Pharmacogenomics in diverse ancestry populations: implications for medication safety and efficacy, health equality and pharmacovigilance

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Statement of originality

I, Emma Forton Magavern, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below. I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material. I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis. I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

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Details of collaboration and publications: this research was done in collaboration with the Genes & Health study using Genes & Health cohort data. Dr Magavern conceptualized the studies, undertook the quantitative and qualitative analyses (including the computation coding required for these), and wrote the papers generated. She did not participate in the Genes & Health participant recruitment or quantitative data resource generation. Where Genes & Health curated data is used it is specified throughout the text. Dr Magavern led all focus groups and study design, data generation, curation and analysis of the qualitative work

presented. A complete list of publications generated from this work can be found in the publication section.

TABLE OF CONTENTS

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ABSTRACT

Background: Personalized prescribing with genetic information can decrease adverse drug reactions (ADRs) and increase therapeutic efficacy. Health inequality is a well acknowledged problem, and British south-Asians suffer from disproportionate multimorbidity contributing to polypharmacy and are under-represented in research.

Aims: To characterise the prevalence of well validated pharmacogene variants in the Genes & Health (G&H) British-Bangladeshi and British-Pakistani population, and link these with medication exposure and real-world clinical outcome events to assess safety and efficacy outcomes. Furthermore, to engage this community in qualitative research around pharmacogenomics implementation and research acceptability.

Methods: The G&H study cohort (N = 44,396) was used to associate validated polymorphisms in two genes central to drug metabolism (*CYP2C19* and *SLCO1B1*), and Factor V Leiden (FVL), a known prothrombotic mutation, with therapeutic efficacy and adverse drug reactions, controlling for confounders as co-variates in multivariable logistic regression analyses. Thematic analysis of focus groups was undertaken to characterise participants attitudes toward pharmacogenomics.

Results: The G&H cohort have a high prevalence of loss-of-function polymorphisms in the pharmacokinetic *CYP2C19* gene. In clopidogrel exposed participants, poor metabolizer state was associated with therapeutic failure in participants who had experienced a myocardial infarction. Presence of the *SLCO1B**5 allele, a genetic proxy for increased statin exposure, was associated with lower prevalence of young onset cataracts in participants exposed to statins. The absolute risk of thrombosis associated with FVL and oestrogen use was non trivial in the context of multimorbidity. Public acceptability for pharmacogenomics implementation and research hinge on trust and trust is linked

with medication compliance. Pharmacogenomic testing may increase the likelihood of compliance on top of a direct gene-drug affect.

Conclusions: Personalised prescribing may improve clinical care for ancestry cohorts underrepresented in trial data. Pharmacogenes are useful tools to interrogate observational data for purported links between medications and adverse drug events.

INTRODUCTION

Trends in medication use, variation in drug response and associated cost of ADRs

UK epidemiologic data shows that the population is aging. People are living longer lives with more years lived with morbidity[1]. Multimorbidity, the presence of two or more long term conditions, is increasing and can lead to polypharmacy, the use of multiple medications, which can increase risk of adverse drug reactions (ADRs) due to volume of exposure and drug-drug interaction[2,3]. This has led to an increase in number of prescriptions dispensed nationally between the last two census points [4,5]. An estimated 3.8 million people in England alone take 8 or more medicines[2]. There is interindividual variation in drug response, with some individuals suffering from ADRs or not benefiting from the medication they take. It was famously estimated by a senior executive at GlaxoSmithKline that 90% of drugs only work in 30-50% of patients. Adverse reactions to medications represent 6.5% of hospital admissions in the UK and cost up to an estimated 2.2 billion pounds a year to the NHS, representing a huge economic burden alongside the impact on individuals[6–8]. Though many non-genetic factors contribute to these ADRs, some of these events arise due to interaction between genetic variants and medicines.

Pharmacogenomics

Some of the recognized interindividual variability in medication response can be explained by these interactions between genes and medications. This is referred to as pharmacogenomics (PGx). Though Drug-Gene interactions are one of the many clinically relevant factors responsible for interindividual variation in drug response, they are largely not considered in current main-stream clinical practice. Therefore, there is great potential to increase efficacy and reduce ADRs, reducing morbidity and

mortality and avoiding associated costs[9]. There is also a potential to mitigate drug-drug-gene interactions which may become more relevant in the context of polypharmacy trends cited above.

Genetic variants, or polymorphisms, can impact on medication safety and efficacy through either pharmacokinetic or pharmacodynamic mechanisms[10]. Examples of different types of variants are single nucleotide polymorphisms (SNPs), insertion-deletions (indels), structural variants such as copy number variants (CNVs), or mitochondrial variants, all of which can impact of medication safety and efficacy. Examples, some of which are explored in more detail, below include SNPs in *CYP2C19* that impact on clopidogrel efficacy, CNVs in the *CYP2D6* gene that lead to different CYP2D6 metaboliser phenotypes, with implications for antidepressants, indels in the *DYPD* gene that impact risk of 5-fluorouracil toxicity, and *MT-RNR1*, a mitochondrial variant associated with aminoglycoside induced ototoxicity.

Pharmacokinetics is often described as "what the body does to the drug". This can be understood via the body's absorption, distribution, metabolism, and excretion of a drug. Pharmacokinetic mediated pharmacogenetic interactions often involve hepatic cytochrome P450 enzymes crucial to the metabolism of many medications. Such enzymes are responsible for the conversion of inactive prodrug to active metabolite in some cases. An example of this is clopidogrel, an P2Y12 inhibiting antiplatelet agent used to treat cardiovascular, cerebrovascular, and peripheral vascular disease. Clopidogrel is an inactive prodrug and requires CYP2C19 to convert to the active metabolite[11]. In other cases, a cytochrome P450 enzyme is responsible for the hepatic mediated clearance of therapeutics. An example of this is CY2C19s role in the

clearance of several antidepressants in 2 classes: serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)[12,13]. Though these two examples of gene-drug interaction involve the same pharmacogene, in the case of clopidogrel poor metabolizers would be exposed to less active metabolite and have decreased efficacy, while in the case of CYP2C19 interaction with antidepressants poor CYP2C19 metabolizers are exposed to higher levels of systemic drug exposure, and a higher potential risk of ADRs[13–15].

Pharmacodynamics is often described as "what the drug does to the body". This can be understood as on target and off target effects. Excessive on-target effects can lead to toxicity in the form of mechanistically predictable "Type A" adverse drug reactions. Off-target effects can lead to "type B" adverse drug reactions, which can be harder to predict mechanistically. These include immune mediated adverse drug reactions. A well understood example of this type of drug-gene interaction is the occurrence of immunologically confirmed abacavir hypersensitivity syndrome in those who have the HLA-B*57:01 allele and are exposed to abacavir[16]. Abacavir is a nucleoside analog reverse-transcriptase inhibitor used to treat human immune deficiency virus. Prior to routine PGx testing before prescribing abacavir, between 5 and 7% of patients taking abacavir developed a hypersensitivity syndrome characterized by gastro-intestinal upset, rash, systemic symptoms, and fever[17]. In its most severe manifestation this could sadly be fatal. Genetic testing and treating the presence of a HLA-B*57:01 allele as a contraindication to abacavir use was a triumph of precision medicine and made immunologically confirmed cases of hypersensitivity reactions a thing of the past[17]. It has therefore become a gold standard example of clinical gains from PGx implementation, and de-risking medication by genetic risk stratification for ADR.

Unfortunately, there are not any other examples of uniformly implemented PGx in the UK to date outside of the highly personalised field of oncology.

The Clinical Pharmacogenetics International Consortium (CPIC) has developed consensus-based guidelines for gene-drug pairs where testing within healthcare may reveal the cause of an adverse reaction or inefficacy (response mode testing) or enable pre-emptive testing to avoid harm[18]. Large scale biobank analysis from the UK has shown that virtually all of us (99.5%) have at least one variant that can impact on medication response according to CPIC evidence-based guidelines[19]. English longitudinal primary care prescribing data shows that 89% of people over 70 years had been prescribed at least one drug linked with a pharmacogene, and 1 in every four patients over 70 years old had been exposed to at least 5 drugs with a validated drug-gene interaction[20]. With the publication of the PREPARE trial, an open label, multicentre, controlled, cluster-randomised crossover implementation study that showed a 30% reduction in ADRs with pre-emptive genotype guided therapy, the question is more how than if PGx should be implemented clinically[9]. A major concern and limitation of evidence generated to date is the bias in data due to unequal representation in research of diverse ancestry participants.

<u>The importance of pharmacogenomics studies in diverse populations</u>

We already know there are ancestry specific heightened risks of adverse drug reactions e.g. specific HLA haplotypes in East Asians leading to increased risk of Steven's Johnson Syndrome and G6PD deficiency may lead to haemolysis in African communities[21,22]. This underscores the need for a comprehensive inventory of pharmacogenomic variants across all communities.

To date the majority of PGx discoveries arise from studies of populations of European heritage[23]. The focus of this proposal is on the importance of exploring the real-world health associated outcomes of several validated PGx variants in the UK British-South Asian community of Bangladeshi and Pakistani ancestry. It is vital to do this because South Asian communities in the UK have high rates of several common diseases such as diabetes, cardiovascular disease, metabolic syndrome, and mental illness leading to a heightened risk of multimorbidity and poly-pharmacy which may place them at risk of a PGx reaction. Furthermore, South Asian populations have not been proportionately represented in research and clinical trials historically. Such studies form the bases of regulatory decisions for medication licensure and therefore there is the potential for built-in inequity in health outcomes from use of any drug that interacts with a pharmacogene with significant trans-ancestry differences in prevalence. Many of the most well characterized pharmacogenes are already known to have significant trans-ancestry differences in prevalence of clinically relevant single nucleotide polymorphisms. Elucidating potential health equity implications of these known differences may help to work toward greater health equality.

There is also increasing awareness that where there is a gene-drug interaction, and the prevalence both of the disease and pharmacogene vary between ancestry groups, traditional randomized controlled trials can be confounded if they do not control for relevant genetic polymorphisms. This is heralding a new era in drug discovery with recall by genotype studies. However, there is also a post-hoc pharmacovigilance potential in observational data with genotype information. Studying validated

pharmacokinetic variant gene-drug association with potential ADRs in on-drug compared to off-drug cohorts offers a novel approach to the use of observational data, which reduces potential for confounding.

The Genes & Health cohort

Genes & Health (G&H) is a population cohort study, including those of British-Bangladeshi and British-Pakistani ancestry living in East London [24]. This is an important ethnic cohort as South Asian population represents almost 25% of the world's population and a rapidly growing demographic in the UK, now representing 10% of the national population[25]. Furthermore, the East London South Asian UK population is disproportionately affected by cardio-metabolic disease and multimorbidity and suffers from a shorter life expectancy than counterparts[26,27]. Some of this can be attributed to disproportionate rates of socioeconomic deprivation[24]. In addition, South Asian ancestry populations are under-represented in both genomics studies and clinical trials which provide the data that underpin therapeutic licensure by regulators[23,28,29].The British South Asian ancestry population suffers from high rates of multimorbidity and will therefore be exposed to polypharmacy. This means they are more likely to experience adverse drug events, drug-drug interactions, and drug-gene as compared with other populations due to exposure to higher numbers of medications.

The importance of public acceptability work alongside pharmacogenetic validation studies in diverse cohorts

Public acceptability work must take place in parallel with research which validates PGx variants in diverse ancestry cohorts and discovery of ancestry specific pharmacogene variants. This is because relationships between under-represented communities and scientific communities have often been fraught with mistrust. To ensure PGx benefits patients from

diverse communities we must work to ensure representation in scientific research but also extensive consultation to support a successful PGx implementation programme.

METHODS

The quantitative analyses presented in this thesis utilize the G&H resource. An overview of the methods common to the different studies presented within the scope of this work is shown here. Further details specific to each study are presented within each chapter.

The methods of data collection for the G&H resource have been previously described [24]. In summary, greater than 44,000 volunteers (at the time of these analyses) were recruited, donated saliva for DNA extraction, completed questioners and gave consent to link to their electronic health records. Participants were genotyped, as previously described on the Illumina GSAMD-24v3-0-EA genotyping chip, and imputation was undertaken using the TOPMED-r2 dataset[30]. The Genome Research Consortium human build 38 was used. All work with the G&H cohort was undertaken in the Trusted Research Environment (TRE). Detailed clinical characteristics of the G&H cohort have been published[24]. A major strength of this resource for PGx research is the complete medication data supplied by primary care linkage for participants from the following clinical commissioning groups (CCGs): Barking, Havering and Redbridge (BHR), Tower Hamlets (TH), Waltham Forest (WF) and Newham (N).

G&H curated phenotypes were used. These phenotypes were defined using ICD10 codes, SNOMED codes, and Office of Population Censuses and Surveys (OPCS) codes from linkage with electronic health records, including Barts Health, NHS digital, Bradford teaching hospitals and primary care CCGs. The methodology and code used to generate these curated phenotypes is based on UK Biobank (UKB) methodology and available via the G&H website (https://www.genesandhealth.org/)[31,32]. ICD-10 codes were identified in Barts health secondary care data, Bradford Teaching Hospitals NHS Trust, and NHS Digital Hospital Episode Statistics, and Mortality. Primary care and secondary care SNOMED codes were then mapped to the ICD-10 code lists to capture the first recording of the code (1:1 mapping).

G&H has made available to all users in the TRE curated principal components as published in a prior analysis[30]. These are used as co-variates to control for population stratification in several of the studies described in this thesis.

Multivariable logistic regression was utilised in several of the studies presented. Assumptions of this model satisfied for these analyses include: linearity, no outliers, independence and no multicollinearity.

We have noted that several of the variants used are in Hardy-Weinberg disequilibrium. Assumptions of Hardy-Weinberg equilibrium include: random mating, no gene flow, infinite population size, no mutation, and no natural selection. We believe that this disequilibrium is most likely the result of demonstrated endogamy in this population, leading to high frequency loss of heterozygosity[33].

AIMS AND HYPOTHESIS

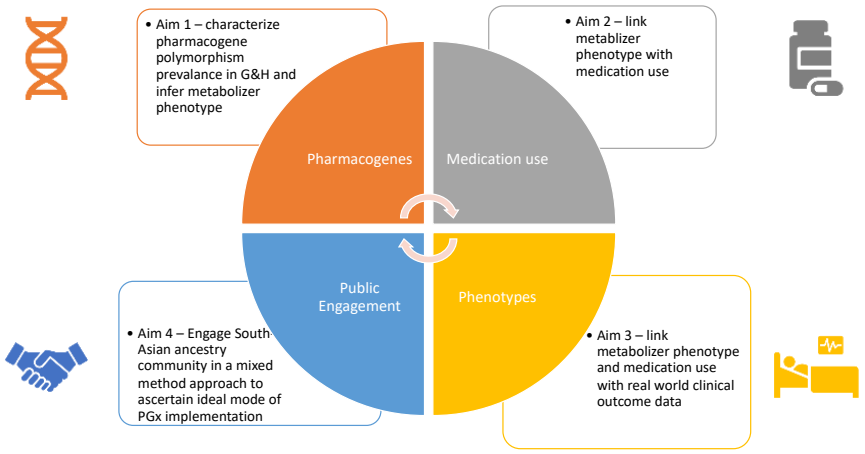
Aims:

1. To use the G&H study to characterise the prevalence of well validated pharmacogene variants in a British-Bangladeshi and British-Pakistani population and infer linked metabolism phenotype.

2. To use the G&H study to link pharmacogene variants and inferred metabolizer phenotypes with primary care prescribing data to establish drug exposure.

3. To link G&H study participants inferred metabolism phenotype and medication exposure with real world national outcome data to assess safety and efficacy outcomes by genotype.

4. To engage the UK South-Asian community in qualitative research around pharmacogenomics implementation and research acceptability in collaboration with G&H.



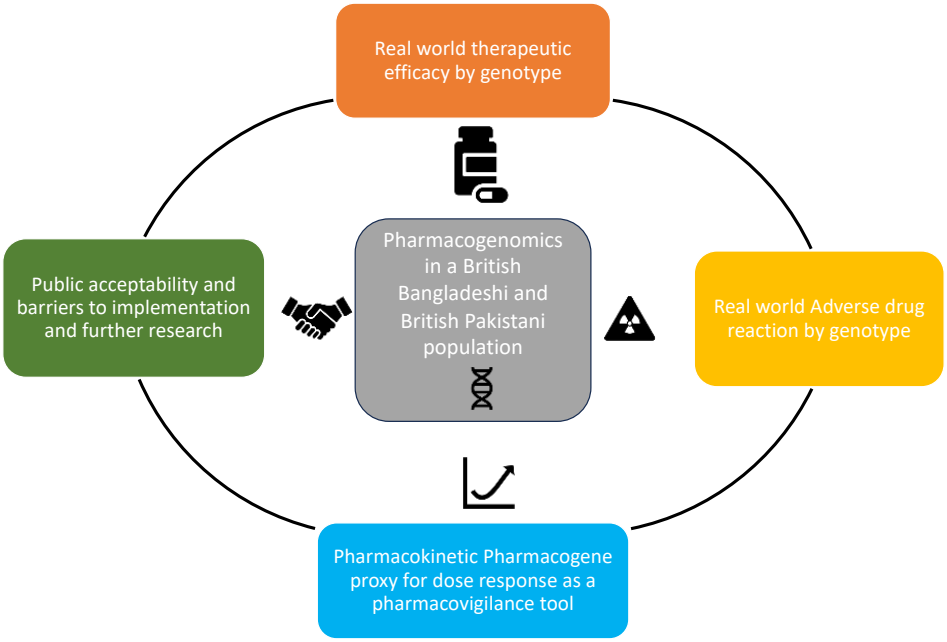
Hypothesis:

We postulated that the burden of multimorbidity and polypharmacy in the British-Bangladeshi and British-Pakistani community may demonstrate the potential real-world impact of pharmacogenes on health outcomes in an understudied population and underserved population. We hypothesize that lack of representation in research means that this cohort may have different pharmacogene allele prevalence from populations engaged in the clinical trials which generate the evidence underpinning medication risk/benefit profile.

<u>This study will be outlined in six chapters</u>:

1. <u>Chapter 1</u>: Association of validated pharmacokinetic polymorphisms in the *CYP2C19* gene with risk of failed secondary prevention for myocardial infarction in participants prescribed clopidogrel.

2. Chapter 2: Association of inferred CYP2C19 metaboliser state with GI bleeds and antidepressant use, to inform potential to decrease GP bleeds with CPIC pre-emptive genotype guidance.
3. Chapter 3: Use of *SLCO1B1*5* as a genetic proxy for increased stain exposure to interrogate a dose response relationship between statin use and cataracts.
4. Chapter 4: The association of Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism: considering the implications of additive relative risk in addition to a shifting baseline absolute risk profile due to multimorbidity.
5. Chapter 5: Equal Access to Pharmacogenomics Testing: The Imperative for Population Wide Access in the UK NHS. An exploration of which subpopulations are participating in pilot pharmacogenomics programmes in UK clinical care in the NHS, and why extrapolation may prove problematic.
6. Chapter 6: A thematic analysis of British South-Asian ancestry participants views of pharmacogenomics clinical implementation and research to inform future work.



Ethics

The G&H resource was accessed for this research after approval by the G&H Access Review Committee. G&H operates under ethical approval, 14/LO/1240, from London South East NRES Committee of the Health Research Authority, dated 16 September 2014.

The qualitative research described in this thesis was done in collaboration with G&H and with institutional ethics approval. It was approved by the Queen Mary University of London Research Ethics Committee (QMERC22.353). Written informed consent was obtained for participation in the study. Participants were given a 50 GBP voucher to thank them for their time and participation.

Section 1

Characterization of known CPIC Pharmacogenes and association with clinical phenotypes in the G&H population

CHAPTER 1

Characterization of well validated *CYP2C19* genotypes and association with recurrent myocardial infarction in the G&H population

1.1 INTRODUCTION: *CYP2C19* genotypes and association with recurrent myocardial infarction

Pharmacogenomics is the use of genetic information to understand differences in response to medications, namely variability in dose requirement, efficacy, and toxicity. This can be due to differences in genes that impact on the pharmacodynamics or pharmacokinetics of a medication.

1.11 Cytochrome P450 2C19 (CYP2C19)

CYP2C19 is a hepatic enzyme crucial to the two-stage sequential oxidation of clopidogrel (inactive prodrug) to the active metabolite[11]. The *CYP2C19* gene which codes for the enzyme is highly polymorphic. Three key variants are referred to as *2, *3 and *17[34]. The *2(c.681G>A) and *3 (c.636G>A) allele both results in an early stop codon, and therefore a truncated and non-functional protein (loss of function (LOF))[15]. The *17 (c.-806C>T) is a transition in the promoter region that increases enzyme expression and activity, thereby conferring gain of function leading to increase active metabolite[15]. Pharmacokinetic studies have demonstrated lower active metabolite concentrations leading to decreased platelet response to clopidogrel in intermediate (IMs) and poor metabolizers (PMs); the inverse is true of rapid and ultra-rapid metabolizers, in a dose dependent fashion[35,36]. Poor and intermediate metabolizers have been linked with higher risk of further cardiovascular events on clopidogrel, while some studies have suggested rapid or ultra-rapid metabolizers may have a higher risk of bleeding[35,37]. Although there are known to be substantial transethnic differences in the prevalence of validated SNPs *2, *3, *17, many ethnic subgroups have not been investigated to date in resources with clinical outcome data.

1.12 Clopidogrel

Clopidogrel is an P2Y12 inhibiting antiplatelet medication licensed to treat acute coronary syndrome (ACS), stroke and peripheral vascular disease[38]. Even though the European Cardiology Society and national guidelines have advocated the use of ticagrelor or prasugrel (non CYP2C19 dependent P2Y12 antagonists) over clopidogrel due to clinical trials showing superior efficacy, clopidogrel remains widely used[39,40]. This may be due to concerns about the higher bleed risk and increased cost of ticagrelor and prasugrel.

1.13 Regulatory and consortia guidance

Regulatory bodies and PGx consortium have given disparate guidance. The US Food and Drug Administration (FDA) recommends considering an alternate drug in PMs, while the European Medicines Agency (EMA) merely discourages the co-use of CYP2C19 inhibiting drugs with clopidogrel[38,41]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends an alternate therapy in IMs or PMs generally but classifies PMs and those who have percutaneous coronary intervention (PCI), as populations at higher risk of treatment failure within that group. [15]. The Dutch Pharmacogenetics Working Group (DPWG) recommends an alternate drug for PMs in those undergoing PCI, and an alternate drug or increased dose of clopidogrel for IMs undergoing PCI[42].

1.14 Lack of diverse representation in evidence base

People of diverse ethnic ancestry may have different population prevalence of genetic loci leading to different response to the same therapeutic agent between populations. A prospective pharmacogenomics approach to prescribing, in which genotype is checked prior to medication prescription, is not standard of care at present. The case for implementation therefore must be proved as an improvement on current standards. Thus, the assumption is that we are at equipoise at baseline without implementation of pharmacogenomics. This may be a flawed assumption and the burden of prescribing without prospective genotype may not be equally bourn by diverse ethnic groups. One of the underlying causes is that medications have historically been trialled in Caucasian ethnicity populations. The regulatory approval outcome studies of clopidogrel in ACS did not include representative participation from communities at higher risk of an adverse drug reaction based on genetic data [38,43–49](Table 1).

Table 1: Studies supporting clopidogrel licensure as listed in the European Medicines Agency summary of product characteristics[38,43–49] . The only study with a substantial Asian population was focused on stroke rather than myocardial ischemia and undertaken in East Asia.

Studies supporting clopidogrel licensure (EMA)

Study	Year	Ethnic group representation	Indication
CAPRIE study	1996	91%-98% of all subgroups "white"	Atherosclerotic vascular disease
CURE study	2001	Not specified	Acute coronary syndromes without ST elevation
CLARITY study	2005	89.5% "white"	ST elevation myocardial infarction
COMMIT study	2006	Not specified	Myocardial infarction
ACTIVE-A	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
CHANCE study	2013	Not specified but conducted in China	TIA or minor ischemic stroke
POINT study	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

1.2 AIMS AND HYPOTHESIS: *CYP2C19* genotypes and association with recurrent myocardial infarction

- The purpose of this study was to investigate the prevalence of variants in the highly polymorphic *CYP2C19* gene in the G&H cohort and to see if genetically inferred CYP2C19 metaboliser type was associated with decreased therapeutic efficacy of clopidogrel for secondary prevention in a sub-cohort with ischemic heart disease. CYP2C19 is a hepatic enzyme involved in the metabolism of clopidogrel from a prodrug to its active metabolite. Few studies have looked at metabolizer genotypes and their relationship with clinical efficacy in South Asian populations.

- We hypothesized, based on existing global genetic data, that the G&H population with high rates of ischemic heart disease may also have high rates of genetically predictable inefficacy from clopidogrel. We further postulated that a validation study in this cohort would reproduce the relationship between diplotype and efficacy demonstrated in primarily European ancestry population.

1.3 METHODS: *CYP2C19* genotypes and association with recurrent myocardial infarction

1.31 Genotype/Imputation quality control

As our metabolizer status was determined by 3 SNPs, quality control checks were undertaken for these variants. The *2 SNPs was imputed, and the imputation quality was very high as assessed by imputation quality metric (INFO) score (0.99). The *3 allele and *17 allele were genotyped. INFO score, MAF, HWE, and missingness for these 3 SNPs are in table 2. There was not substantial missingness. The population was not in Hardy-Weinberg equilibrium (HWE) for the *2 and *17 allele, likely due to previously reported relatedness (random mating is an assumption of HWE). However, the 3 SNPs used did not deviate from HWE in the subpopulation studied for clinical outcomes (those that had an MI and were treated with clopidogrel) (table 2).

Table 2: Genotype and imputation metrics

SNP	***2**	***3**	***17**
Mutation	c.681G>A	c.636G>A	c.-806C>T
Chromosome location	chr10:94781859	chr10:94780653	chr10:94761900
Rs	rs4244285	rs4986893	rs12248560
MAF	0.3412	0.006	0.152
HWE p-value (N=44,396)	4.0e-14	0.17	1.5e-10

HWE p-value MI analysis (N=697)	0.45	1	0.53
Proportion of sample missing (N=44,396)	0.00045	0.001509	0
INFO Score	0.99		

1.32 Characterization of *CYP2C19* genotype, diplotype, and phenotype in G&H Cohort

The *CYP2C19* genotypes were ascertained by characterizing population prevalence of the known PGx *2, *3 and *17 alleles influencing enzymatic function. SNPs were extracted from the data set using PLINK 2.0[50,51]. The *2 allele was defined as c.681G>A, rs4244285 (chr10:94781859). The *3 allele was defined as c.636G>A, rs4986893 (chr10:94780653). The *17 allele was defined as (c.-806C>T), rs12248560 (chr10:94761900).

Subsequent analysis was done using Rstudio[52]. Any participant with one LOF SNP (either *2 or *3) was designated as an intermediate CYP2C19 metabolizer. Any participant with two LOF SNPs was characterized as a poor metabolizer. Any participant with one *17 allele (in absence of a *2 or *3 allele) was designated a rapid metabolizer, and those with two *17 alleles were designated as ultra-rapid metabolizers. The prevalence of these genotypes, diplotypes, and corresponding phenotypes were then compared with published population prevalence data provided by CPIC and with those represented in major recent randomized control trials (RCTs) looking at pharmacogenomics implementation.

1.33 Linking CYP2C19 predicted phenotypes with recurrent myocardial infarction in participants prescribed clopidogrel

Curated data sets from G&H (as described prior in the methods section) were used for clinical phenotypes including acute myocardial infarction (MI) (ICD 10 code I21),

subsequent MI (ICD 10 I22), Diabetes mellitus (DM)(E10; type 1 diabetes mellitus, E11; type 2 diabetes mellitus, E13; other specified diabetes mellitus, E14; unspecified diabetes mellitus), Dyslipidaemia (ICD 10 code E78), Obesity (ICD10 code E66), Chronic Kidney Disease (CKD) (ICD10 code N18) and (Hypertension (HTN) ICD 10 code I10).

The prevalence of clopidogrel prescription in the population who had experienced an acute MI was first ascertained using the G&H curated acute MI phenotype. The medication data was obtained from the primary care prescribing data via those CCGs that are linked with G&H (BHR, TH, WF and N). We therefore limited our analyses to only those participants who had medication data available from these CCGs (84.4% of the initial cohort). The cohort who had been prescribed 75mg clopidogrel in their GP records were then assessed for subsequent MI events. The presence of known cardiovascular disease (CVD) risk factors in the recurrent MI cohort (including obesity, HTN, DM, dyslipidaemia, CKD, and smoking status) was also recorded. The co-morbidity phenotypes were curated by G&H as described above. Smoking status was defined in primary care records by using SNOMED codes to distinguish never-smokers from those who had ever smoked. Participants were classed as ever having smoked if they had a code in any of the smoking or ex-smoking categories, and never having smoked if they didn't have any codes associated with smoking or ex-smoking and had a code of never or currently not smoking. PCI with stent insertion was defined by presence of ICD 10 code Z955, "presence of coronary angioplasty implant and graft" and was found by searching Barts Health electronic data from the research database in the G&H TRE.

1.34 Statistical methods

Fisher's Exact Test was used to compare baseline characteristics of those who had a recurrent MI from those who did not in the index acute MI population.

Multivariable logistic regression was performed to look for association of *CYP2C19* diplotypes with recurrent MI in those who had been prescribed clopidogrel by the GP in the secondary prevention dose (75mg). Four levels were used for the CYP2C19 inferred metabolizer type variable: poor, intermediate, and ultra-rapid metabolizers, with normal and rapid metabolizers as the reference group. Adjustments were made for sex, age at enrolment, and known CVD comorbidities (DM, HTN, dyslipidaemia, obesity, CKD, having ever-smoked). Given that the published literature suggests possibly higher risk of in-stent-thrombosis in poor or intermediate metabolizers on clopidogrel and that there were a lower percentage of those who had stents prescribed clopidogrel, we also adjusted for stent insertion[53]. There were 14 participants in the acute MI group, which included 1 participant in the recurrent MI group, for which no PCI data was available. These participants were removed for logistic regression incorporating PCI data. The participant in the recurrent group who was excluded from this analysis for the missing data was a normal metabolizer. The 39 participants with recurrent MIs who had been prescribed clopidogrel were unrelated as assessed by G&H curated KING analysis[54]. Multicollinearity was assessed using the variance inflation factor of the car package in Rstudio[55]. Sensitivity analysis was undertaken using the principal component analysis inferred ethnicity curated by G&H. 20 G&H curated principal components were co-variates in a second logistic regression to control for population stratification.

1.4 RESULTS: *CYP2C19* genotypes and association with recurrent myocardial infarction

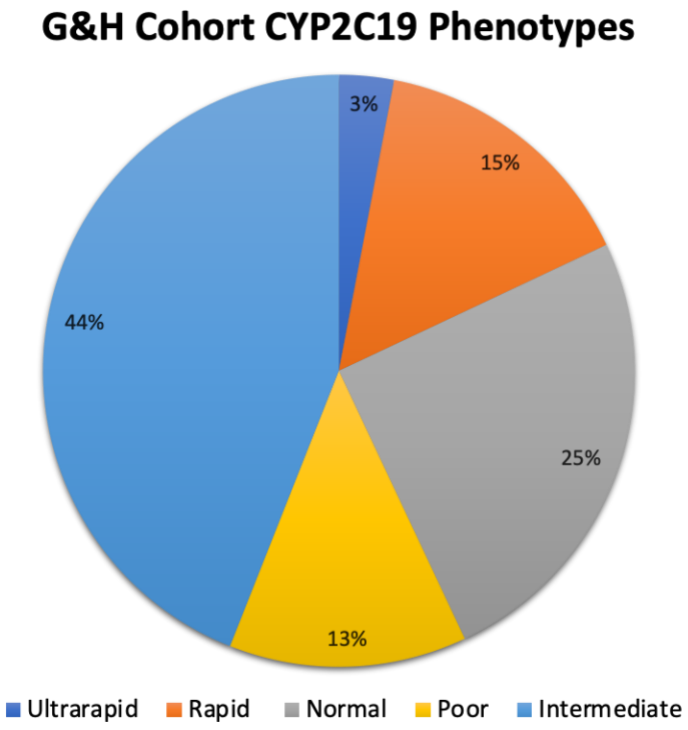
1.41 Characterization of *CYP2C19* genotypes in G&H cohort

The *2 allele was very common in the G&H cohort, with 56% (24949 /total population N 44,396) of the population having at least one copy present. The *3 allele was less common, with 1.2% (532/44,396) having at least one copy. 27.6% of the cohort had at least 1 copy of the *17 increased function allele (12,264/44,396).

1.42 *CYP2C19* diplotypes and inferred metabolizer phenotypes

Denoting as any participants carrying at least one LOF allele (*2 or *3), 57% of the cohort are intermediate or poor metabolizers. 5,816 (13%) carry two LOF alleles and are poor metabolisers while a further 19,479 (44%) carry one LOF allele and are intermediate metabolisers (Figure 1).

Figure 1: Inferred CYP2C19 metabolizer phenotypes in G&H cohort population.



2.7% (1,197/44,396) were homozygous for the *17 allele and were therefore designated ultra-rapid metabolizers. Figure 1 illustrates that normal CYP2C19 metabolizers then represent only 25% of this population. This is a concern because it diverges from representation of SNP prevalence in largely European ancestry landmark clinical trials on PGx in the context of clopidogrel and CYP2C19 in acute MI. Table 3 compares this cohort metabolizer status with expected in European and Central/South Asian populations, and those reported in major recent PGx clinical trial cohorts assessing efficacy of precision genomic guided clopidogrel therapy [56–60].

Table 3: Comparison with biogeographic and trial cohorts [56–60] . The TAILOR PCI and POPular Genetics trials were the two major randomized controlled trials to assess a genomic guided approach to antiplatelet prescribing in ischemic heart disease[59,60]. The Clinical Pharmacogenetics International Consortium (CPIC) considers a large number of *alleles, while we only considered only the three most validated variants for clinical impact (*2 and *3 together account for 99% of all LOF). Each row value is rounded to the nearest whole number.
* = not specified.

Comparison with biogeographic and trial cohorts

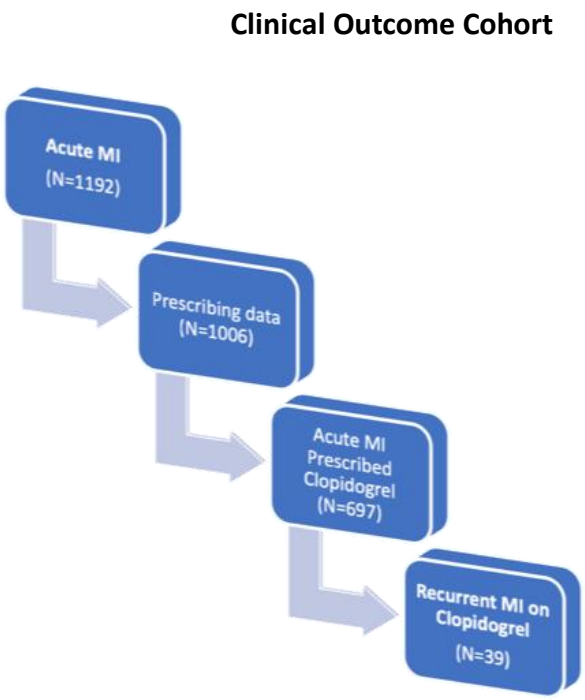
Phenotype	G&H Cohort	CPIC Central/South Asian	CPIC European	TAILOR PCI Trial	POPular Genetics Trial
Rapid or Ultrarapid	18%	21%	32%	*	*
Normal	25%	30%	40%	*	67%
Poor	13%	8%	2%	*	3%
Intermediate	44%	41%	26%	*	29%
Poor or Intermediate	57%	49%	29%	35%	31%

1.43 Prevalence of clopidogrel prescriptions in cohort with acute MI

Medication data was available for those participants with linked primary care records (participating CCGs), which represented 84.4% of the acute MI cohort (1006/1192). We only

included participants with prescribing data in our analysis. As antiplatelet choice post-MI is led by tertiary centres there is not expected to be any bias based on CCG linkage. The percentage of those who had an acute MI who were prescribed clopidogrel was 69.3% (697/1006) (Figure 2).

Figure 2: Linking medication data with clinical outcomes. Medication data was linked for 84.4% of those in G&H diagnosed with an acute MI: of those 69% were prescribed clopidogrel in primary care records. The recurrence of MI in those prescribed clopidogrel was 5.6%.



For the subgroup who had a stent inserted it was lower, 44.2% (410/928). Of those 697 participants who had an acute MI and were prescribed clopidogrel by their GP, 39 of them had recurrent MIs (5.6%) (Figure 2). Characteristics of the cohort with acute myocardial infarction (MI) are noted in Table 4. Those with recurrent MIs were older and more likely to have PCI.

Table 4: Comparison of cardiovascular risk factors and outcomes in the Genes & Health cohort who had acute myocardial infarction (MI) and were prescribed clopidogrel. It shows separately the subgroup who had a recurrent MI and those who did not. The comparison of characteristics was done using fisher's exact test comparing those prescribed clopidogrel who had a recurrent MI with those who did not.

Comparison of Characteristics

Characteristic	Acute MI – Prescribed Clopidogrel (697)	No Recurrent MI (658)	Recurrent MI (39)	P value
Male	80% (556/697)	79% (520/658)	92% (36/39)	0.06
Diabetes	71% (493/697)	70% (460/658)	85% (33/39)	0.07
Hypertension	91% (633/697)	90% (595/658)	97% (38/39)	0.25
Dyslipidemia	90% (625/697)	89% (587/658)	97% (38/39)	0.17
Obesity	46% (218/697)	31% (206/658)	31% (12/39)	1
Chronic Kidney Disease	38% (267/697)	38% (247/658)	51% (20/39)	0.09
Smoker	90% (624/697)	90% (589/658)	90% (35/39)	1
Percutaneous Coronary Intervention	60% (410/683)	59% (380/645)	79% (30/38)	0.02*
Mean Age at enrollment	61 years old	60 years old	67 years old	<0.0001**

1.44 Linking CYP2C19 phenotypes with clinical outcomes: recurrent myocardial infarction in cohort prescribed clopidogrel

Multivariable logistic regression adjusting for age, sex, cardiovascular co-morbidities, smoking and stent insertion showed a significant relationship between poor CYP2C19 metabolizers (OR 3.1, CI 1.2-8.1, p-value, 0.02) and UM CYP2C19 metabolizers (OR 10, CI 1.9-47, p-value 0.003), and recurrent MI. The p value for intermediate metabolizers (N = 15) was not statistically significant with p-value 0.36 (Table 5).

Table 5: Risk of repeat MI in cohort prescribed clopidogrel. Multivariable logistic regression analysis was used and adjusted for age, gender, cardiovascular disease risk factors (smoking,

diabetes mellitus, hypertension, obesity, dyslipidaemia, chronic kidney disease) and percutaneous coronary intervention.

Risk of recurrent MI

Risk factor	Risk of Recurrence of MI (Odds Ratio)	95% CI	P-value
Poor CYP2C19 metabolizer	3.1	1.2-8.1	0.019 *
Intermediate metabolizer	1.5	0.65-34	0.356
Ultra-rapid metabolizer	10	1.9-47	0.003 *
Increased Age at recruitment	1.04 (per year)	1.01-1.08	0.009 *

Reclassification of *2/*17 or *3/*17 from intermediate to normal metabolizers for sensitivity analysis did not change results. Apart from *CYP2C19* diplotype, increased age at recruitment was the only other factor found to increase risk of a subsequent ischemic event in the cohort prescribed clopidogrel (Table 6). The diagnosis of obesity, HTN, dyslipidaemia, DM, CKD or ever-smoking status was not significantly independently associated with recurrent MI risk in the cohort prescribed clopidogrel (though prevalence of all known risk factors was high). Multicollinearity was not found to be present. Sensitivity analyses to correct for genetically determined sub-ancestry group (British-Bengali vs British-Pakistani) did not alter the findings (p for interaction 0.8). 20 principal components curated by G&H were controlled for to ensure our results were not biased by population stratification (Table 6).

Table 6: Risk of repeat MI in cohort prescribed clopidogrel – adjusted for principal components. Multivariable logistic regression analysis was used and adjusted for age, gender, cardiovascular disease risk factors (smoking, diabetes mellitus, hypertension, obesity,

dyslipidaemia, chronic kidney disease) and percutaneous coronary intervention. 20 Principal components were also controlled for in this model.

Risk of recurrent MI – Controlled for Principal Components

Risk factor	Risk of Recurrence of MI (Odds Ratio)	95% CI	P-value
Poor CYP2C19 metabolizer	3.7	1.3-10	0.012 *
Intermediate metabolizer	1.8	0.75-4.5	0.201
Ultra-rapid metabolizer	20	3-110	0.001 *
Increased Age at recruitment	1.05 (per year)	1.02-1.09	0.005 *

Table 7 shows the number of patients in the acute MI and recurrence cohort stratified by metabolizer status.

Table 7: Ischemic events in those prescribed clopidogrel stratified by CYP2C19 Metabolizer type. The percentage to experience a recurrent MI decrease steadily from poor metabolizers to rapid metabolizers as expected, with decreased generation of active metabolite expected to impact efficacy. The higher percentage of ultra-rapid metabolizers to experience a recurrence likely represents therapeutic intolerance.

CYP2C19 Metabolizer status of the G&H cohort prescribed clopidogrel

Events	Poor Metabolizer	Intermediate Metabolizer	Normal Metabolizer	Rapid Metabolizer	Ultrarapid Metabolizer	Total N=
Acute MI	90	301	199	96	11	697
Subsequent MI	9	15	9	3	3	39
Percentage	**10.0%**	**5.0%**	**4.5%**	**3.1%**	**27.3%**	**5.6%**

As the primary interest for clinical implementation is *CYP2C19* LOF variants and clopidogrel resistance, the 11 ultra-rapid metabolizers were excluded and LOF diplotypes changed to a linear variable where the unit was LOF allele (0, 1, or 2). This was undertaken to elucidate the impact of LOF alleles more clearly in absence of the UR diplotype which is an outlier in the trend of interaction between metabolizer type and clinical outcome (Table 8). The results show an OR of 1.9 (CI 1.2-3.3 (p-value - 0.01)) per LOF allele.

Table 8: Risk of repeat MI in cohort prescribed clopidogrel. Multivariable logistic regression analysis was used and adjusted for age, gender, cardiovascular disease risk factors (smoking, diabetes mellitus, hypertension, obesity, dyslipidaemia, chronic kidney disease) and percutaneous coronary intervention, as well as 20 principal components. CYP2C19 LOF diplotypes were parametrized to a continuous variable where the unit was LOF alleles, 0 for none, 1 for one (intermediate metabolizer), 2 for 2 (poor metabolizer)

CYP2C19 LOF relationship with recurrent MI risk in logistic regression

Risk factor	Risk of Recurrence of MI (Odds Ratio)	95% CI	P-value
CYP2C19 LOF allele	1.9	1.2-3.3	0.01*
Increased Age at recruitment	1.05 (per year)	1.01-1.09	0.01 *

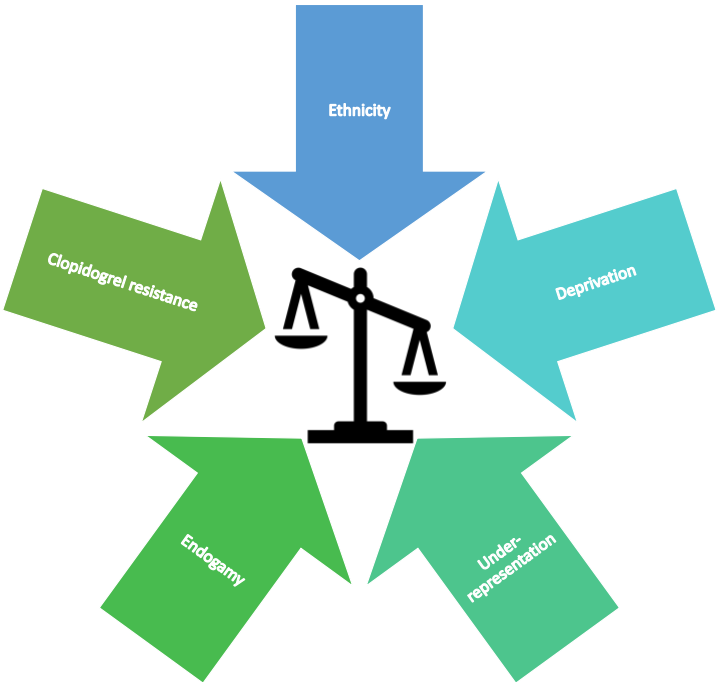
1.5 DISCUSSION: *CYP2C19* genotypes and association with recurrent myocardial infarction

This study demonstrates that the prevalence of genetically inferred poor and intermediate CYP2C19 metabolizers is higher in this British-South Asian ancestry cohort than previously known based on estimates of South Asian populations, and substantially higher than has been

shown in people of European ancestry. This is due to the high prevalence of the *CYP2C19* *2 allele in the G&H population. This work demonstrates the value of using real-world cohort study data to link CYP2C19 poor metabolizers with clopidogrel resistance. Although the *2 allele in this cohort may be particularly prevalent due to non-random mating, the prevalence of poor and intermediate metabolizers is known to be very high in Asian populations generally[58]. Marriage practices and kinship structure among south Asian sub-populations may enrich certain variants in subgroups. Cardiovascular disease is known to be more prevalent in south Asian populations as compared with east Asian counterparts.

Given the increased cardio-metabolic risk in this cohort, these participants therefore have both a higher risk of having an indication for clopidogrel and a higher risk of clopidogrel failure due to increased prevalence *CYP2C19* LOF genotypes than counterparts of European ancestry (Figure 3).

Figure 3: Tipping the scales- Intersection of risk factors amplify risk of CV disease and of resistance to clopidogrel, contributing to health inequality.



Our findings highlight the potential risks of assuming therapeutic potential from licensing trials for diverse communities by extrapolation of benefits and risks from studies in largely Caucasian European ancestry populations. It is further problematic that large RCTs assessing potential benefit of genotype guided prescribing of clopidogrel don't proportionately represent diverse world populations. It is interesting to note also that although PM diplotype was significantly associated with risk of recurrent MI in this cohort, the mere diagnosis of known CVD risk factors (obesity, diabetes, dyslipidaemia, hypertension, CKD, having ever smoker) were not. This is perhaps not surprising as they all have coronary artery disease already.

British- South Asians in the G&H cohort are very likely to receive clopidogrel, with more than two in every three participants with an acute MI in the G&H cohort receiving clopidogrel. International data suggests that this high prevalence of clopidogrel prescribing may be representative[61,62]. A recent large Canadian cohort study in ACS patients who underwent PCI showed that 63.6% were prescribed clopidogrel (though prescribing did decrease slightly over time)[62]. One potential explanation for the continued prevalence of clopidogrel prescription is cost. In the UK, for example, the cost of 1 month of ticagrelor is 54.60 GBP as compared with clopidogrel, 1.24 GBP[63,64]. These factors underline the relevance of continued attention to clopidogrel pharmacogenomics.

A pragmatic and often cited counter argument to genotype guided antiplatelet prescribing is universal prescription of ticagrelor or prasugrel. However, the POPular genetics RCT trial has conclusively demonstrated that a genotype guided de-escalation of antiplatelet therapy, where poor or intermediate CYP2C19 metabolizers are given ticagrelor or prasugrel and others are

given clopidogrel, is non-inferior to universal ticagrelor/prasugrel prescription in terms of thrombotic events[60]. Importantly, the risk of bleeding was significantly reduced with this approach (hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P=0.04)[60]. Therefore, if bleeding can be reduced and an equally efficacious medication used which costs less, genotyping seems likely to be cost-effective, particularly in the context of decreasing costs associated with genetic testing and/or a panel PGx approach. Indeed, real world health economic data published by the IGNITE -PGx group suggests that it would be[65]. These authors demonstrate that genotype guided escalation of therapy, using clopidogrel as the base case, was cost-effective compared with universal prescription of ticagrelor [65].

While these data convincingly demonstrate an increased risk of failed secondary prevention for CYP2C19 poor metabolizers prescribed clopidogrel, lack of signal for the intermediate metabolizers shouldn't be taken as conclusive, given the limitations of the study that may mask such a signal (lack of timeline data, compliance data, lack of consideration of pheno-conversion by drug-drug interaction). In the context of prior work showing that the lack of clopidogrel efficacy in carriers of LOF alleles is dose dependent a finer tuned approach would likely be needed to detect a signal in intermediate metabolizers if one is indeed present. Likewise, the fact that only 60% of this cohort had PCI and only 44% of the PCI cohort overall was prescribed clopidogrel would be anticipated to lead to a weaker signal, as prior research suggests risk associated with in stent thrombosis.

The data for risk to the small number of ultra-rapid metabolizers in this cohort, taken in combination with prior pharmacokinetic studies and clinical trial data, suggests that they are at higher risk of discontinuation due to adverse effects such as major bleeds but we cannot confirm such adverse events with the data available in the G&H TRE. The risk of clopidogrel

discontinuation in *17/*17 ultra-rapid metabolizers hasn't been assessed in clinical studies; future RCTs should also genotype for *17 and assess for, not only disproportionate adverse events, but also discontinuation rates in this subgroup. The number of patients who were Ums was very small (3 with recurrent MI) and these findings would benefit from validation in other studies. Nonetheless this may be an important finding in that it may capture a compliance risk that may not be equally represented in a controlled trial environment, which would have implications clinically (ie support giving a non CYP2C19 dependent antiplatelet to Ums). The large OR associated with UM status, if due to discontinuation, would be consistent with pharmacokinetic and platelet aggregation evidence that suggests PMs may still have some active metabolite and thus some benefit from clopidogrel. In other words, that being a PM taking clopidogrel probably offers more protection than not taking clopidogrel or an alternative anti-platelet agent[66] . All three of the UM participants who had recurrent MIs had stents *in situ*, which would heighten the risk of clopidogrel discontinuation.

1.51 Clinical implications

Given the prevalence of PGx genotypes at the *CYP2C19* locus in the G&H cohort, this study supports targeted genotyping in the South Asian population to guide antiplatelet prescription. It confirms that those who are poor metabolizers have an elevated risk of failed secondary prevention when receiving clopidogrel after an MI. It combines this with new data showing higher than expected poor and intermediate metabolizer diplotypes in this British-South Asian cohort. In light of these results, caution should be used in extrapolating results from trials of European populations to diverse populations worldwide, as conclusions may not be valid. Our results highlights risk inherent in prescribing medications to populations that vary widely from those including in studies used for licensure and post-marketing surveillance. Particularly in comparing safety and efficacy of clopidogrel to non CYP2C19 dependent

antiplatelet agent the ethnic cohort is likely to have an impact in the context of the above results. Indeed, differences in data comparing efficacy of clopidogrel to ticagrelor may well be due to differences in ethnic representation. The PLATO trial, which included 6% Asian participants in the clopidogrel arm found a lower risk of the primary MACE endpoint in the ticagrelor group (in 9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001)[67]. The risk of recurrent MI alone was significant but of a magnitude just over 1% (5.8% vs. 6.9%, P=0.005)[67]. A large Canadian cohort study found no difference in the efficacy of clopidogrel vs ticagrelor for secondary prevention but did not look at ethnic composition of the cohort[62]. These results were reproduced by a large retrospective US based cohort study, which found no difference in the efficacy of clopidogrel vs ticagrelor for secondary prevention, but only included 1.2% Asians in the study[61]. A Danish RCT published this year, which concurred that ticagrelor and clopidogrel did not have different efficacy in secondary prevention after PCI for ACS (cumulative incidence percentage [CIP] 5·6% vs. 6·0%; wIRR 1·06, 95% CI 0·92-1·22) did not publish or analyse ethnic make-up of the cohort. Given the biogeographic cohort it seems likely to have been overwhelmingly European[68].

Lack of action in terms of more diverse representation in trial cohorts and research cohorts risks perpetuating existing inequalities. More effort should be made to encourage publication of ethnic composition of research/trial cohorts especially in a setting where a PGx interaction between gene variants and a drug is probable.

1.52 Limitations

Although the use of this real-world data has many advantages there are also some limitations. We did not have access to the dates of the index presentation and recurrent MI in the TRE. Therefore, we cannot confirm that the recurrence of myocardial infarction was during the timeframe that the participants were prescribed clopidogrel. Furthermore, the risk of in-stent thrombosis after PCI is highest in the first 3 months post stent insertion and this was not analysed due to lack of timeline data. Limitation regarding timeline is mitigated by 2 factors: 1-build in temporality between index event and re-current MI and 2-the limited duration of dual antiplatelet therapy post MI (usually 1 year).

Cause specific mortality data may also have refined our model, as a composite end-point of recurrent MI or cardiovascular death could be considered but this data was not available.

Furthermore, we did not consider co-prescriptions that may cause pheno-conversion (i.e.CYP2C19 inhibiting medication taken by a normal metabolizer which may convert them to an intermediate metabolizer). Co-morbidities may also cause pheno-conversion, for example diabetes is known to be associated with decreased CYP2C19 function[69].

We did not have access to the NHS digital raw data to assess adverse events which may lead to clopidogrel discontinuation, for example significant gastrointestinal or intracranial bleed.

The lack of these data would be expected to hide any existing association between genotype and outcomes, meaning that it is expected our analysis would under–represent rather than over-represent a signal.

1.53 Conclusions

This study makes an important contribution to the expanding knowledge base of *CYP2C19*-clopidogrel pharmacogenomics and has implications for clinical practice. The most salient of these is that prescribing ticagrelor unless contra-indicated, as advised by existing national and international professional guidelines, is likely to have a disproportionate benefit in this British-Bangladeshi and British-Pakistani population. It is hard to imagine not taking action on any other treatment alteration for which an appreciable odds ratio of adverse outcomes could be found in an event cohort of 38 participants, which is supported by well-established mechanistic, pharmacokinetic and translational data, and advocated for by existing guidelines. Furthermore, a genotype guided approach would likely be particularly beneficial to this British-South Asian cohort and work toward addressing health inequality. High quality health economic studies have shown it is affordable.

This is a case study which illustrates how socio-economic deprivation, ethnic differences in pharmacogenes, and poor representation in research can intersect to compound ill health in an already disadvantaged subpopulation. The sociology principle of the *Matthew effect* whereby both advantage and disadvantage accrue over time bears consideration. Further analysis of such effects in clinical medicine are needed.

1.6 VISUAL REPRESENTATION OF WORK: *CYP2C19* genotypes and association with recurrent myocardial infarction

Graphical Abstract of this work produced with support of JACC advances illustrator. I designed the graphic representation, and she made the image more sophisticated and improved the layout.

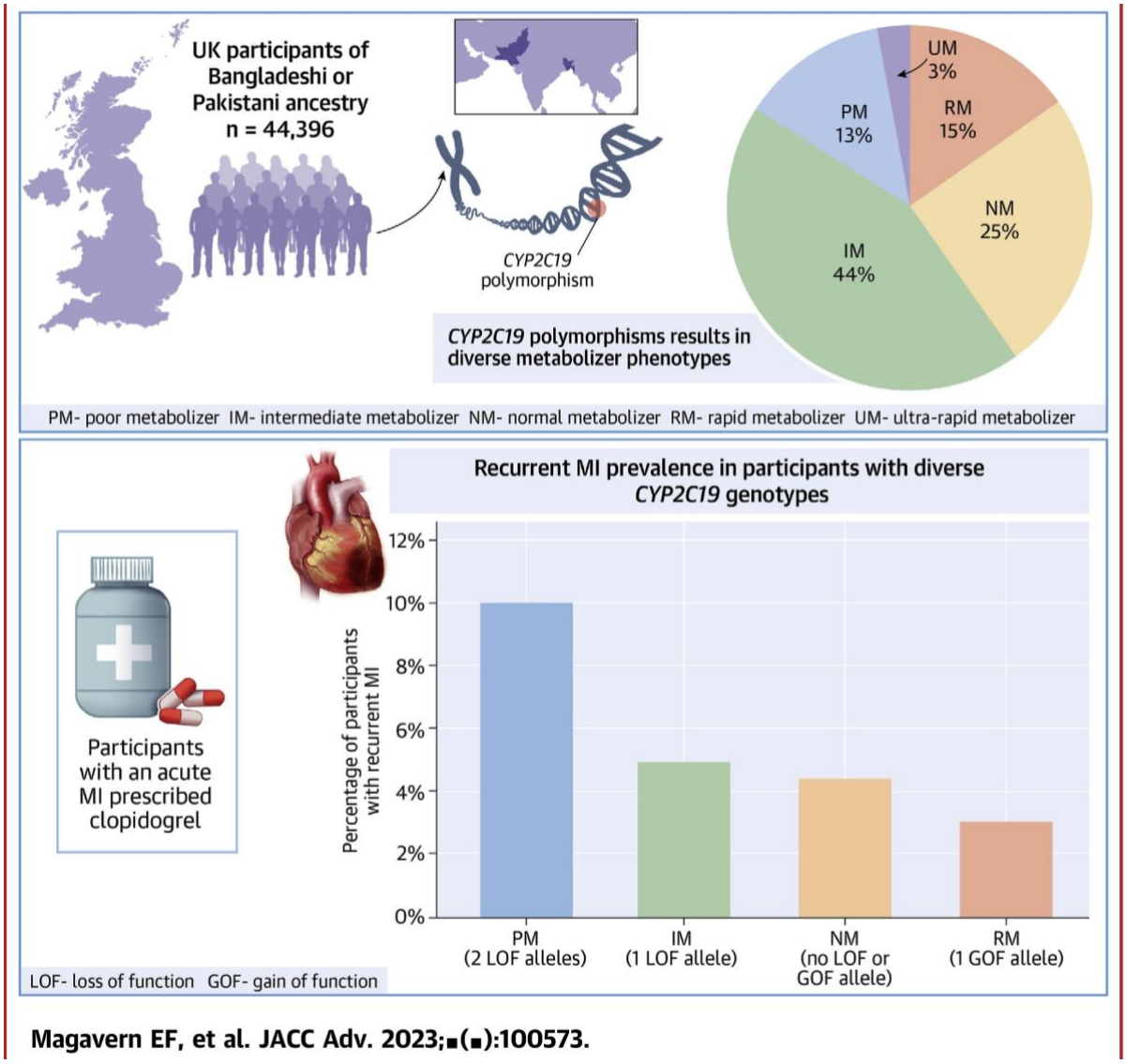


Illustration of an oral presentation of this work by Sandra Hawgate courtesy of the London Genetics Network

The work presented in this chapter has been published in *JACC: Advances*. It received recognition from the editorial office as one of the Journal's Top Ten Original Research Articles for 2023. This publication and the acknowledgment of impact from the editorial office can be found in appendix 5.

CHAPTER 2

Relationship between CYP2C19 metabolized antidepressants and GI bleeds in G&H population

2.1 INTRODUCTION: CYP2C19 metabolized antidepressants and GI bleeds

Genetic polymorphism can explain some of the variation in medication response and predisposition to adverse drug reactions[70] . This is referred to as pharmacogenomics (PGx). Evidence generated from PGx research has resulted in guidance of varying strength from regulators and international consortia[34]. There can be significant transethnic differences in prevalence of pharmacogene polymorphisms impacting medication efficacy and adverse drug events[34].

2.11 CYP2C19 and antidepressant metabolism

CYP2C19 is a hepatic enzyme that is principally responsible for metabolizing several serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)[34]. Asian

populations are known to have high prevalence of poor and intermediate CYP2C19 metabolizers due to high prevalence of the *2 and *3 *CYP2C19* loss of function (LOF) alleles[34,58].

As previously shown, the *2 allele is very common in the Genes & Health (G&H) population cohort of UK-South Asian ancestry participants (56% of the population having at least one copy)[71]. This contributes to a high percentage of poor or intermediate metabolizers (those with at least one of the *2 or *3 SNPs). 13% of the G&H population are inferred CYP2C19 poor metabolizers and 57% are intermediate metabolizers based on diplotypes informed by presence of the *2 and *3 LOF alleles[71] . 2.7% are inferred ultra-rapid metabolizers (homozygous for the *17 GOF allele)[71] .

2.12 Antidepressants and gastrointestinal bleeds

SSRIs have reproducibly been associated with increased risk of gastrointestinal bleed (GIB) in observational studies and meta-analysis [72]. The mechanism is postulated to be the effect of serotonin in platelet aggregation. Serotonin is stored in platelet granules after uptake from plasma and released when platelets are activated[73]. Once released from platelets serotonin activates receptors on platelet membranes, augmenting platelet aggregation. It also enhances other aspects of the coagulation cascade induced by adenosine diphosphate, thrombin, collagen, and epinephrine and increases intracellular calcium concentrations, which induces a platelet shape-change conducive to coagulation[73]. Depletion of intraplatelet serotonin by SSRIs has been shown to inhibit platelet plug formation[75]. TCAs also block the re-uptake of serotonin, but there has been conflicting evidence regarding TCAs association with GIB[74]. Tertiary amines, such as amitriptyline, have serotonergic activity and are metabolized to

secondary amines, which have less serotonergic activity, by CYP2C19[12]. GIBs are a significant cause of morbidity and mortality, and associated healthcare costs[76–78].

2.13 Consortia guidance and evidence gap

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance suggest initiation of lower doses of these medications for those who are poor CYP2C19 metabolizers (classification of recommendation moderate or optional) based on pharmacokinetic data[12,79]. Effect of metabolizer state on gastrointestinal GIB risk for those on CYP2C19 dependent SSRI and TCAs has never been studied to our knowledge. Therefore, it remains unknown if this potentially serious adverse effect might be mitigated by a precision approach to prescribing based on *CYP2C19* diplotype, in which lower doses of these antidepressants are prescribed to those with one or two LOF alleles. This is increasingly relevant as there is more uptake of *CYP2C19* point of care testing in the context of antiplatelet use and therefore more patients who may know their genotype and inferred metabolizer phenotype at point of prescribing antidepressants.

2.2 AIMS AND HYPOTHESIS: CYP2C19 metabolized antidepressants and GI bleeds

- The aim of our study was to explore a possible association between CYP2C19 genetically predicted metabolizer status and GIB in individuals exposed to antidepressants.
- We hypothesised that if GIB was a dose dependent response to the serotonergic effects of antidepressants metabolised by CYP2C19 there may be an association between *CYP2C19* LOF genotypes and GIB prevalence in participants exposed to relevant antidepressants.

2.3 METHODS: CYP2C19 metabolized antidepressants and GI bleeds

2.31 Characterization of *CYP2C19* genotype and inferred phenotype

These methods have been characterized in a prior study[71] . The *CYP2C19* genotype was assessed by characterizing population prevalence of the known PGx *2 (loss of function (LOF)), *3 (LOF) and *17 (gain of function (GOF)) alleles influencing enzymatic function[71] . SNPs were extracted from the data set using PLINK 2.0[50,51]. The *2 allele was defined as c.681G>A, rs4244285 (chr10:94781859). The *3 allele was defined as c.636G>A, rs4986893 (chr10:94780653). The *17 allele was defined as (c.-806C>T), rs12248560 (chr10:94761900). Quality control metrics of these SNP in the sub-population of interest are shown here (Table 1):

Table 1: SNP characteristics

SNP	***2 (imputed)**	***3 (genotyped)**	***17 (genotyped)**
HWE in cohort prescribed SSRI/TCA (N 10,612)	0.02	0.32	0.14
MAF (N 10,612)	0.35	0.007	0.15
Fractional missingness (N 10,612)	0.0004	0.002	0
INFO Score	0.99		

Abbreviations: Hardy-Weinberg equilibrium (HWE), minor allele frequency (MAF)

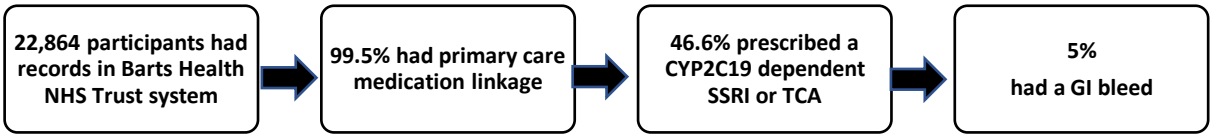
Subsequent analysis was done in Rstudio[52]. Participants with one LOF SNP (either *2 or *3) were inferred intermediate CYP2C19 metabolizers. Those with two LOF SNPs were inferred poor metabolizers. Participants with one *17 allele (in absence of a *2 or *3 allele) were

inferred rapid metabolizers, and those with two *17 alleles were inferred ultra-rapid metabolizers.

2.32 Medication data from primary care

Medication data was obtained from the primary care via linkage with participating CCGs. These include: BHR,TH,WF and N. Participants who had medication data available from these CCGs were included in our analyses (99.5% of participants with records in Barts Health NHS Trust system (22753/22864)) (Figure 1).

Figure 1 – Study overview. Overview of cohort and CYP2C19 dependent SSRI and TCA prescriptions. 5% of the cohort prescribed a CYP2C19 dependent SSRI or TCA had a GIB.



Abbreviations: National Health Service (NHS), *selective serotonin reuptake inhibitor* (SSRI), tricyclic antidepressant (TCA), gastrointestinal (GI).

CYP2C19 dependent SSRIs studied included: sertraline, citalopram, escitalopram. CYP2C19 dependent TCAs studied included: amitriptyline, clomipramine, doxepin, imipramine, Trimipramine. As there were fewer medications in the SSRI group, these were associated with outcomes independently and as a pooled group. Due to the higher number of medications in the TCA group these mediations were pooled for exposure. Exposure to

medication was defined by 1 or more prescription for a medication being used chronically rather than acutely from primary care records.

2.33 Ascertainment of environmental exposures

Smoking status was defined in primary care records as described in prior analysis by using SNOMED codes to distinguish never-smokers from those who had ever smoked[71]. Participants were identified as never having smoked if they had a never-smoked or current non-smoker code and had no codes associated with current smoker, ex-smoking, or smoking cessation. Alcohol use was defined by presence of ICD 10 code Z721, "alcohol use" or ICD10 code Z714 "alcohol abuse counselling" and was found by searching Barts Health electronic data from the research database in the G&H TRE.

2.34 Linking CYP2C19 inferred phenotypes with GIB

We used the Barts Health NHS trust tertiary data linkage to study relationship between *CYP2C19* inferred phenotype and inpatient GIB. GIB occurrence was defined by ICD10 codes K920 (hematemesis), K921 (Melaena), K922 (gastrointestinal haemorrhage, unspecified).

Due to the association of alcoholic liver disease and liver failure with GIB risk and phenoconversion, we also controlled for these phenotypes. Curated data sets from G&H were used for clinical phenotypes including alcoholic liver disease (ALD) (ICD10 code K70), and Fibrosis and cirrhosis of liver (Chronic liver disease (CLD)) (K74).

Presence of conditions which are common indications, or associated with common indications, for SSRIs/TCAs was ascertained using the G&H curated phenotypes. These

included: Diabetes (ICD10 codes E10, E11, E13, E14), Depressive episode (ICD10 code F32), recurrent depressive disorder (ICD10 code F33), anxiety disorders (ICD10 code F41), reaction to severe stress and adjustment disorders (ICD10 code F43), and obsessive-compulsive disorder (ICD10 code F42).

2.35 G&H Curated Principal Components

The first two principal components were used to control for population stratification in our analysis.

2.36 Statistical methods

Multivariable regression was used to test for association between prevalence of GIB and SSRI/TCA use. Alcoholic liver disease, chronic liver disease, gender and age at enrolment were controlled for (all were significant in univariable and multivariable regression). The cohort prescribed a SSRI or TCA was stratified by inferred metabolizer phenotype and fisher's exact test was performed to look for differences in prevalence of GIB. This was done without adjusting for any other variables to simulate the potential use of diplotype stratification in clinical practice. Fisher's exact test was also used to compare binary characteristics between those who were and were not prescribed CYP2C19 metabolized SSRIs and TCAs. A t-test was used to compare the mean age of participants at enrolment.

Multivariable regression was next used to test for association between CYP2C19 phenotypes and GIB in the cohort who had been prescribed antidepressants, adjusting for age at recruitment, gender, CLD and ALD. We also controlled for the first two principal components to avoid bias from population stratification. Four levels were used for the

CYP2C19 inferred metabolizer type variable: poor, intermediate, and ultra-rapid metabolizers, with normal and rapid metabolizers as the reference group.

Sensitivity analyses were undertaken to control for lifetime prescription of other medications which may impact on GI bleed risk including direct oral anticoagulants (DOACs), coumarins, nonsteroidal anti-inflammatory agents (NSAIDs), aspirin, clopidogrel and proton pump inhibitors (PPIs), as well as for smoking and alcohol use.

2.4 RESULTS: CYP2C19 metabolized antidepressants and GI bleeds

2.41 Prevalence of TCA and SSRI prescriptions

In total 10,612 participants, 47% of the cohort had been prescribed at least one CYP2C19 dependent SSRI or TCA (Table 2).

Table 2 -medication exposures

Medication	**N prescribed medication (total N=22,753)**
Sertraline	12.3% (2,800)
Citalopram	14.5% (3,301)
Escitalopram	1.2% (271)
SSRIs pooled	22.3% (5,064)
TCAs	37.2% (8,463)
SSRIs and TCAs pooled	46.6% (10,612)

Abbreviations: *selective serotonin reuptake inhibitor* (SSRI), tricyclic antidepressant (TCA).

* *TCAs studied included: amitriptyline, clomipramine, doxepin, imipramine, trimipramine.*

CYP2C19 dependent TCAs were prescribed to 37% of the cohort, while 22% had been prescribed a CYP2C19 dependent SSRI. Of the individual SSRIs, escitalopram was prescribed less frequently than sertraline and citalopram. Table 3 shows characteristics of those prescribed these SSRIs or TCAs, as well as prevalence of conditions which are among prescribing indications.

Table 3

Participant characteristics stratified by exposure to CYP2C19 dependent SSRI/TCA.

Characteristic	**Cohort not prescribed a CYP2C19 dependent SSRI or TCA (N 12,141)**	**Cohort prescribed a CYP2C19 dependent SSRI or TCA (N 10,612)**	**P value**
Female Sex	62% (7517)	68% (7179)	<0.0001
Diabetes	18% (2140)	31% (3262)	<0.0001
Depression	3% (317)	19% (2037)	<0.0001
Anxiety	9% (1119)	35% (3755)	<0.0001
Stress/Adjustment Disorder	6% (697)	18% (1876)	<0.0001
Obsessive Compulsive Disorder	0.2% (19)	1% (102)	<0.0001
Chronic liver disease	0.4% (54)	1% (101)	<0.0001
Alcoholic liver disease	0.1% (6)	0.2% (17)	0.01
Average Age at Recruitment	39 years old (+/- 14)	46 years old (+/- 14)	<0.0001

Diabetes mellitus has been included as TCAs may be used to treat neuropathic pain. Women are over-represented in this cohort, at 68%. Anxiety (35%) and diabetes mellitus (31%) were highly prevalent. Only 19% had a diagnosis of a depressive episode or recurrent depression.

2.42 Association of SSRIs and TCAs with GIB

864 participants (4%) had a GIB. 534 of the participants with a GIB had been prescribed a CYP2C19 metabolized SSRI or TCA (62%). Logistic regression was used to study the association between SSRI and TCA prescriptions and GIB. ALD, CLD, age at enrolment and gender were controlled for. All 3 CYP2C19 dependent SSRIs as well as pooled TCAs and pooled TCA or SSRI prescription were significantly associated with GIB (Table 4).

Table 4

Association of SSRI/TCAs with GIB
Multivariable regression analyses controlled for age at enrolment, gender, chronic liver disease, alcoholic liver disease.

Medication	**OR**	**CI**	**P-value**
Sertraline	1.6	1.3-1.9	<0.0001
Citalopram	1.5	1.3-1.8	<0.0001
Escitalopram	1.7	1.0-2.7	0.04
SSRIs pooled	1.7	1.4-1.9	<0.0001
TCAs	1.6	1.4-1.8	<0.0001
SSRIs and TCAs pooled	1.8	1.5-2.0	<0.0001

Abbreviations: *selective serotonin reuptake inhibitor* (SSRI), tricyclic antidepressant (TCA).

* *TCAs studied included: amitriptyline, clomipramine, doxepin, imipramine, trimipramine.*

The ORs were very similar, ranging from 1.5 to 1.7 in the individual SSRI class medications, and 1.8 (CI 1.5-2.0, p<0.00001) in the pooled SSRI or TCA group (Table 4). The OR for pooled SSRI (1.7) and pooled TCA (1.6) association with GIB were similar with overlapping confidence intervals (CIs), suggesting no difference in risk between the two groups.

The observed association of antidepressant use with increased GIBs should be contextualised by the slightly older and more morbid population prescribed SSRIs and TCAs as compared

with participants not prescribed these medications, which is a potential source of confounding (Table 3). However, the purpose of this first stage analysis was merely to replicate prior findings associating antidepressant use with increased incidence of GIB in this participant cohort prior to the genetic stratification of participants prescribed antidepressants. As the aim of our study is to explore association between CYP2C19 genetically predicted phenotype and GIB in those exposed to antidepressants, the indication bias in prescribing does not impact these results, presented below.

2.43 GIB risk stratified by CYP2C19 metabolizer state for those prescribed a CYP2C19 dependent SSRI or TCA

Stratification by CYP2C19 metabolizer state in those prescribed a SSRI or TCA did not show any significant impact of metabolizer state on GIB risk (p 0.56 for poor metabolizers and p 0.53 for intermediate metabolizers) (table 5A).

Table 5

No significant association between poor or intermediate CYP2C19 metabolizer status and GIB risk.

5.A - Fisher's exact comparisons stratified by metabolizer status for the sub-cohort prescribed SSRIs or TCAs (N=10,612).

CYP2C19 status	**Total (N=10,612)**	**No Bleed (N=10,078)**	**Bleed (N=534)**	**P value**
Poor metabolizer	13.4% (1424)	13.4% (1348)	14.2% (76)	0.56
Intermediate metabolizer	44.9% (4770)	44.9% (4523)	46.3% (247)	0.53
Ultra-rapid metabolizer	2.4% (255)	2.5% (249)	1.1% (6)	0.06

Multivariable logistic regression in the sub cohort prescribed antidepressants, adjusting for CLD, ALD, age at recruitment, gender, and principal components, showed no significant

association between poor or intermediate CYP2C19 metabolizer status and GIB prevalence (p 0.54 for poor metabolizers, p 0.62 intermediate metabolizers) (table 5B).

5.B - Multivariable logistic regression analysis for relationship between metabolizer state and GIB in sub cohort prescribed SSRI/TCAs. Controlled for age at enrolment, gender, CLD, ALD and 2 principal components.

Variable	**OR**	**CI**	**P**
Poor Metabolizer	1.1	0.8-1.4	0.54
Intermediate metabolizer	1.0	0.9-1.3	0.62
Ultrarapid metabolizer	0.5	0.2-1.0	0.08
Age at enrolment (per year)	1.02	1.01-1.02	<0.0001
Female Sex	0.6	0.5-0.8	<0.0001
ALD	4.5	1.4-12.8	0.007
CLD	2.6	1.4-4.4	0.0009

Sensitivity analyses controlling for life-time use of medications known to be CYP2C19 metabolized (clopidogrel, PPIs) and other commonly prescribed medications likely to impact on GIB risk (aspirin, NSAIDs, DOACs) did not change the results (results shown in table 6).

Table 6: Sensitivity analyses in the cohort prescribed CYP2C19 dependent antidepressants. This multivariable regression analysis expands on that shown in table 5B and includes medication and environmental exposures associated with GI bleed and/or CYP2C19 metabolism. Controlled for age at enrolment, gender, CLD, ALD and 2 principal components.

Exposure	**Number of participants**	**OR**	**CI**	**P value**
Poor CYP2C19 metabolizer	1424	1.1	0.8-1.4	0.68
Intermediate CYP2C19 metabolizer	4770	1.0	0.8-1.3	0.76
Ultrarapid CYP2C19 metabolizer	255	0.4	0.2-1.0	0.07
Aspirin	3531	1.1	0.9-1.3	0.46
NSAIDs	10020	1.1	0.7-1.8	0.66
DOACs	187	0.8	0.4-1.5	0.54
Coumarins	130	1.9	1.0-3.4	0.04
Clopidogrel	979	1.0	0.8-1.4	0.78
PPI	9418	2.2	1.4-3.4	<0.001

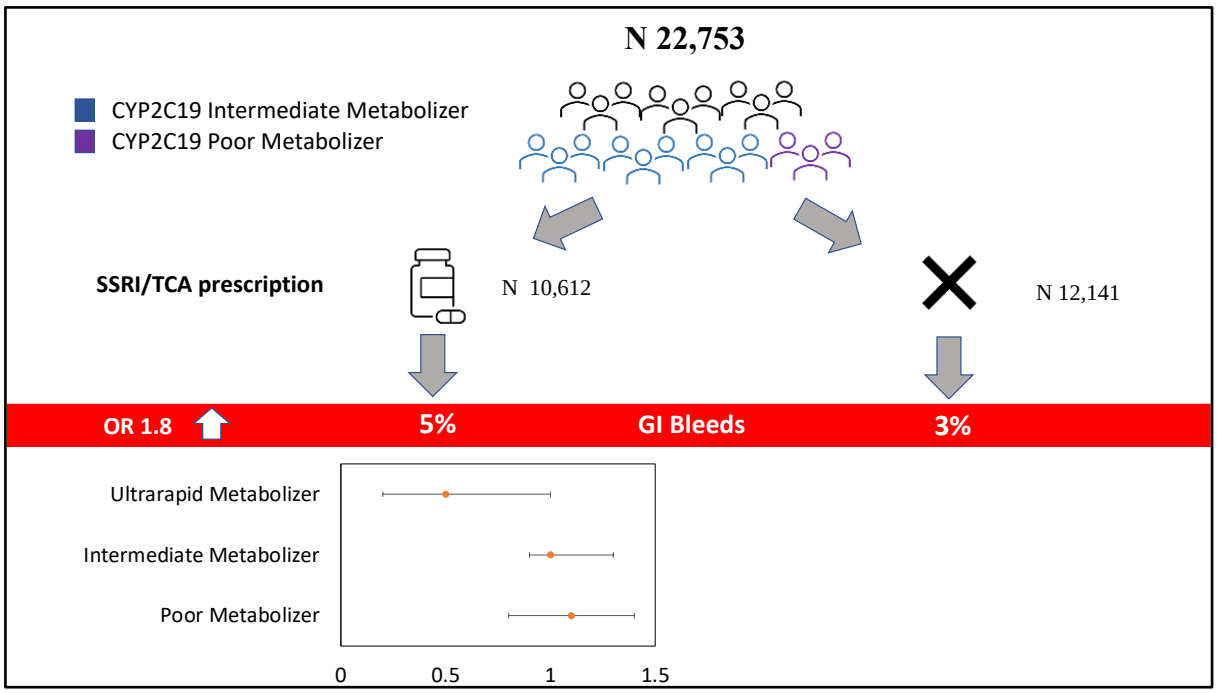
Current or past smoker	7210	0.9	0.7-1.1	0.31
Alcohol use	28	1.8	0.4-5.3	0.37

Abbreviations: Non-steroidal anti-inflammatory drugs (NSAIDS), Direct oral anticoagulants (DOAC), Proton pump inhibitor (PPI)

2.5 DISCUSSION: CYP2C19 metabolized antidepressants and GI bleeds

This study finds a strong association between SSRI/TCA use and GIB. This agrees with prior published studies regarding SSRIs and confirms bleed prevalence associated with CYP2C19 dependent TCAs. Several SSRIs and TCAs are metabolized principally by the CYP2C19 enzyme and international consortia recommend lower starting doses in poor metabolizer as they may suffer adverse events disproportionately due to increased levels of active metabolite[12,79]. This is the first study to look for an association between poor CYP2C19 metabolizer state with GIB for those who are on long term therapy with a CYP2C19 metabolized SSRI or TCA. Our study on a cohort of 22,753 participants found no association between CYP2C19 poor or intermediate inferred metabolizer status and GIB in those prescribed antidepressants (Figure 2).

Figure 2 – **Study Results**: **No increased proportion of GIB in participants with *CYP2C19* loss of function alleles in the cohort prescribed SSRI/TCA.** SSRI/TCA use was associated with a higher risk of GIB. 5% of participants who were prescribed a CYP2C19 metabolized SSRI/TCA had a GIB compared with 3% of the cohort who were not prescribed a CYP2C19 metabolized SSRI/TCA. Poor metabolizers, who would be given a lower dose of medication based on precision prescribing guidelines, were not more likely to have had a GIB among those taking antidepressants



Abbreviations: selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), gastrointestinal (GI).

This study also shows, for the first time to our knowledge, the vast scale of prescribing of these CYP2C19 dependent drugs in the UK based Pakistani and Bangladeshi ancestry population. While the nature of this secondary care data is not well suited to undertake association studies with non-severe adverse drug reactions (which may impact quality of life and compliance), or therapeutic inefficacy, other research has suggested that a precision medicine approach to prescribing may mitigate ADRs[80,81] . This study shows the vast number of people in this cohort who would benefit from a precision approach if such a conclusion is confirmed in clinical trials. As two in every three participants (7179/10612) prescribed one of these medications was female, any benefit of a precision prescribing approach would be disproportionately impactful in the female population. Since women are underrepresented

generally in research it is quite likely that any ADR disproportionately affecting women would be under detected.

2.51 Clinical implications

Precision dosing of antidepressants based on *CYP2C19* diplotype is not likely to mitigate the GIB risk associated with use of these SSRIs and TCAs. Since pharmacokinetic data shows significantly higher drug exposure in poor metabolizers, an association between the antidepressants and GIB seems unlikely to be dose dependent and an approach of low dose initiation for patients at high bleed risk may not be helpful[12,79].

2.52 Limitations

Our study is cross-sectional and the timing of GIB and relationship with length of medications exposure was largely unknown, due to the way the GP prescriptions and bleed events were recorded. Due to this limitation, we were not able to assess potential interaction between antidepressants and other medications or environmental exposures such as alcohol intake or cigarette smoking at the time of the GIB. Very few participants were recorded as using or abusing alcohol in Barts Health NHS trust records, which is partly a result of limitations of recording in secondary care records and partly a result of the fact that many of the cohort are assumed to be practicing Muslims[24]. However, ALD and CLD were controlled for in our analysis. Attempts to quantify life-time use of aspirin, NSAID and PPI use from primary care prescription records only may be incomplete as these medications are available over the counter.

While the SSRIs included do not have guidance from CPIC dependent on *CYP2D6*, the tricyclic antidepressant guidance would be impacted by CYP2D6 metabolizer status as well,

if known, which we are not able to assess from the array data. However, due to the difficulties in characterizing *CYP2D6* genotypes and ready availability of *CYP2C19* as a POC test it is clinically relevant to ask if *CYP2C19* genotype knowledge implemented as PGx for antidepressants is likely to impact on any associated bleed risk. Furthermore, the tertiary amines have more serotonergic activity than the secondary amines resulting from CYP2C19 metabolism ([12]). This serotonergic activity was the mechanism of interest in associating TCAs with GI bleed risk in the context of published literature associating SSRIs with GI bleed.

2.53 Conclusions

Our findings are in agreement with prior studies showing a significant association, with a clinically meaningful effect, between CYP2C19 dependent SSRI and TCAs use and GIB. This seems to be a class effect. In the cohort who had been prescribed antidepressants there was no difference in GIB prevalence between different CYP2C19 metabolizer groups. Therefore, our data suggest that GIB risk would not be mitigated by precision dosing based on CYP2C19 testing. Furthermore, given differences in exposure to medication between different metabolizer states based on prior pharmacokinetic studies, this adverse event association seems unlikely to be dose related (though of course it could be related to peak concentration rather than clearance). This data needs to be interpreted in the context of methodologic limitations and further, more granular, studies are needed.

The work presented in this chapter has been published in *The British Journal of Clinical Pharmacology*. This publication can be found in appendix 5.

CHAPTER 3

*SLCO1B1*5* mediated association between statins and cataracts in G&H participants

3.1 INTRODUCTION: *SLCO1B1*5* mediated association between statins and cataracts

3.11 Statins

Statins are Hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors indicated in the treatment of primary and secondary prevention for cardiovascular disease as well as dyslipidemia[82]. They are among the most prescribed medications, second only to proton pump inhibitors in a study of English prescribing patterns[83]. A large USA based study showed that in 2013, 27.8% of adults over the age of 40 were prescribed a statin[84]. As a result of this widespread use, adverse drug reactions associated with statins have attracted significant attention[85].

3.12 Purported association between statin use and cataracts

Cataracts are a leading cause of blindness world-wide, particularly problematic in low-income and middle-income countries with less access to surgical interventions[86]. The reported association between statin use and cataract risk is controversial and bi-directional[85].

A postulated mechanism of statin induced cataractogenesis is inhibition of the synthesis of cholesterol which is needed to maintain transparency of the lens of the eye. Supporting evidence includes studies where high doses of statins given to dogs induced cataracts, and the fact clinical phenotypes associated with monogenic forms of familial hypocholesterolaemia include cataract formation[90]. However, cataracts are also known to be associated with inflammation, and multiple sources of evidence have linked statins with decreased inflammation[92]. The mechanisms by which statins decrease inflammation has remained a mystery.

While some large observational studies, randomized control trials, and meta-analyses have found statins to have a protective effect on cataracts, others have found an association with increased risk of cataracts, and many studies have found no significant association in either direction[85,87–89,91,93]. Though a systematic review and meta-analysis of observational studies suggested a small increase in cataracts associated with statin use (OR: 1.11 (95% CI: 1.02-1.21); $P = 0.017$), results were heterogeneous and likely impacted by residual confounding[94].

Observational studies can be confounded by the presence of cardio-metabolic risk factors for cataracts which are also indications for statins, and randomized controlled trials include selective populations and don't control for population level genetic differences. The sole study to use genetics as a tool to assess the relationship between statins and cataracts mimicked the LDL lowering effect of statins in isolation. As statins are known to have diverse mechanisms of action, including decreased inflammatory proprieties independent of LDL impact, this approach will model only one aspect of statin association with cataracts[95,96].

3.13 *SLCO1B1*

The solute carrier organic anion transporter family member 1B1 (*SLCO1B1)* gene encodes the transporter protein OATP1B1[97]. OATP1B1 is responsible for the active intrahepatic transport, and subsequent clearance, of statins[97]. *SLCO1B1*5* is a polymorphism associated with increased exposure to statins as shown in pharmacokinetic studies, and increased risk of statin related adverse drug events, such as myopathy and myalgia[97–99]. *SLCO1B1*5* prevalence varies substantially between different ethnic groups. The literature reports *SLCO1B1*5* as present in 1% of African populations, 4% of South Asians, 12% of East Asians, 13% of Americans, and 16% of Europeans[100,101]. South Asian ancestry populations suffer from a particularly high prevalence of cardiometabolic disease, therefore exploring statin related adverse drug reactions in this population is important[26].

3.2 AIMS AND HYPOTHESIS: *SLCO1B1*5* mediated association between statins and cataracts

- The aim of our study was to use a genetic proxy for increased statin exposure by presence of the *SLCO1B1*5* allele in a large cohort of more than 36 thousand participants to elucidate the relationship between statins and cataracts.
- Association between *SLCO1B1*5* and cataract risk in statin users has not been characterized, and we hypothesized that stratification by *SLCO1B1*5* genotype in statin users and non-users would clarify the relationship between statin use and cataracts.

3.3 METHODS: *SLCO1B1*5* mediated association between statins and cataracts

3.31 Characterization of *SLCO1B1* genotype

The *SLCO1B1*5* genotype was extracted from the data set using PLINK 2.0[50,51]. The *5 allele was defined as c.521T>C, rs4149056 (chr12:21178615 (GRCh38)). The population was in HWE for this SNP and there was no substantial missingness (table 1). The MAF of the allele was 0.04 (table 1). Subsequent analysis was done in Rstudio[52].

Table 1- Characteristics of *5 Genotype

Cohort	**HWE *5**	**Fractional Missingness *5**	**MAF *5**
Ever-prescribed Statin Cohort (N=102,704)	1	0.0003	0.045
Never-prescribed Statin (N=23,809)	0.2	8e-5	0.043
Total Cohort (N=36,513)	0.32	0.0002	0.044

3.32 Statin use data from primary care

Medication use was assessed from linkage with primary care via participating CCGs as prior described (BHR, TH,WF,N). Our study population was constituted by N=36,513 individuals who had genetic and clinical data, including medications (Figure 1). Participants were assigned to the ever-used statins group if they had any record of a statin on the ordinary prescription list (vs short term prescriptions) from primary care. Participants who did not meet this criterion were assigned to the never-used statin sub-group. Type of statins used included all those available in the UK: atorvastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin (Figure 2A). Pharmacokinetic data shows that there is agent specific variation in the increase in area under the curve associated with the SLCO1B1*5 allele and statin exposure[99,102] . The effect is most pronounced for simvastatin and atorvastatin[103]. Pooling

statins as a class exposure was chosen to optimize power but may also bias against or under-estimate agent specific signal detection. Statin dose was not assessed for this project as we did not have the date of cataract diagnosis so we could not say what current or recent dose of statins had been when a cataract was diagnosed. The use of a binary exposure defined by a repeat prescription for a statin was therefore chosen and utilised as detailed above.

3.33 G&H curated phenotypes

G&H curated phenotypes were used in this analysis. The methods used to generate these have been previously described in the common methods section of this thesis. Non-senile cataracts were defined by ICD10 code H26. Senile cataracts were defined by ICD10 code H25. Diabetes (DM) included E10; type 1 diabetes mellitus, E11; type 2 diabetes mellitus, E13; other specified diabetes mellitus, E14; unspecified diabetes mellitus. Dyslipidaemia was defined by ICD 10 code E78. Obesity was defined by ICD10 code E66. Chronic Kidney Disease was defined by ICD10 code N18. Hypertension was defined by ICD 10 code I10. Ischemic heart disease (IHD) was defined by ICD 10 codes I21; acute myocardial infarction, I24; other acute ischemic heart diseases, and I25; chronic ischemic heart disease. Peripheral vascular disease (PVD) was defined by ICD10 code I73.

3.34 G&H Curated Principal Components

G&H has curated principal components as referenced in a prior publication [30]. The first two of these were used to control for population stratification in our analysis.

3.35 Statistical Methods

Multivariable logistic regression was used to test for association between statin use and cataracts, adjusting for population characteristics and potential confounders by inclusion of

the listed cardio-metabolic conditions and characteristics as variables. Multivariable logistic regression was used to test association between *SLCO1B1*5* containing diplotypes and cataracts, adjusting for age at recruitment, gender, cardiometabolic risk factors, and two principal components in sub-groups having ever or never been prescribed statins. Fisher's exact test was used to compare cohort characteristics.

3.4 RESULTS: *SLCO1B1*5* mediated association between statins and cataracts

3.41 cohort characteristics

The average age at enrolment was 41 years old (+/- 14 years) and 45% of participants were males. The cohort was characterized by a high prevalence of cardio-metabolic conditions including obesity (17%), diabetes (16%), hypertension (19%), and dyslipidaemia (21%) (table 2).

Table 2 - Cohort demographics, genotype, and disease prevalance

Medication use	**All participants (N 36,513)**	**Prescribed Statin (N 12,704)**	**Not Prescribed Statin (N 23,809)**	**P value**
Average age at enrolment (SD)	41 years old (+/- 14 years)	53 years old (+/-12 years))	34 years old (+/-10 years)	< 2.2 e-16
Male % (n)	45 (16465)	58 (7395)	38 (9070)	< 2.2 e-16
Obesity % (n)	17 (6140)	23 (2928)	13 (3212)	< 2.2 e-16
Diabetes % (n)	16 (6024)	42 (5377)	3 (647)	< 2.2 e-16
Hypertension % (n)	19 (6801)	46 (5861)	4 (940)	< 2.2 e-16
Dyslipidaemia % (n)	21 (7576)	54 (6831)	3 (745)	< 2.2 e-16
CKD % (n)	5.9 (2155)	15 (1935)	0.9 (220)	< 2.2 e-16
PVD % (n)	1.3 (477)	2 (274)	0.9 (203)	< 2.2 e-16
IHD % (n)	7.5 (2741)	21 (2629)	0.5 (112)	< 2.2 e-16
Cataracts (all) % (n)	5.4 (1973)	14 (1764)	0.9 (209)	< 2.2 e-16
Cataracts, non-senile% (n)	4.6 (1686)	12 (1507)	0.8 (179)	< 2.2 e-16

*SLCO1B1*5* homozygote or heterozygote % (n)	8.6 (3122)	8.8 (1115)	8.4 (2007)	0.3

Abbreviations: CKD (chronic kidney disease); IHD (ischemic heart disease); PVD (peripheral vascular disease).

3.42 Statin exposure

35% of G&H participants with linked medication data **(**12,704/36,513) had been prescribed a statin as an ordinary medication in primary care (Table 2, Figure 1).

Figure 1 – Study cohort overview

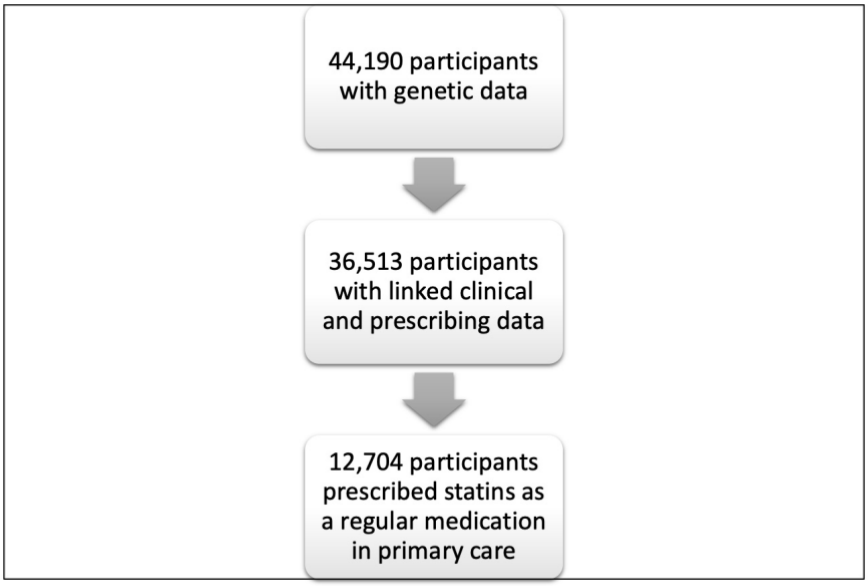
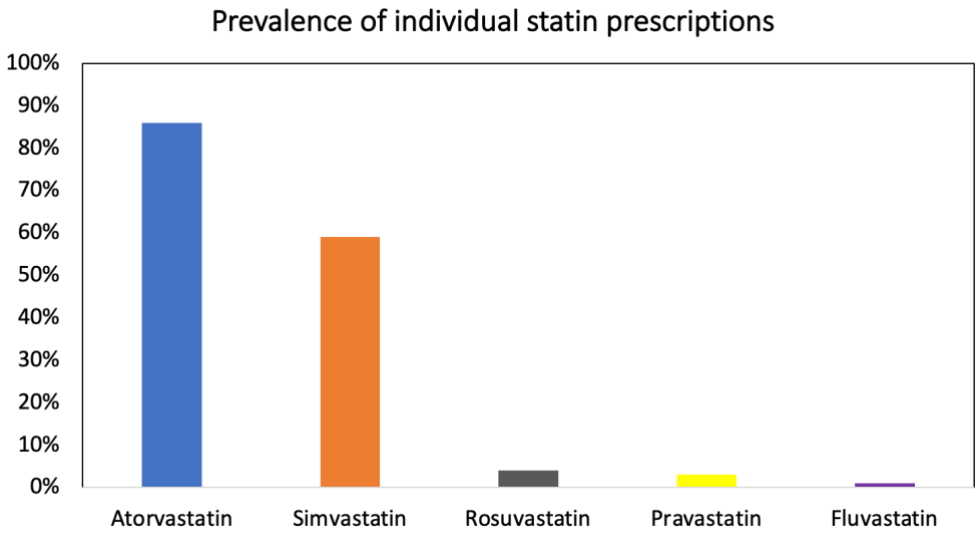


Figure 2A illustrates the prevalence of individual medications within the statin class. Atorvastatin and simvastatin were the most commonly prescribed agents. Fluvastatin was not commonly prescribed. Some participants had been prescribed multiple different statins (Figure 2B). 54% had only been prescribed 1 agents, while 41% had been prescribed 2

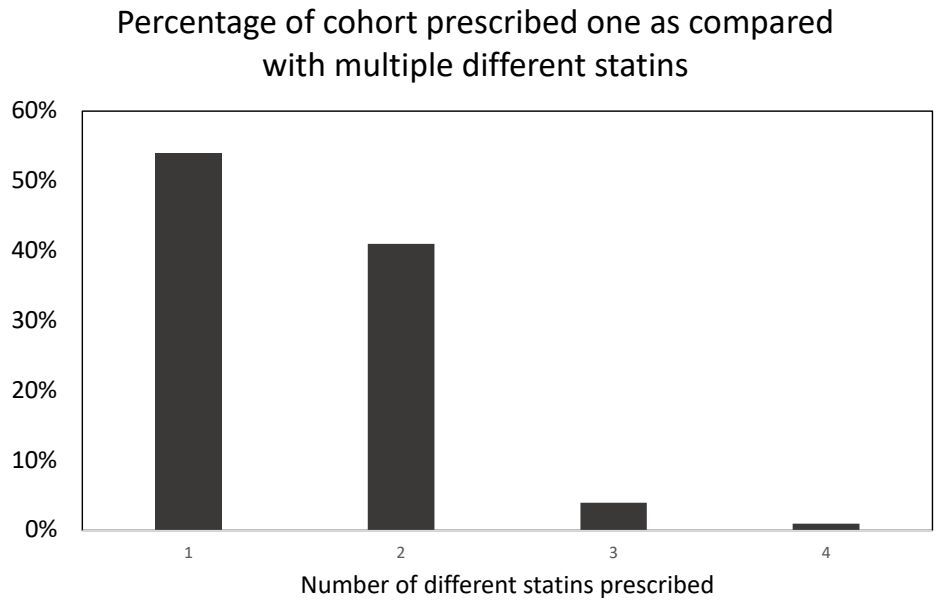
different statins and 4% had been prescribed 3 different types of statin. It was rare to have been prescribed 4 or 5 different types of statins (Figure 2B).

Figure 2A and 2B –Statin prescribing prevalence and prevalence of exposure to multiple different statins.

2A -Prevalance of exposure to specific statin agents within the cohort prescribed statins, in descending order of prevalence.



2B -Prevalence of multiple different statin agent exposures in primary care. In the cohort prescribed statins (N 12704) it was common to have been prescribed 2 different agents within the class of statins. The odds of having been prescribed more than 1 different statin did not differ in presence or absence of *SLCO1B1**5 allele using fisher exact test (OR 9.0, CIO 0.8-1.0, p 0.14**).**



3.43 Cataract prevalence

1686 Participants (5%) had a non-senile cataract. 995 Participants (3%) had a senile cataract. When stratified by statin use, 12% of participants who had been prescribed statins had a diagnosis of non-senile cataract, compared with 0.8% of those not prescribed a statin. Cohort characteristics stratified by statin use and by genotype are outlined in table 3.

Table 3 - Cohort demographics stratified by genotype in:
Participants prescribed statins (N 12704) and participants not prescribed statins (N 23809)

	Stratification of participants prescribed statin by genotype (N 12704)			**Stratification of participants not prescribed statin by genotype (N** 23809)		
Genotype	*SLCO1B1*5* present (N 1115)	*SLCO1B1*5* absent (N 11589)	P value	*SLCO1B1*5* present (N 2007)	*SLCO1B1*5* absent (N 21802)	P value
Obesity % (n)	21 (234)	23 (2694)	0.09	14 (273)	13 (2939)	0.9
Diabetes % (n)	39 (430)	43 (4947)	0.008	3 (59)	3 (588)	0.5
HTN % (n)	44 (491)	46 (5370)	0.15	4 (86)	3 (854)	0.4
Dyslipidaemia % (n)	51 (570)	54 (6261)	0.06	3 (59)	3 (686)	0.7
CKD % (n)	15 (162)	15 (1773)	0.5	0.8 (16)	0.9 (204)	0.6
PVD % (n)	2 (22)	2 (252)	0.7	0.8 (16)	0.9 (187)	0.9

IHD % (n)	20 (224)	21 (2405)	0.6	0.7 (14)	0.4 (98)	0.1
Cataracts (all) % (n)	10 (115)	14 (1649)	0.0002	0.8 (17)	0.9 (192)	1
Cataracts, non-senile % (n)	8 (94)	12 (1413)	0.0002	0.6 (12)	0.8 (167)	0.5
Male % (n)	59 (656)	58 (6739)	0.68	40 (797)	38 (8273)	0.1
Average age at enrolment	53 years old	53 years old	0.06	34 years old	34 years old	0.7

3.44 Association between statin prescriptions and cataracts

The association between statin use and non-senile cataracts was not independent after controlling for confounding conditions associated with both CV and cataract risk, and population stratification (table 4).

Table 4- Association of statin use with non-senile cataracts adjusted for confounders: Dyslipidaemia, Obesity, Hypertension, CKD, PVD, Diabetes, IHD, age at recruitment, sex, and two principal components.

	OR	CI	P value
Statin Use	**1.0**	**0.8-1.2**	**0.97**
Dyslipidaemia	1.7	1.4-1.9	2.6e-10
Obesity	1.2	1.1-1.4	0.005
Hypertension	2.0	1.7-2.4	2.8e-16
CKD	1.3	1.1-1.5	0.0004
PVD	1.3	0.9-1.8	0.12
Diabetes	2.0	1.7-2.3	2e-16
IHD	0.8	0.7-0.9	0.003
Age at recruitment (Years)	1.1	1.1-1.1	<2e-16
Female sex	1.1	1.0-1.3	0.06

Abbreviations: CKD (chronic kidney disease); IHD (ischemic heart disease); PVD (peripheral vascular disease).

8 % of the whole studied population had a *SLCO1B1*5* allele. Only 0.2% of the cohort were homozygous for the *5 allele. There was no significant difference in *SLCO1B1*5* genotype between those prescribed only 1 statin as compared with those prescribed more than 1 different type of statin (OR 0.9 CI 0.8-1.0, p value 0.14).

3.45 Association between *SLCO1B1*5* and cataracts in statin exposed stratified cohorts

In the cohort who had been prescribed statins, 8% of those with a *SLCO1B1*5* allele had a diagnosis of non-senile cataract as compared with 12% of those without a *SLCO1B1*5* allele (table 3). The presence of the *SLCO1B1*5* genotype was significantly associated with a lower risk of non-senile cataract, controlling for age at enrolment, gender, principal components, and co-morbidities (OR 0.7 (CI 0.5-0.9, p 0.007) (Table 5).

Table 5- Multivariable logistic regression assessing association between *SLCO1B1*5* genotype presence and non-senile cataract diagnosis in the on-statin cohort. Adjusted for Dyslipidaemia, Obesity, Hypertension, CKD, PVD, Diabetes, IHD, as well as age at enrolment, gender, and two principal components.

	OR	CI	P value
SLCO1B1*5	**0.7**	**0.5-0.9**	**0.007**
Dyslipidaemia	1.7	1.4-2.0	2.3e-10
Obesity	1.2	1.0-1.4	0.02
Hypertension	1.9	1.6-2.2	7.1e-12
CKD	1.3	1.1-1.5	0.0006
PVD	1.2	0.8-1.6	0.3
Diabetes	2.0	1.7-2.3	<2e-16
IHD	0.8	0.7-1.0	0.01
Age at recruitment (per year)	1.1	1.1-1.1	<2e-16
Female sex	1.1	1.0-1.3	0.04

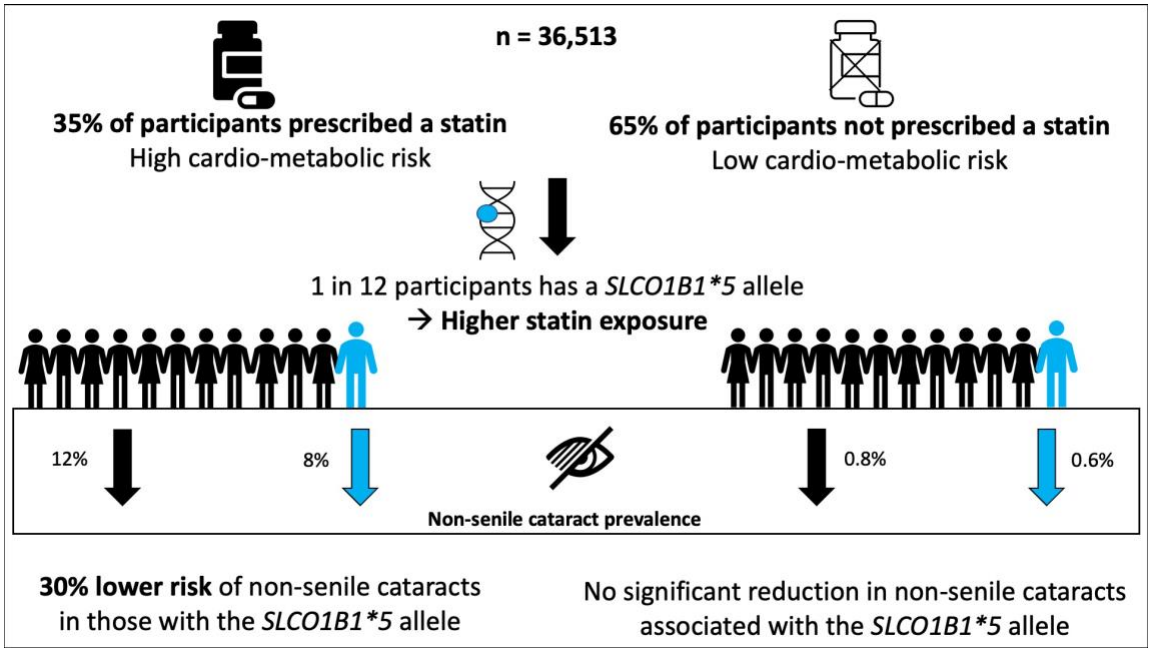
Abbreviations: CKD (chronic kidney disease); IHD (ischemic heart disease); PVD (peripheral vascular disease).

The significant association between *SLCO1B1*5* genotype and non-senile cataract diagnosis was not present in the subgroup not prescribed statins (p 0.5). The association between *SLCO1B1*5* genotype and senile cataract diagnosis was not significant (p 0.2).

3.5 DISCUSSION: *SLCO1B1*5* mediated association between statins and cataracts

Our study found an association between statin use and a high prevalence of non-senile cataracts, but this appeared to be entirely explained by the burden of cardiometabolic risk factors (which was expectedly higher in individuals who were prescribed statins). In a large cohort of UK based South Asian ancestry participants who were prescribed statins, individuals carrying a *SLCO1B1*5* allele had a 30% lower risk of developing non-senile cataract in comparison with individuals who did not carry this polymorphism known to lead to higher systemic exposure to statins (Figure 3).

Figure 3 – Study results overview. The *SLCO1B1*5* allele was present in 8% of participants. 35% of the study population were prescribed statins. In the cohort prescribed statins, there was a 30% lower odds of non-senile cataracts diagnosis in those with a *SLCO1B1*5* allele as compared with those who did not have a *SLCO1B1*5* allele. There was no significant reduction in cataract risk in those with a *SLCO1B1*5* not exposed to statins.



As the *SLCO1B1*5* allele has been linked with muscle related ADRs, we have undertaken this two-step analysis to show that the *SLCO1B1*5*-statin association with decreased cataract prevalence is not likely to be due to decreased exposure to statin through lower doses or non-compliance in those with *SLCO1B1*5*. If the protective SNP-drug effect seen were due to less statin exposure in those with a *SLCO1B1*5* allele we would expect to see an association of statin use with cataracts independent of confounding factors in the first step of the analysis. We show that such an association is not present.

Our findings add a significant piece of the puzzle in the controversy regarding association between statins and cataracts, demonstrating that pharmacogene association with statins are responsible for decreased non-senile cataract risk by higher exposure to statins. This is proof of concept that stratification by pharmacogene in observational on-drug cohorts can be helpful in clarifying drug association with putative adverse drug events. The G&H South Asian ancestry cohort is uniquely suited for this study due to high rates of cardiometabolic disease, and therefore a high-risk profile for non-senile cataracts.

These novel results represent the first exploration of pharmacogene-statin interaction in association with cataracts and are reassuring given the prevalence of statin prescription in the G&H community and broader population. They also account for conflicting results in the literature of bi-directional statin association with cataracts. Many prior studies have not reported on ethnic composition of the study cohort, so it is difficult to assess potential implications of our findings in interpretation of prior work. On a population level the protective effect of statins associated with *SLCO1B1*5* would be amplified in European ancestry populations and minimal in African ancestry populations, due to diverse prevalence of *SLCO1B1*5* in these populations, if prescription rates and co-morbidities are constant.

Therefore, it seems unlikely to be accidental that the sole RCT reporting a protective effect of statins on cataracts included a 99.7% Caucasian cohort[91,104]. It also seems quite likely that pooling studies from diverse populations without controlling for ancestry may yield conflicting results, particularly if both disease prevalence and allele prevalence vary across populations. None of the prior studies have included pharmacogenomic data.

Though the *SLCO1B1*5* genotype was protective in association with non-senile cataracts there was no significant association with senile cataracts. This may be simply because the numbers of participants with senile cataracts were smaller and therefore this study was underpowered to find an association, if present, or may be because the pathophysiology of senile vs non-senile cataracts is different.

3.51 Clinical implications

This study suggests that individuals with a *SLCO1B1*5* allele who are prescribed statins are at lower risk of developing a non-senile cataract. Those at high risk of non-senile cataract from cardiometabolic conditions may reduce this risk by a third if they take a statin. It thus highlights potential therapeutic opportunities in cataract prevention. It also underlines potential to use observational cohort data in conjunction with pharmacogene information to elucidate purported adverse drug reactions, an approach which had not been applied prior to this question.

Compliance to medications may be variable and dependant on numerous factors, including strength of counselling and depth of information available to patients. Certainly, knowledge of pharmacogenetic background and of dramatic reduction in risk of developing a potentially disabling condition may have a significant impact on patients' attitude toward statins, and

thereby compliance. There is international consensus that pharmacogenomic testing is entering mainstream cardiovascular medicine, and therefore patients may well know if they have a *SLCO1B1*5* allele in the near future[103].

3.52 Limitations

This study was not equipped to differentiate the association between individual statins and non-senile cataracts, as opposed to class effect. This was due to limited number of non-senile cataract events and unequal prescription of individual statins to individuals in the cohort. Likewise, due to unequal distribution of different statin agents and dosages as well as lack of timeline data this study was not equipped to assess effects of different dosages.

The results presented here have pooled participants who are homozygous for the *SLCO1B1*5* allele and those who are heterozygous. This was because of limited number of participants homozygous for the *SLCO1B1*5* allele in this population (only 26 participants with linked clinical and medication data were homozygous for *SLCO1B1*5* and had been prescribed a statin).

The dates of events were not available. Thus, we are unable to link time of statin use and time of cataract. We did not quantify time on statin prior to cataract for the same reason (due to lack of timeline data). However, the presence of the statin medication as a regular rather than short term medication assumes chronic use.

Despite these limitations, the relationship between the *SLCO1B1*5* genotype and reduced non-senile cataract risk only existed in the cohort who had been prescribed statins and was

not apparent in the larger cohort of those not prescribed statins. This argues against a relationship between the genotype and the outcome which is not drug mediated.

3.53 Conclusions

Our study shows an association between statin use and increased risk of non-senile cataracts is due to confounders linked with both cardiovascular/metabolic and cataract pathophysiology, in keeping with previous research. We hereby demonstrate on a large cohort that the *SLCO1B1*5* genotype, known to lead to increased statin exposure, is significantly associated with decreased risk of non-senile cataracts in those taking statins. Although our novel results will need to be validated in other cohorts, they emphasize a new approach to a controversial question, utilizing a well characterized pharmacogene, and can provide two important clinical points. The first is re-assurance to patients and cardiometabolic clinicians who take and prescribe statins regularly, that this study agrees with several prior studies in concluding that statin use is not associated independently with increased risk of cataracts. The second is support for a protective association between statins and cataracts for those at high risk of non-senile cataracts due to comorbidities and exposed to higher concentration of drug. Furthermore, stratification of on-drug cohorts by validated pharmacogenomic variants is a useful tool to support or repudiate adverse drug events in observational cohorts. The population level protective effect of *SLCO1B1*5* in statin users, would be more pronounced in ethnic cohorts with higher prevalence of the *5 allele, such as European ancestry populations, assuming equal prescribing prevalence and morbidity burden.

The work presented in this chapter has been published in *The Pharmacogenomics Journal*. This publication can be found in appendix 5.

CHAPTER 4

Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism in G&H participants

4.1 INTRODUCTION: Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism

4.11 Venous thromboembolism

Incidence of venous thromboembolism (VTE) varies by age and ethnicity, with estimates ranging from 104 to 183 events per 100,000 person-years in European ancestry populations [105]. There is some evidence of lower incidence in East Asian populations[105]. VTE results in significant morbidity and mortality, contributing to impaired quality of life and high health care costs[106–108]. Mortality from pulmonary embolism is significant and noted recently to be up-trending among younger patients (25-64 years old) in the USA[109,110].

4.12 Oestrogen use

Oestrogen containing oral combined contraception (OCP) and hormone replacement therapy (HRT) are commonly used by pre- and post-menopausal women. Data from the USA suggests that more than 80% of sexually active women had taken oral contraceptives, almost all of which were combination therapies containing oestrogen[111,112]. OCPs and oestrogen containing

HRT are known to increase the relative risk of venous thromboembolism (VTE) significantly, though the absolute risk of VTE remains low[113,114].

4.13 Factor V Leiden

Factor V Leiden (FVL) is caused by a single nucleotide polymorphism in the *F5* gene (1691G>A substitution) and leads to a pro-thrombotic state, which has a synergistic increase in VTE risk with exogenous oestrogen use[115,116]. The mechanism of thrombophilia in FVL is a resistance to activated protein C, which is an endogenous anticoagulant[115]. The *F5* gene encodes the coagulation factor V protein. The substitution of adenine for guanine at nucleotide 1691 in FVL causes a single amino acid change of arginine to glutamine in factor V at amino acid 506[120]. This amino acid change in factor V is at the location where activated protein C normally cleaves to inactivate factor V[120]. Therefore, in FVL the variant means the cleavage site is eliminated and activated protein C cannot inactivate the prothrombotic factor V. Prevalence of FVL is known to vary across trans-ancestorial groups, with highest prevalence in European ancestry and a lower prevalence in Asian populations[117,118].

4.14 Multimorbidity

Multimorbidity is increasing, and it remains unclear how intersection of multiple common medical conditions, exogenous oestrogen use, and FVL may alter risk of VTE[119]. To address this gap in knowledge we analysed the G&H cohort of Bangladeshi and Pakistani ancestry participants in the United Kingdom (UK). Although Asian populations are known to have lower prevalence of the FVL allele, as compared with European ancestry populations, the G&H cohort suffers from high rates of cardio-metabolic morbidity and a large percentage of

women are likely to be exposed to exogenous oestrogen across their lifetime. It is also a population that is grossly under-represented in clinical and preclinical research cohorts.

4.15 The shifting context of pharmacogenomics in the NHS

Pharmacogenomic panels are being considered for routine use in national clinical care in the United Kingdom's National Health Service, therefore revisiting utility of *F5* pharmacogenomic testing to inform choice of contraception and hormone replacement therapy is timely[121]. Pharmacogenomic panel testing shifts the issue of FVL testing from a population screening question and reframes it as a medicine optimisation tool. Furthermore, prior health economic models used to estimate cost of genetic testing are obsolete in this context. These models have considered the cost of testing for FVL in isolation. The direction of travel following the PREPARE trial for pre-emptive clinical implementation of pharmacogenomics is pharmacogene panel testing, where the incremental cost of adding a SNP is negligible. The true cost of implementation, however, is more than the cost of testing, and will be in integration of PGx information into clinical decision support and clinical pathways. The costs that may be associated with this on a national level are so far unclear. However, in a panel context incremental cost for testing and clinical integration of results for one variant would be anticipated to be low.

These UK NHS specific implementation systems are already being formed around *CYP2C19* testing for clinical care in the UK, though specific to the contexts of mavacamten use in hypertrophic obstructive cardiomyopathy and clopidogrel use for secondary prevention after ischemic stroke. We have contributed to some of this work by the creation of national resources for healthcare practitioners (https://www.genomicseducation.hee.nhs.uk/genotes/in-

the-clinic/results-patient-with-hypertrophic-cardiomyopathy-with-known-cyp2c19-genotype-requiring-mavacamten/) and patients (https://www.nw-gmsa.nhs.uk/patients/patient-information-and-resources).

4.2 AIMS AND HYPOTHESIS: Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism

- The aim of this study was to clarify how intersection of multiple common medical conditions, exogenous oestrogen use, and FVL contribute to cumulative risk of VTE in a British South-Asian ancestry cohort.
- We hypothesised that as multimorbidity increases, particularly in deprived populations, the baseline risk of VTE would be raised.

4.3 METHODS: Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism

4.31 Characterization of F5 genotype

The *F5* SNP RS6025 (defining the presence of FVL) was genotyped on the chip as above and was extracted using PLINK 2.0[50,51]. Details of this SNP are shown in table 1. Though population as a whole was not in Hardy Weinberg equilibrium (HWE) for this SNP (this population is known to be endogamous), HWE was not violated in the population of women taking exogenous oestrogens. The minor allele frequency for the population was 0.014 (table 1). There was not any substantial missingness. Subsequent analysis was done in Rstudio [52]. Participants who were homozygous or heterozygous for FVL were pooled for analysis due to low numbers of homozygotes prescribed oestrogen (only 1).

Table 1 – variant characteristics defining Factor V Leiden

Rs ID	RS6025
Chromosome location	1:169549811 (GRCh38)
Allele change	C>T
MAF (N=20,048)	0.014
Missingness (fractional) (N=20,048)	0.001
HWE in Female G&H cohort (N=20,048)	0.002
HWE in only women exposed to oestrogens (N=5970)	0.6

4.32 Medication data

Medication data was acquired via linkage with primary care prescribing records. Not all participants had linked prescribing data available. Participating primary care clinical CCGs have been outlined above. Medication data was available for 85% of the total female population with linked genotype and clinical data (20,048/23,711). Participants without linked medication data were excluded from our analysis. Analysis relating to oestrogen containing medication use was thus undertaken in this cohort of 20,048 women.

4.33 Exogenous oestrogen use

Use of oestrogen contained in oral combined contraceptives was extracted from primary care prescribing records, using only those prescriptions listed as ordinary (as compared with short term) prescriptions. The following brand name OCP medications were included to target OCP use: Bimizza, Gedarel, Mercilon, Akizza, Femodetter, Millinette, Sunya, Cimizt, Marvelon, Dretine, Lucette, Yacella, Yasmin, Yiznell, Femodene, Katya, Levest, Microgynon, Ovranette, Rigevidon, Elevin, Maexeni, Cilique, Lizinna, Brevinor, Norimin, Norinyl, Zoely, Logynon, TriRegol, Synphase, Qlaira. The non-brand names for oestrogens contained in these OCPs

were also included: ethinylestradiol and estradiol, including non-oral formulations. A cut off participant age was not used (due to lack of confirmation of each woman's age at menopause and age at time of prescription), thus our population may include women using oestrogens as HRT. As these oestrogens have been associated with VTE in the context of use as OCP or HRT, this is a valid approach. None of the branded HRT patch therapies, gels, or pessaries were included.

4.34 G&H curated phenotypes

This analysis used G&H curated phenotypes for the medical co-morbidities of interest. The methods underlying generation of these phenotypes is described in the common methods section of the thesis.

DM included E10; type 1 diabetes mellitus, E11; type 2 diabetes mellitus, E13; other specified diabetes mellitus, E14; unspecified diabetes mellitus. Dyslipidaemia was defined by ICD 10 code E78. Obesity was defined by ICD10 code E66. CKD was defined by ICD10 code N18. HTN was defined by ICD 10 code I10.

Venous thromboembolic events were identified from the above phenotypes using the following ICD 10 codes: Pulmonary embolism (I26), Phlebitis and thrombophlebitis (I80), Portal vein thrombosis (I81), Other venous embolism and thrombosis (I82).

4.35 G&H Curated Principal components

The G&H study team has prior published work using principal component analyses and made these available as curated parameters in the G&H trusted research environment[30]. The first 20 of these principal components were used for this analysis to control for the influence of

population stratification. We included 20 principal components to control adequately for population stratification following sensitivity analyses which showed some meaningful stratification up to this point.

4.36 Statistical Methods

Fisher's exact test was used for comparison of discrete baseline characteristics between groups, and two sample t-test was used to test for difference in mean value between the two groups for continuous variables. Fisher's exact test was used to compare prevalence of VTE in sub-cohorts. Multivariable logistic regression was used to test for association between prevalence of VTE and oestrogens use, FVL allele presence, and prevalence of common medical co-morbidities in the female sub-cohort. The first model included each medical condition specified as a co-variate. The second model included multimorbidity as a multilevel variable to assess risk associated with presence of 1, 2, 3 or 4 of the following conditions in the same participant: Obesity, hypertension, dyslipidaemia, chronic kidney disease. These four conditions were used as they are common conditions, often co-occur, and each were independently significantly associated with increased VTE prevalence in the first step multivariate logistic regression analysis described above. This was a cross sectional analysis as dates of events were not available.

4.4 RESULTS: Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism

4.41 *F5* genotype and exogenous oestrogen

In this study cohort 2.8% of women had at least 1 copy of the Factor V Leiden polymorphism, and 30% had been prescribed oestrogens (table 2). In the sub cohort of women prescribed oestrogens 2.6% had a FVL polymorphism (table 2).

Table 2. Percentage of G&H cohort with 1 *F5* mutation (heterozygotes) and 2 *F5* Leiden mutation (homozygotes).

Number of *F5* Leiden mutations	**1 Heterozygous**	**2 Homozygous**	**All *F5* Leiden carriers**
All Women (N 20,048)	2.7% (547)	0.05% (11)	2.8% (558)
Women prescribed oestrogen (N 5,970)	2.5% (152)	0% (1)	2.6% (153)

Table 3 shows the cohort characteristics and VTE events stratified by presence of FVL.

Table 3 - Female cohort characteristics and VTE events. P values from fisher's exact test for discrete variables and t-test for continuous variables. * p value <0.05,

** p value <0.001

Characteristics and co-morbid conditions	**Prevalence in all Women (N 20,048)**	**Prevalence in Women with FVL** (N 558)	**Prevalence in Women without FVL** (N 19,490)	**P value**
Diabetes mellitus	15% (3,068)	15% (82)	15% (2,986)	0.7
Obesity	22% (4,410)	27% (150)	22% (4,260)	0.006*
Primary Hypertension	16% (3,298)	16% (89)	16% (3,209)	0.8
Dyslipidaemia	16% (3,192)	17% (97)	16% (3,095)	0.3
Chronic Kidney Disease	4% (831)	4% (24)	4% (807)	0.8
Mean Age at enrolment (years)	39 years old (+/- 13.2)	39 years old (+/- 13.9)	39 years old (+/- 13.1)	0.5

VTE events				
Pulmonary embolism	0.5% (96)	0.9% (5)	0.5% (91)	0.2
Phlebitis and thrombophlebitis	1.7% (340)	3.9% (22)	1.6% (318)	0.0003**
Other venous embolism and thrombosis	0.1% (23)	0.4% (2)	0.1% (21)	0.1
Portal vein thrombosis	0.05% (10)	0% (0)	0.05% (10)	1
Total number of participants with VTE	2.2% (439)	4.7% (26)	2.1% (413)	0.0003**
Oestrogen prescription	30% (5,970)	27% (153)	30% (5,817)	0.2

4.42 VTE events

The relative risk of VTE in women carrying a factor V Leiden mutation who had been prescribed oestrogen was more than double women who did not have a factor V Leiden mutation (4.6% vs 2.1%, significant on fisher's exact testing *p* 0.047, OR 2.2, 95% CI 0.9-4.9). The majority of the 439 VTE events were phlebitis and thrombophlebitis (76%). Of those women prescribed oestrogens, 21% of the participants with VTE (27/129) had a pulmonary embolism (0.5% of all women prescribed oestrogen) (table 4).

Table 4. Female cohort characteristics and VTE events. P values from fisher's exact test for discrete variables and t-test for continuous variables. * *p* value <0.05, ** *p* value <0.001

Characteristics and co-morbid conditions	**Prevalence in all Women (N 20,048)**	**Prevalence in Women prescribed oestrogens** (N 5,970)	**Prevalence in Women not prescribed oestrogens** (N 14,078)	**P value**
Diabetes mellitus	15% (3,068)	11% (639)	17% (2,429)	<0.0001**
Obesity	22% (4,410)	21% (1,231)	23% (3,179)	0.002*
Primary Hypertension	16% (3,298)	11% (628)	19% (2,670)	<0.0001**
Dyslipidaemia	16% (3,192)	11% (627)	18% (2,565)	<0.0001**

Chronic Kidney Disease	4% (831)	2% (111)	5% (720)	<0.0001**
Mean Age at enrolment (years)	39 years old (+/- 13.2)	37 years old (+/- 9.6)	40 years old (+/- 14.3)	<0.0001**
VTE events				
Pulmonary embolism	0.5% (96)	0.5% (27)	0.5% (69)	0.8
Phlebitis and thrombophlebitis	1.7% (340)	1.8% (108)	1.6% (232)	0.4
Other venous embolism and thrombosis	0.1% (23)	0% (0)	0.2% (23)	0.0004**
Portal vein thrombosis	0.05% (10)	0% (1)	0.1% (9)	0.3
Total number of participants with VTE	2.2% (439)	2.2% (129)	2.2% (310)	0.9
FVL (homozygous or heterozygous)	2.7% (558)	2.6% (153)	2.9% (405)	0.22

4.43 Morbidity

Prevalence of common medical co-morbidities in the cohort prescribed oestrogens are shown above in table 4. Those who had been prescribed oestrogens were young at enrolment (mean age 37), with 21% obesity, 11% diabetes mellitus, 11% primary hypertension, 11% dyslipidaemia, and 2% chronic kidney disease. Those prescribed oestrogens were significantly younger and less likely to have a diagnosis of obesity, diabetes mellitus, primary hypertension, dyslipidaemia or chronic kidney disease as compared with the cohort who had not been prescribed oestrogens. However, there was no significant difference in FVL prevalence between the two groups.

4.44 Association of FVL, oestrogen and multimorbidity with VTE events

Oestrogen use was independently associated with VTE (OR 1.3, CI 1.1-1.7, p value 0.009), as was FVL carrier status (OR 2.2, 1.4-3.3, p 0.0002), and age (OR 1.01 (per year), 1.01-1.02 p 0.002) (table 5A). Obesity (OR 1.5, CI 1.2-1.9, p 0.0001), HTN (OR 1.8, CI 1.3-2.4, p

<0.0001), dyslipidaemia (OR 1.7, CI 1.3-2.2, 0.0002), and CKD (OR 2.0, CI 1.5-2.7, p <0.0001) were also associated independently with higher VTE prevalence (table 5A).

Diagnosis of any one medical condition including obesity, dyslipidaemia, HTN and CKD was independently associated with VTE with an OR 1.6 (1.2-2.0, p 0.001); two co-occurring medical conditions OR 2.7 (2.0-3.7, p <0.00001); three co-occurring conditions OR 5.3 (3.8-7.4, p<0.00001); four co-occurring conditions OR 8.1 (4.9-13.0, p <00001) (table 5B).

Table 5A&5B – Multivariable logistic regression in female cohort (**N 20,048**) examining associations with VTE. * *p* value <0.05, ** *p* value <0.001

5.A

Exposure	**OR for VTE**	**95% CI**	**P value**
FVL carrier	2.2	1.4-3.3	0.0002**
Oestrogen use	1.3	1.1-1.7	0.009*
Obesity	1.5	1.2-1.9	0.0001**
Hypertension	1.8	1.3-2.4	<0.0001**
Dyslipidaemia	1.7	1.3-2.2	0.0002**
Chronic Kidney Disease	2.0	1.5-2.7	<0.0001**
Diabetes mellitus	1.0	0.8-1.4	0.86
Age at enrolment	1.01 (per year)	1.01-1.02	0.002*

5.B – Multivariable logistic regression testing for association between VTE and multiple of the 4 common medical conditions found the be significant above (obesity, HTN, CKD, dyslipidaemia). * *p* value <0.05, ** *p* value <0.001

Exposure	**OR for VTE**	**95% CI**	**P value**
FVL Leiden carrier	2.2	1.4-3.3	0.0002**
Oestrogen use	1.3	1.1-1.7	0.01*
Multimorbidity: (Obesity, Dyslipidaemia, Hypertension, Chronic kidney disease)			
1 condition	1.6	1.2-2.0	0.001*
2 conditions	2.7	2.0-3.7	<0.0001**
3 conditions	5.3	3.8-7.4	<0.0001**
4 conditions	8.1	4.9-13.0	<0.0001**
Age at enrolment	1.02 (per year)	1.01-1.03	0.0001**

Odds ratio (OR), Confidence interval (CI)
20 principal components were included as covariates to control for population stratification

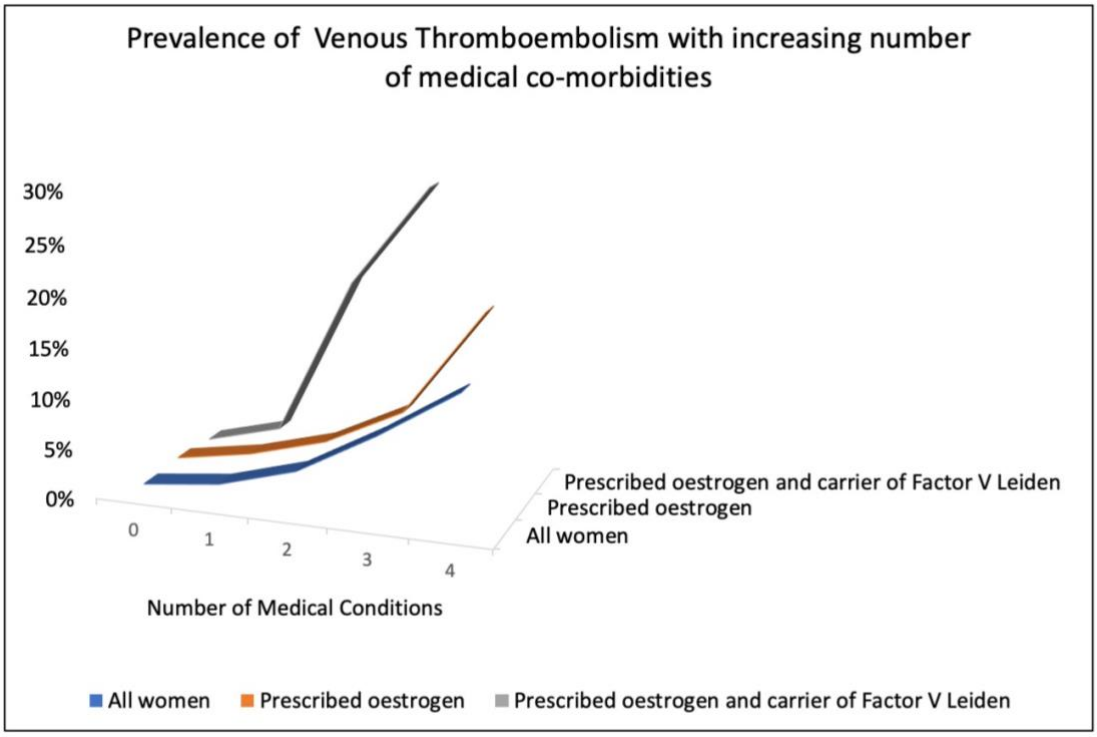
When VTE events were stratified by multimorbidity status, prevalence of VTE increases with number of conditions (Table 6). Our results show that the absolute risk of VTE in this cohort is not trivial in those women with two or more co-existent medical conditions in the absence of oestrogen use, ~4% with two condition rising to ~14% with four co-morbid conditions. This risk is amplified with the same trends in those proscribed oestrogens, though a smaller percentage of participants with multiple co-morbidities were prescribed oestrogen compared with the baseline population (Table 6).

Table 6: Multimorbidity impact. The below table outlines VTE prevalence in participants with increasing numbers of 4 common medical co-morbidities associated with VTE in this cohort: Obesity, Hypertension, Dyslipidaemia, Chronic kidney disease. Statistically significant difference with *p* value <0.05 by fisher's exact test in comparison with the column to the left noted by *. ** denotes *p* value <0.001

Number of at risk general medical co-morbidities	**0**	**1**	**2**	**3**	**4**
Women (N 20,048**)**	63% (12688)	22% (4386)	9% (1799)	5% (953)	1% (222)
VTE prevalence in Women	**1.2%** (157/12688)	**2.1%**** (92/4386)	**4.3%**** (78/1799)	**8.6%**** (82/953)	**13.5%*** (30/222)
Women prescribed Oestrogen (N 5970)	68.5% (4088)	22.4% (1337)	6.6% (396)	2.1% (128)	0.4% (21)
VTE prevalence in Women prescribed Oestrogen	**1.4%** (59/4088)	**2.7%*** (36/1337)	**4.8%*** (19/396)	**8.6%** (11/128)	**19.0%** (4/21)
Women prescribed Oestrogen in presence of Factor V Leiden (N 153)	63% (97)	22% (33)	10% (16)	5% (7)	0% (0)
VTE prevalence in Women prescribed Oestrogen in presence of Factor V Leiden	**1%** (1/97)	**3%** (1/33)	**19%** (3/16)	**29%** (2/7)	NA

In the sub-cohort prescribed oestrogens who carry a FVL mutation there was an increase in VTE prevalence affecting those with more than 1 medical co-morbidity disproportionately (Table 6, Figure 1).

Figure 1 – Prevalence of VTE. Prevalence of VTE in women increases with increasing number of co-existent medical co-morbidities identified on the x-axis (obesity, hypertension, chronic kidney disease, dyslipidaemia). There in an increase in VTE in those women prescribed oestrogens that follows the same trend, increasing with number of medical co-morbidities. In those prescribed oestrogen and carrying a Factor V Leiden mutation there is a steep increase in VTE risk in those women with more than one medical co-morbidity.



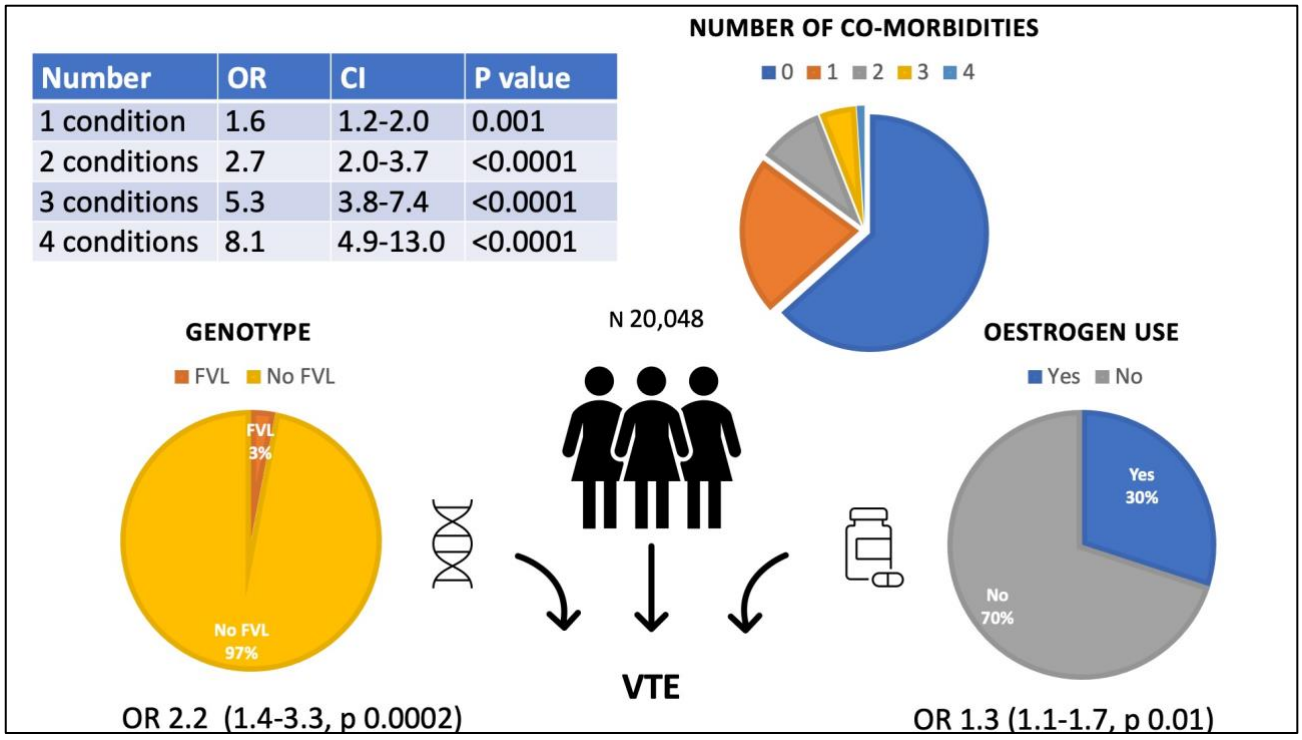
19% of those carrying a FVL mutation with 2 medical co-morbidities had a VTE event (compared with ~5% VTE prevalence in those prescribed oestrogens and having 2 medical co-morbidities overall) (Table 6). Likewise, in a dose dependent fashion, those with 3 medical co-morbidities who carried a FVL mutation had a 29 % prevalence of VTE

(compared with ~9% in those with 3 medical co-morbidities prescribed oestrogen overall) (Table 6, Figure 1).

4.5 DISCUSSION: Factor V Leiden, oestrogen and multimorbidity association with venous thromboembolism

Our study shows an independent, statistically significant, and clinically meaningful increase in VTE prevalence in women who have FVL, had been prescribed oestrogen, or had a diagnosis of obesity, HTN, CKD, or dyslipidaemia. We demonstrated a cumulative significant association with VTE where several of these medical co-morbidities was present in combination, ranging from an OR 1.6 for 1 condition (CI 1.2-20, p0.001) to OR 8.1 (CI 4.9-13.0, p2e-16) for a participant with all 4 identified medical co-morbidities (not an uncommon patient to encounter in clinical practice) (Figure 2).

Figure 2 – Study results overview



This is the first such study to look at cumulative risk of common medical conditions, oestrogen use and FVL on VTE prevalence in a South Asian ancestry western population. While independently these factors have all been associated with VTE to various degrees, prior studies have not aggregated commonly co-occurring medical conditions. Furthermore, South Asian ancestry populations in western countries are known to suffer from high rates of cardiometabolic morbidity[122].

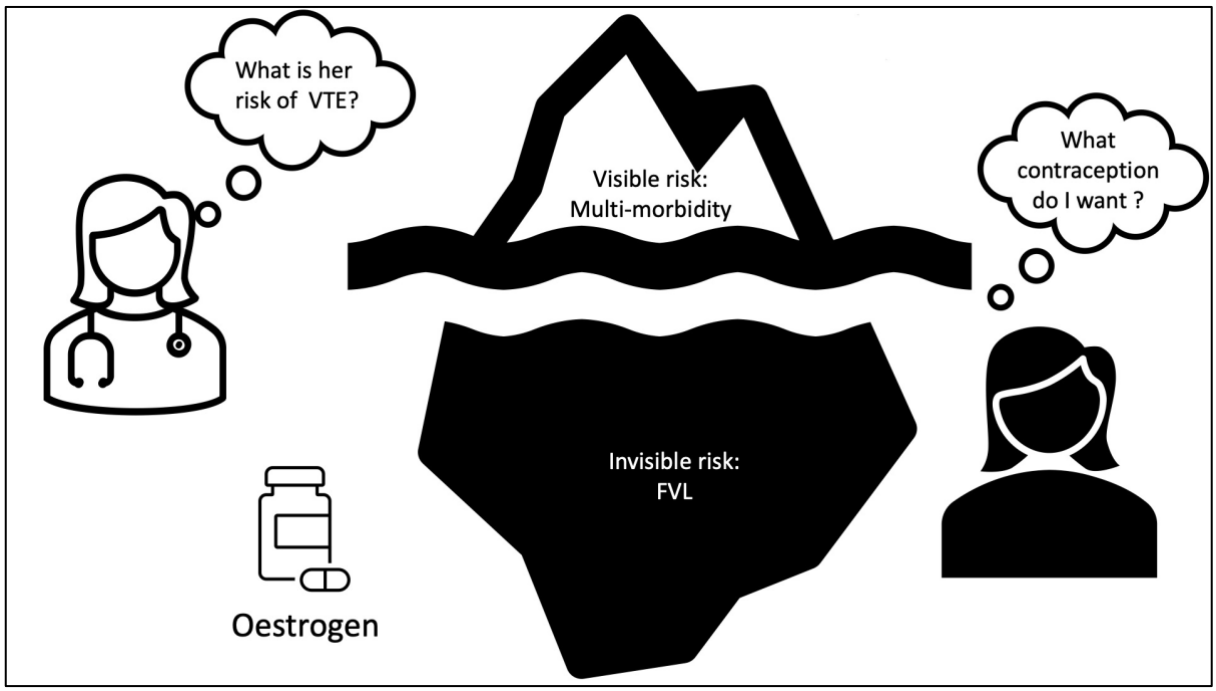
Our results show that the prevalence of VTE in this cohort is not trivial in those women with two or more co-existent medical conditions; rising to almost 1 in every 6 women with 4 co-morbid conditions in the absence of oestrogen use. In the sub-cohort who had been prescribed oestrogen the prevalence of VTE was nearly 1 in 5 for those women with all 4 medical conditions. In the presence of FVL the prevalence of VTE with 3 medical conditions was nearly 1 in every 3 women. These absolute risks argue against prior dogma which resulted in a decision not to offer testing for FVL prior to oestrogen prescription[113].

Nearly one in every three women in this study cohort had been prescribed oestrogens. The high prevalence of exposure to oestrogens emphasizes the importance of elucidating multifactorial VTE risk.

VTE risk is known to be multifactorial, with inherited, acquired, and environmental risk factors. However, the contribution of multimorbidity with chronic and commonly overlapping cardiovascular and metabolic conditions to VTE has not been well studied. It is important to elucidate the cumulative impact of multimorbidity with exogenous oestrogen use and FVL to optimize informed choice of oestrogen containing medication use. Future studies should explore the impact of overlap multimorbidity FVL and oestrogen use in other geographic, socioeconomic and ancestral populations. Further work should be done to understand the various aspects of multi morbidity that may be contributing to VTE risk such as lifestyle habits and environmental exposures associated with the studied medical conditions.

Prior concerns were raised about women being denied contraception due to detection of FVL[113]. However, there are many safe and effective non-oestrogen containing choices for contraception and an estimation of non-trivial VTE risk does not need to be a contraindication to use. In fact, there is an increasing emphasis on wholistic decisions making rather than treating all thrombophilia as contraindications to OCP use[123]. FVL inclusion in a pharmacogenomic panel medicines optimization approach could therefore enable more personalized risk assessment and enable patients to make more informed decisions (Figure 3).

Figure 3 – Clinical implications: as populations become increasingly multimorbid the invisible genetic risk of VTE posed by FVL is more relevant.



The population morbidity landscape has changed in the past several decades, as have contraception options and doctor patient decision making models. People are living longer but with more of life lived with co-morbidities[124]. Projections suggest this will continue, with individuals experiencing four or more diseases estimated to reach 17% by 2035 [3]. Women are having children later in life and are more likely to have medical comorbidities during reproductive years than in the past[125,126]. Contraception options have expanded, and there is now more emphasis on shared decision making and informed consent.

The healthcare provider landscape is shifting toward pre-emptive pharmacogenomic testing for commonly used non-specialist prescribed medications: The PREPARE trial demonstrated reduction of ADRs by 30% using a panel approach in European centres. In the UK, point of

care genomic testing for *mtRNR1* has been initiated prior to aminoglycoside use in neonatal sepsis, and NICE is expected to shortly release guidelines recommending *CYP2C19* testing in stroke[9,127,128]. Therefore, a future when pre-emptive pharmacogenomic panels are readily available in routine care may be near at hand.

These factors combine mean that a large number of women who are likely to consider taking exogenous oestrogens in their lifetime may have an elevated baseline risk of VTE due to co-morbidities and other multifactorial additional risk factors, and that pharmacogenomic panel information may be available to help inform personalised discussion of VTE risk. Including FVL in such a panel would continue the shifting ideology of medicines optimization and shared decision making based on informed consent.

4.51 Limitations

Due to the overall low prevalence of VTE and of FVL, the number of women who had a FVL allele, had been prescribed oestrogen and had a VTE event was small (7 women). Therefore, it would be ideal to replicate this data in a larger cohort. Furthermore, due to limitations of the data available, this is a cross sectional study. This approach and lack of longitudinal data is likely to decrease our signal and mean that we are underestimating the effect of oestrogen on VTE and accounts for the lower OR associated with VTE from oestrogen use in our study versus prior studies. However, this biases our model against signal detection, it does not compromise the validity of the significant associations we have presented. Furthermore, though the medical conditions considered could plausibly lead to increased VTE risk, there is not a plausible pathway for VTE to lead to the occurrence of these medical co-morbidities. We also did not analyse drug-drug interactions.

4.52 Clinical implications

As multimorbidity increases it is important to examine cumulative risk of VTE from multiple common medical conditions, aging, genetic risk prior to prescribing oestrogen. FVL disproportionately increases VTE risk for those with multiple common medical co-morbidities taking oestrogen contained in oral contraceptives due to additive risk. If these results are validated in other cohorts, it would suggest that not only obesity and hypertension, but also dyslipidaemia and chronic kidney disease should be considered and possibly even screened for before initiating oestrogen therapy. Our cohort data suggests that clinicians are already less likely to prescribe oestrogens to multimorbid patients, but that they are not likely to prescribe oestrogens to those with FVL (as it is not clinical practice to test for FVL in the absence of an unexplained thrombotic event or family history). This suggests the practice of asking about family history of VTE prior to prescribing oestrogen is not significantly decreasing the percentage of patients with FVL being prescribed oestrogens.

4.53 Conclusions

FVL should be part of a pharmacogenomic panel to support medicine optimization as one factor in wholistic patient centred decision making regarding exogenous oestrogen use. Even in lower prevalence genetic populations FVL may be an important contributor to VTE in the context of increasing medical multimorbidity due to population level usage of oestrogens. This is likely to be particularly important in deprived populations, as evidence suggests deprived people are disproportionately likely to be multimorbid[129].

The work presented in this chapter has been published in *iScience*. This publication can be found in appendix 5.

Section 2

Bias in cohort demographics of NHS PGx implementation data

CHAPTER 5

Equal Access to Pharmacogenomics Testing: The Imperative for Population Wide Access in the UK NHS

5.1 Genomics in the NHS

The United Kingdom's (UK's) National Health System (NHS) has a proud heritage of providing equal access to healthcare of a high standard that is free to all at the point of care. It is also an international leader in genomic medicine thanks to the creation of genomics England and mechanism of integration of genomics services with centralized national healthcare[121]. As part of this tradition, NHS England (NHSE) has committed to reviewing evidence for national implementation of PGx over the next one to three years [121].

The foundation of such evidence for implementation is likely to be highly commendable trials and pilots undertaken both in the UK and internationally[130–132] . However, where pilots are focused in one geographical region or targeted at only one demographic, medicine optimization lags and preventable iatrogenic harm continue to affect non pilot populations. It's also possible that the pilot populations may not represent the highest risk patient populations. In this research letter we outline concerns regarding current unequal availability of pharmacogenomic tests newly implemented in the NHS in a non-centralized fashion.

5.2 Aminoglycoside induced ototoxicity

The Pharmacogenetics to Avoid the Loss of Hearing (PALOH) trial demonstrated that a point of care testing for the mitochondrial genetic variant which can predispose to hearing loss if given an aminoglycoside antibiotic is safe and does not delay emergency treatment for sepsis in the neonatal intensive care unit context [131]. The effect of this result at present is anticipated roll out for neonates in select hospitals in the Manchester area, with reference to potential national implementation for neonates[127]. While this is an important opportunity to trial integration of POC testing in routine care in a pilot population it is hard to ethically reconcile a lack of timely national roll-out by the NHS to other age groups.

Avoiding aminoglycoside induced ototoxicity (AIO) in neonates is undoubtedly a valuable priority given the role that hearing plays in development. However, it is not clear what percentage of AIO is currently occurring in paediatric as compared with adult clinical care settings. Although gentamicin is used in neonatal sepsis, aminoglycosides are often used to treat infection in adults as well, and it is expected that the adult population would have more exposure to antibiotic therapy as compared with children.

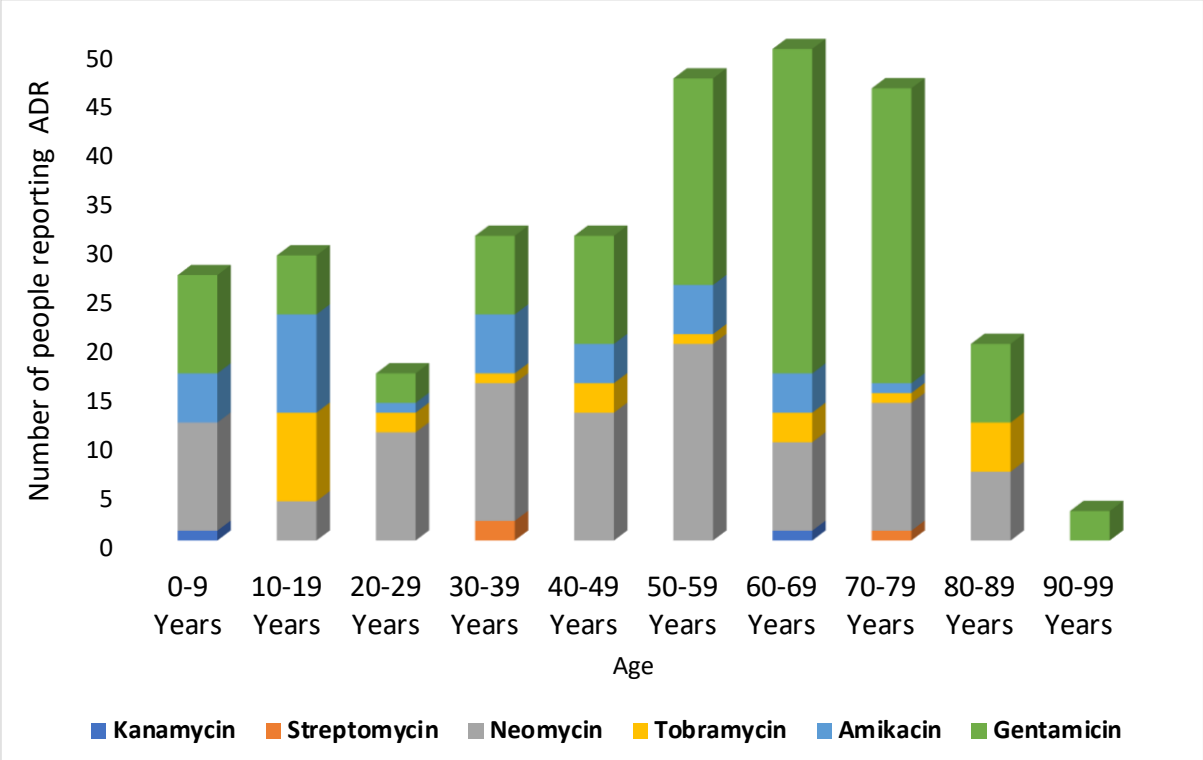
5.3 Yellow card reporting

The Medicines and Healthcare products Regulatory Agency (MHRA) of the UK has used a yellow card reporting system for reporting of adverse drug reactions (ADRs) since the 1960s. Health professionals as well as patients can report using this system[133]. Some of this reporting data from yellow cards is publicly available on the website [134].

Review of this data (from the 1960s through to September 20th 2022) shows that of those who report an age for an ear related ADR (excluding those specified as external or middle ear)

only 9% were under the age of 10, the remaining 91 % were greater than 10 years old and the highest age prevalance reported was in the 50-79 year old age groups[134](Figure 1).

Figure 1 – Data from MHRA Yellow Card reports from 1960s-2022. Data extracted from the Interactive Drug Analysis Profiles (https://yellowcard.mhra.gov.uk/idaps)[134]. ADRs related to the inner ear/CN VIII and hearing, or aural disorders NEC, and excluding external or middle ear reactions were included in the below chart. 87 individuals reporting ADRs meeting these criteria did not specify age (22% of the overall cohort). Please refer to the MHRA website for the "Essential Context for Understanding this Interactive Drug Analysis Profile"(Data accessed Nov 23 2022)[135].



22% of relevant yellow cards did not specify the age of the patient[134]. Exact ages were not provided, only decade-based grouping, so we are unable to say what percentage of these ADRs in <10-year-old were in fact in neonates[134].

Genetic predisposition is not the only factor contributing to ototoxicity in response to aminoglycosides, but PGx intervention can improve on current practice and thereby presumably reduce such harms[136]. Interestingly, almost as many ADRs were reported as associated with neomycin (126) as with gentamicin (160). In the under 10 age group there were 11 reports associated with neomycin use and 10 associated with Gentamicin use. None of the neomycin reports were linked with intravenous use, suggesting use mainly in outpatient settings. Therefore, the approach of targeting NICUs seems unlikely to impact on these ADRs. There may be systemic bias in yellow card reporting, and almost certainly there is profound under-reporting, but it seems highly improbable that AIO in neonates and young children would be disproportionately under-reported with respect to other age groups.

5.4 *CYP2C19* testing for clopidogrel use after ischemic stroke

Another example is *CYP2C19* testing to pre-emptively detect lack of response to clopidogrel. A trust in Scotland has recently become the first to implement such PGx testing in the context of stroke[132]. However, the burden of *CYP2C19* loss of function alleles, leading to decreased clopidogrel efficacy, varies greatly across diverse ancestral groups and Asian populations are at particularly high risk of therapeutic failure[15]. In this context it is again worrying that there is not a central mode of implementation happening in a more accelerated fashion. Furthermore, pilot implementation in Tayside, where the population is 98.07% white may not be representative of potential benefits in London, where the population is 18.5% Asian, or in sub-regions of London, such as Newham, where the Asian population (43.5%) approximates 1 in every 2 people[137–139].

PGx is concerned with medicines optimization, and therefore preventing iatrogenic harm or increasing pharmacologic intervention efficacy. International consortia have compiled

evidence for actionable gene-drug pairs[18,140]. Technology has developed such that costs of pre-emptive PGx panels are broadly considered affordable[141]. There is an ethical imperative to implement validated and affordable PGx testing in an equitable and nationally funded pathway as soon as possible to avoid unequal access to improvements in care offered by PGx testing. If we start stratifying access to more advanced technologies in care by age, geographic region, or local resources or enthusiasm, we risk worsening health inequalities.

5.5 Interface between representation in data and health equality

PGx has the potential, due to differing prevalence of pharmacogene polymorphisms in diverse ancestral groups, to balance the scale where there has been historic underrepresentation of certain groups in research. However, the opposite could also transpire and PGx could conceivably further tip the scale where inequality already exists by promoting advances in personalized medicine for those who already enjoy the best health.

Clinical pharmacologists are uniquely well suited to support a broad PGx implementation campaign[142]. As a community we must ensure proportionate representation in data underpinning PGx implementation and make testing accessible in a fair and timely manner.

The work presented in this chapter has been published in *The British Journal of Clinical Pharmacology*. This publication can be found in appendix 5.

Section 3

Public acceptability of pharmacogenomic implementation and research generated from implementation data

CHAPTER 6

British South-Asian ancestry participants views of pharmacogenomics clinical implementation and research: a thematic analysis

6.1 INTRODUCTION: Views of pharmacogenomics clinical implementation and research

6.11 The British-south Asian ancestry population

The South Asian ancestry population is a rapidly growing demographic in the UK, now representing 10% of the national population[25]. South Asian ancestry populations are under-represented in both genomics studies and clinical trials which provide the data that underpin therapeutic licensure by regulators[23,28,29]. The UK South Asian ancestry population suffers from high rates of multimorbidity and will therefore be exposed to polypharmacy. This means they are more likely to experience adverse drug events and drug-drug interactions as compared with other populations due to exposure to higher numbers of medications.

6.12 Pharmacogenomics

Pharmacogenomics (PGx) uses genetic information to predict some of the interindividual variability in response to therapeutics and can help to personalize medication choice to get the right drug to the right patient at the right dose and the right time. PGx can therefore increase efficacy, decrease ADRs, and mitigate drug-drug interactions. The potential benefits of (PGx for the UK-south Asian ancestry population are substantial, so it is vital engage the

community in discussions about PGx clinical implementation and use of generated clinical data for future research.

6.13 Pharmacogenomics and health equality

PGx has potential to address some inequalities by nature of ancestral variation in polymorphism prevalence. For example, it would personalize therapy for those who are poor CYP2C19 metabolizers (higher prevalence in Asian and Oceanic ancestry populations) or ultra-rapid CYP2D6 metabolizers (more likely in those of Oceanic, Ashkenazi Jewish and middle eastern populations)[58,143]. However, PGx implementation could make inequalities worse if historically under-represented ancestral groups, such as the South Asian ancestry population, do not engage with the PGx research that will flow from clinical implementation[144]. This is because unless there is research engagement from diverse ancestral groups, PGx polymorphisms cannot be validated in diverse populations, and polymorphisms specific to non-European ancestral groups may be missed.

6.14 Implementation in the NHS

The NHS has committed to examining the evidence for PGx implementation in the next 1 to 3 years as part of the national genomic medicine strategy[121].The benefit of patient and public engagement (PPE) in clinical service development is well established. Systematic review shows that care process outcomes emerged from high-level enagagement[145]. Furthermore, engagement can improve the relevance and credibility of research, aligning the research community and research population, and improve accountability to the research population[146].

PPE is critical to shaping and driving PGx implementation. Enhanced research participation from historically underrepresented communities is vital to the goal of using PGx to address health inequality. This is particularly important when there might be disproportionate benefit to historically under-represented communities and potential trust barriers to be overcome.

6.2 AIMS AND HYPOTHESIS: Views of pharmacogenomics clinical implementation and research

- The objective of this qualitative study was to understand British-Bangladeshi and British-Pakistani participants attitudes toward PGx clinical implementation and potential barriers and facilitators in relation to PGx data sharing for research.
- We hypothesized that focus groups would allow broad ranging discussions which would generate consensus themes to guide further work on public acceptability of PGx in this population.

6.3 METHODS: Views of pharmacogenomics clinical implementation and research

6.31 Recruitment

Due to the lack of any prior PGx public acceptability work in this cohort demographic, focus groups were chosen as a methodology to canvas public input with minimal assumptions.

We recruited to focus groups from existing participants in the Genes & Health cohort study[24]. Genes & Health participants were originally recruited 2015-present in community and healthcare settings[24]. Inclusion criteria were age 16 or older and self-identified as Bangladeshi or Pakistani ancestry. 150 participants who had recently engaged with follow-up

studies locally were sent an SMS inviting them to join the focus groups. This was supplemented with invites extended directly to recent or future participants by telephone.

6.32 Demographic data

Demographic information was collected from participants in a brief survey administered prior to the discussion. Four focus groups were conducted with 9-12 participants per group. Two groups were mixed gender, one was male only and one was female only. Simultaneous interpretation was available to participants in Urdu and Bengali.

6.33 Format of focus groups

A brief introduction was given on pharmacogenomics and then PGx clinical implementation and use of clinically generated PGx information for research were discussed.

The focus groups took a semi-structured approach using a topic guide which asked questions about PGx implementation, concerns about taking a PGx test, and sharing clinical PGx data with third parties for research (the topic guide is provided in appendix 2). A literature review was undertaken to inform the topic guide development. Though information regarding public and patient perspectives of PGx is scant and high level there are common themes in the literature which served as a starting point for the semi-structured topic guide used (Table 1)[12–22].

Table 1: A review of common themes from studies investigating pharmacogenomic implementation from the perspectives of patient/public, prescriber, or a mixed group[147–157].

Study population	**Patients/Public**	**Prescribers**	**Mixed**

Common themes	Holistic approach to diagnosis and medication use Concern re prevalence of ADRs at present – PGx could help Cost effectiveness was a concern Storage and privacy of genetic information was a concern Patients would want a high level of information and valued effective communication Participant driven counselling needed Trust was important, trust in research, trust in doctors, trust in pharmacists Experience with healthcare and health was important to inform significance/relevance Perceived potential harms ie less effective or more expensive medication, insurance implications Want to receive information specifically tailored to their health vs general PGx info	Education of primary care workforce Ethical, legal and social aspects - impact on patients Health economics Informatics Testing timeframe Patient acceptability Adherence perceived as much bigger problem than PGx Sensitivity to all thing genetics related in tribal settings	Education for public and clinicians Lack of evidence for clinical utility Reimbursement Data registration and sharing Decision support tools Responsibilities ie doctor vs pharmacist Cost effectiveness Infrastructure to support testing and interpretation Turnaround time of testing Effect on family members

A clinician investigator led the focus groups, enabling participants to ask questions about the topic (ie: how genetic testing samples would be collected). Focus groups were recorded and abridged transcription was performed.

6.34 Thematic analysis

The data was analysed thematically, using an inductive approach, to describe perceived utility of and barriers to clinical PGX implementation and subsequent PGx research [158]. A member checking session was held to discuss the results of the thematic analysis.

6.4 RESULTS: Views of pharmacogenomics clinical implementation and research

6.41 Focus group demographics

There were 42 participants across the four groups, 64% female. 26% were born in the UK or Europe. 52% were born in Bangladesh and 17% in Pakistan. 36% reported university level education. More detailed information to characterize each focus group is shown in Table 2.

Table 2: Detailed demographic information for focus group participants. Some participants did not respond to some questions; therefore, percentages do not always add up to 100%.

Focus Group	1	2	3	4
Number of participants	12	12	10	8
Female Gender (%)	70% (9)	100% (12)	60% (6)	0% (0)
Average age	37 years	42 years	33 years	35 years

(Range)	(18-45)	(23-59)	(21-43)	(16-48)
Spoken Language				
English	67% (8)	42% (5)	50% (5)	50% (4)
Bengali	17% (2)	58% (7)	50% (5)	13% (1)
Urdu	17% (2)	0% (0)	0% (0)	38% (3)
Born in				
UK	25% (3)	8% (1)	50% (5)	0% (0)
Bangladesh	25% (3)	83% (10)	50% (5)	50% (4)
Pakistan	33% (3)	0% (0)	0% (0)	38% (3)
India	8% (1)	0% (0)	0% (0)	0% (0)
Other	0	8% (1)	0% (0)	0% (0)
University education	75% (9)	25% (3)	30% (3)	25% (2)
Country of education				
UK	25% (3)	0% (0)	50% (5)	25% (2)
Bangladesh	25% (3)	25% (3)	10% (1)	25% (2)
Pakistan	33% (4)	0% (0)	0% (0)	0% (0)
India	8% (1)	0% (0)	0% (0)	0% (0)
Other	0% (0)	8% (1)	0% (0)	0% (0)

6.42 Themes arising from analysis

Main themes that emerged are shown in Table 3.

Table 3

	Themes	Sub-themes
Clinical implementation (1.0)	Benefits (1.1)	***Which medicine 'suits' me (1.1)*** Reduced side effects, higher efficacy, more personalised to each individual and diverse communities
	Communication (1.2)	***Communication to support clinical PGx implementation (1.2)*** Simplicity, Person communicating, differentiate from diagnostic testing /disease prediction
	Timing (1.3)	***Timing of testing in the clinical pathway: Who would benefit the most and how should testing eligibility reflect that? (1.3)*** When to offer, at what stage of illness/health
		Testing in primary care. (1.31) Where in care setting/journey
	Custodian of data (1.4)	***Maximizing benefits of clinical PGx testing: transfer of information across care settings. (1.4)*** Who keeps test results, how do they travel
	Cost (1.5)	***Balancing benefits against costs (1.5)*** Direct costs, indirect costs
	Trust (1.6)	***The role of trust in clinical PGx implementation: 'GP they trust' (1.6)*** Factors contributing to lack of trust, how to build trust
	Education and Outreach (1.7)	***Education to support clinical PGx implementation (1.7)*** Educational needs and baseline awareness
		Outreach and engagement (1.71) where to outreach, use local community members to lead engagement
		Education and misinformation – lessons learnt from the covid-19 pandemic (1.72) Emerging evidence and shifting practice through the lens of the covid-19 pandemic
Research (2.0)	Benefits (2.1)	***Benefits of research using PGx clinical data: 'whatever is necessary to help the community' (2.1)*** Improved medicines use in future, for this community specifically
	Trust (2.2)	***Trust in PGx research: protective and harmful factors (2.21)*** Concerns around sharing data with different groups or institutions
		Lack of trust leads to concerns about data misuse (2.22)
		Lack of trust in profit driven research (2.23)
		Feeding back research results facilitates trust (2.24)
		Trust in therapeutics through the lens of the covid-19 pandemic (2.25)
	Education (2.3)	***Education to facilitate PGx research (2.3)*** Lack of understanding of genes/DNA

	Data sharing facilitators (2.4)	***Factors supporting PGx data sharing for research. (2.4)*** Trust, lack of conflict of interest, benefit sharing
	Barriers to Data sharing and Safeguards (2.5)	***Barriers to sharing clinical PGx data for research and potential safeguards (2.5)*** Concerns about privacy, data ownership and data misuse for profit. Gating of information, protective legislation and grouping of potential access groups were suggested safeguards.

For PGx clinical implementation these were: benefits, communication, timing of testing in the clinical care pathway, custodianship of data, cost, trust, education and outreach. Themes that emerged from discussion of sharing clinical PGx data for research purposes were: benefits, trust, education, data sharing facilitators, barriers to data sharing and safeguards. Themes were consistent across all groups, and all groups emphasized trust as primary and interlaced with all other themes.

The relationships between these themes are Illustrated in figure 1 (Figure 1- mind map).

Figure 1: Mind Map of focus group theme and sub-theme interactions

These key themes are expanded with sub-themes, to illustrate participant insights (Table 3).

1 PGx clinical implementation

1.1 Benefits of clinical PGx implementation: which medicine 'suits' me

Pharmacogenomics was perceived to be beneficial to individuals, by making medication choice more tailored, with less trial and error: "*which medicine suits me, I think that would be a good idea*". There was particular interest in implementing PGx for gene-drug pairs where

there are known to be high prevalence of polymorphisms in South Asian ancestry groups, and therefore a higher risk of inefficacy or toxicity in this community. Risk of ADRs were perceived to be a big concern in taking medications, and to impact on compliance. There were concerns that ADRs can be worse or more long-lasting that the original treatment indication, and that if participants knew of someone who reacted badly to a medication, they would not want to take it:

> "*For example, I take a medicine and I react really badly to it. Everyone in this room might sit there and think, wow, she's taking that medication and she's had a really bad reaction. Maybe I shouldn't take that medicine*."

Participants felt that PGx had the potential to mitigate this reaction by reassuring people that genetic risk of ADRs had been checked.

The potential to avoid broad contraindications with a more targeted approach was raised by several participant anecdotes. For example, one participant suggested that with more precise PGx stratification we might better understand which asthmatics are likely to have a bad reaction to ibuprofen and not withhold it from those who are not likely to have an ADR.

Communication

1.2 *Communication to support clinical PGx implementation*

Participants felt that limited information was desired for clinical PGx use at the point of care. There was a strong preference for use of simple language to communicate PGx. Participants thought that the easiest way of conveying the utility of PGx was to identify which medicines "*suit*" you/your body. Participants generally agreed that for clinical indication a minimal explanation of PGx testing to inform medication choice (similar to a routine blood test) was sufficient. Many participants didn't think it was necessary or helpful to include the fact that

DNA/genetics are being tested. For example, as one participant reflected elderly people might not understand what genes are in comparison to younger people. Given this, they suggested presenting PGx as something that would help clinicians make sure that the medicines they prescribe are "*more suitable for you*" would result in an explanation that would make sense to a wider range of people. This sentiment of offering PGx clinically for medicine optimization without detailed discussion of genetics was echoed by the majority of participants across all focus groups.

There was a strong preference that communication around PGx be led by GPs. GPs were described as trusted sources of information and having the skill and resources to support communication where language and literacy barriers are present: "*GP can explain very well"*.

Timing

1.3 Timing of testing in the clinical pathway: Who would benefit the most and how should testing eligibility reflect that?

PGx was viewed as particularly helpful to those who suffer from polypharmacy. People taking many medications were perceived as most likely to benefit from PGx testing, by decreasing risk of side effects and drug-drug interactions. In addition to identifying polypharmacy as increasing risk of ADRs, participants felt that enhancing efficacy from medication for those with the most morbidity was important, regardless of age. In the words of one participant, which provoked broad agreement "*you could have someone that is like half the age and has already been using so many different medicines. They aren't working for them and they wanna know why it's not working*."

Due to the shared view amongst participants that the greatest beneficiaries of PGx implementation would be those with the most morbidity, they proposed the idea of a secondary prevention speciality clinic. They felt that this would mean that people at high risk would be able to benefit from PGx innovations "*as soon as possible*" rather than having to wait potentially many years for pre-emptive PGx to be rolled out across everyday clinical practice for all people via NHS primary care.

While benefits of more personalized medicine were thought to be particularly promising for multimorbid patients, if resources allowed participants liked the idea of PGx panel testing for all at birth, so that the information would be there pre-emptively to optimize medication choice throughout life. Several participants suggested they would welcome PGx testing as a part of routine neonatal testing: "*you know the kids are born and then they offer the next day the hearing test …in the hospital without leaving? You can offer [PGx] at the same time*." Participants had no concerns about doing PGx testing on babies, provided sample extraction was not painful or harmful. Parents were much more concerned with the risks of a perceived trial and error prescribing approach that did not consider genetic data which could indicate high ADR risk.

1.31 Testing in primary care.

Participants felt strongly that pre-emptive PGx testing via the GP was preferable to point of care testing in hospital at the time of indication for therapeutic (ie in the example of CYP2C19 testing to help guide anti-platelet choice after a myocardial infarction). The reasons were multifactorial; the GP was first point of contact, had all patient information, provided continuity of care, and was perceived to communicate well. Participants liked the idea of having PGx testing before there was a treatment indication, and felt primary care was

the right place for this kind of anticipatory testing. There was also a concern that anything viewed as not essential may not reliably happen in acute care settings. Furthermore, participants thought of primary care as a less threatening and more personal setting where there was a higher likelihood of receiving information about test results and being in a state to understand that information, as compared with hospitals. "*Going to the GP… it's a lot more personal than going to a hospital… if you're at a hospital it just kind of feels alien*". They also felt that need for acute care was associated with fear: "*people go in hospital when [they are] in danger…I can call the GP and book an appointment… when you go to hospital [there's] always danger there*". Participants felt that due to the acute nature of secondary care communication was limited, and patients were often unaware of investigations ordered. As one participant surmised: "*We don't even know probably half of the things they do. No one questions about the medicine or why they're taking the blood test. There's no choice*".

Custodian of data

1.4 Maximizing benefits of clinical PGx testing: transfer of information across care settings.

Benefits of PGx were thought to be greatest if PGx results could be effectively shared across care settings, particularly primary and secondary care but also community pharmacy settings. Some participants felt that integration across care settings of existing analogous data is not good. One parent illustrated this with an anecdote:

> "*I have an example: One of my sons [is] allergic [to] ibuprofen. So, this information I can see …the GP shared with me…but always I have to tell [them] in a hospital, don't give ibuprofen to him, because he has a reaction with that*".

However, another participant gave examples of successful programs where important medical information travels with patients, suggesting the same could be done with PGx: "*Shouldn't be*

a problem because you already have medical bracelets and tags for people with different…conditions… so they could be identified if some something was to happen to them in public you can see that necklace or bracelet."

Participants liked the idea of an NHS app having PGx information that could travel with the patient and allow self-advocacy. For example, in the words of one participant:

> "*It should be the GP as well as the patient who has that information because… sometimes… the GP don't really listen properly… if she knows what her needs are… she can show it and say this is what it is. This is my genetic result*" (translated from Bengali).

Some participants saw community pharmacists as care providers that could give more personalized advice if they had access to PGx results. This could take some strain off primary care. However, others perceived sharing clinical PGx data with private chemists as a risk that could lead to inflated prices.

Cost

1.5 Balancing benefits against costs

The benefits of clinical PGx implementation, particularly as pre-emptive testing for all nationally, were weighed against the risk of overburdening resource limited NHS services and clinicians, which participants felt protective of. There was trust in the NHS and NHS clinicians and a perception that the benefit of PGx implementation would need to outweigh added financial strain and time constraints on these institutions and professionals.

There was a feeling that any preventive endeavour would be lower priority, as compared with testing which responded to clinical need. In the words of one participant, which the other participants expressed agreement with:

> *"you know they're suggesting a GP visit should cost people money…what about the cost of the test… would it cause too much pressure? …In advance you are doing a testing… Maybe you need it in the future or not…still you are doing it … they're asking for less pressure on the NHS then you're putting so much more pressure on the NHS."*

Many participants felt that streamlined logistics of PGx implementation were crucial to ensure the inconvenience of participation wasn't perceived to outweigh the benefits.

A further concern to the integrity of existing services and professionals was any added threat of litigation. This concern further highlighted the protective feeling participants had toward the NHS, and the requirement that the benefits outweigh the all-inclusive costs:

> *"Could this open up the NHS or the GP to liable action, i.e. being sued. Because they have the genetic markers there. You gave the medicine, but now obviously they got it wrong…Patient then sues the GP/ brings action against the NHS because you've given me a wrong medicine, even though you've had my genetic markers."*

Trust

Trust was a central theme in discussion of clinical PGx implementation and was impacted by and impacted on communication and education.

1.6 The role of trust in clinical PGx implementation: 'GP they trust'

There were strong feelings of trust in the national health system and health care providers, particularly primary care practitioners. Examples of broadly shared articulated trust in GP were common. Despite this trust, participants commonly cited concerns about side effects leading to medication non-compliance. "*Some people are quite scared of taking any medication because of all the side effects. Even if they get the medication from the GP… they're going to ask how many side effects [and then] don't take it".*

Participants thought that a more personalised approach to prescribing using genetic information would enhance trust in prescribers and prescriptions, because people would have more confidence in the selection of therapeutics knowing it was aligned with their personal test results. "*After genetic test when doctor will prescribe medicine obviously there're going to involve more trust on this*". Participants thought that this enhanced trust would improve medication compliance, as demonstrated by one participant:

> *"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.*"

Ancestry specific representation in research generated evidence for therapeutics was noted to build trust in a clinical setting: "*If you get a medication out and say we tested it on these kind of… people… and that was beneficial. This drug was good for Asian community… S' it's better to take that."* The implication was that participants know that ancestry is sometimes linked with response to medication. Therefore, proportionate ancestry representation in evidence base assessing efficacy and ADRs builds trust in clinical practice by demonstrating that a specific medicine has a favourable risk-benefit profile in their community. Due to

trans-ancestry variation in pharmacogene polymorphisms and historically non-diverse clinical trial cohorts this is an important point in how clinical PGx implementation interfaces with trust.

Interestingly, there were no concerns from participants around misuse of data within clinical care pathways. Participants unanimously felt that their clinical data was secure through standard NHS data protection pathways and that PGx data would be no different. In the words of two participants: "*I think the GDPR legislation makes me comfortable with sharing my information with the GP and the NHS, so I don't see any hindrance…sharing my information*"; " *the current GDPR is quite broad*". However, participants felt that any sharing of personal data with private entities such as chemists could result in price gouging if, for example, pharmacies discovered they were serving a population who were much more likely to respond well to one specific medication. This was a widely shared concern.

Education and Outreach

1.7 Education to support clinical PGx implementation

There was consensus that national roll out of pharmacogenomic testing should be accompanied by public health level education, with outreach, and clear communication to facilitate trust. It was clear from the focus group discussions that it is important to differentiate diagnostic genetic testing or genetic testing to predict disease risk from PGx testing. There was a general concern from participants that the level of genetic literacy in the UK-South Asian community is low. There was a feeling that people with more lived experience of disease and medication use were more likely to understand and be interested in PGx.

1.71 Outreach and engagement

Participants universally acknowledged that GPs would not be able to discuss PGx with each person. This was an impetus for support for a broader public health and outreach awareness campaign proposed by participants.

Forums such as local mosques, Islamic centres, schools, fairs, shopping centres and GP surgeries were suggested to disseminate information about pharmacogenomics. "*The mosque …some Islamic mosques have community services [centres] as well… the kids there are learning…the elders are coming there…women are coming there…mosques have a community system…the ladies are very much involved in that.*"

Multi language leaflets and videos were enthusiastically suggested, as was propagation of information via social media. The importance of leadership in the community, and community and family links, were paramount. Therefore, secular and faith leaders and heads of family were perceived to play a key role in propagating information. There was also a suggestion from participants in every group that information can be disseminated in families by incorporating education about genetics generally and PGx specifically in schools. "*Getting children to understand…maybe they can go home to their parents…if you come to schools and talk about it*".

1.72 Education and misinformation – lessons learnt from the covid-19 pandemic

Participants framed their experience with dissemination of new medical information through experiences with covid vaccines. There was a broadly shared view that misinformation around the covid-19 pandemic and vaccines had eroded trust between the community and

health care. There was perceived to be a new reluctance to engage in any non-essential clinical tests:

> "*You know covid changed everything. Do you think that people will go for the blood test or genetic test that don't know why you are using this, why we need this? So you need to educate them what is the importance for them. Otherwise' it's very hard for the Asian community to come*."

The pandemic highlighted a need for high quality accessible information regarding new developments in therapeutics related clinical care ("*to spread information and minimize misinformation*" in the words of one participant), and ability to understand which demographics different forms of information was reaching. Misinformation was a concern, particularly via social media platforms, where it can be widely disseminated: "*There's so much data on the internet, and so much information it can be false*". Education with outreach were seen as a solution to the problem of misinformation. Social media was seen as an effective tool to combat misinformation and democratise knowledge via accessible multi-media campaign.

6 2 Sharing clinical PGx data for research purposes.

Themes that emerged from discussion of sharing clinical PGx data for research purposes were: benefits, trust, education, data sharing facilitators, barriers to data sharing and safeguards.

Benefits

2.1 Benefits of research using PGx clinical data: 'whatever is necessary to help the community'.

Research that could be generated from use of PGx clinical data was felt to be beneficial to the community with some risks to the individual privacy. Participants felt favourably about contributing data to support research which would benefit the community, and the good of the community had a central role in discussion. As one participant said, and others echoed: "*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*". However, there were strong feelings about privacy and concerns that any data sharing may breach privacy and open potential for misuse:

> "*I think data protection is very important in our lives…Yeah like how we said it should be between …researchers and GP…I don't think I would like everyone to know… what benefits me… I would like to have privacy ourselves as well*".

These privacy concerns were counterbalanced by the benefits of community representation in research to develop community specific knowledge. A participant highlighted concern that research on medicine is only done in some people, but then the medicine is used in all people, and participants agreed broadly that it is reassuring to be treated with medicine when the evidence base for medicine use included their community. "*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?*" (translated from Urdu).

Participants felt more favourably about taking medication that had been trialled in their ancestry group and felt that ancestry specific research could drive changes in medication or supplement taking behaviour. For example, a participant gave an example of impact on behaviour driven by community specific research: most people in the community didn't take vitamin D supplements, and then research that south Asians often lack vitamin D was

disseminated. This research specific to the south Asian community then convinced many people in the community to take vitamin D: "*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".*

Benefits of data sharing to generate further research specific to the south Asian community was perceived as outweighing the potential risks of data misuse generally, particularly with appropriate safeguards: "*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*."

Trust

2.21 Trust in PGx research: protective and harmful factors

Willingness to share clinical data for research purposes revolved around trust. Participants felt that more personalized therapy through PGx clinical implementation would enhance trust and therefore contribute to increased willingness to engage with and share data for research. Trust was engendered by institutional affiliations (ie NHS, medical practitioners, national regulatory bodies such as the Medicines Healthcare Regulatory Association (MHRA)). Trust was supported by safeguards in data protection and de-identification of data used for research. Participants also found the non-diagnostic nature of PGx testing reassuring, and keeping the scope of PGx testing to non-disease diagnostic genes was a factor that enhanced trust: "*I feel if like it's really narrowed down in front of you it would be safer …".* Trust in the individual recruiting to research was also a factor. Trust leading to research engagement could be gained by endorsement of a family member, faith leader, or community leader: "*If my relative did it, I might [do it]. Some people trust in relatives…People trust more family*".

Trust was harmed by insecure data, a history of data breach or association with individuals or institutions that were not trusted. Lack of consistency in information and profit as a motivating factor were other factors which harmed trust.

2.22 Lack of trust leads to concerns about data misuse

Misuse of data by non-trusted entities was a concern. This was a central disincentive to research participation: "*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*" (Translated from Urdu). Concerns regarding the specific nature of potential data misuse ranged from breaches of privacy and financial exploitation to the potential for malicious actors to use genomics data for racially motivated genocide.

> "*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"*.

This latter was perceived by some participants to be hyperbolic, and the level of time, knowledge and resources needed to misuse data in such a nefarious way were cited as protective: "*to get to the point of …killing hundreds of thousands… is far-fetched. We'd need to dissect …an entire genome, which would take a very long time, and a lot of work*."

2.23 Lack of trust in profit driven research

Participants across all groups expressed concern that pharmaceutical industry was not trustworthy due to profit as motivating factor. "*Medicine is about helping people and saving lives…They've developed the drugs but they're big businesses as well*…". Some extended this

logic to private chemists and pharmacists working at chemists, as profit was felt to be the bottom line. The perceived conflict of interest created by profit as a primary goal was felt to lead to risk of misuse of information.

There were concerns about benefit hoarding for profit. Many participants across all groups worried that if industry were to get PGx data for research they would find a way to profit at the expense of the community and withhold benefits from the community. Several participants felt there was a risk of price gouging if a therapeutic was found to be particularly beneficial to their community:

> "*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."* Another participant in a different group expressed the same sentiment: "*If this information is being delivered to industry, will it affect the cost of the medicine?… if we're getting a tablet for 1 pound we might then get it for 3 pounds*" (translated from Urdu).

There was a negative view toward proprietary patents as tools to restrict availability of therapeutics. There was a concern that if lifesaving medications were discovered from genetic data, patents would mean that the medicine would not be affordable or accessible to the participant communities that had contributed data to the research.

However, trust in national regulators was seen by some participants to counterbalance the risk of unrestrained industry: "*business is business at the end of the day. Some businessmen are OK. If the regulator doesn't allow, then they won't get it [the medication]. They need to allow it first*."

2.24 Feeding back research results facilitates trust

Feeding back research results was crucial to ongoing research engagement through building trust: "*if someone sees a result then they will become more involved*". Participants agreed that if research results were fed back it would support education and engagement and facilitate trust via grassroots community communication. As one participant said of receiving feedback on how she contributed to a study: "*And then you would speak to, like, your friends and family…They would open up. They would be like, wow, that's so cool… It would build trust between communities*." Some participants felt that personalized feedback on an individual level had an even more powerful impact, and there were suggestions that researchers could build trust further by contacting individual participants to make them aware of how their data had contributed to a study.

2.25 Trust in therapeutics research through the lens of the covid-19 pandemic

Participants expressed their experience with trust, and mistrust, in therapeutics and research through the lens of the covid-19 pandemic. Participants reported a change in context and trust toward therapeutics research due to covid. There was broad agreement that lack of trust had manifested in strongly divided opinions on the safety and efficacy of the covid-19 vaccine:

> "*for example…, covid injection, half of the people …didn't have it…a lot of people I know, they didn't go for that injection…it's their choice end of the day…but there's a reason why they didn't have it…because they don't trust maybe, they didn't believe".*

Lack of trust toward the covid-19 vaccine within the south-Asian community was widely felt to be prompted by the pace of research and social media reports of trusted health care practitioners refusing covid-19 vaccination. Because of the nature of the pandemic, some participants saw covid vaccines and treatments as initially experimental or offered without a

full understanding of possible effects. However, it was felt that this mistrust would not extend PGx research focused on optimizing personal risk/benefit profile for existing medications.

Education

2.3 Education to facilitate PGx research

In contrast to the skeletal information desired for clinical PGx use at the point of care, participants felt that a lot of information and education was needed to responsibly organize sharing of the generated clinical data for research. "*for research: you have to make sure you understand it perfectly and it has to be accurate information given to you. Clinical, that's something you just do…easier to do…research you have to be really accurate.*"

Participants highlighted lack of awareness of research, and lack of scientific and genetic literacy as significant barriers to research engagement. *"this is the reason there is a less data from these groups: because the lack of education and they don't participate if they don't understand anything."* Language barriers were also cited as key hurdles to engagement of this community in research.

However, participants also perceived a lot of interest in advancing health and medication related knowledge in the community and suggested that community ties offered vehicles to public engagement. The public health engagement campaign suggestions outlined above around national PGx roll out were echoed strongly in the discussion of education to facilitate data PGx sharing for research. Engaging with local community members for grass-roots education was advised by participants. But some participants perceived the lack of scientific literacy to be a significant barrier to community exchange of information:

> "*How to educate those people? Like when you speak to other people they don't know, like when she will leave from here, what she would say to her neighbour … what is*

that genetic information to do with the medication? We take medication everyday" (translated from Urdu).

Many participants expressed interest in being trained to be community champions and volunteered to disseminate PGx information to facilitate research engagement: "*in East London mosque they have events and things… I'm here today. I understand. I will go and spread to my friends and family. So, it's like word of mouth will get spread*."

2.4 Data sharing facilitators

Data sharing was the key concept on which research from a hypothetical clinical PGx service hinged. Participants required prompting to distinguishing PGx testing for clinical use from sharing clinical data for research.

2.4 Factors supporting PGx data sharing for research.

Data sharing was desirable if the researchers did not have a financial stake, and benefits would be shared. There was a common perception that without research use of medicine will not improve, but an understanding that the risk is to the participating individuals while the benefit would be for future individuals:

> "*If you don't share it, you don't advance really. So, you have to come to some sort of compromise where you are sharing the results they need, or do you want to just not share it and be stuck and not give two hoots about what happens in the future. You have to draw that line somewhere*.".

The perceived "good" of the research purpose was a key motif: "*So the point is how it works when we share for the good purpose, not for the bad purpose. So, it can help, so definitely [we should] share*". There was broad consensus across individuals and groups that the idea of

good as compared with bad purpose had an association with the trustworthiness of the researchers: "*we have a concern, so we can only share these things [PGx data] with trusty [trustworthy] ones and [make ourselves aware*]." The perceived trustworthiness of both individual researchers and associated institutions were determining factor in weighing willingness to share clinical PGx data for research purposes.

Health care professionals, academic institutions, and the regulatory body (the MHRA) were considered trustworthy and therefore participants were happy to share PGx data with these groups for research with the protection of standard data de-identification and data protection.

Barriers to data sharing and safeguards

2.5 Barriers to sharing clinical PGx data for research and potential safeguards

Participants across all groups broadly acknowledged that some people would not like to share data as a rule, due to privacy concerns: *"There are people with those [privacy] concerns and those concerns are very real".* Data ownership was an important topic linked with privacy, and many participants wanted to maintain control over access to their data *"It's my information. That's mine, do you know what I mean, it's an invasion of privacy where you don't have control over who gets to see your information."*

As compared with healthcare practitioners and academics, there were very different perspectives on sharing PGx data for research with industry. Concerns revolved around trust, as outlined above. Most participants felt that industry has an inherent conflict of interest as a profit driven private enterprise and therefore could not be trusted to prioritize benefit sharing/the health of the community over potentially exploitive options: "*pharmaceutical*

companies are only thinking about their profits then it's not good to share our information with them".

Others felt that there is an inherent risk to not doing research: "*without research there will be always risk, there's no cure*". Some perceived the benefits of data sharing for industry use to outweigh potential harms: *"It improves the medicine, so it improves the patient care*".

Confidentiality and anonymization of data were important safeguards to protect privacy. "*It's anonymous isn't it…so the people who are doing it, they don't know who it is. They have to have that barrier that [data] is confidential and not to be leaked to anyone*." Well-articulated policies around data protection and management of any breach of data protection were perceived by many participants to be crucial safeguards: *"It's important what they're going to do with the data but also if there is a breach of data, what happens… if they find that information was leaked to the public…what they do*".

Transparency about potential conflicts of interest and opportunities to opt out of data sharing with non-trusted research partners were desirable.

> "*I think everyone should be given the option to opt in and opt out, so I think that's potentially a way of going forward … so you [can] opt in for pharmaceuticals or universities and … and so on…You can label them as non-profit organisation and for-profit organisations and so. That would build confidence in the person that is being involved in the research*."

Safeguards against financial exploitation due to knowledge of individual or community PGx data would be protective.

6.5 DISCUSSION: Views of pharmacogenomics clinical implementation and research

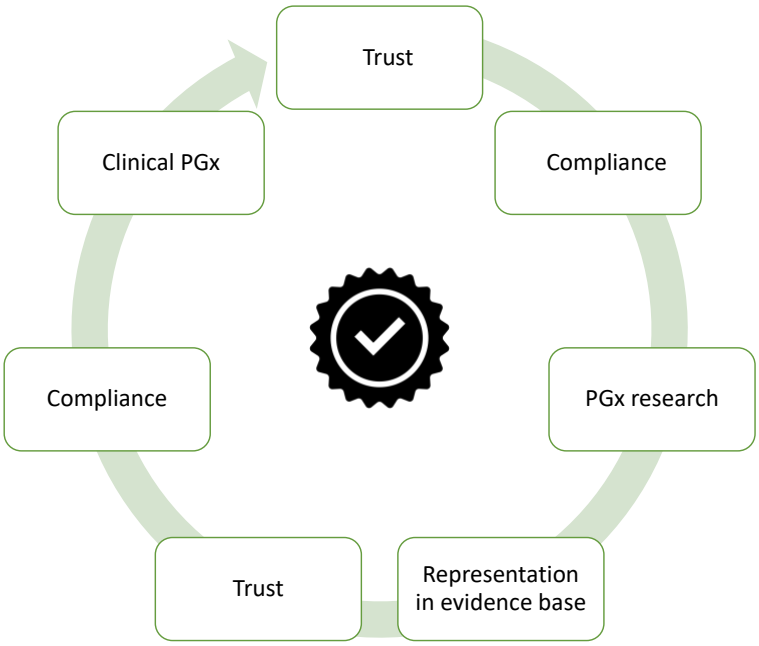
6.51 Key cross-cutting themes

There were key cross-cutting themes common to discussion of both clinical implementation and use of clinical data for research. These included: benefits, the central role of trust, concerns about baseline education and desire for public heath level campaign to address this perceived need, and data sharing/custodianship. These echoed existing themes in the literature around the central importance of public awareness, education, trust, and data custodianship (supplementary table 1). However, the interaction between the key themes across clinical application and research domains was rich, particularly around trust, and adds some novel detailed insight around building trust within this population.

Pharmacogenomics implementation with appropriate population wide education and clinician communication was perceived to have the potential to enhance trust in clinical care systems by personalizing therapy to individuals, particularly those from under-represented ancestorial groups. This increased trust was thought likely to contribute to increased medication compliance. Trust drives willingness to share data and engage with research, and participants linked increased trust in clinical prescribing with increased willingness to share data toward advancing PGx because they could see PGx benefits in action (ie there is clinical value proven from PGx research). Representation of the South-Asian ancestry group in therapeutic evidence base through research increases trust in the evidence base for medicine use and may increase compliance with therapeutics. Therefore, participants constructed a circular trust building and benefit model that could see a well implemented PGx roll out promote increased medication compliance via trust in clinical systems and increased research representation,

which would then feed information back into clinical practice, further supporting trust (Figure 2).

Figure 2: A circular trust building and benefit model of pharmacogenomics.



The relationship between participants and GPs were key to promoting this model of trust, as was feeding back utility of research to those who choose to participate, public health level education campaigns, and stakeholder guided data gating.

Therefore, if the NHS decides to adopt panel PGx testing nationwide, educational and engagement initiatives should proceed the roll out, with accessible materials in multiple languages that can be disseminated either by championing individuals or via multi-

media/social media. Engaging with community leaders to disseminate information is a valuable approach, as well as optimizing intergenerational information sharing by educating those in school.

Success of a national PGx programme program is likely to hinge on the level of trust built into the rollout. Some of that trust is engendered already by trusted individuals, professionals, and associations, but some must be earned by education and engagement initiatives with the public. The covid-19 pandemic demonstrated how easily misinformation can be disseminated and erode trust. The unanimous emphasise on mistrust kindled by the covid-19 pandemic have implications for PGx, particularly in BAME groups, not prior discussed to our knowledge. These findings highlight the importance of building from existing trusted relationships with GPs and carefully considering stakeholder suggested safeguards to preserve trust.

Trust can be supported by robust and transparent policies around protection of data, management of data security breaches, and stakeholder input on proposed data sharing. Sharing any data which could be used by private entities for fiscal gain is likely to be a particular source of contention and therefore should be continually informed by stakeholder consultation. Policies that would protect against price gouging as a result of proprietary gains from clinical PGx data sharing for research should be considered.

This study suggests that pre-emptive PGx roll out via primary care is the preferred approach in the long term, but participants highlighted secondary care prevention clinics as a high benefit population in which to pilot panel PGx testing.

6.52 Strengths and limitations of this study

This is the first study to engage UK participants of South-Asian ancestry in discussion of facilitators and barriers to pharmacogenomics implementation and research. Further research should be done quantitatively to canvas large scale public awareness and attitudes to PGx clinical implementation, utility, and sharing PGx data for research in this community. The study was made possible by collaboration with the Genes & Health research team and their links and pre-existing trust building with the community. However, participants recruited from a cohort who have chosen to participate in a large-scale genetic research study may not be representative in their attitudes toward PGx.

6.53 Clinical implications

This participant data from an under-characterized and disproportionately morbid population within the UK is valuable to influence policy on PGx implementation. Inclusive engagement studies can increase the likelihood that PGx implementation would become a tool to improve the health of this group at high risk of polypharmacy and support underpinnings for data sharing to generate PGx research specific to this under-represented population. Such a stakeholder informed approach will support PGx to be a tool which reduces instead of exacerbating health inequality.

The work presented in this chapter has been published in *The Pharmacogenomics Journal*. This publication can be found in appendix 5.

CONCLUSIONS OF THE THESIS

The studies in this thesis highlight several key points about use of real-world data on medication prescription and health outcomes coupled with genetic data. The first is validation of real-world therapeutic efficacy association with genotype, as in the case of *CYP2C19* and clopidogrel use for secondary prevention after myocardial infarction. The second is the utility of stratification by genotypes to look for association with purported adverse drug reactions in an observational dataset. An excess of events stratified by genotype suggest possibility to mitigate such events with PGx testing. The third is the use of pharmacogene proxies for higher drug exposure as a pharmacovigilance tool. As in the case of the *SLCO1B1*-statin work presented, if individuals exposed to higher amounts of medication have an associated outcome and this association is not present in non-drug exposed participants it can support or refute a hypothesis of causality.

The use of these strategies to probe gene-drug interactions and impact on patients in British-Bangladeshi and British-Pakistani communities is crucial. This is because, as demonstrated by the FVL multimorbidity study and the statin study, baseline levels of multimorbidity that deviate from prior research study cohorts may alter the real-world relevance of gene-drug interactions by impact on baseline event risk. Furthermore, the G&H community has a prevalence of pharmacogene alleles which is not comparable to those in European ancestry trial populations, as demonstrated in the *CYP2C19* diplotype characterisation and demonstrated impact on efficacy of clopidogrel use for secondary MI prevention. To ensure PGx targets health inequality and promotes health equality, research must highlight real world impact of not performing PGx testing in these communities and benefits of further characterising known pharmacogenes in these under-represented populations. It is very likely

that there are many important rare variants in such pharmacogenes in this population which have not yet been characterised and may not be well covered by array data.

The discussion with G&H participants from the British-Bangladeshi and British-Pakistani communities was extremely informative. The emphasis on trust and the relationship between trust, representation and medication compliance are dense, important, and require further exploration. Medication adherence is a substantial barrier to achieving optimal control over many chronic diseases which contribute to substantial multimorbidity, such as HTN, DM, and heart failure, to name only a few. There was participant consensus that merely the knowledge of a PGx test having been performed would lead to higher medication adherence due to higher confidence that medication was well suited to the individual. This would not be a small add-on benefit to PGx testing if proven to be true in prospective studies testing behavioural modifications in response to PGx testing. Furthermore, being presented with evidence of benefit specific to the participant community was associated by participants with more adherent medication behaviour. A barrier to testing this behavioural aspect of PGx response is that clinical trial patients are widely acknowledged to be much more adherent to prescribed medication that a typical patient population. If adherence has a component that's mediated by trust and representation in research, it is conceivable that underrepresented populations are less adherent and that this may contribute to known health inequality. Therefore, it's wholly conceivable that a pilot study in an underserved population would see benefits that are above and beyond those seen in a clinical trial if there is an incremental benefit from medication adherence. However, data suggesting a relationship between ancestry and adherence may be biased by gene-drug and other drug interactions that could lead to lower tolerance in ancestry groups not represented in research and trial cohorts. Quantitative studies are needed to unpack this information and tease out gene-drug

interaction contributing to lower mediation adherence via non-tolerance from the behavioural contribution to adherence which may be mediated by increased trust simply due to PGx testing. Therefore, further research as discussed in more detail below should focus on 1- genetic association with compliance in specific gene-drug pairs, 2- quantification of current medication adherence and association with attitudes toward PGx testing, 3- testing the impact of PGx on medication adherence in a prospective clinical setting. Furthermore, forthcoming exome data will allow for characterisation of novel rare variants in known pharmacogenes from this population.

WORK IN PROGRESS AND FUTURE WORK

Public acceptability of PGx

Planned ongoing and future work should focus heavily on assessing public acceptability to inform PGx implementation as part of the new NHS England PGx Network of Excellence (NOE). We have obtained institutional ethics approval from QMUL as part of a mixed methods analysis in conjunction with the focus groups and provisional approval from G&H's executive committee to disseminate a survey based on the thematic analysis presented in chapter 6 of this thesis to G&H participants. This will quantify feedback around many key themes that emerged from the focus group discussion. We will aim for 500 completed responses, and weight invitations from a pilot phase to elicit representative responses from the cohort according to age and gender. The survey has been developed in partnership with the G&H team and community advisory board as well as external advisors and citizen scientists (and can be found in Appendix 3). This will provide large scale quantitative feedback on the themes discussed in the focus groups and explore the identified themes around medication use and compliance, ADRs, trust, communication and PGx. It will characterize awareness of PGx and characterize facilitators and barriers to PGx implementation, and PGx data sharing for research. The survey is set to go out early in the new year and we anticipant analysis will be able to start in March.

The following hypotheses will be tested:

- Those with poor compliance may be more likely to be compliant if provided with PGx information
- Participants reporting experience with side effects, inefficacy or polypharmacy may be more likely to want PGx testing
- Those with less medication exposure may have more concerns about PGx testing

- Concerns linked with PGx testing may be related to education level
- Those who are aware of the MHRA and ability to report ADRs may be less likely to be concerned about data misuse and more likely to share data for research
- Those who report a non-English language as their primary spoken language might think communication is more important
- Those who report a non-English language as their primary spoken language might be less likely to share data for research
- Those who report a non-English language as their primary spoken language might be more concerned about data misuse.

Furthermore, we have worked with Professor Rachel Conyers' team in Melbourne at the Murdoch Children's Research Institute to develop a separate survey to assess attitudes toward PGx in adolescent and young adults who have cancer and/or are immunosuppressed. With detailed input from patient and carer collaborators, we have developed surveys for patients and carers to allow us to assess how attitudes around PGx decisions may relate to autonomy in this context. My participation in this work was funded by the Dunlop prize award from the British Pharmacological Society and The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists. It also has been fully developed and has ethical approval and will be disseminated in January.

<u>Follow up analyses planned</u>

Following the lead from the focus group participant highlighted themes, I will try to assess the behavioural and genetic impact of pharmacogenomic on medication adherence. Participants have suggested that simply having a PGx test will make them more likely to be adherent to medication, which would be a large potential benefit on top of any benefit gained

in adherence due to alleviating non-tolerance from a gene-drug interaction. The survey that we have prepared for dissemination in G&H will shed light quantitatively on the behavioural component. Given the results for the *CYP2C19* ultrarapid metabolisers prescribed clopidogrel for secondary prevention after a myocardial infarction, I would like to examine the genetic architecture of medication adherence. Therefore, I am currently undertaking a study of the genetic architecture of clopidogrel adherence. I further would like to construct a polygenic risk score from these GWAS results and test it for association with major adverse cardiovascular events in the large date set held by Regeneron. This collaboration is being discussed now with Regeneron. The NHSE NOE may offer further opportunity to assess adherence behaviour in a PGx trial capacity, though clinical trial patients are well acknowledged to be vastly more adherent than other patients. The G&H population has now also had exome sequencing. This data will shortly be available to academic researchers. I have written a proposal which will capitalise on this data to fully profile known pharmacogenomics variants, including structural variants, and to explore novel pharmacogenetic variants with predicted deleterious effects. This comprehensive PGx profiling will allow prediction of excess morbidity and mortality associated with diplotypes predicting non-typical medication response and allow extrapolated health economic analysis of potential cost-savings for PGx use in this population (appendix 4).

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PUBLICATIONS

Magavern EF, Caulfield MJ. Equal access to pharmacogenomics testing: The ethical imperative for population-wide access in the UK NHS. Br J Clin Pharmacol. 2023 May;89(5):1701-1703. doi: 10.1111/bcp.15689. Epub 2023 Feb 20. PMID: 36808131.

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Magavern EF, Jacobs B, Warren H, et al. CYP2C19 Genotype Prevalence and Association With Recurrent Myocardial Infarction in British–South Asians Treated With Clopidogrel. JACC Adv. null2023, 0 (0) . https://doi.org/10.1016/j.jacadv.2023.100573

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Magavern, EF, Durrani, F, Raza, M, Lerner, R, Islam, MR, Genes & Health Research Team, Clinch, M, Caulfield, MJ. British South-Asian ancestry participants views of pharmacogenomics clinical implementation and research: a thematic analysis. Pharmacogenomics J. https://doi.org/10.1038/s41397-023-00317-8

Submitted manuscripts and manuscripts in revision:

Magavern, EF, Kapil, V, Saxena, M, Gupta, A, Caulfield, MJ. Use of Genomics to Develop Novel Therapeutics and Personalize Hypertension Therapy. Under review at *ATVB*.

Cipriani, V, Vestito, L, **Magavern, EF** … Caulfield, MJ, Smedley, D. Rare disease gene association discovery from burden analysis of the 100,000 Genomes Project data. Under review at *Nature Medicine*.

Tamargo, J, Agewall, S, Borghi, C, Ceconi, C, Cerbai, E, Dan, GA, Ferdinandy, P, Lerkevang Grove, E, Rocca, B, **Magavern, EF**, Sulzgruber, P, Semb, AG, Sossalla, S, Niessner, A, Kaski, JC, Dobrev, D. New pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2023. Under review at *EHJ-CVP*.

PRIZES

Prize	Organization/Event	Year
Dunlop prize winner	British Pharmacological Society and The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists	2023
Harvey Prize winner	Royal Society of Medicine	2023
Runner up for prize: best poster clinical pharmacology	World Congress of Basic & Clinical Pharmacology	2023

PRESENTATIONS

Event	Location	Date
UK Pharmacogenetics & Stratified Medicine Network	London, UK	June 2022
Open Targets Pharmacogenomics network drug target workshop	London, UK	October 2022
International Society of Cardiovascular Pharmacotherapy	Bucharest, Romania	October 2022
London Genetics Network	London, UK	December 2022
Cambridge Genomics MSc	Cambridge, UK	February 2022/2023
Festival of Genomics	London, UK	January 2023
SGUL Interventional Cardiology department	London, UK	April 2023
World Congress of Basic & Clinical Pharmacology	Glasgow, Scotland	July 2023
European Society of Cardiology Congress	Amsterdam, the Netherlands	August 2023

Royal Society of Medicine Vascular Medicine and PVD day	London, UK	September 2023
G2MC Congress 2023	Geneva, Switzerland	October 2023
Digital Health AI & Data 2023 (Panel)	London, UK	October 2023
Murdoch Children's Research Institute	Melbourne, Australia	October 2023
EuroCVP 2023	Florence, Italy	November 2023
Dunlop prize talk	Glasgow, Scotland	November 2023

SCIENCE COMMUNICATION

During my PhD I had the great opportunity to work with the DNA& team from the genetics society to produce a Pharmacogenomics episode:
https://open.spotify.com/episode/5pKoLlHpE5LXXa7w0LwYDc?si=ead3c88c3a0f4e3e&nd=1&utm_medium=organic&_branch_referrer=H4sIAAAAAAAAA7WNWwrCMBREV5N%2BtrVpVYQiQi2CXUD9kpjc2NCYXPKguHtTwSUI8zHMcDhTCOgPReHRBiXfOUPMtTJzcURnReShtQgmI1Uto9b36HQ7rQihJ1L1Keud%2F2huX2kCVN4KSK3Bqx30Bc%2FNMI5st5TDcus4ob1XhHbABOX7PaeslDVQ%2BFqY1g%2FG5%2F%2BaSLU1Iu2bTAIL0UFr3ZMZxT8dluAtDwEAAA%3D%3D&product=open&%24full_url=https%3A%2F%2Fopen.spotify.com%2Fepisode%2F5pKoLlHpE5LXXa7w0LwYDc%3Fsi%3Dead3c88c3a0f4e3e&feature=organic&_branch_match_id=1021689456835909625

Appendix 1:

ABBREVIATIONS

Acute coronary syndrome (ACS)
Adverse drug reactions (ADRs)
Alcoholic liver disease (ALD)
Aminoglycoside induced ototoxicity (AIO)
Barking, Havering and Redbridge (BHR)
Cardiovascular disease (CVD)
Chronic kidney disease (CKD)
Chronic liver disease (CLD)
Clinical commissioning groups (CCGs)
Clinical Pharmacogenetics International Consortium (CPIC)
Confidence interval (CI)
Cytochrome P450 2C19 (CYP2C19)
Diabetes mellitus (DM)
Direct oral anticoagulant (DOAC)
Dutch Pharmacogenetics Working Group (DPWG)
European Medicines Agency (EMA)
Factor V Leiden (FVL)
Food and Drug Administration (FDA)
Gain of function (GOF)
Gastrointestinal (GI)
Gastrointestinal bleed (GIB)
Genes & Health (G&H)
Hardy-Weinberg equilibrium (HWE)
Hazard ratio (HR)
Hormone replacement therapy (HRT)
Hydroxymethylglutaryl-Coenzyme A (HMG-CoA
Hypertension (HTN)
Imputation quality metric score (INFO)
Intermediate metabolizer (IM)
Ischemic heart disease (IHD
Loss of function (LOF)
Medicines and Healthcare products Regulatory Agency (MHRA)
Minor allele frequency (MAF)
Myocardial infarction (MI)
National Health Service (NHS)
Network of Excellence (NOE)
Newham (N)
NHS England (NHSE)
Nonsteroidal anti-inflammatory drug (NSAID)
Odds ratio (OR)
Office of Population Censuses and Surveys (OPCS)
Oral combined contraception (OCP)
Patient and public involvement and engagement (PPE)
Percutaneous coronary intervention (PCI)
Peripheral vascular disease (PVD)
Pharmacogenomics (PGx)

Poor metabolizer (PM)
Proton pump inhibitor (PPI)
Randomized control trials (RCTs)
Serotonin reuptake inhibitors (SSRIs)
Single nucleotide polymorphisms (SNPs)
Solute carrier organic anion transporter family member 1B1 (*SLCO1B1)*
Tower Hamlets (TH)
Tricyclic antidepressants (TCAs)
Trusted Research Environment (TRE)
UK Biobank (UKB)
United Kingdom (UK)
Venous thromboembolism (VTE)
Waltham Forest (WF)

Appendix 2:

Topic guide for focus groups

Session introduction and overview – introductory information given about PGx, and the example of *CYP2C19* testing for clopidogrel was discussed.

1. Do you think it is a good idea to test people to see if their *CYP2C19* gene works properly? If so, why?
2. If you think it is a good idea, when would you prefer to be told this information:
   -By you GP during a routine appointment in which your heart attack risk was explored?
   -After a heart attack when you are being treated in hospital?
   -What is your reason for choosing one of these options over the other?
3. If you knew this genetic information about yourself, what would you like to be able to do with it?
   -For example, would you like to be able to share it with healthcare providers or pharmacists?
4. If you would like to be able to share it with people, how would you like to do this? For example, stored on an app on your phone?
5. Would you like information like this to be stored on your electronic healthcare records so healthcare professionals who prescribe medication were aware of it? Doctors in hospital? GPs? Pharmacists? Please explain your answers to this question.
6. Do you have any worries about using genetic information to inform the medicines you and others are prescribed? Please explain any concerns you have or why you are not worried about this. What factors would make you decline a PGx test?
7. Do you have any suggestions for how healthcare professionals can explain PGx results to patients well?
8. If you had a side effect to a medication, would you be willing to report your symptoms to the NHS?
   -If yes/no, why?
9. If you were willing to record your medicine responses, how would you prefer to do this? For example, by speaking to someone such as your GP, a person who works in a hospital? Or by a phone app or an online form?

-What is the reason for your answer?

Expanding the Evidence

10. Can you think of any reasons why people would not want to be involved in PGx research?

11. How might we work with people to encourage them to become involved in PGx research? Are there any concerns that may be particular to your community?

12. Would you be willing to have genetic information related to medication effects shared with academic researchers so they could design or improve medications safety and effectiveness?

    -Would you be willing for your genetic information to be shared with the medication regulators in the UK when they look at reports of people who have suffered harms from medications?

        If yes/no, why?

    -Would you be willing for your genetic information to be shared with pharmaceutical companies when they are developing treatments.

        If yes/no, why?

Appendix 3:

Survey for pharmacogenomics public acceptability in Genes & Health:

"Genetics and Medication"

Appendix 4:

G&H Exome PGx profiling project proposal

Appendix 5:

Copy of Publications comprising PhD work