Companion diagnostics and precision medicine : Regulatory and update barriers to patient access

A Perspective from the Genetics Lab

Geneva, September 27th, 2018

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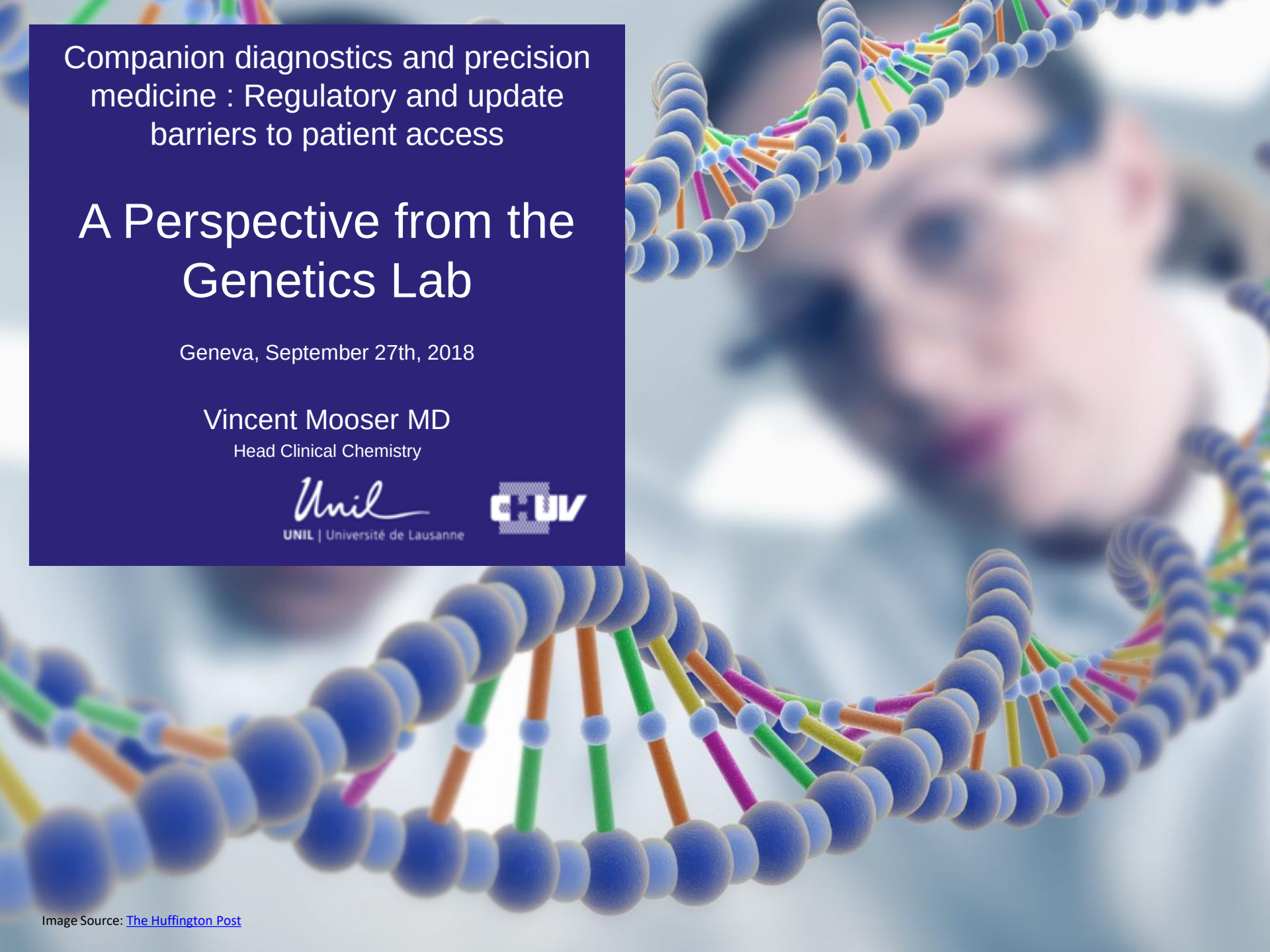
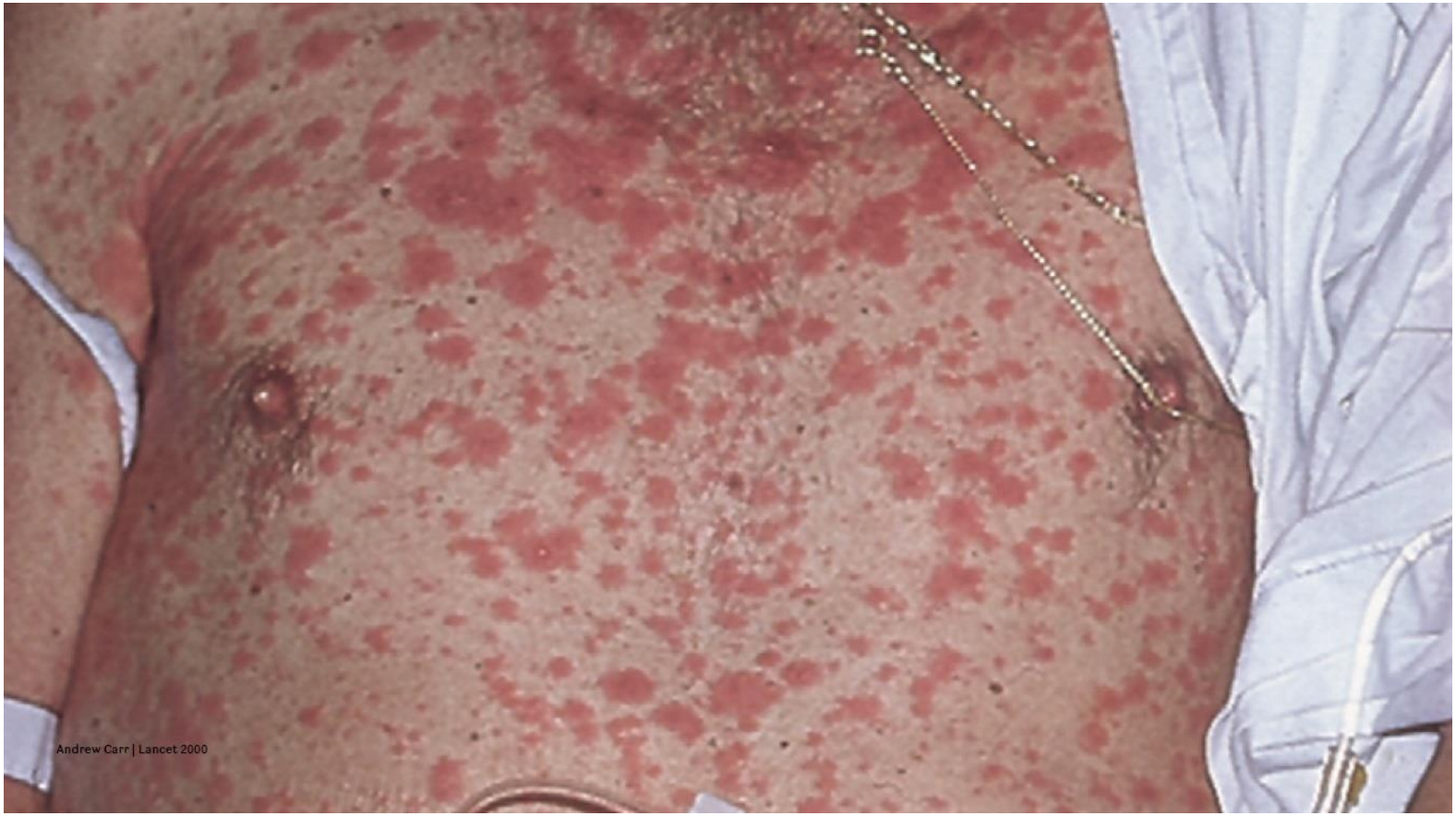


Image Source: The Huffington Post


Andrew Carr | Lancet 2000

Abacavir : Hypersensitivy Reaction in Phase II Trials

Antiretroviral effect and safety of abacavir alone and in combination with zidovudine in HIV-infected adults

Michael S. Saag, Anders Sonnerborg*, Ramon A. Torres†, Danny Lancaster‡, Brian G. Gazzard§, Robert T. Schooley¶, Carmen Romero**, Dennis Kelleher††, William Spreen††, Stephen LaFon†† and the Abacavir Phase 2 Clinical Team

N = 3 patients, out of 76, with hypersensitivity reaction

F204 AIDS 1998, Vol 12 No 16

HSR to Abacavir : First Extensive Analysis

CLINICAL THERAPEUTICS®/VOL. 23, NO. 10, 2001

Hypersensitivity Reactions During Therapy with the Nucleoside Reverse Transcriptase Inhibitor Abacavir

Seth Hetherington, MD,[1] Sue McGuirk, PhD,[2] Gwendolyn Powell, MD,[1] Amy Cutrell, MS,[1] Odin Naderer, PharmD,[1] Bill Spreen, PharmD,[1] Steve Lafon, MSc,[1] Gill Pearce, PhD,[2] and Helen Steel, MD[2]

[1]GlaxoSmithKline, Research Triangle Park, North Carolina, and [2]GlaxoSmithKline,

Results: A total of 1803 cases were identified, 1302 in the 30,595 patients participating in clinical trials or the expanded-access program and 501 in patients from the post marketing experience. On review, 176 (9.8%) of these cases were considered definitive and the remainder probable. Based on the 1302 cases identified in clinical trials or the expanded-access program, the calculated incidence of hypersensitivity was 4.3%. Symp

HSR to Abacavir : First Genetic Association

Articles

Association between presence of *HLA-B*5701, HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

S Mallal, D Nolan, C Witt, G Masel, A M Martin, C Moore, D Sayer, A Castley, C Mamotte, D Maxwell, I James, F T Christiansen

Methods MHC region typing was done in the first 200 Western Australian HIV Cohort Study participants exposed to abacavir. Definite abacavir hypersensitivity was identified in 18 cases, and was excluded in 167 individuals with more than 6 weeks' exposure to the drug (abacavir tolerant). 15 individuals

Lancet 2002; **359:** 727–32

HSR to Abacavir : Second Report on Genetic Association

Genetic variations in *HLA-B* region and hypersensitivity reactions to abacavir

Seth Hetherington, Arlene R Hughes, Michael Mosteller, Denise Shortino, Katherine L Baker, William Spreen, Eric Lai, Kirstie Davies, Abigail Handley, David J Dow, Mary E Fling, Michael Stocum, Clive Bowman, Linda M Thurmond, Allen D Roses

Lancet 2002; **359:** 1121–22

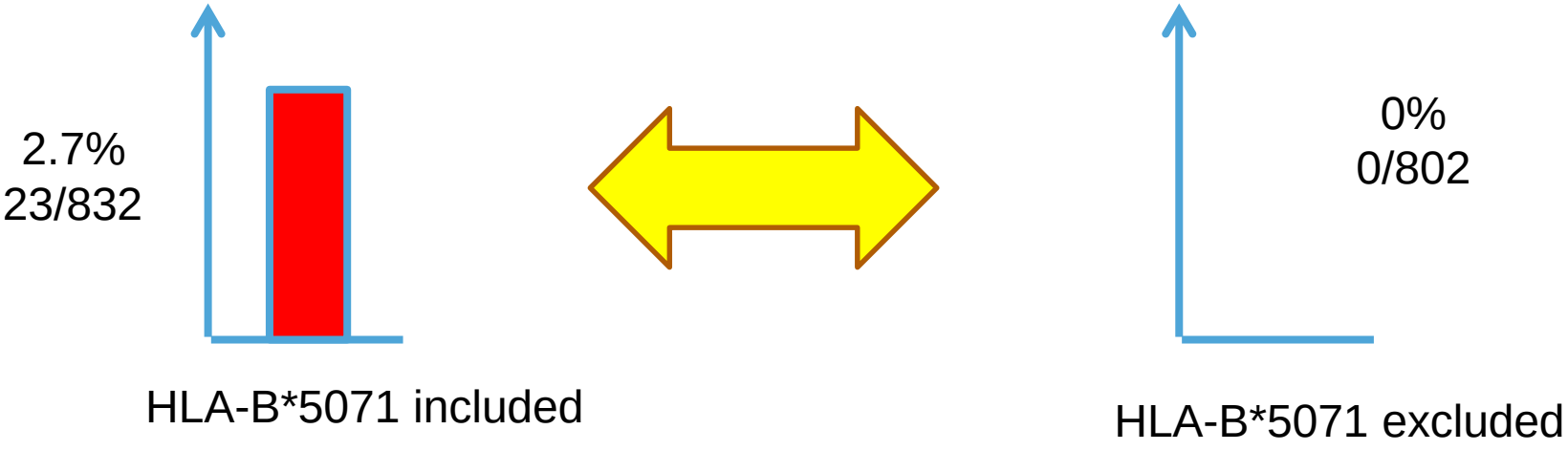
→ Replication in second, independent dataset

Abacavir and HLA B*5701 : The Predict Trial

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

HLA-B*5701 Screening for Hypersensitivity to Abacavir



Abacavir and HLA B*5701 : FDA Change in Label

On July 18, 2008, the FDA approved changes to the package insert for Ziagen (abacavir sulfate) highlighting information about the association of the HLA-B*5701 allele (a part of a gene) and hypersensitivity reactions (HSR) caused by abacavir-containing therapy.

Modification du 1er janvier 2017

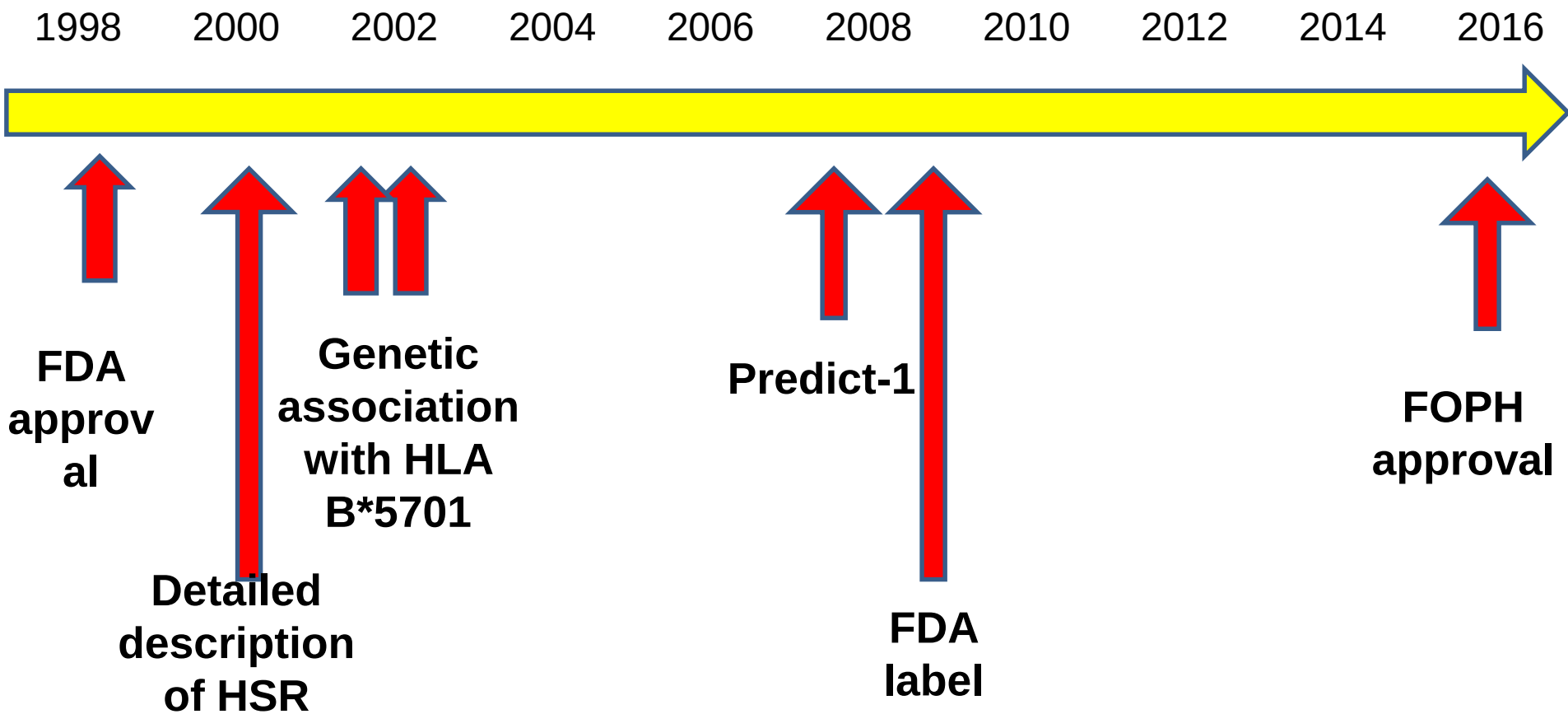
No. pos.	NP	Dénomination (Analyses de génétique moléculaire)	Limitation	Domaine de laboratoire
2150.00		**Autres**		
2150.10	93	Analyse pharmacogénétique	Limitations : 1. Uniquement au moment où il y a indication à l'administration d'un médicament, ou lors de survenue d'un effet secondaire médicamenteux ou d'une efficacité thérapeutique diminuée ou absente en cours de traitement avec un médicament, pour lequel il existe une relation scientifiquement démontrée entre des effets secondaires médicamenteux significatifs (y compris les effets toxiques) ou une efficacité thérapeutique diminuée ou absente et les mutations génétiques examinées 2. Uniquement lorsque les mutations génétiques recherchées ne servent pas à poser un diagnostic, à rechercher une prédisposition à une maladie génétique ou à réaliser une typisation tissulaire HLA sans lien avec l'administration du médicament. 3. Prescription de l'analyse par tous les médecins sans distinction du titre de spécialité selon la « Liste de la Société Suisse de Pharmacologie et Toxicologie cliniques (SSPTC) des analyses pharmacogénétiques courantes que peuvent prescrire tous les médecins sans distinction du titre de spécialité», version 1.0 du 09.06.2016 (www.bag.admin.ch/ref) 4. Pour les médicaments ne figurant pas dans la liste de la SSPTC, prescription de l'analyse uniquement par des médecins titulaires du titre postgrade fédéral en pharmacologie et toxicologie cliniques selon la loi fédérale du 23 juin 2006 sur les professions médicales	C G

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

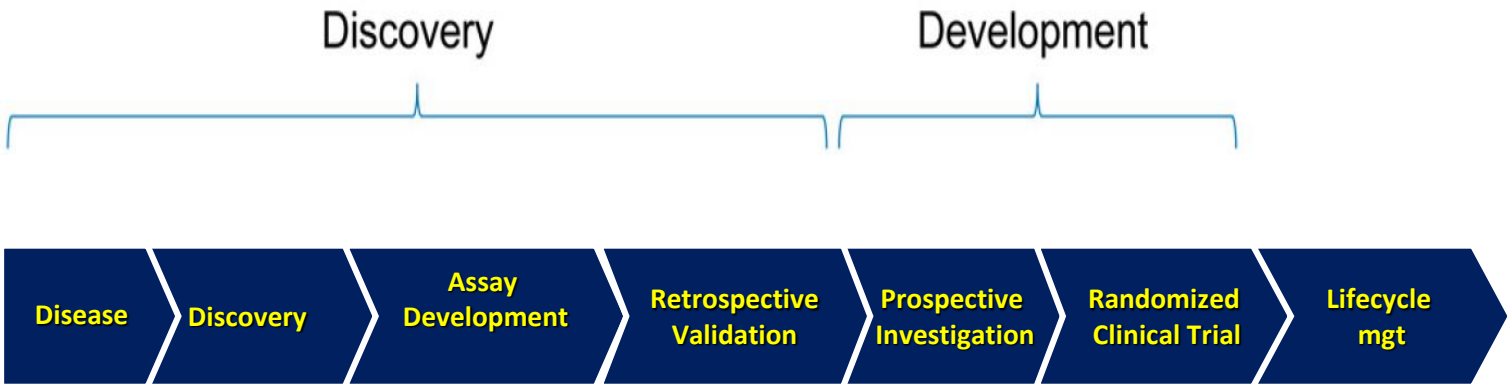
médicament	**gène**
abacavir	HLA-B*5701
carbamazépine	HLA-A*3101 et HLA-B*1502
6-mercaptopurine, azathioprine	TPMT
5-fluorouracile, capécitabine	DPYD
irinotécan	UGT1A1

Liste éditée par le comité exécutif de la SSPTC le 9.06.2016
Numéro de version 1.0

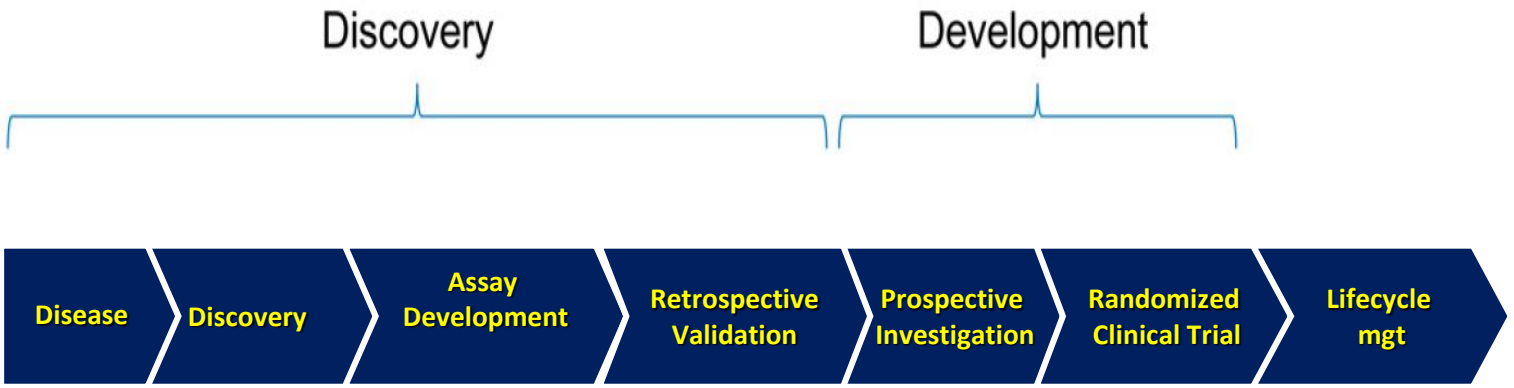
Abacavir and HLA B*5701 : A 20-Year Story



The road to a new biomarker



The road to a new biomarker



Analytical validity

Clinical validity

Clinical utility

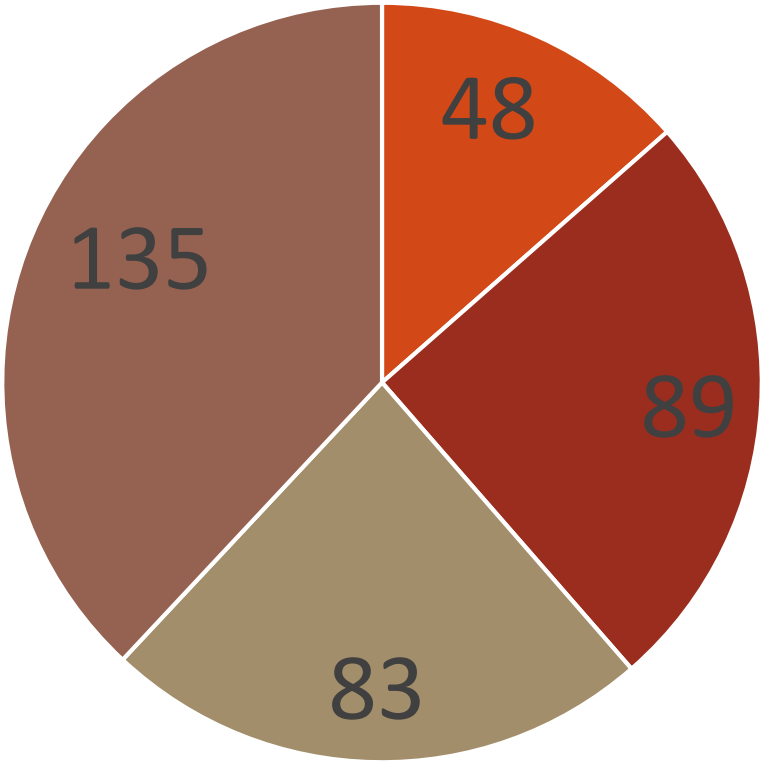
canton de vaud

CHUV

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.
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.

Distribution of 355 Gene-Drug Couples according to CPIC Level



REVIEW OF THERAPEUTICS

Impact of Pharmacogenetics on Efficacy and Safety of Statin Therapy for Dyslipidemia

Whitney D. Maxwell,[1] Laura B. Ramsey,[2] Samuel G. Johnson,[3,4] Kate G. Moore,[5] Michael Shtutman,[6] John H. Schoonover,[1] and Marina Kawaguchi-Suzuki[7,8*]

Proteins involved in statin transport and elimination

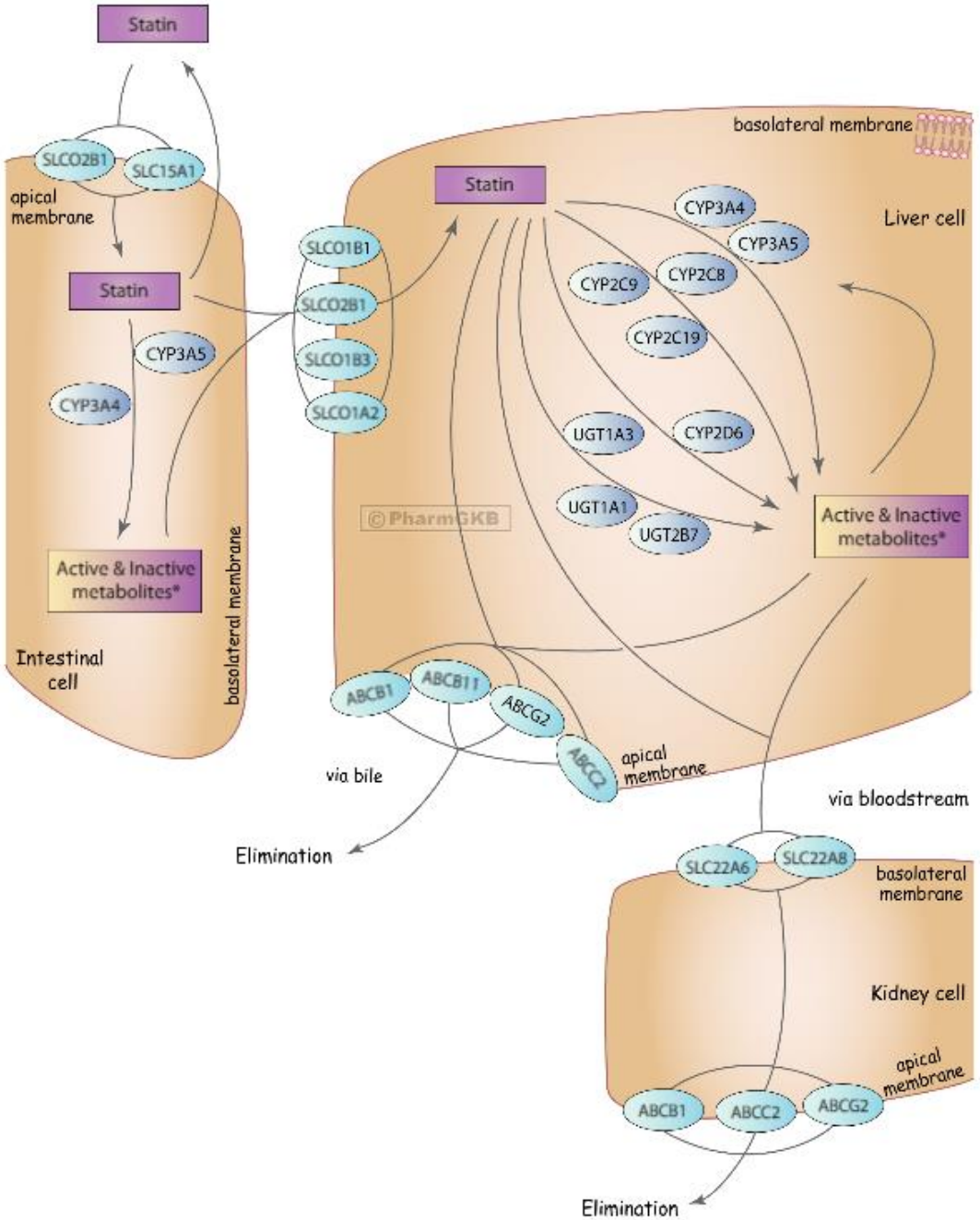


Table 1. Summary of Key Pharmacogenetic Variants Associated with Statin Efficacy or Safety

Gene	Allele	rs ID	Allele frequency, %	No. of study participants	Efficacy/ Safety	Variant effect	Associated with clinical outcomes[a]	Associated with surrogate marker[b]
Simvastatin								
ABCB1	3435T>C	rs1045642	52.6	114	Safety	Myopathy↓		X
			54.0	85	Efficacy	Greater Tc↓		X
	1236T>C	rs1128503	43.5	85	Efficacy	Greater Tc↓ and LDL ↓		X
			44.0	114				
	2677G>T/A	rs2032582	51.0	85	Efficacy	Greater Tc↓		X
	A>C	rs3789244	42.3	1883	Efficacy	↑MI risk	X	
	A>T	rs1922242	35.2			↓MI risk		
APOA5	1131C	rs662799	16.0	657	Efficacy	Less LDL↓		X
APOC1	G>A	rs4420638	19.0	1976	Efficacy	LDL↓		X
APOE	388T>C (ε_4)	rs429358	20.3	966	Efficacy	ACM↓	X	
CETP	118 + 279G>A (*TaqB B2*)	rs708272	50.0	99	Efficacy	HDL↑		X
	1264G>A (I405V)	rs5882	27.5	180	Efficacy	Less HDL↑ and TG↓		X
CLMN	A>T	rs8014194	24.0	1976	Efficacy	Tc↓		X
CYP3A4	352A>G (*4)	rs55951658	3.3	16	Efficacy	Greater TG↓ and Tc↓		X
	522–191C>T (*22)	rs35599367	3.6	646	Safety	PK parameters (↑conc)		X
			4.7	273	Efficacy	↓dose required		X
			10.6	80	Efficacy	Greater Tc↓ and LDL↓		X
CYP3A5	219–237A>G (*3)	rs776746	8.4 (for *1)	69	Efficacy	Less Tc↓ and LDL↓ (for *1)		X
SLCO1B1	521T>C (*5, *15, *17)	rs4149056	15.2	66	Efficacy	Less Tc↓		X
			NP	32	Safety	PK parameters (↑AUC, C_{max})		X
			10.6	646	Safety	PK parameters (↑conc)		X
			15.0	175	Safety	Myopathy↑		X
			14.6	192	Safety	ADR↑	X	
SCAP	2392G>A	rs12487736	48.0	99	Efficacy	Greater Tc↓ and TG↓		X

Finally, more evidence on cardiovascular and safety outcomes are needed for all statins to demonstrate the benefits of pharmacogenomic testing in clinical practice.

In addition, the cost-effectiveness of pharmacogenetic testing for polymorphisms related to statin therapy is yet to be fully evaluated.

OPEN

The Pharmacogenomics Journal (2017) 17, 395–402

www.nature.com/tpj

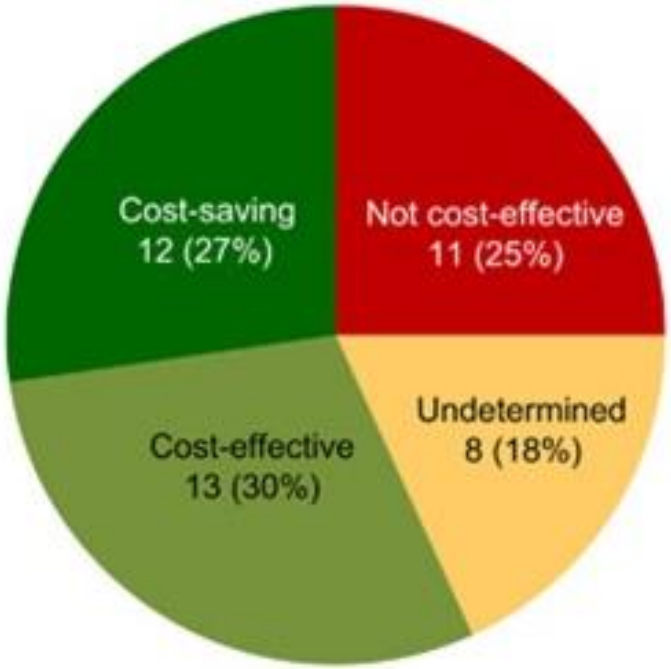
REVIEW

Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet?

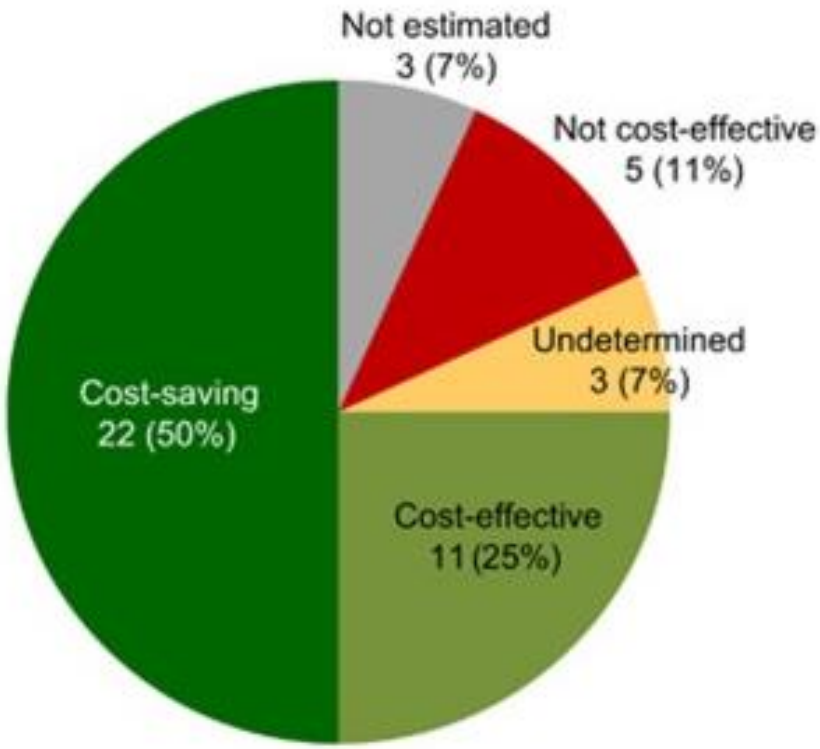
M Verbelen[1], ME Weale[2] and CM Lewis[1,2]

Cost-effectivenes for PGX Testing for 44 drugs

PGX testing with costs



PGX testing at no cost



Legend

Cost-saving/dominant	Cost-effective	Undetermined	Not cost-effective	Not estimated
PGx was more effective at lower cost	PGx was more effective at acceptable additional cost	Reviewed study did not reach unequivocal conclusion	PGx was not cost-effective	Study did not report enough detail to estimate impact on conclusion

Conclusion

1. Genetic association ≠ clinical utility
2. Strong evidence sufficient to modify medical practice available only for a minority of drug – gene couples
3. Major concern for diagnostic lab : clinical-grade quality
4. Major need to invest into development (as opposed to discovery) of companion diagnostics
5. Evolution towards pre-emptive PGX testing → Cost-effectiveness.