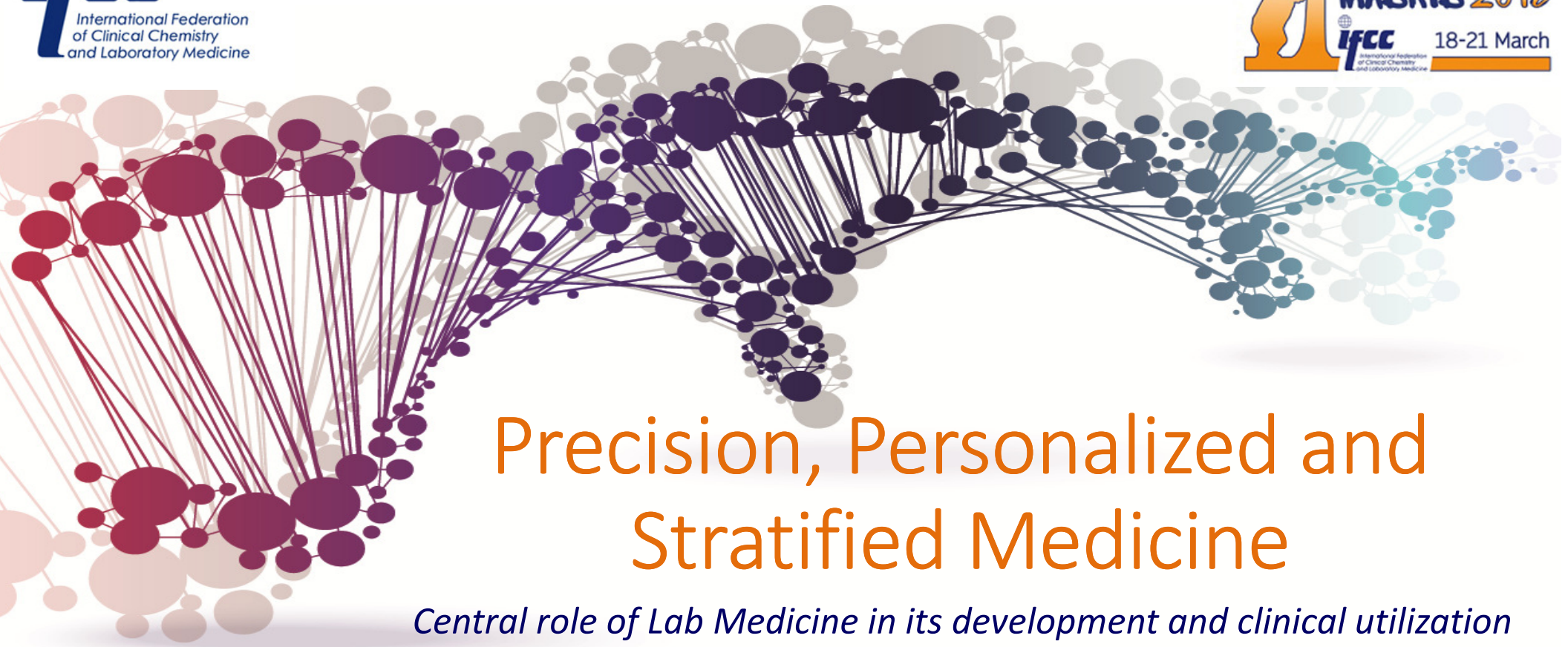
IFCC International Federation of Clinical Chemistry and Laboratory Medicine

General Conference MADRID 2016 IFCC 18-21 March



Precision, Personalized and Stratified Medicine

Central role of Lab Medicine in its development and clinical utilization

Where do we stand, where can we go?

Pharmacogenetics

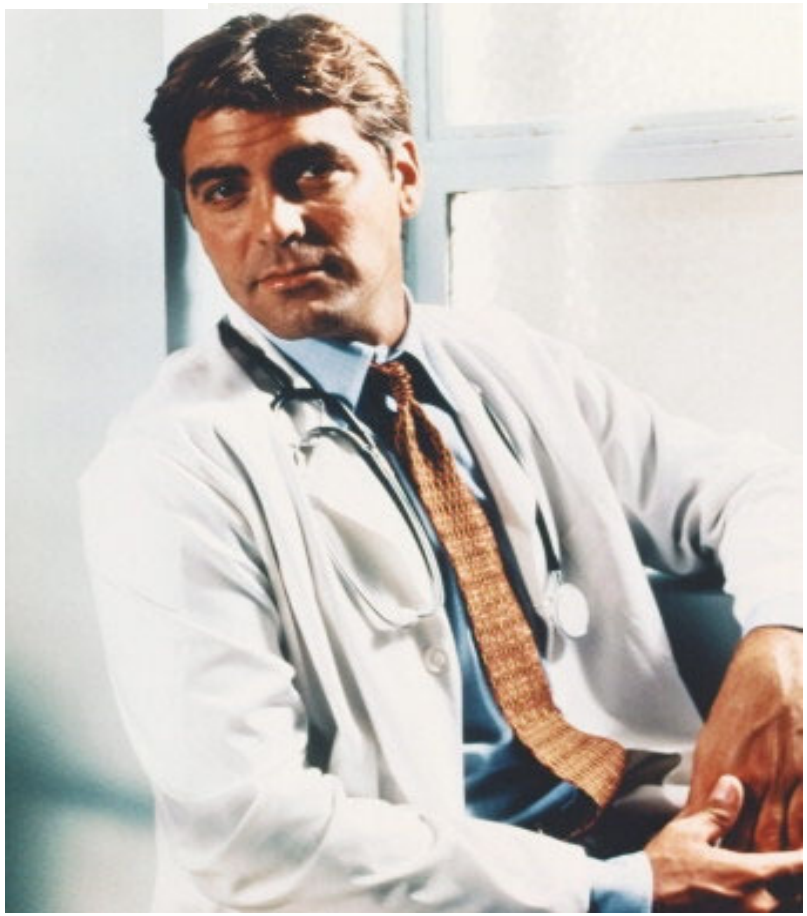
DNA analysis

to explain/ to predict

the response of to drug therapy

Personalized Medicine

Precision Medicine

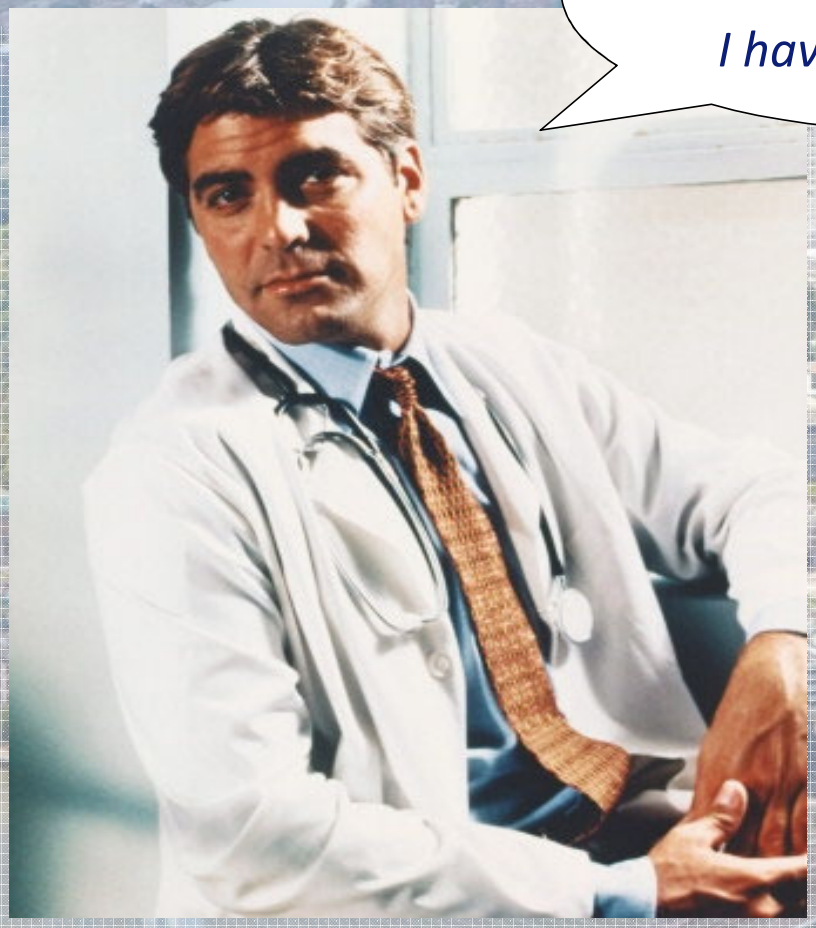


Pharmacogenetics

*Can **YOU** still do without…..?*

Off course,

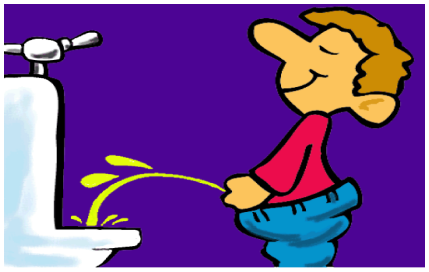
Because I have been working without pharmacogenetics for years!

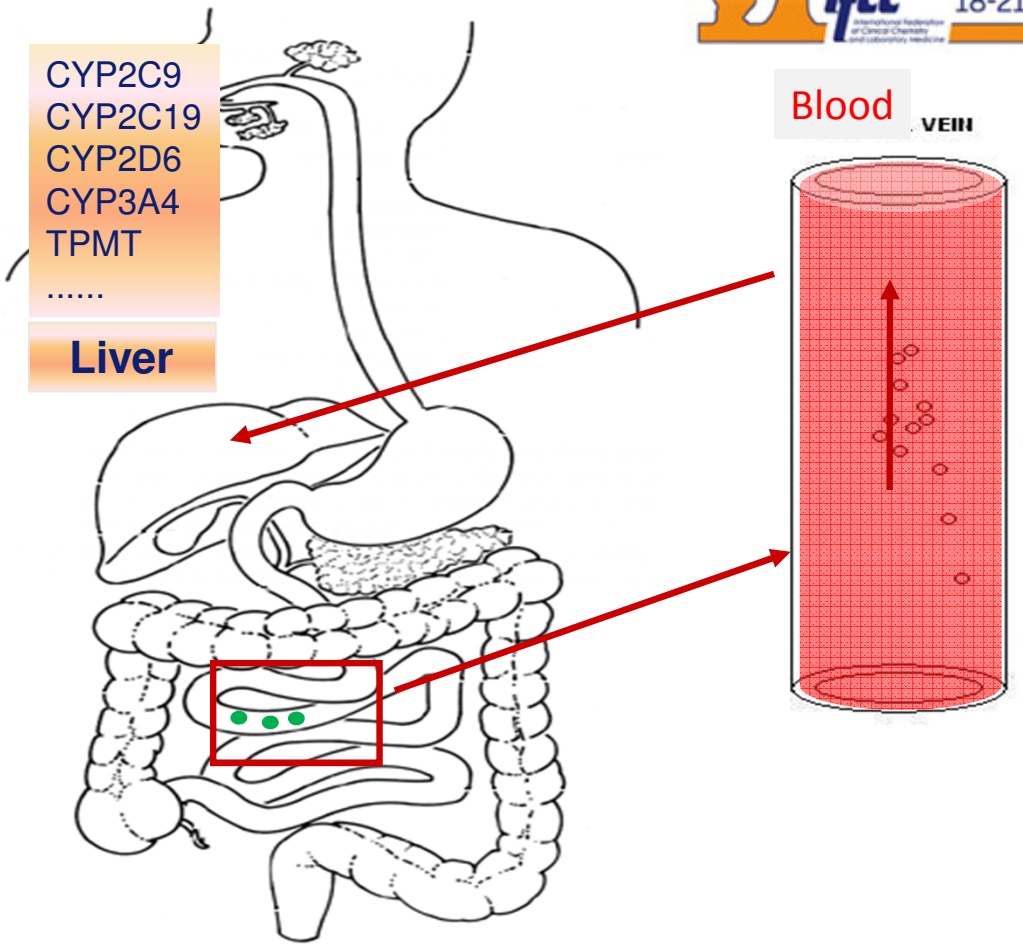


Prof van Schaik,

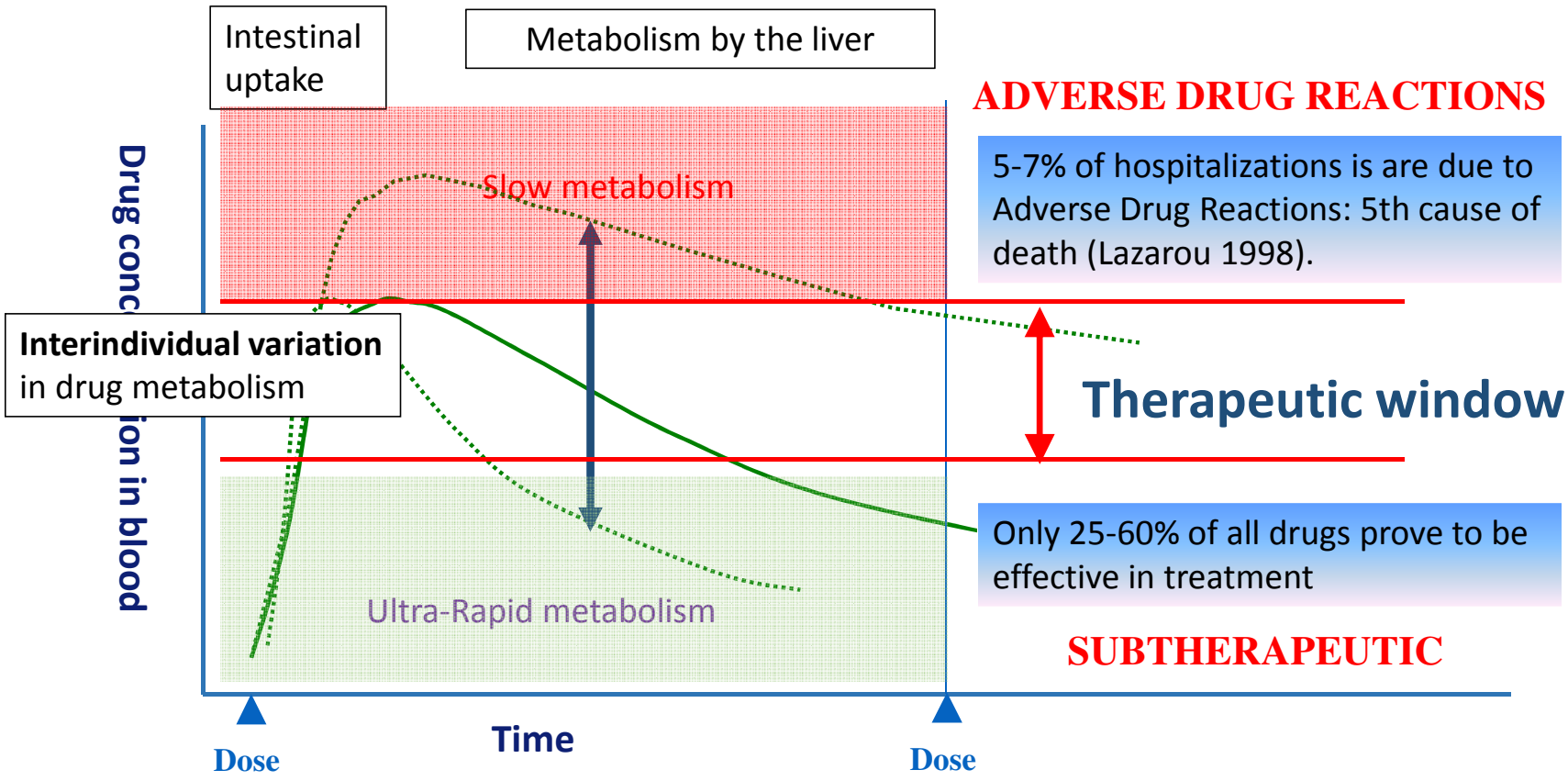
I have a problem….

Metabolism of drugs





Metabolism of drugs

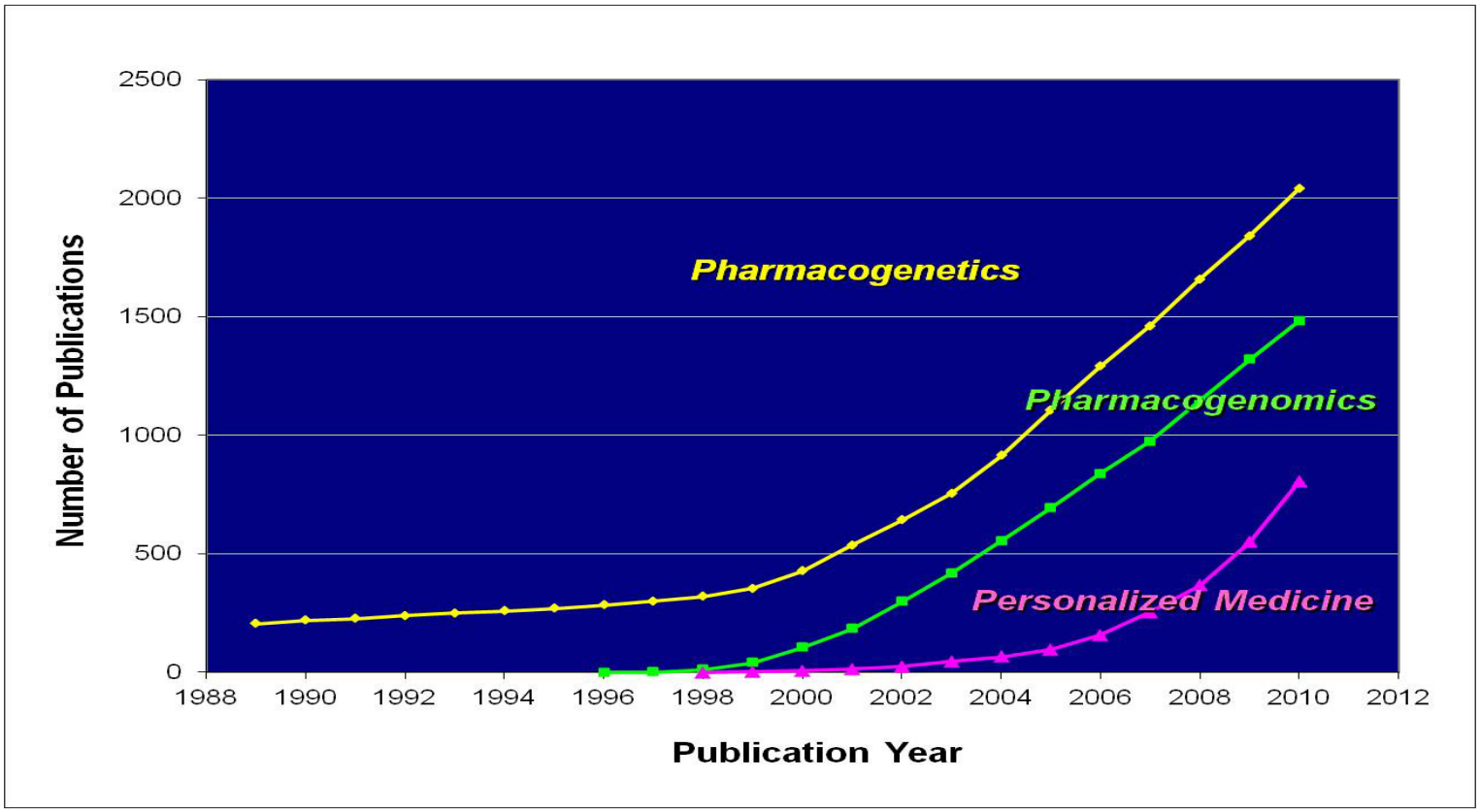


ADVERSE DRUG REACTIONS

5-7% of hospitalizations is are due to Adverse Drug Reactions: 5th cause of death (Lazarou 1998).

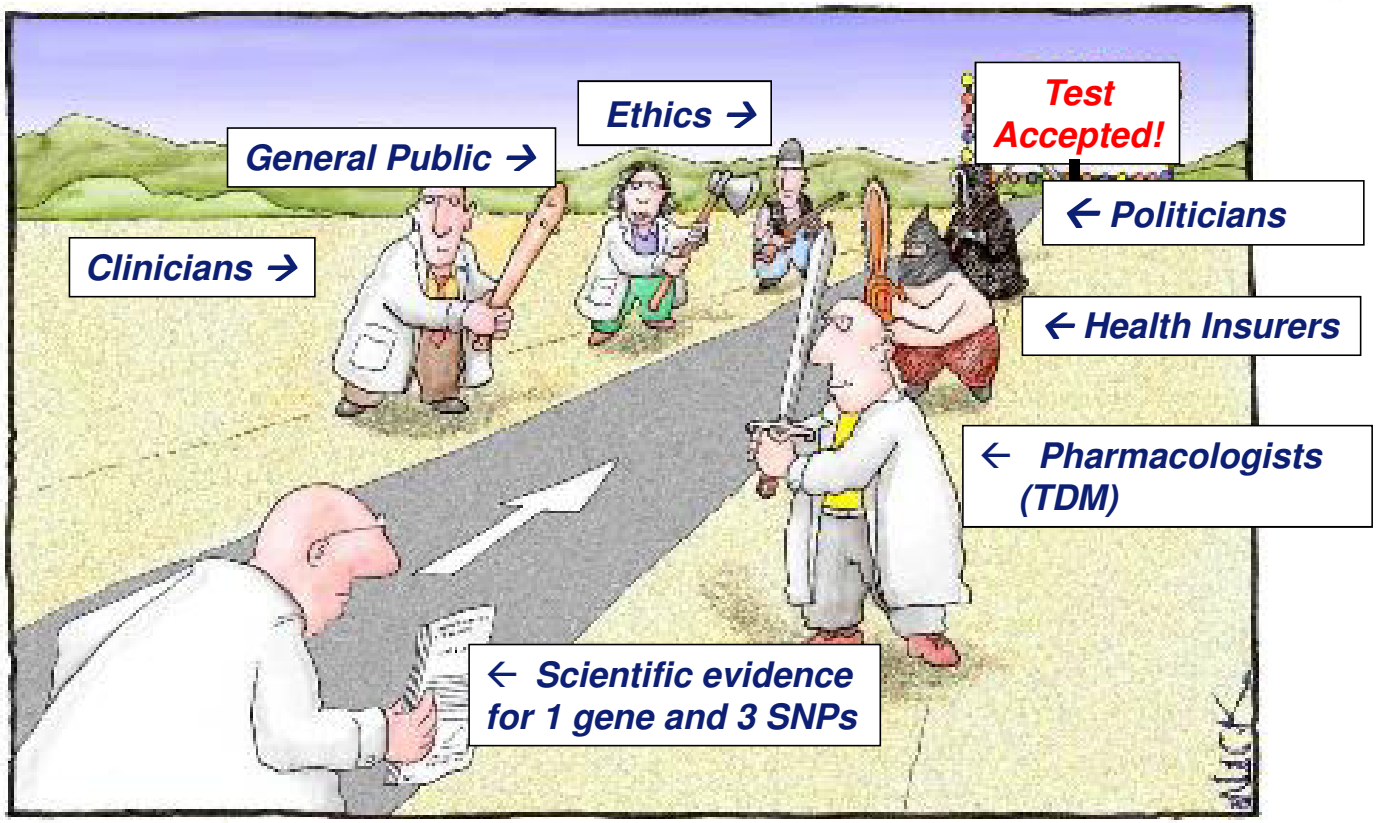
Only 25-60% of all drugs prove to be effective in treatment

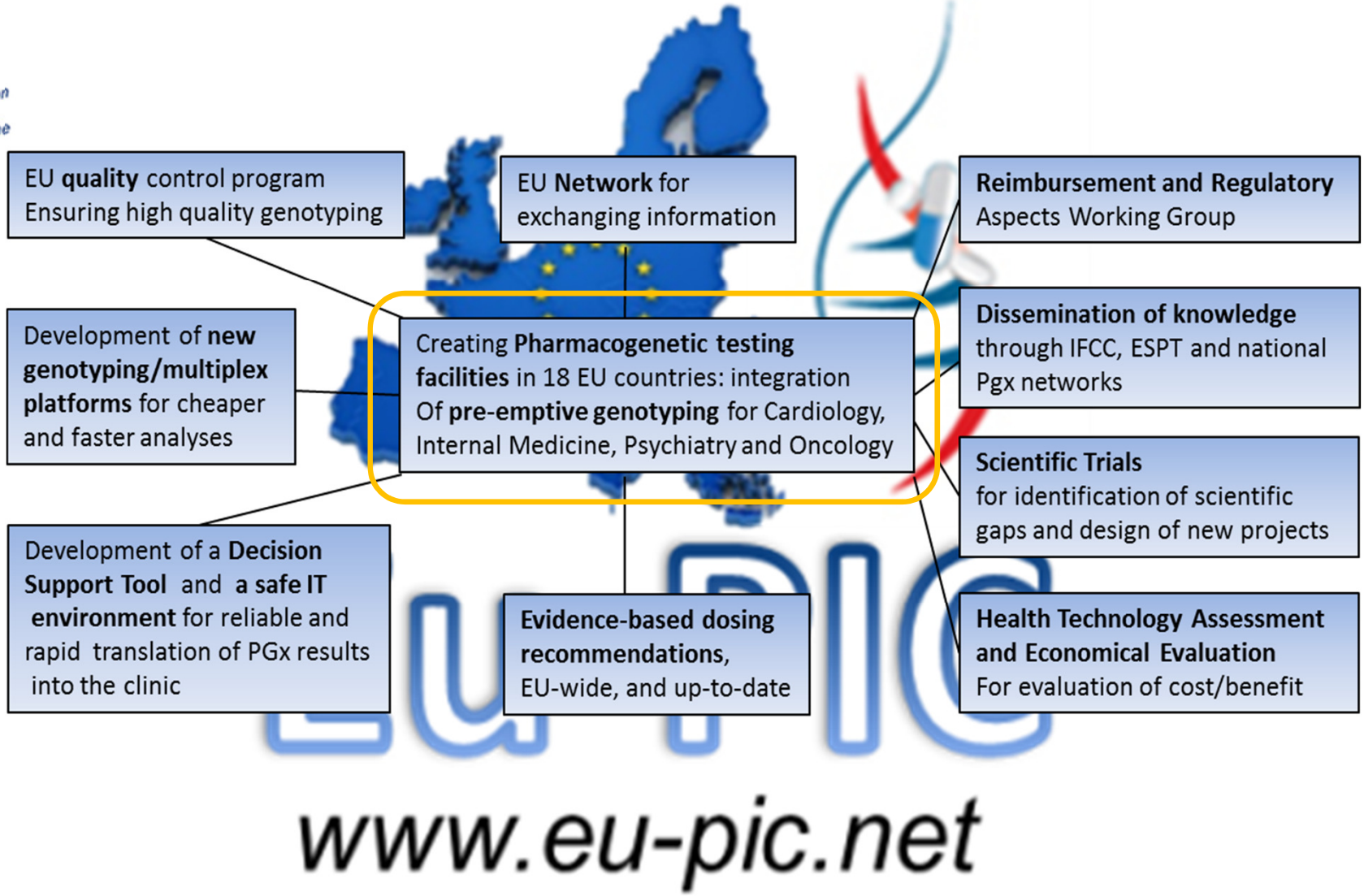
SUBTHERAPEUTIC



2015:
808
1,573
4,077
2,029
8,487

Pharmacogenomics: Can we make it happen?



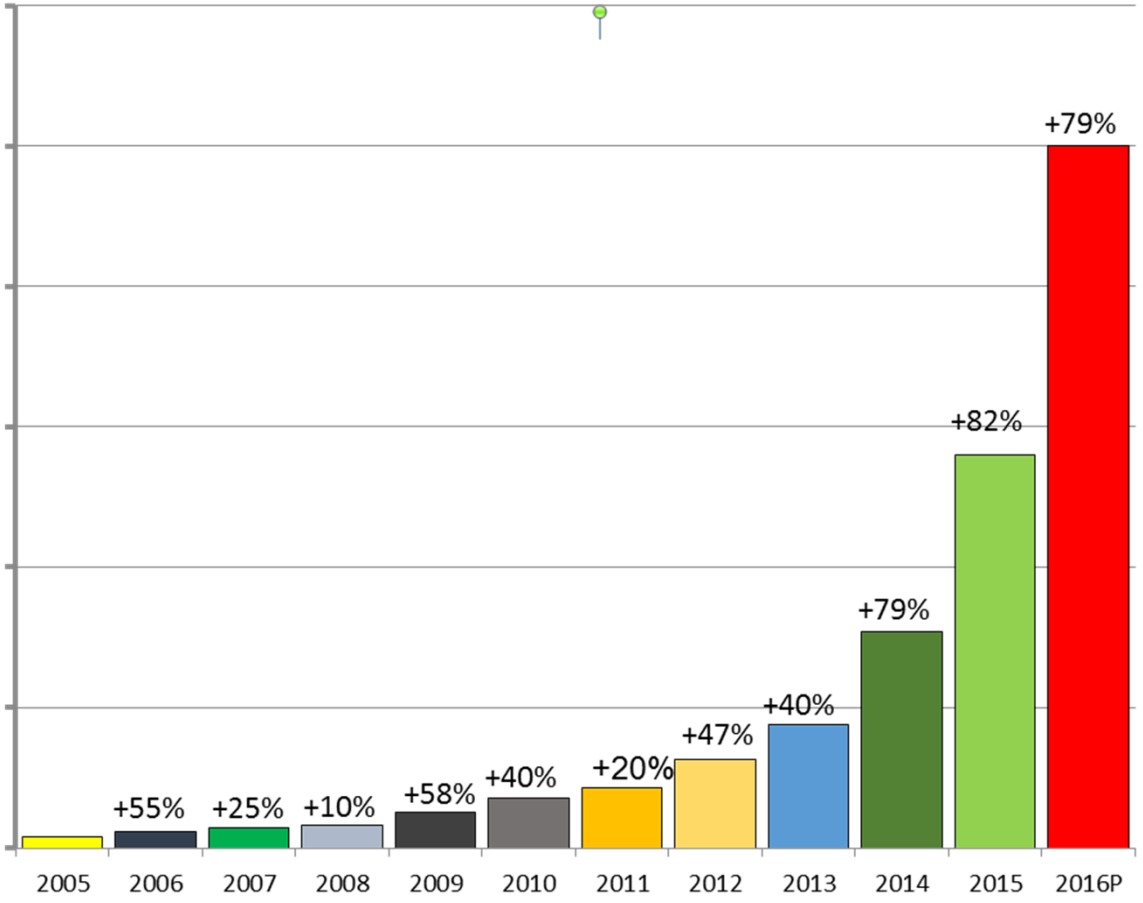

EU **quality** control program
Ensuring high quality genotyping
EU **Network** for
exchanging information
Reimbursement and Regulatory
Aspects Working Group
Development of **new genotyping/multiplex platforms** for cheaper and faster analyses
Creating **Pharmacogenetic testing facilities** in 18 EU countries: integration
Of **pre-emptive genotyping** for Cardiology, Internal Medicine, Psychiatry and Oncology
Dissemination of knowledge
through IFCC, ESPT and national Pgx networks
Scientific Trials
for identification of scientific gaps and design of new projects
Development of a **Decision Support Tool** and **a safe IT environment** for reliable and rapid translation of PGx results into the clinic
Evidence-based dosing recommendations,
EU-wide, and up-to-date
Health Technology Assessment and Economical Evaluation
For evaluation of cost/benefit
www.eu-pic.net

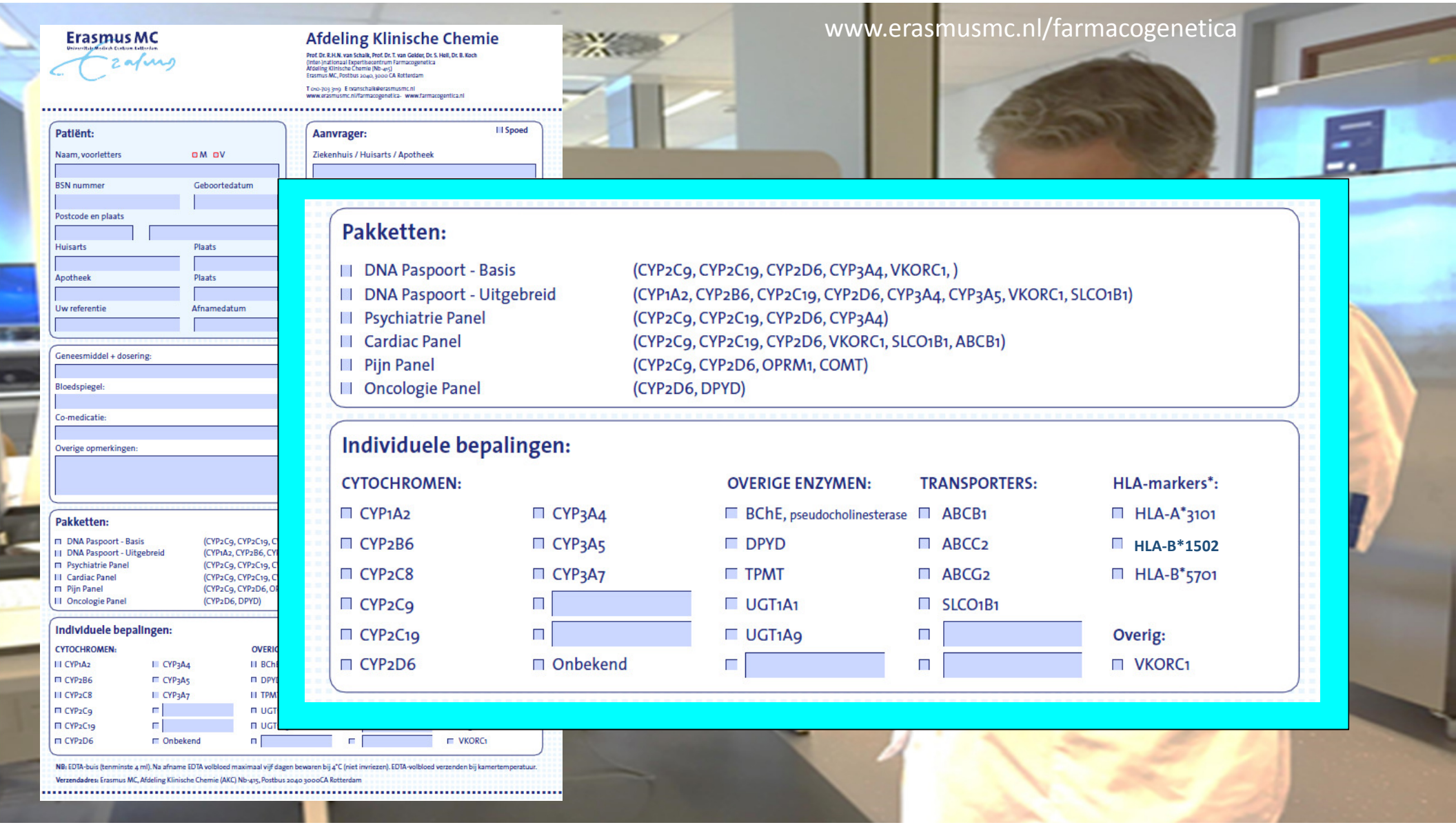
IFCC
International Federation of Clinical Chemistry and Laboratory Medicine

PGx Diagnostics

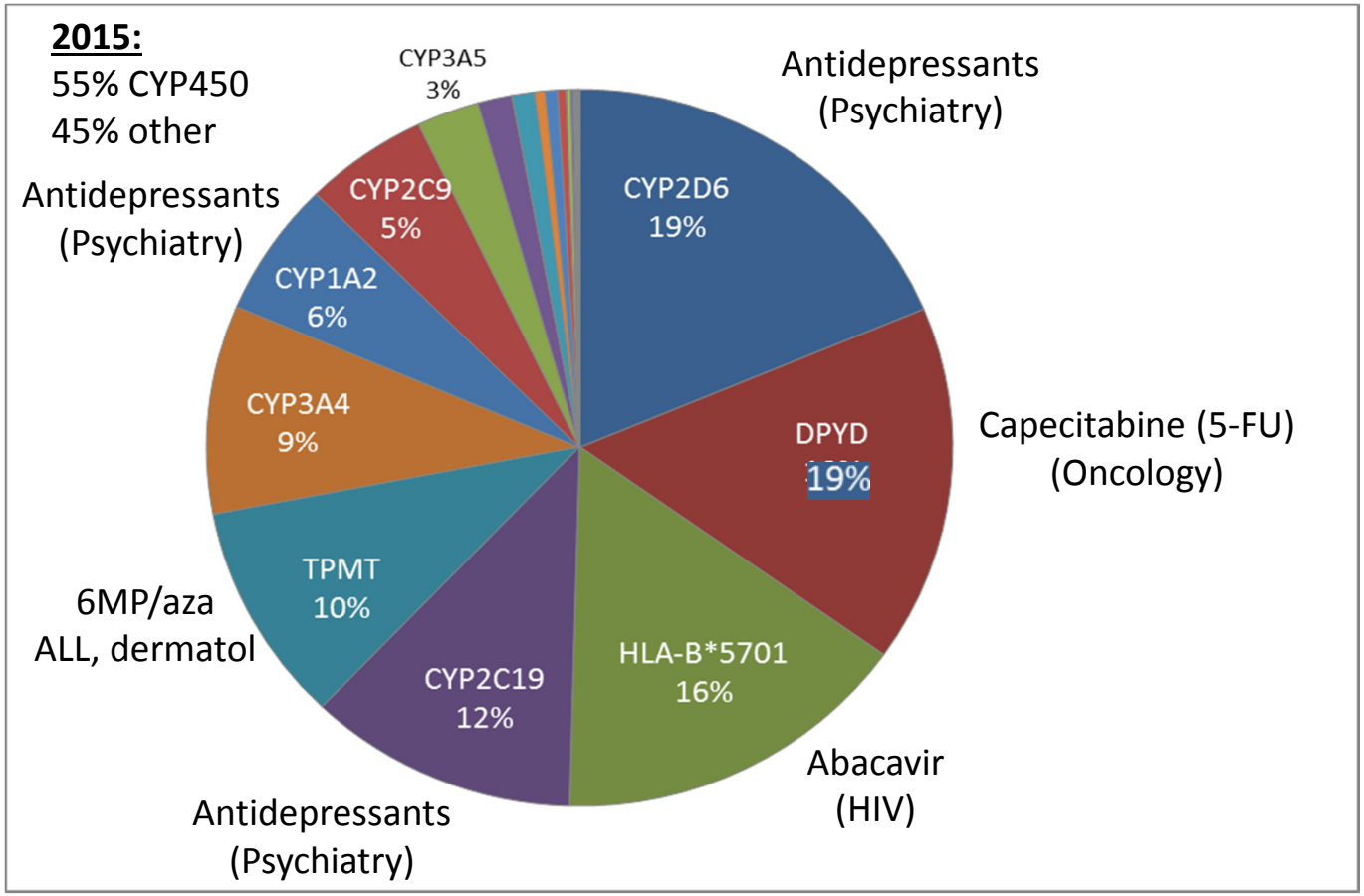
1. Netherlands
2. Austria
3. Belgium
4. Denmark
5. Finland
6. France
7. Germany
8. Greece
9. Hungary
10. Italy
11. Luxemburg
12. Portugal
13. Serbia
14. Slovenia
15. Sweden
16. Switserland
17. Turkey
18. United Kingdom

PGx request at Erasmus MC

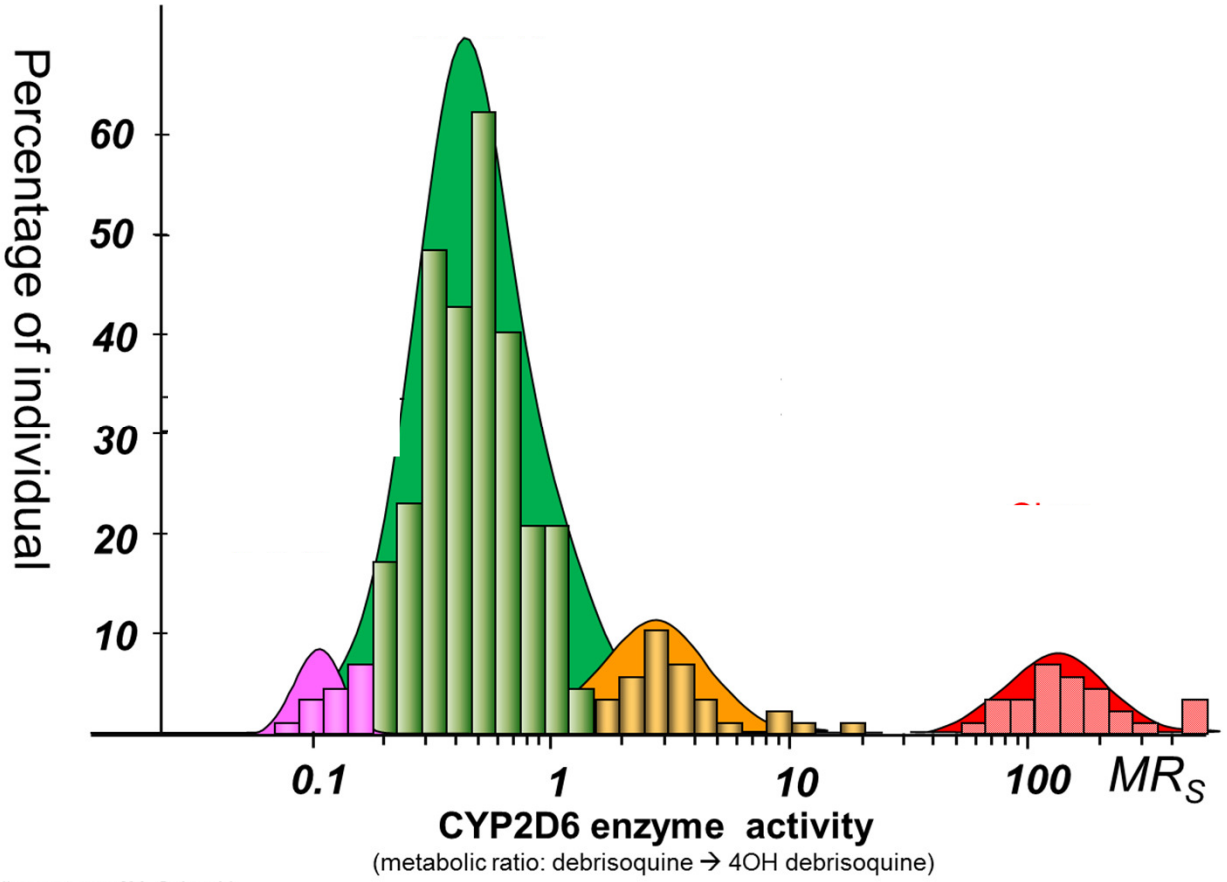



www.erasmusmc.nl/farmacogenetica
Erasmus MC
Afdeling Klinische Chemie
Patiënt:
Naam, voorletters
M V
BSN nummer
Geboortedatum
Postcode en plaats
Huisarts
Plaats
Apotheek
Plaats
Uw referentie
Afnamedatum
Aanvrager:
Spoed
Ziekenhuis / Huisarts / Apotheek
Geneesmiddel + dosering:
Bloedspiegel:
Co-medicatie:
Overige opmerkingen:
Pakketten:
DNA Paspoort - Basis (CYP2C9, CYP2C19, CYP2D6, CYP3A4, VKORC1,)
DNA Paspoort - Uitgebreid (CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, SLCO1B1)
Psychiatrie Panel (CYP2C9, CYP2C19, CYP2D6, CYP3A4)
Cardiac Panel (CYP2C9, CYP2C19, CYP2D6, VKORC1, SLCO1B1, ABCB1)
Pijn Panel (CYP2C9, CYP2D6, OPRM1, COMT)
Oncologie Panel (CYP2D6, DPYD)
Individuele bepalingen:
CYTOCHROMEN:
CYP1A2
CYP2B6
CYP2C8
CYP2C9
CYP2C19
CYP2D6
CYP3A4
CYP3A5
CYP3A7
Onbekend
OVERIGE ENZYMEN:
BChE, pseudocholinesterase
DPYD
TPMT
UGT1A1
UGT1A9
TRANSPORTERS:
ABCB1
ABCC2
ABCG2
SLCO1B1
HLA-markers*:
HLA-A*3101
HLA-B*1502
HLA-B*5701
Overig:
VKORC1
NB: EDTA-buis (tenminste 4 ml). Na afname EDTA volbloed maximaal vijf dagen bewaren bij 4°C (niet invriezen). EDTA-volbloed verzenden bij kamertemperatuur.
Verzendadres: Erasmus MC, Afdeling Klinische Chemie (AKC) Nb-415, Postbus 2040 3000CA Rotterdam

PGx test distribution at Erasmus MC

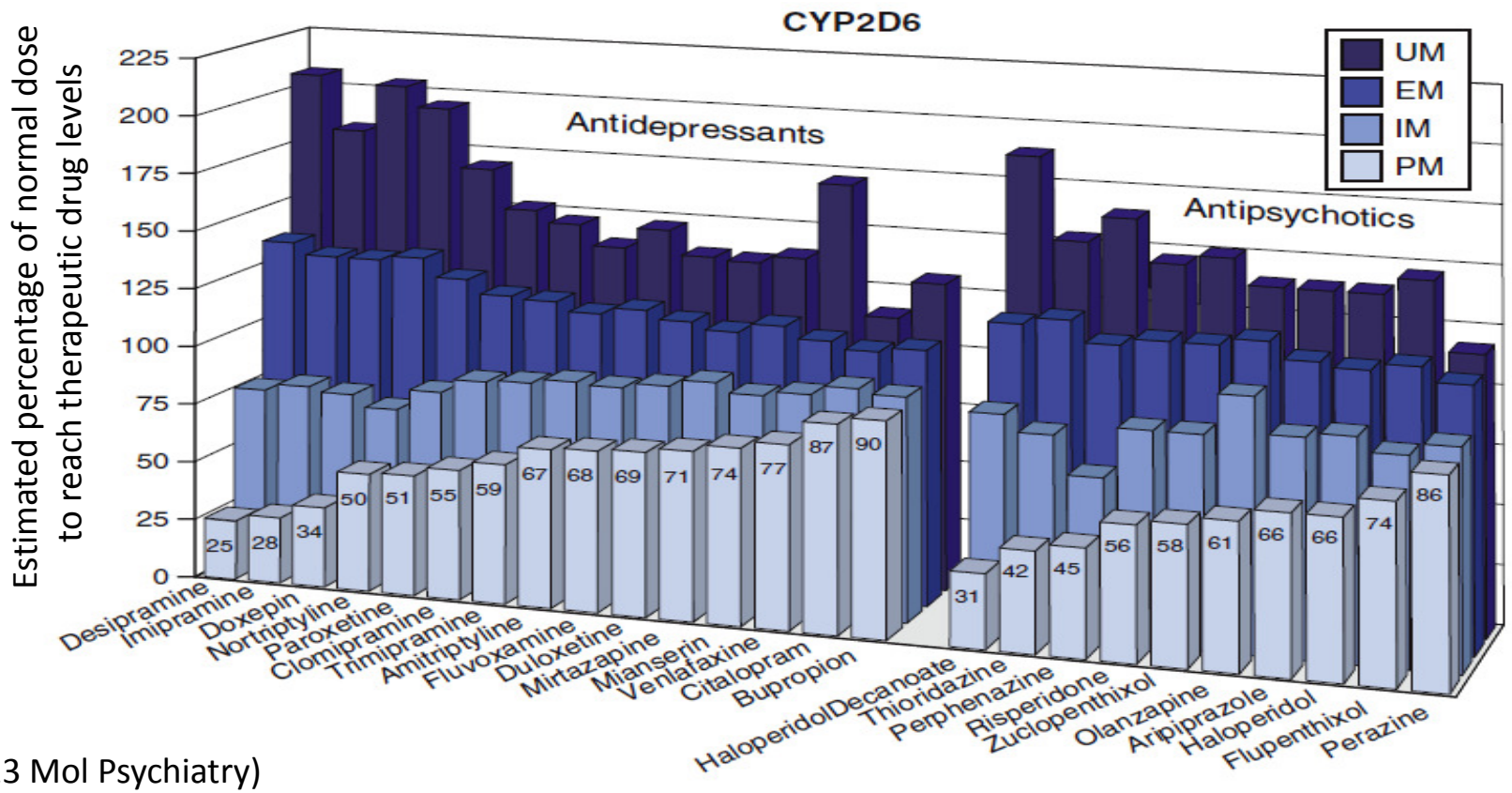


CYP2D6 activity distribution



(Slide (adapted) ;courtesy of M. Schwab)

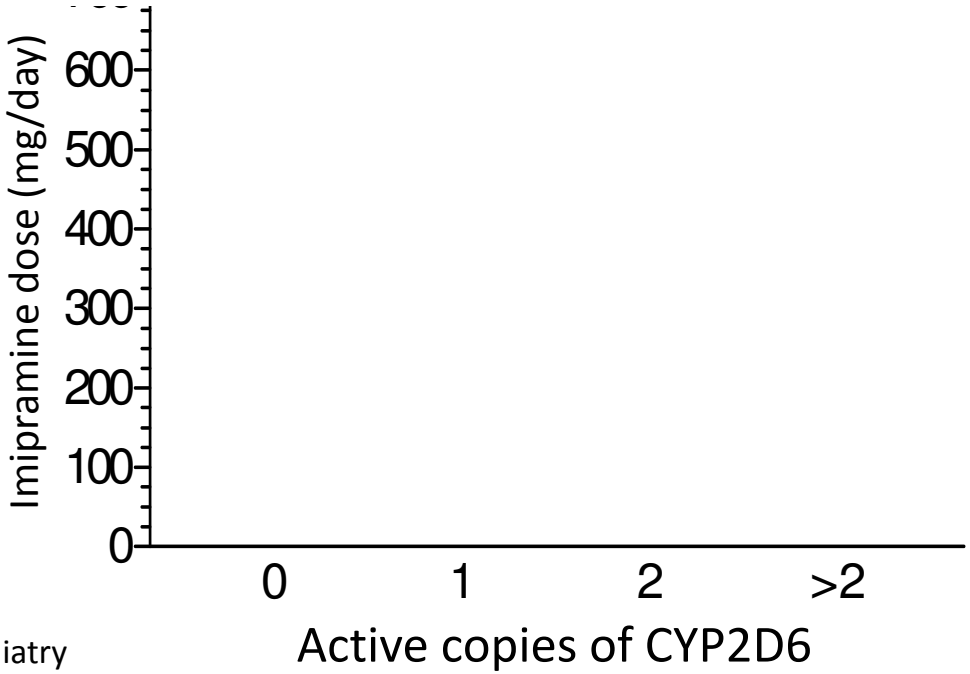
CYP2D6 and psychoactive drugs



(Stingl 2013 Mol Psychiatry)

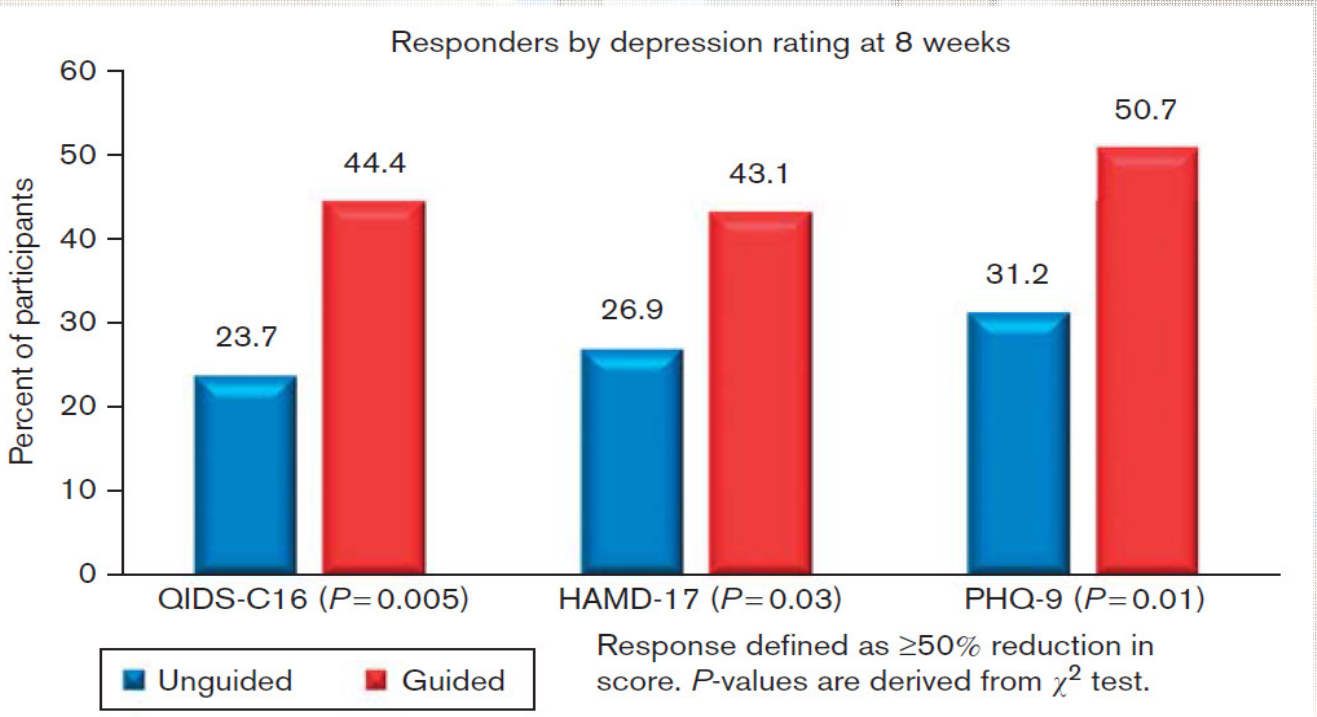
Imipramine metabolism

Imipramine —CYP2C19→ Desipramine —CYP2D6→ 2OH-desipramine



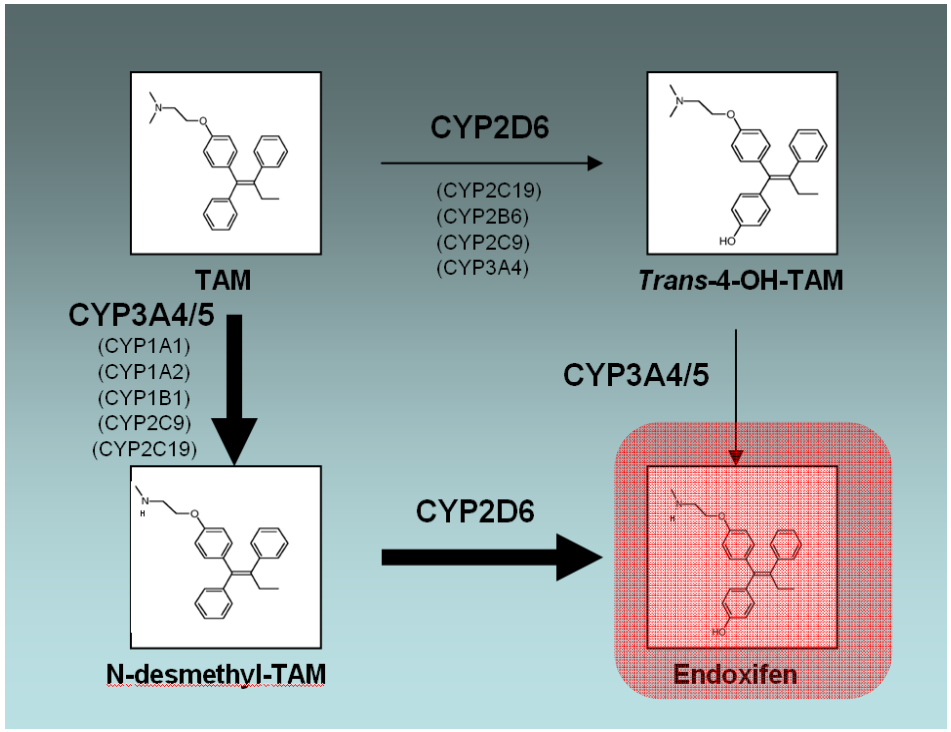
Paul Schenk et al 2008 Mol Psychiatry

Effect of PGx guided therapy

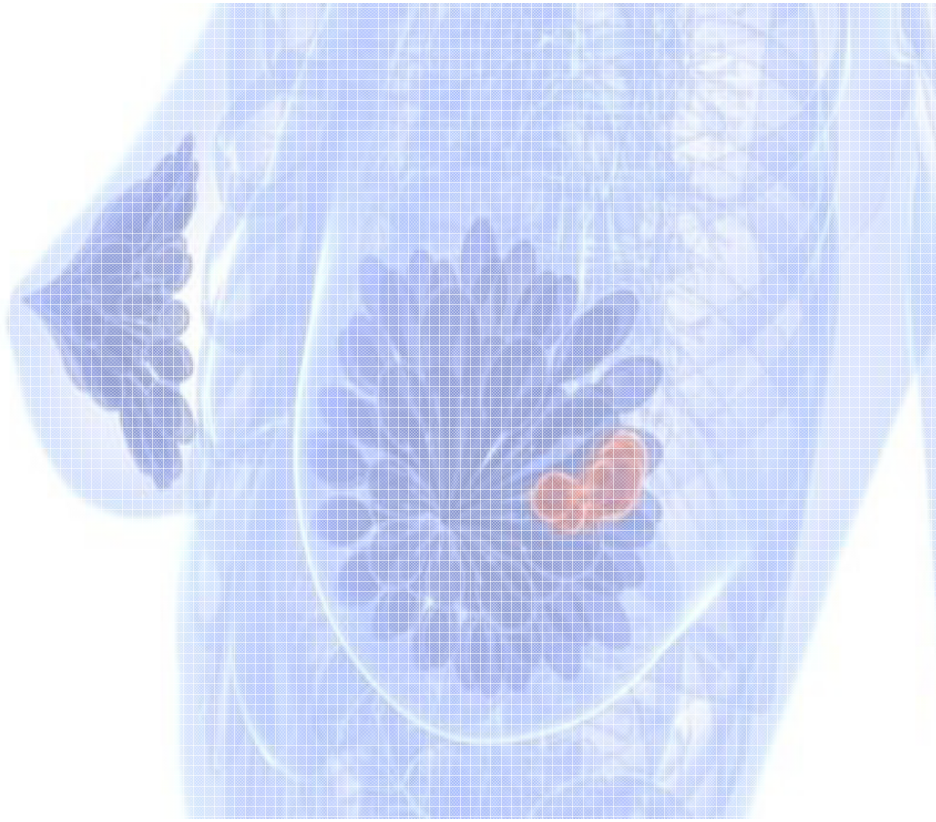


(Hall Flavin 2013 Pharmacogenomics)

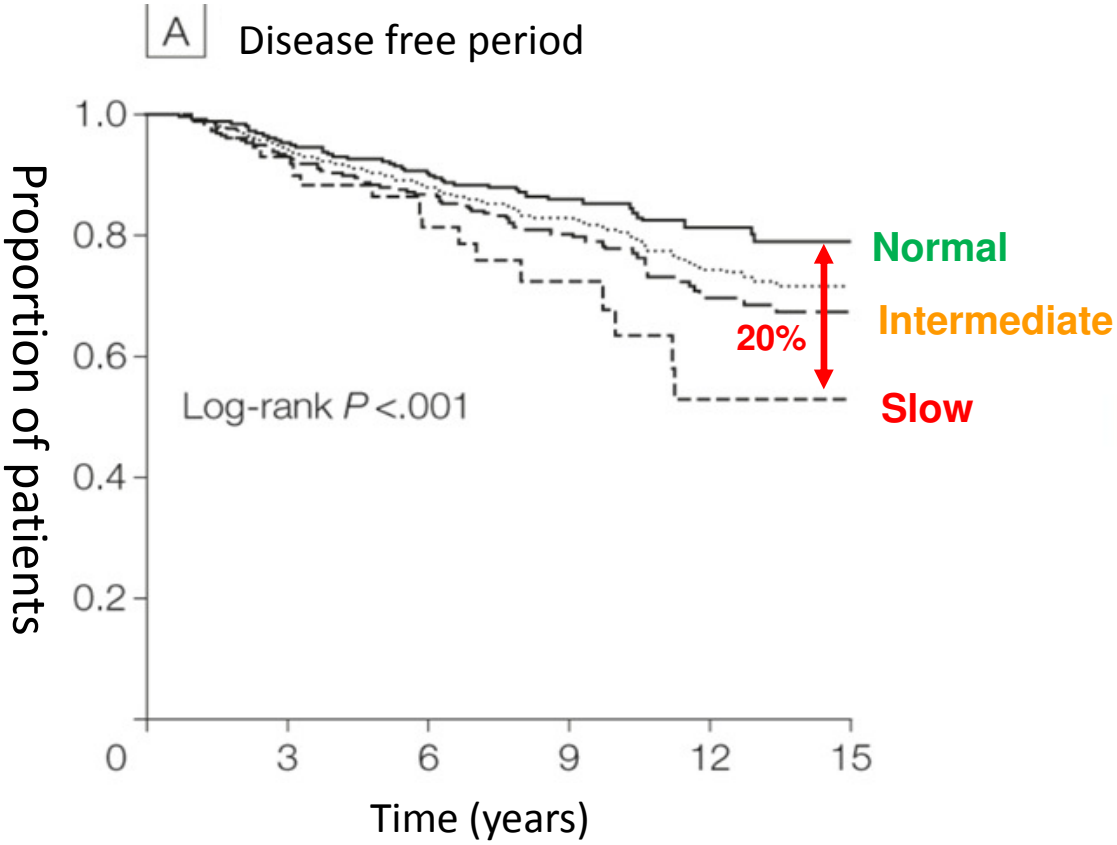
Breast cancer and Tamoxifen

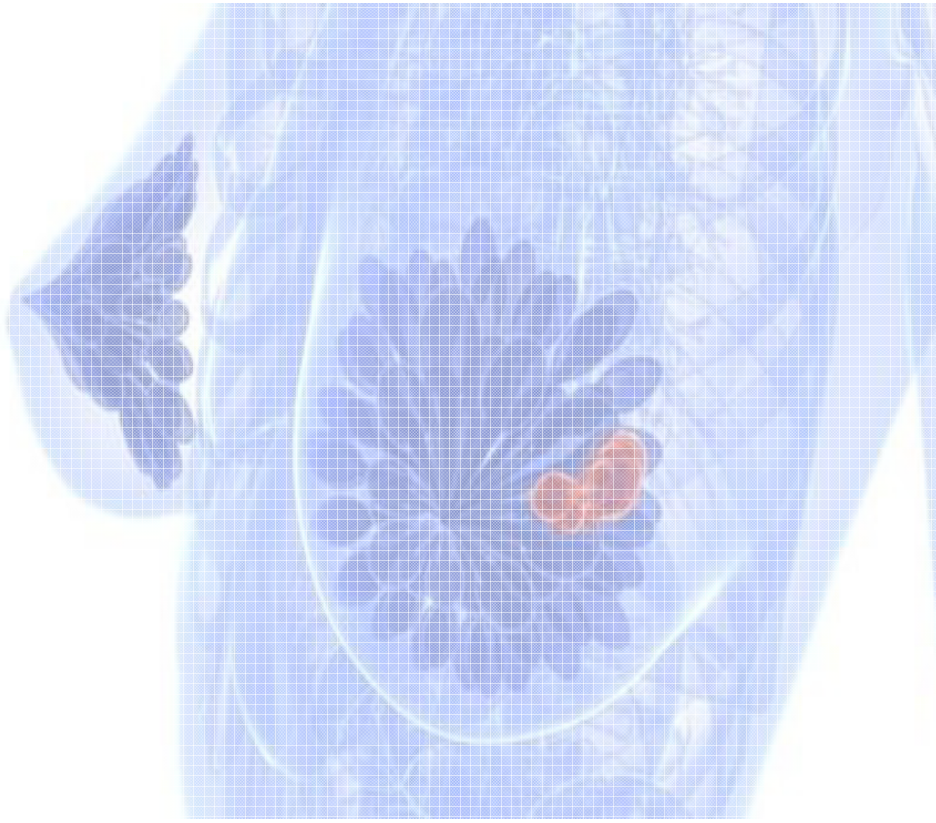


Effective metabolite



CYP2D6 and tamoxifen





(Schroth et al 2009 JAMA)

Published Articles: contradictory results…..

y	n	Genotyping	Endpoint	result
Kiyotani et al.Pharmacogen Genom 2010	167	*4, *5, *10, *21, *36, *41	RFS	+
Goetz et al. JCO 2005	190	*4		
Schroth et al. JCO 2007	206	*4, *5, *10, *41		
Lim et al. JCO 2007	21	*10		
Ramon y Cajal et al. Breast Cancer Res Treat 2010	91	*4, *5, *41		
Bijl et al. Breast Cancer Res Treat 2009	85	*4		
Schroth et al. JAMA 2009	**1325**	***3, *4, *5, *6, *10, *41**		
Kiyotani et al. JCO 2010	282	*4, *5, *10, *10-*10, *14, *21, *36, *41		
Lammers et al. Br J Cancer 2010	102	*3, *4, *5, *6, *10, *41		
Xu et al. Ann Oncol 2008	152	*10		
Newman et al. Clin Cancer Res 2008	115	*3, *4, *5, *41		
Stingl et al. Curr Med Res Opin 2010	496	*4		
Leyland-Jones et al. San Antonio 2010 (abstract)	1243	*4	DFS	-
Rae et al. San Antonio 2010 (abstract)	588	*3, *4, *6, *10, *41	RR	-
Dezentje et al. JCO 2010	747	?	DFS	-
Nowell et al. Breast Cancer Res Treat 2005	162	*3, *4, *6	PFS	-
Wegman et al. Breast Cancer Res 2005	76	*4	RR	invers
Wegman et al. Breast Cancer Res 2007	677	*4	DFS	invers

Hardy Weinberg equilibrium

Minor allele frequency: 10%

	Expected	Observed
Wild type	90%	87%
Heterozygote	9%	11%
Homozygote mut	1%	2%

P>0.05

Rae et al: Not in Hardy Weinberg Equilibrium ($p< 10^{-91}$)

POINT/COUNTERPOINT

CPT Aug 2013

CYP2D6 Genotype Should Not Be Used to Determine Endocrine Therapy in Postmenopausal Breast Cancer Patients

JM Rae[1,2]

Not ready for clinical implementation

Big study, no effect for CYP2D6

CYP2D6 Genotype and Tamoxifen Activity: Understanding Interstudy Variability in Methodological Quality

MJ Ratain[1–3], Y Nakamura[1–4] and NJ Cox[1–3,5]

Ready for clinical implementation

Plausability, many positive studies, fits with PK Endoxifen, study Rae not in HW

Province M et al 2013 CPT

ACCEPTED ARTICLE PREVIEW

(Preview online Sept 23, 2013)

Abstract

The International Tamoxifen Pharmacogenomics Consortium (ITPC) was established to address the controversy over *CYP2D6* status and clinical outcomes in tamoxifen therapy. We performed a meta-analysis on data from 4,973 tamoxifen treated patients (twelve globally-distributed sites). Using strict eligibility requirements (postmenopausal women with estrogen receptor (ER) positive breast cancer receiving 20 mg/day tamoxifen for 5 years, Criterion 1), CYP2D6 poor metabolizer status was associated with poorer Invasive Disease-Free Survival (IDFS: HR=1.25; 95% CI 1.06, 1.47; P=0.009).

Clopidogrel needs activation by CYP2C19

N ENGL J MED 360;4 NEJM.ORG JANUARY 22, 2009

The NEW ENGLAND JOURNAL of MEDICINE

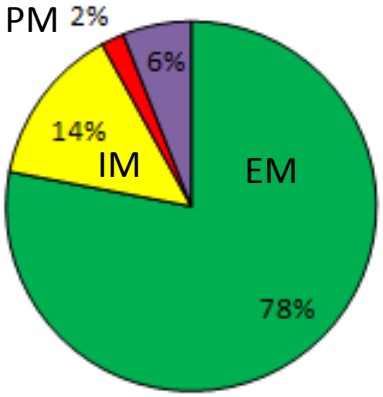
ORIGINAL ARTICLE

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

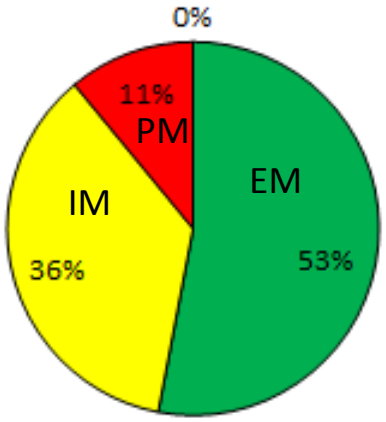
Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

CONCLUSIONS

Among patients with an acute myocardial infarction who
grel, those carrying *CYP2C19* loss-of-function alleles had a hi
cardiovascular events than those who were not. This effect v
among the patients undergoing percutaneous coronary inter
gov number, NCT00673036.)



Caucasians



Asians

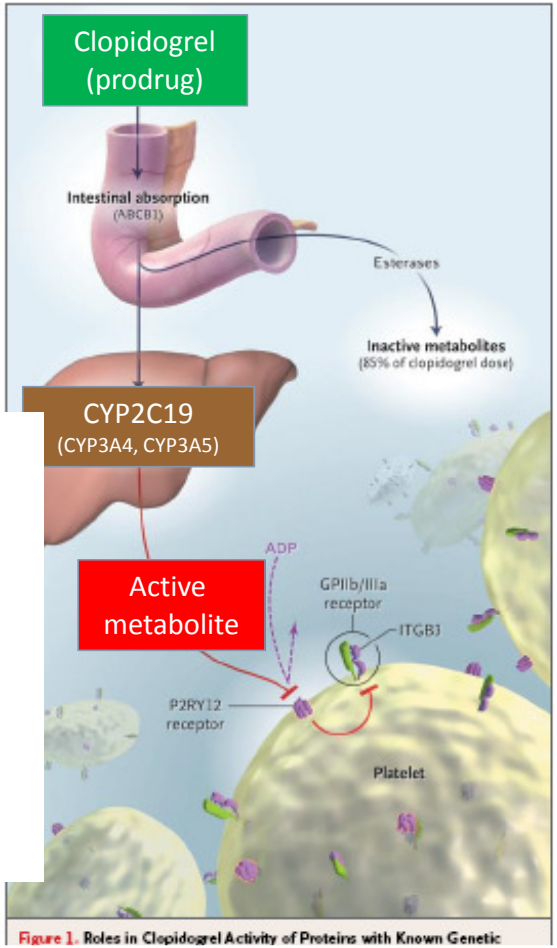
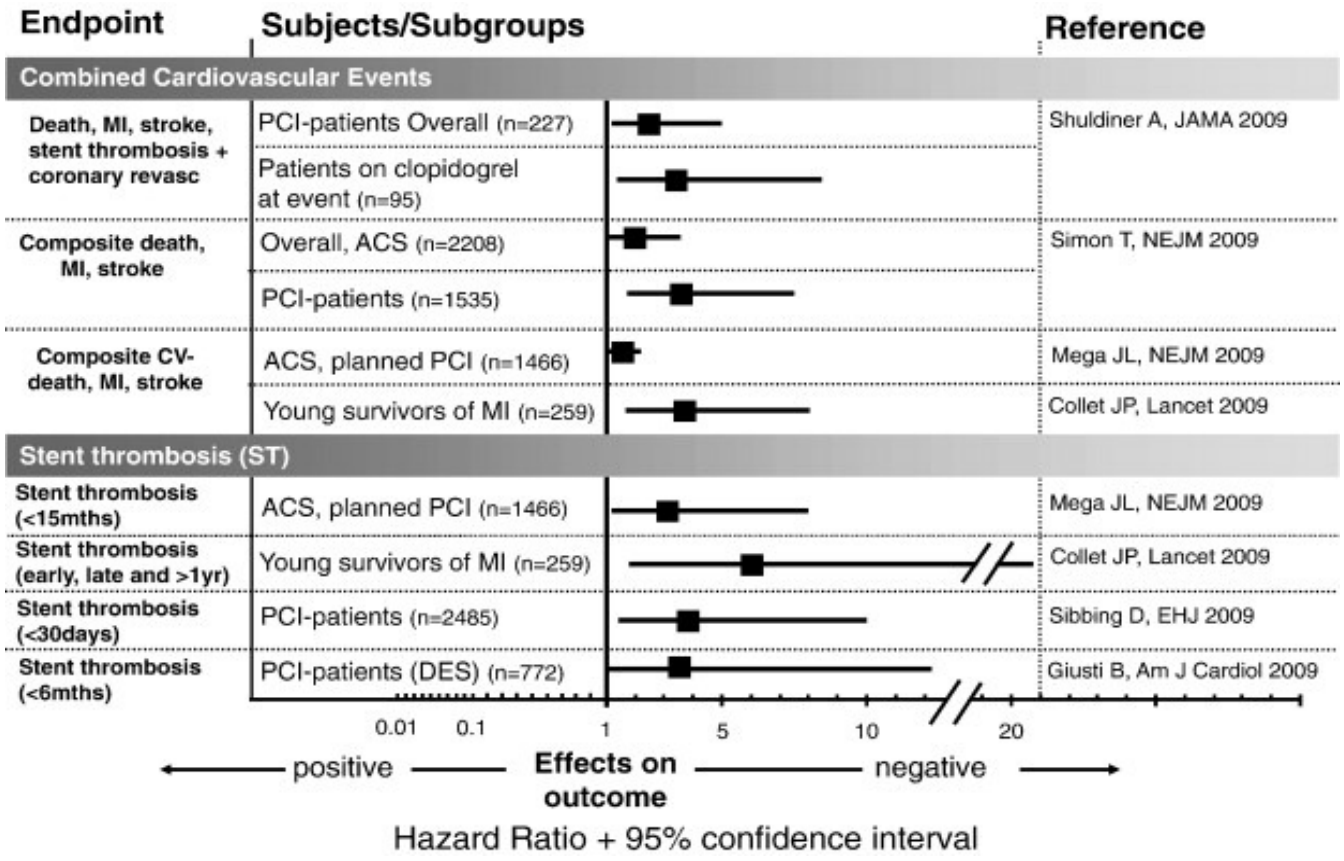


Figure 1. Roles in Clopidogrel Activity of Proteins with Known Genetic

Meta-analysis (Geisler et al 2011 CPT)

CY2C19*2 carriers are at risk



Test for CYP2C19 variants:

Negative → clopidogrel (€)

Positive → prasugrel (€€€)

FDA Boxed Warning on Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally

action.[1/5] At present, genetic testing cannot be recommended in routine clinical practice due to insufficient prospective data. In con-

syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function

- Tests are available to identify a patient's CYP2C19 genotype and ca

European Heart Journal doi:10.1093/eurheartj/ehv320

2015 ESC Guidelines for th... of acute cor...

...ome ...ister ...enda

...ask Force for the Management of Acute C... Patients Presenting without Persistent ST-... European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairpe... Carlo Patrono* (co-Chairperson) (Italy), Jean-Philippe... Christian Mueller† (Switzerland), Marco Valgimigli† (T... Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands)... Carlos Brotons (Spain), Derek P. Chew (Australia), Bar... Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), P... Ulf Landmesser (Germany), Julinda Mehilli (Germany), D... Robert F. Storey (UK), and Stephan Windecker (Switze...

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EMA drug label (3).

The EMA-drug label contains the following wording:

Section 4.4: Cytochrome P450 2C19 (CYP2C19)

"Pharmacogenetics: In patients who are poor CYP2C19 metaboli doses forms less of the active metabolite of clopidogrel and has a Tests are available to identify a patient's CYP2C19 genotype."

DNA passport for Drug Therapy

Erasmus MC

Nederlands Expertisecentrum Farmacogenetica
Afd. Klinische Chemie
Erasmus MC Rotterdam

Farmacogenetica Profiel

Bij een afwijkend
aangepaste doser
uw arts of apothek
KNMP-Kennisbank

Naam: Test Erasmus MC/RvS **Geb. datum: 01/01/1980**

BSN: 12345678 **Uitgifte kaart: 14/07/2014**

Gen:	Uitslag:	Metabolisme	Prev.:[1]	Getest op:
CYP1A2	*1/*1	Normaal	45%	*1C, *1F, *1K
CYP2B6	*4/*6	Intermediair	25%	*4, 5, 6, 7, 8, 9, 13, 16, 18
CYP2C9	*1/*2	Intermediair	17%	*2, 3
CYP2C19	*1/*1	Normaal	80%	*2, 3, 17
CYP2D6	*1/*2xN	Ultrasnel	3%	25 varianten (AmpliChip)
CYP3A4	*1/*1	Normaal	80%	*1B,1G,3-6,10,12,17,18,20,22
CYP3A5	*3/*3	Nonexpressor	80%	*3, *6
BChE	U/S	Normaal	99%	A, K, F1, F2, H, J, Sc, Silent
DPYD	*1/*2A	Intermediair	2%	*2A
HLA-B*5701	NEG	Normaal	96%	
TPMT	*1/*1	Normaal	89%	*2, 3A, 3B, 3C
VKORC1	AA	Gevoelig	20%	-1639G>A

[1] *In blanke bevolking. Kan afwijken bij andere etniciteiten*

KNMP | Kennisbank

Home > Medicatiebewaking > Farmacogenetica > IMIPRAMINE CYP2D6 PM-IM-UM

farmacogenetica

- UM
- IMIPRAMINE CYP2D6 PM-IM-UM
- KINIDINE CYP2D6 PM-IM-UM
- METHYLFENIDAAT CYP2D6 PM-IM-UM
- METOPROLOL CYP2D6 IM-PM-UM
- MIRTAZAPINE CYP2D6 PM-IM-UM
- NORTRIPTYLINE CYP2D6 IM-PM-UM
- OLANZAPINE CYP2D6 IM-PM-UM
- OXYCODON CYP2D6 PM-IM-UM
- PAROXETINE CYP2D6 IM-PM-UM
- PIMOZIDE CYP2D6 PM-IM-UM
- PROPAFENON CYP2D6 PM-IM-UM
- QUETIAPINE CYP2D6 PM-IM-UM
- RISPERIDON CYP2D6 UM-IM-PM

Inhoud

- CYP2D6 PM
  - Apothekertekst
  - Balietekst
  - Voorschrijvertekst
  - Ziekenhuistekst
  - Achtergrondinformatie
  - Literatuur
  - Geneesmiddelen
- CYP2D6 IM
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  - Ziekenhuistekst
  - Achtergrondinformatie
  - Literatuur
  - Geneesmiddelen

IMIPRAMINE CYP2D6 PM-IM-UM

CYP2D6 PM

Apothekertekst

Het genetisch polymorfisme leidt tot een verlaagde metabole capaciteit van CYP2D6 waardoor de plasmaconcentraties van imipramine en de actieve metaboliet kunnen stijgen.

Advies:

1. verlaag de dosering tot 30% van de normale dosering en monitor de plasmaconcentraties van imipramine en desipramine voor het instellen van de onderhoudsdosering

Balietekst

De omzetting van imipramine door het enzym CYP2D6 is verlaagd als gevolg van een genetische variatie.

Overleg met de apotheker.

1. verlaag de dosering tot 30% van de normale dosering en monitor de plasmaconcentraties van imipramine en desipramine voor het instellen van de onderhoudsdosering