Implémentation clinique de la pharmacogénétique

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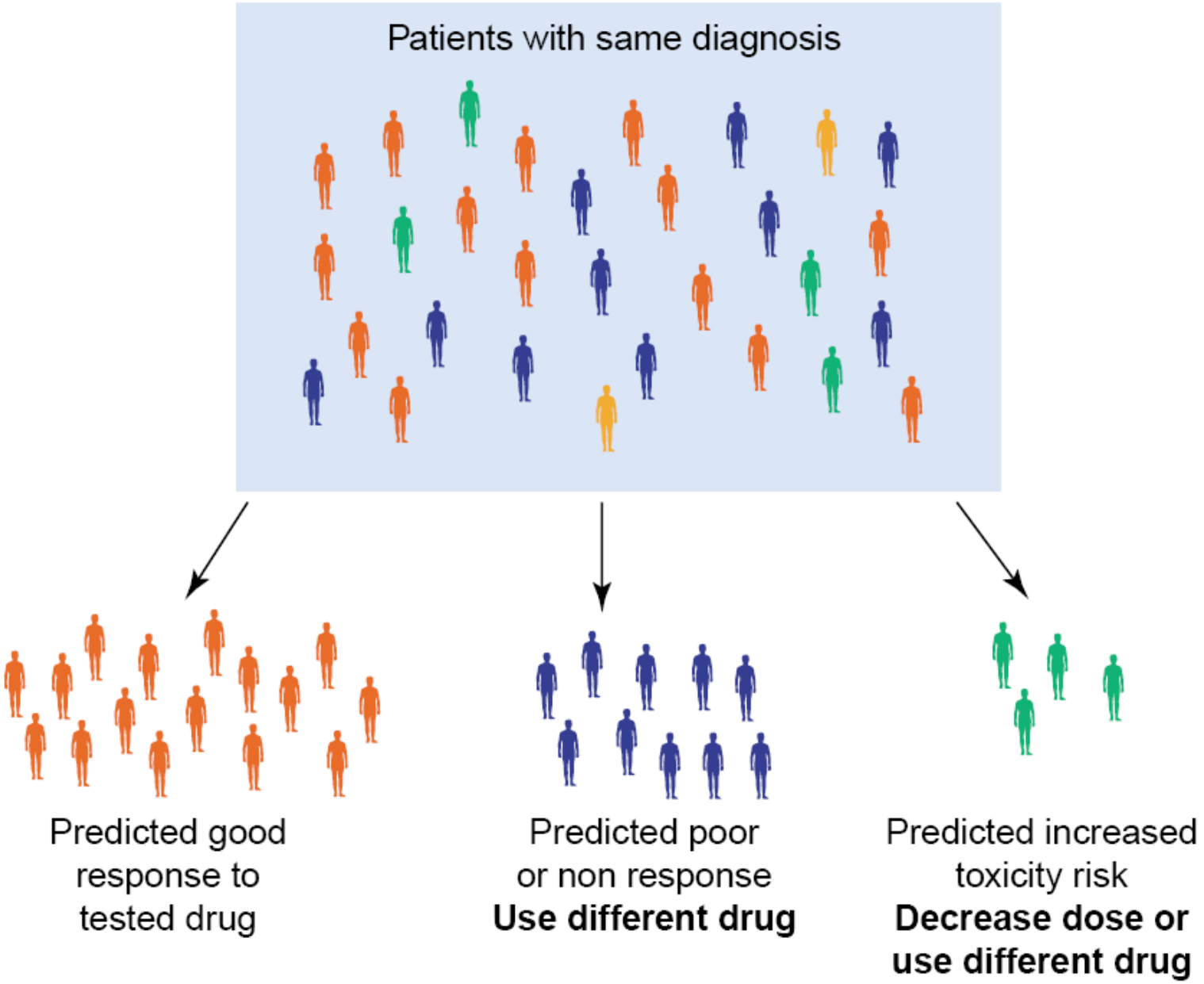
Pharmacogenetics: the future of the pharmacotherapy ?

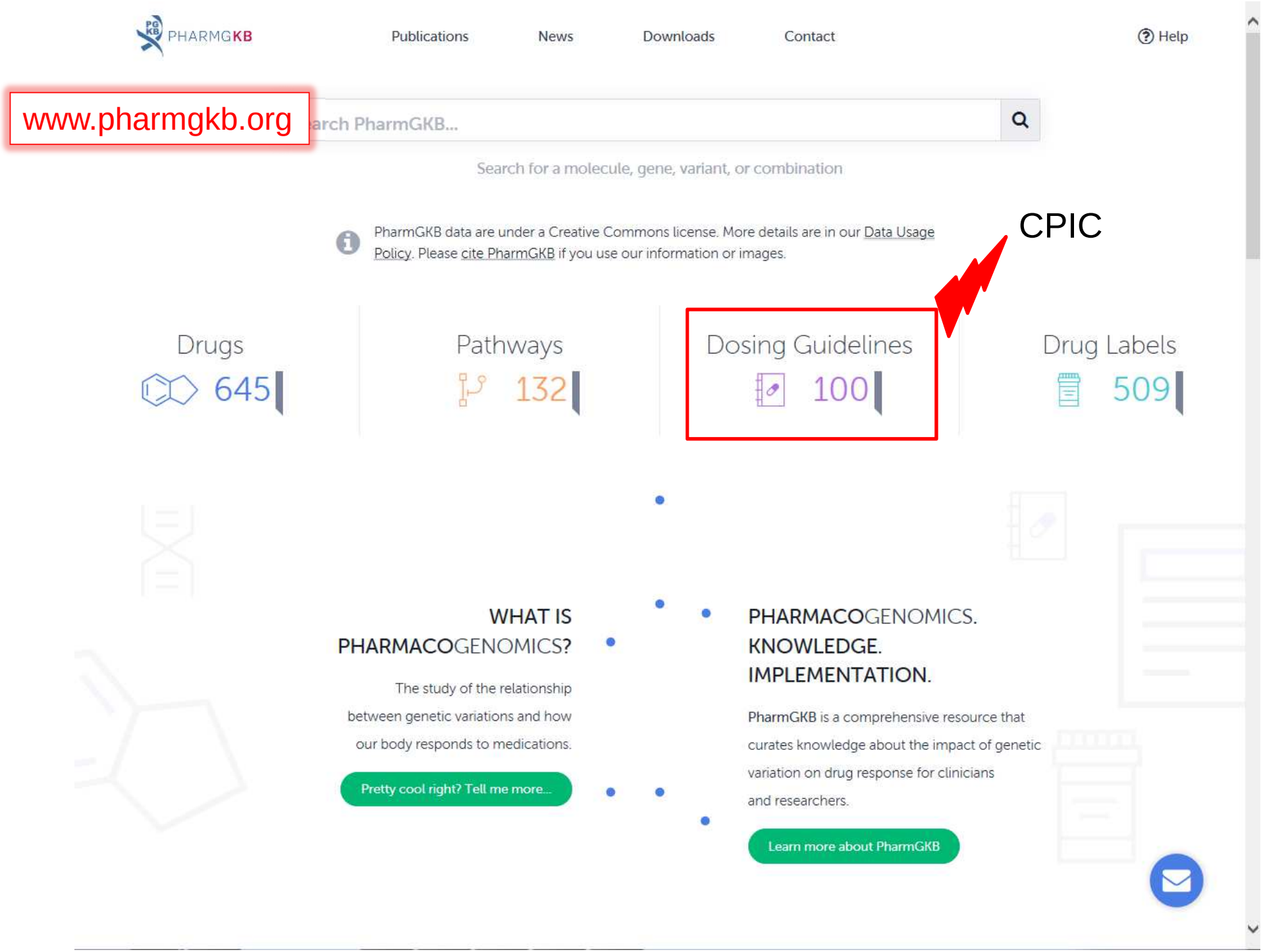
"Here is my sequence…"

(The New Yorker, 2000)


Patients with same diagnosis
Predicted good response to tested drug
Predicted poor or non response
Use different drug
Predicted increased toxicity risk
Decrease dose or use different drug
TRENDS in Genetics

Pharmacogenetics(-genomics) and its scope

	CONSTITUTIVE genetic variants	DISEASE (tumoral) genetics
Responders vs non-responders	+	+++
Individualized dosing	++	(-)
Identify patients at risk for ADRs	+++	(-)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CPIC
Drugs
645
Pathways
132
Dosing Guidelines
100
Drug Labels
509
WHAT IS PHARMACOGENOMICS?
The study of the relationship between genetic variations and how our body responds to medications.
Pretty cool right? Tell me more...
PHARMACOGENOMICS. KNOWLEDGE. IMPLEMENTATION.
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.
Learn more about PharmGKB

Dosing Guidelines

PharmGKB annotates PGx-based drug dosing guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and other professional societies. PharmGKB annotations present a brief summary of the genotype-based dosing recommendations.

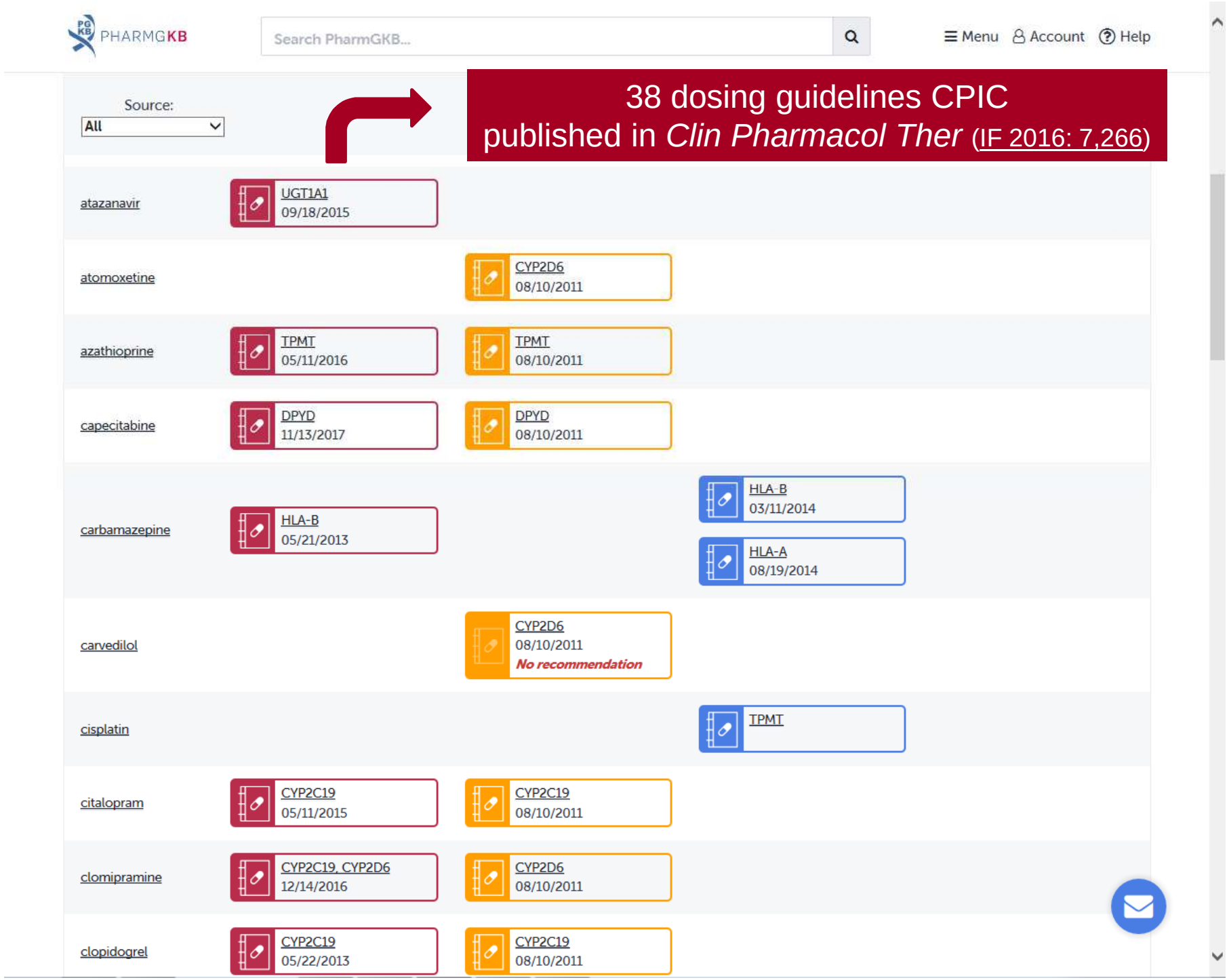
We welcome any information regarding published PGx dosing guidelines - please contact us.

YouTube Guideline Videos. PharmGKB has recorded short video introductions of some CPIC dosing guidelines. The full video overview of a guideline can be seen on the individual guideline page, when available.

Source: All

Filter

DRUG	CPIC	DPWG	CPNDS	OTHER
abacavir	HLA-B 09/30/2014	HLA-B 08/10/2011		
acenocoumarol		VKORC1 08/10/2011 CYP2C9 08/10/2011		
allopurinol	HLA-B 06/12/2015			HLA-B 10/01/2012
amitriptyline	CYP2C19, CYP2D6 12/14/2016	CYP2D6 08/10/2011		
aripiprazole		CYP2D6 08/10/2011		
atazanavir	UGT1A1 09/18/2015			


PHARMGKB
Search PharmGKB...
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Source:
All
38 dosing guidelines CPIC
published in *Clin Pharmacol Ther* (IF 2016: 7,266)
atazanavir
UGT1A1
09/18/2015
atomoxetine
CYP2D6
08/10/2011
azathioprine
TPMT
05/11/2016
TPMT
08/10/2011
capecitabine
DPYD
11/13/2017
DPYD
08/10/2011
carbamazepine
HLA-B
05/21/2013
HLA-B
03/11/2014
HLA-A
08/19/2014
carvedilol
CYP2D6
08/10/2011
No recommendation
cisplatin
TPMT
citalopram
CYP2C19
05/11/2015
CYP2C19
08/10/2011
clomipramine
CYP2C19, CYP2D6
12/14/2016
CYP2D6
08/10/2011
clopidogrel
CYP2C19
05/22/2013
CYP2C19
08/10/2011

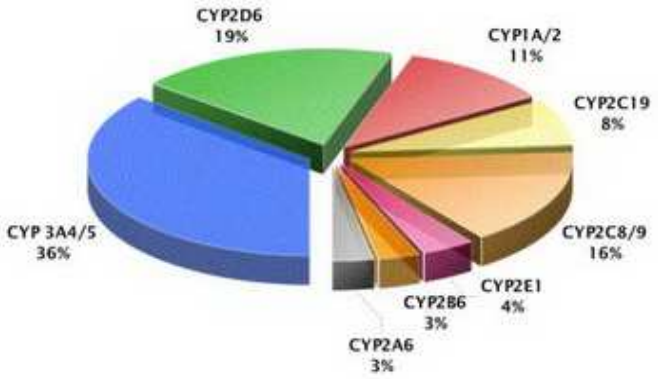
Eu-PIC

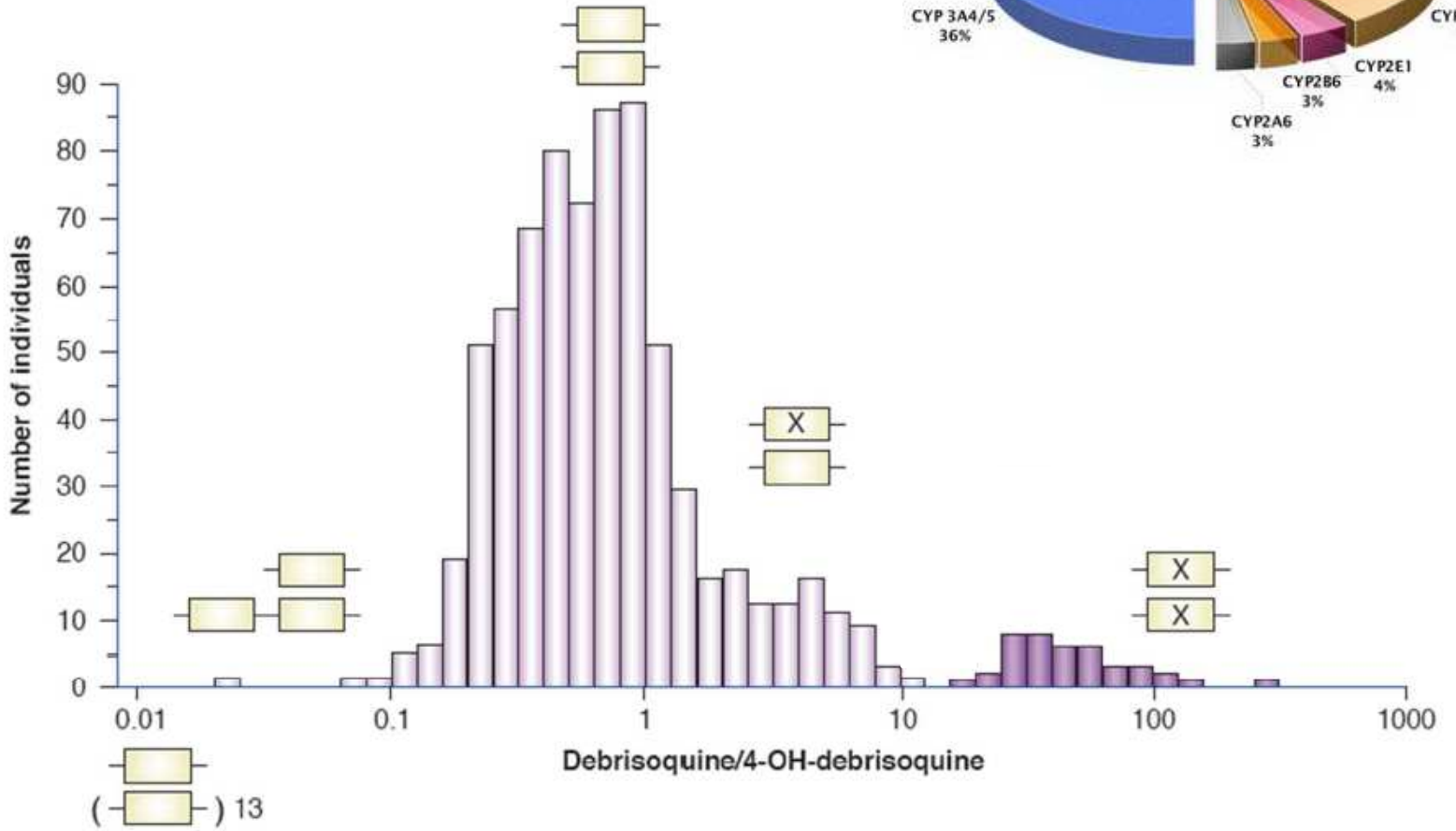
www.eu-pic.net

RNPGx

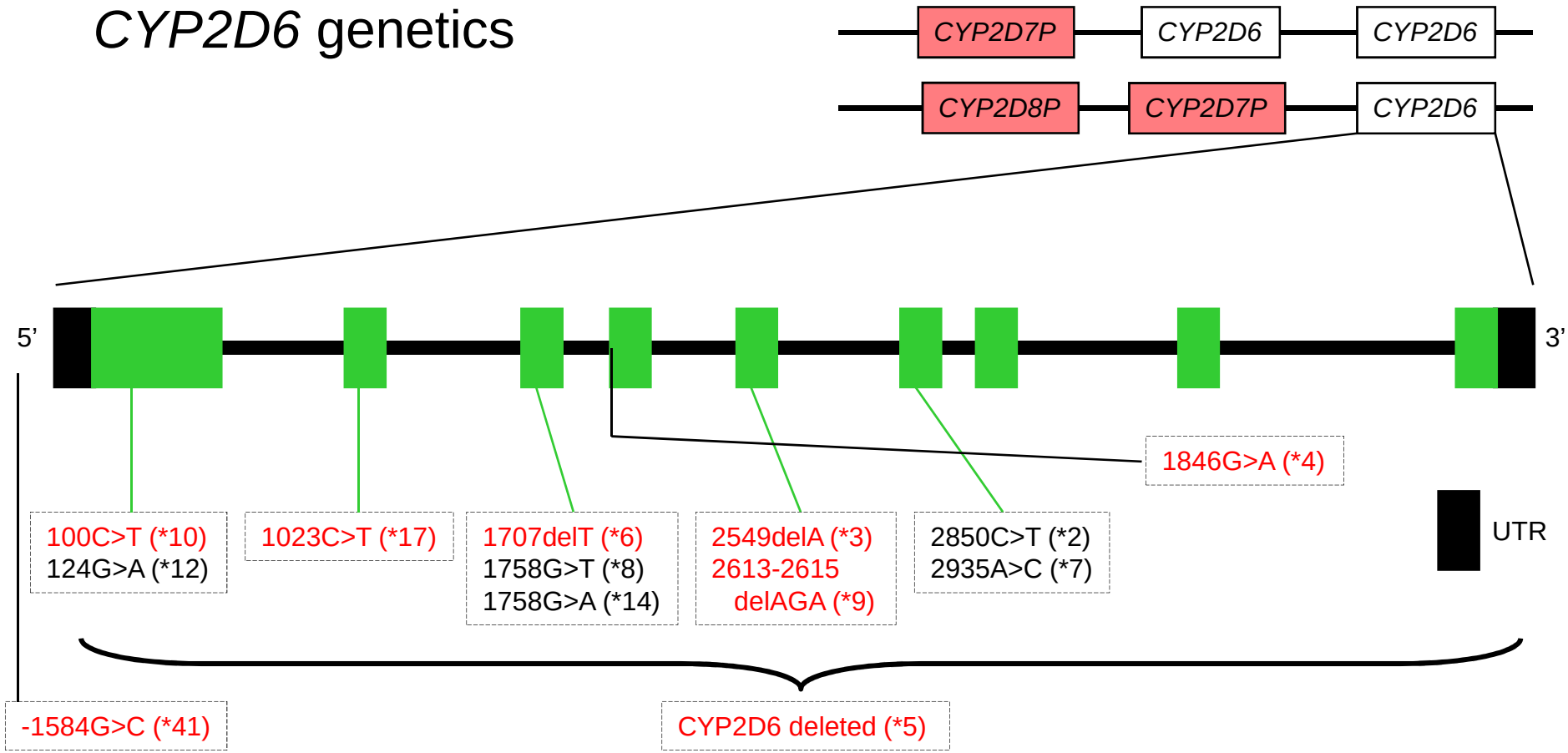
RÉSEAU NATIONAL DE PHARMACOGÉNÉTIQUE

CYP2D6 pharmacogenetics





CYP2D6 genetics



113 different alleles (http://www.cypalleles.ki.se, September 2018)

*CYP2D6*3* (259 frameshift)
*CYP2D6*4* (splicing defect)
*CYP2D6*5* (gene deletion)
*CYP2D6*6* (118 frameshift)
*CYP2D6*9* (K281del)
*CYP2D6*10* (P34S)
*CYP2D6*17* (T107I)
*CYP2D6*41* (expression ⬇)

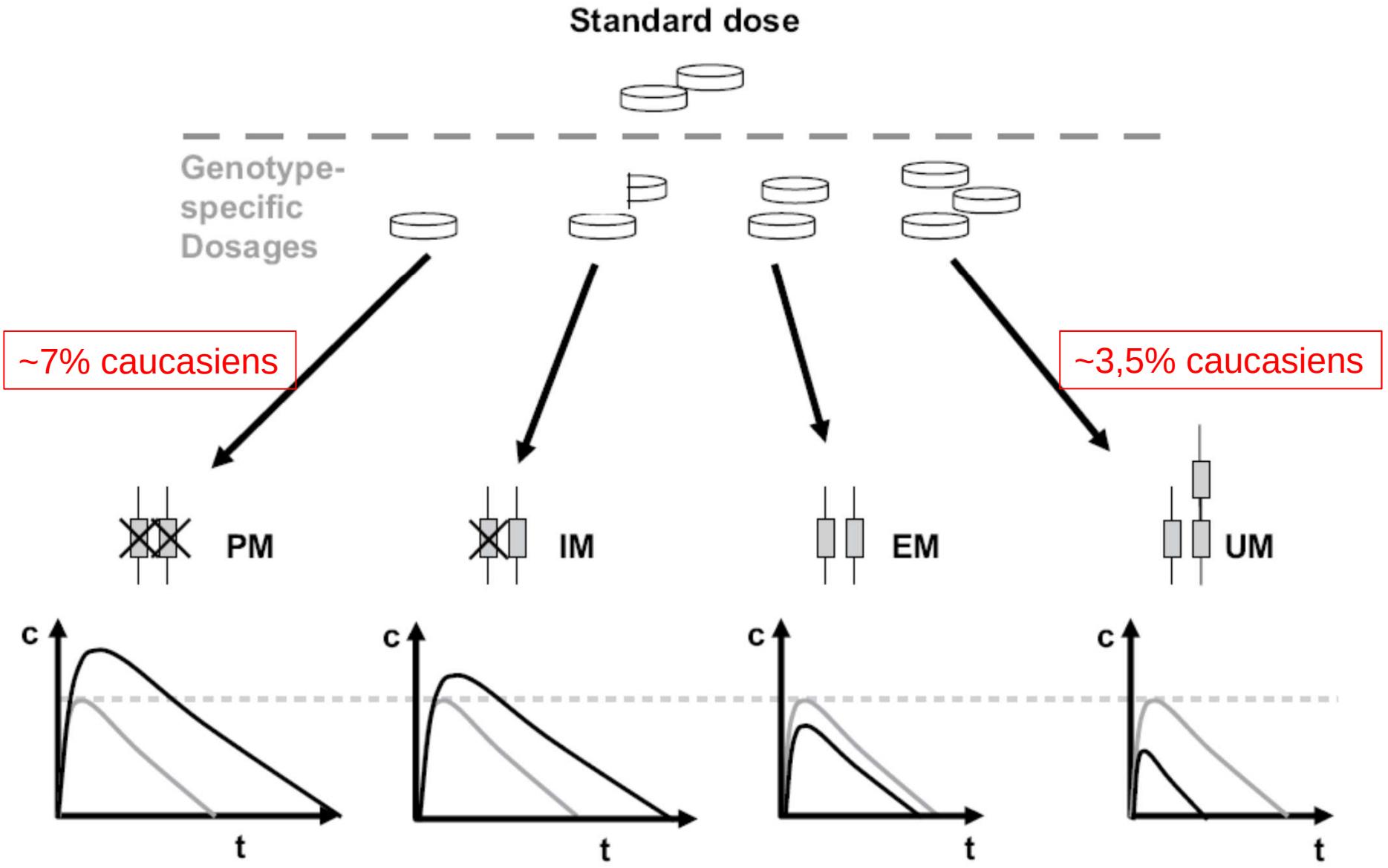
Translation of genotype (AS) into a qualitative measure of phenotype (genotype-based phenotype)

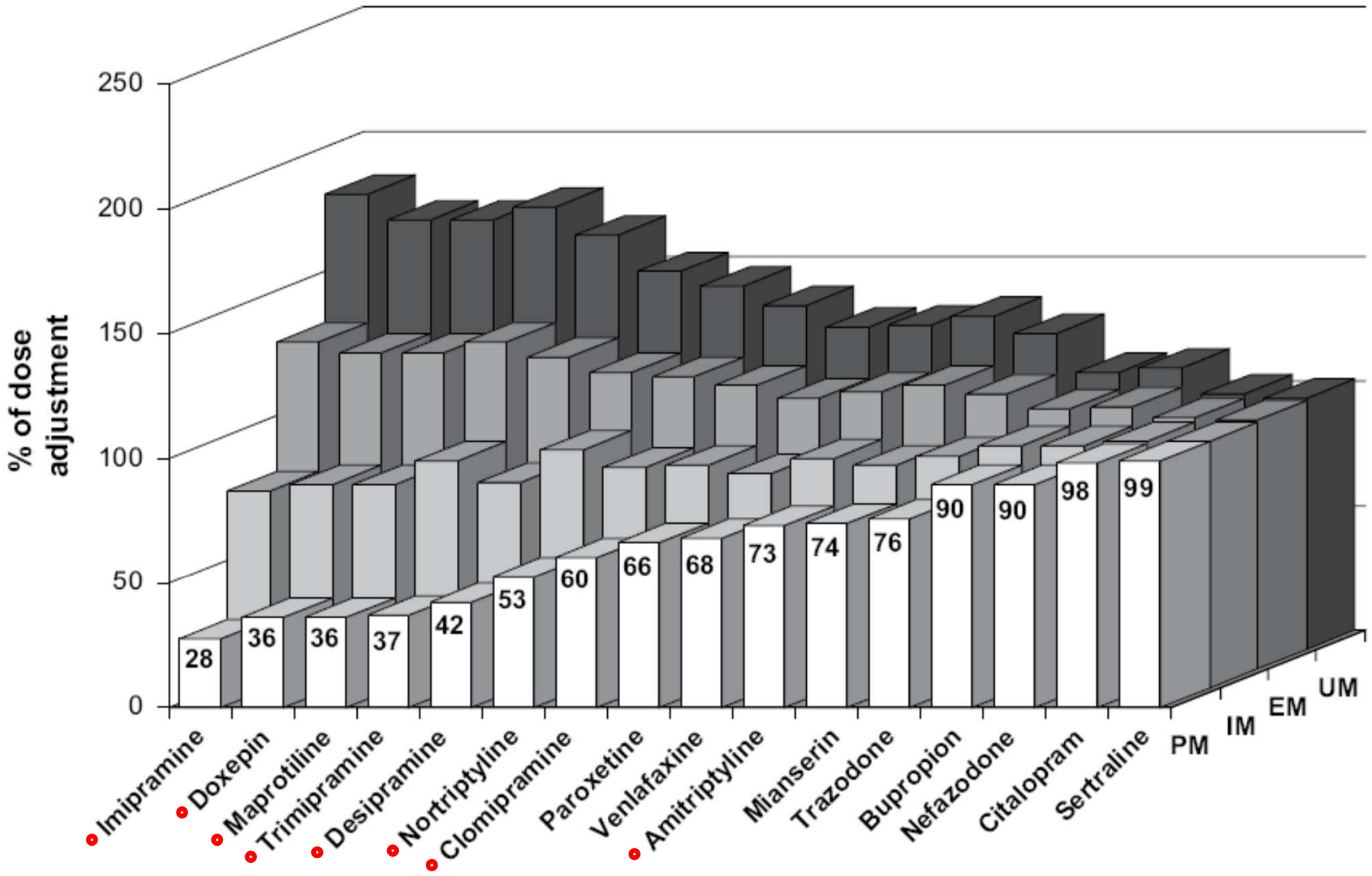
	PM	IM	EM	UM	Reference
Model 1	0	0,5	1 1,5 2	>2	*
Model 2	0	0,5 1 (0,5+0,5)	1 (1+0) 1,5 2	>2	**
Model 3	0	0,5 1	1,5 2	>2	***

* Clinical Pharmacogenetics Implementation Consortium (CPIC) for codeine, http://www.pharmgkb.org/guideline/PA166104996
** Luminex 2D6v3 FDA approved kit, http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGCYP2D6/
*** Dutch Pharmacogenetics Working Group Guidelines (DPWG) for codeine, http://www.pharmgkb.org/guideline/PA166104970

Haufroid et al. *Clin Toxicol* 2015; 53: 501-10.

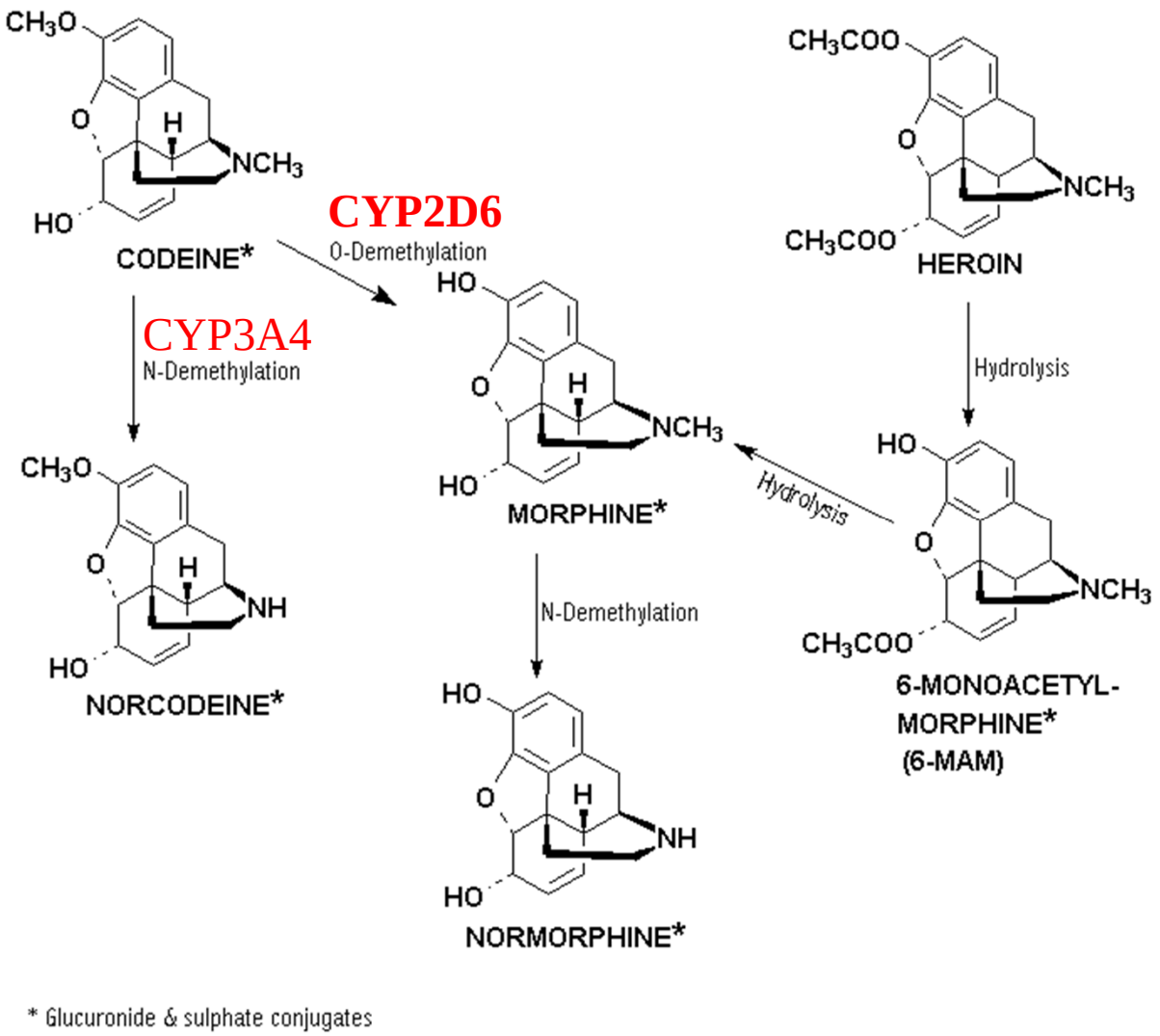
population-based versus individualization of dosing





Seeringer et al. *Clin Lab Med* 2008; 28: 619

le cas de la codéine…



* Glucuronide & sulphate conjugates

Case report:

62-year-old man / history of chronic lymphocytic leukemia
Emergency room for fatigue, dyspnea, fever and cough

Initial diagnosis: bilateral pneumonia with yeast infection

Treatment: ceftriaxone, clarithromycin
voriconazole
oral codeine (25 mg, 3 times a day)

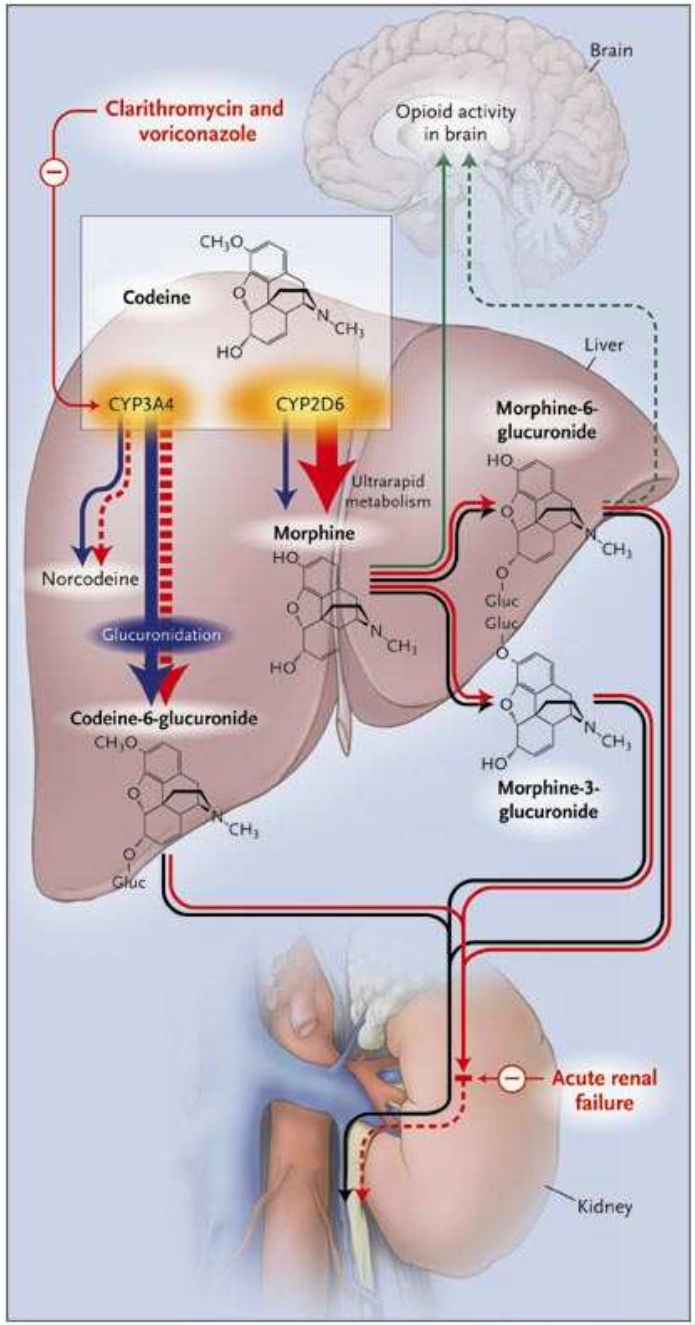
Day 4: patient's level of consciousness deterioration!

Intravenous administration of naloxone; rapid improvement

Biological results:

Codeine:	*114 µg/L (Nl: 13-75 µg/L, with extensive CYP2D6)*
Codeine glucuronide:	*361 µg/L (Nl: 700-1670 µg/L)*
Morphine:	***80 µg/L (Nl: 1-4 µg/L!)***

Gasche et al. *N Engl J Med* 2004; 351: 2827.



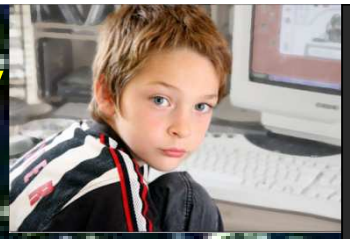
Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

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.

Gasche Y et al. N Engl J Med 2004;351:2827-2831

The NEW ENGLAND JOURNAL of MEDICINE

A DNA tragedy



Genetic tests to prevent adverse drug reactions may save tens of thousands of lives a year, but for a troubled boy named mickael they came too late

The death of nine-year-old Michael Adams-Conroy didn't seem at first like a signal event in medicine.
It seemed like homicide.

FLUOXETINE: DEATH IN A CHILD WITH POLYMORPHISM OF CYTOCHROME P450 2D6

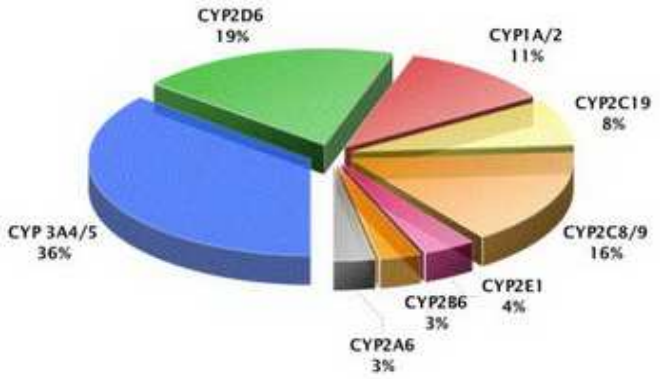
A 9-year-old died due to fluoxetine toxicity. Genetic tests confirmed that he had a gene defect at the CYP2D6 locus, which made him a poor metabolizer of fluoxetine.

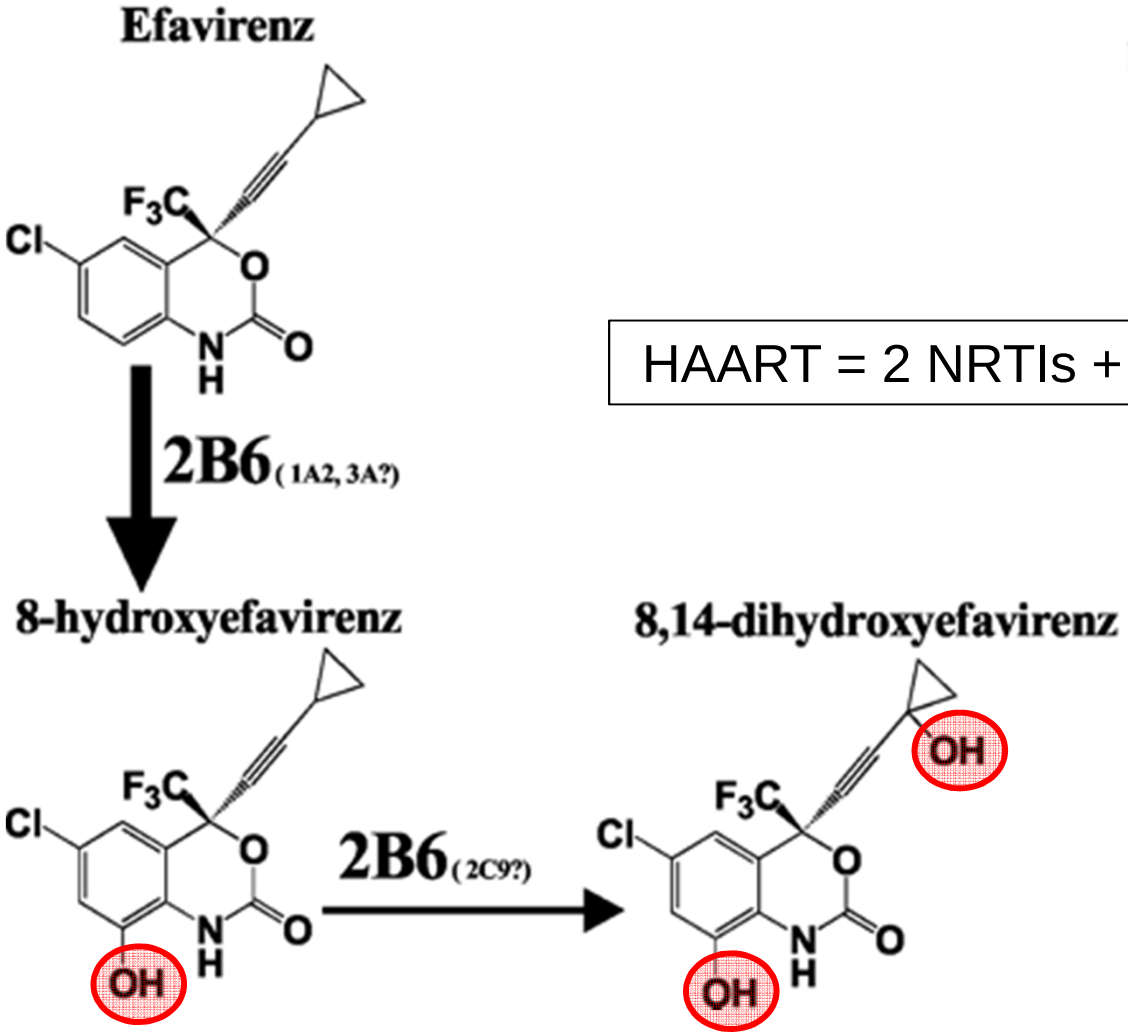
Sallee et al. *J Child Adolesc Psychopharmacol.* 2000;10:27-34.

…While recuperating from what seemed to be flu, Michael went into a prolonged grand mal seizure and died. His grieving parents, Jayne and Neil, soon got another shock: an autopsy showed a massive overdose of Prozac in Michael's blood and tissues, raising the specter of a murder charge against them …
Thus began the Adams-Conroys' painful pilgrimage to a medical frontier known as pharmacogenetics, the study of how genetic influences responses to drugs…"

Forbes Magazine (October 30, 2000)

CYP2B6 pharmacogenetics



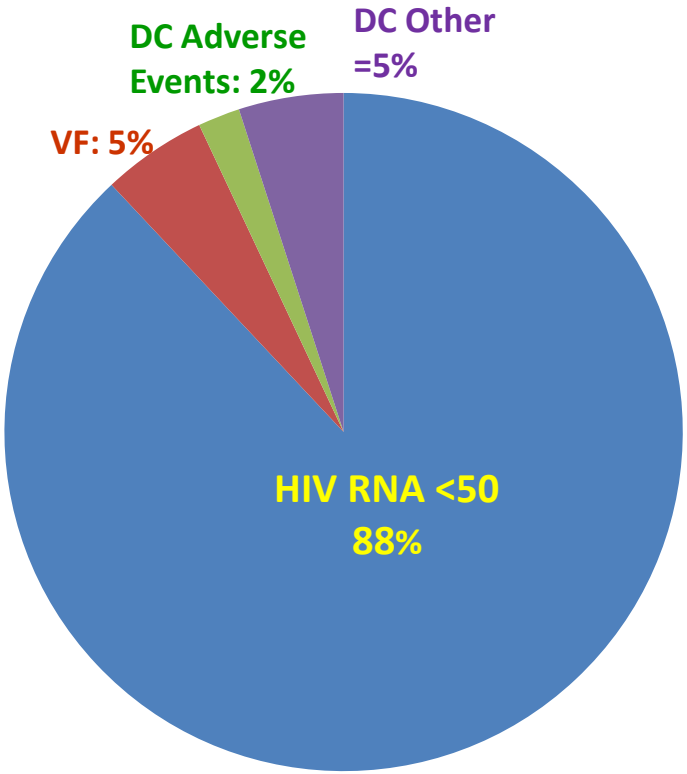


HAART = 2 NRTIs + NNRTI or PI

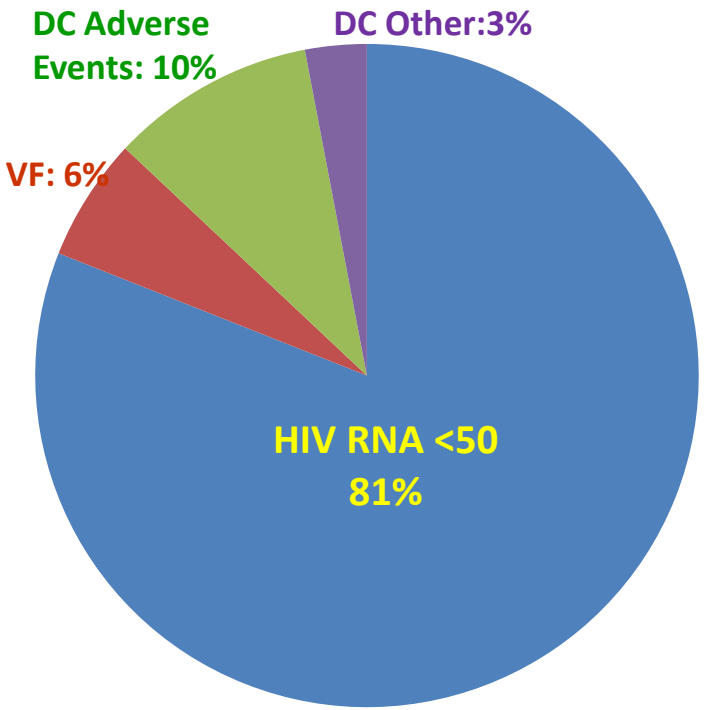
SINGLE Trial: DTG vs EFV

Week 48 efficacy:AE results

ABC/3TC/DTG

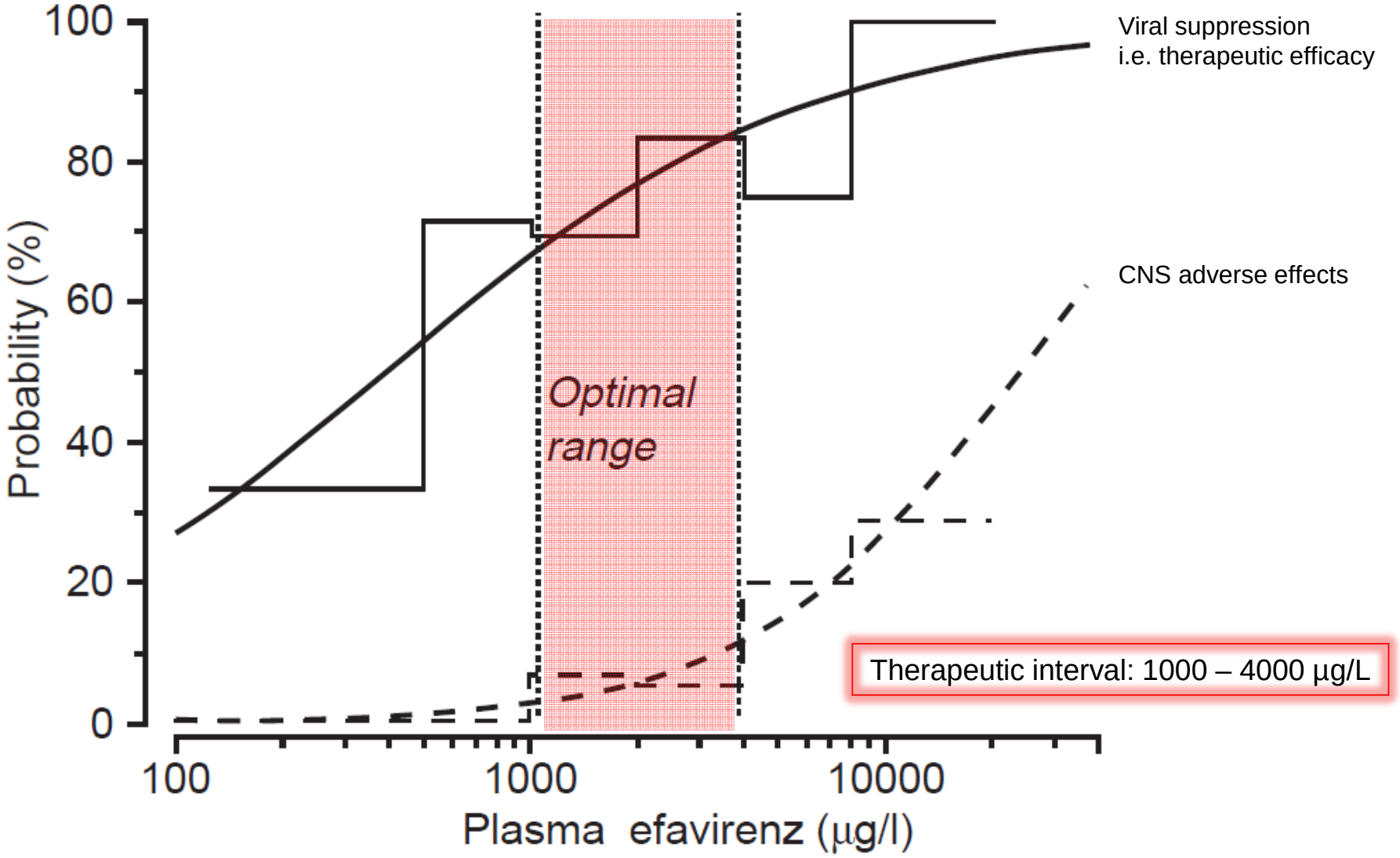


TDF/FTC/EFV600



Ref: Dolutegravir FDA prescribing information

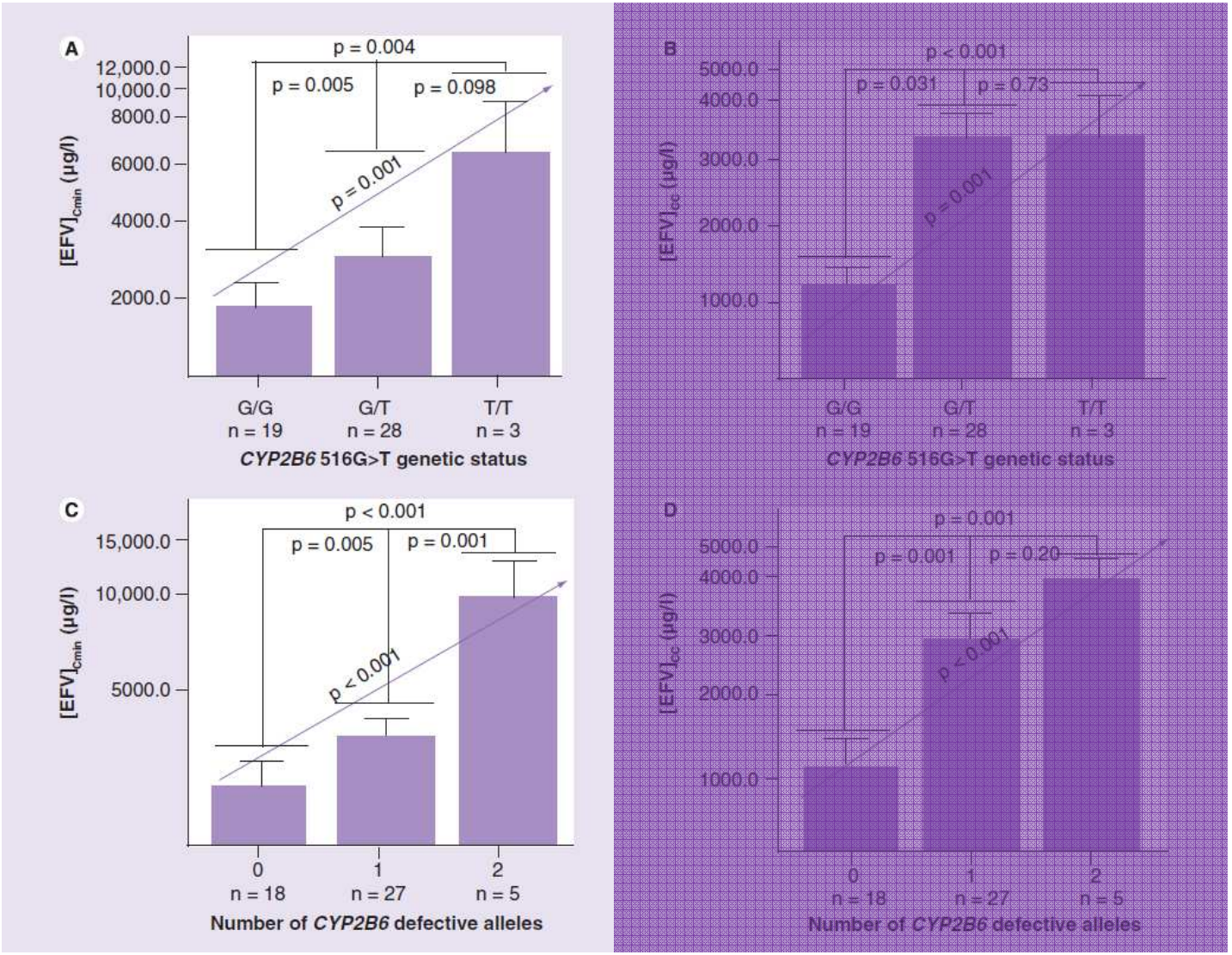
Slide courtesy of Pr Anton Pozniak (London)



Marzolini et al. *AIDS* 2001; 15: 71

*CYP2B6*6*

*CYP2B6*6*
*CYP2B6*11*
*CYP2B6*18*



Elens et al. *Pharmacogenomics* 2010; 11: 1223

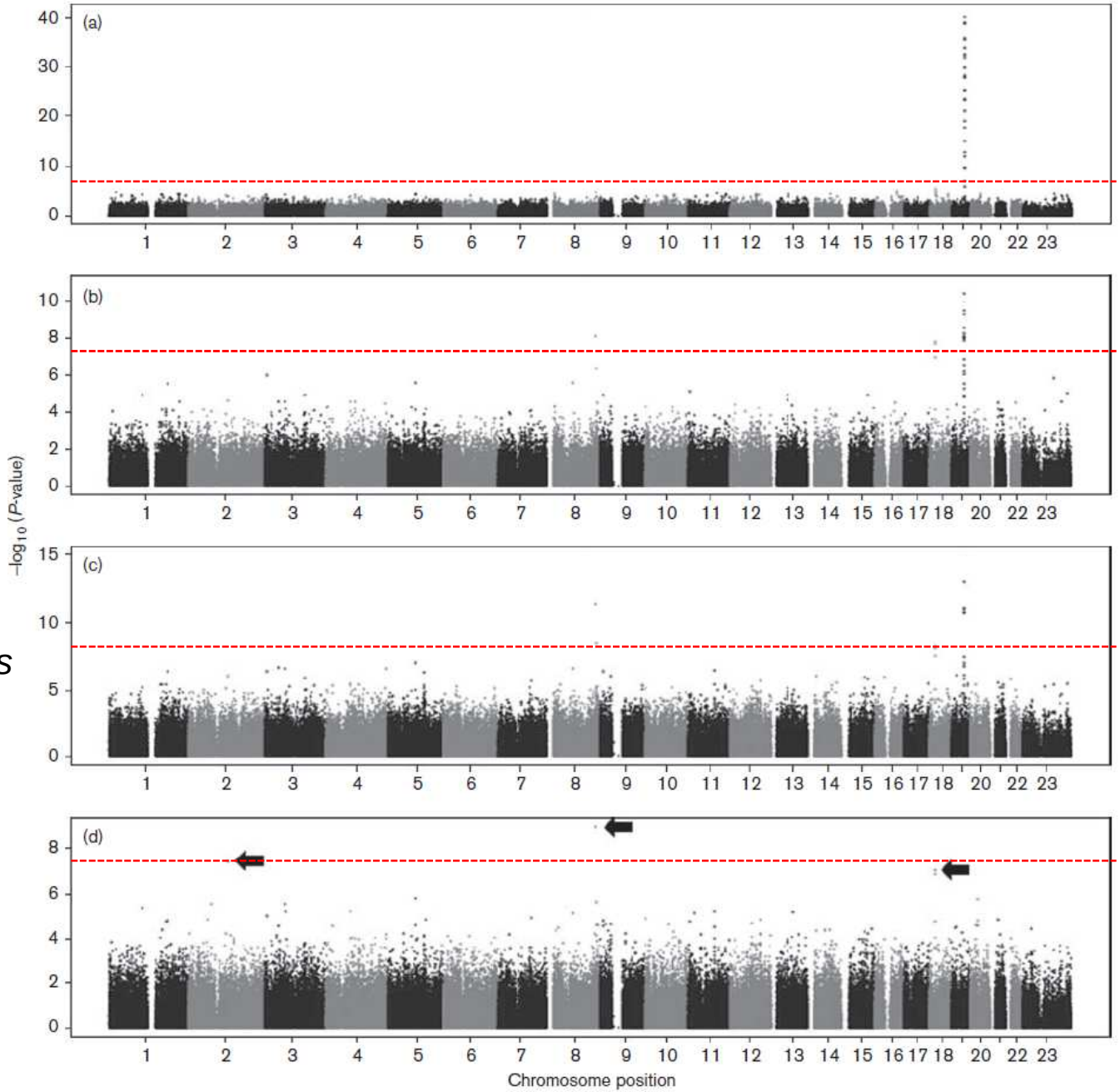
GWAS

EFV C_{min}

(b)
*CYP2B6*6 adjustment*

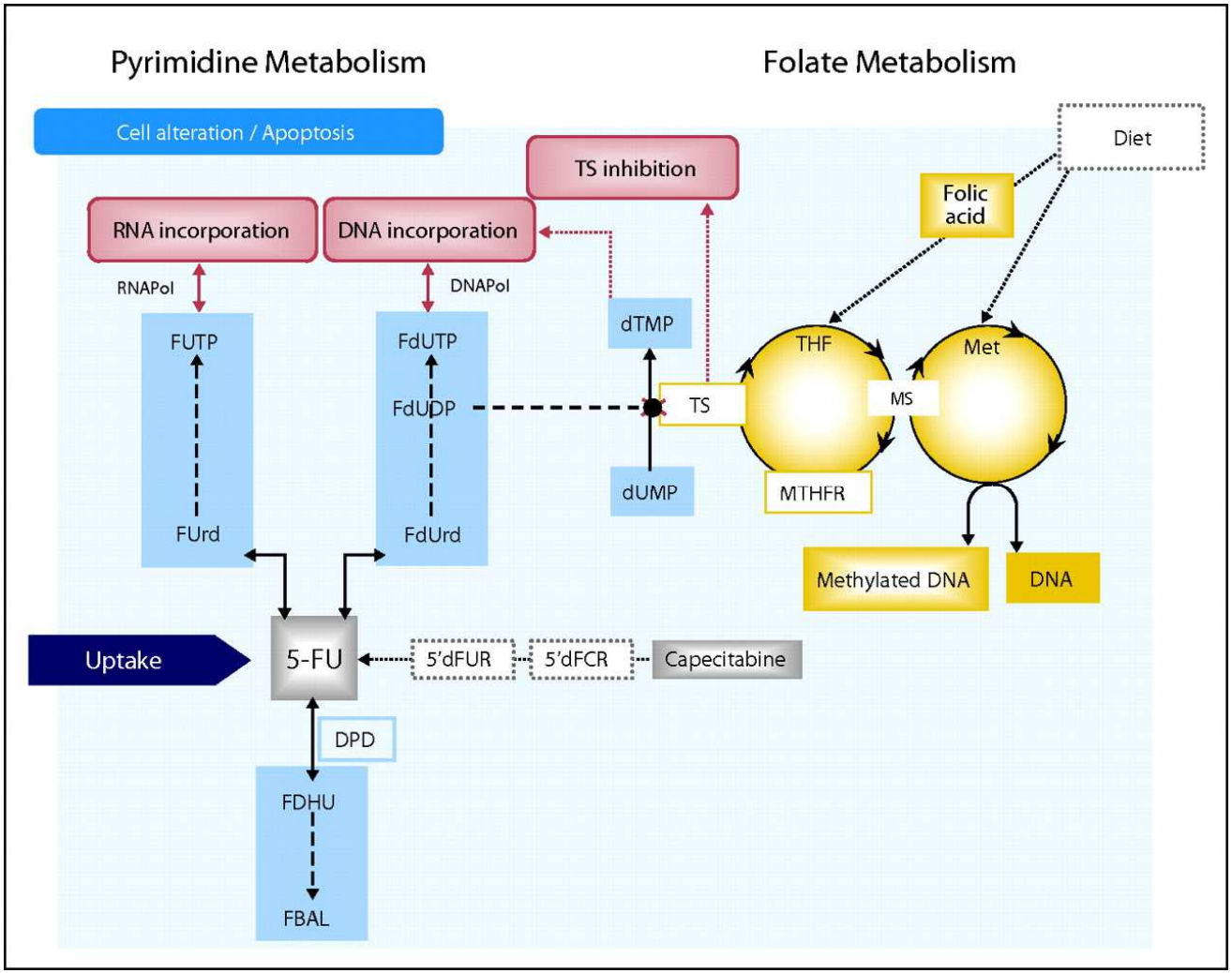
(c)
*CYP2B6*6*
*CYP2B6*18 adjustments*

(d)
*CYP2B6*6*
*CYP2B6*18*
rs4803419 adjustments



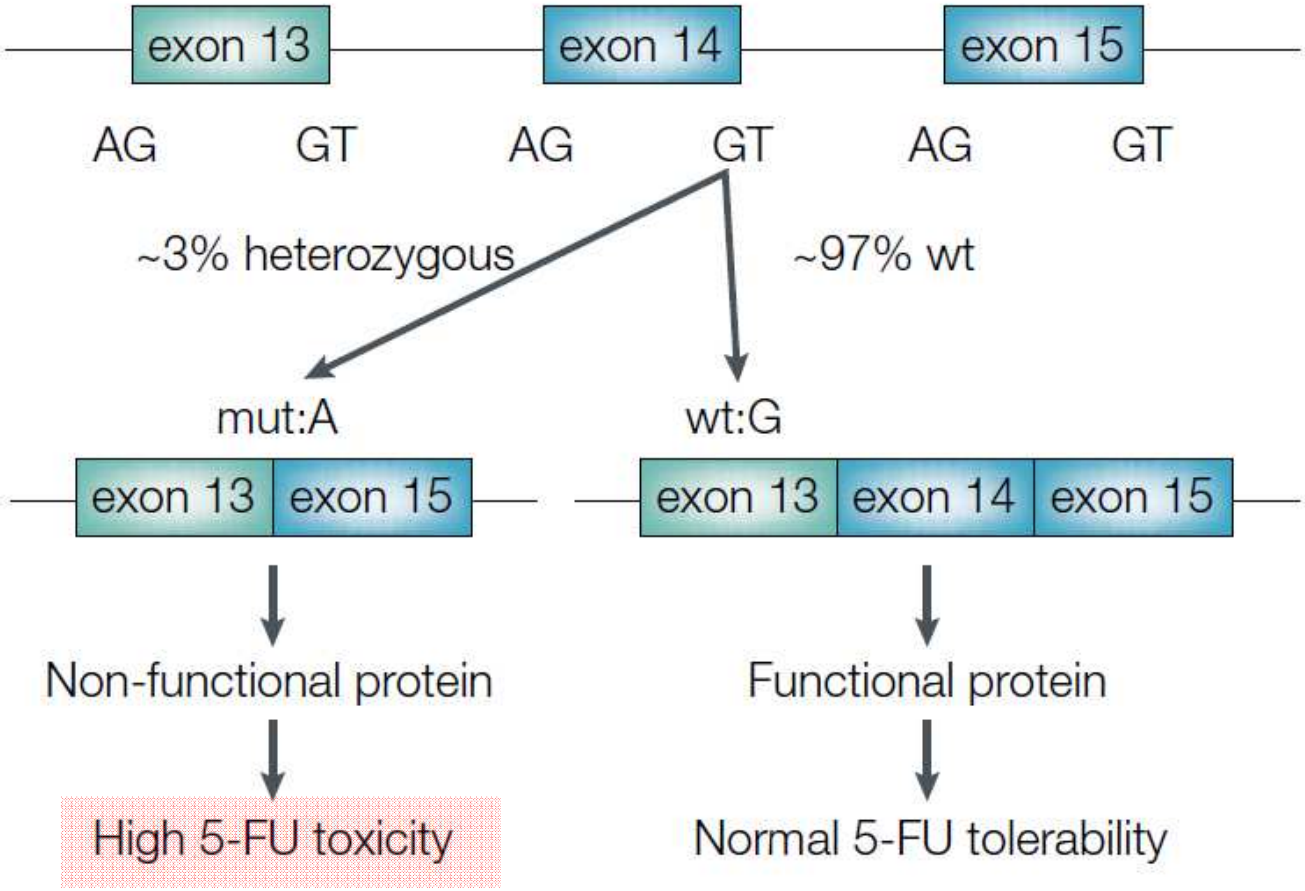
Holzinger et al. *Pharmacogenetics and Genomics* 2012; 22: 858

DPYD and fluoropyrimidine toxicity



Schwab et al. *J Clin Oncol* 2008; 26: 2131

*DPYD*2A* (IVS14+1) results in exon 14 skipping



DPYD genetics (2017 update from CPIC)

Strong Evidence supporting function (the four main)

Haplotype	rsID	Nucleotide change	Protein change	Allele functional status	Activity score	References	PMID
***2A**	rs3918290	c.1905+1G>A	N/A	**No function**	0	Offer 2013	23328581
*5	rs1801159	c.1627A>G	p.I543V	Normal	1	Offer 2013	23328581
*9A	rs1801265	c.85T>C	p.C29R	Normal	1	He 2008	18452418
***13**	rs55886062	c.1679T>G	p.I560S	**No function**	0	Offer 2013	23328581
	rs67376798	c.2846A>T	p.D949V	**Decreased**	0.5	Offer 2014	24648345
HapB3	rs75017182, rs56038477, rs56276561	c.1129-5923C>G, c.1236G>A, c.483+18G>A	N/A p.E412E N/A	**Decreased**	0.5	Nie 2017	28295243

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update

Ursula Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12]

Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer ~3 to 8% of Caucasian population	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer ~0,2% of Caucasian population	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2915–2922, 2017
doi:10.1093/annonc/mdx411
Published online 2 August 2017

REVIEW

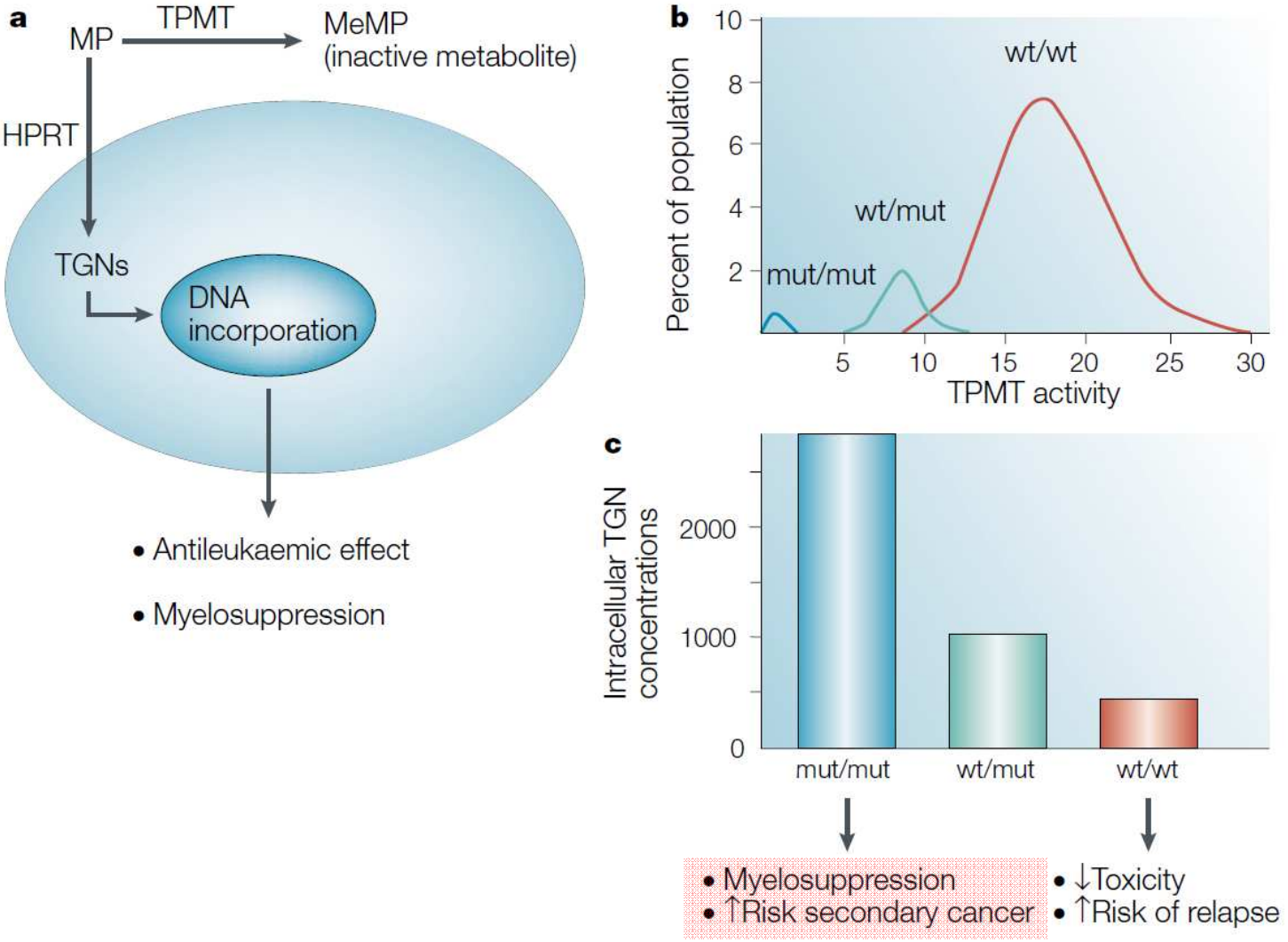
DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update

L. M. Henricks[1,2], F. L. Opdam[1,2], J. H. Beijnen[3,4], A. Cats[5] & J. H. M. Schellens[1,2,4*]

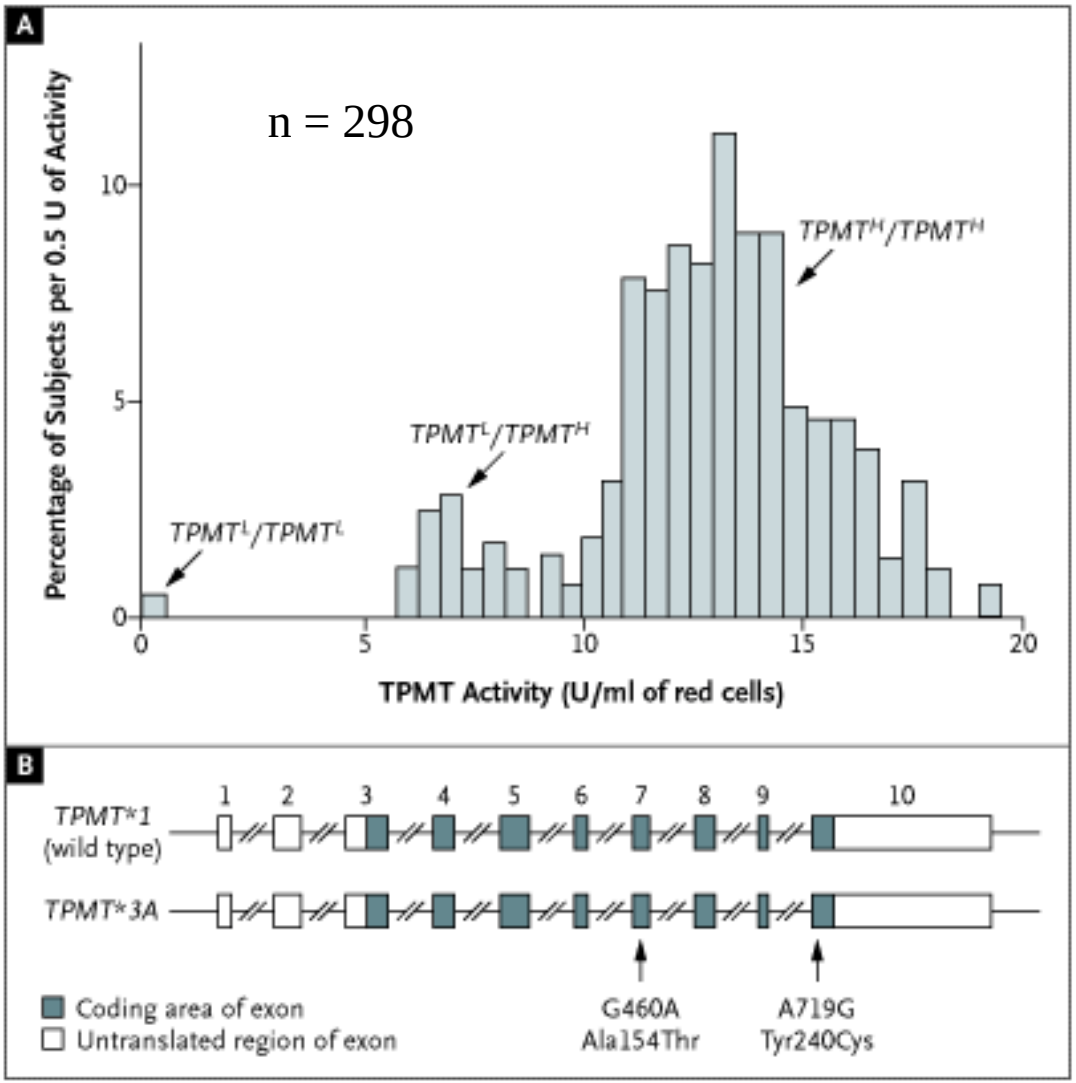
[1]Division of Pharmacology; [2]Department of Clinical Pharmacology, Division of Medical Oncology; [3]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Amsterdam; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht; [5]Department of Gastroenterology and Hepatology, Division of Medical Oncology

*Correspondence to: Prof. Jan H. M. Schellens, Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands. Tel: +31-20-512-2446; E-mail: j.schellens@nki.nl

TPMT and 6-mercaptopurine toxicity



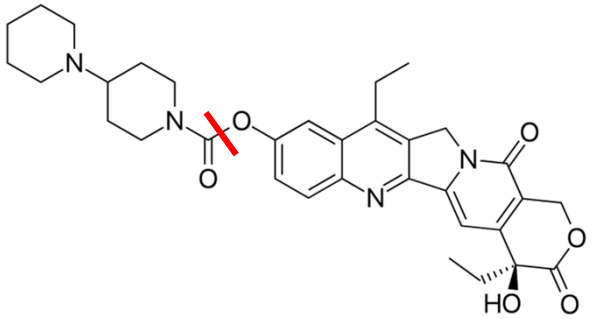
TPMT pharmacogenetics

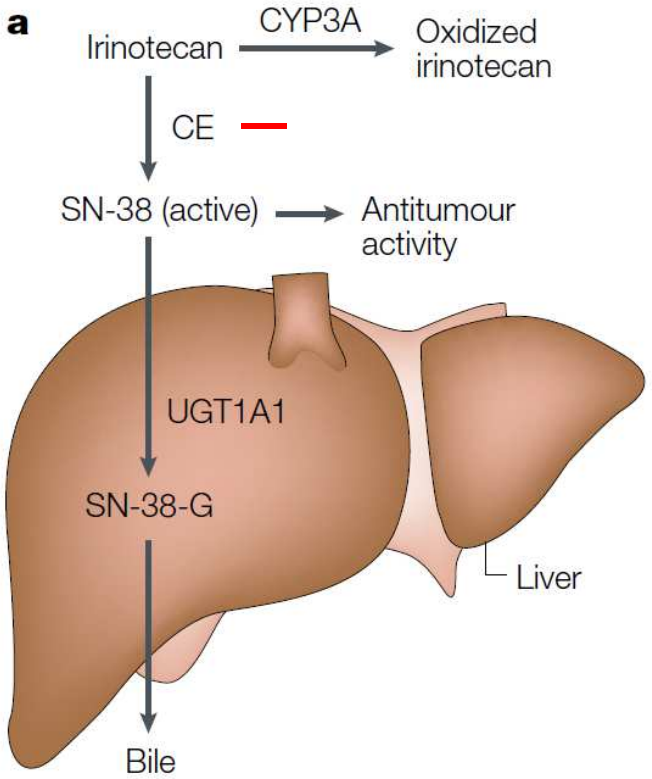


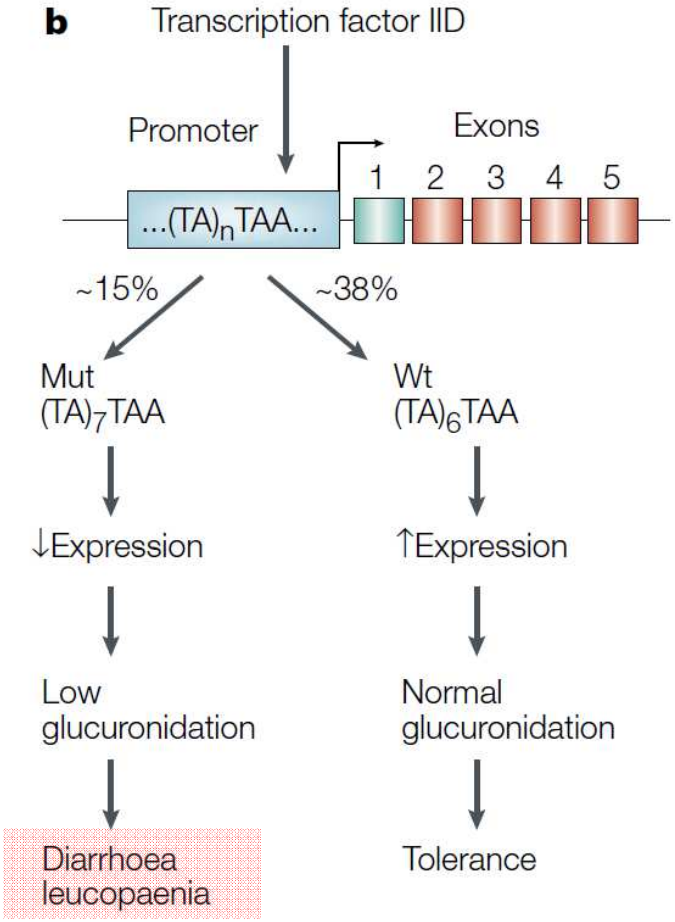
*TPMT*1*	wild-type
*TPMT*2*	238 G>C
*TPMT*3A*	460 G>A 719 A>G
*TPMT*3B*	460 G>A
*TPMT*3C*	719 A>G

TPMT deficiency
(Caucasians)
1 out of 300 (0.3%)

UGT1A1 and irinotecan toxicity







UGT1A1 and common exons allele nomenclature (view change log)

UGT1A common exons (2-5) SNPs are highlighted in grey.

Allele naming	Protein	Nucleotide Change Reference sequence : AF297093	Amino Acid Change	Exon	Effect	Phenotype[1]	Enzyme activity		Genbank	Reference	Notes
							In vivo	*In vitro*			
UGT1A1*1	UGT1A1.1				Wild-type					Ritter JK.,	
UGT1A1*2	UGT1A1.2	877(T>A)/878-890del	Frameshift/Del	2	Frameshift	CN1	Absent	Absent		Ritter JK, Sappal BS,	
UGT1A1*3	UGT1A1.3	1124(C>T)	S375F	4		CN1	Inactive	Inactive		Bosma PJ,	
UGT1A1*4	UGT1A1.4	1069(C>T)	Q357X	3		CN1	Inactive	Inactive		Bosma PJ,	
UGT1A1*5	UGT1A1.5	991(C>T)	Q331X	2	Exon 2 deletion	CN1	Absent	Inactive		Bosma PJ,	
UGT1A1*6	UGT1A1.6	211(G>A)	G71R	1			Reduced	Reduced		Aono S,	
UGT1A1*7	UGT1A1.7	1456(T>G)	Y486D	5		CN2	Reduced	Reduced		Aono S,	
UGT1A1*8	UGT1A1.8	625(C>T)	R209W	1		CN2	4.4%	Reduced		Bosma PJ; Huang CS,	
UGT1A1*9	UGT1A1.9	992(A>G)	Q331R	2		CN2	Reduced	Reduced		Moghrabi N,	
UGT1A1*10	UGT1A1.10	1021(C>T)	R341X	3		CN1	Absent	Absent		Moghrabi N,	
UGT1A1*11	UGT1A1.11	923(G>A)	G308E	2		CN1	Inactive	Absent		Erps LT, Labrune P,	
UGT1A1*12	UGT1A1.12	524(T>A)	L175Q	1		CN2	38.4%	Reduced		Seppen J,	
UGT1A1*13	UGT1A1.13	508-510del	F170del	1		CN1	Inactive	Inactive		Ritter JK,	
UGT1A1*14	UGT1A1.14	826(G>C)	G276R	1		CN1	Inactive	Inactive		Seppen J,	
UGT1A1*15	UGT1A1.15	529(T>C)	C177R	1		CN1	Inactive	Inactive		Seppen J,	
UGT1A1*16	UGT1A1.16	1070(A>G)	Q357R	3		CN1	Absent	Absent		Labrune P,	
UGT1A1*17	UGT1A1.17	1143(C>G)	S381R	4		CN1	Absent	Absent		Labrune P,	
UGT1A1*18	UGT1A1.18	1201(G>C)	A401P	4		CN1	Absent	Absent		Labrune P,	
UGT1A1*19	UGT1A1.19	1005(G>A)	W335X	3		CN1	Absent	Absent		Labrune P,	
UGT1A1*20	UGT1A1.20	1102(G>A)	A368T	4		CN1	Absent	Absent		Labrune P,	
UGT1A1*21	UGT1A1.21	1223insG	Frameshift	4	Frameshift	CN1	Absent	Absent		Labrune P,	
UGT1A1*22	UGT1A1.22	872(C>T)	A291V	2		CN1	Absent	Absent		Labrune P,	
UGT1A1*23	UGT1A1.23	1282(A>G)	K426E	4		CN1	Absent	Absent		Labrune P,	
UGT1A1*24	UGT1A1.24	1309(A>T)	K437X	5		CN1	Absent	Absent		Labrune P,	
UGT1A1*25	UGT1A1.25	840(C>A)	C280X	1		CN1	Absent	Absent		Aono S,	
UGT1A1*26	UGT1A1.26	973delG	Frameshift	2	Frameshift	CN2	Absent	Absent		Seppen J,	
UGT1A1*27	UGT1A1.27	686(C>A)	P229Q	1		Gilbert	Reduced	Reduced		Aono S,	
UGT1A1*28	UGT1A1.28	A(TA)6TAA to A(TA)7TAA		Promoter		Gilbert	Reduced	Reduced		Bosma PJ,	UGT1A1 TATA box
UGT1A1*29	UGT1A1.29	1099(C>G)	R367G	4		Gilbert	Reduced	Reduced		Aono S,	
UGT1A1*30	UGT1A1.30	44(T>G)	L15R	1		CN2	Reduced	Reduced		Seppen J,	
UGT1A1*31	UGT1A1.31	1160(CC>GT)	P387R	4		CN1	Absent	Absent		Ciotti M,	
UGT1A1*32	UGT1A1.32	1006(C>T)	R336W	3		CN1	0-10%	Absent		Ciotti M,	
UGT1A1*33	UGT1A1.33	881(T>C)	I294T	2		CN2	40-55%			Ciotti M,	
UGT1A1*34	UGT1A1.34	928(A>G)	M310V	2		CN2	26%-51%			Ciotti M,	

Internet | Mode protégé : désactivé 100%

UGT1A1*14	UGT1A1.14	826(G>C)	G276R	1		CN1	Inactive	Inactive		Seppen J.	
UGT1A1*15	UGT1A1.15	529(T>C)	C177R	1		CN1	Inactive	Inactive		Seppen J.	
UGT1A1*16	UGT1A1.16	1070(A>G)	Q357R	3		CN1	Absent	Absent		Labrune P.	
UGT1A1*17	UGT1A1.17	1143(C>G)	S381R	4		CN1	Absent	Absent		Labrune P.	
UGT1A1*18	UGT1A1.18	1201(G>C)	A401P	4		CN1	Absent	Absent		Labrune P.	
UGT1A1*19	UGT1A1.19	1005(G>A)	W335X	3		CN1	Absent	Absent		Labrune P.	
UGT1A1*20	UGT1A1.20	1102(G>A)	A368T	4		CN1	Absent	Absent		Labrune P.	
UGT1A1*21	UGT1A1.21	1223insG	Frameshift	4	Frameshift	CN1	Absent	Absent		Labrune P.	
UGT1A1*22	UGT1A1.22	872(C>T)	A291V	2		CN1	Absent	Absent		Labrune P.	
UGT1A1*23	UGT1A1.23	1282(A>G)	K426E	4		CN1	Absent	Absent		Labrune P.	
UGT1A1*24	UGT1A1.24	1309(A>T)	K437X	5		CN1	Absent	Absent		Labrune P.	
UGT1A1*25	UGT1A1.25	840(C>A)	C280X	1		CN1	Absent	Absent		Aono S.	
UGT1A1*26	UGT1A1.26	973delG	Frameshift	2	Frameshift	CN2	Absent	Absent		Seppen J.	
UGT1A1*27	UGT1A1.27	686(C>A)	P229Q	1		Gilbert	Reduced	Reduced		Aono S.	
UGT1A1*28	UGT1A1.28	A(TA)6TAA to A(TA)7TAA		Promoter		Gilbert	Reduced	Reduced		Bosma PJ.	UGT1A1 TATA box
UGT1A1*29	UGT1A1.29	1099(C>G)	R367G	4		Gilbert	Reduced	Reduced		Aono S.	
UGT1A1*30	UGT1A1.30	44(T>G)	L15R	1		CN2	Reduced	Reduced		Seppen J.	
UGT1A1*31	UGT1A1.31	1160(CC>GT)	P387R	4		CN1	Absent	Absent		Ciotti M.	
UGT1A1*32	UGT1A1.32	1006(C>T)	R336W	3		CN1	0-10%	Absent		Ciotti M.	
UGT1A1*33	UGT1A1.33	881(T>C)	I294T	2		CN2	40-55%			Ciotti M.	
UGT1A1*34	UGT1A1.34	928(A>G)	M310V	2		CN2	26%-51%			Ciotti M.	
UGT1A1*35[1]	UGT1A1.35	1292(T>C)	I431T	4		CN2	61%-81%			Ciotti M.	
UGT1A1*36	UGT1A1.36	A(TA)6TAA to A(TA)5TAA		Promoter			Increased	Increased		Beutler E.	
UGT1A1*37	UGT1A1.37	A(TA)6TAA to A(TA)8TAA		Promoter		CN2	Reduced	Reduced		Beutler E.	
UGT1A1*38	UGT1A1.38	1213(A>G)/ A(TA)6TAA to A (TA)8TAA	N400D	4		CN2				Labrune P.	Originally designated UGT1A1*64
UGT1A1*39	UGT1A1.39	1201(G>C)/1309(A>T)	A401P/K437X	4; 5		CN1				Labrune P.	
UGT1A1*40	UGT1A1.40	872(C>T)/1282(A>G)	A291V/K426E	2; 4		CN1				Labrune P.	
UGT1A1*41	UGT1A1.41	120-121delCT	Frameshift	1	Frameshift	CN1				Ciotti M.	
UGT1A1*42	UGT1A1.42	1388(A>C)/N A(TA)7TAA	E463A	5		CN2				Chalasani N.	
UGT1A1*43[1]	UGT1A1.43	698(T>G)	L233R	1		-				Gagne JF.	Originally designated UGT1A1*35
UGT1A1*44	UGT1A1.44	115(C>G)	H39D	1		CN1				Kadakol A.	
UGT1A1*45	UGT1A1.45	222(C>A)	Y74X	1		CN1				Kadakol A.	
UGT1A1*46	UGT1A1.46	517delC	Frameshift	1	Frameshift	CN1				Kadakol A.	
UGT1A1*47	UGT1A1.47	722-723delAG	Frameshift	1	Frameshift	CN1				Kadakol A.	
UGT1A1*48	UGT1A1.48	674(T>G)/722-723delAG	V225G/Frameshift	1	Frameshift	CN2				Kadakol A.	
UGT1A1*49	UGT1A1.49	1043delA	Frameshift	3	Frameshift	CN1				Kadakol A.	
UGT1A1*50	UGT1A1.50	1220delA/N	Frameshift/N	4	Frameshift	CN1				Kadakol A.	
UGT1A1*51	UGT1A1.51	1127(A>G)/N	H376R/N	4		CN2				Kadakol A.	
UGT1A1*52	UGT1A1.52	1130(G>T)	G377V	4		CN2				Kadakol A.	

Internet | Mode protégé : désactivé
100%

intensified dose in *28/*28 patients. The administration of an intensified dose (240 mg/m2) is only possible in *1/*1 patients, as well as in *1/*28 patients, in the absence of additional risk factors and under strict medical surveillance.

This...analysis is limited by the fact that other UGT1A1 deficient variants are relevant in non-Caucasian populations, particularly the *6 and *27 alleles in Asian populations.

The joint working group also provided a decision tree to guide irinotecan dosing based on *UGT1A1* genotype:

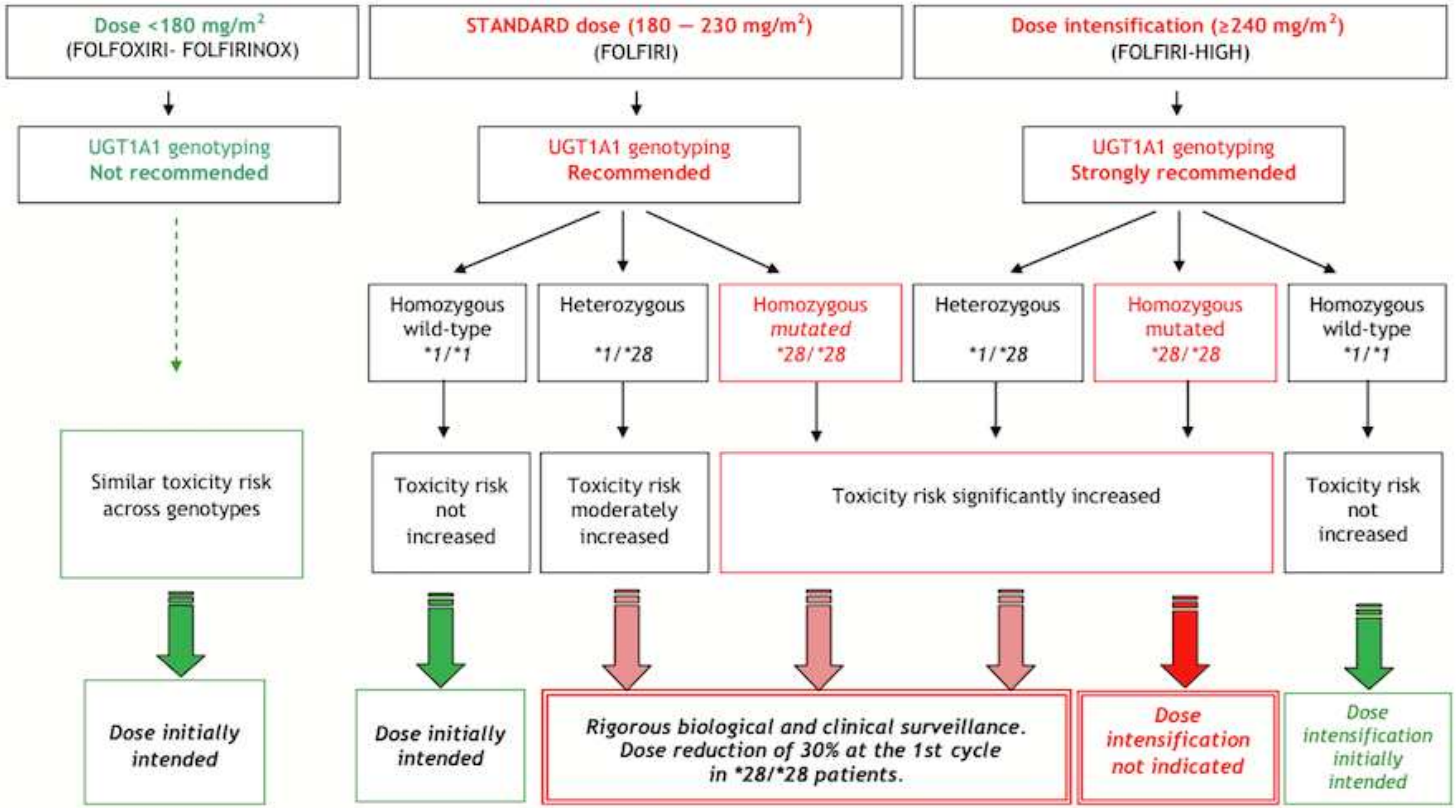


Figure 1 Decision tree for UGT1A1 genotyping depending on initially intended irinotecan dose.

Reprinted with permission from Etienne-Grimaldi et al. UGT1A1 genotype and irinotecan therapy: general review and implementation in routine practice. Fundamental & Clinical Pharmacology (2015)

Guideline History

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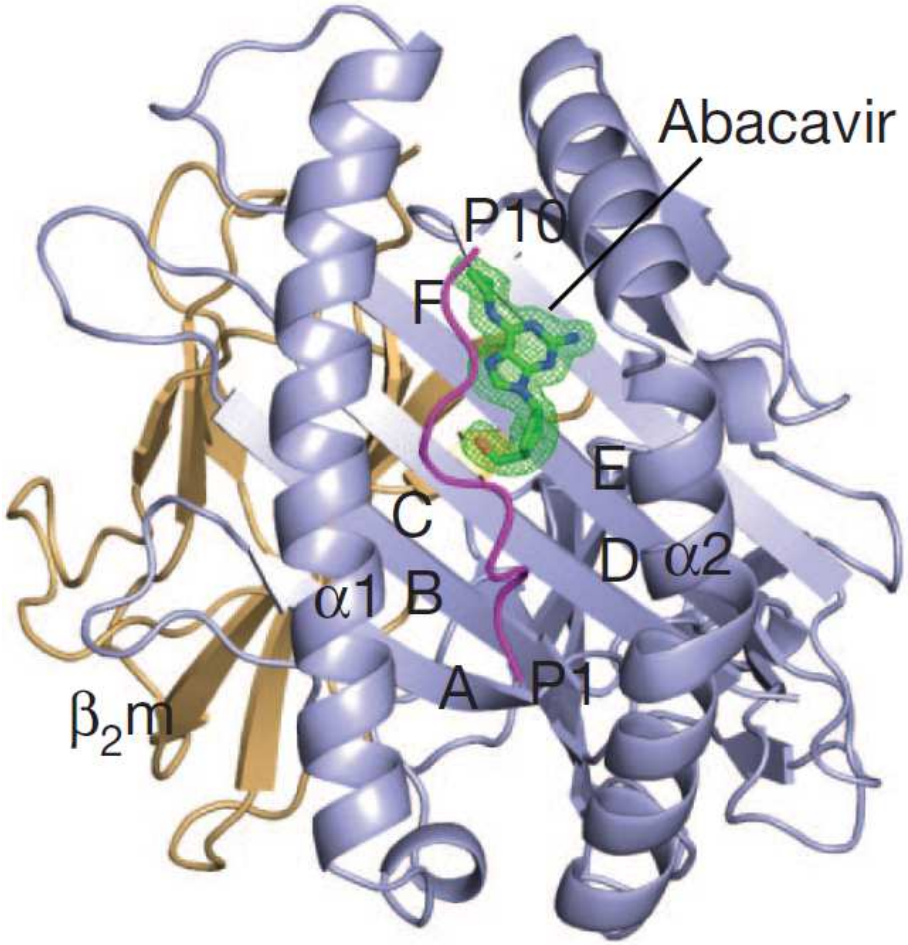
*HLA-B*57:01 and Abacavir hypersensitivity*



*HLA-B*57:01* is necessary but not sufficient by itself for HSR

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)*
Clinically diagnosed hypersensitivity reaction				
Total population that could be evaluated				
Hypersensitivity reaction	30	36	66	Sensitivity: 45.5 (33.1–58.2)
No hypersensitivity reaction	19	762	781	Specificity: 97.6 (96.2–98.5) PPV: 61.2 (46.2–74.8) NPV: 95.5 (93.8–96.8)
White subgroup				
Hypersensitivity reaction	29	32	61	Sensitivity: 47.5 (34.6–60.7)
No hypersensitivity reaction	19	638	657	Specificity: 97.1 (95.5–98.3) PPV: 60.4 (45.3–74.2) NPV: 95.2 (93.3–96.7)
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)
White subgroup				
Hypersensitivity reaction	22	0	22	Sensitivity: 100 (84.6–100)
No hypersensitivity reaction	25	666	691	Specificity: 96.4 (94.7–97.6) PPV: 46.8 (32.1–61.9) NPV: 100 (99.4–100)

* The white subgroup included the two and three patients reporting both categories of white ancestry in the prospective-screening group and the control group, respectively. NPV denotes negative predictive value, and PPV positive predictive value.

Mallal et al. *N Engl J Med* 2008; 358: 568

FDA black box warning in 2008 and CPIC guidelines

Home Drugs Drug Safety and Availability Postmarket Drug Safety Information for Patients and Providers

Drugs

Information for Healthcare Professionals: Abacavir (marketed as Ziagen) and Abacavir-Containing Medications

[For additional information about these drugs, see Information on Abacavir and Abacavir-containing Medications[1].]

FDA ALERT [7/24/2008]: Serious and sometimes fatal hypersensitivity reactions (HSR) caused by abacavir therapy are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*5701. Abacavir HSR is a multi-organ syndrome characterized by 2 or more clinical signs or symptoms that can include fever, rash, gastrointestinal symptoms, respiratory symptoms and constitutional symptoms.

FDA has reviewed data from 2 studies that support the recommendation for pre-therapy screening for the presence of the HLA-B*5701 allele and the selection of alternative therapy in positive subjects. Genetic tests for HLA-B*5701 are already available and all patients should be screened for the HLA-B*5701 allele before starting or restarting treatment with abacavir or abacavir-containing medications. Avoidance of abacavir therapy in HLA-B*5701 positive patients will significantly decrease the risk of developing clinically-suspected abacavir HSR. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only under exceptional circumstances when the potential benefit outweighs the risk.

Development of clinically-suspected abacavir HSR requires immediate and permanent discontinuation of abacavir therapy in all patients, including patients negative for HLA-B*5701. This new safety information will be reflected in updated product labeling.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this when additional information or analyses become available.

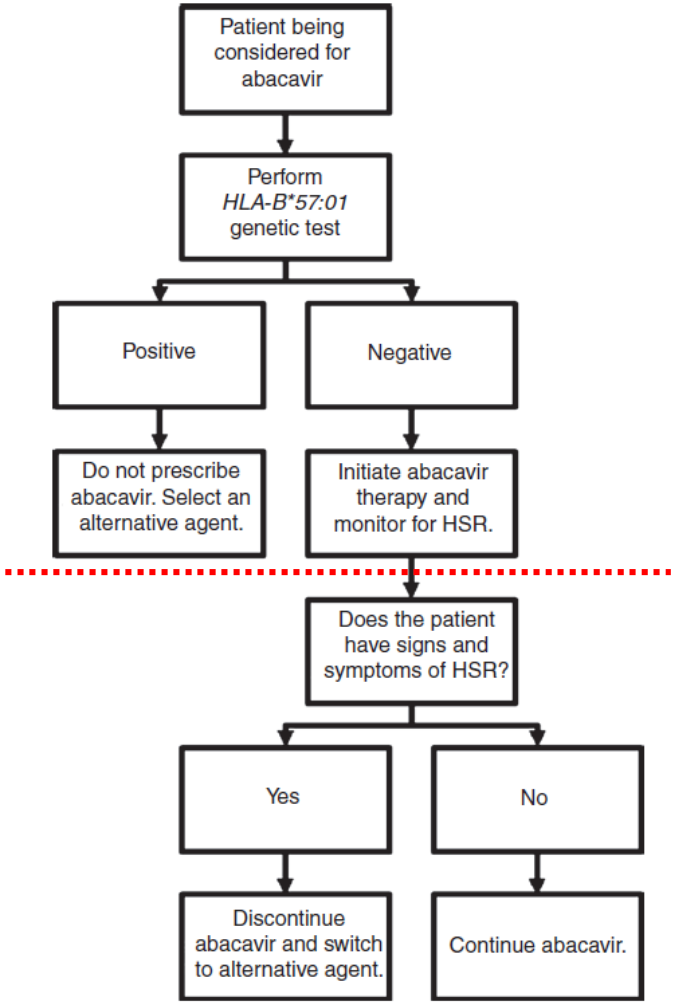
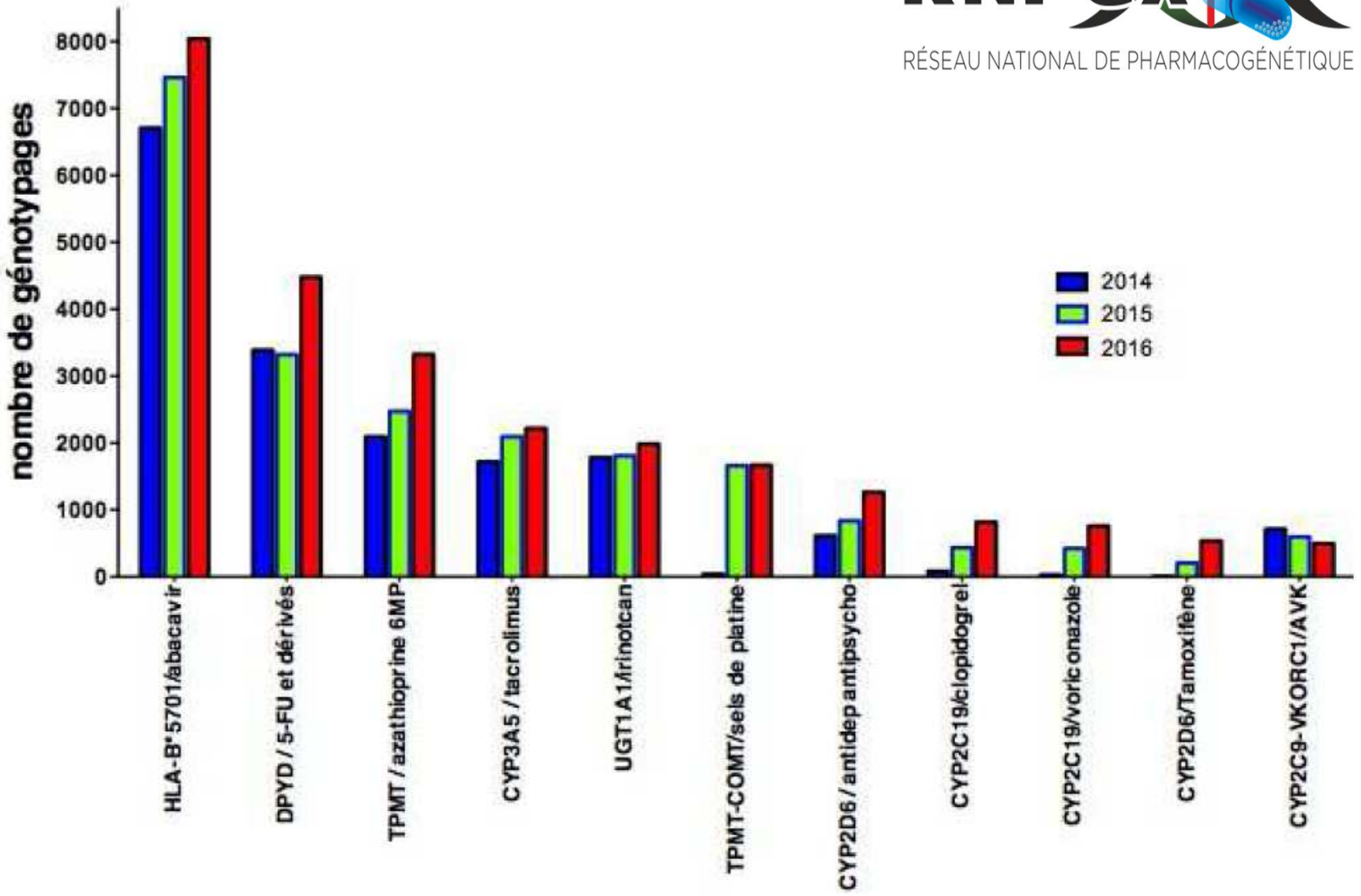


Figure 1 Treatment algorithm for clinical use of abacavir based on *HLA-B*57:01* genotype. HLA-B, human leukocyte antigen B; HSR, abacavir hypersensitivity reaction.

RNPGx

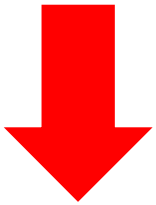
RÉSEAU NATIONAL DE PHARMACOGÉNÉTIQUE



Pharmacogenetics as a standard of care in pharmacotherapy?

Today:

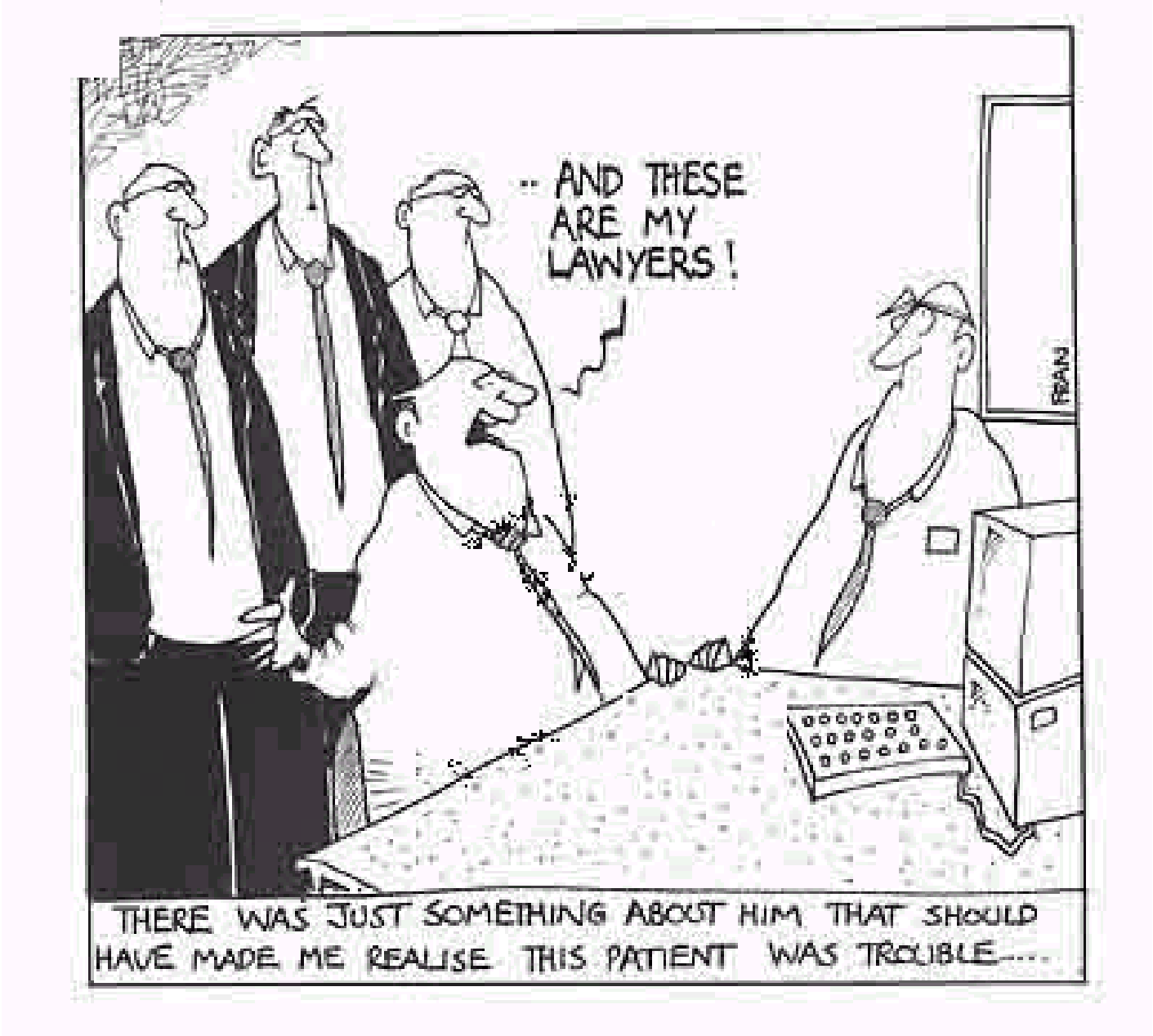
Do we have to perform **pre-emptive genotyping** (or any alternative approach to assess enzyme / protein activity) before initiating therapy?



Tomorrow:

Do we have to use genotype-guided dose individualization guidelines **when patient genotype is available** before initiating therapy?

How long can you do WITHOUT pharmacogenetics ?!?

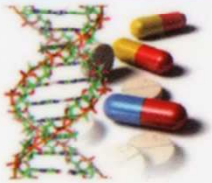


Transfer of information…

Erasmus MC
Universitair Medisch Centrum Rotterdam

Nederlands Expertisecentrum Farmacogenetica
Afd. Klinische Chemie
Erasmus MC Rotterdam

Farmacogenetica Profiel



Contact: farmacogenetica@erasmusmc.nl
Telefoon: 010-7033119
www.erasmusmc.nl/farmacogenetica
www.farmacogenetica.nl

Bij een afwijkend metabolisme zou voor een aantal geneesmiddelen mogelijk een aangepaste dosering beter passen. Dit … uw arts of apotheker. Doseringsvoorstell… KNMP-Kennisbank Farmacogenetica.

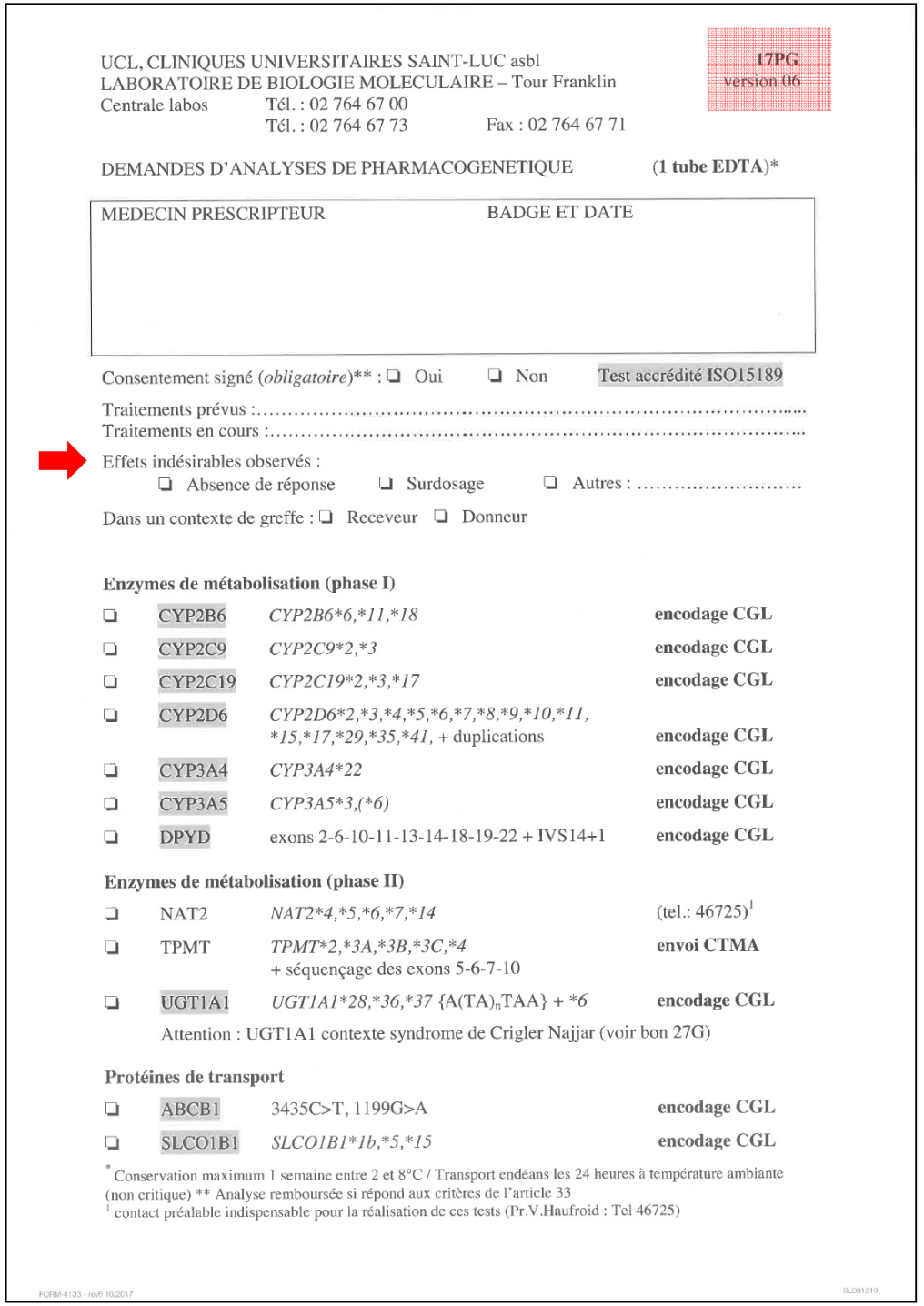
Naam: Test Erasmus MC/RvS — Geb. datum: 01/01/1980
BSN: 12345678 — Uitgifte kaart: 14/07/2014

Gen:	Uitslag:	Metabolisme	Prev.:[1]	Getest op:
CYP1A2	*1/*1	Normaal	45%	*1C, *1F, *1K
CYP2B6	*4/*6	Intermediair	25%	*4, 5, 6, 7, 8, 9, 13, 16, 18
CYP2C9	*1/*2	Intermediair	17%	*2, 3
CYP2C19	*1/*1	Normaal	80%	*2, 3, 17
CYP2D6	*1/*2xN	Ultrasnel	3%	25 varianten (AmpliChip)
CYP3A4	*1/*1	Normaal	80%	*1B,1G,3-6,10,12,17,18,20,22
CYP3A5	*3/*3	Nonexpressor	80%	*3, *6
BChE	U/S	Normaal	99%	A, K, F1, F2, H, J, Sc, Silent
DPYD	*1/*2A	Intermediair	2%	*2A
HLA-B*5701	NEG	Normaal	96%	
TPMT	*1/*1	Normaal	89%	*2, 3A, 3B, 3C
VKORC1	AA	Gevoelig	20%	-1639G>A

[1] *In blanke bevolking. Kan afwijken bij andere etniciteiten*

Slide courtesy of Pr Ron VanSchaik (Rotterdam)

En routine aux CUSL



UCL, CLINIQUES UNIVERSITAIRES SAINT-LUC asbl
LABORATOIRE DE BIOLOGIE MOLECULAIRE – Tour Franklin
Centrale labos Tél. : 02 764 67 00
Tél. : 02 764 67 73 Fax : 02 764 67 71

17PG
version 06

DEMANDES D'ANALYSES DE PHARMACOGENETIQUE (**1 tube EDTA**)*

MEDECIN PRESCRIPTEUR BADGE ET DATE

Consentement signé (*obligatoire*)** : ❑ Oui ❑ Non Test accrédité ISO15189

Traitements prévus :.....
Traitements en cours :.....

Effets indésirables observés :
❑ Absence de réponse ❑ Surdosage ❑ Autres : .....

Dans un contexte de greffe : ❑ Receveur ❑ Donneur

Enzymes de métabolisation (phase I)

❑	CYP2B6	*CYP2B6*6,*11,*18*	**encodage CGL**
❑	CYP2C9	*CYP2C9*2,*3*	**encodage CGL**
❑	CYP2C19	*CYP2C19*2,*3,*17*	**encodage CGL**
❑	CYP2D6	*CYP2D6*2,*3,*4,*5,*6,*7,*8,*9,*10,*11, *15,*17,*29,*35,*41,* + duplications	**encodage CGL**
❑	CYP3A4	*CYP3A4*22*	**encodage CGL**
❑	CYP3A5	*CYP3A5*3,(*6)*	**encodage CGL**
❑	DPYD	exons 2-6-10-11-13-14-18-19-22 + IVS14+1	**encodage CGL**

Enzymes de métabolisation (phase II)

❑	NAT2	*NAT2*4,*5,*6,*7,*14*	(tel.: 46725)[1]
❑	TPMT	*TPMT*2,*3A,*3B,*3C,*4* + séquençage des exons 5-6-7-10	**envoi CTMA**
❑	UGT1A1	*UGT1A1*28,*36,*37* {A(TA)$_n$TAA} + **6*	**encodage CGL**

Attention : UGT1A1 contexte syndrome de Crigler Najjar (voir bon 27G)

Protéines de transport

❑	ABCB1	3435C>T, 1199G>A	**encodage CGL**
❑	SLCO1B1	*SLCO1B1*1b,*5,*15*	**encodage CGL**

* Conservation maximum 1 semaine entre 2 et 8°C / Transport endéans les 24 heures à température ambiante (non critique) ** Analyse remboursée si répond aux critères de l'article 33
[1] contact préalable indispensable pour la réalisation de ces tests (Pr.V.Haufroid : Tel 46725)

FORM-4133 - rev6 10.2017 SL001219