MRI scan	$2,611
Echocardiogram	$1,300
10 "Most Important" Lab Tests*	$ 319
Crestor 1 year supply from Costco	$3,222
Xarelto 1 year supply from Costco	$4,444
3 Pharmacogenetic tests Quest^	$ 975
Whole Genome Sequence	**$ 999**

* A "package" significantly discounted via DirectLabs.com
\+ vary widely, these are average US charges from centers w/ data available on the web
^ 3 SNPs which account for 0.00000000001% of the genome

Complimentary pharmacogenetics

WES, WGS data in clinical genetics

WGS data in oncology

CPCT
Center for Personalized Cancer Treatment

Genomics england

THE PRECISION MEDICINE INITIATIVE

mijndnamedicatiepas.nl

DE VOLKSKRANT
DINSDAG 16 JANUARI 2018 25

Wetenschap

Leidse patiënten krijgen dna-paspoort

Hoe patiënten geneesmiddelen afbreken hangt mede af van genetische aanleg. Kennis van die dna-variaties kan voorkomen dat mensen problemen krijgen door een mismatch. Daarom wordt die informatie gedeeld.

Ellen de Visser
Amsterdam

den. Vorig jaar gebeurde dat bij enkele duizenden patiënten. Het LUMC gaat nu voor het eerst aan preventie doen, van hun dna tot problemen kan leiden, krijgt de arts automatisch een waarschuwing. betrokken enzym afwijkt, dan kan een medicijn in te hoge of te lage concentratie in hun bloed terechtkomen. Gevolg: Europees onderzoek, onder leiding van het LUMC, moet uitwijzen of het afstemmen van medicijnen op het dna van pa-

Boodschap

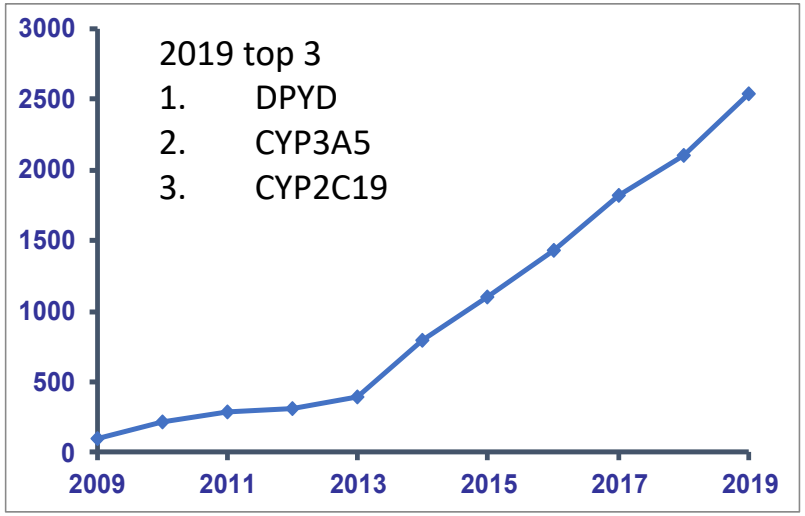
- Farmacogenetica is één van de tools om de behandeling te individualiseren
- Kijk bij problemen met medicatie welke PGx variant mogelijk relevant is en overweeg een test
- Adviezen beschikbaar van KNMP, NHG, anderen
- NL = uniek met integratie PGx adviezen bij voorschrijven en afleveren geneesmiddelen
- Er is een belangrijke rol weggelegd voor de apotheker

j.j.swen@lumc.nl
www.lumc.nl/org/kft/Farmacogenetica/

Pharmacogenetics @ LUMC

Prospective test:

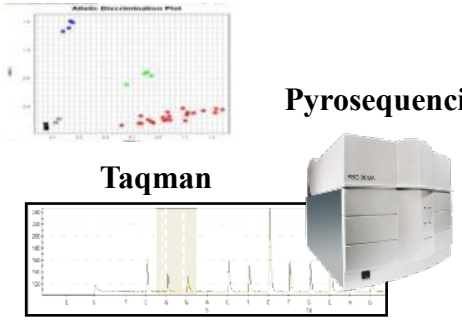
- Oncology: patients receiving CAP or 5-FU tested for *DPYD* (rs3918290, rs55886062, rs67376798, rs56038477)
- Nephrology: kidney transplant patients tested for *CYP3A5* (rs776746, rs10264272).
- Psychiatry: patients with a therapy resistant depression, referred to LUMC for ECT, tested for *CYP2D6,* and *CYP2C19*.
- Cardiology: CYP2C19
- PGx consultation service for outpatients



On request: VKORC1, CYP2C9, SLCO1B1, UGT1A1, THYMS, ABCB1, NAT1, NAT2, CYP3A4, CYP2B6 other….

Workflow example: Individualization of fluoropyrimidine therapy

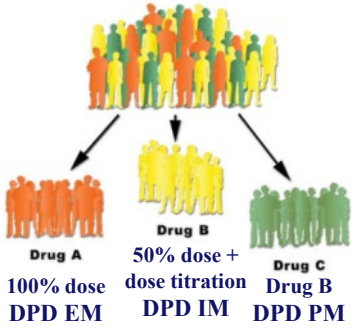
Rx fluoropyrimidine



Genotyping with 2 independent techniques

Technical approval

Interpretation and Consult: Hospital Pharmacist



Individualized Dose Recommendation