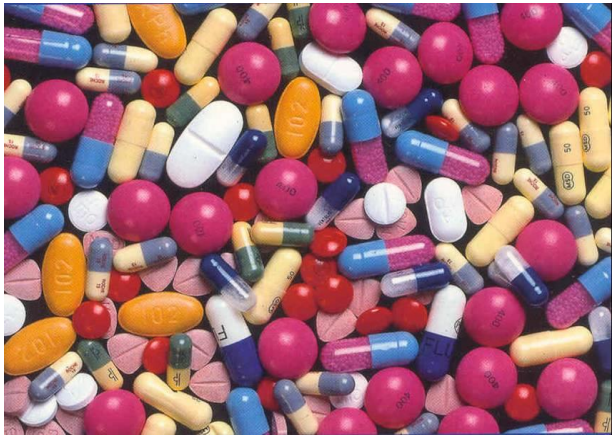
Pharmacogenetic testing: why and when?



Nederlandse Vereniging voor KLINISCHE FARMACOLOGIE en Biofarmacie

COIG 2013 – Bunnik

Teun van Gelder

Afdelingen Interne Geneeskunde en Apotheek

Erasmus Medisch Centrum, Rotterdam

Outline

1. Pharmacogenetics
2. Example 1: metformin (Glucophage)
3. Example 2: abacavir (Ziagen)
4. Example 3: tamoxifen (Nolvadex)
5. Conclusions

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Same symptoms

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Same symptoms

Same findings

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Same symptoms

Same findings

Diagnose the same disease

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Same symptoms

Same findings

Diagnose the same disease

Start same (standard dose) drug therapy

Erasmus MC

Drug therapy - Current clinical practice

Two patients

Same symptoms

Same findings

Diagnose the same disease

Start same (standard dose) drug therapy

… Find different effects!

Erasmus MC

Causes for variability in drug response

Non-compliance

Underlying disease (kidney and liver function)

Age, gender

Drug – drug interactions

Environmental factors (smoking, diet)

Erasmus MC

Causes for variability in drug response

Non-compliance

Underlying disease (kidney and liver function)

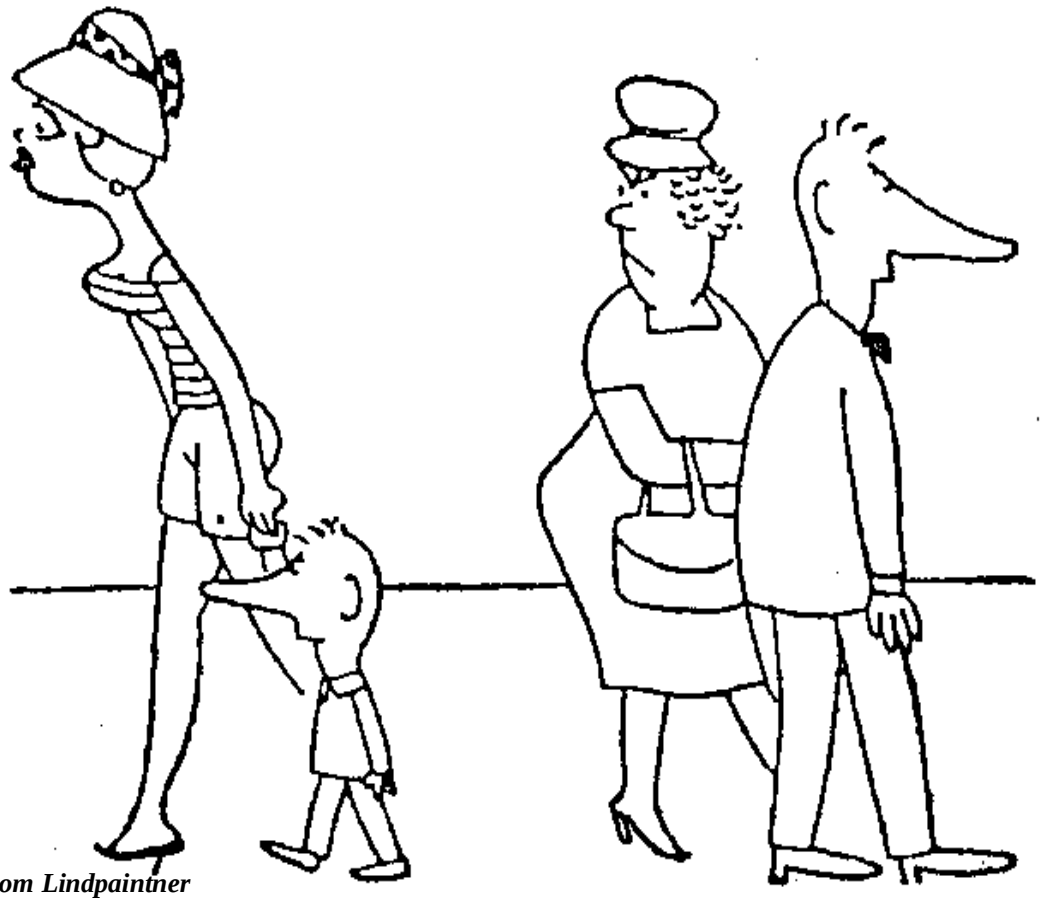
Age, gender

Drug – drug interactions

Environmental factors (smoking, diet)

Genetics (pharmacokinetics and pharmacodynamics)

Erasmus MC



Adapted from Lindpaintner

Erasmus MC

Human genome sequence variation

- Single nucleotide polymorphisms (SNPs) are the most common class of human DNA sequence variation
- SNP may alter protein function or expression
- More than 1.4×10^6 SNPs in human genome
- Average gene contains 6-8 SNPs

→ An estimated 20-95% of variability in drug disposition and effects is attributed to genetic differences between individuals

Erasmus MC

Pharmacogenetics

insight review articles

Pharmacogenetics and the practice of medicine

Allen D. Roses

Genetics Directorate, Glaxo Wellcome plc, Greenford, Middlesex UB6 0HE, UK, and Duke University Medical Center, Durham, North Carolina 27710, USA

NATURE | VOL 405 | 15 JUNE 2000 | www.nature.com

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

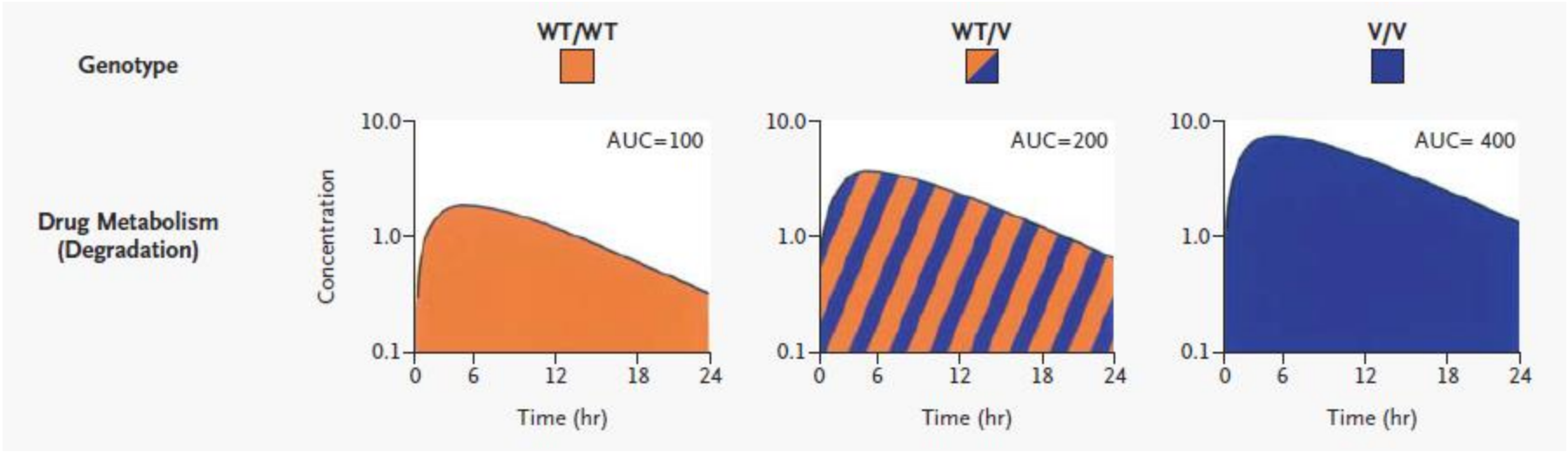
Alastair J.J. Wood, M.D., *Editor*

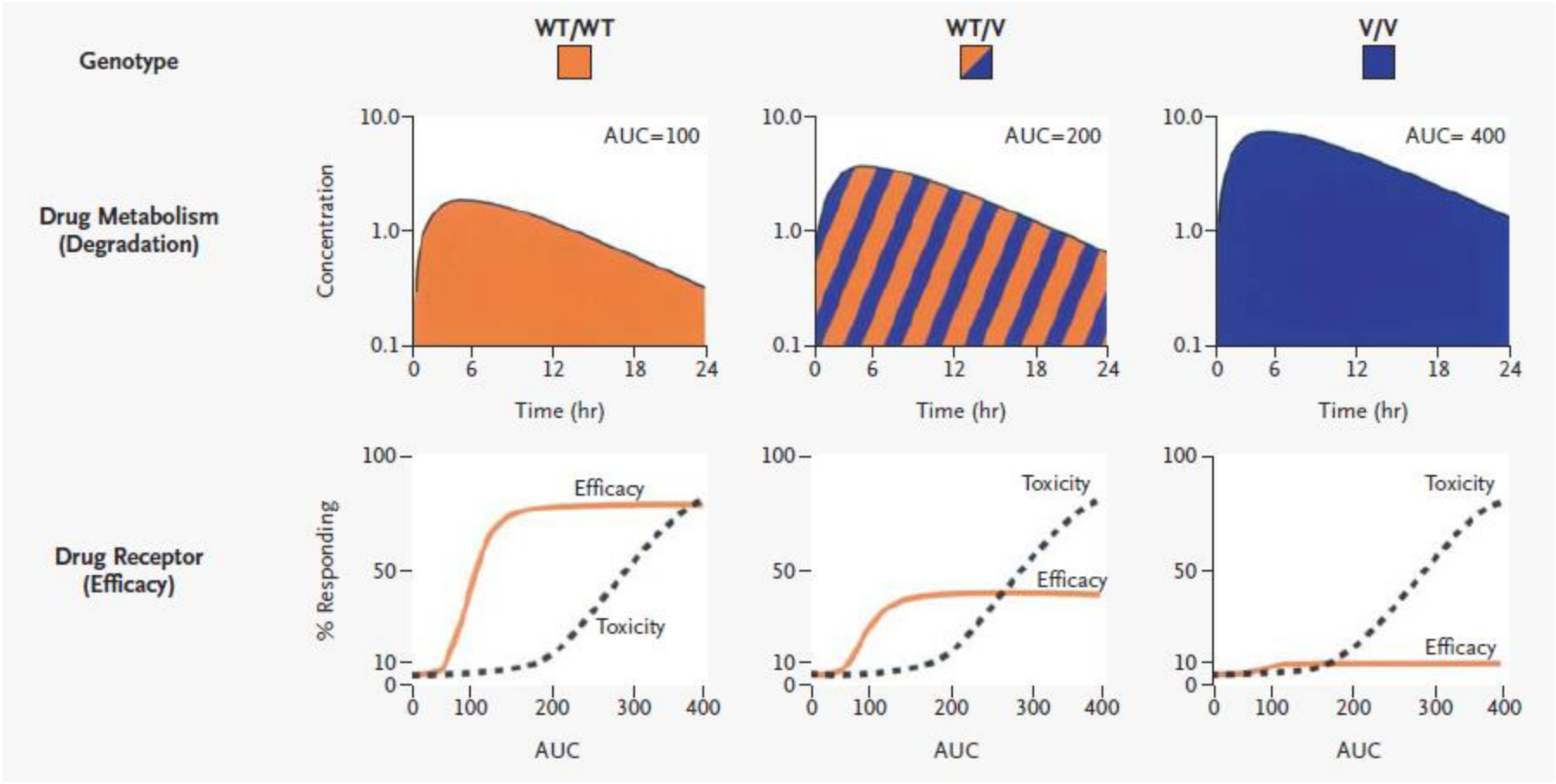
Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects

William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

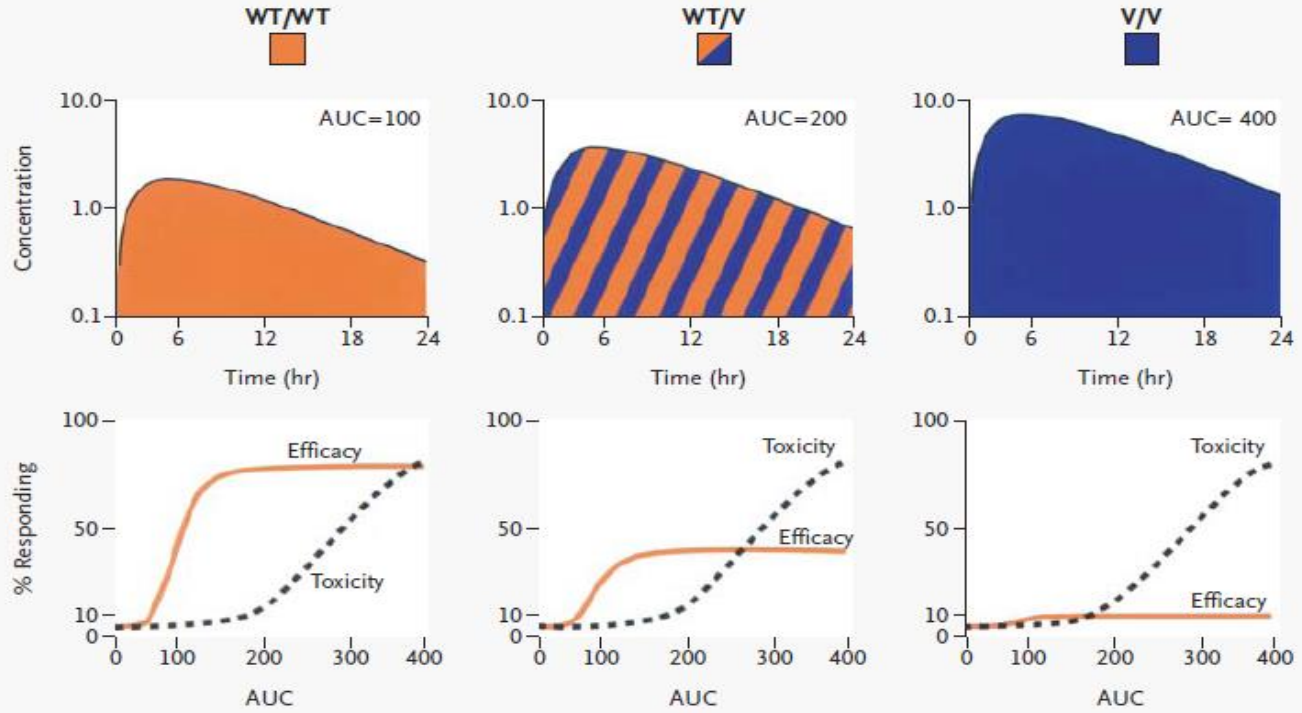
N ENGL J MED 348;6 WWW.NEJM.ORG FEBRUARY 6, 2003

Erasmus MC


Genotype
WT/WT
WT/V
V/V
Drug Metabolism (Degradation)
Concentration
10.0
1.0
0.1
AUC=100
AUC=200
AUC= 400
0
6
12
18
24
Time (hr)


Genotype
WT/WT
WT/V
V/V
Drug Metabolism (Degradation)
Concentration
AUC=100
AUC=200
AUC= 400
10.0
1.0
0.1
0
6
12
18
24
Time (hr)
Drug Receptor (Efficacy)
% Responding
100
50
10
0
Efficacy
Toxicity
0
100
200
300
400
AUC

Erasmus MC



Polygenic Drug Response

Metabolism genotype		Receptor genotype	Response: Efficacy	Response: Toxicity
■	+	■	65%	Low (5%)
■	+	◪	32%	Low
■	+	■	9%	Low
◪	+	■	79%	Moderate (15%)
◪	+	◪	40%	Moderate
◪	+	■	10%	Moderate
■	+	■	80%	High (80%)
■	+	◪	40%	High
■	+	■	10%	High

Goals of a pharmacogenetic approach

1. Help choose the most appropriate drug for each individual

2. Select an optimal dose

3. Identify those at risk from atypical adverse drug reactions

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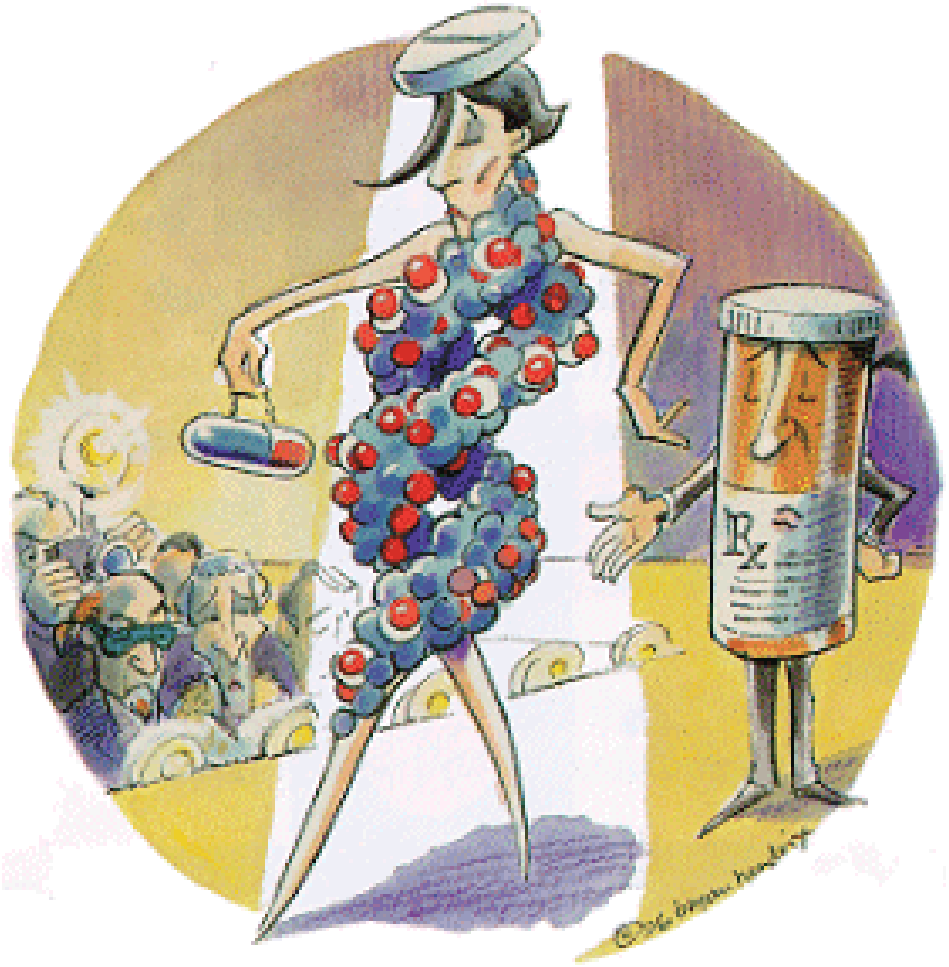
Introducing pharmacogenetics into medicine:

Revolution?

Or

Evolution?



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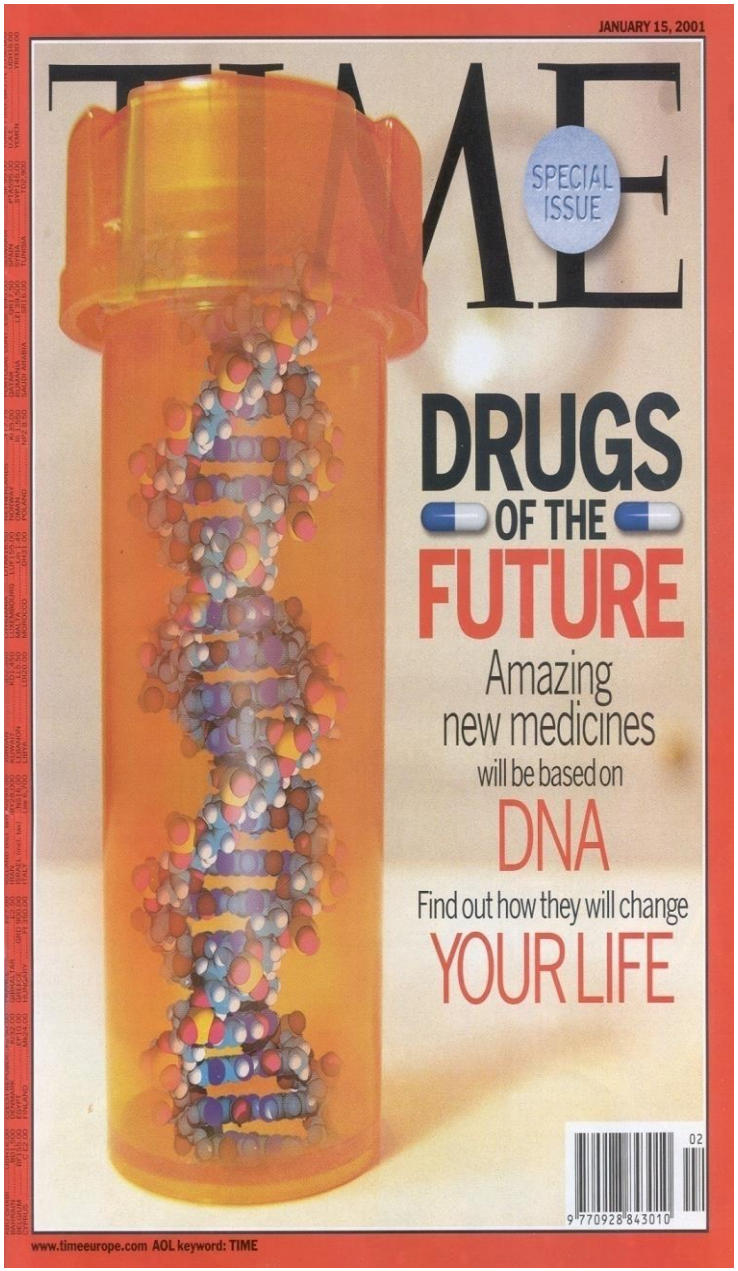
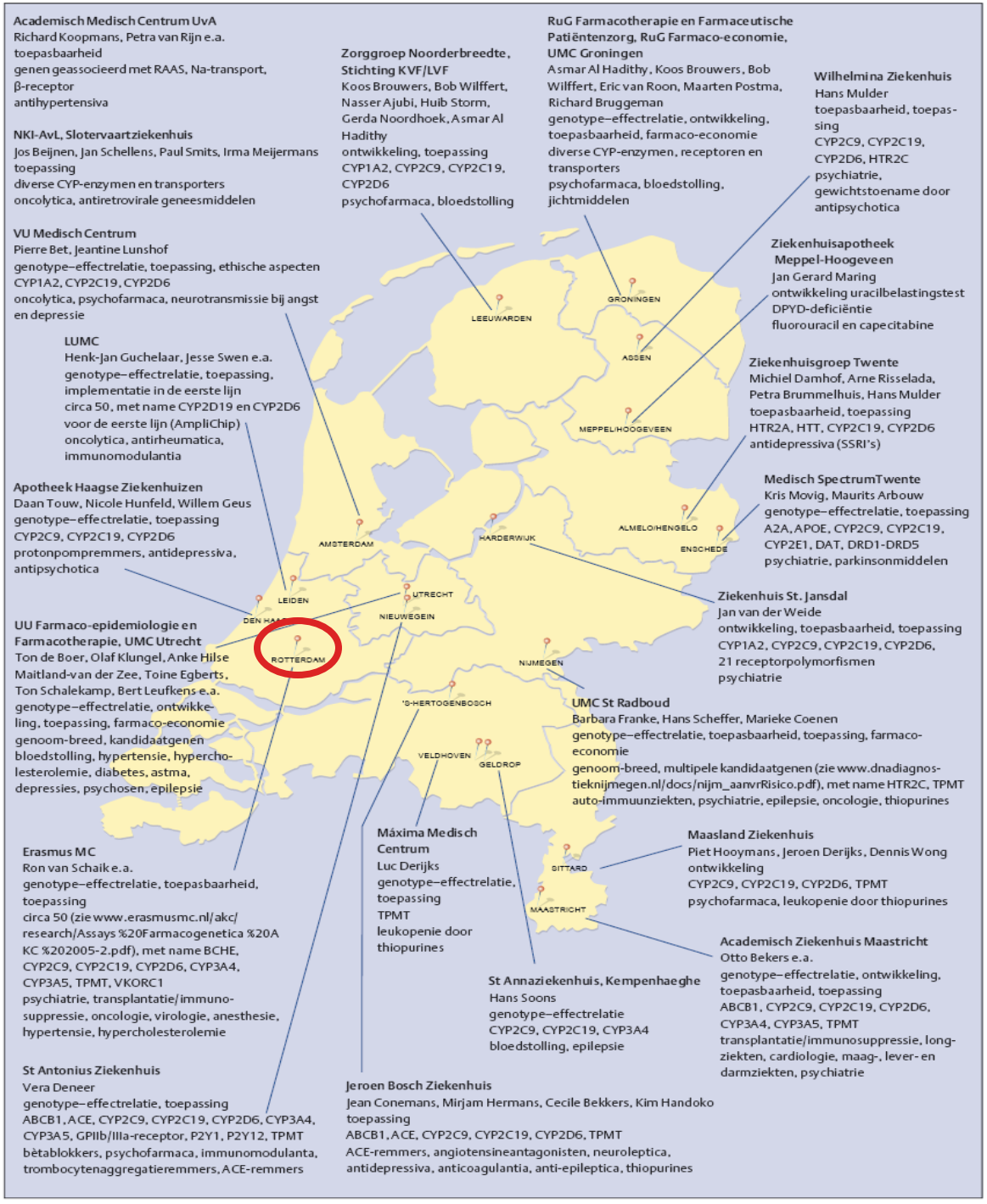

JANUARY 15, 2001
TIME
SPECIAL ISSUE
DRUGS
OF THE
FUTURE
Amazing new medicines will be based on
DNA
Find out how they will change
YOUR LIFE
02
9 770928 843010
www.timeeurope.com AOL keyword: TIME

Erasmus MC


Academisch Medisch Centrum UvA
Richard Koopmans, Petra van Rijn e.a.
toepasbaarheid
genen geassocieerd met RAAS, Na-transport, β-receptor
antihypertensiva
NKI-AvL, Slotervaartziekenhuis
Jos Beijnen, Jan Schellens, Paul Smits, Irma Meijermans
toepassing
diverse CYP-enzymen en transporters
oncolytica, antiretrovirale geneesmiddelen
VU Medisch Centrum
Pierre Bet, Jeantine Lunshof
genotype–effectrelatie, toepassing, ethische aspecten
CYP1A2, CYP2C19, CYP2D6
oncolytica, psychofarmaca, neurotransmissie bij angst en depressie
LUMC
Henk-Jan Guchelaar, Jesse Swen e.a.
genotype–effectrelatie, toepassing, implementatie in de eerste lijn
circa 50, met name CYP2D19 en CYP2D6 voor de eerste lijn (AmpliChip)
oncolytica, antirheumatica, immunomodulantia
Apotheek Haagse Ziekenhuizen
Daan Touw, Nicole Hunfeld, Willem Geus
genotype–effectrelatie, toepassing
CYP2C9, CYP2C19, CYP2D6
protonpompremmers, antidepressiva, antipsychotica
UU Farmaco-epidemiologie en Farmacotherapie, UMC Utrecht
Ton de Boer, Olaf Klungel, Anke Hilse Maitland-van der Zee, Toine Egberts, Ton Schalekamp, Bert Leufkens e.a.
genotype–effectrelatie, ontwikkeling, toepassing, farmaco-economie
genoom-breed, kandidaatgenen
bloedstolling, hypertensie, hypercholesterolemie, diabetes, astma, depressies, psychosen, epilepsie
Erasmus MC
Ron van Schaik e.a.
genotype–effectrelatie, toepasbaarheid, toepassing
circa 50 (zie www.erasmusmc.nl/akc/research/Assays%20Farmacogenetica%20AKC%202005-2.pdf), met name BCHE, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, TPMT, VKORC1
psychiatrie, transplantatie/immunosuppressie, oncologie, virologie, anesthesie, hypertensie, hypercholesterolemie
St Antonius Ziekenhuis
Vera Deneer
genotype–effectrelatie, toepassing
ABCB1, ACE, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, GPIIb/IIIa-receptor, P2Y1, P2Y12, TPMT
bètablokkers, psychofarmaca, immunomodulanta, trombocytenaggregatieremmers, ACE-remmers
Zorggroep Noorderbreedte, Stichting KVF/LVF
Koos Brouwers, Bob Wilffert, Nasser Ajubi, Huib Storm, Gerda Noordhoek, Asmar Al Hadithy
ontwikkeling, toepassing
CYP1A2, CYP2C9, CYP2C19, CYP2D6
psychofarmaca, bloedstolling
RuG Farmacotherapie en Farmaceutische Patiëntenzorg, RuG Farmaco-economie, UMC Groningen
Asmar Al Hadithy, Koos Brouwers, Bob Wilffert, Eric van Roon, Maarten Postma, Richard Bruggeman
genotype–effectrelatie, ontwikkeling, toepasbaarheid, farmaco-economie
diverse CYP-enzymen, receptoren en transporters
psychofarmaca, bloedstolling, jichtmiddelen
Wilhelmina Ziekenhuis
Hans Mulder
toepasbaarheid, toepassing
CYP2C9, CYP2C19, CYP2D6, HTR2C
psychiatrie, gewichtstoename door antipsychotica
Ziekenhuisapotheek Meppel-Hoogeveen
Jan Gerard Maring
ontwikkeling uracilbelastingstest DPYD-deficiëntie
fluorouracil en capecitabine
Ziekenhuisgroep Twente
Michiel Damhof, Arne Risselada, Petra Brummelhuis, Hans Mulder
toepasbaarheid, toepassing
HTR2A, HTT, CYP2C19, CYP2D6
antidepressiva (SSRI's)
Medisch SpectrumTwente
Kris Movig, Maurits Arbouw
genotype–effectrelatie, toepassing
A2A, APOE, CYP2C9, CYP2C19, CYP2E1, DAT, DRD1-DRD5
psychiatrie, parkinsonmiddelen
Ziekenhuis St. Jansdal
Jan van der Weide
ontwikkeling, toepasbaarheid, toepassing
CYP1A2, CYP2C9, CYP2C19, CYP2D6, 21 receptorpolymorfismen
psychiatrie
UMC St Radboud
Barbara Franke, Hans Scheffer, Marieke Coenen
genotype–effectrelatie, toepasbaarheid, toepassing, farmaco-economie
genoom-breed, multipele kandidaatgenen (zie www.dnadiagnostiek.nijmegen.nl/docs/nijm_aanvrRisico.pdf), met name HTR2C, TPMT
auto-immuunziekten, psychiatrie, epilepsie, oncologie, thiopurines
Máxima Medisch Centrum
Luc Derijks
genotype–effectrelatie, toepassing
TPMT
leukopenie door thiopurines
Maasland Ziekenhuis
Piet Hooymans, Jeroen Derijks, Dennis Wong
ontwikkeling
CYP2C9, CYP2C19, CYP2D6, TPMT
psychofarmaca, leukopenie door thiopurines
Academisch Ziekenhuis Maastricht
Otto Bekers e.a.
genotype–effectrelatie, ontwikkeling, toepasbaarheid, toepassing
ABCB1, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, TPMT
transplantatie/immunosuppressie, longziekten, cardiologie, maag-, lever- en darmziekten, psychiatrie
St Annaziekenhuis, Kempenhaeghe
Hans Soons
genotype–effectrelatie
CYP2C9, CYP2C19, CYP3A4
bloedstolling, epilepsie
Jeroen Bosch Ziekenhuis
Jean Conemans, Mirjam Hermans, Cecile Bekkers, Kim Handoko
toepassing
ABCB1, ACE, CYP2C9, CYP2C19, CYP2D6, TPMT
ACE-remmers, angiotensineantagonisten, neuroleptica, antidepressiva, anticoagulantia, anti-epileptica, thiopurines
LEEUWARDEN
GRONINGEN
ASSEN
MEPPEL/HOOGEVEEN
ALMELO/HENGELO
ENSCHEDE
AMSTERDAM
HARDERWIJK
LEIDEN
UTRECHT
NIEUWEGEIN
ROTTERDAM
NIJMEGEN
'S-HERTOGENBOSCH
VELDHOVEN
GELDROP
SITTARD
MAASTRICHT

Erasmus MC

Questionaire for the audience

For routine patient care I have requested genotyping of a patient prior to initiating drug therapy:

A. Never

B. Once or twice

C. A few times per year

D. Regularly

Questionaire for the audience

For routine patient care I have requested genotyping of a patient after to initiating drug therapy (adverse event, non-responsiveness):

A. Never

B. Once or twice

C. A few times per year

D. Regularly

Erasmus MC

Erasmus MC Rotterdam

Pharmacogenetic testing :

1. Dr R van Schaik, clinical chemist, Head Pharmacogenetics Core Lab (AKC)
2. Dr B Koch, hospital pharmacist, Head Pharmacy Lab
3. Dr T van Gelder, internist – clinical pharmacologist

To be answered:

- Is there a good rationale for testing?
  - Evidence for testing prior to R/? Correct gene?
  - If adverse event: interactions?
- Interpretation of the result of testing

Erasmus MC

www.erasmusmc.nl/farmacogenetica

Reason for genotyping request:

Drug
Dose
Conc.
Co-med.

- ☐ Screening prior to therapy
- ☐ High blood levels
- ☐ Low blood levels
- ☐ No effect
- ☐ Side effects

CONSULT

Dr. van Schaik (klinisch chemicus)
email: r.vanschaik@erasmusmc.nl
(+31) 10 7033119

Prof. van Gelder
(internist-klinisch farmacoloog)
email: t.vangelder@erasmusmc.nl
(+31) 10 7033202

☐ Cito Fax

Gene to be tested:

- ☐ CYP1A2
- ☐ CYP2B6
- ☐ CYP2C8
- ☐ CYP2C9
- ☐ CYP2C19
- ☐ CYP2D6 - (33 variants, AmpliChip)
- ☐ CYP2D6 - (14 variants, DNA chip)
- ☐ CYP2E1
- ☐ CYP3A4
- ☐ CYP3A5
- ☐ ABCB1 (MDR-1)
- ☐ DPYD
- ☐ HLA-B*1502
- ☐ HLA-A*3301
- ☐ HLA-B*5701
- ☐ IL-28B
- ☐ SLCO1B1
- ☐ TPMT
- ☐ UGT1A1
- ☐ Pseudocholinesterase (BChE) (4)

☐ Unknown to me: please advice.

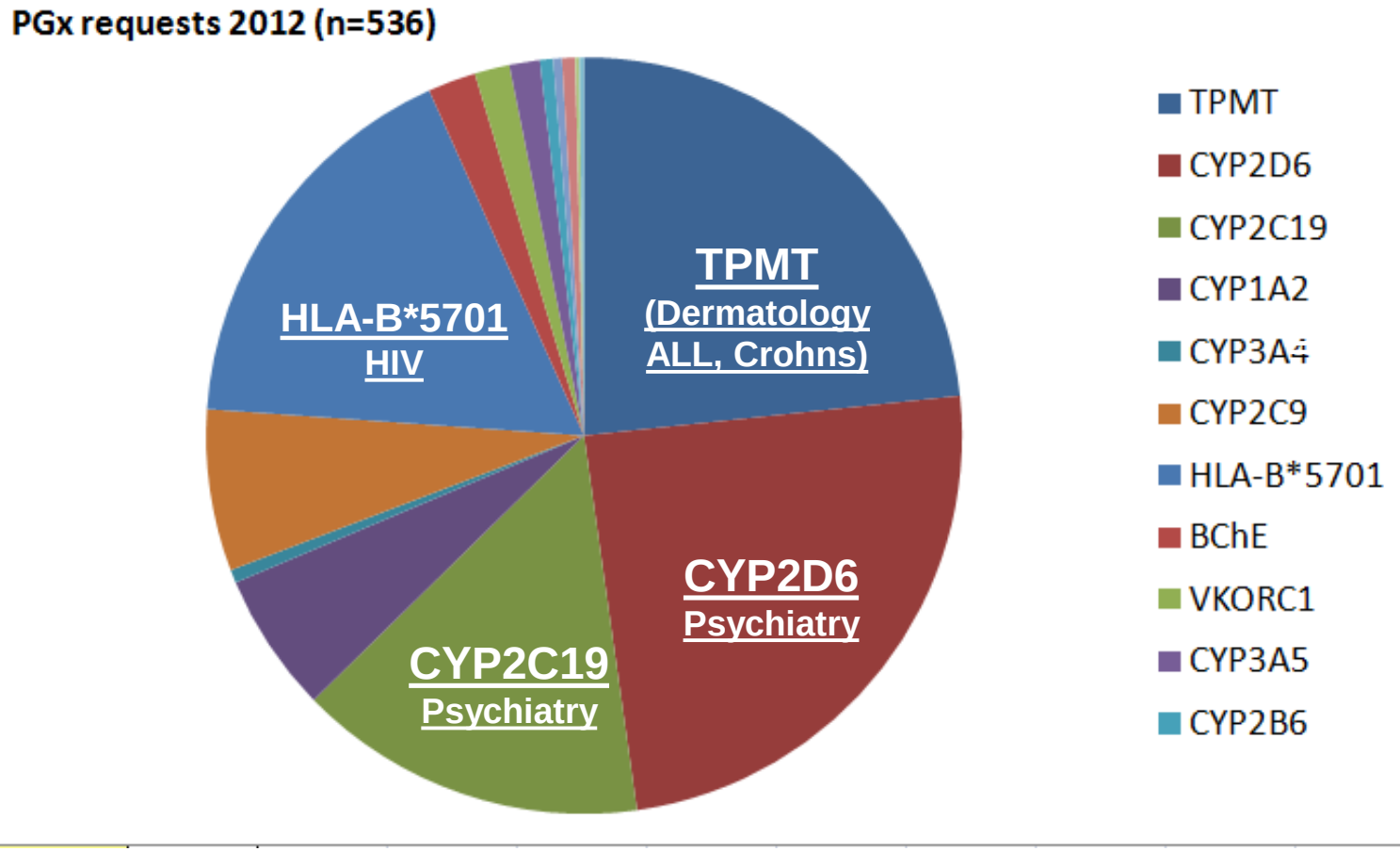
☐ Other gene, being:

Consulted with:

Niet invullen! T.b.v. interne registratie AKC:

☐ PORD DNAnr
PIDNR
Monsternr

PGx testing in 2012



Erasmus MC

Metformine

Studies binnen ERGO cohort (Rotterdam study)

- Afd Pharmacoepidemiologie
- (Matthijs Becker, Loes Visser, Bruno Stricker)

98 incidente metformine gebruikers

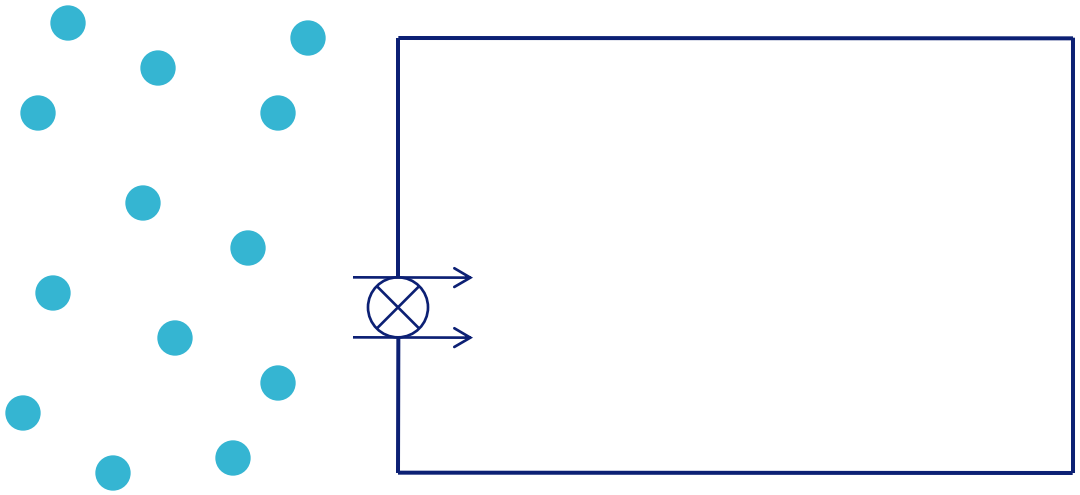
HbA1c en genotype bekend

- OCT1 : (organic cation transporter 1) transporteert cel in
- MATE1: (multidrug and toxin extrusion 1) efflux pomp

Erasmus MC

Metformine & OCT1 (organic cation transporter 1)

13% heeft een **slecht** werkende OCT1 pomp



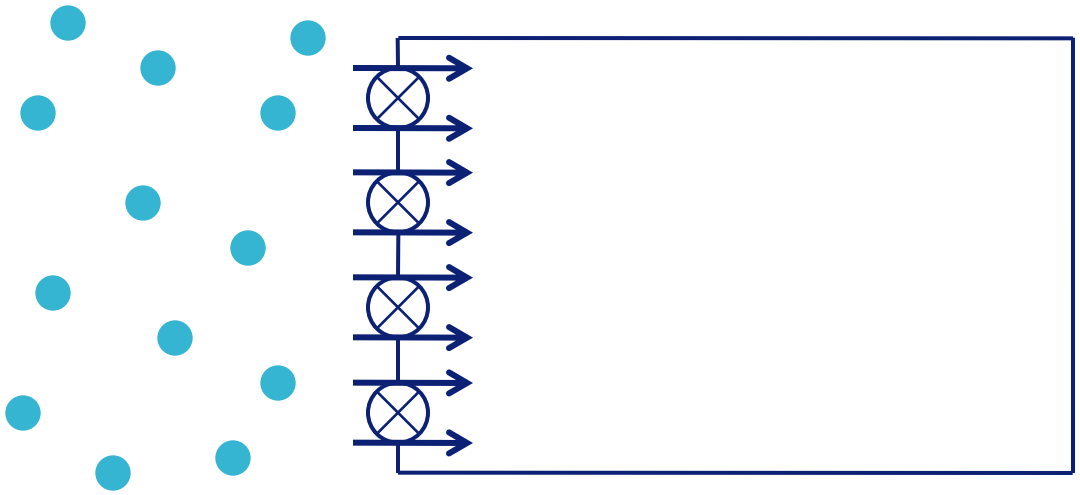
Levercel

(M.L. Becker 2009)

Erasmus MC

Metformine & OCT1 (organic cation transporter 1)

48% heeft een **goed** werkende OCT1 pomp

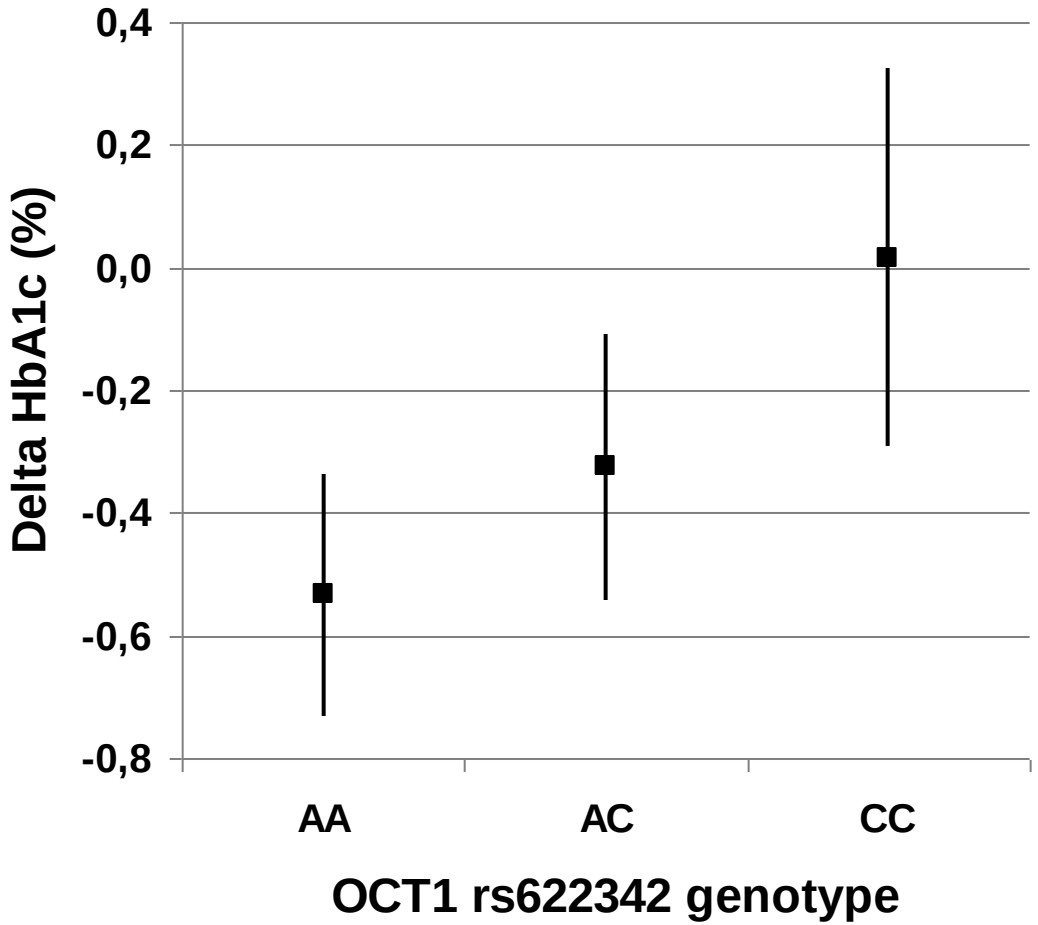


Levercel

(M.L. Becker 2009)

Erasmus MC

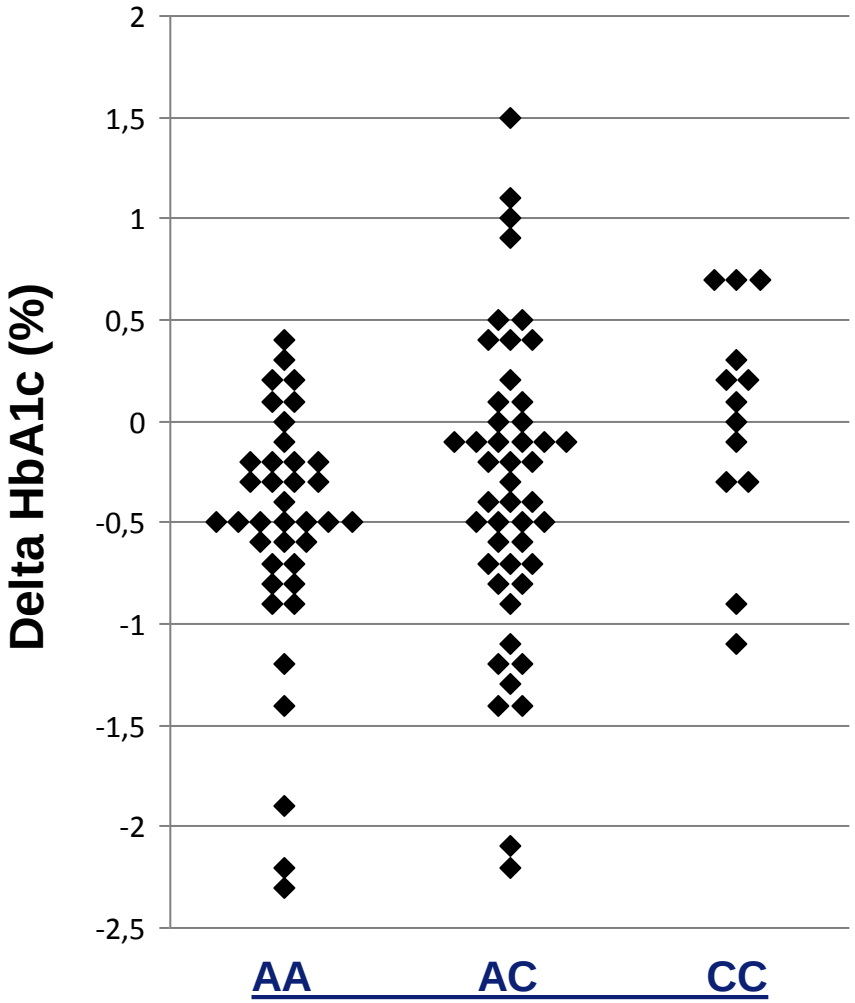
Metformin & OCT1 (organic cation transporter 1)



(M.L. Becker 2009)

Erasmus MC

Metformin & OCT1 (organic cation transporter 1)

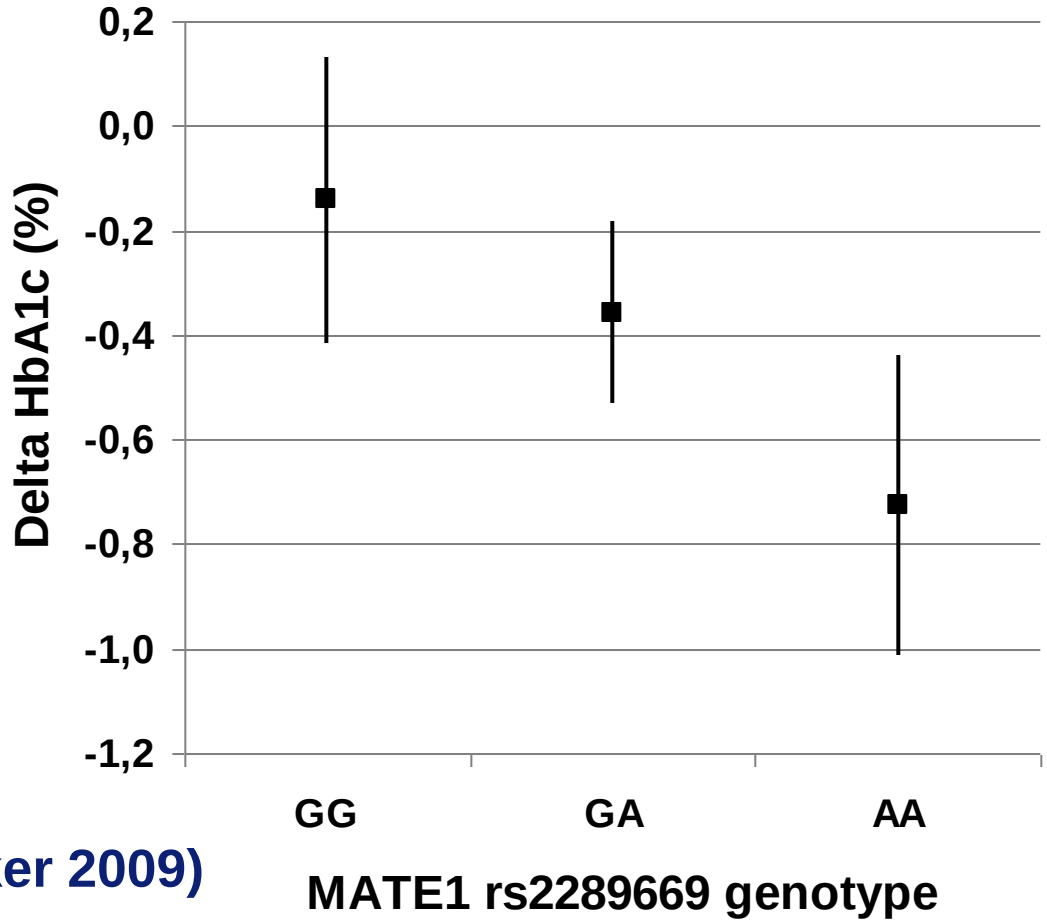


Explained variance: 5.3 %

(M.L. Becker 2009)

Erasmus MC

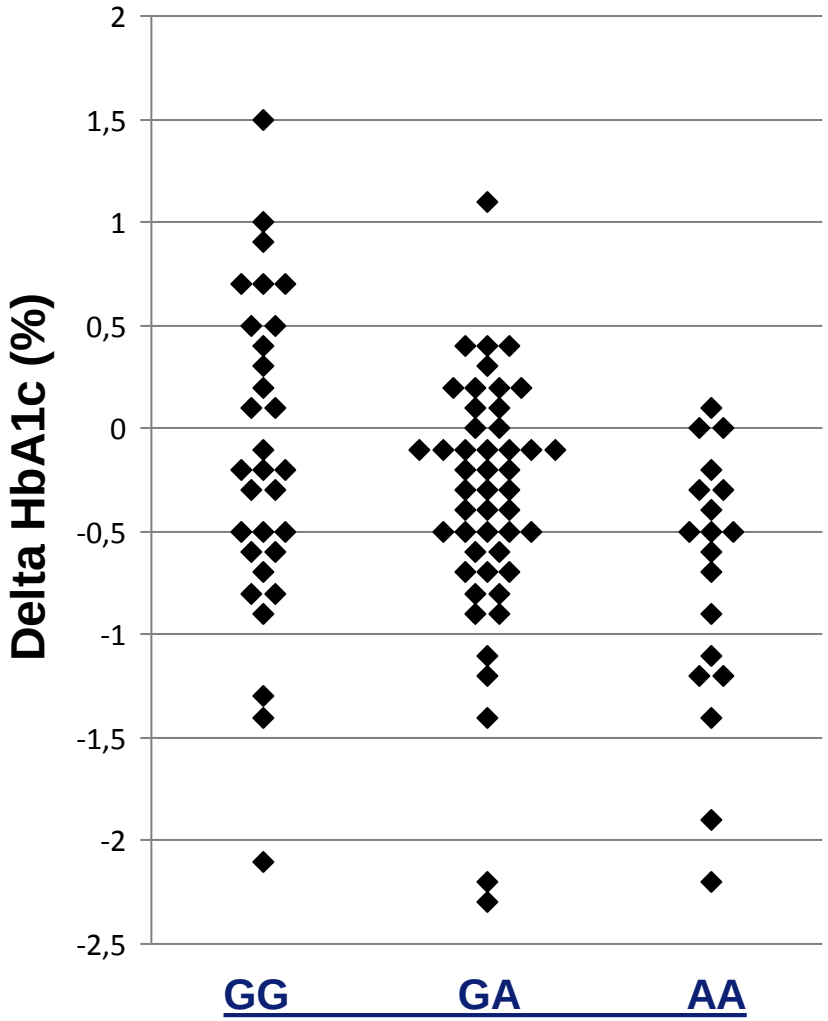
Metformin & MATE1 (multidrug and toxin extrusion 1)



(M.L. Becker 2009)

Erasmus MC

Metformin & MATE1 (multidrug and toxin extrusion 1)



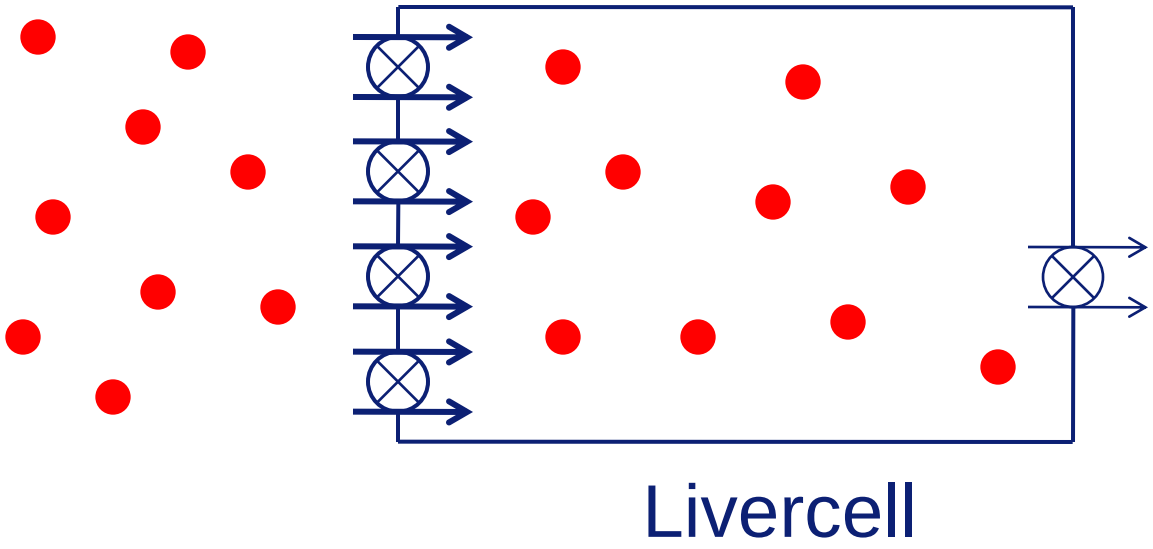
Explained variance: 7.0 %

(M.L. Becker 2009)

Erasmus MC

Metformin, OCT1 & MATE1

High influx (OCT1), low efflux (MATE1)

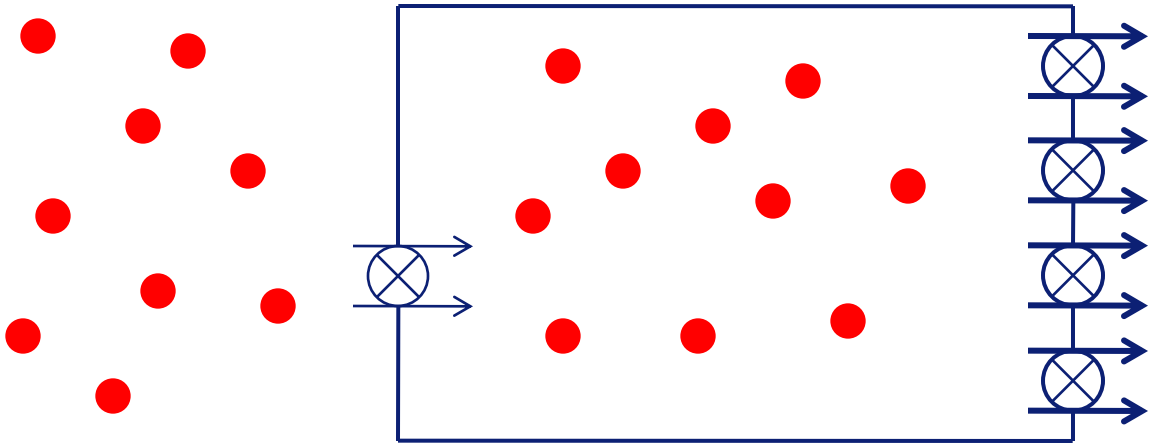


Very high metformin concentration

Erasmus MC

Metformin, OCT1 & MATE1

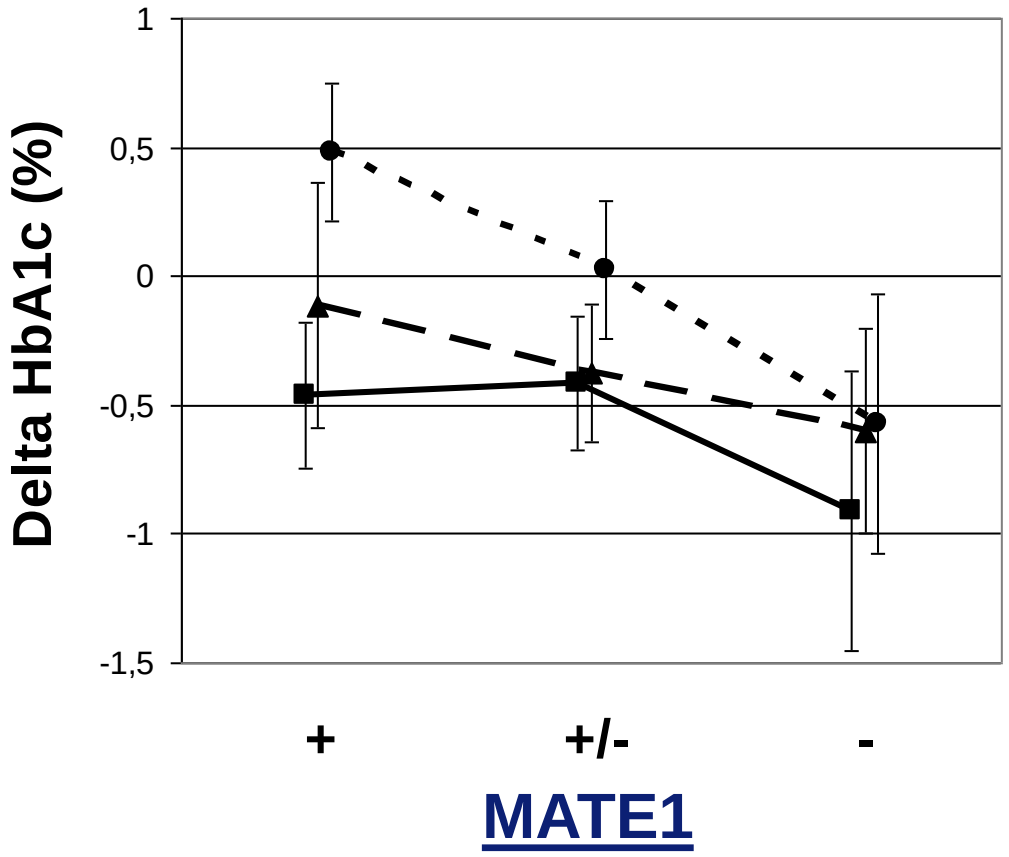
Low influx (OCT1), high efflux (MATE1)



Liver cell

Very low metformin concentration

Metformin, OCT1 & MATE1



Explained variance: 25.1%

OCT1

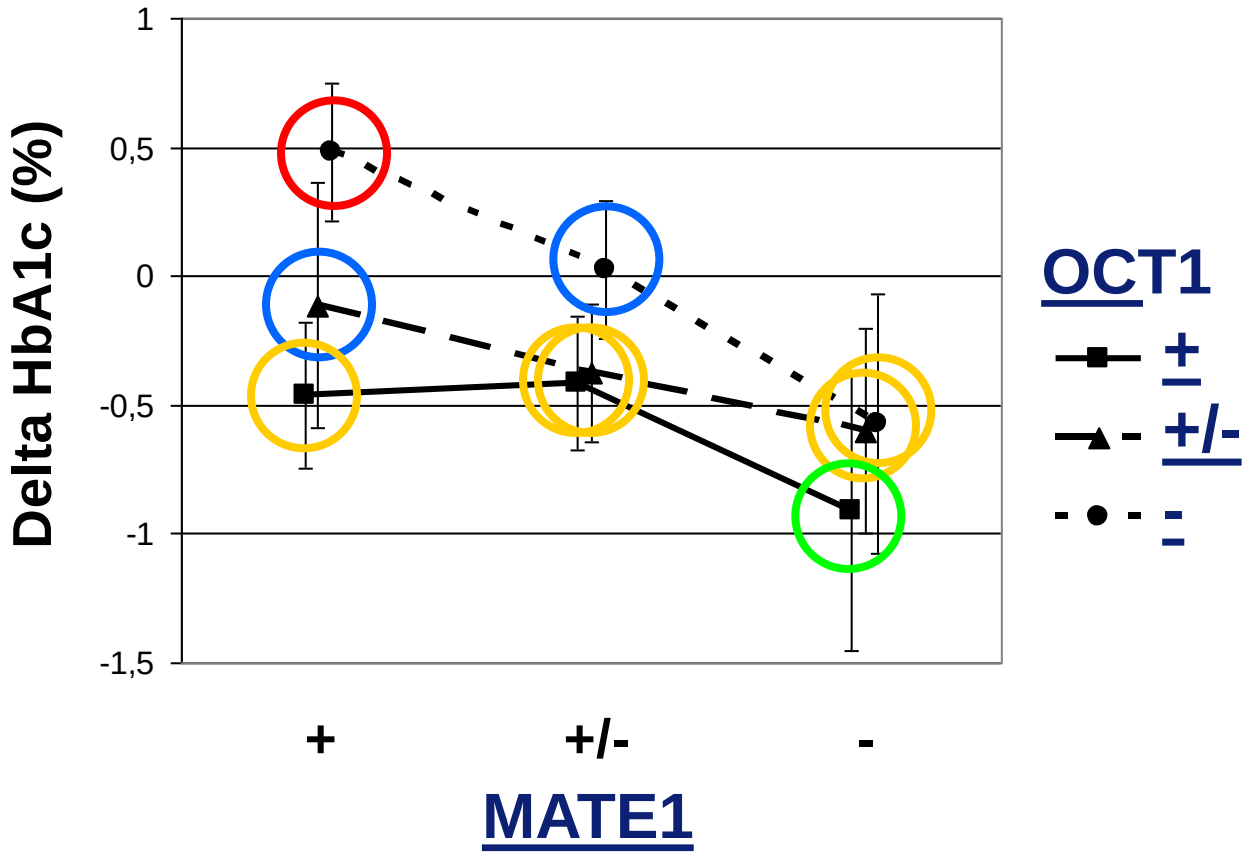
+

+/-

-

(M.L. Becker 2009)

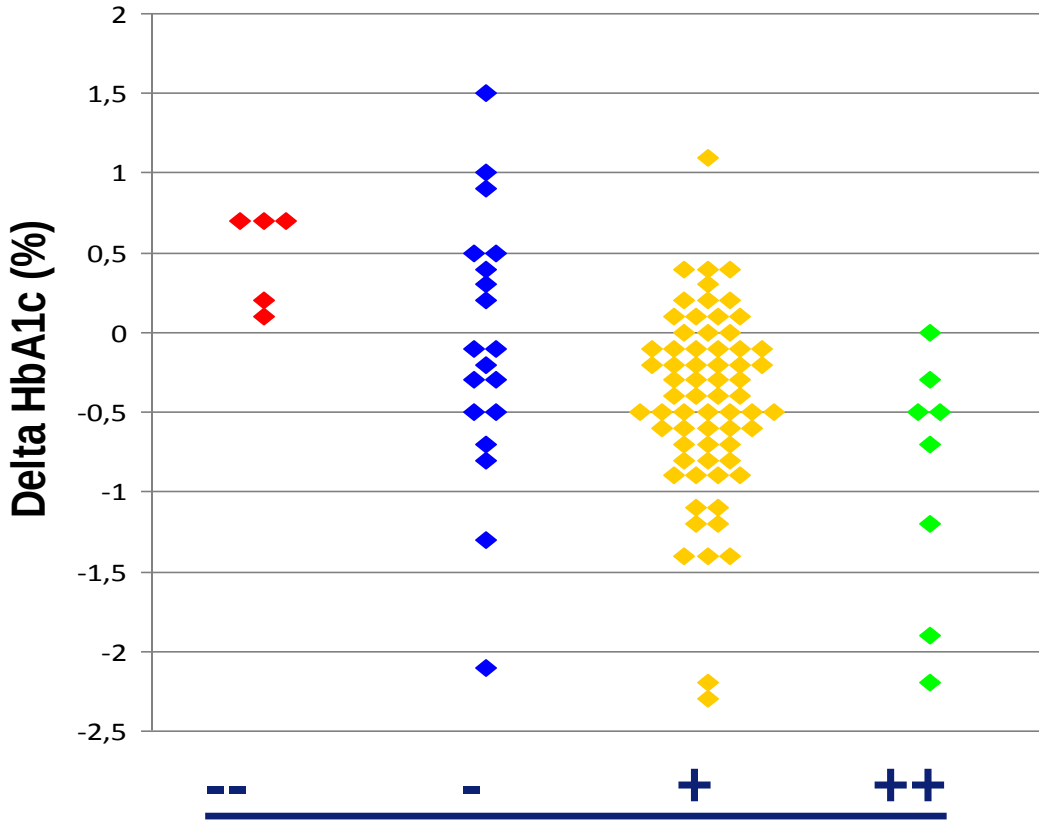
Metformin, OCT1 & MATE1



(M.L. Becker 2009)

Erasmus MC

Metformin, OCT1 & MATE1



Expected metformin respons

(M.L. Becker 2009)

Erasmus MC

Metformine

Studies binnen ERGO cohort (Rotterdam study) laten zien dat bij een subgroep van patiënten te voorspellen is dat zij op metformine behandeling een zeer matige respons zullen hebben

Nog onduidelijk of een hogere dosis dit kan opheffen (wellicht leidt dit tot meer bijwerkingen), dan liever een ander oraal anti-diabeticum?

Afd Pharmacoepidemiologie

(Matthijs Becker, Loes Visser, Bruno Stricker)

Erasmus MC

Example 3: Abacavir

Abacavir : 5-8% will develop hypersensitivity reaction

- usually within 6 weeks of initiation of treatment
- unrelated to dose
- can be fatal in rare cases
- less frequent in blacks
- familial reports

Erasmus MC

Association between presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

Mallal et al. Lancet 2002;359:727-732.

Association between HLA antigens and hypersensitivity:

- study in 200 individuals in Australia
- HLA-B57.01 presence in general population : 4-5%

		HLA-B57.01 present
Abacavir hypersensitive	18/195	14/18 (78%)
Abacavir tolerant	167/195	4/195 (2%)

Erasmus MC

Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study

Rauch A, ... Mallal S. CID 2006;43:99-102

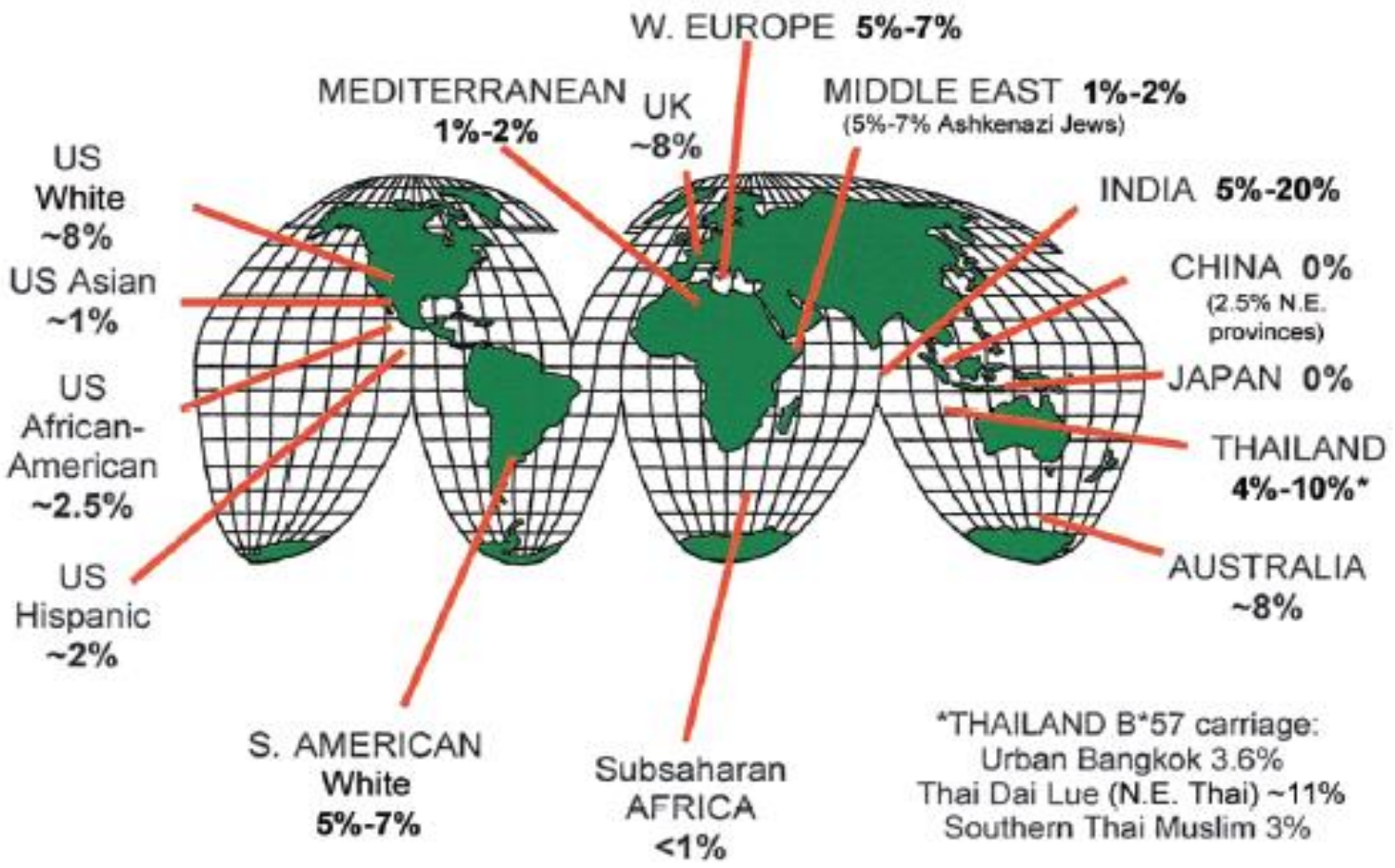
Prospective pharmacogenetic screening

Abacavir-naive patients

- Testing for HLA-B*57.01
- If positive: no abacavir treatment

Erasmus MC

Prevalence of HLA-B*57.01 in the world



CID 2006;43:103-5

Erasmus MC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

STUDY OBJECTIVE AND END POINTS

The objective of the study was to test the hypothesis that prospective pharmacogenetic screening for HLA-B*5701 and the exclusion of those patients carrying the allele from abacavir treatment reduces the incidence of hypersensitivity reaction to abacavir as compared with that in an unscreened population. The primary end points were

N Engl J Med 2008;358:568-79.

Erasmus MC

Study design

Prospective, randomized study

A. Prospective-screening group: only start abacavir in HLA-B*5701-negative patients.

B. Retrospective-screening group: start abacavir in all patients, without prior HLA-B*5701-testing (only retrospective testing).

N Engl J Med 2008;358:568-79.

Erasmus MC

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

N Engl J Med 2008;358:568-79.

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Conclusions:

HLA-B*5701-screening reduced the risk of hypersensitivity reactions to abacavir.

This study shows that a pharmacogenetic test can be used to prevent a specific toxic effect of a drug.

N Engl J Med 2008;358:568-79.

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Actueel nieuws
Publicaties
Geneesmiddelen
Registratiezaken
Homeopathie
Kruiden
Medische hulpmiddelen
Geneesmiddelen-informatiebank

ACTUEEL GENEESMIDDELEN VOOR MENSEN

10 maart 2008 - Belangrijke veiligheidsinformatie over abacavir (Ziagen, Kivexa en Trizivir)

Naar aanleiding van nieuwe gegevens heeft het wetenschappelijk comité voor geneesmiddelen voor humaan gebruik (CHMP), waarin het CBG vertegenwoordigd is, besloten dat de productinformatie voor Ziagen, Kivexa en Trizivir aangepast dient te worden met betrekking het optreden van overgevoeligheidsreacties op abacavir. Dit is de eerste keer dat een indicatie van een geregistreerd geneesmiddel wordt aangepast, om door het vooraf genetisch screenen van patiënten de veiligheid in de klinische praktijk te verhogen. Screening op het HLA-B*5701-allel voorafgaand aan de behandeling en het vervolgens vermijden van het gebruik van abacavir bij HLA-B*5701-positieve patiënten, verminderde significant het optreden van overgevoeligheidsreacties op abacavir, zo blijkt uit een recent gepubliceerd prospectief onderzoek. Symptomen van deze soms levensbedreigende reacties treden gewoonlijk op binnen de eerste 6 weken na de start van de behandeling met abacavir.

Mede op basis van deze gegevens zijn in de productinformatie de volgende wijzigingen in de indicatie opgenomen:

NIEUWSARCHIEF GENEESMIDDELEN VOOR MENSEN

29 april 2008
Europese registratie van geneesmiddelen in april 2008

28 april 2008
Bericht voor registratiehouders van geneesmiddelen die mesilaten, (di) isetionaten, tosilaten of besilaten bevatten

23 april 2008
DHPC over abacavir (Ziagen, Kivexa en Trizivir) en didasonine (Videx)

22 april 2008
Aangepaste instructie voor bereiding en kwaliteitscontrole Nanocoll

Naar Nieuwsarchief »

NIEUWSBRIEVEN

Tamoxifen

Tamoxifen heeft een anti-oestrogene werking.

Tamoxifen wordt toegepast bij bepaalde vormen van borstkanker.

Door het geven van tamoxifen kan de groei van de tumor of van metastasen vaak een tijd geremd worden.

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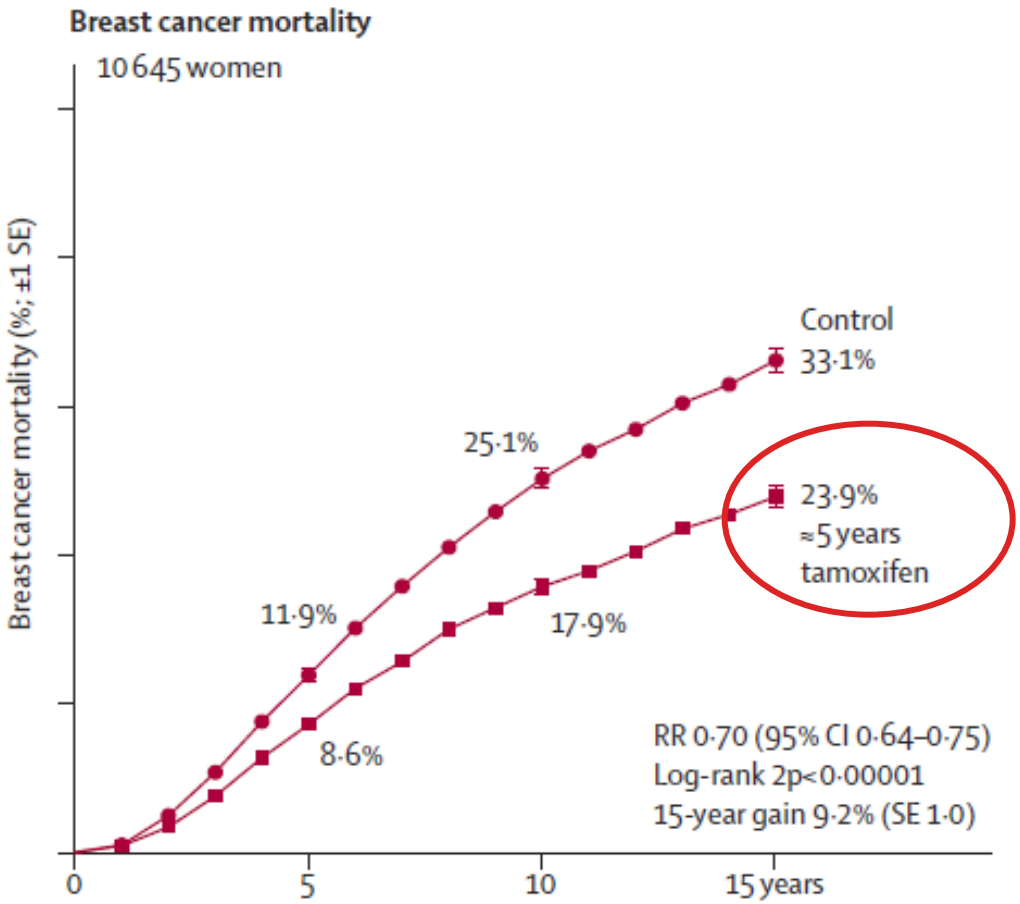
Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

Lancet 2011; 378: 771–84

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**



Erasmus MC

CYP2D6 speelt belangrijke rol bij vorming endoxifen

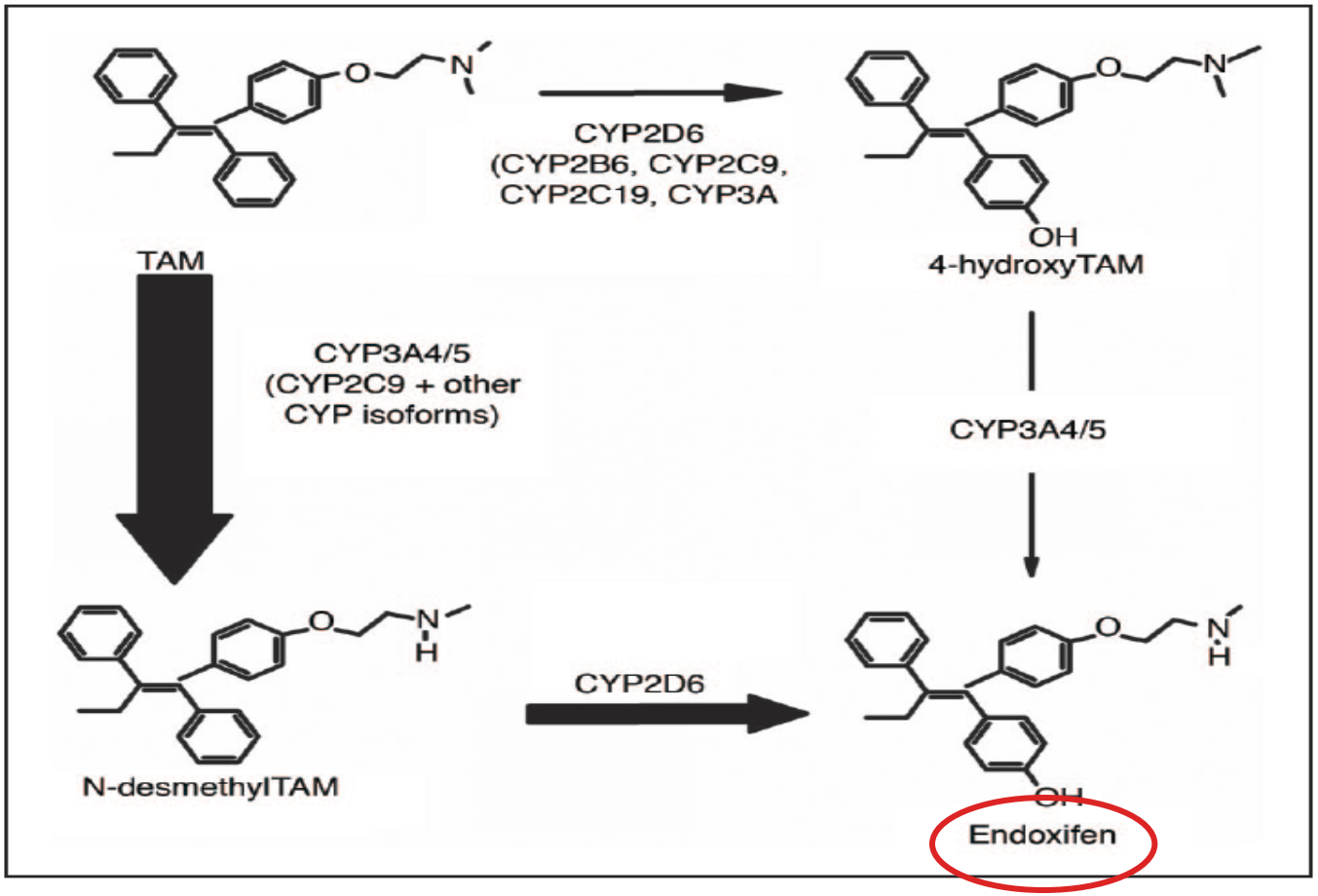


Fig 1. Selected transformation pathways of tamoxifen and the main CYP enzymes involved. The relative contribution of each pathway to the overall oxidation of tamoxifen is shown by the thickness of the arrow, and the principal P450 isoforms responsible are highlighted in larger fonts.

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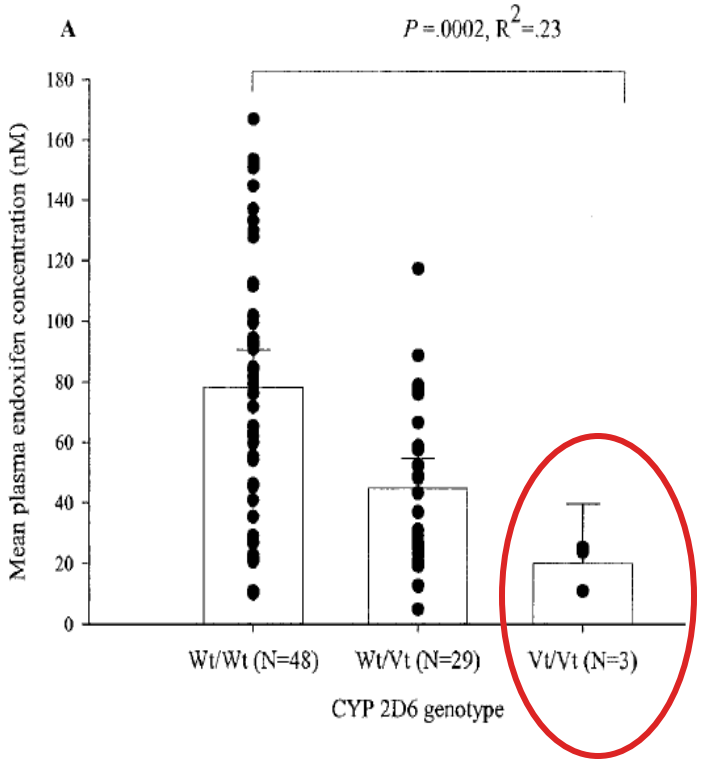
CYP2D6 Variant allel dragers maken minder endoxifen

Genotype group	N	Mean concentration, nM (95% CI) Endoxifen
CYP2D6		
Wt/Wt	48	78.0 (65.9 to 90.1)
Wt/Vt†	29	43.1 (33.3 to 52.9)
Vt/Vt‡	3	20.0 (11.1 to 28.9)
P		<.001



Journal of the National Cancer Institute, Vol. 97, No. 1, January 5, 2005

Erasmus MC

VOLUME 23 · NUMBER 36 · DECEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY

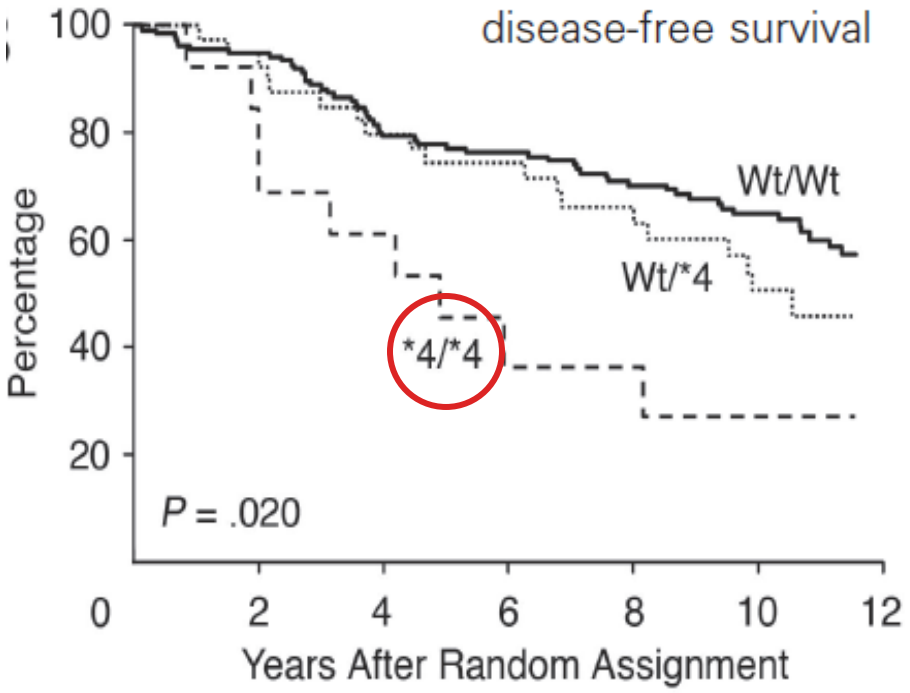
ORIGINAL REPORT

Pharmacogenetics of Tamoxifen Biotransformation Is Associated With Clinical Outcomes of Efficacy and Hot Flashes

Matthew P. Goetz, James M. Rae, Vera J. Suman, Stephanie L. Safgren, Matthew M. Ames, Daniel W. Visscher, Carol Reynolds, Fergus J. Couch, Wilma L. Lingle, David A. Flockhart, Zeruesenay Desta, Edith A. Perez, and James N. Ingle

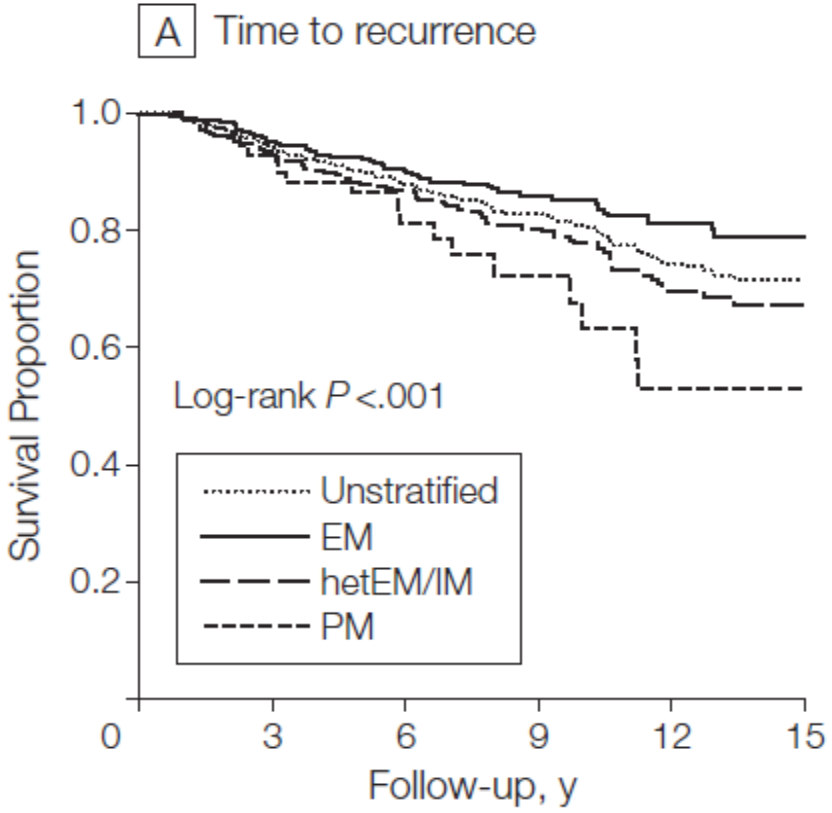
Table 2. Genotype and Allele Frequencies (q) for CYP2D6 (*4) and CYP3A5*3

	No.	%	
CYP2D6 (*4), n = 190			q = 0.17
wt/wt	137	72.1	
wt/*4	40	21.1	
*4/*4	13	6.8	



Association Between CYP2D6 Polymorphisms and Outcomes Among Women With Early Stage Breast Cancer Treated With Tamoxifen

JAMA. 2009;302(13):1429-1436



No. at risk

Unstratified	1325	1075	649	346	166	62
EM	609	496	289	161	81	31
hetEM/IM	637	491	307	154	70	24
PM	79	60	31	17	9	4

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Table 2. "Positive" studies on mainly Caucasian breast cancer patients using adjuvant tamoxifen: higher recurrence in Poor Metabolizers

Author (population)	Study design	*N*	Results
Goetz et al. 2005 (29)	*4/*4 vs. 1/*1 + *1/*4	190	RFS HR, 1.86; *P* = 0.08
Goetz et al. 2007 (ref. 46; trial)			RFS HR, 1.74; *P* = 0.02 (+ CYP2D6 inhibitors)
Schroth et al. (ref. 30; non-trial)	Rest (*4,*5, *10, *41)* vs. *1/*1	197	EFS HR, 1.89; *P* = 0.02
Gonzalez-Santiago et al. (ref. 31; non-trial) †	*4/*4 + *1/*4 vs. *1/*1	84	RFS HR, 2.82; *P* = 0.05

Abbreviations: *N*, number of patients; RFS, recurrence-free survival; EFS, event-free survival; HR, adjusted hazard ratios.

Table 3. "Negative" studies on mainly Caucasian breast cancer patients using adjuvant tamoxifen: lower recurrence in Poor Metabolizers

Author (population)	Study design	*N*	Results
Wegman et al. 2005 (ref. 33; trial)	*4/*4 + *1/*4 vs. 1/*1	76	DRFS HR, <1; nonsignificant
Wegman et al. 2007 (ref. 34; partly trial)	*4/*4 vs. *1/*4 or 1/*1	677	RFS HR, <1; *P* = 0.055
Nowell et al. (ref. 32; nontrial)	*4/*4 + *1/*4 vs. 1/*1	162	PFS HR, 0.67; *P* = 0.19

Abbreviations: DRFS, distant recurrence-free survival; PFS, progression-free survival.

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Vincent O. Dezentjé, Henk-Jan Guchelaar, Johan W.R. Nortier, et al. *Clin Cancer Res* 2009;15:15-21.

Samenvattend:

Tamoxifen moet worden omgezet in endoxifen voor effectiviteit.

CYP2D6 zorgt voor deze omzetting naar endoxifen.

CYP2D6 PMs maken minder endoxifen en hebben (in een aantal studies) een slechter resultaat van de behandeling.

...Zou u een CYP2D6 genotypering laten uitvoeren alvorens uw moeder/zus/echtgenote met tamoxifen gaat beginnen ???

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Onbeantwoorde vragen:

Als CYP2D6 PM genotype wordt vastgesteld, kan dan de uitkomst worden verbeterd door:

- een hogere dosis tamoxifen te geven?
- een andere behandeling te geven?

Is de endoxifen concentratie een goede leidraad voor de behandeling, en is het beter om te doseren op geleide van die concentraties, ipv het genotype te bepalen?

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The Netherlands: recommendations for 53 drugs

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[3], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 89 NUMBER 5 | MAY 2011

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Dose recommendations in Netherlands

The Royal Dutch Association for the Advancement of Pharmacy

established the Pharmacogenetics Working Group

with the objective of developing pharmacogenetics-based therapeutic (dose) recommendations

based on systematic review of the literature

and assisting physicians and pharmacists by integrating the recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance.

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Dose recommendations for 53 drugs and 11 genes:

The drugs were associated with genes coding for

CYP2D6 (n = 25)

CYP2C19 (n = 11)

CYP2C9 (n = 7)

thiopurine-S-methyltransferase (TPMT) (n = 3)

dihydropyrimidine dehydrogenase (DPD)(n = 3)

vitamin K epoxide reductase (VKORC1) (n = 2)

Uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1)

HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL) (all n = 1).

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Therapeutic (dose) recommendations

were formulated for 39 (73.6%) of the 53 drugs

for clozapine, flupenthixol, and olanzapine, a gene–drug interaction with CYP2D6 was considered, but no evidence was found in the literature, and hence no recommendations were required

for 11 of the drugs (20.8%), a gene–drug interaction was present, but no therapeutic (dose) recommendation was deemed necessary

Limitations:

Pharmacogenetics was not the primary objective for most of the studies assessed; therefore, many of the studies were underpowered, with insufficient sample size per genotype or phenotype.

The end points assessed were often pharmacokinetic ones and the result of single-dose experiments in healthy volunteers— not representative of the conditions in daily clinical practice.

Very few studies on added value of pharmacogenetic testing (similar to the randomized trial for abacavir)

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Nortriptyline	270	PM	3	C	Yes	Reduce dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–127
		IM	4	C	Yes	Reduce dose by 40% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–124, 126, 128–132
		UM	3	C	Yes	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	39, 123, 124, 128
Olanzapine	201	PM	3	AA	No	No	133–135
		IM	3	AA	No	No	134, 136, 137
		UM	—	—	No	No	—
Oxycodone	78	PM	3	B	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug—not tramadol or codeine—or be alert to symptoms of insufficient pain relief	138–142
		IM	3	AA	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug—not tramadol or codeine—or be alert to symptoms of insufficient pain relief	140
		UM	1	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (NOT tramadol or codeine) or be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention)	143

Clinical decision support at Vanderbilt University

Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project

JM Pulley[1], JC Denny[2,3], JF Peterson[2,3], GR Bernard[3,4], CL Vnencak-Jones[5,6], AH Ramirez[3], JT Delaney[3], E Bowton[4], K Brothers[5], K Johnson[2,5], DC Crawford[7,8], J Schildcrout[9], DR Masys[2,3], HH Dilks[7], RA Wilke[3], EW Clayton[5,10], E Shultz[2,3], M Laposata[3,6], J McPherson[3], JN Jirjis[2,3] and DM Roden[3,11]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 92 NUMBER 1 | JULY 2012

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Pharmacogenetic testing

Conventional	Vanderbilt
Reactive	Pre-emptive
Patient needs drug	Sample all patients
Genotype	Deposit genetic info
Interpret test	If patients needs drug
Change prescription	Individualized R/
Delay of hrs/days	Available if needed

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Hoe kan rol farmacogenetica worden vergroot?

1. Kennis bij voorschrijvers
2. Studies die laten zien dat klinische uitkomst verbetert
3. Vergoeding kosten test
4. Technische (analytische) vooruitgang
5. Farmacogenetische substudies
6. Informed consent
7. Registratie voor (genetische) subpopulatie?

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