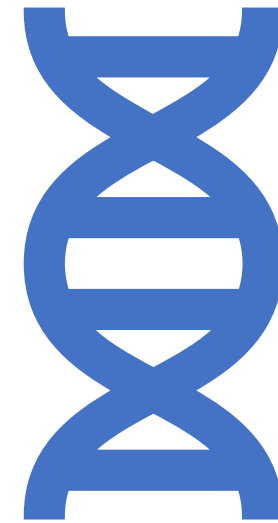


# Implementation and equity: EDI and pharmacogenetics

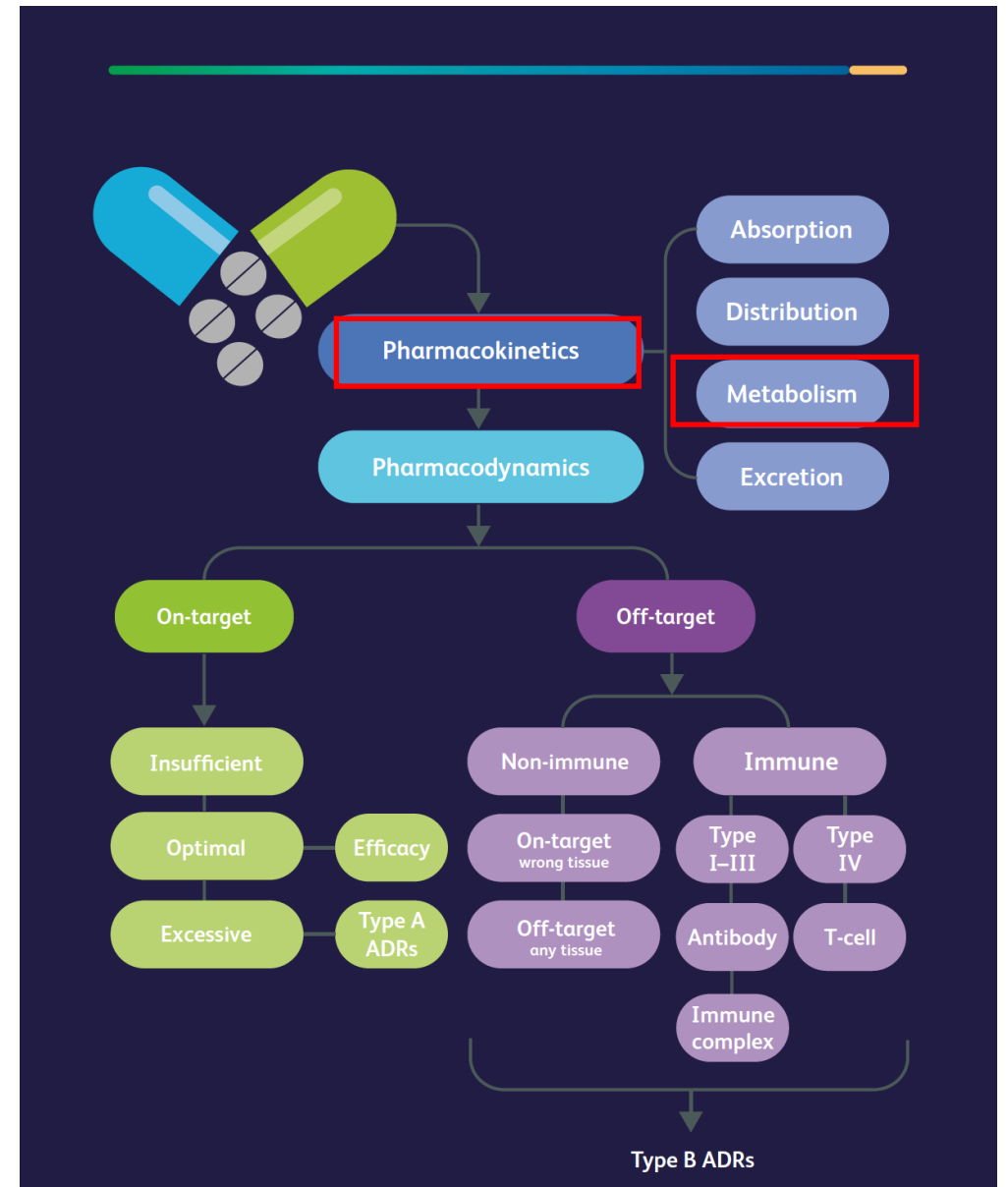
Dr E F Magavern  
NIHR Academic Clinical Lecturer  
William Harvey Research Institute  
Queen Mary University of London



# Pharmacogenomics

Using genetic information based on understanding of gene-drug interaction to alter prescribing

- Genes can impact
  - therapeutic pharmacokinetics - what body does to the drug or
  - pharmacodynamics - what the drug does to the body



Royal College of Physicians and British Pharmacological Society. Personalised prescribing: using pharmacogenomics to improve patient outcomes. Report of a working party. London: RCP and BPS, 2022.

## CYP450 metaboliser genotype/ phenotype

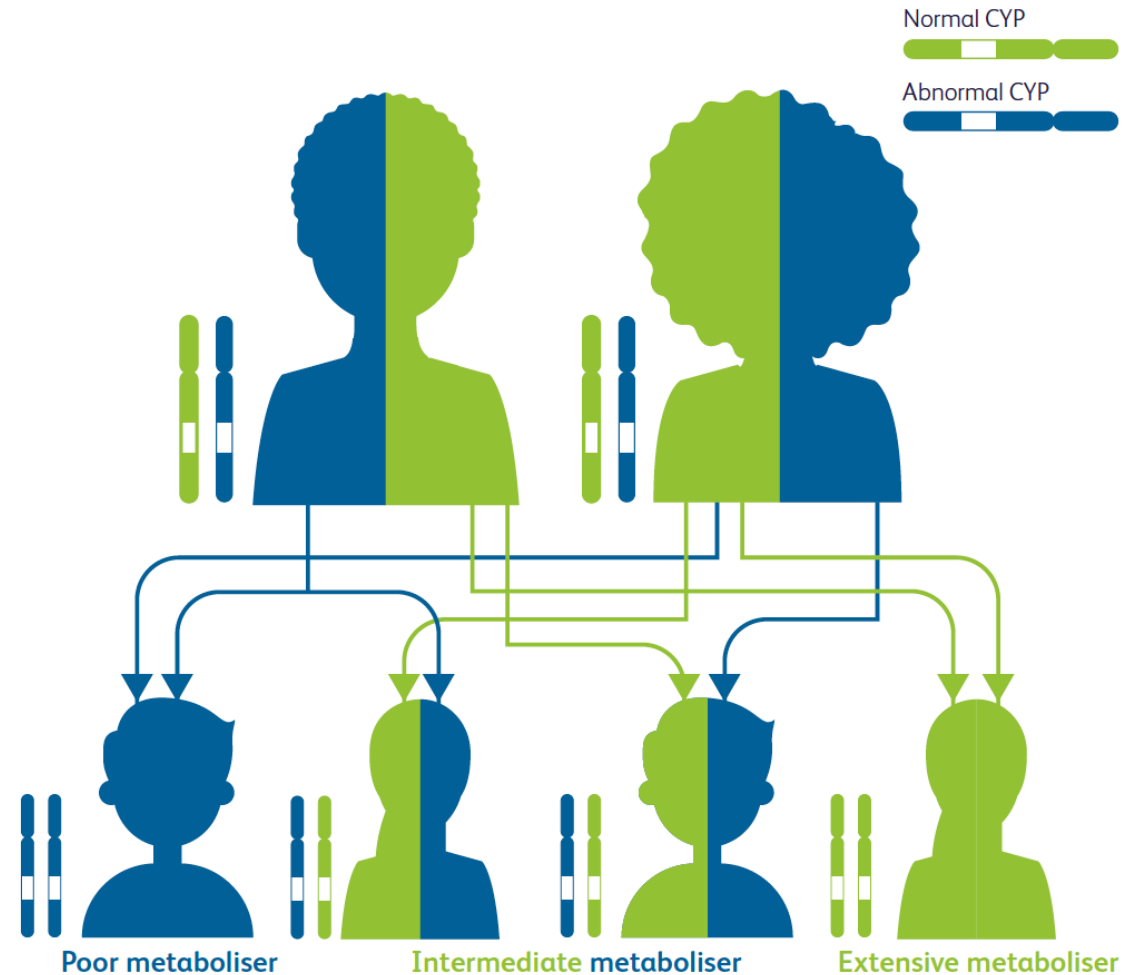


Fig 4. Cytochrome P450 pharmacogenetic variation leading to changes in enzyme activity and thereby metaboliser status

Royal College of Physicians and British Pharmacological Society. Personalised prescribing: using pharmacogenomics to improve patient outcomes. Report of a working party. London: RCP and BPS, 2022.

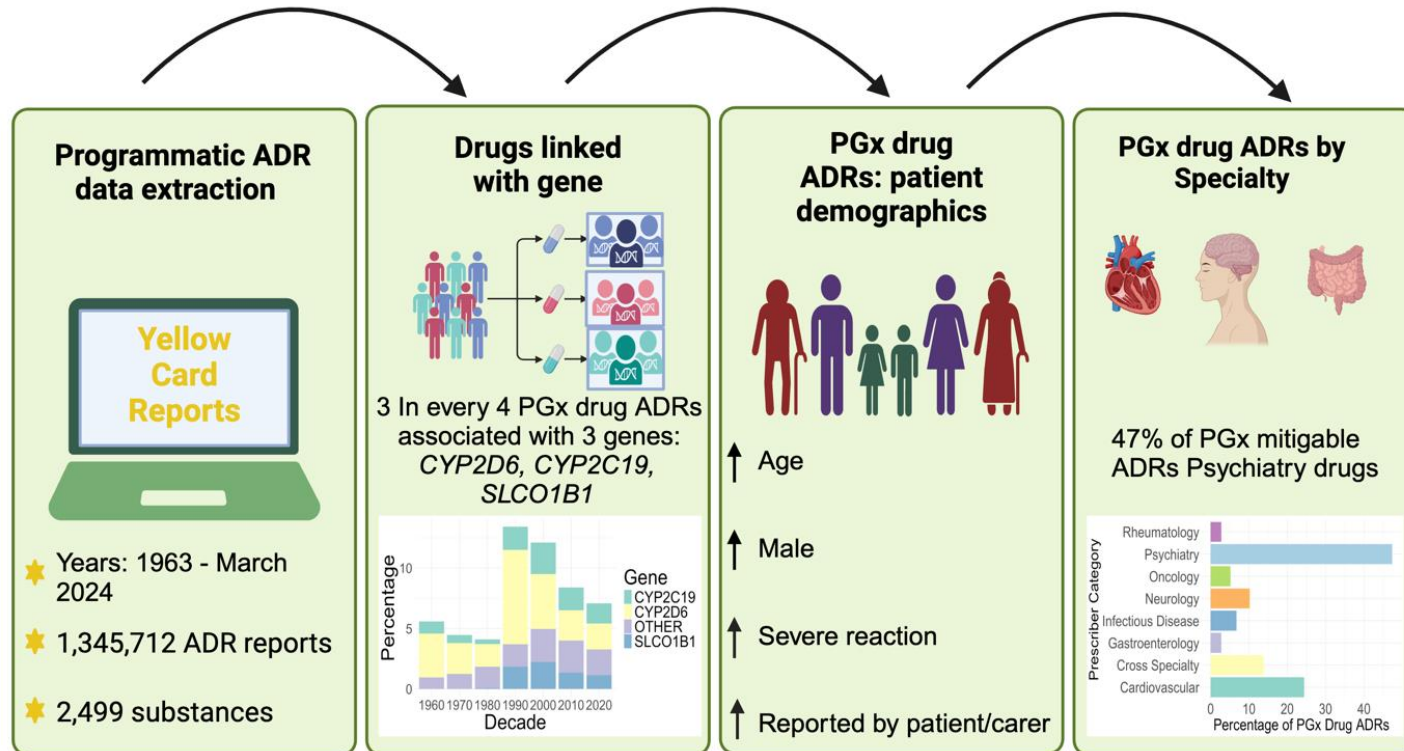
# The scale of the problem - ADRs

- Growing number of prescriptions (50% more in 10 year period nationally)
  - Longer life expectancy → ↑poly-morbidity → ↑polypharmacy
  - **£530 million** per annum
  - **6.5% of all acute admissions** nationally
  - Some of this avoidable harm could be modified using pharmacogenomics... limited number of gene-drug pairs
- > **Scope of PGx mitigatable ADRs at population scale?**



# PGx mitigatable ADRs - scale

- Objective: To elucidate the **scale** of **potential ADR mitigation** by pharmacogenomics (PGx) implementation in the UK from retrospective **pharmacovigilance data**
- Data: **Yellow Card ADR** reports to the Medicines and Healthcare Products Regulatory Agency (**MHRA**) from **1963-2024**



9% of overall ADRs

Psychiatric medication = 47%

Cardiovascular medications = 24%

Emma F Magavern, Maia Megase, Jack Thompson, Gabriel Marengo, Julius Jacobsen, Damian Smedley, Mark J Caulfield.

*Pharmacogenetics and adverse drug reports: insights from a national database from the United Kingdom.* Manuscript Under review

Biogeographical groups	CYP2D6 atypical metabolisers	CYP2C19 atypical metabolisers
African American/Afro-Caribbean	22%	40%
American	10%	24%
Central/South Asian	15%	52%
East Asian	34%	59%
European	19%	33%
Latino	14%	23%
Near Eastern	28%	29%
Oceanian	22%	94%
Sub-Saharan African	25%	37%

Emma F Magavern, Maia Megase, Jack Thompson, Gabriel Marengo, Julius Jacobsen, Damian Smedley, Mark J Caulfield.  
*Pharmacogenetics and adverse drug reports: insights from a national database from the United Kingdom.* Manuscript Under review

# Population prevalence of pharmacogenes and exposure




How likely am I to have a pharmacogene?

How likely am I to be prescribed the drug?

Both likely to be higher in underrepresented groups due to intersection of lack of representation in evidence base and increased risk of multimorbidity with known health inequality

# Personalized prescribing

## Promise

-  efficacy
-  toxicity
-  compliance
- Dose guidance
- Efficient choice of medication and dose

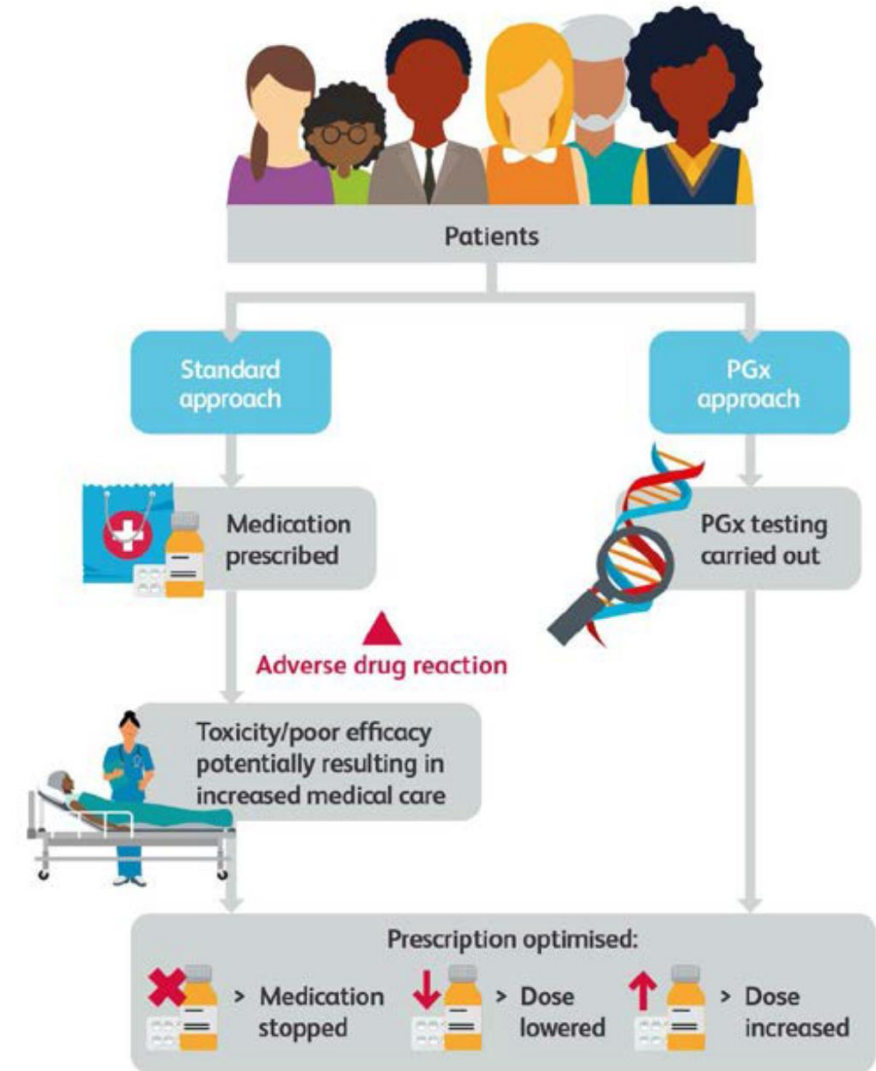
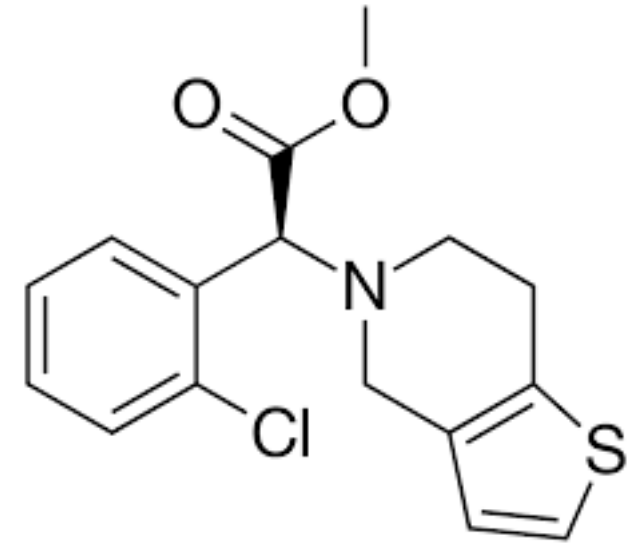


Fig 8. Comparing pharmacogenomic and standard approaches to prescribing



# Clopidogrel

- **Antiplatelet agent**
- **P2Y<sub>12</sub> inhibitor**
- **Used for secondary prevention after myocardial infarction**



# Clopidogrel

## Poor Metabolizers can't form the active metabolite

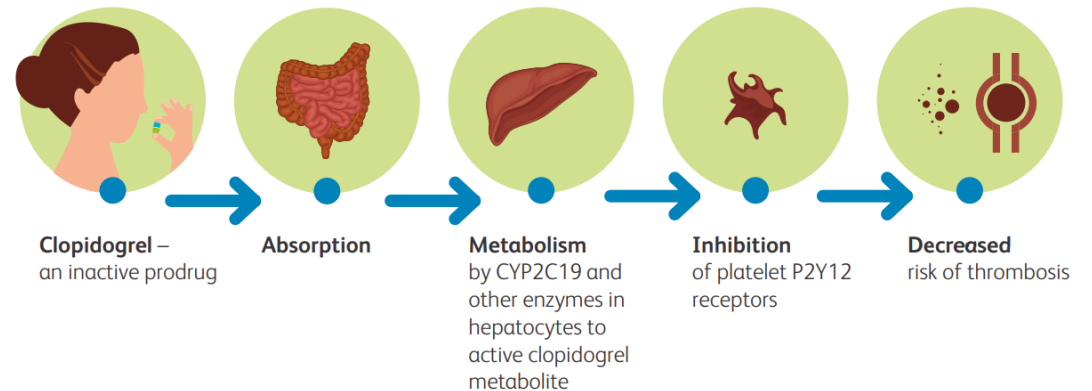
### Reduced efficacy

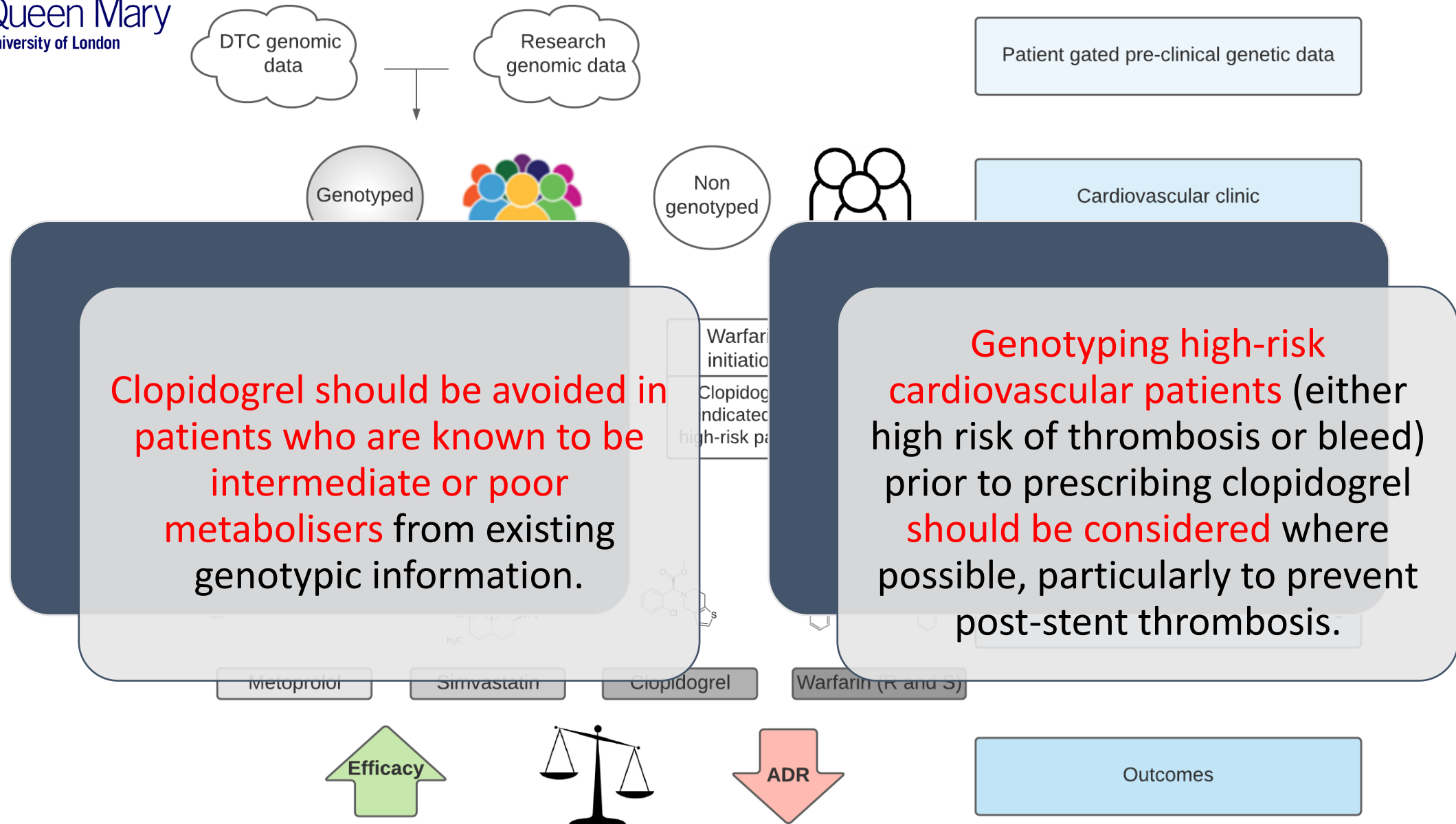
- **Prodrug** -> Transformed to active metabolite in two sequential **CYP2C19** dependent steps.

- LOF variant in **CYP2C19**  
->high on-treatment platelet reactivity  
->increased risk of ischaemic events

1/3 European ancestry population

– significant trans-ethnic variation





REVIEW ARTICLE | Originally Published 20 June 2024 |

Check for updates

## CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association

Naveen L. Pereira, MD, FAHA, Chair, Sharon Cresci, MD, FAHA, Vice Chair, Dominick J. Angiolillo, MD, PhD, Wayne Batchelor, MD, MHS, Quinn Capers IV, MD, Larisa H. Cavallari, PharmD, Dana Leifer, MD, FAHA, ... [SHOW ALL](#) ... on behalf of the American Heart Association Professional/Public Education and Publications Committee of the Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council | [AUTHOR INFO & AFFILIATIONS](#)

Circulation • Volume 150, Number 6 • <https://doi.org/10.1161/CIR.0000000000001257>

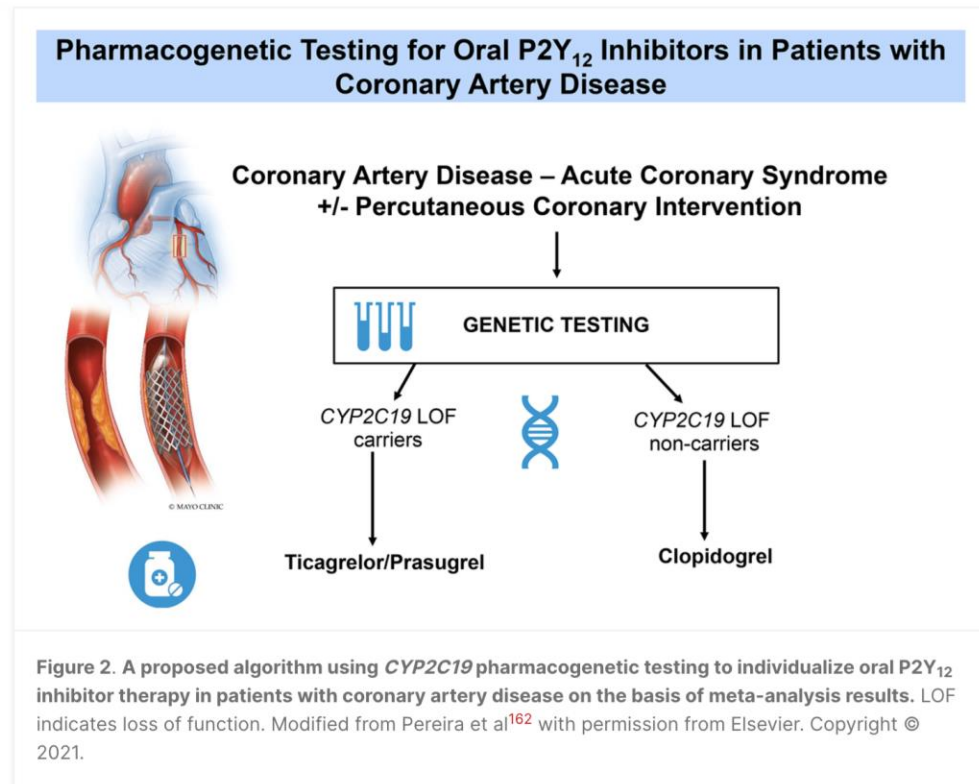
3,935 / 1



PDF/EPUB



# Upshot: Genotype is beneficial, but the crux is implementation



Highlighted:

- clinician and patient perceptions
- recommendations provided by clinical guidelines that incorporate recently published clinical evidence
- adoption by health care organizations by providing seamless
- integration in the EHR with
- supportive tools to understand results,
- reimbursement by insurance companies, and
- easy and timely availability of genetic testing.

# NICE guidance for PGx guided antiplatelet therapy

## Ischemic stroke

[Home](#) > [NICE Guidance](#) > [Conditions and diseases](#) > [Cardiovascular conditions](#) > [Stroke and transient ischaemic attack](#)

### CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack

Diagnostics guidance [DG59] Published: 31 July 2024 [Register as a stakeholder](#)

[Guidance](#) [Tools and resources](#) [Information for the public](#) [History](#)

[Overview](#)  
**1 Recommendations**  
2 The diagnostic tests  
3 Committee discussion  
4 Implementation  
5 Diagnostics advisory committee members and NICE project team

#### Guidance

[Download guidance \(PDF\)](#)

< Next >

### 1 Recommendations

1.1 Use CYP2C19 genotype testing to assess if clopidogrel is a suitable antiplatelet drug for people who have just had an ischaemic stroke or a transient ischaemic attack (TIA). CYP2C19 genotype testing is only recommended if:

- quality-assurance processes and arrangements are in place for point-of-care tests
- shared decision making for doing the test is established (see [NICE guidance on shared decision making](#)).

When interpreting test results, healthcare professionals should take into account that the prevalence of different CYP2C19 genotypes may vary between ethnic groups.

Laboratory-based testing



# Adverse Drug Reactions

- Mavacamten -> **CYP2C19** and CYP3A4
- Good oral bioavailability
- Mainly metabolized by **CYP2C19**
- **CYP3A4** more important in **CYP2C19** poor metabolizers

Regulator guidance to test **CYP2C19 genotype** based on Phase 1 PK data in **EU and UK**, but not FDA



European Heart Journal (2023) 44, 4622–4633  
https://doi.org/10.1093/eurheartj/ehad637

**STATE OF THE ART REVIEW**  
Heart failure and cardiomyopathies

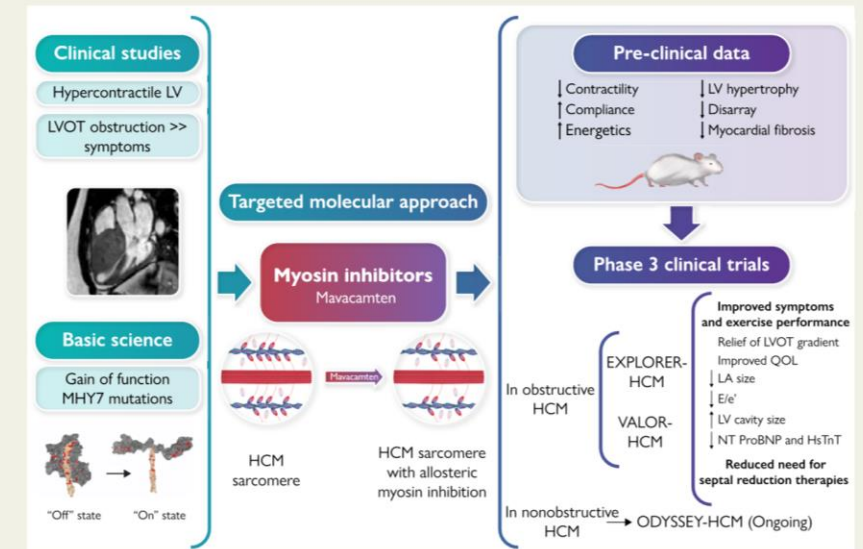
## Mavacamten: a first-in-class myosin inhibitor for obstructive hypertrophic cardiomyopathy

Eugene Braunwald<sup>1,2\*</sup>, Sara Saberi<sup>3</sup>, Theodore P. Abraham<sup>4</sup>, Perry M. Elliott<sup>5</sup>, and Iacopo Olivetto<sup>6</sup>

<sup>1</sup>Division of Cardiovascular Medicine, TIMI Study Group, Brigham and Women's Hospital, 60 Fenwood Road, Boston, MA 02115, USA; <sup>2</sup>Department Medicine, Harvard Medical School, Boston, MA, USA; <sup>3</sup>Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, MI, USA; <sup>4</sup>UCSF HCM Center of Excellence, University of California San Francisco, San Francisco, CA, USA; <sup>5</sup>Institute of Cardiovascular Science, University College London, London, UK; and <sup>6</sup>Meyer Children's Hospital, University of Florence, Florence, Italy

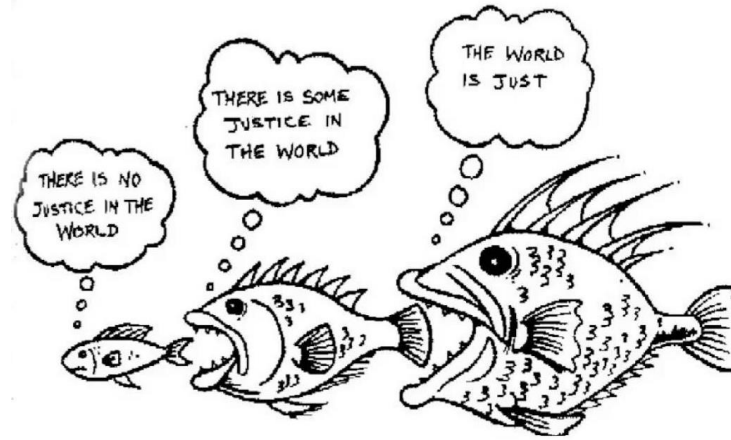
Received 6 April 2023; revised 9 August 2023; accepted 11 September 2023; online publish-ahead-of-print 7 October 2023

### Graphical Abstract



BUT

## *Social justice*



- Most genetic studies and PGx data do not adequately address admixed populations and populations of Black, Asian and minority ethnic (BAME) backgrounds, including indigenous peoples.
- Relations of the mainstream research community and establishment with some ethnic minority groups such as indigenous people has been fraught with mistrust.
- Risk of increasing health inequality?



Representing our local clinical population in  
my research

# UK Genes & Health participant cohort (N 44,190)

- ❖ South Asian: Bangladeshi, Pakistani ancestry
- ❖ Important ethnic cohort for PGx/implementation in clinical practice in the UK
- ❖ Under-represented in both clinical trial and genetic study cohorts
- ❖ 4x more likely to have cardio-metabolic disease

G&H population not represented in  
medication data

# PGx to address health inequality:

No South Asian representation (25% global population)

## Studies supporting Clopidogrel licensure (EMA)

Study	Year	Ethnic group representation	Indication
<b>CAPRIE study</b>	1996	91%-98% of all subgroups "white"	Atherosclerotic vascular disease
<b>CURE study</b>	2001	Not specified	Acute coronary syndromes without ST elevation
<b>CLARITY study</b>	2005	89.5% "white"	ST elevation myocardial infarction
<b>COMMIT study</b>	2006	Not specified	Myocardial infarction
<b>ACTIVE-A</b>	2009	9.6-9.9% north America 30.5-31.2% western Europe and Israel 32.7% Eastern Europe 20.5-20.8% South America 4.2-4.3% Asia-Pacific 1.6-1.7% South Africa	Atrial Fibrillation
<b>CHANCE study</b>	2013	Not specified but conducted in China	TIA or minor ischemic stroke
<b>POINT study</b>	2018	74.9-75.2% "white" , 20-20.7% "black" , 2.8-3.3% "Asian" , 6.2-6.3% "Hispanic" , 1.5-1.6% "other"	TIA or minor ischemic stroke

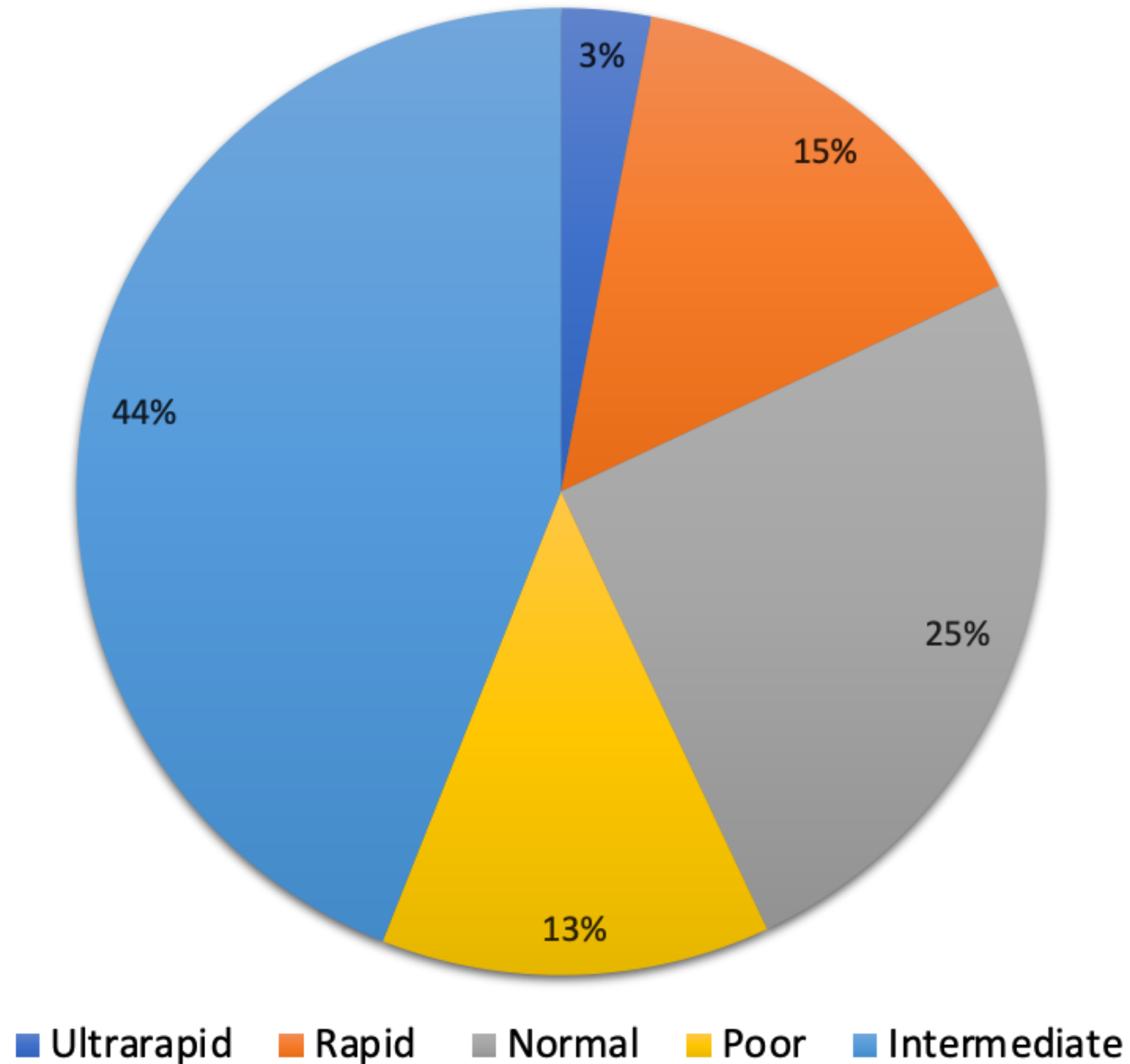
# Analyses linking genetic data with health outcome data **lacking** in **South Asian populations**

## ❑ **Validation study** aims:

- To **assess *CYP2C19* genotypes** in a **British-South Asian ancestry** cohort and
- To correlate inferred **metabolizer phenotypes with recurrent MI events** in participants prescribed clopidogrel.

## G&H Cohort CYP2C19 Phenotypes

= 57 %  
poor or  
intermediate  
metabolizer



# British-South Asian cohort: Nearly 2 in every 3 have a *CYP2C19* LOF SNP

## Comparison with biogeographic and trial cohorts

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

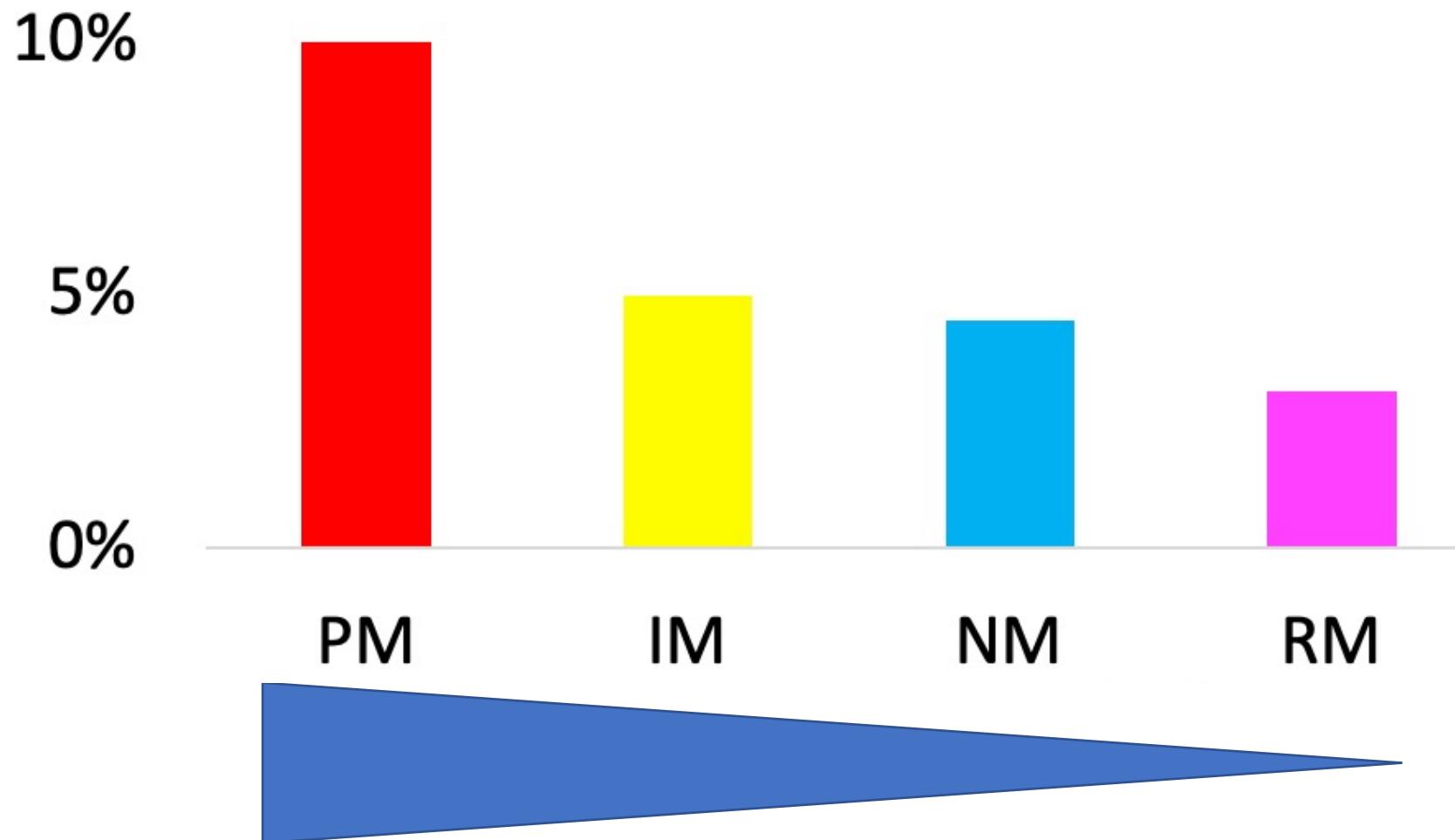
# Risk of recurrent MI in G&H population prescribed Clopidogrel

Risk factor	Risk of Recurrence of MI (Odds Ratio)	95% CI	P-value
Poor CYP2C19 metabolizer	3.7	1.3-10	0.012 *



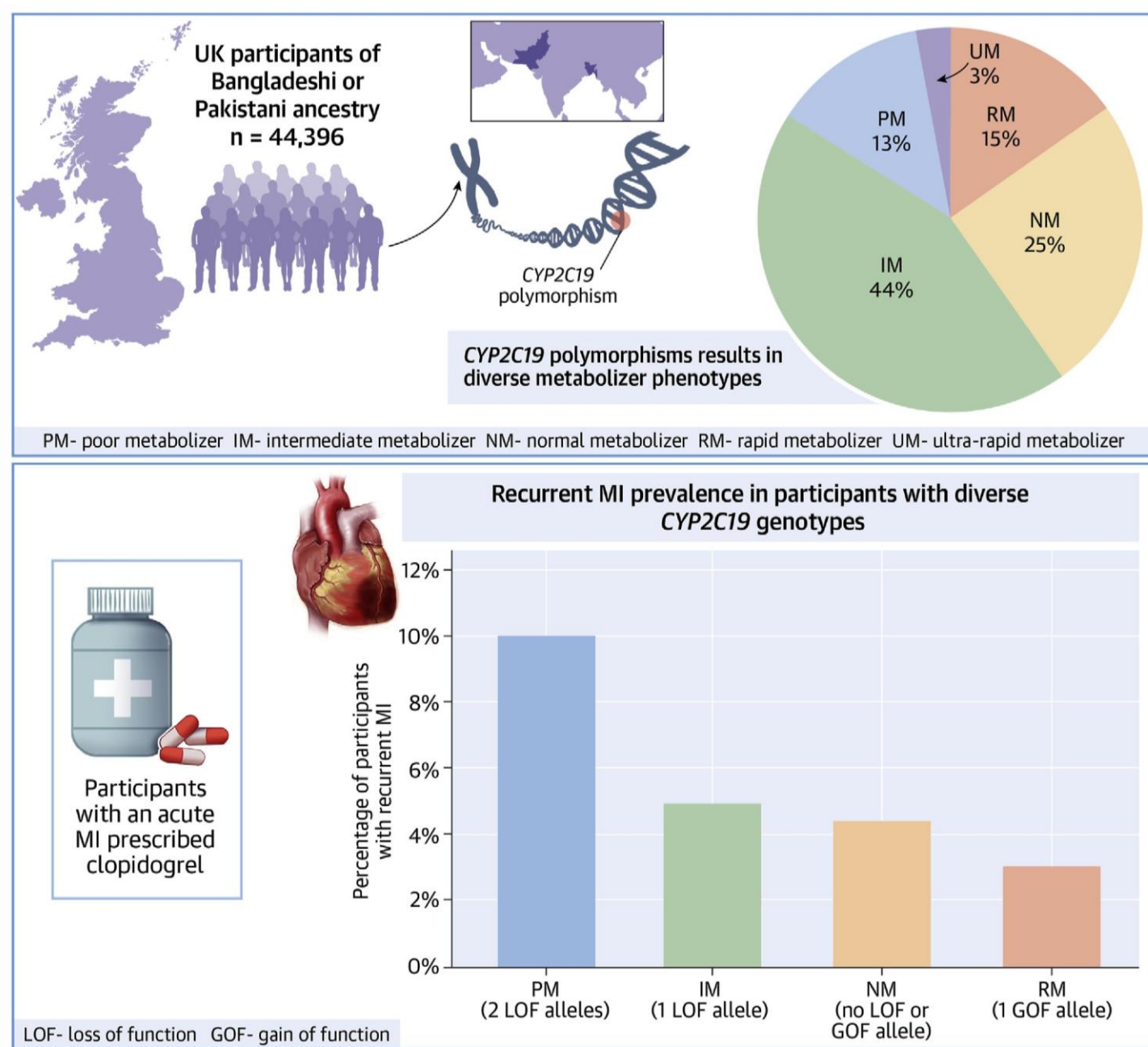
# CYP2C19 Metabolizer status of cohort prescribed Clopidogrel:

Recurrent MI



# Summary

- ❑ This UK South-Asian ancestry population has a **high prevalence of *CYP2C19* LOF alleles**
- ❑ This is known to lead to poor activation of clopidogrel
- ❑ And is linked with increased risk of **recurrent myocardial infarction from real world health outcome data**



# Take home messages

Important to attain **proportionate representation of global populations**

–Engagement-> trust is key



Need to scrutinize the **broader socio-economic, cultural and political context** to avoid worsening health inequalities



Important to look at populations with differing:

Pharmacogene variant prevalence

Disease prevalence

Medication exposures

AND

To implement PGx we need to solve rather than  
increase the representation problem

# These PK pathways are common to many different medication – re use of PGx data?

European Heart Journal

## Cardiovascular Pharmacotherapy

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European Heart Journal

### Article Contents

#### The premise

Mavacamten

CYP2C19

The problem

I'm not an ICC specialist—Why do I care about this?

That sounds scary, what can I do about it?

JOURNAL ARTICLE

CORRECTED PROOF

## CYP2C19 genetic testing for Mavacamten and ischaemic stroke treatment: What does the result mean for cardiovascular prescribers in the UK and Europe? FREE

Emma F Magavern ✉, John H McDermott, Mark J Caulfield, William G Newman

[Author Notes](#)

*European Heart Journal - Cardiovascular Pharmacotherapy*, pvae040,

<https://doi.org/10.1093/ehjcvp/pvae040>

**Published:** 23 August 2024 **Article history** ▼

# Transition from evidence to practice – we need input from patients....



**"Can you prescribe marijuana to help relieve the boredom of sitting in your waiting room?"**





## Who we heard from

- Subset of **Genes & Health (G&H) study cohort** participants
  - ✓ participants who had recently engaged with follow-up studies locally were invited by text, telephone, or face to face invitation
- G&H is a **large community-based genetics study from the UK**
- Participants are of **Bangladeshi or Pakistani ancestry**



# Why we chose this population

- **Underrepresented** in genomic studies and therapeutics trials.
- High rates of **multi-morbidity**  
➡ **polypharmacy**
- **Objective**: elucidate British South-Asian ancestry **community perspectives on PGx**



# What we did together



- ☐ Four **focus groups**, semi-structured
  - ✓ 9-12 participants in each group
  - ✓ Two mixed gender, one male only, one female only
  - ✓ Recruited from the Genes & Health study
  - ✓ Brief demographic survey taken before discussion
- ☐ Simultaneous **interpretation** was available to participants in **Urdu and Bengali**
- ☐ Focus groups were **recorded**
- ☐ Abridged **transcription**
- ☐ Thematic **analysis** undertaken

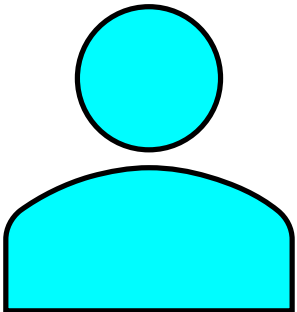
# Demographics survey

- ❖ 42 participants
- ❖ 64% female
- ❖ 26% born in the UK or Europe
- ❖ 52% born in Bangladesh; 17% in Pakistan
- ❖ 36% reported university level education
- ❖ Primary spoken language:
  - 52% **English**
  - 36% **Bengali**
  - 12% **Urdu**

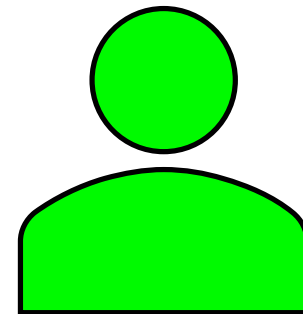


# Clinical implementation: Benefits

*“to ensure that you get the right medicine...[don't want] trial and error on my kid... I want [the GP] to give him specific medicine that will make him better. Not two weeks later, oh that didn't work. Let's try something else.”*

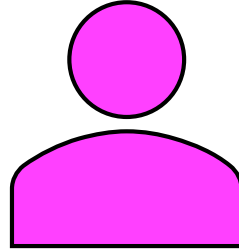


*“which medicine suits me, I think that would be a good idea”*

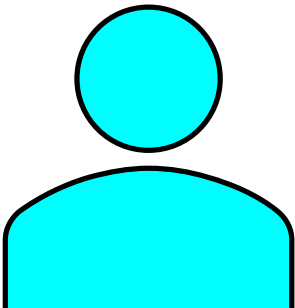


# Clinical implementation: Trust

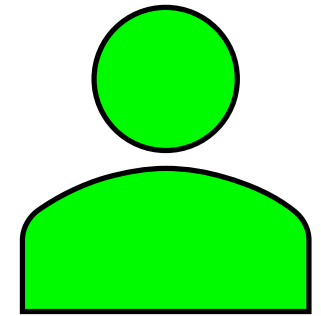
*'GP they trust'*



*"After genetic test when doctor will prescribe medicine obviously there're going to involve more trust on this".*

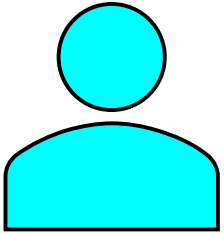


*"For example, if I go doctor then they just prescribe me paracetamol? Yeah. If they tell me. OK have 100 [dose]. Maybe I'm gonna have 20 or 30. But after the blood test or whatever test done. If he give me 100 then I'm gonna say yeah I'm gonna finish the 100 because it's been done by test... In the first time, he gave me 100, I'm not gonna take it."*

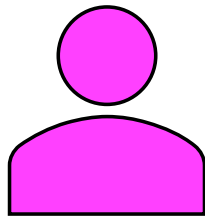


# Research: Benefits

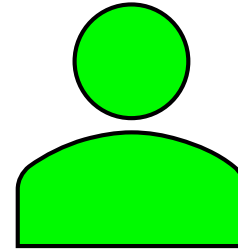
*“What’s the point in just having the blood test done and not going for research. I think that goes hand in hand...I would take it... Whatever is necessary to help the community”.*



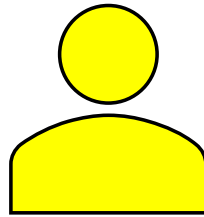
*“They got some information Asian people lack vitamin D. Apparently it's in the genes or something...majority of the Asian people, my family members, all of them, they take vitamin D”.*



*“if it benefits the community by sharing the data... with their permission, with their consent, if this is shared in the research team that’s fine also... keeping data secure, confidential with her permission.”*



*“When scientists do research there is one portion of the population but how [do] they apply that information onto the big portion of the population?”*



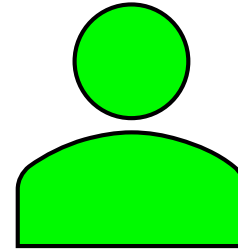
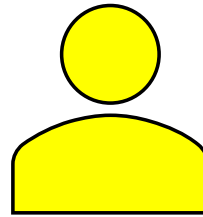
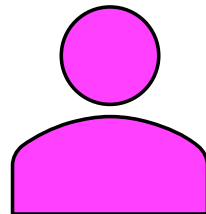
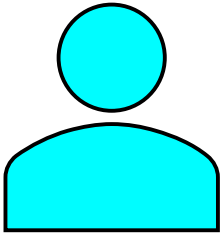
# Research: Trust

*“In theory... if someone wants to target a ...specific group of people like south Asians... if I target that gene it could set off a virus that could only affect these people...I think I’ve seen it in a film, when they target a specific gene ... they set this gas off but it will only effect people with this gene...South Asian genes”.*

*“People really don't want to share their information. They might have doubt on the people using to do research. That's why they don't want to share”*

*“If my relative did it, I might [do it]. Some people trust in relatives...People trust more family”.*

*“but when the makers know that then they will increase the prices. And you know we are very careful about our health so we will spend money.”*



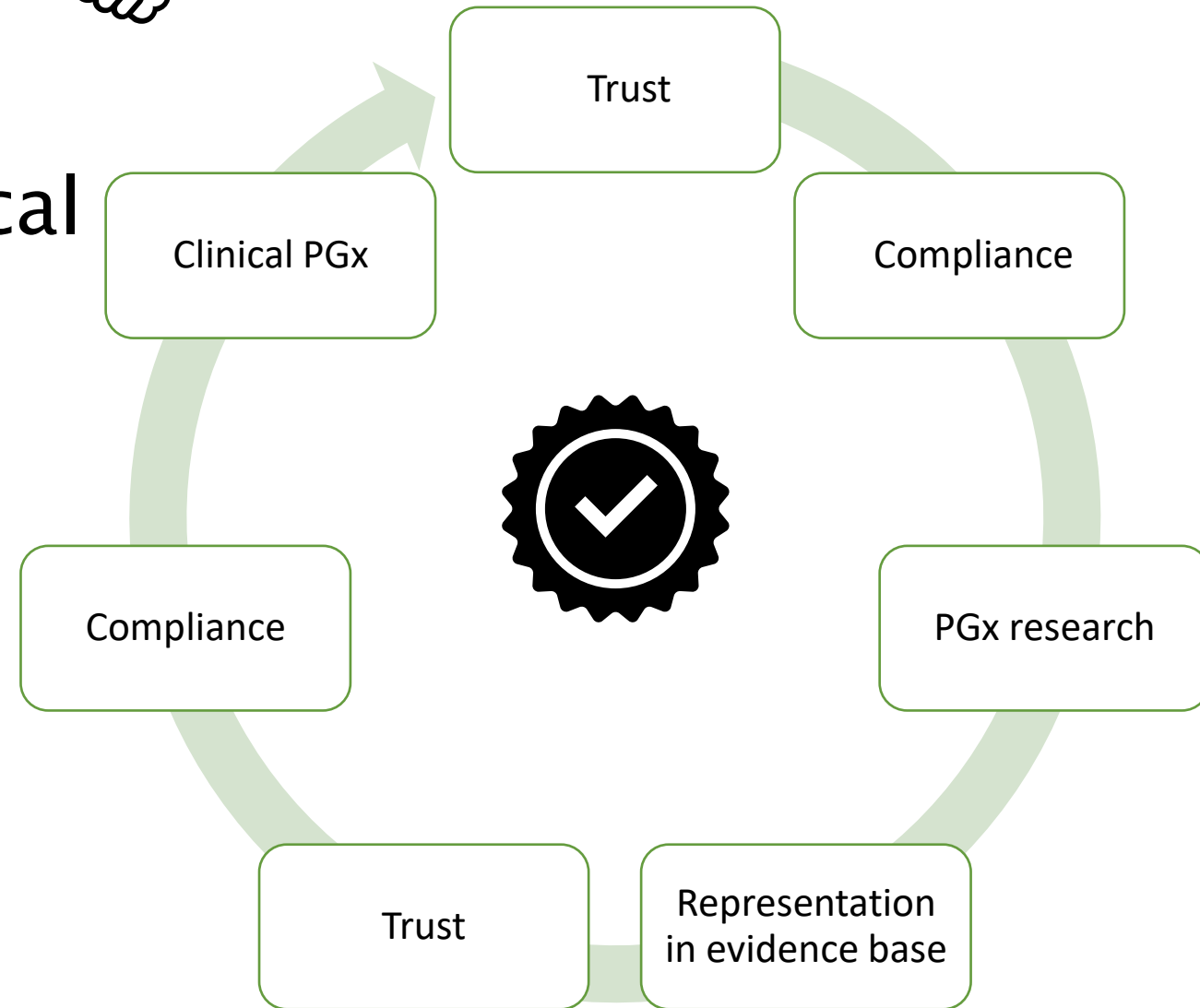


- **Implementation of pharmacogenomics** was perceived to be beneficial to individuals BUT pose a risk of overburdening resource limited systems.
- **Pharmacogenomic research** was perceived to be beneficial to the community, with concerns about data privacy and misuse.
- **Data sharing** was desirable if the researchers did not have a financial stake, and benefits would be shared. Participants feared price gouging.

# Trust



- ❖ **the key condition** for the acceptability of both clinical implementation and research
- ❖ **Trust** was linked with **medication compliance**.
- ❖ **Education, outreach, and communication** facilitate trust.





# Patient Resources

Hosted by the NHS England Pharmacogenomics Network of Excellence

<https://www.nw-gmsa.nhs.uk/patients/patient-information-and-resources>

# Acknowledgements

**RCP/BPS team involved in PGx report**

**Prof Mark Caulfield**

**Prof Damian Smedley**

**Dr Megan Clinch**

**Maia Megase**

**Jack Thompson**

**Gabriel Marengo**

**Julius Jacobsen**

## **G&H participants**

**G&H research team**

**G&H engagement team**

**Prof David van Heel**

**Dr Sarah Finer**

**Dr Helen Warren**

**Dr Ben Jacobs**



## **Funders:**

**NIHR Barts BRC**

**Barts Charity**



**Queen Mary**  
University of London





# Questions and Discussion

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