Using Human Genomic Variation for Individualisation of Drug Treatment

Munir Pirmohamed
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University of Liverpool
Current Paradigms

- Physicians “personalise” treatments
- We use the best evidence available to us (usually from RCTs – population based studies) to treat the patient (i.e. individual) consulting us
- From a population perspective, that has proven benefits
- But from an individual perspective, it is less satisfactory and is CRUDE
  - Cannot predict whether the patient will improve
  - Cannot predict whether the patient will develop adverse effects
<table>
<thead>
<tr>
<th>Condition</th>
<th>Efficacy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>30</td>
</tr>
<tr>
<td>Asthma</td>
<td>60</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57</td>
</tr>
<tr>
<td>HCV</td>
<td>47</td>
</tr>
<tr>
<td>Cancer</td>
<td>25</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
</tbody>
</table>

Source: Physicians Desk Reference

“The vast majority of drugs - more than 90 per cent – only work in 30 or 50 per cent of the people,”
Adverse Drug Reactions (Side Effects)

- Adverse drug reactions are common
- Vary in severity

TOXIC EPIDERMAL NECROLYSIS
A Modern Concept of Personalised Medicine

- Environmental factors
- Drug variability
- Molecular definition
- Phenotypic definition

Current standard

Phenotypic definition
A Modern Concept of Personalised Medicine

- Environmental factors
- Drug variability
- Molecular definition
- Phenotypic definition

Disease stratification
Current standard
A Modern Concept of Personalised Medicine

- Drug variability
- Molecular definition
- Phenotypic definition

Pharmacogenomics
Disease stratification
Current standard
A Modern Concept of Personalised Medicine

- Environmental factors
- Drug variability
- Molecular definition
- Phenotypic definition

Personalised Medicine
Pharmacogenomics
Disease stratification
Current standard
Pharmacogenomic Variation in Drug Response

**Pharmacokinetics**
- Absorption
- Distribution
- Metabolism
- Excretion

**Pharmacodynamics**
- Ion channels
- Receptors
- Enzymes
- Nucleic acid

**Drug Response**
Using Human Genomic Variation for Individualisation of Drug Treatment

When it works......
Human Leucocyte Antigens (HLA)

- On short arm of chromosome 6
- Involved in the pathogenesis of immune-mediated adverse drug reactions
- Since 2001, 23 different HLA associations have been reported with ADRs affecting skin and liver
Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

Clinical phenotype
Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

Clinical phenotype

Clinical genotype

Association with HLA-B*5701
Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

Clinical phenotype

Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity
Dyfrig A. Hughes\(^a\), F. Javier Vilar\(^b\), Charlotte C. Ward\(^a\), Ana Alfrevic\(^a\), B. Kevin Park\(^a\) and Munir Pirmohamed\(^a\)
Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

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<table>
<thead>
<tr>
<th>Country</th>
<th>Pre testing</th>
<th>Post testing</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>7%</td>
<td>&lt;1%</td>
<td>Rauch et al, 2006</td>
</tr>
<tr>
<td>France</td>
<td>12%</td>
<td>0%</td>
<td>Zucman et al, 2007</td>
</tr>
<tr>
<td>UK (London)</td>
<td>7.8%</td>
<td>2%</td>
<td>Waters et al, 2007</td>
</tr>
</tbody>
</table>
Effect of Pharmacogenetics on Drug Usage

Data courtesy of Prof Saye Khoo
Change in Peptide Repertoire

Immune self-reactivity triggered by drug-modified HLA-peptide repertoire

Patricia T. Illing\textsuperscript{1,2}, Julian P. Vivian\textsuperscript{3}, Nadine L. Dudek\textsuperscript{2}, Lyudmila Kostenko\textsuperscript{1}, Zhenjun Chen\textsuperscript{1}, Mandvi Bharadwaj\textsuperscript{1}, John J. Miles\textsuperscript{4,5}, Lars Kjer-Nielsen\textsuperscript{1}, Stephanie Gras\textsuperscript{3}, Nicholas A. Williamson\textsuperscript{2}, Scott R. Burrows\textsuperscript{4}, Anthony W. Purcell\textsuperscript{2\ast}, Jamie Rossjohn\textsuperscript{3,5\ast}, & James McCluskey\textsuperscript{1,6\ast}

Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire

David A. Ostrov\textsuperscript{a}, Barry J. Grant\textsuperscript{b}, Yuri A. Pompeu\textsuperscript{c}, John Sidney\textsuperscript{d}, Mikkel Harndahl\textsuperscript{e}, Scott Southwood\textsuperscript{d}, Carla Oseroff\textsuperscript{d}, Shun Lu\textsuperscript{a}, Jean Jakoncic\textsuperscript{f}, Cesar Augusto F. de Oliveira\textsuperscript{g}, Lun Yang\textsuperscript{h}, Hu Mei\textsuperscript{h}, Leming Shi\textsuperscript{h}, Jeffrey Shabanowitz\textsuperscript{i}, A. Michelle English\textsuperscript{i}, Amanda Wriston\textsuperscript{i}, Andrew Lucas\textsuperscript{i}, Elizabeth Phillips\textsuperscript{i}, Simon Mallal\textsuperscript{i}, Howard M. Grey\textsuperscript{d,1}, Alessandro Sette\textsuperscript{d}, Donald F. Hunt\textsuperscript{i}, Soren Buus\textsuperscript{e}, and Bjoern Peters\textsuperscript{d,1}

Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity

Michael A. Norcross\textsuperscript{a}, Shen Luo\textsuperscript{a}, Li Lu\textsuperscript{a}, Michael T. Boyne\textsuperscript{b}, Mary Gomartelli\textsuperscript{c}, Aaron D. Rennels\textsuperscript{c}, Janet Woodcock\textsuperscript{d}, David H. Margulies\textsuperscript{c}, Curtis McMurtrey\textsuperscript{f}, Stephen Vernon\textsuperscript{f}, William H. Hildebrand\textsuperscript{f} and Rico Buchli\textsuperscript{c}
Peptides from untreated cells standard peptide profile

ABC treated cells show novel self-peptides (20-25%) with Ile/Leu occupying C-terminal anchor protein

No change in peptide profile with closely related allotypes

Illing et al, 2013, Curr Opin Immunol
Using Human Genomic Variation for Individualisation of Drug Treatment

When it makes sense....
Eculizumab – humanised monoclonal antibody binds to C5 inhibiting its activation

3% of patients have a poor response

Missense mutation identified in C5 in these patients

Eculizumab able to block C5-mediated hemolysis in nonmutant RBCs but not those carrying variant

Somatic mutation leads to deficiency of GPI anchored proteins (CD55, CD59)

Susceptible to C5 mediated haemolysis
Eculizumab – humanised monoclonal antibody binds to C5 inhibiting its activation

3% of patients have a poor response

Missense mutation identified in C5 in these patients

Eculizumab able to block C5-mediated hemolysis in nonmutant RBCs but not those carrying variant
Using Human Genomic Variation for Individualisation of Drug Treatment

More often than not, it is difficult......
Sources of Variation

- Increasing number of examples of pharmacodynamic genetic variation which are being used in clinical practice
- Pharmacokinetic variation has been more difficult to implement
  - The most successful has been TPMT and bone marrow suppression with 6MP and azathioprine
- PK and PD factors work together to affect response – accounting for both can improve prediction
  - Warfarin dose prediction
Warfarin

- Number of users UK: **600,000**
- Dose (mg) range per day: **0.5-20**
- Fold variability in dose: **40**
- Major bleeding rate per 100-person years: **2.6**
- Ranking in ADR list: **3**

Approved for human use in 1954
Variation in Dose Requirements

**UK prospective cohort data**

![Histogram showing variation in dose requirements](image)

<table>
<thead>
<tr>
<th>INR</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>4.11</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>3.78</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>15.78</td>
</tr>
<tr>
<td>&gt;4.1</td>
<td>99.26</td>
</tr>
</tbody>
</table>

Only 50% of bleeds occur with INR > 2.5; 50% occur at levels below this

Hylek et al, 2007

**Centre for Drug Safety Science**
Determinants of Anticoagulation Control

- Drug interactions (5–10%)
- Other factors (30–40%)
- CYP2C9 (up to 15%)
- VKORC1 (up to 25%)
- Age, height, weight (10–20%)

McLeod and Jonas, 2009
Determinants of Anticoagulation Control

One of the most highly replicated genotype-phenotype associations

McLeod and Jonas, 2009

- Drug interactions (5–10%)
- Other factors (30–40%)
- CYP2C9 (up to 15%)
- VKORC1 (up to 25%)
- Age, height, weight (10–20%)
GWAS Warfarin Mean Weekly Dose (UK Prospective Cohort; n=714)
Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*
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
## 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 Staafberg, 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

### Main findings

**ITT ANALYSIS (n= 211 vs 216)**

<table>
<thead>
<tr>
<th>Genotyped arm</th>
<th>Standard dosing (control) arm</th>
<th>Adjusted Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%TTR</td>
<td>%TTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67.4%</td>
<td>60.3%</td>
<td>7%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

**PER-PROTOCOL (n=166 vs 184)**

<table>
<thead>
<tr>
<th>Genotyped arm</th>
<th>Standard dosing (control) arm</th>
<th>Adjusted Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%TTR</td>
<td>%TTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.9%</td>
<td>62.3%</td>
<td>6.6%</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

### PRIMARY OUTCOME MEASURE:

Percent time within therapeutic INR range 2.0-3.0 (TTR) during 12 weeks following the initiation of warfarin therapy
Differences Between Genotyped-Guided Group and Control Group

**International Normalized Ratio**

- **Control group**
- **Genotype-guided group**

**Time in Therapeutic Range**

- **Genotype-guided group**
- **Control group**
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., Ph.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*

No difference between genotyped and control arms

Two Conflicting Prospective, RCTs on Warfarin PGx Provide No Definitive Guidance to Physicians

Do Pharmacogenetics Have a Role in the Dosing of Vitamin K Antagonists?

Bruce Furie, M.D.

“The conclusions of the three studies are similar”
How can we explain the differences?
Dosing Algorithms

EU-PACT

- Day 1-3: Loading dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 3 months: AC clinics (computerised dosing)

COAG

- Day 1-3: Maintenance dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 1 month: Protocol driven
Dosing Algorithms

EU-PACT
- Day 1-3: Loading dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 3 months: AC clinics (computerised dosing)

COAG
- Day 1-3: Maintenance dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 1 month: Protocol driven

- S-warfarin elimination half-life: 18-35 hours
- Time to steady state: 90-175 hours
- Time to steady state shortened by loading dose
- Dose revision algorithm on day 4 dependent on INR
- What proportion of patients will have had a change in INR by day 4?
Dosing Algorithm – Day 1

- COAG algorithm did not include CYP2C9 on day 1 (“dosing patients with CYP2C9 *2 or *3 variants at lower doses during the first day of therapy may not lead to improvement in AC and could lead to worse anticoagulation”). **BASED ON MAINTENANCE DOSE.**
Dosing Algorithm – Day 1

- COAG algorithm did not include CYP2C9 on day 1 ("dosing patients with CYP2C9 *2 or *3 variants at lower doses during the first day of therapy may not lead to improvement in AC and could lead to worse anticoagulation"). **BASED ON MAINTENANCE DOSE.**

SNPs in CYP2C9, but not VKORC1, associated with time to stable warfarin dose, time to therapeutic INR and INR >4 at end of week 1
Ethnic Heterogeneity

- COAG was more heterogeneous (67% white, 27% Black, 6% Hispanic) than EU-PACT (97% Caucasian)
- Blacks did worse in genotype arm than in clinical group (-8% difference)

<table>
<thead>
<tr>
<th>Allele</th>
<th>Location</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>European</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caucasians</td>
</tr>
<tr>
<td>CYP2C9*2</td>
<td>Exon 3</td>
<td>0.10</td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>Exon 7</td>
<td>0.06</td>
</tr>
<tr>
<td>CYP2C9*5</td>
<td>Exon 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CYP2C9*6</td>
<td>Exon 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CYP2C9*8</td>
<td>Exon 3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CYP2C9*11</td>
<td>Exon 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CYP2C9 rs7089580</td>
<td>Intronic</td>
<td>0.24</td>
</tr>
<tr>
<td>VKORC1 -1639A</td>
<td>5-UTR</td>
<td>0.40</td>
</tr>
<tr>
<td>VKORC1 rs61162043</td>
<td>5-UTR</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Control Arms in the Two Trials

- EU-PACT: fixed dosing which reflects current clinical care
- COAG: clinical algorithm (includes all factors apart from genetics)
- Interpreted as genetics does not add anything over and above clinical factors – some have advocated use of clinical algorithm
- Clinical algorithm has never been tested in a RCT
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- Clinical algorithm has never been tested in a RCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time</th>
<th>Genotyped arm %TTR</th>
<th>Control arm %TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>COAG</td>
<td>4 weeks</td>
<td>45.2</td>
<td>45.4</td>
</tr>
<tr>
<td>EU-PACT</td>
<td>4 weeks</td>
<td>54.6</td>
<td>45.7</td>
</tr>
<tr>
<td>COAG</td>
<td>12 weeks</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>EU-PACT</td>
<td>12 weeks</td>
<td>67.4</td>
<td>60.3</td>
</tr>
</tbody>
</table>
Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY investigators
## Comparison Between COAG and EU-PACT

<table>
<thead>
<tr>
<th>Total no of variants</th>
<th>Genotype guided</th>
<th>Clinically guided</th>
<th>Total</th>
<th>Genotyped</th>
<th>Non-genotyped</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>204 (40%)</td>
<td>189 (38%)</td>
<td>393 (39%)</td>
<td>63 (28%)</td>
<td>57 (27%)</td>
<td>120 (27%)</td>
</tr>
<tr>
<td>1</td>
<td>178 (35%)</td>
<td>186 (37%)</td>
<td>364 (36%)</td>
<td>113 (50%)</td>
<td>115 (54%)</td>
<td>228 (52%)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>128 (25%)</td>
<td>125 (25%)</td>
<td>253 (25%)</td>
<td>50 (22%)</td>
<td>40 (19%)</td>
<td>90 (21%)</td>
</tr>
</tbody>
</table>

Higher frequency of allelic variants in EU-PACT compared to COAG, mostly in CYP2C9
EU-PACT: Effect of Number of Variants on % Time in Therapeutic Range (TTR)

<table>
<thead>
<tr>
<th>Total number of variants</th>
<th>Genotyped arm (n=211) %TTR</th>
<th>Control arm (n=216) %TTR</th>
<th>Adjusted Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61.83</td>
<td>59.31</td>
<td>2.03</td>
<td>0.588</td>
</tr>
<tr>
<td>1</td>
<td>68.56</td>
<td>61.83</td>
<td>7.38</td>
<td>0.005</td>
</tr>
<tr>
<td>2 or more</td>
<td>71.95</td>
<td>57.32</td>
<td>11.05</td>
<td>0.009</td>
</tr>
</tbody>
</table>

RELY DATA: a 10% improvement in %TTR leads to a 20% improvement in clinical outcomes
Algorithm incorporating CYP2C9 and VKORC1 genotypes

No difference at 3 months, but %TTR was higher in genotyped arm in first 4 weeks

Combined data from acenocoumarol (n=190) and phenprocoumon (n=83) giving total of 273 in genotype group

Assessed individually, this would be an under-powered trial
Differences in Vitamin K antagonists

- Warfarin
- Phenprocoumon
- Acenocoumarol
Evidence standards differ between non-genetic and genetic tests

3 examples given:
- Drug exposure
- Prevention of adverse drug reactions
- Health technology assessment
Drug Exposure: Differential Evidential Standards

- Example: Aztreonam SmPC
  - “after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m²”

- Many different examples in hepatic and renal impairment with dose instructions based on PK studies and occasionally PK-PD modelling

- No need for RCTs – in fact, would be impractical

- However, a genetic polymorphism leading to same degree of change in drug exposure is often ignored and/or RCT data are required for implementation
Differential Evidence Standards

- Unfamiliarity with genetic tests
- Lack of experience in interpretation
- Perceived cost of genetic testing
- Lack of availability of tests
- Poor turnaround time
Differential Evidence Standards

- Unfamiliarity with genetic tests
- Lack of experience in interpretation
- Perceived cost of genetic testing
- Lack of availability of tests
- Poor turnaround time

Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

12 December 2011
EMA/CHMP/37646/2009
Committee for Medicinal Products for Human Use (CHMP)

recommendations on dosing evaluation in patients with polymorphisms in known metabolic pathways
Tivantinib: selective, oral, non-ATP competitive, small-molecule inhibitor of c-Met
Response to a drug, efficacy or toxicity, is a complex phenotype.
Systems Pharmacology Approaches

Warfarin Dose Prediction

Environment

Pharmacokinetic

Pharmacodynamic

Individual Dose

Age, BMI, drug interactions

CYP2C9*2, CYP2C9*3

VKORC1

50-60% prediction

Alcohol, smoking, Co-morbidities, Other factors

Other P450 enzymes Phase II enzymes Transcription factors

Clotting factor levels, Other key proteins, Metabolome, microRNA

Missing Prediction?
Summary

- Translation into clinical practice is difficult
- Pathway for translation – one size does not fit all
- RCTs are not the ultimate answer to translating biomarkers into clinical practice
- Systems approaches need to be investigated, accompanied by mechanistic analysis
Routine whole-genome sequencing of babies by 2019?

By Daniel MacArthur  February 12, 2009  |  12:15 pm  |  Categories: Genetic Future

I’m slowly catching up on genomics news from the last week – this story in particular has been getting a lot of press.

The executive summary: Jay Flatley, CEO of genomic technology manufacturer Illumina, predicts that whole-genome sequencing of newborns will become routine within a decade.

Flatley has an obvious financial interest in this prediction coming true, since Illumina provides the most commercially successful next-generation sequencing platform currently on the market, the Genome Analyzer, and has recently invested heavily in emerging “third-generation” sequencing technologies (by

Acknowledgements

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• B Kevin Park
• Ana Alfirevic
• Andrea Jorgensen
• Girvan Burnside
• Eunice Zhang
• Javier Vilar

EU-PACT (Mia Wadelius, Ann Daly, Farhad Kamali, Anke Hilse Maitland, and many others)

Funders:

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• Dept of Health (NHS Chair of Pharmacogenetics)
• MRC Centre for Drug Safety Science
• Wolfson Foundation
• WT, DH, NIHR