Genomics Education Programme

NHS Health Education England

Implementing pharmacogenomics in Europe – incentives & challenges

Richard Turner

Health Education England Genomics & Innovation Fellow

Clinical Pharmacology & Therapeutics Registrar

UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

U-PGx | Ubiquitous Pharmacogenomics

- H2020, €15 million
- 10 EU countries, 16 beneficiaries
- Implement pre-emptive PGx testing in a real world clinical setting across 7 EU sites
- Evaluate **implementation metrics**, **patient outcomes** and **cost effectiveness**
- Jan 2016 – Dec 2020 (5 years)

H.J. Guchelaar (Coordinator), J.J. Swen, M. Kriek
Leiden University Medical Center

M. Pirmohamed, R. Turner

M. Ingelman-Sundberg

J. Stingl

M. Samwald
G. Sunder-Plassmann

C. Mitropoulou

D. Steinberger

M. van Rhenen, K.C. Cheung

M. Karlsson
S. Jönsson

G. Toffoli
E. Cecchin

C.L. Davila Fajardo

V.H.M. Deneer

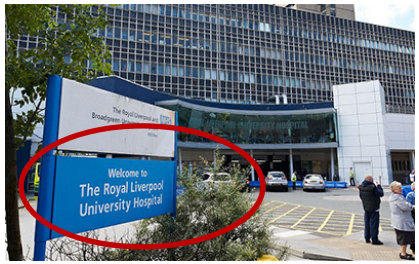
G. Patrinos

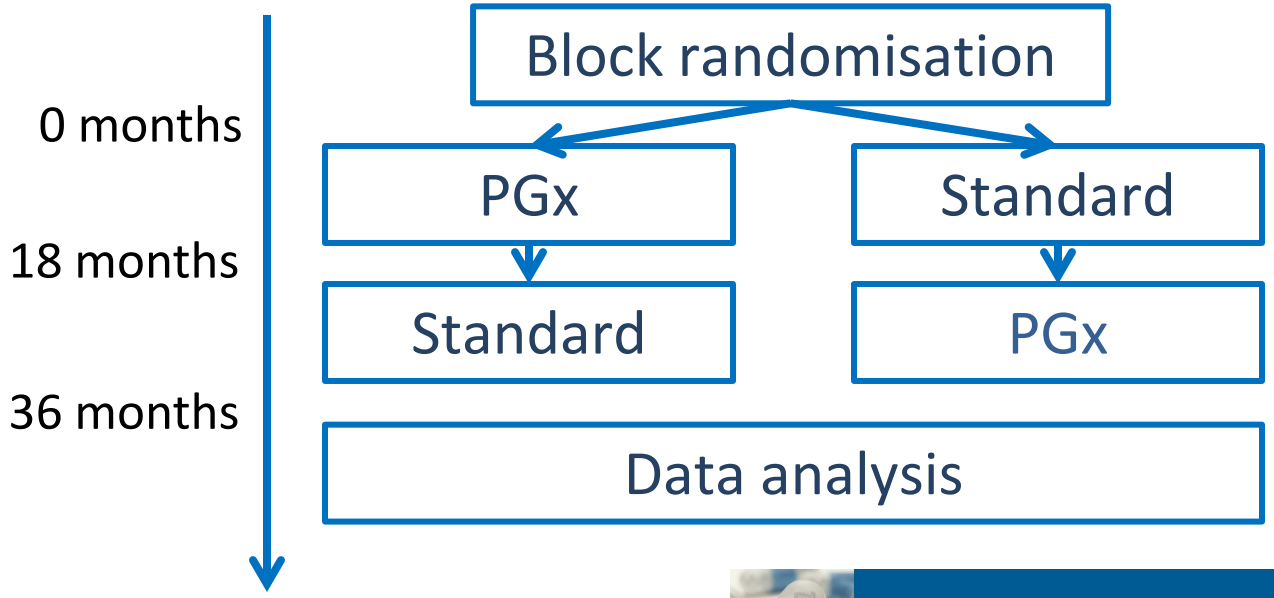
V. Dolžan

M. Schwab
E. Schaeffeler

A. Cambon-Thomsen

U-PGx Implementation Project



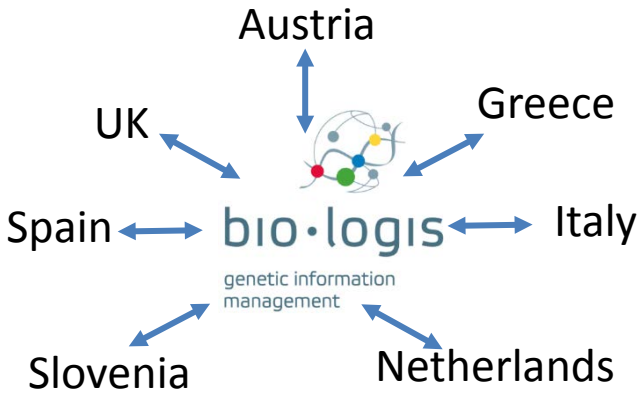


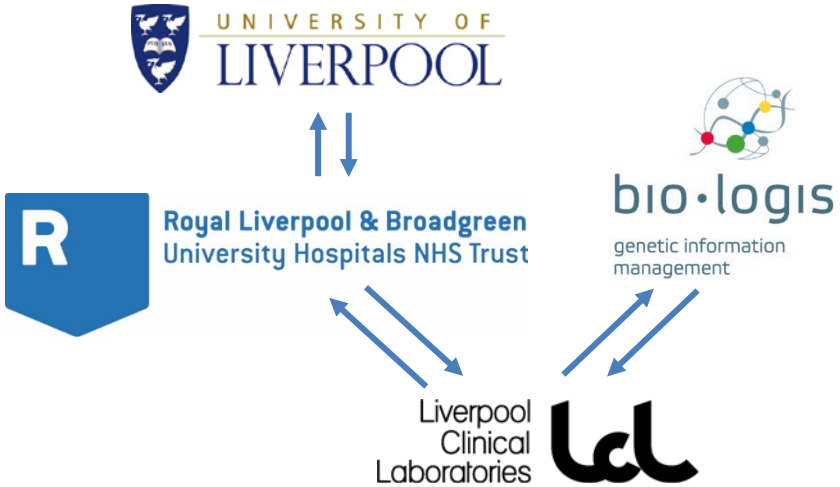
Operational factors

Ethical approvals

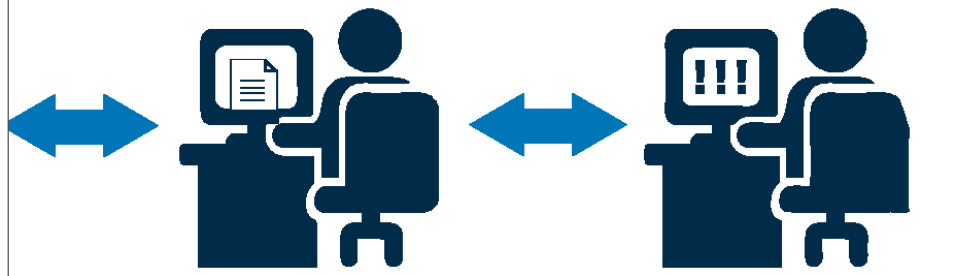
Language/acceptability

Genotype interpretation





Clinical decision support

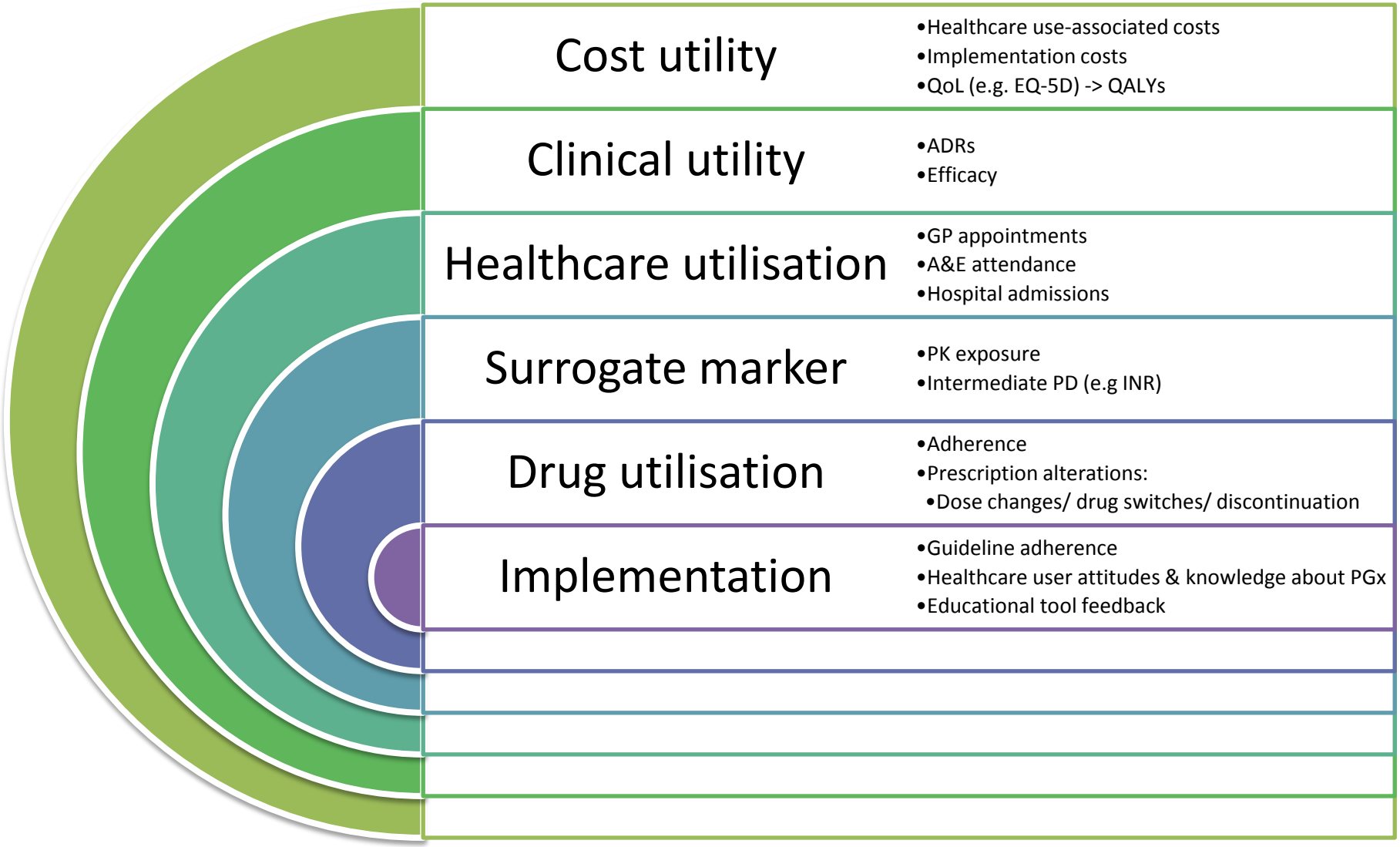


Interpretive, passive CDS ***inside*** the EHR system

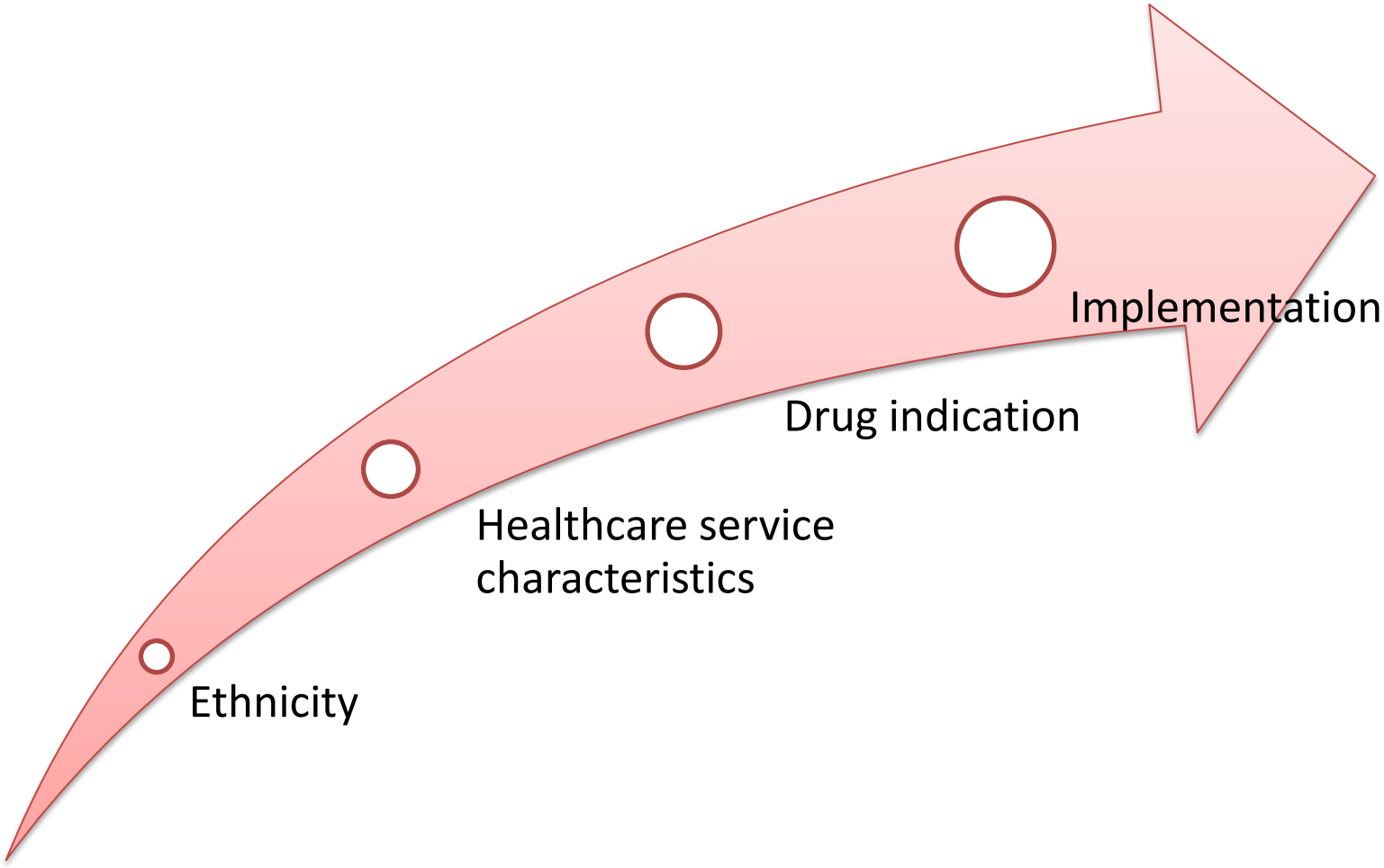
Interruptive, active CDS inside EHR/e-prescription system

Dr Samwald: http://safety-code.org/

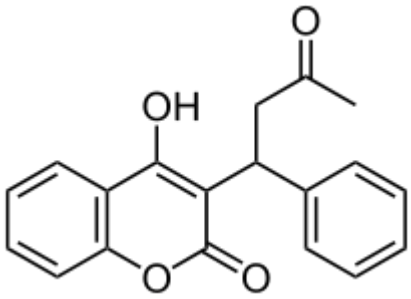
Outcomes


Cost utility
•Healthcare use-associated costs
•Implementation costs
•QoL (e.g. EQ-5D) -> QALYs
Clinical utility
•ADRs
•Efficacy
Healthcare utilisation
•GP appointments
•A&E attendance
•Hospital admissions
Surrogate marker
•PK exposure
•Intermediate PD (e.g INR)
Drug utilisation
•Adherence
•Prescription alterations:
•Dose changes/ drug switches/ discontinuation
Implementation
•Guideline adherence
•Healthcare user attitudes & knowledge about PGx
•Educational tool feedback

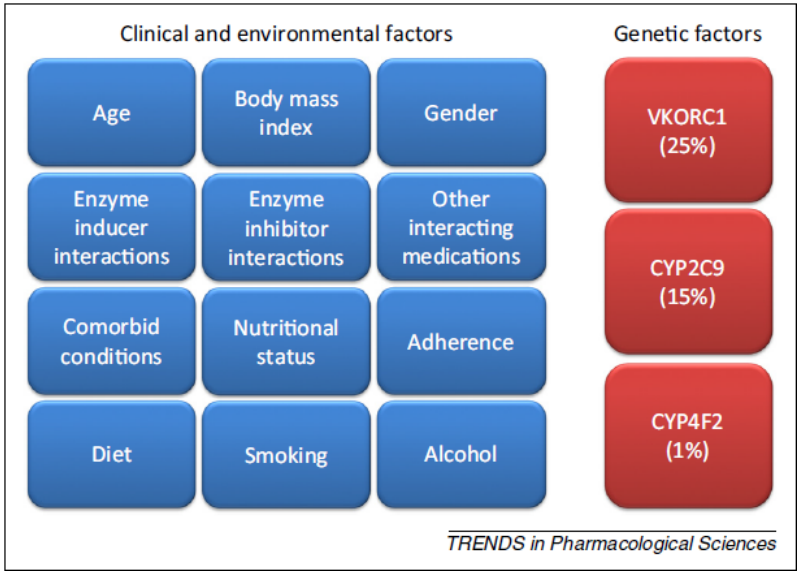
Data sharing – factors that may affect clinical utility



Warfarin



- ~1% of UK population on warfarin
- 40x fold variation in dose between patients
- 3rd most common cause of ADRs leading to hospitalisation



Pirmohamed *et al*, 2015

Warfarin RCTs

PGx | Clinical

EU-PACT

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*

N Engl J Med 2013; 369:2294-2303 | December 12, 2013 | DOI: 10.1056/NEJMoa1311386

12 week TTR

67.4% **60.3%**

P<0.001

COAG

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Stephen E. Kimmel, M.D., Benjamin French, Ph.D., Scott E. Kasner, M.D., Julie A. Johnson, Pharm.D., Jeffrey L. Anderson, M.D., Brian F. Gage, M.D., Yves D. Rosenberg, M.D., Charles S. Eby, M.D., Rosemary A. Madigan, R.N., M.P.H., Robert B. McBane, M.D., Sherif Z. Abdel-Rahman, Ph.D., Scott M. Stevens, M.D., Steven Yale, M.D., Emile R. Mohler, III, M.D., Margaret C. Fang, M.D., Vinay Shah, M.D., Richard B. Horenstein, M.D., Nita A. Limdi, Pharm.D., Ph.D., James A.S. Muldowney, III, M.D., Jaspal Gujral, M.B., B.S., Patrice Delafontaine, M.D., Robert J. Desnick, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Henny H. Billett, M.D., Robert C. Pendleton, M.D., Nancy L. Geller, Ph.D., Jonathan L. Halperin, M.D., Samuel Z. Goldhaber, M.D., Michael D. Caldwell, M.D., Ph.D., Robert M. Califf, M.D., and Jonas H. Ellenberg, Ph.D., for the COAG Investigators*

N Engl J Med 2013; 369:2283-2293 | December 12, 2013 | DOI: 10.1056/NEJMoa1310669

4 week TTR

45.2% 45.4%

ns

GIFT

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty

The GIFT Randomized Clinical Trial

Brian F. Gage, MD, MSc[1]; Anne R. Bass, MD[2]; Hannah Lin, BA[1,3]; Scott C. Woller, MD[4,5]; Scott M. Stevens, MD[4,5]; Noor Al-Hammadi, MBChB, MPH[1]; Juan Li, MPH[1]; Tomás Rodríguez Jr, MS[1]; J. Philip Miller, AB[1]; Gwendolyn A. McMillin, PhD[5]; Robert C. Pendleton, MD[5]; Amir K. Jaffer, MD, MBA[6]; Cristi R. King, BS[1]; Brandi DeVore Whipple, BS[1]; Rhonda Porche-Sorbet, MS[1]; Lynnae Napoli, BS[5]; Kerri Merritt, BA[2]; Anna M. Thompson, BA[1,7]; Gina Hyun, MD[1,8]; Jeffrey L. Anderson, MD[4,5]; Wesley Hollomon, MD, MBA[2]; Robert L. Barrack, MD[1]; Ryan M. Nunley, MD[1]; Gerard Moskowitz, PhD[1]; Victor Dávila-Román, MD[1]; Charles S. Eby, MD[1]

4 week major bleeding, INR≥4, VTE, death

10.8% **14.7%**

P=0.02

Ethnicity-specific PGx

- COAG RCT: 67% White, 27% African American, 6% Hispanic (only 36% had ≥1 variant allele)
- EU-PACT RCT: 97% White (52% had ≥1 variant allele)

- Africa American patients did worse in genotype arm than in clinical group (TTR 35% vs 43%)

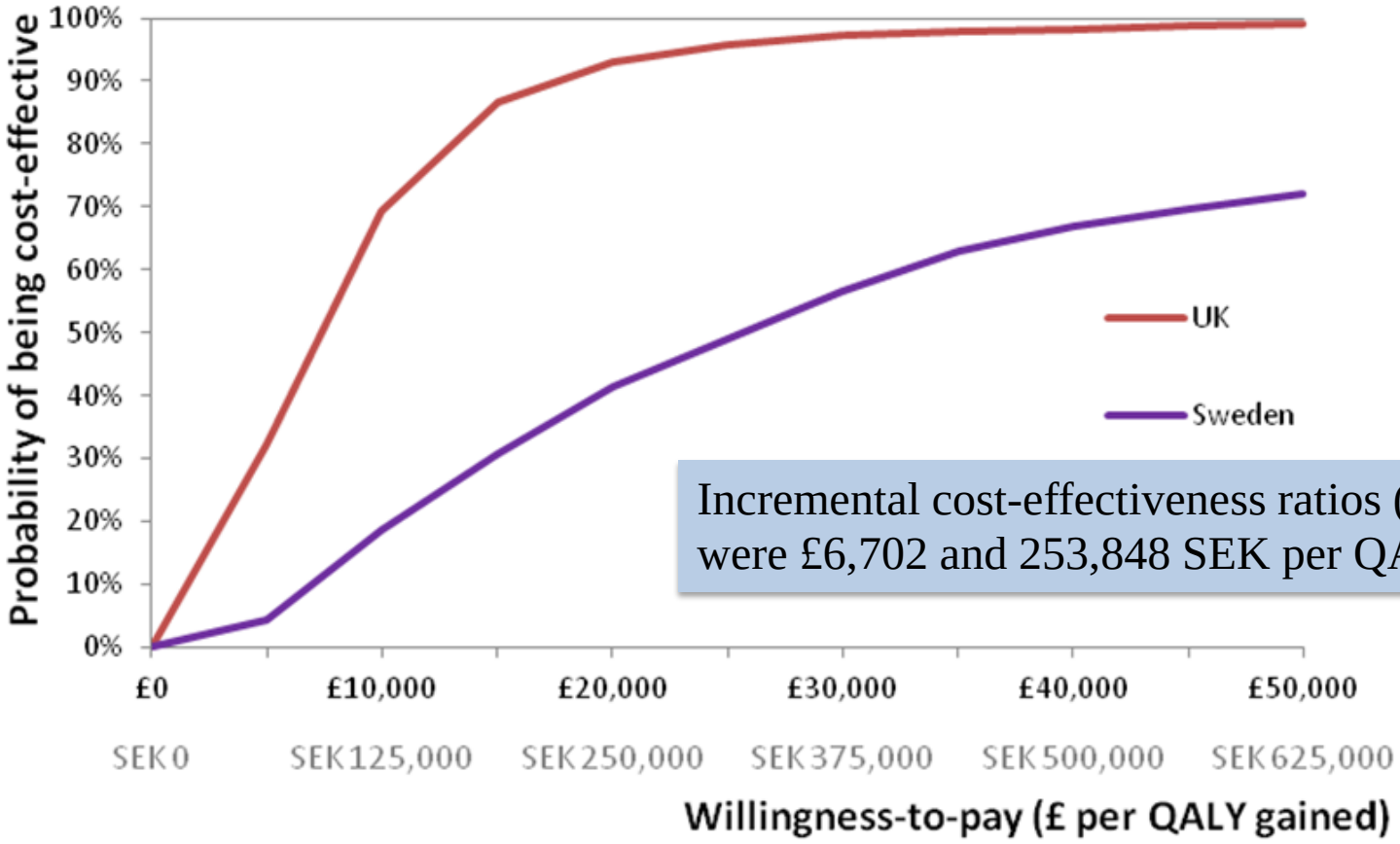
Allele	Location	Frequency		
		European Caucasians	*US Hispanics*	*African–Americans*
*CYP2C9*2*	Exon 3	0.10	0.07	0.02
*CYP2C9*3*	Exon 7	0.06	0.05	0.01
*CYP2C9*5*	Exon 7	<0.01	<0.01	0.01
*CYP2C9*6*	Exon 5	<0.01	<0.01	0.01
*CYP2C9*8*	Exon 3	<0.01	<0.01	0.06
*CYP2C9*11*	Exon 7	<0.01	<0.01	0.04
CYP2C9 rs7089580	Intronic	0.24	0.11	0.23
VKORC1 -1639A	5-UTR	0.40	0.46	0.11

Cavallari *et* Perera 2012; 8(4):563-576

ORIGINAL ARTICLE

Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden

TI Verhoef[1,2], WK Redekop[3], S Langenskiold[4,5], F Kamali[6], M Wadelius[7], G Burnside[8], A-H Maitland-van der Zee[2], DA Hughes[9] and M Pirmohamed[8]



Incremental cost-effectiveness ratios (ICERs) were £6,702 and 253,848 SEK per QALY gained

Warfarin PGx Implementation Processes

- Initial discussion with Ethics committee who confirmed service evaluation
- RD&I involvement at outset due to Innovation – no gold standard guidance to follow
- 3 Trusts for implementation: all with different processes

- Approval in some organisations took more than 6 months
- Lack of clarity about information governance processes
- Unable to get access to all data in anticoagulation clinics for control purposes even when anonymised

100,000 Genomes Project

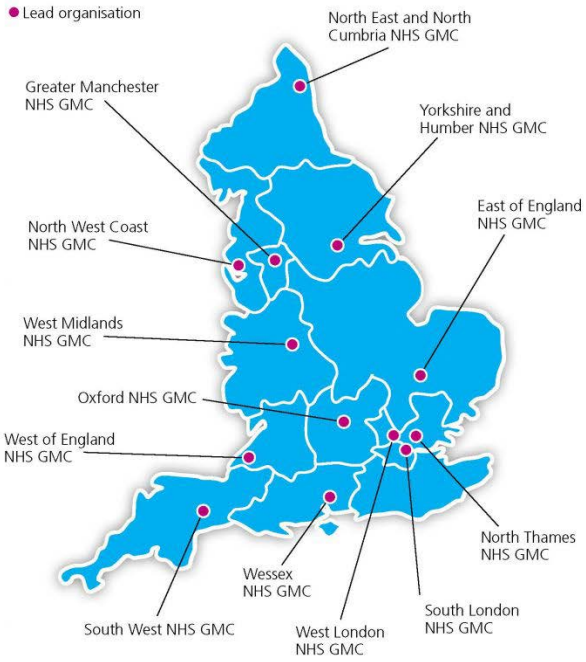
Genomics england

NHS Genomic Medicine Centres

NHS England

Paving the way to personalised medicine

- 70,000 patients
- Rare diseases
- Cancer



NHS

Public Health England

Sequencing centres

Management Infrastructure

Identities

Relationships

Operations

Research Infrastructure

Data storage

Virtual data centres

GeCIP

Researchers

Clinical Interpretation

Industry

Adapted from: Genomics England: https://www.genomicsengland.co.uk/the-100000-genomes-project/data/data-types-and-storage/

Collaboration & Data sharing

Acknowledgements

University of Liverpool

- Prof Sir Munir Pirmohamed

Leiden University Medical Center

- Prof Henk-Jan Guchelaar
- Dr Jesse Swen

Medical University of Vienna

- Dr Matthias Samwald

U-PGx consortium

Funders

- H2020
- HEE
- MRC
- WT, DH, NIHR, EU-FP7

UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

Richard.Turner@liverpool.ac.uk

Genomics Education Programme

Published in final edited form as:
Clin Pharmacol Ther. 2012 May ; 91(5): 774–776. doi:10.1038/clpt.2012.21.

Clopidogrel: A Case for Indication-Specific Pharmacogenetics

JA Johnson[1], **DM Roden**[2], **LJ Lesko**[1], **E Ashley**[3], **TE Klein**[4], and **AR Shuldiner**[5]

- Clopidogrel – *CYP2C19*2*
- Several meta-analyses undertaken
- *CYP2C19*2* carriage consistently associated with stent thrombosis
- Risk of MACE in *CYP2C19*2* carriers dependent on baseline risk

	Holmes *et al*, 2011	Mega *et al*, 2010
**2 carrier*	1.18 (1.09-1.28)	1.57 (1.13-2.16)
**1/*2*	0.94 (0.80-1.10)[1]	1.55 (1.11-2.27)
**2/*2*	1.52 (1.04-2.21)[1]	1.76 (1.24-2.50)