Pharmacogenetics Implementation in the UK

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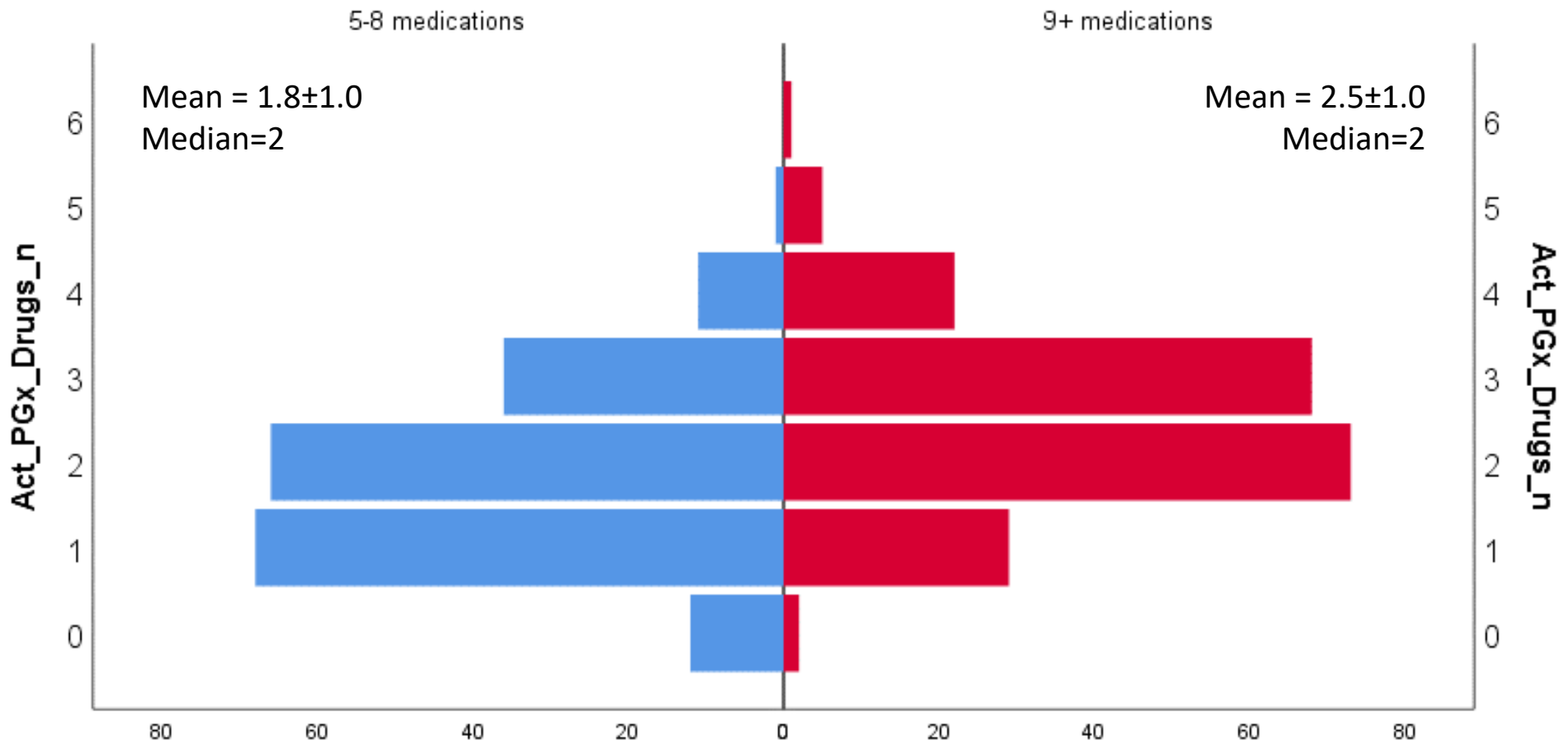
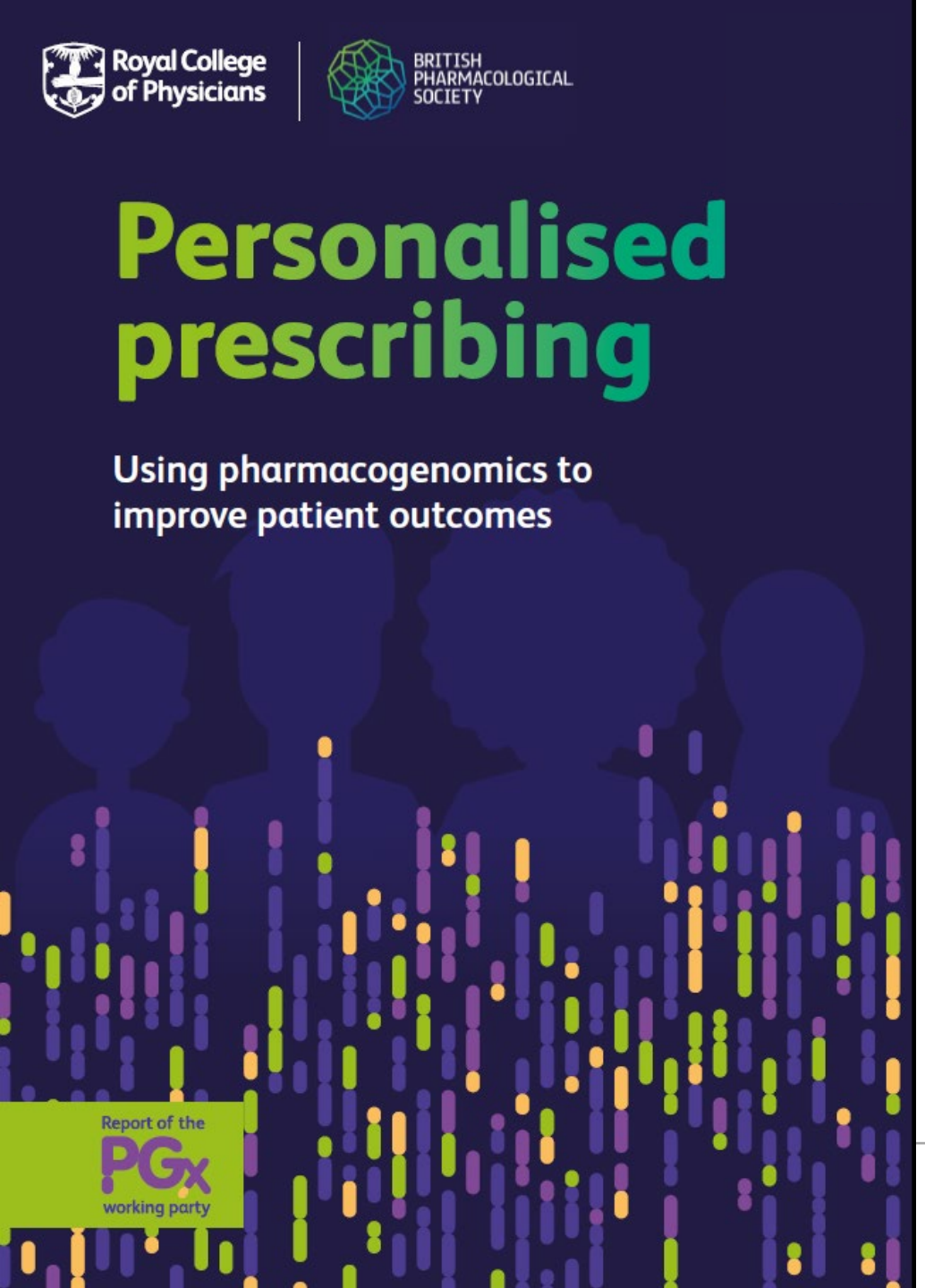
Pharmacogenomic Variation

Country	Number studied	Number of genes evaluated	Proportion carrying at least one actionable genotype or diplotype	Reference
Australia	5408	4	95.9%	*J Neural Transm (Vienna)* **126**, 5-18 (2019)
Canada	98	19	96.9%	*NPJ Genom Med* **2**, 19 (2017)
Estonia	42092	11	99.8%	*Genet Med* **21**, 1345-1354 (2019)
Netherlands	498	11	99.4%	*Front Genet* **10**, 567 (2019)
Qatar	6045	15	99.5%	*NPJ Genom Med* **7**, 10 (2022)
UK	487,409	14	99.5%	*Clin Pharmacol Ther* **109**, 1528-1537 (2021)
UK	713	11	98.7%	*BMC Med* **18**, 367 (2020)
US	9,589	6	91.4%	*Clin Pharmacol Ther* **95**, 423-31 (2014)
US	1,013	5	99.0%	*J Mol Diagn* **18**, 438-445 (2016)

Pirmohamed, Nature Reviews Genetics, 2023; 24: 350-62

Polypharmacy Cohort: Actionable PGx Drugs





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

Abacavir Hypersensitivity: The Poster Child

Association between presence of *HLA-B*5701, HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

S Mallal, D Nolan, C Witt, G Masel, A M Martin, C Moore, D Sayer, A Castley, C Mamotte, D Maxwell, I James, F T Christiansen

Lancet 2002; **359:** 727–32

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

N Engl J Med 2008;358:568-79.

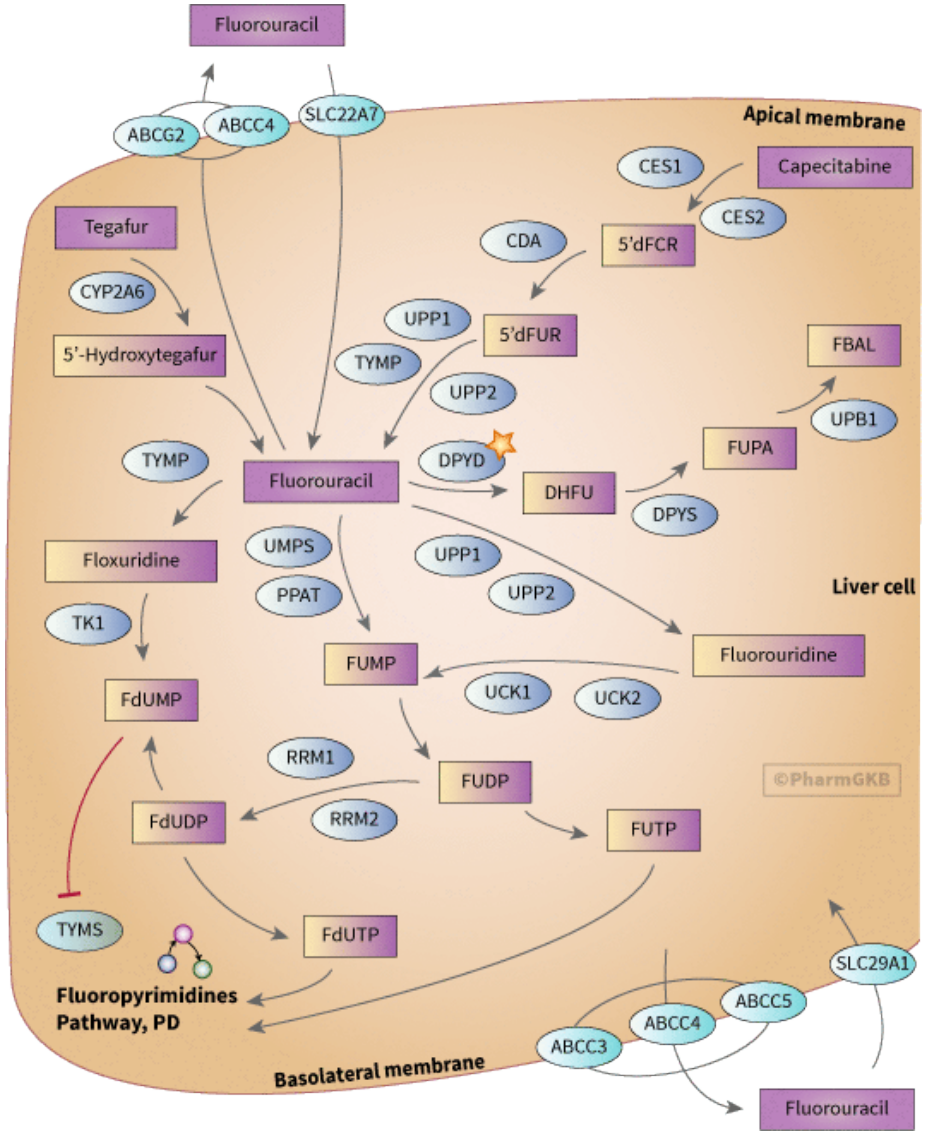
Cost-effectiveness analysis of HLA *B*5701* genotyping in preventing abacavir hypersensitivity

Dyfrig A. Hughes[a], F. Javier Vilar[b], Charlotte C. Ward[a], Ana Alfirevic[a], B. Kevin Park[a] and Munir Pirmohamed[a]

Pharmacogenetics 2004, 14:335–342

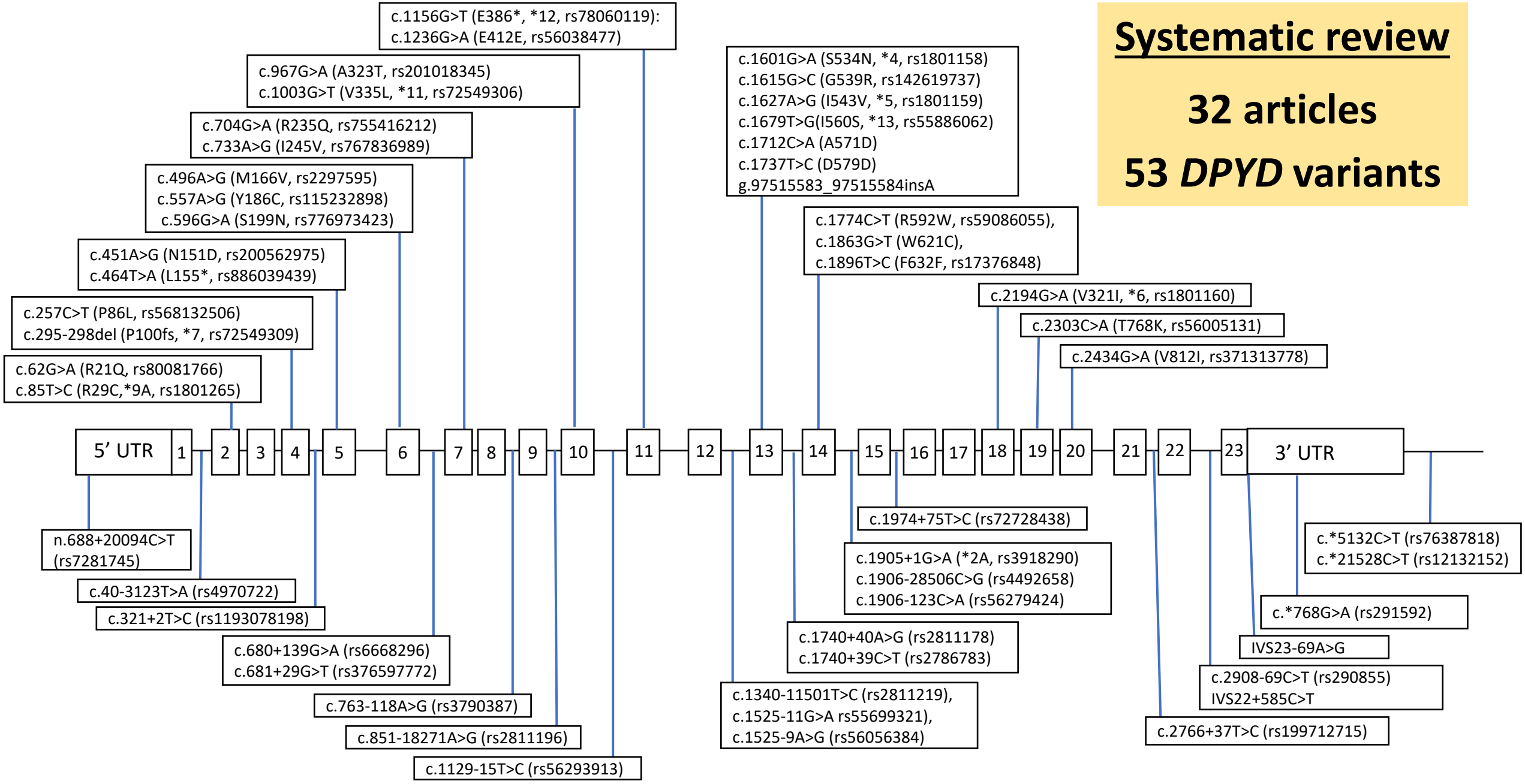
- Pre-prescription genotyping is a cost-effective strategy
- Implemented in the UK from 2006 (before PREDICT-1)
- Incidence has decreased from 5% to <1%

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 England, 38,000 tests per year
- Derived from European populations
- Non-European ancestry inevitably labelled as wild type


Systematic review
32 articles
53 DPYD variants
c.1156G>T (E386*, *12, rs78060119):
c.1236G>A (E412E, rs56038477)
c.967G>A (A323T, rs201018345)
c.1003G>T (V335L, *11, rs72549306)
c.704G>A (R235Q, rs755416212)
c.733A>G (I245V, rs767836989)
c.496A>G (M166V, rs2297595)
c.557A>G (Y186C, rs115232898)
c.596G>A (S199N, rs776973423)
c.451A>G (N151D, rs200562975)
c.464T>A (L155*, rs886039439)
c.257C>T (P86L, rs568132506)
c.295-298del (P100fs, *7, rs72549309)
c.62G>A (R21Q, rs80081766)
c.85T>C (R29C,*9A, rs1801265)
c.1601G>A (S534N, *4, rs1801158)
c.1615G>C (G539R, rs142619737)
c.1627A>G (I543V, *5, rs1801159)
c.1679T>G(I560S, *13, rs55886062)
c.1712C>A (A571D)
c.1737T>C (D579D)
g.97515583_97515584insA
c.1774C>T (R592W, rs59086055),
c.1863G>T (W621C),
c.1896T>C (F632F, rs17376848)
c.2194G>A (V321I, *6, rs1801160)
c.2303C>A (T768K, rs56005131)
c.2434G>A (V812I, rs371313778)
5’ UTR
1
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9
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11
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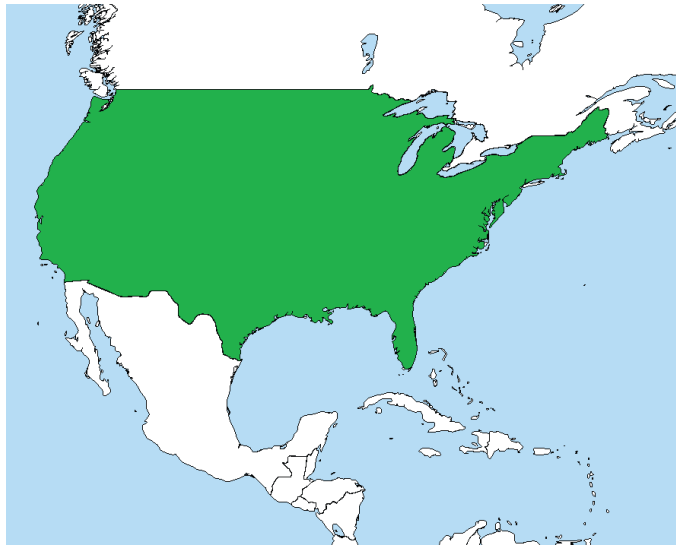
13
14
15
16
17
18
19
20
21
22
23
3’ UTR
n.688+20094C>T
(rs7281745)
c.40-3123T>A (rs4970722)
c.321+2T>C (rs1193078198)
c.680+139G>A (rs6668296)
c.681+29G>T (rs376597772)
c.763-118A>G (rs3790387)
c.851-18271A>G (rs2811196)
c.1129-15T>C (rs56293913)
c.1340-11501T>C (rs2811219),
c.1525-11G>A rs55699321),
c.1525-9A>G (rs56056384)
c.1740+40A>G (rs2811178)
c.1740+39C>T (rs2786783)
c.1905+1G>A (*2A, rs3918290)
c.1906-28506C>G (rs4492658)
c.1906-123C>A (rs56279424)
c.1974+75T>C (rs72728438)
c.2766+37T>C (rs199712715)
c.2908-69C>T (rs290855)
IVS22+585C>T
IVS23-69A>G
c.*768G>A (rs291592)
c.*5132C>T (rs76387818)
c.*21528C>T (rs12132152)

African American



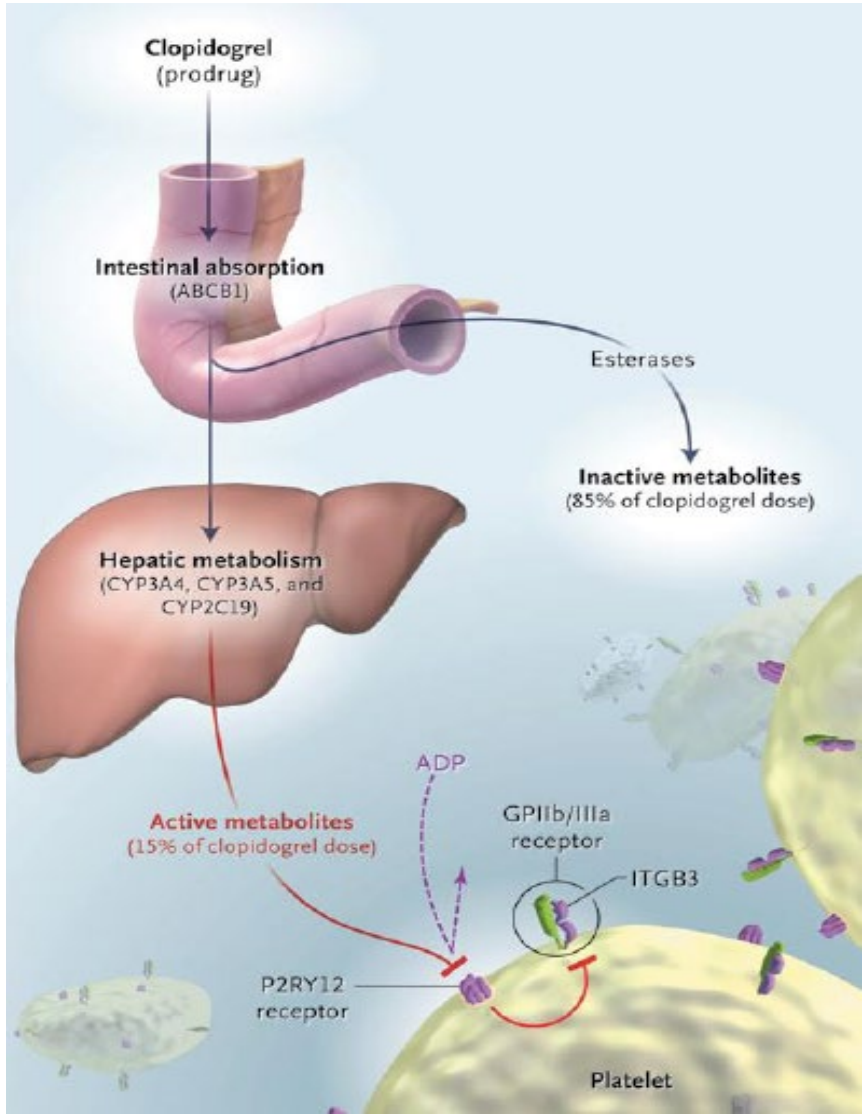
African America

- 19 variants
- USA: 3 case studies, 1 cohort study

c.557A>G reported in all 3 cases studies

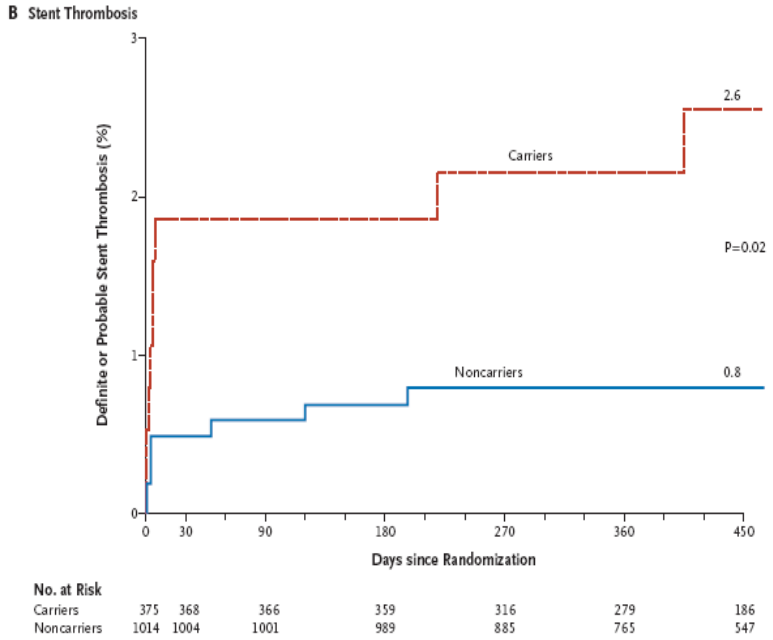
- Tyrosine to cysteine substitution at protein position 186
- Decreased enzyme function (CPIC evidence level: Moderate)
- 2% frequency in African reference populations
- Included in *DPYD* testing panel in several labs in the USA
- UK census 2021: 2.4 million (4.2% population) identified within “Black, Black British, Caribbean or African” ethnic groups
- Beneficial to include **c.557A>G** in NHS *DPYD* testing

Clopidogrel activation and action



Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.



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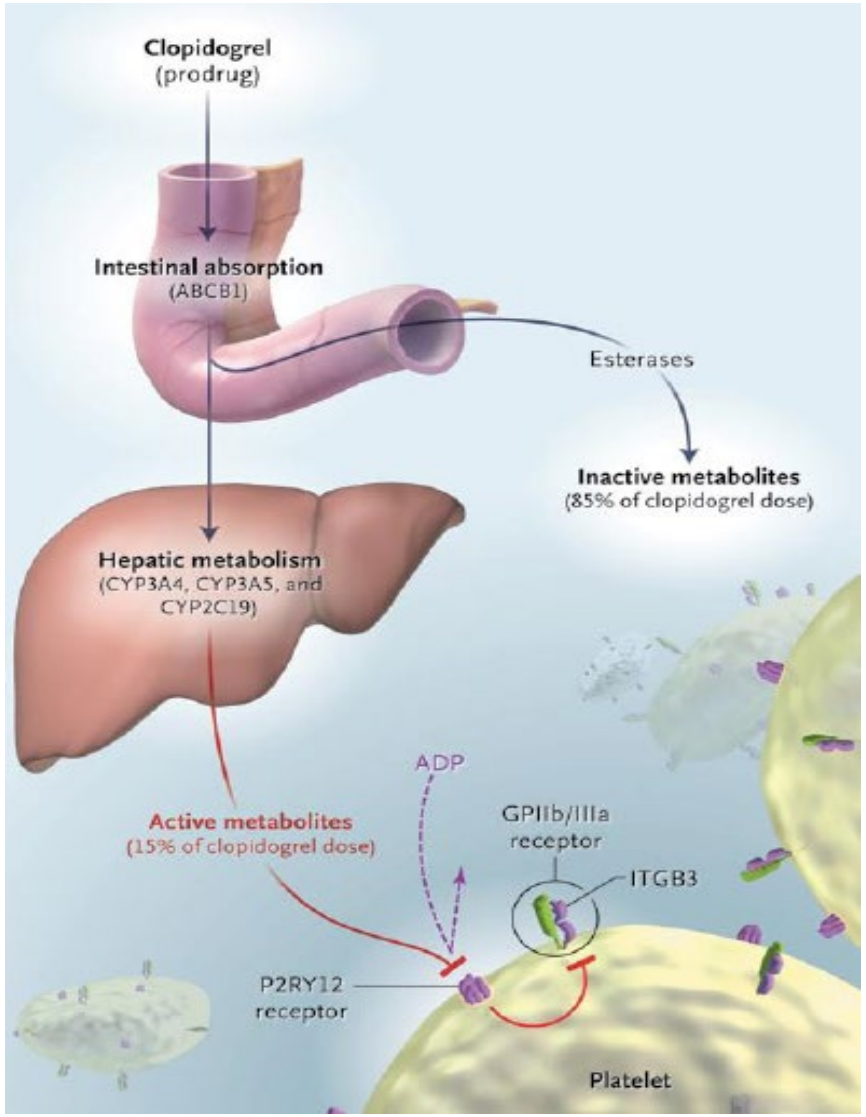
Clopidogrel and CYP2C19



Stroke Medicine:

- 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** (31 July 2024)
- Available at https://www.nice.org.uk/guidance/dg59

Potential Labelling Issues

- Will the SmPC and PiL need to change?
- Who will initiate the change? (efficacy rather than safety – depends on definition of safety)
- Wording tricky:
  - Only with recent stroke
  - But not in patients with ACS (where clopidogrel is recommended in those over 70 years of age, and those at high risk of bleeding)
- Use of ticagrelor is off-label
- How to handle phenocopy issues?

CYP2C19 Genotype Prevalence and Association With Recurrent Myocardial Infarction in British–South Asians Treated With Clopidogrel

Emma F. Magavern, MD, MSc,[a] Benjamin Jacobs, BM BCh, MSc,[b] Helen Warren, PhD,[a]
Gherardo Finocchiaro, MD, PhD,[c] Sarah Finer, MBBS, PhD,[d] David A. van Heel, BM BCh, MA, PhD,[b]
Genes & Health Research Team, Damian Smedley, PhD,[a] Mark J. Caulfield, MD[a]

- British South Asian population: Bangladeshi and Pakistani (n=44,396)
- Loss of 2 CYP2C19 alleles (poor metabolisers) 13% - cf with 2.4% in Europeans
- Poor metabolisers more likely to have recurrent myocardial infarction (OR 3.1, P=0.019)

TABLE 1 Comparison With Biogeographic and Trial Cohorts[27-31]

Phenotype	G&H Cohort	CPIC Central/ South Asian	CPIC European	TAILOR PCI Trial	POPular Genetics Trial
Rapid or ultrarapid	18%	21%	32%	a	a
Normal	25%	30%	40%	a	67%
Poor	13%	8%	2%	a	3%
Intermediate	44%	41%	26%	a	29%
Poor or intermediate	**57%**	**49%**	**29%**	**35%**	**31%**

Models of Testing

- **Reactive genetic testing**
  - Current model
  - Order test when needed, and wait for result
- **Pre-emptive genetic testing**
  - Order a panel test and store genetic information in the healthcare record
  - No need to wait for test result, as it is already available
  - Fits in better with the clinical pathway

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

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†*

Lancet 2023; 401: 347–56

The NHS England PROGRESS Programme

PROGRESS

Pharmacogenetics Roll Out - Gauging Response to Service

Who should have pharmacogenomic testing?
Which gene drug pairs should we implement?
In what clinical contexts?

What are patient and public attitudes towards pharmacogenomic testing and data re-use?
How might patients access their data?

How does any "intervention" fit into a complex healthcare environment?
How do we scale?

PPIE Acceptability

Genetic Variation

Genotype to Phenotype

Development of Technological Solutions

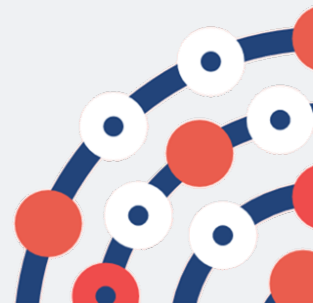
Implementation

Personalised Medicine

Health Economic Evaluation

What should our genetic testing approaches be?
How do we surface the data in a clinically relevant format + timeframe?

How do you assess the cost effectiveness of pharmacogenomic testing?
How can the benefits of data re-use be quantified?



PROGRESS Study

- Primary care based
- Focusing on 4 medicine classes:
  - Selective Serotonin Reuptake Inhibitors [citalopram, escitalopram, fluvoxamine, paroxetine, sertraline]
  - Tricyclic Antidepressants (prescribed for pain or depression) [amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine]
  - Statin Therapy [atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin]
  - Proton Pump Inhibitors [esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole]
- Primary Outcome: The Pharmacogenetic Clinical Utility Metric (Defined as the proportion of patients across the study cohort with a CPIC Level 1A variant related to the medicine which triggered recruitment to the study) – determined through genetic testing as part of study

UK Regulatory Science and Innovation Network in Pharmacogenomics

Challenge area 1	Including PGx information in drug labels and developing guidelines
Challenge area 2	Embedding PGx information in EHRs and creating intelligent decision support systems
Challenge area 3	Regulation of pharmacogenomic diagnostic tests
Challenge area 4	Cost effectiveness for the NHS (reactive to pre-emptive)

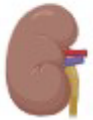
AIM
Proportionate, forward-looking, inclusive and responsive regulatory pathways that enhance innovation

Summary

Age and sex

Disease(s)

Concomitant drugs



Renal function

Hepatic function

Pharmacogenetic testing

- Clinical and laboratory information is required to ensure that patients get the right drug at the right dose
- We already use a lot of information
- Pharmacogenetics represents an additional piece of information to further refine prescribing