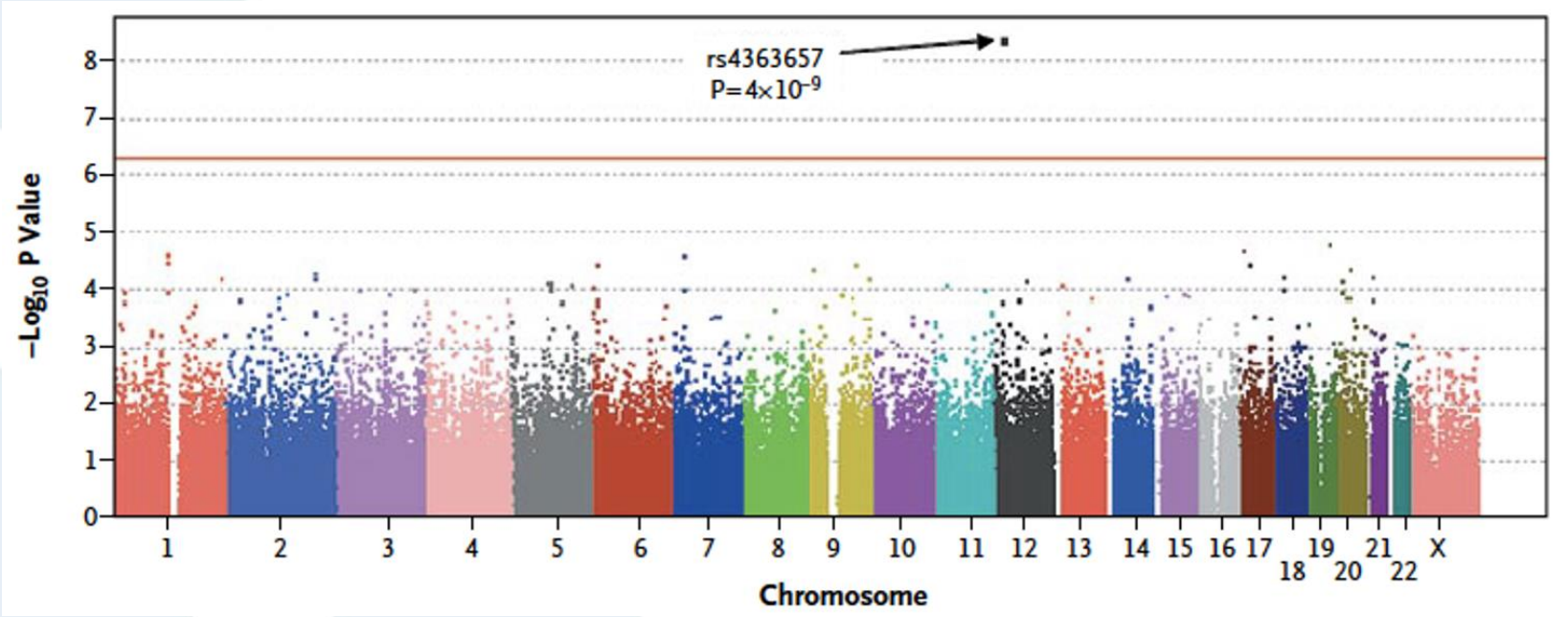
Publikumsvortrag Hirslanden 09.02.2021

GENETIK UND DIGITAL HEALTH - DIE ZUKUNFT DER MEDIZIN



CLINICAL PHARMACOGENETICS

Stefan Russmann, MD

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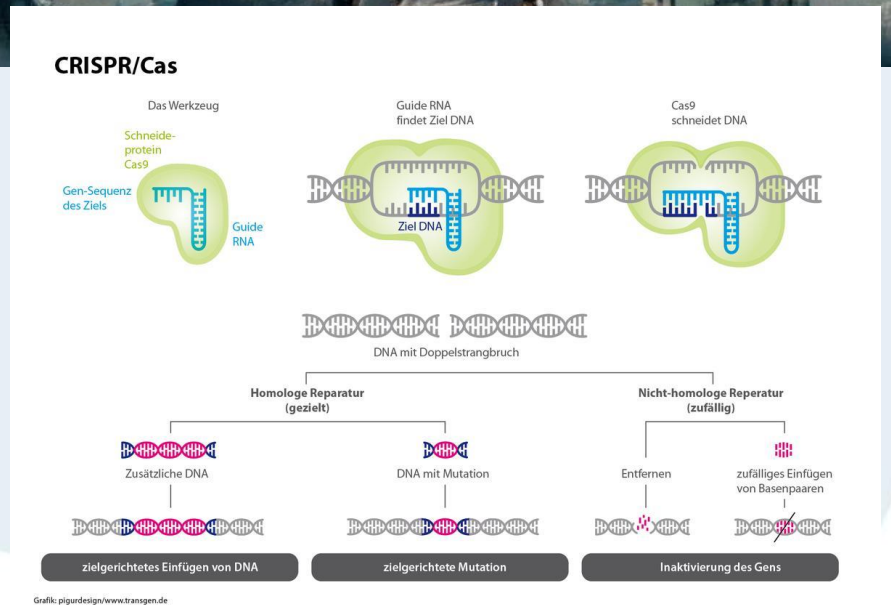
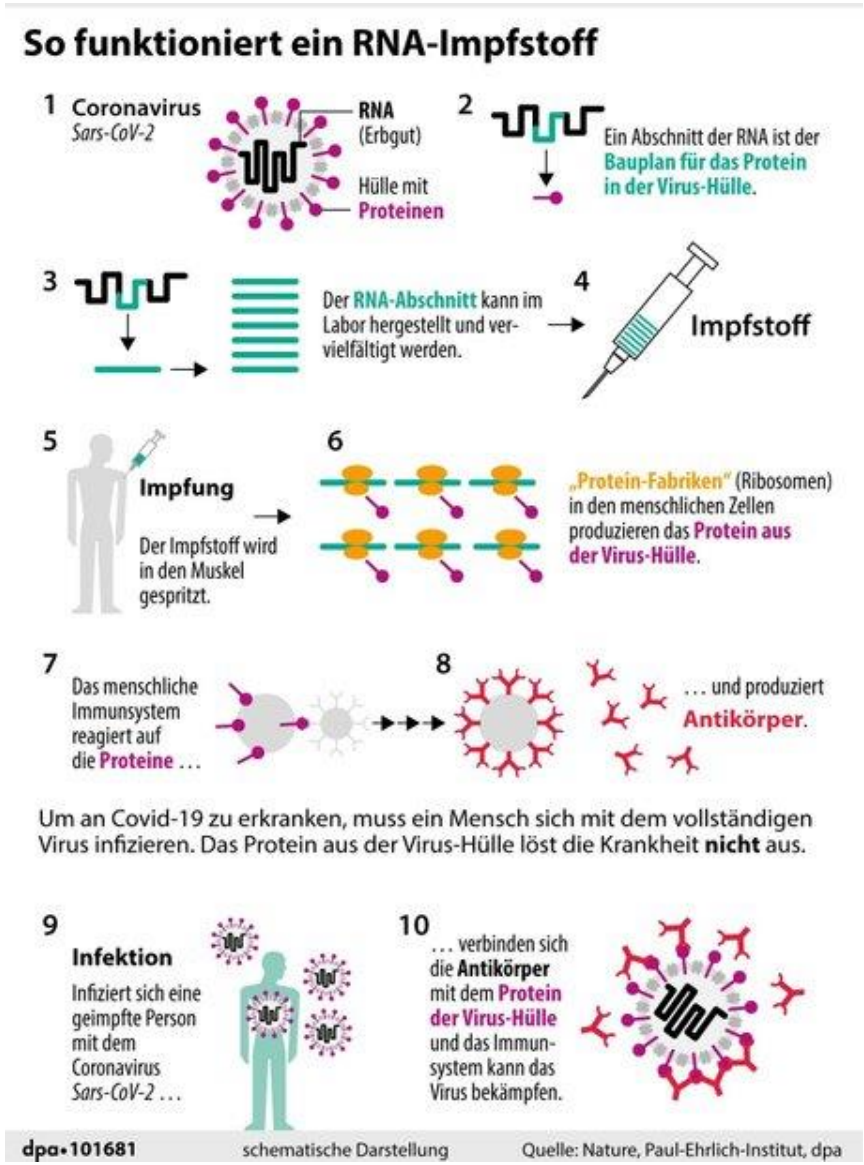
HIRSLANDEN

CRISPR/Cas9 - genetics goes Hollywood…





Potential benefits of genetics-driven pharmacotherapy

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- Faster drug development
- Higher specificity
- Higher efficacy
- Higher efficiency
- Improved safety
- Lower costs
- ...

Lung cancer as an example for genetic medicine

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Genetic risk factors

-> screening

Genetics of cancer cells

-> selection of therapy (e.g. Iressa® / EGFR)
-> implications for clinical studies

Genetics of drug metabolizing enzymes

-> selection of therapy
-> implications for clinical studies

Genetic modification of mammalian cells

-> e.g. replacement of inactive tumor-suppressing genes

PRINCIPLES OF CLINICAL PHARMACOLOGY
PHARMACOKINETIC AND PHARMACODYNAMIC PROCESSES

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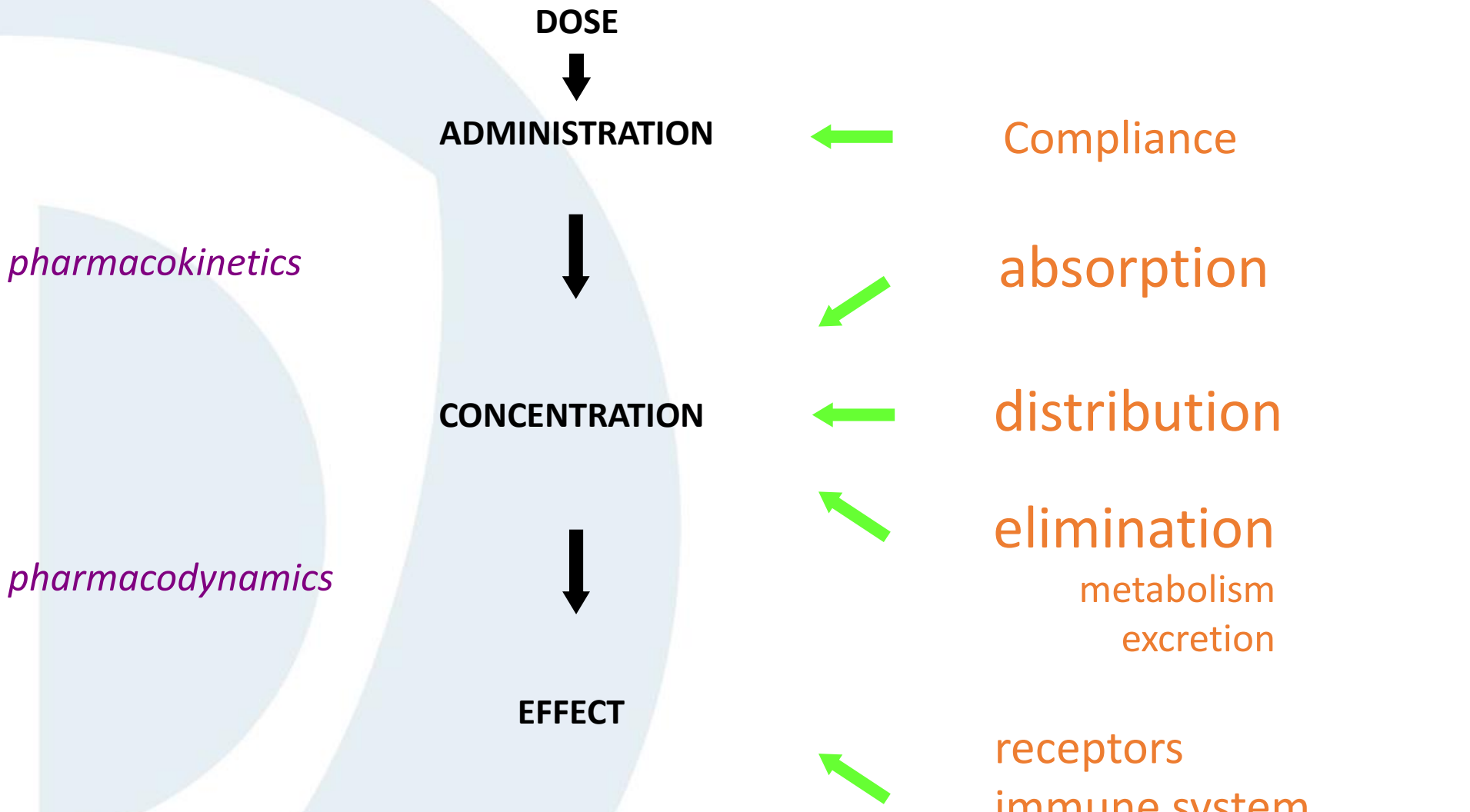

Clinical pharmacology and pharmacogenetics

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compliance	*example tamoxifen...*
absorption	ABCB1
distribution	ABCB1 SLCO1B1
elimination	
metabolism	CYP450 1A2 / 2C9 / 2B6 / 2C19 / 2D6 / 3A4 / 3A5 / 4F2 POR TPMT DPYD
excretion	ABCB1 SLCO1B1
receptors	OPRM1
immune system	*HLA variants* *B*57:01 / B*58:01 / B*15:02 / A*31:01*
mechanism of action	COMT VKORC1

Example of pharmacogenetic profile (16 gene PGx panel)

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PHARMACOGENETIC ID CARD

Felix Muster name			1976-09-16 date of birth (y/m/d)	male gender
GENE	**GENOTYPE**	**EFFECT**	**EXAMPLES OF AFFFECTED DRUGS**	
ABCB1	CGC/TTT	drug-dep. alt. efficacy		
COMT	low/im	slow metabolism		
CYP1A2	*1F/*1F	very fast metabolism	clozapine, coffeine, zolmitriptane, ropinirol	
CYP2B6	*1/*6	slow metabolism	efavirenz, bupropion, methadone, pethidine	
CYP2C9	*1/*1	normal metabolism		
CYP2C19	*1/*1	normal metabolism		
CYP2D6	*1/*2	normal metabolism		
CYP3A4	*1/*1	normal metabolism		
CYP3A5	*3/*3	normal metabolism		
CYP4F2	C/T	slow metabolism		
DPYD	*1/*1	normal metabolism		
OPRM1	A/G	drug-dep. alt. efficacy	morphine	
POR	*28/*28	fast metabolism		
SLCO1B1	*1a/*1a	normal drug efficacy		
TPMT	*1/*1	normal metabolism		
VKORC1	G/A	increased drug efficacy	acenocoumarol, phenprocoumon, warfarin	

Genetic analyses may not detect all known mutations of a gene. List of affected drugs is not comprehensive.
Consequences of pharmacogenetics on medication should be discussed with consulting physician.

Frequency distribution of pharmacogenetic phenotypes in the study population (N=135)

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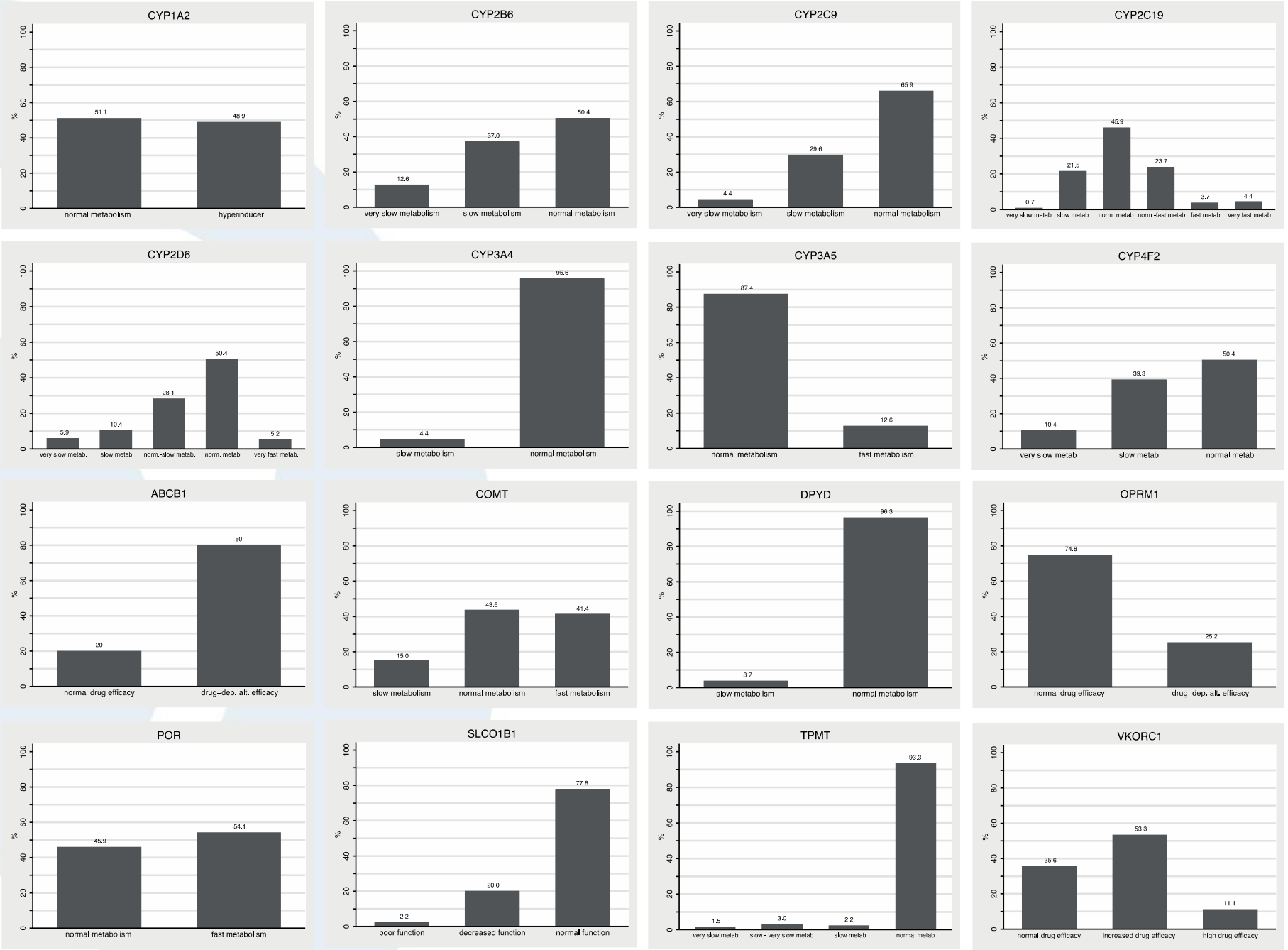
Russmann et al. 2020, under review



Integrated drug-drug and drug-gene interaction check

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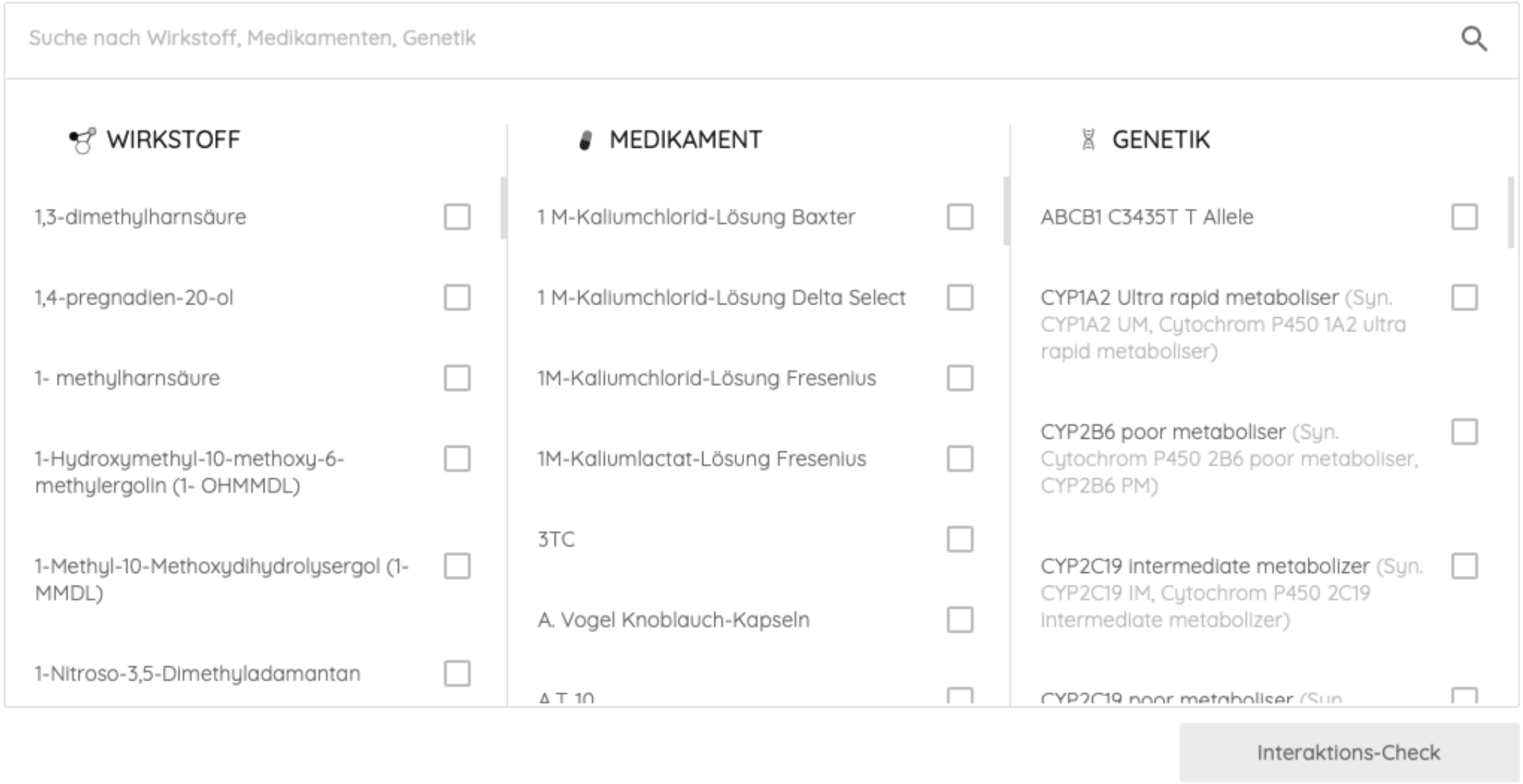

source: MediQ

Beispiel PGx bei neuen Medikamenten

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Brexpiprazol

- Indikation: Schizophrenie bei Erwachsenen
- Wirkungsmechanismus: partiell agonistische Aktivität an serotonergen 5-HT1A und dopaminergen D2 Rezeptoren, antagonistische Aktivität an serotonergen 5-HT2A Rezeptoren
- Veränderungen des Nüchtern-Gesamtcholesterins, des LDL-Cholesterins und des HDL-Cholesterins vergleichbar bei Patienten unter REXULTI und unter Placebo

Bexpiprazol Pharmakokinetik

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- Metabolismus durch CYP3A4 und CYP2D6
- Metaboliten ohne bekannte pharmakologische Wirkung
- $t_{½\ ss}$ = 91.4 h
- **CYP2D6 poor metabolizer: AUC 1.8fach erhöht**
- C_{max} und AUC bei Frauen 40-50% höher als bei Männern

  Beurteilung: «statistisch signifikant, klinisch nicht relevant»
- GFR <30 ml/min: AUC um 69% erhöht (nach 2 Einzeldosen)

Bexpiprazol klinische Pharmakogenetik (Fachinformation)

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Dosisanpassungen für langsame CYP2D6 Metabolisierer und bei gleichzeitiger Anwendung von CYP Hemmern oder Induktoren

	Angepasste Dosis
Langsame CYP2D6 Metabolisierer	
Bekannte langsame CYP2D6 Metabolisierer	Gabe der halben üblichen Dosis
Bekannte langsame CYP2D6 Metabolisierer, die mässige/starke CYP3A4 Hemmer einnehmen	Gabe eines Viertels der üblichen Dosis
Patienten, die CYP2D6 Hemmer und/oder CYP3A4 Hemmer einnehmen	
Starke CYP2D6 Hemmer	Gabe der halben üblichen Dosis
Starke CYP3A4 Hemmer	
Starke/mässige CYP2D6 Hemmer mit starken/mässigen CYP3A4 Hemmern	Gabe eines Viertels der üblichen Dosis
Patienten, die CYP3A4 Induktoren einnehmen	
Starke CYP3A4 Induktoren*	Verdoppelung der üblichen Dosis über 1–2 Wochen

* Wird der gleichzeitig verabreichte CYP3A4 Induktor abgesetzt, muss die Dosierung über 1-2 Wochen auf das ursprüngliche Niveau reduziert werden.

PHARMACOGENETICS OF STATIN-INDUCED MYOPATHY

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

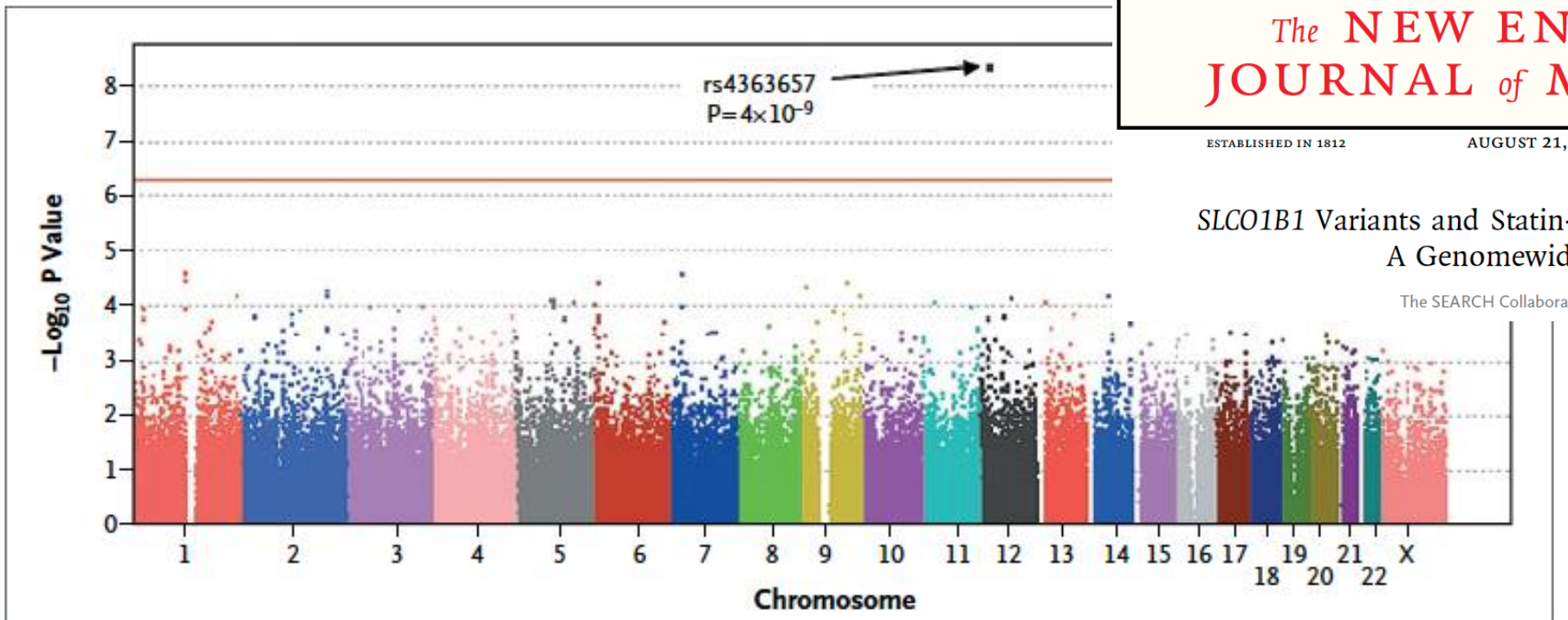

Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

N Engl J Med. 2008 Aug 21;359(8):789-99

Pharmacogenetics of SLCO1B1 and statins - clinical implications?

N Engl J Med. 2008 Aug 21;359(8):789-99

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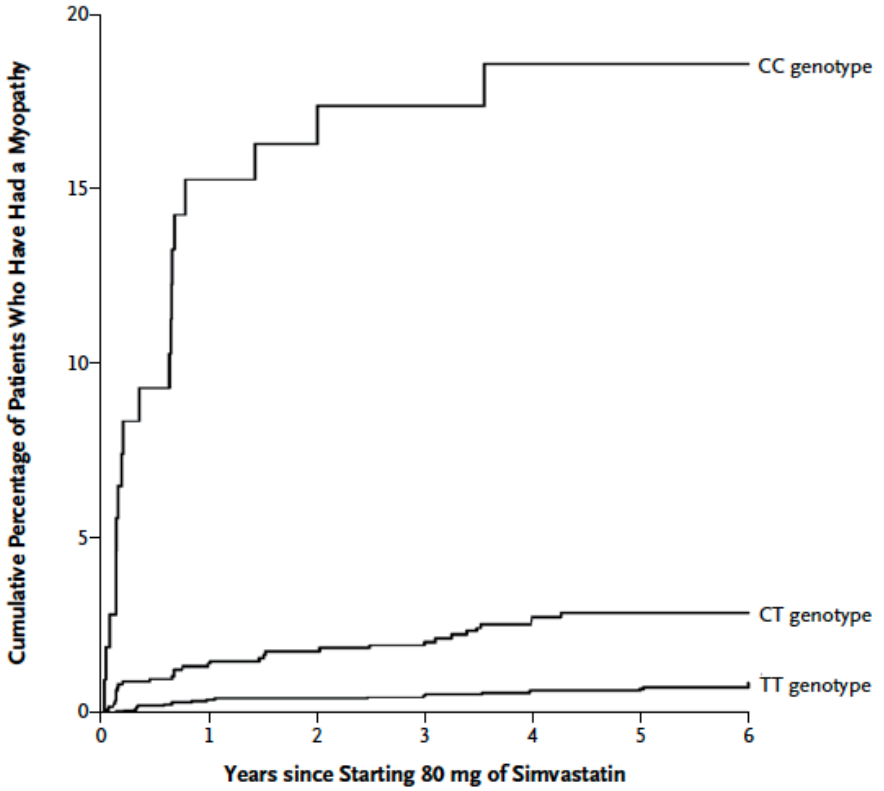

Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy							
		Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Figure 3. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to *SLCO1B1* rs4149056 Genotype.

Pharmacogenetics of SLCO1B1 and statins - clinical implications?

N Engl J Med. 2008 Aug 21;359(8):789-99

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VIEWPOINT

Prediction, Not Association, Paves the Road to Precision Medicine

Danilo Bzdok, MD, PhD
Mila–Quebec Artificial Intelligence Institute, Montreal, Quebec, Canada; and

In the 20th century, evidence-based medicine has put clinical practice on much more solid ground. For instance, randomized clinical trials have provided strong evidence on useful interventions, thanks to double-blind treatment application and tests for treatment as-

tee replicability. The higher the association found in a given sample, the lower the chance of observing a similarly strong association in participant samples recruited later. The reason involves sampling variability; many if not most published associations with impres-

PHARMACOGENETICS of CLOPIDOGREL

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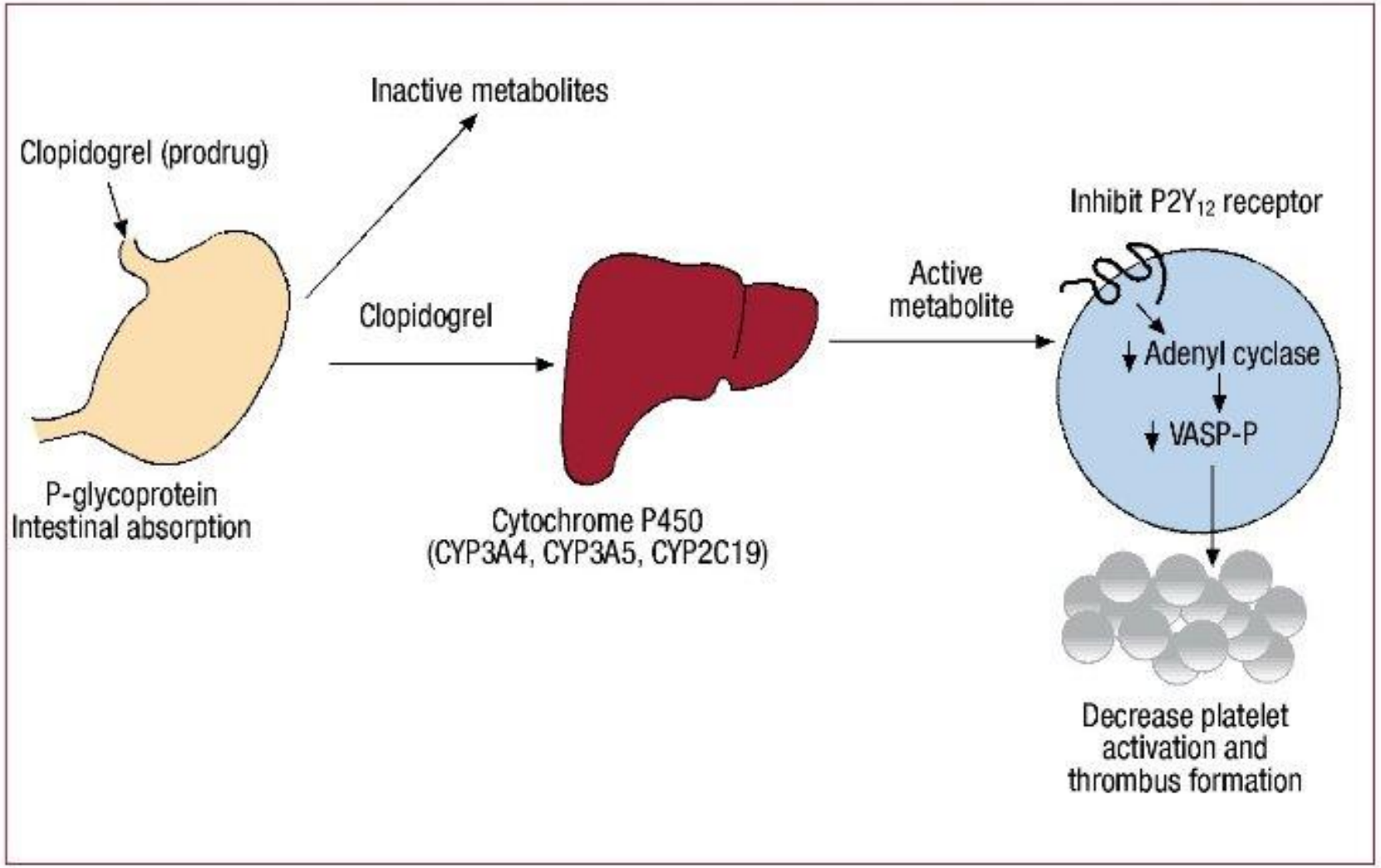
BIOACTIVATION OF CLOPIDOGREL VIA CYP2C19



PHARMACOGENETICS of CLOPIDOGREL

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

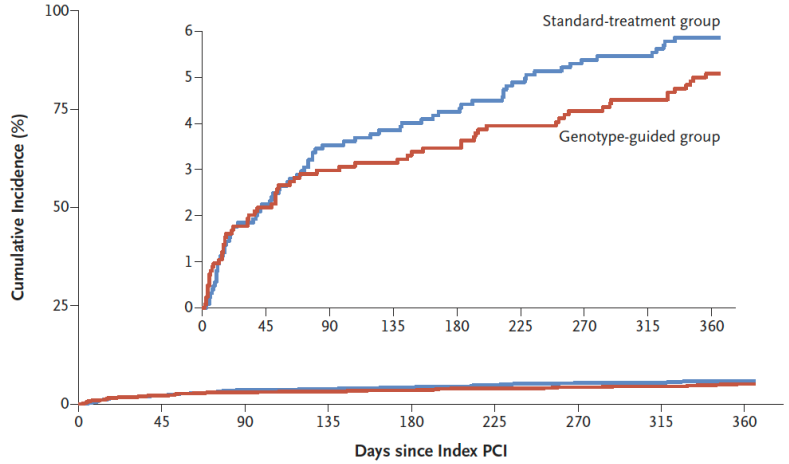
Daniel M.F. Claassens, M.D., Gerrit J.A. Vos, M.D., Thomas O. Bergmeijer, M.D., Renicus S. Hermanides, M.D., Ph.D., Arnoud W.J. van 't Hof, M.D., Ph.D., Pim van der Harst, M.D., Ph.D., Emanuele Barbato, M.D., Ph.D., Carmine Morisco, M.D., Ph.D., Richard M. Tjon Joe Gin, M.D., Folkert W. Asselbergs, M.D., Ph.D., Arend Mosterd, M.D., Ph.D., Jean-Paul R. Herrman, M.D., Ph.D., Willem J.M. Dewilde, M.D., Ph.D., Paul W.A. Janssen, M.D., Ph.D., Johannes C. Kelder, M.D., Ph.D., Maarten J. Postma, Ph.D., Anthonius de Boer, M.D., Ph.D., Cornelis Boersma, Pharm.D., Ph.D., Vera H.M. Deneer, Pharm.D., Ph.D., and Jurriën M. ten Berg, M.D., Ph.D.

CONCLUSIONS

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Organization for Health Research and Development; POPular Genetics ClinicalTrials.gov number, NCT01761786; Netherlands Trial Register number, NL2872.)

This article was published on September 3, 2019, at NEJM.org.

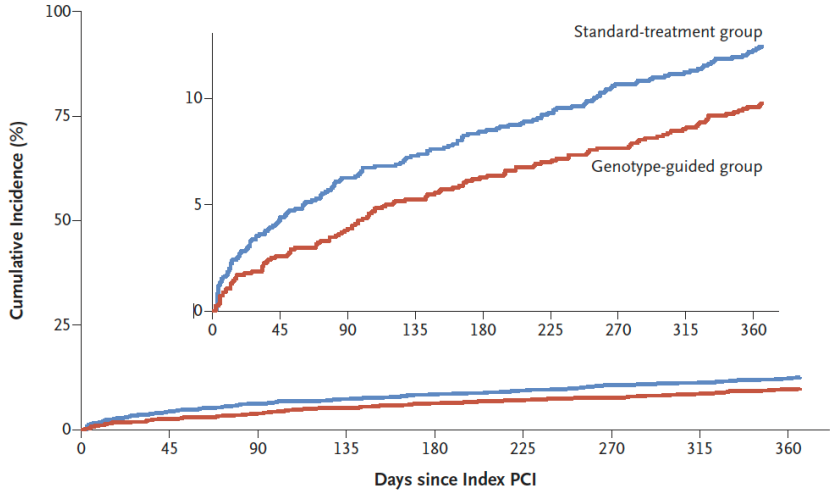
A Primary Combined Outcome



No. at Risk

Standard-treatment group	1246	1218	1202	1198	1193	1185	1179	1178	1173
Genotype-guided group	1242	1213	1203	1201	1197	1191	1187	1184	1177

B Primary Bleeding Outcome



No. at Risk

Standard-treatment group	1246	1193	1168	1155	1141	1130	1113	1106	1094
Genotype-guided group	1242	1208	1193	1175	1162	1153	1145	1134	1121

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-020-03050-4

PHARMACOGENETICS

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Implementation and management outcomes of pharmacogenetic CYP2C19 testing for clopidogrel therapy in clinical practice

Stefan Russmann[1,2,3,4] · Ali Rahmany[1,3,4] · David Niedrig[1,5] · Karl-Dietrich Hatz[6] · Katja Ludin[7] · Andrea M. Burden[4] · Lars Englberger[8] · Roland Backhaus[9] · Andreas Serra[2] · Markus Béchir[3]

Table 3 Association of recurrent thrombotic events under clopidogrel therapy with CYP2C19 genotype and other factors

	OR*	(95% CI)	*p*
Univariate analysis			
CYP2C19 IM or PM	1.9	(0.4–8.7)	0.40
Multivariate analysis			
CYP2C19 IM or PM	2.2	(0.3–14.4)	0.41
Age	0.9	(0.1–1.0)	0.08
Female gender	0.5	(0.05–5.87)	0.48
Diabetes	3.3	(0.4–25.2)	0.26
Peripheral artery disease	3.6	(0.4–34.1)	0.26
Cerebrovascular disease	1.3	(0.2–9.5)	0.78
Dual platelet inhibition (aspirin in addition to clopidogrel)	0.6	(0.1–4.6)	0.64

*Odds ratio for recurrent thrombotic event under clopidogrel therapy from univariate analysis and multivariate logistic regression analysis; in the multivariate analysis, age is modeled as a continuous variable, and all other variables are binary

PHARMACOGENETICS of TAMOXIFEN

- Bioactivation of tamoxifen into active metabolite endoxifen primarily via CYP2D6

- Several studies demonstrated higher recurrence rates of breast cancer under tamoxifen therapy in carriers of CYP2D6 poor metabolizer genetic variants

Options for clinical management

- PGx
- TDM endoxifen
- Dose adjustment of tamoxifen
- Alternative therapy with anastrozol

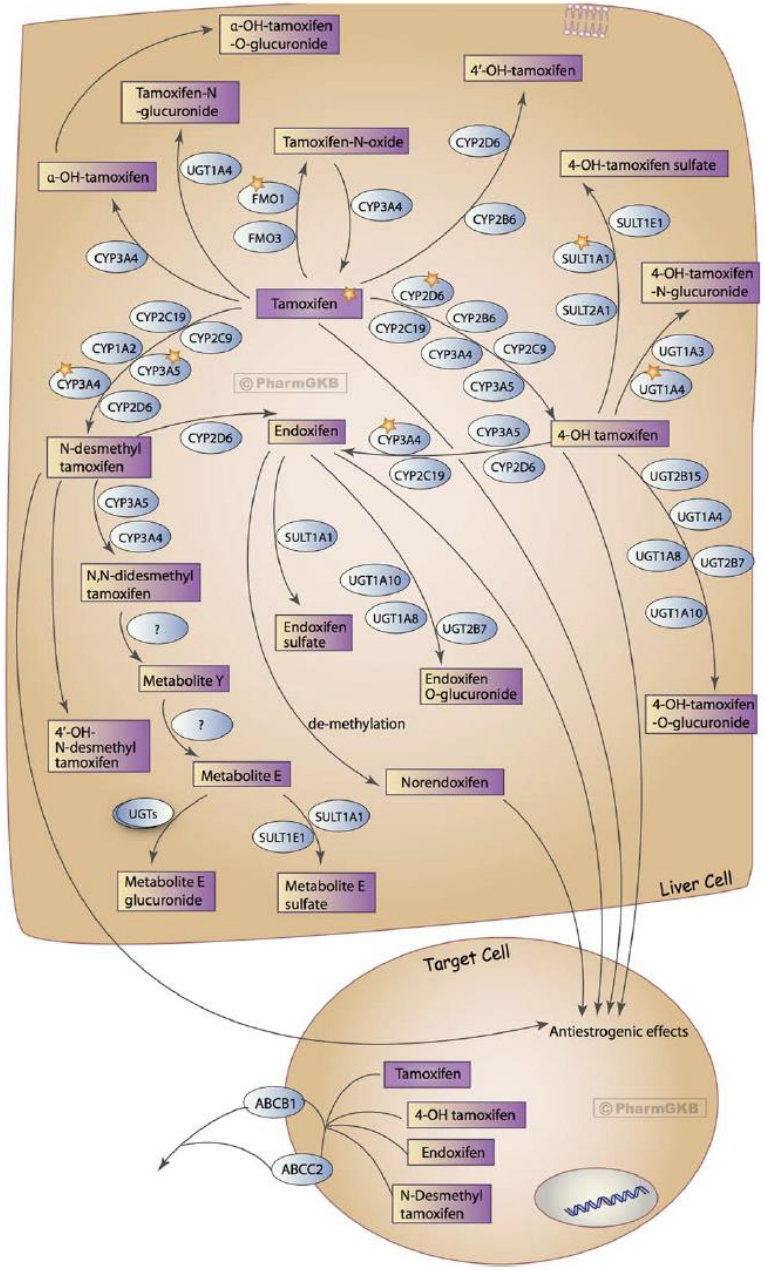

Figure 1 Tamoxifen pathway, pharmacokinetics.[57] Permission has been given by PharmGKB and Stanford to use figure.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy

Matthew P. Goetz[1], Katrin Sangkuhl[2], Henk-Jan Guchelaar[3], Matthias Schwab[4,5,6], Michael Province[7], Michelle Whirl-Carrillo[2], W. Fraser Symmans[8], Howard L. McLeod[9], Mark J. Ratain[10], Hitoshi Zembutsu[11], Andrea Gaedigk[12], Ron H. van Schaik[13,14], James N. Ingle[1], Kelly E. Caudle[15] and Teri E. Klein[2]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 00 NUMBER 00 | MONTH 2018

CONCLUSIONS

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- Clinical pharmacogenetics has arrived in today's routine clinical care
  -> yes, we can !

- Disease genetics and drug genetics have a major impact on drug development and study design
  -> genetic subgroup indications and post-hoc analyses in clinical studies

- Diseases, therapy outcomes and clinical decisions are always multifactorial
  -> don't underestimate the limitations and complexity of pharmacogenetics for clinical decisions

- Highly specialized up to date knowledge is required for genetic-guided medicine
  -> digital health solutions are required and have great potential to support the further implementation of pharmacogenetics in clinical practice

- Implementation of pharmacogenetics is currently also limited by cost-benefit considerations
  -> technological progress and scaling effects have a major impact on costs and benefits

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