

Pharmacogenomics: A Clinical Perspective

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Lost in Translation

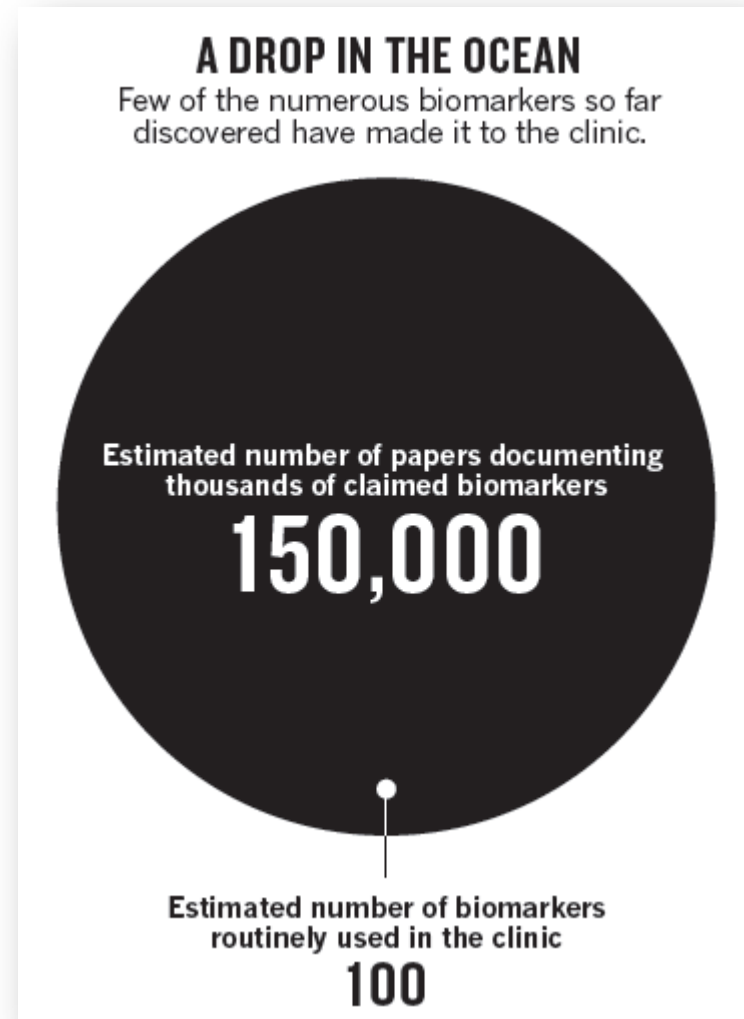


- Only one in 20 findings in basic science result in a product
- Only one in 7 discoveries make it to clinical practice
- Takes an average of 17 years to make it to practice



Predictive Testing

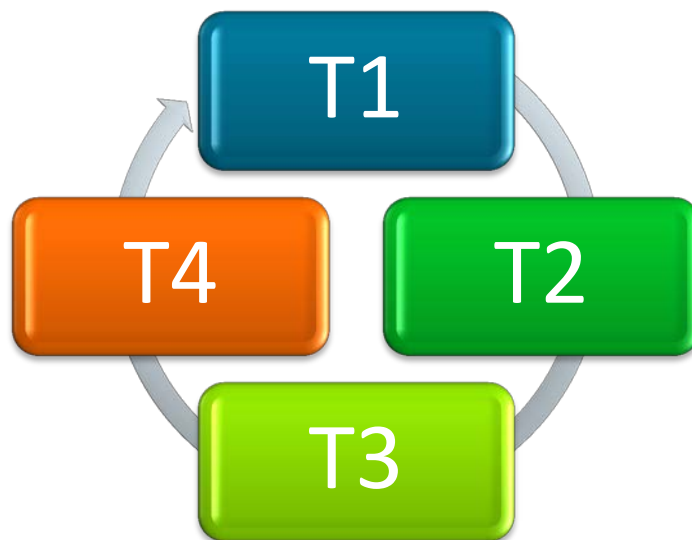
- Area that has been criticised for lack of progress – very few tests in clinical practice
- Many reasons for this
 - ▶ Poor clinical phenotyping
 - ▶ Poor genotyping strategies
 - ▶ Small sample sizes
 - ▶ Population stratification
 - ▶ Poor study designs
- Many different strategies are now being put into place: from technological to implementation



Poste, Nature, 2011



Bridging the Translational Gaps



- **T1** – Basic Discovery Process
- **T2** – Taking your discovery into populations
- **T3** – implementing your discovery into clinical practice
- **T4** – impact on public health



T1: Discovery and Clinical Validity

- The position for most discoveries
- Complicated by the “winner’s curse”
- Lack of replication and contradictory data
- Overestimation of effect size leads to inadequately powered replication studies
- Lack of standardisation of phenotypes
- Systematic reviews and meta-analyses may be important in identifying issues



The Phenotype Standardization Project: Improving Pharmacogenetic Studies of Serious Adverse Drug Reactions

M Pirmohamed¹, GP Aithal², E Behr³, A Daly⁴ and D Roden⁵

Phenotype Standardization for Immune-Mediated Drug-Induced Skin Injury

M Pirmohamed¹, PS Friedmann², M Molokhia³, YK Loke⁴, C Smith⁵, E Phillips⁶, L La Grenade⁷, B Carleton⁸, M Papaluca-Amati⁹, P Demoly¹⁰ and NH Shear¹¹

Case Definition and Phenotype Standardization in Drug-Induced Liver Injury

GP Aithal¹, PB Watkins², RJ Andrade^{3,4}, D Larrey⁵, M Molokhia⁶, H Takikawa⁷, CM Hunt⁸, RA Wilke⁹, M Avigan¹⁰, N Kaplowitz¹¹, E Bjornsson¹² and AK Daly¹³

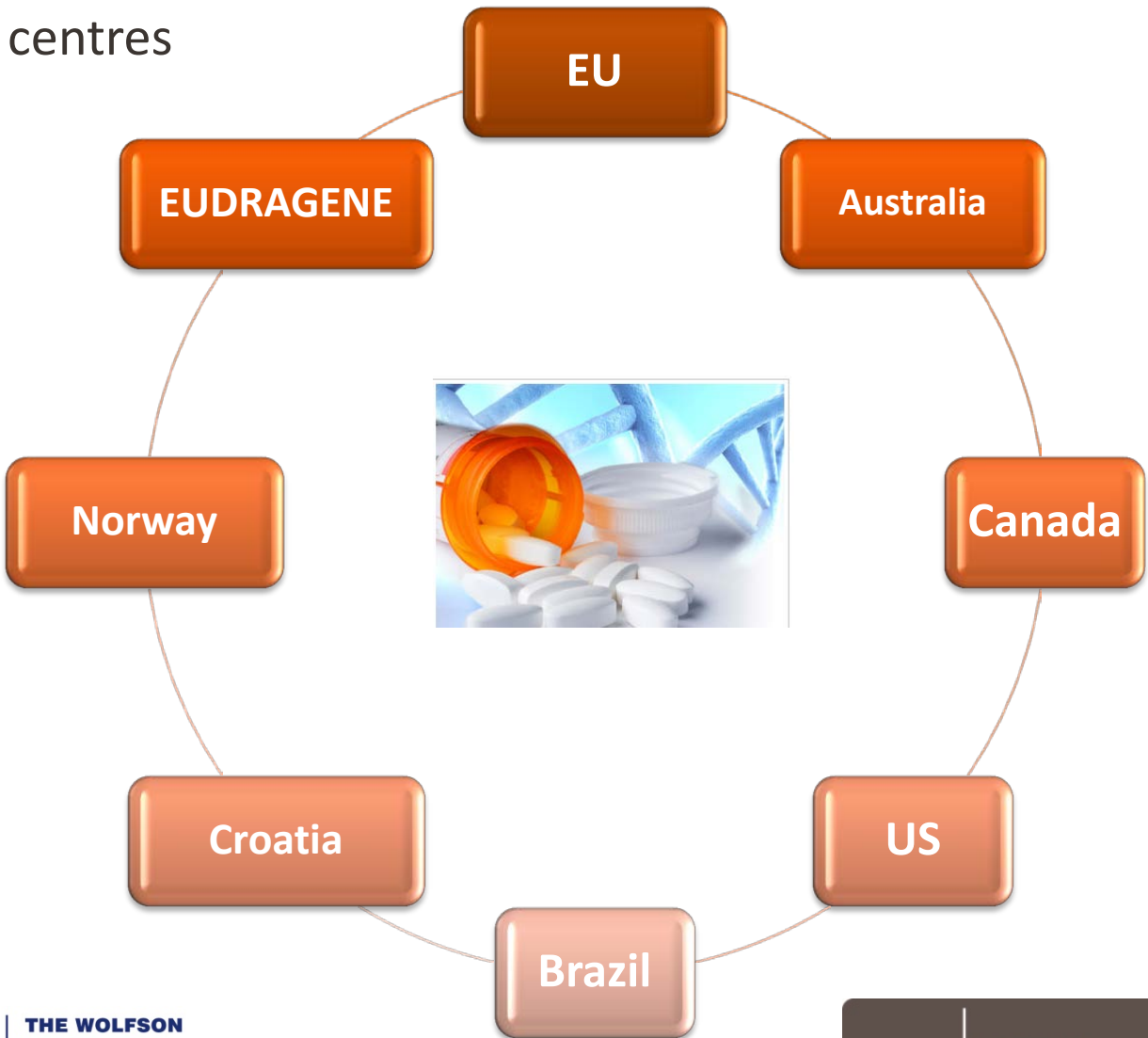
The International Serious Adverse Events Consortium (iSAEC) phenotype standardization project for drug-induced torsades de pointes

Elijah R. Behr^{1*}, Craig January², Eric Schulze-Bahr³, Andrew A. Grace⁴, Stefan Kääh⁵, Monica Fiszman⁶, Shaniece Gathers⁷, ShaAvhrée Buckman⁸, Ashraf Youssef⁹, Munir Pirmohamed¹⁰, and Dan Roden^{11*}



InTernational Consortium on Drug Hypersensitivity (ITCH)

- 12 international centres
- 50 UK centres
- 1500 patients



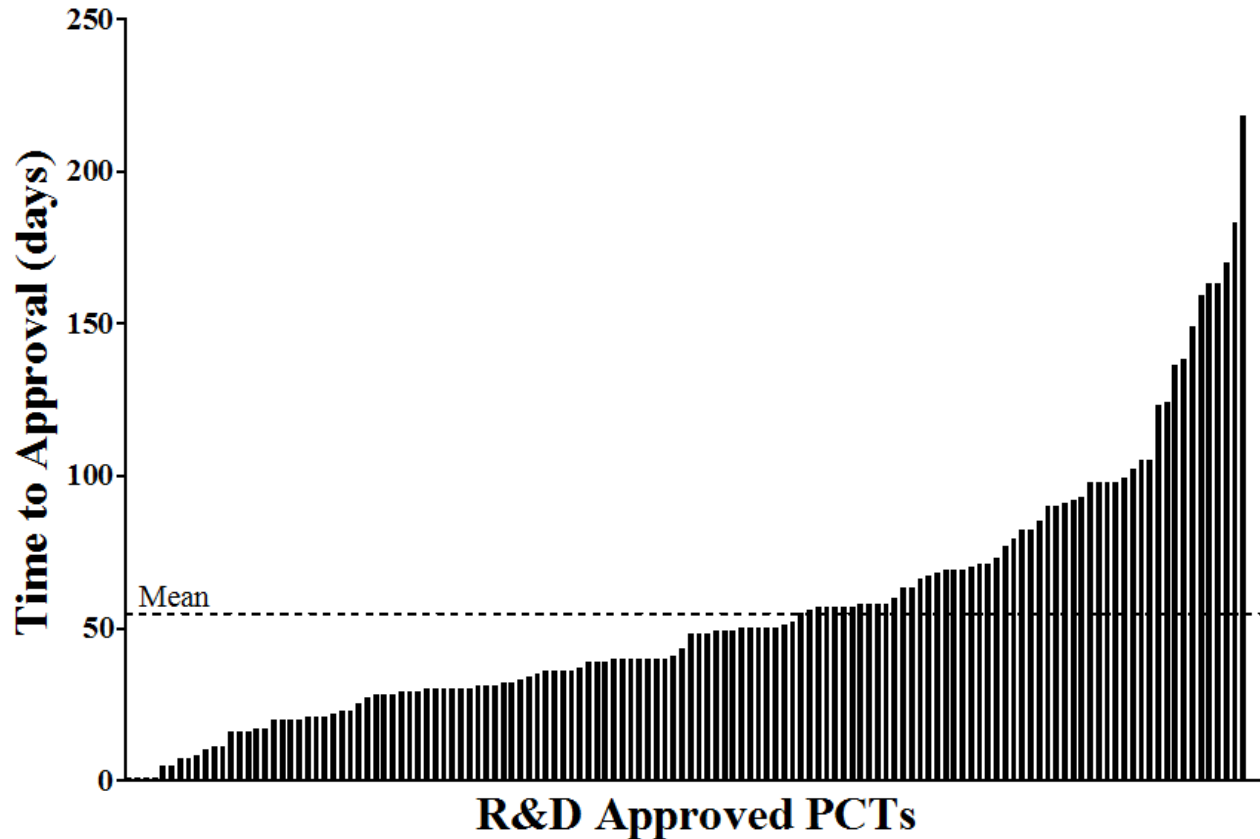
Sponsored by the International Serious Adverse Event Consortium (iSAEC)

Electronic Medical Records: Clinical Practice Research Datalink

- Previously GPRD
- 12 million patient records (March 2011)
Increased to 52 million with the transition to CPRD
- Feasibility study using statin myopathy as paradigm
- 641,703 patients prescribed a statin
- 127,209 with concurrent CPK measurement



The R&D Governance Burden



Statin myopathy
Identified via CPRD
Link to DNA samples

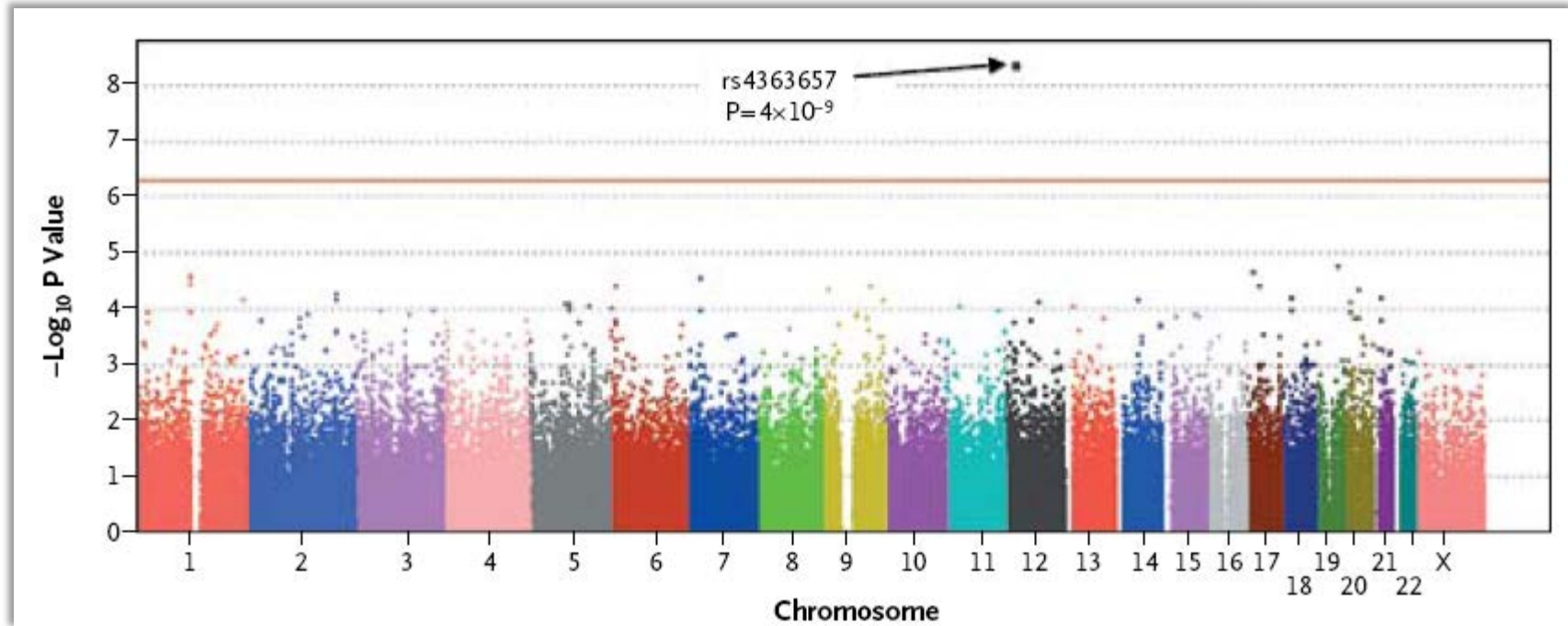
132 R&D approvals



SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

N Engl J Med 2008;359.

The SEARCH Collaborative Group*



1. Implicated SNP is in the SLCO1B1 gene (transporter)
2. Shown with simvastatin 40mg and 80mg



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SLCO1B1 Genetic Variant Associated With Statin-Induced Myopathy: A Proof-of-Concept Study Using the Clinical Practice Research Datalink

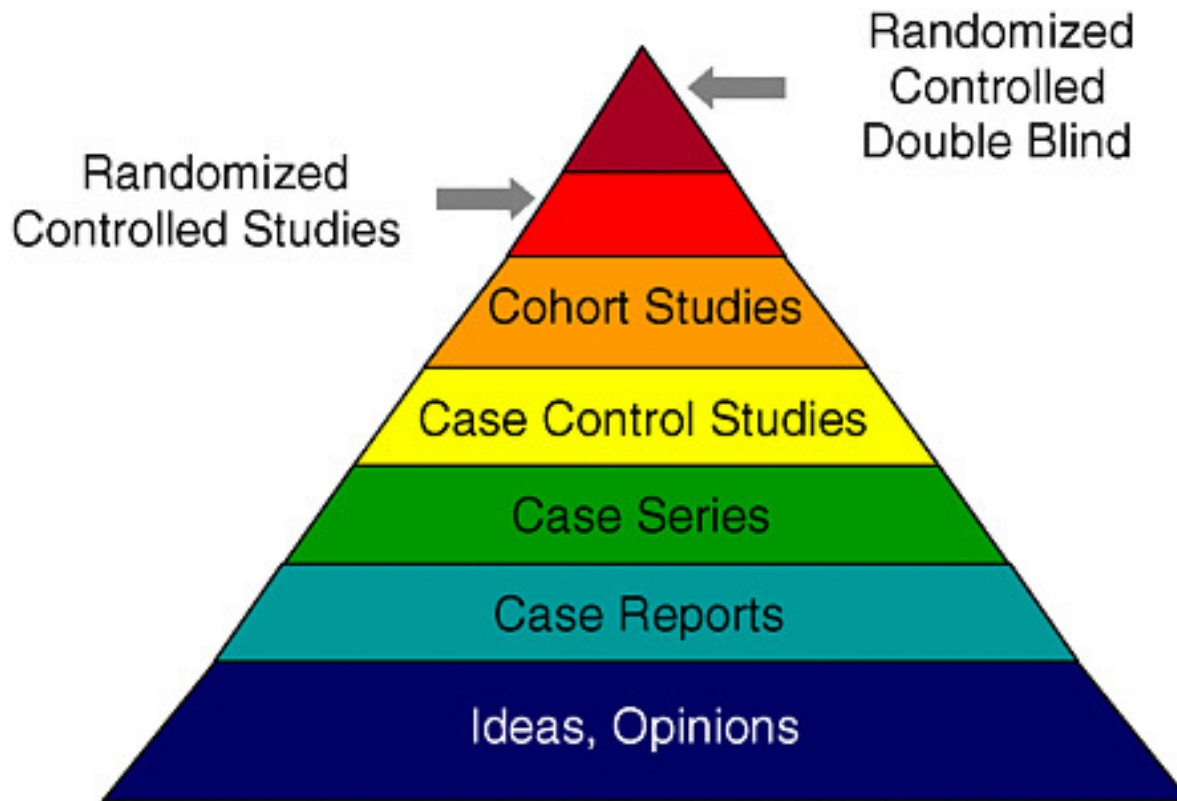
DF Carr¹, H O'Meara¹, AL Jorgensen², J Campbell³, M Hobbs³, G McCann³, T van Staa³⁻⁵ and M Pirmohamed¹

		<u>Genotype Frequency</u>					<u>Per C-allele OR (95%CI)</u>
		<u>n</u>	<u>T/T</u>	<u>T/C</u>	<u>C/C</u>	<u>p</u>	
All Statins (n=448)	Tolerant	372	0.70	0.27	0.03	-	-
	All Myopathy	76	0.53	0.39	0.08	0.005	2.08 (1.35-3.23)
	Severe Myopathy	23	0.35	0.44	0.21	0.0003	4.47 (1.84-10.84)
Simvastatin Only (n=281)	Tolerant	222	0.66	0.32	0.02	-	-
	All Myopathy	59	0.49	0.42	0.09	0.014	2.13 (1.29-3.54)
	<40mg/day	24	0.63	0.37	0.00	0.997	1.03 (0.45-2.36)
	≥40mg/day	35	0.40	0.46	0.14	0.0002	3.23 (1.74-5.99)
	Severe Myopathy	18	0.28	0.50	0.22	0.0004	4.97 (2.16-11.43)
	<40mg/day	5	0.40	0.60	0.00	0.778	1.84 (0.34-9.86)
	≥40mg/day	13	0.23	0.46	0.31	0.0004	6.28 (2.38-16.60)



Hierarchy of Evidence

What type of evidence is required for demonstration of clinical utility?



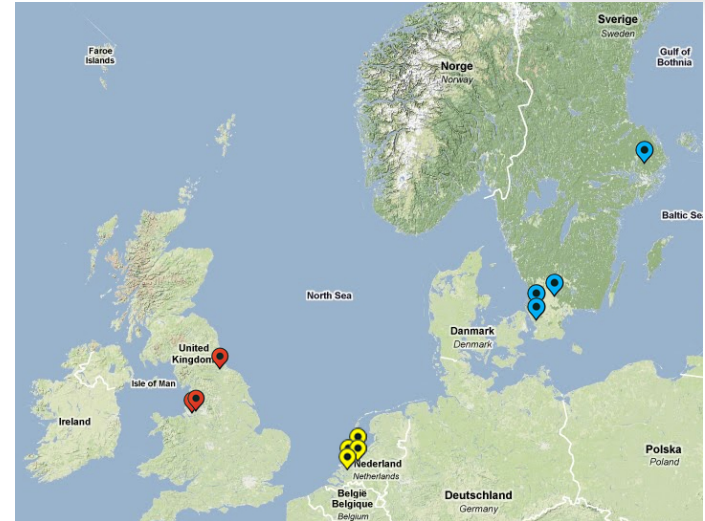
Efficacy end-points
versus
Safety end-points



Pharmacogenetic-Based Dosing: Warfarin Randomised Controlled Trial



- FP7 sponsored EU trials
- 454 patients
 - 226 in genotype arm
 - 228 in standard care arm
- Point of Care test for genotyping



**European Union
Pharmacogenetics of
AntiCoagulant Therapy**

Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project

JM Pulley¹, JC Denny^{2,3}, JF Peterson^{2,3}, GR Bernard^{3,4}, CL Vnencak-Jones^{5,6}, AH Ramirez³, JT Delaney³, E Bowton⁴, K Brothers⁵, K Johnson^{2,5}, DC Crawford^{7,8}, J Schildcrout⁹, DR Masys^{2,3}, HH Dilks⁷, RA Wilke³, EW Clayton^{5,10}, E Shultz^{2,3}, M Laposata^{3,6}, J McPherson³, JN Jirjis^{2,3} and DM Roden^{3,11}

The promise of “personalized medicine” guided by an understanding of each individual’s genome has been fostered by increasingly powerful and economical methods to acquire clinically relevant information. We describe the operational implementation of prospective genotyping linked to an advanced clinical decision-support system to guide individualized health care in a large academic health center. This approach to personalized medicine entails engagement between patient and health-care provider, identification of relevant genetic variations for implementation, assay reliability, point-of-care decision support, and necessary institutional investments. In one year, approximately 3,000 patients, most of whom were scheduled for cardiac catheterization, were genotyped on a multiplexed platform that included genotyping for *CYP2C19* variants that modulate response to the widely used antiplatelet drug clopidogrel. These data are deposited into the electronic medical record (EMR), and point-of-care decision support is deployed when clopidogrel is prescribed for those with variant genotypes. The establishment of programs such as this is a first step toward implementing and evaluating strategies for personalized medicine.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 92 NUMBER 1 | JULY 2012



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Carbamazepine Hypersensitivity

- More complicated than abacavir hypersensitivity
- Different phenotypes
 - ▶ Skin (mild → blistering)
 - ▶ Liver
 - ▶ Systemic (DRESS)
- Predisposition varies with ethnicity and phenotype
 - ▶ HLA-B*1502 (Chinese)
 - ▶ HLA-A*3101 (Caucasian)

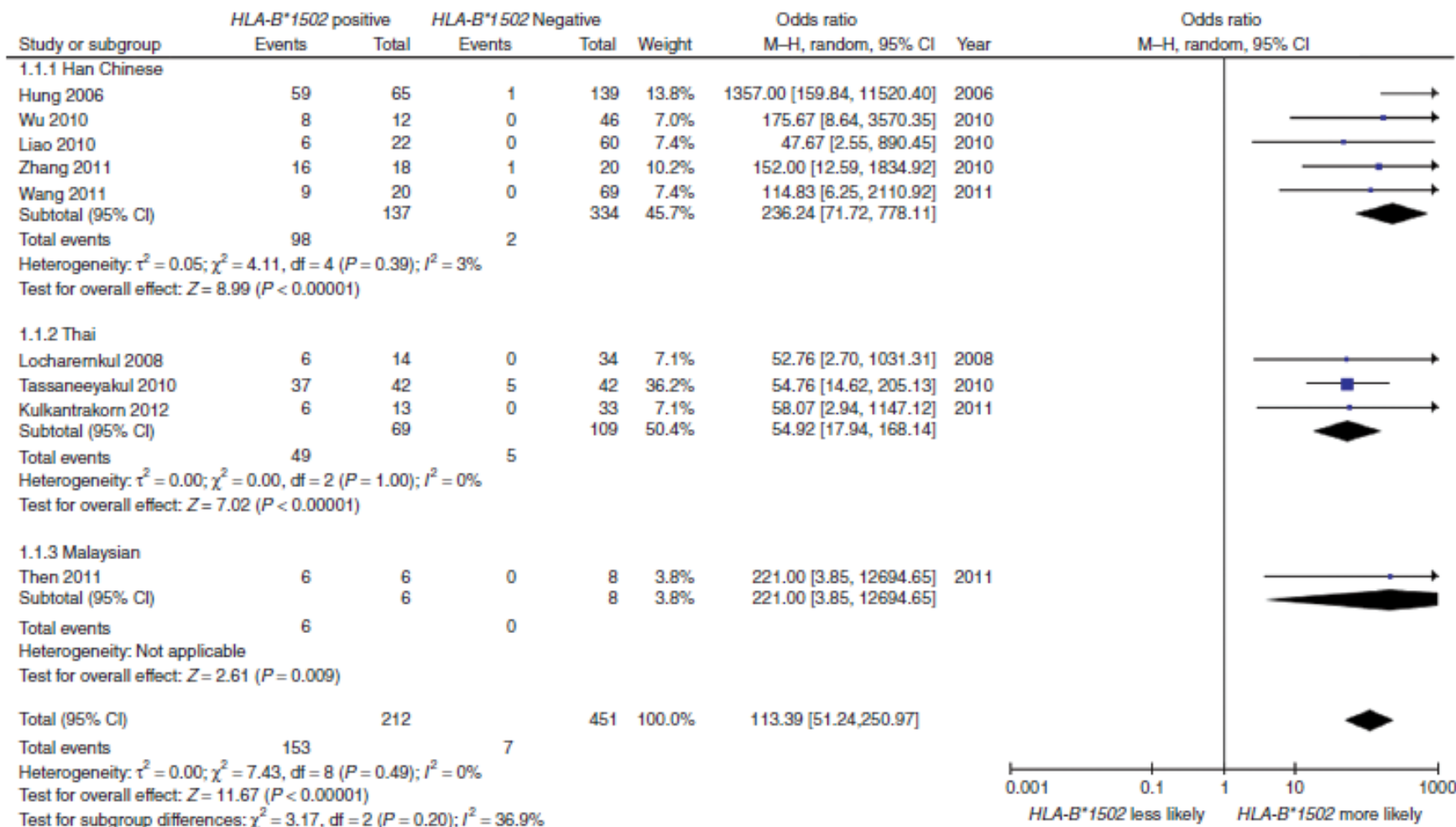


HLA Genotype and Carbamazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review

CPT, 2012

VL Yip¹, AG Marson², AL Jorgensen³, M Pirmohamed¹ and A Alfirevic¹

HLA-B*1502





The NEW ENGLAND JOURNAL of MEDICINE

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Keyword, Tr

ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro,

N Engl J Med 2011;364:1126-33.

- To prospectively identify subjects at risk for SJS
- 4877 CBZ naive subjects from 23 hospitals
- 372 (7.7%) were HLA-B*1502 were positive – NOT given CBZ
- No patients developed SJS (compared with historical controls)



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Harveian Oration

De testimonio: on the evidence for decisions about the use of therapeutic interventions

Michael Rawlins

Lancet 2008; 372: 2152-61

“Hierarchies of evidence should be replaced by accepting—indeed embracing—a diversity of approaches.....

...It is a plea to investigators to continue to develop and improve their methods; to decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgment.”



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Conclusions

- Pathway for translation – one size does not fit all
- **Efficacy pharmacogenomics**
 - ▶ Difficult
 - ▶ Likely need for RCTs to show clinical utility especially when effect size is not high
 - ▶ However, it will be interesting to see the effect of pre-emptive genotyping on uptake into clinic
- **Safety pharmacogenomics**
 - ▶ Pathway will depend on frequency of the adverse effect, the severity and the effect size
 - ▶ For rare events, observational data, which has been replicated, should be adequate, but there needs to be much clearer guidance

