New Tools and Research strategies in
Personalized Health EPFL

Pharmacogenomics & personalized therapies

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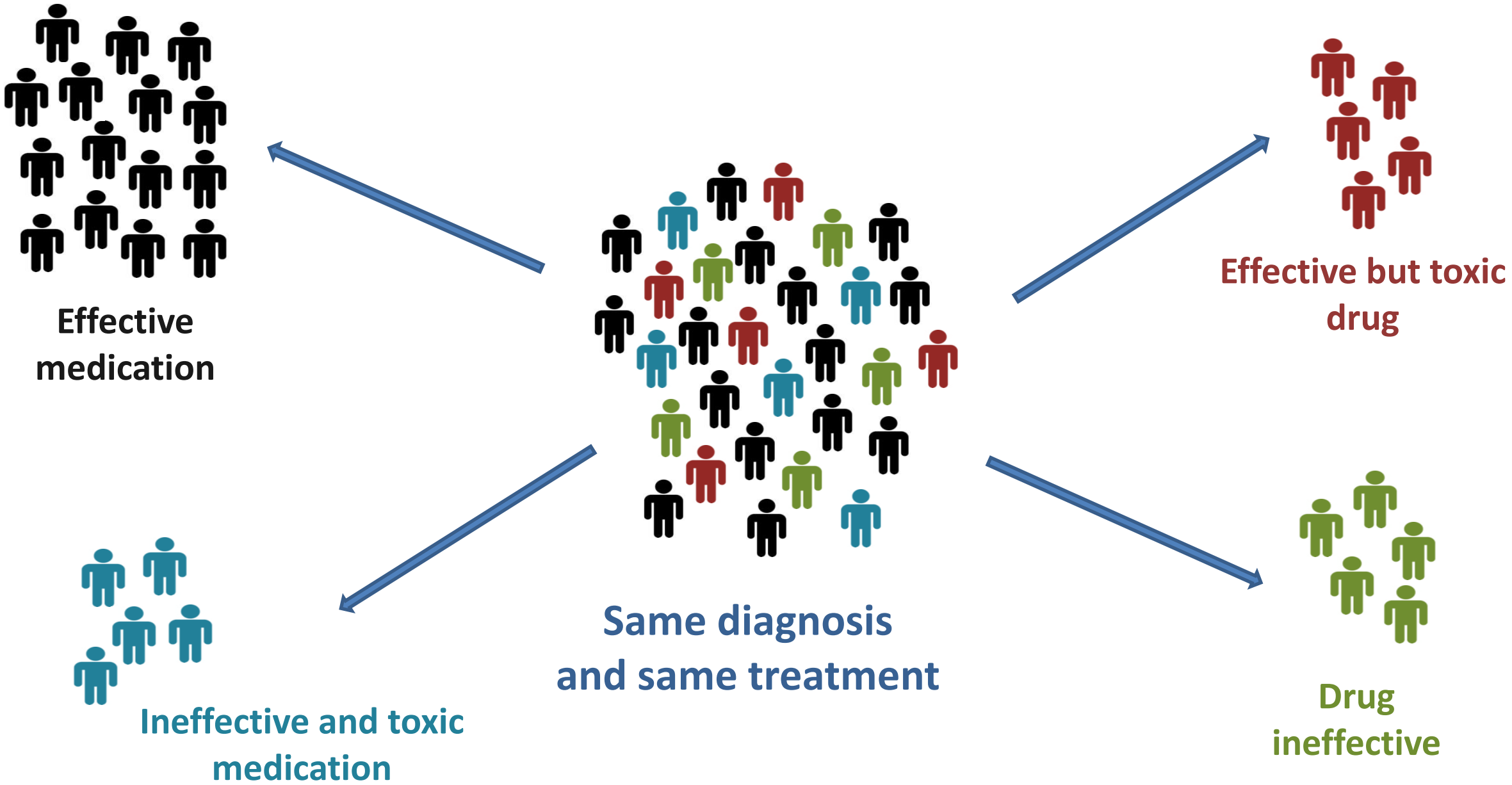
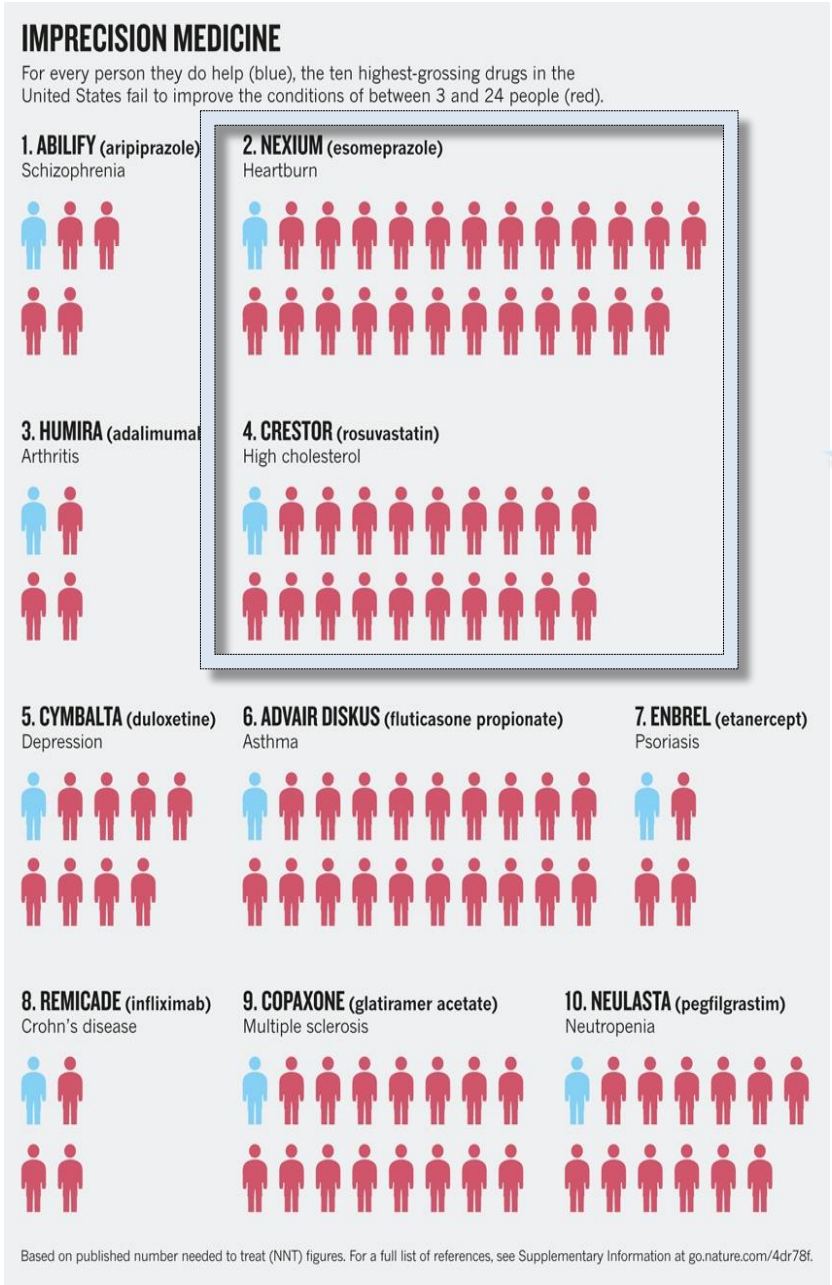
VARIABILITY OF DRUG RESPONSE





IMPRECISION MEDICINE

Number of **people to be treated** for **a person to** benefit.

1 for 20 à 25

Top 10 best-selling drugs in the US

Shork. Nature. 2015

ADVERSE DRUG REACTIONS

5-10%

Hospital admissions

4 ème

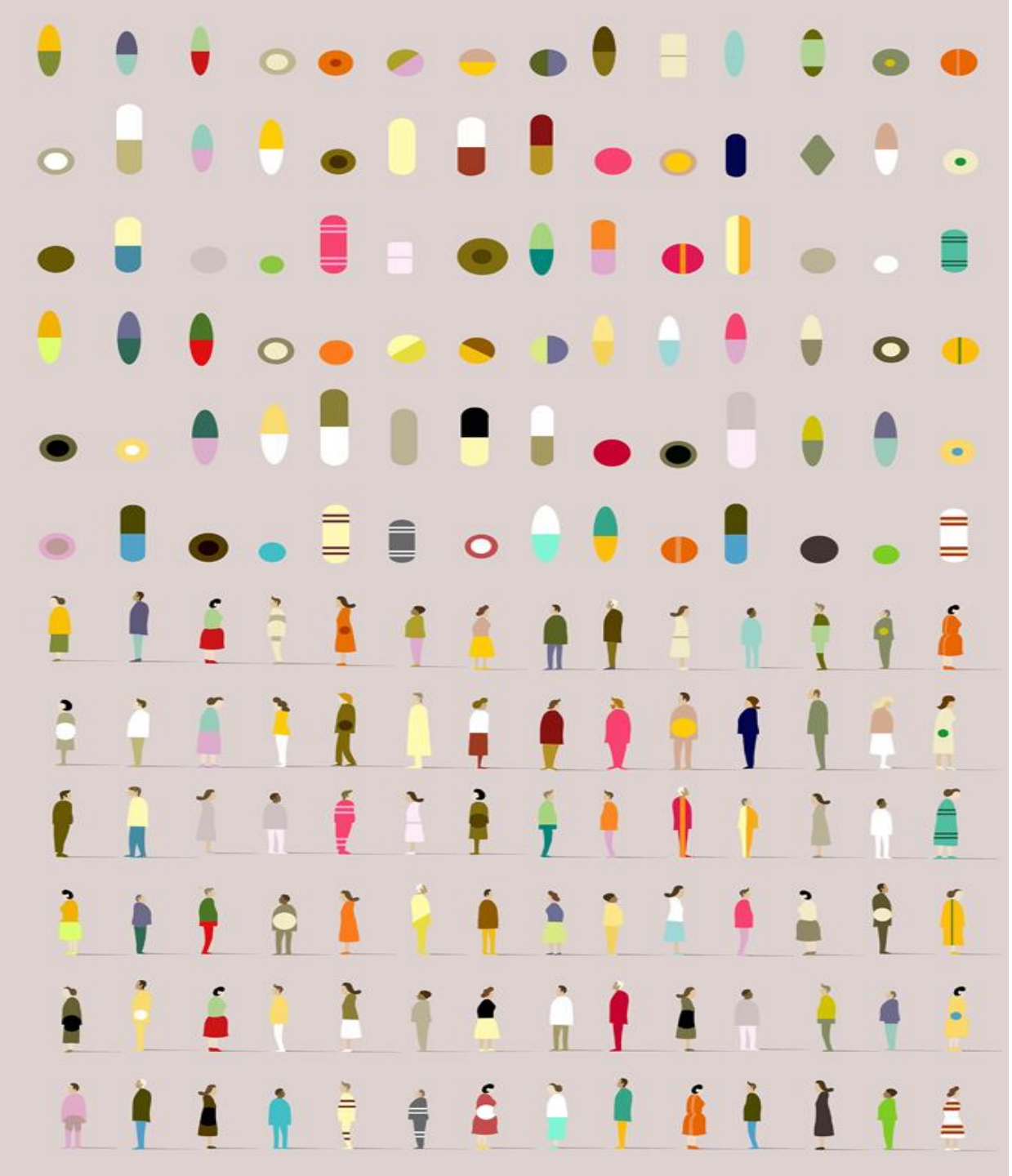
Cause of death (USA)

4 billion

Annual costs

Preventable in **50%** of cases

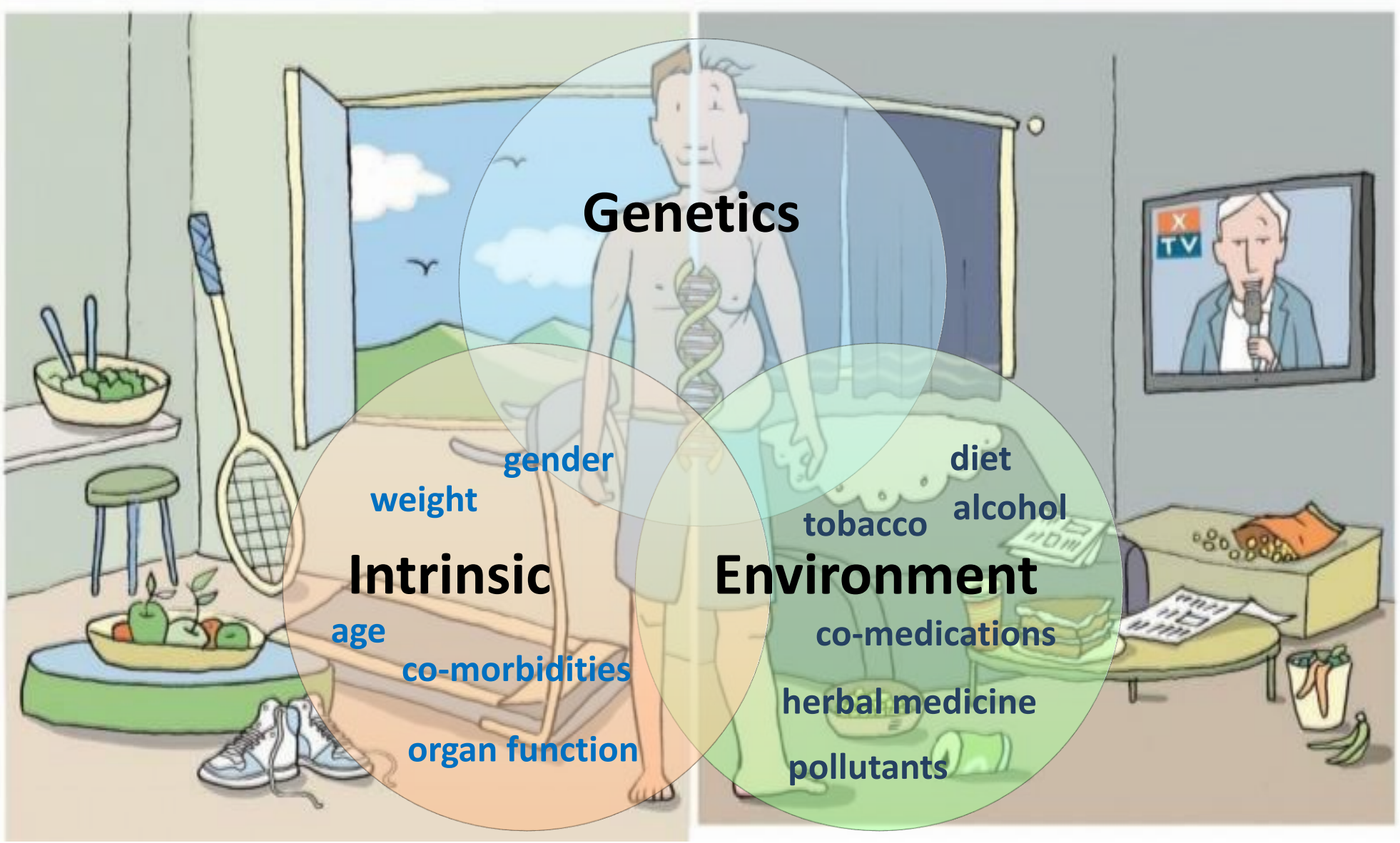
Lazarou et al JAMA 1998; Wasserfallen et al Eur J Intern Med. 2001; Pirmohamed M et al BMJ 2004

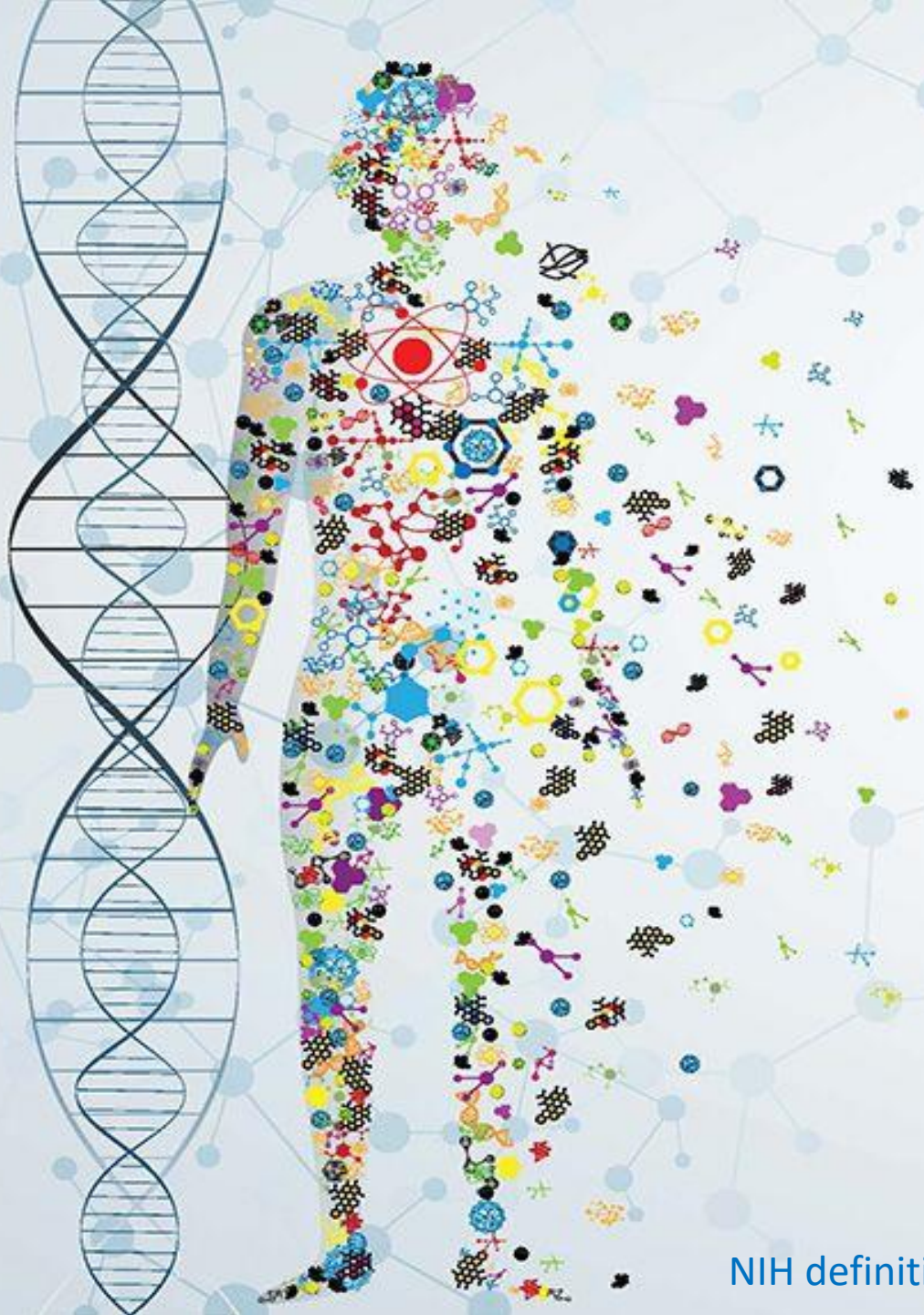


"One-size-fits-all

Personalised therapies

SOURCES OF VARIABILITY





PRECISION MEDICINE

Emerging approach for **treatment** and disease **prevention,** which takes into account the **variability** of individuals at the level of their **genes, environment** and **lifestyle**.

NIH definition

https://medlineplus.gov/genetics/understanding/precisionmedicine/definition/

THE PRECISION MEDICINE INITIATIVE

All of Us℠ The Precision Medicine Initiative®
THE FUTURE OF HEALTH BEGINS WITH YOU

"I want the country that eliminated polio and mapped the human genome to lead **a new era of medicine - one that delivers the right treatment at the right time**. So tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes and to give all of us access to the personalized information we need to keep ourselves and our families healthier. We can do this.

https://allofus.nih.gov

President Barack Obama, State of the Union Address, January 20, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 26, 2015

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

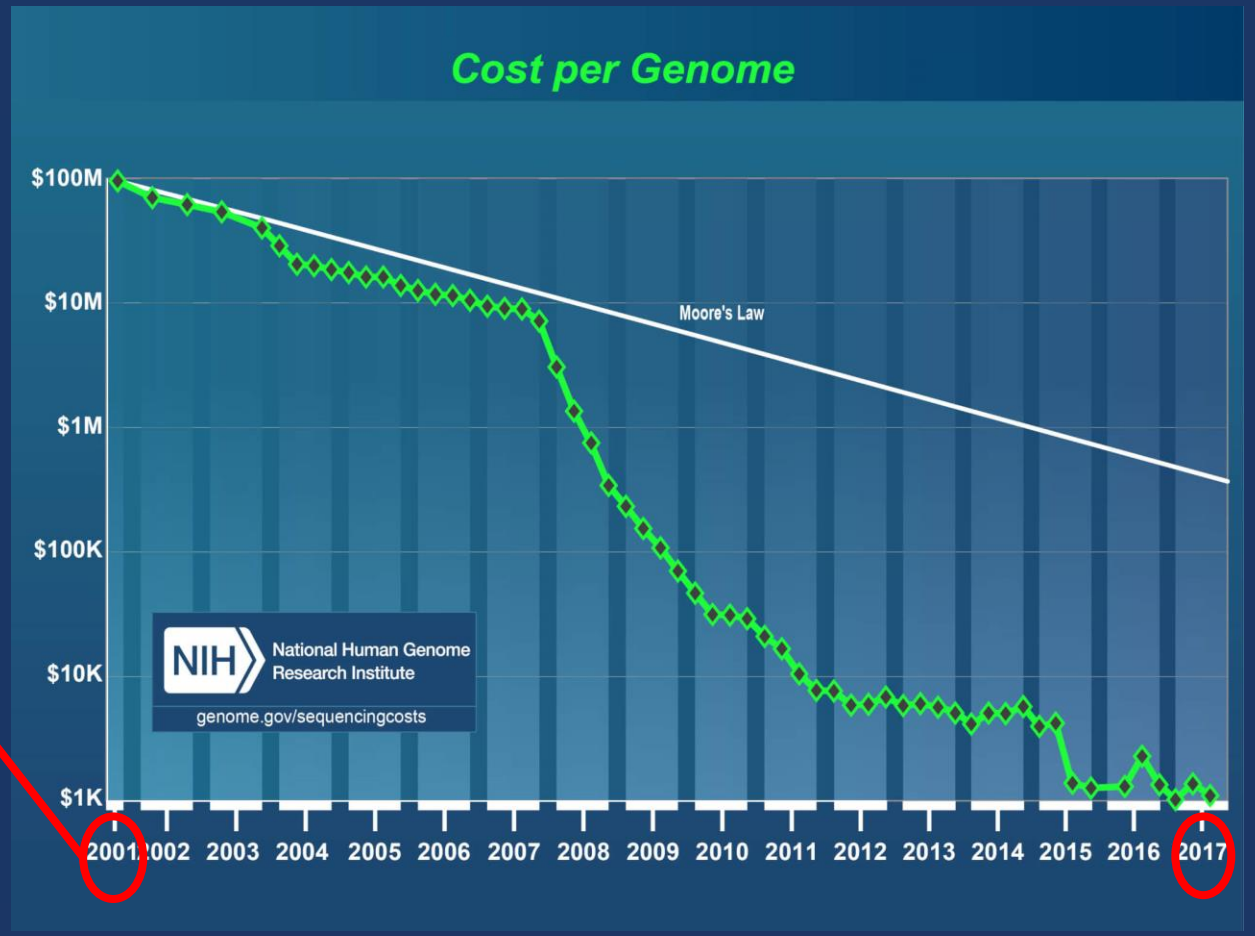
> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

Mission statement: to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.

WHY NOW?

The **time is right** because of:

Sequencing of the human genome



WHY NOW?

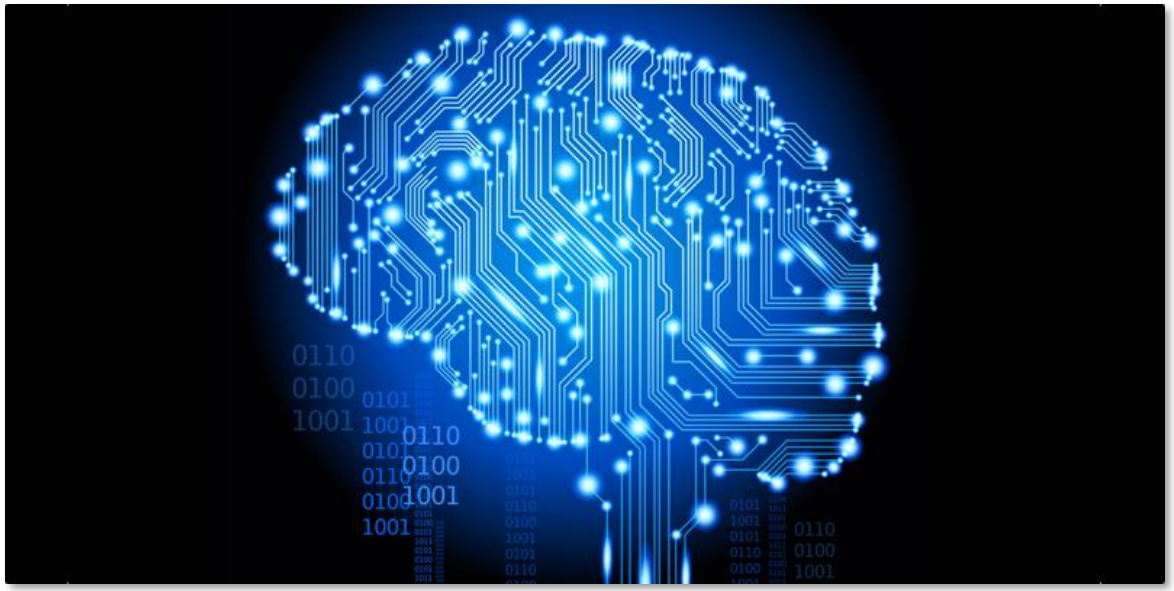
The **time is right** because of:

Sequencing of the human genome

Improved technologies for biomedical analysis

New tools for using large datasets

https://allofus.nih.gov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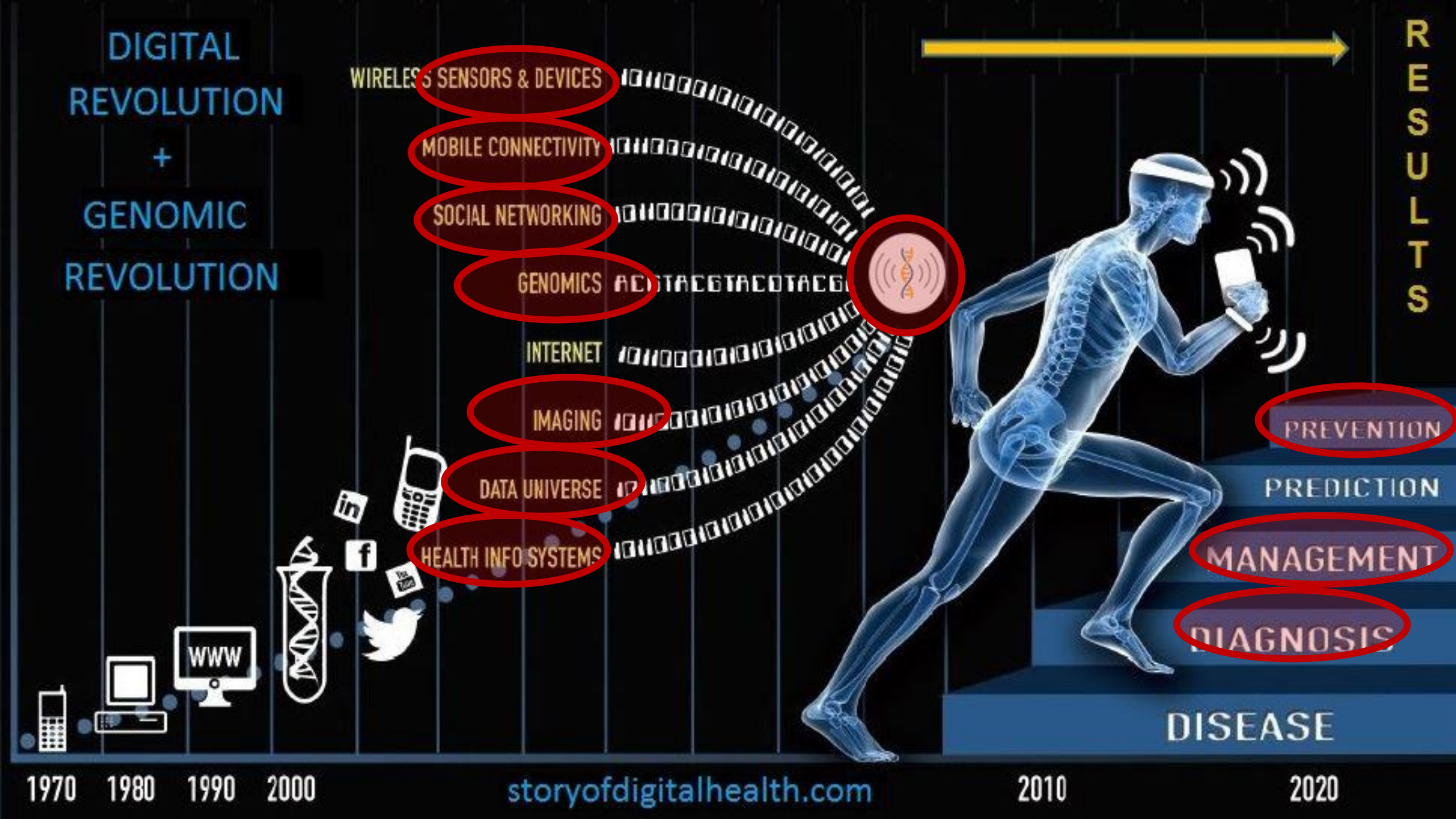
EHR
Systems


DIGITAL REVOLUTION
+
GENOMIC REVOLUTION
WIRELESS SENSORS & DEVICES
MOBILE CONNECTIVITY
SOCIAL NETWORKING
GENOMICS
INTERNET
IMAGING
DATA UNIVERSE
HEALTH INFO SYSTEMS
WWW
RESULTS
PREVENTION
PREDICTION
MANAGEMENT
DIAGNOSIS
DISEASE
1970
1980
1990
2000
storyofdigitalhealth.com
2010
2020

https://allofus.nih.gov

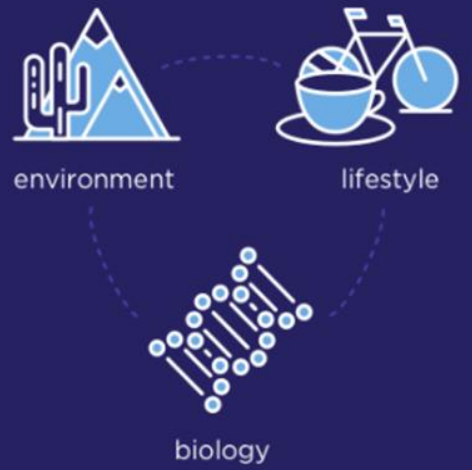
NIH National Institutes of Health
All of Us Research Program

ABOUT FUNDING NEWS, EVENTS, & MEDIA

We are building a research program of 1,000,000+ people

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all of us.

ABOUT THE SCALE & SCOPE



Research focuses on the intersection of 3 factors

characterization of biologic specimens and behavioral data linked to the EHR

We are actively partnering with others to create a groundbreaking national research resource platform

Create a research cohort of **> 1 million American volunteers** who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.

Pioneer **a new model for doing science** that emphasizes **engaged participants, responsible data sharing, and privacy protection.**

Research based upon the cohort data will:

- Advance **pharmacogenomics,** the right drug for the right patient at the right dose
- Identify new targets for **treatment and prevention**
- Test whether **mobile devices** can encourage healthy behaviors

https://allofus.nih.gov

Accès à la littérature spécialisée

Culture scientifique

Interprofessionnalité

Qualité en médecine

Santé personnalisée

Swiss Personalized Health Network

Système de santé durable

Swiss Personalized Health Network

Le Swiss Personalized Health Network (SPHN) est une initiative nationale dont l'objectif est de promouvoir la médecine et la santé personnalisées en Suisse. L'ASSM dirige la mise en œuvre de l'initiative à la demande de la Confédération. Le SPHN mettra sur pied l'infrastructure nécessaire à l'utilisation des quantités énormes de données de santé pour la recherche et l'innovation.

Des chercheurs de l'EPF, des universités et des hôpitaux universitaires sont à l'origine de l'initiative «Swiss Personalized Health Network». L'objectif du SPHN est de garantir une harmonisation des systèmes d'informations et des types de données des institutions participantes et de permettre l'échange de données de santé indispensable à la recherche. Ainsi, la Suisse peut exploiter le potentiel du «Big data» en faveur de → la médecine et de la santé personnalisées.

Début 2016, le ↗ Secrétariat d'État à la formation, à la recherche et à l'innovation (SEFRI) a chargé l'ASSM de l'instauration du SPHN. Conformément à la convention de prestations pour les années 2017 à 2020, l'ASSM est responsable des aspects organisationnels, juridiques et financiers du SPHN. La Confédération met à disposition un montant de CHF 68 millions, dont CHF 18 millions sont destinés au financement du projet BioMedIT dirigé par le ↗ SIB Swiss Institute of Bioinformatics. Le principe des fonds complémentaires («matching funds») s'applique à toute les contributions financières, c'est-à-dire que les institutions participantes doivent apporter leurs contributions propres à hauteur des fonds fournis par SPHN. Le financement reflète ainsi la relation entre contributions et bénéfices, fournis ou générés par les partenaires du réseau.

CONTACT

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Directeur SPHN
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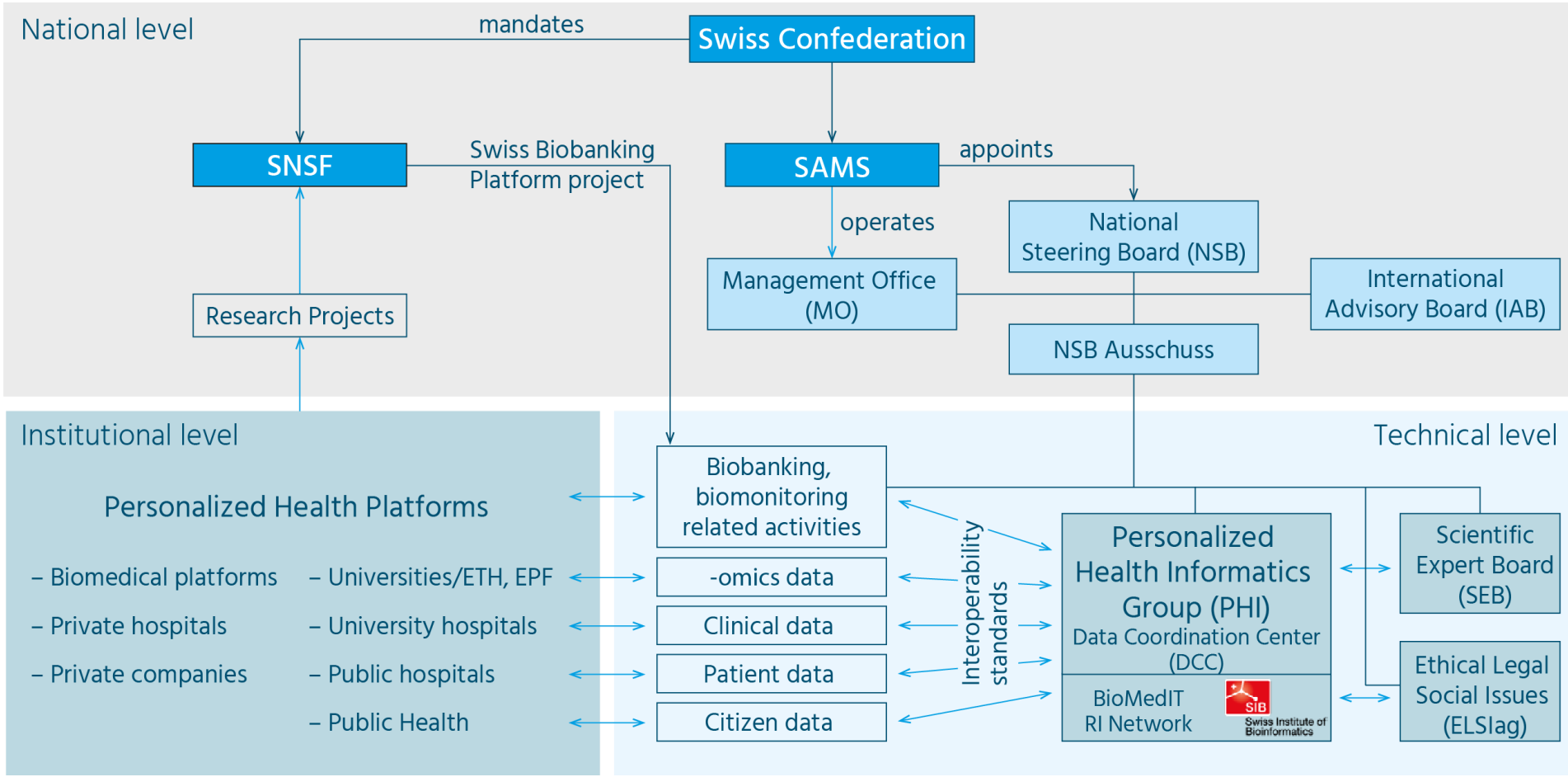
https://www.samw.ch/fr/Projets/Swiss-Personalized-Health-Network.html

Swiss Personalized Health Network

The Swiss Personalized Health Network (SPHN) is a national initiative designed to promote the development of personalized medicine and personalized health in Switzerland. The Swiss Academy of Medical Sciences heads the implementation of the Initiative on behalf of the Federal Government. SPHN will build the infrastructure necessary to exploit the diversity of health-related data for research and innovation.

The Swiss Government has allocated a total of CHF 68 millions to the initiative.



Period 2017-2020

CHF 68 million

BioMed IT

CHF 18 million

Project financing (NSB) CHF 50 million

Infrastructure implementation

Infrastructure development

Drivers

Three funding instruments

Period 2021-2024

- The Swiss Government renewed the mandate of the Swiss Academies of Medical Sciences (SAMS) and the SIB Swiss Institute of Bioinformatics for **a second SPHN funding period for 2021 to 2024**.

- From a total budget of 66.9 Mio CHF:
  - 50 Mio are under the responsibility of the NSB and the SAMS
  - 16.9 Mio is dedicated to BioMedIT

PHARMACOGENOMICS

Study of the influence of genetic variations on drug response

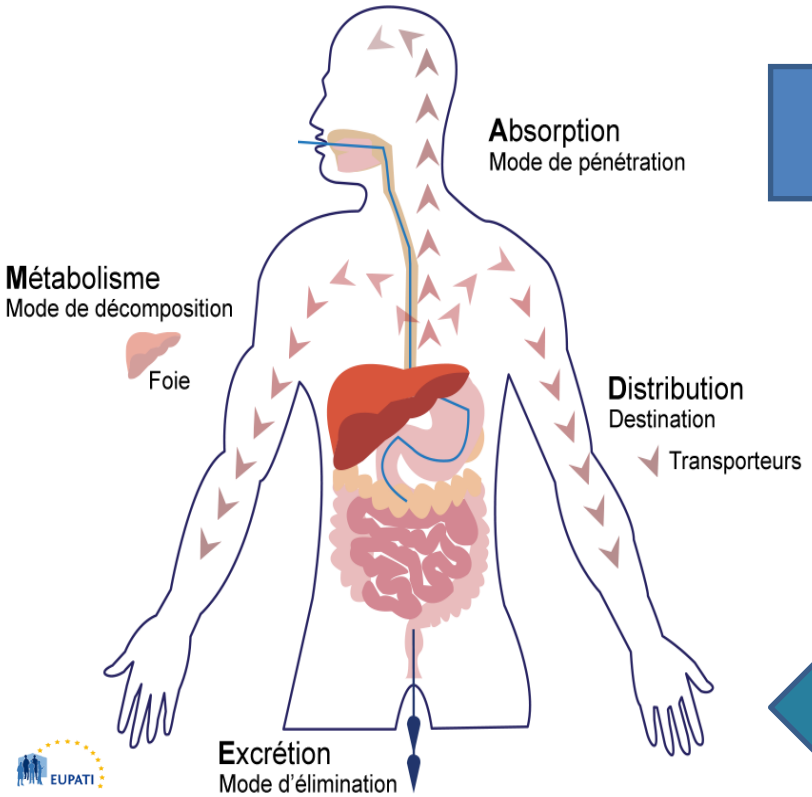
Abbasi J, JAMA 2016;316:1533-35.

Objectives of pharmaco genomics

Individualising drug therapy

- ✓ Improving the effectiveness of treatments
- ✓ Reducing the incidence of adverse effects
- ✓ Reducing treatment costs for the health system

PHARMACOGENOMIC FACTORS



PHARMACOCINETICS

Drug carriers

Enzymes of metabolism

PHARMACODYNAMICS

Receptors Ion channels

Enzymes

ORGANISM

DRUG

PHARMACOGENOMIC FACTORS

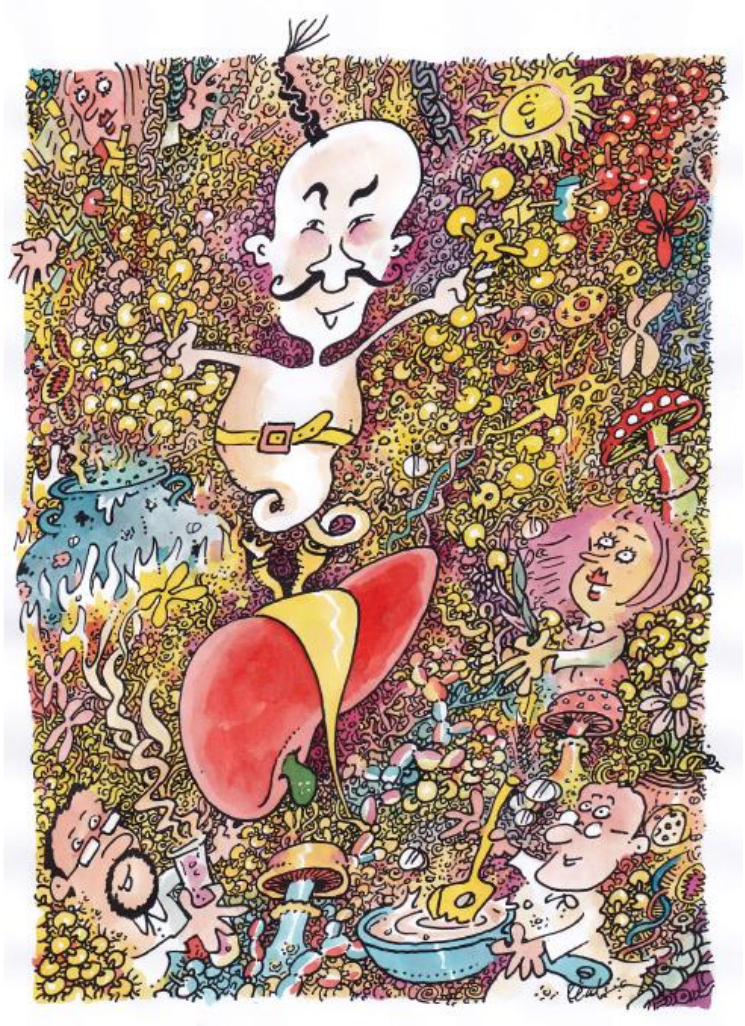
Pharmacokinetics

e.g:
Cytochromes P-450 (CYP)
N-acetyltransferase (NAT)
Thiopurine methyltransferase (TPMT)
P-glycoprotein (ABCB1)

Pharmacodynamics

e.g:
Mu opioid receptor 1 (OPRM1)
Vitamin K epoxide reductase C (VKORC1)
Catechol-O-methyltransferase (COMT)
HLA

CENTRAL ROLE OF CYP450



Pharmacology

biotransformation of drugs

Chemistry

stereoselective and regioselective oxygenation

Toxicology

detoxification, activation of pro-carcinogens

cytochromes P450

Plants and phytotherapy

metabolism of terpenes, alkanoids, phytoalexins

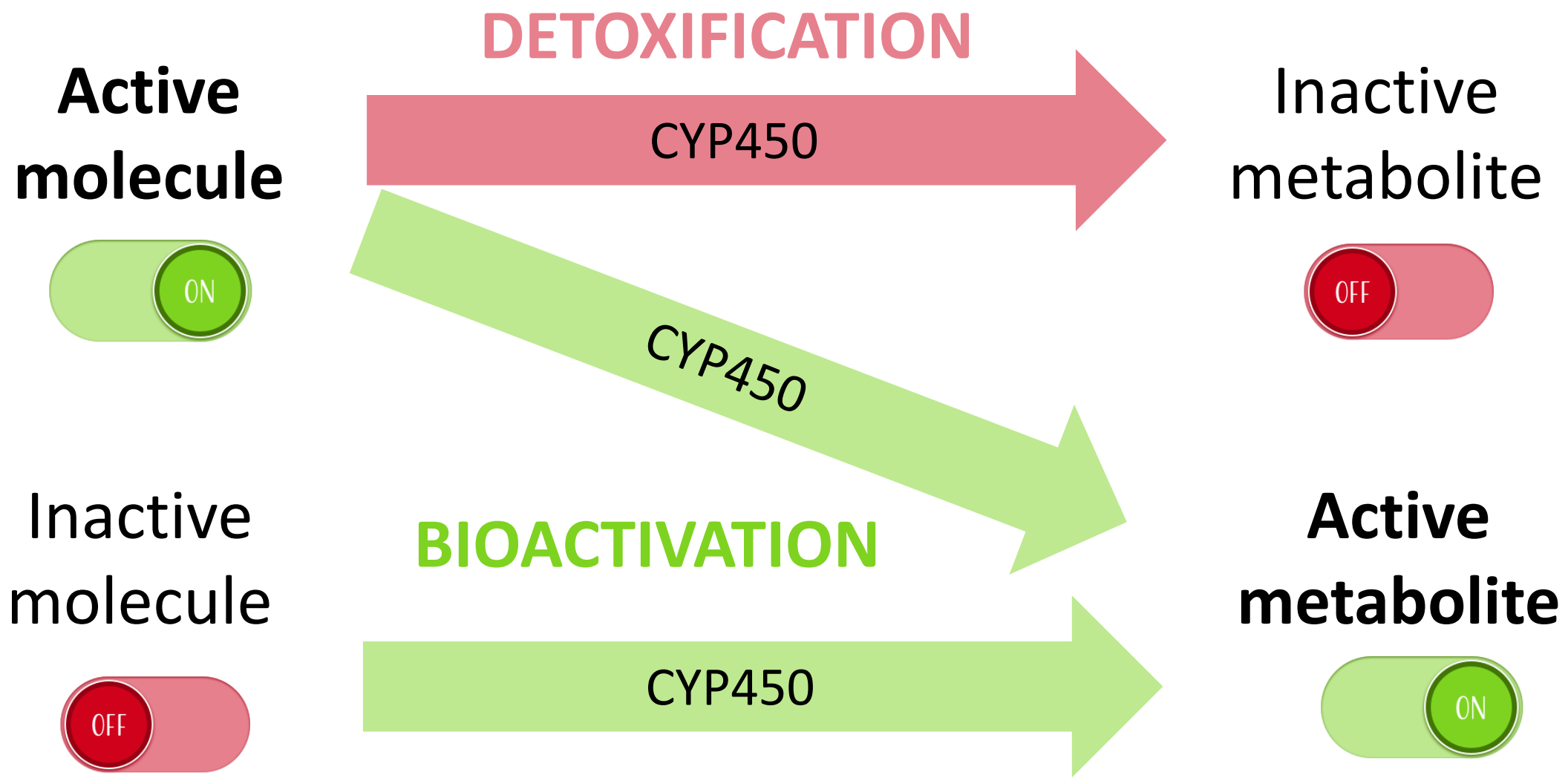
Physiology

metabolism and biosynthesis of endobiotics

Environmental Sciences

herbicide metabolism, pesticides, biomonitoring

CYP450 METABOLISM



WHY MEASURE CYP450 ACTIVITY?

Isoenzyme	Extent of variability
CYP 1A2	40x
CYP 2B6	50x
CYP 2C	25-100x
CYP 2D6	>1000x
CYP 3A	90x

Rendic & DiCarlo. *Drug Metab Rev* 1997, 29, 413-80.
Wojnowski. *Ther Drug Monit* 2004, 26, 192-9.


CO-DAFALGAN®
PARACETAMOL + CODEIN
500 mg / 30 mg
Gegen Schmerzen
UPSA
16 FILMTABLETTEN


Codicalm
Hustensirup
Sirop antitussif
Sciroppo antitussivo
LOT 50847
EXP 06/2020


20 ml gouttes
Resyl® plus
Contre la toux
NOVARTIS


20 Tabletten
No N143
Codein Knoll®
Antitussivum
ABBOTT


coop vitality
Bronchialpastillen mit Codein
Codeini phosphas hemihydricus 3 mg
Hustenstillend und beruhigend bei Reizhusten
ohne Zucker gesüsst mit Sorbit, Aspartam und Acesulfam K
24 Pastillen


Pecto-calmine® N
Guaifenesin, Codein phosphat hemihydrat, Ephedrin HCl, Polygala-Flüssigextrakt
Erwachsene und Kinder ab 14 Jahren
Hustenstiller
bei Husten, Bronchitis
und Reizhusten
Sirup
200 ml

Ne donnez plus de codéine aux enfants

Valérie Piguet le 25 janvier 2018

Chez les enfants de moins de 12 ans, la codéine comporte des risques d'effets indésirables graves, voire mortels.

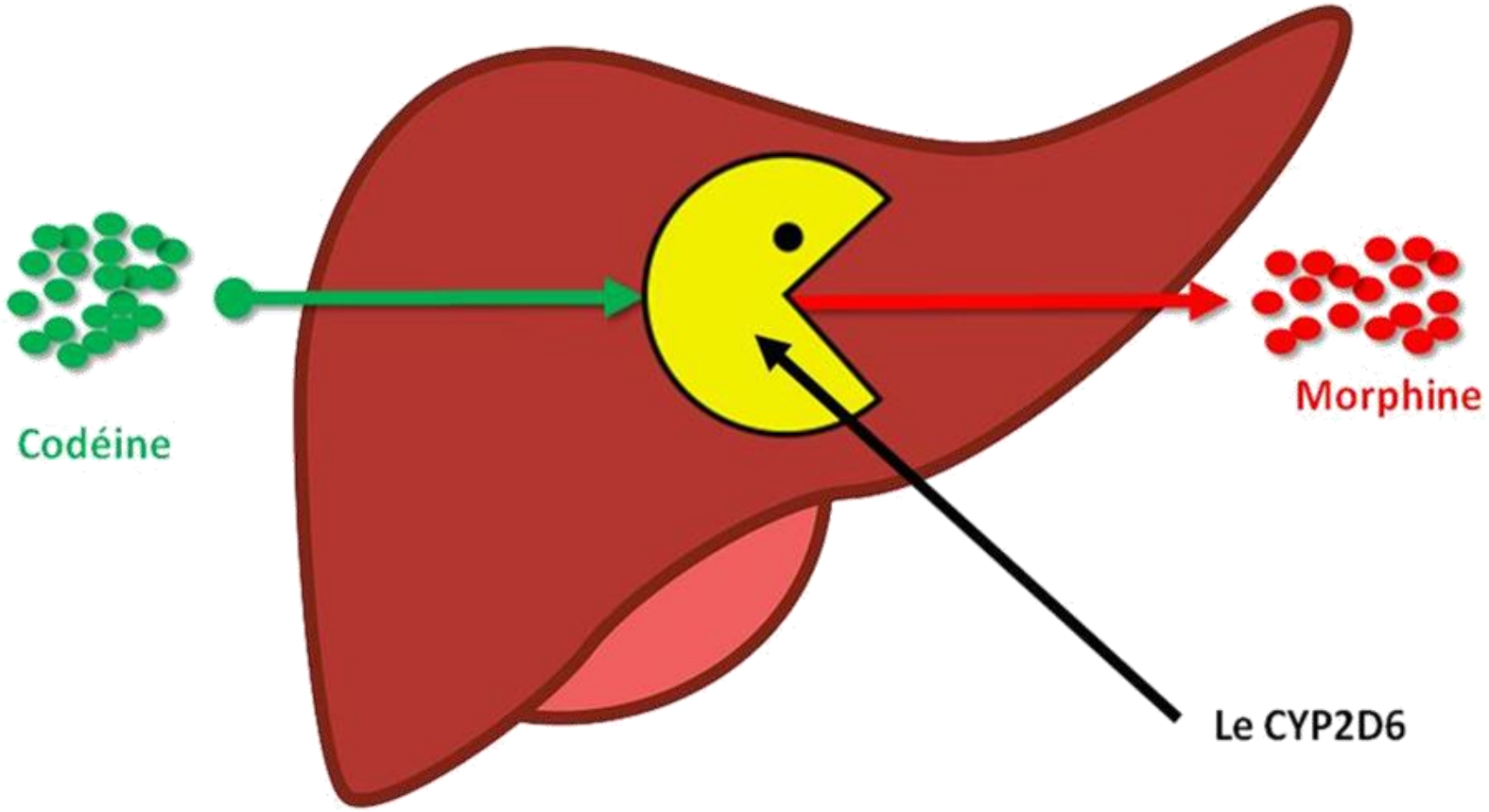
Explications

Médicament efficace, la **codéine** a pendant très longtemps été utilisée chez l'enfant pour traiter la toux ou la douleur. On la trouve encore actuellement sous forme de comprimés ou de sirop ou même combinée avec d'autres médicaments. Et elle peut s'acheter en « vente-libre », c'est-à-dire sans ordonnance, malgré l'interdiction de vente pour les enfants de moins de 12 ans.

> Si votre enfant a moins de 12 ans, votre pédiatre n'a plus le droit de lui prescrire de médicament contenant de la codéine, et votre pharmacien n'a plus le droit de vous en vendre sans ordonnance. Pourquoi?

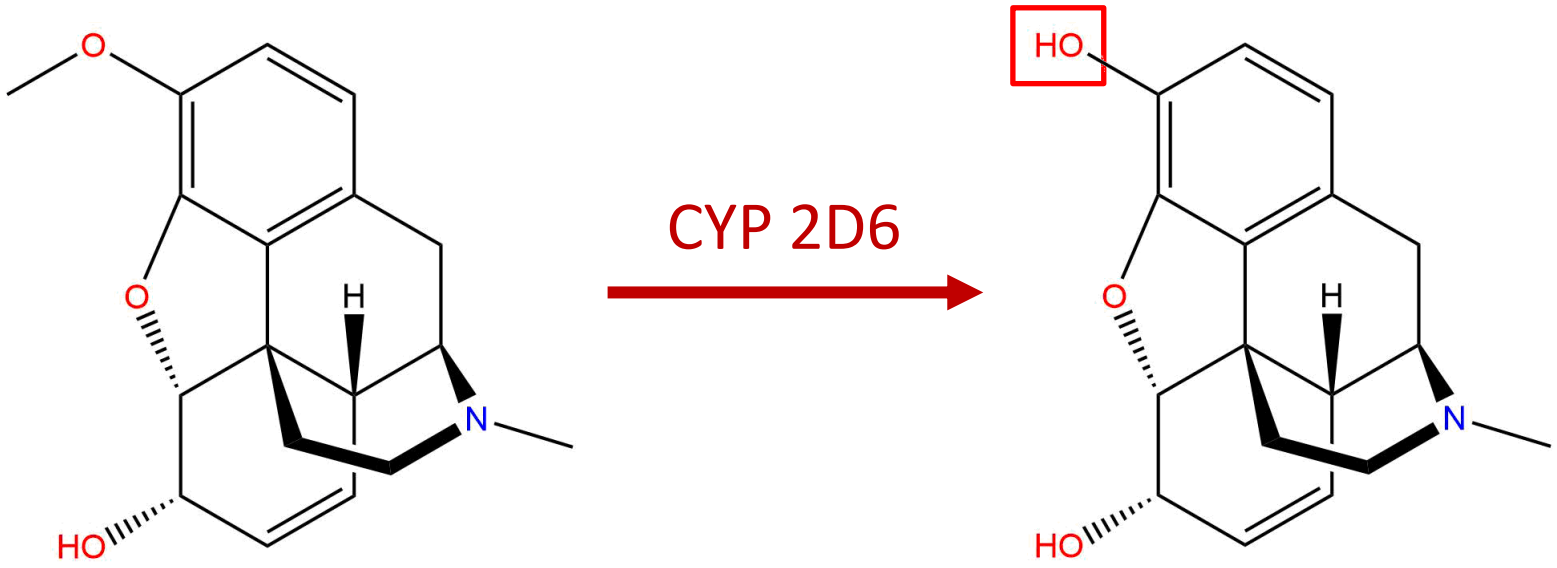
https://www.atelierantalgie.com/blog/2018/01/25/ne-donnez-plus-de-codeine-aux-enfants/

Codeine and CYP2D6



https://www.atelierantalgie.com/

Bioactivation of codeine

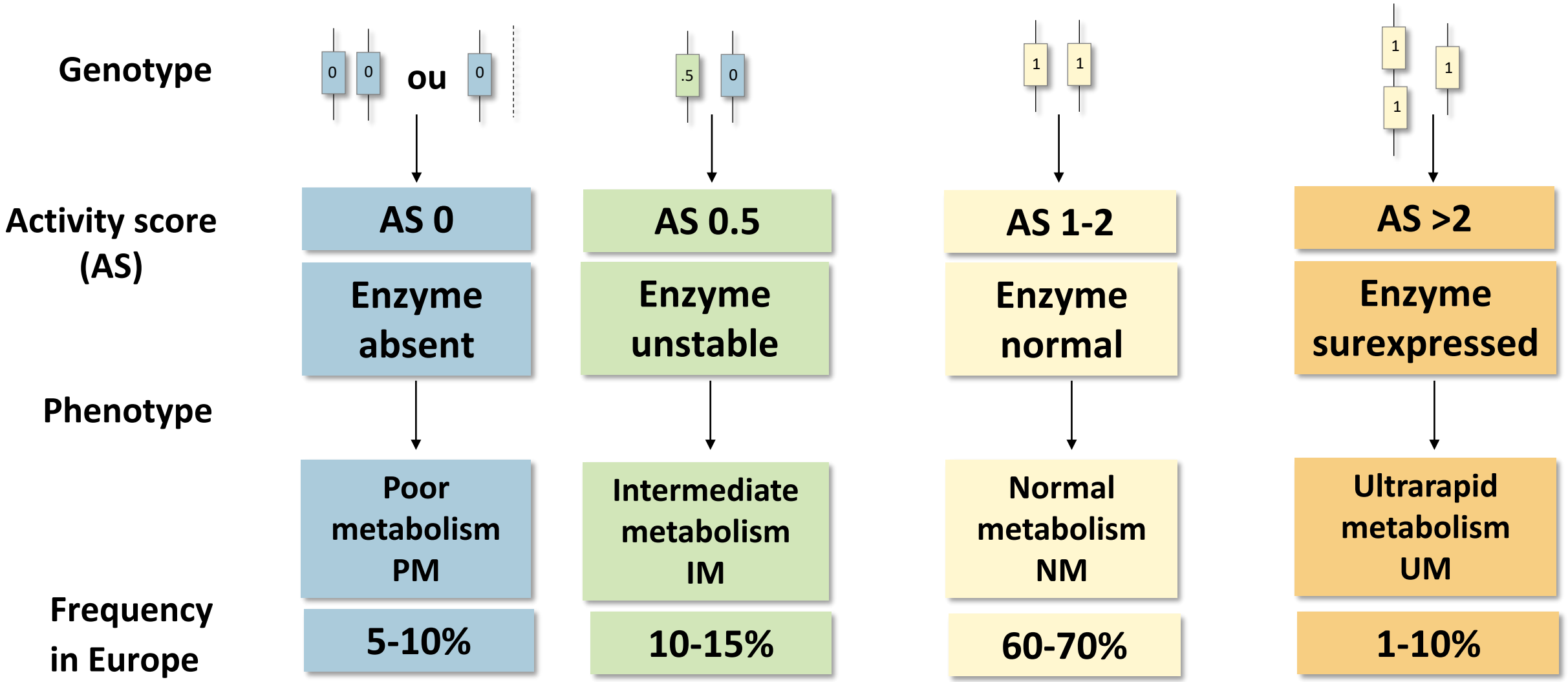


codeine

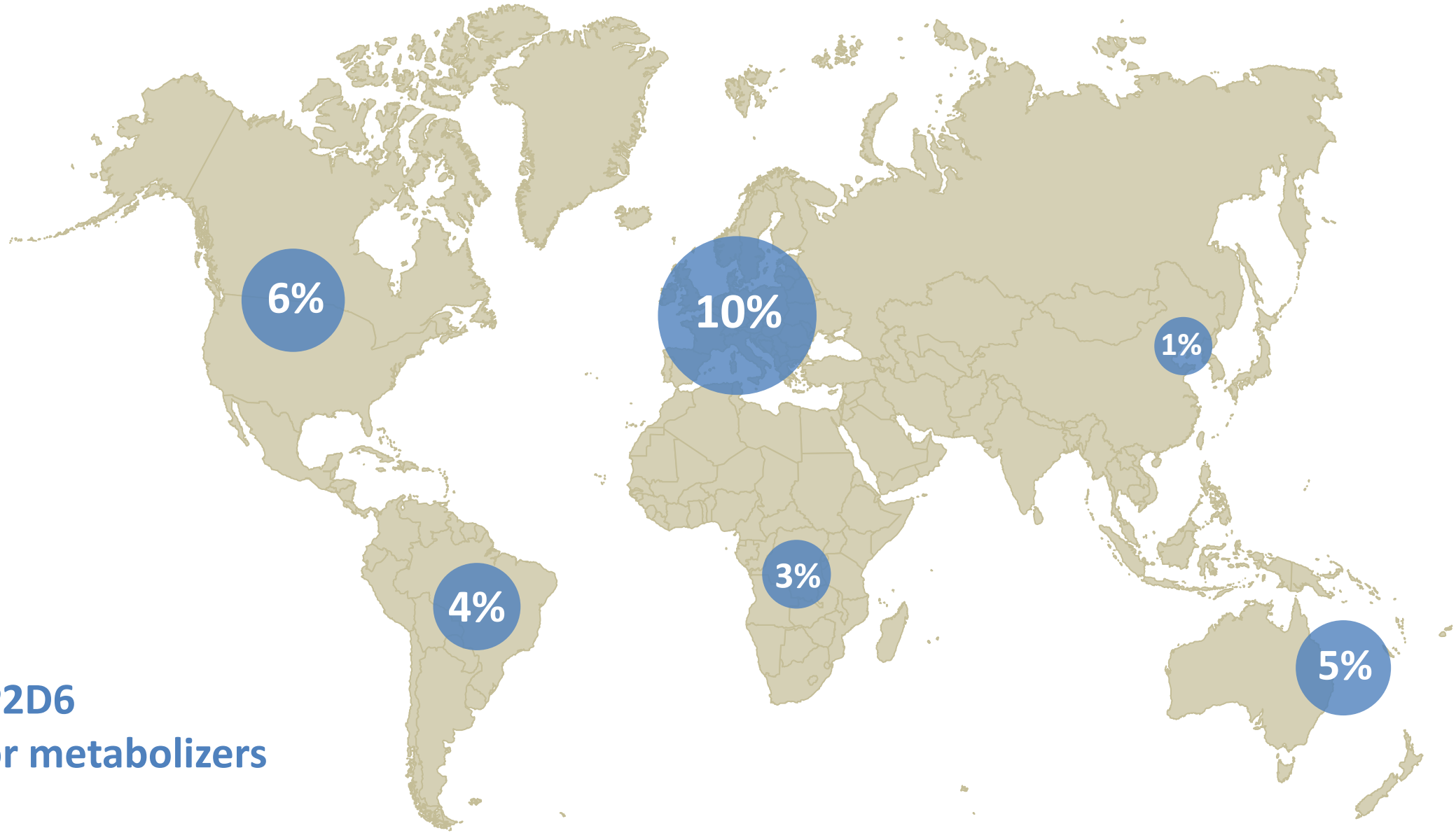
morphine

Dayer P et al. Biochem Biophys Res Commun. 1988;152: 411-6.
Desmeules J et al. Eur J Clin Pharmacol. 1991;41: 23-6.

Polymorphism of CYP2D6

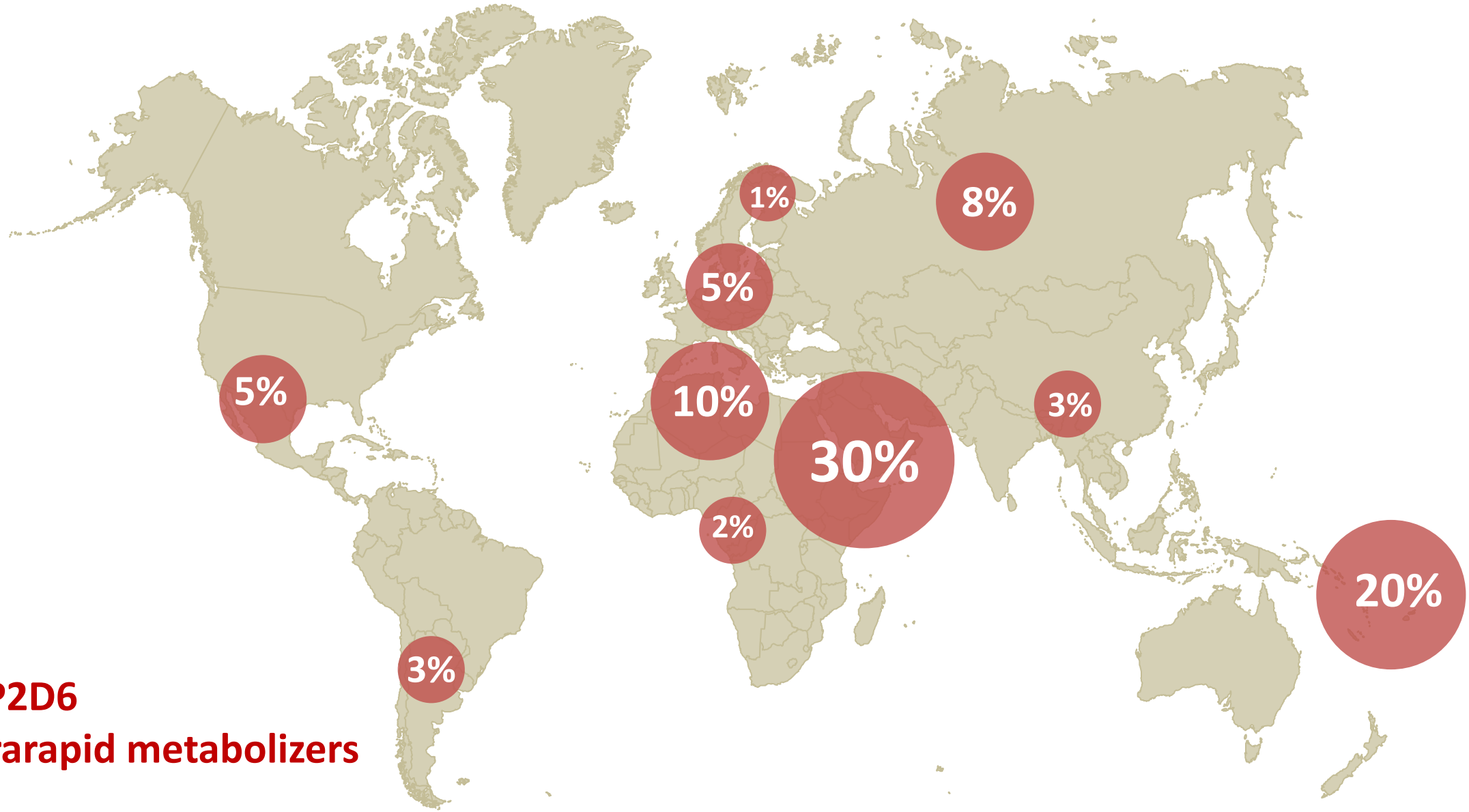


Polymorphism of CYP2D6



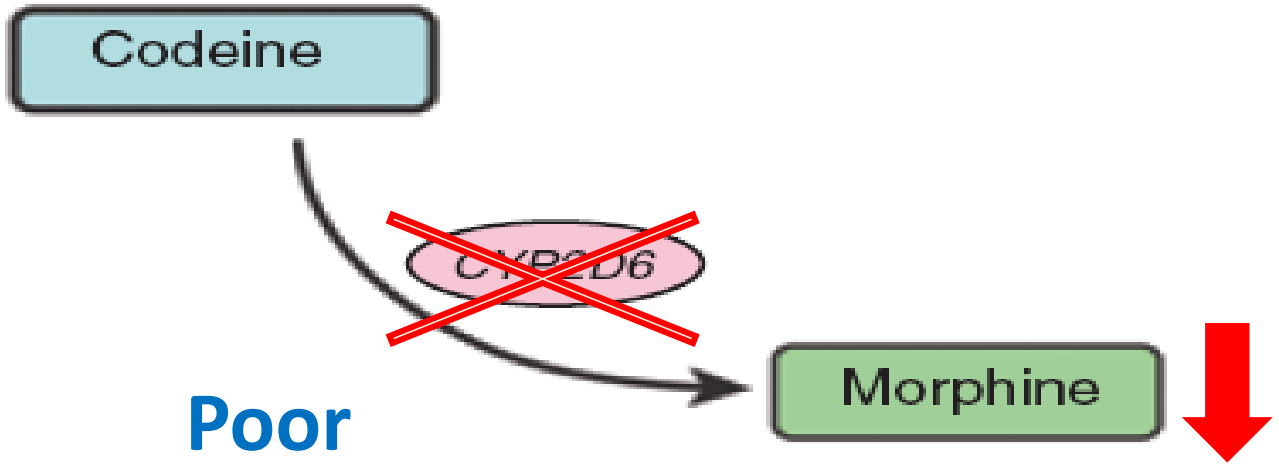
CYP2D6
Poor metabolizers

Polymorphism of CYP2D6



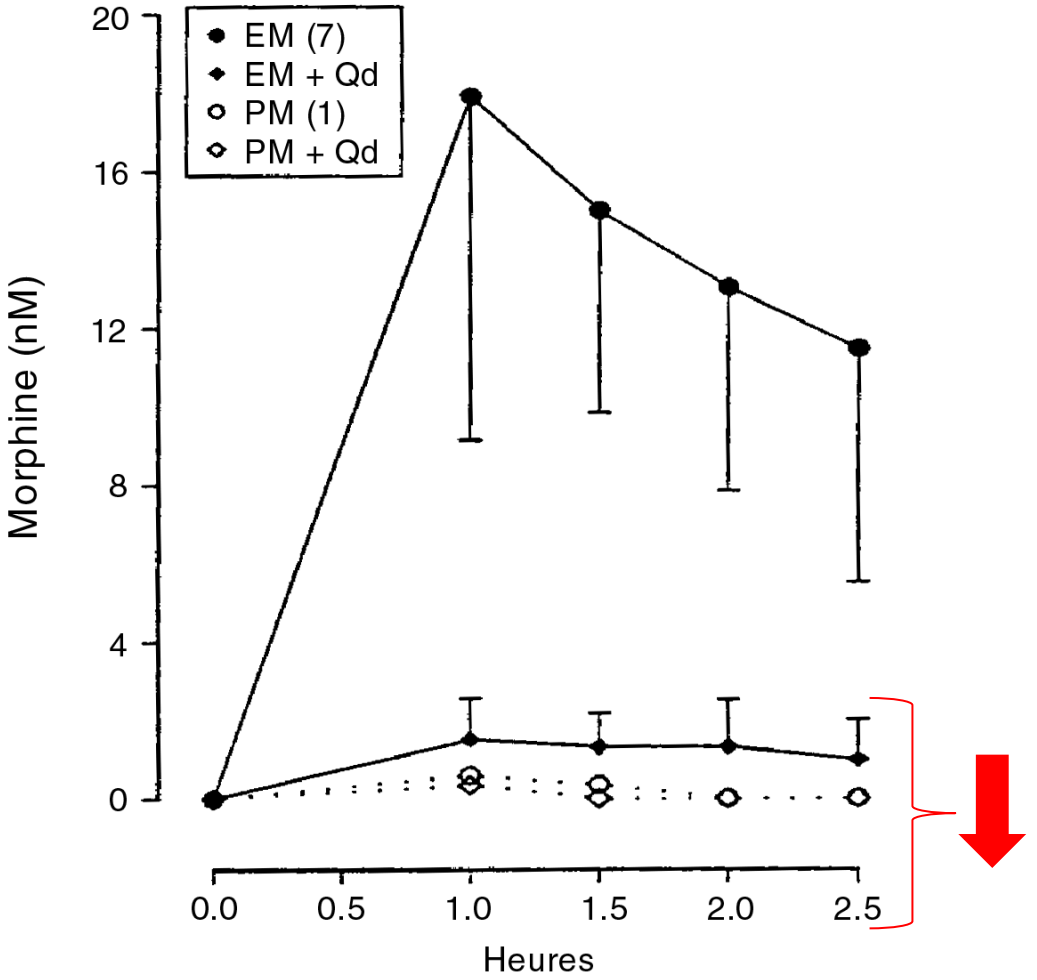
CYP2D6
ultrarapid metabolizers

CODEIN AND CYP2D6 POOR METABOLISM



Poor metabolizer

Reduced analgesic efficacy (experimental pain models in healthy volunteers)



Desmeules et al Eur J Clin Pharmacol 1991, 4:1 79-86

CYP2D6 AND CODEINE ANALGESIA

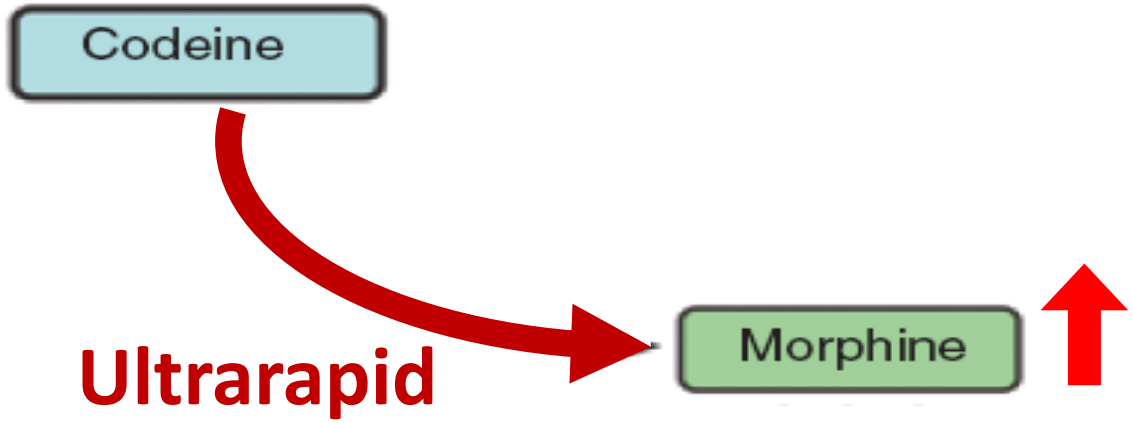
	All Patients	EMs	hetEMs	PMs
Three-d postoperative pain scores				
AUC mean (±SD)	238 (±106)	226 (±102)	226 (±100)	232 (±41)
Mean (±SD)	3.5 (±1.6)	3.3 (±1.5)	3.4 (±1.5)	3.4 (±1.0)
Median	3.4	3.1	3.4	3.3
Range	1.1–7.2	1.2–6.3	1.1–6.9	3.8–4.0
Count of women ≥4 mean VAS score	16	4	8	1
Day 2 (peak) postoperative pain scores				
AUC mean (±SD)	92 (±41)	85 (±39)	89 (±39)	84 (±27)
Mean (±SD)	3.6 (±1.7)	3.3 (±1.5)	3.5 (±1.6)	2.9 (±0.9)
Median	3.7	3.1	3.7	2.9
Range	0.8–7.7	1.1–6.4	0.8–7.0	2.3–3.6
Count of women ≥4 mean VAS score	18	5	10	0
3-d Codeine dose (mg)				
Median	180	180	180	450
Range	30–840	60–840	30–660	120–780
3-d Codeine dose (mg/kg)				
Median	2.4	2.2	2.4	4.6
Range	0.4–11.1	0.8–10.8	0.4–11.1	1.6–7.7

Doses x2.5

n= 45 post-caesarean women treated with codeine and genotyped for CYP2D6

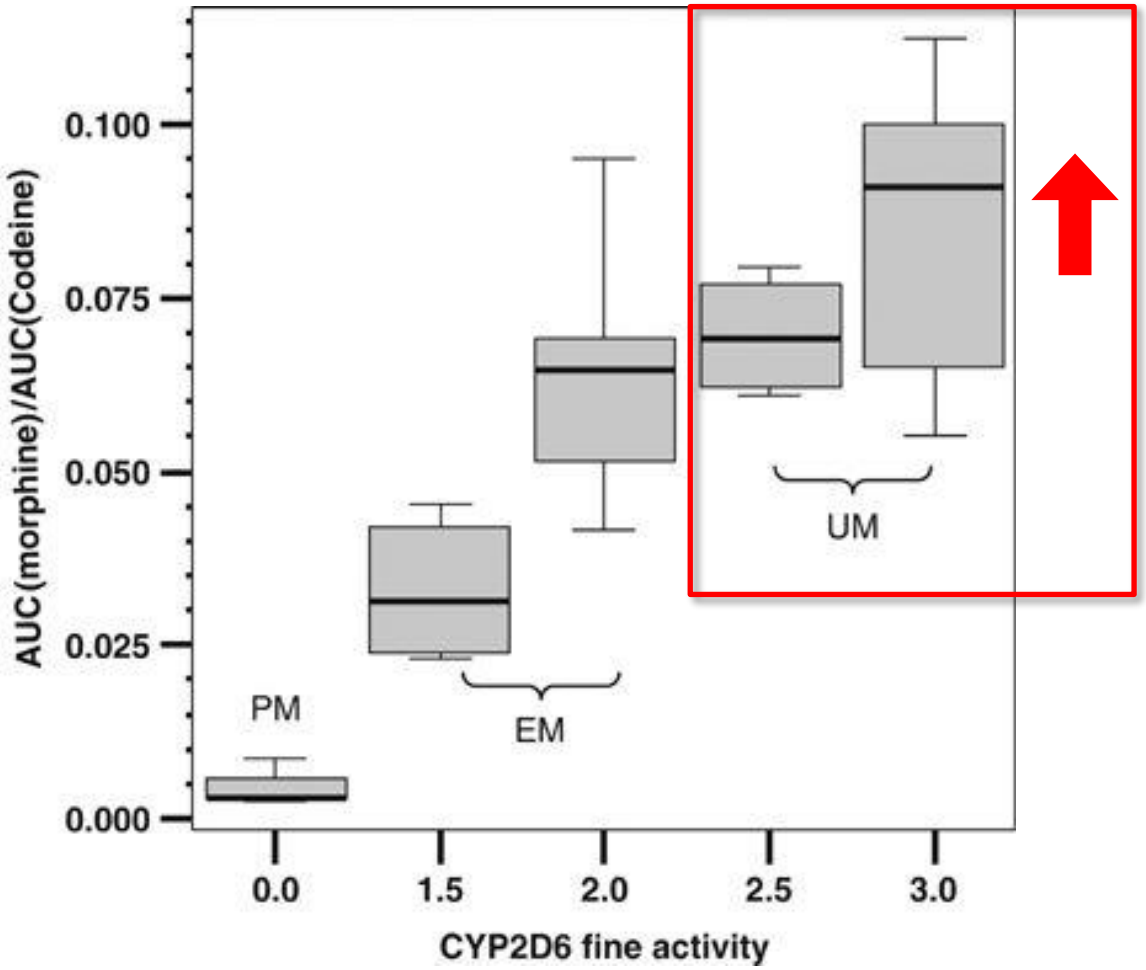
VanderVaart S et al. Ther Drug Monit. 2011;33:425-32.

CODEINE AND CYP2D6 UM



Ultrarapid metaboliser UM

Increased toxicity?



Kirchheiner et al Pharmacogenomic J 2007

TOXICITY OF CODEIN AND CYP2D6

Cases	Indication	Toxicity
CYP2D6 ultra-rapid metabolizers	Episiotomy (mother)	Death
	Severe muscle pain (mothers)	Mothers: sedation, nausea, dizziness; Children: dizziness, feeding difficulties
	Tonsillectomy	Death
	Tonsillectomy	Apnea
	Tonsillectomy	Severe respiratory depression
	Adenotonsillectomy	Death
	Adenotonsillectomy	Death

Dalen et al 1997, Koren et al 2006, Madadi et al 2007, Voronov et al 2007, Madadi et al 2009, Kelly et al 2012, Orliaguet et al 2015

U.S. FOOD & DRUG ADMINISTRATION

FDA Warning on Codeine Use by Nursing Mothers
May Increase Chance of Serious Side Effects in Infants **2007**

The U.S. Food and Drug Administration (FDA) is concerned that nursing infants may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of codeine. The agency has reviewed all available information on this subject since a medical journal reported the death of a 13-day old breastfed infant who died from morphine overdose. The morphine levels in the mother's milk were abnormally high after taking small doses of codeine to treat episiotomy pain. A genetic test showed that the mother was an ultra-rapid metabolizer of codeine.

FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy **2013**

FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women **2017**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

swissmedic

FDA Drug Safety Communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older **2018**

CPIC
Clinical Pharmacogenetics Implementation Consortium

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy

Kristine R. Crews[1,*], Andrew A. Monte[2], Rachel Huddart[3], Kelly E. Caudle[1], Evan D. Kharasch[4], Andrea Gaedigk[5,6], Henry M. Dunnenberger[7], J. Steven Leeder[5,6], John T. Callaghan[8], Caroline Flora Samer[9], Teri E. Klein[3], Cyrine E. Haidar[1], Sara L. Van Driest[10], Gualberto Ruano[11], Katrin Sangkuhl[3], Larisa H. Cavallari[12], Daniel J. Müller[13], Cynthia A. Prows[14], Mohamed Nagy[15], Andrew A. Somogyi[16] and Todd C. Skaar[8]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 110 NUMBER 4 | October 2021

Table 2 Codeine therapy recommendations based on CYP2D6 phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.[b]	Strong
Extensive metabolizer	Normal morphine formation	15–60 mg every 4 h as needed for pain (label recommendation)	Strong
Intermediate metabolizer	Reduced morphine formation	Begin with 15–60 mg every 4 h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopioid. Monitor tramadol use for response.	Moderate
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.[b]	Strong

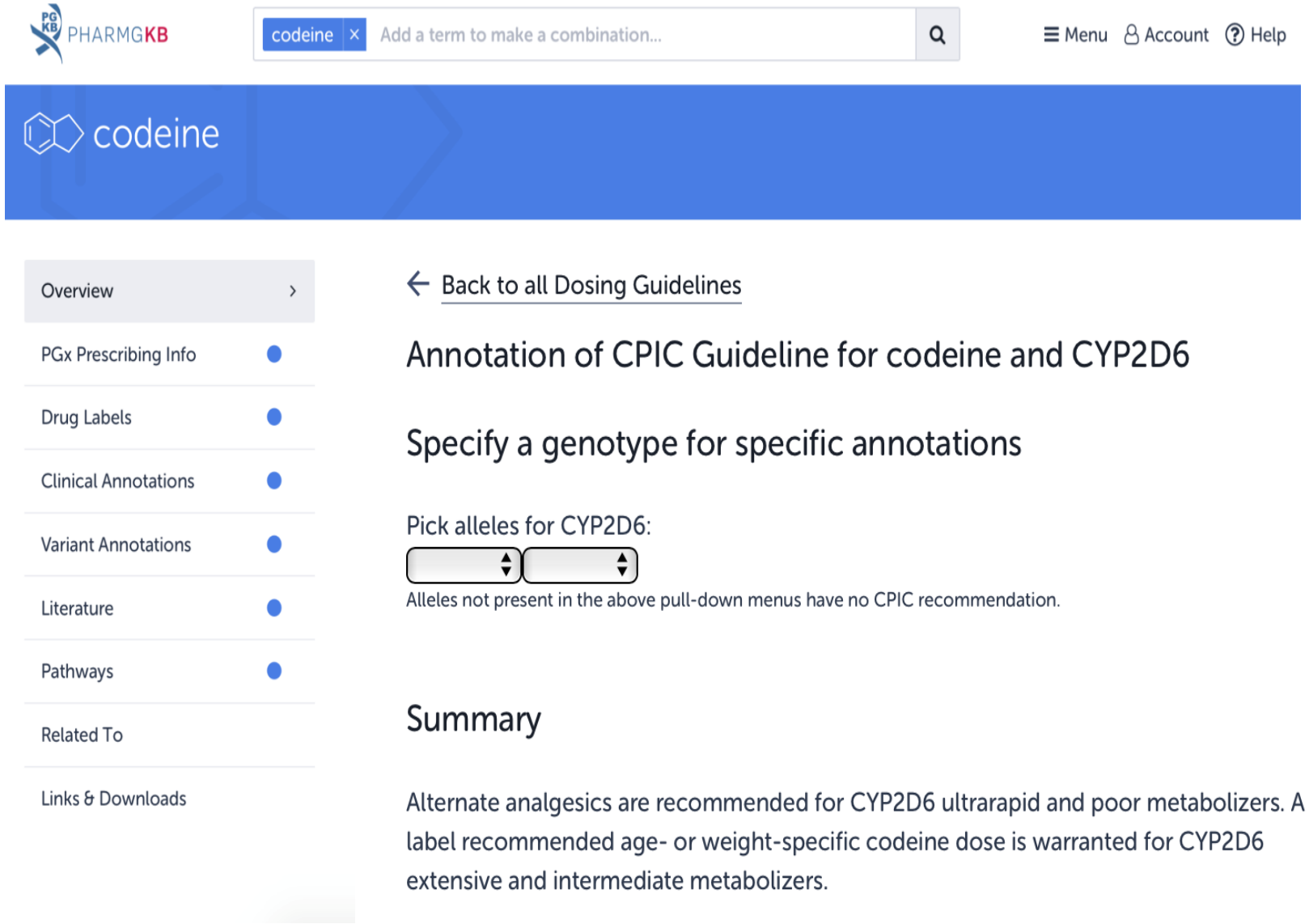
Recommendations for codeine treatment according to CYP2D6 genotype

1 in 5 Europeans should not receive codeine

CPIC Clinical Pharmacogenetics Implementation Consortium

CPIC Guidelines

Crews K et al, Clin Pharmacol Ther. 2014; 95:376-82.



PHARMaco**G**enomics**K**nowledge**B**ase

http://www.pharmgkb.org/

Codeine

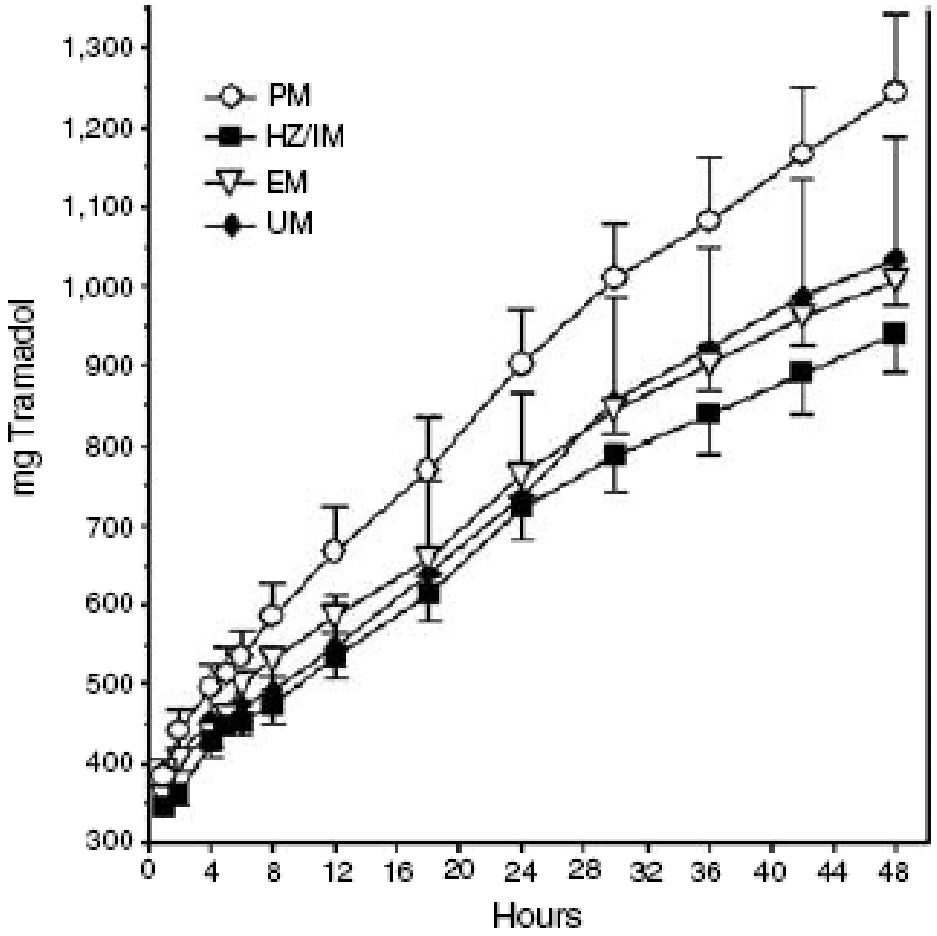
Oxycodone

Tramadol

Bio-activation of opioids by CYP2D6

Substance	Active metabolite	Reference
codeine	morphine	Dayer et al, Biochem Biophys Res Comm 1988
tramadol	M1	Paar et al, Clin Invest 1992
hydrocodone	hydromorphone	Otton et al , Clin Pharmacol Ther 1993
oxycodone	oxymorphone	Cleary et al, J Pharmacol Exp Ther 1993
dihydrocodeine	dihydromorphine	Fromm et al, J Pharmacol Exp Ther 1995
ethylmorphine	morphine	Xu et al, Biochem Pharmacol 1995

CYP2D6 and postoperative tramadol analgesia

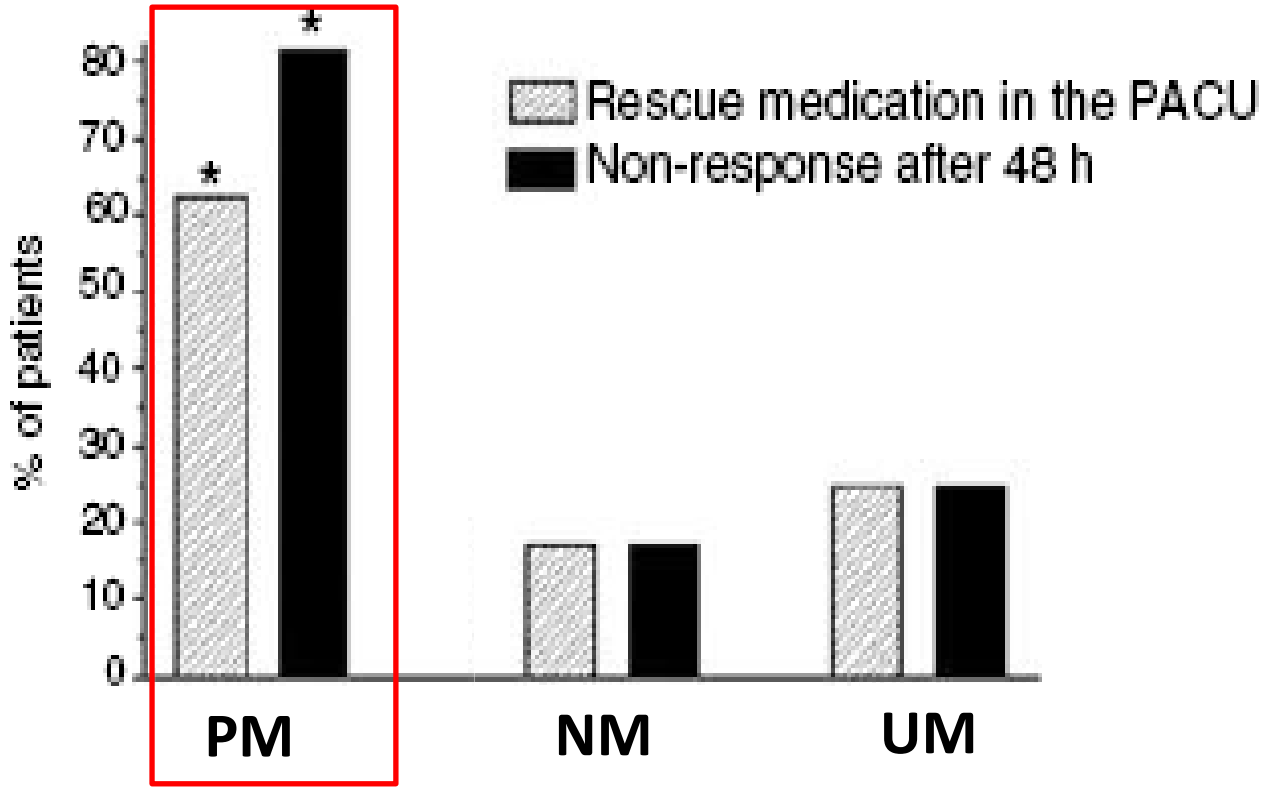


Cumulative tramadol consumption over 48 hours
PM > IM > NM > UM

n= 187 patients after major abdominal surgery

Stamer U et al, Clin Pharmacol Ther 2007

Quadrupled therapeutic resistance in CYP2D6 poor metabolizers

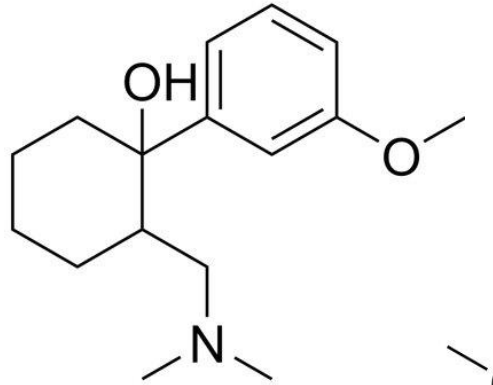


n= 187 major abdominal surgeries

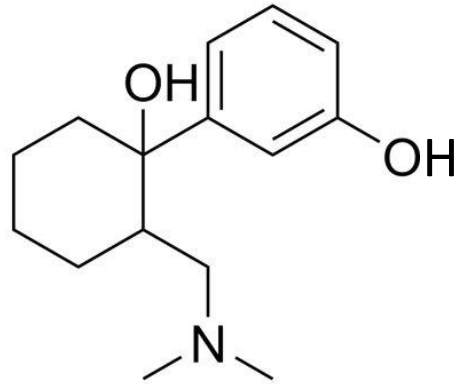
Stamer U et al, Clin Pharmacol Ther 2007

TRAMADOL: DUAL MODE OF ACTION

tramadol



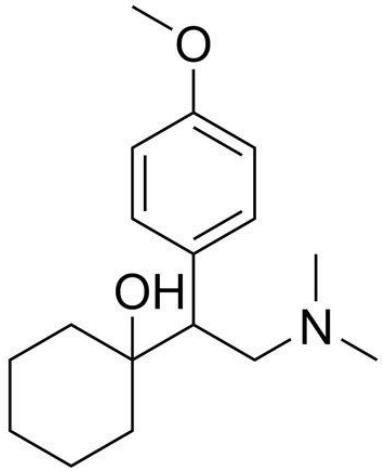
CYP2D6



M1

↑ monoaminergic

CYP2D6 poor metabolizers



Venlafaxine

↑ opioidergic

CYP2D6 ultrarapid metabolizers

2 phenotypes <-> 2 different drugs

frontiers in Pharmacology

REVIEW
published: 05 March 2018
doi: 10.3389/fphar.2018.00148

Check for updates

When the Safe Alternative Is Not That Safe: Tramadol Prescribing in Children

*Frédérique Rodieux[1], Laszlo Vutskits[2,3,4], Klara M. Posfay-Barbe[5], Walid Habre[4,6], Valérie Piguet[1], Jules A. Desmeules[1,7] and Caroline F. Samer[1]**

Front Pharmacol. 2018 Mar 5;9:148. doi: 10.3389/fphar.2018.00148.

OPIOIDS AND CYP2D6

- ✓ A subset of patients (CYP2D6 PMs and UMs) **should not receive** codeine, oxycodone or tramadol due to reduced analgesic effects or increased toxicity

Association studies

Hypothesis driven

Candidate gene approach

Risk: negative study if false hypothesis

Hypothesis generating

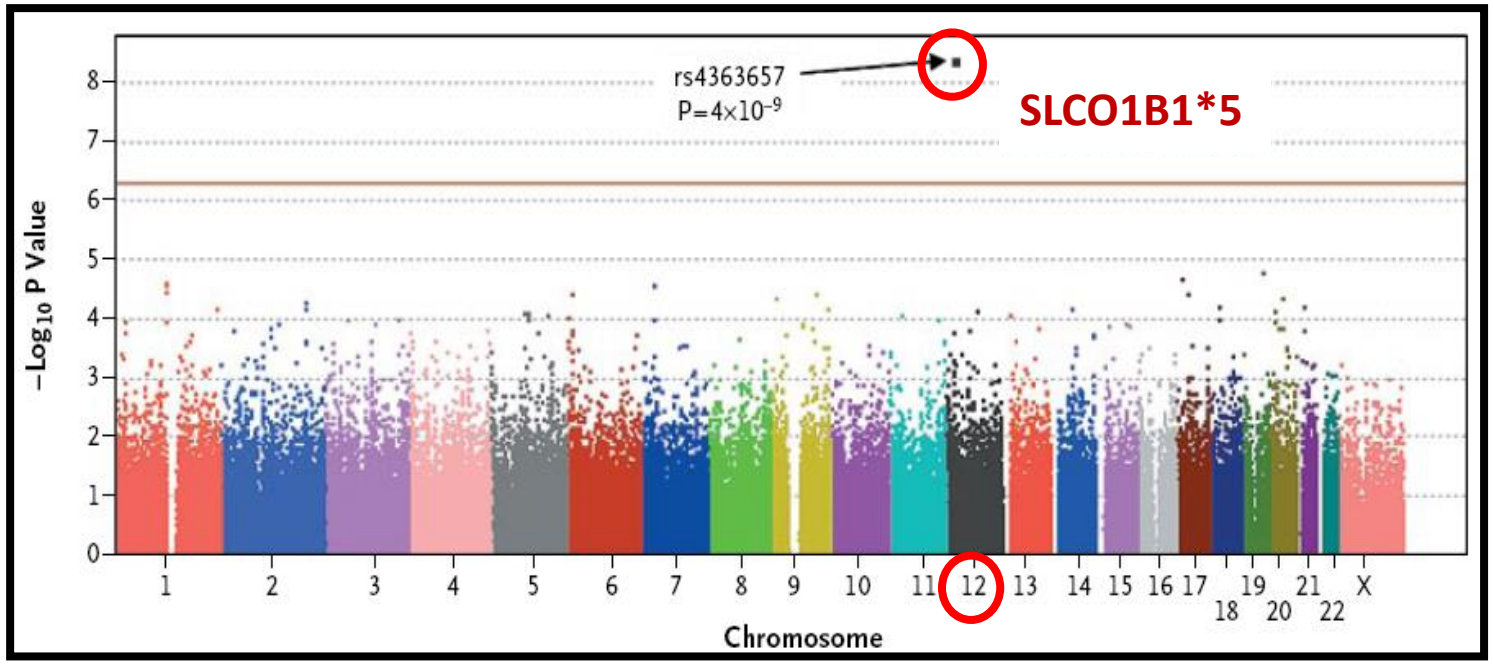
GWAS

10 -10^{56} SNPs

Risk: insufficient power, false positives

GWAS : statin induced myopathies

- 6’000 patients taking simvastatin 80 mg/d
- 85 cases of myopathy vs 90 matched controls
- 300’000 genetic markers (GWAS)



Replicated in an independant dataset
(simvastatine 40 mg/d)

SLO1B1*5 ⚠

Risk increase:

4.5 fold (1 mutation)

17 fold (2 mutations)

60% myopathies attributed to the C allele

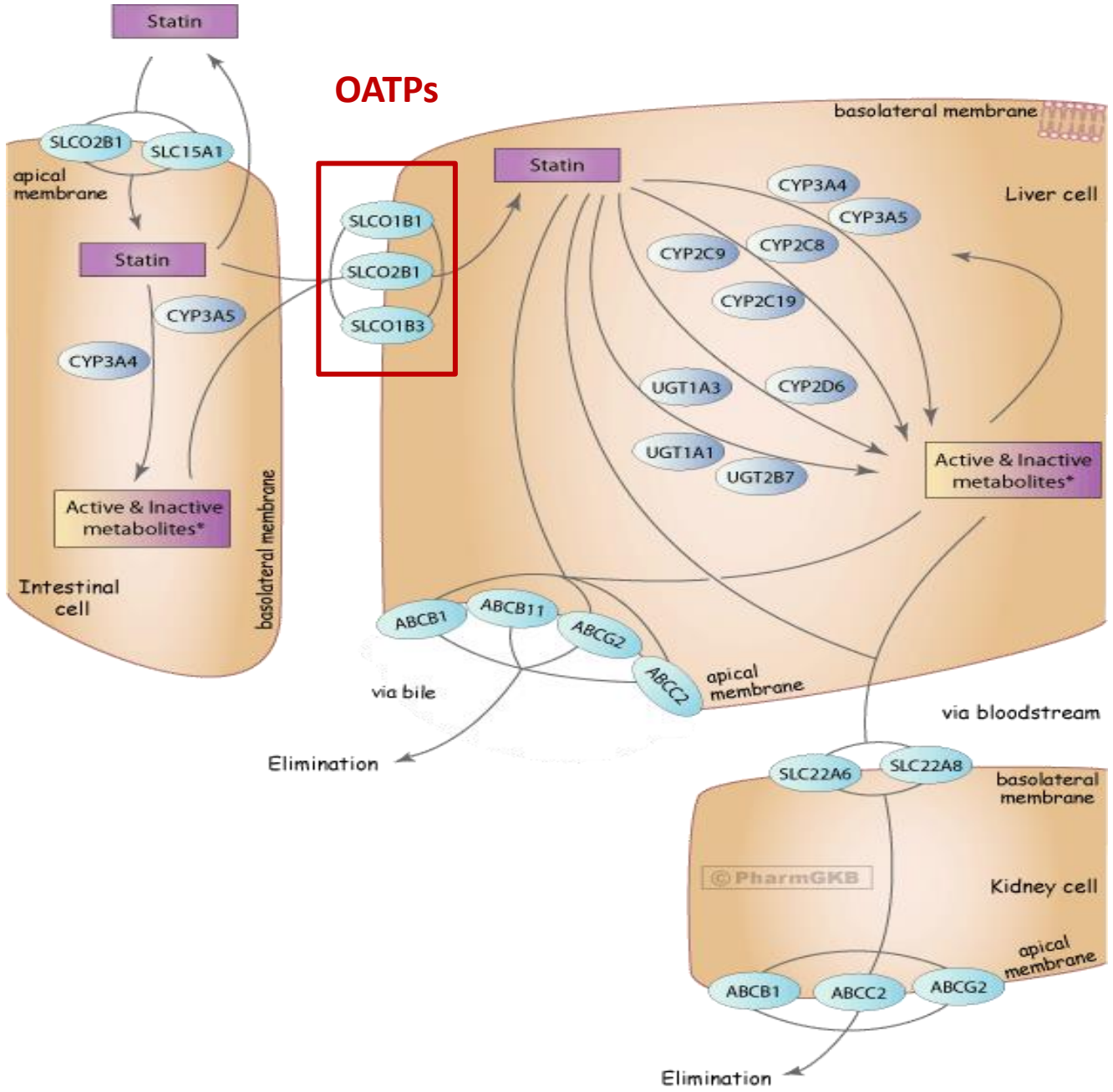
SEARCH collaborative group. NEJM 2008,359:789-99

SLCO1B1

- SLCO1B1 (*solute carrier organic anion transporter family member 1B1*) gene codes for **OATP1B1 tansporter**
- Facilitates the uptake of statine **into hepatocytes**
- Many polymorphisms identified incl. **SLCO1B1*5**

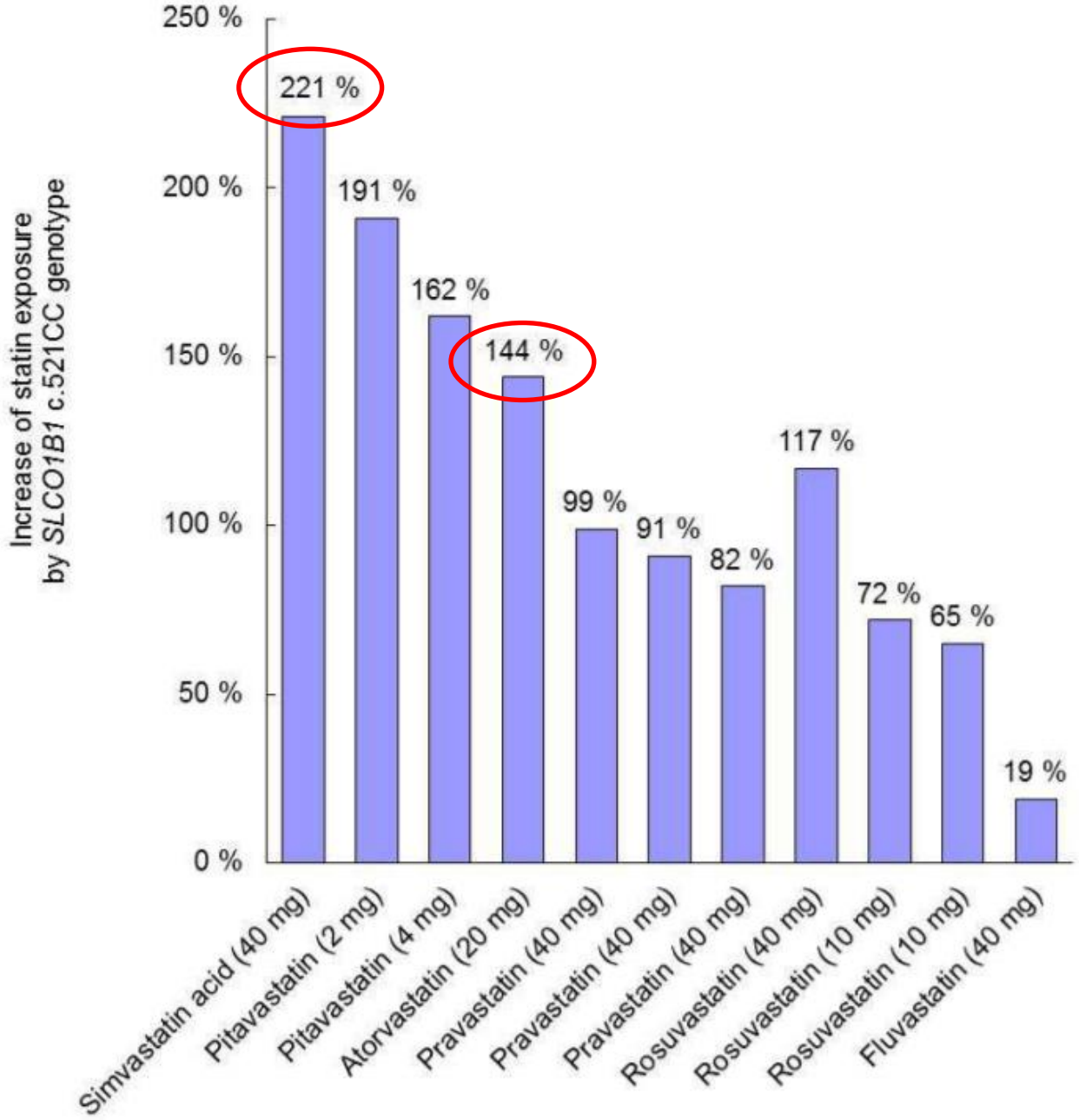
-> in Europe:

27% (heterozygotes)
1% (homozygotes)



https://www.pharmgkb.org/pathway/PA145011108

The impact of SCLO1B1*5 varies by statin



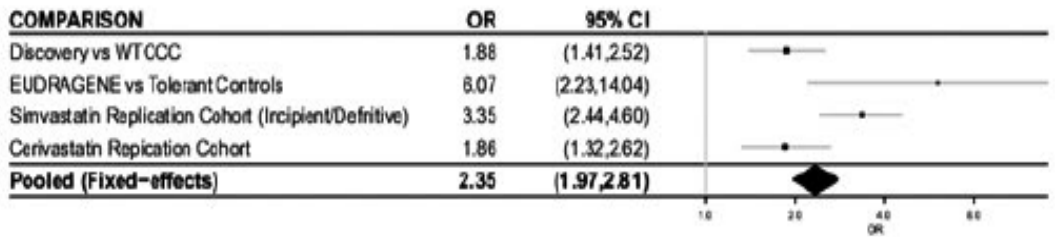
European Heart Journal - Cardiovascular Pharmacotherapy 2022, 8: 85-99.

SLCO1B1*5 and statin induces myopathies: meta-analysis

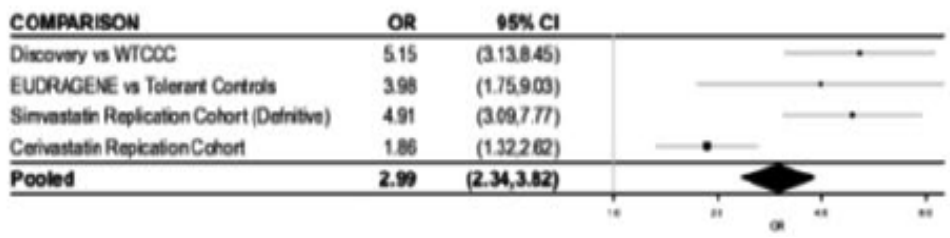
All myopathies

Severe myopathies

all statins

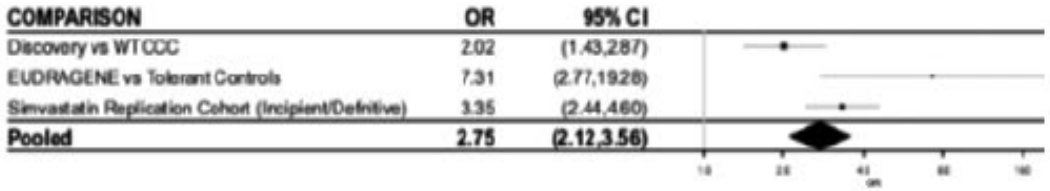


OR 2.35

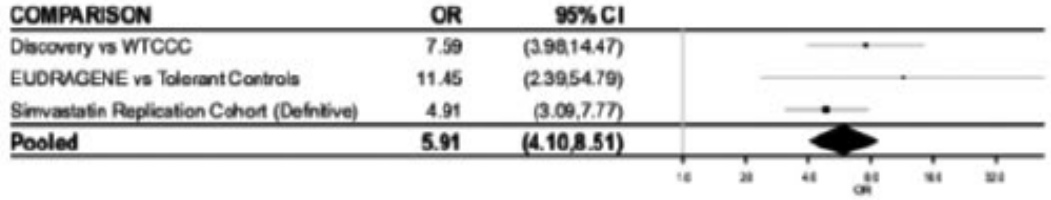


OR 2.99

Simva statin



OR 2.75 $P = 2.01 \times 10^{-14}$



OR 5.91 $P = 1.46 \times 10^{-21}$

Carr DF et a, Clin Pharmacol Ther 2019. 106(6): 1353-61.

SLCO1B1 GENOTYPE AND STATIN DOSE RECOMMENDATIONS

	SLCO1B1 c.521T>C genotype (SLCO1B1*5)			
	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

Reduce the dose by 4 times!

Niemi M, Clin Pharm Ther 2010, 87(1): 130-133.

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2022) **8**, 85–99
doi:10.1093/ehjcvp/pvab018

2022

The role of pharmacogenomics in contemporary cardiovascular therapy: a position statement from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

EUROPEAN SOCIETY OF CARDIOLOGY

Key clinical positions:

- Avoid high-dose simvastatin (80 mg) and consider an alternative statin of equivalent LDL lowering efficacy in patients known to be homozygous for the *SLCO1B1*5* reduced function variant.
- Recommendations: prospective genotyping prior to simvastatin initiation is recommended where possible.

European Heart Journal – Cardiovascular Pharmacotherapy 2022, 8: 85-99.

STATIN-INDUCED MYOPATHIES

- ✓ A subgroup of patients is at increased risk of **toxicity**
- ✓ Hypothesis **generated** by a GWAS
- ✓ Available recommendations for dosage **adjustment**

HYPERSENSITIVITY TO ABACAVIR

- HIV nucleoside reverse transcriptase inhibitor (NRTI)
- Hypersensitivity reaction: 5-9%.
  - Idiosyncratic
  - Quick start
  - Multi-organ, non-specific symptoms
  - Reversible on discontinuation of abacavir
  - Rechallenge can be fatal

Hetherington S et al, Clin Ther 2001, 23: 1603-14.

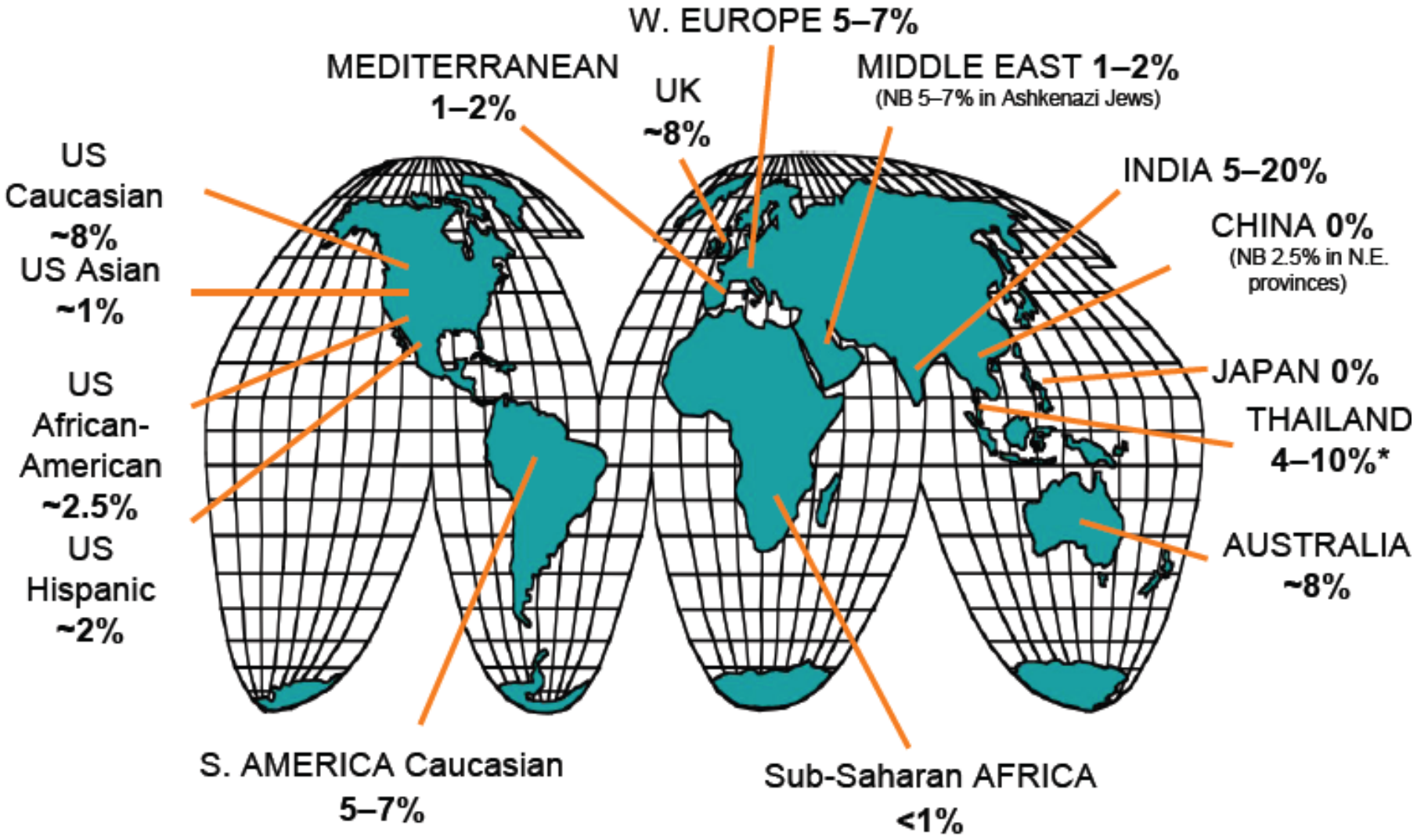
HLA PREDICTIVE OF HYPERSENSITIVITY TO ABACAVIR

Contribution of combined or individual loci of 57.1 ancestral haplotype to susceptibility to abacavir

HLA type	Abacavir hypersensitive (n = 18)	Abacavir tolerant (n = 167)	Odds ratio (95% CI)	*P* value
*HLA-B*5701*	14 (78%)	4 (2%)	**117** (29–481)	< 0.0001
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73 (20–268)	< 0.0001
*HLA-B*5701, HLA-DR7, HLA-DQ3*	13 (72%)	0 (0%)	822 (43–15675)	< 0.0001

Mallal S. NEJM 2008, 358: 568-79

ALLELE FREQUENCY HLA-B*5701



* THAILAND B*57 carriage: Urban Bangkok 3.6%;
Thai Dai Lue (N.E. Thai) ~11%; Southern Thai Muslim 3%

Phillips EJ. *Clin Infect Dis* 2006; **43**:103–105

Table 4. Performance Characteristics of HLA-B*5701 Screening for Hypersensitivity Reaction to Abacavir in the Control Group.*

Subgroup	Positive for HLA-B*5701	Negative for HLA-B*5701	Total	Performance Characteristic for Hypersensitivity Reaction
	number of patients			*percent (95% CI)*
Immunologically confirmed hypersensitivity reaction				
Total population that could be evaluated				
Hypersensitivity reaction	23	0	23	Sensitivity: 100 (85.2–100)
No hypersensitivity reaction	25	794	819	Specificity: 96.9 (95.5–98.0) PPV: 47.9 (33.3–62.8) NPV: 100 (99.5–100)

50% HLB*5701 positive patients will not develop hypersensitivity to abacavir

Mallal S. NEJM 2008, 358: 568-79

Ziagen®

■ VIIV HEALTHCARE

OEMéd

Composition

Principe actif: Abacavirum (ut abacaviri sulfas).

Excipients

Comprimés filmés: excip. pro compresso obducto.

Solution buvable: sorbitolum (0,5%), saccharinum, propylenglycolum, aromatica, vanillinum et ethylvanillinum, Conserv.: methylis parahydroxybenzoas (E 218), propylis parahydroxybenzoas (E 216), excip. ad solutionem.

Forme galénique et quantité de principe actif par unité

Comprimés filmés sécables à 300 mg.

Solution buvable à 20 mg/ml.

Indications/Possibilités d'emploi

L'usage de Ziagen est indiqué, en association avec d'autres antirétroviraux, pour le traitement des adultes et enfants infectés par le virus de l'immunodéficience humaine (VIH-1).

Avant de débuter un traitement contenant de l'abacavir, le dépistage de l'allèle HLA-B*5701 doit être réalisé chez tout patient infecté par le VIH, quelle que soit son origine ethnique. L'abacavir ne doit pas être utilisé chez les patients porteurs de l'allèle HLA-B*5701, à moins qu'aucune autre alternative thérapeutique ne soit disponible chez ces patients, en tenant compte des antécédents thérapeutiques et des tests de résistance (voir rubriques «Mises en garde et précautions» et «Effets indésirables».

Posologie/Mode d'emploi

Posologie usuelle

Ziagen peut être pris au cours ou en dehors des repas.

Les comprimés doivent être idéalement avalés sans les écraser, afin de garantir l'administration de la dose complète.

Ziagen est également disponible sous forme de solution buvable pour les patients dans l'incapacité d'avaler des comprimés.

Pour les patients dans l'incapacité d'avaler des comprimés, une autre alternative est d'écraser les comprimés et de les mélanger à une petite quantité de nourriture semi-solide ou de liquide, le tout devant être ingéré immédiatement (voir rubrique «Pharmacocinétique»).

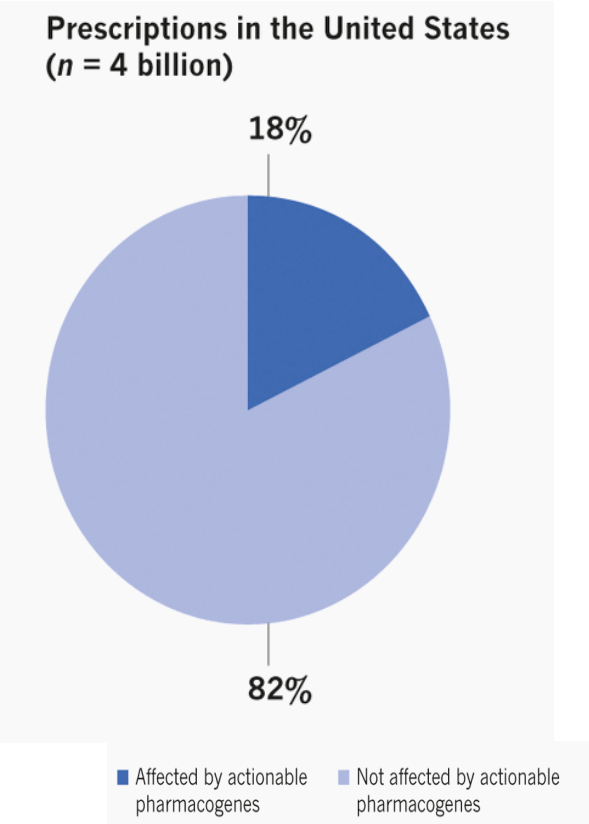
Adultes et adolescents pesant plus de 30 kg

La posologie recommandée de Ziagen est de 600 mg par jour. Cette dose peut être administrée soit sous la forme de 300 mg (un comprimé ou 15 ml de solution buvable) deux fois par jour, soit sous la forme de 600 mg (2 comprimés) une fois par jour.

HYPERSENSITIVITY TO ABACAVIR

- ✓ A subgroup of patients is at risk of fatal idiosyncratic **toxicity**
- ✓ Genetic diagnostic testing is **available** and **required** prior to prescription
- ✓ Indicated in the professional information of the medicine

There are currently ~ 20 genes whose variants have an impact on 150 medicines



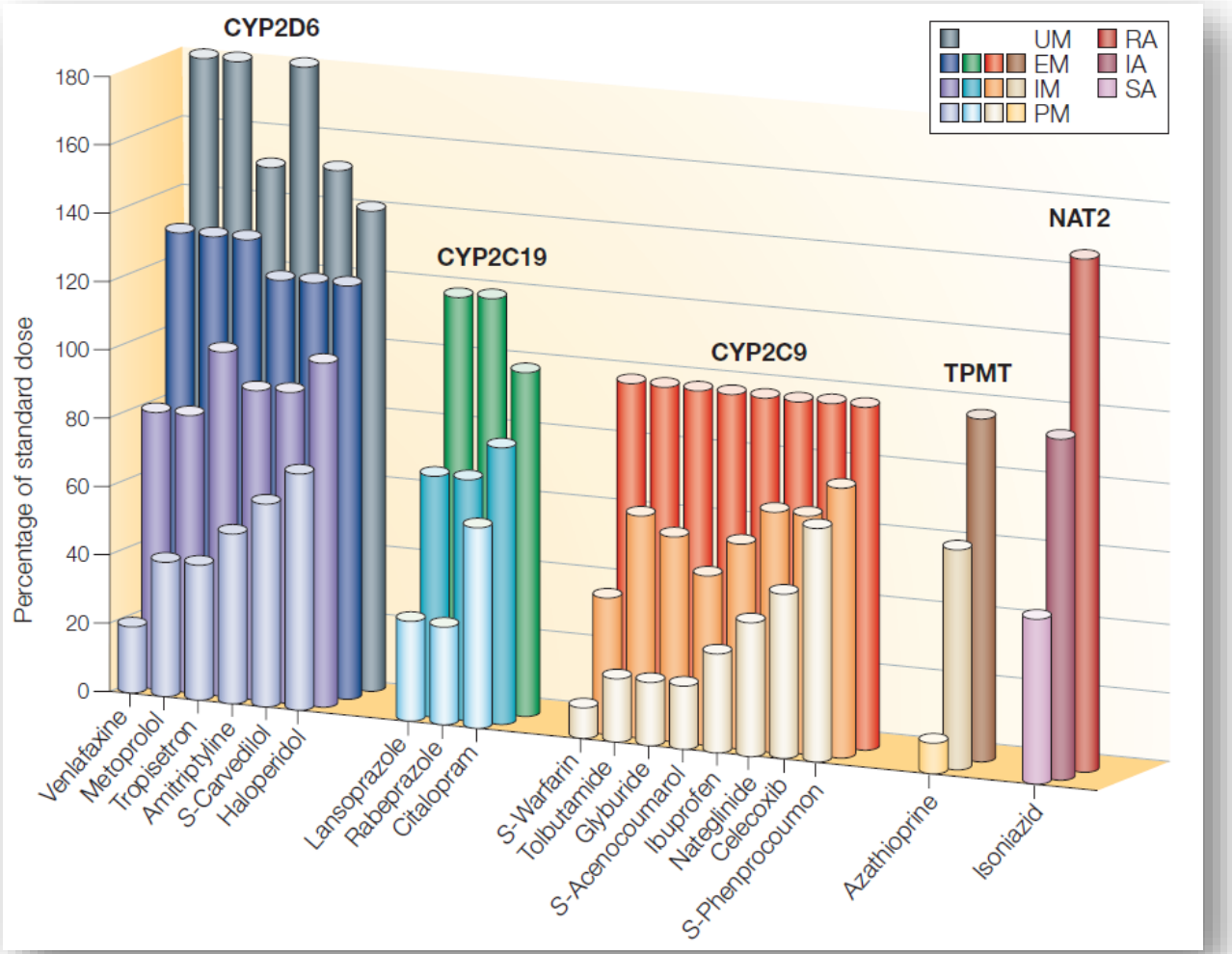
- Cancer
- Cardiovascular diseases
- Infectious diseases
- Psychiatric illnesses
- Pain
- Transplantation

U.S. FOOD & DRUG ADMINISTRATION

Relling and Evans, 2015 Nature 526:343-350

FDA Table of PGx Biomarkers in Drug Labeling

DOSE ADJUSTMENTS AND PHARMACOGENES



Kirchheiner J et al, Nat Rev Drug Discovery 2015

PharmGKB

PHARMacoGenomicsKnowledgeBase

Clinical

DOSING GUIDELINES	100
DRUG LABELS	509
CLINICAL ANNOTATIONS	3,931

Canadian Pharmacogenomics Network for Drug Safety

CPIC Clinical Pharmacogenetics Implementation Consortium

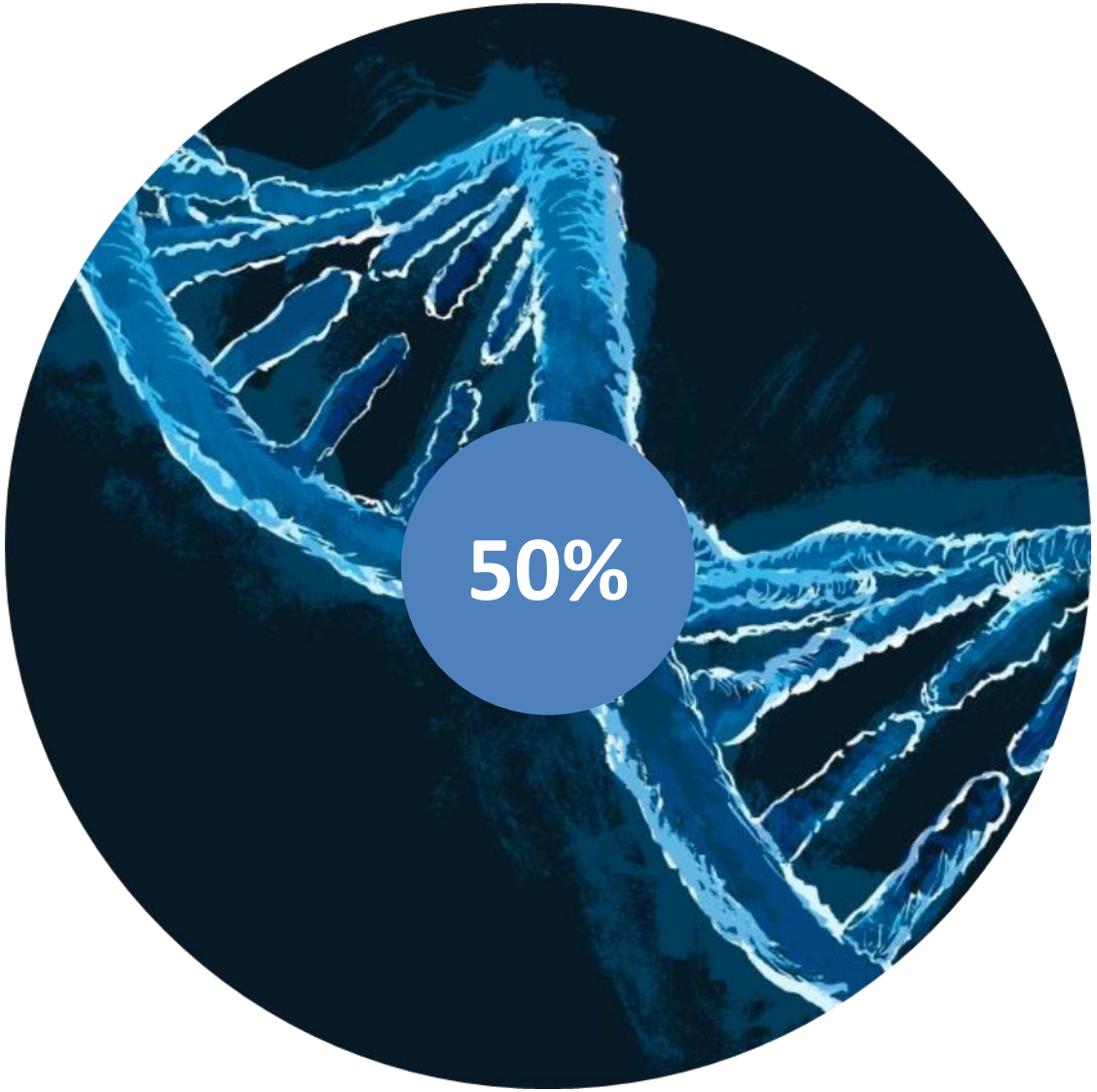
DPWG

Dutch Pharmacogenetics Working Group

https://www.pharmgkb.org/guideline

OPTIMISATION POTENTIAL

50% of patients over 65 will receive a treatment within 4 years that could be optimised by pharmacogenomics



Schildcrout JS et al, *Clin Pharmacol Ther* 2012

Drug	Polymorphism frequency	Risk
Codeine	CYP2D6 (20%)	Inefficacy/ toxicity
Statins	SLCO1B1 (1-15%)	Myopathies
Clopidogrel	CYP2C19 (7-10%)	Reduced efficacy
Acenocoumarol	VKORC1 (30%) CYP2C9 (3-20%)	Bleeding
Tacrolimus	CYP3A5 (20%)	50% initial dose reduction
AZA et 6MP	TPMT (6%)	Myelotoxicity

91% of patients carried at least one of these genetic variants

Clin Pharmacol Ther 2014; 95 : 423–431

Genotyping

Phenotyping

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Office of Public Health

REIMBURSEMENT OF PHARMACOGENOMIC TESTS

since January 2017

Analysis List January 1st 2017

2150.10	93	Analyse pharmacogénétique

Reimbursed by health insurance if:

1. Usefulness and association with clinical outcomes are scientifically demonstrated
2. The test is linked to the prescription of a drug that falls within the scope of

The tests on the SSCPT list can be prescribed by any doctor

All other tests require a specific indication by an FMH specialist in clinical pharmacology and toxicology

SGKPT SSPTC

SOCIETE SUISSE DE PHARMACOLOGIE ET TOXICOLOGIE CLINIQUES

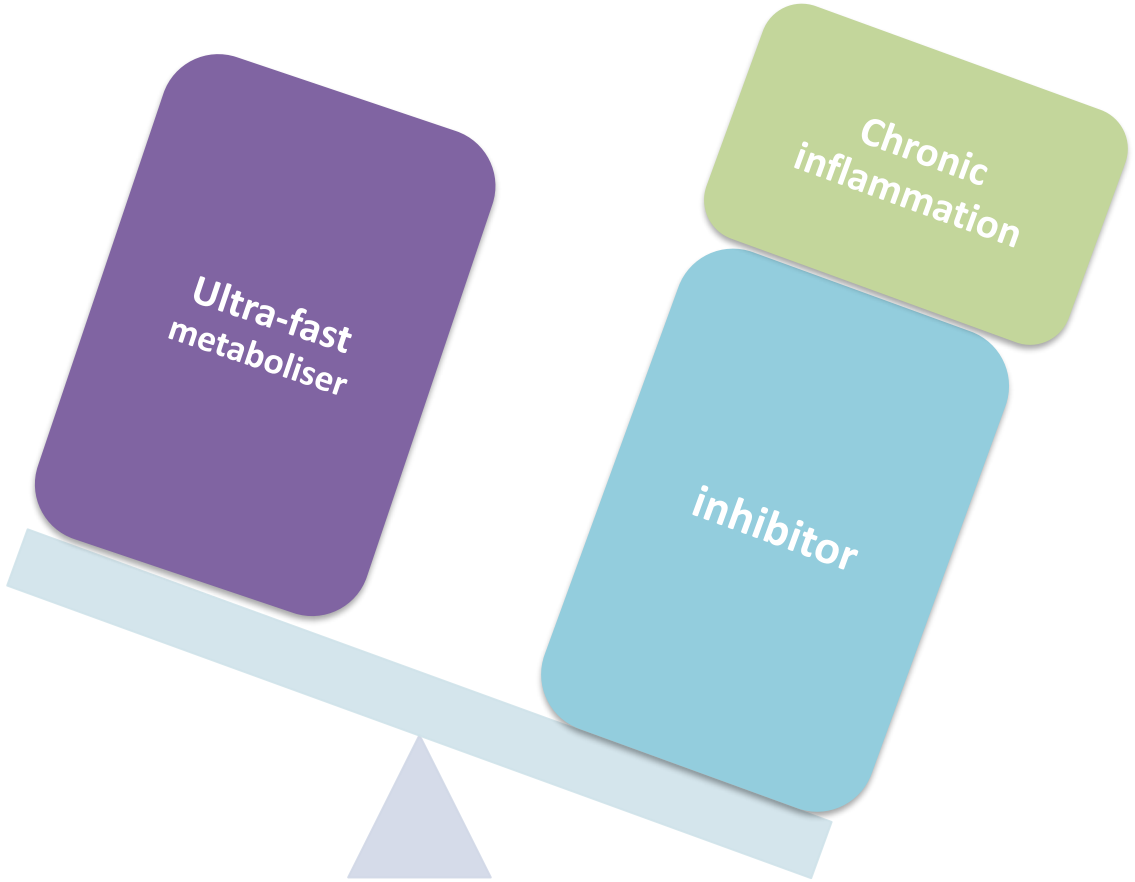
SCHWEIZERISCHE GESELLSCHAFT FÜR KLINISCHE PHARMAKOLOGIE UND TOXIKOLOGIE

Liste de la Société Suisse de Pharmacologie et Toxicologie cliniques (SSPTC) des analyses pharmacogénétiques courantes que peuvent prescrire tous les médecins sans distinction du titre de spécialité :

médicament	gène
abacavir	HLA-B*5701
carbamazépine	HLA-A*3101 et HLA-B*1502
6-mercaptopurine, azathioprine	TPMT
5-FU, capecitabine	DPYD
irinotécan	UGT1A1

CYP450 PHENOTYPING

Reduced activity



Phenoconversion

Discrepancy between genotype-based **prediction** of metabolism and **actual ability** to metabolise drugs due to **non-genetic** factors

Br J Clin Pharmacol. 2015; 79: 222-240.

HOW TO MEASURE CYP ACTIVITY?

Phenotyping

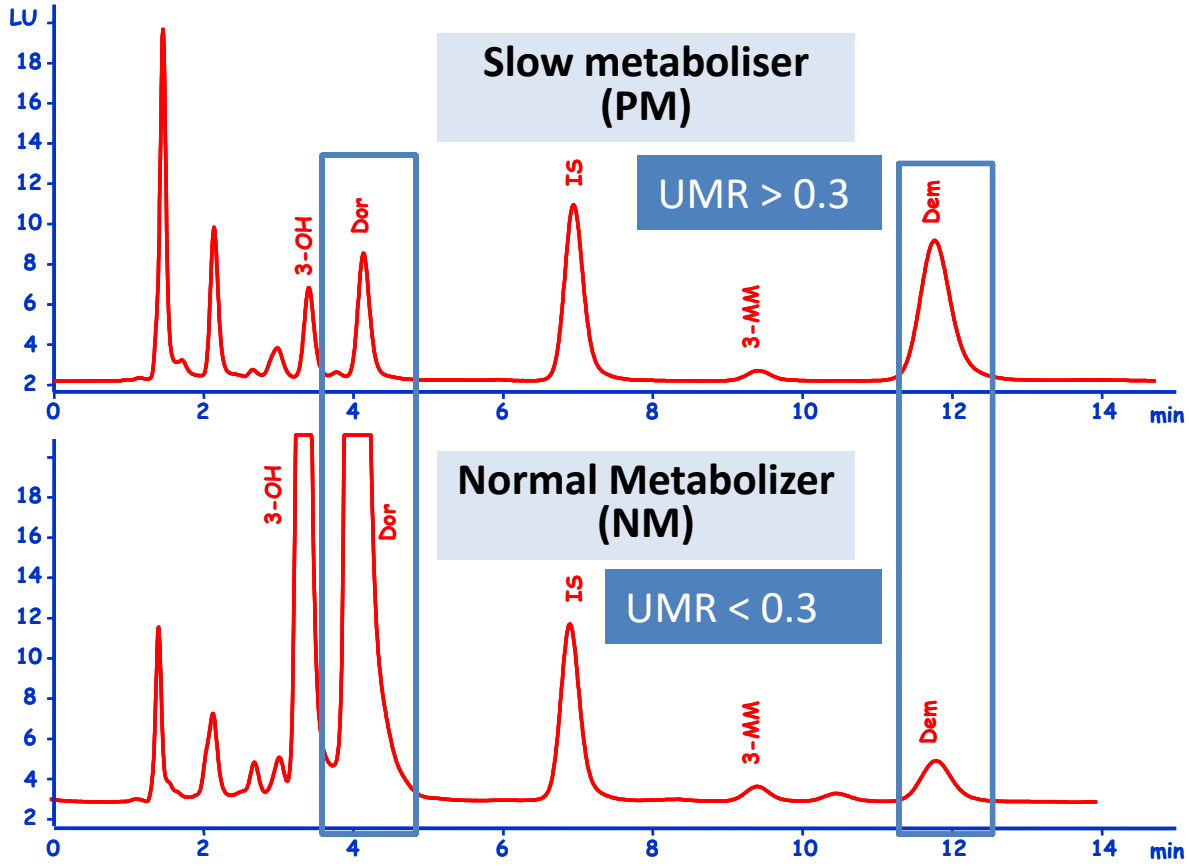
test substrate → **CYP** → **metabolite**

Phenotyping metrics

Ex: metabolic ratio (MR) [substrate]/[metabolite].

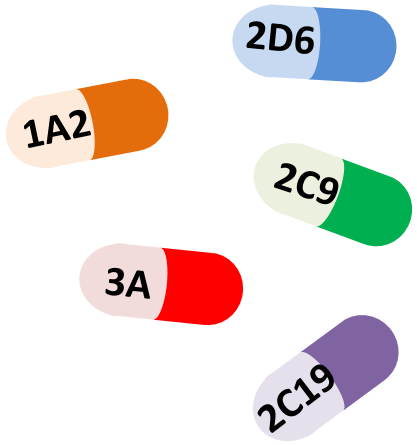
dextrormetorphan (DEM) → **CYP2D6** → **dextrorphan (DOR)**

UMR dextromethorphan (DEM)/dextrorphane (DOR)



PHENOTYPING COCKTAIL

Simultaneous administration of multiple test substrates



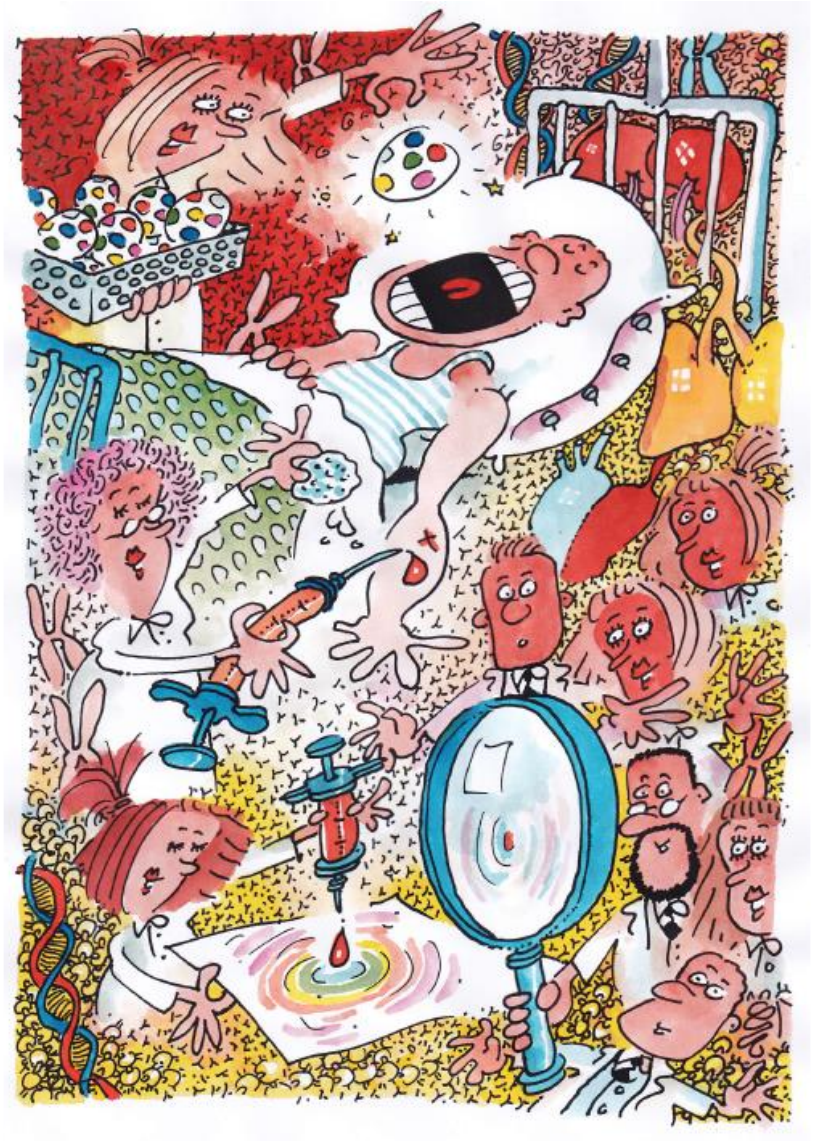
Cocktail

Simultaneous measurement of multiple enzyme activities

+/- drug carriers

CONDITIONS:

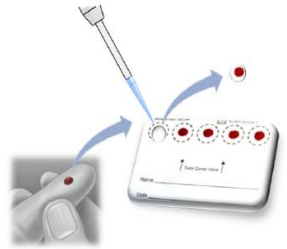
- enzyme-selective substrates
- **no interactions** between substrates



GENEVA COCKTAIL

midazolam (1 mg)
flurbiprofen (10 mg)
dextromethorphan (10 mg)
omeprazole (10 mg)
caffeine (50 mg)
bupropion (25 mg)
fexofenadine (25 mg)

2h
capillary sample



Blotting paper

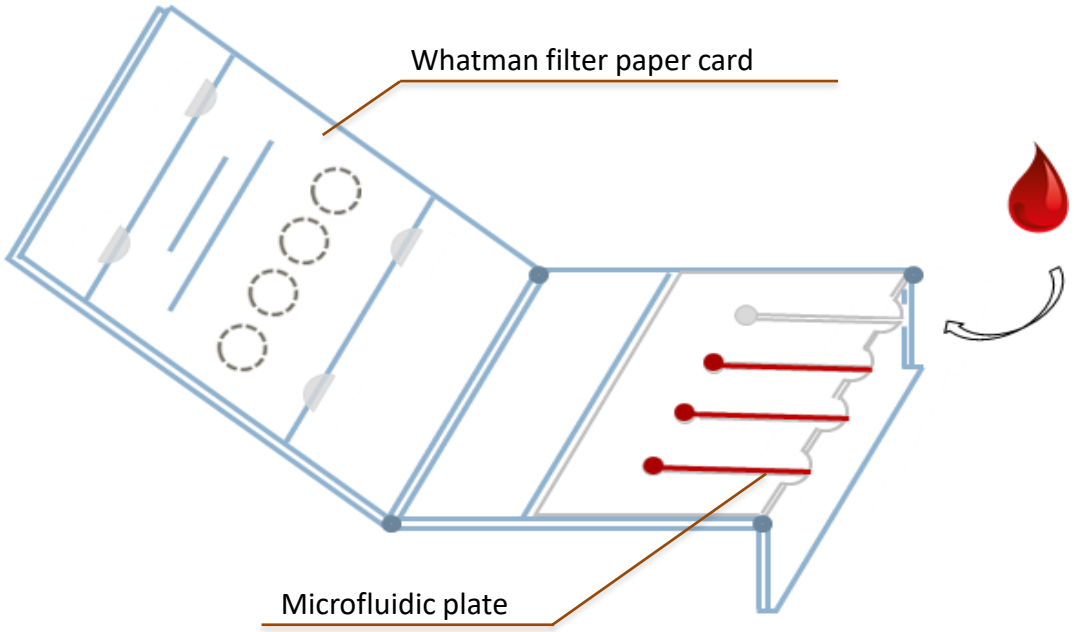
- ✓ Low blood volume (5-10 µl)
- ✓ Simple preparation
- ✓ Sent by post and stable in the air for at least 15 days

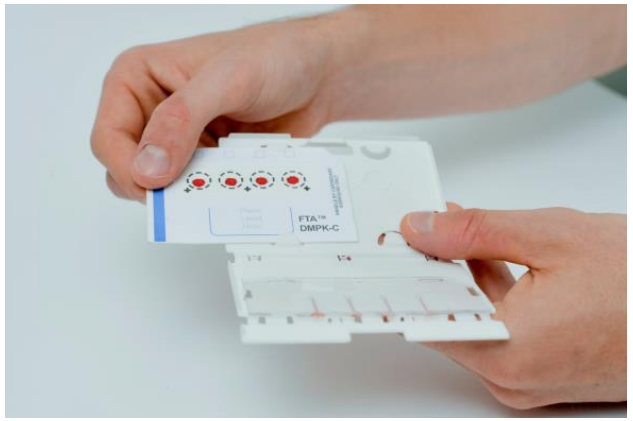
Measuring activity

CYP3A
CYP2C9
CYP2D6
CYP2C19
CYP1A2
CYP2B6
P-gp

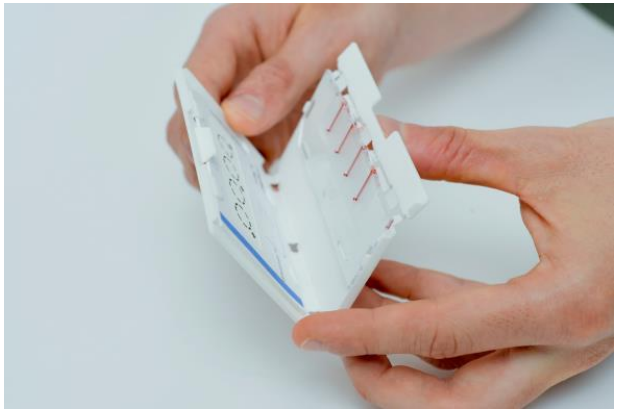
Bosilkovska M, Samer C et al, Clin Pharmacol Ther 2014

i-DBS TECHNOLOGY



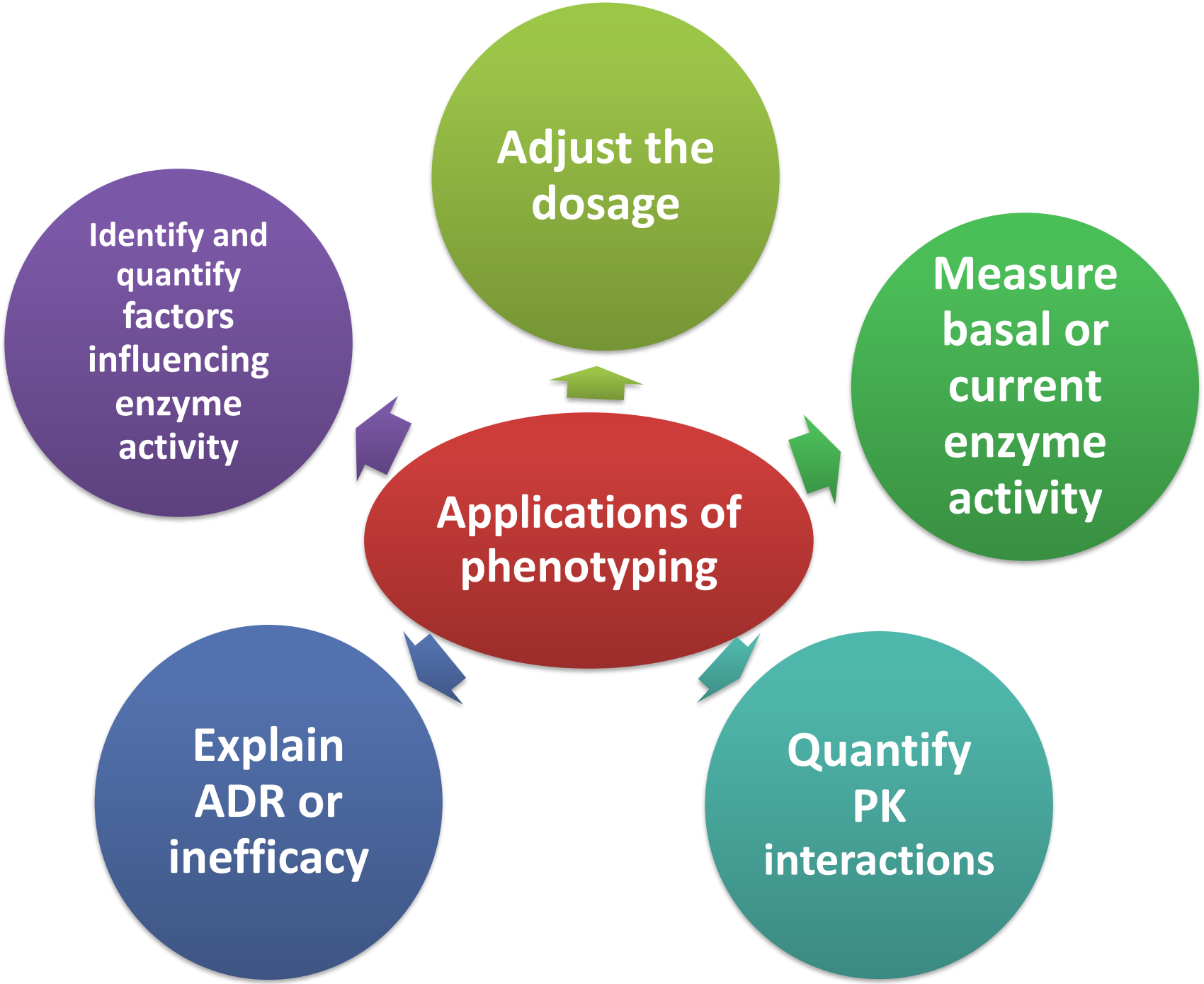


Microfluidic device for self-sampling



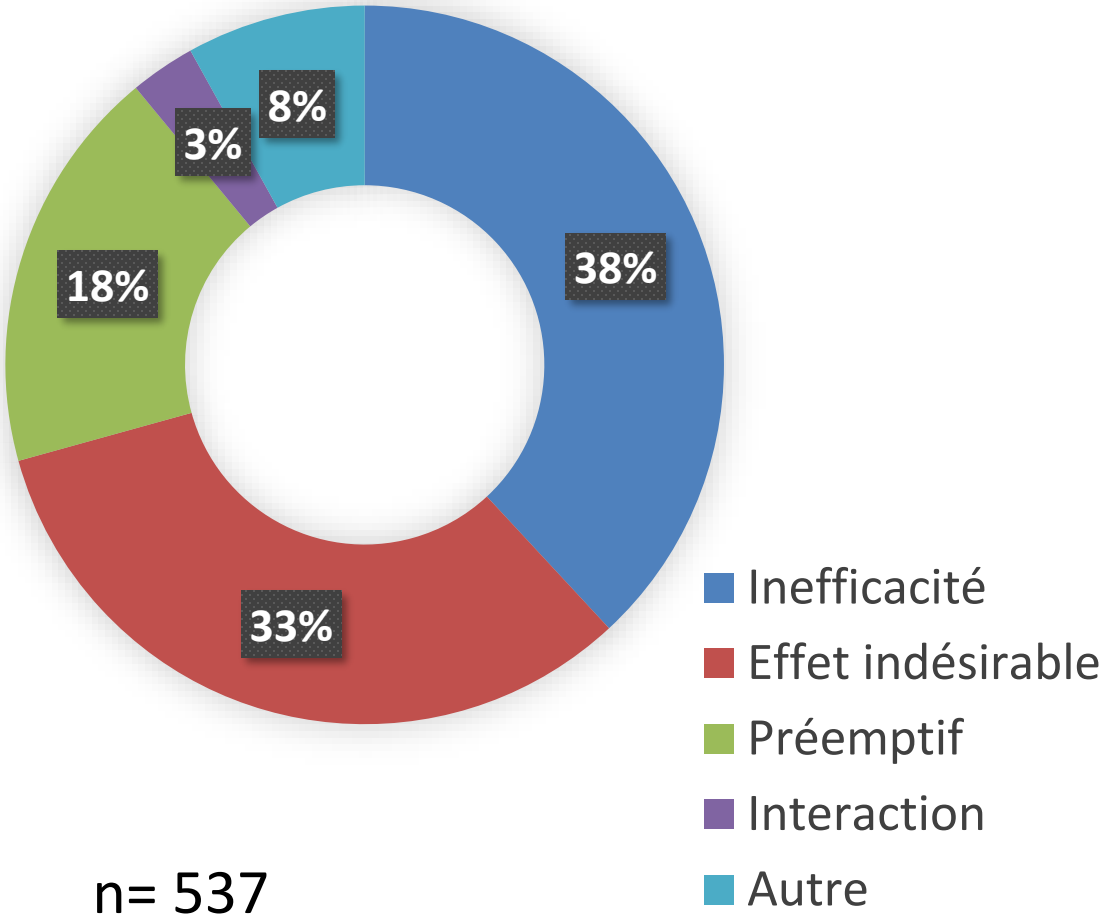
Patent WO/2013/144743 A1
Device and Method for Dried Fluid Spot Analysis

HemaXis DBS System


Adjust the dosage
Identify and quantify factors influencing enzyme activity
Measure basal or current enzyme activity
Applications of phenotyping
Explain ADR or inefficacy
Quantify PK interactions

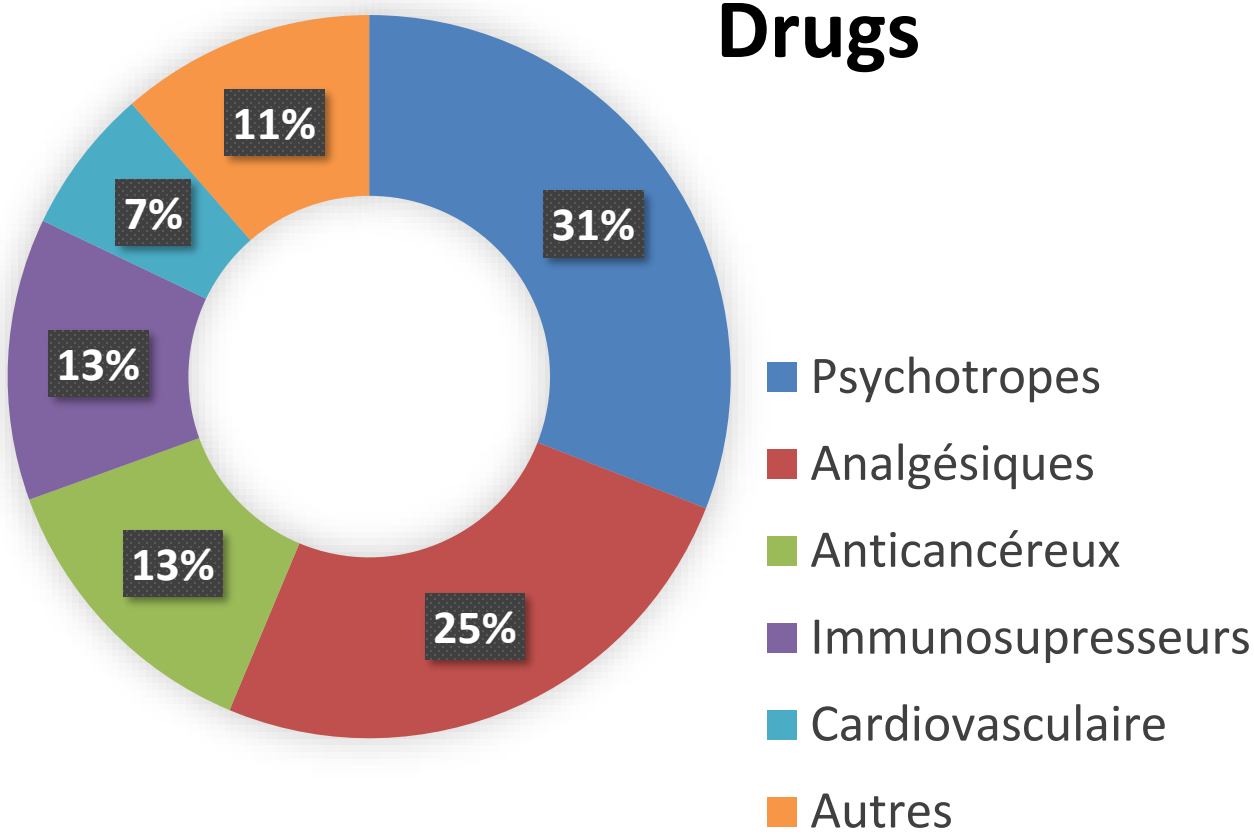
Genotyping and phenotyping at HUG

Indications



n= 537

Drugs

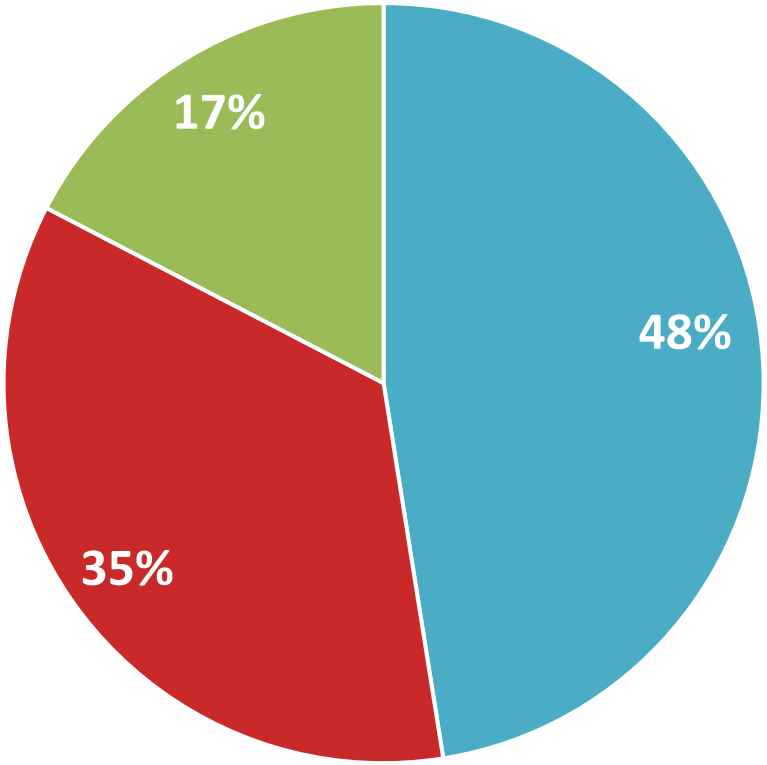


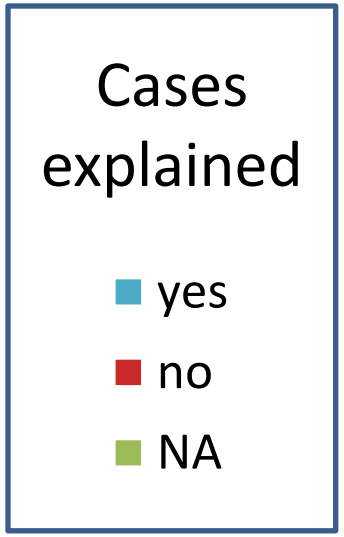
Ing Lorenzini K et al, Frontiers Pharmacol 2021 doi.org/10.3389/fphar.2021.730637

CLINICAL IMPLEMENTATION

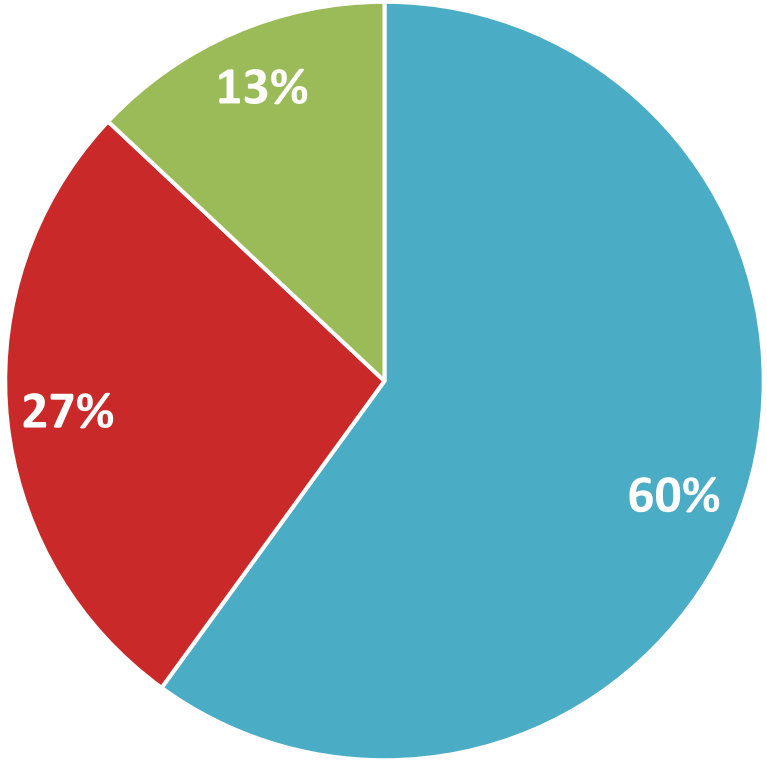
Retrospective analysis 948 patients

genotyping





phenotyping + genotyping



Hôpitaux Universitaires Genève

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

NEJM 2004

Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

Yvan Gasche, M.D., Youssef Daali, Pharm.D., Ph.D., Marc Fathi, Ph.D., Alberto Chiappe, Silvia Cottini, M.D., Pierre Dayer, M.D., and Jules Desmeules, M.D.

Severe and persistent morphine-induced respiratory depression associated with ATP-Binding Cassette Subfamily B Member 1 and catechol-*O*-methyltransferase genetic defects

Eur J Anaesthesiol. 2018

A case report

Gaspard Aebischer, Kuntheavy Ing Lorenzini, Simon Tomala, Jules Desmeules, Youssef Daali and Caroline F. Samer

"Late" Withdrawal Syndrome after Carbamazepine *In Utero* Exposure in a CYP2C9 Slow Metabolizer Newborn

Front Pharmacol. 2017

*Evangelia Passia[1], Nathalie Rock[2], Riccardo E. Pfister[2], Kuntheavy R. Ing Lorenzini[3], Jules Desmeules[3] and Caroline F. Samer[3]**

Rivaroxaban-Induced Hemorrhage Associated with *ABCB1* Genetic Defect

Front Pharmacol. 2016

Kuntheavy Ing Lorenzini[1], Youssef Daali[1], Pierre Fontana[2], Jules Desmeules[1] and Caroline Samer[1]*

AIDS. 2012 Nov 28;26(18):2417-8. doi: 10.1097/QAD.0b013e32835a11ba.

Serotonin syndrome following drug-drug interactions and CYP2D6 and CYP2C19 genetic polymorphisms in an HIV-infected patient.

AIDS 2012

I Lorenzini K, Calmy A, Ambrosioni J, Assouline B, Daali Y, Fathi M, Rebsamen M, Desmeules J, Samer CF.

CLINICAL COMMUNICATION TO THE EDITOR

Am J Med 2021

THE AMERICAN JOURNAL of MEDICINE®

Mixing Drugs and Genetics: A Complex Hemorrhagic Cocktail

"Pharmacogenomics will undoubtedly become a very compelling part of medical practice. The limiting factor right now is that oftentimes, if you are ready to write a prescription, you do not want to wait a week to find out the genotype before you decide whether you've got the right dose and the right drug. But if everybody's DNA sequence is already in their medical record and it is simply a click of the mouse to [find] out all the information you need, then there is going to be a much lower barrier to beginning to incorporate that information into drug prescribing. If you have the evidence, it will be hard, I think, to say that this is not a good thing. And once you've got the sequence, it's not going to be terribly expensive. And it should improve outcomes and reduce adverse events."

—Francis Collins

NIH director

U-PGx | Ubiquitous Pharmacogenomics

Horizon 2020: **15 Mio €**

PREPARE

PREemptive
Pharmacogenetic Testing to
Prevent
Adverse Drug
REactions

OUR FOCUS

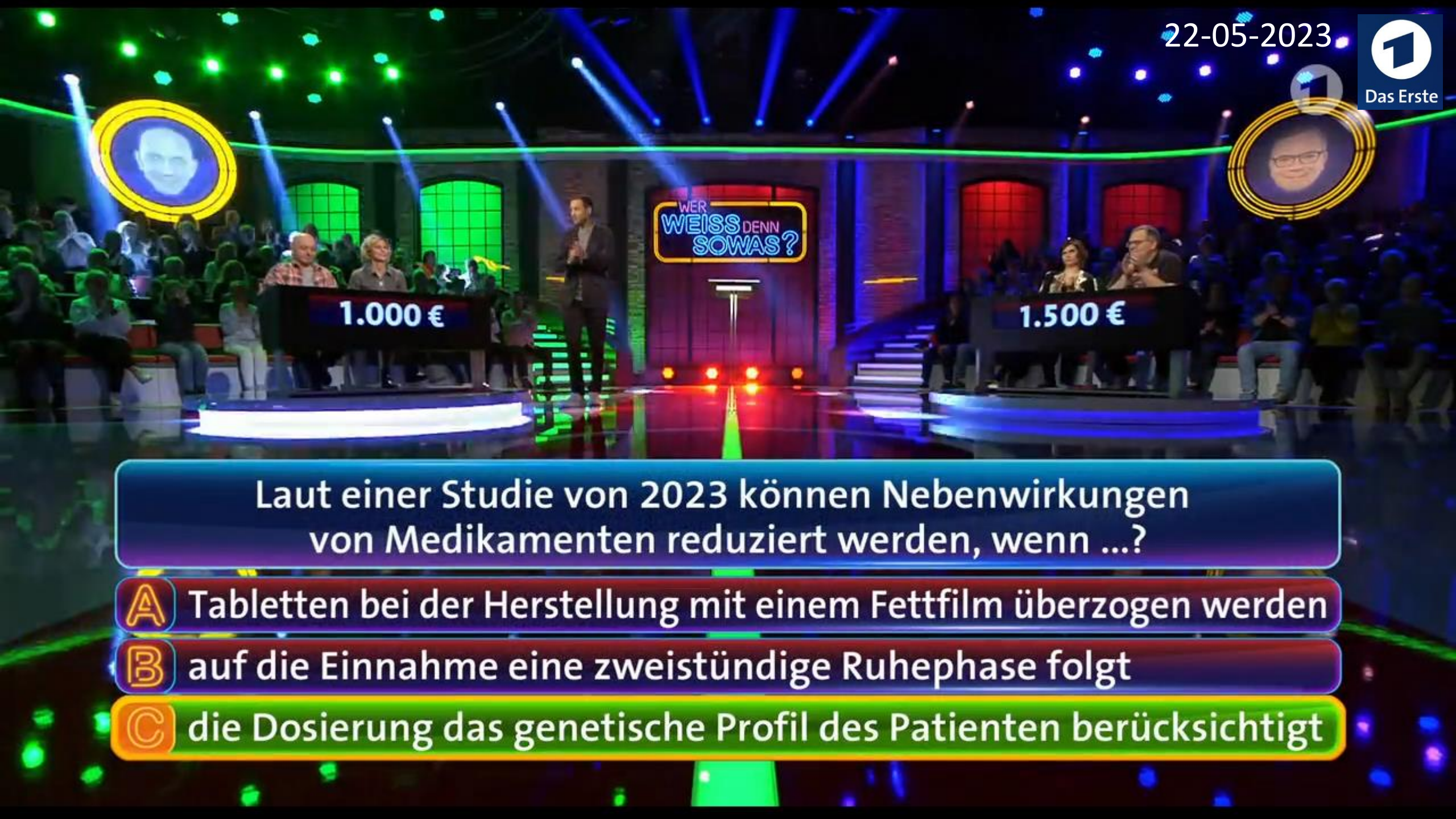
We want to make effective treatment optimization accessible to every European citizen

U-PGx: UBIQUITOUS PHARMACOGENOMICS

THE "PREPARE" CLINICAL STUDY

PHARMACOGENOMICS EDUCATIONAL MATERIAL

PHARMACOGENOMICS GUIDELINES


22-05-2023
Das Erste
WER WEISS DENN SOWAS?
1.000 €
1.500 €
Laut einer Studie von 2023 können Nebenwirkungen von Medikamenten reduziert werden, wenn ...?
A Tabletten bei der Herstellung mit einem Fettfilm überzogen werden
B auf die Einnahme eine zweistündige Ruhephase folgt
C die Dosierung das genetische Profil des Patienten berücksichtigt

A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Lancet 2023; 401: 347–56

- International multicenter, randomized, cluster-controlled, crossover study (Austria, Greece, Italy, Netherlands, Slovenia, Spain and UK).
- Genotype-guided drug treatment (n=3342) vs standard care (n=3602)
- Pharmacogenetic panel of 12 genes (50 SNPs)
- Clinically relevant adverse events : 21% vs 28% (OR 0·70 [95% CI 0·61–0·79]; p <0·0001)

-> **<u>Reduces adverse effects by 30%.</u>**

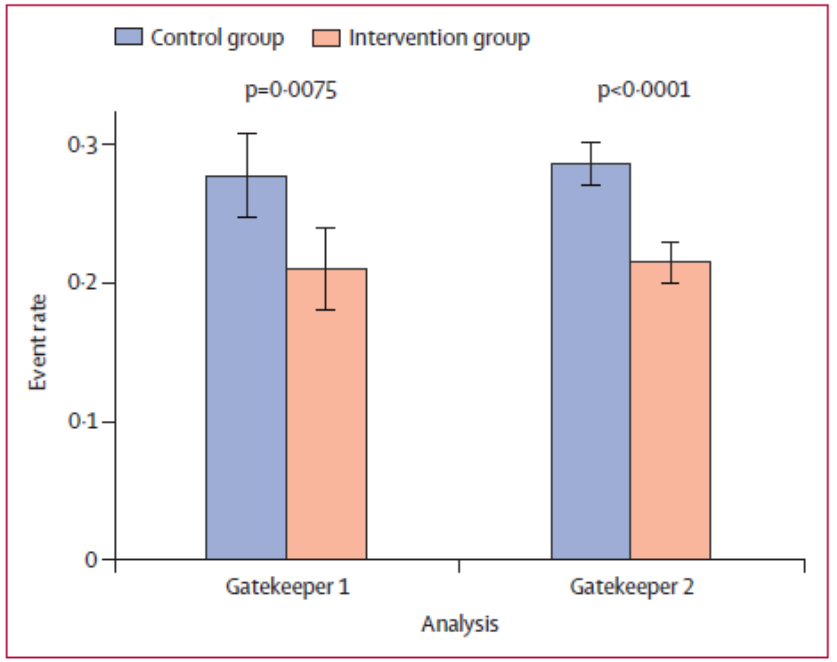


Figure 2: Frequency of causal clinically relevant adverse drug reactions in patients with an actionable test result

Swen J et al, Lancet 2023, 401: 346-56.

Clinical trials: rephrasing the questions

- Does the intervention work in the general population?
- Is the intervention beneficial or harmful for particular patients?
- Is it useful to consider genotype?

CLINICAL RESEARCH AND PRECISION MEDICINE

Designing clinical trials **strategically** to **increase the information** obtained from each study:

- ✓ Testing **specific subgroups** and **identifying populations likely to respond** to treatment to demonstrate efficacy in fewer subjects (a priori genetic screening, enrichment strategies)
- ✓ Demonstrate benefits **without exposing non-responders**
- ✓ **Identify and understand *outliers*** (plasma concentrations or clinical response)

Shi MM et al, Drug Metab Disp 2001, 29: 591-5.

STUDY DESIGNS AND BIOMARKERS

Retrospective

Examples:

- Approved but less favourable benefit-risk ratio than competitor
- Nested study nested within a completed controlled trial

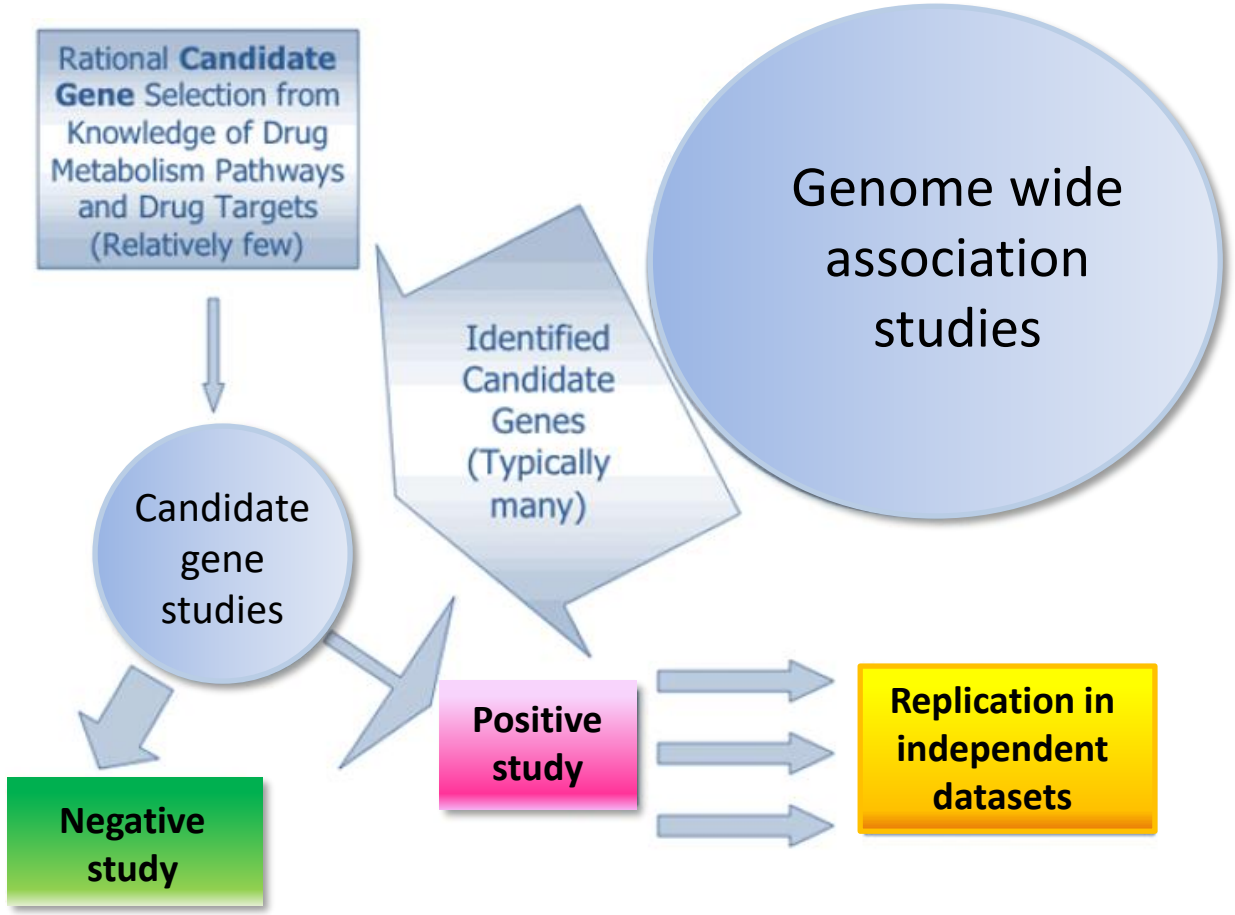
Wang SJ, Pharmaceut Statist 2007, 283-96.

STUDY DESIGNS AND BIOMARKERS

Prospective

- Key question: Is there a genomic biomarker present at baseline that can be used to predict therapeutic effect?
- Enrichment design: genomic marker used to exclude patients (requires a validated diagnostic test)

Wang SJ, Pharmaceut Statist 2007, 283-96.



Candidate Gene Studies	Genome-Wide Studies
Rational selection of genes for study increases biological plausibility of findings, however novel genes cannot be identified.	Analysis of whole genome allows identification of genes not previously known to be important in response to drug.
Limited number of genes reduces possibility of false discovery.	Large number of analyses means significant risk of false discovery.
Expense reduced if candidate genes selected prove to be relevant to outcome.	Increased expense following up on large number of positive findings.
Moderate sample size may be adequate.	Large sample sizes are needed because of the large number of comparisons made.

COMPANION DIAGNOSTICS TESTS

- Based on biomarkers developed in parallel with the targeted drug development process = model for **co-development** of drug diagnostics.
- Provide essential information for patient classification, and anticipation of effects and adverse events.
- The marketing of predictive biomarker tests is increasing significantly.

INFORMATION IN THE PACKAGE LEAFLETS OF MEDICINES

- Inform prescribers about the impact (or lack thereof) of genotype on treatment response
- Indicate whether a genomic test is available and, if so, indicate whether a test
  - should be considered
  - is recommended
  - is necessary

Section of Label	Types of Information
INDICATIONS AND USAGE	PGx information related to proper patient selection (e.g., the need for PGx testing)
DOSAGE AND ADMINISTRATION	Dosing recommendations for subgroups of patients based on genetic makeup
BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and/or ADVERSE REACTIONS	PGx information affecting drug safety
WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULATIONS	Genotype(s) that are known to be associated with an adverse reaction in a specific population
DRUG INTERACTIONS	Relevant information concerning the role of genetic variations in drug-drug interactions, and the clinical consequences of the combination of genetic polymorphisms in protein(s) in the context of the drug's metabolism, transport, and action
CLINICAL PHARMACOLOGY	PGx impact on PK or PD
CLINICAL STUDIES (if studied and the evidence is substantial; or if observed neutral findings (i.e., lack of a pharmacogenetic effect) would be pertinent clinical information)	Efficacy differences related to PGx

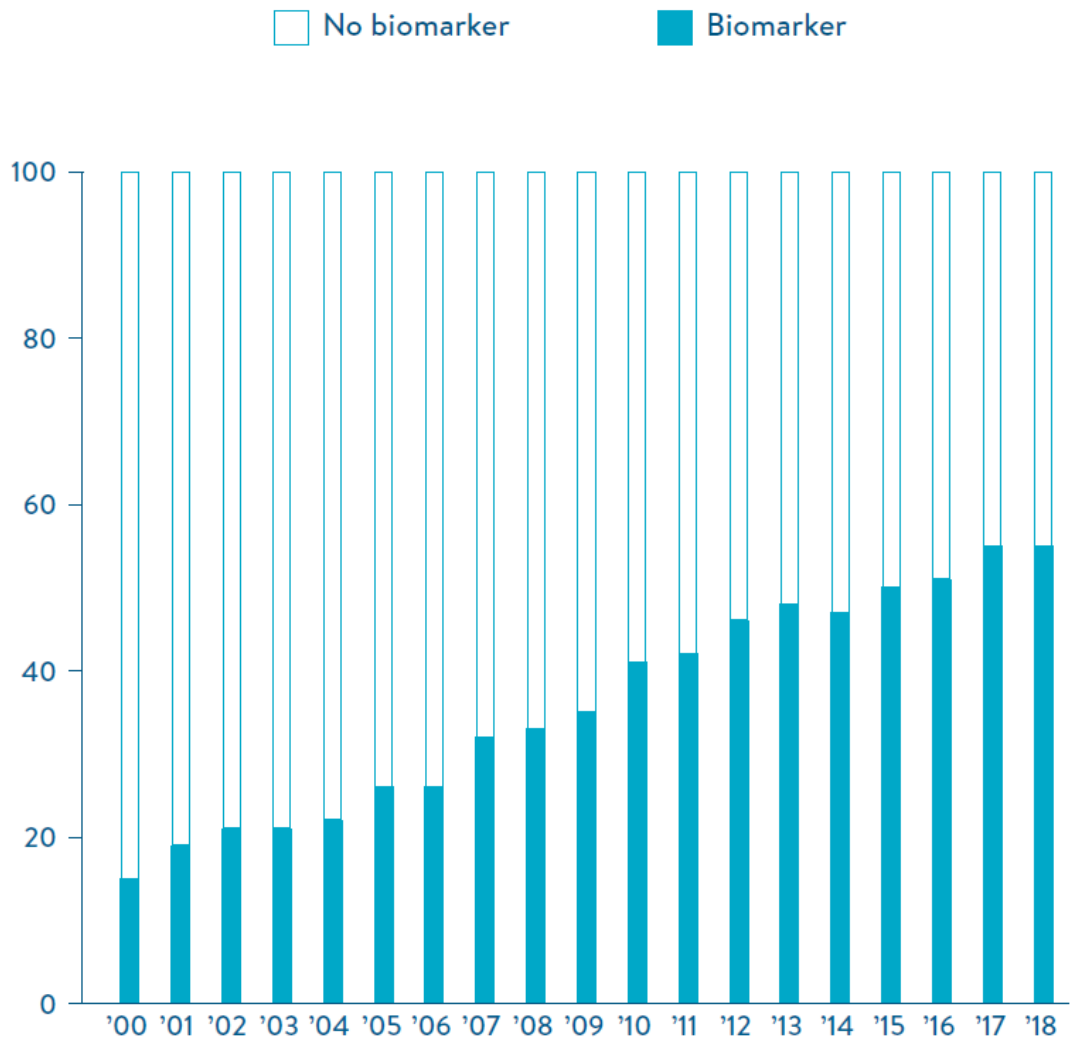
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf

PGX BIOMARKERS ON DRUG PACKAGE INSERTS (FDA)

Biomarker	Drug	Test required	Label Sections
ALK	Crizotinib		Indications and Usage, Warnings and Precautions
BRAF	Vemurafenib		Indications and Usage, Warning and Precautions
JRC5	Maraviroc	YES	Indications and Usage, Warnings and Precautions
CD20 antigen	Tositumomab		Indications and Usage
c-Kit	Imatinib	YES	Indications and Usage
CYP2C9, VKORC1	Warfarin		Dosage and Administration, Precautions
DPD	Capecitabine, Fluorouracil		Contraindications
EGFR, KRAS	Cetuximab, Panitumumab	YES	Indications and Usage, Warnings and Precautions
ER	Fulvestrant, Tamoxifen	YES	Indications and Usage
ER/PGR	Exemestane, Letrozole	YES	Indications and Usage
ERBB2 (HER2)	Everolimus, Lapatinib, Pertuzumab, Trastuzumab*	*YES	Indications and Usage
G6PD	Rasburicase		Contraindications
HLA-B*5701	Abacavir	YES	Contraindications
Ph Chromosome	Dasatinib, Nilotinib, Imatinib		Indications and Usage
TPMT	Mercaptopurine, Thioguanine		Dosage and Administration, Contraindications/precautions

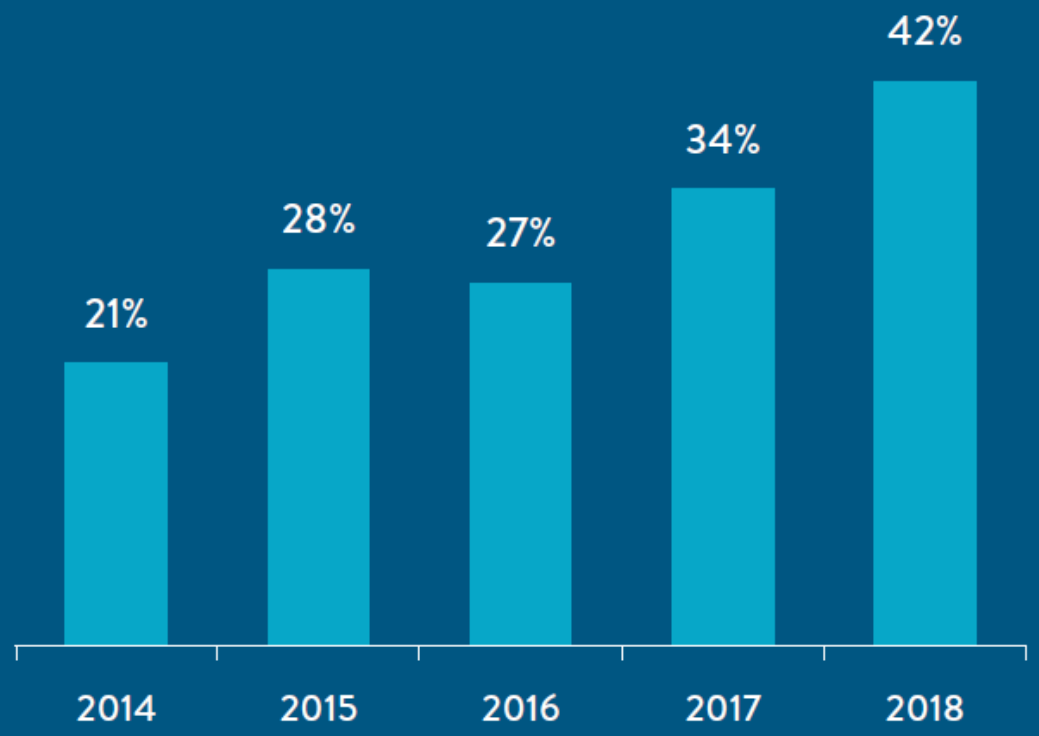
55% of oncology studies involved the use of biomarkers in 2018 compared to **15%** in 2000

FIGURE 1A: Percentage of oncology trials, by use of biomarkers (2000–2018)



Sources: AACT; L.E.K. biomarker database

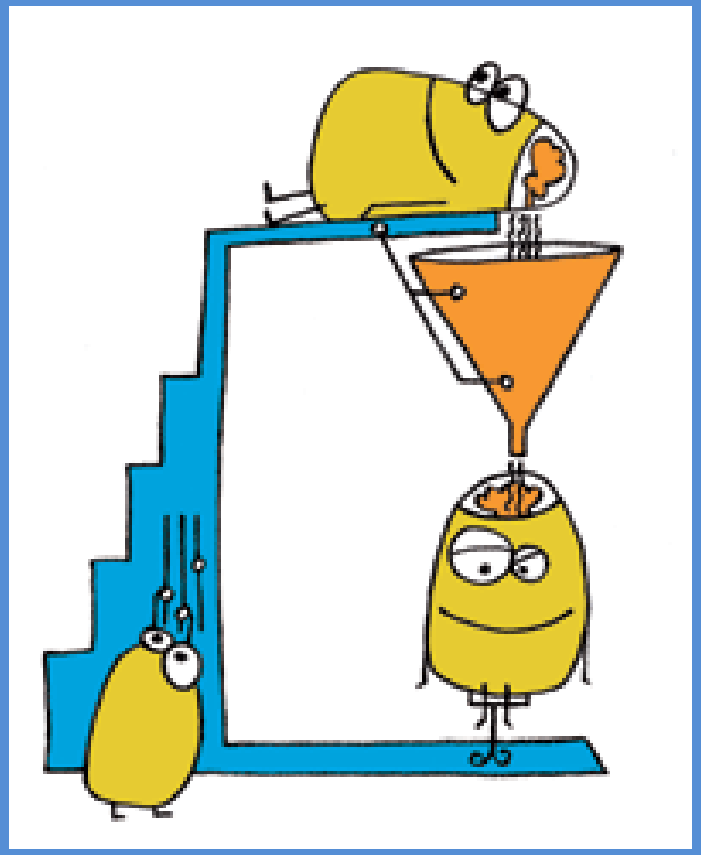
Personalized Medicines Top 30% of FDA Approvals for Second Year in a Row



Methodology: PMC defines personalized medicine as an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans. When evaluating NMEs, PMC categorizes personalized medicines as those therapeutic products for which the label includes reference to specific biological markers, identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients.

42% of drug approvals (n=25) by the FDA in 2018

PHARMACOGENOMIC KNOWLEDGE



Interest of doctors
98% of doctors believe that pharmacogenomics could help them better predict response to treatment

But... lack of knowledge
Only 10% of doctors consider their knowledge and available tools to be adequate

Stanek E et al, Clin Pharmacol Ther 2012, 91:450-8.

PHARMacoGenomicsKnowledgeBase

PharmGKB

Online resource compiling knowledge on the impact of genetic variation on drug response for clinicians

Clinical

CLINICAL GUIDELINE ANNOTATIONS	188
DRUG LABEL ANNOTATIONS	822
FDA DRUG LABEL ANNOTATIONS	391
CLINICAL ANNOTATIONS	5,007

Research

PATHWAYS	194
VIPs (Very Important Pharmacogenes)	68
VARIANT ANNOTATIONS	25,593
ANNOTATED DRUGS	745

DPWG
Dutch Pharmacogenetics Working Group

CPIC
Clinical Pharmacogenetics Implementation Consortium

Canadian Pharmacogenomics Network for Drug Safety

https://www.pharmgkb.org

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This course will provide you with the key knowledge and tools to understand the fundamentals and practical implications of precision medicine, its opportunities and challenges. It will address precision-medicine era diagnostics, treatment selection, genetic counseling, public health interventions, and biomedical research. It will also deal with data science and ethical issues.

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Antoine Geissbuhler
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Idris Guessous
Professor, Head of Division
Division of Primary Care Medicine

Caroline Samer
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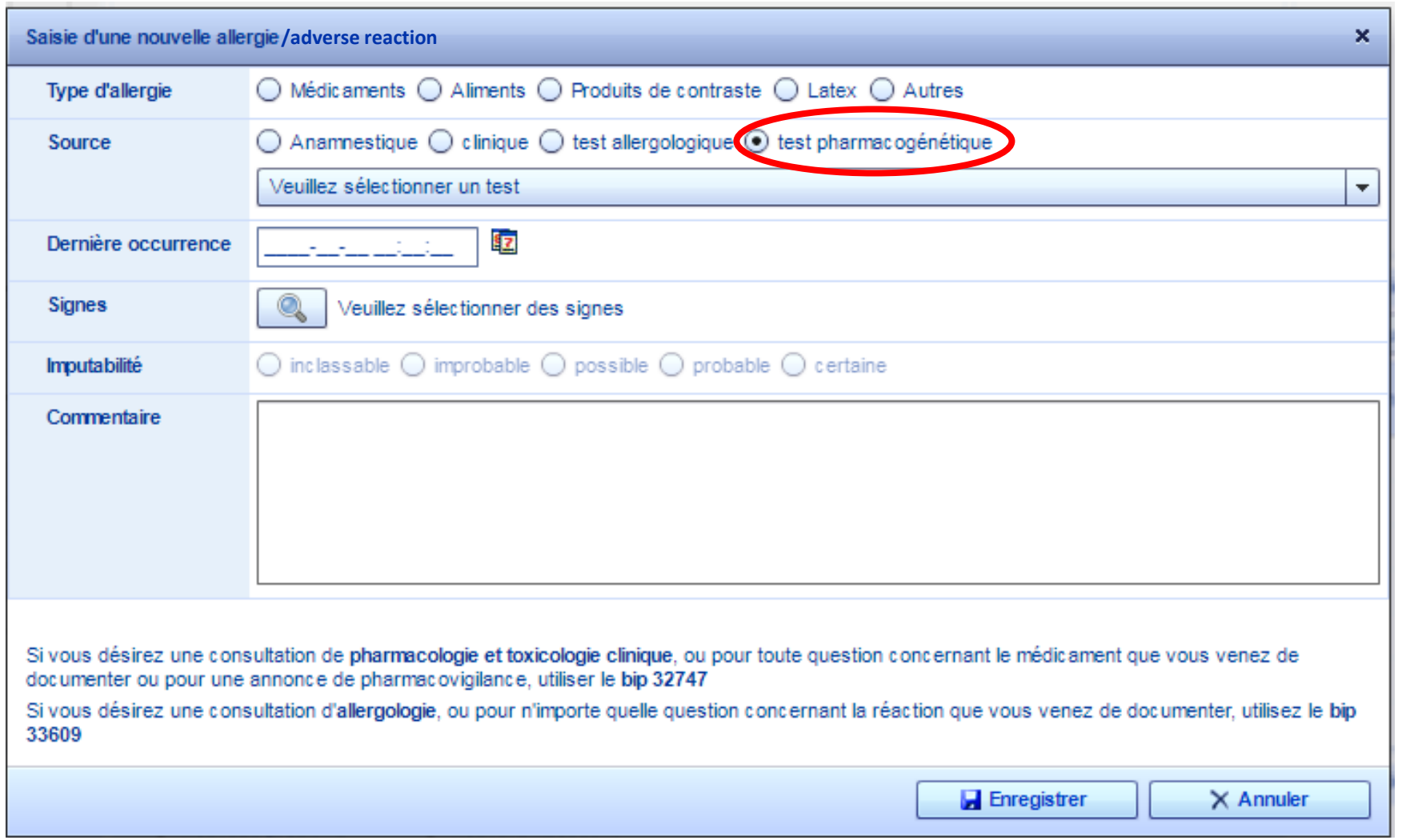
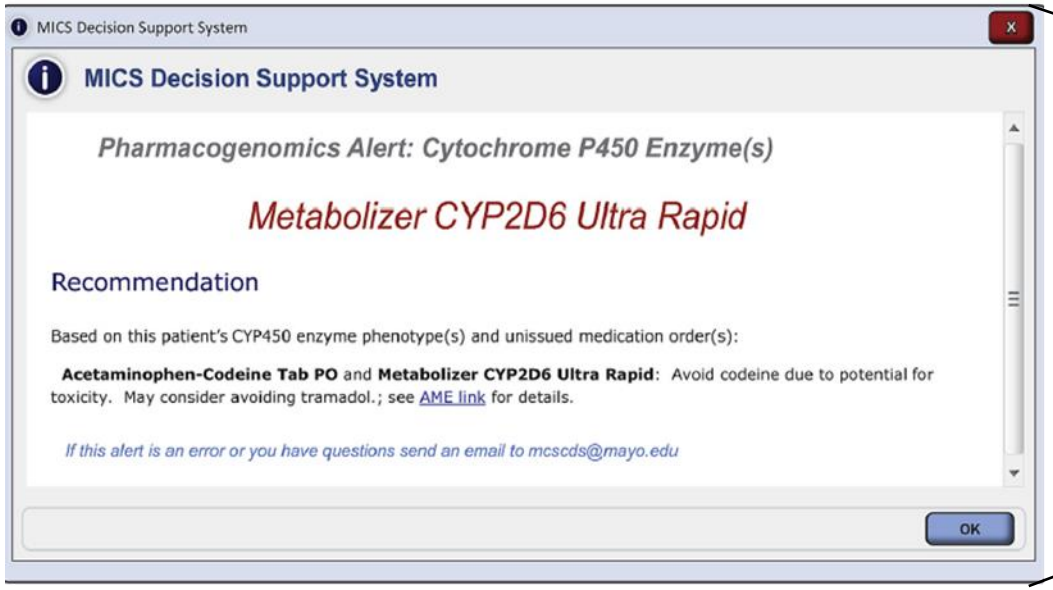
Dossier Patient Intégré
Hôpitaux Universitaires Genève

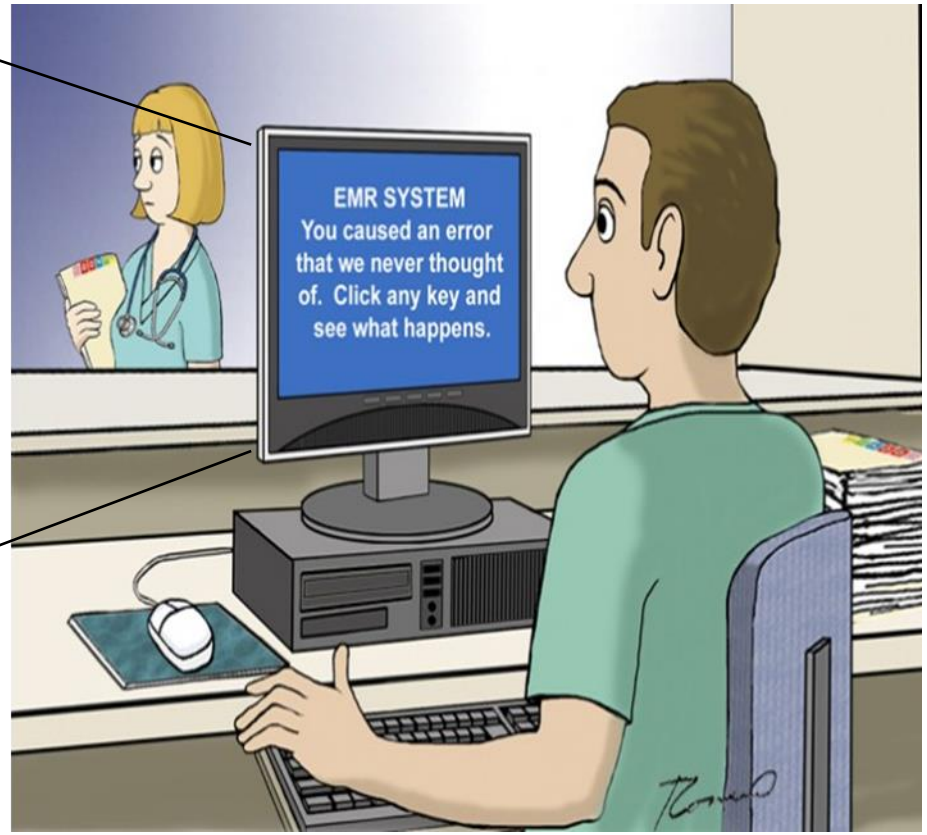
MEDICAL HEALTH RECORDS



DPA PdG R C T VG P Pb NdS NdS2 F F2 Lab Img RD EC2 EC DI RAO PS E VCS TC

CLINICAL DECISION SUPPORT TOOLS





Inclusion of pharmacogenetic data in electronic medical records (clinical decision support tools)

Informations pratiques

Consultation sur rendez-vous

Unité de pharmacogénomique et thérapies personnalisées
Secrétariat
☎ 022 372 99 33

Horaire

Du lundi au vendredi, de 8h à 12h

Réf. 47 9932 • D-MA • Des traitements personnalisés • Novembre 2019
Photo: Julien Gregorio, Dessin: Simon Tschopp

Service de pharmacologie et toxicologie cliniques
Bâtiment Louise Morier
Rue Gabrielle-Perret-Gentil 4
1205 Genève

Accès

Tram 12, 18,
arrêt « Augustins »

Bus 1, 5, 7, 35,
arrêt « Hôpital »

Léman Express,
arrêt « Genève-Champel »

Parkings

H-Cluse et H-Lombard

Cette brochure, testée auprès des patient·e·s, a été réalisée par le Service de pharmacologie et toxicologie cliniques en collaboration avec le Groupe d'information pour les patient·e·s et les proches (GIPP).

INFORMATION TO PATIENTS

HUG Hôpitaux Universitaires Genève

Pharmacogenomic profile

Last name, First name:

Genotype: CYP 2D6 *5/*4

Phenotype: slow metabolizer CYP2D6

Turn over the card for more information

If you have any questions, please contact the Pharmacogenomics and Personalised Therapy Unit,
Clinical Pharmacology and Toxicology Department,
University Hospitals of Geneva

Tel. 022 372 99 [illegible]6 - Fax 022 372 99 45

Be careful when using the following medicines:

Antidepressants: selective and non-selective serotonin reuptake inhibitors, tricyclics
Antipsychotics: aripiprazole, haloperidol, risperidone, zuclopenthixol
Beta-blockers: metroprolol, carvedilol
Opioids: codeine, oxycodone, tramadol
Miscellaneous: atomoxetine, ondansetron, tamoxifen

Drug information and dosage

INFORMATION TO PATIENTS

HUG Hôpitaux Universitaires Genève

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Genotype: CYP 2D6 *5/*4

Phenotype: slow metabolizer CYP2D6

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Clinical Pharmacology and Toxicology Department,
University Hospitals of Geneva

Tel. 022 372 99 36 - Fax 022 372 99 45

"This is my pharmacogenomic profile!

From pharmacogenomics to pharmaco-omics – individualized care for every patient

Pharmacogenetics

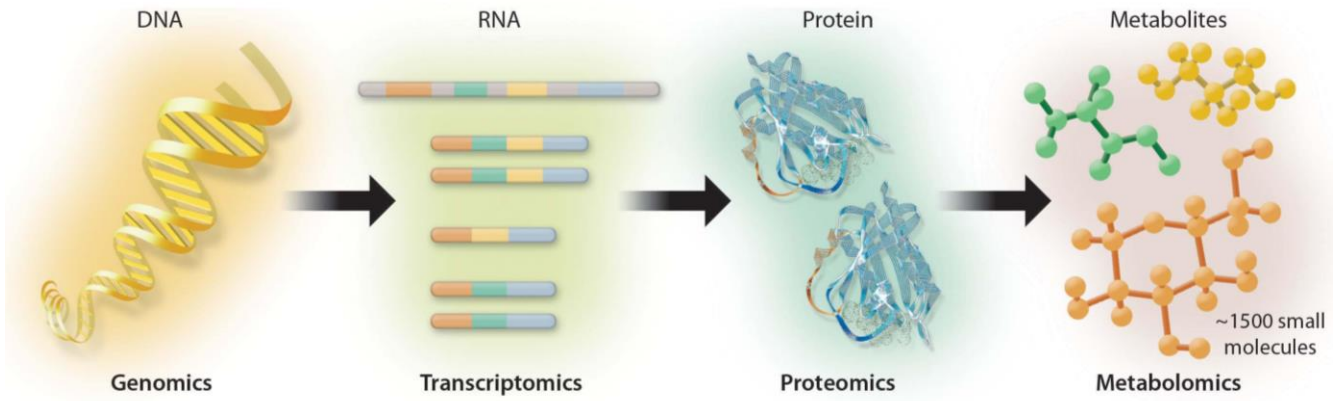
- Reactive observational studies
- Family-based studies
- Candidate gene studies
- Randomized controlled trials

Pharmacogenomics

- Genome-wide association studies
- High-throughput sequencing
- Population comparative studies
- High-throughput functional validation

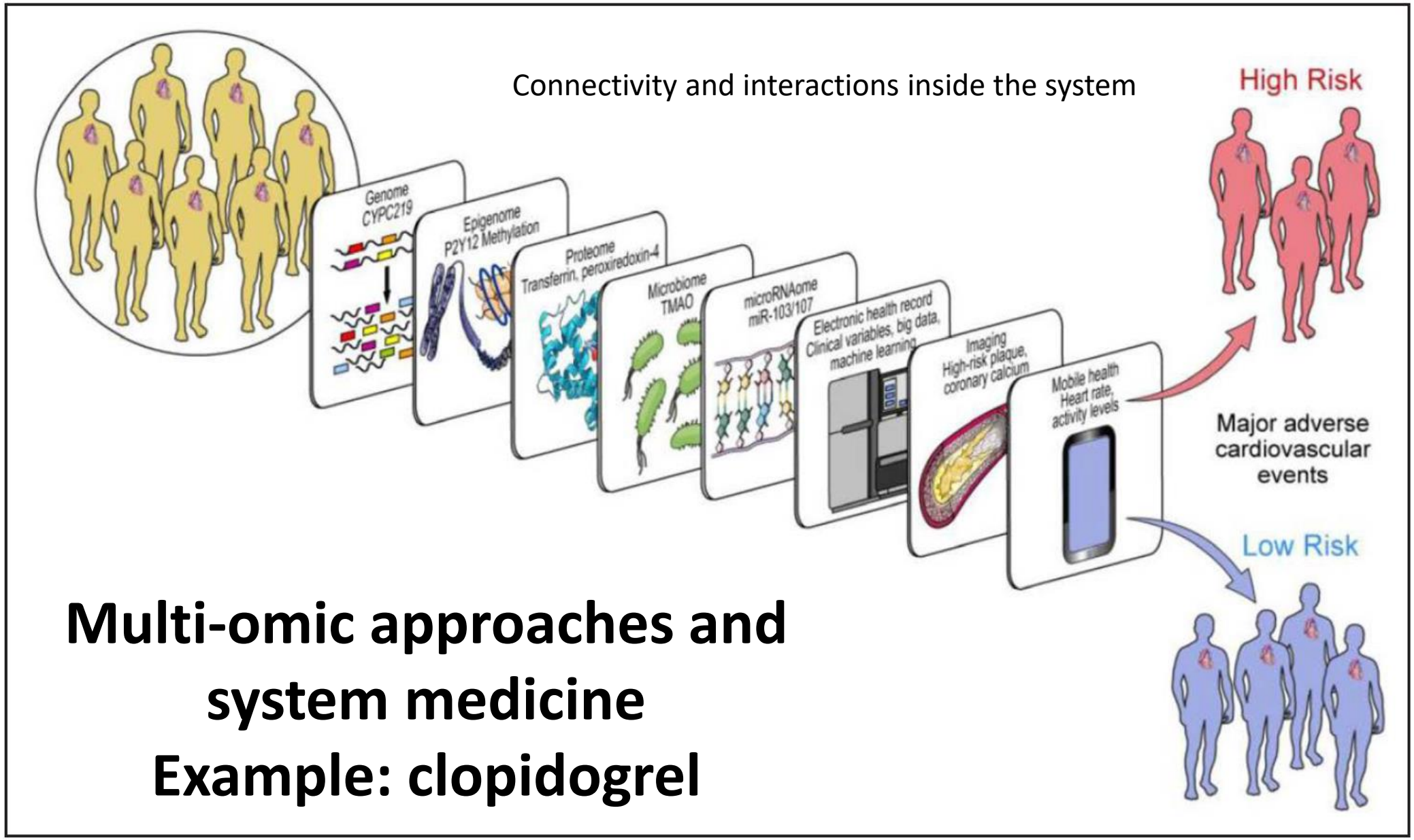
Pharmaco-omics

- Electronic health records
- Transcriptome, proteome, metabolome, epigenome
- Machine learning
- *In silico* approaches



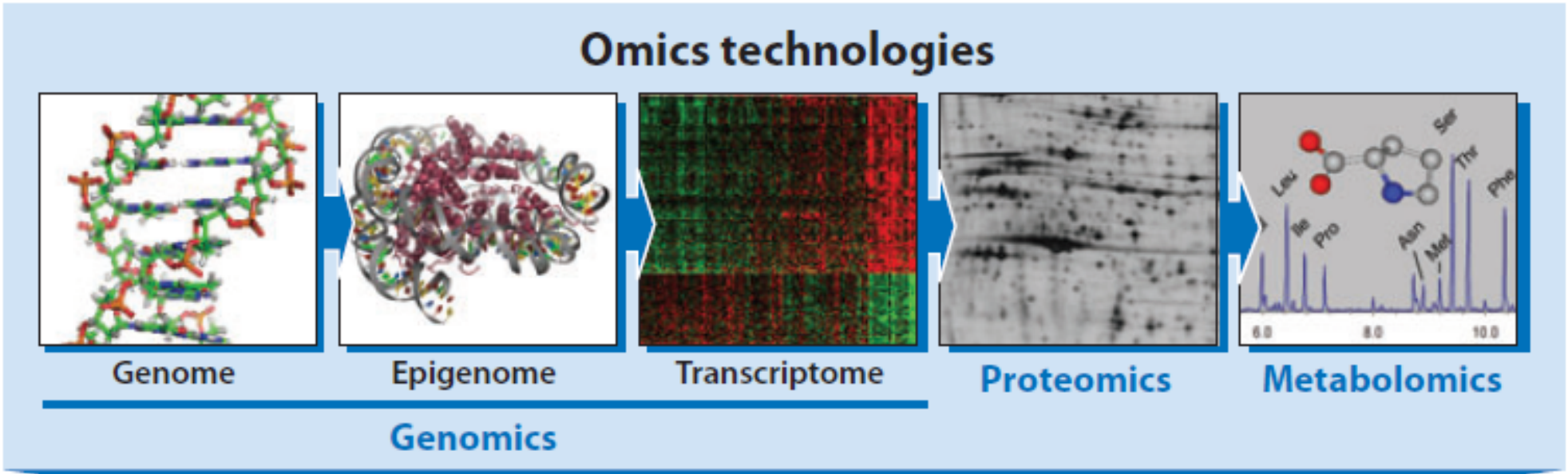
Auwerx C et al, HGG Advances 2022

Weinshilboum R. Mayo Clin Proc. 2017;92:1711-22



Multi-omic approaches and system medicine
Example: clopidogrel

Brown SA, Pereira N, J Pers Med 2018, doi: 10.3390/jpm8010008



BIOMARKERS

Family history
Medical history

Predicted drug-response profile

Assigned diagnosis
Comorbidities
Lab values
Medications (DDI)
Lifestyle (smoking, alcohol, exercise, nutrition, etc)
Microbiome

Electronic health record database
Therapeutic decision-support tools

Treatment decision

Meyer UA, Annu Rev Pharmacol Toxicol 2013

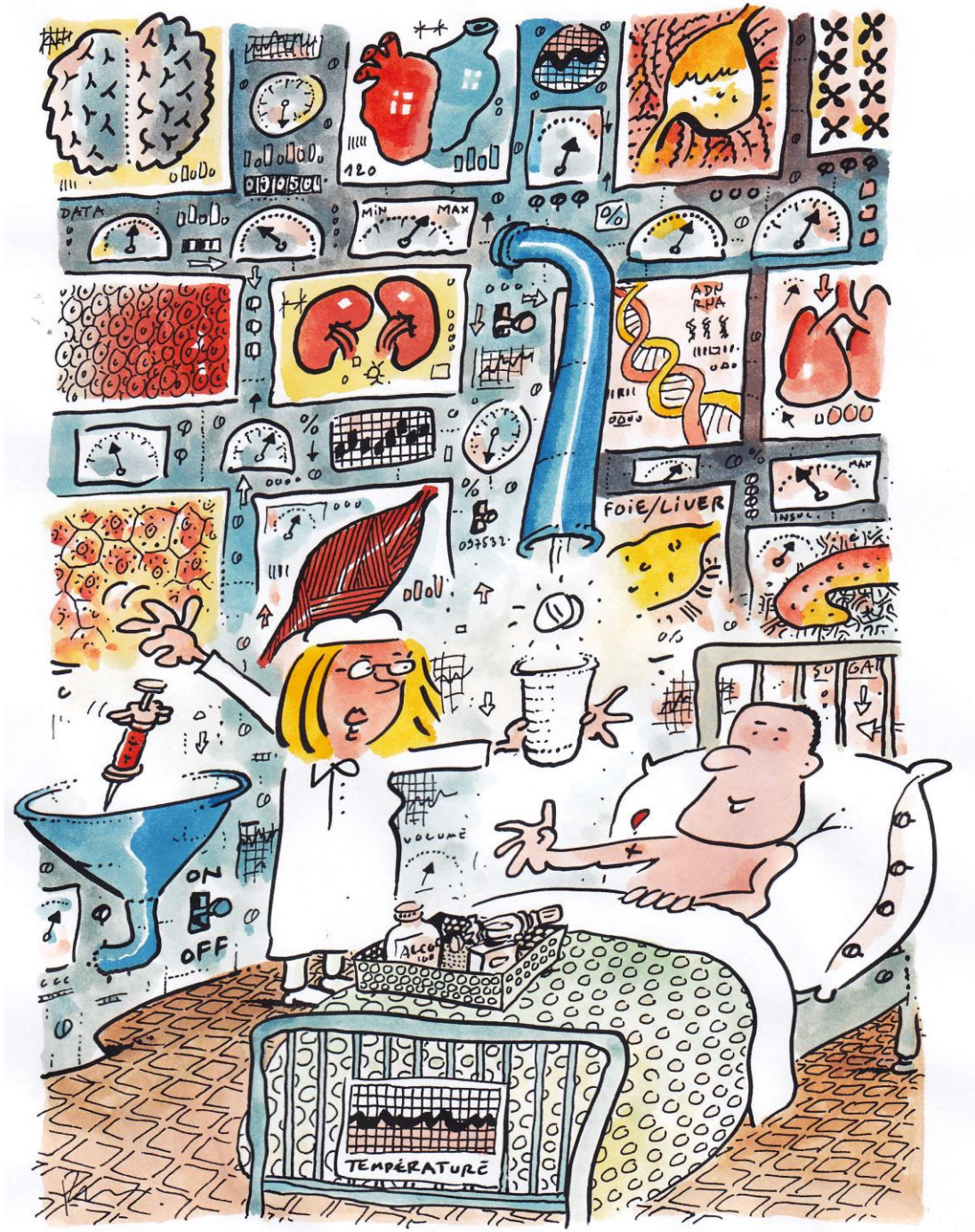
CONCLUSIONS

- ✓ A **better understanding of the** etiology of diseases :
  «The right medicine for the right disease»
- ✓ More efficient **drug development** -> design of specific clinical trials
- ✓ Better prediction of toxicity and efficacy, **therapeutic individualisation**
- ✓ Less **"trial and error"** -> Choice of drug and dose
- ✓ **Drug labelling** -> contraindications, warnings, recommendation for genetic testing
- ✓ **Diagnostic tools** available (phenotyping, genotyping) to allow assessment of genes and environment

OUTLOOK

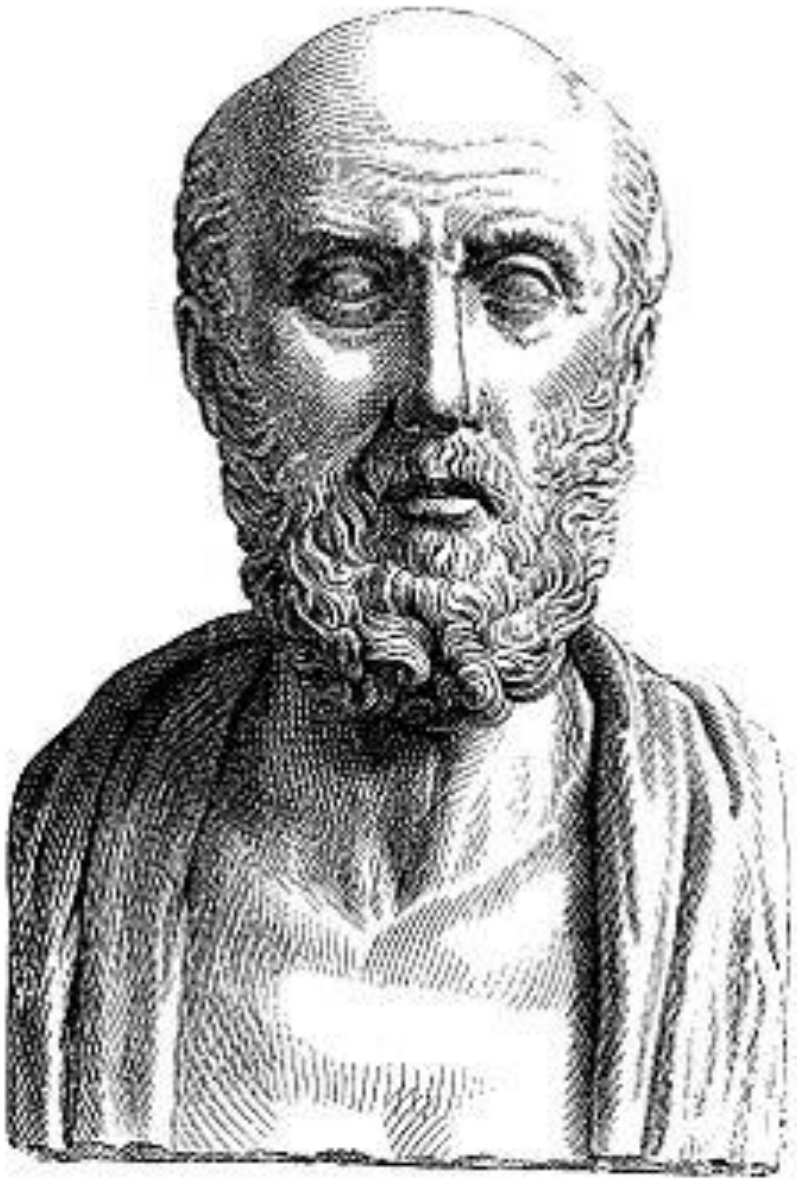
- ✓ Discovery of new genes and new therapeutic targets (GWAS, whole genome sequencing)
- ✓ Assessment of interactions between genes, diseases and environment
- ✓ Cost-effectiveness evaluations (clinical validity and utility)
- ✓ Raise awareness among physicians and patients (education, clinical decision support tools) to increase clinical implementation

La Clairvoyance
René Magritte
1936



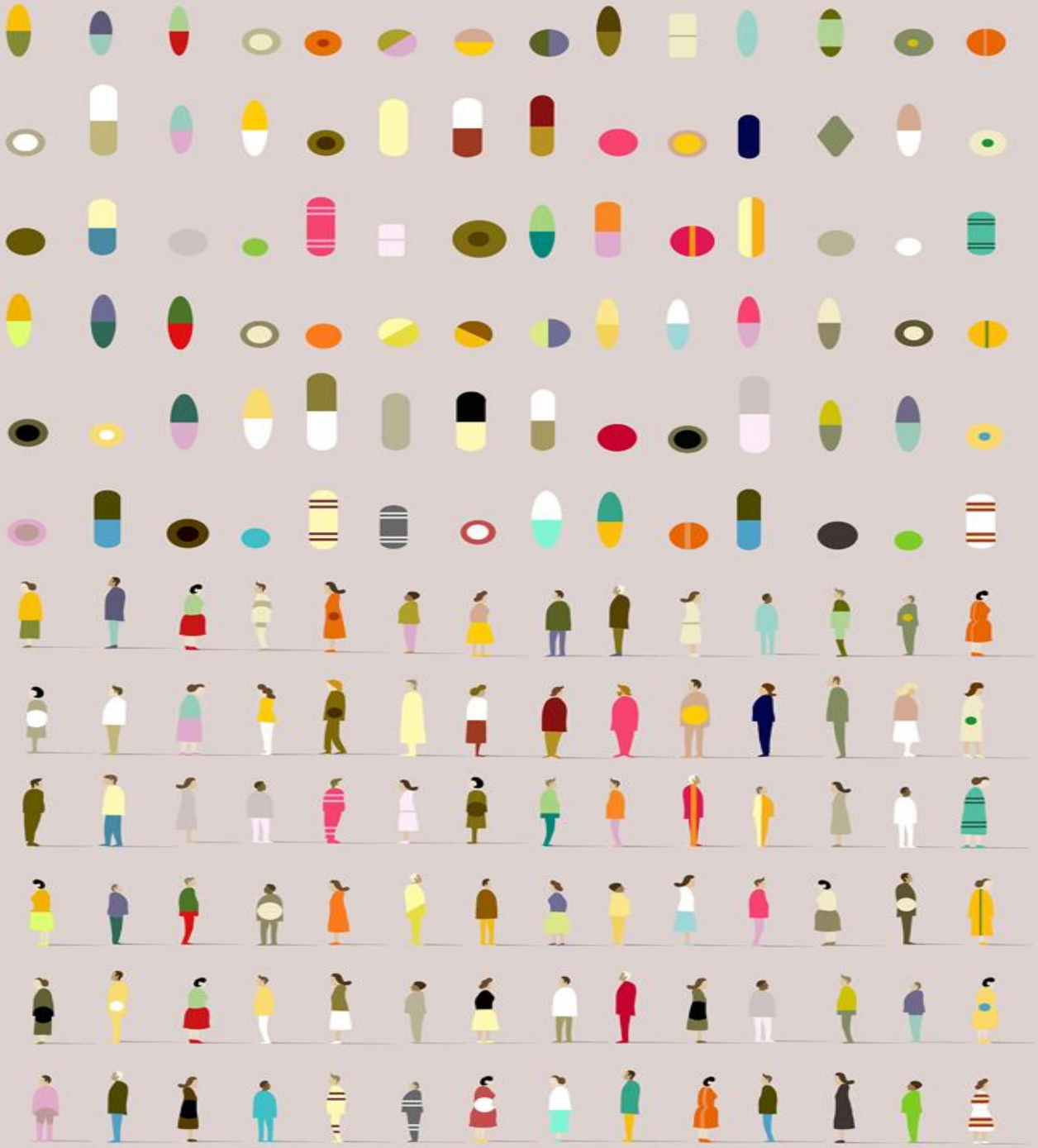
The right drug at the right dose to the right patient

PERSONALIZED MEDICINE



"It is *more important to know what kind of* ***person*** *has the disease than to know what kind of* ***disease*** *the person has*".

Hippocrates 460-370 BC



Questions?

Caroline.Samer@hcuge.ch