The Promise and Challenges of Implementing Pharmacogenomics to improve Population Health: Where are we Heading with Pre-emptive Pharmacogenomic Screening?

Munir Pirmohamed

David Weatherall Chair of Medicine, and NHS Chair of Pharmacogenetics

Email: munirp@liverpool.ac.uk

UNIVERSITY OF LIVERPOOL

English Medicines Landscape

1 million patients every 36 hours

1.1 billion community prescriptions

£20 billion annual cost

8000 hospital inpatients with ADRs

>£2.1 billion annual cost

237 million medication errors

Variability in Drug Response

Efficacy

90% of drugs only work in 30-50% of patients

Safety

6.5% of all hospital admissions are due to ADRs

UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

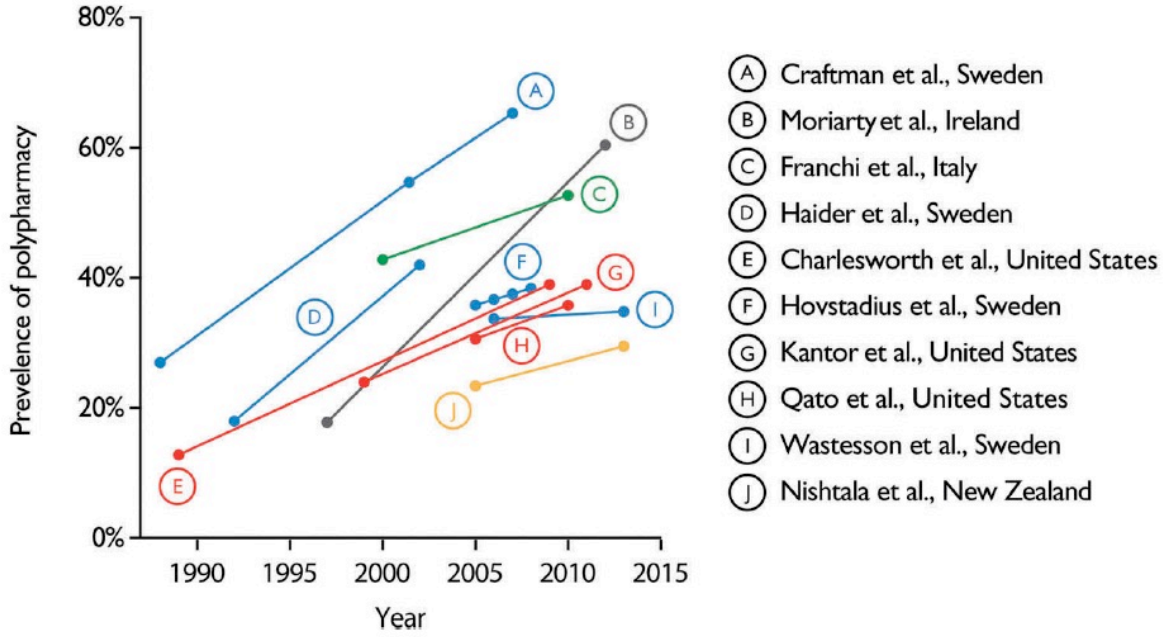
Polypharmacy

Good for you, good for us, good for everybody

A plan to reduce overprescribing to make patient care better and safer, support the NHS, and reduce carbon emissions

Published 22 September 2021

- **15% of patients on 5 or more medicines, 7% on ≥ 8**
- Elderly, those with disabilities and minority ethnic backgrounds disproportionately affected



To cite this article: Jonas W. Wastesson, Lucas Morin, Edwin C.K. Tan & Kristina Johnell (2018) An update on the clinical consequences of polypharmacy in older adults: a narrative review, Expert Opinion on Drug Safety, 17:12, 1185-1196, DOI: 10.1080/14740338.2018.1546841

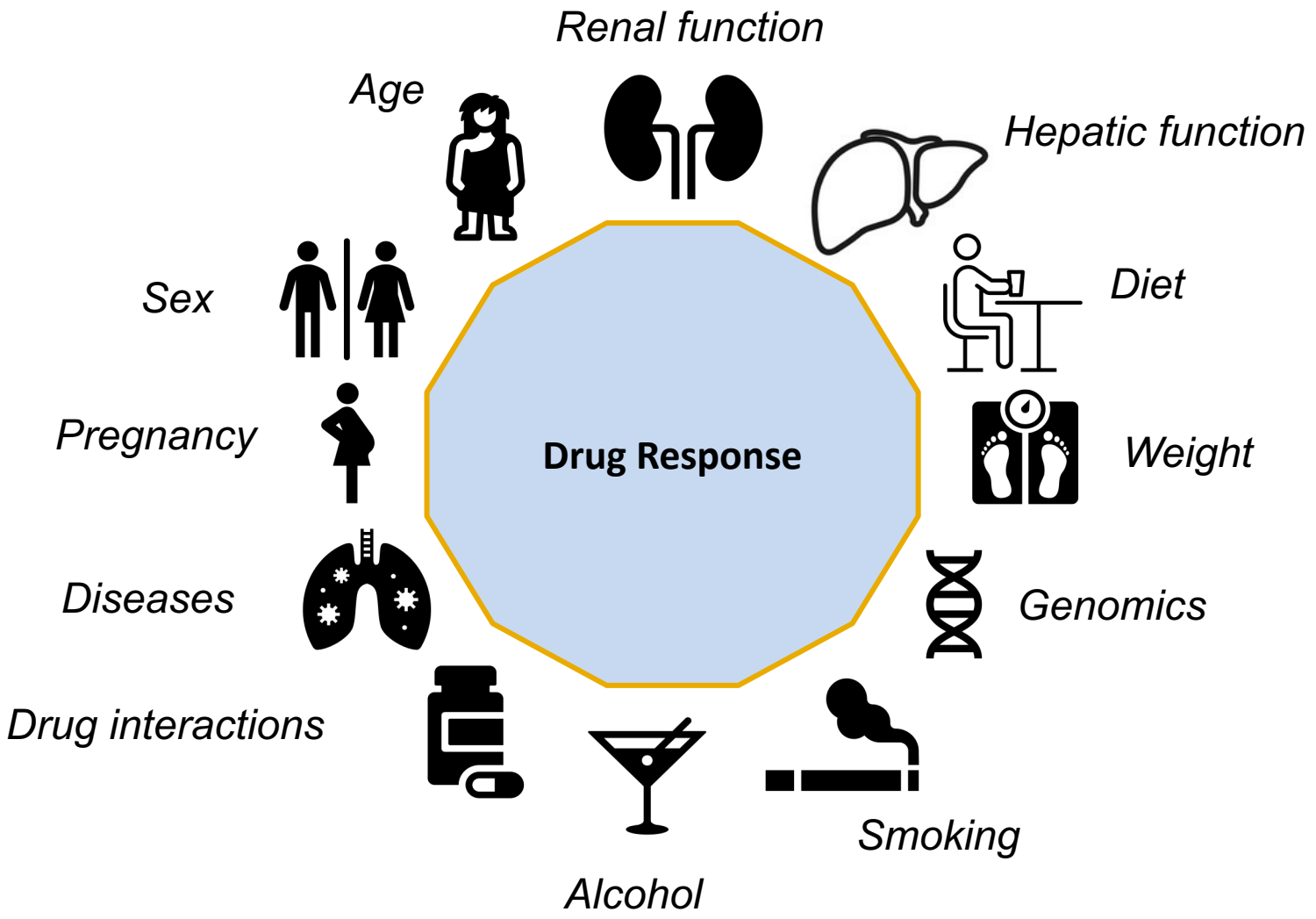
Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions

BMJ Open 2022;**12**:e055551

Rostam Osanlou ,[1,2] Lauren Walker,[1,2] Dyfrig A Hughes ,[3] Girvan Burnside,[4] Munir Pirmohamed [1,2]

- ADRs accounted for 16.5% of hospital admissions
- Those with ADRs take more medicines and have more co-morbidities
- Mortality rate 0.34%
- Length of stay 6 days
- Cost to NHS England £2.21 billion per annum

Variability in Drug Response



Definition

Current definition

- The study of variations of DNA and RNA characteristics as related to drug response

Broader definition

- The study of genomic technologies to enable the discovery and development of novel drugs, and the optimisation of drug dose and choice in individual patients to maximise efficacy and minimise toxicity

Friedrich Vogel

Pharmacogenomics: current status and future perspectives

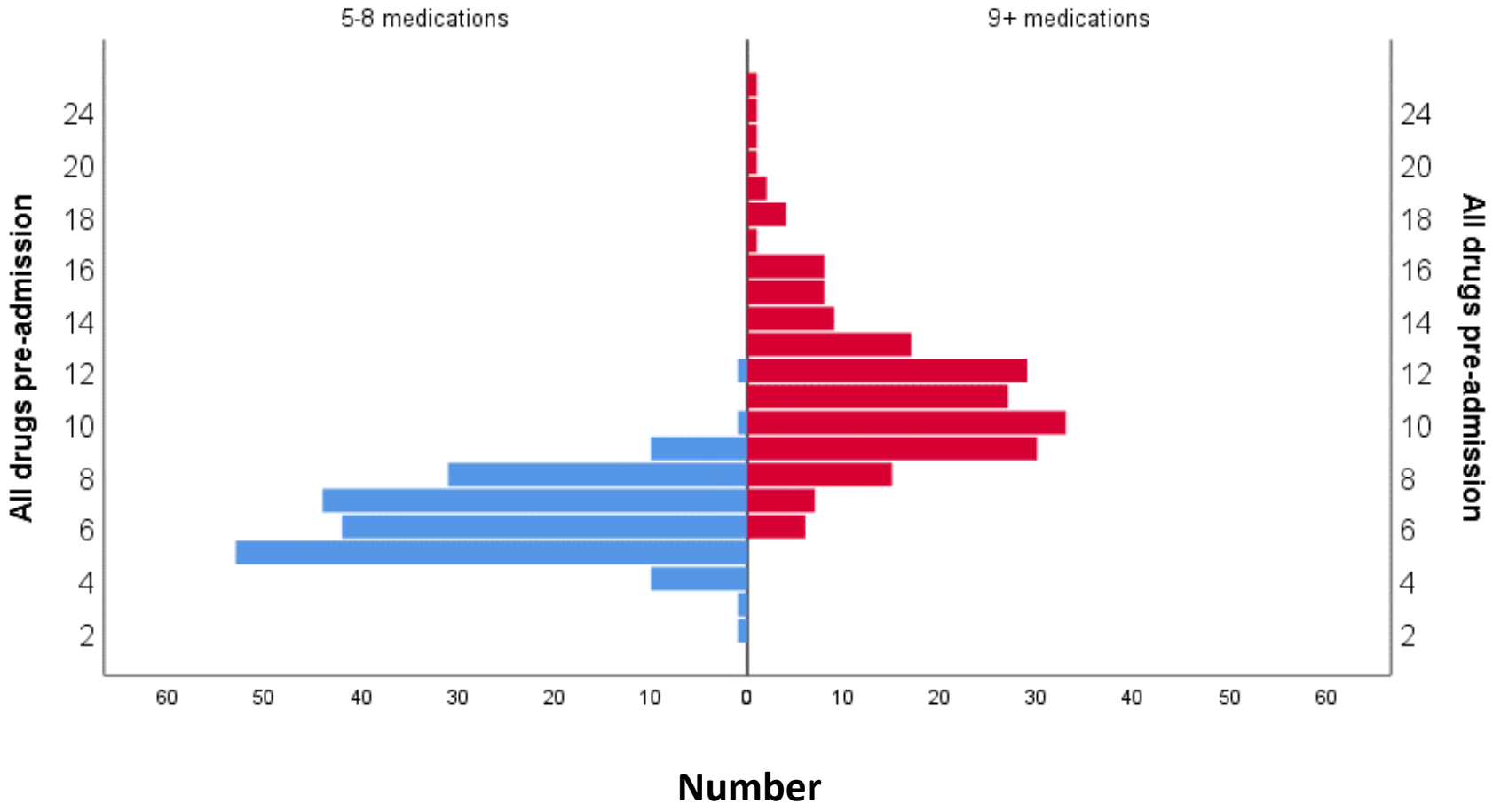
Munir Pirmohamed

https://doi.org/10.1038/s41576-022-00572-8

Pharmacogenomic Variation

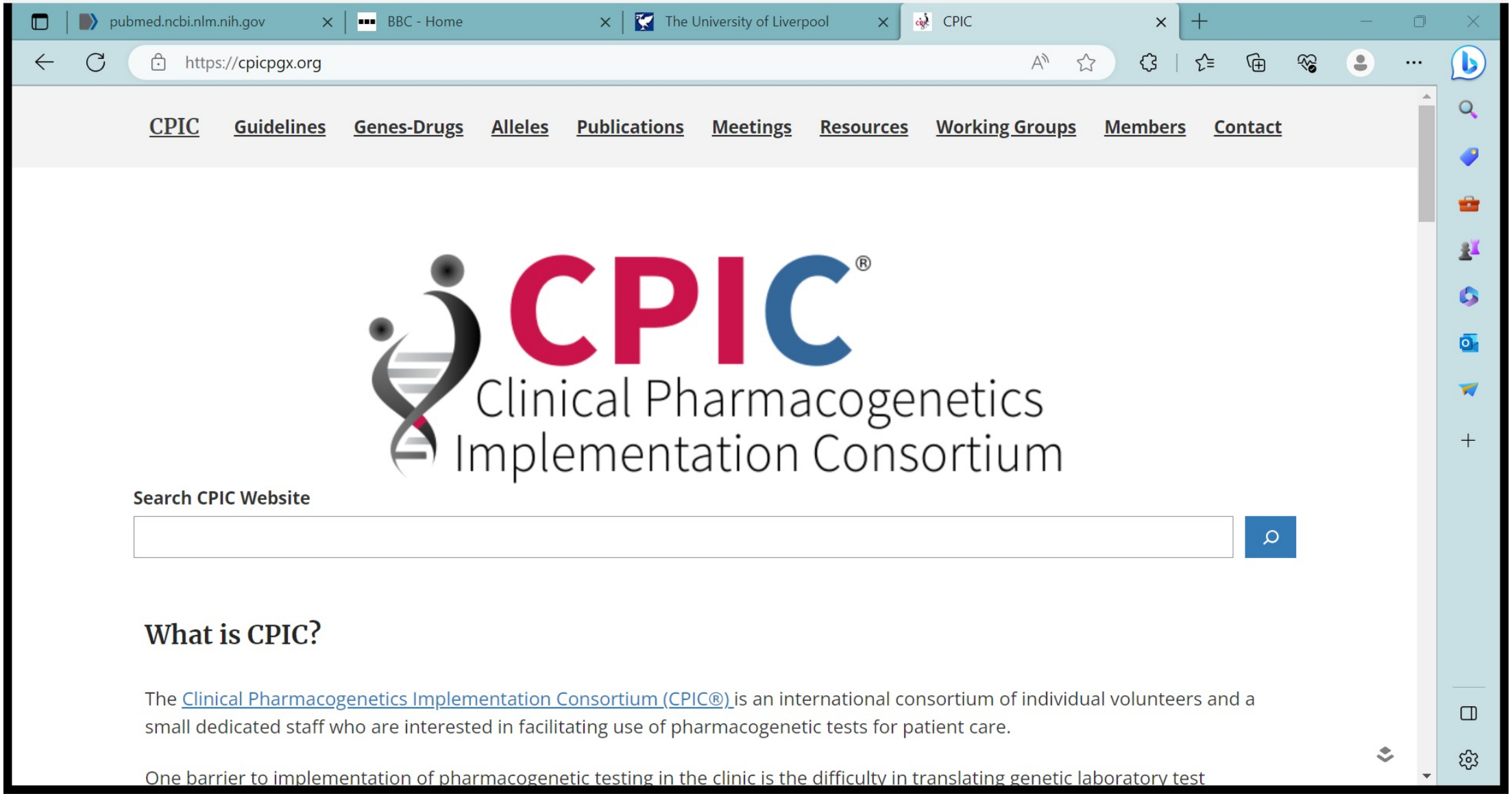
Country	Number studied	Proportion carrying at least one actionable genotype or diplotype	Reference
Australia	5408	95.9%	*J Neural Transm (Vienna)* **126**, 5-18 (2019)
Canada	98	96.9%	*NPJ Genom Med* **2**, 19 (2017)
Estonia	42092	99.8%	*Genet Med* **21**, 1345-1354 (2019)
Netherlands	498	99.4%	*Front Genet* **10**, 567 (2019)
Qatar	6045	99.5%	*NPJ Genom Med* **7**, 10 (2022)
UK	487,409	99.5%	*Clin Pharmacol Ther* **109**, 1528-1537 (2021)
UK	713	98.7%	*BMC Med* **18**, 367 (2020)
US	9,589	91.4%	*Clin Pharmacol Ther* **95**, 423-31 (2014)
US	1,013	99.0%	*J Mol Diagn* **18**, 438-445 (2016)

Polypharmacy Cohort (n=400)

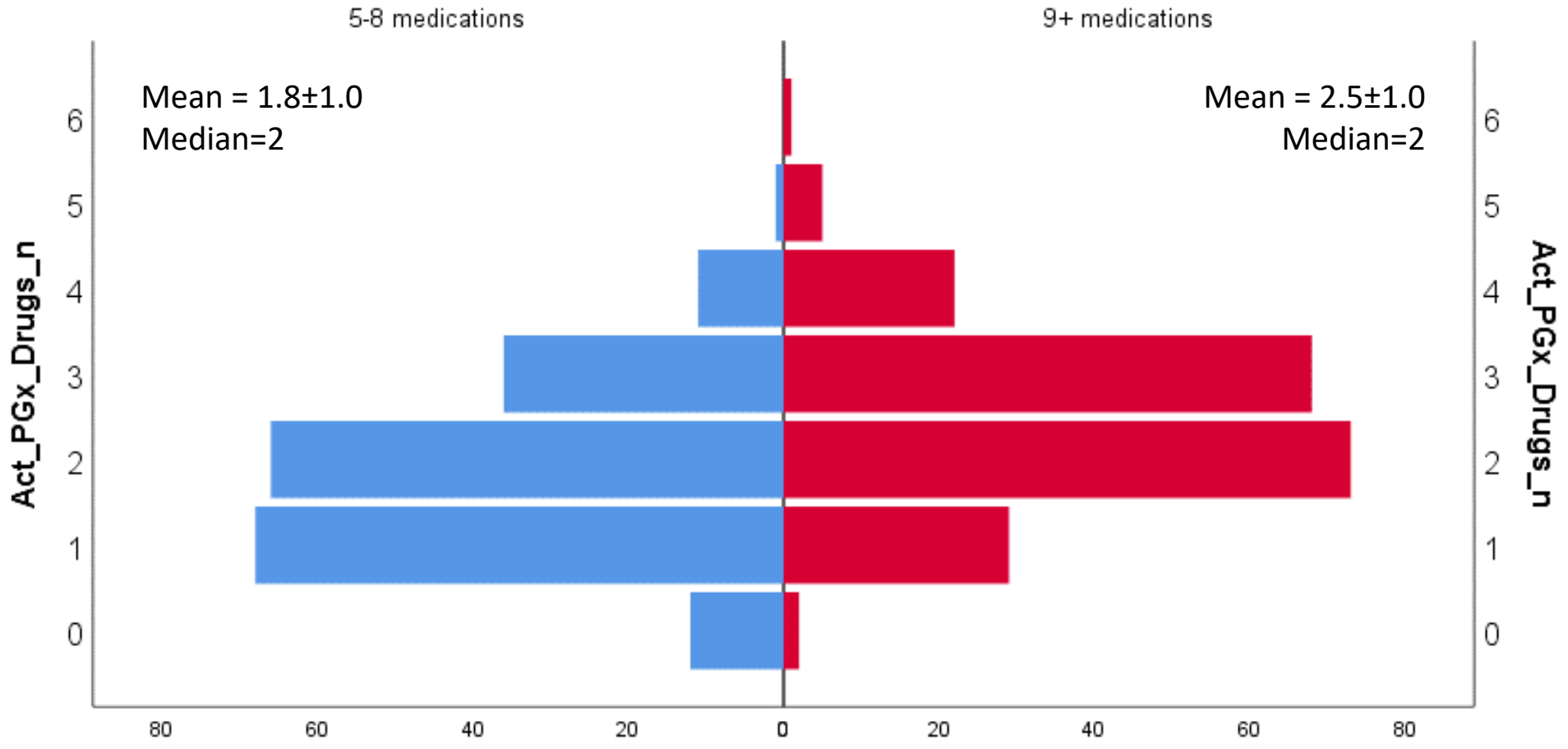


- Prospective cohort
- Admitted to hospital
- Followed up through EHR
- Unpublished preliminary data

Unpublished


pubmed.ncbi.nlm.nih.gov
BBC - Home
The University of Liverpool
CPIC
https://cpicpgx.org
CPIC
Guidelines
Genes-Drugs
Alleles
Publications
Meetings
Resources
Working Groups
Members
Contact
CPIC®
Clinical Pharmacogenetics Implementation Consortium
Search CPIC Website
What is CPIC?
The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.
One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test

Polypharmacy Cohort: Actionable PGx Drugs



Three Examples with Distinct Issues

1

Efficacy

- Clopidogrel

2

Dose

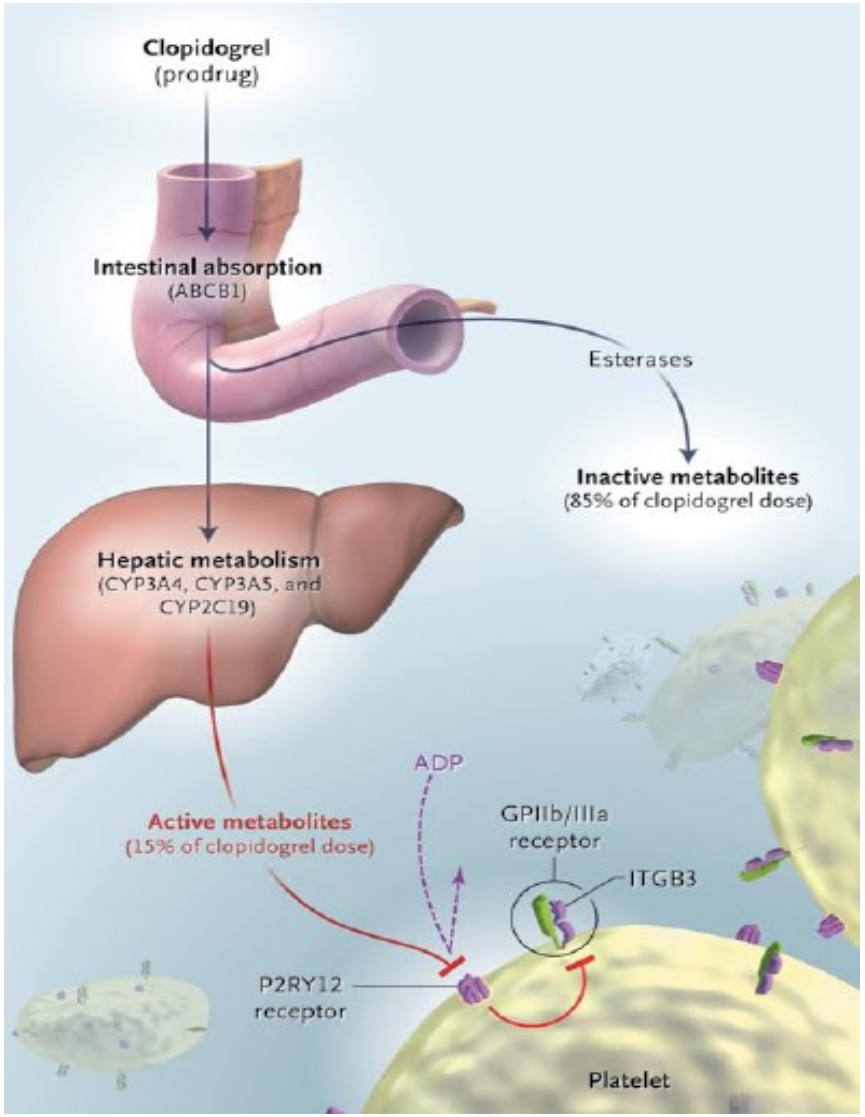
- Warfarin

3

Safety

- HLA alleles

Clopidogrel and CYP2C19

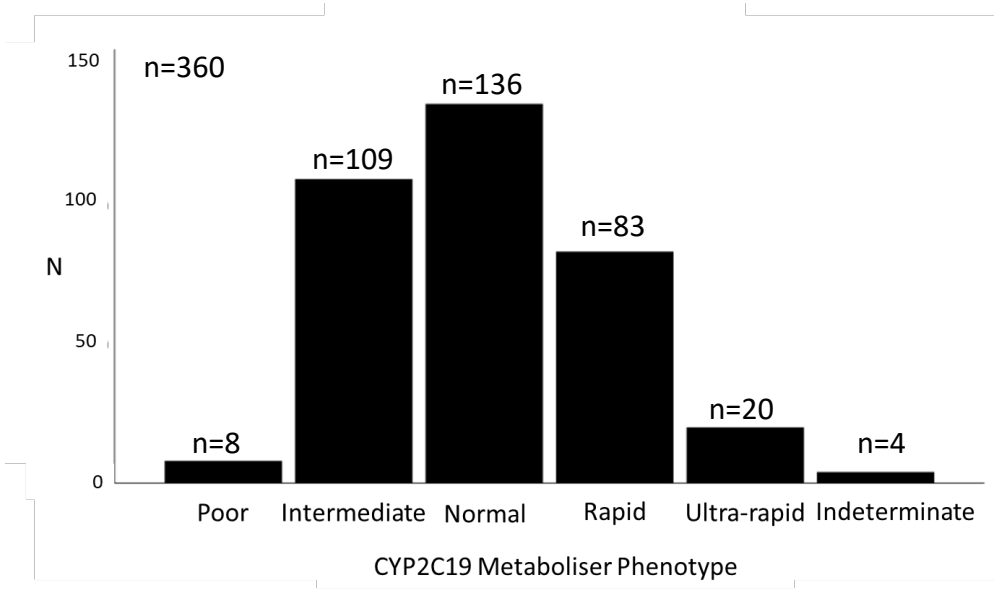


- Clopidogrel – pro-drug. Requires activation by CYP2C19
- Recent RCT data in coronary artery disease
- But still not in major guidelines (including AHA and ESC)

- Greater acceptance by stroke physicians and this is now the main area for implementation in the UK
- **Recent approval by NICE for stroke/TIA indication**

CYP2C19 Polymorphism Data

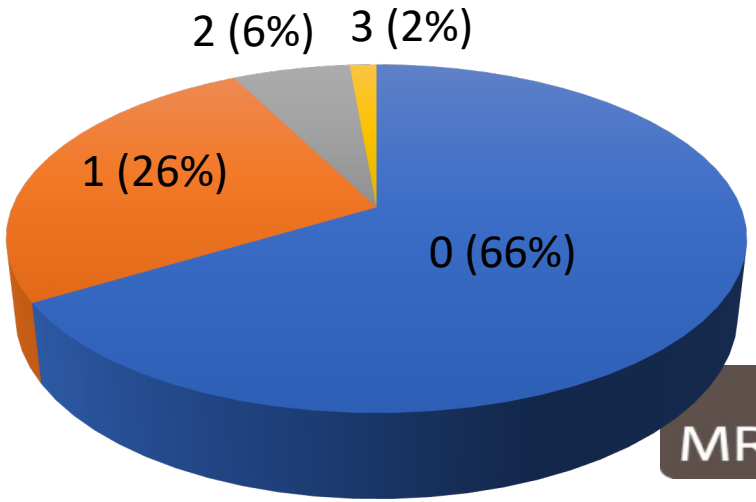
CYP2C19 Metaboliser Phenotype



Actionable *CYP2C19* Drug-gene pairs

Drug	Patients receiving	Drug-gene pairs (n)
Amitriptyline	44	15
Citalopram	31	19
Clomipromine	1	1
Clopidogrel	52	11
Escitalopram	2	2
Lansoprazole	141	51
Omeprazole	112	40
Pantoprazole	4	1
Sertraline	48	14
		154

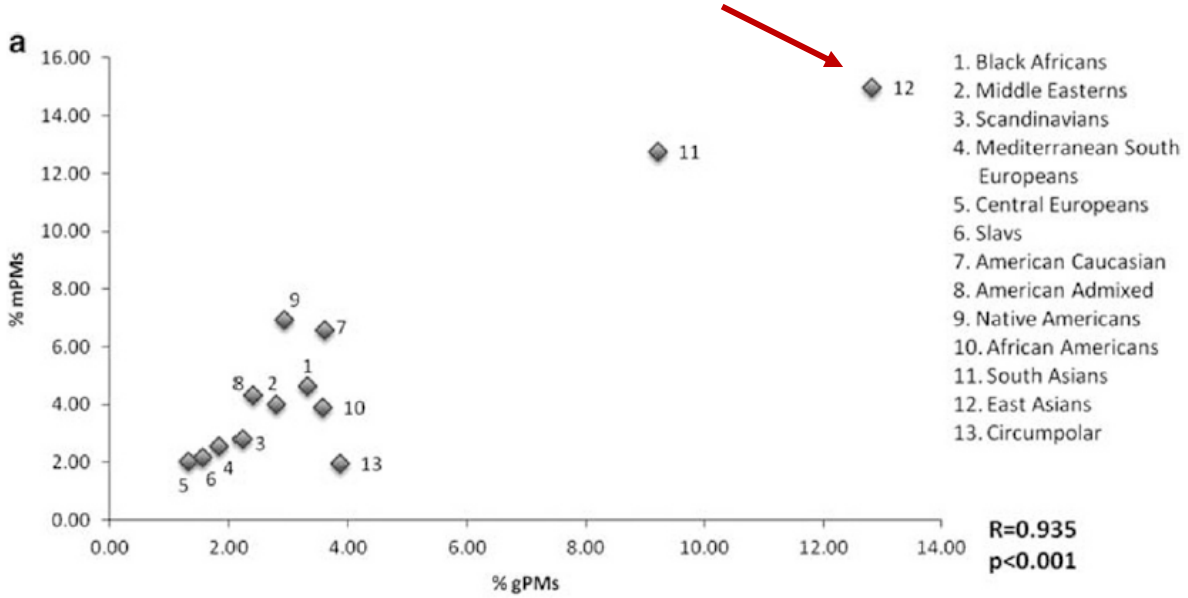
CYP2C19 Drug-gene pairs per patient

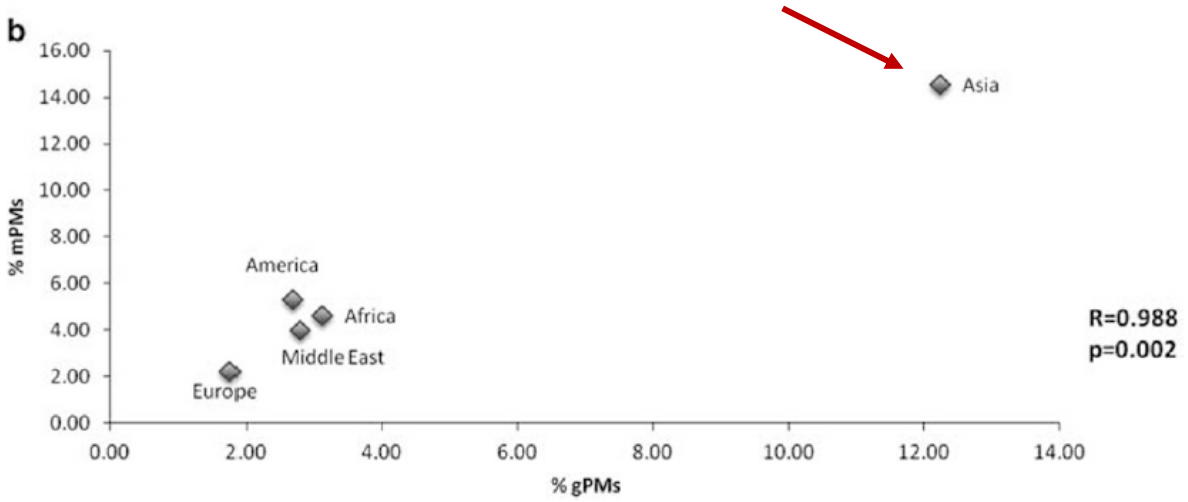


UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Cytochrome P450 2C19 (CYP2C19)





Interethnic variation of *CYP2C19* alleles, 'predicted' phenotypes and 'measured' metabolic phenotypes across world populations

I Fricke-Galindo[1,2], C Céspedes-Garro[1,3], F Rodrigues-Soares[1,4], MEG Naranjo[1], Á Delgado[1], F de Andrés[1], M López-López[5], E Peñas-Lledó[1] and A LLerena[1]

The Pharmacogenomics Journal (2016) 16, 113–123

- 202 substrates listed on DrugBank
- Important substrates
  - Clopidogrel
  - Citalopram
  - Voriconazole
  - Omeprazole
  - Phenytoin
  - Proguanil

MRC | Centre for Drug Safety Science

Unintended Consequences

(Reuters) - A judge in Hawaii on Monday ordered Bristol-Myers Squibb Co and Sanofi SA to pay more than $834 million to the state for failing to warn non-white patients properly of health risks from its blood thinner Plavix.

Article

https://doi.org/10.1038/s41467-023-37209-

Clinically important alterations in pharmacogene expression in histologically severe nonalcoholic fatty liver disease

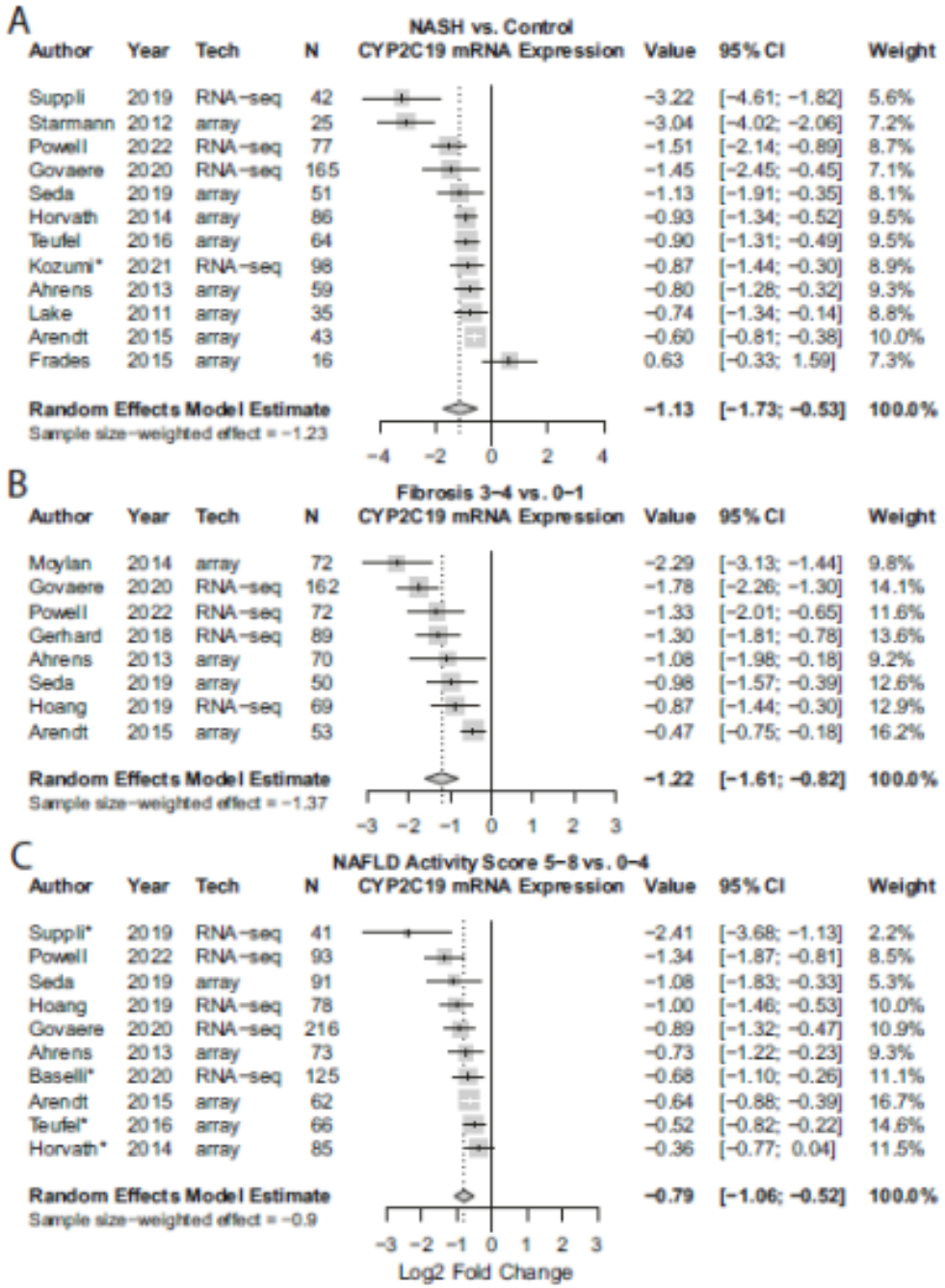
Received: 20 July 2022

Accepted: 7 March 2023

Published online: 17 March 2023

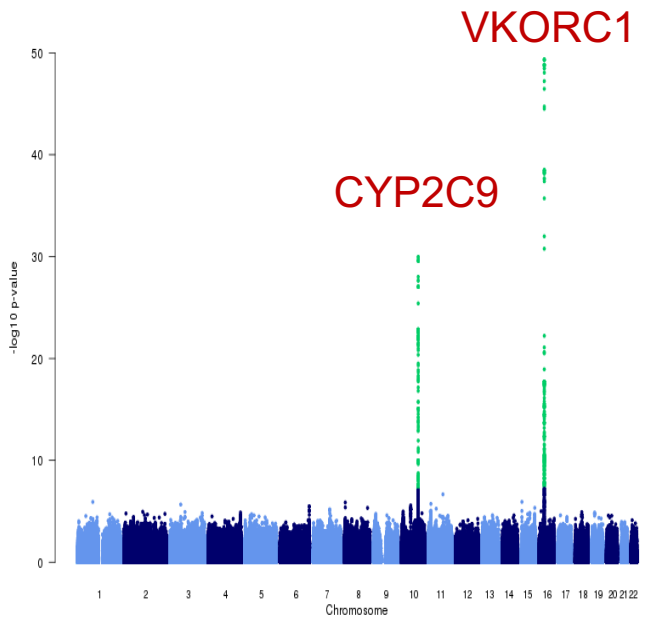
Nicholas R. Powell[1], Tiebing Liang[2], Joseph Ipe[1], Sha Cao[2], Todd C. Skaar, Zeruesenay Desta[1], Hui-Rong Qian[3], Philip J. Ebert[3], Yu Chen[3], Melissa K. Thomas[3] & Naga Chalasani[2]

- Decrease in CYP2C19 mRNA in different NAFLD phenotypes
- Confirmed by meta-analysis in 16 studies
- Decrease by 43-58% in CYP2C19 mRNA
- Equivalent to an intermediate metaboliser
- NAFLD patients shown previously to have reduced effect to clopidogrel
- NAFLD often excluded from trials



UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

Warfarin



DISCOVERY

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%

ALGORITHM (PRS)

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*

CLNICAL UTILITY

Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: a matched cohort study

Andrea L. Jorgensen[1*], Clare Prince[2], Gail Fitzgerald[2], Anita Hanson[2], Jennifer Downing[3,6], Julia Reynolds[4], J. Eunice Zhang[3], Ana Alfirevic[3] and Munir Pirmohamed[5]

IMPLEMENTATION

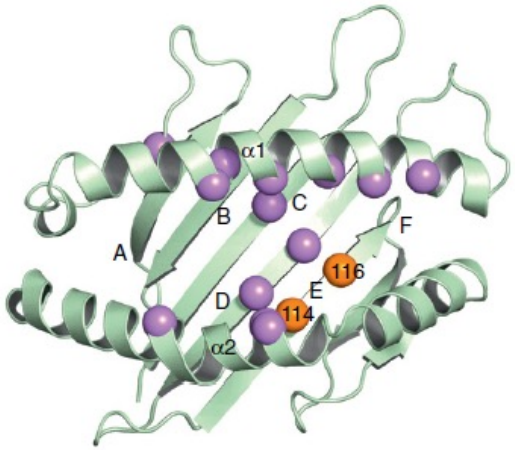
Difficulties in Implementing Warfarin Pharmacogenomics

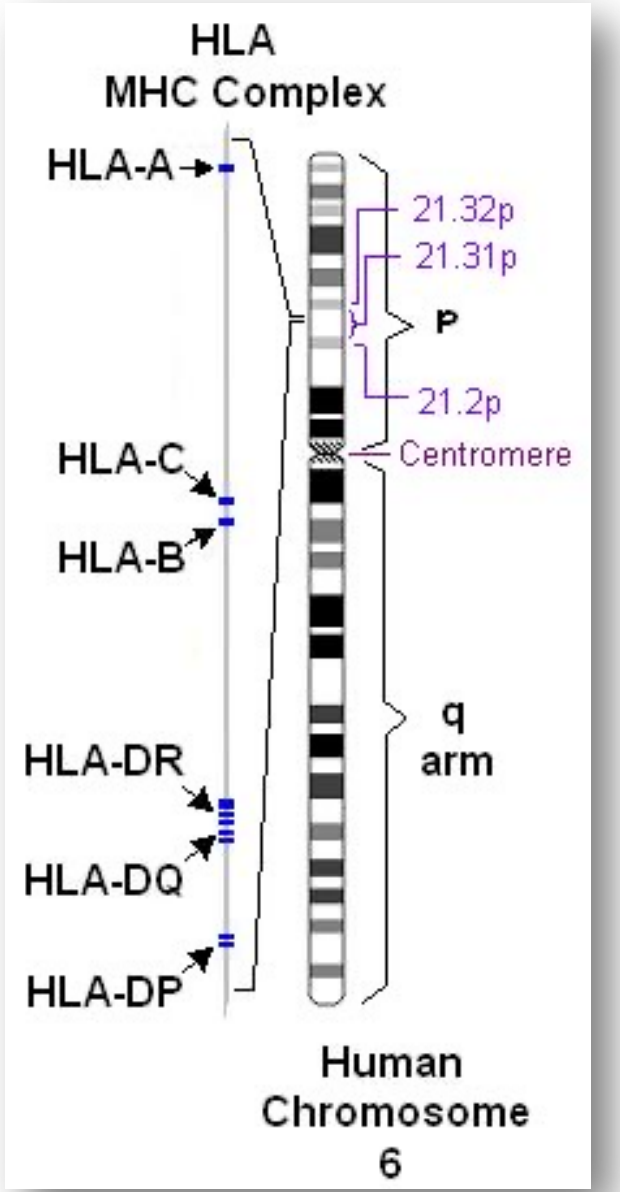
- Difficulties in changing clinician behaviour
- INR thought to be adequate
- EU-PACT vs COAG
- No recommendation in clinical guidelines
- Lack of availability of genotyping platforms
- Introduction of DOACs
- Pandemic hastening change in prescribing behaviour
- Lack of diversity in data

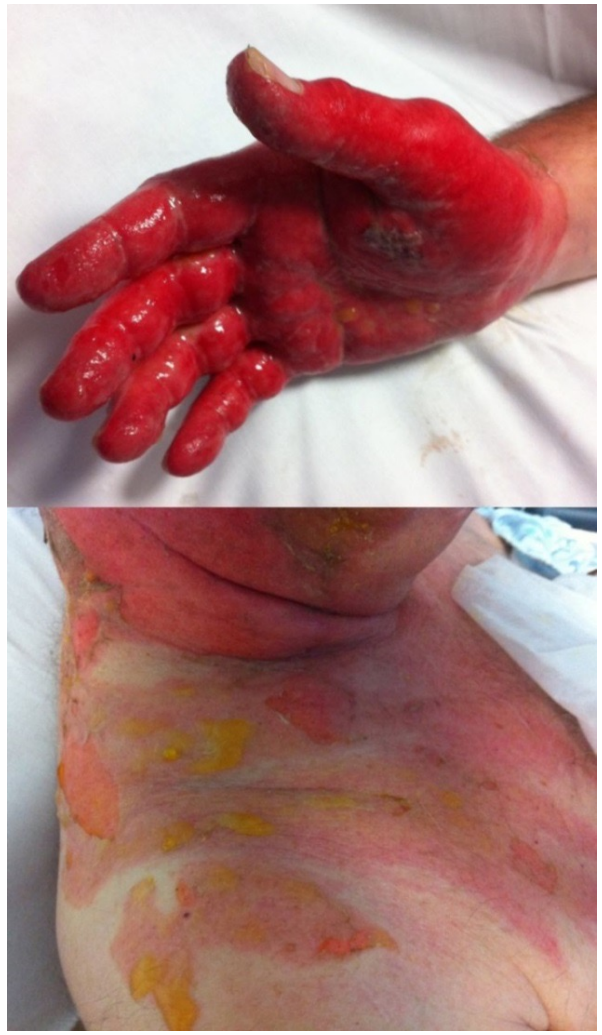
Human Leucocyte Antigens (HLA)

- On short arm of chromosome 6
- More than 200 genes
- Associated with more than 100 diseases
- Involved in the pathogenesis of immune-mediated adverse drug reactions

HLA-B*57:01 and Abacavir Hypersensitivity







UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

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

Carbamazepine Hypersensitivity

- Different phenotypes of carbamazepine hypersensitivity
  - Skin (mild → blistering)
  - Liver
  - Systemic (DRESS)
- HLA-B*15:02 – replication and cohort studies have shown utility in SE Asian patients
- HLA-A*31:01 – replication and cohort studies have shown utility in several different ethnic groups worldwide

Clinical Pharmacogenetics Implementation Consortium Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

Elizabeth J. Phillips[1], Chonlaphat Sukasem[2,3], Michelle Whirl-Carrillo[4], Daniel J. Müller[5,6], Henry M. Dunnenberger[7], Wasun Chantratita[8,9], Barry Goldspiel[10], Yuan-Tsong Chen[11,12], Bruce C. Carleton[13], Alfred L. George Jr.[14], Taisei Mushiroda[15], Teri Klein[4], Roseann S. Gammal[16,17] and Munir Pirmohamed[18]

Difficulties in Implementation

Study 1 (Chen et al[120])

- Based in Hong Kong
- Government paid for testing
- Physicians switched to other antiepileptic drugs instead of undertaking genetic testing
- The overall incidence of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) did not change, although carbamazepine-induced SJS/TEN decreased

Study 2 (Lin et al[121])

- Based in Taiwan
- Nationwide screening introduced
- Incidence of carbamazepine-induced SJS/TEN decreased by 87% over 10 years but the use of carbamazepine also decreased by 83%
- Only 25% of new carbamazepine users were screened for *HLA-B*15:02*

Study 3 (Sung et al[122])

- Based in Singapore
- Genotyping introduced 2013 with a 75% subsidy
- Phenytoin not recommended as a substitute
- Led to a 92% reduction in carbamazepine-induced SJS/TEN
- Number of new carbamazepine users decreased by one-third

Taken from Immunol Allergy Clin N Am: https://doi.org/10.1016/j.iac.2022.01.006

Reducing severe cutaneous adverse and type B adverse drug reactions using pre-stored human leukocyte antigen genotypes

Clin Transl Allergy. 2022;e12098.
https://doi.org/10.1002/clt2.12098

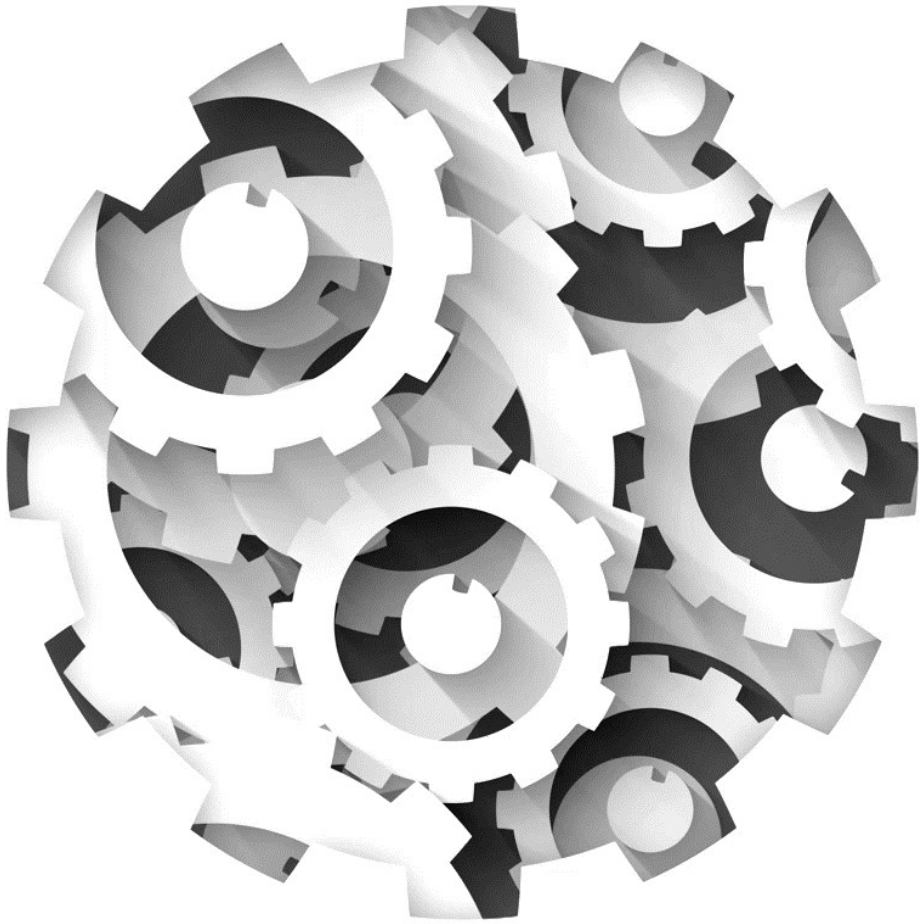
Kye Hwa Lee[1] | Dong Yoon Kang[2] | Hyun Hwa Kim[2] | Yi Jun Kim[3] | Hyo Jung Kim[4] | Ju Han Kim[5] | Eun Young Song[6] | James Yun[7,8] | Hye-Ryun Kang[2,9]

- Use of pre-stored HLA information from transplant recipients
- *HLA-B*57:01*, *HLA-B*58:01*, *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*13:01*, *HLA-B*59:01*, and *HLA-A*32:01*
- 11,988 HLA-tested transplant recipients
  - 4092 (34.1%) had high risk alleles
  - 4538 (38.2%) were prescribed risk drugs
  - 580 (4.8%) experienced type B ADRs
- Availability of pre-emptive HLA information has the potential to prevent serious hypersensitivity reactions

HLA Allele Panel

- Able to genotype for multiple HLA alleles
- Move from reactive to pre-emptive
- Cheaper than single locus testing
- Cost dominant in health economic analysis
- Turnaround time ~48 hours
- Dynamic – change alleles as required

Implementation

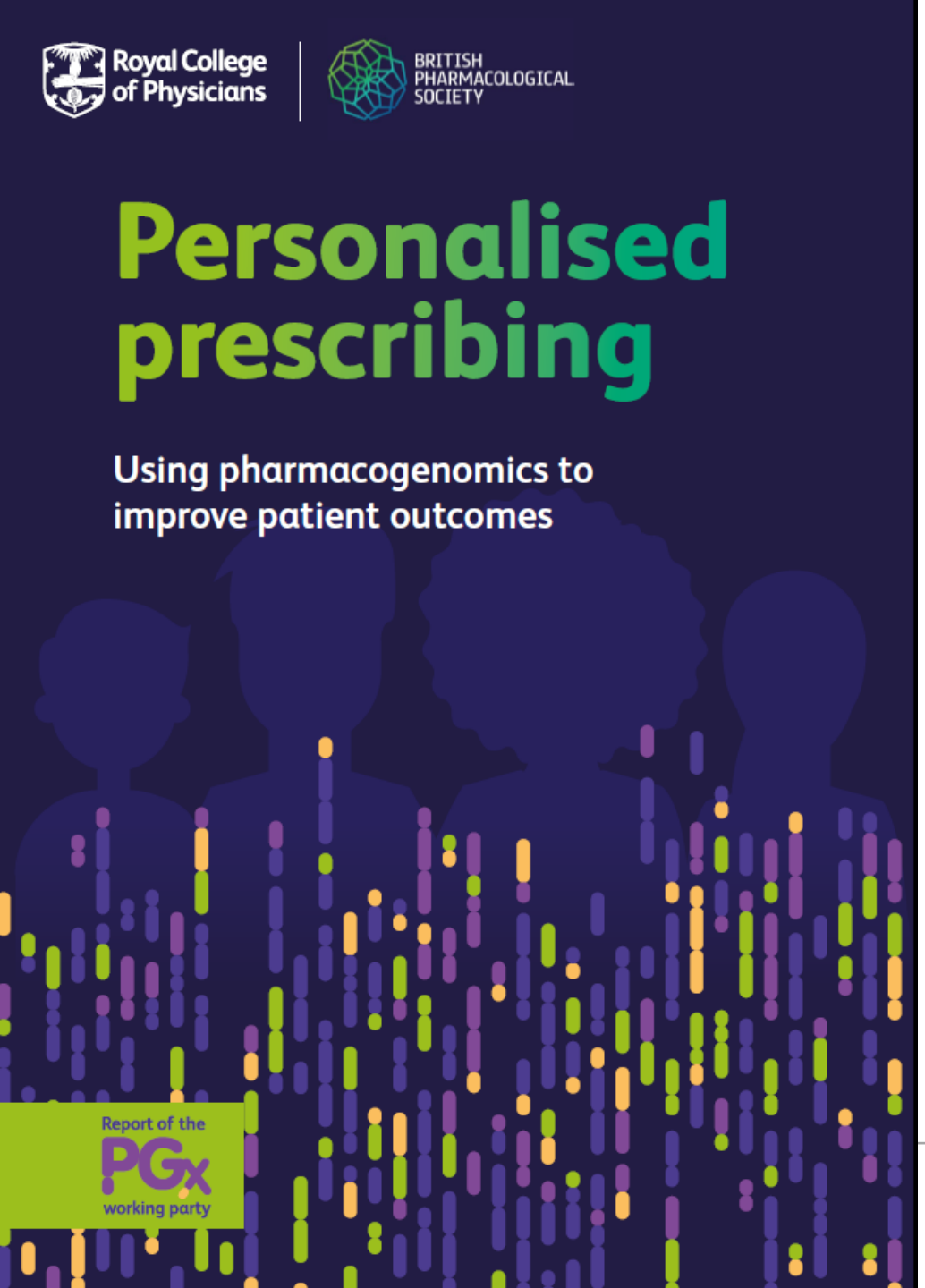


Characterizing pharmacogenetic programs using the consolidated framework for implementation research: A structured scoping review

John H. McDermott[1,2]*, Stuart Wright[3], Videha Sharma[4], William G. Newman[1,2], Katherine Payne[3] and Paul Wilson[5]

Front. Med. 9:945352.
doi: 10.3389/fmed.2022.945352

104 manuscripts → 40 distinct programmes → 95% high income countries → 66% were in the USA



Report published by Royal College of Physicians and the British Pharmacological Society

shorturl.at/bBGSZ

Recommendations

Implementation in all sectors and centrally funded

Agile (respond to advances) and continually evaluated

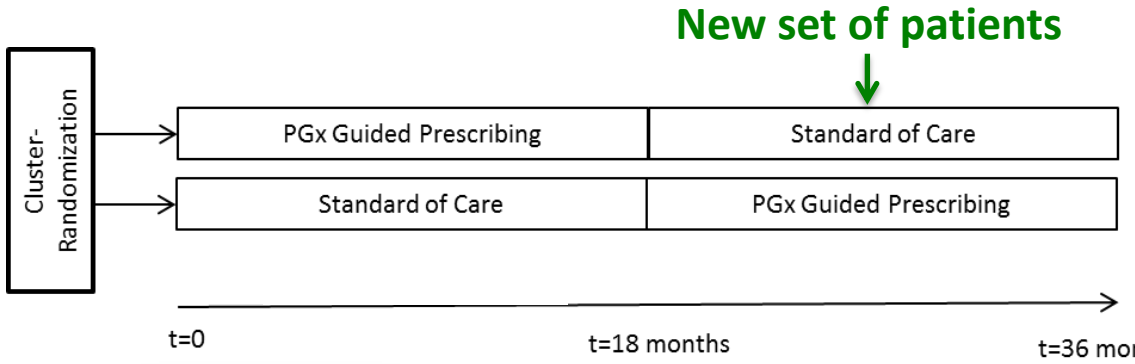
Comprehensive education and training package

Support for clinicians

Further research funding still needed

Clear lines of communication

*PRE*emptive *P*harmacogenomic testing for preventing *A*dverse drug *Re*actions (PREPARE)



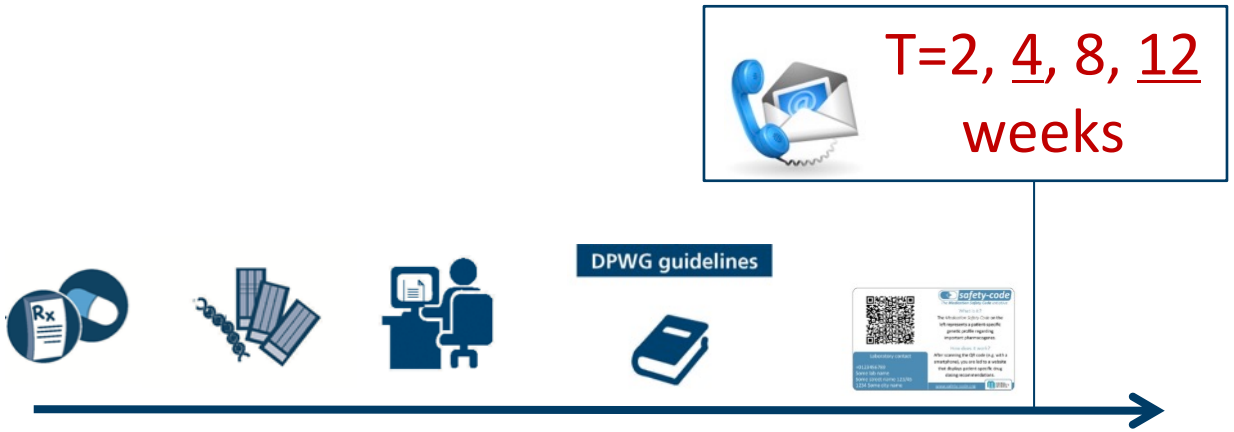
Spain, Greece, Slovenia

Netherlands, UK, Austria, Italy

NCT03093818

Each site has its own therapeutic focus

Patient Journey Study Arm



eCRF: ProMise

Research Nurse Follow-up

Baseline (± 1 week)*
4 weeks (± 1 week) *
12 weeks (± 1 week)*
End of Study (± 4 weeks)

*For every newly prescribed drug of interest

LIM

Online Survey Follow-up

2 weeks*
8 weeks*

*For every newly prescribed drug of interest

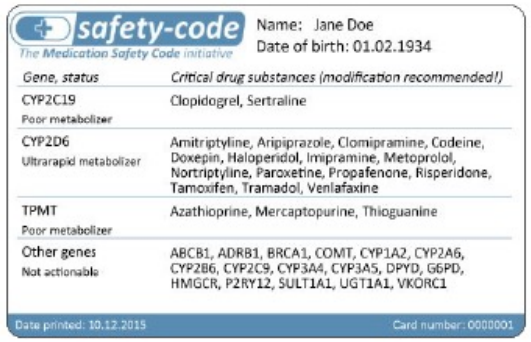
Ubiquitous Pharmacogenomics

Genotyping platform

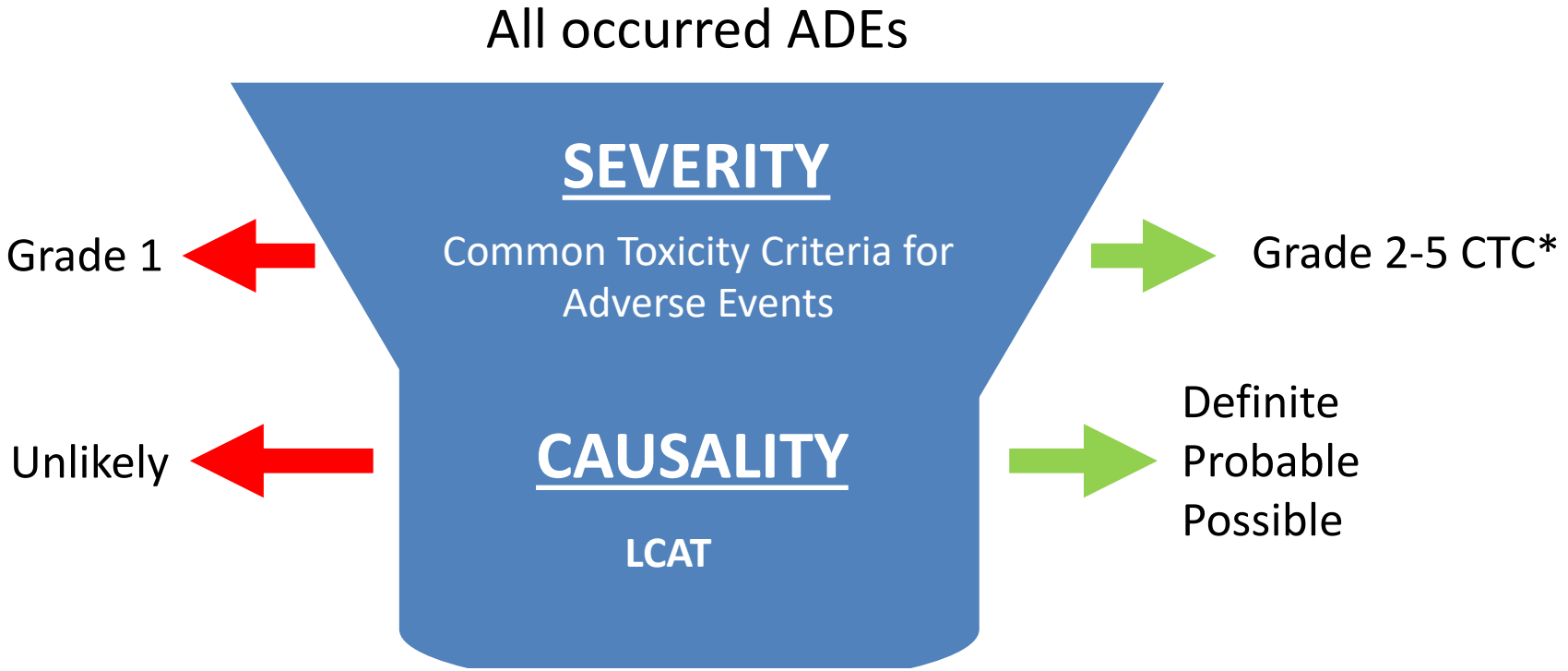
- 12 genes (including CYP2D6 and SLCO1B1)
- 44 variants
- 39 drugs

Pharmacogenomic Card

Scan QR code



Primary endpoint



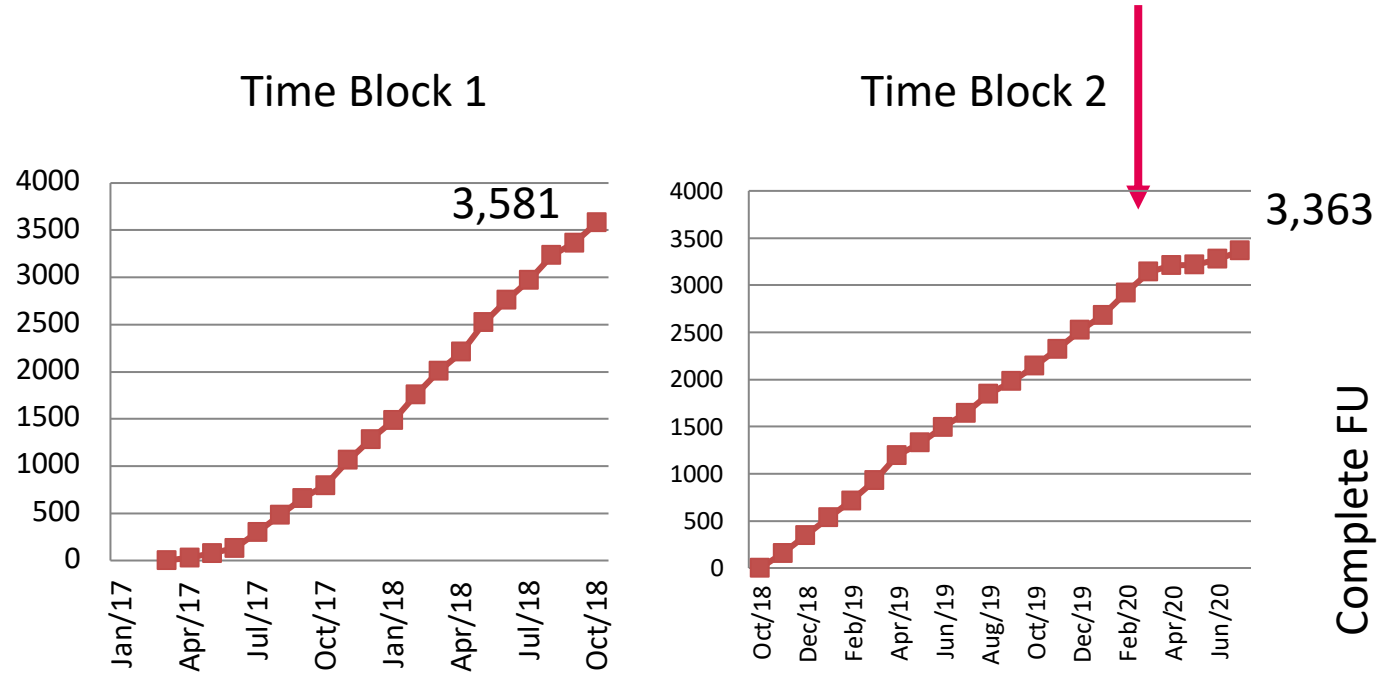
Clinically relevant ADRs, caused by the index drug

*For oncology patients only hematological toxicities of grade 4-5 and non-hematological toxicities of grade 3-5 will be considered clinically relevant

Timeline

Total: 6,944 patients

Feb 2020 Covid



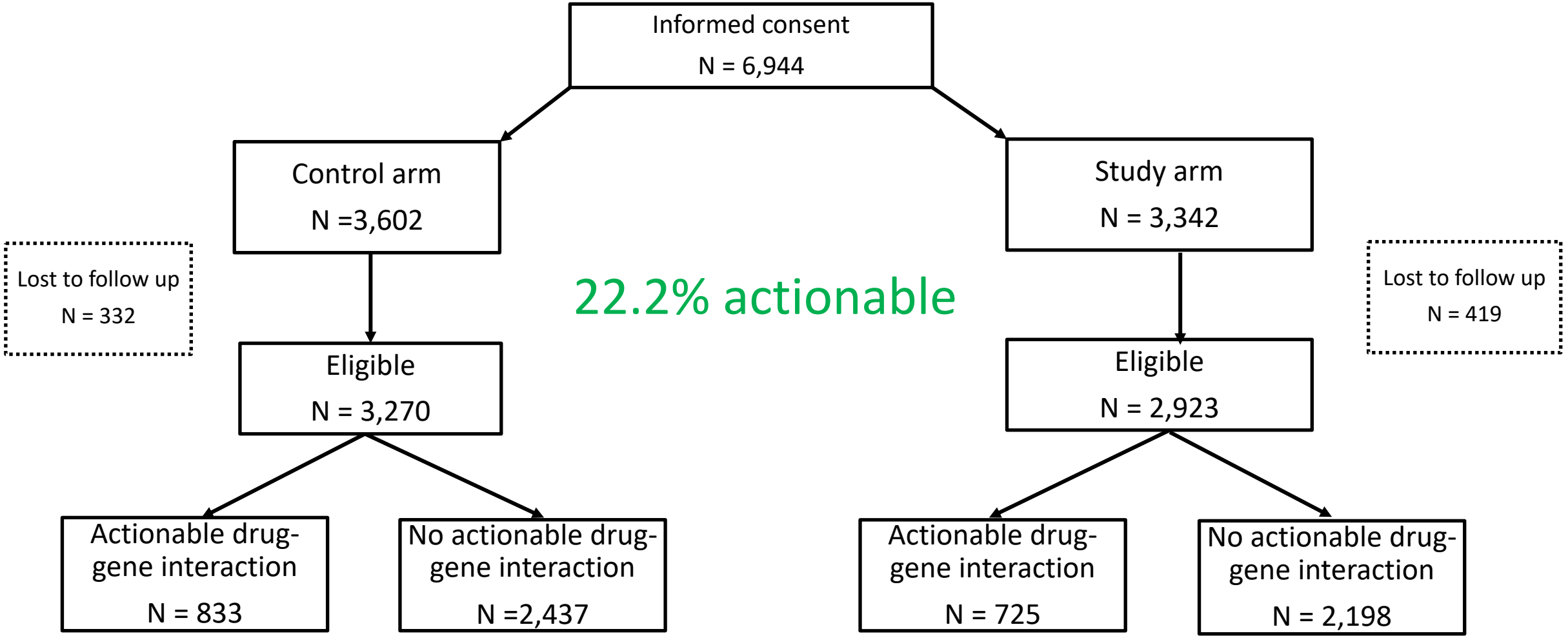
- Data Cleaning
- Severity + Causality Assessments
- Genotyping controls
- Drug-Genotype assessment
- LAREB re-assessments
- Preparation of analyses

Jan 1 2016 | Mar 7 2017 | Oct 1 2018 | Jun 30 2020 | Sep 2020 | Now

CRO AVIANO

cross-over

Patient flow



A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Lancet 2023; 401: 347–56

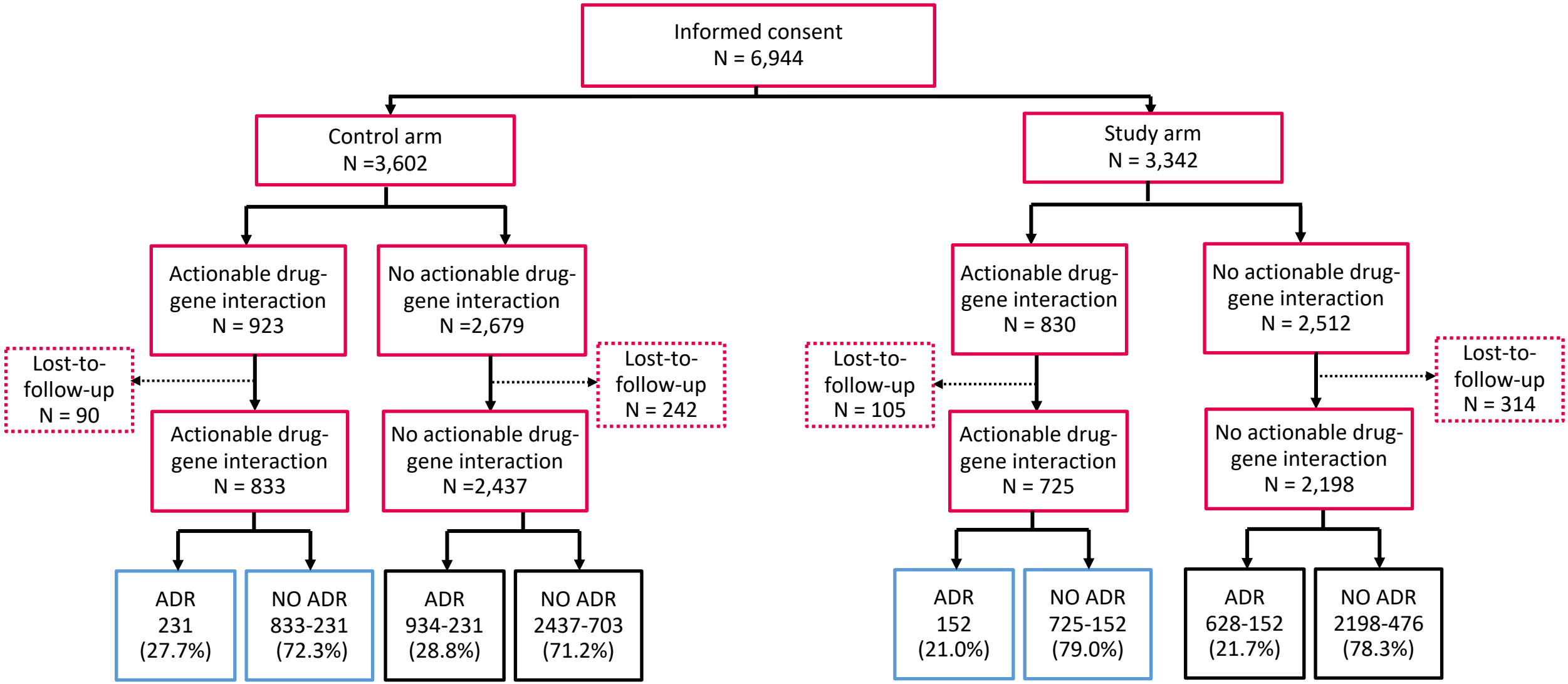
Jesse J Swen, Cathelijne H van der Wouden*, Lisanne EN Manson*, Heshu Abdullah-Koolmees, Kathrin Blagec, Tanja Blagus, Stefan Böhringer, Anne Cambon-Thomsen, Erika Cecchin, Ka-Chun Cheung, Vera HM Deneer, Mathilde Dupui, Magnus Ingelman-Sundberg, Siv Jonsson, Candace Joefield-Roka, Katja S Just, Mats O Karlsson, Lidija Konta, Rudolf Koopmann, Marjolein Kriek, Thorsten Lehr, Christina Mitropoulou, Emmanuelle Rial-Sebbag, Victoria Rollinson, Rossana Roncato, Matthias Samwald, Elke Schaeffeler, Maria Skokou, Matthias Schwab, Daniela Steinberger, Julia C Stingl, Roman Tremmel, Richard M Turner, Mandy H van Rhenen, Cristina L Dávila Fajardo, Vita Dolžan, George P Patrinos, Munir Pirmohamed, Gere Sunder-Plassmann, Giuseppe Toffoli, Henk-Jan Guchelaar, on behalf of the Ubiquitous Pharmacogenomics Consortium†

Primary analysis in patients with an actionable test result:

- clinically relevant adverse drug reaction occurred in 152 (**21·0%**) of 725 patients in the study group and 231 (**27·7%**) of 833 patients in the control group
- Odds ratio of **0.70** (95% CI 0.54-0.91); P=0.0075)

30% reduction in adverse drug reactions

Gatekeeping Analysis

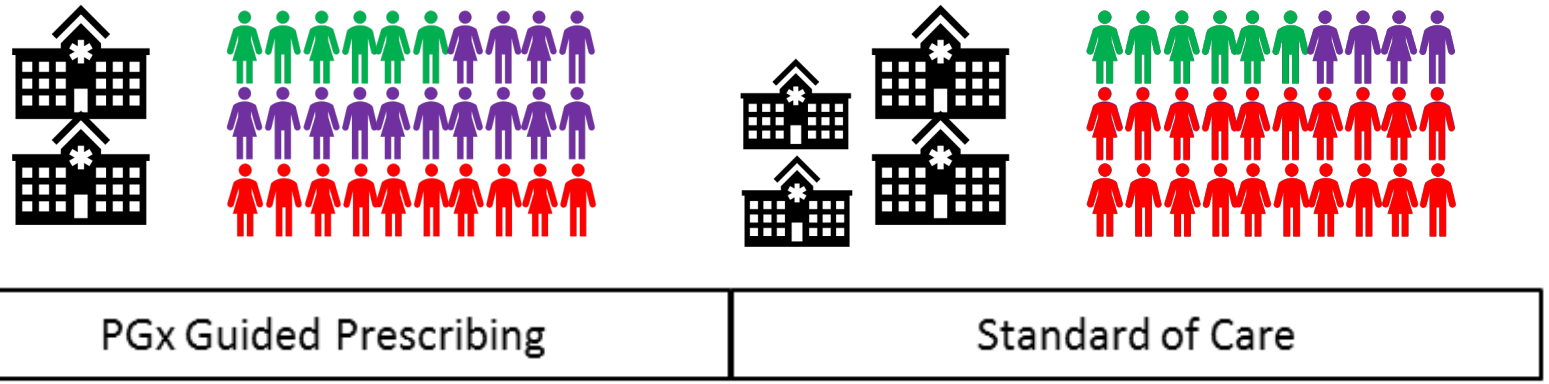


Confounding Effect of Case-Mix

Low toxicity profile

High toxicity profile

Real-world design: addition of centers and changes in drugs and guidelines

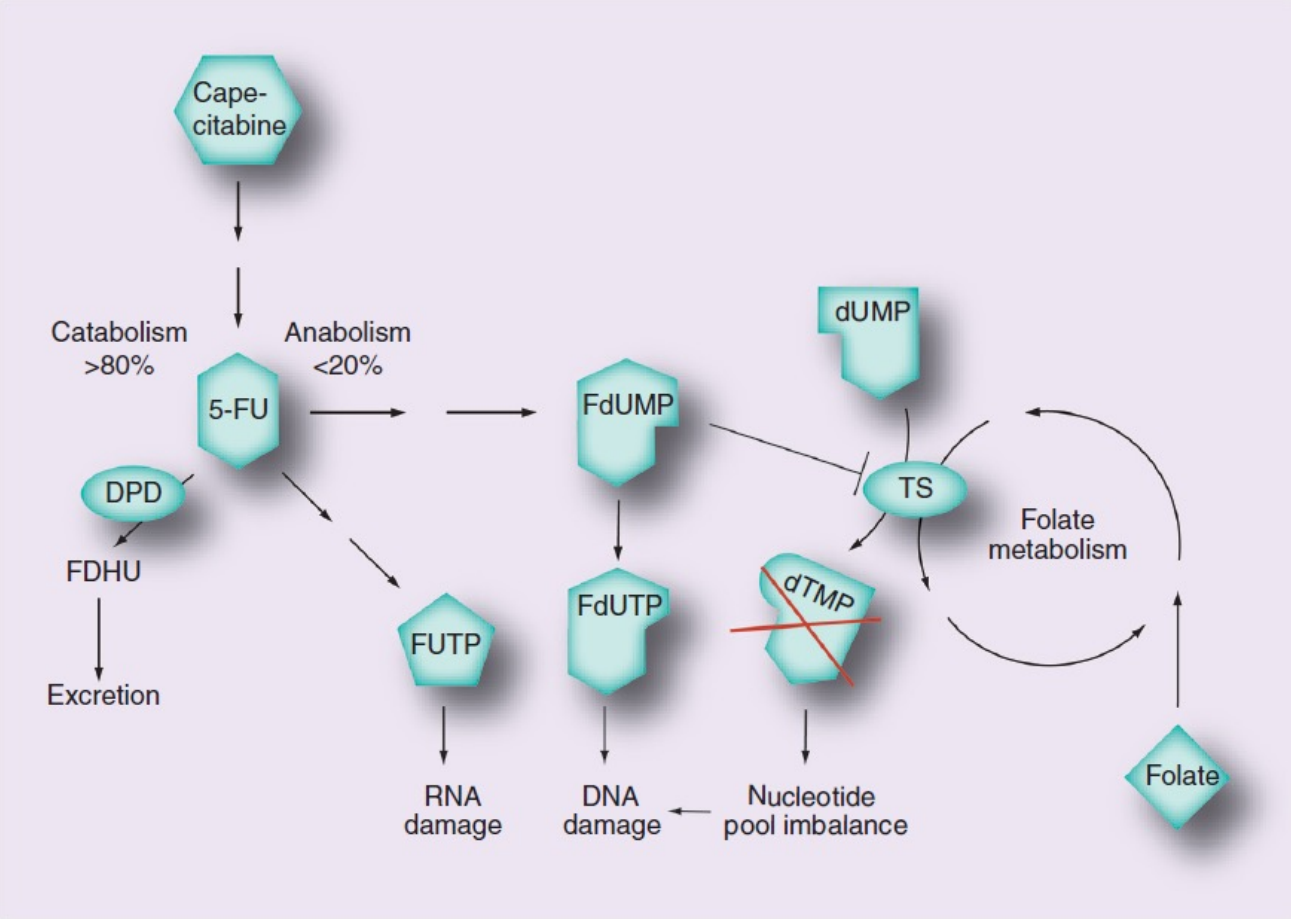


- Post-hoc analysis including index drug and an index drug-by-country interactions:
  - Effect **decreases** from 0.30 to 0.13 (OR 0.87 95CI 0.70-1.12) **in all patients**
  - Effect **increases** from 0.30 to 0.39 (OR 0.61 95CI 0.51-0.74) **in actionables**
- Changes in drugs and centers (case-mix) main contributor to effect seen on gatekeeping analysis
- Effect of genotype panel still evident after correction for case mix

Reflections

- Large effect size because the panel contained well characterised drug-gene associations
- Efficacy unlikely to be impacted as guidelines based on effect of polymorphisms on drug exposure
- 70% of prescribers adopted the recommendations, 30% did not
- Test results available within 7 days, and so some patients initiated on original drugs may already have had the ADR before test result available
- We accepted grade 2-5 ADRs. Mild and moderate ADRs are important because they affect patient quality of life and impact adherence

5-Fluorouracil

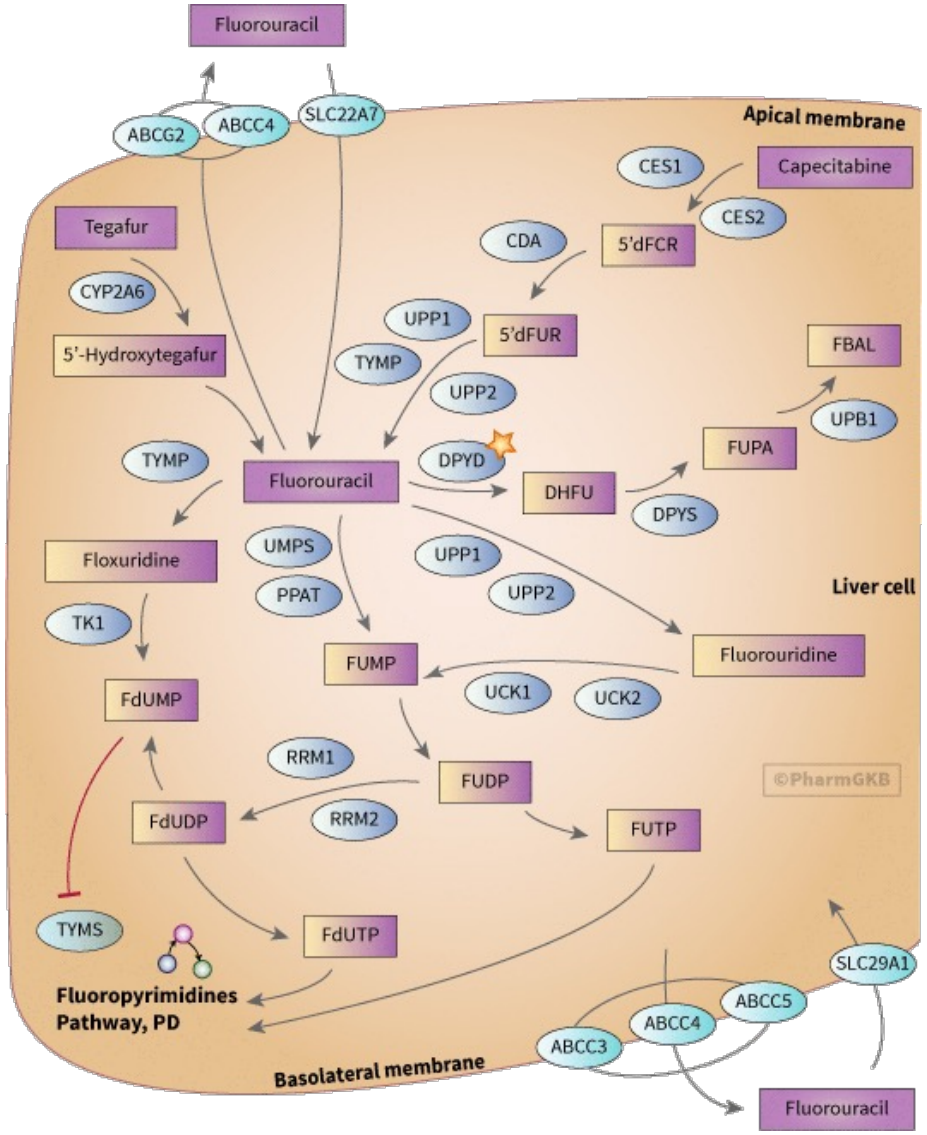


- Toxicity: haematological, GI and skin
- Used in 30% of chemotherapy regimens

- Dihydropyrimidine dehydrogenase (DPYD) the important catabolic pathway
- Subject to polymorphisms which vary with ethnicity

Other drugs metabolised by DPD:
Capecitabine, tegafur, 5-flucytosine

Dihydropyrimidine Dehydrogenase Polymorphisms



Variant	Frequency (%)
DPYD∗2; rs3918290	0.65
DPYD∗13; rs55886062	0.03
HapB3; rs75017182 + rs56038477	1.3
D949V; rs67376798	0.32

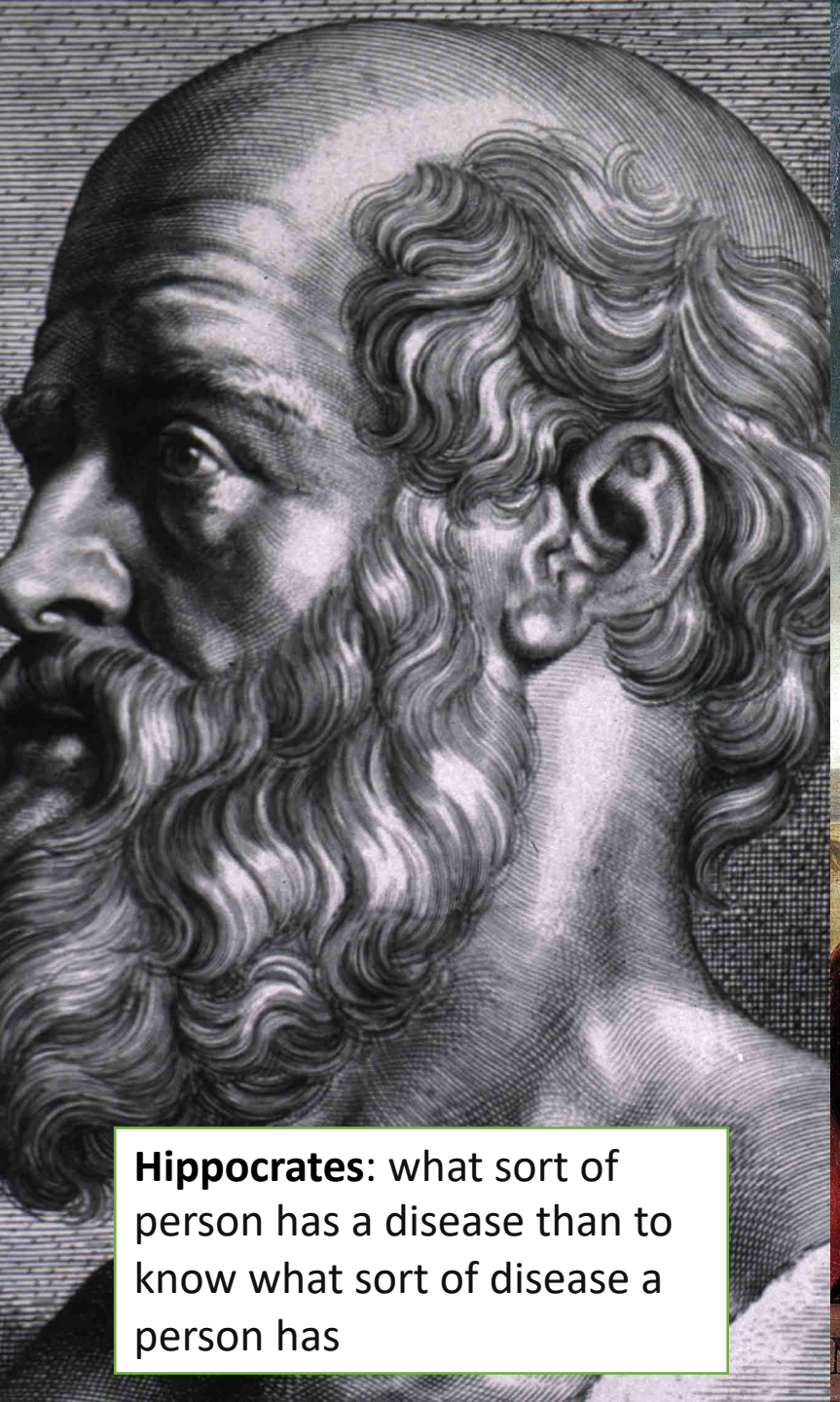
- 4 polymorphisms tested
- In the UK, 38,000 tests per year
- Derived from European populations
- Non-European ancestry inevitably labelled as wild type

DPYD International Study

- International study with the aim to recruit patients who have had Grade 3, 4, or 5 toxicity from the use of 5FU or its analogues
- Focusing on non-Northern European ancestry populations
- Sequence based analysis of DPYD
- Assessment of functionality of the identified mutations
- In the UK, provide evidence to increase the variants tested to reduce race inequalities
- Of value to other countries as they introduce or expand DPYD testing now or in the future
- If anybody interested in collaborating on this, then please contact me (munirp@liverpool.ac.uk)

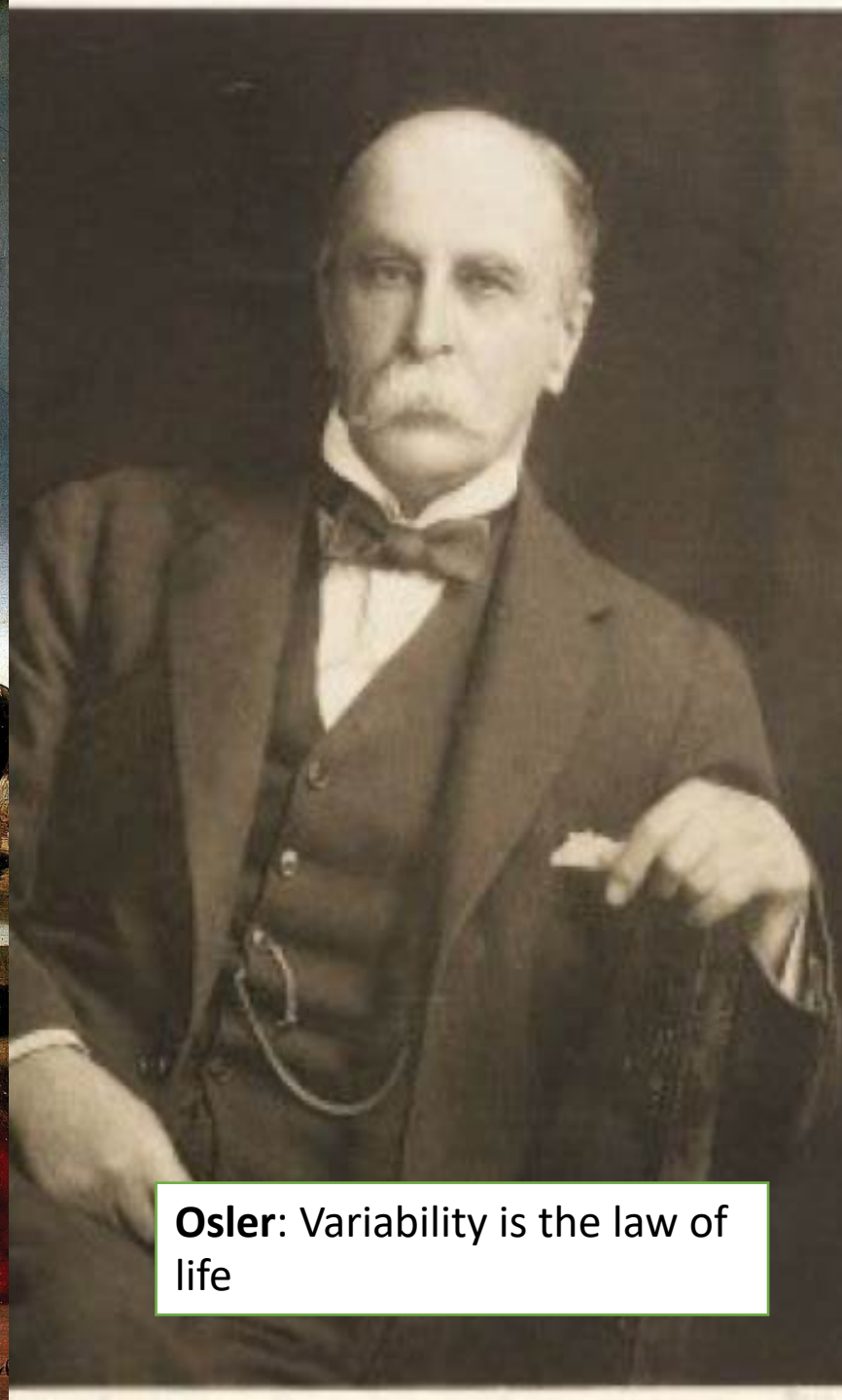
Pre-emptive Pharmacogenomics

- More efficient than reactive, and fits in better with existing clinical pathways
- When?
  - When first prescribed a medicine with PGx guidance
  - At a certain age, e.g. above 50
  - Newborn genome sequencing
- How do we assess utility over the long-term?

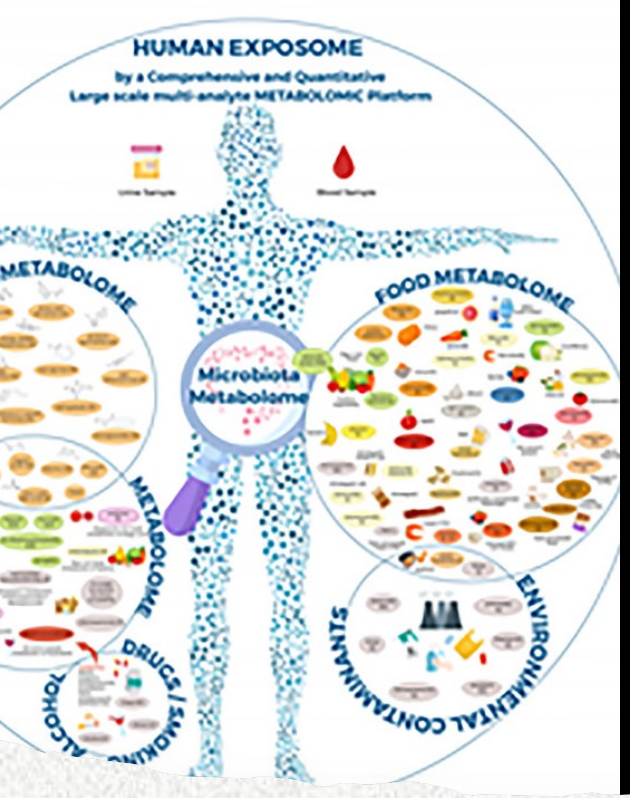


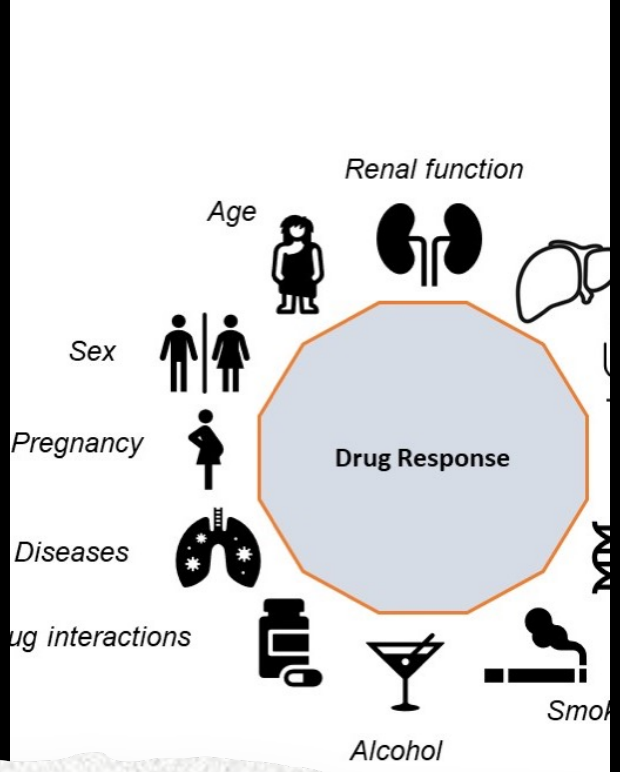
Hippocrates: what sort of person has a disease than to know what sort of disease a person has

Paracelsus: The dose is either the remedy or poison

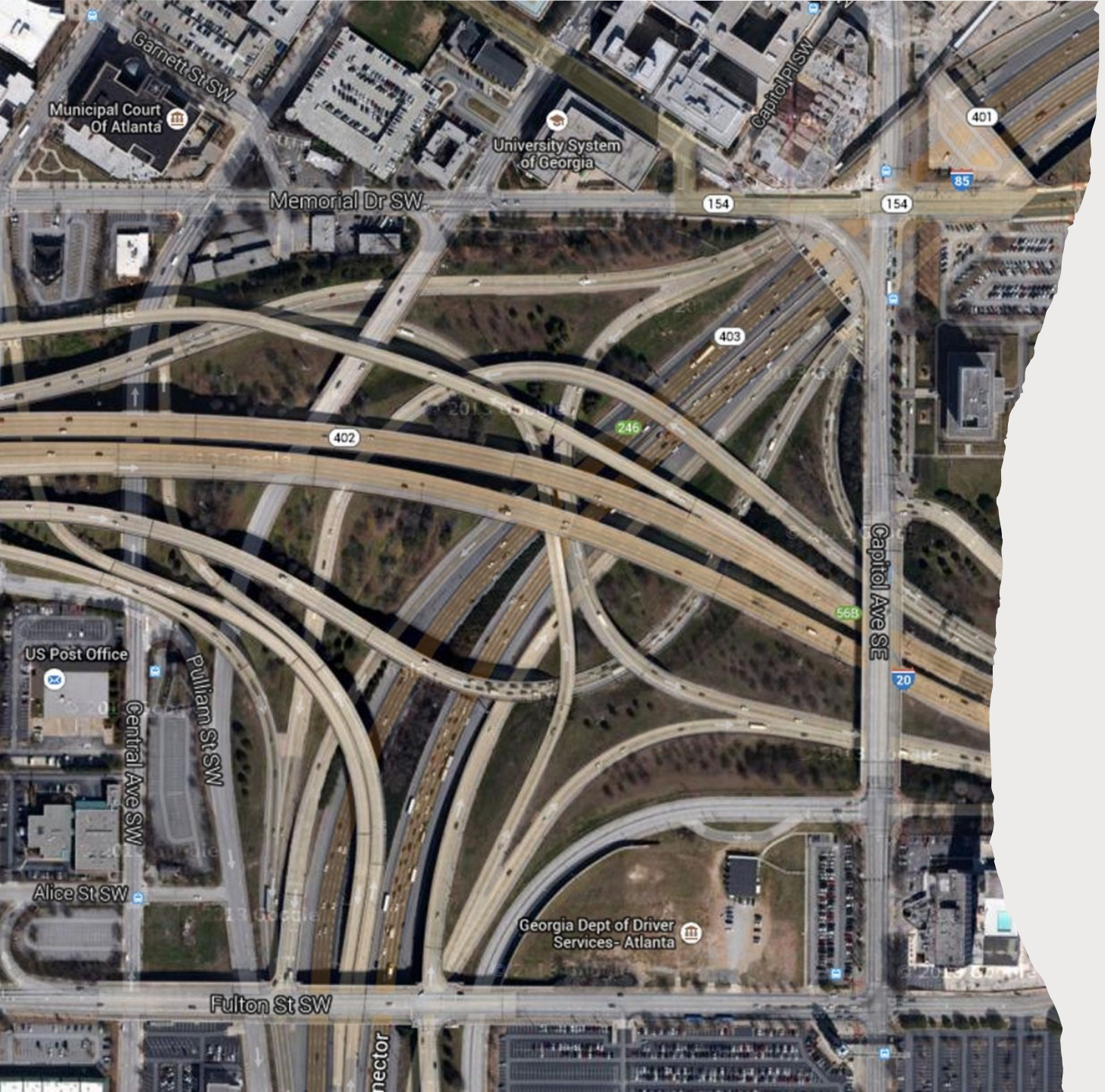


Osler: Variability is the law of life





Variability in Response



Summary

- An important purpose of clinical pharmacology and pharmacogenetics is to improve the benefit-harm ratio of medicines
- We need to deal with complexity – pharmacogenomics is only one aspect of the complexity
- We currently deal with one factor, but most patients have multiple issues which need to evaluated and controlled at the same time
- In research, new technologies allow us to start to deal with complexity

Acknowledgements

The University of Liverpool

- Eunice Zhang
- Dan Carr
- Richard Turner
- Ana Alfirevic
- Anita Hanson
- Andrea Jorgensen
- Vicky Rollinson
- Innocent Asiimwe
- Plus, many others

- **Funders: Dept of Health (NHS Chair of Pharmacogenetics), MRC, WT, DH, NIHR, EU-FP7**

- **UPGx Consortium (H2020 funding)**
  - EU funded (grant number 668353)
  - >150 people have worked on this (www.upgx.eu)
  - Particular thanks to Henk-Jan Guchelaar and Jesse Swen who led the Consortium

NIHR Global Research Group on warfarin (War-PATH):Catriona Waitt, Karen Cohen, and many others