Medicina Personalizada de Precisión

De la teoría
a la práctica

Módulo I

De la Biología Molecular a la Medicina: Fundamentos de la Medicina Personalizada de Precisión

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25/09/2017

Estructura

1) Farmacogenética y Farmacogenómica

- Conceptos básicos

MPP y PGt/ PGx
Revelancia social, económica, sistemas sanitarios
Fármacos ineficaces y tóxicos
Variación genética en genes ADME

- Identificación de marcadores PGt: estrategias

Biomarcadores

Genes candidatos → genoma completo
Genotipado → secuenciación

- Implementación

Consorcios, sociedades, agencias reguladoras

2) Casos prácticos

Codeína en infancia y lactancia materna
Toxicidad de carbamazepina
*CYP3A4*20* en población española
Respuestas extraordinarias

3) Conclusiones generales

Conceptos básicos

Medicina Personalizada de Precisión

Identificación y aplicación del abordaje **preventivo, diagnóstico y terapéutico más efectivo y más seguro** para cada paciente

Paciente

Estratificación

Mayor beneficio al paciente

Sostenibilidad del sistema sanitario

Clasificar a los pacientes en **sub-poblaciones** con distinta:

- Susceptibilidad a desarrollar una enfermedad
- Biología y/o el pronóstico
- Respuesta a un determinado tratamiento

Intervenciones preventivas o terapéuticas específicas

Medicina Personalizada de Precisión

Farmacogenética y Farmacogenómica

Paciente

Estratificación

Mayor beneficio al paciente

Sostenibilidad del sistema sanitario

+

Fármacos

Intervenciones específicas basadas en biomarcadores

Farmacogenética y Farmacogenómica

Farmacogenética (PGt)

Estudio de variaciones en la **secuencia del DNA** relacionadas con la respuesta a un fármaco

Variaciones inter-individuales del DNA relacionadas con la farmacocinética y farmacodinámica de fármacos (disposición y acción) y que pueden influir en la respuesta clínica

Farmacogenómica (PGx)

Estudio de variaciones en las características del **DNA y RNA** relacionadas con la respuesta a un fármaco

La aplicación de las **tecnologías genómicas** para determinar la susceptibilidad a enfermedades, descubrimiento de fármacos, acción farmacológica, disposición de fármacos y respuesta terapéutica

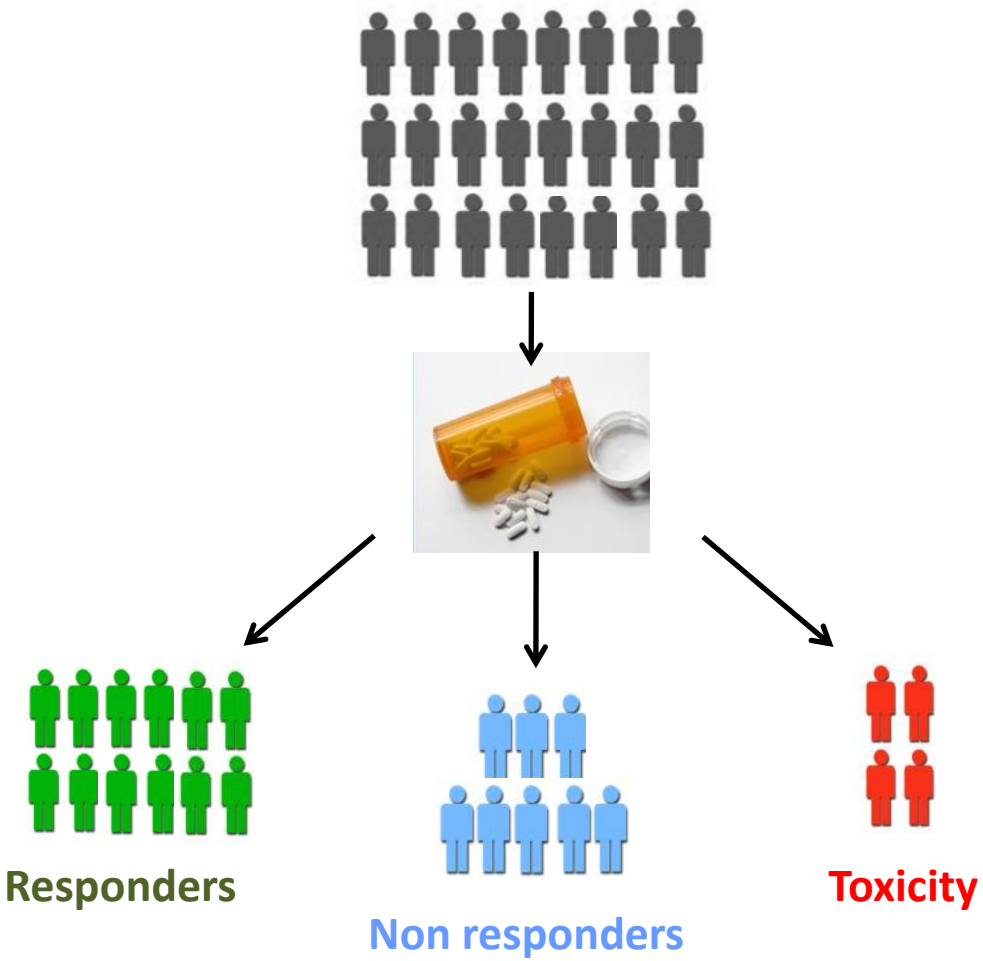
Intervenciones específicas basadas en biomarcadores

Farmacogenética y Farmacogenómica

Biomarcadores

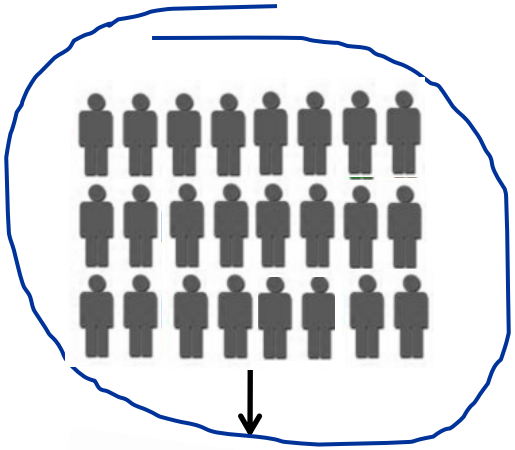
Traditional medicine

Drug treatments based on general population



Personalized medicine

Drugs and doses tailored to each patient



Causes?

- **Improve eficacy**
- **Decrease toxicity**

We are all “zebras”

*“When you hear hoofbeats, think of **horses**, not zebras”*

Precision Medicine is modifying this principle

Precision Medicine sees the zebra in all of us and focuses not on what makes us part of the herd, but what makes us a **unique** (or unique group!)

Fármacos ineficaces

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

30 APRIL 2015 | VOL 520 | NATURE | 609

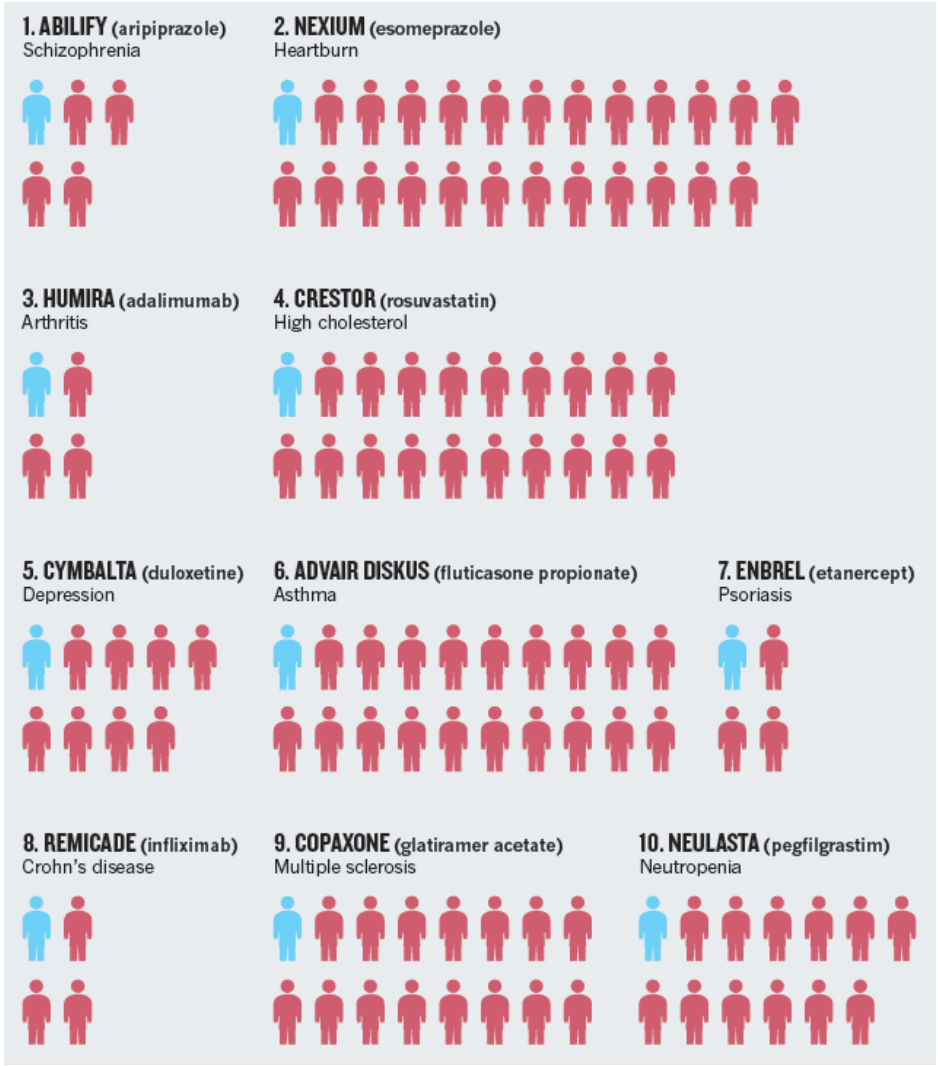
Fármacos ineficaces

IMPRECISION MEDICINE

10 highest-grossing drugs USA

Drugs do help

Fail to improve conditions



Fármacos tóxicos

Reacción adversa a medicamentos (***Adverse Drug Reaction, ADR***)**:** cualquier respuesta a un medicamento nociva y no intencionada

ADRs→ increasing morbidity and mortality and health care cost worldwide

- 5-7% of all hospital admissions due to ADR
- 0.15-0.3% are fatal
- 250,000 admissions per year in UK
- Cost to NHS £466 million/ year (UK)
- 72% were (possibly or definitely) preventable

Pirmohamed, BMJ 2004, 329:15 Hitchen, BMJ 2006, 332:1109 Lazarou, JAMA 1998, 279 (15): 120

Factors that influence drug response

Environmental

Physiopathologic

Genetic

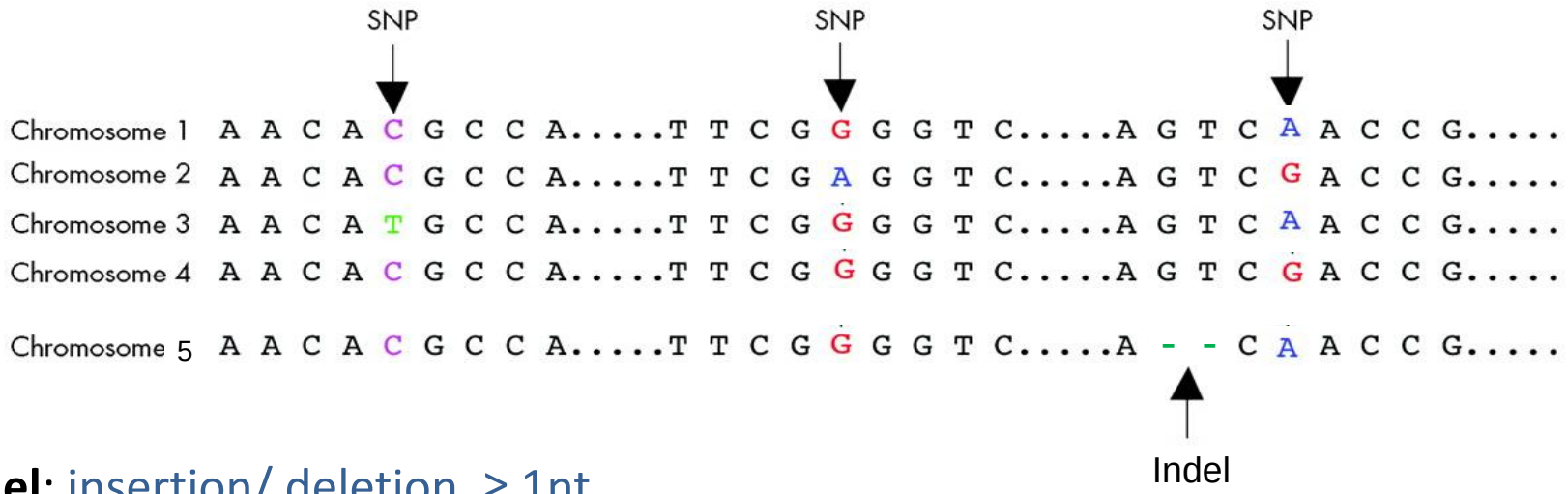
Predictive markers

Pharmacogenomics

Genetic variation

Individual differences are defined by 0.1% genome that varies

- SNP: single nucleotide polymorphism, 1 nt



- Indel: insertion/ deletion, ≥ 1nt

- CNV: copy number variation, 10-5000 kb

Genetic variation

Intragenic regions

- **Promotor** (transcription)
- **5´UTR** (translation)
- **Coding region** (nonesense, missense)
- **Introns** (splicing)
- **3´UTR** (mRNA stability, microRNA)

Intergenic regions

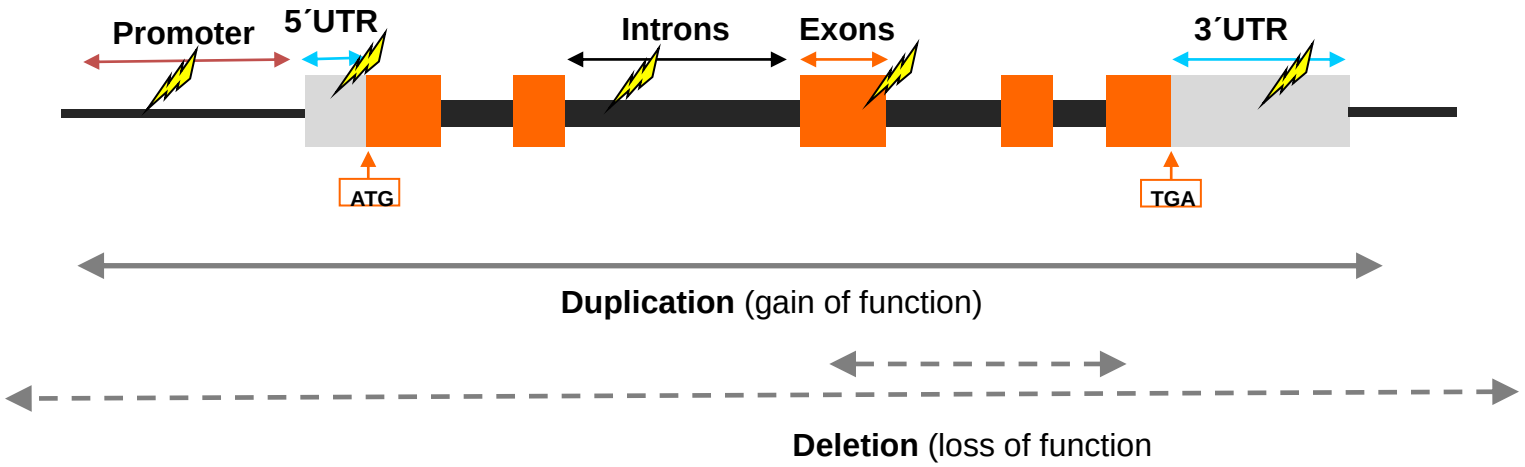
(75% of the genome)

"junk" DNA

- **Regulatory regions**
- **Enhancers**

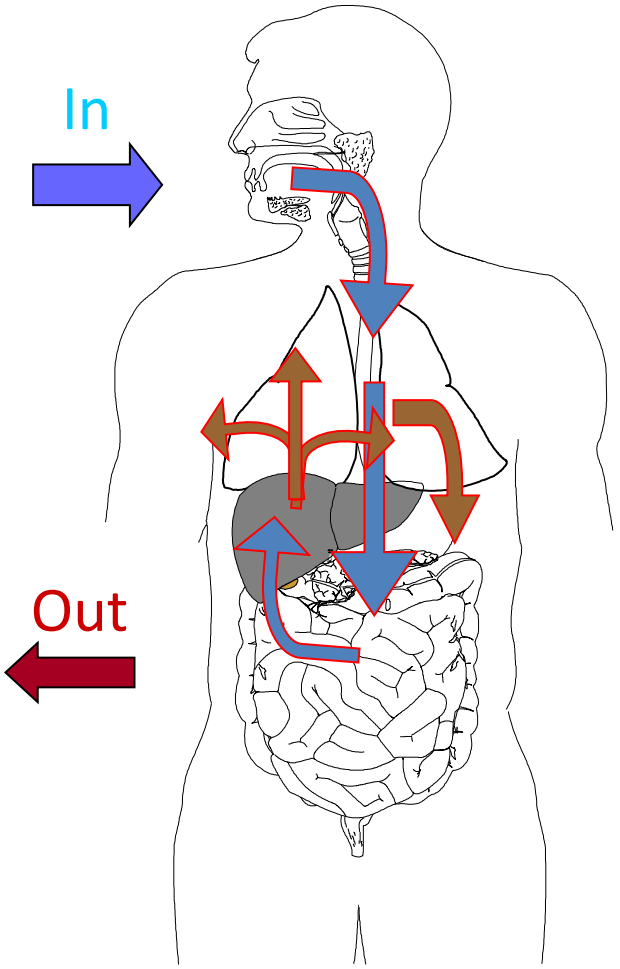
Alteration in quantity-activity of proteins

Genetic regulation



Xenobiotic: pharmacokinetics & pharmacodynamics

Xenobiotic



PK

- Absorption
- Distribution
- Metabolism
- Excretion

PD

- Target binding
- Mechanism of action (signal transduction)

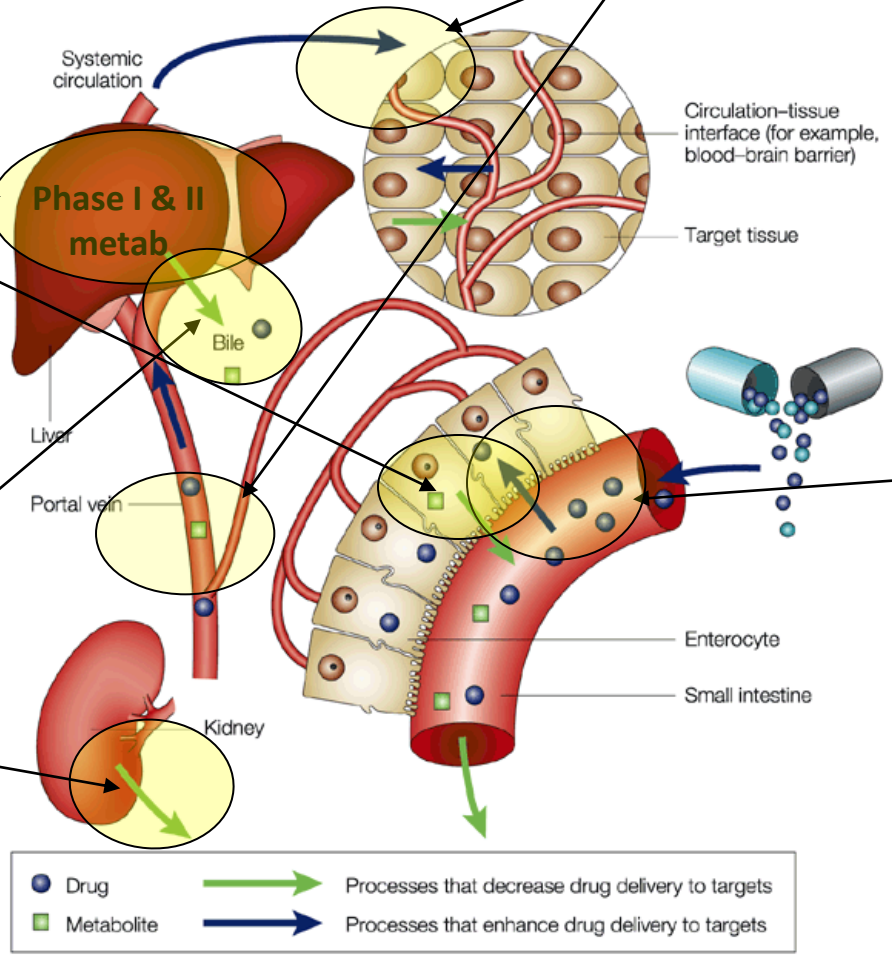
Pharmacokinetics: ADME

Distribution

If oral ad: from intestine to liver, and then systemic circulation.
Drug binding to plasma proteins.

Metabolism

Biotransformation to more water soluble compounds (Phase I & II).
In intestine (oral ad) first pass metabolism decreases absorption.



Absorption

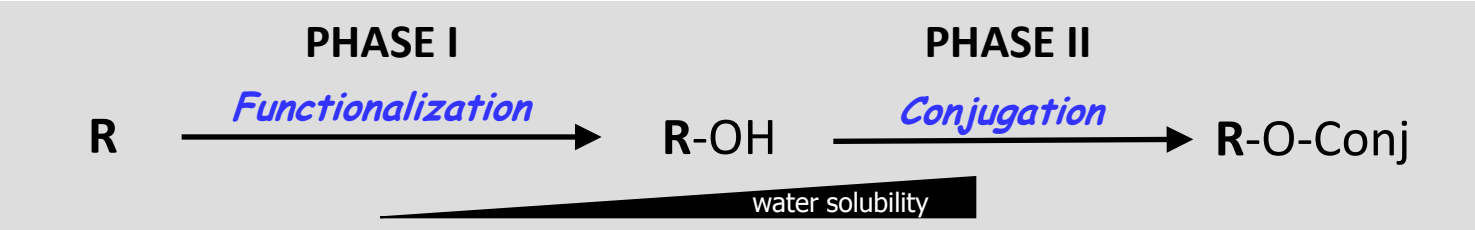
Depends on administration: oral, iv…

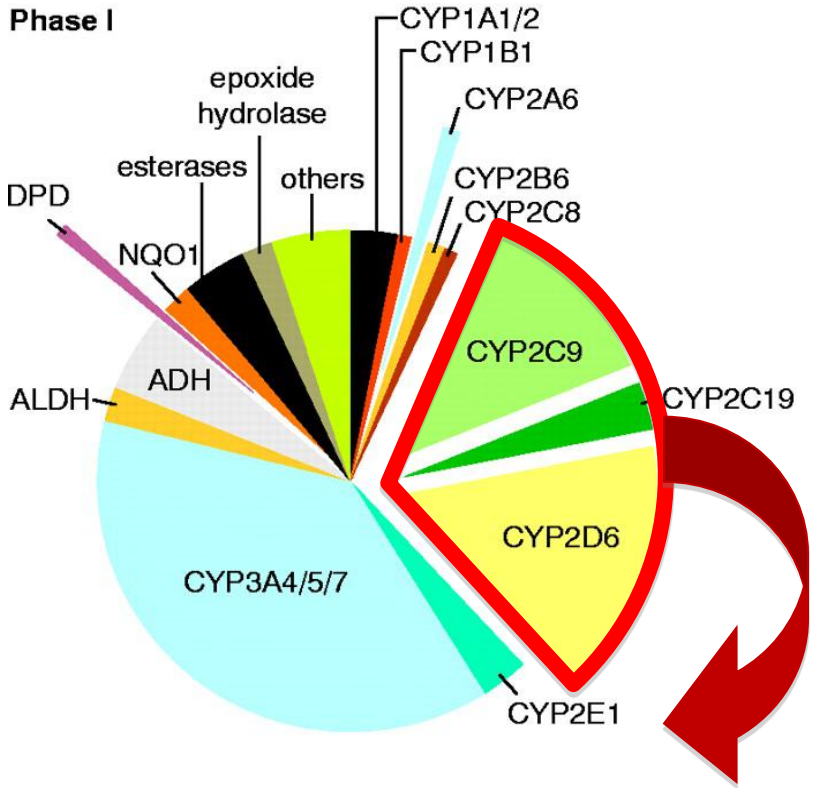
Excretion

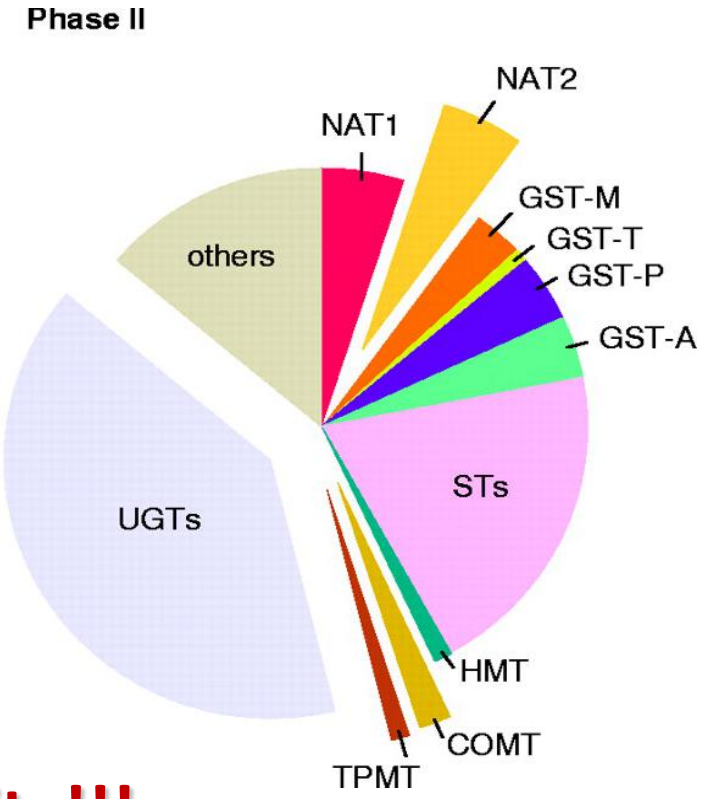
Elimination of drugs/ metabolites in the liver or in the kidney

Roden *et al* 2002. Nature Reviews Drug Discovery, 1, 37-44.

Major drug metabolizing enzymes







Large inter-individual variability!!!

High genetic variability in CYPs 1-3

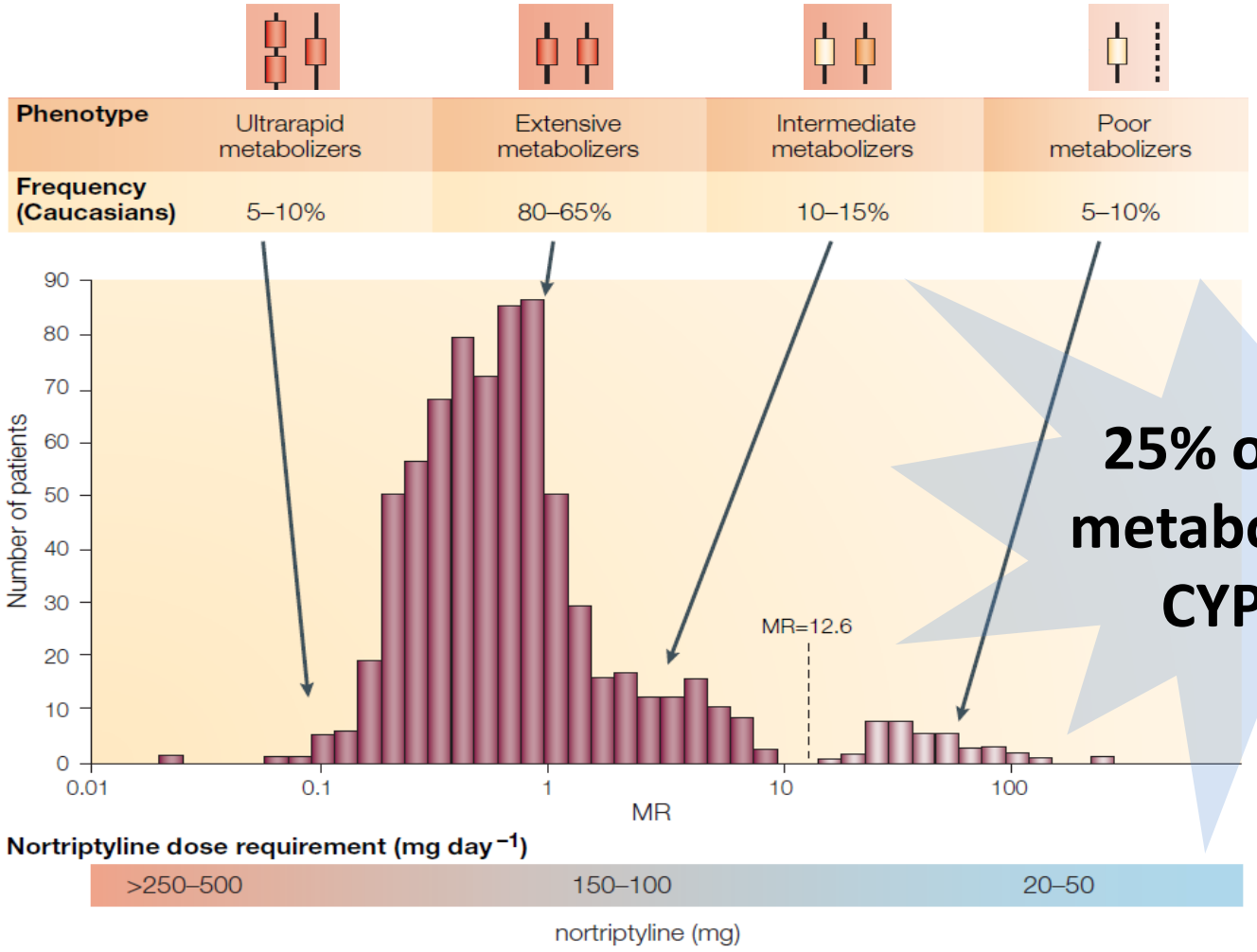
Common Name	Variant type	Variant	Consequence	MAF Eur	MAF Asian	MAF Afr
CYP2C9*2	SNV	rs1799853	Decreased enz activity	10-15	0-0.1	2 -4
CYP2C9*3	SNV	rs1057910	Decreased enz activity	4-10	4-7	1-2
CYP2C19*2	SNV	rs4244285	Not active enzyme (alt splicing)	11-13	27-31	13-22
CYP2C19*17	SNV	rs12248560	Increased activity	18	4	18
CYP2D6*4	SNV	rs1800716	Not active enzyme (alt splicing)	15-21	0.5-1	1-3
CYP2D6*9	SNV	rs4986895	Decreased enz activity	2-3	3	0
CYP2D6*10	SNV	rs5030655	Decreased enz activity	1-2	38-70	3-9
CYP2D6*17	SNV	rs4987150/ rs16947	Decreased enz activity	0-1	0.5	20-34
CYP3A4*22	SNV	rs35599367	Decreased activity	2-4		
CYP3A4*20	SNV	rs67666821	No activity	1	0	0
CYP3A5*3	SNV	rs776746	Not active enzyme (alt splicing)	88-95	73-76	28-35
CYP2D6xN (N=2, 3, 4, 5 or 13)	CNV	Multiplication/ Deletion		4-9	5-7	5-7
CYP2D6*3	SNV	rs35742686	Not active enzyme (frameshift)	0.7-4	0.1-0.8	0-0.5
CYP2D6*6	SNV	rs5030655	Not active enzyme (frameshift)	1	-	0

Some times large inter-ethnic variabilities

No phenotype unless exposed to drug

CYP2D6 variability

Alleles with different protein = 109
Premature stop codons, splicing defects, missense, CNV (deletion, duplication, multiplication)



25% of drugs metabolized by CYP2D6!

Nat Rev Genet. 2004;5(9):669-76

CYP2D6 variability

Alleles with different protein = 109
Premature stop codons, splicing defects, missense, CNV (deletion, duplication, multiplication)

Common Name	Variant	Activity	Minor Allele Frequency (%)		
			Eur.	Asian	Afr.
CYP2D6*4	rs1800716	None	15-21	0.5-1	1-3
CYP2D6*9	rs4986895	Decreased	2-3	3	0
CYP2D6*10	rs5030655	Decreased	1-2	38-70	3-9
CYP2D6*17	rs4987150	Decreased	0-1	0.5	20-34

CYP2D6 variability

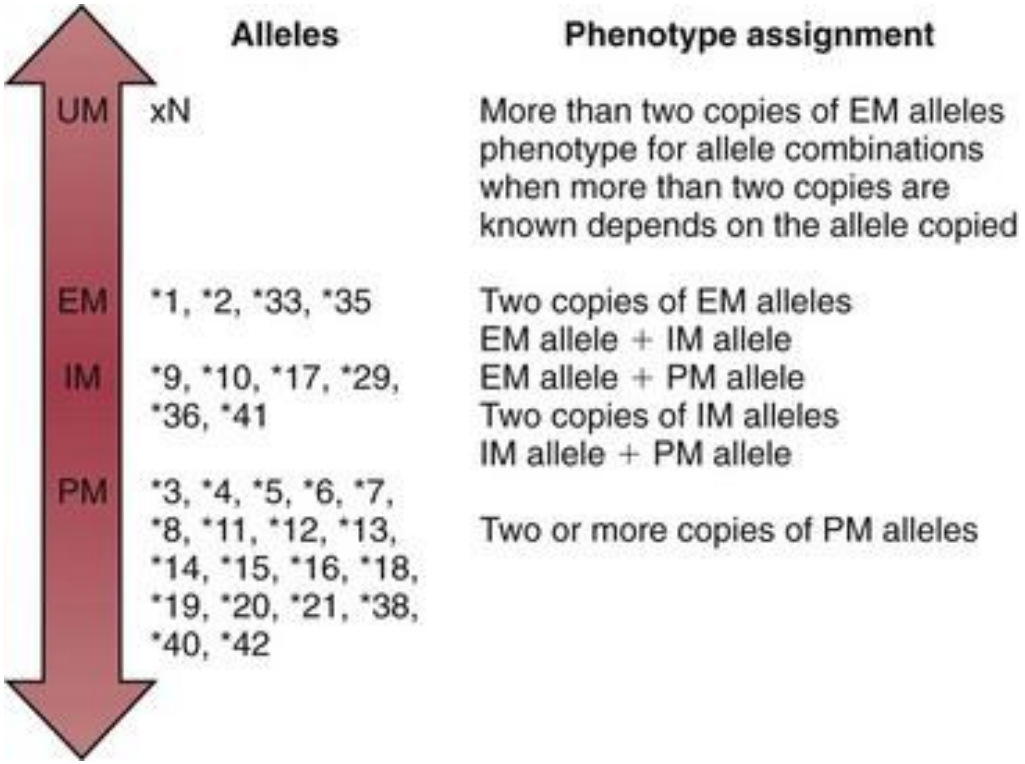
Population

Ultra-rapid Metabolizer (1-5%)*

Extensive Metabolizer (35%)

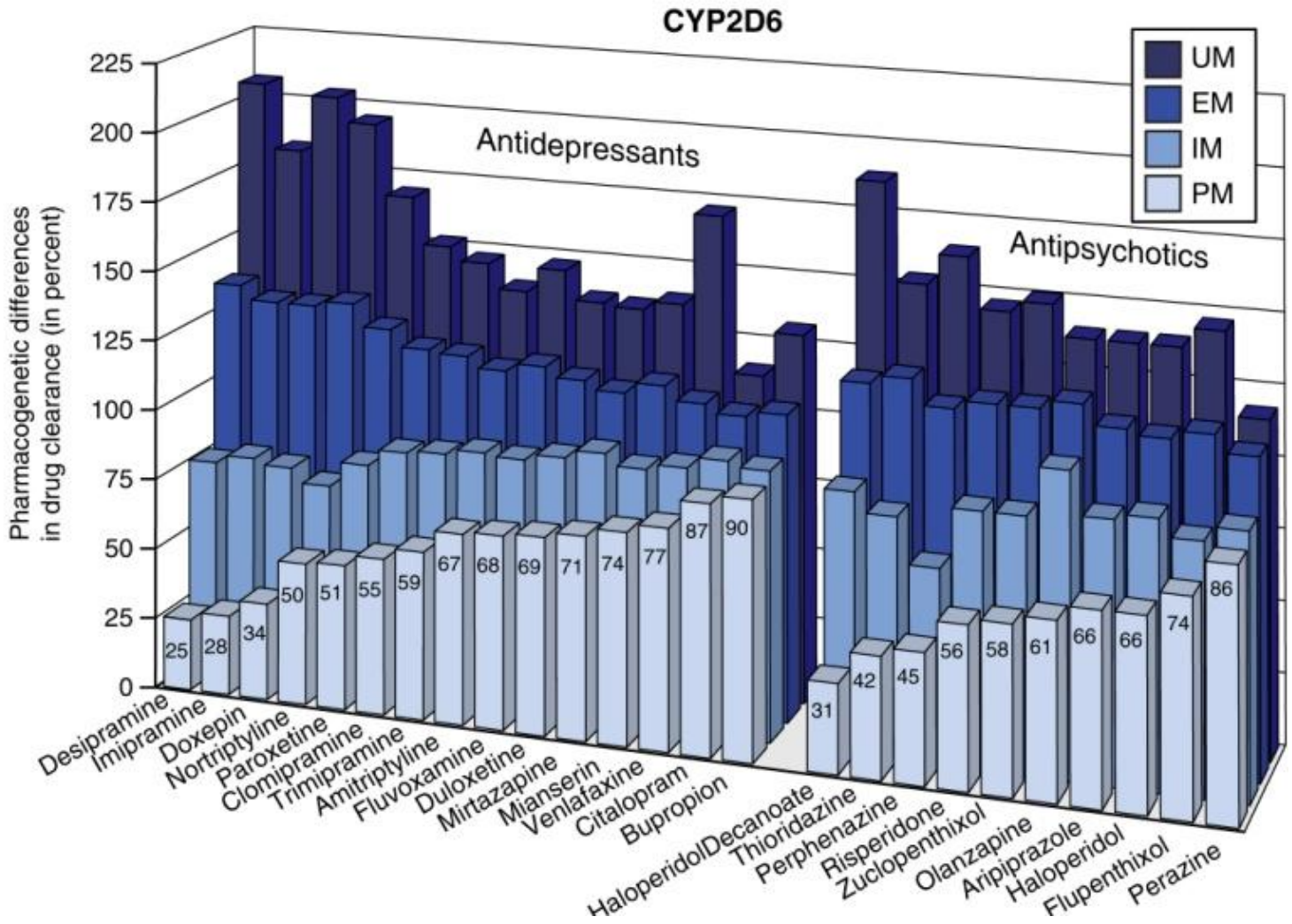
Intermediate Metabolizer (50%)

Poor Metabolizer (10%)



* Caucasians

CYP2D6: clinical consequences



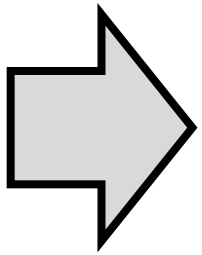
Molecular Psychiatry (2013) **18**, 273-287

CYP2D6: clinical consequences

ANTIDEPRESSANT METABOLISM BY CYP ENZYME[8]

CYP Enzyme	*Primarily Metabolized*	*Substantially Metabolized*	*Minimally Metabolized*
2D6	desipramine doxepin fluoxetine nortriptyline paroxetine venlafaxine	amitriptyline bupropion duloxetine imipramine mirtazapine trazodone	citalopram escitalopram fluvoxamine sertraline
2C19	amitriptyline citalopram clomipramine escitalopram	doxepin imipramine moclobemide notriptyline sertraline	venlafaxine
1A2	fluvoxamine	clomipramine duloxetine imipramine	amitriptyline mirtazapine
2C9	None	amitriptyline fluoxetine	sertraline

Wall CA, Oldenkamp C, Swintak C. *Primary Psychiatry*. Vol 17, No 5. 2010.



Clinical guidelines needed

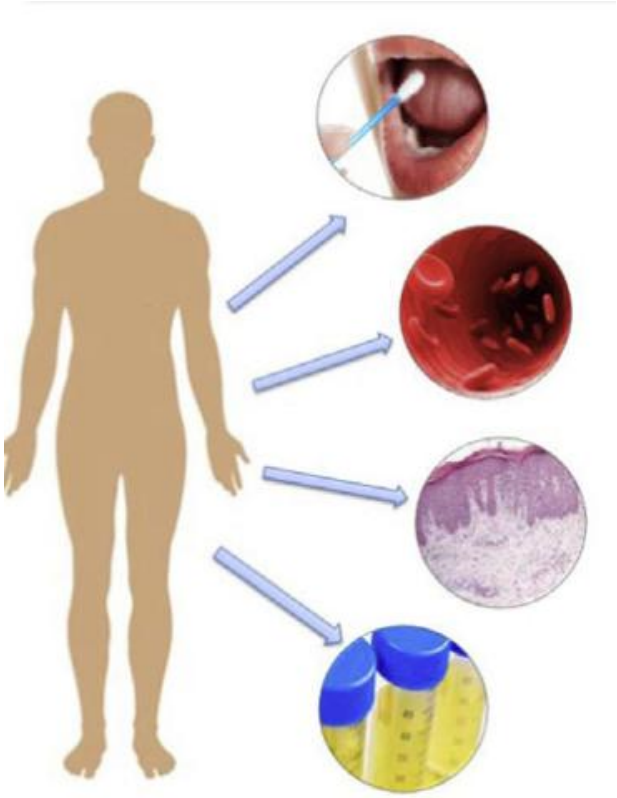
Identificación de biomarcadores: estrategias en PGt/ PGx

What is a biomarker?

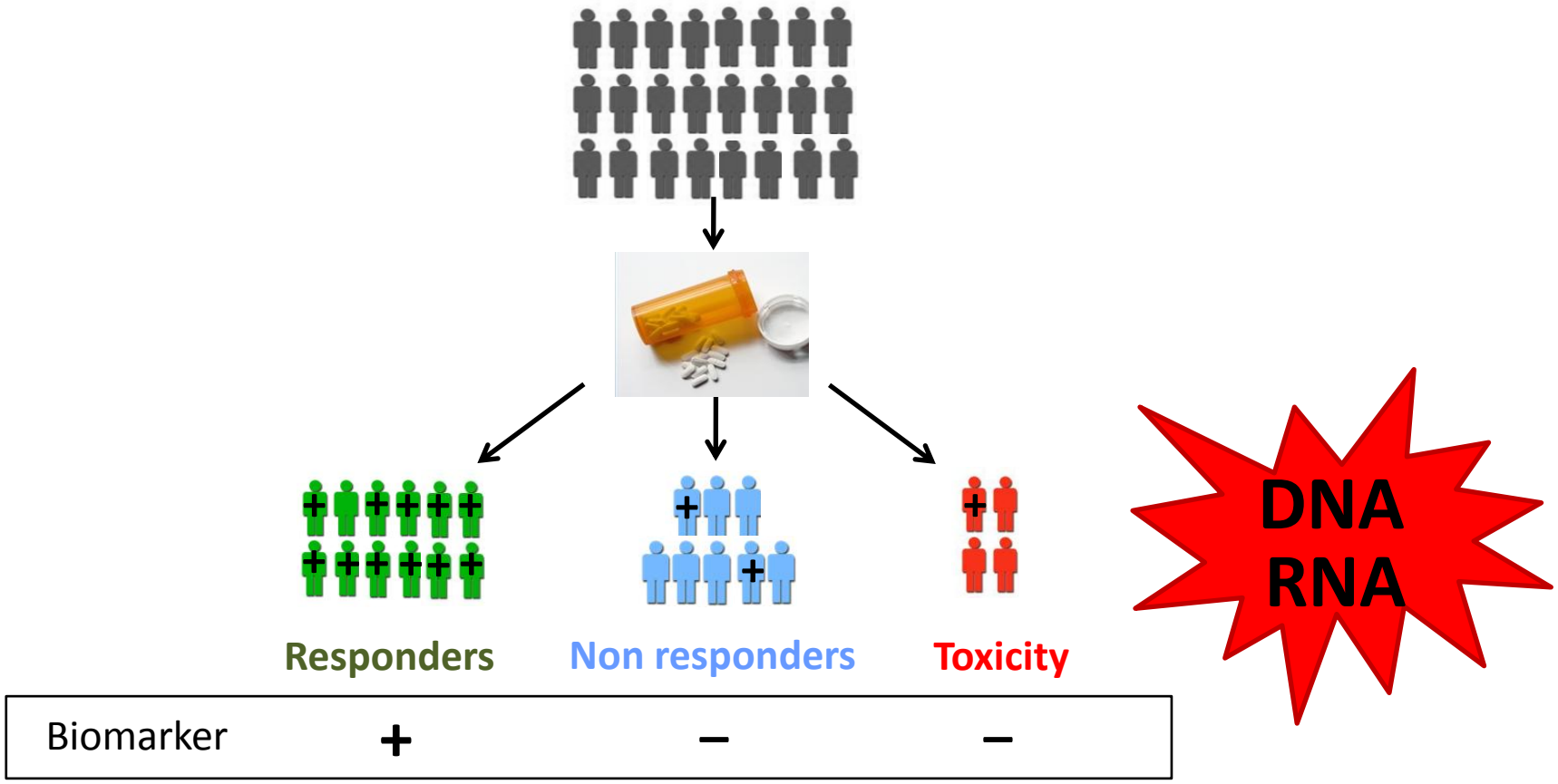
- **A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention**

- **Types**
  - Diagnostic
  - Prognostic
  - Predictive

- **Characteristics**
  - Specific: highly enriched in patients with outcome
  - Sensitive: easily quantificable
  - Robust: rapid, simple, accurate, reproducible
  - Non-invasive



Biomarkers to classify patients

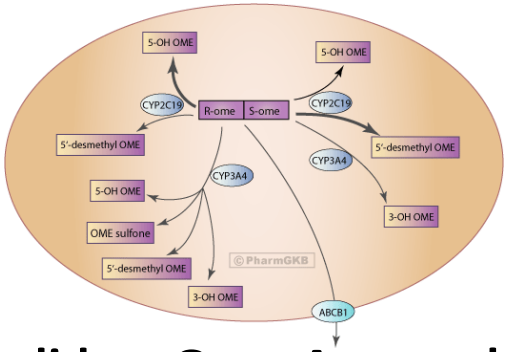


Where and how to find biomarkers?

(Strategies, techniques)

Strategies for biomarker identification in PGx

Search for markers of drug outcome



Candidate Gene Approaches

Genome Wide Approaches

Reduced false positives

Risk of excluding important genes

Functional variants

PK/ PD

Biological-pathway

~ 1 Million SNP each individual

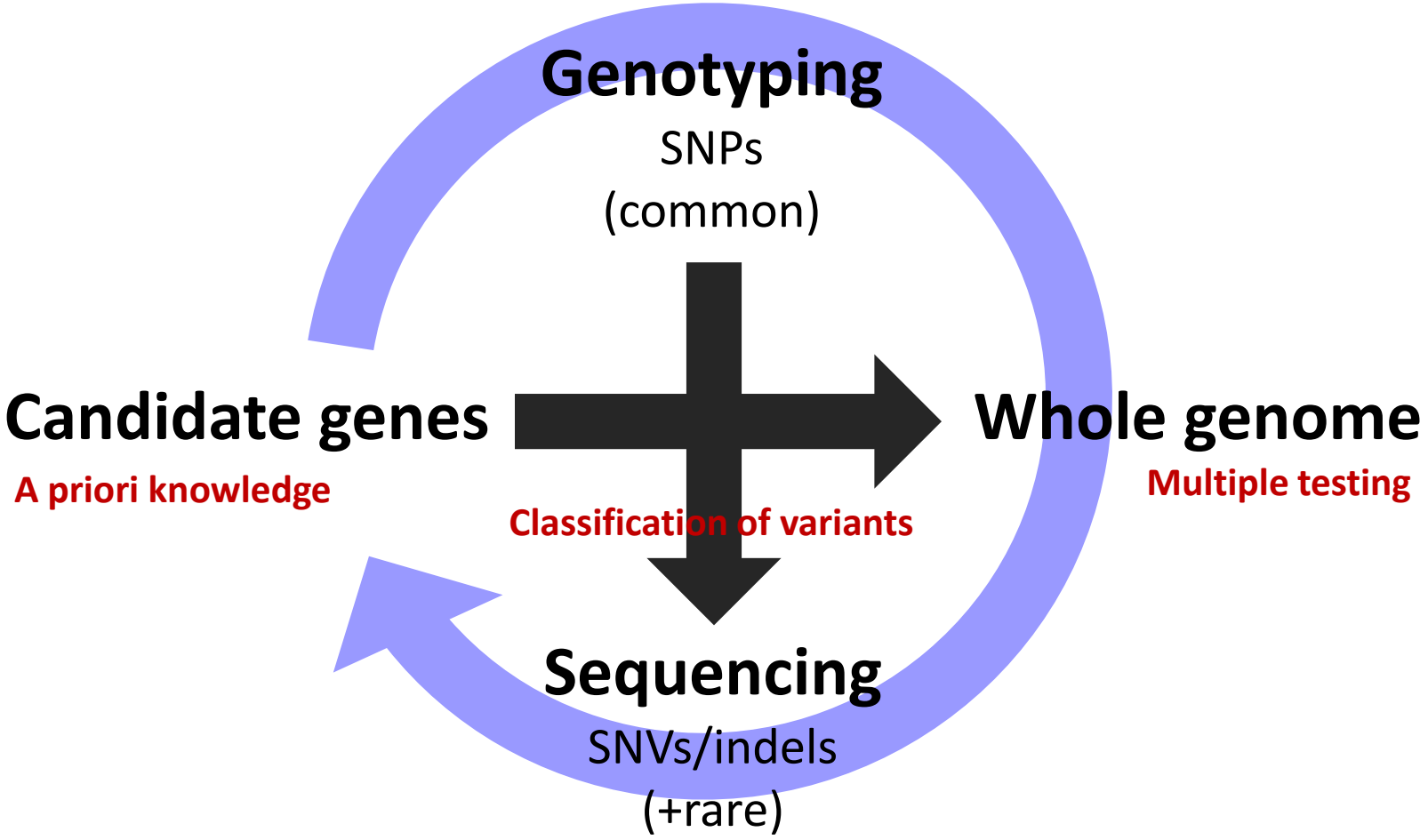
~ 20,000 genes

"Hypothesis free"

Novel mechanisms, genes...

Large nº of false positive

Strategies to identify pharmacogenomic markers



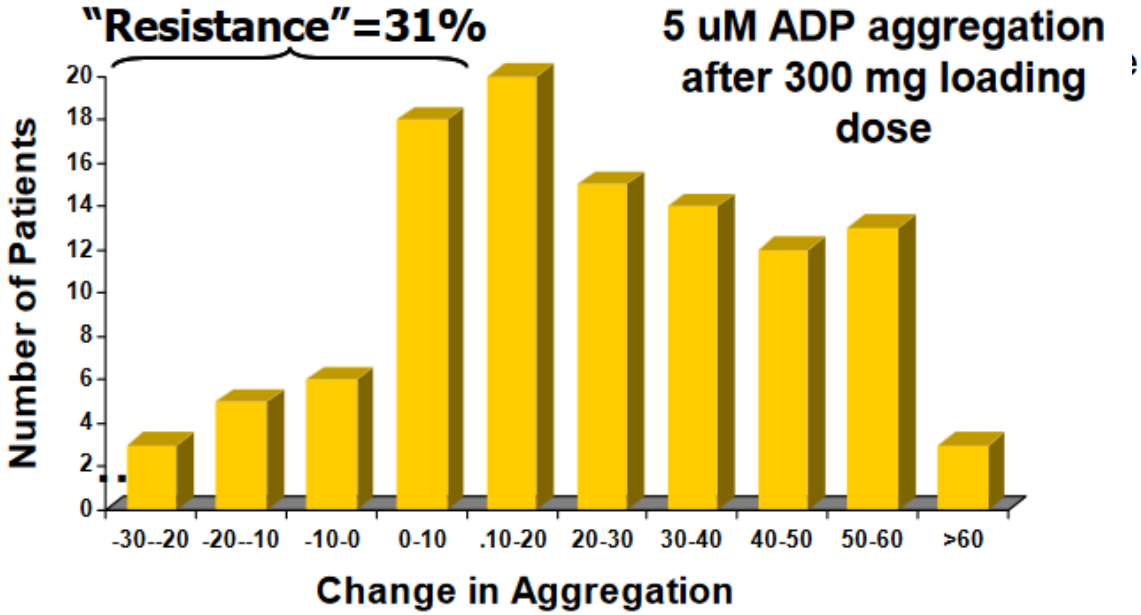
Phenotype definition & assessment

Genotyping candidate gene strategies: clopidogrel

Clopidogrel

- Thienopyridine drug that irreversibly inhibits platelet aggregation via the P2Y12 (ADP) receptor

Responses are highly variable

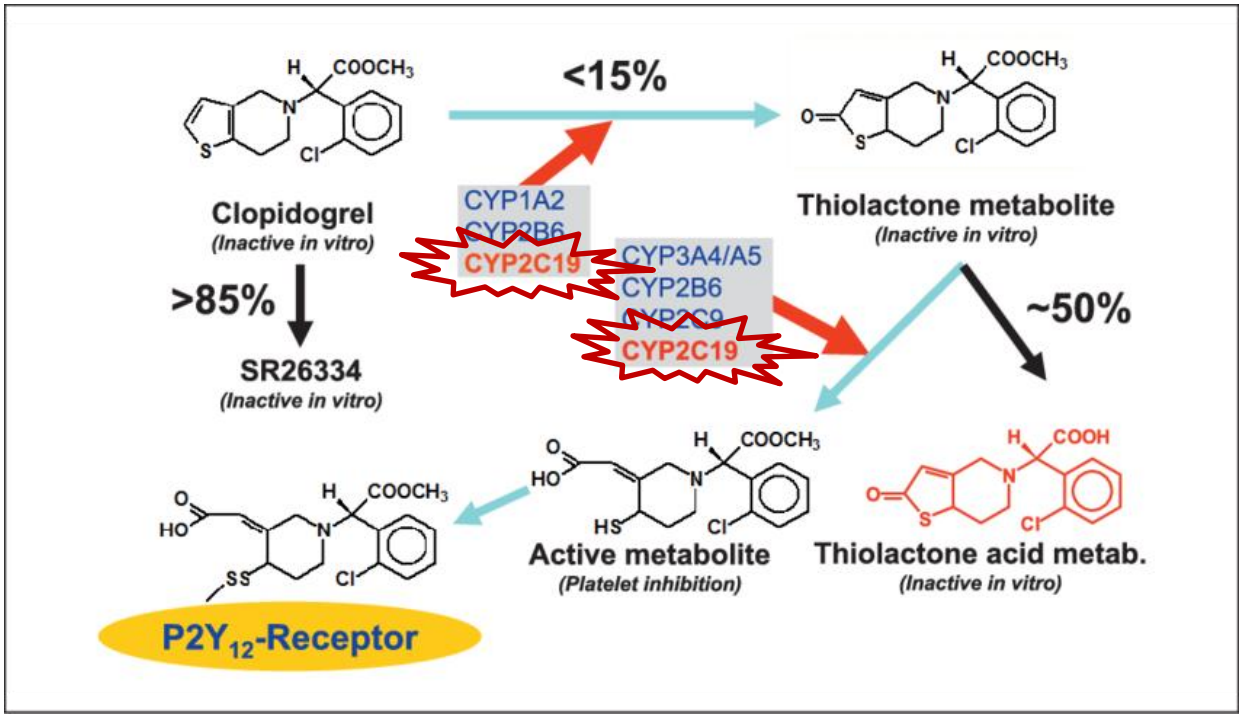


Gurbel Circulation 2003; 107: 2908

Genotyping candidate gene strategies: clopidogrel

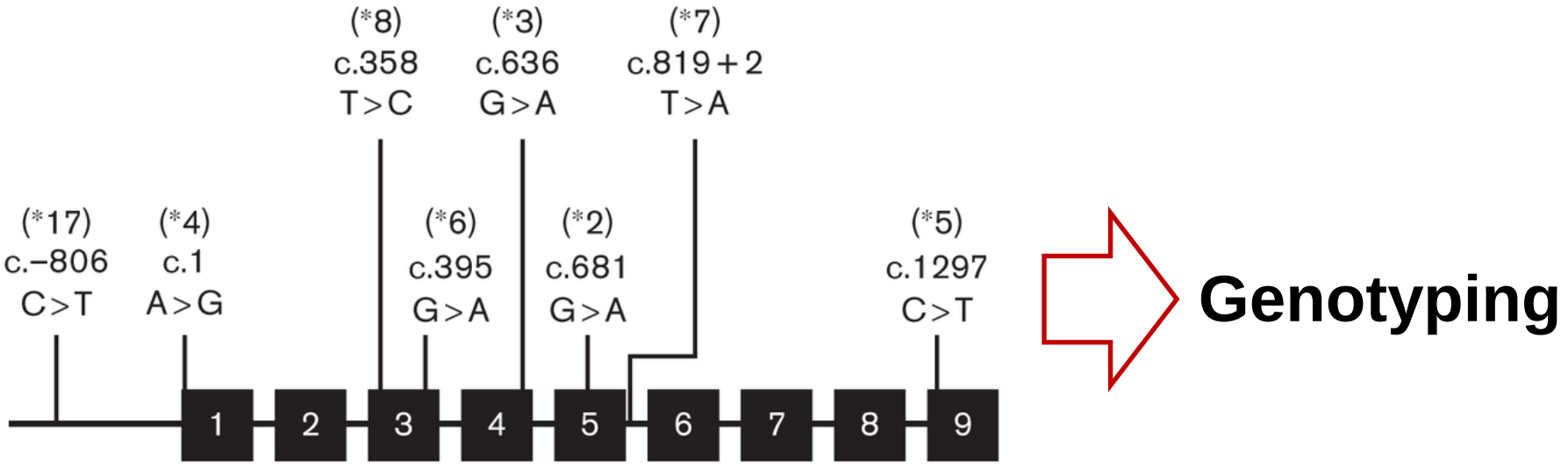
Clopidogrel

A priori knowledge: 2-step metabolism



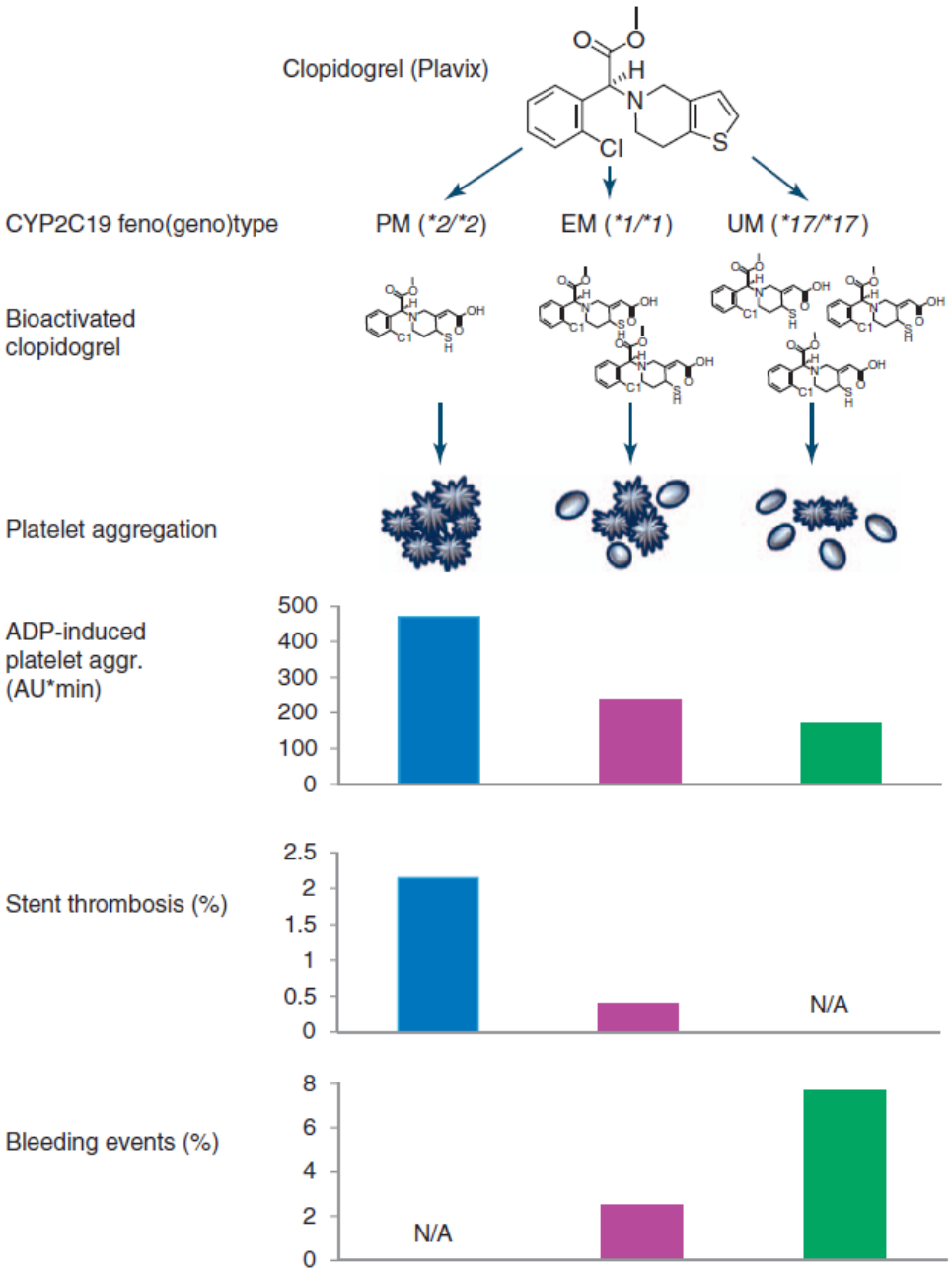
CYP2C19 is a highly polymorphic enzyme

Genotyping candidate gene strategies



CYP2C19 is a highly polymorphic enzyme

Clopidogrel Pharmacogenetics



Clopidogrel Pharmacogenetics

Guidelines for *CYP2C19* genotype and clopidogrel therapy

CPIC
Clinical Pharmacogenetics Implementation Consortium

Table 2 Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[a]
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[b]	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[a]See **Supplementary Materials and Methods** (Strength of Therapeutic Recommendations) online. [b]The *CYP2C19*17* allele may be associated with increased bleeding risks (ref. 15).
ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

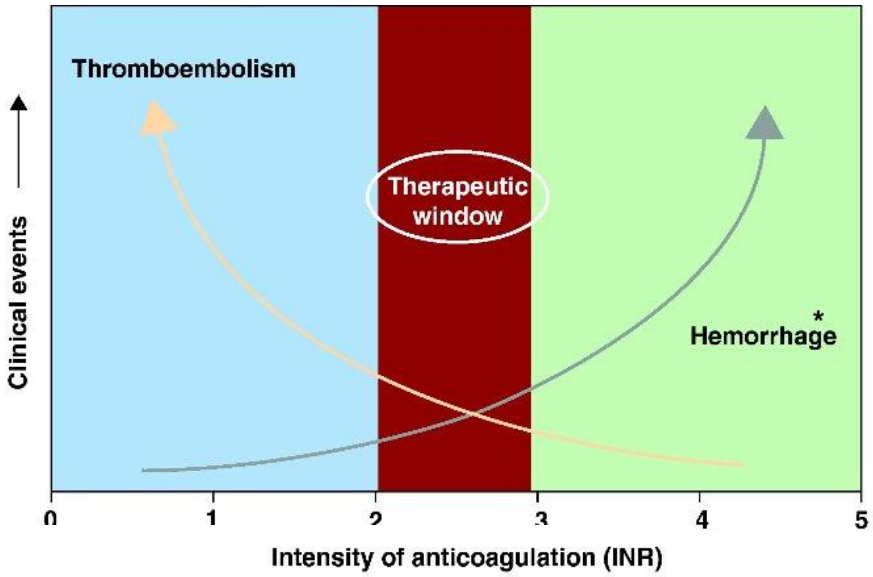
Genome Wide Association Studies (GWAS)

Warfarin

- Anticoagulant normally used in prevention of thrombosis and thromboembolism
- Initially introduced as a pesticide against rats and mice in 1948
- Approved as a medication in 1954. Most prescribed oral anticoagulant in USA
- Activity is monitored by blood testing for the international normalized ratio (INR)

Low INR:
No protection for thromboembolic events

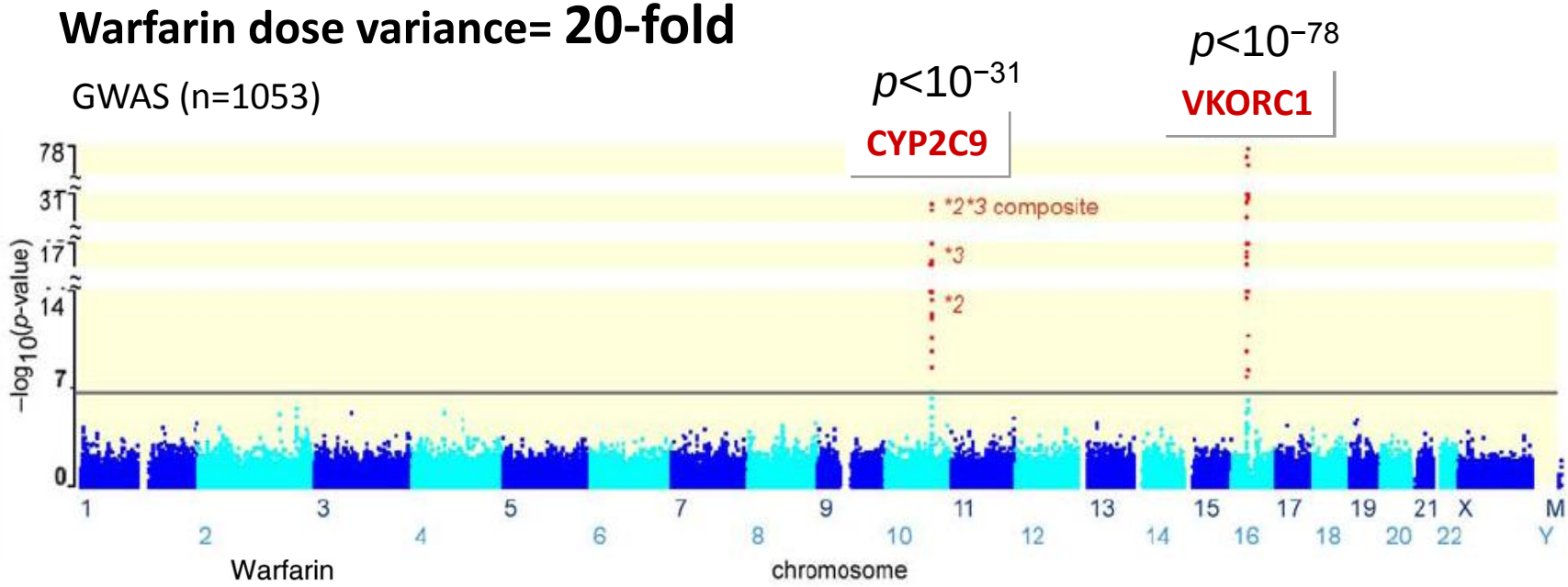
High INR:
increased risk of bleeding

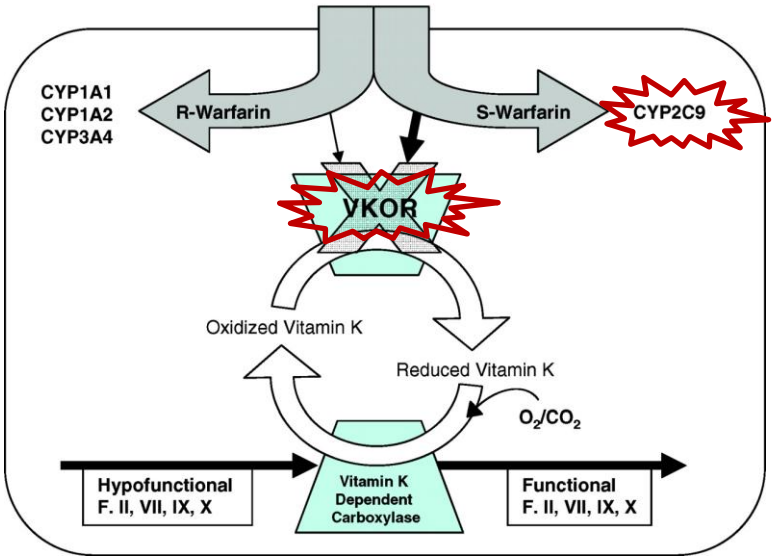


Genetic variation affecting warfarin dose

Warfarin dose variance= 20-fold

GWAS (n=1053)

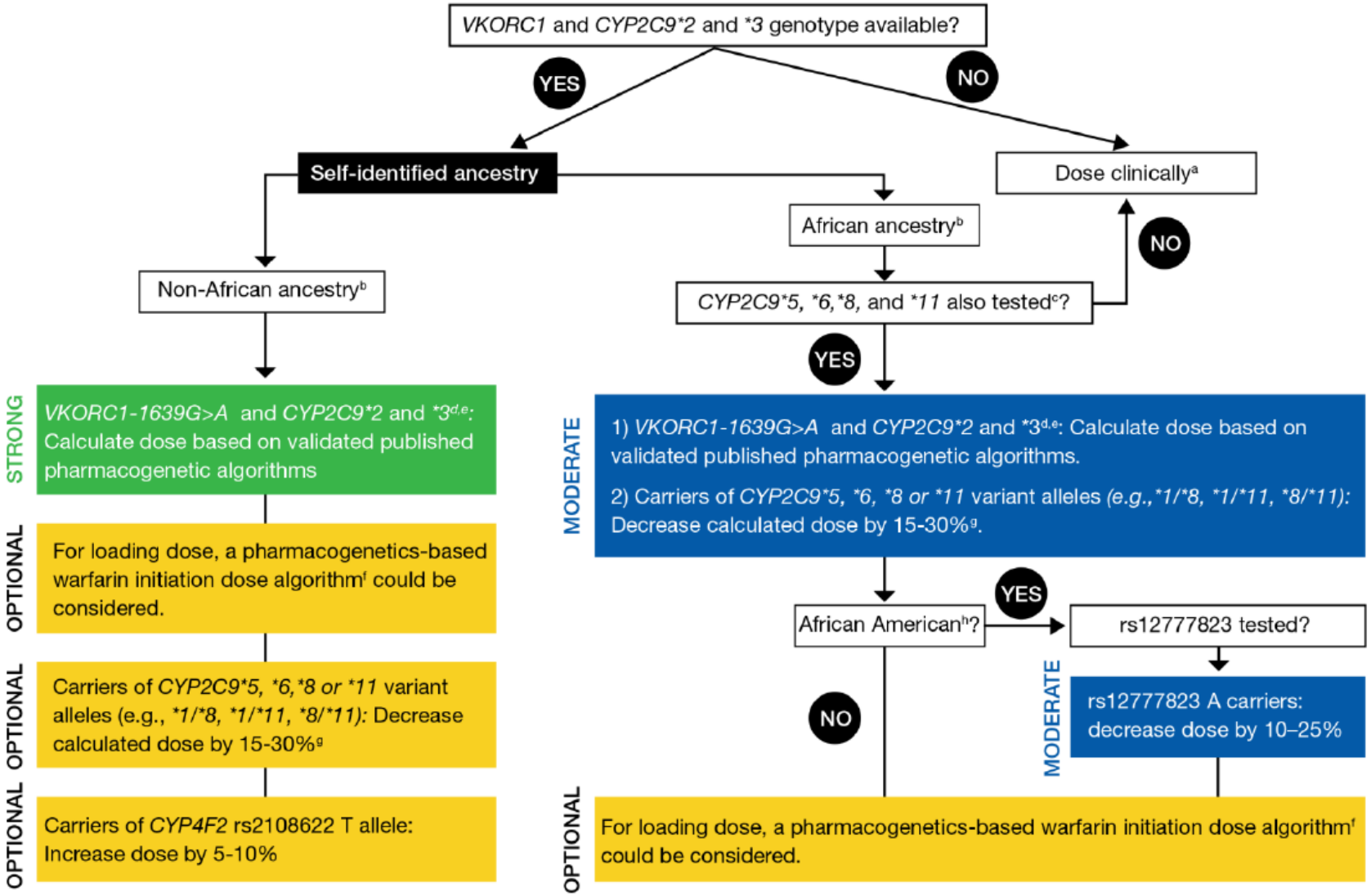




Warfarin dose variance	
• **Genetic Factors**	**44%**
VKORC1	30%
CYP2C9	12%
• **Non-genetic Factors**	**15%**

Takeuchi *et al.* 2009

Warfarin Pharmacogenetics



Next generation sequencing: comercial ADME panels

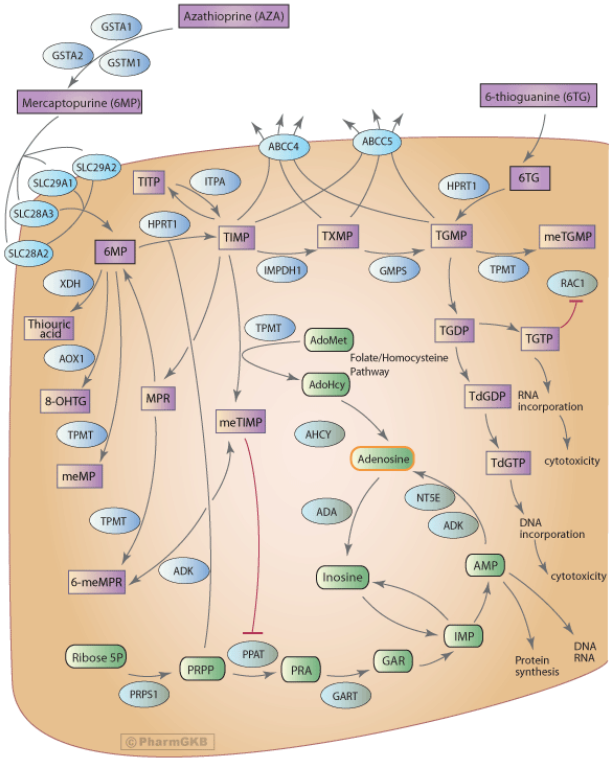
- Otogenetics human drug related genes: **352 ADME genes**

- RainDance ADMESeq™ Research Screening Panel: **242 key drug metabolism-linked genes**

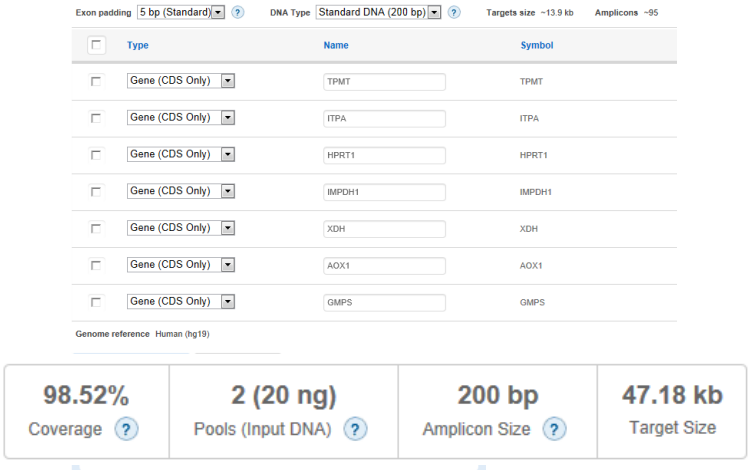
RainDance ADMESeq™ Research Screening Panel													
ABCB1	ABCC9	ALDH2	CDA	CYP11B2	CYP2C19	CYP4F12	FMO3	GSTM4	NAT2	RALBP1	SLC29A2	SULT4A1	UGT2B17
ABB10	ABCG2	ALDH3A1	CES1	CYP17A1	CYP2C8	CYP4F2	FMO4	GSTM5	NNMT	SCN5A	SLC5A6	TAP1	UGT2B4
ABCB11	ACE	ALDH3A2	CES2	CYP19A1	CYP2C9	CYP4F3	FMO5	GSTO1	NQO1	SLC10A1	SLC7A5	TAP2	UGT2B7
ABCB4	ADH1A	ALDH3B1	CHST10	CYP1A1	CYP2D6	CYP4F8	G6PD	GSTP1	NR1I2	SLC13A1	SLC7A7	TBXAS1	UGT8
ABCB5	ADH1B	ALDH3B2	CHST11	CYP1A2	CYP2E1	CYP51A1	GPX1	GSTT1	NR1I3	SLC15A2	SLCO1A2	TPMT	VDR
ABCB6	ADH1C	ALDH4A1	CHST13	CYP1B1	CYP2F1	CYP7A1	GPX3	HLA-B	NR3C1	SLC16A1	SLCO1B1	TYMS	VKORC1
ABCB7	ADH4	ALDH5A1	CHST2	CYP20A1	CYP2J2	CYP7B1	GPX4	HMGCR	OTC	SLC19A1	SLCO1B3	UGT1A	XDH
ABCB8	ADH5	ALDH6A1	CHST3	CYP21A2	CYP2R1	CYP8B1	GPX5	HNMT	P2RY1	SLC22A1	SLCO2B1	UGT1A1	XRCC1
ABCB9	ADH6	ALDH7A1	CHST4	CYP24A1	CYP2S1	DPYD	GPX6	IL28B	P2RY12	SLC22A2	SULT2B1	UGT1A10	
ABCC1	ADH7	ALDH8A1	CHST5	CYP26A1	CYP39A1	DRD2	GPX7	KCNH2	PARP1	SLC22A3	SPG7	UGT1A3	
ABCC10	ADHFE1	ALDH9A1	CHST6	CYP26C1	CYP3A4	EGFR	GSTA1	KCNJ11	PON1	SLC22A4	SRRT	UGT1A4	
ABCC11	ADRB1	ALOX5	CHST7	CYP27A1	CYP3A43	EPHX1	GSTA2	KRAS	PON2	SLC22A5	SULT1A1	UGT1A6	
ABCC12	ADRB2	AOX1	CHST8	CYP27B1	CYP3A5	EPHX2	GSTA3	LDLR	PON3	SLC22A6	SULT1B1	UGT1A7	
ABCC2	AHR	ARG (RERE)	CHST9	CYP2A13	CYP3A7	ERCC1	GSTA4	MAOA	POR	SLC22A8	SULT1C2	UGT1A8	
ABCC4	ALDH1A1	ASL	COMT	CYP2A6	CYP46A1	ERCC2	GSTA5	MAOB	PPARA	SLC28A1	SULT1C4	UGT1A9	
ABCC5	ALDH1A2	ASNA1	CPS1	CYP2A7	CYP4A11	F5	GSTM1	MTHFR	PPARD	SLC28A2	SULT1E1	UGT2A1	
ABCC6	ALDH1A3	ASS1	CYP11A1	CYP2B6	CYP4B1	FMO1	GSTM2	NAGS	PPARG	SLC28A3	SULT2A1	UGT2B11	
ABCC8	ALDH1B1	ATP7A	CYP11B1	CYP2C18	CYP4F11	FMO2	GSTM3	NAT1	PTGIS	SLC29A1	SULT2B1	UGT2B15	

Next generation sequencing: Custom panels

- **Select genes** (coding region, UTR, introns, regions with variations)
- **Enrichment** (PCR based/ array capture): bias
- **Define sequencing depth** (germline/ somatic)



Online design



Whole Exome/Genome Sequencing for PGt

Pre-emptive PGts: opportunistic pharmacogenetic screening

n= 98 children; WGS

67 pharmacogenetic loci

Reference SNP (haplotype)	Gene
rs1801131; rs1801133	*MTHFR*
rs67376798; rs3918290	*DPYD*
rs12248560, rs28399504, rs41291556, rs17884712, rs4986893, rs4244285	*CYP2C19*
rs1799853, rs9332131, rs1057910, rs28371686	*CYP2C9*
rs1800497	*ANKK1*
rs1954787	*GRIK4*
rs2306283; rs4149056	*SLCO1B1*
rs9923231	*VKORC1*
rs2108622	*CYP4F2*
rs12979860	*IFNL3*
rs1051266	*SLC19A1*
rs4633; rs4818; rs4680	*COMT*

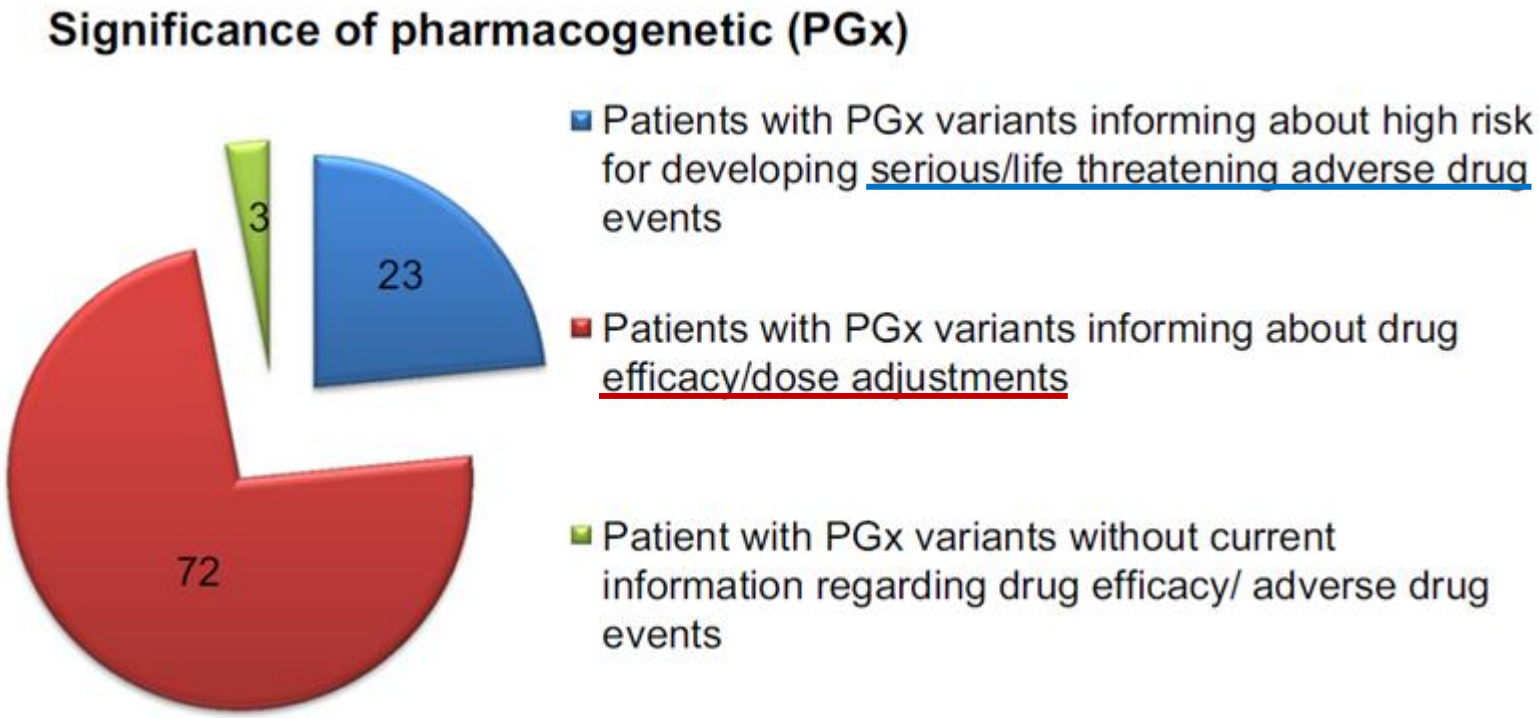
Reference SNP (haplotype)	Gene
rs1135840, G4125_4133 T (rs765776661), rs28371731 (rs4987144), rs72549346, rs72549347 (rs147960066), rs2837172, rs72549349, rs5030867, rs16947, rs5030656 rs72549351, rs72549352, rs35742686, rs72549353 (rs758320086), rs72549354, rs72549356 (rs553846709), rs3892097, rs5030865, rs5030655, rs1058164, rs61736512, rs28371706, rs5030863 (rs201377835), rs72549357 (rs774671100), rs5030862, rs1065852, rs769258, rs28735595, rs1080985	*CYP2D6*
rs2228001	*TMEM*
rs2231142, rs2231137	*ABCG2*
rs1142345, rs1800584, rs1800460, rs1800462	*TPMT*
rs1061235 (HLA- A* 31:01), rs2395029 (HLA-B* 57:01)	*HLA*
rs1045642, rs2032582, rs1128503	*ABCB1*
rs776746	*CYP3A5*

Cohn, Genomic Med 2017

Whole Exome/Genome Sequencing for PGt

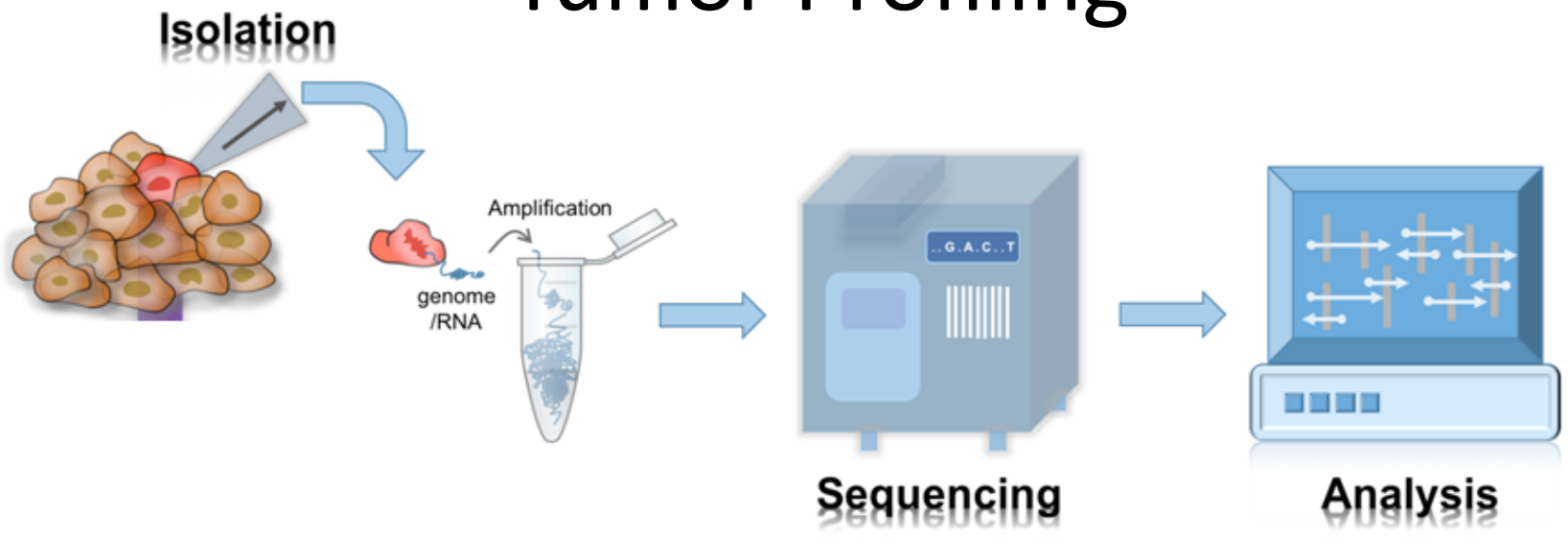
Pre-emptive PGts: opportunistic pharmacogenetic screening

n= 98 children; WGS



Cohn, Genomic Med 2017

Tumor Profiling



NCI-MATCH Trial (Molecular Analysis for Therapy Choice)

Reaches 6,000-patient tumor sequencing goal 2 years early

NCI National Clinical Trials Network

Phase II precision medicine trial that seeks to determine the effectiveness of treatment that is directed by genomic profiling in cancer.

The study attempts to demonstrate that matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of its type. Such discoveries could be eligible to move on to larger, more definitive trials.

Basket trials **“Big data”**

Implementación

Implementation of PGt testing

Barriers for implementation

- Lack of large clinical trials (std treatment vs genetically selected patients)
- Lack of cost-benefit estimations
- Poor PGt education

Facilities for implementation

- Technology (high throughput technologies, lowering costs)
- Genomic knowledge is constantly increasing (personal genomes)
- Benefit for the individual/ society (cost-beneficial for Health System)

Implementation of PGt testing

- **Associations, consortia, societies** (PharmGKB, CPIC, uPGx, ESPT, SEFF)

- **PGt data bases** (gene-drug effect), **guidelines** (CPIC, Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group)

- **Research** (cost-benefit studies, new markers, improved accuracy)

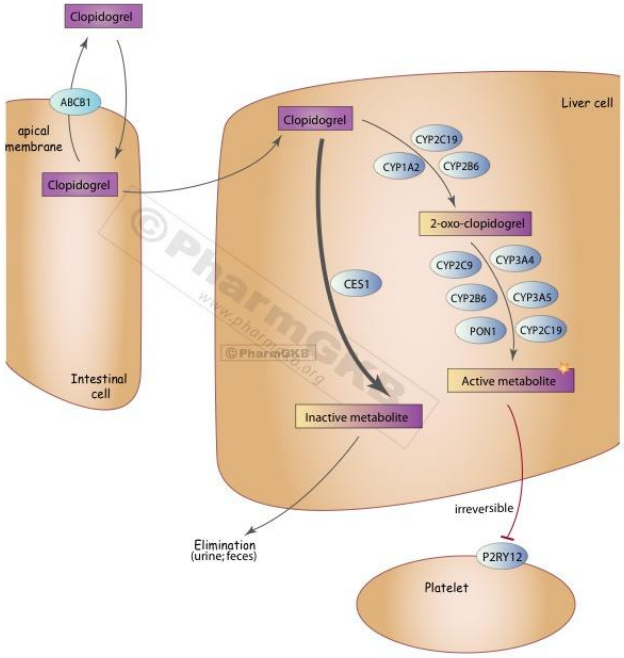
- **Regulatory agencies (EMA, FDA)**, PGt markers in drug labels

Knowledge is constantly growing

PharmGKB

https://www.pharmgkb.org/

Drugs	Pathways	Dosing Guidelines	Drug Labels
621	119	96	476



Dosing Guidelines

These dosing guidelines take into consideration patient genotype and have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG, manually curated by PharmGKB), or other professional society (PRO, manually curated by PharmGKB).

	SOURCE	GENES	TITLE
Read Now	CPIC	CYP2C19	Annotation of CPIC Guideline for clopidogrel and CYP2C19
Read Now	DPWG	CYP2C19	Annotation of DPWG Guideline for clopidogrel and CYP2C19

Clinical Pharmacogenetics Implementation Consortium (CPIC)

https://cpicpgx.org/

Clasification of gene-drug pairs

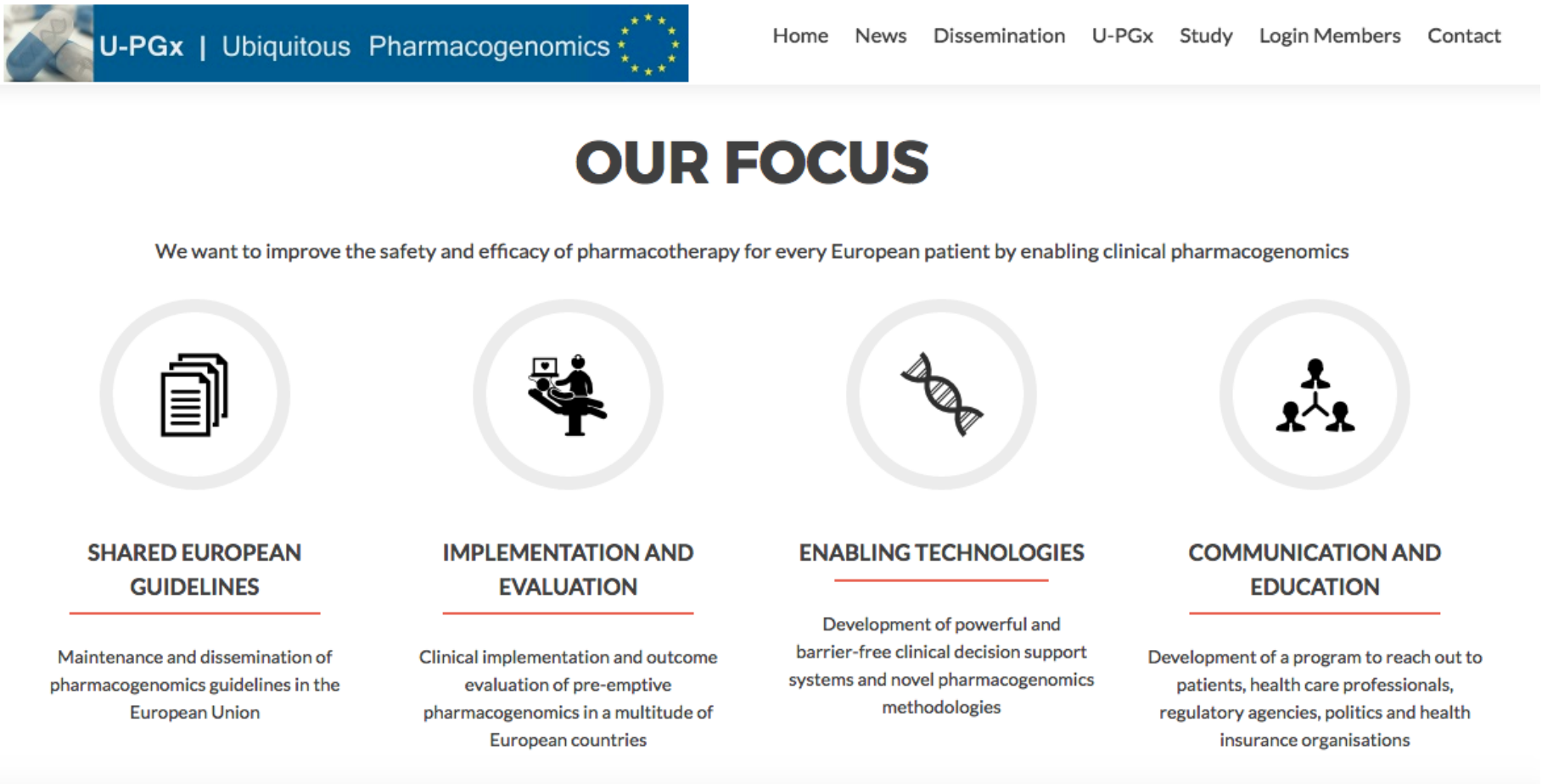
CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

Clinical Pharmacogenetics Implementation Consortium (CPIC)

Clasification of gene-drug pairs

# (N=352)	GENE (UNIQUE = 127)	DRUG (UNIQUE = 223)	GUIDELINE	CPIC LEVEL	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	1A	Testing required	• 22378157 • 24561393
2	HLA-B	allopurinol	Guideline	A	1A		• 23232549 • 26094938
3	CYP2C19	amitriptyline	Guideline	A	1A		• 23486447 • 27997040
4	CYP2D6	amitriptyline	Guideline	A	1A	Actionable PGx	• 23486447 • 27997040
5	UGT1A1	atazanavir	Guideline	A	1A		• 26417955
6	TPMT	azathioprine	Guideline	A	1A	Testing recommended	• 21270794 • 23422873

Ubiquitous Pharmacogenomics (uPGx)



PREPARE (**Pre**emptive Pharmacogenomic Testing for **P**reventing **A**dverse Drug **Re**actions) is a clinical study initiated to implement and evaluate the impact of pharmacogenomic testing on therapy outcomes in seven European clinical centres.

Societies PGx

European Society of Pharmacogenomics and Personalized Therapy

http://www.esptnet.eu/

Aims

- To transcend the boundaries of single nations or single corporations, in developing the field of PGX and personalized medicine.

- To provide a forum for consensus, in the broadest sense, to offer a European view at the highest possible scientific and technical level, aiming to improve quality of care for the patient and maintain his health.

- To disseminate information on "best practice" at various levels of technology, clinical practice and economic development.

- To promote a vision of PGX and personalized medicine that extends beyond traditional narrow perceptions of the field.

- To improve patient understanding and health.

- To inform clinicians and patients on the appropriate use of PGX.

- To promote, inform and offer an independent view of PGX and personalized medicine to clinicians, regulators, the public and other stakeholders.

Societies PGx

Sociedad Española de Farmacogenética y Farmacogenómica

http://www.seff.es/

Objetivos

- Contribuir al desarrollo y difusión de los conocimientos científicos PGt/PGx

- Asesorar y colaborar con organismos públicos e instituciones privadas para el desarrollo científico, técnico y la protección jurídica de la PGt/PGx

- Instar al cumplimiento de las directrices marcadas por la propia sociedad relativas a la homologación de técnicas aplicables, control y garantías de calidad de las mismas, y en general a todo cuanto se refiera al uso de técnicas genómicas con fines asistenciales.

-Impulsar colaboración entre profesionales implicados en los campos de la PGt/PGx para aumentar la calidad y cantidad de la investigación en estas áreas, y principalmente fomentar la aplicación clínica de los descubrimientos en estos campos

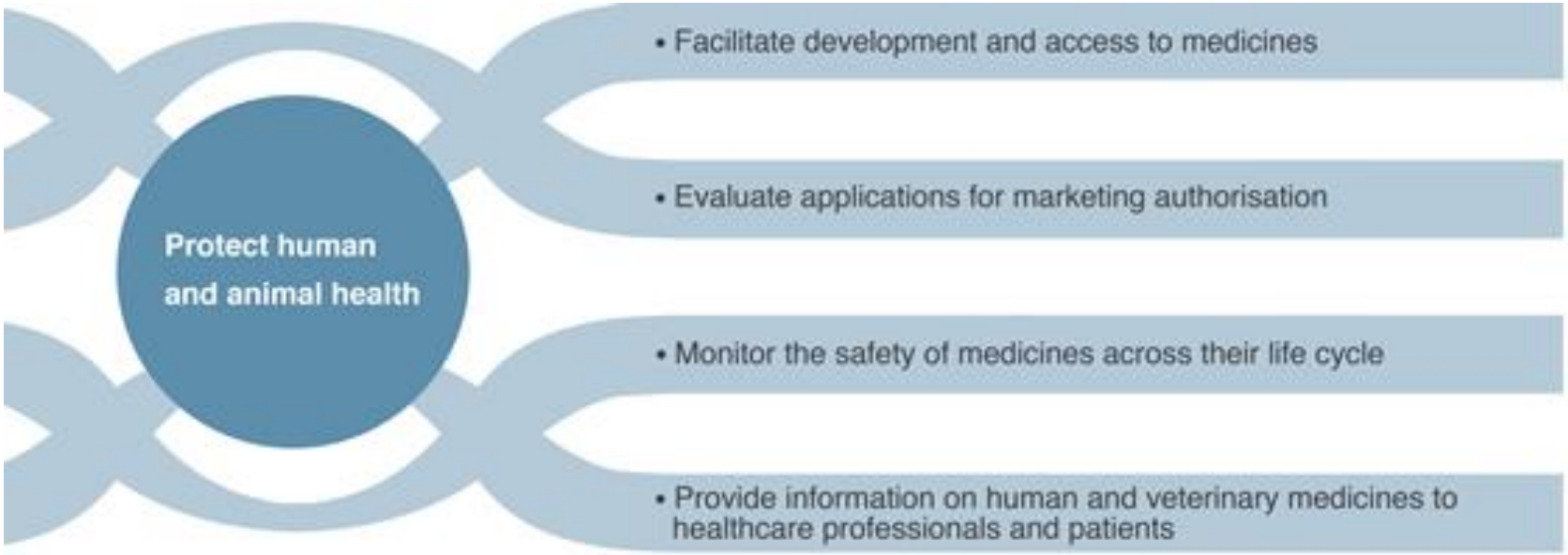
-Promover las relaciones y cooperaciones entre sus socios, así como con otras sociedades o grupos científicas de áreas afines.

-Organizar reuniones científicas y contribuir a la formación continuada de los profesionales del ámbito de la salud, en PGt/PGx.

Regulatory agencies

- **USA→ Food and Drug Administration (FDA)**
- **Europe→ European Medicines Agency (EMA)**

The mission of the EMA is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the EU



➢The EMA **Pharmacogenomics Working Party** provides recommendations to the Committee for Medicinal Products for Human Use (CHMP) on all matters relating directly or indirectly to pharmacogenomics.

Regulatory agencies

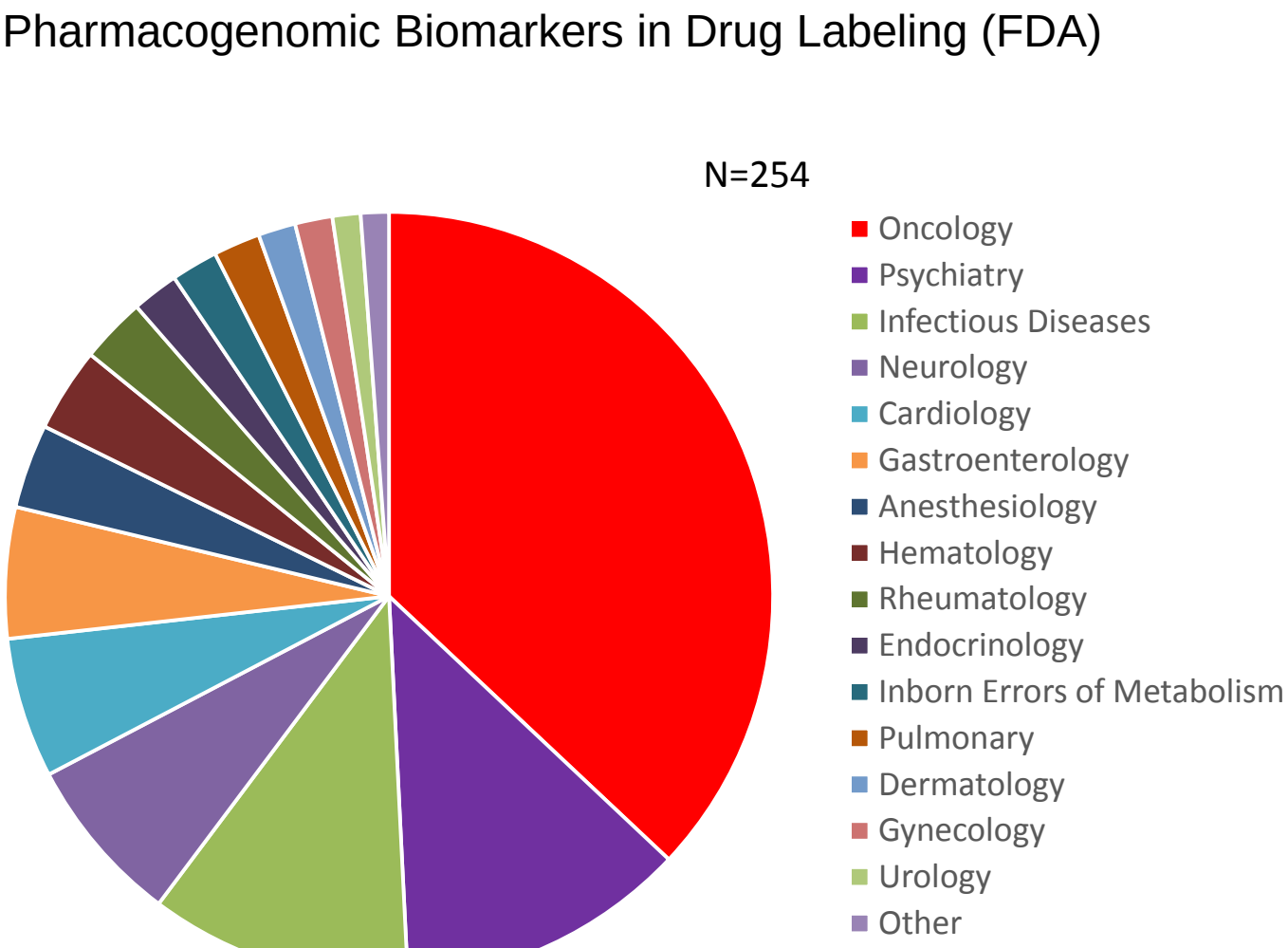
Pharmacogenomic Biomarkers in Drug Labeling (FDA)

n=254

Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes
- Trial design features

Regulatory agencies

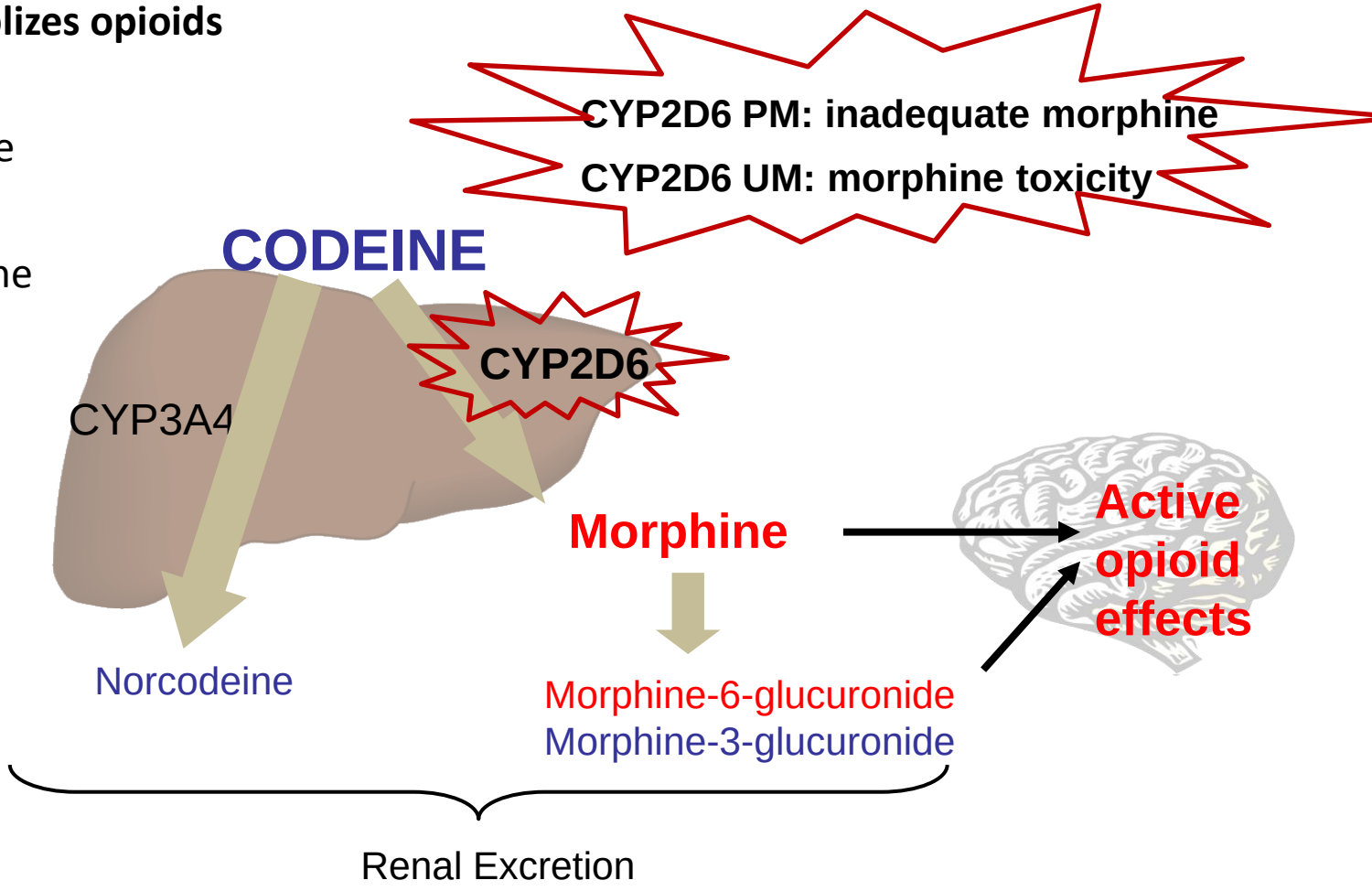


Casos prácticos

Codeine in infancy and breastfeeding

CYP2D6 metabolizes opioids

- Codeine
- Hydrocodone
- Oxycodone
- Propoxyphene
- Tramadol



Reynolds Clin Lab Med 2008;28:581

Codeine in infancy and breastfeeding

Case Report

Lancet 2006; 368: 704

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL.[1] The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1·9–20·5 ng/mL at doses of 60 mg every 6 h.

Genotype analysis was done for cytochrome P450 2D6 (*CYP2D6*), the enzyme catalysing the O-demethylation of codeine to morphine.[2] The mother was heterozygous for a *CYP2D6*2A* allele with *CYP2D6*2×2* gene duplication, classified as an ultra-rapid metaboliser. This genotype

Morphine Overdose from Codeine

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

Our review of several decades of adverse event reports submitted to FDA* from January 1969 to May 2015 identified **64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years**. This includes only reports submitted to FDA, so there may be additional cases about which we are unaware. We also identified nine cases of serious breathing problems, **including three deaths, with the use of tramadol in children** younger than 18 years from January 1969 to March 2016 (see Data Summary). The majority of serious side effects with both codeine and tramadol occurred in children younger than 12 years, and **some cases occurred after a single dose of the medicine.**

Morphine Overdose from Codeine

Nota informativa

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

Agencia Española de Medicamentos y Productos Sanitarios
AEMPS

CODEÍNA: NUEVAS RESTRICCIONES DE USO COMO ANTITUSÍGENO EN PEDIATRÍA

(Recomendaciones del Comité para la Evaluación de Riesgos en Farmacovigilancia europeo-PRAC)

Fecha de publicación: 13 de marzo de 2015

Categoría: MEDICAMENTOS DE USO HUMANO, SEGURIDAD.
Referencia: MUH (FV) 3/2015

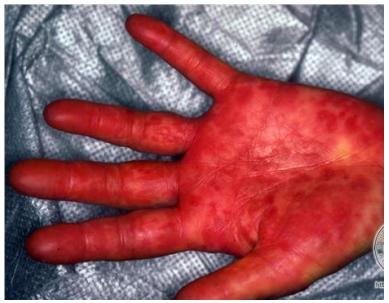
Tras la revisión del balance beneficio-riesgo de codeína para el tratamiento de la tos asociada a procesos catarrales en población pediátrica se han recomendado las siguientes restricciones de uso:

- ***No utilizar codeína en menores de 12 años de edad, en pacientes metabolizadores ultrarrápidos del CYP2D6 ni en mujeres durante la lactancia.***
- ***No se recomienda el uso de codeína en pacientes de 12 a 18 años de edad que presenten compromiso de la función respiratoria.***

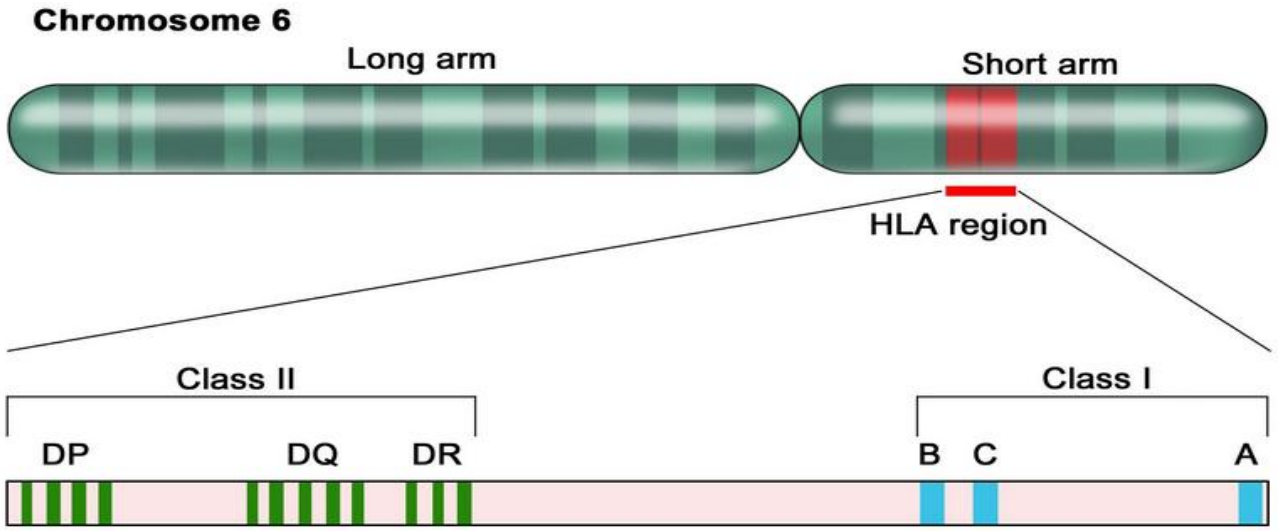
No identificados

Toxicity of carbamazepine

*HLA-B*15:02* allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis



- Life-threatening cutaneous disorders
- Mortality that can be as high as 30%
- Immune mediated etiology



Toxicity of carbamazepine

Table 1 **Frequency of *HLA* alleles in patients with Stevens–Johnson syndrome**

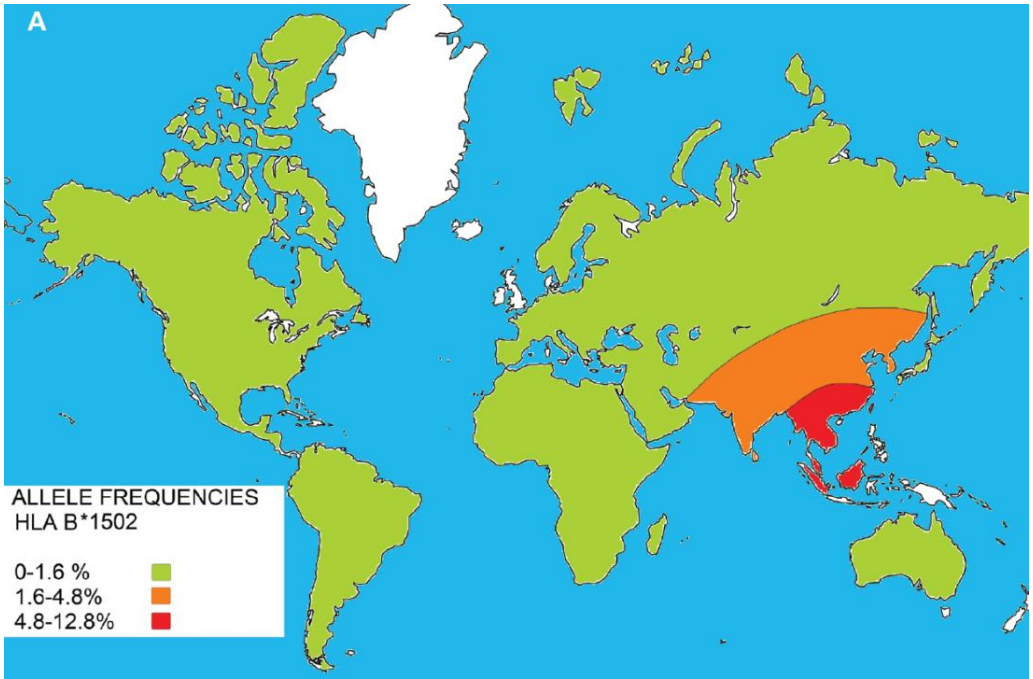
HLA allele	*CBZ–SJS*	*CBZ-tolerant*	*Normal*
*B*1502*	44 (100%)	3 (3%)*	8 (8.6%)†

Stevens–Johnson syndrome (CBZ–SJS; $n = 44$), and in carbamazepine-tolerant ($n = 101$) and normal subjects ($n = 93$).

*Odds ratio (CBZ–SJS/CBZ-tolerant): 2,504 (95% CI, 126–49,522); corrected P value $P_c = 3.13 \times 10^{-27}$.

†Odds ratio (CBZ–SJS/normal): 895 (95% CI, 50–15,869); $P_c = 1.38 \times 10^{-21}$.

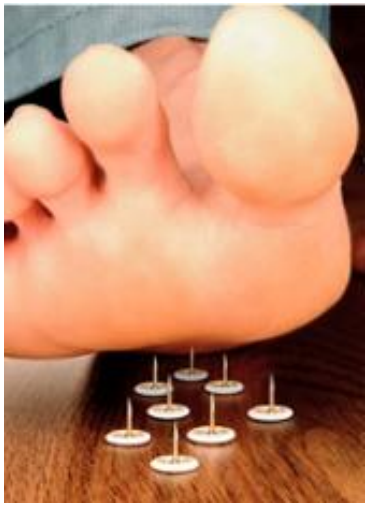
Nature 2004;428(6982):486

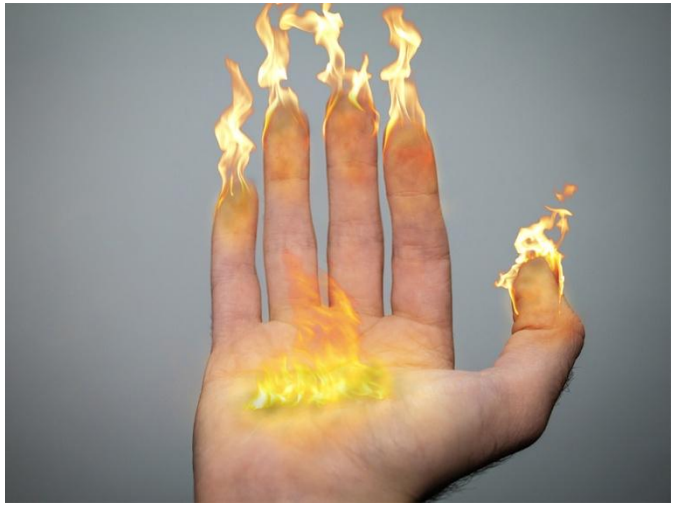


Drug-induced peripheral neuropathy

- **40%** of cancer patients suffer neuropathy (treatments)
- Neuropathy **limits the dose and efficacy** of these drugs
- Affects **quality of life**, sometimes permanently
- Genetic component, but **no markers** of neuropathy risk in clinic

Feet or hands



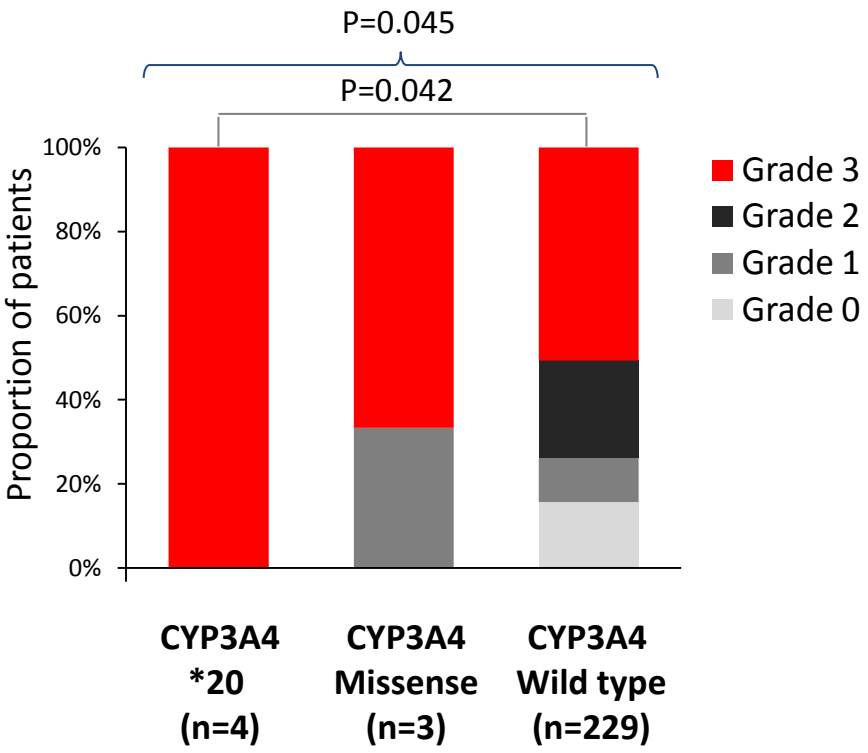


Numbness, tingling
Pain (sharp, throbbing)
Pain (freezing, burning)
Extreme sensitivity to touch
Lack of coordination
Falling
Muscle weakness

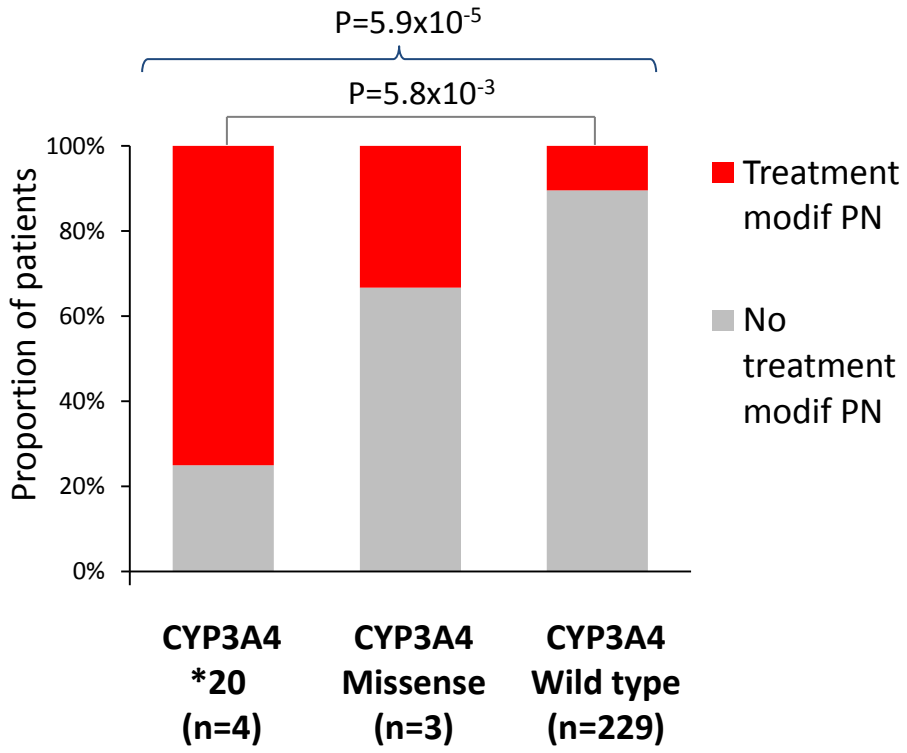
Paclitaxel-induced neuropathy

*CYP3A4*20* allele

Maximum neuropathy grade



Treatment modifications caused by neuropathy

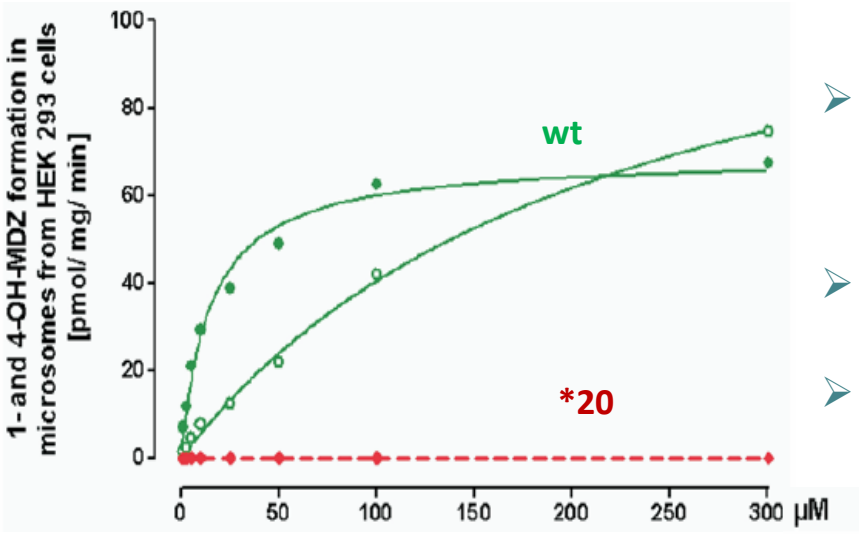


Apellániz-Ruiz, Clin Cancer Res. 2015;21(2):322-8

*CYP3A4*20* allele

(rs67666821)

- *CYP3A4* has little genetic variation (no coding variant MAF>1%)
- Loss of function (LOF) alleles are very rare
- The LOF allele *CYP3A4*20* discovered in 2006 and defined as **rare allele**

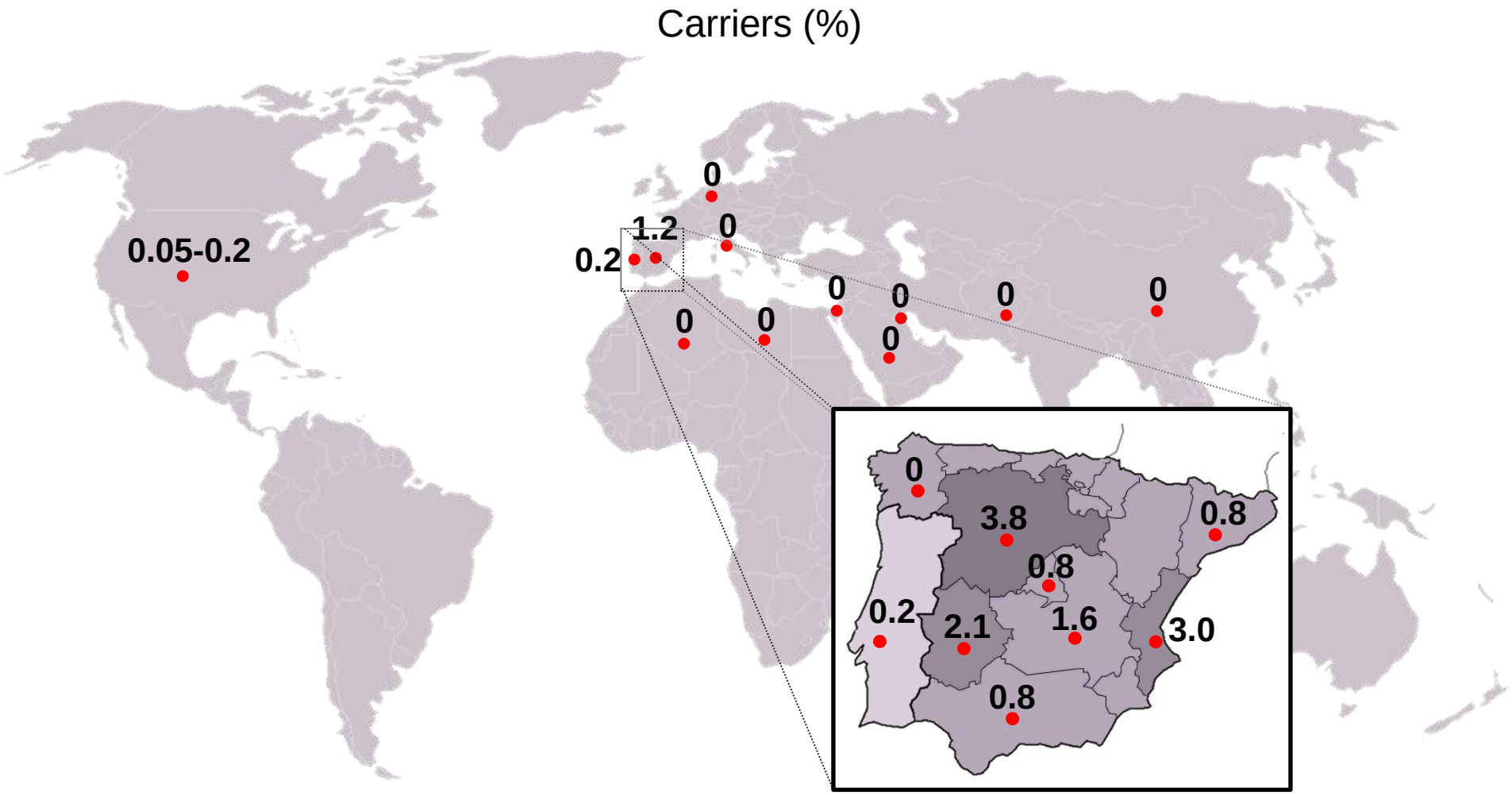


- Carrier with 6-fold higher exposure to CYP3A4 drug.

  Brazilian with Spanish mother
- CYP3A4.20 inactive protein
- Rare (ExAC: 34 het/ 60,625 indiv; MAF=0.03%)

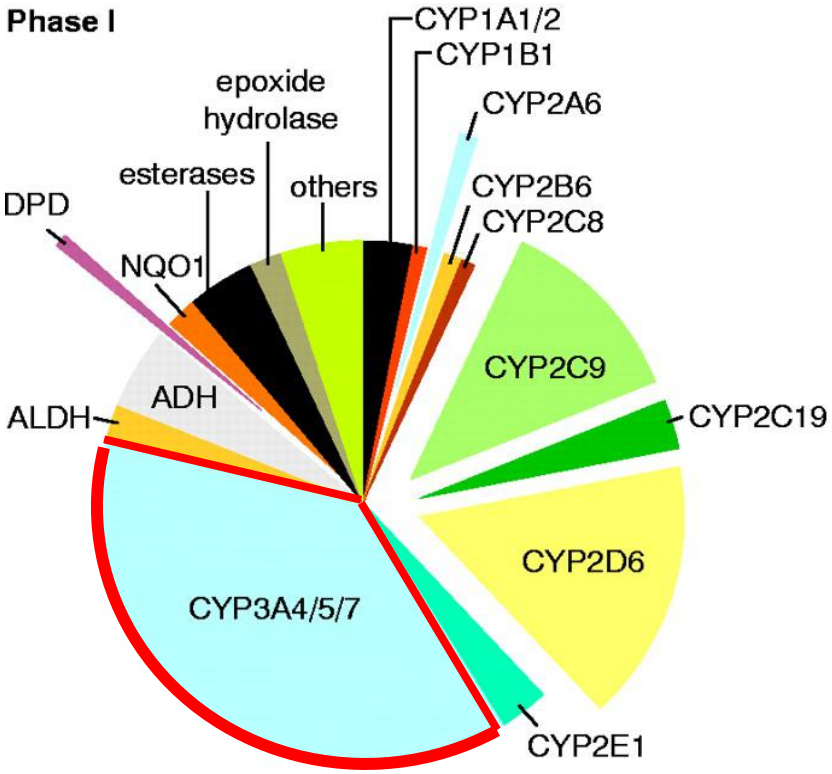
Westlind-Johnsson, Clin Pharmacol Ther. 2006;79:339

Worldwide distribution of *CYP3A4*20* allele



Apellaniz-Ruiz, Pharmacogenomics J. 2015;15:288

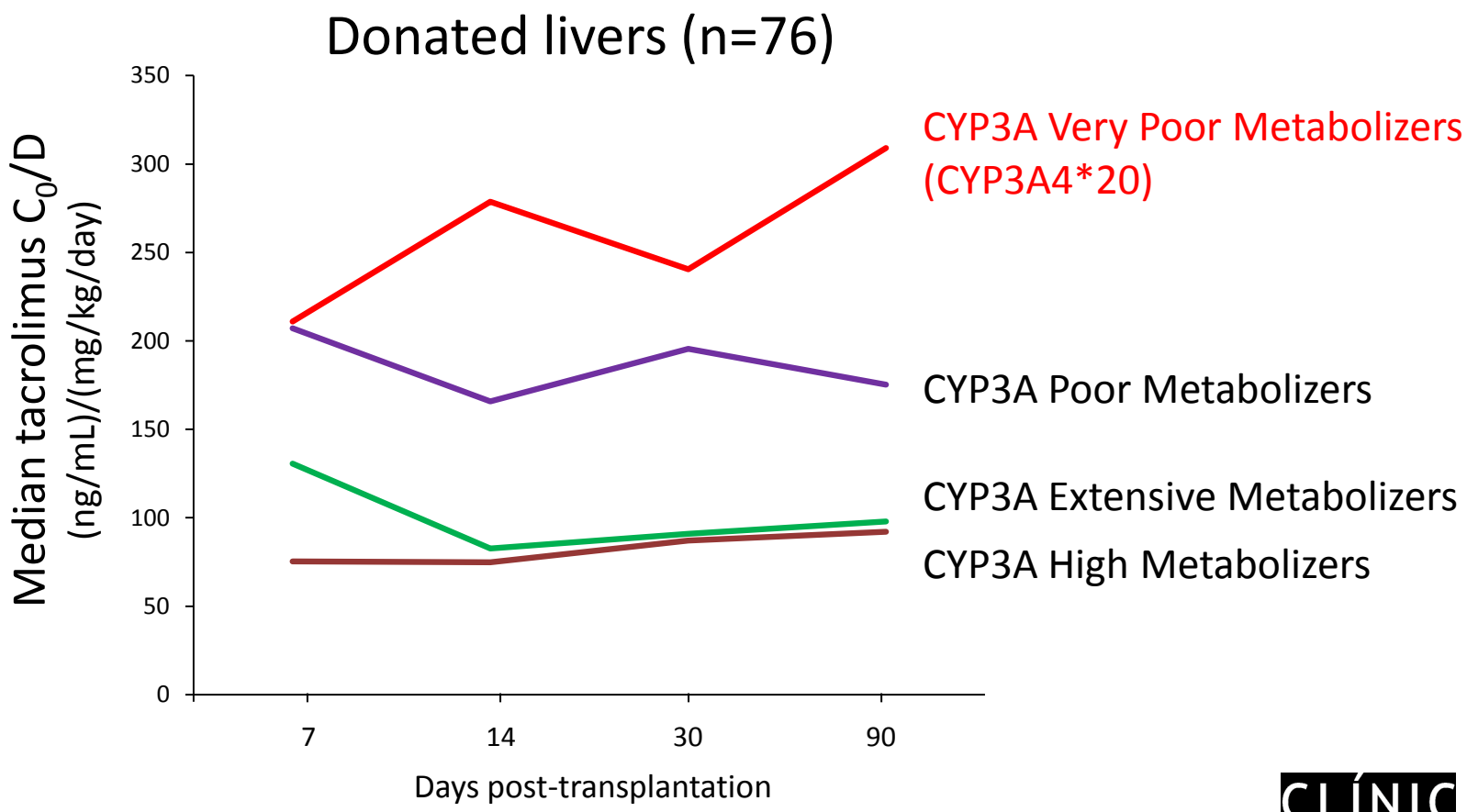
CYP3A4 substrates



Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

Clinical impact of *CYP3A4*20* on tacrolimus PK

Tacrolimus therapy in liver transplant

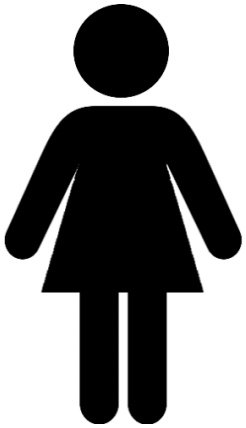


Gomez-Bravo *et al. (in press)*

CLÍNIC BARCELONA Hospital Universitari

M. Brunet

Extraordinary responses



34 years old

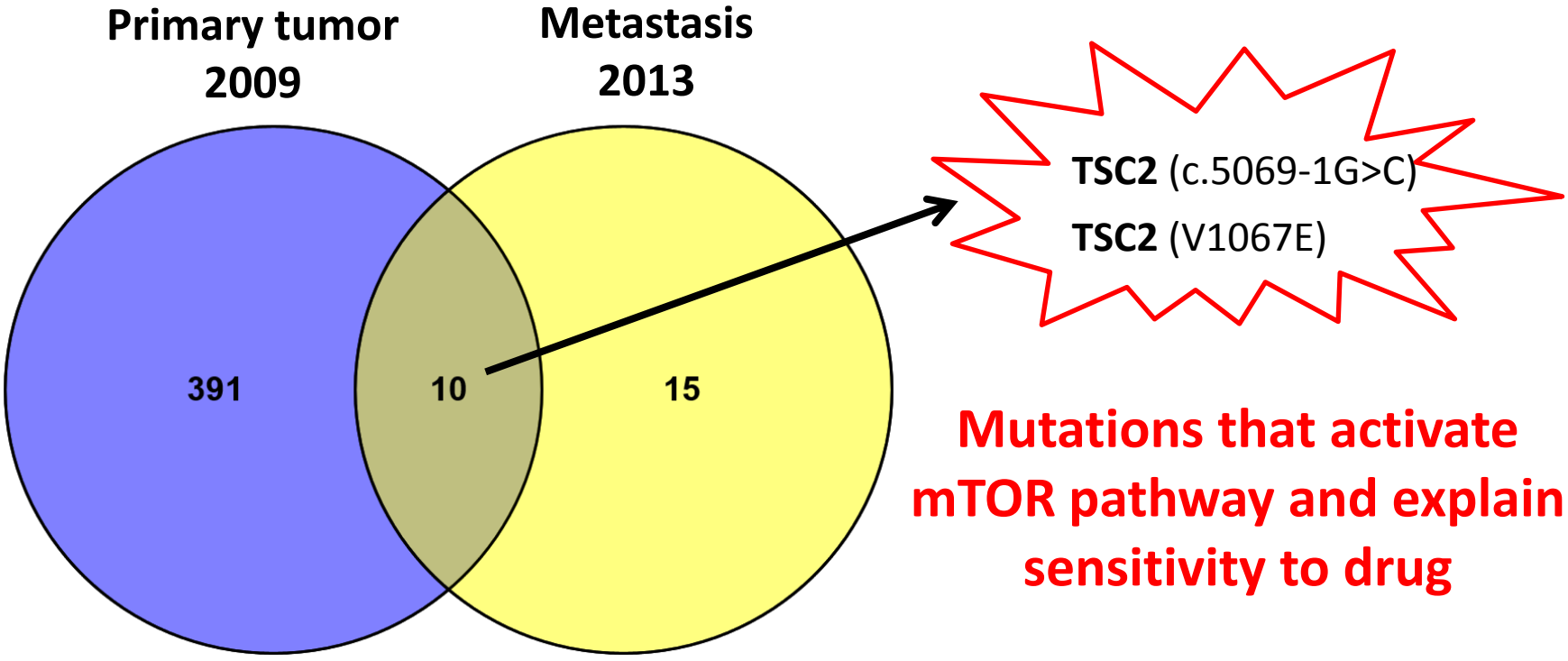
- Diagnosed with **metastatic chromophobe renal cancer** (Mtx femur and lungs>5)– 2008
- **Temsirolimus as first line** –15 months later **>80% of reduction in primary tumor & Complete Response in Mtx**
- Nephrectomy– 2009
- Disease free, 2011 stops Temsirolimus stop and starts follow up
- 2013 retroperitoneal adenopathy (Mtx) – surgery
- Dec 2016 –renal tumor Mtx in femur
- **Temsirolimus treatment on-going.** After one dose, pain disappeared, again in response; no toxicity

Whole Exome Sequencing

Maroto, JNCCN (in revision)

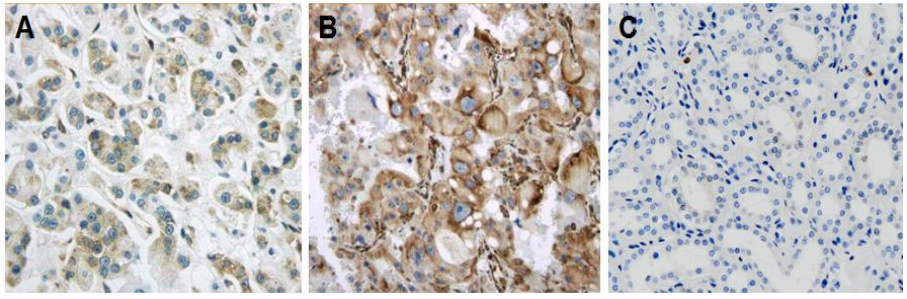
HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA
Pablo Maroto
Georgia Anguera

Whole exome sequencing (WES) of tumors



Mutations that activate mTOR pathway and explain sensitivity to drug

IHC pS6 tumors and normal kidney



Conclusions

- PGt/ PGx will result in safer, more efficient and better drugs. However, there are important challenges ahead
- Large studies and solid evidences are needed for the advancement of the field
- Initial pharmacogenetic examples are simple (one gene) but future lies in complex responses (many genes, interactions, environment). New technologies will be a driving force
- These advancements will drastically change medicine as we currently know it. Conventional medicine evolution to Personalized Medicine