

Pharmacogenetics Implementation: European Perspectives

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Europe



No of countries in
Europe: 44

No of countries in
the EU: 28

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Case Study 1

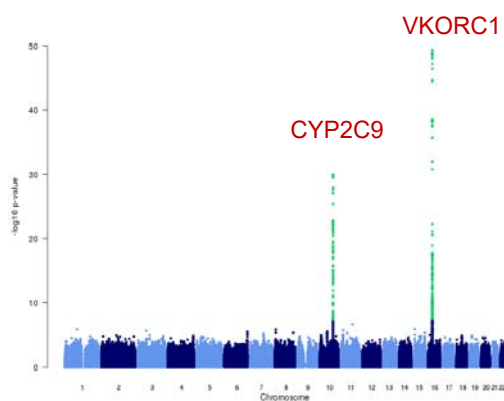
WARFARIN



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GWAS Warfarin Mean Weekly Dose (UK Prospective Cohort; n=714)



Total = 57.9%

Age: 11.2%

Height: 3.56%

Weight: 5.98%

Interacting meds: 0.98%

Sum of interacting meds: 2.2%

VKORC1: 25.61%

CYP2C9: 16.65%

CYP4F2: 0.49%



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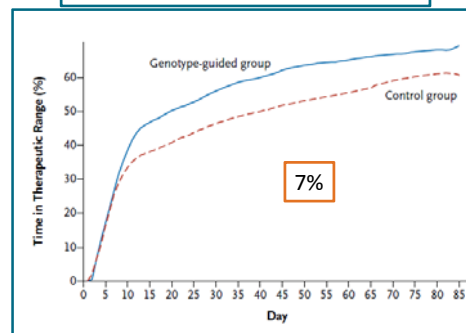
A Randomized Trial of Genotype-Guided Dosing of Warfarin

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.,
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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*

N Engl J Med 2013;369:2294-303.

DOI: 10.1056/NEJMoa1311386

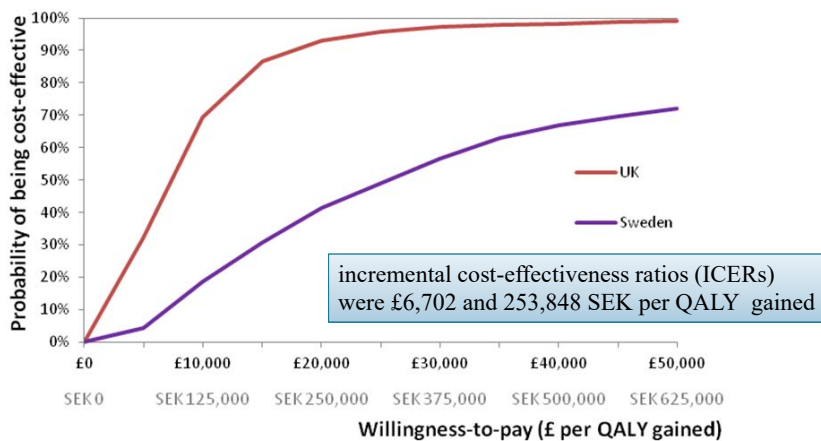
Time in Therapeutic Range



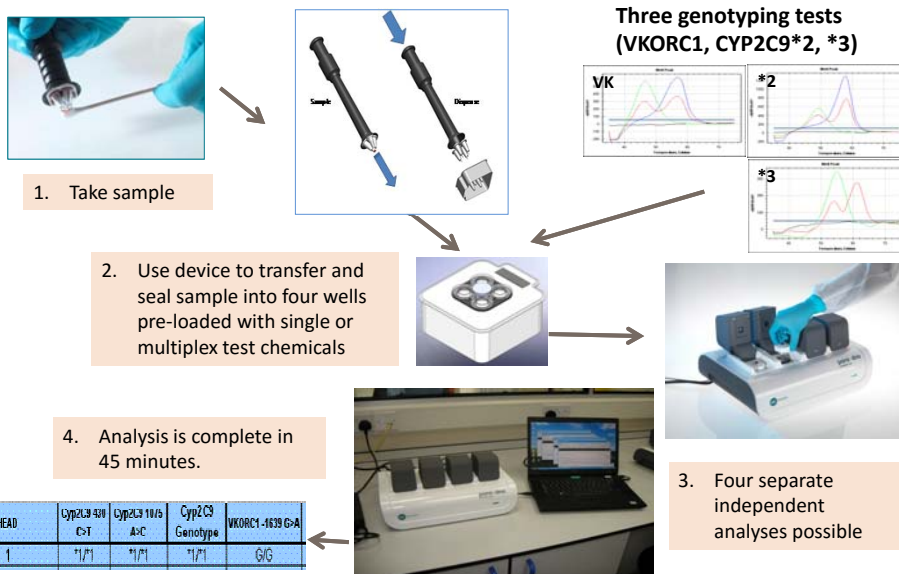
EU-PACT: Relevance of Findings

- Comparison of genotype-guided dosing to current clinical practice in the UK and Sweden
- Pharmacokinetically defined algorithms taking into account the need to individualise loading doses according to carriage of variants
- Use of a point-of-care genotyping platform to allow for genotyping of CYP2C9 and VKORC1 at the start
- Homogeneous population
- After day 5, the use of current clinically available computerised dosing software for maintenance

EU-PACT Cost Effectiveness



ParaDNA: Point of Care Device



Courtesy of LGC, Commercial in Confidence



Clinics in Chester, Warrington and Liverpool

University of Liverpool

NIHR Collaboration for Leadership in Applied Health Research and Care North West Coast


INNOVATION AGENCY
 Academic Health Science Network for the North West Coast


LIVERPOOL HEALTH PARTNERS

Patient quote:
 He said: "The old way of prescribing warfarin is more hit and miss; this is bespoke medication, calculated on my gene type."
 "My mum went on warfarin eight months ago and she was back and forward to the clinic at least four times on a weekly basis before they got the dose right. I went back once, which meant I could go back to work quicker, feeling well enough to go back to normal life. I think this a win-win, for me and for the health service."


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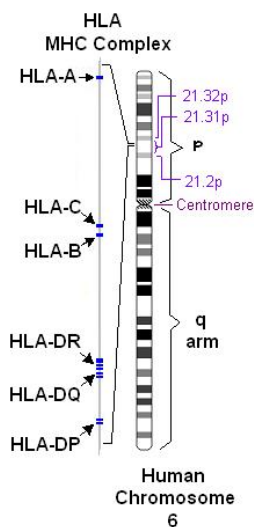
Direct Oral Anticoagulants

- Total cost to NHS England for 2014/15: £89.3m
- Prescription spend on DOACs rising (2014/15 cf 2013/14):
 - ▶ Apixaban 504%
 - ▶ Dabigatran 48%
 - ▶ Rivaroxaban 183%
- Patent expiry 2023
- Spending on DOACs is likely to increase (>£300 million in 2016)
- **Likely to reach £1 billion in 2020 – 5.5% of total NHS drug budget**



Case Study 2

HLA



HLA Alleles Recommended for Testing in Drug Labels

HLA-B*57:01



Abacavir hypersensitivity

HLA-B*15:02



Carbamazepine-induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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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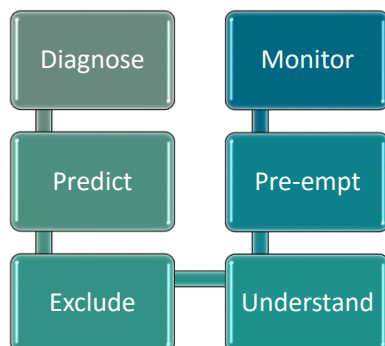
Special Issue: Precision Medicine

Review

Genomics of Adverse Drug Reactions

Ana Alfirevic¹ and Munir Pirmohamed^{1,*}

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

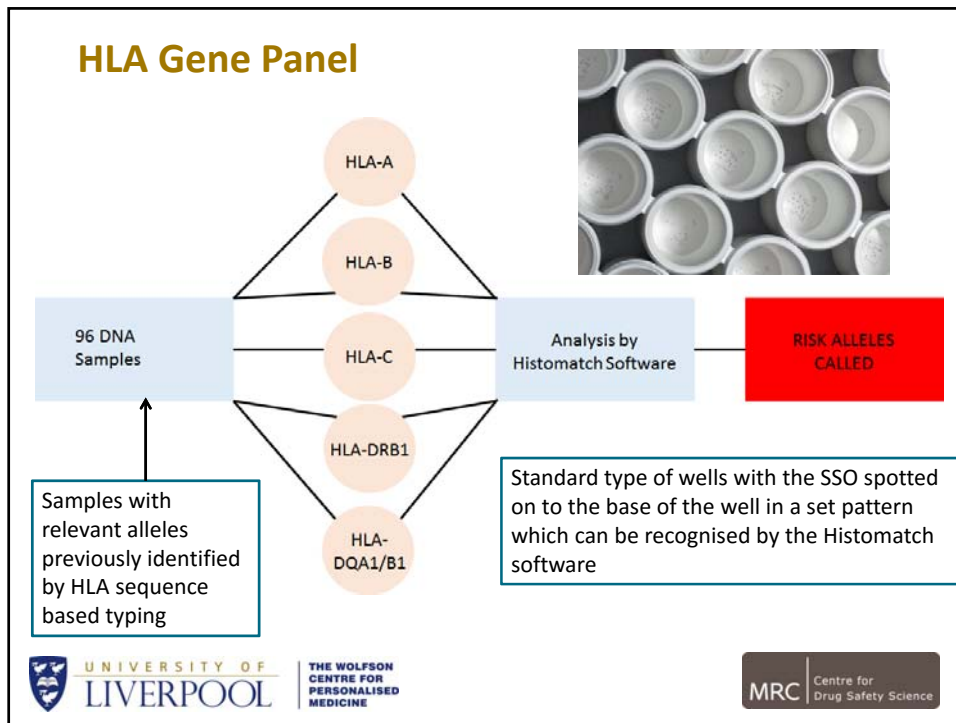


Genomic testing can be used for more than prediction



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HLA Platform

MCD
AUTOMATED MOLECULAR DIAGNOSTICS

Mr SPOT

Histomatch software

48 hour turnaround time

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Clinical Decision Support


Please select your drug and/or alleles of interest

Drug				Allele			
abacavir	allopurinol	amoxicillin-clavulanate	antituberculosis drugs	A*31:01	A*33:03	A*68:01	B*13:01
aspirin	carbamazepine	clozapine	dapsone	B*15:02	B*35:05	B*44:03	B*56:02
flucloxacillin	lamotrigine	lapatinib	lumiracoxib	B*57:01	B*58:01	C*04:01	C*08:01
nevirapine	NSAID and 'multi-ingredient cold medication'	oxcarbazepine	phenytoin	DQA1*01:02	DQA1*02:01	DQB1*02:01	DQB1*05:02
statins	sulfamethoxazole	sulfasalazine	ticlopidine	DQB1*06:02	DQB1*06:04	DQB1*06:09	DRB1*07:01
ximelagatran				DRB1*11:01	DRB1*13:02	DRB1*15:01	


Database last updated: 07 March 2017



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Clinical Decision Support

HLA Clinical Decision Support Tool

[Home](#) > [CDST results](#)

Information for carbamazepine

A*31:01


HLA-CDST recommendation: -Filler Text-Warning message-/Filler text-

Show supporting information


B*15:02

HLA-CDST recommendation: -Filler text-Warning message-/Filler Text-


Show supporting information



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Case Study 3

The Horizon 2020 U-PGx project Ubiquitous Pharmacogenomics in the EU

Implement pre-emptive PGx testing in a real world clinical setting across 7 EU sites using DPWG guidelines

Evaluate patient outcome and cost effectiveness in a RCT

Thanks to the U-PGx team and HJ Guchelaar for the slides



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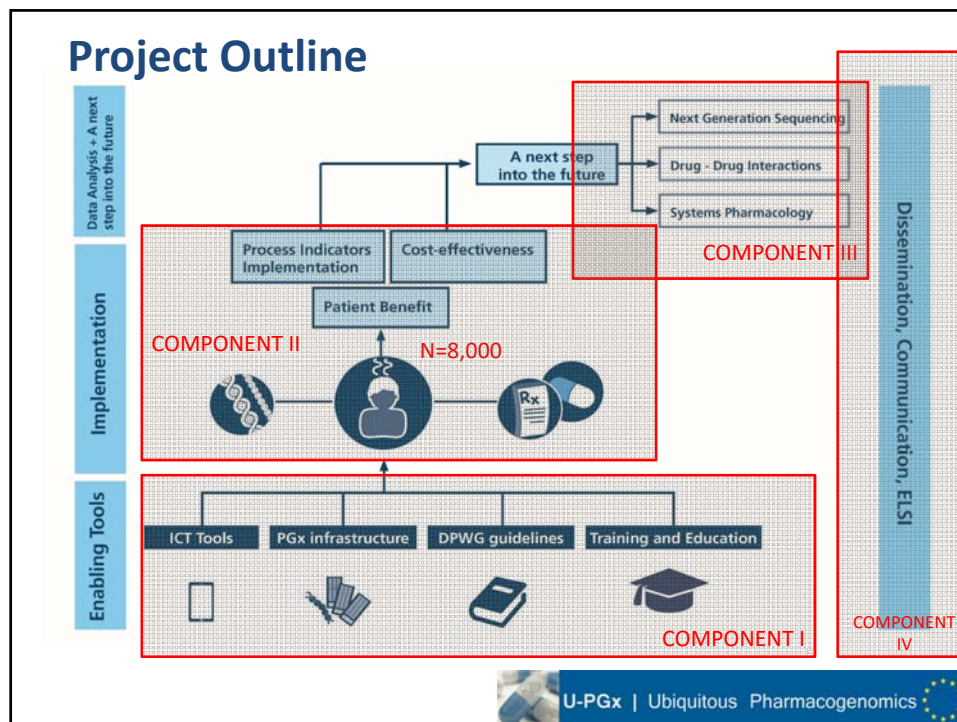
Aim

- Implement pre-emptive PGx testing in a real world clinical setting across 7 EU countries;
- For acceptance, **it is essential that implementation is supported by evidence** demonstrating clear benefit of the pre-emptive PGx strategy.
- Therefore, in this project we will evaluate **patient outcome** and **cost effectiveness** using solid **scientific methodology**.



U-PGx | Ubiquitous Pharmacogenomics





II: Implementation

Objective:

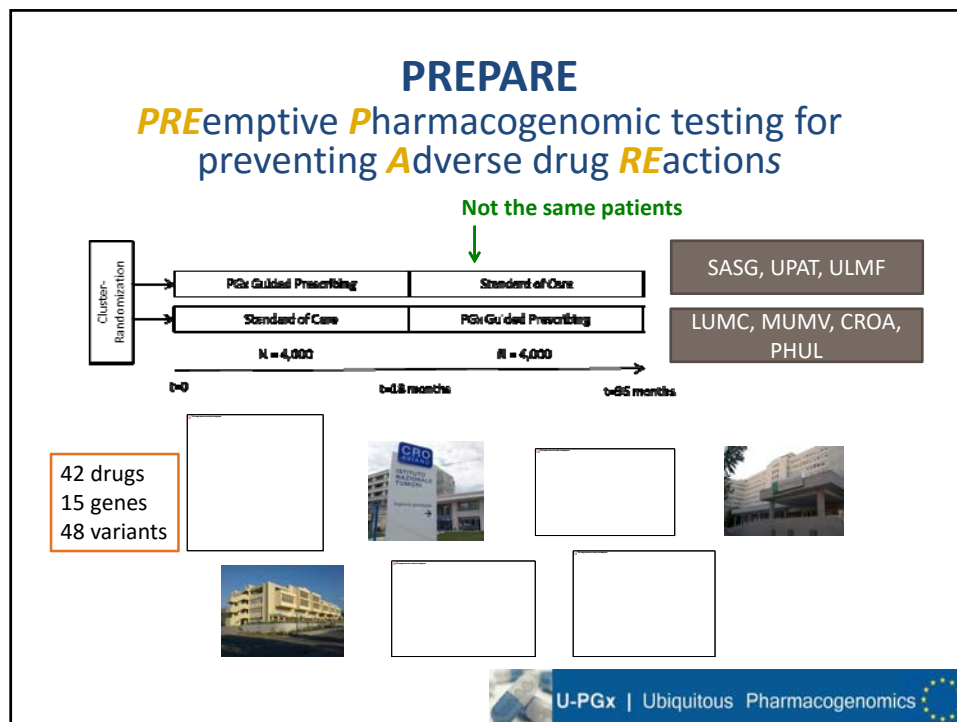
To investigate a pre-emptive genotyping approach of a panel of PGx variants covering 13 important pharmacogenes as a new model of personalized medicine.

Design:

Open randomized cross-over trial in 7 countries including 8,000 patients.

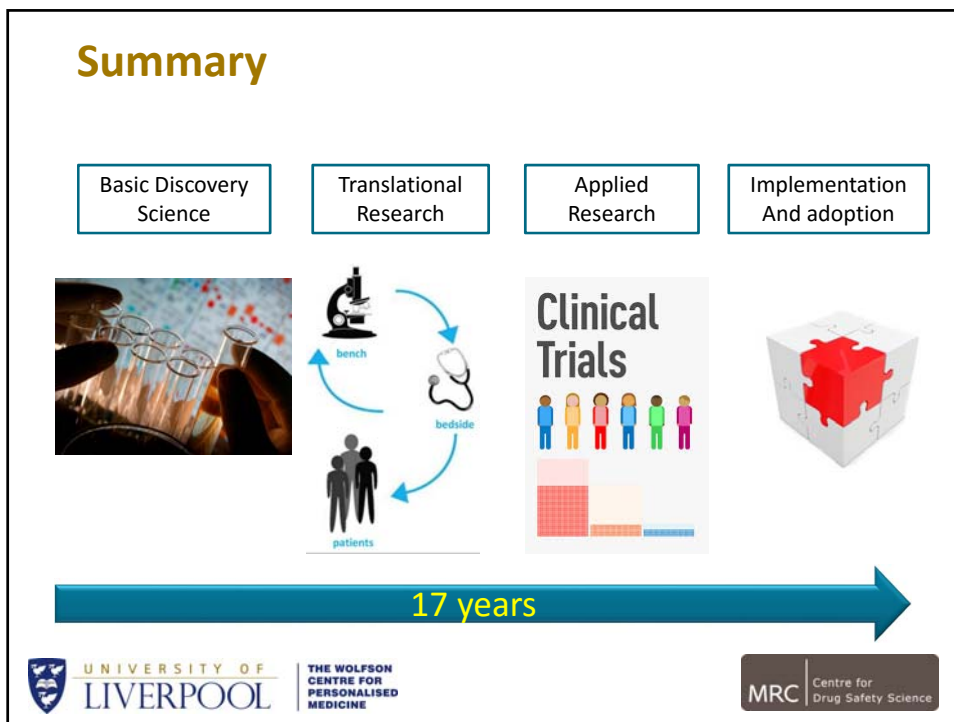
Outcomes:

Primary	Clinical outcome
Secondary	Process indicators for implementation
	Cost-effectiveness
	Patient reported outcomes



Current status

- ❑ ICT tool developed → **msc card**
- ❑ PGx genotyping platform selected → **LGC SNPLine**
- ❑ PGx panel selected → **15 pharmacogenes; 48 variants; incl. genotype-phenotype translation**
- ❑ Guidelines translated → **English and local languages; validated**
- ❑ Training and education materials developed
 - ▶ Promotional video (www.upgx.eu)
 - ▶ eLearnings for participants (nurses, pharmacists, clinicians)
- ❑ First U-PGx Pharmacogenomics Day Granada; 2nd in Vienna 12 May
- ❑ Study protocol finished
 - ▶ IRB approval: Spain, UK, Greece, Italy, Slovenia, Netherlands; Austria pending
- ❑ eCRF in progress; test-run dummy patients
- ❑ SOPs completed e.g. logistics, causality assessment, genotyping



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- Andrea Jorgensen
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- Panagiotis Deloukas
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- **EPIGEN**
- **EU-PACT**
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Warfarin: LGC
HLA: MC Diagnostics

**INDUSTRY
COLLABORATION**

