Pharmacogenetics of Adverse Drug Reactions

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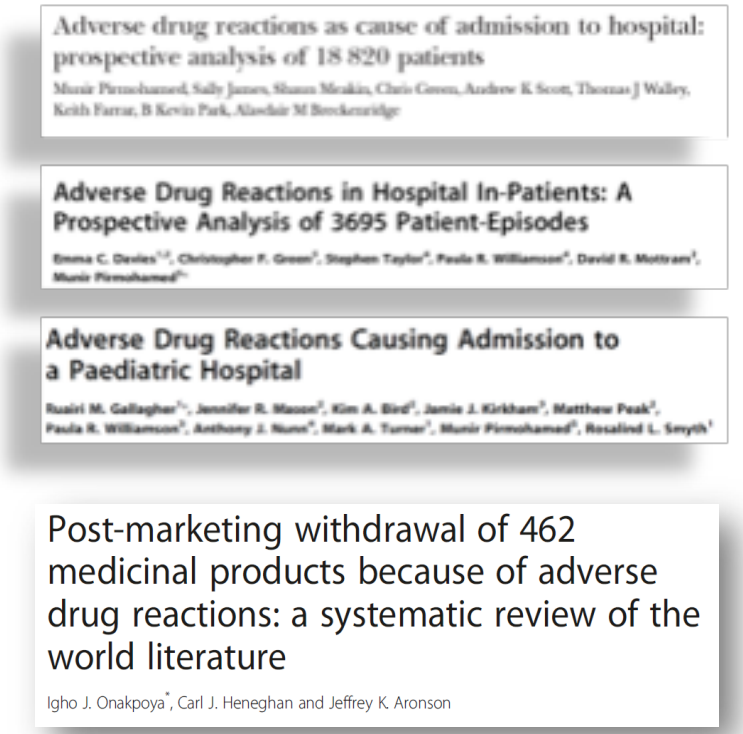
: @MPUoL

Drug Safety is an Important Issue

- Admissions to hospital:
  - Adult – 6.5%
  - Children – 2.9%
- ADRs in hospital
  - Adults – 14.7%
  - Children - 17.7%
- Cost
  - £1.6 billion per year to NHS
  - Huge cost to Industry



Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

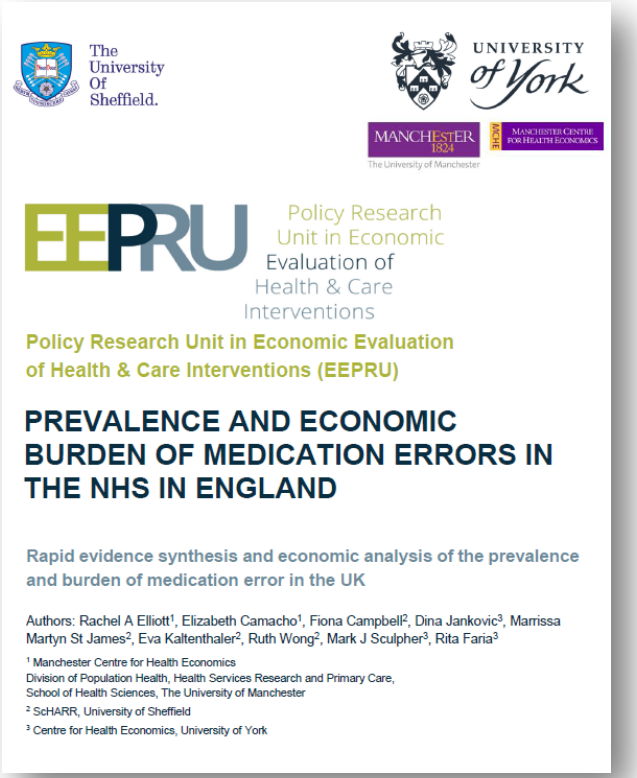
Munir Pirmohamed, Sally James, Shaun Meakin, Chris Green, Andrew K Scott, Thomas J Walley, Keith Farrar, B Kevin Park, Alasdair M Breckenridge

Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes

Adverse Drug Reactions Causing Admission to a Paediatric Hospital

Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature

Igho J. Onakpoya*, Carl J. Heneghan and Jeffrey K. Aronson



The University Of Sheffield.

UNIVERSITY of York

MANCHESTER 1824 The University of Manchester

Manchester Centre for Health Economics

EEPRU Policy Research Unit in Economic Evaluation of Health & Care Interventions

Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU)

PREVALENCE AND ECONOMIC BURDEN OF MEDICATION ERRORS IN THE NHS IN ENGLAND

Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK

Authors: Rachel A Elliott[1], Elizabeth Camacho[1], Fiona Campbell[2], Dina Jankovic[3], Marrissa Martyn St James[2], Eva Kaltenthaler[2], Ruth Wong[2], Mark J Sculpher[3], Rita Faria[3]

[1] Manchester Centre for Health Economics
Division of Population Health, Health Services Research and Primary Care,
School of Health Sciences, The University of Manchester

[2] ScHARR, University of Sheffield

[3] Centre for Health Economics, University of York

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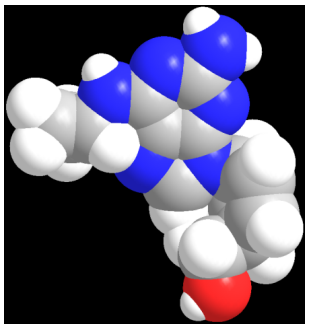
Adverse Drug Reactions: Classification

ON TARGET REACTIONS

- Predictable from the known primary or secondary pharmacology of the drug
- Clear dose-dependence relationship within the individual

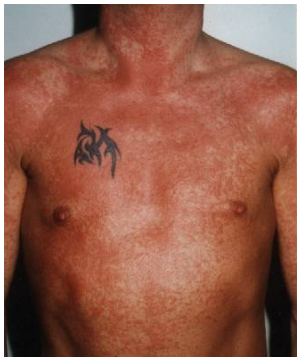
Type A



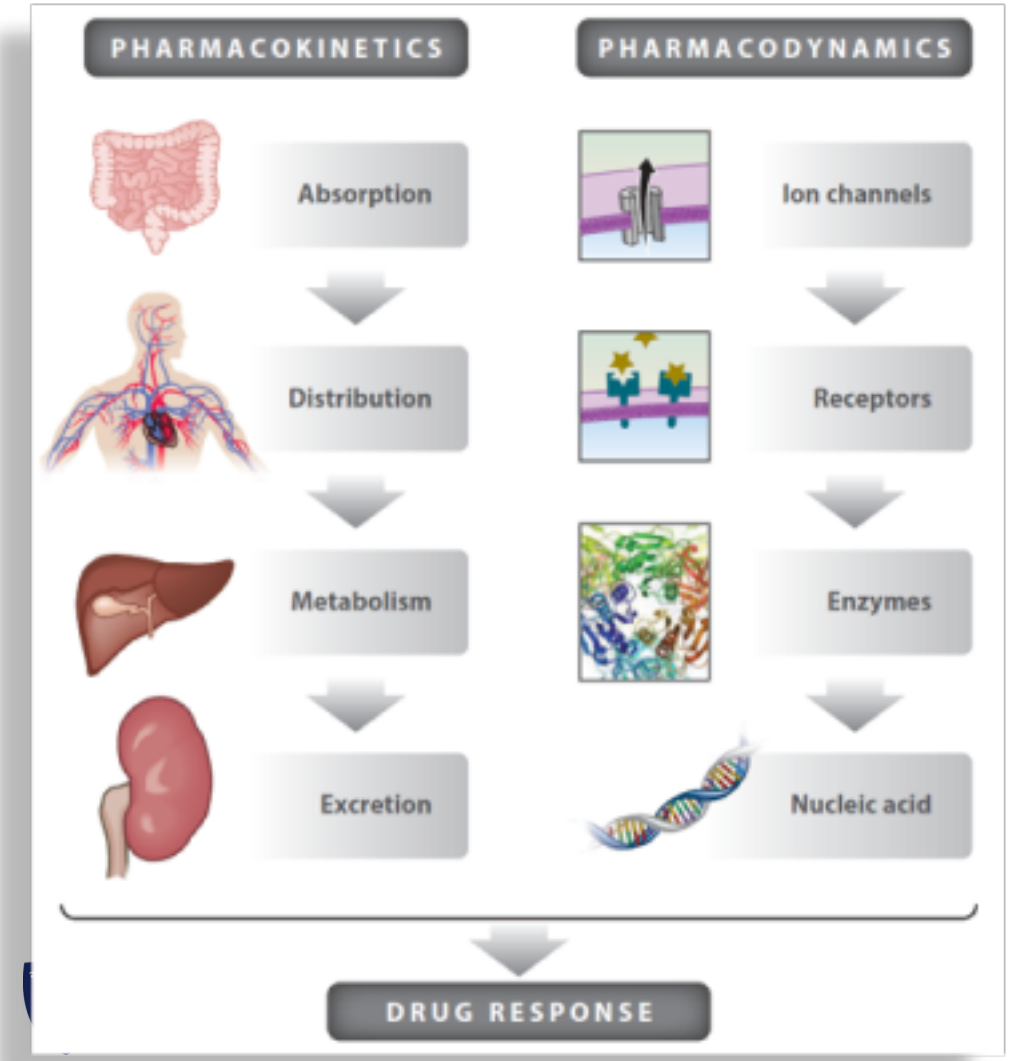
OFF TARGET REACTIONS

- Not predictable from a knowledge of the basic pharmacology of the drug and can exhibit marked inter-individual susceptibility
- Complex dose-dependence

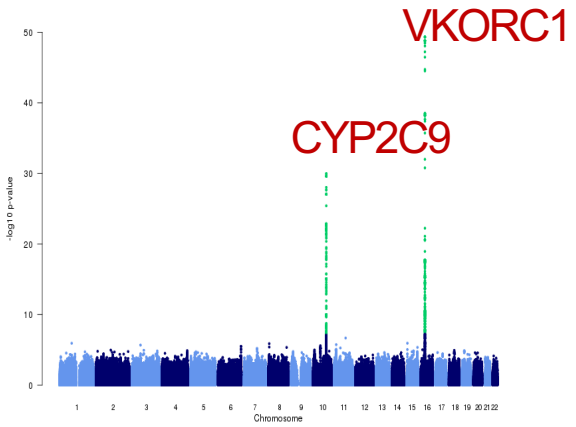
Type B



Variation in Drug Response



- **Both PK and PD factors may act together to increase risk of ADRs**



A Randomized Trial of
Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

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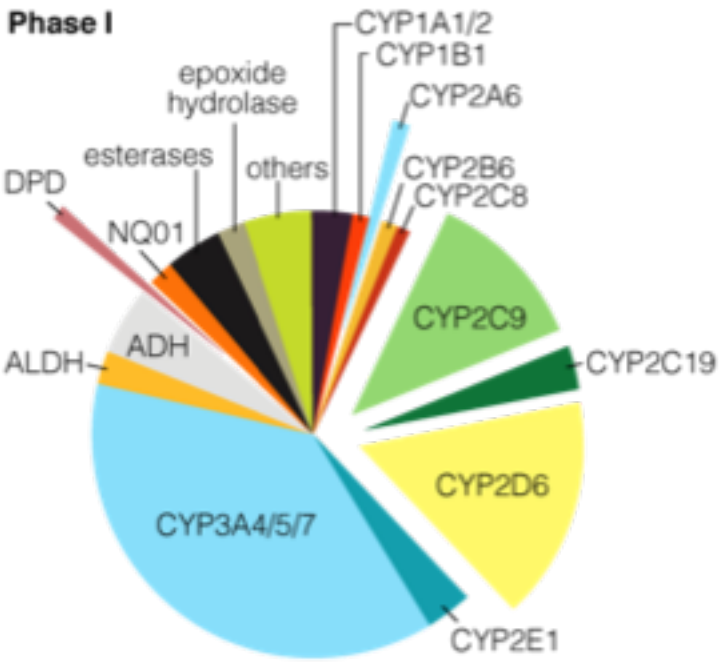
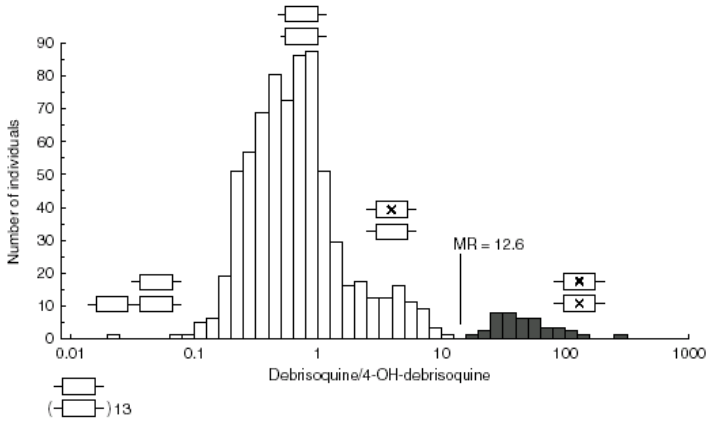
Phase I Enzyme Gene Polymorphisms



Evans and Relling, 1999

CYP2D6: Responsible for metabolism of 25% of drugs, including antidepressants and antipsychotics

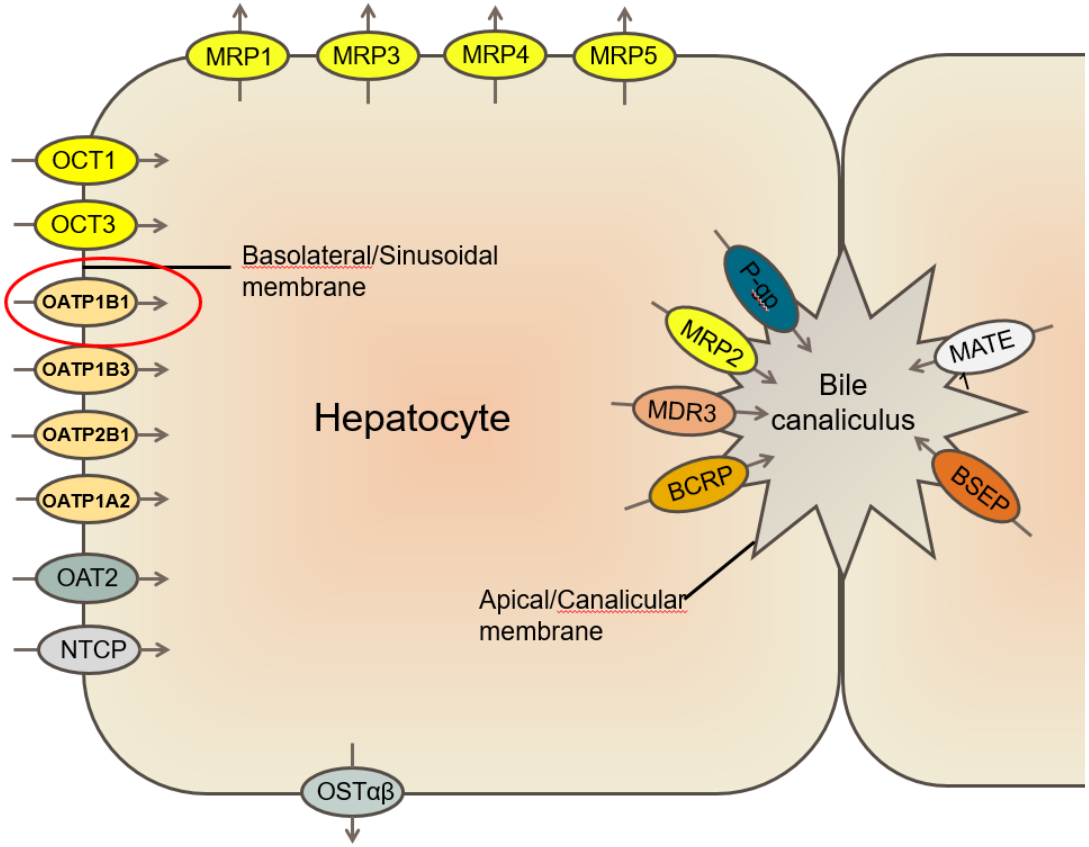


8% are poor metabolisers
2% ultra-rapid metabolisers (29% Ethiopians)

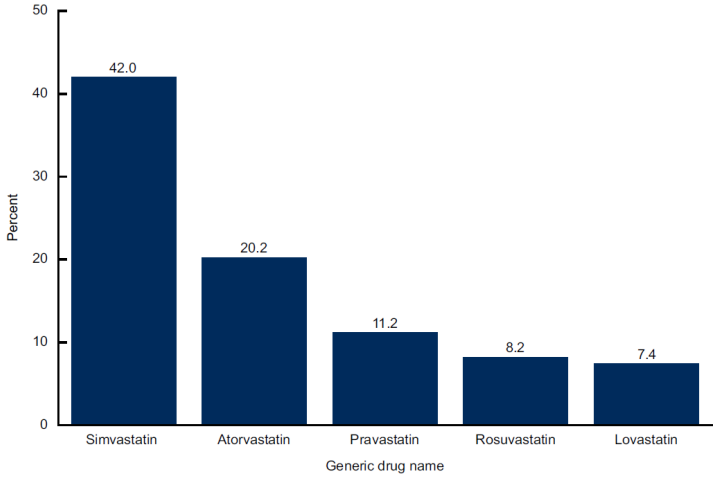
ADVERSE DRUG REACTION:

1. *Increased drug concentrations*, e.g. metoprolol induced bradycardia
2. *Drug accumulation,* e.g. Perhexilene induced hepatotoxicity and neuropathy

Transporters



SLCO1B1 and Statins

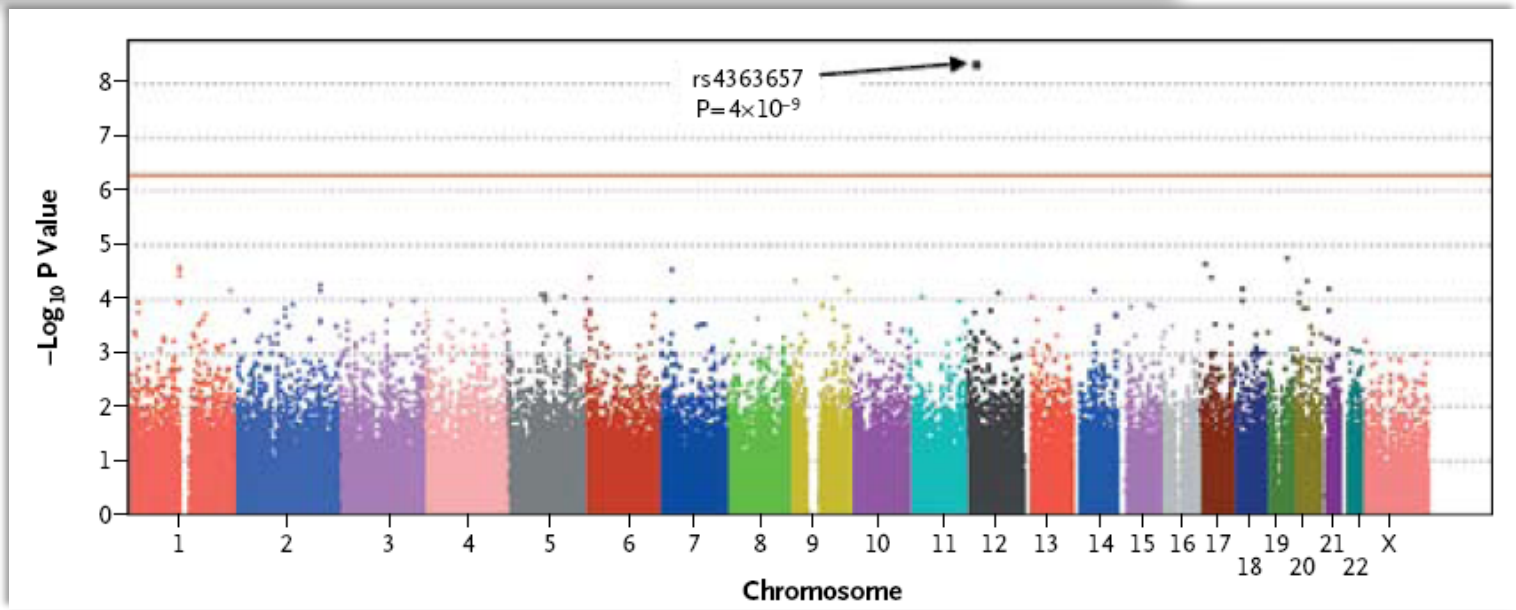


200 million people worldwide

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

N Engl J Med 2008;359.



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

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

Clin Pharmacol Ther. 2013 Dec;94(6):695-701

DF Carr[1], H O'Meara[1], AL Jorgensen[2], J Campbell[3], M Hobbs[3], G McCann[3], T van Staa[3–5] and M Pirmohamed[1]

			SLC01B1 p.V174A Genotype frequency				
		n	T/T	T/C	C/C	*P*	Per C-allele OR (95% CI)
All statins (*n* = 448)	Tolerant[a]	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)
	<40 mg/day	24	0.63	0.37	0.00	0.997	1.03 (0.45–2.36)
	≥40 mg/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)
	<40 mg/day	5	0.40	0.60	0.00	0.778	1.84 (0.34–9.86)
	≥40 mg/day	13	0.23	0.46	0.31	**0.0004**	6.28 (2.38–16.60)
Atorvastatin only (*n* = 121)	Tolerant	110	0.78	0.2	0.02	—	—
	All myopathy	11	0.64	0.36	0.00	0.613	1.91 (0.56–6.54)
	Severe myopathy	3	1.00	0.00	0.00	0.507	N/A

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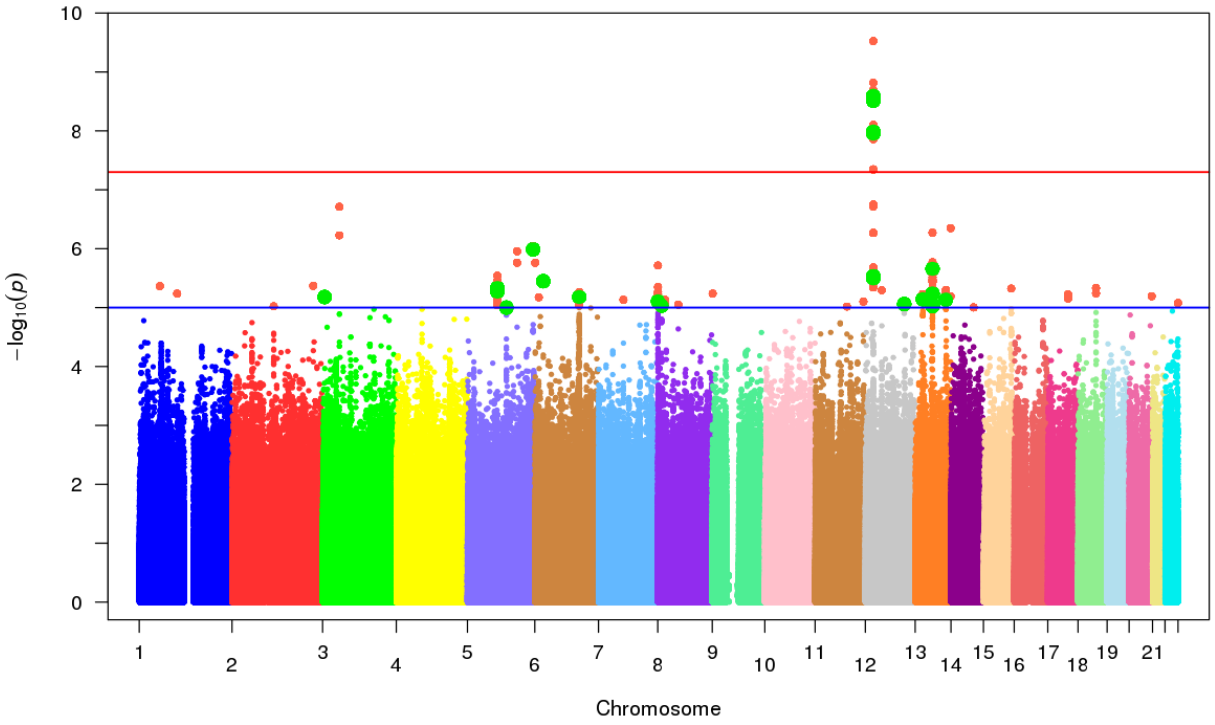
Statin Myopathy GWAS (n=135)

Cases (n=32) vs. WTCCC (n=2,501)



GWAS identified 12 SNPs with $p<5x10^{-5}$

Replication attempted in:

- EUDRAGENE cohort – 19 cases
- SEARCH collaborative simvastatin cohort (Oxford) – 141 cases
- Cerivastatin cohort (Bruce Psaty) – 172 cases

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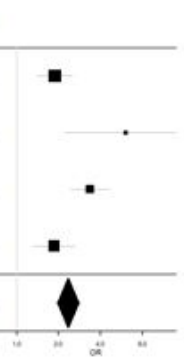
SLCO1B1 and Statin Myopathy

All Myopathy

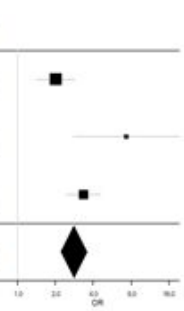
All Statins

COMPARISON	OR	95% CI
Discovery vs WTCCC	1.88	(1.41,2.52)
EUDRAGENE vs Tolerant Controls	6.07	(2.23,14.04)
Simvastatin Replication Cohort (Incipient/Definitive)	3.35	(2.44,4.60)
Cerivastatin Repication Cohort	1.86	(1.32,2.62)
Pooled (Fixed-effects)	**2.35**	**(1.97,2.81)**



Simvastatin

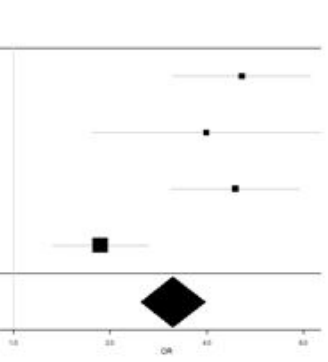
COMPARISON	OR	95% CI
Discovery vs WTCCC	2.02	(1.43,2.87)
EUDRAGENE vs Tolerant Controls	7.31	(2.77,19.28)
Simvastatin Replication Cohort (Incipient/Definitive)	3.35	(2.44,4.60)
Pooled	**2.82**	**(2.24,3.54)**



Severe Myopathy

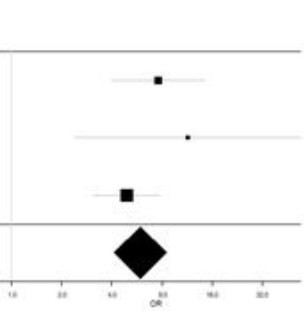
All Statins

COMPARISON	OR	95% CI
Discovery vs WTCCC	5.15	(3.13,8.45)
EUDRAGENE vs Tolerant Controls	3.98	(1.75,9.03)
Simvastatin Replication Cohort (Definitive)	4.91	(3.09,7.77)
Cerivastatin Repication Cohort	1.86	(1.32,2.62)
Pooled	**3.14**	**(2.49,3.96)**



Simvastatin

COMPARISON	OR	95% CI
Discovery vs WTCCC	7.59	(3.98,14.47)
EUDRAGENE vs Tolerant Controls	11.45	(2.39,54.79)
Simvastatin Replication Cohort (Definitive)	4.91	(3.09,7.77)
Pooled	**5.91**	**(4.10,8.51)**



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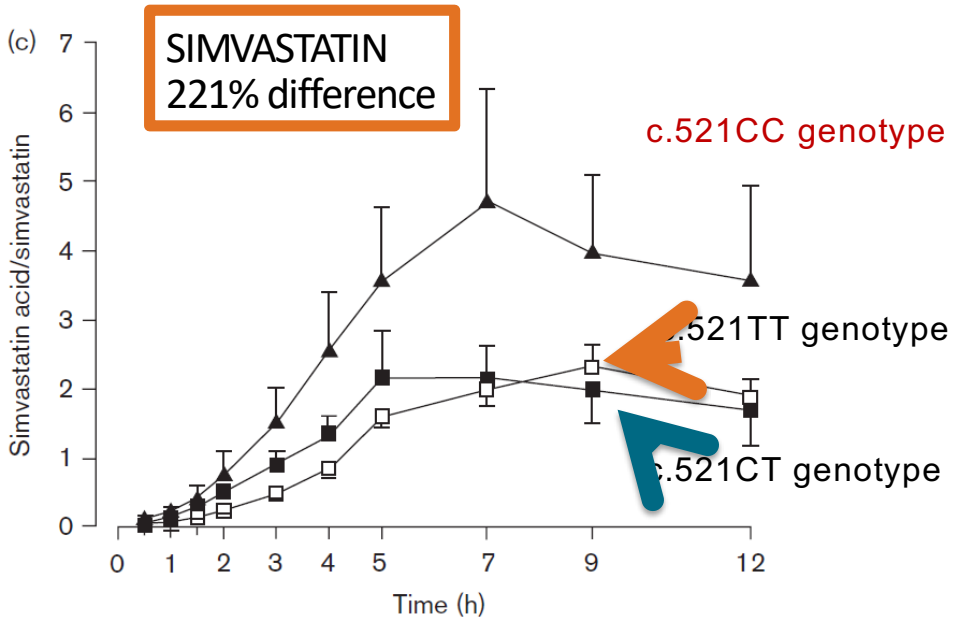
Effect of SLCO1B1 Polymorphism on Statin Pharmacokinetics

Niemi et al, Various papers

Statin	AUC (CC vs TT)
Atorvastatin	2.45-fold (+145%)
Fluvastatin	1.19-fold (+19%, NS)
Lovastatin	to 84% (-16%, NS)
Lovastatin acid	2.86-fold (+186%)
Pitavastatin	3.08-fold (+208%)
Pravastatin	1.91-fold (+91%)
Rosuvastatin	1.62-fold (+62%)
Simvastatin	1.43-fold (+43%, NS)
Simvastatin acid	3.21-fold (+221%)



SmPC – do not use 80mg simvastatin in SLCO1B1 rs4149056 CC homozygotes

SLCO1B1 c.521T>C genotype

	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

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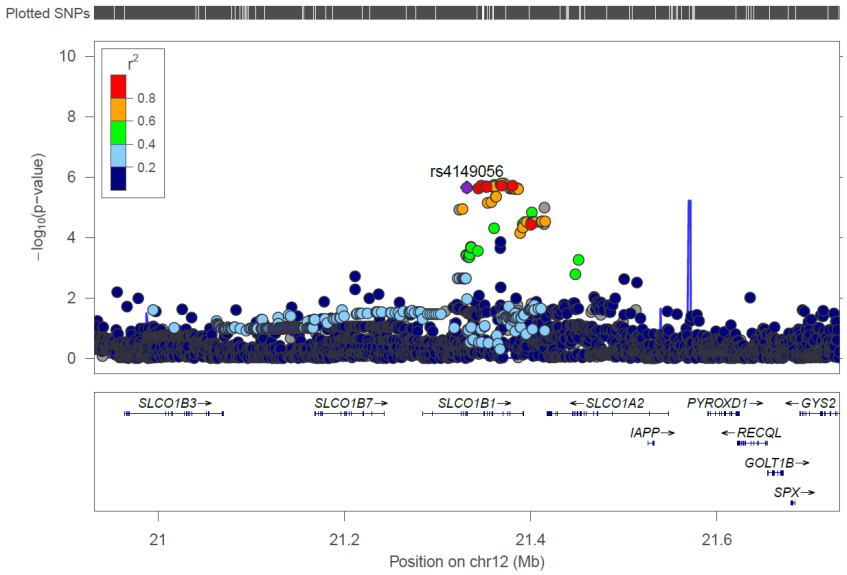
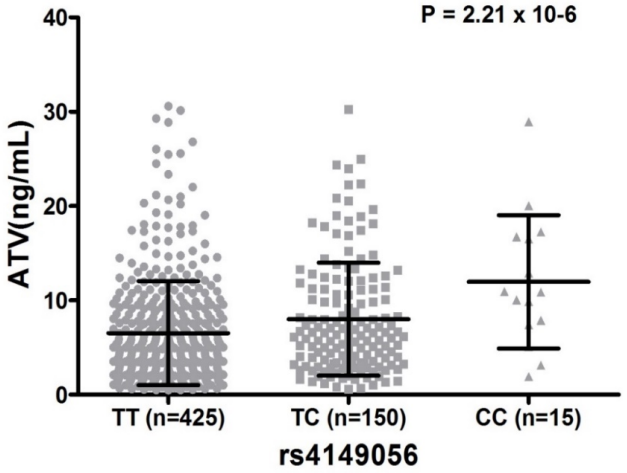
GWAS of Atorvastatin Concentrations in Patients with Acute Coronary Syndrome





- Up to 1500 patients
- Prospective cohort
- Recruited at time of ACS
- 80mg atorvastatin daily
- Followed up for 2 years+
- Longitudinal blood sampling

***Adjusted* risk** of muscle symptoms if discharged on ATV 80mg at one month:

- *SLCO1B1* rs4149056 (V174A) (dominant): **OR = 3.40 (1.07-10.81), p=0.039**

Adjusted risk of suboptimal statin therapy if discharged on ATV 80mg by one month:

- *SLCO1B1* rs4149056 (V174A) (additive): **OR = 1.59 (1.10-2.31), p=0.015**

Risk of MACE if discharged on ATV 80mg by one month:

- *SLCO1B1* rs4149056 (V174A) (additive): OR = 1.08 (0.79-1.48), p=NS

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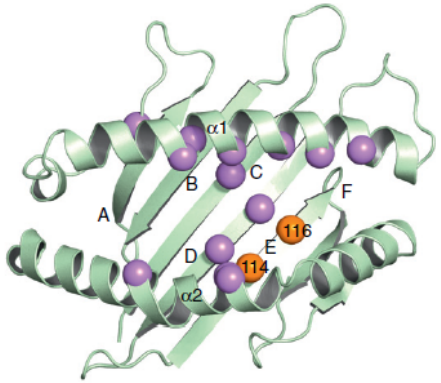
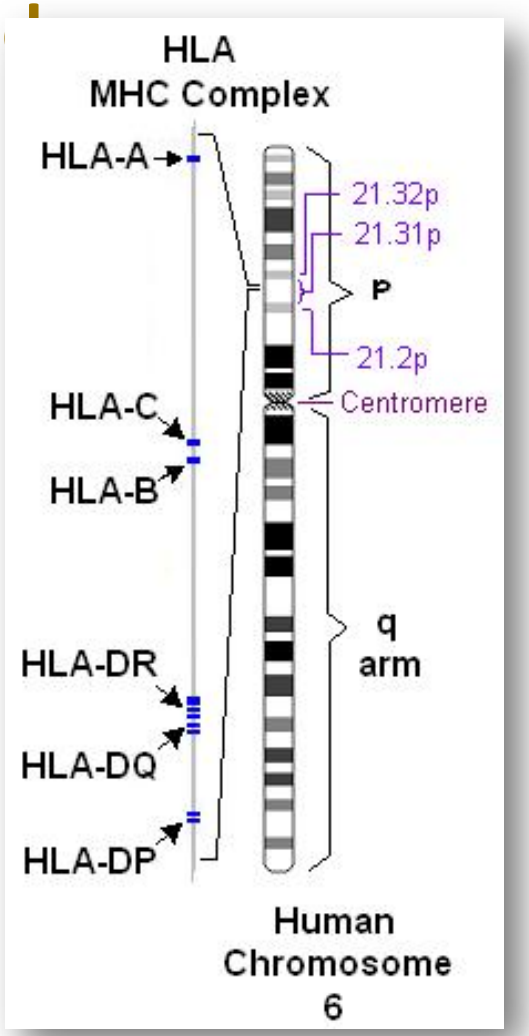
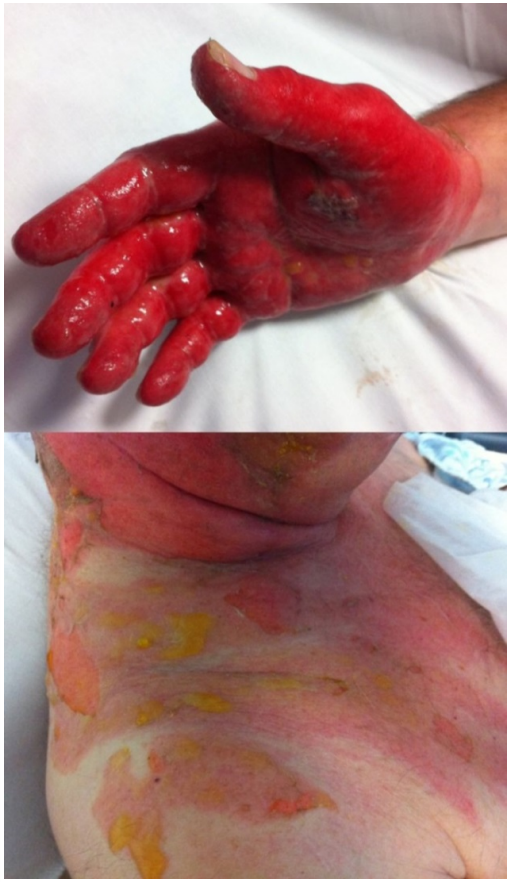
Serious Adverse Drug Reactions an
Human Leucocyte Antigens (HLA)

- On short arm of chromosome 6
- Involved in the pathogenesis of immune-mediated adverse drug reactions



Abacavir hypersensitivity
*HLA-B*57:01*
Decrease incidence from 7% to <1%





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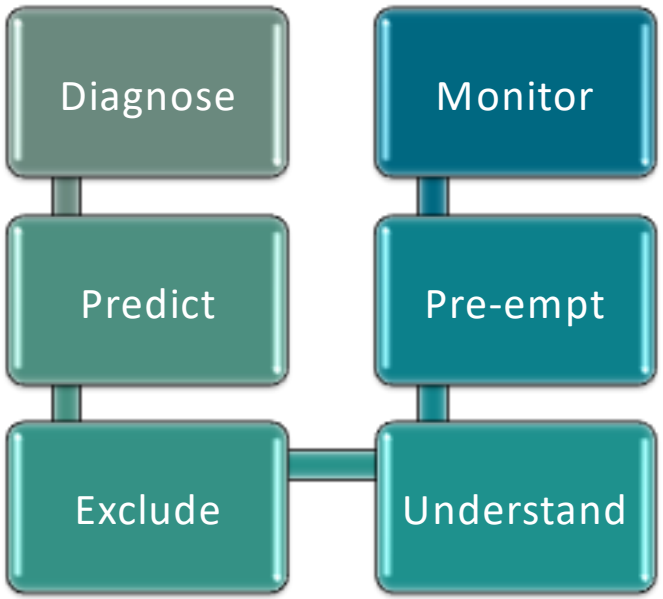
Special Issue: Precision Medicine

Review

Genomics of Adverse Drug Reactions

Ana Alfirevic[1] and Munir Pirmohamed[1,*]

Trends in Pharmacological Sciences, January 2017, Vol. 38, No. 1



Genomic testing can be used for more than prediction

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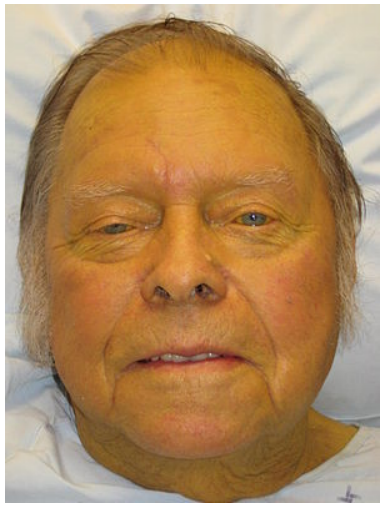
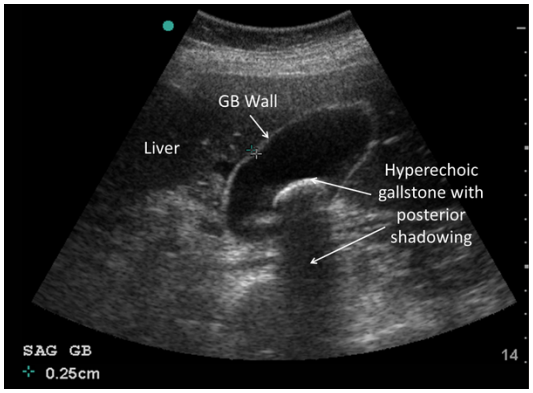
Example of the Use for Diagnosis



- 66 year old man
- Presents with Jaundice
- Patient on flucloxacillin for cellulitis
- Ultrasound – gallstones

- What is the diagnosis?



- HLA-B*57:01 strong association with flucloxacillin hepatitis
- 100% negative predictive value
- Patient was negative for HLA-B*57:01
- Treatment – cholecystectomy
- Not allergic to flucloxacillin – GP informed. Important as patient with history of recurrent cellulitis.

Associations of Serious Adverse Drug Reactions with HLA Alleles

A*31:01 Carbamazepine	**A*33:03** Ticlopidine	**A*68:01** Lamotrigine	**A*02:06** Cold medicines	**B*13:01** Dapsone Trichlorethylene	**B*15:02** Carbamazepine Phenytoin
B*35:05 Nevirapine	**B*44:03** Cold Medicines	**B*56:02** Phenytoin	**B*57:01** Abacavir Flucloxacillin	**B*58:01** Allopurinol	**C*04:01** Nevirapine
C*08:(01) Nevirapine	**DRB1*07:01** Ximelagatran Lapatinib Asparaginase	**DRB1*11:01** Statins	**DRB1*13:02** Aspirin	**DRB1*15:01** Lumiracoxib Co-amoxiclav	**DQA1*01:02** Lumiracoxib
DQA1*02:01 Lapatinib	**DQB1*02:01** Ximelagatran Clometacin	**DQB1*05:02** Clozapine	**DQB1*06:02** Co-amoxiclav Lumiracoxib	**DQB1*06:04** Ticlopidine	**DQB1*06:09** Aspirin

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HLA Panel Analytic Validation

- Platform was able to call risk alleles with 100% accuracy at all the loci (n=187 healthy volunteers) using sequence based typing as the standard

Number of Risk Alleles per sample	Number of Samples	% of samples
0	28	15.0
1	39	20.9
2	14	7.5
3	46	24.6
4	34	18.2
5	11	5.9
6	6	3.2
7	8	4.3
8	1	0.5

85% have at least 1 risk allele

Use
- At time needed
- Store data on EHR
- Pre-emptive genotype

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Funded by NIHR

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Clinical Decision Support

Please select your drug and/or alleles of interest

Drug

abacavir	allopurinol	amoxicillin-clavulanate	antituberculosis drugs
aspirin	carbamazepine	clozapine	dapsone
flucloxacillin	lamotrigine	lapatinib	lumiracoxib
nevirapine	NSAID and 'multi-ingredient cold medication'	oxcarbazepine	phenytoin
statins	sulfamethoxazole	sulfasalazine	ticlopidine
ximelagatran			

Allele

A*31:01	A*33:03	A*68:01	B*13:01
B*15:02	B*35:05	B*44:03	B*56:02
B*57:01	B*58:01	C*04:01	C*08:01
DQA1*01:02	DQA1*02:01	DQB1*02:01	DQB1*05:02
DQB1*06:02	DQB1*06:04	DQB1*06:09	DRB1*07:01
DRB1*11:01	DRB1*13:02	DRB1*15:01	

Reset Submit

Database last updated: 07 March 2017

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NHS National Institute for Health Research

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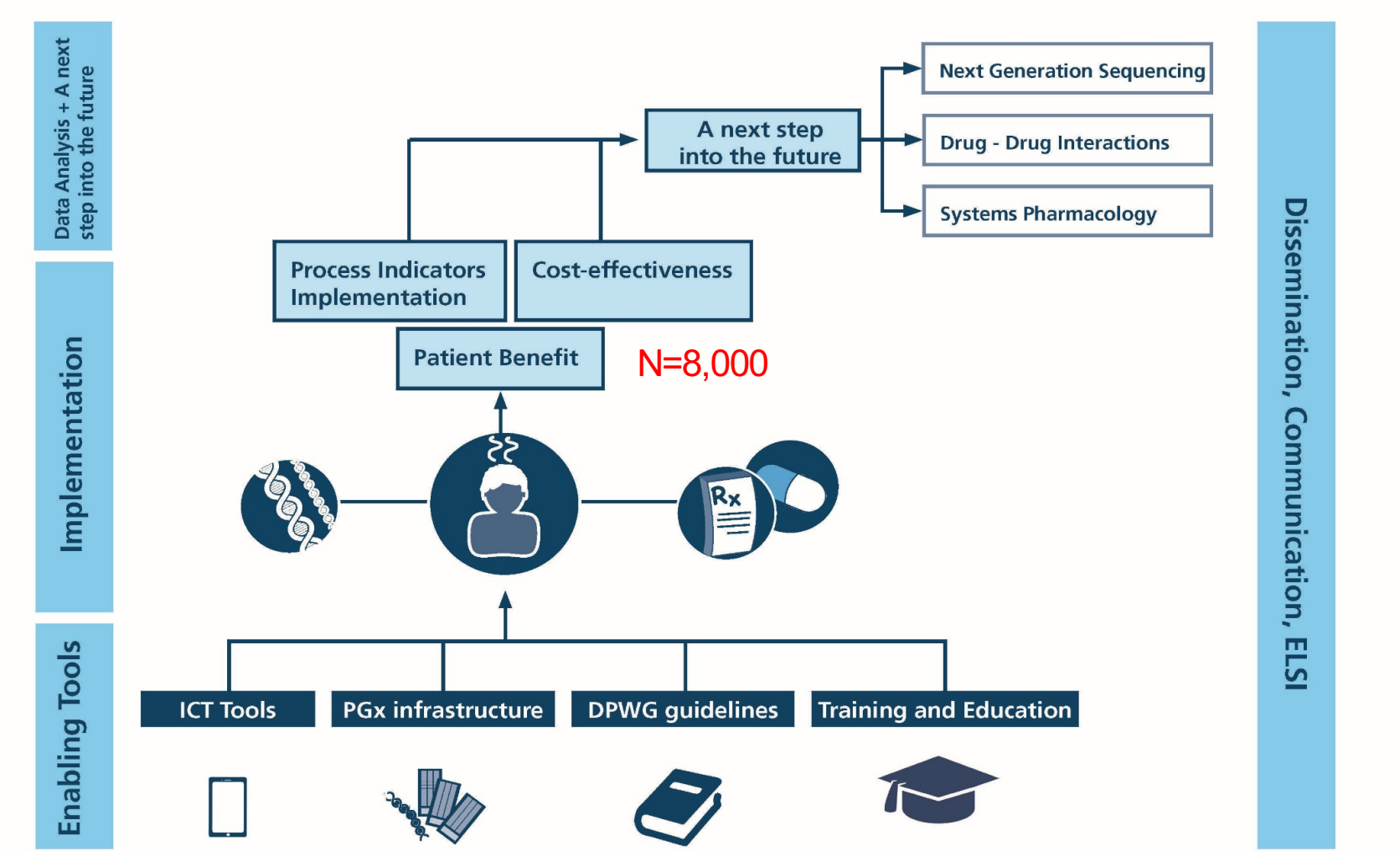
U-PGx | Ubiquitous Pharmacogenomics

- €15 million, H2020, 10 EU countries
- Implement pre-emptive PGx testing in a real world clinical setting across 7 EU sites
- Evaluate **patient outcome** and **cost effectiveness** using solid **scientific methodology**
- Start 1-1-2016, 5 years

- **H-J Guchelaar (Coordinator),**
- JJ Swen, M Kriek, LUMC
- M Pirmohamed, R Turner, UOL
- J Stingl, FDMD
- M Ingelman-Sundberg, KI
- M Karlsson, S Jönsson, PBUU
- M Schwab, E Schaeffeler, IKP
- VHM Deneer STZHM
- M Samwald, G Sunder-Plassmann, MUWV
- M van Rhenen, KC Cheung, KNMP
- C Mitropoulou, GHXF
- D Steinberger, BIOL
- CL Davila Fajardo, SAS
- G Patrinos, UPAT
- V Dolžan, ULMF
- A Cambon-Thomsen, UPS
- G Toffoli, E Cecchin, CROA

Project Outline

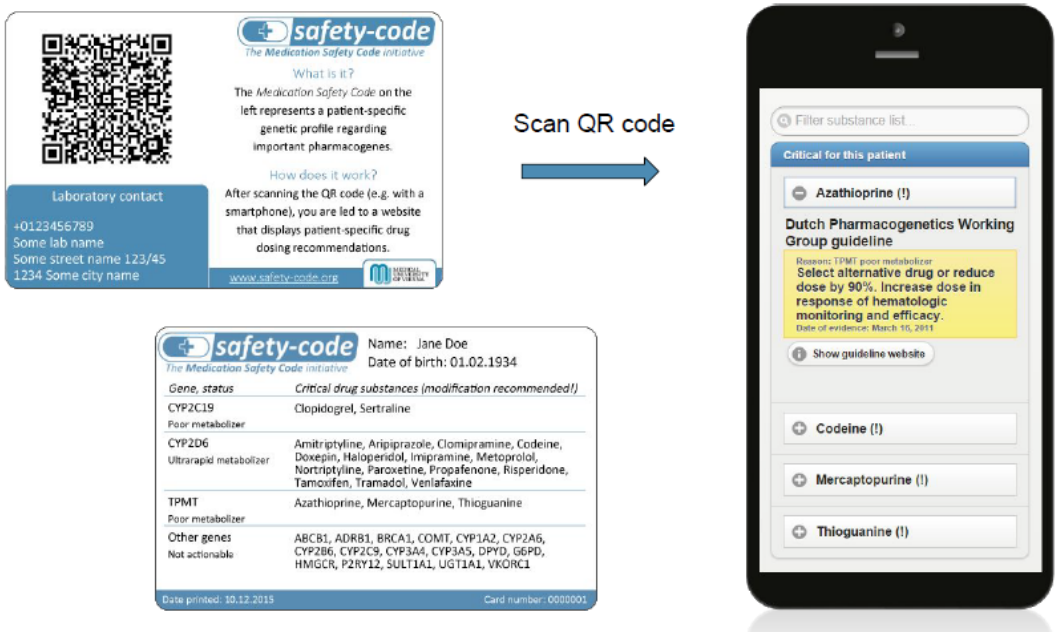


Ubiquitous Pharmacogenomics

Genotyping platform

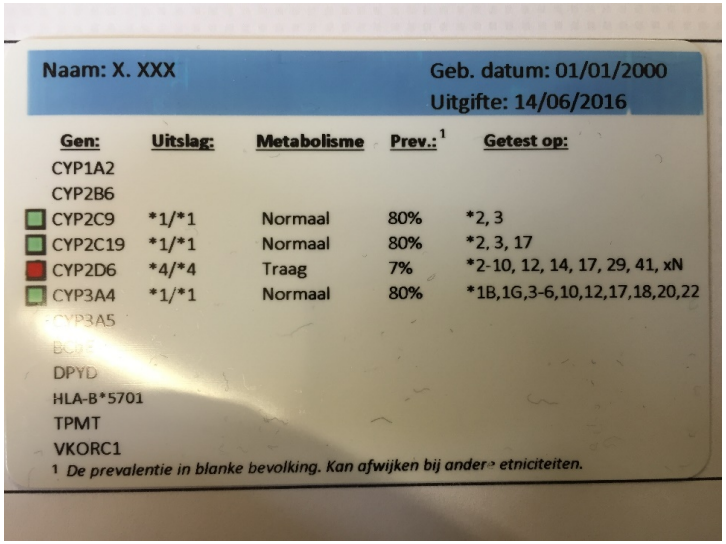
- 12 genes (including CYP2D6 and SLCO1B1)
- 44 variants
- 39 drugs

Pharmacogenomic Card

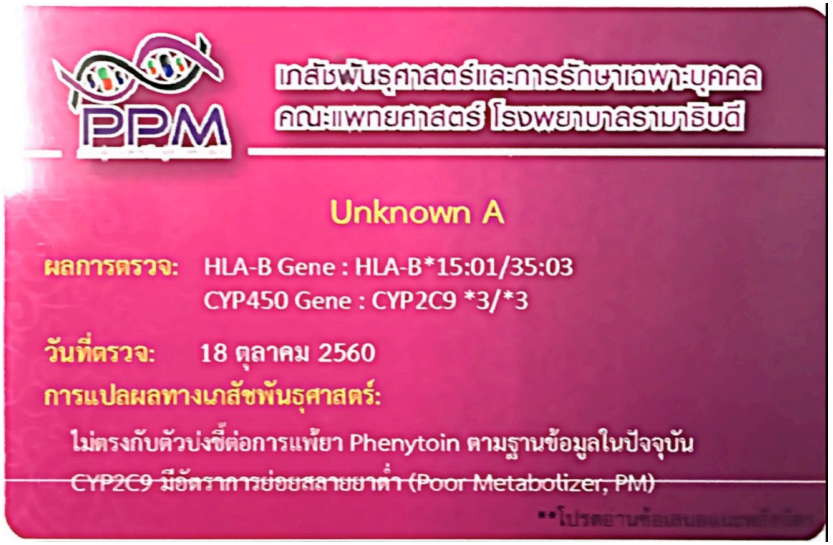


Conclusions

- Pharmacogenomics is important in identifying predisposing factors for adverse drug reactions: both pharmacokinetic and pharmacodynamic factors are important
- Genetic variants need to be combined with other clinical factors, and not used in isolation
- Implementation to avoid ADRs is a major focus in many countries



Netherlands



Thailand

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