Markus Paulmichl MD

Pharmakogenetik: Regulatorische und Klinische Aspekte

Kühtai

2023

Center for
Personalized Medicine
Humanomed, Klagenfurt, Austria

Sapienza Università di Roma; Medical Faculty
Department of Personalized Medicine, Italy

Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties.

Markus Paulmichl MD; Chair of the Pharmacogenomic Working Party of EMA (now member of the MWP)

Co-founder of PharmGenetix

Pharmakogenetik: Regulatorische und Klinische Aspekte

- Regulatorische und Juridische Aspekte der PGx
- Ökonomische Aspekte der PGx
- Die Klinik am Beispiel der Psychiatrie
- Die Implementierung der PGx in den klinischen Alltag

Pharmakogenetik: Regulatorische und Klinische Aspekte

- Regulatorische und Juridische Aspekte der PGx
- Ökonomische Aspekte der PGx
- Die Klinik am Beispiel der Psychiatrie
- Die Implementierung der PGx in den klinischen Alltag

Overview
Research and development
Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Geriatric medicine
Innovation in medicines

Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

Current effective version	**Adopted guideline**
Reference number	EMA/CHMP/37646/2009
Published	02/02/2012
Effective from	01/08/2012
Keywords	Pharmacogenetics, pharmacokinetics, clinical development
Description	This document addresses the influence of pharmacogenetics on drug pharmacokinetics, encompassing considerations and requirements for the design and conduct of investigations during drug development.

OPINION

Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective

Marc Maliepaard, Charity Nofziger, Marisa Papaluca, Issam Zineh, Yoshiaki Uyama, Krishna Prasad, Christian Grimstein, Michael Pacanowski, Falk Ehmann, Silvia Dossena and Markus Paulmichl

Abstract | Pharmacogenetics, one of the cornerstones of personalized medicine, has the potential to change the way in which health care is offered by stratifying patients into various pretreatment categories, such as likely responders, likely non-responders or likely to experience adverse drug reactions. In order to advance drug development and regulatory science, regulatory agencies globally have promulgated guidelines on pharmacogenetics for nearly a decade. The aim of this article is to provide an overview of new guidelines for the implementation of pharmacogenetics in drug development from a multiregional regulatory perspective — encompassing Europe, the United States and Japan — with an emphasis on clinical pharmacokinetics.

Pharmacogenetics — the study of the associations between the genetics of individuals and their response to drugs, which is a subset of pharmacogenomics (BOX 1, note 1) — has become an important tool for drug development and in regulatory review[1–5]. So far, results from studies with a pharmacogenetics component have been used for several purposes including the following: elucidating the molecular or mechanistic basis for lack of drug efficacy or occurrence of adverse drug reactions (ADRs); clarifying variability in clinical response to drugs by ruling out the role of pathways involving the protein products of well-known polymorphic genes as clinically significant contributors to variable drug pharmacokinetics (PK) and/or pharmacodynamics (PD) parameters; estimating the magnitude of potential drug–drug interactions (DDIs); and designing clinical trials to test for greater treatment effect in genetic subpopulations[5].

Recently, the European Medicines Agency (EMA) published a guideline on the role of pharmacogenetics methodologies in the evaluation of drug PK properties and the US Food and Drug Administration (FDA) published a draft guidance on the use of clinical pharmacogenetics in early-phase clinical studies. These documents, along with similar guidelines from the equivalent agency in Japan (the Pharmaceuticals and Medical Devices Agency (PMDA)), are expected to affect drug development by providing a framework for using pharmacogenetics data throughout a drug's life cycle: from the preclinical phase to post-marketing pharmacovigilance. After providing brief background information on how genetic variations can affect drug response, the aim of this article is to describe the guidelines from the EMA, the FDA and the PMDA, focusing on critical issues for the use of pharmacogenetics during drug development related to drug PK parameters. These include the use of threshold values to guide decisions on the implementation of pharmacogenetics in different phases of drug development, and requirements for DNA sampling, genotyping and phenotyping (TABLE 1). This article also aims to compare the current guidelines from each agency and highlight future perspectives.

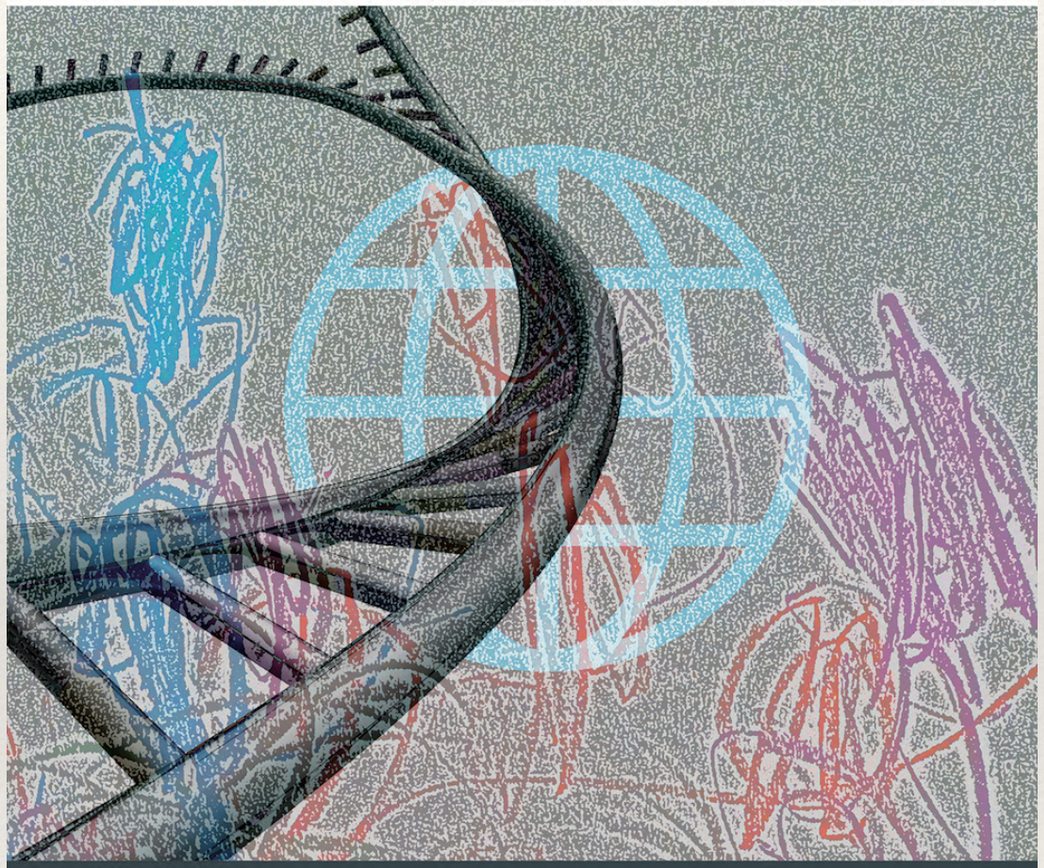
Genetic variants and drug response

The responses to virtually all drugs can vary between individuals owing to intrinsic factors (such as age, health and genetics) and/or extrinsic factors (such as diet, the use of concomitant drugs and adherence) that may affect drug PK and/or PD parameters. In recent years, our understanding of the influence of genes on interindividual differences in drug response has developed rapidly with the availability of the human genome sequence and technologies that allow high-throughput genotyping[3,4,6]. Examples of genetic variants that influence drug response include single nucleotide polymorphisms (SNPs), insertions and deletions, and copy number variations.

An individual's response following administration of a drug depends on several factors. First, genes relevant to the drug's absorption, distribution, metabolism and excretion (ADME), which determine PK properties; second, genes that encode drug targets — either intended or unintended — and their associated pathways, which determine PD properties; and third, genes that influence disease susceptibility or progression (examples of each category are given in TABLE 2). Although genetic variants affect both the PK and PD parameters of drugs, thereby contributing to heterogeneous clinical outcomes (that is, toxicity and/or efficacy), this article focuses on how genetic variants affect PK parameters because the study of genetic variants related to PK properties, especially in terms of drug metabolism, is a relatively mature field in which sufficient data and experience within the regulatory agencies are available to provide detailed guidance. For certain drugs, for example, in oncology, genetic variants directly related to PD parameters may be more important than genetic variants related to PK properties in influencing variability in drug response, but we have fewer examples to form the basis for regulatory guidance, and the strategy for drug development is often more complex than linking a genetic factor to drug concentrations.

The ADME properties of a drug are determined by a complex interplay of systemic (such as cardiovascular) and molecular factors (such as drug transport proteins

nature REVIEWS
february 2013 volume 12 no. 2
www.nature.com/reviews
DRUG DISCOVERY
THE SCIENCE AND BUSINESS OF DRUG DISCOVERY AND DEVELOPMENT



TARGETING EOSINOPHILS
Opportunities in allergy, inflammation and beyond

Pharmacogenetics in the evaluation of new drugs
A multiregional regulatory perspective

Table 4 | **Summary of differences between the three regulatory guidelines on pharmacogenetics**

Issue	Regulatory agency		
	European Medicines Agency	**Pharmaceutical and Medical Devices Agency, Japan**	**US Food and Drug Administration**
Development phases covered in guideline or guidance	Preclinical and clinical development (Phases I–IV; focusing on PK)	Clinical development (Phases I–IV)	Early clinical development (Phases I and II)
Banking of DNA samples	Highly recommended	Encouraged*	Strongly encouraged
Genomic testing	Required‡	Recommended	Recommended
In vitro cut-off values§	>50%	None	None
In vivo cut-off values§	>25%	None	None

*Does not apply to category A (see main text for more details). ‡Is a firm requirement only when *in vitro* (>50%) or *in vivo* (>25%) cut-off values are met. §For when pharmacogenetics-related testing is required in pharmacokinetics (PK) studies.

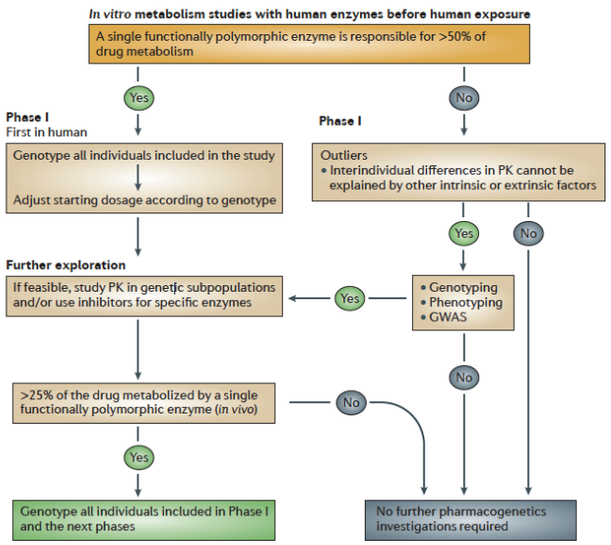


Figure 1 | **The European Medicine Agency's decision-making tree for *in vitro* studies prior to human exposure and Phase I studies.** For polymorphic enzyme systems for which well-validated *in silico* physiologically based pharmacokinetic (PK) models have been developed, pharmacogenetics differences in humans may be predicted and used as a guide for clinical study design with respect to pharmacogenetics investigation. GWAS, genome-wide association study.

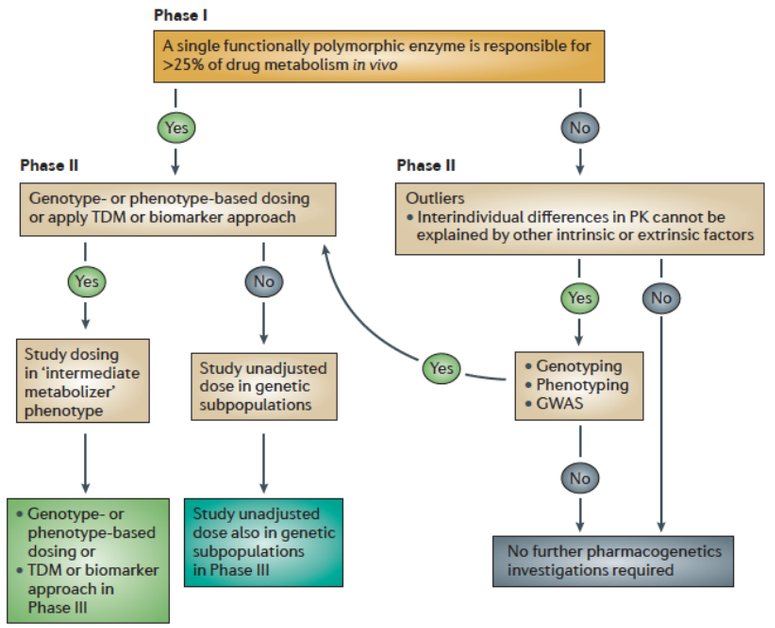


Figure 2 | **The European Medicine Agency's decision-making tree for Phase I and Phase II studies.** For polymorphic enzyme systems for which well-validated *in silico* physiologically based pharmacokinetic (PK) models have been developed, pharmacogenetics differences in humans may be predicted and used as a guide for clinical study design with respect to pharmacogenetics investigation. GWAS, genome-wide association study; TDM, therapeutic drug monitoring.

Overview
Research and development
Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Geriatric medicine
Innovation in medicines

ICH E18 Guideline on genomic sampling and management of genomic data

Current effective version	**Adopted guideline** Adopted guideline enters into effect 28/02/2018 - see below
Reference number	EMA/CHMP/ICH/11623/2016
Published	06/10/2017
Effective from	28/02/2018
Keywords	Genomic sampling, genomic data, clinical studies
Description	This document provides guidance on genomic sampling and management of genomic data from interventional and non-interventional clinical studies.

Overview
Research and development
Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Geriatric medicine
Innovation in medicines
Non-pharmaceutical products
Orphan designation

Addendum on terms and concepts of pharmacogenomic features related to metabolism to the Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

Current effective version	**Concept paper**
Reference number	EMA/CHMP/644998/2016
Published	07/07/2017
Keywords	Phenotype, genotype, methodologies, pharmacokinetics, metabolism
Description	This addendum to the guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009) intends to provide clear definitions of terms used for metabolic phenotyping, as well to propose concepts regarding the translation of genotypes into the predicted metabolic phenotype, of significant importance for the correct treatment of patients.

Overview
Research and development
Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Geriatric medicine
Innovation in medicines
Non-pharmaceutical products

Key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

Current effective version	**Adopted guideline**
Reference number	EMA/CHMP/281371/2013
Published	20/11/2015
Effective from	01/04/2016
Keywords	Pharmacogenomics, pharmacovigilance, biomarkers, genomic variations
Description	This document addresses the influence of pharmacogenomics on pharmacovigilance activities. It includes considerations on how to evaluate the pharmacovigilance related issues for medicinal products with pharmacogenomic associations, and how to translate the results of these evaluations to appropriate treatment recommendations in the labelling..

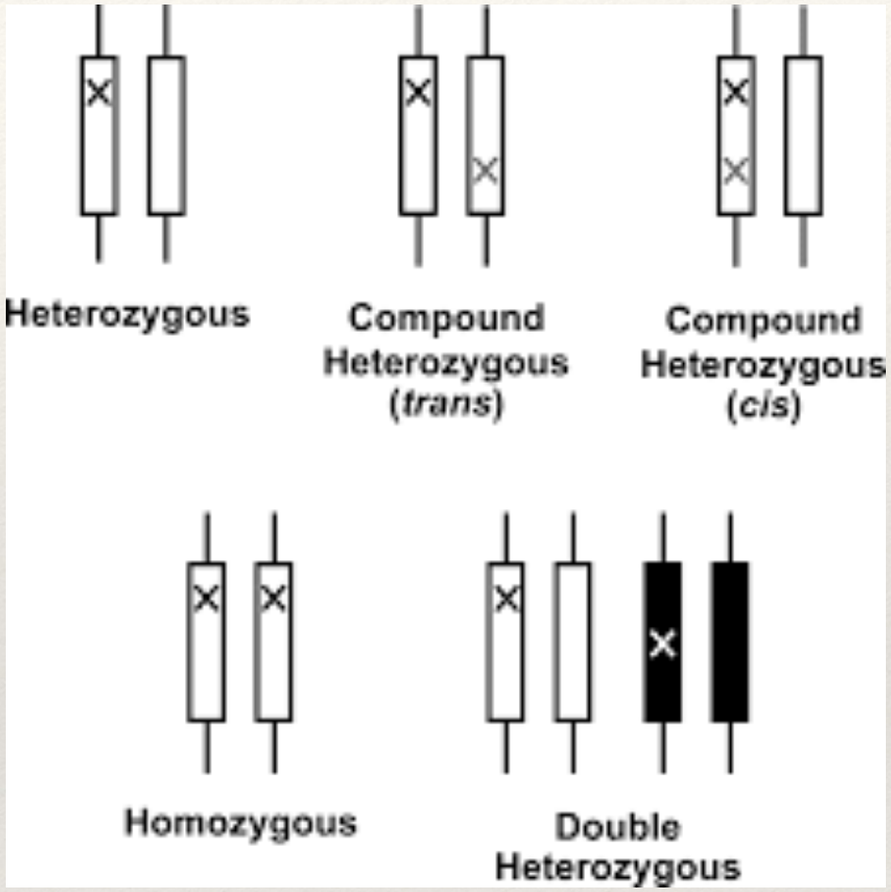
Overview
Research and development
Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Geriatric medicine
Innovation in medicines

Good pharmacogenomic practice

Current effective version	**Adopted guideline** Adopted guideline enters into effect 01/09/2018
Reference number	EMA/CHMP/718998/2016
Published	19/03/2018
Keywords	Pharmacogenomics, good practices, pharmacogenomic analyses, biomarkers, study design, pharmacokinetics, DNA sequencing
Description	This document describes requirements related to the choice of appropriate genomic methodologies during the development and the life-cycle of a drug. It discusses the principles for a robust clinical genomic dataset. It also highlights the key scientific and technological aspects for the determination and interpretation of the genomic biomarker data and their translation into clinical practice.

Content of the ‚Good PGx Practice' Guideline Important for polymorphic genes i.e. CYP2D6

- Preanalytics
- Analytics
  - **cis/trans heterozygous**
  - **NGS specific; 30 X minimum coverage**
  - **Allele Drop-Out**
  - **How many SNPs?**
  - **Hybrids**
  - **CNVs**
  - Liquid biopsies
  - Inter Patient Verification (IPV)
  - Reporting and *-nomenclature
  - Accreditation
- Sample repository for retrospective studies



NGS specific issues:
Minimum coverage **30x** (6x)
Mean coverage 150x (**30x**)
Cave: Allele drop out
Cave: Gene Homology

For which drugs is PGx information available?

≈ 35% of all drugs EMA has granted market authorization do have PGx relevant Bio-Markers mentioned in important sections of their SmPC[1]

≈37.7% of all drugs marketed in Austria do have PGx relevant Bio-Markers mentioned in important sections their SmPC[2]

1 **Pharmacogenomic information in drug labels: European Medicines Agency perspective.**
Ehmann F, Caneva L, Prasad K, **Paulmichl M**, Maliepaard M, Llerena A, Ingelman-Sundberg M, Papaluca-Amati M.
Pharmacogenomics J. 2015 Feb 24. doi: 10.1038/tpj.2014.86. [Epub ahead of print]

2 Doctoral Thesis of Norma Anwar, PMU, 2015

Haftung für Ärzte bei Nichttestung?

- Testing required:
  Bei Abgabe von Medikamenten, die nur nach pharmakogenetischer Testung verschrieben werden dürfen, liegt bei Nichtbeachtung der Testverpflichtung zwangsläufig ein Behandlungsfehler vor.

- Testing recommeded/Actionable PGx:
  Kommt es bei einer Nichttestung in Fällen, in denen der Test zwar nicht zwingend vorgeschrieben ist, aber in der Fachinformation entsprechende Hinweise zum Handlungsbedarf vermerkt sind, zu entsprechenden Nebenwirkungen, liegt möglicherweise ein Behandlungsfehler vor, wenn der Patient nicht nachweislich auf das Risiko bei einer Nichtdurchführung des Tests aufmerksam gemacht wurde.

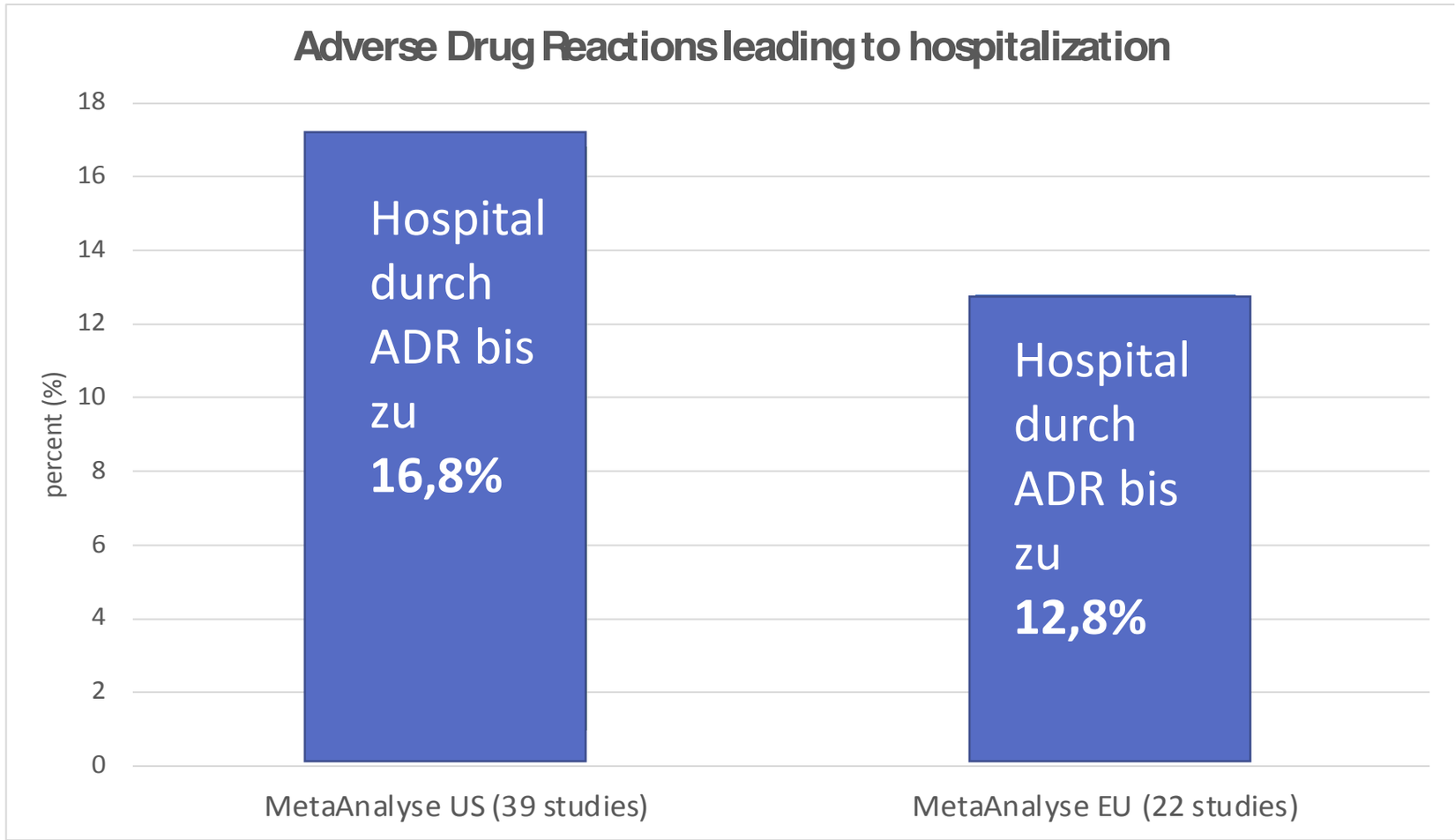
Prof. Dr. med. Markus Paulmichl
Facharzt für Pharmakologie und Toxikologie
Leiter der Abteilung Personalisierte Medizin, Privatklinik Maria Hilf GmbH, Klagenfurt
Allgemein beeidigter und gerichtlich zertifizierter Sachverständiger für die Bereiche 02.03, 02.23 und 02.46

Pharmakogenetik in der Beurteilung von medizinischen Behandlungsfehlern bei der Medikamentenverschreibung

Pharmakogenetik: Regulatorische und Klinische Aspekte

- Regulatorische und Juridische Aspekte der PGx
- Ökonomische Aspekte der PGx
- Die Klinik am Beispiel der Psychiatrie
- Die Implementierung der PGx in den klinischen Alltag

Meta-Studien zeigen, dass Adverse Drug Reactions (ADRs) häufig Hospitalisierung verursachen



Formica D. et al., EXPERT OPINION ON DRUG SAFETY 2018, VOL. 17, NO. 7, 681–695

Studien zum ökonomischen Benefit

2016, SanDiego, 112 polypharmacy patients [1)]	Medication cost savings related to the identified reduction and replacement opportunities exceeded the cost of testing and are **estimated to be US$1300** (year 2016 cost) **per patient annually**.	less drug
2015, Prosp. generated cohort, 2168 cases, 10,880 contr. [2)]	Patients receiving **PGx testing saved $1035.60 in total medication** costs over 1 year compared to the usual care cohort (P = 0.007). PGx testing **improved adherence** compared to standard of care.	better adherenc e
2016, San Diego [3)]	Applying PGx guided recommendations across the patient population resulted in the **elimination and/or replacement of one to three drugs** and an estimated annual **saving of US$621 per patient**.	less drug
2015, College of Pharmacy, Univ. of Utah, 1025 patients [4)]	Pre-emptive screening via panel-based approach resulted in a signif. **reduction in hospitalizations** (9.8% vs 16.1%, P = 0.027) and patient **visits to the emergency** department (4.4% vs 15.4%, P = 0.0002).	less hospit al
2010, Medco Health Solutions, Mayo Clinic, 3584 patients [4)]	CYP2C9 and VKORC1 genotyping of warfarin recipients resulted in **31% fewer hospitalizations** overall and a **43% lower risk** of hospitalization for bleeding or thromboembolism.	less hospit al

1. Sugarman EA et al., Drugs Aging 2016 Dec;33(12):929-936 2. Winner JG, et al. Curr Med Res Opin. 2015;31(9):1633–43. , 3. Saldivar JS, et al. Pharmgenomics Pers Med. 2016;9:1–6.,
4. Brixner D, et al., J Med Econ. 2016;19(3):213–28., 5. Epstein RS, et al., J Am Coll Cardiol. 2010;55(25):2804–12.

Pharmakogenetik: Regulatorische und Klinische Aspekte

- Regulatorische und Juridische Aspekte der PGx
- Ökonomische Aspekte der PGx
- Die Klinik am Beispiel der Psychiatrie
- Die Implementierung der PGx in den klinischen Alltag

Studien zum klinischen Benefit

2021, Review of 43 PGx studies between 2007 and 2020 [1)]	Pharmacogenetic multi-gene panel tests within MTM (medication therapy management) demonstrate an approximate **50% decrease in emergency visits and hospitalizations** in elderly polypharmacy patients	poly-phar
2019, Seven of University of Florida Health primary care clinics, 375 enrolled patients [2)]	Within the same subgroup of IM/PMs prescribed tramadol or codeine at baseline, CYP2D6-guided group experienced a **30% reduction in composite pain intensity** compared with the usual care group.	PAI N
2019, Meta-analysis of 5 randomized controlled trials (RCT), 1737 participants [3)]	Pharmacogenetic-guided therapy **1.71 times more likely** to achieve **symptoms remission** relative to individuals who received usual treatment.	psyc h
2016, Netherlands Cancer Inst., Slotervaart Hosp., Canisius W.Hosp., 2038 patients [4)]	The risk of 5-FU-induced toxicity was significantly reduced **from 73%** in historical controls (n = 48) **to 28% by genotype-guided dosing** (P < .001); drug-induced death was reduced from 10% to 0%.	ONK O
2015, AssureRx Health, Mayo Clinic, 258 patients [5)]	Gene-guided treatment raised the odds of **clinical response by 2.3-fold**, the guided group had a **53% greater improvement** in depressive symptoms.	psyc h

1.Hayashi M et al., es Social Adm Pharm 2021 Aug 20;S1551-7411(21)00313-2 , 2. Smith DM, et al., Genet Med. 2019;0(0)., 3. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW., Pharmacogenomics. 2019;20(1):37–47.
4. Deenen MJ, et al., J Clin Oncol. 2016; 34(3):227–34., 5. Altar CA, Carhart J, Allen JD, Hall-Flavin D, Winner J, Dechairo B., Mol Neuropsychiatry. 2015; 1(3):145–55.

Braucht es Studien um PGx zu implementieren?

Nichtbefolgung führt zu Strafen!

Actionable PGx	EMA	Annotation of EMA Label for duloxetine and CYP2D6	CYP2D6	duloxetine

Nichtbefolgung kann Haftungsansprüche zur Folge haben!

SSRI & SNRI:

Jeffrey Bishop regarding PGx and Psychiatry

- Effective treatments are available, but drugs are usually chosen by trial & error
  - "Response" rates for antidepressants, antipsychotics, and mood stabilizers ~40-70%
    - Inter-individual variability is high
  - One year discontinuation rates for antidepressants and antipsychotics 32-74%
    - Inadequate response and side effects
  - Many drug and non-drug treatment options
    - Need to improve our ability to optimize the selection and dosing of available treatments

1. Lieberman et al. Am J Psychiatry 2003. PMID: 12900300
2. Lieberman et al. N Engl J Med 2005. PMID: 16172203
3. Mullins et al. Pharmacotherapy 2005. PMID: 15899727

University of Minnesota
College of Pharmacy

- PM or UM patients 3-6x more likely to discontinue treatment at 45 days or 1 year

CPIC Meeting June 2019 Memphis

SSRI UND SNRI

SSRIs (Serotonin-Wiederaufnahme-Hemmer) und **SNRIs** (Serotonin-Noradrenalin-Wieder-aufnahme-Hemmer) werden **bevorzugt über CYPs abgebaut**.

WIRKSTOFF	MEDIKAMENT	ABBAU **I - primär** I - sekundär I - beteiligt	ANALYSE-PAKET
Citalopram #+$!	Pram, Seropram, Citalostad, Celexa, Ran-Citalo	**CYP2C19**	PSYCH I
		CYP3A4	PSYCH II
Duloxetin !	Dulasolan, Yentreve, Cymbalta	**CYP2D6**	CYP2D6
		CYP1A2	PSYCH II
Escitalopram +$	Cipralex, Lexapro, Pramulex	**CYP2C19, CYP2D6**	PSYCH I
		CYP3A4	PSYCH II
Fluoxetin !	Felicium, Mutan, Prozac, Sarafem, FXT, Fluoxibene	**CYP2D6**	CYP2D6
		CYP2C9	PSYCH II
Fluvoxamin +	Luvox, Riva-Fluvox, Floxyfral	**CYP2D6**	CYP2D6
		CYP1A2	PSYCH II
Mirtazapin	Mirtabene, Mirtel, Mirtaron	**CYP2D6**	CYP2D6
		CYP3A4, CYP1A2	PSYCH II
Paroxetin #+$!	Seroxat, Paxil, Pexeva, Parocetan, Ennos	**CYP2D6,** CYP2C19	PSYCH I
		CYP3A4, CYP1A2	PSYCH II
		CYP3A5	PSYCH III
Sertralin +$!	Gladem, Tresleen, Adjuvin, Zoloft	**CYP2C19**	PSYCH I
		CYP2B6, CYP3A4	PSYCH II
Venlafaxin $	Efectin, Effexor	**CYP2D6, CYP2C19**	PSYCH I
		CYP3A4	PSYCH II

EMA/FDA Test Levels: Antidepressants

	PGX LEVEL	SOURCE	GENES	TITLE
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for amitriptyline and CYP2D6
Read Now	Actionable PGx	FDA	CYP2C19, CYP2D6	Annotation of FDA Label for citalopram and CYP2C19,CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for clomipramine and CYP2D6
Read Now	Actionable PGx	FDA	CYP2C19, CYP2D6	Annotation of FDA Label for escitalopram and CYP2C19,CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for duloxetine and CYP2D6
Read Now	Actionable PGx	FDA	CYP2C19, CYP2D6	Annotation of FDA Label for escitalopram and CYP2C19,CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for fluvoxamine and CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for imipramine and CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for nortriptyline and CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for protriptyline and CYP2D6
Read Now	Actionable PGx	FDA	CYP2D6	Annotation of FDA Label for trimipramine and CYP2D6
Read Now	Actionable PGx	PMDA	CYP2C19, CYP2D6	Annotation of PMDA Label for escitalopram and CYP2C19,CYP2D6
Read Now	Actionable PGx	HCSC	CYP2C19	Annotation of HCSC Label for citalopram and CYP2C19
Read Now	Actionable PGx	HCSC	CYP2D6	Annotation of HCSC Label for nortriptyline and CYP2D6

Sertralin dosing according CPIC

← Back to all Dosing Guidelines

Annotation of DPWG Guideline for sertraline and CYP2C19

Summary

Reduce sertraline dose by 50% for patients with CYP2C19 poor metabolizer genotypes (PM), and be extra alert to adverse drug events in patients with CYP2C19 intermediate metabolizer genotypes (IM).

Reduction by 50%

Annotation

The Royal Dutch Pharmacists Ass… …rmacogenetics Working Group has evaluated therapeutic dose recommendations for sertraline based on *CYP2C19* genotype [Article:21412232].

PHENOTYPE (GENOTYPE)	THERAPEUTIC DOSE RECOMMENDATION	LEVEL OF EVIDENCE
CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Reduce dose by 50%.	Published controlled studies of moderate quality* relating to phenotyped and/or genotyped patients … having relevant pharmacokinetic or clinic…

CLINICAL RELEVANCE

Clinical effect (statistically significant difference): long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; adverse drug events resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); … normalized ratio 4.5-6.0; neutropenia 1.0-1.5x109/l; leucopenia … thrombocytopenia 50-75x109/l

However: NO indication on how the tests should be performed

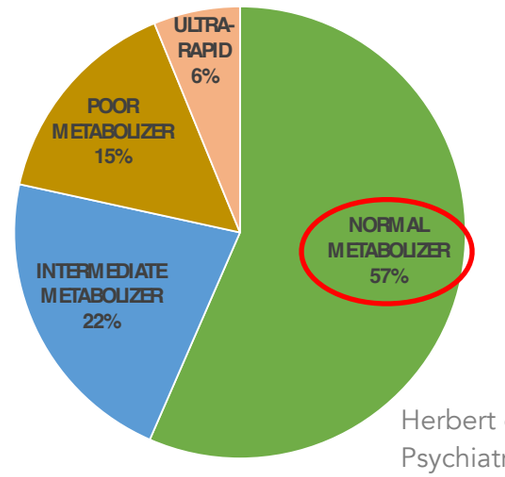
CYP2D6 spielt eine Schlüsselrolle: hoch polymorphes Enzym

	Total	No	Redu.	Incr.	allele specificity	Hybrids	Functional Test (Promoter & Intron & Exon)	Allele drop-out
TOT care & Psych	All (178)	All (60)	All (19)	All	YES	All	All	All
Lab1	3	1	1	(-)	-	-	-	-
Lab2 NGS	O	O	O	O	-	-	-	-
Lumin.	7	-	3	(-)	-	-	-	-
Stratip.	12	8	2	(-)	-	-	-	-
Biolog.	19	13	4	(-)	-*	-	-	-

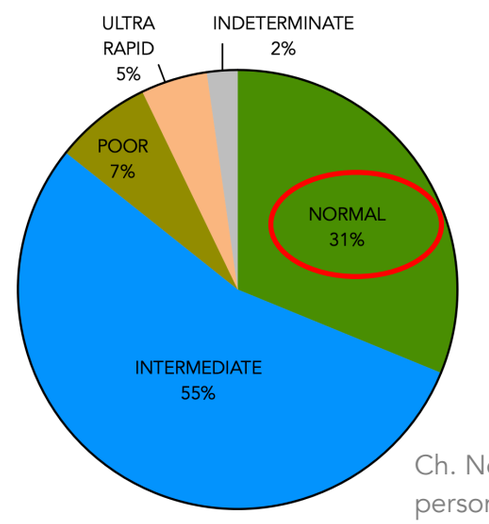
O = according EMA Guideline **should no be used**

* Use of Haplotypes

CYP2D6 Phänotyp Häufigkeit



Herbert et al., J Psychiatr Res. 2018 Jan;96:265-272

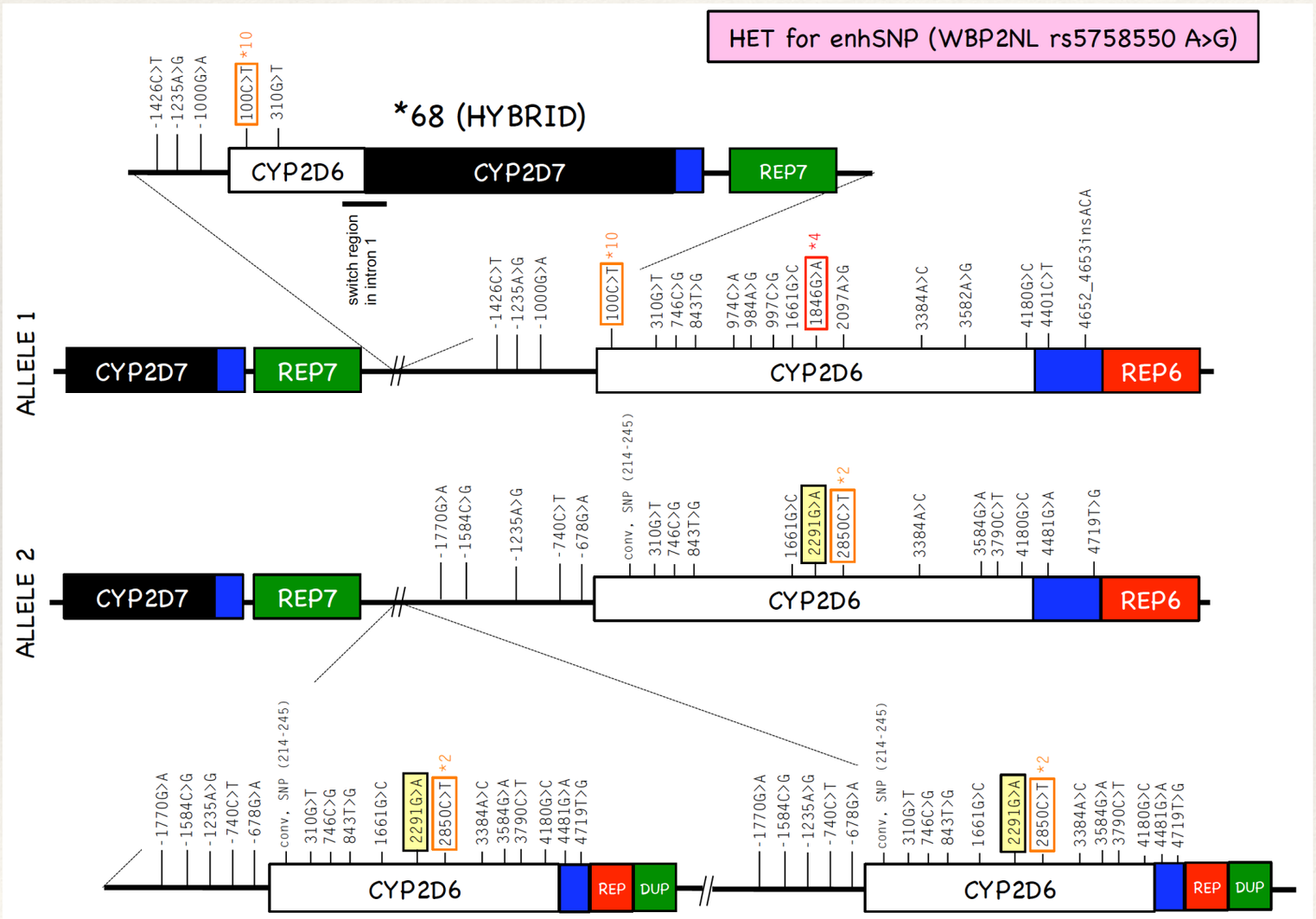


Ch. Nofziger, 2022 personal communication

CNV (CYP2D6)

Fluoxetin (3 years 20 mg; 3 month ago reduction to 10 mg)

CYP2D6, CYP2C9



Patient is a Ultra-Rapid Metabolizer for CYP2D6

Change Fluoxetin to
Sertralin (2B6, **2C19**, 3A4)
Citalopram (**2C19**, 3A4)
both
Selective Serotonin Reuptake Inhibitors (SSRI)

Editorial

For reprint orders, please contact: reprints@futuremedicine.com

Pharmacogenomics

Accurately genotyping *CYP2D6*: not for the faint of heart

Charity Nofziger*,[1] & Markus Paulmichl[2,3]

[1]PharmGenetix Gmbh, Niederalm, Austria

[2]Center for Health & Bioresources, Austrian Institute of Technology, Vienna, Austria

[3]NESMOS Department, University of Rome Sapienza, Rome, Italy

*Author for correspondence: Tel.: +43 501015 300; charity.nofziger@me.com

"achievement of a 100% accurate *CYP2D6* genotype may constitute only half of the proverbial uphill battle."

First draft submitted: 20 June 2018; Accepted for publication: 5 July 2018; Published online: 18 July 2018

Pharmakogenetik: Regulatorische und Klinische Aspekte

- Regulatorische und Juridische Aspekte der PGx
- Ökonomische Aspekte der PGx
- Die Klinik am Beispiel der Psychiatrie
- Die Implementierung der PGx in den klinischen Alltag

From the PGx analysis to the PGx guided prescription

From here....

CYP2D6*4 heterozygot	-	Intermediate metabolizer
CYP3A5*3 homozygot	-	poor metabolizer

- Learn PGx
- Know about PGx relevant drugs
- Know DDI
- Take into consideration PGx information in the SmPC
- Consider PGx databases
- Be informed about the original literature
- Translate into actionable prescription

... to dosing and prescription

Legende	Bedeutung
✕	Ziehen Sie die Verwendung eines alternativen Wirkstoffes in Betracht
↓↓↓	Ziehen Sie die Verwendung einer sehr viel niedrigen (>= 75%) Dosierung in Betracht; Prodrugs können eine sehr viel geringere Wirkung zeigen
↓↓	Ziehen Sie die Verwendung einer viel niedrigen (>= 50%) Dosierung in Betracht; Prodrugs können eine viel geringere Wirkung zeigen
↓	Ziehen Sie die Verwendung einer niedrigen (>= 25%) Dosierung in Betracht; Prodrugs können eine geringere Wirkung zeigen
✓	Dosieren Sie wie in der Fachinformation angegeben
↑	Substrate können eine niedrige Wirkung haben; bei Prodrugs ziehen Sie eine geringere Dosierung in Betracht
↑↑	Substrate können eine viel niedrige Wirkung haben; bei Prodrugs ziehen Sie eine viel geringere Dosierung in Betracht
↑↑↑	Substrate können eine sehr viel niedrige Wirkung haben; bei Prodrugs ziehen Sie eine sehr viel geringere Dosierung in Betracht

Medikamente

Medikation:	Dosierungshinweis
Agomelatin	↑
Alprazolam	↓
Amitriptylin	✕
Aripiprazol	✓
Bromazepam	↑
Brotizolam	✓
Bupropion	↓↓↓
Citalopram	✕
Clobazam	↑↑
Clomipramin	✕
Clozapin	✕
Desipramin	✓
Diazepam	↑
Doxepin	✕
Duloxetin	↑
Escitalopram	✕
Flunitrazepam	✓
Fluoxetin	✓
Fluvoxamin	✓

Von der Blutabnahme und Labor-Analyse…
zur angewandten personalisierten Medizin

PGxOPTIMIZER

DNA-Extraktion

PGx-Analyse

- >25 Gene
- Copy number
- >160 SNPs
- Allel-drop-out
- Hybrid-Analyse
- Allel-Spezifität
- Deletionen

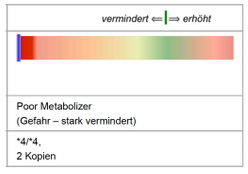
Techn. Befund

*CYP2C9 *8 MUT*
*CYP2D6 *4/*4*
CYP2D19 WT
*CYP3A5 *3 MUT*
CYP3A4 WT
*SLCO1B1. *3 MUT*
...

Interpretation

- poor
- intermediate
- normal
- ultra rapid

CYP2D6



Dosis-Empfehlung

WIRKSTOFF	EINZELMEDIKATION
Siponimod	↓
Ticagrelor	✓
Fluvastatin	↓↓ ⚠
Pantoprazol	↑

PGx-Medikamenten-**Interaktions-Prüfung**

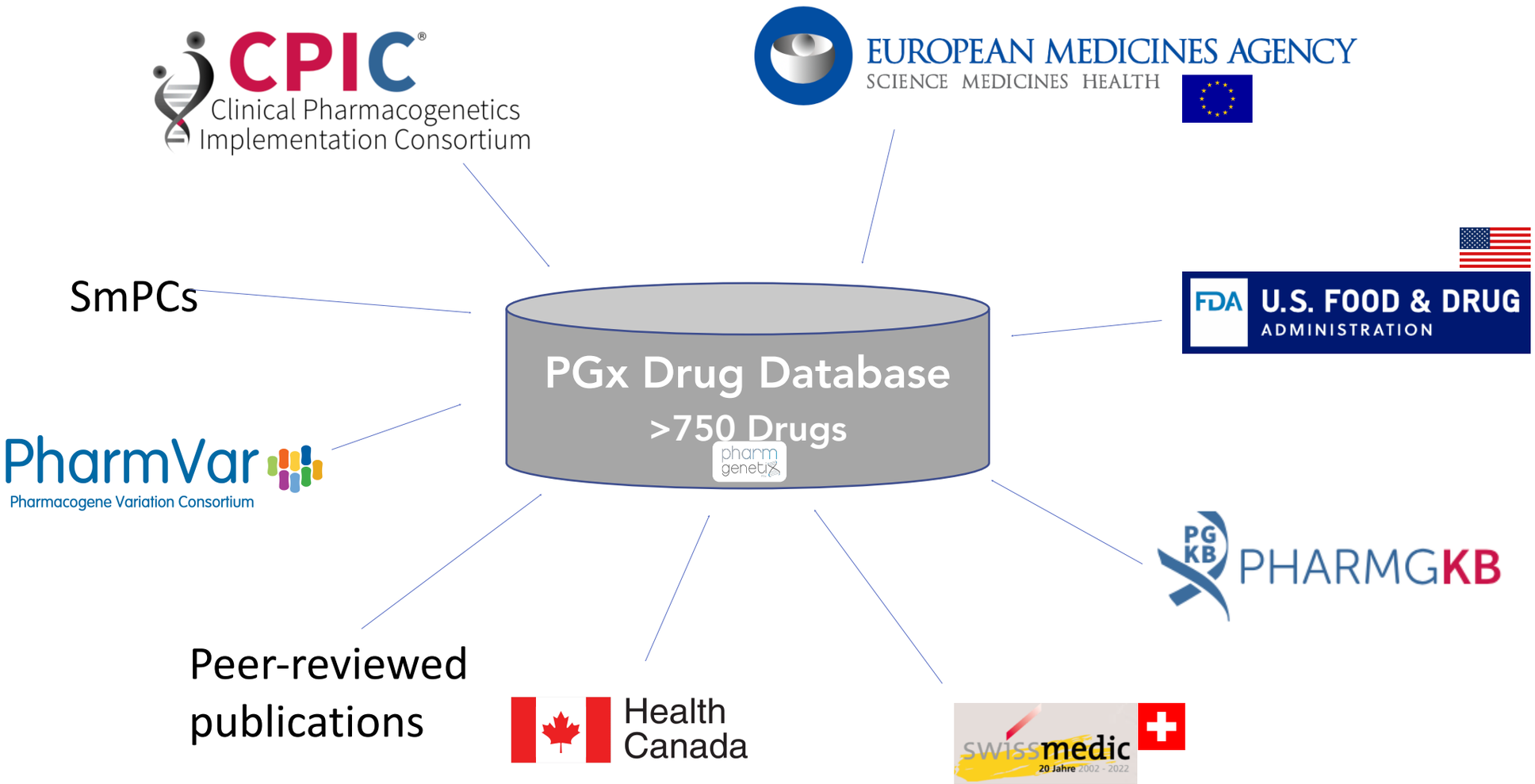
INTERAKTION
✕
↑↑
✕ ⚠
↑

Optimierungs-Vorschlag

ERSATZKOMBI 1
↓ Siponimod
✓ Ticagrelor
✓ Cerivastatin
↑ Lansoprazol

PGx-Medikamenten-Datenbank

Eine umfassende PGx-Wirkstoff-Datenbank ist der Kern für PGx-Befunde



Bei der Optimierung von Polypharmazie werden oft >1 Million Kombinationen durchgerechnet

Polypharmazie mit 8 Medikamenten,
je Klasse durchschn. 6 Alternativen

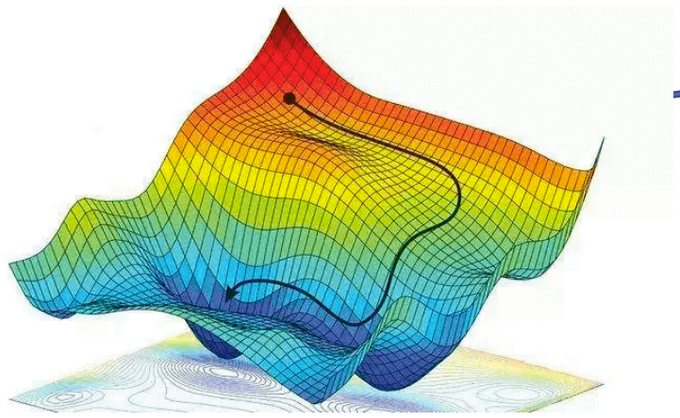
1.679.616
Optionen

14 Minuten
Berechnungszeit

DRUG	MONOTHERAPY	INTERACTION
Siponimod	↓	✕
Fluvastatin	↓↓ ⚠	✕ ⚠
Tamsulosin	↓	✕
Dexibuprofen	↓	✕
Pantoprazole	↑	↓
Clopidogrel	↓	✕
Fluoxetine	↓↓↓	✕
Tramadol	✕	✕

REPLACEMENT 1
✓ Siponimod
✓ Pravastatin
✓ Alfuzosin
✓ Ketoprofen
↑ Lansoprazole
↑ Clopidogrel
↓ Citalopram
✓ Tilidin

Integration von AHI /
Augmented Human
Intelligence - Methoden



4 Sekunden
Berechnungs
zeit

Der PGx-Optimizer ist eine einzigartige Befundungs-Software, welche personalisierte Medikamenten-Interaktionen berücksichtigt und alternative Verschreibungs-Optionen berechnet

PGxOPTIMIZER®

Medizinprodukt

CE

SRN: AT-MF-000013749

qualityaustria

SYSTEMZERTIFIZIERT

ISO 9001:2015 NR.20045/0

ISO 13485:2016 NR.00284/0

Oh, **this is the end** / My only friend, the end

(The Doors, 1967)

paulmichl@me.com