Pharmacogenomics in the precision medicine era

24-11-2022

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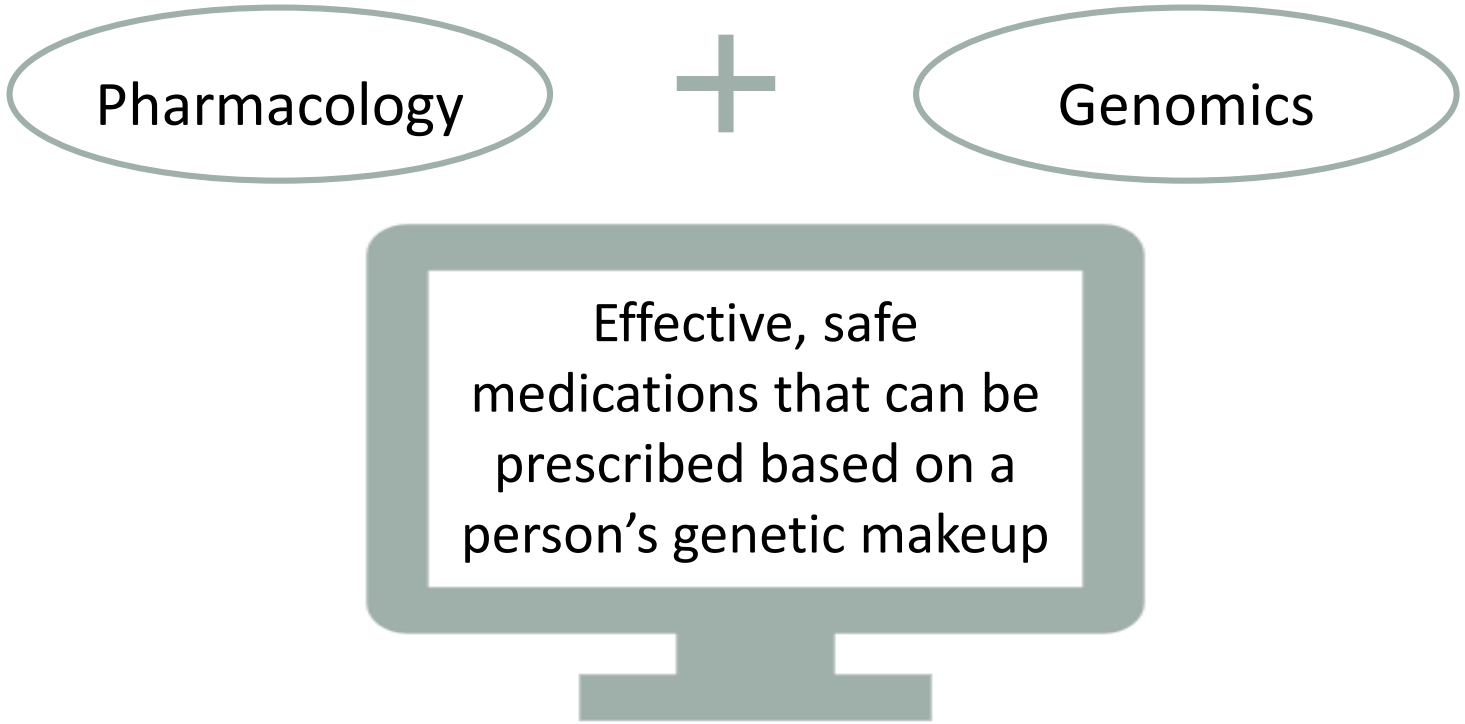
CONTENT

- Introduction
- Real time PCR – melting curve analysis
- Real time PCR – Taqman probes
- Other techniques

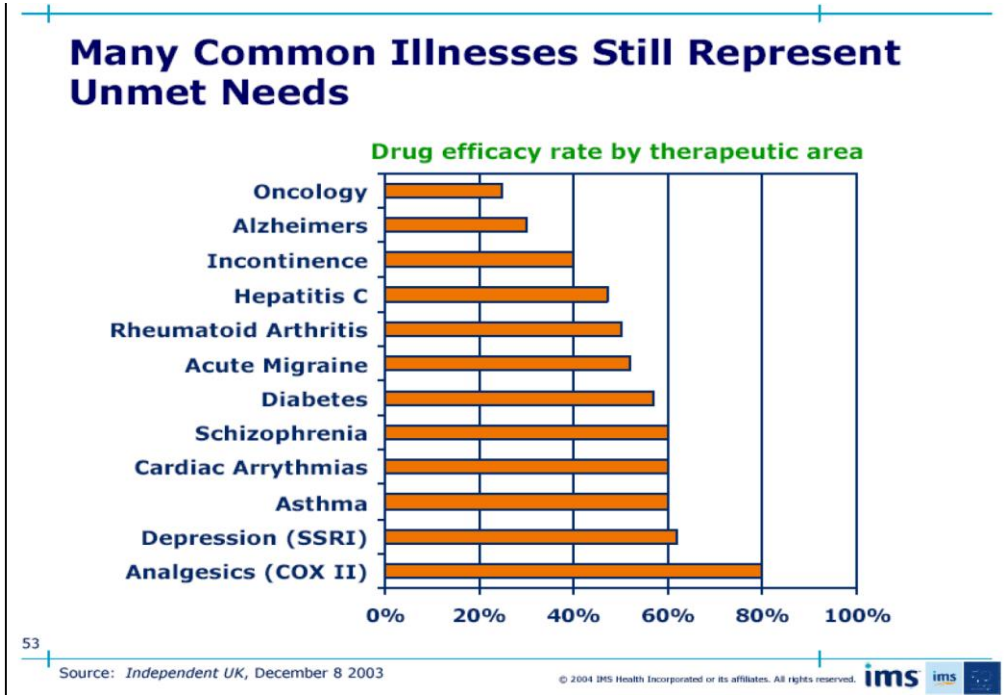
PHARMACOGENOMICS

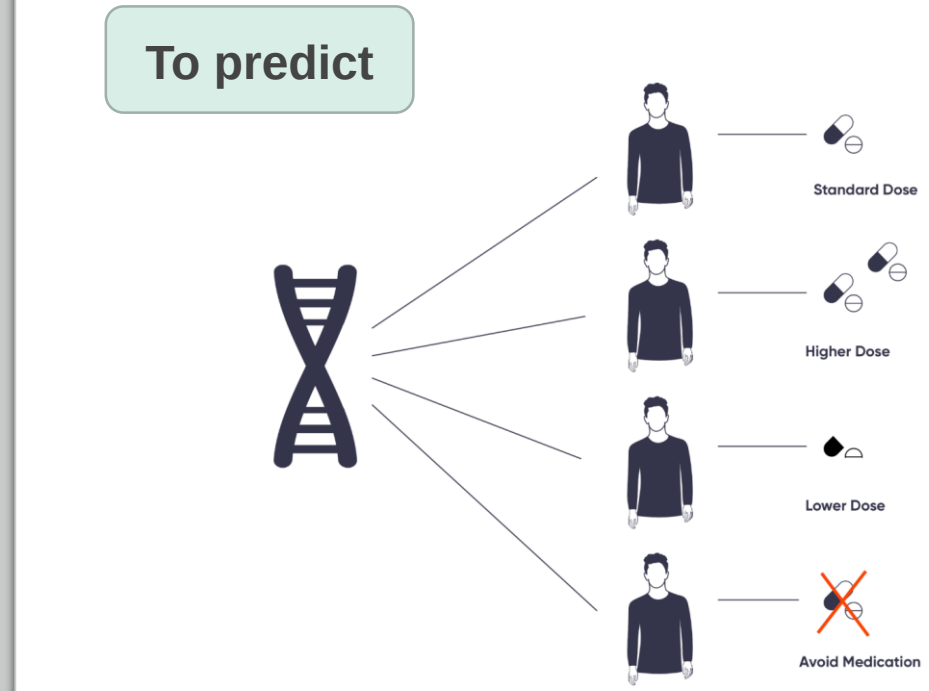
- Pharmacogenomics is the study of how genes affect a person's response to drugs



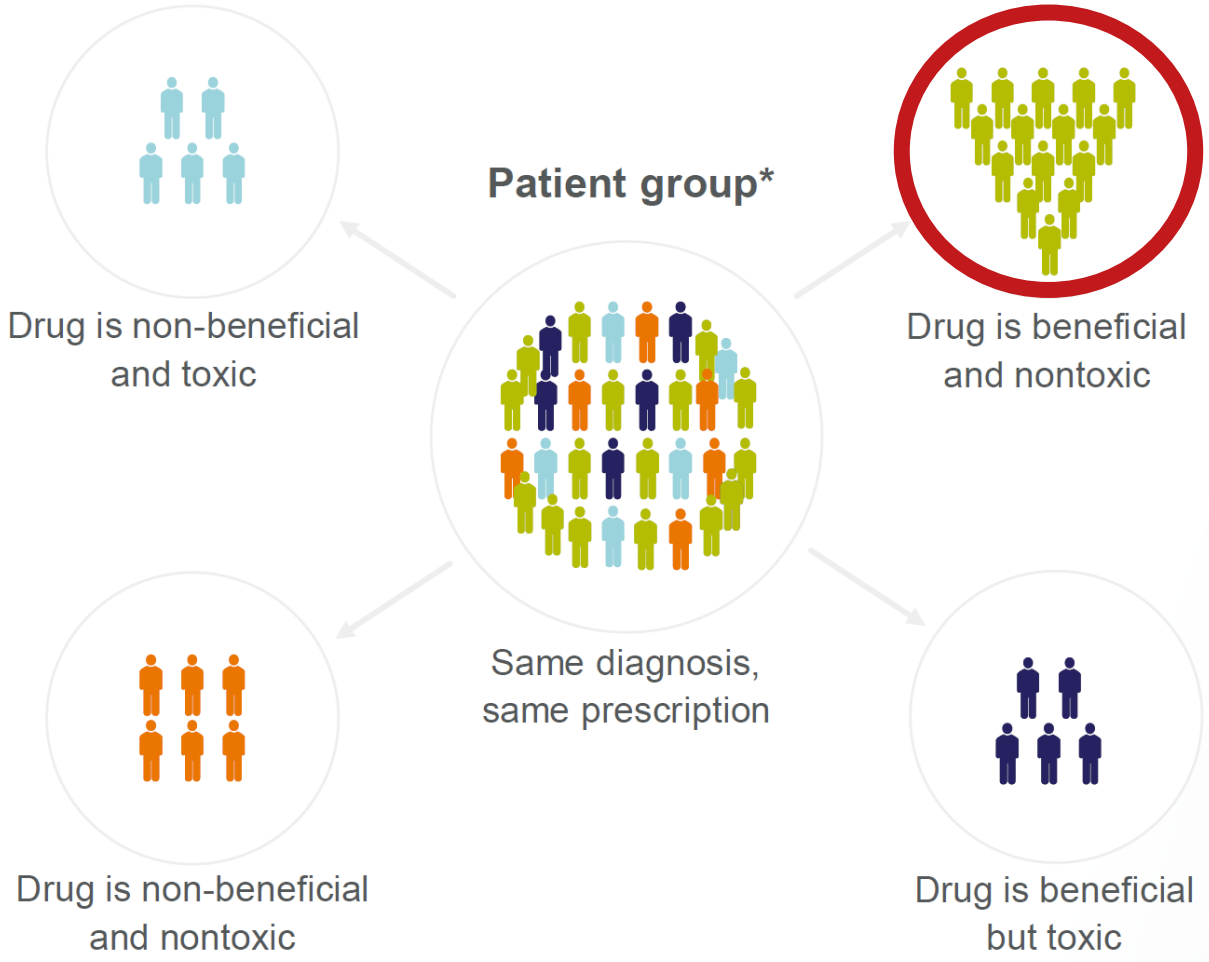
PRECISION MEDICINE

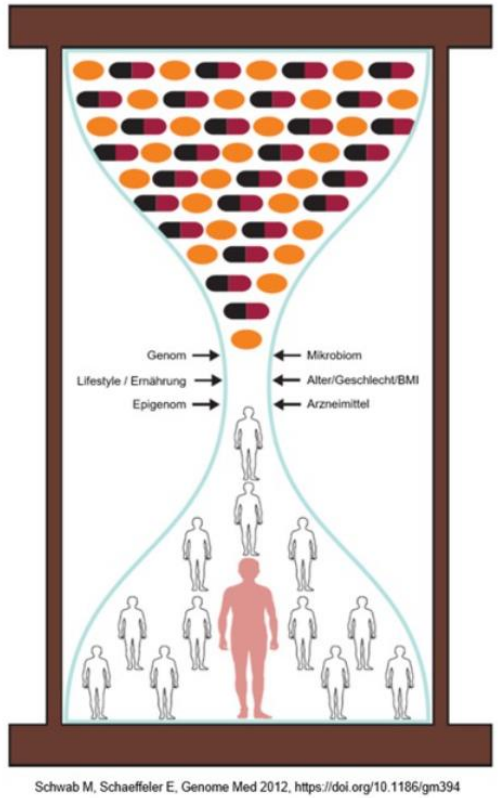
- Statistics demonstrate that over 4 billion prescriptions are issued each year in the US, however, only around 50% of them show the expected therapeutic efficacy. In the US alone, the direct and indirect cost of chronic pain management can range from $560 to 635 billion annually





Pharmacogenetic test

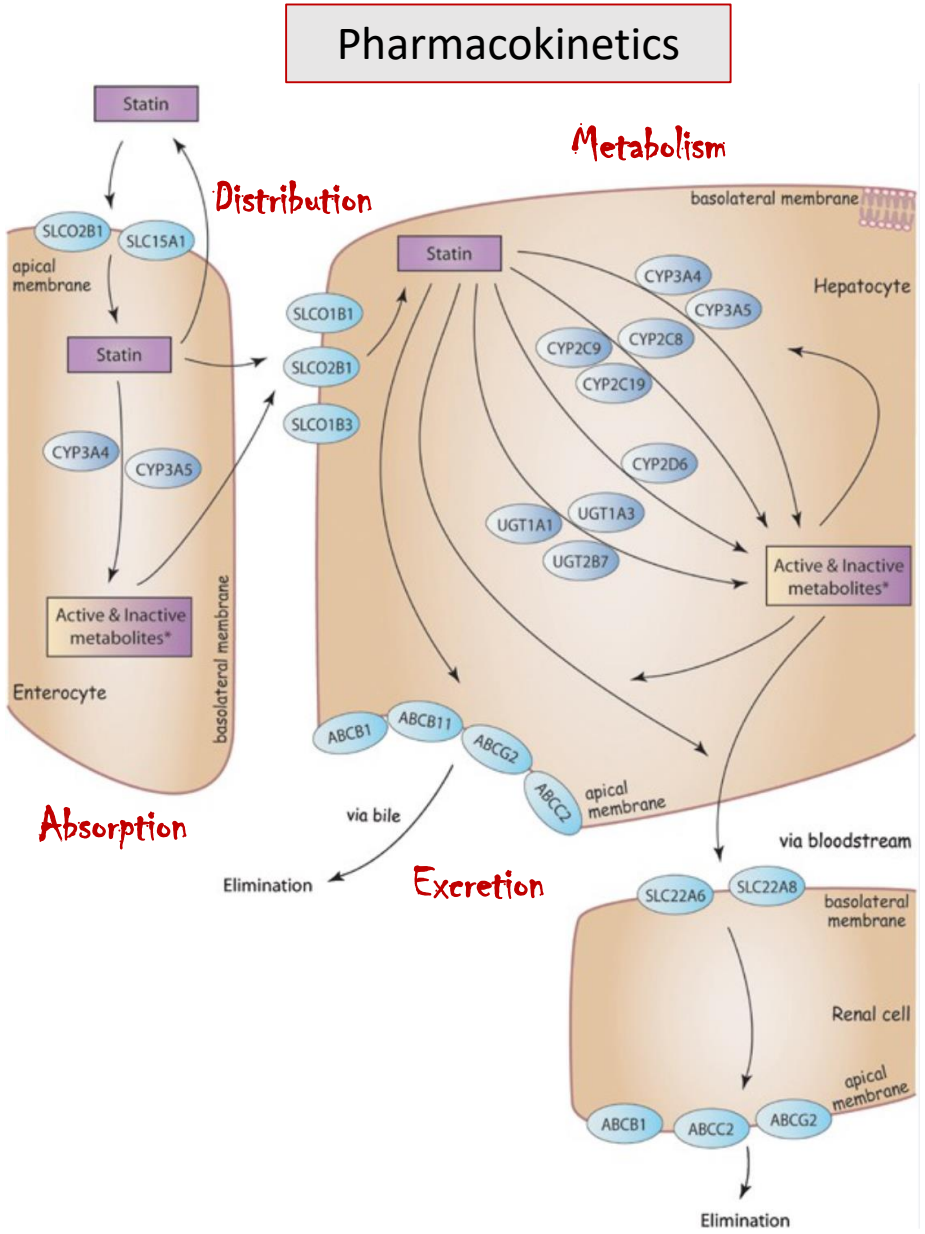


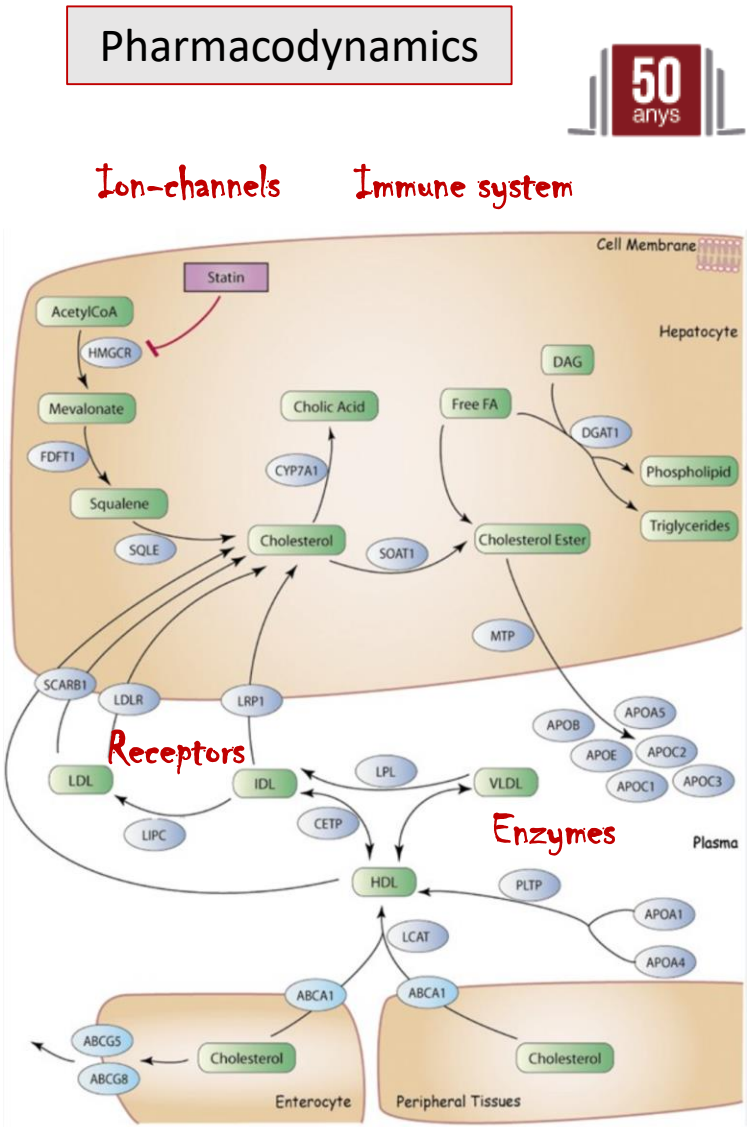


Schwab M, Schaeffeler E, Genome Med 2012, https://doi.org/10.1186/gm394

- Drug
- Genomics
- Lifestyle
- Epigenomics
- Microbiome
- Sex, age, BMI

METABOLIC PATHWAYS





Mangravite, L., Thorn, C. & Krauss, R. Clinical implications of pharmacogenomics of statin treatment. *Pharmacogenomics J* **6**, 360–374 (2006). https://doi.org/10.1038/sj.tpj.6500384

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Level Definitions for CPIC Genes/Drugs

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.
A/B	Preliminary review indicates it is likely that the definitive CPIC level will be either A or B.	Full evidence review needed to assess level of evidence, but prescribing actionability is likely	Full review by expert guideline group to assign strength of recommendation
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.

CPIC GUIDELINES

A = 118
A + B = 167

GUIDELINES	DRUGS	GENES
CFTR and Ivacaftor		
CYP2B6 and efavirenz		
CYP2C19 and Clopidogrel		
CYP2C19 and Proton Pump Inh		
CYP2C19 and Voriconazole		
CYP2C9 and NSAIDs		
CYP2C9, HLA-B and Phenytoin		
CYP2C9, VKORC1, CYP4F2 and Warfarin	warfarin	CYP2C9 CYP4F2 VKORC1
CYP2D6 and Atomoxetine		
CYP2D6 and Ondansetron and		
CYP2D6 and Tamoxifen		
CYP2D6, CYP2C19 and Selectiv		
CYP2D6, CYP2C19 and Tricycli		
CYP2D6, OPRM1, COMT, and C		
HLA-A, HLA-B and Carbamazepine and Oxcarbazepine	carbamazepine oxcarbazepine	HLA-A HLA-B
HLA-B and Abacavir		
HLA-B and Allopurinol		
IFNL3 and Peginterferon-alpha-based Regim		
MT-RNR1 and Aminoglycosides		
RYR1, CACNA1S and Volatile anesthetic agen		
SLCO1B1, ABCG2, CYP2C9, and Statins		
CYP3A5 and Tacrolimus	tacrolimus	CYP3A5
DPYD and Fluoropyrimidines	capecitabine fluorouracil tegafur	DPYD
G6PD	aminosalicylic acid aspirin chloramphenicol chloroquine chlorpropamide glipizide glyburide hydroxychloroquine mafenide mepacrine mesalazine methylene blue moxifloxacin nalidixic acid nicorandil nitrofural nitrofurantoin norfloxacin ofloxacin	G6PD
TPMT, NUDT15 and Thiopurines	azathioprine mercaptopurine thioguanine	NUDT15 TPMT
UGT1A1 and Atazanavir	atazanavir	UGT1A1

FDA U.S. FOOD & DRUG ADMINISTRATION

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Propranolol	Cardiology	CYP2D6	Clinical Pharmacology
Quinidine	Cardiology	CYP2D6	Precautions
Rivaroxaban	Cardiology	F5 (Factor V Leiden)	Clinical Studies
Tafamidis	Cardiology	TTR	Clinical Pharmacology, Clinical Studies
Ticagrelor	Cardiology	CYP2C19	Clinical Pharmacology
Cevimeline	Dental	CYP2D6	Precautions
Abrocitinib	Dermatology	CYP2C19	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Dapsone (1)	Dermatology	G6PD	Warnings and Precautions, Use in Specific Populations, Patient Counseling Information
Dapsone (2)	Dermatology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions, Adverse Reactions, Patient Counseling Information
Fluorouracil (1)	Dermatology	DPYD	Contraindications, Warnings
Ustekinumab	Dermatology and Gastroenterology	IL12A, IL12B, IL23A	Warnings and Precautions
Chlorpropamide	Endocrinology	G6PD	Precautions
Evinacumab-dgnb (1)	Endocrinology	LDLR	Clinical Studies
Glimepiride	Endocrinology	G6PD	Warnings and Precautions, Adverse Reactions

50 anys

https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

PHARMACOGENOMIC PANEL

Cardio

- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4
- CYP3A5
- VKORC1
- SLCO1B1
- MTHFR
- F2
- F5
- APOE

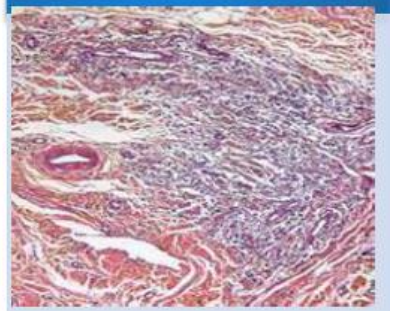
Pain

- CYP2C9
- CYP2C19
- CYP1A2
- CYP2B6
- CYP2D6
- CYP3A4
- CYP3A5
- OPRM1

Psych

- CYP2C9
- CYP2C19
- CYP1A2
- CYP2D6
- CYP3A4
- CYP3A5
- COMT
- ANKK1/DRD2

Oncology

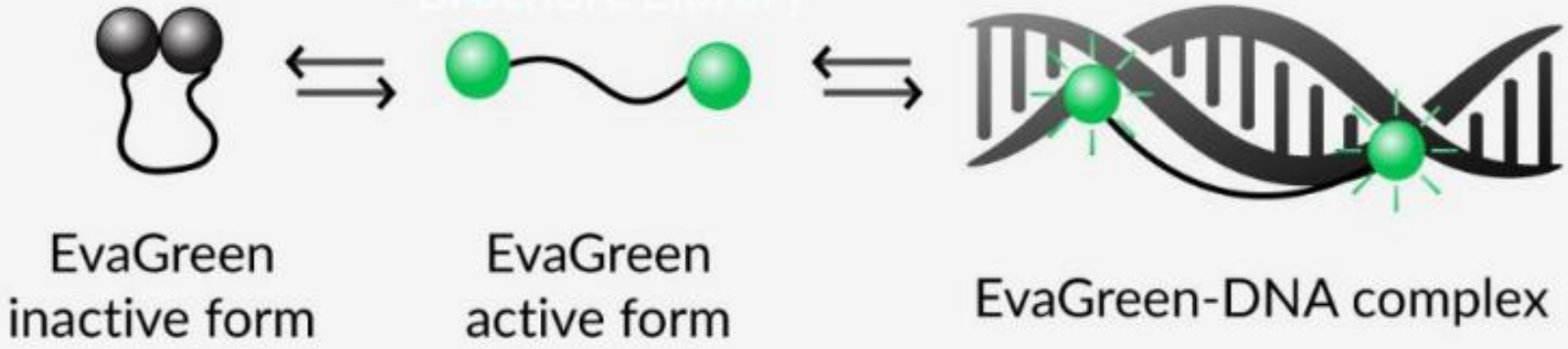


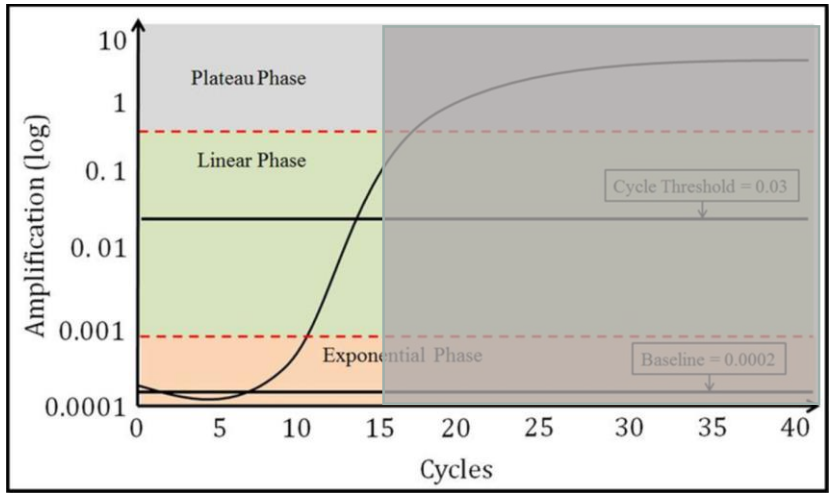
- ABCG2
- CYP2C8
- DPYD
- HTR2A
- HTR2C
- SLC6A4
- TPMT
- UGT1A1

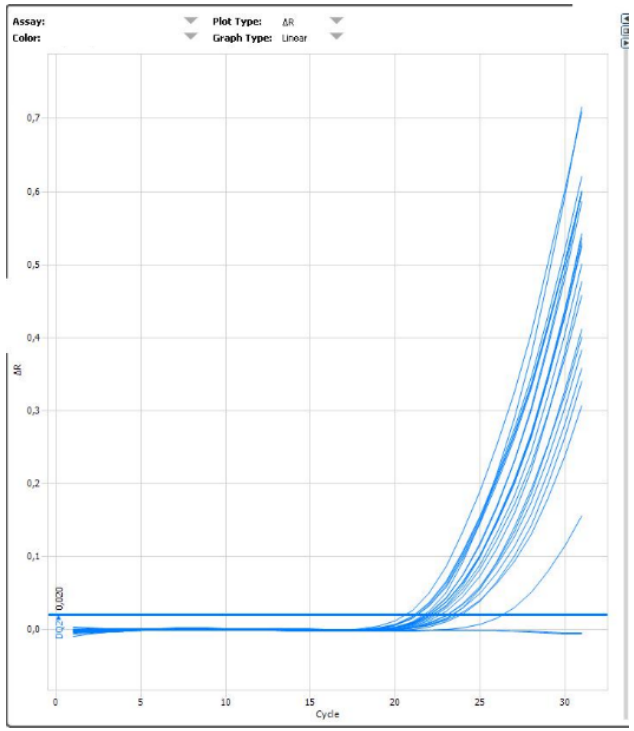
ThermoFisher SCIENTIFIC

REAL TIME PCR
melting curve analysis

- HLA alleles
- Carrier / non-carrier
- Multiplex
- HRM systems




Plateau Phase
Linear Phase
Exponential Phase
Cycle Threshold = 0.03
Baseline = 0.0002
Amplification (log)
10
1
0.1
0.01
0.001
0.0001
0
5
10
15
20
25
30
35
40
Cycles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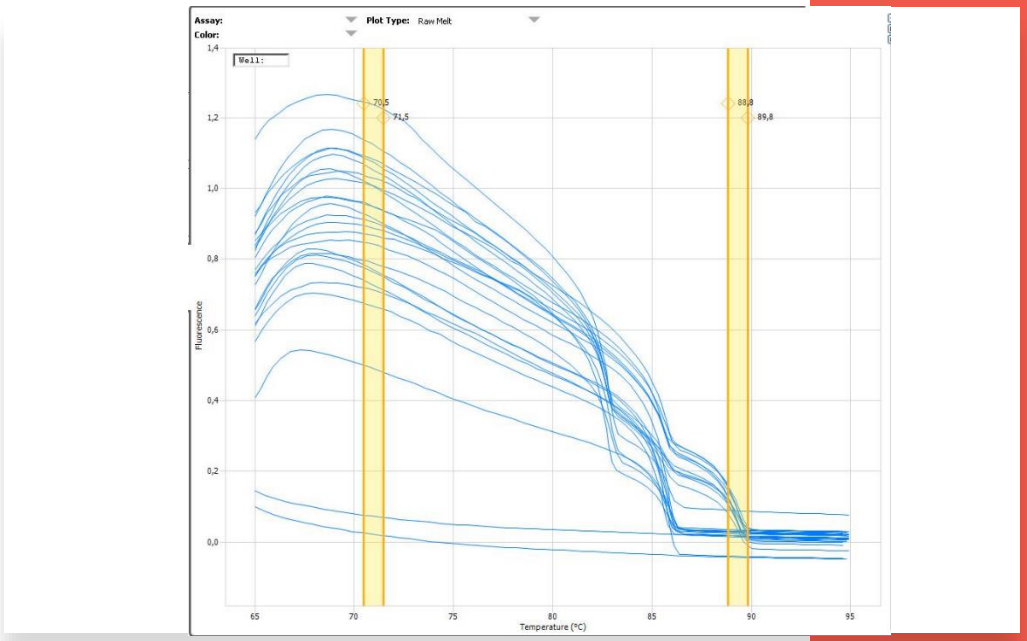
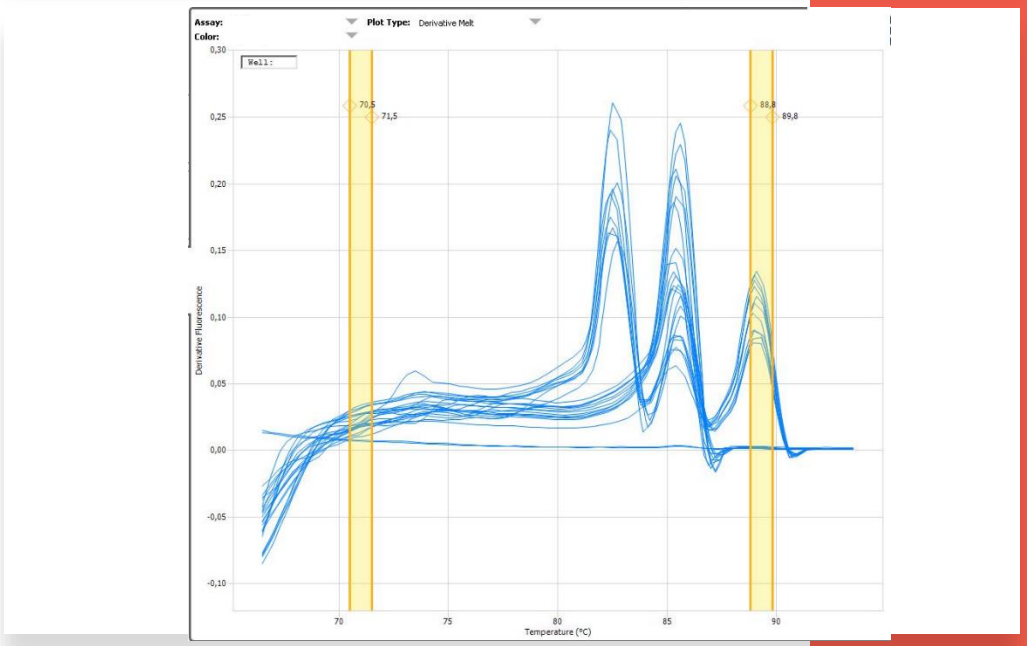
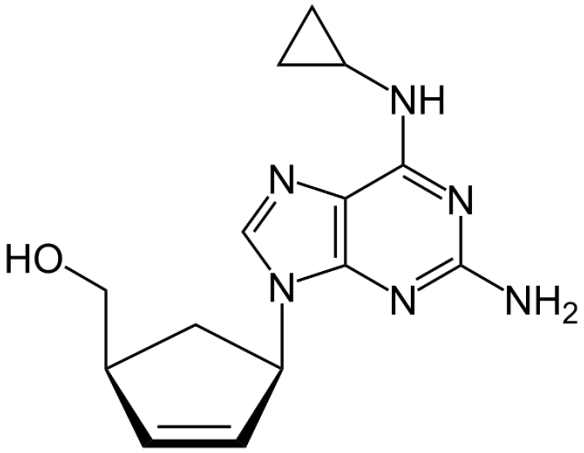
Color:
Plot Type: ΔR
Graph Type: Linear
ΔR
Cycle


Assay:
Color:
Plot Type: Raw Melt
Well:
70,5
71,5
88,8
89,8
Fluorescence
Temperature (°C)


Assay:
Color:
Plot Type: Derivative Melt
Well:
70,5
71,5
88,8
89,8
Derivative Fluorescence
Temperature (°C)



ABACAVIR; HLA-B*57:01

used in conjunction with other antiretrovirals in the treatment of HIV infection

Table 2 Recommended therapeutic use of abacavir in relation to *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for abacavir	Classification of recommendations[a]
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

HLA-B, human leukocyte antigen B.

Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Abacavir Dosing

MA Martin[1], TE Klein[2], BJ Dong[3], M Pirmohamed[4], DW Haas[5–7] and DL Kroetz[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 91 NUMBER 4 | APRIL 2012

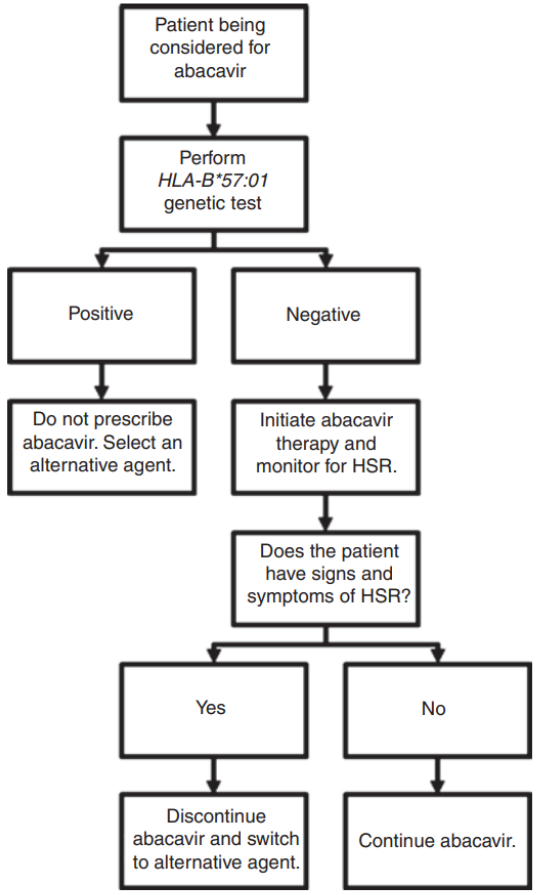
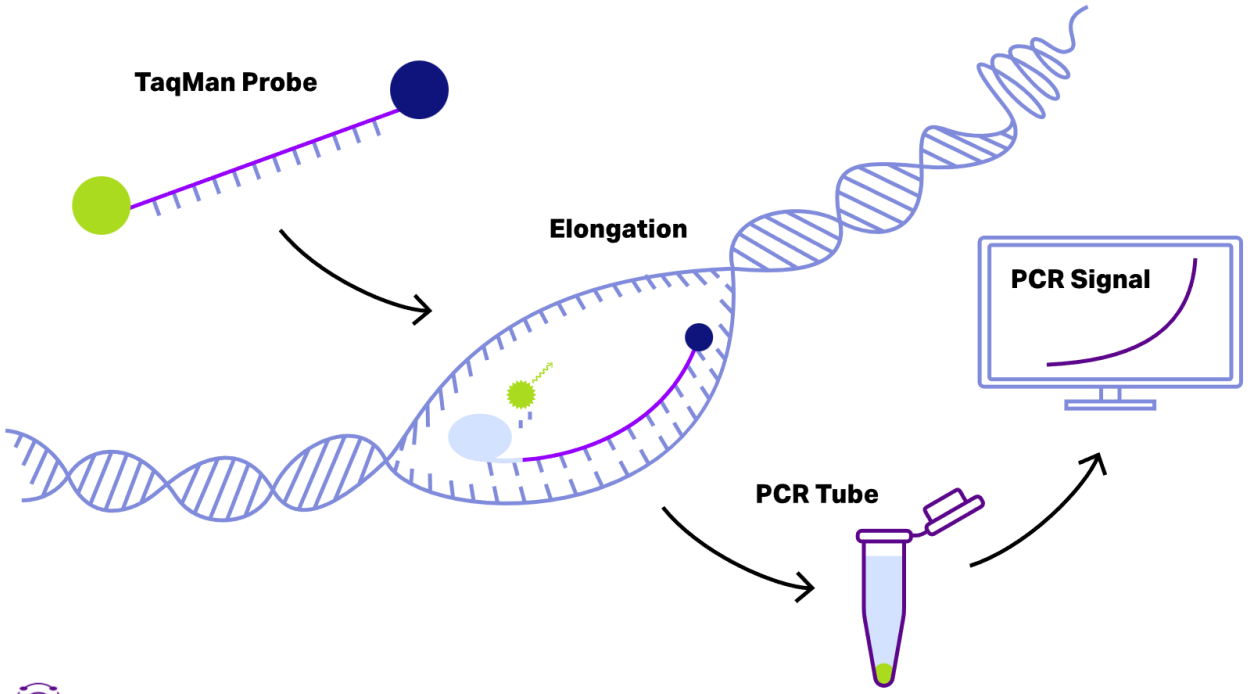


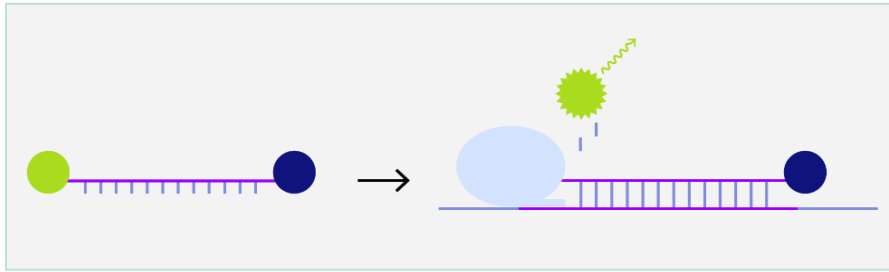
Figure 1 Treatment algorithm for clinical use of abacavir based on *HLA-B*57:01* genotype. HLA-B, human leukocyte antigen B; HSR, abacavir hypersensitivity reaction.

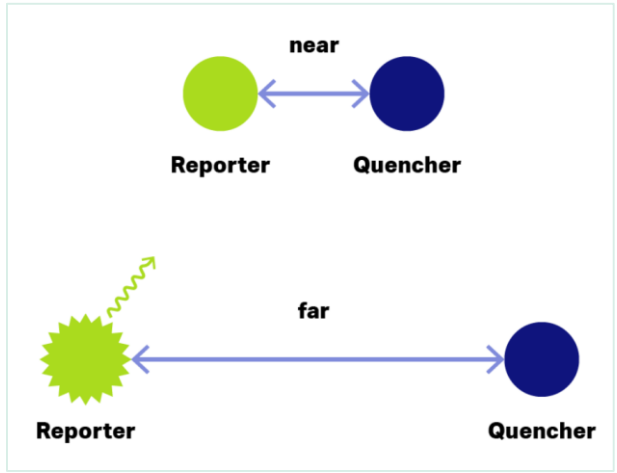
REAL TIME PCR
TaqMan probes

- Homozygote / heterozygote / wild type
- Single nucleotide variant
- Primer annealing + elongation in the same step

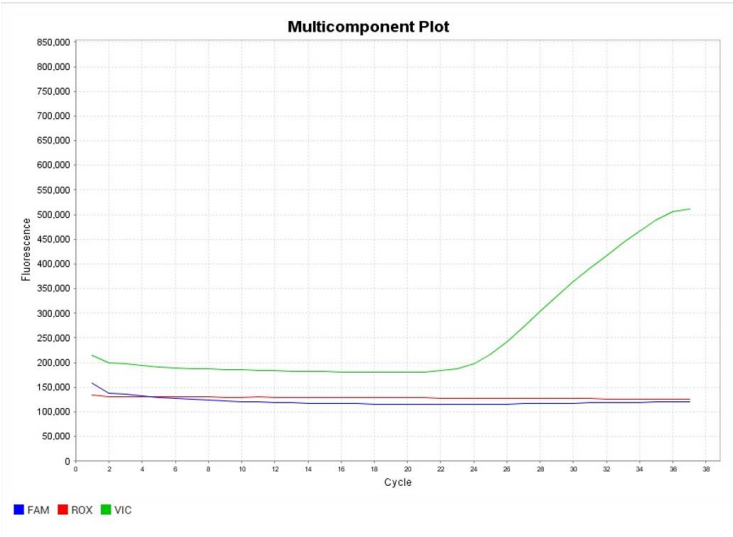


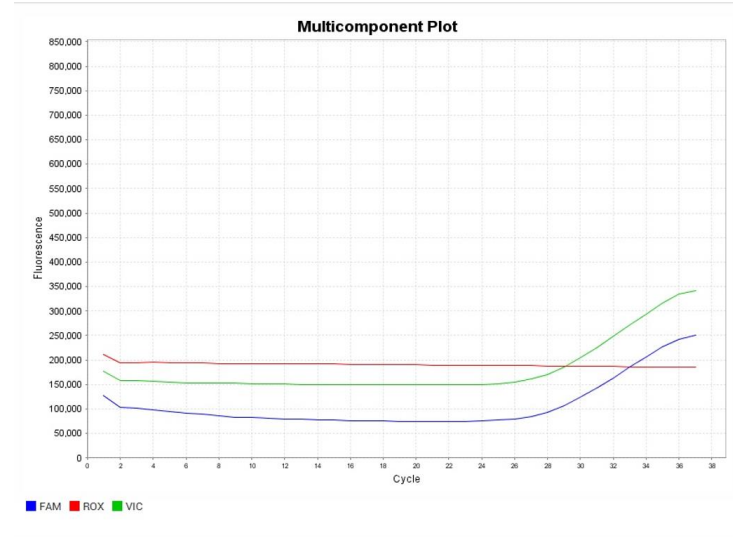
kilobaser



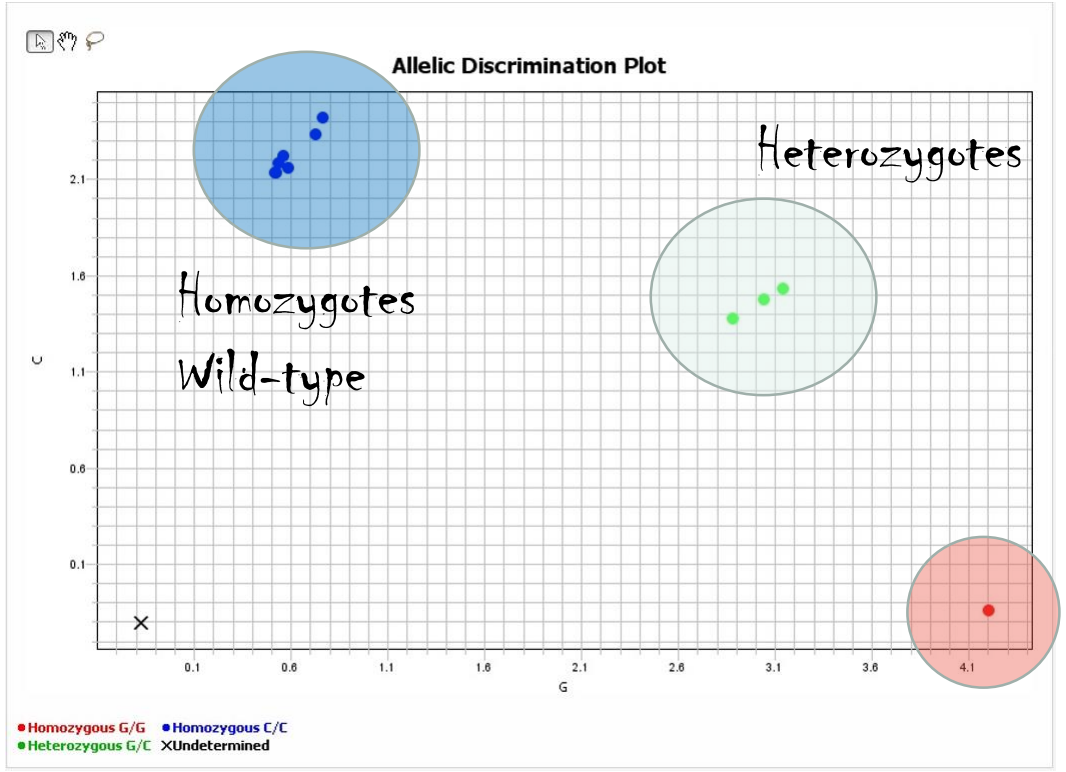


REAL TIME PCR
TaqMan probes

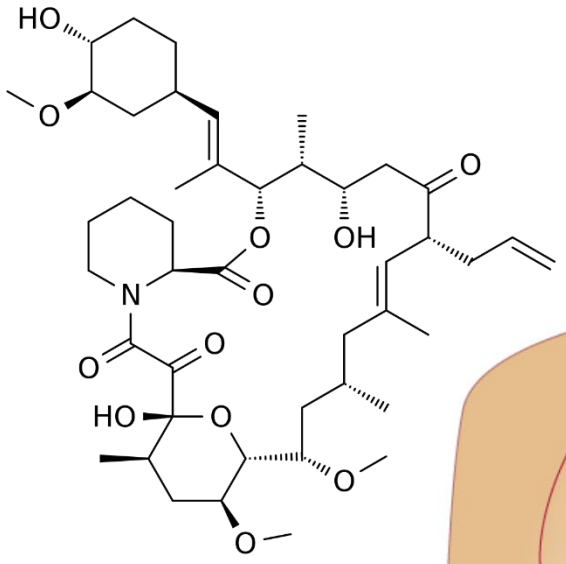


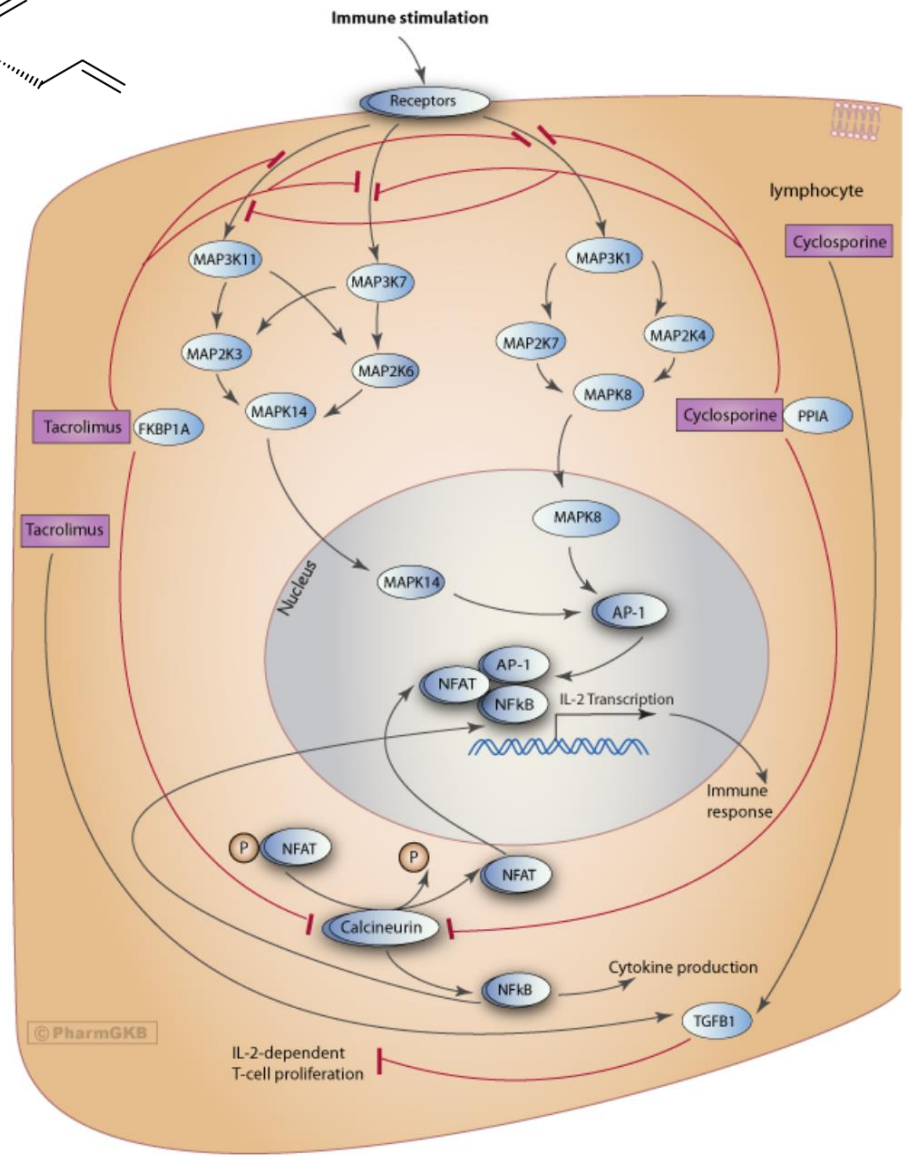


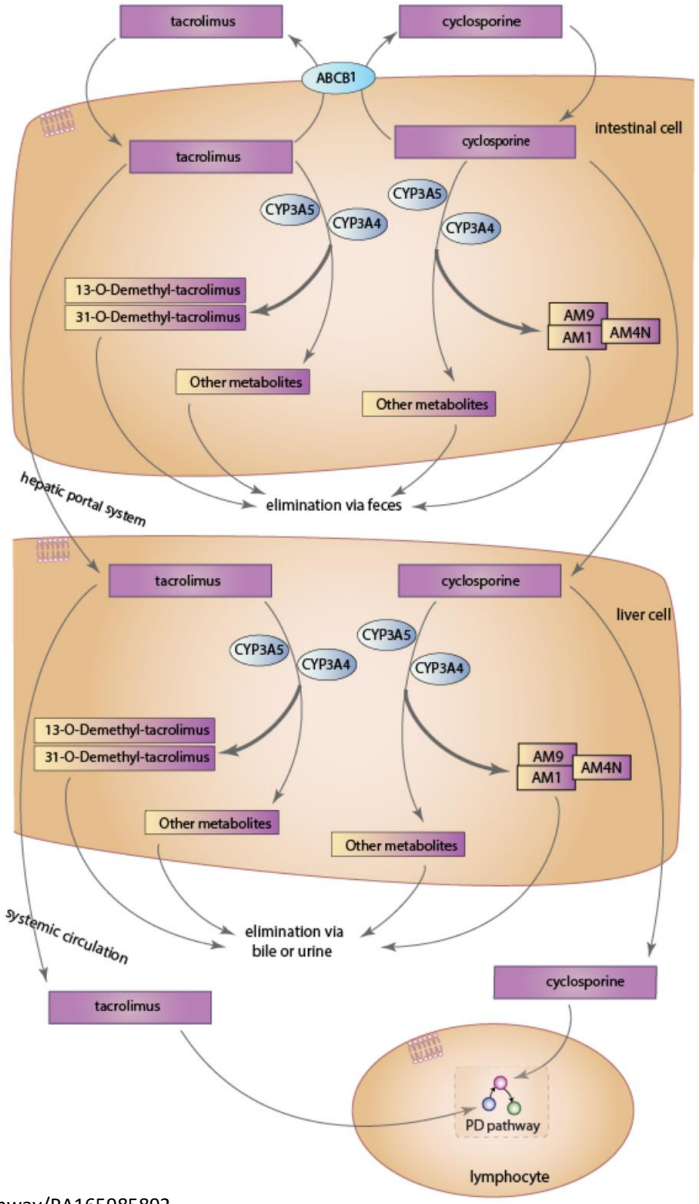
REAL TIME PCR
TaqMan probes



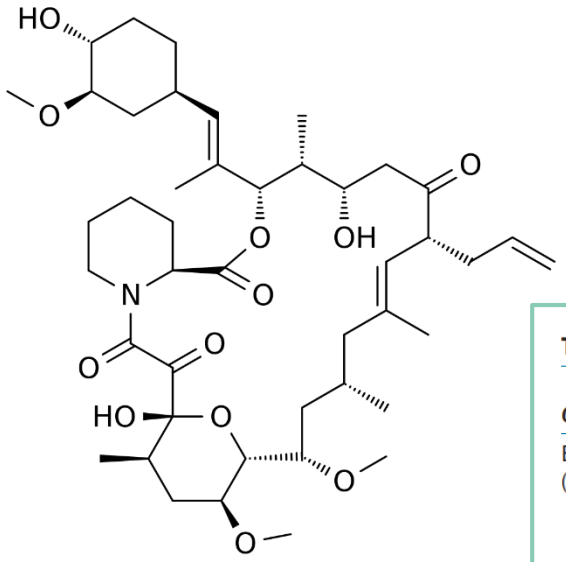
TACROLIMUS; CYP3A5







https://www.pharmgkb.org/pathway/PA165985892



TACROLIMUS; CYP3A5

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing

KA Birdwell[1,2], B Decker[3], JM Barbarino[4], JF Peterson[2,5], CM Stein[2,6], W Sadee[7], D Wang[7], AA Vinks[8,9], Y He[10], JJ Swen[11], JS Leeder[12], RHN van Schaik[13], KE Thummel[14], TE Klein[4], KE Caudle[15] and IAM MacPhee[16]

VOLUME 98 NUMBER 1 | JULY 2015 | www.wileyonlinelibrary/cpt

Table 1 Assignment of likely metabolism phenotypes based on *CYP3A5* diplotypes

Likely phenotype	Genotypes	Examples of diplotypes[a]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

TACROLIMUS; CYP3A5

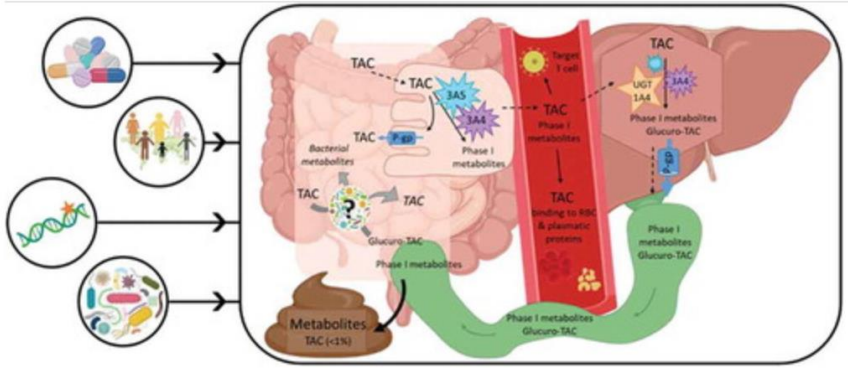
drug–drug interactions

ageing and ethnicity

CYP3A5 pre-emptive genotyping strategy

Expert opinion

The management of TAC concentration in transplanted kidney patients is as critical as it is challenging. Recommendations based on rigorous scientific evidences are lacking as knowledge of potential predictors remains limited outside of DDIs. Awareness of these limitations should pave the way for studies looking at demographic and pharmacogenetic factors as well as gut microbiota composition in order to promote tailored treatment plans. Therapeutic approaches considering patients' clinical singularities may help allowing to maintain appropriate concentration of TAC.



$$CL/F(l\,h^{-1}) = 38.4 \times [(0.86, \text{if days 6–10}) \text{ or } (0.71, \text{if days 11–180})] \times [(1.69, \text{if CYP3A5*1/*3 genotype}) \text{ or } (2.00, \text{if CYP3A5*1/*1 genotype})] \times (0.70, \text{if receiving a transplant at a steroid sparing centre}) \times [(\text{age in years}/50)^{-0.4}] \times (0.94, \text{if CCB is present})$$

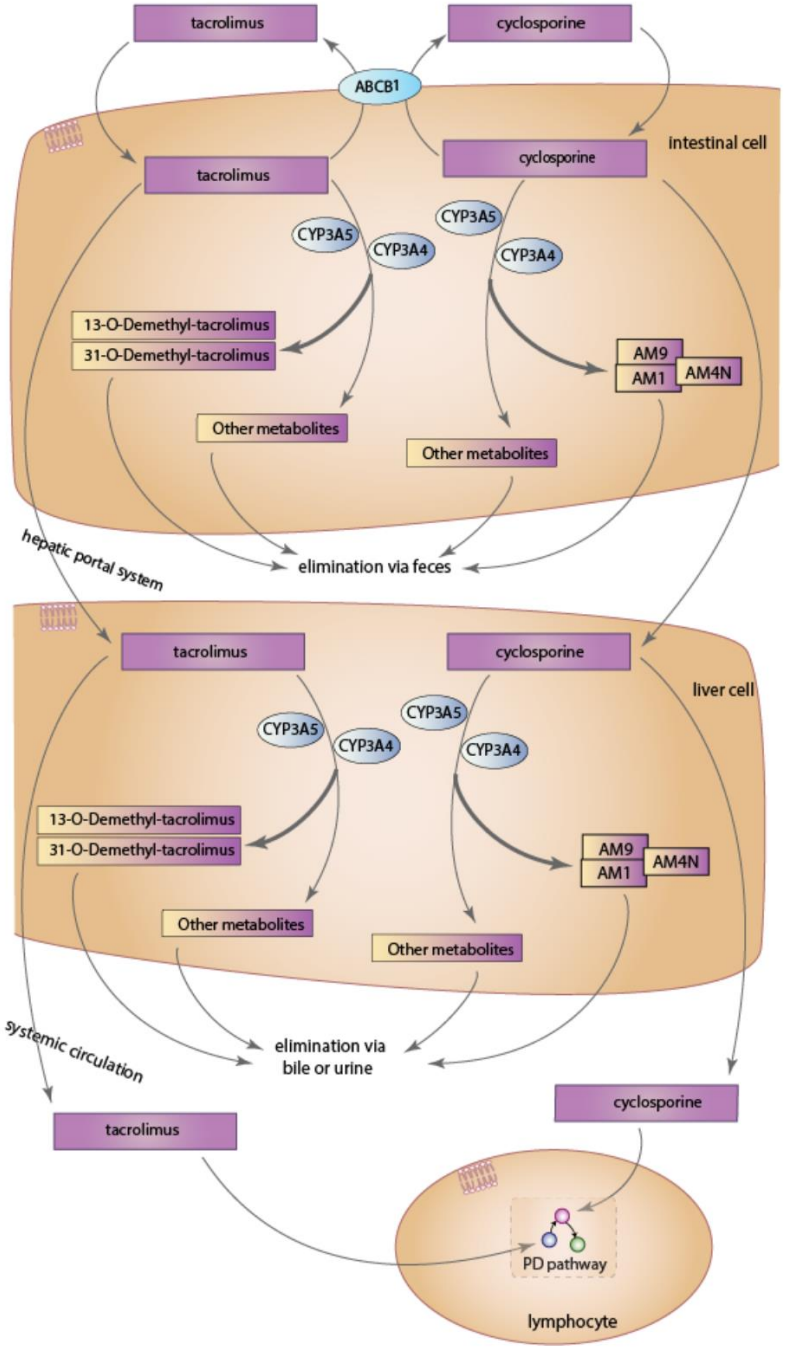
The total daily dose (TDD) requirement is then calculated from the estimated tacrolimus CL/F above and the desired goal trough concentration.

$$TDD\,(mg) = [CL/F(l\,h^{-1}) \times \text{tacrolimus trough goal } (ng\,ml^{-1}) \times 24\,h]/1000$$

Alexandra L Degraeve et al. (2020) Predictors of tacrolimus pharmacokinetic variability: current evidences and future perspectives, Expert Opinion on Drug Metabolism & Toxicology, 16:9, 769-782, DOI: 10.1080/17425255.2020.1803277

Passey C, Birnbaum AK, Brundage RC, Oetting WS, Israni AK, Jacobson PA. Dosing equation for tacrolimus using genetic variants and clinical factors. Br J Clin Pharmacol. 2011 Dec;72(6):948-57.

TACROLIMUS; CYP3A4



# (N=463)	GENE (UNIQUE = 119)	DRUG (UNIQUE = 285)	GUIDELINE	CPIC LEVEL	CPIC LEVEL STATUS
347	CYP3A4	tacrolimus		C	Provisional

Statin-associated musculoskeletal symptoms; *SLCO1B1*

KIF6 gene as a pharmacogenetic marker for lipid-lowering effect in statin treatment.

Ruiz-Iruela C, Padró-Miquel A, Pintó-Sala X, Baena-Díez N, Caixàs-Pedragós A, Güell-Miró R, Navarro-Badal R, Jusmet-Miguel X, Calmarza P, Puzo-Foncilla JL, Alía-Ramos P, Candás-Estébanez B.

PLoS One. 2018 Oct 10;13(10):e0205430. doi: 10.1371/journal.pone.0205430. eCollection 2018.

Being a carrier of the c.2155T> C variant of the *KIF6* gene negatively impacts patient responses to simvastatin, atorvastatin or rosuvastatin

Genetic contribution to lipid target achievement with statin therapy: a prospective study.

Ruiz-Iruela C, Candás-Estébanez B, Pintó-Sala X, Baena-Díez N, Caixàs-Pedragós A, Güell-Miró R, Navarro-Badal R, Calmarza P, Puzo-Foncilla JL, Alía-Ramos P, Padró-Miquel A.

Pharmacogenomics J. 2020 Jun;20(3):494-504. doi: 10.1038/s41397-019-0136-7. Epub 2019 Dec 6.

PMID: 31806882

ABCA1, *CYP2D6*, and *CETP* genotyping could be used to help predict which statin and dosage is appropriate in order to improve personalized medicin

Influence of 6 genetic variants on the efficacy of statins in patients with dyslipidemia.

Cano-Corres R, Candás-Estébanez B, Padró-Miquel A, Fanlo-Maresma M, Pintó X, Alía-Ramos P.

J Clin Lab Anal. 2018 Oct;32(8):e22566. doi: 10.1002/jcla.22566. Epub 2018 May 7.

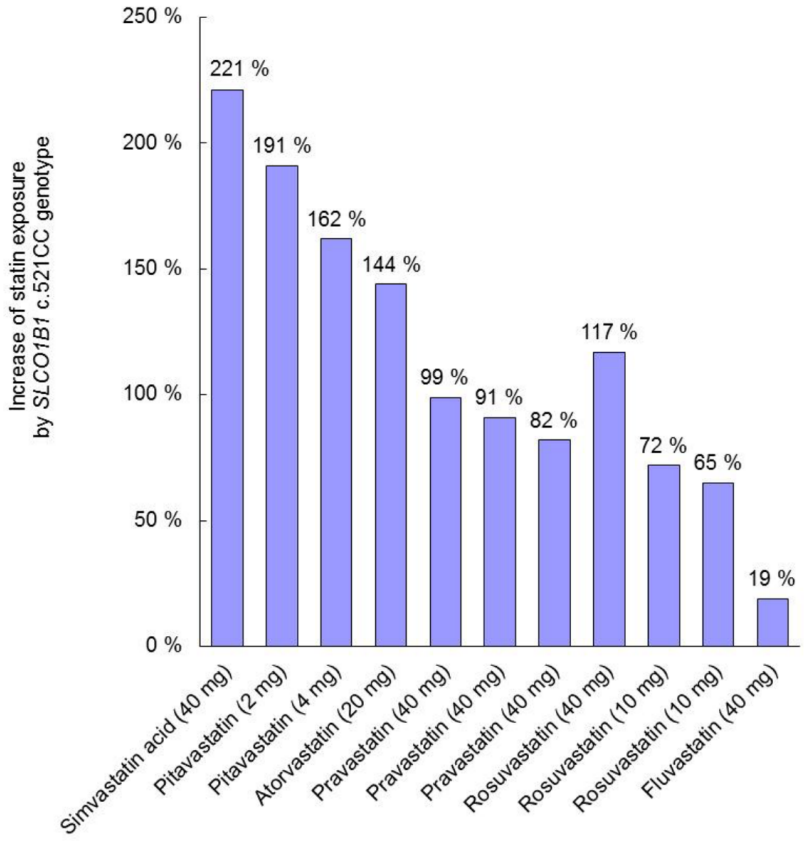
HMGCR c.1564-106A > G variant was associated with less statin efficacy to decrease cholesterol.

SLCO1B1, ABCG2, CYP2C9, HMGCR, CYP3A4/5, ABCB1, APOE, CETP, COQ2, LDLR, KIF6, LPA, HMGCR

Statin-associated musculoskeletal symptoms; *SLCO1B1*

# (N=463)	GENE (UNIQUE = 119)	DRUG (UNIQUE = 285)	GUIDELINE	CPIC LEVEL	CPIC LEVEL STATUS	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
10	SLCO1B1	atorvastatin	Guideline	A	Final	1A	Informative PGx	• 35152405
34	CYP2C9	fluvastatin	Guideline	A	Final	1A		• 35152405
35	SLCO1B1	fluvastatin	Guideline	A	Final	1A		• 35152405
52	SLCO1B1	lovastatin	Guideline	A	Final	1A		• 35152405
80	SLCO1B1	pitavastatin	Guideline	A	Final	1A		• 35152405
83	SLCO1B1	pravastatin	Guideline	A	Final	1A		• 35152405
87	ABCG2	rosuvastatin	Guideline	A	Final	1A		• 35152405
88	SLCO1B1	rosuvastatin	Guideline	A	Final	1A	Actionable PGx	• 35152405
91	SLCO1B1	simvastatin	Guideline	A	Final	1A	Informative PGx	• 22617227 • 24918167 • 35152405

https://cpicpgx.org/genes-drugs/



- The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *SLCO1B1*, *ABCG2*, and *CYP2C9* and statin-associated musculoskeletal symptoms (January 2022)

PEG Interferon-α; *IL28B* (rs12979860 C>T)

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *IFNL3* (*IL28B*) Genotype and PEG Interferon-α–Based Regimens

AJ Muir[1], L Gong[2], SG Johnson[3,4], MTM Lee[5,6,7], MS Williams[8], TE Klein[2], KE Caudle[9] and DR Nelson[10]

VOLUME 95 NUMBER 2 | FEBRUARY 2014 | www.nature.com/cpt

Pegylated interferon-α (PEG-IFN-α or PEG-IFN 2a and 2b)– and ribavirin (RBV)-based regimens are the mainstay for treatment of hepatitis C virus (HCV) genotype 1. *IFNL3* (*IL28B*) genotype is the strongest baseline predictor of response to PEG-IFN-α and RBV therapy in previously untreated patients and can be used by patients and clinicians as part of the shared decision-making process for initiating treatment for HCV infection. We provide information regarding the clinical use of PEG-IFN-α- and RBV-containing regimens based on *IFNL3* genotype.

Table 1 Assignment of probable IFNL3 phenotypes based on genotypes

Observed phenotype	Description	Genotype definitions	Genotype rs12979860
Favorable response genotype	Increased likelihood of response (higher SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with unfavorable response genotype	An individual carrying two favorable response alleles	CC
Unfavorable response genotype	Decreased likelihood of response (lower SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with favorable response genotype	An individual carrying at least one unfavorable response allele	CT or TT

PEG-IFN-α, pegylated interferon-α 2a or 2b; RBV, ribavirin; SVR, sustained virologic response.

PEG Interferon-α; *IL28B* (rs12979860 C>T)

3 CATALUNYA RÀDIO NOTÍCIES ESPORTS CULTURA EL TEMPS 3X3 DIRECTES

Notícies | Últimes notícies | Vídeos | Àudios | Seccions

BARCELONA

Els experts creuen que la nova medicació per a l'hepatitis C pot eradicar la malaltia abans de 15 anys

Uns 80.000 catalans infectats pels genotips 1 i 4 del virus de l'hepatitis C poden beneficiar-se de l'alta eficàcia del nou medicament que s'inclourà al sistema sanitàri públic

Redacció
26/07/2014 - 13.10 | Actualitza 26/07/2014 - 16.02

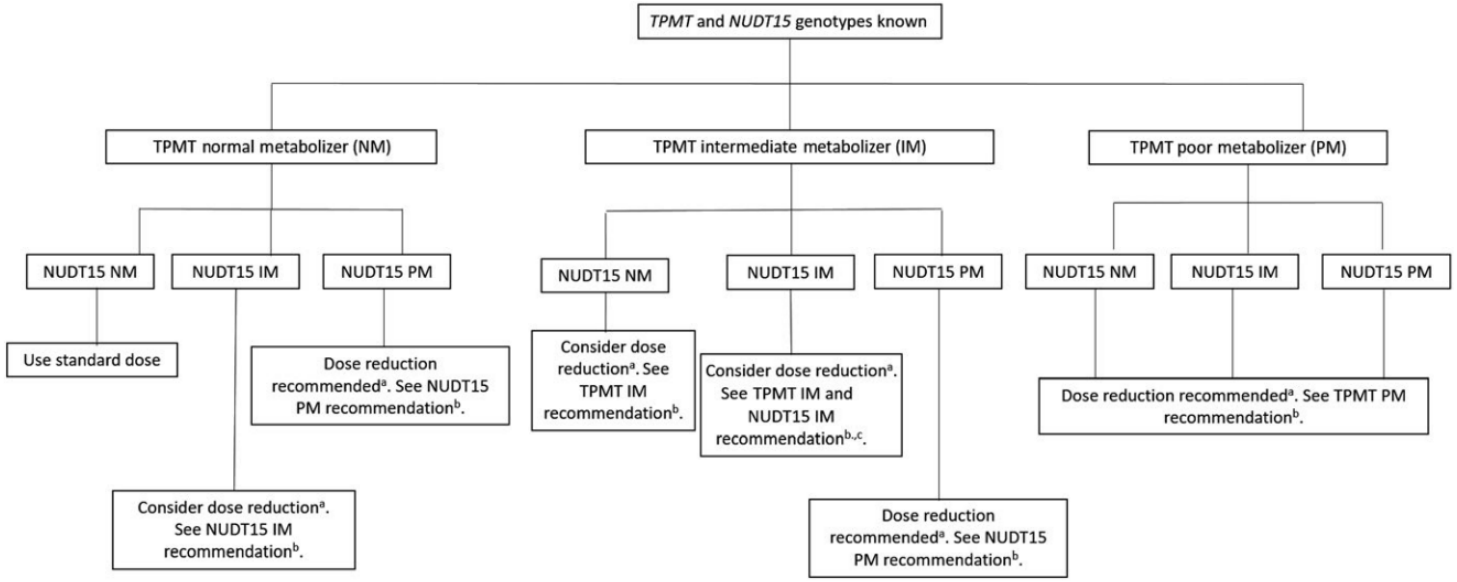
2015 - 2017

BOC: boceprevir
EBR: elbasvir
DCV: daclatasvir
DSV: dasabuvir
GLE: glecaprevir
GZR: grazoprevir
OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir
PEG: peginterferó alfa
PIB: pibrentasvir
RBV: ribavirina
SMV: simeprevir
SOF: sofosbuvir
SOF/LDV: sofosbuvir/ledipasvir
TEL: telaprevir
VEL: velpatasvir
VHB: virus de l'hepatitis B
VHC: virus de l'hepatitis C
VOX: voxilaprevir

TPMT -thiopurine methyltransferase

NUDT15 -nudix (nucleoside diphosphate linked moiety X)-type motif 15-

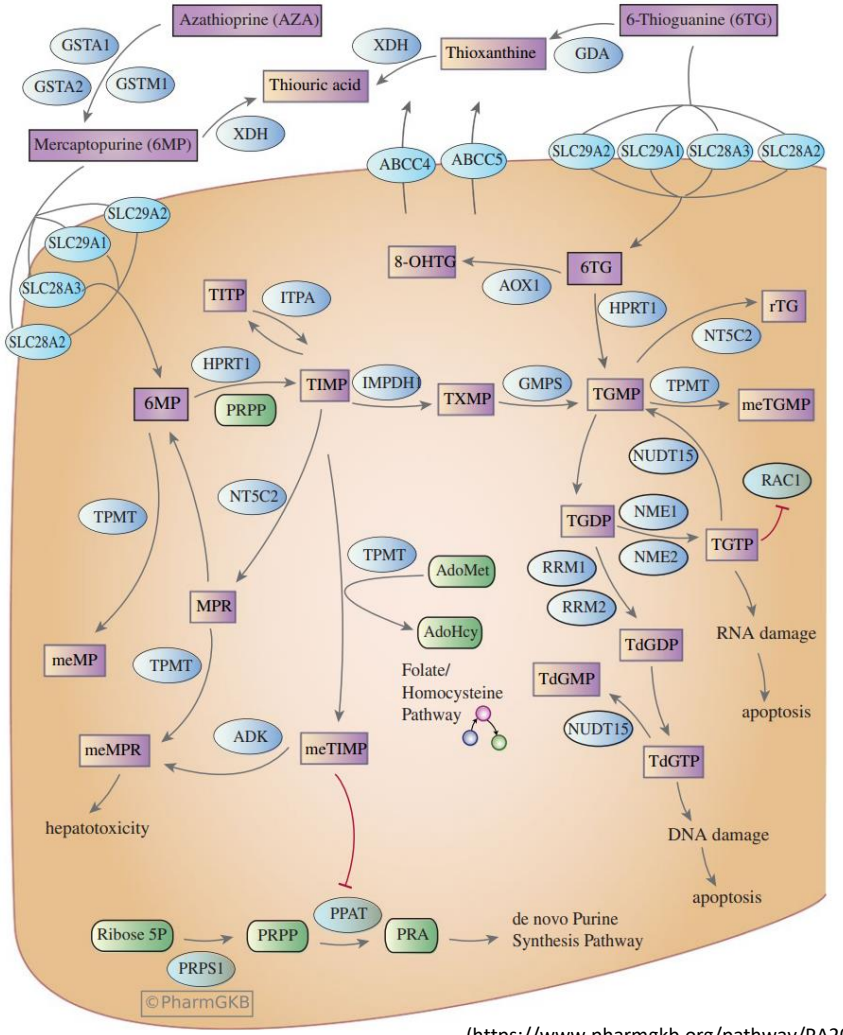
Thiopurine (Azathioprine, Mercaptopurine, Thioguanine) metabolite levels



Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT*15 Genotypes: 2018 Update

Mary V. Relling[1], Matthias Schwab[2,3,4], Michelle Whirl-Carrillo[5], Guilherme Suarez-Kurtz[6], Ching-Hon Pui[7], Charles M. Stein[8], Ann M. Moyer[9], William E. Evans[1], Teri E. Klein[4], Federico Guillermo Antillon-Klussmann[10,11], Kelly E. Caudle[1], Motohiro Kato[12], Allen E.J. Yeoh[13,14], Kjeld Schmiegelow[15,16] and Jun J. Yang[1]

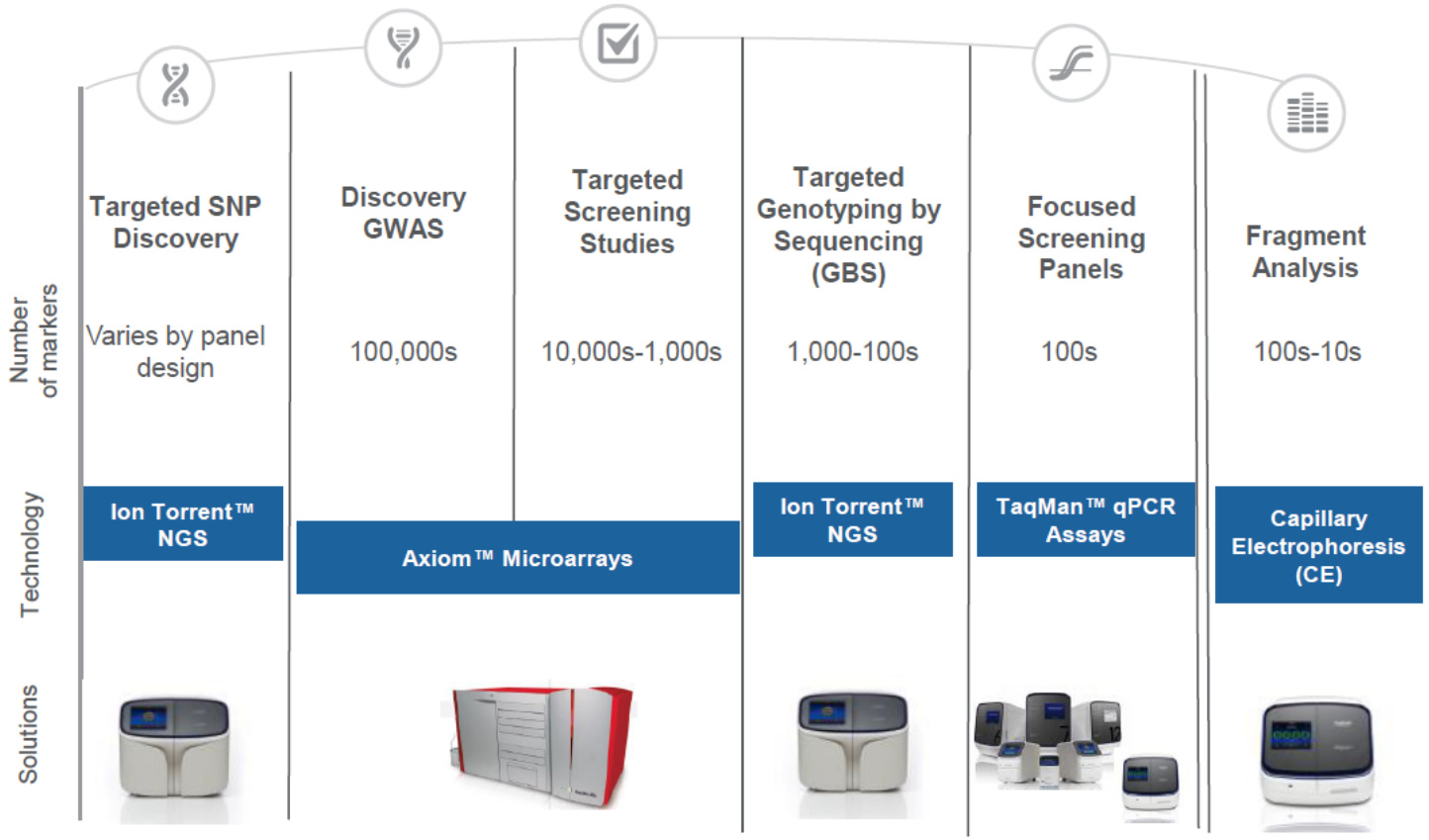
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 105 NUMBER 5 | MAY 2019



(https://www.pharmgkb.org/pathway/PA2040)

OTHER TECHNOLOGICAL SOLUTIONS

- Fragment analysis
- Multiplex TaqMan Assays
- Microarrays
- Next Generation Sequencing



ThermoFisher SCIENTIFIC

ARRAYS

Axiom PharmacoFocus Array -

Achieving the tasks of three different technologies in a single workflow

- Genotyping – including **accurate genotyping of highly predictive markers in regions of high homology** within CYP2C19, CYP2C9, CYP2D6, CYP1A2, CYP2A6, CYP2B6, GSTM1 and SULT1A1

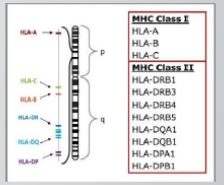
ThermoFisher SCIENTIFIC

- **Copy number analysis** for regions in high evidence genes

CN region	CN states
CYP2A6_5pFlank	0,1,2,3
CYP2A6_intron2-intron4	
CYP2A6_intron5-exon9	
CYP2D6-3pFlank	0,1,2,3
CYP2D6_5pFlank	
CYP2D6_exon9	
GSTM1_gene	0,1,2,3
GSTT1_gene	0,1,2,3
UGT2B17_gene	0,1,2
SULT1A1_gene*	0,1,2,3,4

*copy number analysis in SULT1A1 is offered with separate analysis workflow

- **HLA typing** across 11 HLA loci's which have documented influence in individuals' response to a drug, inclusive of HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01

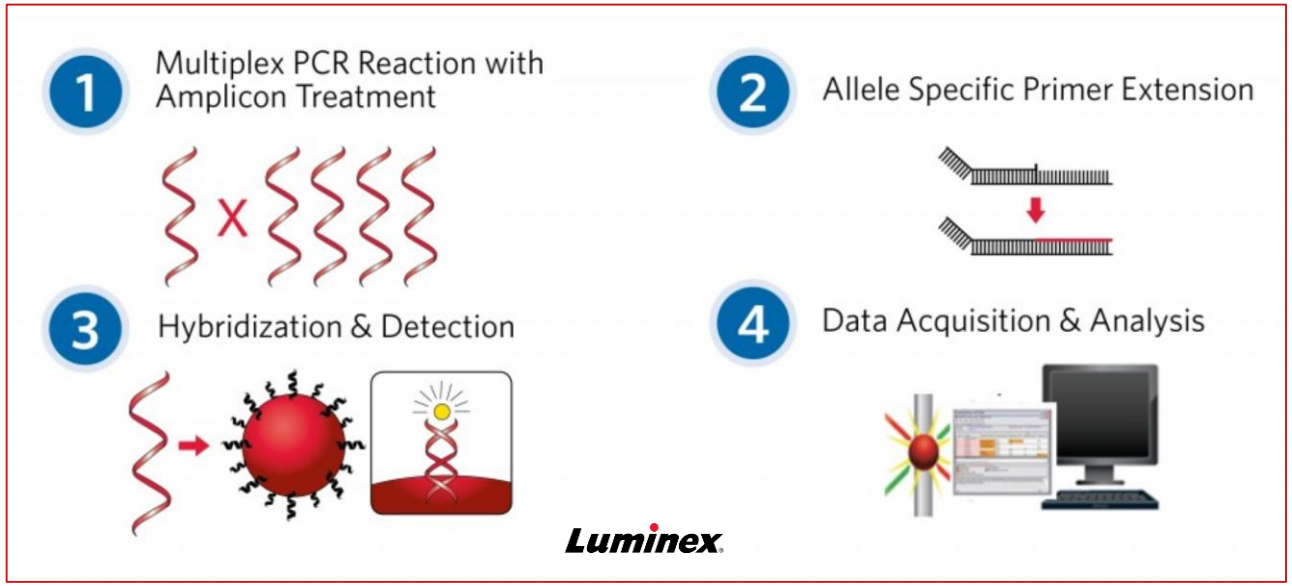


Genes tested:
CYP2B6, CYP2C19, CYP2C9, CYP2C, VKORC1, CYP4F2, CYP2D6, OPRM1, COMT, CYP3A5, DPYD, IFNL3/4, MT-RNR1, RYR1, CACNA1S, SLCO1B1, ABCG2, TPMT, NUDT15, UGT1A1, NAT1, NAT2, BCHE, HLA-A, HLA-B, HLA-DRB1, HLA-DQA1

The test covers more than 120 medications used to treat a wide range of medical conditions, including cardiovascular disease, chronic and acute pain, gastroesophageal reflux disease, general anesthesia, ADD/ADHD, epilepsy, depression, anxiety, and infections.

SNaP-SHOT™
ARIEL
PRECISION MEDICINE

LUMINEX

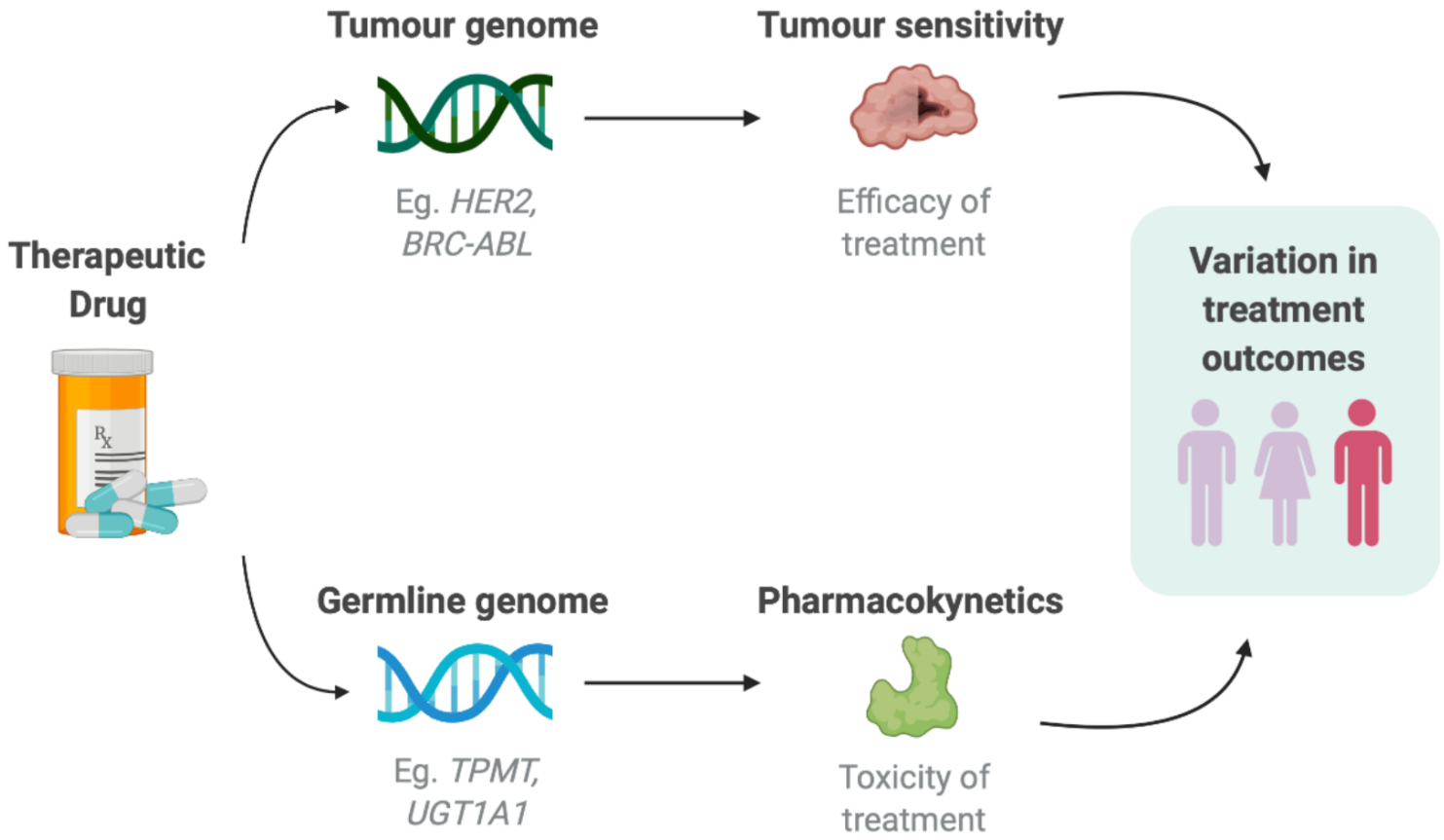


Genotipo de estrella (*)	Mutaciones y polimorfismos† detectados por el equipo de análisis xTAG CYP2D6	
	PCR A	PCR B
*1	Ninguna	Ninguna
*2	**-1584C>G**, 1661G>C	**2850C>T, 4180G>C**
*3		**2549A>del**
*4	100C>T, 1661G>C, **1846G>A**	2850C>T, 4180G>C
*5		**Supresión**
*6	**1707T>del**	4180G>C
*7		**2935A>C**
*8	1661G>C, **1758G>T**	2850C>T, 4180G>C
*9		**2613delAGA**
*10	**100C>T**, 1661G>C	4180G>C
*11	**883G>C**, 1661G>C	2850C>T, 4180G>C
*15	**138insT**	
*17	**1023C>T**, 1661G>C	2850C>T, 4180G>C
*29	**1659G>A**, 1661G>C	2850C>T, **3183G>A**, 4180G>C
*35	-1584C>G, **31G>A**, 1661G>C	2850C>T, 4180G>C
*41	1661G>C	2850C>T, **2988G>A**, 4180G>C
DUP	**Duplicación**	

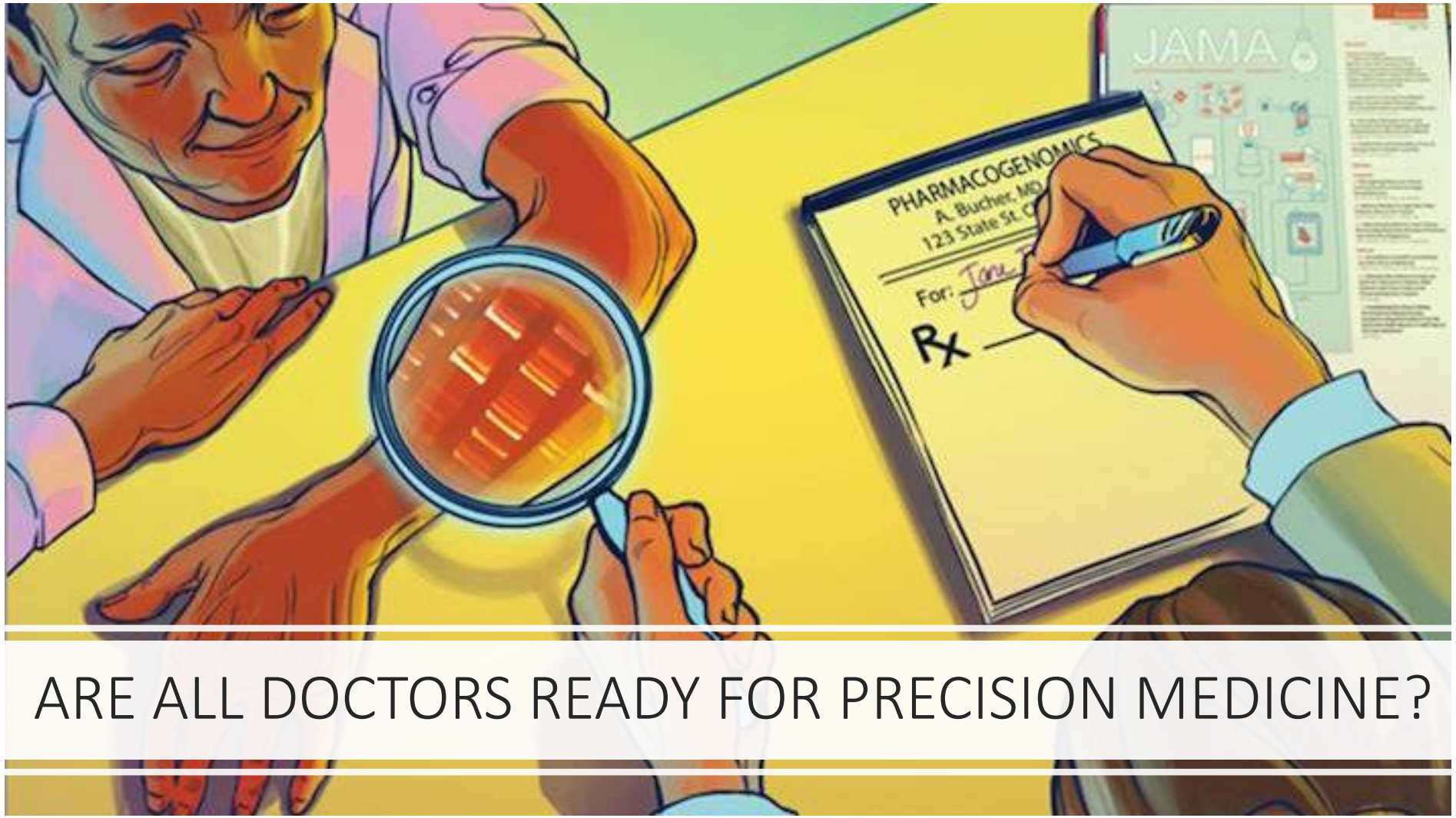
Table 1a. Common Substrates of CYP2C19[5]

Common Substrates of CYP2C19	
Proton Pump Inhibitors	• Lansoprazole/Dexlansoprazole • Omeprazole/Esomeprazole • Rabeprazole • Pantoprazole
Antiepileptics	• S-Mephenytoin • Diazepam • Phenobarbital • Phenytoin • Primidone
Antidepressants	• Amitriptyline • Citalopram • Clomipramine • Moclobemide • Imipramine • Desipramine • Sertraline
Antibiotics	• Chloramphenicol
Antifungals	• Voriconazole
Anticancer	• Nilutamide • Cyclophosphamide • Neniposide
Other	• Clopidogrel • Carisoprodol • Indomethacin • Mephobarbital • R-warfarin* • Hexobarbitol • Nelfinavir • Propranolol • Progesterone • Proguanil

Next Generation Sequencing IN CANCER PHARMACOGENOMICS



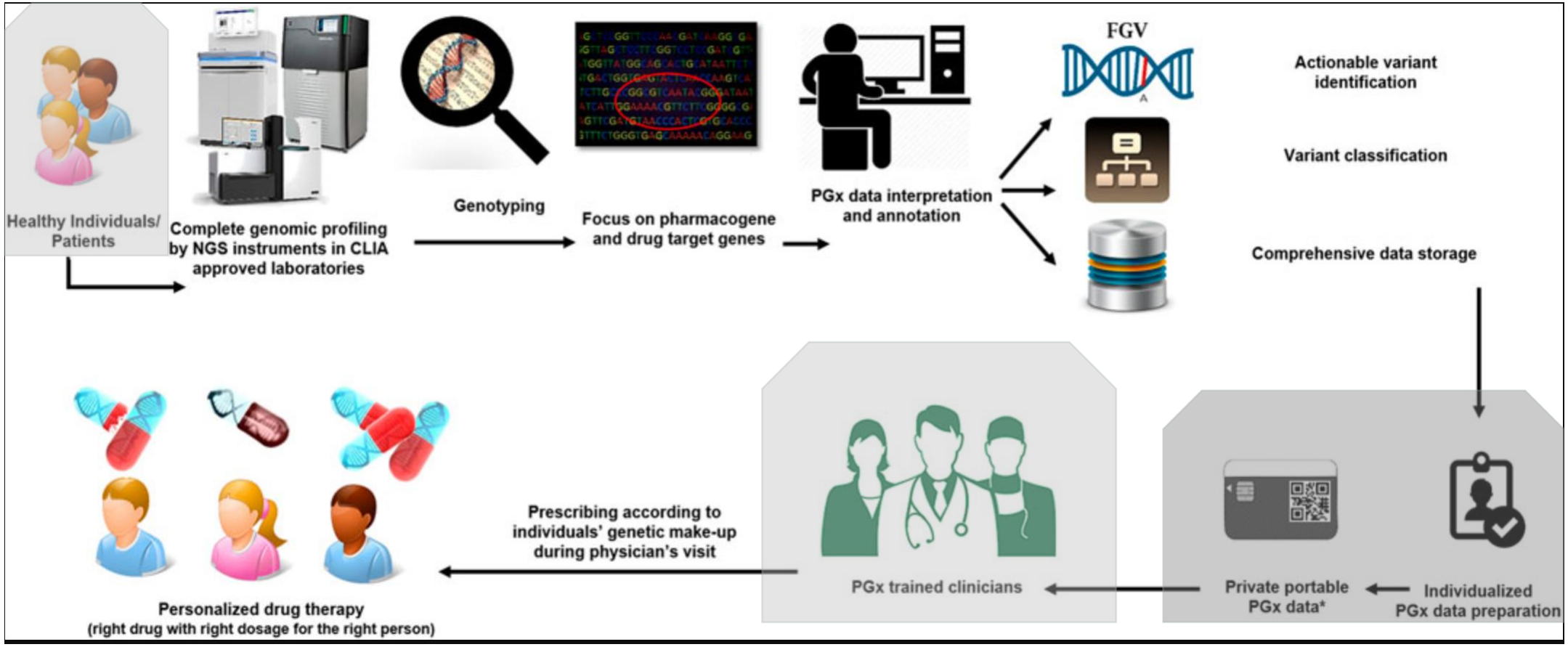
IN THE ERA OF BIG DATA…



ARE ALL DOCTORS READY FOR PRECISION MEDICINE?

https://www.myogenes.com/author/emmanuel/

From whole exome to the pharmacogenomic profile



REVIEW article
Front. Pharmacol., 25 August 2021
Sec. Pharmacogenetics and Pharmacogenomics
https://doi.org/10.3389/fphar.2021.693453
This article is part of the Research Topic
Insights in Pharmacogenetics and Pharmacogenomics: 2021
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Applying Next-Generation Sequencing Platforms for Pharmacogenomic Testing in Clinical Practice

Alireza Tafazoli[1,2], Henk-Jan Guchelaar[3,4], Wojciech Miltyk[1], Adam J. Kretowski[2,5] and Jesse J. Swen[3,4]*