Clinical and Genetic Epidemiology Winter School

15.02.2017

Pharmacogenomics

Part 1 – General PGx

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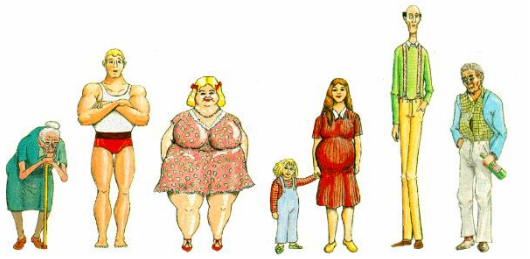
What is ‘omics’ in the biological context?

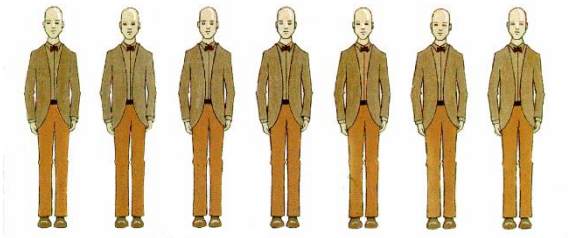
- Genomics (the quantitative study of genes, regulatory and non-coding sequences)
- Transcriptomics (RNA and gene expression)
- Proteomics (protein expression)
- Metabolomics (metabolites and metabolic networks)
- **Pharmacogenomics (the quantitative study of how genetics affects hosts' responses to drugs)**

Goals of Pharmacogenomics

- Identification of novel drug targets
- Facilitated drug development
- Salvage of less effective drugs
- Explanation of interindividual response
- Optimized drug treatment

Individualized treatment *versus* "one fits all"

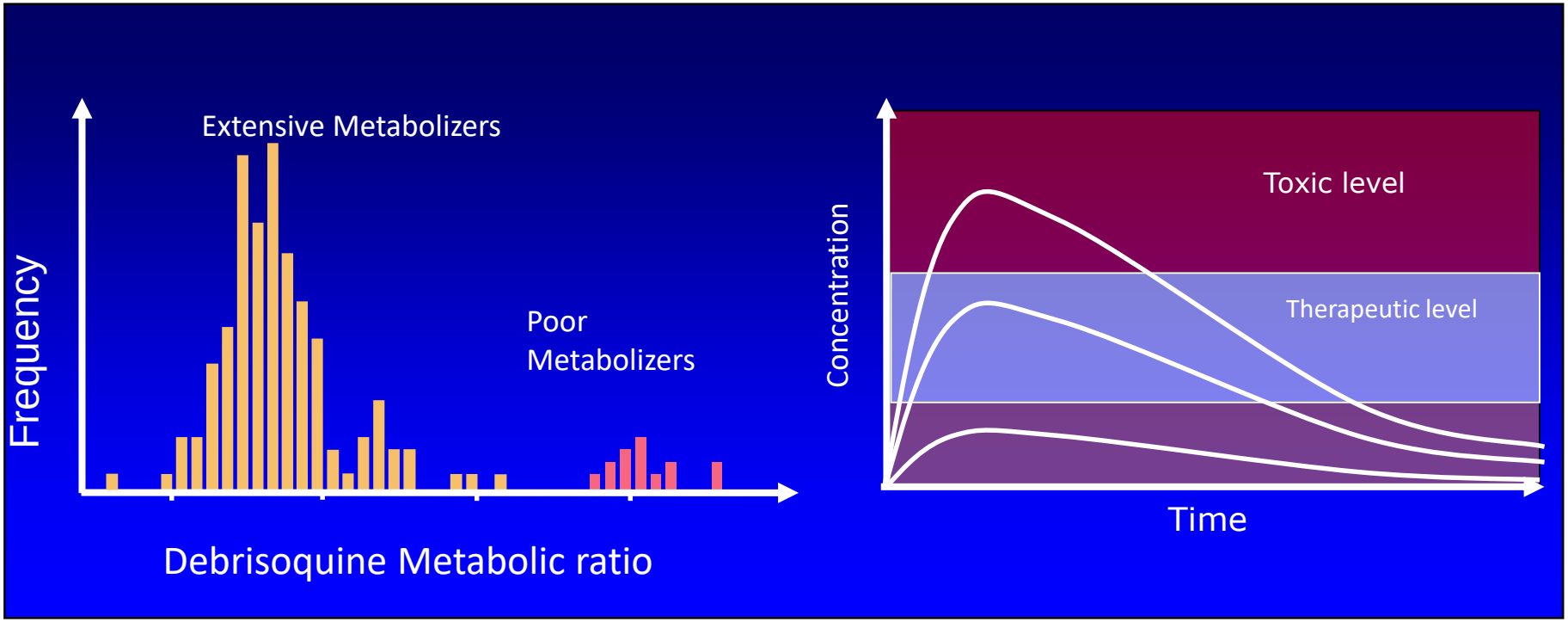




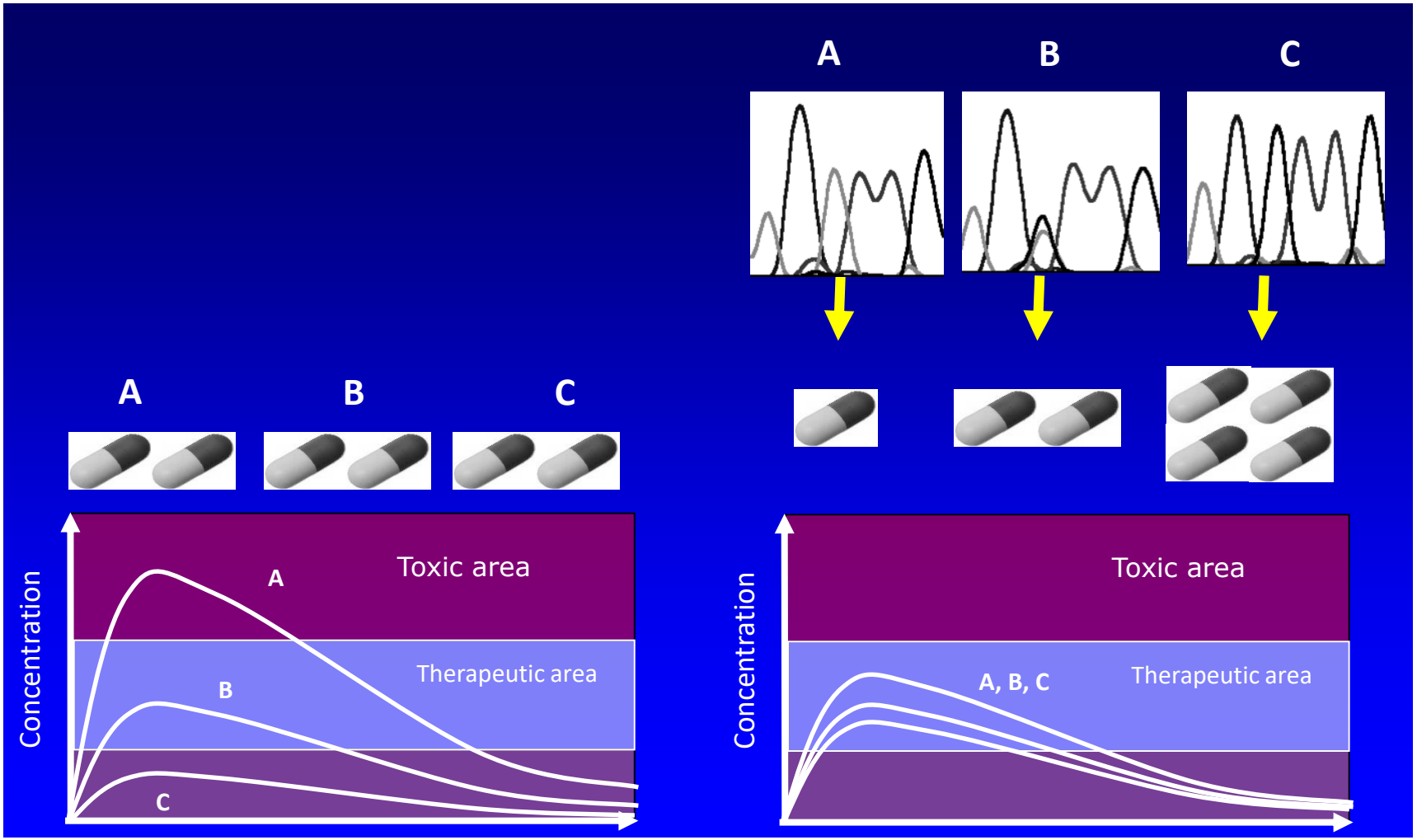
„Classic“ concept of pharmacogenetics

Observation:
Presence of different phenotypes regarding the plasma levels

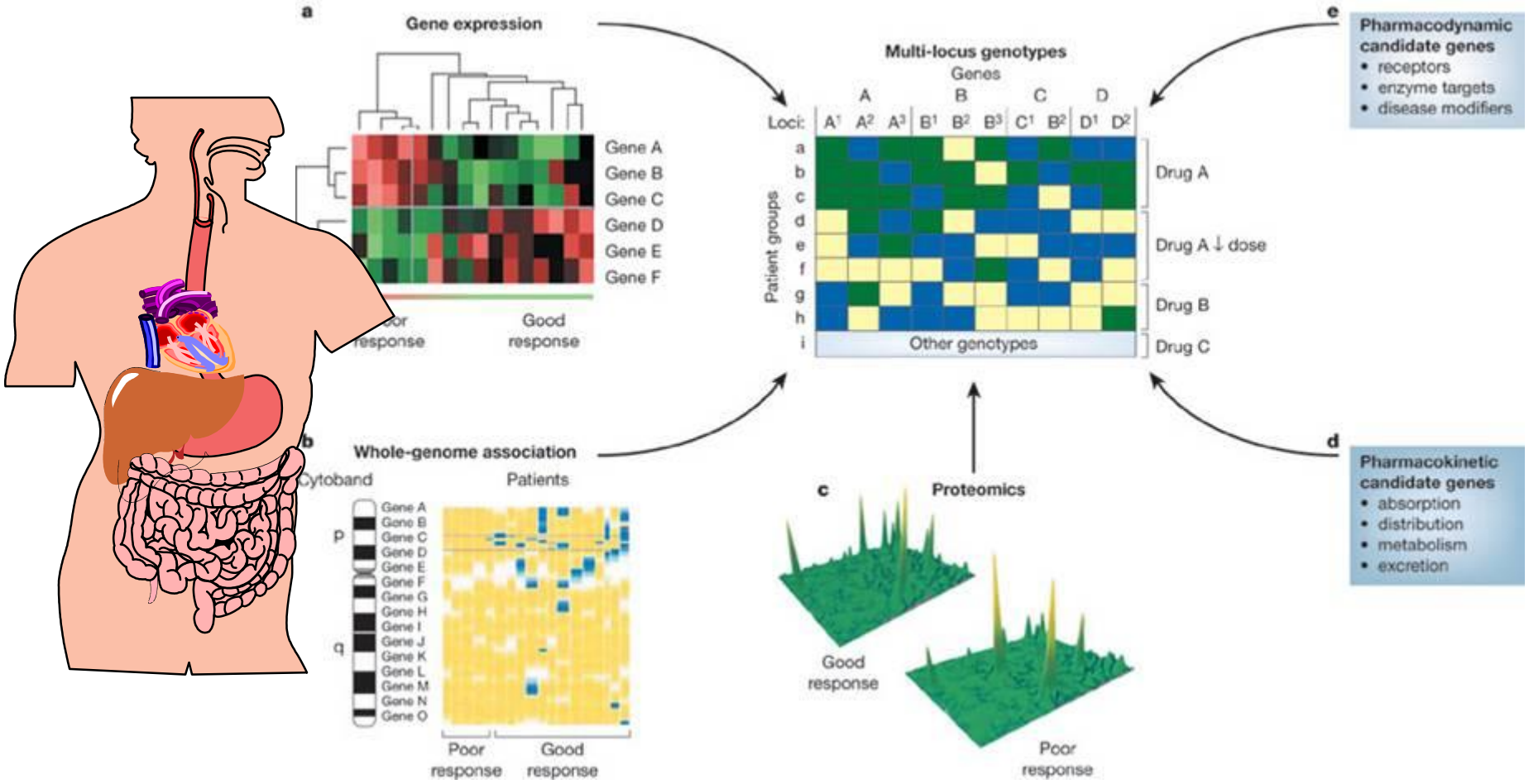
Goal:
Identification of allelic variants, being associated with the different phenotypes



Simple model of dose individualization



Identifying genes influencing polygenic drug response



Evans and Relling, Nature 2004

Biomarkers in individualized therapy

Diagnostic biomarkers

- High specificity – detection of specific disease

Prognostic biomarkers

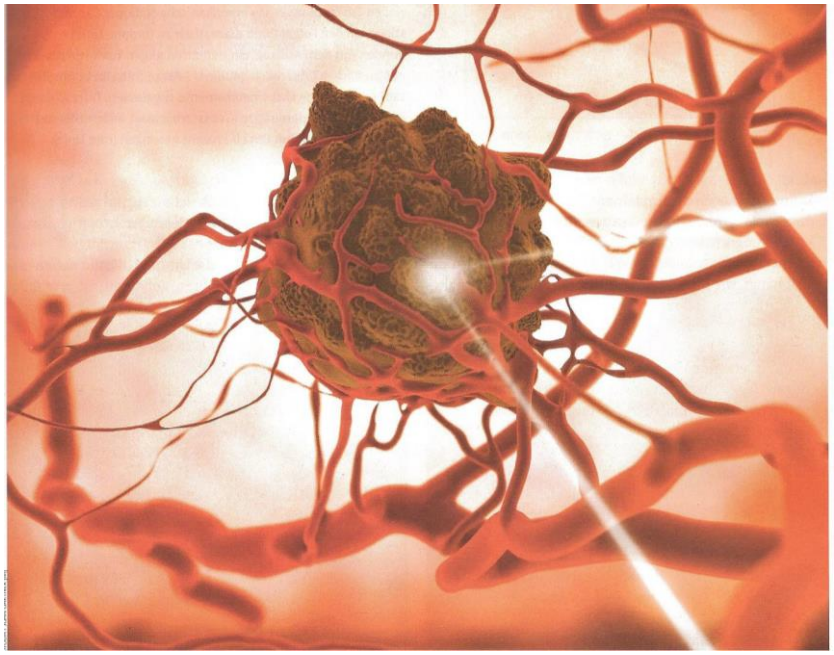
- Differential expression – correlation with patient outcome
- Stratification of high vs. low risk patients
- Guide for patient information and monitoring

Predictive biomarkers

- Differential expression – correlation with treatment response
- Stratifictation to responders and non-responders
- Guide to determine selection of therapeutic regime

Current focus of stratified therapy

(Somatic) tumor gene variants as predictive biomarker



Applying pharmacogenetic testing

Hereditary (inherited) variants (polymorphisms)

Somatic mutations (tumor mutations) do not belong to pharmacogenetics according to the German Gene Diagnostics Act (Gendiagnostikgesetz)

REVIEW

doi:10.1038/nature15817

Pharmacogenomics in the clinic

20 genes that affect about 80 medications

Mary V. Relling[1] & William E. Evans[1]

After decades of discovery, inherited variations have been identified in approximately 20 genes that affect about 80 medications and are actionable in the clinic. And some somatically acquired genetic variants direct the choice of 'targeted' anticancer drugs for individual patients. Current efforts that focus on the processes required to appropriately act on pharmacogenomic variability in the clinic are moving away from discovery and towards implementation of an evidenced-based strategy for improving the use of medications, thereby providing a cornerstone for precision medicine.

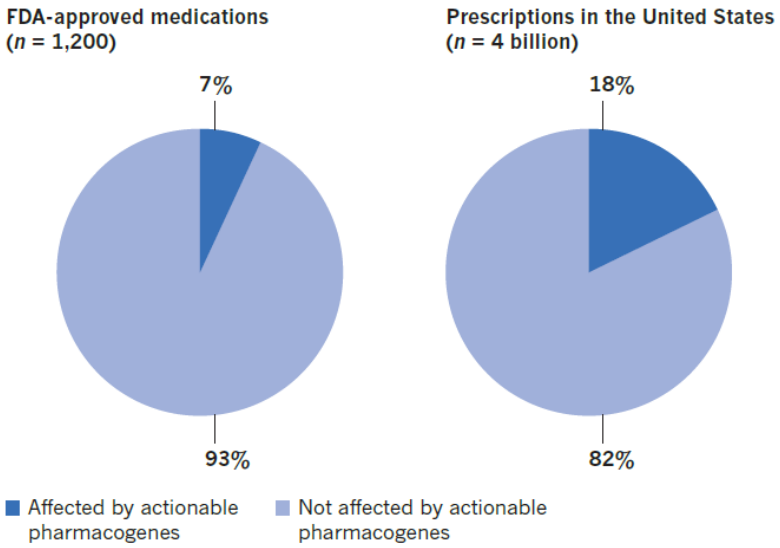
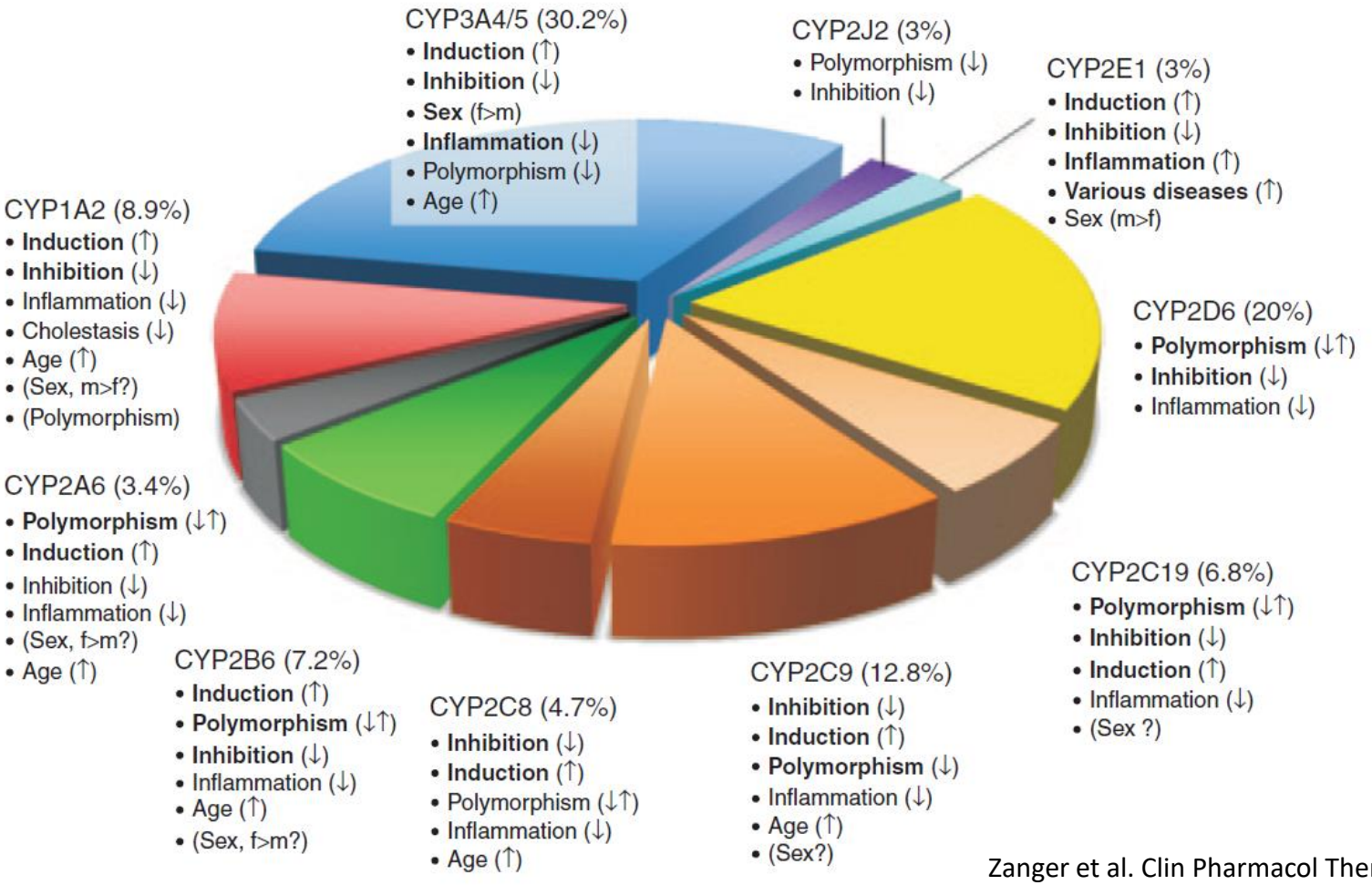


Table 1 | Actionable germline genetic variation and associated medications

Genetic variation	Medications
TPMT	Mercaptopurine, thioguanine, azathioprine
CYP2D6	Codeine, tramadol, tricyclic antidepressants
CYP2C19	Tricyclic antidepressants, clopidogrel, voriconazole
VKORC1	Warfarin
CYP2C9	Warfarin, phenytoin
HLA-B	Allopurinol, carbamazepine, abacavir, phenytoin
CFTR	Ivacaftor
DPYD	Fluorouracil, capecitabine, tegafur
G6PD	Rasburicase
UGT1A1	Irinotecan, atazanavir
SLCO1B1	Simvastatin
IFNL3 (IL28B)	Interferon
CYP3A5	Tacrolimus

Relling & Evans. Nature. 2015;526:343-50.

Factors influencing function of P450-enzymes in human liver



Zanger et al. Clin Pharmacol Ther 2014; 95:258

Pharmacogenetic information in drug labels (EMA)

The Pharmacogenomics Journal (2015) 15, 201–210

www.nature.com/tpj

PERSPECTIVE

Pharmacogenomic information in drug labels: European Medicines Agency perspective

F Ehmann[1], L Caneva [1], K Prasad[2,3], M Paulmichl[2,4], M Maliepaard[2,5,6], A Llerena[2,7], M Ingelman-Sundberg[8] and M Papaluca-Amati[1]

Pharmacogenomics (PGx) has a growing impact on healthcare and constitutes one of the major pillars of personalised medicine. For the purpose of improved individualised drug treatment, there is an increasing effort to develop drugs suitable for specific subpopulations and to incorporate pharmacogenomic drug labels in existing and novel medicines. Here, we review the pharmacogenomic drug labels of all 517 medicinal products centrally approved in the European Union (EU) since the establishment of the European Medicines Agency in 1995. We identified all pharmacogenomic-related information mentioned in the product labels and classified it according to its main effect and function on drug treatment, that is, metabolism, transport and pharmacodynamics, and according to the place of the respective section of the Summary of Product Characteristics (SmPC). The labels are preferentially present in drugs having antineoplastic properties. We find that the number of drugs with pharmacogenomic labels in EU increases now steadily and that it will be an important task for the future to refine the legislation on how this information should be utilised for improvement of drug therapy.

The Pharmacogenomics Journal (2015) **15,** 201–210; doi:10.1038/tpj.2014.86; published online 24 February 2015

Recommendations on pharmacogenetic information in drug labels (EMA)

4.1 Therapeutic indications
If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype , then this should be stated in the indication

4.2 Posology and method of administration
Where necessary, dosage adjustments inpatients with a particular genotype should be stated with cross reference to other relevant sections for further detail as appropriate

4.3 Contraindications
Linked to a particular genotype

4.4 Special warnings and precautions for use
Subjects or patients with a specific genotype or phenotype may either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. This may arise because non-functioning enzyme alleles, alternative metabolizing pathways (governed by specific alleles) or transporter deficiencies. Such situation should be clearly described if known.

Ehmann et al. Pharmacogenomics J 2015;15:201–210

Recommendations on pharmacogenetic information in drug labels (EMA)

4.5 Interactions with other medicinal products
If interactions with other medicinal products depend on polymorphisms of metabolizing enzymes or certain genotypes, this should be stated.

4.8 Undesirable effects
This section may include information on any clinical relevant differences specifically observed in patients with a specific genotype

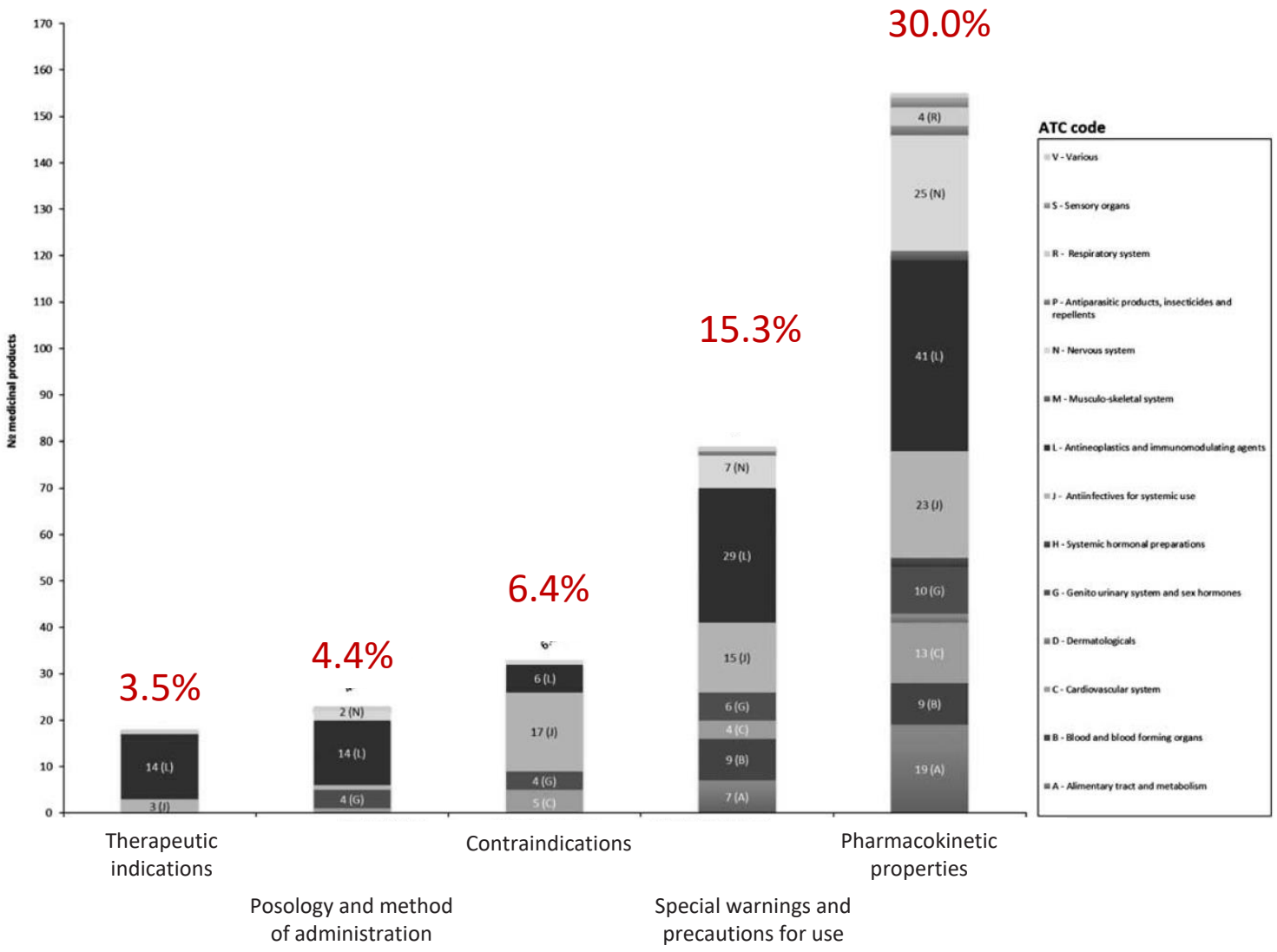
4.9. Overdose
If applicable, counteractive measures based on genetic factors should be described

5.1. Pharmacodynamic properties
Any relevant pharmacogenetic information from clinical studies should be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.

5.2. Pharmacokinetic properties
Variation with respect to polymorphic metabolism should be described, if clinically relevant, in quantitative terms.

Ehmann et al. Pharmacogenomics J 2015;15:201–210

Pharmacogenetic information in drug labels (EMA)



Ehmann et al. Pharmacogenomics J 2015;15:201–210

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/CHMP/281371/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 April 2016
EMA/CHMP/268544/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on good pharmacogenomic practice

Draft

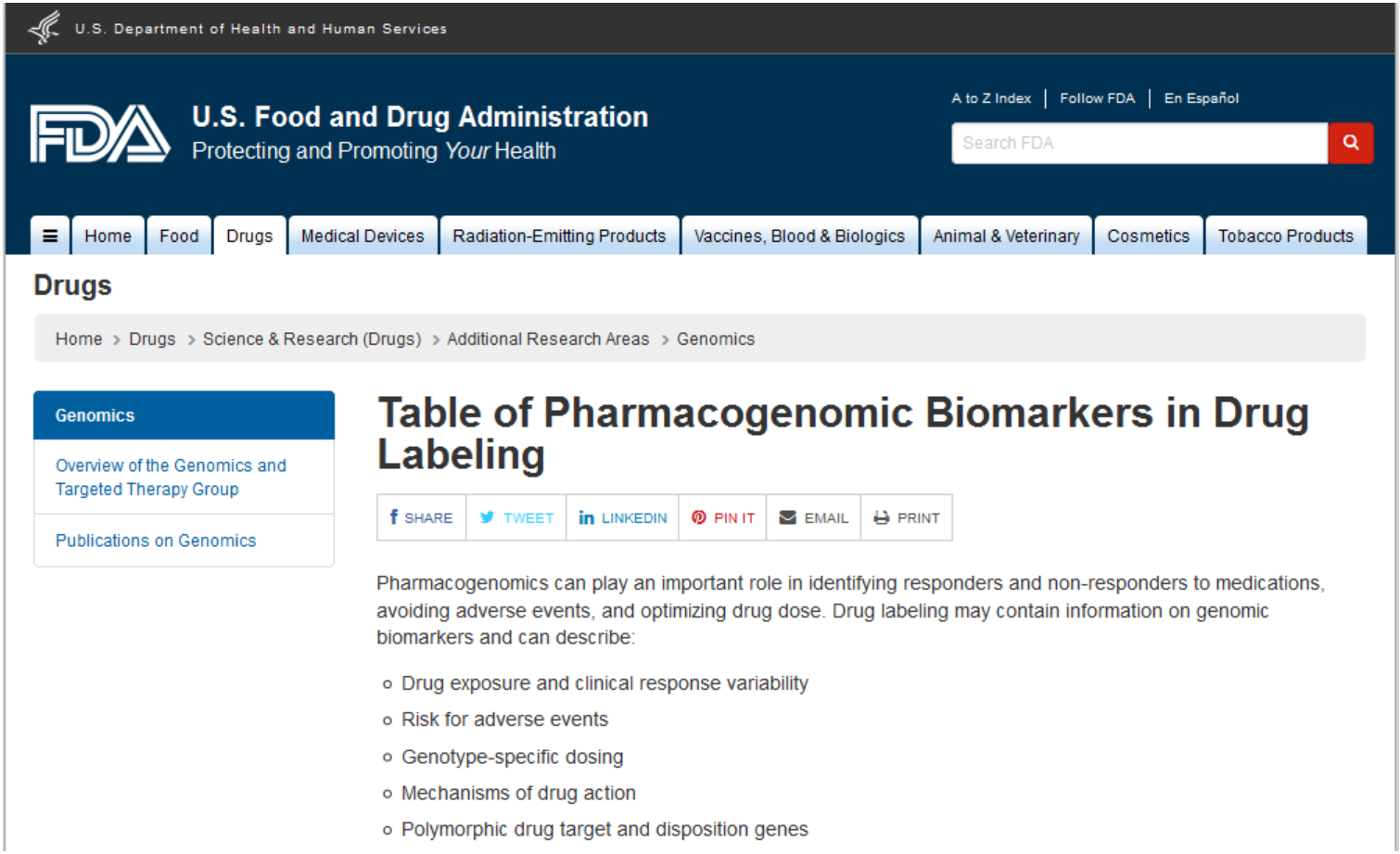
Agreed by Pharmacogenomics Working Party	21 March 2016
Adopted by CHMP for release for consultation	28 April 2016
Start of public consultation	02 May 2016
End of consultation (deadline for comments)	16 September 2016

Indications including pharmacogenomic biomarker implications for drugs evaluated between 1995 and 2014 by the European Medicines Agency

Name	*INN*	*Year of approval*	*PGx biomarker*	*Indication*
SmPC section Therapeutic indications (section 4.1)				
Herceptin	Trastuzumab	2000	HER2	Stomach neoplasms Breast neoplasms
Tyverb	Lapatinib	2008		Breast neoplasms
Afinitor	Everolimus	2009		Carcinoma, renal cell pancreatic neoplasms, breast neoplasms
Kadcyla	Trastuzumab emtansine	2013		Breast neoplasms
Perjeta	Pertuzumab	2013		Breast neoplasms
Ziagen	Abacavir	1999	HLA-B*5701	HIV infections
Trizivir	Abacavir/lamivudine/zidovudine	2000		
Kivexa	Abacavir/lamivudine	2004		
Tarceva	Erlotinib	2005	EGFR	Non-small-cell lung carcinoma pancreatic neoplasms
Iressa	Gefitinib	2009	EGFR	Non-small-cell lung carcinoma
Giotrif	Afatinib	2013	EGFR	Non-small-cell lung carcinoma
Erbitux	Cetuximab	2004	EGFR RAS	Colorectal neoplasms Head and neck neoplasms
Vectibix	Panitumumab	2007	RAS	Colorectal neoplasms
Glivec	Imatinib	2001	BCR-ABL Kit *CD117* FIP1L1-PDGFR	Chronic myelogenous leukaemia Gastrointestinal stromal tumours Myelodysplastic-myeloproliferative diseases Dermatofibrosarcoma Precursor cell lymphoblastic leukaemia-lymphoma Hypereosinophilic syndrome
Sprycel	Dasatinib	2006	BCR-ABL	Chronic myelogenous leukaemia precursor cell lymphoblastic leukaemia-lymphoma
Tasigna	Nilotinib	2007	BCR-ABL	Chronic myelogenous leukaemia
Bosulif	Bosutinib	2013	BCR-ABL	Myelogenous leukaemia
Imatinib (accord, actavis, medac)	Imatinib	2013	BCR-ABL Kit CD117 FIP1L1-PDGFR	Chronic myelogenous leukaemia Myelodysplastic-myeloproliferative diseases Dermatofibrosarcoma Precursor cell lymphoblastic leukaemia-lymphoma Hypereosinophilic syndrome
Iclusig	Ponatinib	2013	T315I mutation BCR-ABL	Lymphoid leukaemia Myeloid leukaemia
Zelboraf	Vemurafenib	2012	*BRAF V600*	Melanoma
Tafinlar	Dabrafenib	2013		
Adcetris	Brentuximab vedotin	2012	CD30	Hodgkin disease lymphoma (non-Hodgkin)
Xalkori	Crizotinib	2012	ALK	Non-small-cell lung carcinoma
Kalydeco	Ivacaftor	2012	CFTR *G551D*	Cystic fibrosis
Caprelsa	Vandetanib	2012	*RET* mutation	Thyroid neoplasms
Trisenox	Arsenic trioxide	2002	PML-RAR-α t(15;17)	Acute promyelocytic leukaemia

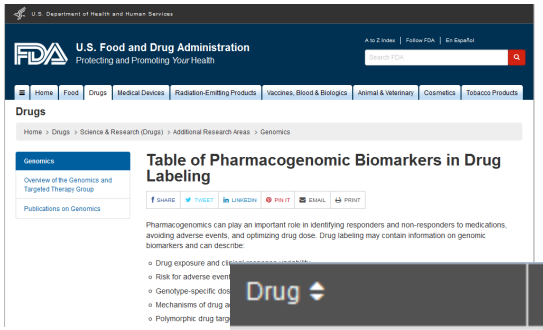
Ehmann et al. Pharmacogenomics J 2015;15:201–210

Pharmacogenetic information in drug labels (FDA)



appr. 150 pairs of drugs and genetic markers

Pharmacogenetic information in drug labels (FDA)



Drug	Therapeutic Area*	Biomarker	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R)positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Amitriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Anastrozole	Oncology	ESR1, PGR	Hormone receptor-positive	Indications and Usage, Adverse Reactions, Drug Interactions, Clinical Studies

Level Definitions for CPIC Genes/Drugs

CPIC Level	Clinical Context	Level of evidence	Strength of Recommendation
A			
B	Genetic information could be used to	Preponderance of evidence	At least one optional action
C	rationale, but no prescribing actions are recommended because (a) dosing based on genetics convincingly makes no difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.		
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

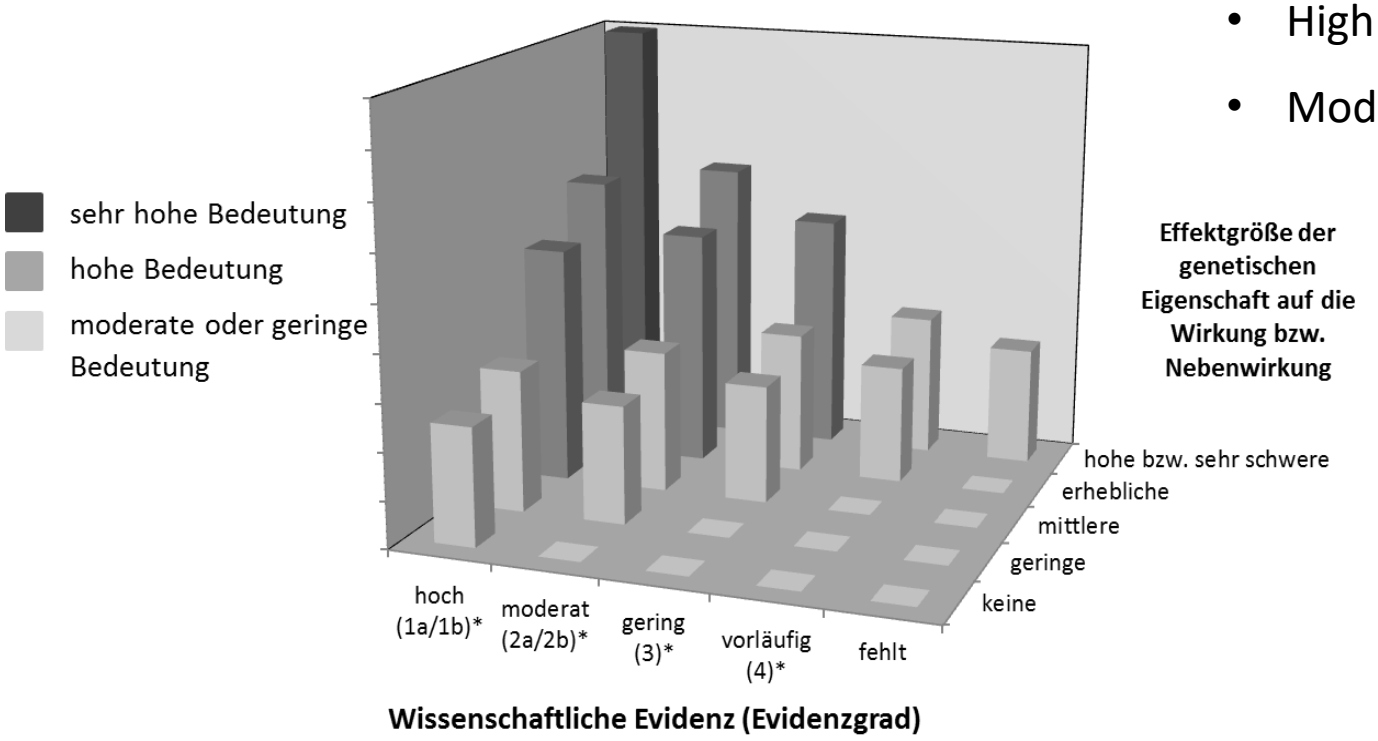
A: Genetic information should be used to change prescribing of the affected drug

B: Genetic information could be used to change prescribing of the affected drug, because alternative therapies/dosing are extremely liekely to be as effective and safe as non-genetically based dosing

Classification of pharmacogenetic diagnostic

ACCE-based recommendations

- Very high significance
- High significance
- Moderate or low significance



Schematische Darstellung für die Beurteilung einer genetischen Eigenschaft hinsichtlich ihrer Bedeutung bei der Anwendung von Arzneimitteln unter Berücksichtigung der vorhandenen wissenschaftlichen Evidenz für die genetische Assoziation (Gen-Arzneimittel-Interaktion) einerseits und dem Effekt dieser Eigenschaft bei Mutationsträgern andererseits.
* PharmGKB „Levels of Evidence“ (3)

Very high significance

of genetic trait in favor of changing prescribing

Consequence:

Mandatory documentation of pharmacogenetic trait

Example of very high significance

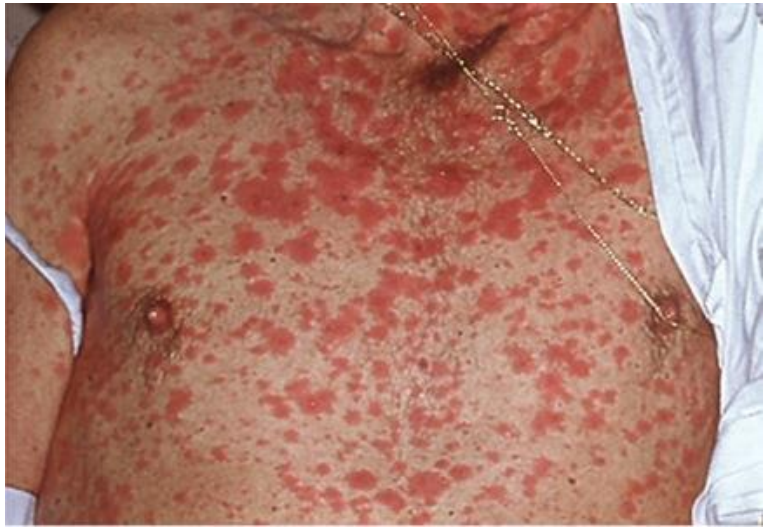
Drug	Area*		Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions

Abacavir

Severe hypersensitivity : 5%

Association to HLA-marker:
(**HLA-B* 5701**): appr. 50%

Negative predictive value >99%



Mandatory documentation of HLA-B*5701 / Abacavir

FACHINFORMATION

ViiV Healthcare

Ziagen® 300 mg Filmtabletten

1. BEZEICHNUNG DES ARZNEIMITTELS

Ziagen 300 mg Filmtabletten

2. QUALITATIVE UND QUANTITATIVE ZUSAMMENSETZUNG

Jede Filmtablette enthält 300 mg Abacavir (als Sulfat).

weder als zweimal tägliche Dosis von 300 mg (eine Tablette) oder als einmal tägliche Dosis von 600 mg (zwei Tabletten) eingenommen werden (siehe Abschnitte 4.4 und 5.1).

Kinder (mit einem Körpergewicht von weniger als 25 kg):

Für Ziagen Tabletten wird eine Dosierung

schwerer Einschränkung der Leberfunktion kontraindiziert (siehe Abschnitte 4.3 und 4.4).

Ältere Patienten

Pharmakokinetische Daten von Patienten über 65 Jahre liegen derzeit nicht vor.

4.3 Gegenanzeigen

Überempfindlichkeit gegen Abacavir oder

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with ZIAGEN:

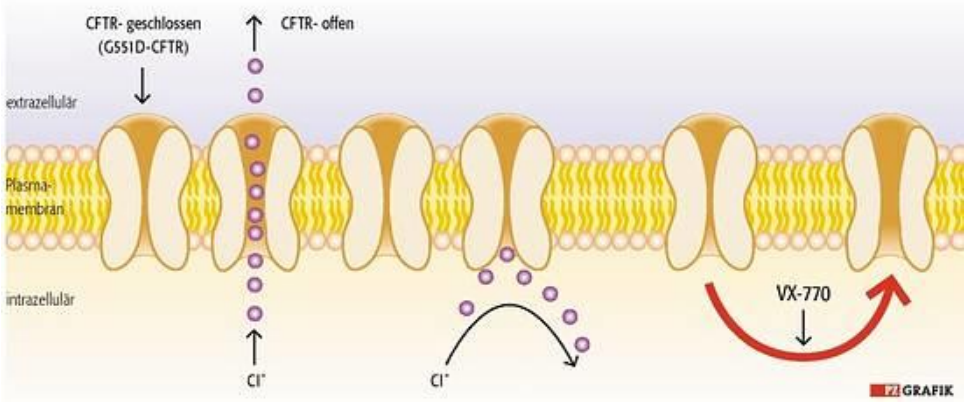
- All patients should be screened for the HLA‑B*5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA‑B*5701 allele assessment.
- ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA‑B*5701-positive patients.
- Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product. NEVER restart ZIAGEN or any other abacavir‑containing product following a hypersensitivity reaction to abacavir, regardless of HLA‑B*5701 status.

Companian diagnostic

Ivacaftor for the treatment of mucoviscidosis

Ivacaftor is a CFTR potentiator. It improves the transport of chloride through the ion channel by binding to the channels directly to induce a non-conventional mode of gating which in turn increases the probability that the channel is open

Overlap to human genetics



High significance

of genetic trait in favor of changing prescribing

Consequence:

Highly recommended genotyping/phenotyping of pharmacogenetic trait

TPMT / Azathioprine bei IBD / ALL

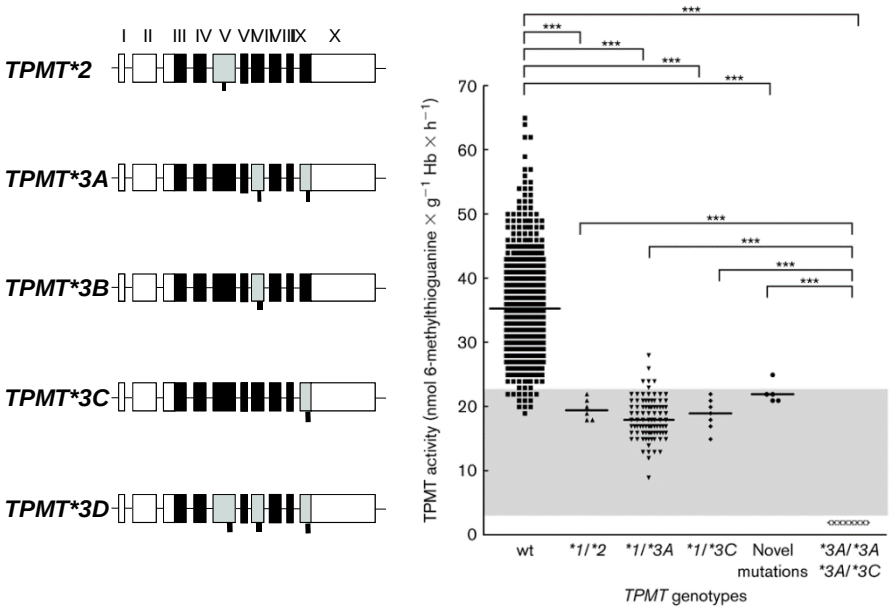
Azathioprine → 6-Mercaptopurine → 6-Methyl-Mercatopurine

Thiopurin S-methyltransferase

XO → 6-Thiourea

HGPRT → 6-Thioguanosine-nucleotides

Danger of panzytopenia!



0.6% Poor metabolizer
= 1 out of 180

100% chance to develop life-threating side effects

Recommendation:

5-10% of standard dose

Schaeffeler *et al*. Pharmacogenetics 2004;14:407-417

Recommendations of BfArM and FDA

Fachinformation Imurek

Etwa 10 % der Patienten haben durch genetischen Polymorphismus eine verminderte Aktivität des Enzyms Thiopurin-Methyltransferase (TPMT). Insbesondere bei homozygoten M
be
my

Ein
ei
nicht alle Patienten mit einem Risiko für eine schwere Toxizität identifizieren können, wird die **Testung auf TMPT-Mangel insbesondere prä-therapeutisch bei hochdosierter Azathioprin-Therapie sowie bei rascher Verschlechterung des Blutbildes empfohlen.**

Drug Label Imuran

TPMT Testing: It is recommended that consideration be given to either genotype or phenotype patients for TPMT. **Phenotyping and genotyping methods are commercially available**.

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ion.

Early drug discontinuation in these patients is advisable.

TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING IMURAN.

There are alternatives for genotyping available

CPIC: Clinical Pharmacogenetics Implementation Consortium

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB and the Pharmacogenomics Research Network. CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC's goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Questions? Send email to cpic@pharmgkb.org.

CPIC Team

Leader	Co-Leader	Coordinator
Mary V. Relling, Pharm.D. St. Jude Children's Research Hospital, Memphis	Teri E. Klein, Ph.D. Stanford University	Kelly Caudle, Pharm.D., Ph.D. St. Jude Children's Research Hospital, Memphis

CPIC Steering Committee

Mary V. Relling, Pharm.D.
St. Jude Children's Resea

Tyndale, Ph.D.
of Toronto and CAMH

33 CPIC Guidelines
(as of 11/2016)

BACKGROUND

One barrier to clinical implementation of pharmacogenetics is the lack of freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines. CPIC provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. The guidelines can center on genes (e.g. thiopurine methyltransferase and its implications for thiopurines) or around drugs (e.g. warfarin and CYP2C9 and VKORC1). Priority is given to genotyping tests that are already offered in CLIA-approved clinical settings.

CPIC GUIDELINES

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The SOP was updated in June 2014: June 2014 CPIC Authorship Update.

Moderate significance of genetic trait in favor of changing prescribing

Consequence:

- Optional genotyping/phenotyping of pharmacogenetic trait?
- Use of pre-emptive genotyping?
- Only information?

Pharmacogenetics in therapeutic areas

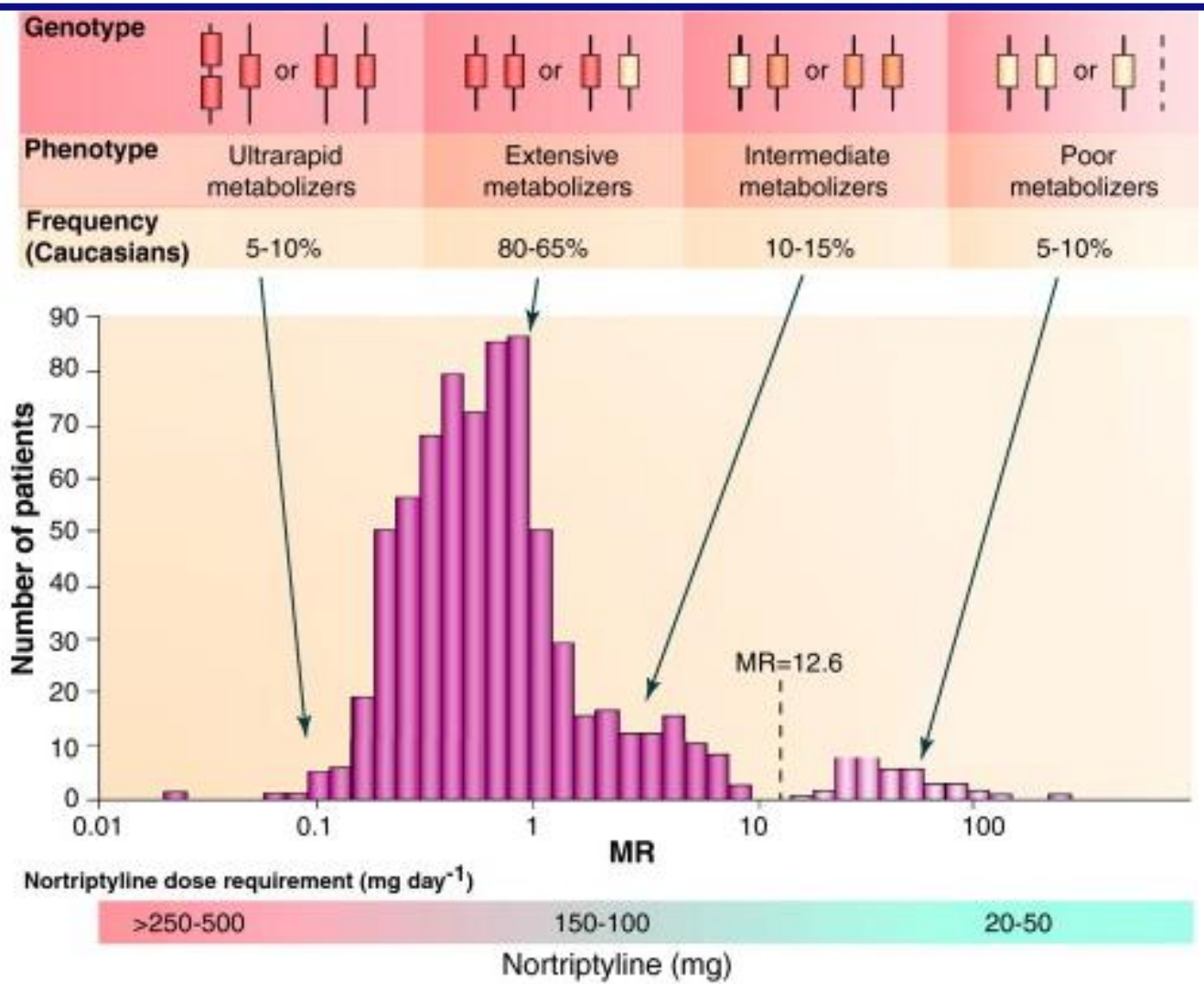
- **Psychiatry**
  - Schizophrenia
  - Depression
- **Anticoagulation**
  - Prevention of stroke
  - Prevention of thrombosis
- **Rare variants**

Pharmacogenetics in psychiatry

Classical concept of pharmacogenetics in psychiatry

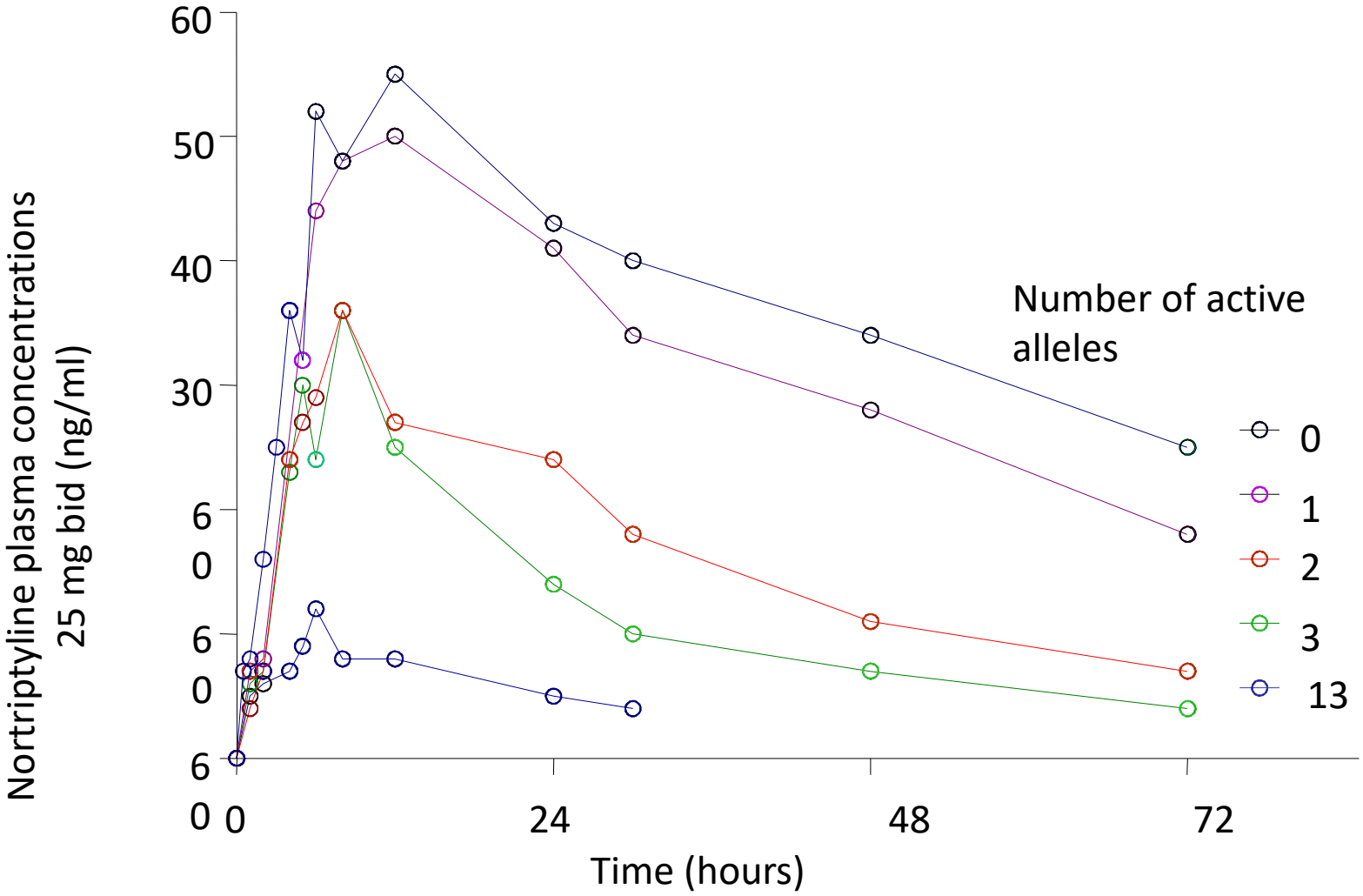
Most studies investigated effects of polymorphic CYP2D6 on the pharmacokinetics of antipsychotics or antidepressants, but not on the clinical outcome

Genotype phenotype relationship of CYP2D6



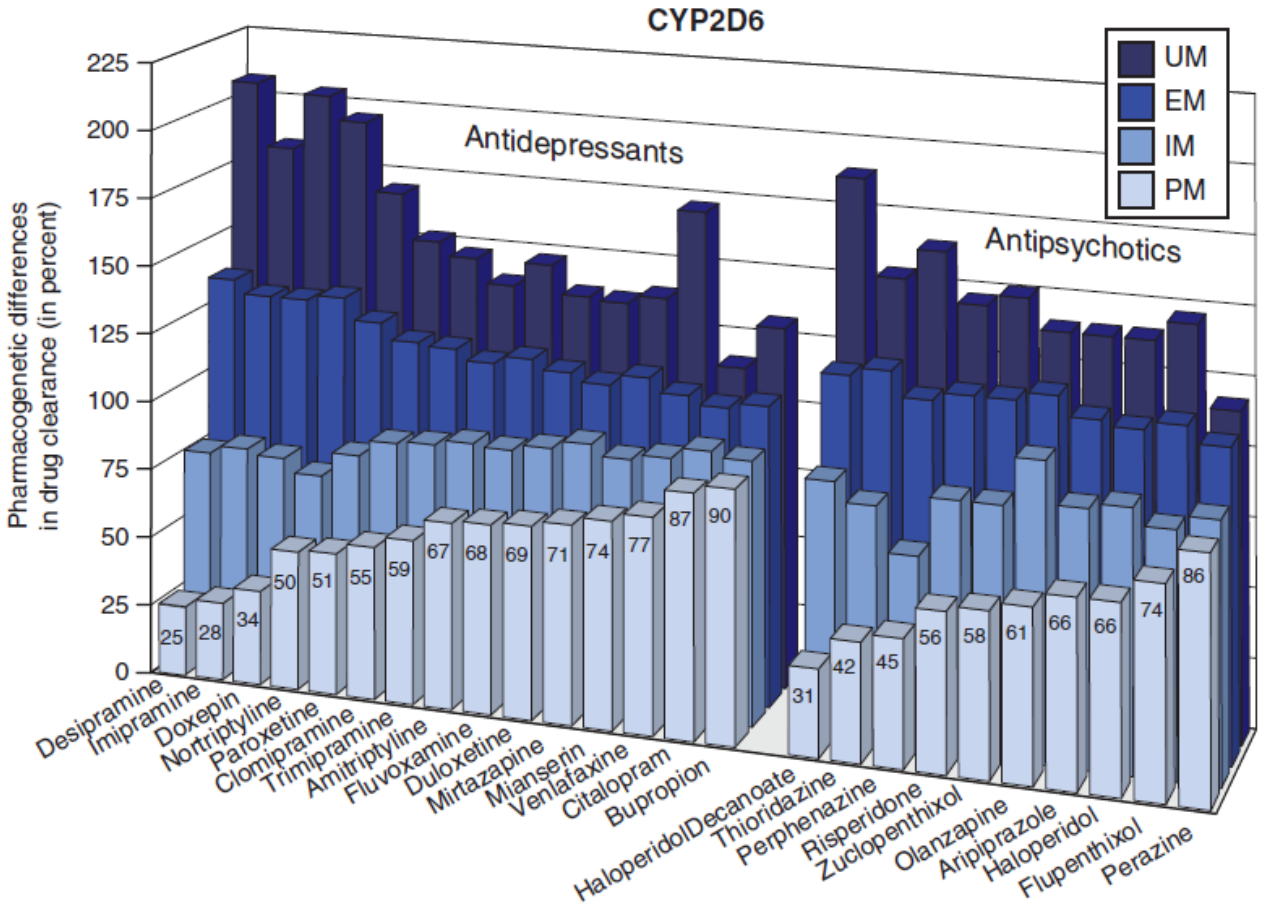
Meyer UA, Nature Rev Genet 2004;5:669-676

Nortriptyline single dose pharmacokinetics related to the number of active CYP2D6 alleles



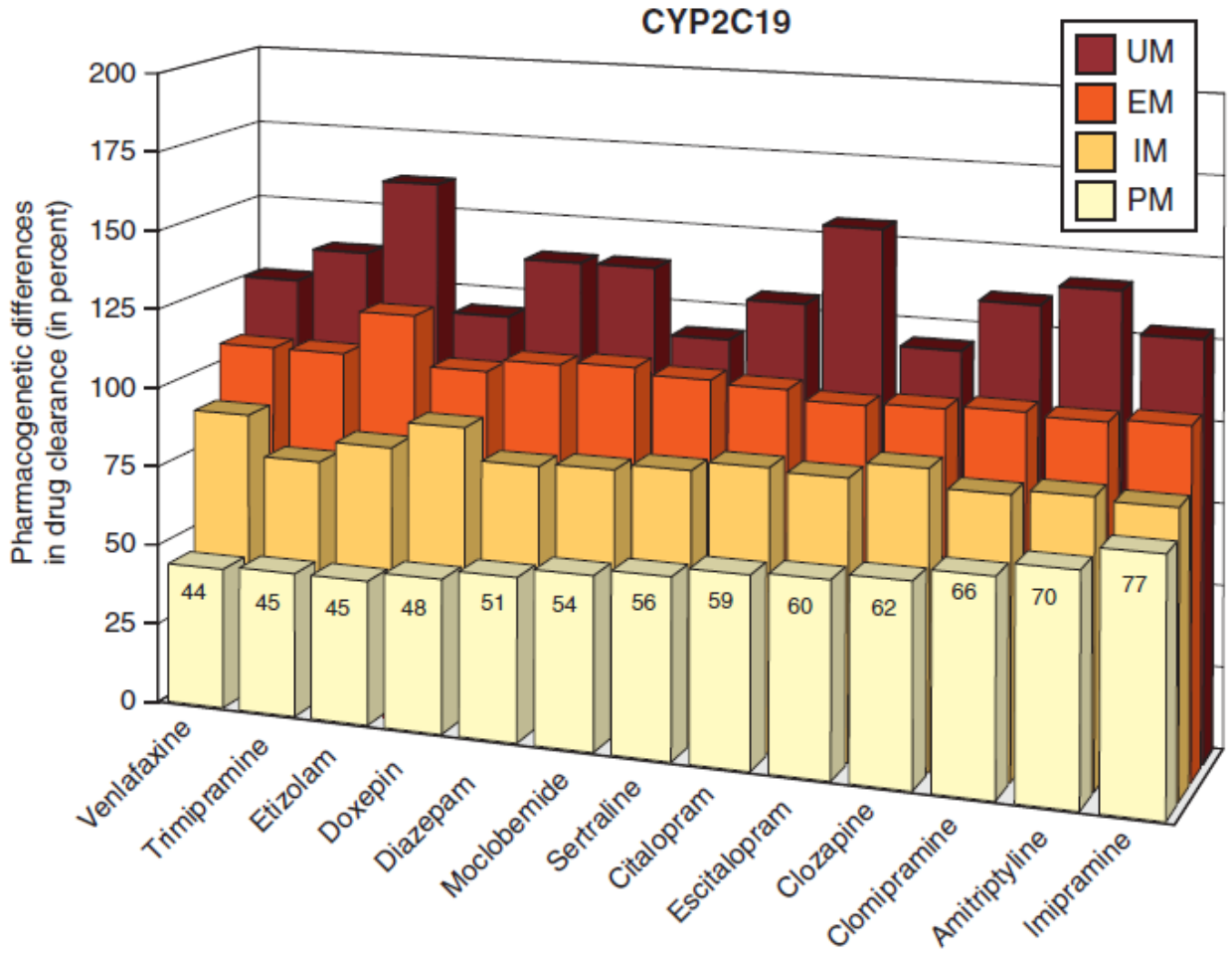
Dalen et al., Clin Pharmacol Ther, 1998; 63:444-52

CYP2D6-dependent clearance of antidepressents and antipsychotics



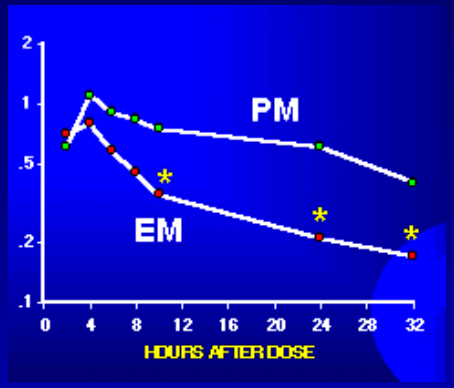
Stingl et al. Molecular Psychiatry 2012

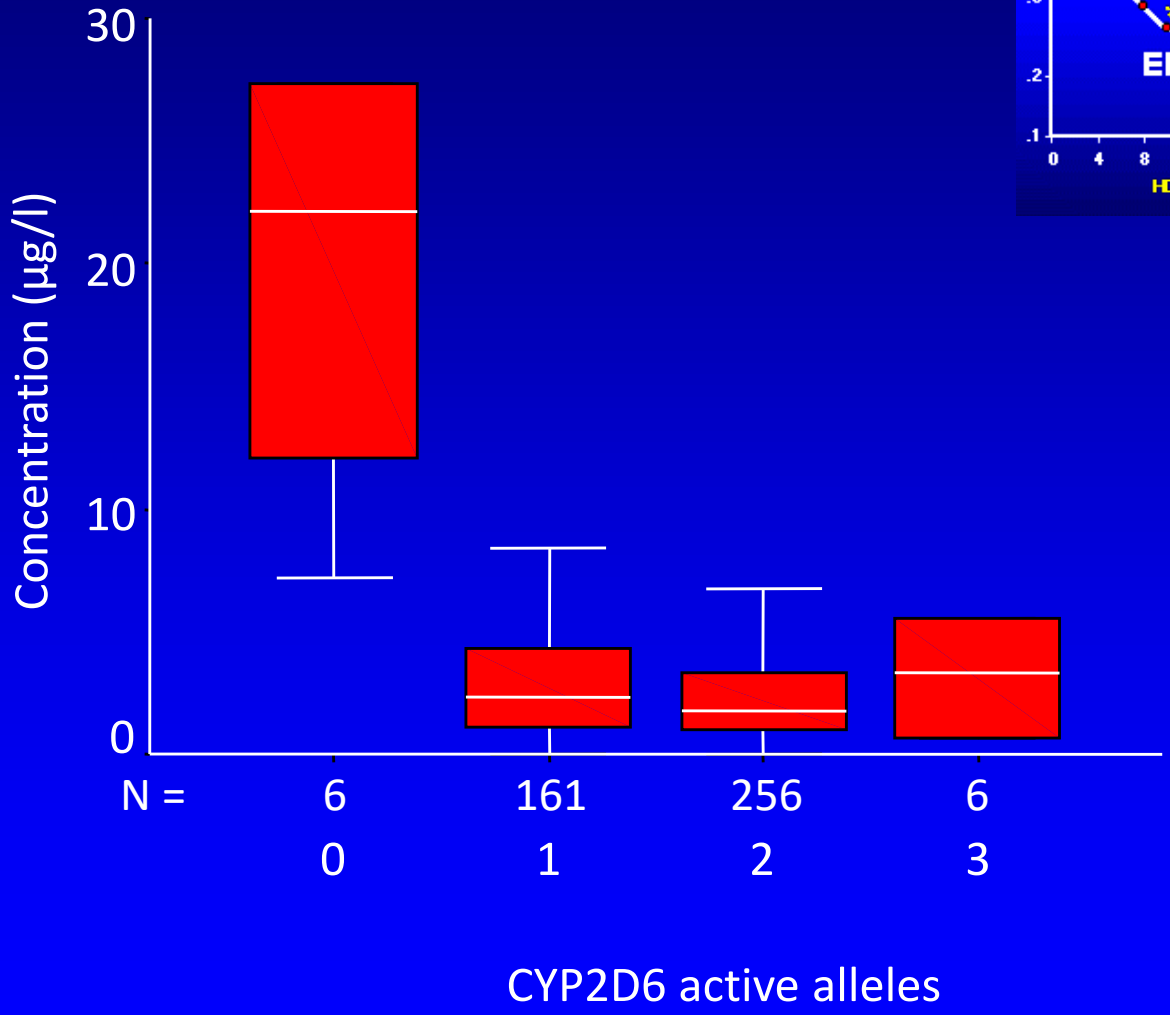
CYP2C19-dependent clearance of antidepressents and antipsychotics



Stingl et al. Molecular Psychiatry 2012

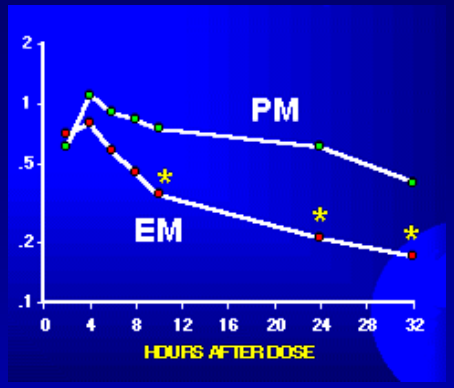
Reduced haloperidol concentrations in dependence of *CYP2D6* genotype

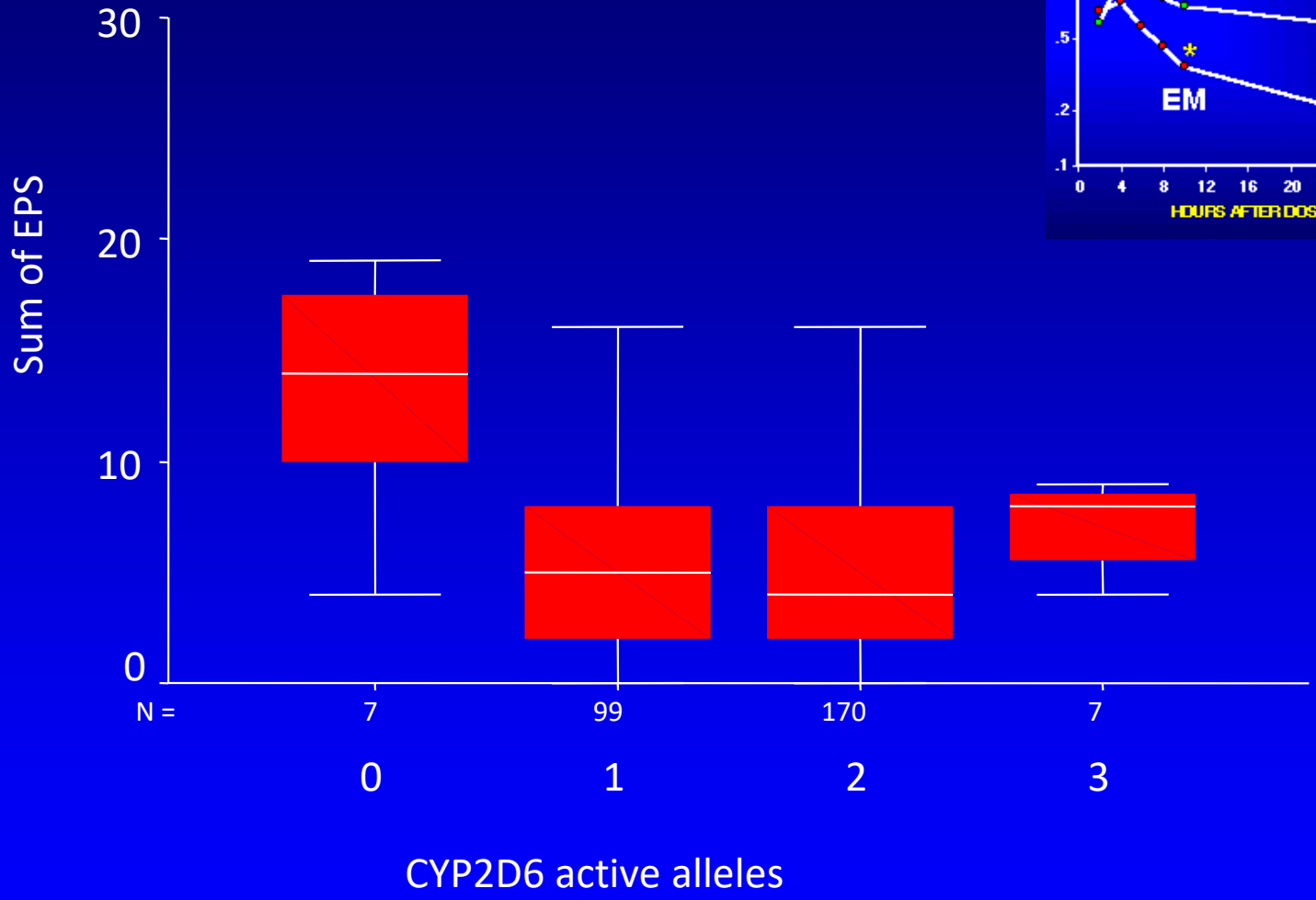




Brockmöller et al. Clin Pharmacol Ther. 2002, 72:438-52

Number of extrapyramidal symptoms caused by haloperidol in dependence of *CYP2D6* genotype





Brockmöller et al. Clin Pharmacol Ther. 2002, 72:438-52

Pharmacogenetics in therapeutic areas

- **Psychiatry**
  - Schizophrenia
  - Depression
- **Anticoagulation**
  - Prevention of stroke
  - Prevention of thrombosis
- **Rare variants**

Pharmacogenetics in the treatment of major depression

Genetics of mood disorders

Molecular Psychiatry (2012) 17, 36–48

www.nature.com/mp

Open

ORIGINAL ARTICLE

Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned

NR Wray[1], ML Pergadia[2], DHR Blackwood[3], BWJH Penninx[4], SD Gordon[1], DR Nyholt[1], S Ripke[5,6], DJ MacIntyre[3], KA McGhee[3], AW Maclean[3], JH Smit[4], JJ Hottenga[4], G Willemsen[4], CM Middeldorp[4], EJC de Geus[4], CM Lewis[7], P McGuffin[7], IB Hickie[8], EJCG van den Oord[9], JZ Liu[1], S Macgregor[1], BP McEvoy[1], EM Byrne[1], SE Medland[1], DJ Statham[1,11], AK Henders[1], AC Heath[2], GW Montgomery[1], NG Martin[1], DI Boomsma[4], PAF Madden[2] and PF Sullivan[10]

Common variants of intermediate or large effect do not have main effects in the genetic architecture of MDD.

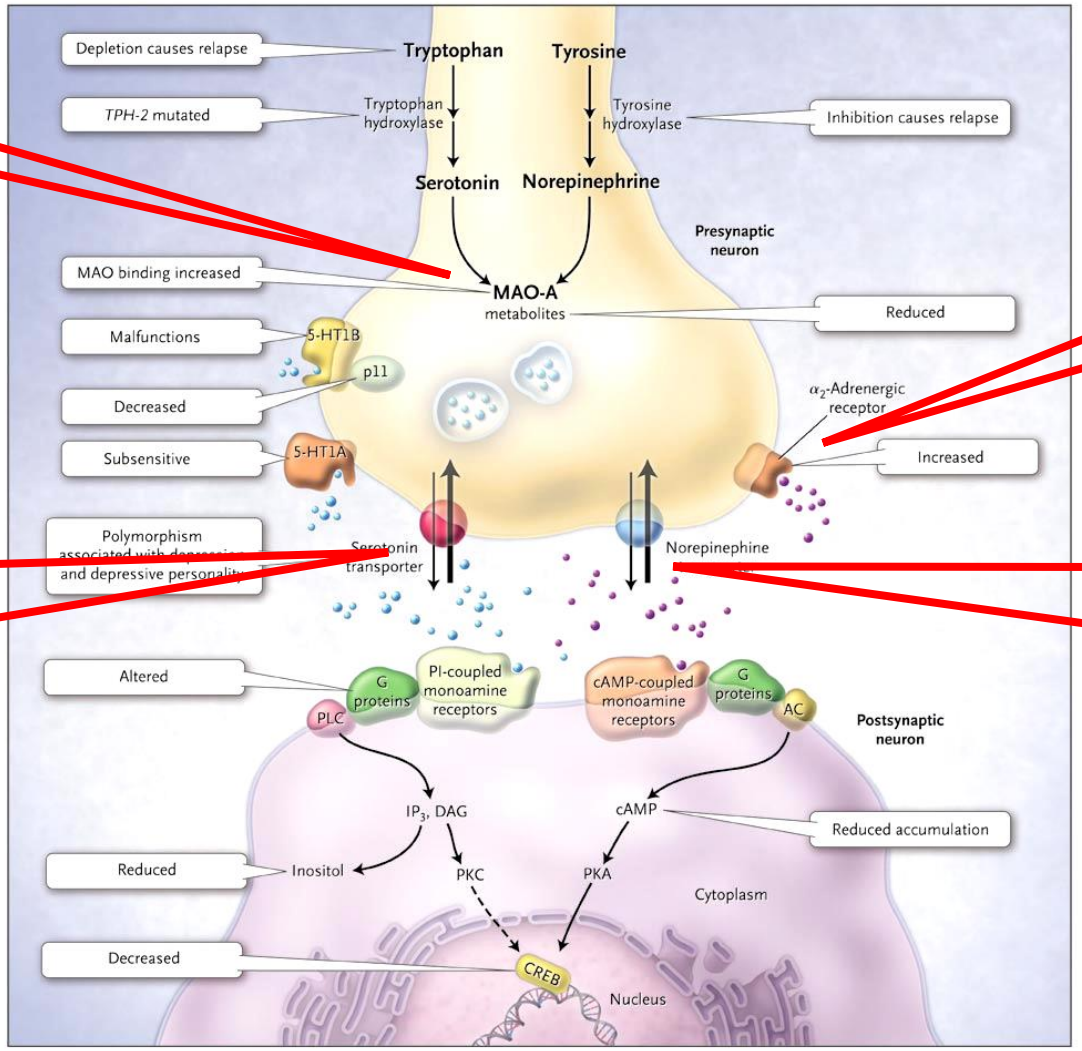
The monoamine deficiency hypothesis

MAO-inhibition

Serotonin reuptake inhibiton

α_2-Inhibition

Norepinephrine reuptake inhibition



Belmaker and Agam N Engl J Med 2008;358:55-68

Serotonin transporter (SLC6A4) polymorphism

44-bp deletion / insertion (short/long)

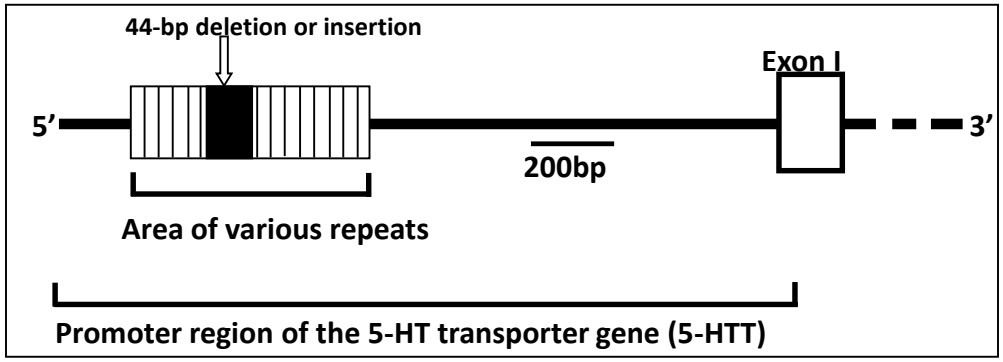
Gene locus: Chromosome 17q11.2 –12

Localization: Promoter region

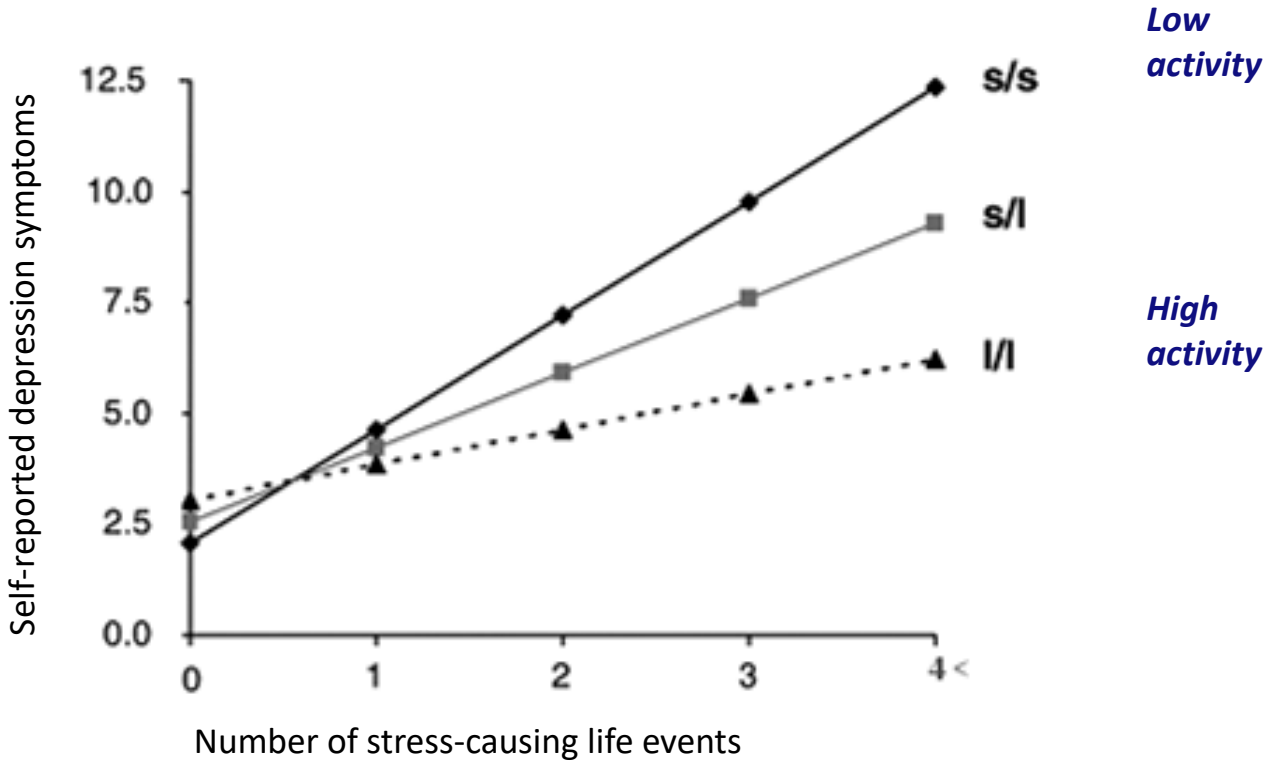
appr. 1 kb upstream of exon 1

Genotype distribution:32% l/l; 49% l/s; 19% s/s

(Science 1996; 274:1527-1531)



Association of 5-HTT s/l-genotype with risk of depression



No direct association between genotype and depressive disorders;
but: s/s genotype interacts statistically significant with an increasing number of negative life-events (P<0,001)

Caspi et al. Science 2003; 301: 386-389

Molecular Psychiatry (2004) 1–5

www.nature.com/mp

ORIGINAL RESEARCH ARTICLE

Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden

HJ Grabe[1], M Lange[2], B Wolff[3], H Völzke[4], M Lucht[1], HJ Freyberger[1], U John[4] and I Cascorbi[2]

[1]*Department of Psychiatry and Psychotherapy, University of Greifswald, Germany;* [2]*Institute of Pharmacology and Toxicology, University of Greifswald, Germany;* [3]*Department of Internal Medicine B, University of Greifswald, Germany;* [4]*Institute of Epidemiology and Social Medicine, University of Greifswald, Germany*

SHIP study:
Cross sectional study in North-East-Germany

Cohort of 4,310 participants

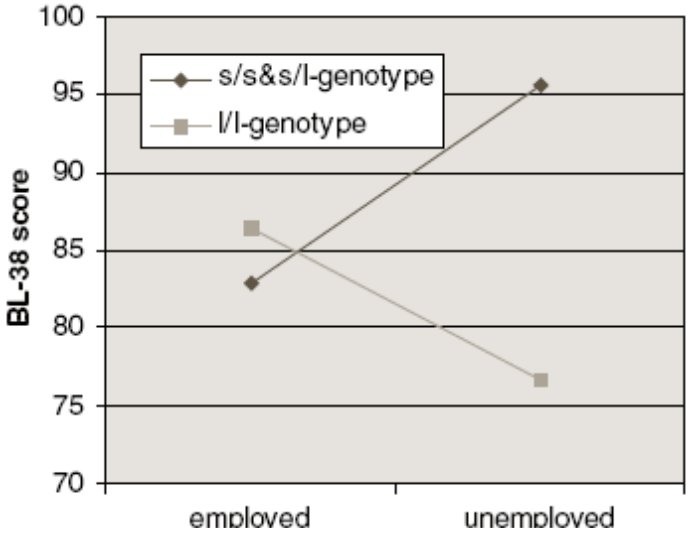
Cases: 505 subjects with moderate or high BL-38 score (>58±2)

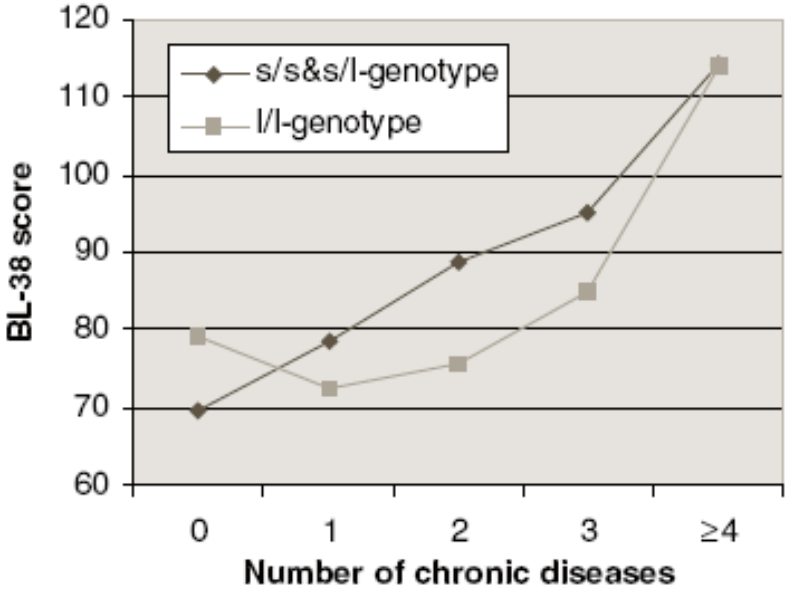
Controls: 505 subjects from total sample

Association of 5-HTT-polymorphism with mental and physical distress

Interaction of SLC2A4 genotype and BL-38 score

(modified Zerssen complaint scale)





Grabe et al. Mol Psychiatry 2005 10:220-4.

Table 6: Relevant pharmacogenetic association studies that focused on *5-HTTLPR* (part 1 of 2)

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Mrazek et al.[175]	*5-HTTLPR*	Citalopram	White non-Hispanic: Int2 VNTRs 12/12 and LL genotype ↑ remission	25	1914
Yoshimura et al.[186]	*5-HTTLPR*	Paroxetine	No association	21	60
Gressier et al.[213]	*5-HTTLPR*	Various antidepressants	In females L allele ↑ response	19	103
Min et al.[191]	*5-HTTLPR*	SSRI, SNRI	*5-HTTLPR* L/L or STin2 12/12 genotype ↑ response to SSRI	25	657
Huezo-Diaz et al.[174]	*5-HTTLPR*	Escitalopram, nortriptyline	L allele ↑ response to escitalopram, > effect in males	20	795
Capozzo et al.[214]	*5-HTTLPR*	Citalopram	l/l carriers ↑ response	8	21
Maron et al.[180]	*5-HTTLPR*	Escitalopram	No associations in response S allele ↑ severe headache	20	135
Ferreira et al.[215]	*5-HTTLPR*	Various	L allele ↓ switch into a manic episode	9	112
Oberlander et al.[196]	*5-HTTLPR*	SSRIs exposed neonates	l/l genotype ↑ respiratory symptoms (respiratory distress and rapid breathing) s/s genotype ↑ neuromotor symptoms	13	37
Lotrich et al.[192]	*5-HTTLPR*	Paroxetine	In s carriers paroxetine concentrations ↑ response (elderly population)	16	110
Schillani et al.[216]	*5-HTTLPR*	Sertraline	L carriers ↑ response	10	11
Smits et al.[163]	*5-HTTLPR*	Various SSRIs	In female s-allele ↓ response	13	214
Stamm et al.[193]	*5-HTTLPR*	Lithium augmentation	s/s genotype ↑ response	14	55
Tanaka et al.[217]	*5-HTTLPR*	Paroxetine	No association with iatrogenic nausea	15	72
Kang et al.[181]	*5-HTTLPR*	Mirtazapine	s/s genotype ↑ response	18	101
Kirchheiner et al.[218]	*5-HTTLPR*	Various	No association	19	77
Kronenberg et al.[219]	*5-HTTLPR*	Citalopram	In children l /l genotype ↑ response	24	312
Hu et al.[177]	*5-HTTLPR*	Citalopram	L(A) allele ↑ side effects	19	1655
Kim et al.[184]	*5-HTTLPR*	Fluoxetine sertraline notriptyline	STin2 12/12 ↑ response to SSRIs S allele ↑ response to SSRIs and to nortriptyline	19	208
Masoliver et al.[220]	*5-HTTLPR*	Various antidepressants	s alleles ↑ manic switch	8	188
Ng et al.[221]	*5-HTTLPR*	Sertraline	No association with response and side effects	16	35
Smeraldi et al.[208]	*5-HTTLPR*	Fluvoxamine	l allele ↑ response 16F *l ↑ partial response 16D *l ↑ response	21	228
Popp et al.[206]	*5-HTTLPR*	Various	STin2 10/10 ↑ side effects s/s genotype ↑ side effects	9	109

Data on association of serotonin transporter and therapy response are inconsistent

Pharmacogenetics in the treatment of antidepressants

- Pharmacogenetics may contribute to the explanation of adverse effects of antidepressants, in particular of tricyclics (TCA)
- Non-response to TCA frequently associated with CYP2D6 ultra-rapid metabolizers
- *Cave: Tricyclics are only rarely prescribed today*
- The efficacy of SSRIs is modestly dependent from *CYP2D6* and *CYP2C19*

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors

JK Hicks[1], JR Bishop[2], K Sangkuhl[3], DJ Müller[4], Y Ji[5], SG Leckband[6], JS Leeder[7], RL Graham[8], DL Chiulli[9], A LLerena[10], TC Skaar[11], SA Scott[12], JC Stingl[13], TE Klein[3], KE Caudle[14] and A Gaedigk[7]

Clin Pharmacol Ther. 2015;98:127-34.

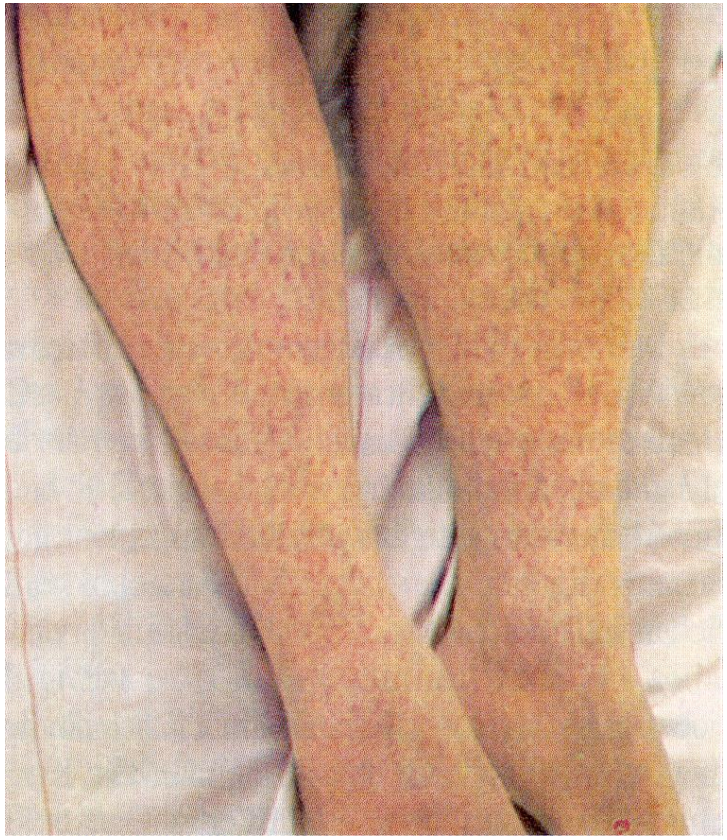
Pharmacogenetics in therapeutic areas

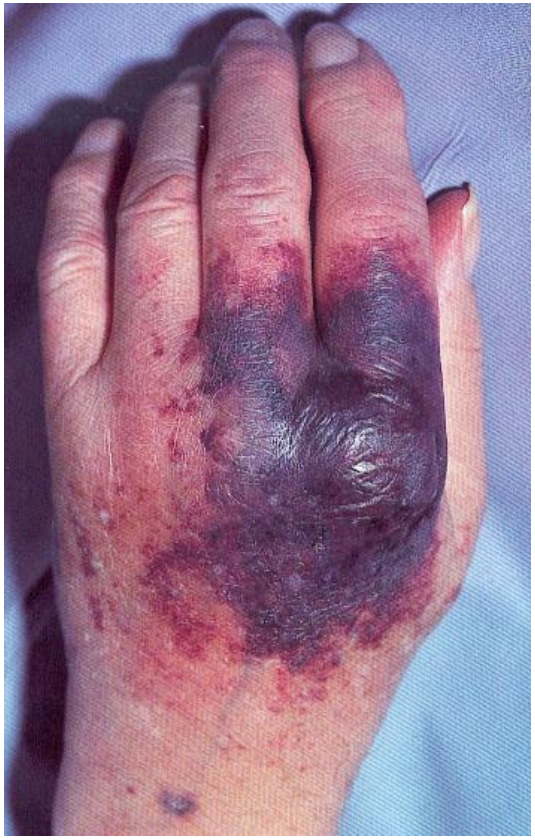
- Psychiatry
  - Schizophrenia
  - Depression

- **Anticoagulation**
  - Prevention of stroke
  - Prevention of thrombosis

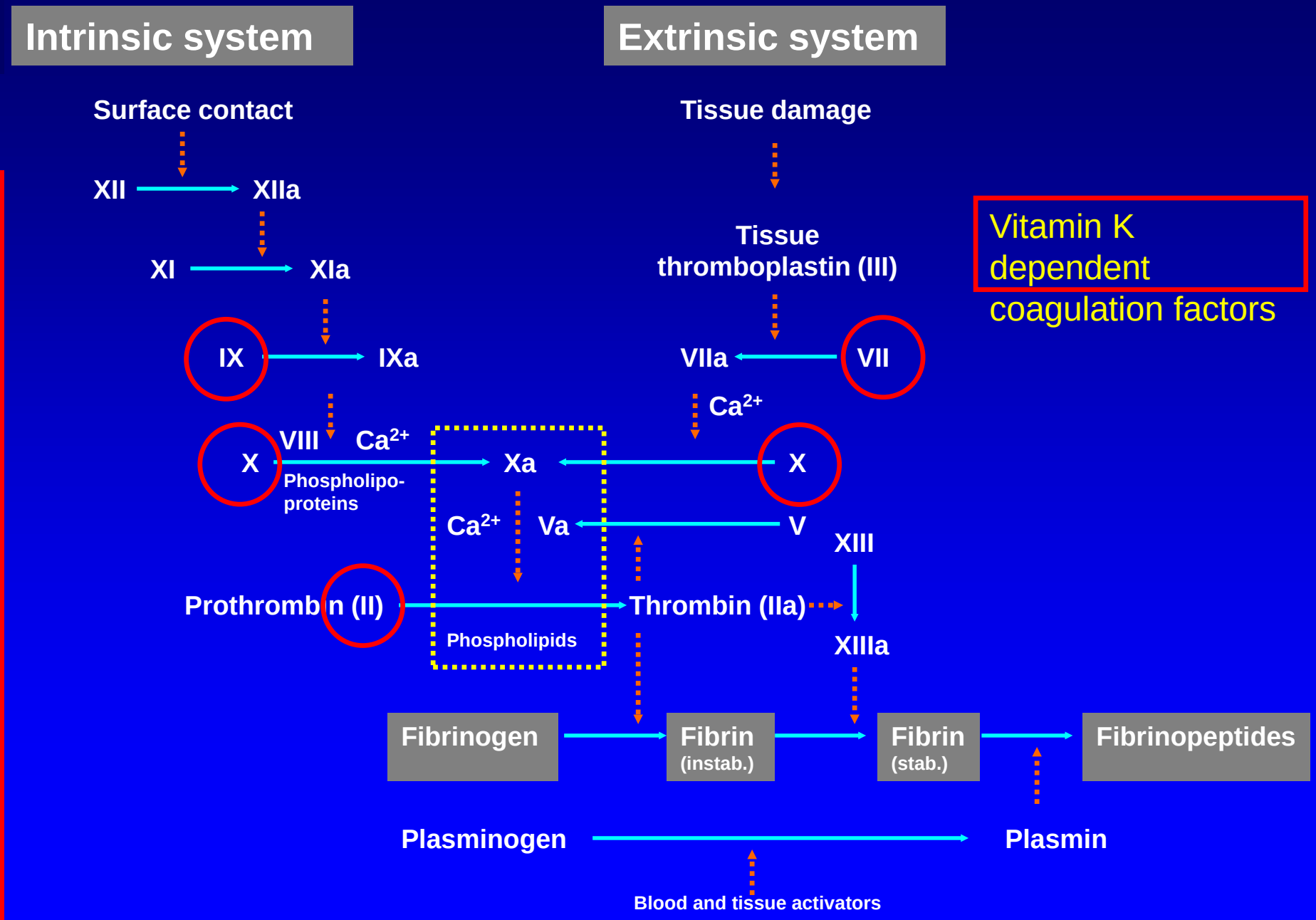
- Rare variants

Pharmacogenetics of anticoagulation

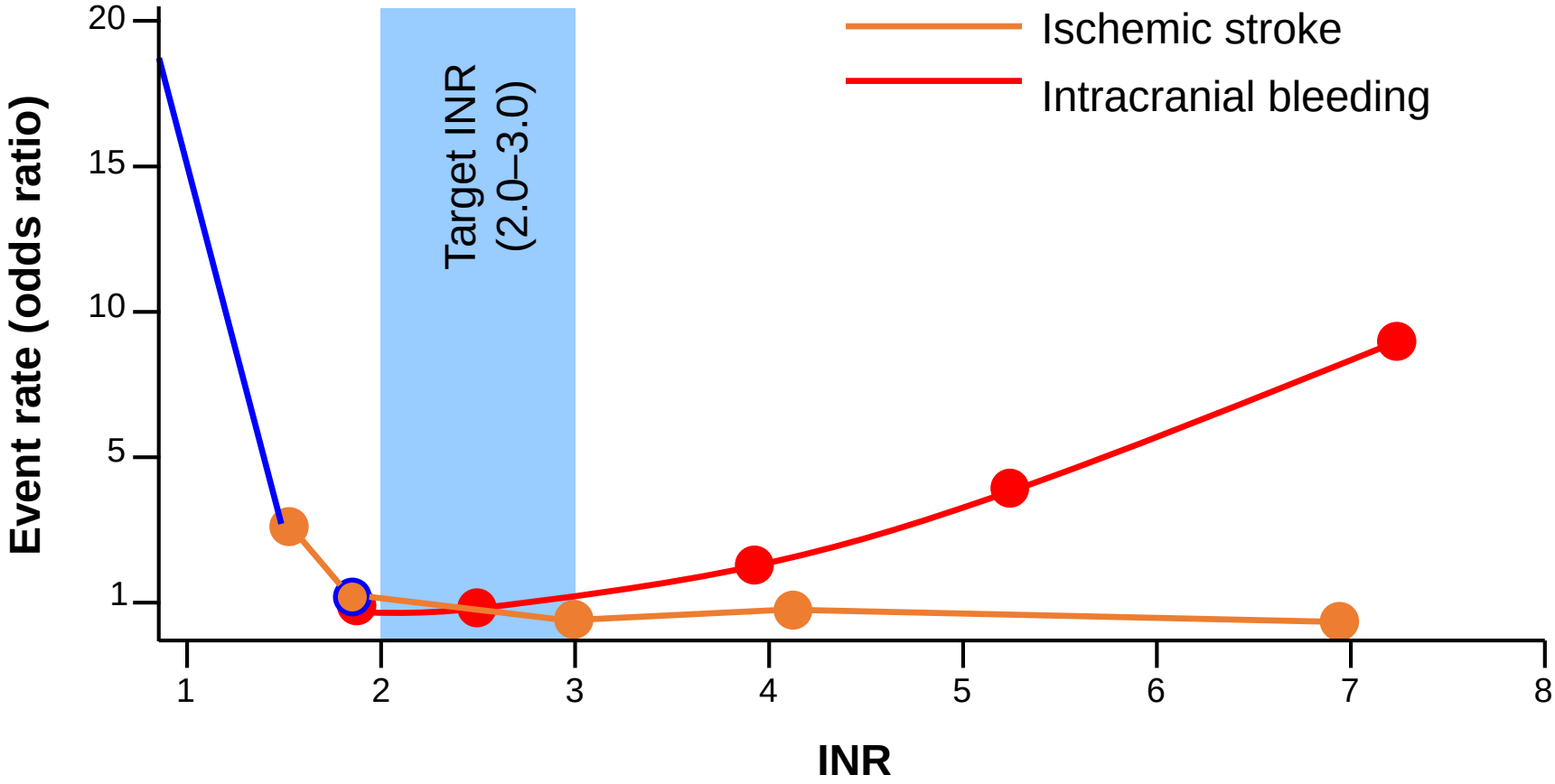




Blood coagulation

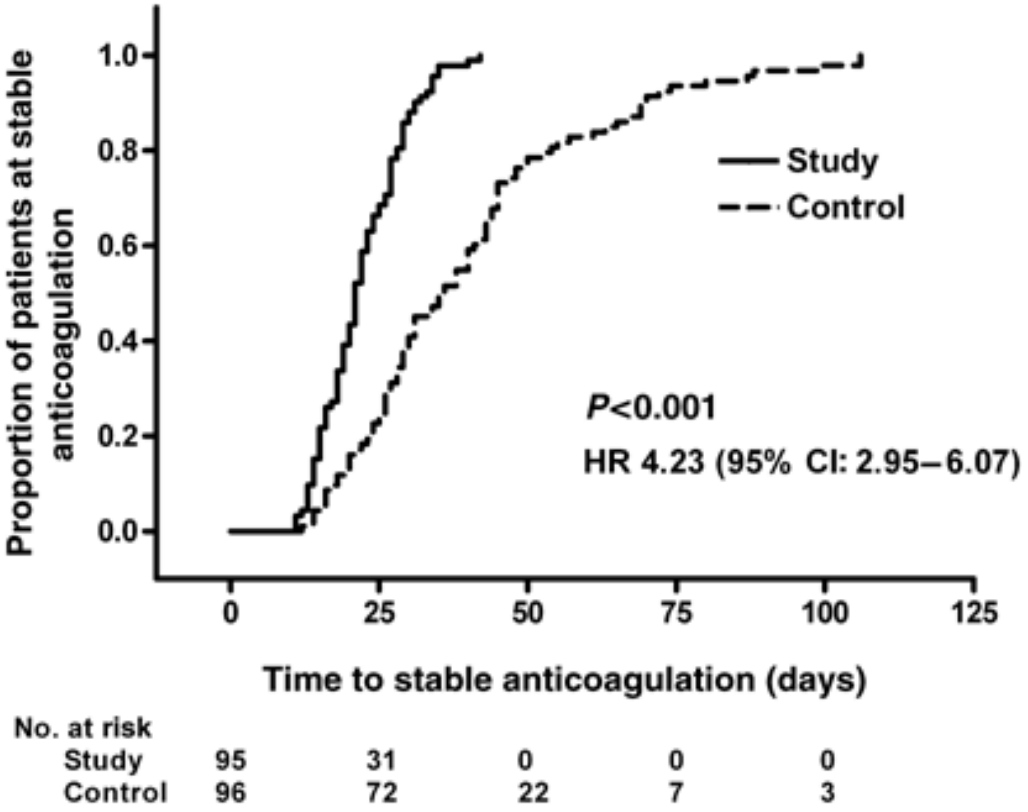


Therapeutic window of vitamin K-antagonists



Adopted to Fuster *el al.*, Eur Heart J. 2006;27:1979-2030

Prospective study on CYP2C9-genotype directed warfarin dosage



Caraco et al, Clin Pharmacol Ther 2007

Re-labelling of Coumadin by FDA in 2007

FOR IMMEDIATE RELEASE
August 16, 2007

Media Inquiries:
Karen Riley, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Approves Updated Warfarin (Coumadin) Prescribing Information

New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients

The U.S. Food and Drug Administration announced today the approval of updated labeling for the widely used blood-thinning drug, Coumadin, to explain that people's genetic makeup may influence how they respond to the drug.

Manufacturers of warfarin, the generic version of Coumadin, are to add similar information to their products' labeling, FDA said.

The labeling change highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. **Testing may help optimize the use of warfarin and lower the risk of bleeding complications from the drug.**

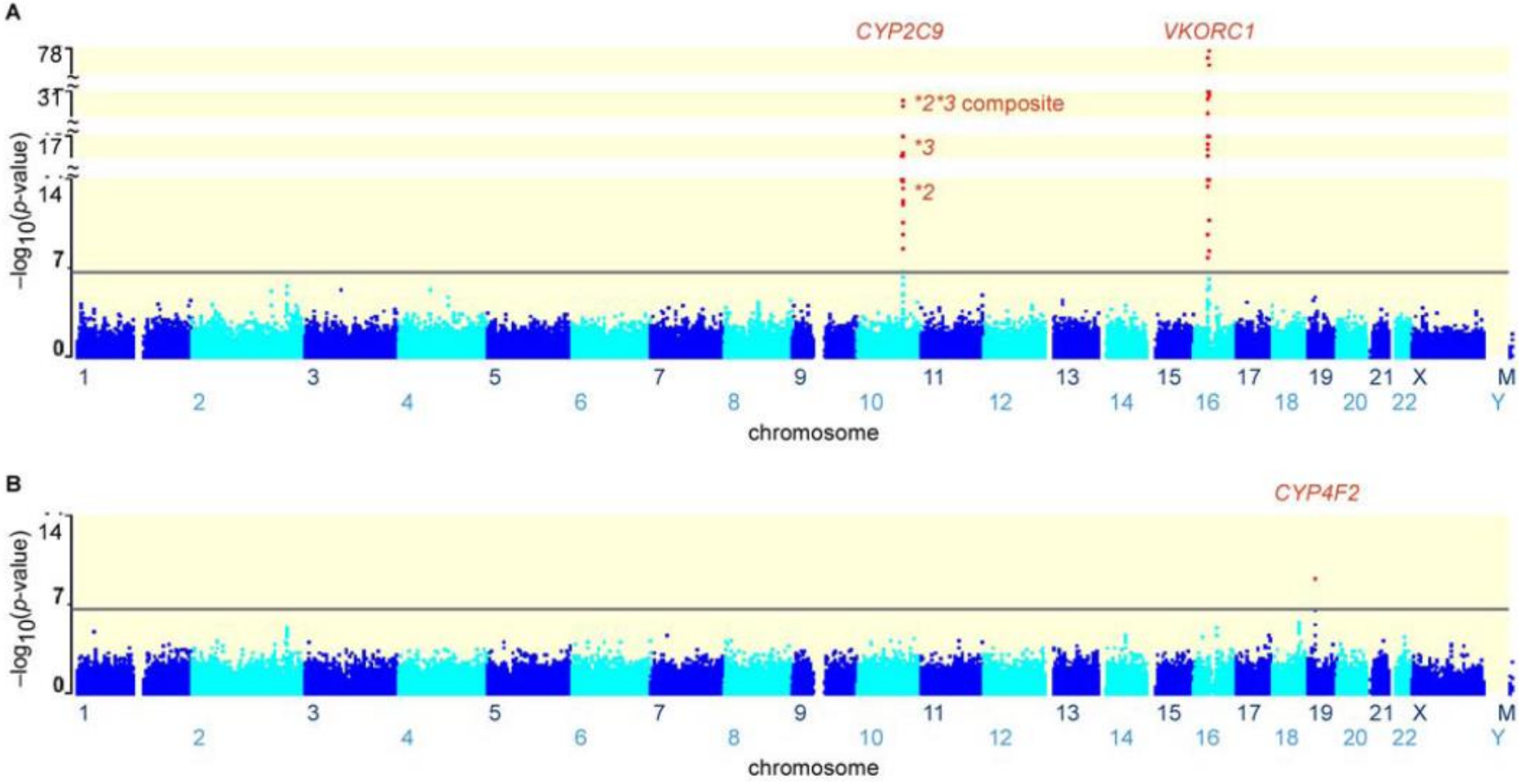
These labeling updates are based on an analysis of recent studies that found people respond to the drug differently based, in part, on whether they have variations of certain genes.

OPEN ACCESS Freely available online PLoS GENETICS

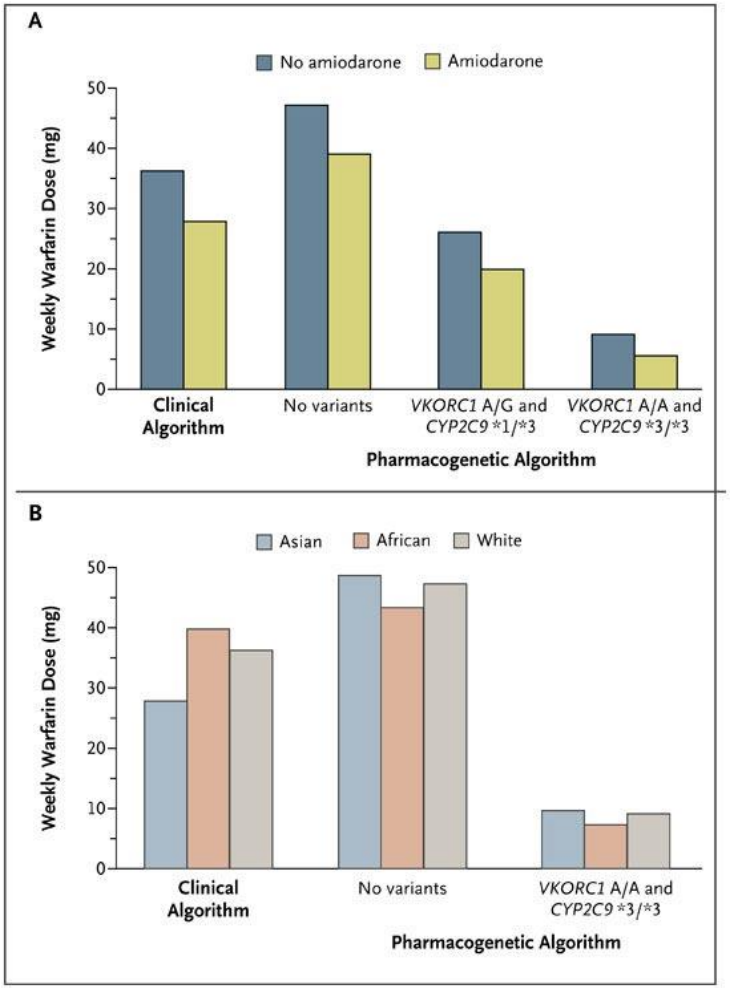
A Genome-Wide Association Study Confirms *VKORC1*, *CYP2C9*, and *CYP4F2* as Principal Genetic Determinants of Warfarin Dose

Fumihiko Takeuchi[1,9], Ralph McGinnis[1,9]*, Stephane Bourgeois[1], Chris Barnes[1], Niclas Eriksson[2], Nicole Soranzo[1], Pamela Whittaker[1], Venkatesh Ranganath[1], Vasudev Kumanduri[1], William McLaren[1], Lennart Holm[3], Jonatan Lindh[3], Anders Rane[3], Mia Wadelius[4], Panos Deloukas[1]*

1 Wellcome Trust Sanger Institute, Hinxton, United Kingdom, **2** Uppsala Clinical Research Centre, Uppsala, Sweden, **3** Department of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, **4** Department of Medical Sciences, Clinical Pharmacology, Uppsala University Hospital, Uppsala, Sweden



Comparisons of Warfarin Doses Predicted According to the Clinical Algorithm and the Pharmacogenetic Algorithm



The International Warfarin Pharmacogenetics Consortium. N Engl J Med 2009;360:753-764

Re-labelling of Coumadin by FDA in 2010

- The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose.
- In all patients, subsequent dosage adjustments must be made based on the results of PT/INR determinations.

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes[†]

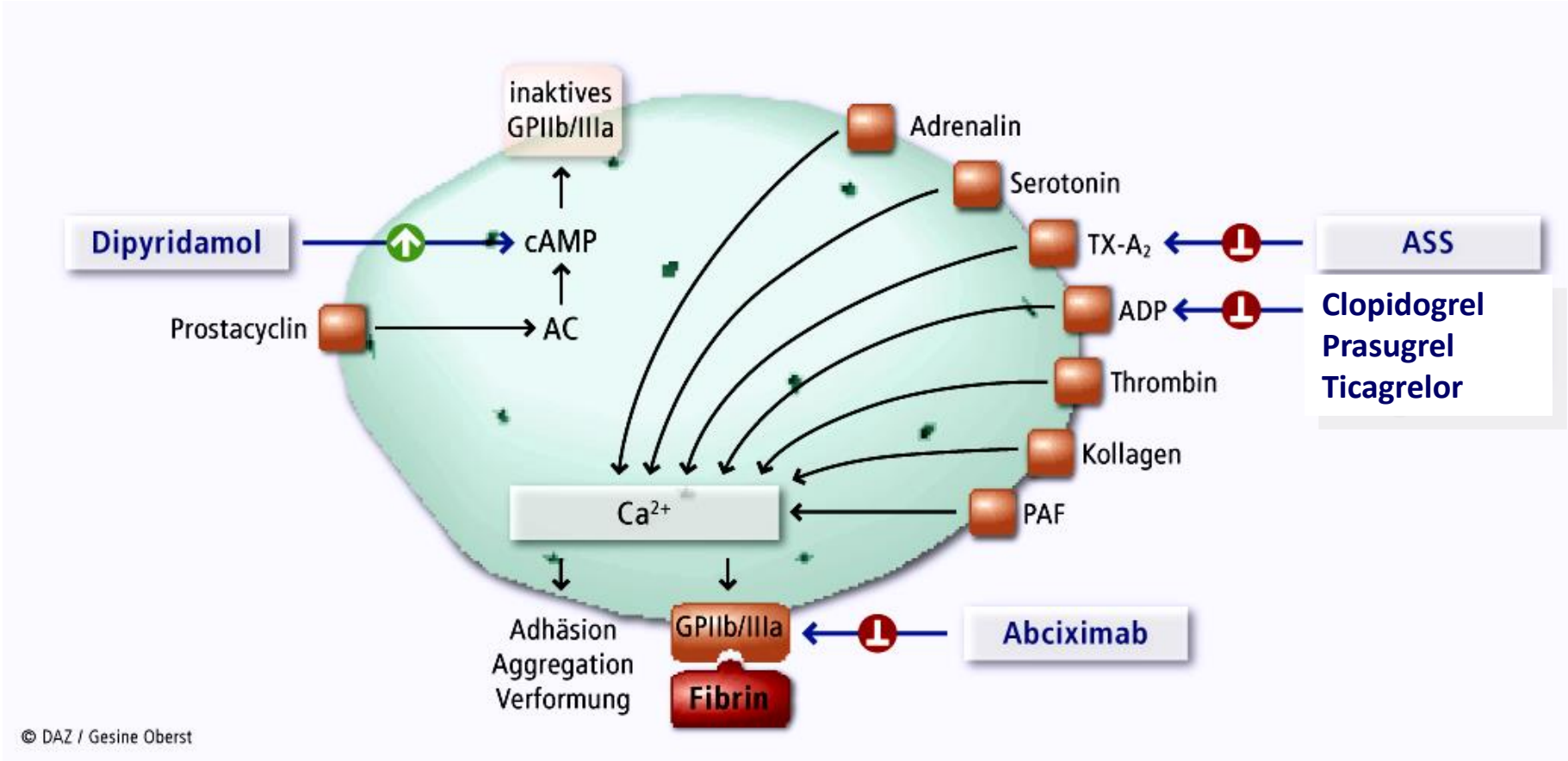
VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

[†]Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

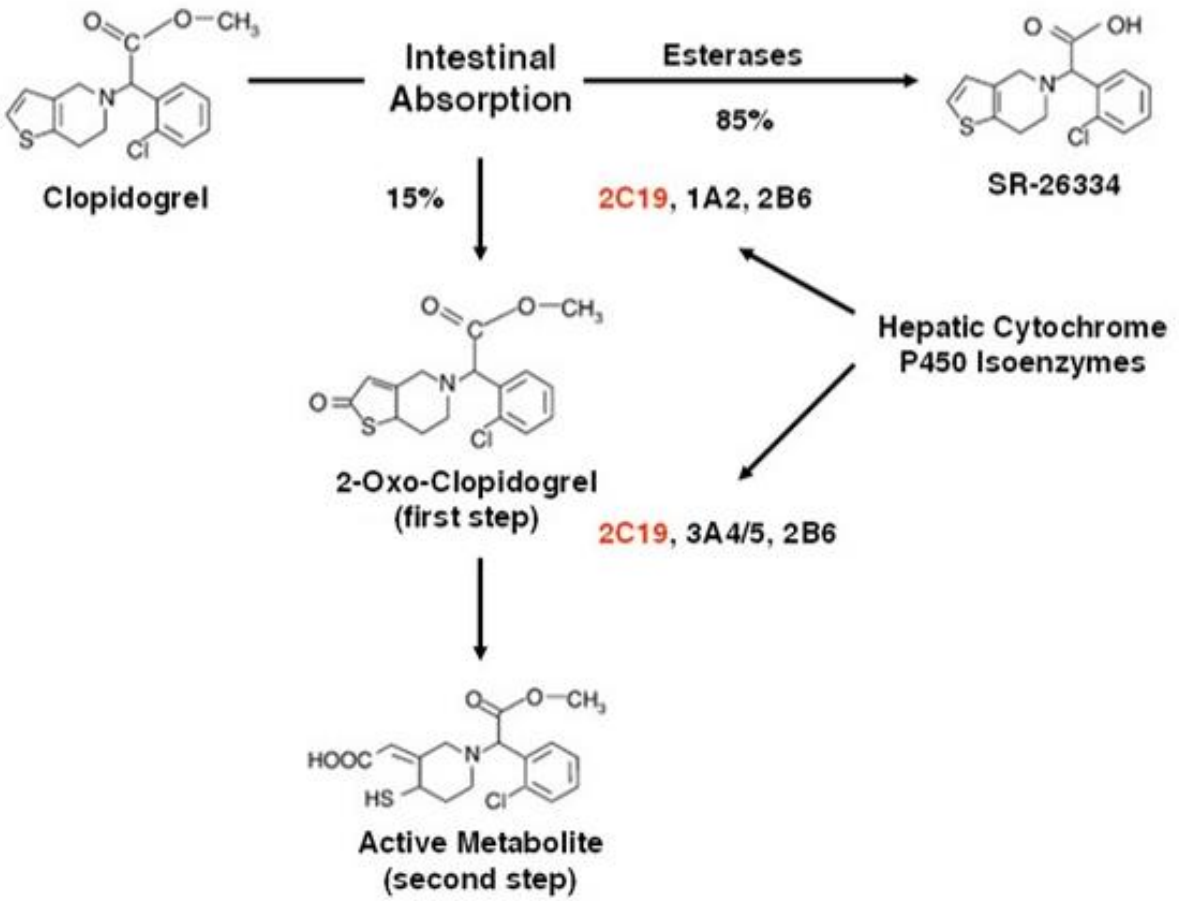
Pharmacogenetics in therapeutic areas

- Psychiatry
  - Schizophrenia
  - Depression
- **Anticoagulation**
  - Prevention of stroke
  - Prevention of thrombosis
- Rare variants

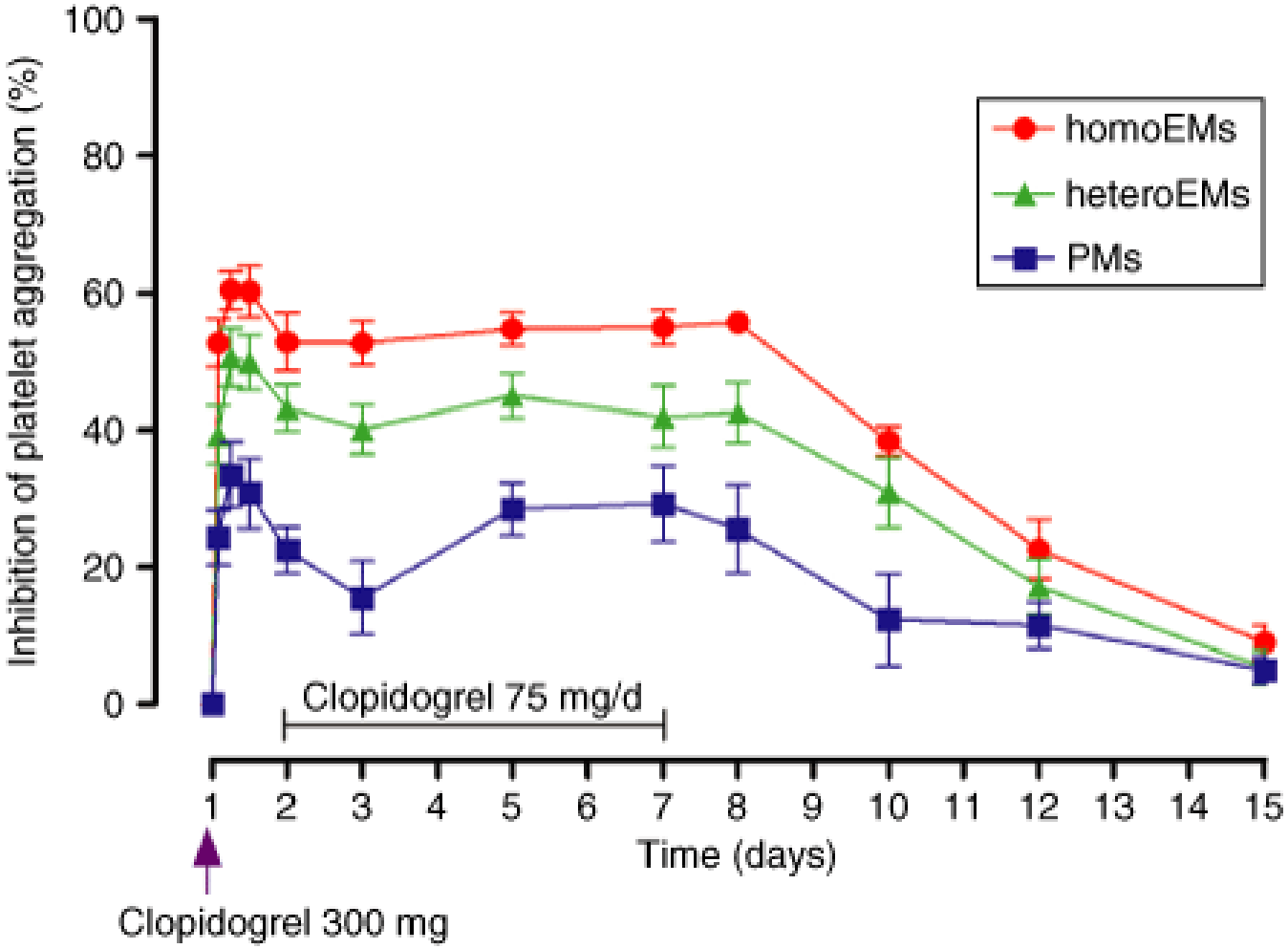
Inhibition of platelet aggregation



Clopidogrel is a prodrug

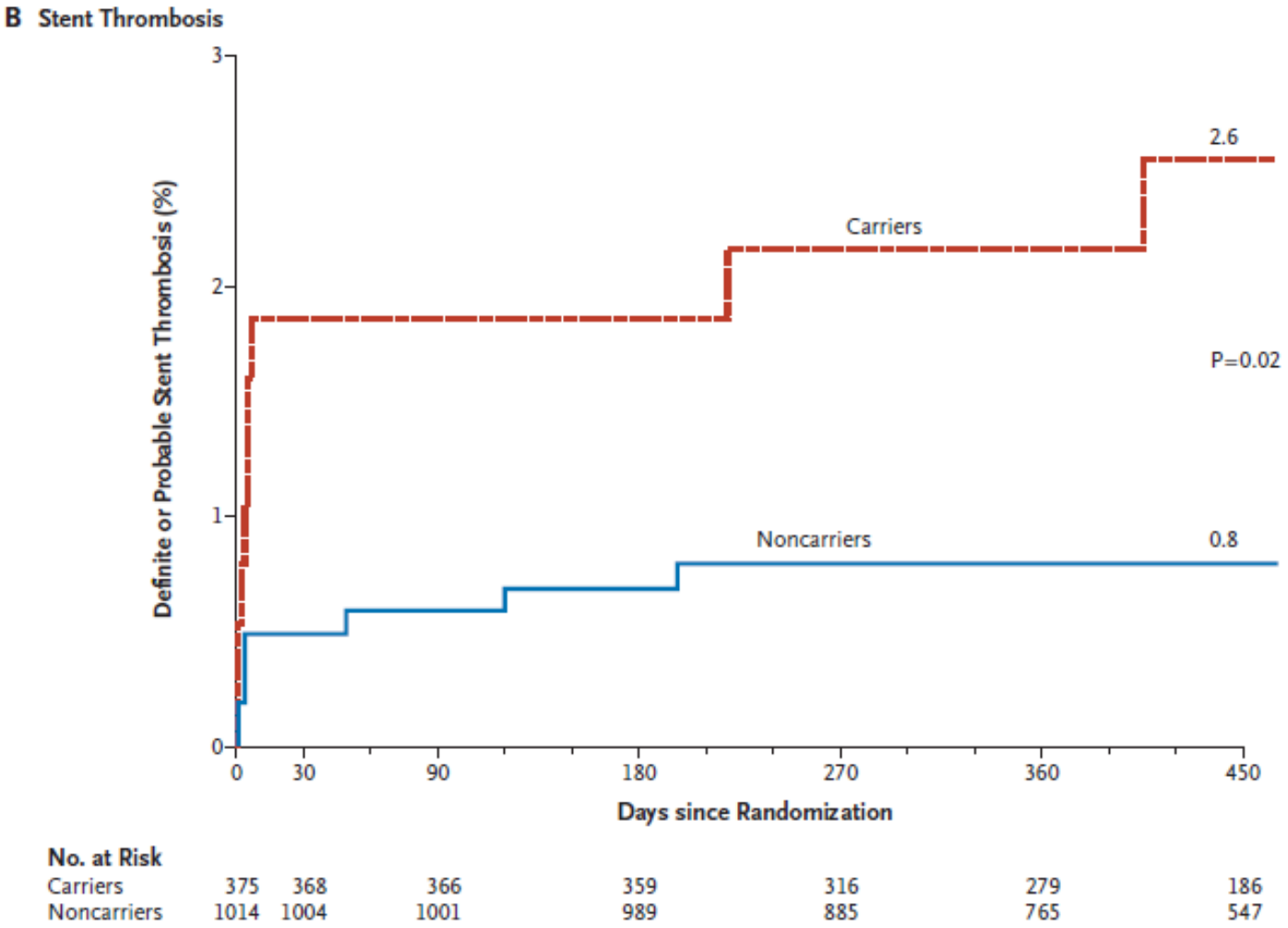


Clopidogrel-mediated inhibition of platelet aggregation is influenced by *CYP2C19*



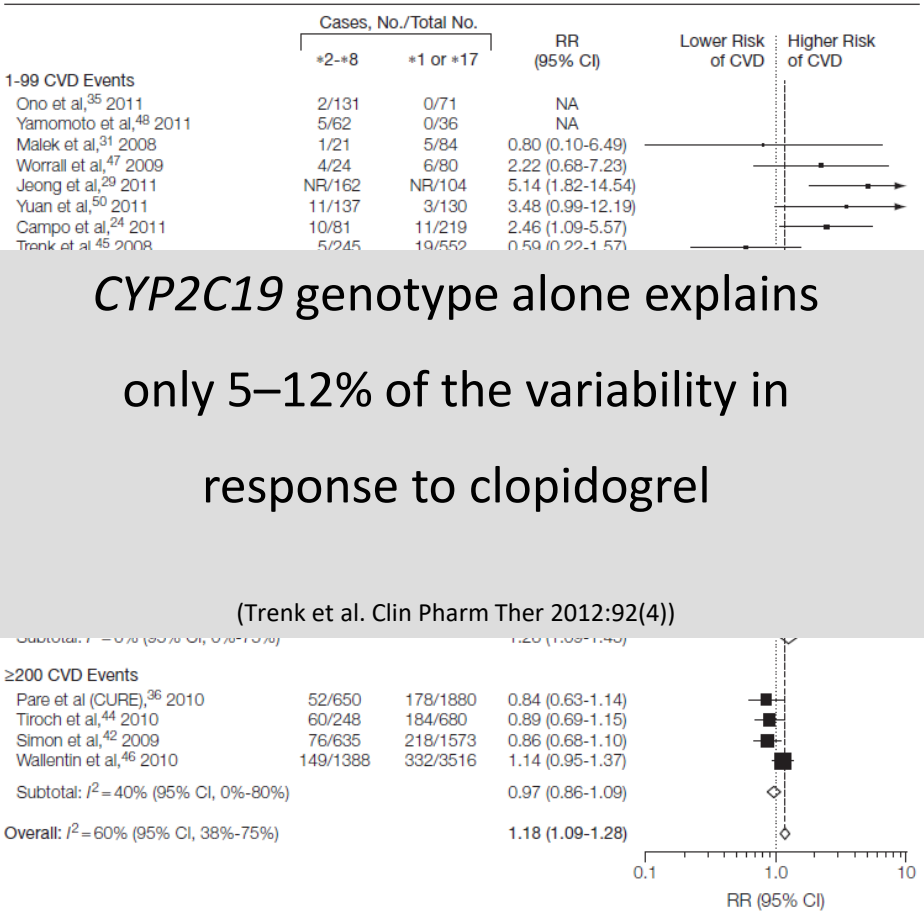
Kim et al. Clin Pharmacol Ther 2008; 84, 236–242

Increased risk of stent thrombosis in *CYP2C19* poor metabolizers



Mega et al. NEJM 2009;360:354-362

Meta-analysis of CYP2C19 Genotype and Risk of Composite Cardiovascular Outcome in Individuals Treated With Clopidogrel: "Treatment-Only" Analysis



CYP2C19 genotype alone explains only 5–12% of the variability in response to clopidogrel

(Trenk et al. Clin Pharm Ther 2012:92(4))

Comparison of any copy of *CYP2C19* *2 through *8 to wild-type (*1) or *17 (reference) is stratified according to the number of events per study (1-99, 100-199, ≥200). Data-marker sizes indicate the weight applied to each study using fixed-effects meta-analysis. CVD indicates cardiovascular disease; NR, not reported; RR, relative risk.

Holmes et al. JAMA. 2011;306:2704-2714

Pharmacogenetics in therapeutic areas

- Psychiatry
  - Schizophrenia
  - Depression
- Anticoagulation
  - Prevention of stroke
  - Prevention of thrombosis
- **Rare variants**

Identification and Characterization of a Defective *CYP3A4* Genotype in a Kidney Transplant Patient With Severely Diminished Tacrolimus Clearance

AN Werk[1], S Lefeldt[2], H Bruckmueller[1], G Hemmrich-Stanisak[3], A Franke[3], M Roos[2], C Küchle[2], D Steubl[2], C Schmaderer[2], JH Bräsen[4,5], U Heemann[2], I Cascorbi[1] and L Renders[2]

Fig. 1A

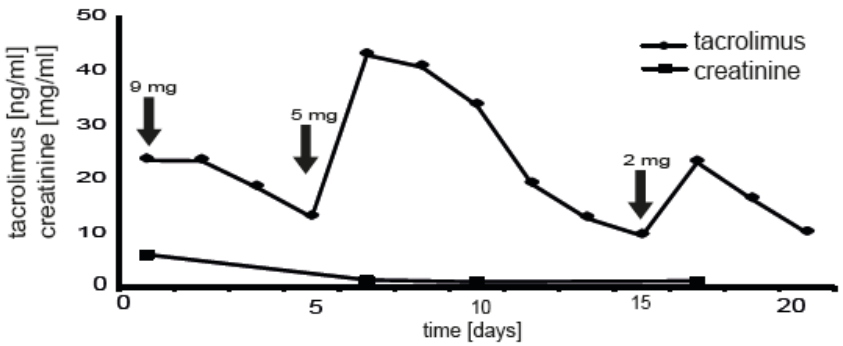
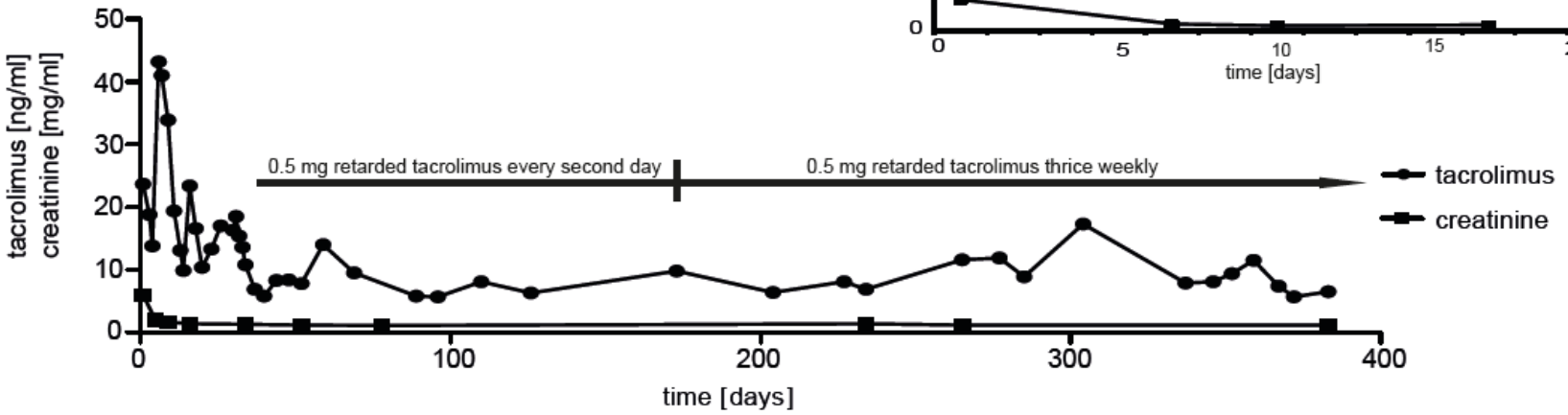
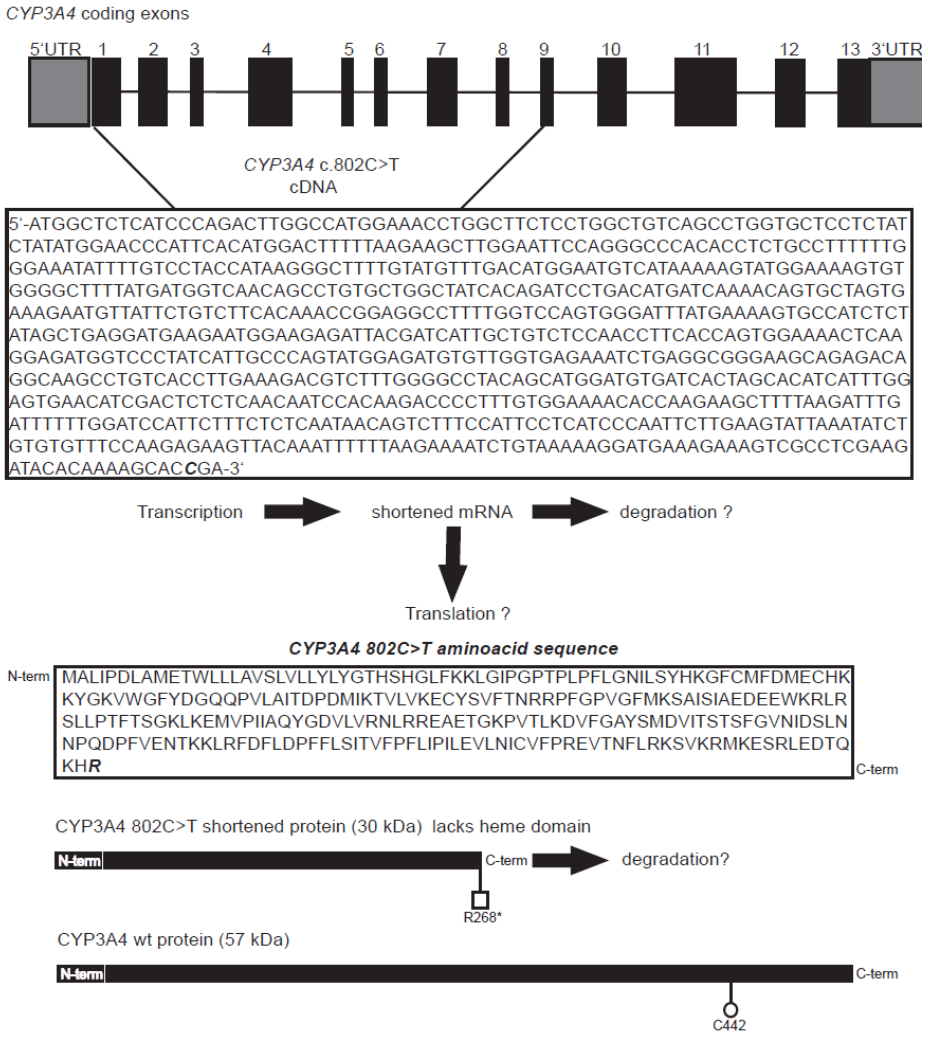


Fig. 1B



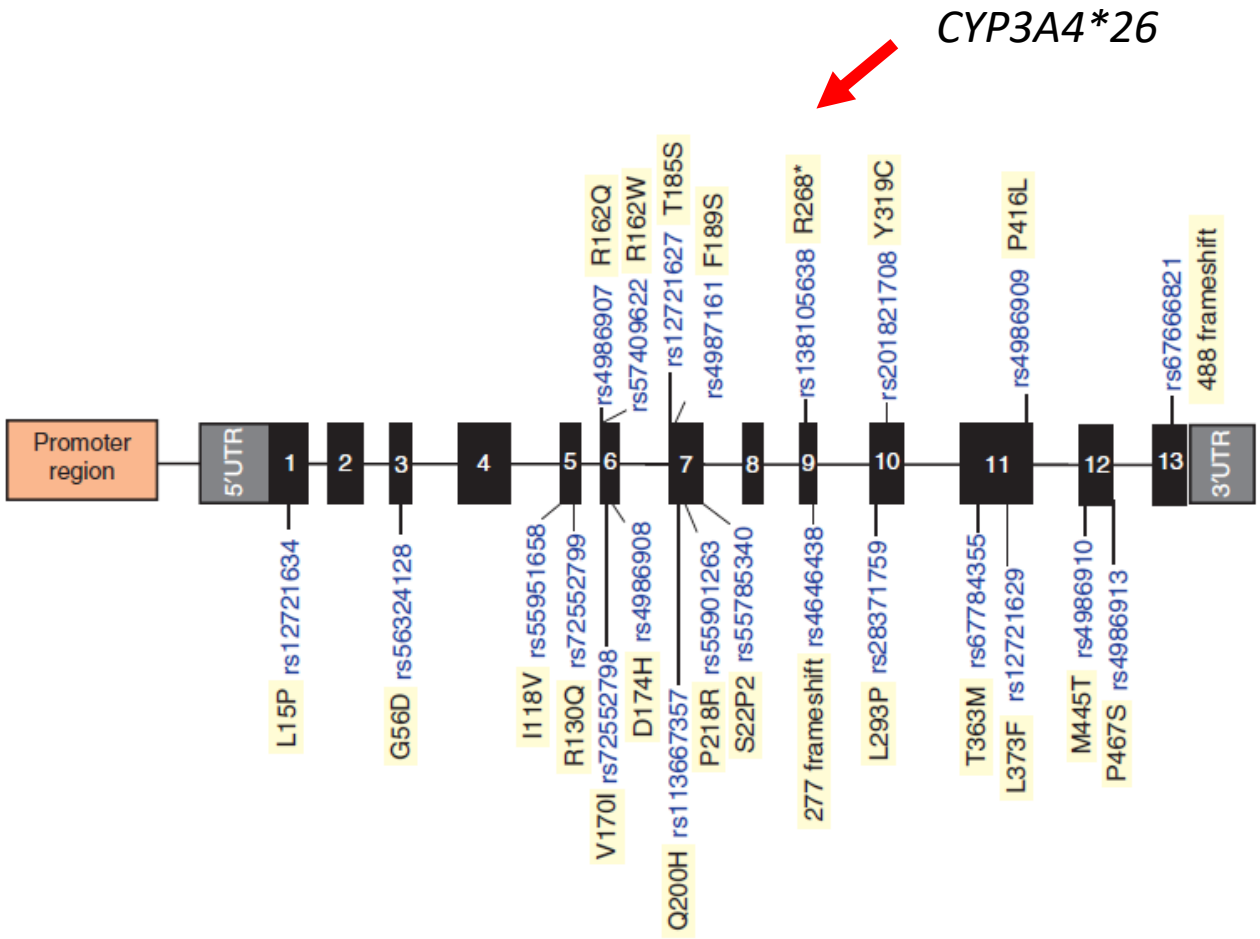
Werk et al. Clin Pharm Ther 2014;95:416-22

Identification of a premature stop codon (*CYP3A4*26*)

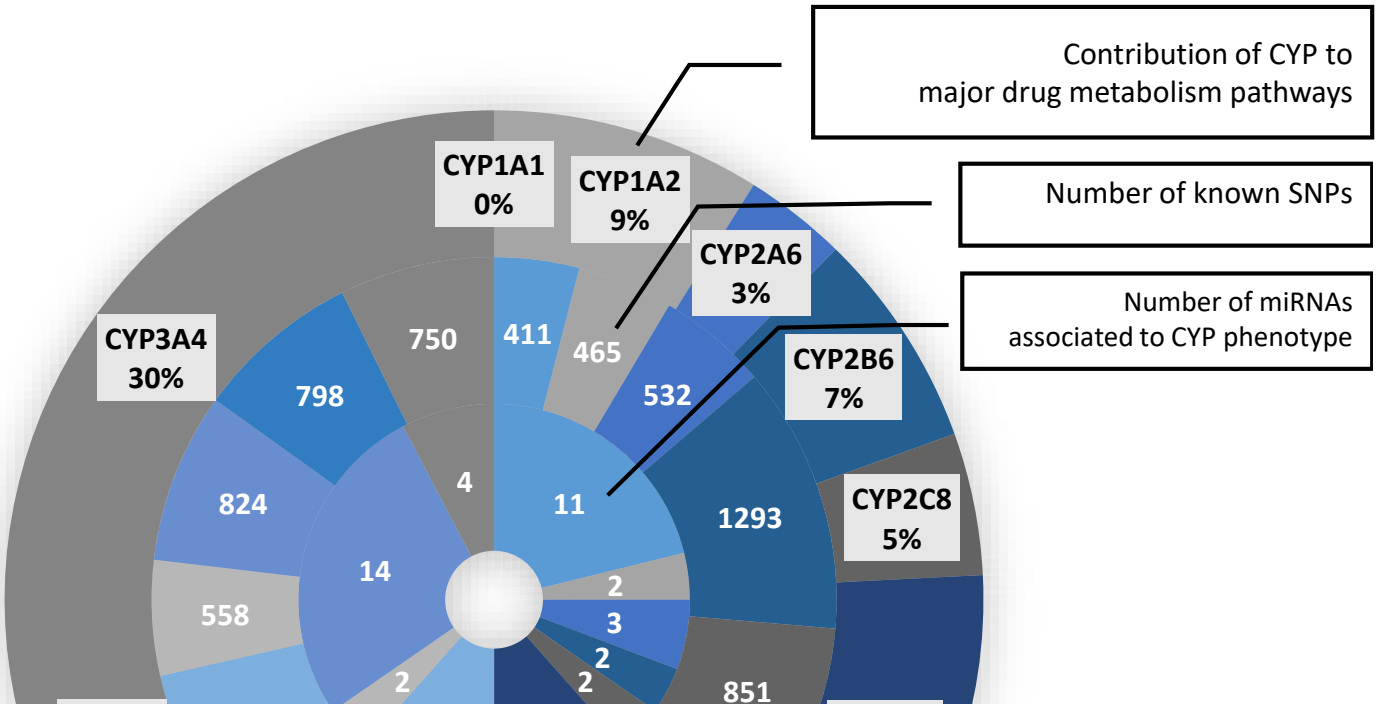


Werk et al. Clin Pharm Ther 2014;95:416-22

Exonic variants of *CYP3A4*



Werk and Cascorbi, Clin Pharmacol Ther. 2014;96:340-8



Trends in Pharmacological Sciences

CellPress

Forum

Precision Medicine and Rare Genetic Variants

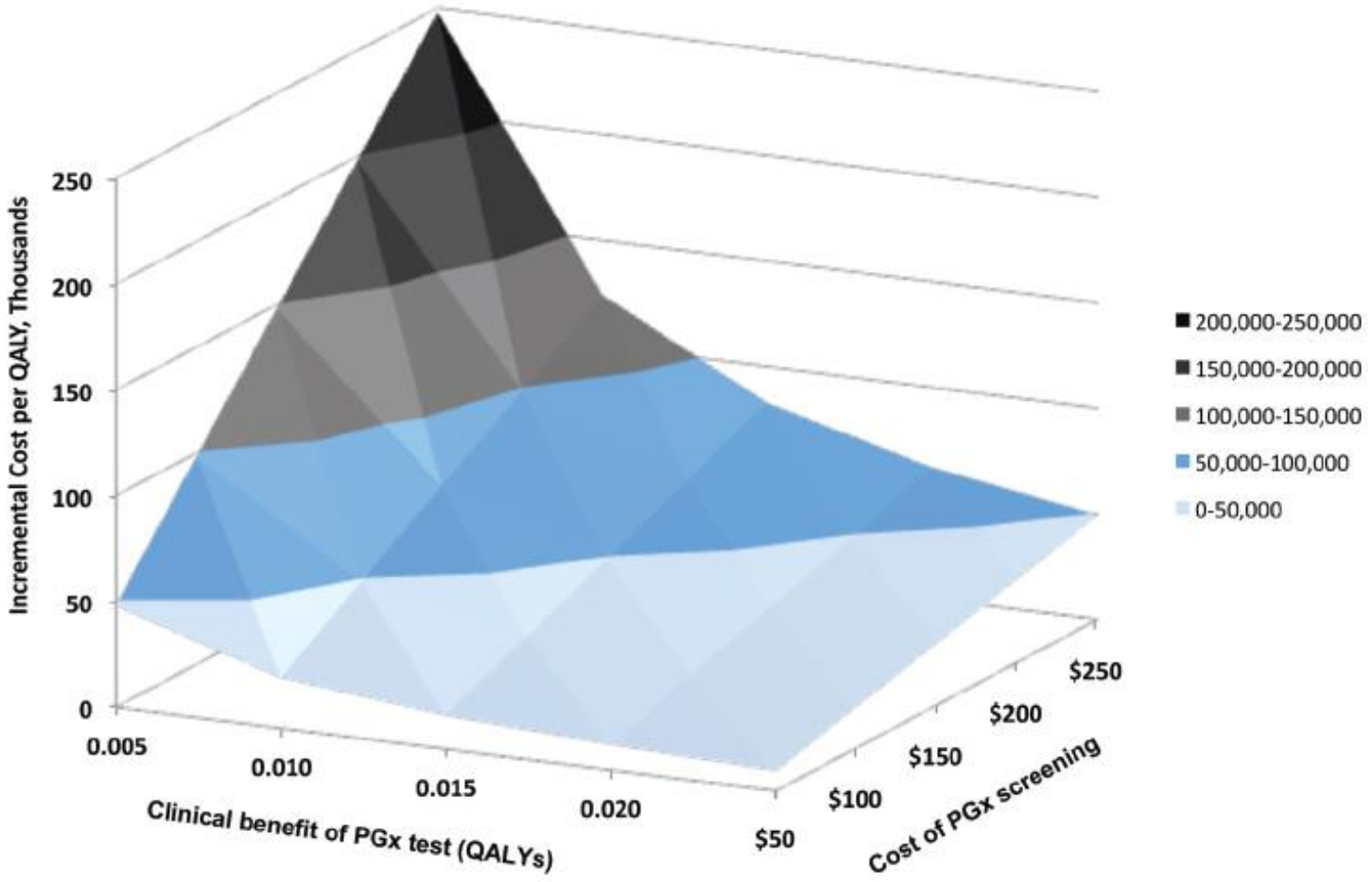
Volker M. Lauschke[1] and Magnus Ingelman-Sundberg[1,*]

and 24 to 30 were implicated in rare diseases [2]. Of the transcribed variants, more than 85% were rare, with minor allele frequencies (MAFs) below 0.5% [3]. When considering only putatively functional variants, this number increases to more than 95%, underlining the importance of rare variants for successful genetically ba treatment of disease [3].

gene can guide treatment with mutation-specific drugs causing specific refolding of the transporter and alleviation of disease symptoms. Variants are analyzed using a candidate panel or an unbiased sequencing approach, with the latter resulting in a significant increase in the number of var-

TIPS 2016;37(2):85–86

Future developments – the question of costs



Definition according to German Gene Diagnostics Act*
Gendiagnostikgesetz GenDG

§ 7 Medical doctor reservations

(1) Diagnostic genetic examinations may only be conducted by medical doctors, and predictive genetic examinations may only be conducted by medical doctors who are certified specialists in human genetics or by other medical doctors who within the framework of their own area of expertise were also able to obtain certification, specialization or additional qualification to conduct genetic examinations.

(2)The genetic analysis of any genetic sample may only be conducted in the course of a genetic examination by the responsible medical doctor or by a persons or institutions commissioned by the responsible medical doctor.

(3) Any genetic counselling as defined in § 10 may only be conducted by medical doctors qualified pursuant to Subparagraph (1), above, who are qualified to perform genetic counselling.

*unauthorized translation www.eshg.org