Annual Review of Pharmacology and Toxicology

Addressing Ancestry and Sex Bias in Pharmacogenomics

Manuel Corpas,[1,2] Moneeza K. Siddiqui,[3] Opeyemi Soremekun,[4] Rohini Mathur,[5] Dipender Gill,[6] and Segun Fatumo[4,7]

[1]School of Life Sciences, University of Westminster, London, United Kingdom

[2]Cambridge Precision Medicine Limited, ideaSpace, University of Cambridge Biomedical Innovation Hub, Cambridge, United Kingdom

[3]Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, United Kingdom

[4]African Computational Genomics (TACG) Research Group, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, Entebbe, Uganda

[5]Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom

[6]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

[7]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom; email: segun.fatumo@lshtm.ac.uk

Annu. Rev. Pharmacol. Toxicol. 2024. 64:1.1–1.12

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-030823-111731

Keywords

pharmacogenomics, underrepresented populations, alleles, haplotypes, biogeographical regions, diversity genomics

Abstract

The association of an individual's genetic makeup with their response to drugs is referred to as pharmacogenomics. By understanding the relationship between genetic variants and drug efficacy or toxicity, we are able to optimize pharmacological therapy according to an individual's genotype. Pharmacogenomics research has historically suffered from bias and underrepresentation of people from certain ancestry groups and of the female sex. These biases can arise from factors such as drugs and indications studied, selection of study participants, and methods used to collect and analyze data. To examine the representation of biogeographical populations in pharmacogenomic data sets, we describe individuals involved in gene-drug response studies from PharmGKB, a leading repository of drug-gene annotations, and showcase

CYP2D6, a gene that metabolizes approximately 25% of all prescribed drugs. We also show how the historical underrepresentation of females in clinical trials has led to significantly more adverse drug reactions in females than in males.

INTRODUCTION

Our understanding of how genetic variants influence drug response has been revolutionized since the release of the human genome project (1). Understanding the genetic composition of individuals has improved our ability to identify beneficial effects of pharmacological treatments as well as harms related to drug addiction, drug dependence or resistance, and adverse drug reactions (ADRs) across entire populations. Predictions of drug reactions and their expected effect have produced important benefits for well-characterized drugs such as those metabolized by cytochrome P450 genes (e.g., *CYP2D6*) (2–4) and anticoagulant drugs such as warfarin (5–7), among many others (8–10).

Despite these incontrovertible advances, our ability to translate pharmacogenomic knowledge into clinical benefit remains inequitable for certain population groups, due to a lack of data sets representing their genetic variation. In terms of sex, females have historically been underrepresented in clinical trials (11–13), meaning that if a drug is tested primarily on males, its effectiveness and safety in females may not be fully understood. This lack of representation for certain groups is a systemic problem affecting not only pharmacogenomics but also genome medicine as a whole, as illustrated by some seminal studies (14, 15).

The first systematic investigation into population biogeographical diversity for genetic studies was published in 2009 (14) and revealed that 96% of participants of all genome-wide association studies (GWASs) existing at that time were of European descent. A similar analysis was replicated in 2016 by Popejoy & Fullerton (16), showing that the representation of non-European participant data from across the globe for GWASs was far from equitable. While Europeans represent only 16% of the global population today, around 78% of data used in GWASs originate from people of European descent. Recent studies have shown that in spite of several calls for more diversity in genomics studies, the gap continues to widen (17–20).

Significant disparities in biogeographical representation of genomic data sources have increasingly triggered international efforts to ensure the benefits of genomic science reach all populations, regardless of ancestry or sex. Greater representation of diverse populations not only is of interest for the underrepresented individuals themselves but also is paramount for uncovering true causal associations between genotype and phenotype, which currently may be confounded by effects such as linkage disequilibrium, where DNA markers occur together more often than can be accounted for by chance because of their physical proximity on a chromosome. The equitable representation of individuals in genomic studies is therefore a question not only of moral imperative but of scientific progress.

Although the lack of data from underrepresented populations has been assessed for GWASs, the extent to which this bias also affects pharmacogenomic data sources remains unknown. There is evidence of dosage algorithms being less accurate for underrepresented populations (21, 22), reflecting participant selection biases in public reference databases. Concurring with previous studies on genetic diversity, we hypothesize that the number of individuals in pharmacogenomic study resources is a proxy for the performance of dosage algorithms in that particular population subgroup.

QUANTIFYING BIOGEOGRAPHICAL BIAS IN PUBLIC DATA SOURCES

In order to establish the degree of bias in publicly available data sources, we downloaded the full contents of PharmGKB (23, 24).[1] PharmGKB is a leading resource that aggregates, curates, and integrates data on pharmacogenomics. PharmGKB constitutes a catalog of genetic variants affecting drug responses. Using PharmGKB as a reference, we are able to relate the number of individuals (cases) from different biogeographical regions associated with drug response annotations. The biogeographical groups reported in PharmGKB are based on a standardized system for annotating populations in pharmacogenetic research (25).

As of December 2022, PharmGKB had 11,198 variant drug annotations. When analyzing the biogeographical groups of the studies from which drug annotations were derived, heterogeneity was found. In total, we counted 509 different biogeographical groups, the vast majority of which consisted of combinations of multiple ancestry groups, which were difficult to categorize. The number of individuals in unclassified groups amounted to a total of 2,509,439 (49.78% of the total number of cases reported for all collected studies within PharmGKB). Heterogeneous groups, where discrete biogeographical groups could not be assessed, were discarded. We cannot rule out that this heterogeneity in annotation of biogeographical groups could lead to a selection bias, which therefore should be acknowledged as potential limitation. The way in which study data are reported by PharmGKB also does not allow us to identify the origin of the studies from which these data are generated. Therefore, the description of biogeographical groups is limited to the number of cases described for each study according to PharmGKB's annotation. The biogeographical groups for which we could assign unequivocal study cases amounted to 2,531,125 individuals (50.22% of all individuals in the collated PharmGKB studies; **Figure 1**). These individuals were assigned to the following biogeographical groups: European, East Asian, Central/South Asian, African American or Afro-Caribbean, Latino, sub-Saharan African, Near Eastern, or American. We found that 63.56% (1,608,723) of these individuals were of European origin, and 28.05% were East Asian (710,073). From the rest, 3.66% were African (sub-Saharan, African American, Afro-Caribbean), 1.55% were Latinos, and 0.1% were indigenous Americans. These proportions appear to be consistent with the findings reported by Popejoy & Fullerton (16), who calculated 3%, 0.54%, and 0.05% of GWAS subjects as being of African, Latino, and indigenous/native descent, respectively. The tendency of an increased representation of East Asians is mirrored in our results, doubling from the 14% observed by Popejoy & Fullerton to 28% in our data set. Similarly, other underrepresented populations had no greater presence than in GWASs. Another limitation of this analysis is that it does not account for the resampling of data sets across independent studies, and it is likely that the cohorts used in publicly available pharmacogenomics studies have been used multiple times. This effect of double counting with current data sets is impossible to estimate, as individual genotype data are anonymized.

The total number of studies (calculated as distinct PubMed IDs) that have been reported so far in PharmGKB amounts to 3,682, involving 1,085 genes and 889 drugs or combinations thereof. In order to assess the implications of pharmacogenomic biases due to the lack of biogeographical representation, we focus our attention on *CYP2D6* and also include warfarin as an example of the issues.

GENOMIC DIVERSITY OF *CYP2D6*

CYP2D6 is a highly polymorphic gene commonly involved in ADRs. The resulting encoded enzyme performs differently depending on the type of variants that it harbors, significantly affecting

[1]The data source and the code developed to analyze the data are available under a Massachusetts Institute of Technology license and can be accessed here: **https://github.com/manuelcorpas/13-PGX-REPO**.

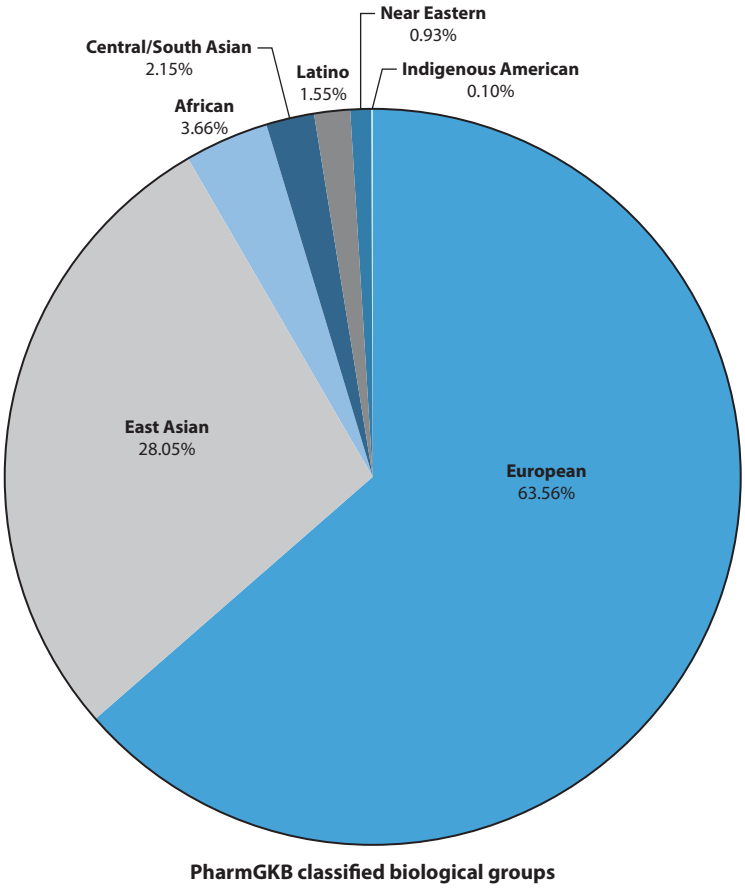

Figure 1

Breakdown of biogeographical groups from PharmGKB studies whose source cohorts have been classified. We found that 63.56% (1,608,723) of these individuals were of European origin, and 28.05% were East Asian (710,073). From the rest, 3.66% were African (sub-Saharan, African American, Afro-Caribbean), 1.55% were Latinos, 0.93% were Near Eastern, and 0.1% were indigenous Americans.

its ability to metabolize prescribed drugs. *CYP2D6* is a very important gene for pharmacogenomics, metabolizing up to 25% of currently prescribed drugs (26), which include antipsychotic drugs, antiarrhythmic agents, tricyclic antidepressants, β-adrenergic receptor antagonists, opioids, and the estrogen receptor antagonist tamoxifen.

The pharmacogenomic effects of *CYP2D6* result in a lack of therapeutic effect or an ADR due to fast metabolization of precursors into the active form. For instance, codeine, a drug metabolized by *CYP2D6*, is regularly prescribed to manage pain crises from sickle cell disease (27), a disease that is overrepresented among Africans. When administered to the patient, codeine converts differently depending on metabolizer status, which is determined by variations in *CYP2D6*. This process leads to significant health impacts as a result. **Table 1** (adapted from 28) shows the different effects that metabolizer status may confer to a patient administered with codeine.

In order to predict codeine drug reactions, it is first necessary to identify the individual's haplotype (group of alleles that tend to occur together). A haplotype is inherited from each parent, and in order to distinguish one combination of variants from another, the numbering system of star

Table 1 Different impacts of the metabolizer status of an individual for the drug codeine

Metabolizer status	Amount of codeine converted to morphine	Impact on the patient/recommendations	Frequency (reference)
Poor	Low (10%)	Insufficient pain relief, change medication	5–10% of Europeans patients, although it is believed that this is reduced in African patients
Intermediate	Reduced	Use label-recommended dose; if not effective, change medication	2–11% of European patients 20–28% of African patients (29)
Extensive	Normal	Use label-recommended dosing	77–92% of European patients ~50% of African patients (30)
Ultrarapid	High (40–51%)	Potential for morphine toxicity, which can translate into fatal concentrations in breast milk; change medication	28% of North Africans, Ethiopians, and Arabs 10% of Caucasians, 3% of African Americans (31)

Table adapted from Reference 28.

alleles is used. An expression of a haplotype in a gene may be called **2* (normal function). Another combination may be called **3* (no function). Whenever genetic testing is performed, the results are noted as two numbers, each one representing a combination of variants in that gene. This haplotype representation is denoted as the two-star allele separated by a slash in the middle (e.g., **2/*3*; intermediate metabolizer). Depending on the haplotype a person has, different metabolizer status can be inferred. Haplotype frequencies vary significantly among different biogeographical groups. **Table 2** shows a biogeographical breakdown of the differing frequency of haplotypes by biogeographical group for the *CYP2D6* gene (32).

In a study by Twesigomwe et al. (33), it was found that for 961 individuals of sub-Saharan African ancestry studied with high-depth whole-genome analysis, more than 5% carried novel (unidentified to date) alleles within this gene. This study also emphasized the need for not just considering one single African population as a general proxy for another when developing pharmacogenomic therapeutics. Greater diversity in *CYP2D6* has been demonstrated in Africa versus Europe or Asia, and alleles that are uniquely African have been identified that can alter drug metabolizer status (34).

We have shown how *CYP2D6* haplotype frequencies vary according to population ancestries, with different ancestries displaying more diverse haplotypes, conditioning optimal dosage level for drug administration. Understudied populations with more diverse haplotype frequencies are therefore more likely to be affected by imprecision when applying pharmacogenomic annotations to dosage administration. Therefore, pharmacogenomics can differ across different ancestral groups, with significant impact on drug efficacy and safety (35–37). However, unequal representation of biogeographical regions is not the only urgent bias to address.

GENOMIC DIVERSITY OF WARFARIN

Warfarin has remained the most commonly prescribed vitamin K oral anticoagulant worldwide since its approval in 1954 (38). Warfarin is prescribed to prevent blood clots, stroke, and heart attacks with genetic variations in *CYP2C9* and *VKORC1* encoding for the enzymes that metabolize and activate it (38). Such variations can affect drug response, leading to variations in drug efficacy and safety, with genetic ancestry playing a determinant role in the diversity of warfarin pharmacology. For example, individuals of African descent may have a higher prevalence of *CYP2C9* and *VKORC1* genetic variants associated with increased warfarin sensitivity (39). In particular, African Americans have been found to be more likely to carry variants of these genes

Table 2 Allele frequencies of the first 20 *CYP2D6* haplotypes broken down by biogeographical group

CYP2D6 Allele	African allele frequency	African American allele frequency	European allele frequency	Middle Eastern allele frequency	East Asian allele frequency	South/ Central Asian allele frequency	Americas allele frequency	Oceanian allele frequency
**1*	32.377	33.631	37.123	40.724	35.585	48.930	50.518	73.000
**2*	19.671	15.608	26.833	21.718	12.664	28.845	22.732	1.200
**3*	0.031	0.278	1.364	0.083	0.001	0.025	0.603	0.180
**4*	3.344	6.387	18.174	7.800	0.648	7.873	10.764	2.480
**5*	6.241	6.375	2.829	2.336	5.170	3.286	2.107	4.320
**6*	<0.001	0.216	0.960	0.576	0.015	<0.001	0.335	<0.001
**7*	<0.001	<0.001	0.094	<0.001	0.001	ND	<0.001	<0.001
**8*	<0.001	<0.001	0.022	<0.001	<0.001	ND	0.055	<0.001
**9*	0.080	0.428	1.997	<0.001	0.167	0.757	1.113	<0.001
**10*	6.615	4.067	2.780	3.490	42.430	17.357	2.566	2.500
**11*	<0.001	<0.001	0.013	<0.001	<0.001	ND	<0.001	<0.001
**12*	<0.001	0.080	0.008	<0.001	<0.001	ND	2.100	ND
**13*	0.510	<0.001	0.187	ND	<0.001	ND	ND	0.400
**14*	0.170	<0.001	<0.001	0.150	0.752	<0.001	0.293	<0.001
**15*	<0.001	<0.001	0.005	ND	<0.001	ND	0.503	<0.001
**17*	19.946	18.138	0.312	1.583	0.010	0.136	2.480	0.050
**18*	<0.001	<0.001	<0.001	<0.001	0.074	ND	<0.001	ND
**19*	<0.001	<0.001	0.013	<0.001	<0.001	ND	0.273	<0.001
**20*	<0.001	<0.001	<0.001	<0.001	<0.001	ND	<0.001	<0.001

Abbreviation: ND, no data. Data from the Clinical Pharmacogenetics Implementation Consortium (32).

that result in decreased metabolism of warfarin and increased sensitivity to its effects, requiring higher doses to achieve therapeutic benefit (40). On the other hand, individuals of East Asian descent may have a higher prevalence of genetic variants associated with decreased warfarin sensitivity (41). It is also suggested that diverse populations such as African Americans, Latinos, and South Asians have different variability in warfarin dosage requirements and a higher risk for warfarin-related adverse events compared to Europeans (42).

The implications of these different dose requirements are therefore significant in clinical care, where overdosing can lead to serious bleeding events, while underdosing can result in inadequate anticoagulation and an increased risk of blood clots. Therefore, determining the appropriate dose of warfarin for an individual patient is crucial to ensure optimal treatment outcomes. Despite this influence in treatment outcomes, most of the studied dosing algorithms and phenotype-genotype relationships still continue to be most specific for Europeans or East Asians (43).

GENDER AND SEX IN PHARMACOGENOMIC STUDIES

Sex (the biological concept) and gender (the social construct) play significant roles in health and health behaviors. Studies have found differential drug efficacy and safety profiles for males and females, from cholesterol-lowering proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (44) to therapies for chronic pain management (45) and mental health (46). Moreover, changing hormonal levels in postmenopausal women can alter biological processes in the body, a fact not often considered in the design of studies examining drug efficacy or safety over a woman's life course.

Post hoc genomic analyses of drug efficacy and safety using randomized controlled trials have become increasingly popular. Pharmaceutical companies see the value in gathering genotypic data on trial participants to better understand the underlying genetic factors that may impact the efficacy and safety of new therapies. This approach has paid rich dividends as scientists in academia and industry are now able to collaborate in large-scale pharmacogenomic studies using high-quality randomized control trial (RCT) data, paving the way for precision medicine (47).

Unfortunately, the representation of women in RCTs is not always equitable and is often skewed in relation to their comparative risk of diseases. For example, in 192 clinical trials of individuals with chronic kidney disease, only 45% of trial participants were women, whereas women are 33% more likely than men to suffer from chronic kidney disease (48). This mismatch in participant-to-prevalence ratios is particularly steep for women of child-bearing ages, who are often explicitly excluded from RCTs for safety reasons. Disentangling the roles of genetics, biology, and environmental effects in this subgroup of women is therefore more challenging, and researchers must then rely on the availability of observational data resources to conduct postauthorization safety studies.

An example in pharmacogenomics where biological sex appears to modify the association of genetic factors on drug efficacy is the PCSK9-R46L variant. PCSK9 is a potent natural regulator of plasma low-density lipoprotein cholesterol (LDL-C) levels. Levels of PCSK9 have been found to be higher in premenopausal women than they are in men and postmenopausal women (49, 50). Pharmacological inhibition of PCSK9 has shown efficacy in reducing LDL-C levels and therefore the risk of major adverse coronary outcomes (51). However, recent trials and large observational studies have shown that inhibition using the agent evolocumab achieves stronger inhibition in men compared to women (45, 52). In certain trials of drug efficacy, fewer women were able to achieve target LDL-C levels as compared to men. A meta-analysis of real-world data settings confirms this finding, with only 25% of women achieving target reductions in LDL-C levels compared to 50% of men (53).

GENDER BIAS IN ADVERSE DRUG REACTIONS

Women experience ADRs nearly twice as often as men, yet the roles of gender and sex as biological and social factors that may increase the risk ADRs are poorly understood (54). Trials do not always report efficacy stratified by gender or sex, and even less frequently for adverse events or safety outcomes (55). Across the globe, there is a combination of cultural and societal reasons why women and men approach health care differently and might be more or less likely to report adverse events to therapies (56).

An example is *CYP2D6* genotype–determined phenotypes and the observed difference in rates of ADRs for opioid users across sexes. According to a study undertaken using the Mayo Clinic Biobank, *CYP2D6* ultrarapid metabolizers are at a significantly greater risk of ADRs, including nausea, rash, and constipation, in response to opioid therapy (57). While there was no difference in drug efficacy (i.e., pain management) in the 2,877 opioid users examined, women were more likely than men to suffer from an ADR ($p = 0.002$). Among women, those who were ultrarapid or rapid metabolizers had a greater risk of ADRs compared to poor metabolizers, but this trend was not observed among men. There are hypothesized differences in *CYP2D6* activity between men and women, with pregnancy-induced changes in liver tissue uncovering potential mechanisms (58). However, it is apparent that more research into both the mechanism and extent of this effect is necessary. For example, do these effects observed in women abate after menopause, and are there observable differences in the extent of pain management?

Capturing information on effects of therapies, including ADRs, is challenging when using observational data resources. For example, in the long-term management of chronic pain using

opioids, women experience a 50–70% increased risk of ADRs compared to men (54). Certain adverse physical and mental health effects of long-term pain management, such as morphine-induced respiratory depression (57, 58), poor self-image, and increased nausea and vomiting, are observed more frequently in women (59, 60). At the same time, there are genes with known effects on opioid metabolism such as *COMT* and *OPRM1*. Indeed, sex modifies the effect of variants in these genes on known ADRs, where males and females with the risk genotypes in *OPRM1* and *COMT* experience different ADRs at significantly different rates (45).

Most drugs withdrawn from the market increased health risks for women (45, 61, 62), which is consistent with the poor representation of women in the trials that led to the approval and use of these drugs. Women represent only 38% of participants in drug efficacy and pharmacokinetic studies (46). Due to greater life expectancy in many regions of the world, women often comprise a higher proportion of the elderly population and are more likely to require polypharmacy and suffer the associated health risks and increased health-care burden. Therefore, the underrepresentation of women in clinical and research studies poses a grave challenge in developing appropriate clinical guidelines. Gender- and sex-stratified approaches would be the logical first step in applying precision medicine to pharmacogenomics, given the known impacts of sex and gender on the efficacy and safety of drugs, health-care interactions, and behaviors.

STEPS TOWARD ADDRESSING ANCESTRY AND SEX BIAS IN PHARMACOGENOMICS

Addressing ancestry and sex biases is crucial to ensuring that pharmacogenomic research is effective and equitable for all people. A concerted effort to include diverse populations is required. This includes people from different ancestral backgrounds as well as both men and women. Moreover, it is also important to avoid language that reinforces stereotypes or biases. For example, using terms such as Caucasian or Oriental can be outdated and offensive. Instead, the use of more neutral terms such as European or East Asian can help. Similarly, using inclusive language to describe gender is important.

In addition to genetics, social factors can also play a role in drug responses. For example, individuals with lower socioeconomic status may not be prescribed medications that are tailored to their genetics. Furthermore, some cultures may view genetic testing as invasive and unnecessary, which could lead to less willingness to participate in clinical trials involving pharmacogenomic testing. It is therefore crucial that these social factors be considered when designing studies (63). This can be achieved by engaging with communities to understand their experiences and concerns to build trust and ensure that research is relevant and impactful. Work with community groups is also necessary to identify research questions and study designs that are sensitive to cultural beliefs and practices.

Assuming that biases in data representation are addressed, widespread implementation of pharmacogenomics will still require numerous barriers to be overcome. The fact that many health-care providers are not familiar with pharmacogenomics and may not be aware of its potential benefits poses a significant barrier as well. For private and public health systems, the implementation of pharmacogenomics not only may be an expensive procedure to implement but also might lead to new inequalities for those patients with fewer resources who might not be able to afford it. Moreover, even if implementation is afforded, there is the challenge of standardization of testing. A myriad of procedures and technologies are available for implementation of pharmacogenomics in many labs. These labs may have different requirements and constraints in terms of which genotyping methods to apply. What to apply and what not remain in a state of flux, not least because of the evolving landscape of possible tests and results derived from them. All of this adds uncertainty in terms of how to comply with regulations related to pharmacogenomic

Table 3 Recommendations for addressing pharmacogenomics biases in ancestry and sex

Recommendation	What it means in practice
Increase awareness and education	Educate health-care providers on existence of ancestry and sex biases in pharmacogenomics Eliminate cultural biases (e.g., stereotypical language) Equalize study design biases (e.g., develop studies that include pregnant women)
Provide more equitable financial support	Avoid discrimination of less-resourced groups
Develop standards for pharmacogenomics implementation	Develop a minimum set of requirements for equality, diversity, and inclusion when testing patients Reduce technology biases (e.g., avoid genetic tests with overrepresentation of European-centric variants)
Address regulatory uncertainty	Reduce uncertainty in terms of how to best comply with regulation related to pharmacogenomic testing (e.g., what technologies to adopt, what quality controls should be necessary)
Augment evidence base	Include more diverse ancestral and sex data sets for more pharmacogenomically relevant drug targets
Facilitate integration into clinical workflows	Reduce barriers to clinical adoption by providing relevant infrastructure, resources, training, and support
Increase transparency	Share data and results openly with the public and obtain informed consent from participants

testing. Regulations for the implementation of testing may be further impaired by a lack of infrastructure, resources, or training to support the integration of pharmacogenomic testing into clinical care. For all of the above reasons, implementing ethical and transparent policies from the outset of research is fundamental (64). Policies may include sharing data and results openly with the public, obtaining informed consent from participants, and ensuring that study designs do not perpetuate biases or stigmatize particular groups.

In **Table 3**, we offer a set of recommendations for addressing pharmacogenomics biases in ancestry and sex.

CONCLUSION

Pharmacogenomics is a powerful tool for achieving precision medicine. Its applications have the power to help improve drug efficacy and avoid ADRs. Such tailor-made pharmacological strategies have the potential to provide personalized tools for titrating the right dose of the right drug to the right patient. We have shown that, to date, most of the data from which pharmacogenomics knowledge is derived are based on European and East Asian males. We observed that traditionally underrepresented biogeographical groups such as Africans, Latinos, and South/Central Asians continue to encompass a minimal fraction of existing pharmacogenomic data sets, in line with the already characterized GWAS data set biases. In this review, we have showcased the pharmacogenomics of *CYP2D6*, the gene that metabolizes the greatest proportion of prescribed drugs. Furthermore, women, who have historically been underrepresented in clinical trials, may present diseases differently than men, leading to gender bias in pharmacogenomics research. With the help of regulatory organizations, it is possible to establish and follow recommendations for how to prescribe different drugs, but it is still required that recommendations embrace the intricacies of existing biases, which have relatively neglected sex- and ancestry-specific genetic differences, resulting in suboptimal pharmacological treatments for these groups. By addressing ancestry and sex bias in pharmacogenomics research, we can improve the accuracy and effectiveness of drug therapies and ensure that all patients receive the best possible care.

DISCLOSURE STATEMENT

At the time of writing, M.C. is associated with Cambridge Precision Medicine Ltd. D.G. is employed part time by Novo Nordisk, unrelated to the submitted work.

ACKNOWLEDGMENTS

S.F. is supported by the Wellcome Trust (220740/Z/20/Z) at the Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit. R.M. is supported by Barts Charity (MGU0504). D.G. is supported by the British Heart Foundation Centre of Research Excellence (RE/18/4/34215) at Imperial College London.

LITERATURE CITED

1. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. 2001. Initial sequencing and analysis of the human genome. *Nature* 409(6822):860–921
2. Lauschke VM, Ingelman-Sundberg M. 2019. Prediction of drug response and adverse drug reactions: from twin studies to next generation sequencing. *Eur. J. Pharm. Sci.* 130:65–77
3. Malki MA, Pearson ER. 2020. Drug-drug-gene interactions and adverse drug reactions. *Pharmacogenom. J.* 20(3):355–66
4. Pirmohamed M. 2014. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. *Annu. Rev. Genom. Hum. Genet.* 15:349–70
5. Wadelius M, Chen LY, Eriksson N, Bumpstead S, Ghori J, et al. 2007. Association of warfarin dose with genes involved in its action and metabolism. *Hum. Genet.* 121(1):23–34
6. Zhang J, Wu T, Chen W, Fu J, Xia X, Chen L. 2019. Effect of gene-based warfarin dosing on anticoagulation control and clinical events in a real-world setting. *Front. Pharmacol.* 10:1527
7. Chan SL, Suo C, Lee SC, Goh BC, Chia KS, Teo YY. 2012. Translational aspects of genetic factors in the prediction of drug response variability: a case study of warfarin pharmacogenomics in a multi-ethnic cohort from Asia. *Pharmacogenom. J.* 12(4):312–18
8. Agúndez JAG, Esguevillas G, Amo G, García-Martín E. 2014. Clinical practice guidelines for translating pharmacogenomic knowledge to bedside. Focus on anticancer drugs. *Front. Pharmacol.* 5:188
9. Huang RS, Ratain MJ. 2009. Pharmacogenetics and pharmacogenomics of anticancer agents. *CA Cancer J. Clin.* 59(1):42–55
10. Carr DF, Turner RM, Pirmohamed M. 2021. Pharmacogenomics of anticancer drugs: personalising the choice and dose to manage drug response. *Br. J. Clin. Pharmacol.* 87(2):237–55
11. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. 2020. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 141(7):540–48
12. Yakerson A. 2019. Women in clinical trials: a review of policy development and health equity in the Canadian context. *Int. J. Equity Health* 18(1):56
13. Anaba U, Ishola A, Alabre A, Bui A, Prince M, et al. 2022. Diversity in modern heart failure trials: Where are we, and where are we going. *Int. J. Cardiol.* 348:95–101
14. Need AC, Goldstein DB. 2009. Next generation disparities in human genomics: concerns and remedies. *Trends Genet.* 25(11):489–94
15. Bustamante CD, De la Vega FM, Burchard EG. 2011. Genomics for the world. *Nature* 475(7355):163–65
16. Popejoy AB, Fullerton SM. 2016. Genomics is failing on diversity. *Nature* 538:161–64
17. Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin AR, Kuchenbaecker K. 2022. A roadmap to increase diversity in genomic studies. *Nat. Med.* 28(2):243–50
18. Kamiza AB, Toure SM, Vujkovic M, Machipisa T, Soremekun OS, et al. 2022. Transferability of genetic risk scores in African populations. *Nat. Med.* 28(6):1163–66
19. Fatumo S, Inouye M. 2023. African genomes hold the key to accurate genetic risk prediction. *Nat. Hum. Behav.* 7:295–96
20. Fatumo S, Yakubu A, Oyedele O, Popoola J, Attipoe DA, et al. 2022. Promoting the genomic revolution in Africa through the Nigerian 100K Genome Project. *Nat. Genet.* 54(5):531–36

21. Hughes JH, Woo KH, Keizer RJ, Goswami S. 2022. Clinical decision support for precision dosing: opportunities for enhanced equity and inclusion in health care. *Clin. Pharmacol. Ther.* 113:565–74
22. Asiimwe IG, Zhang EJ, Osanlou R, Jorgensen AL, Pirmohamed M. 2021. Warfarin dosing algorithms: a systematic review. *Br. J. Clin. Pharmacol.* 87(4):1717–29
23. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, et al. 2021. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther.* 110(3):563–72
24. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, et al. 2012. Pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther.* 92(4):414–17
25. Huddart R, Fohner AE, Whirl-Carrillo M, Wojcik GL, Gignoux CR, et al. 2019. Standardized biogeographic grouping system for annotating populations in pharmacogenetic research. *Clin. Pharmacol. Ther.* 105(5):1256–62
26. Taylor C, Crosby I, Yip V, Maguire P, Pirmohamed M, Turner RM. 2020. A review of the important role of in pharmacogenomics. *Genes* 11(11):1295
27. Solovieff N, Hartley SW, Baldwin CT, Klings ES, Gladwin MT, et al. 2011. Ancestry of African Americans with sickle cell disease. *Blood Cells Mol. Dis.* 47(1):41–45
28. Ahmed S, Zhou Z, Zhou J, Chen S-Q. 2016. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. *Genom. Proteom. Bioinform.* 14(5):298–313
29. Del Tredici AL, Malhotra A, Dedek M, Espin F, Roach D, et al. 2018. Frequency of *CYP2D6* alleles including structural variants in the United States. *Front. Pharmacol.* 9:305
30. PharmGKB. Gene-specific information tables for CYP2D6. *PharmGKB*. **https://www.pharmgkb.org/page/cyp2d6RefMaterials**
31. Dean L, Kane M. 2021. Codeine therapy and *CYP2D6* genotype. In *Medical Genetics Summaries*, ed. VM Pratt, SA Scott, M Pirmohamed. Bethesda, MD: Natl. Cent. Biotechnol. Inf.
32. PharmGKB. 2023. *Gene-specific information tables for CYP2D6*. Inf. Tables, PharmGKB. **https://www.pharmgkb.org/page/cyp2d6RefMaterials**
33. Twesigomwe D, Drögemöller BI, Wright GEB, Adebamowo C, Agongo G, et al. 2023. Characterization of *CYP2D6* pharmacogenetic variation in sub-Saharan African populations. *Clin. Pharmacol. Ther.* 113(3):643–59
34. Rajman I, Knapp L, Morgan T, Masimirembwa C. 2017. African genetic diversity: implications for cytochrome P450-mediated drug metabolism and drug development. *EBioMedicine* 17:67–74
35. Ortega VE, Meyers DA. 2014. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. *J. Allergy Clin. Immunol.* 133(1):16–26
36. Magavern EF, Gurdasani D, Ng FL, Lee SS-J. 2022. Health equality, race and pharmacogenomics. *Br. J. Clin. Pharmacol.* 88(1):27–33
37. Goodman CW, Brett AS. 2021. Race and pharmacogenomics-personalized medicine or misguided practice? *JAMA* 325(7):625–26
38. Viera de Lara D, Oliveira de Melo D, Araujo Silva LC, Gonçalves TS, Lima Santos PCJ. 2022. Pharmacogenetics of clopidogrel and warfarin in the treatment of cardiovascular diseases: an overview of reviews. *Pharmacogenomics* 23(7):443–52
39. Scott SA, Khasawneh R, Peter I, Kornreich R, Desnick RJ. 2010. Combined *CYP2C9*, *VKORC1* and *CYP4F2* frequencies among racial and ethnic groups. *Pharmacogenomics* 11(6):781–91
40. Ndadza A, Muyambo S, Mntla P, Wonkam A, Chimusa E, et al. 2021. Profiling of warfarin pharmacokinetics-associated genetic variants: Black Africans portray unique genetic markers important for an African specific warfarin pharmacogenetics-dosing algorithm. *J. Thromb. Haemost.* 19(12):2957–73
41. Dean L. 2012. Warfarin therapy and *VKORC1* and *CYP* genotypes. In *Medical Genetics Summaries*, ed. VM Pratt, SA Scott, M Pirmohamed. Bethesda, MD: Natl. Cent. Biotechnol. Inf.
42. Kaye JB, Schultz LE, Steiner HE, Kittles RA, Cavallari LH, Karnes JH. 2017. Warfarin pharmacogenomics in diverse populations. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* 37(9):1150–63
43. Asiimwe IG, Pirmohamed M. 2022. Ethnic diversity and warfarin pharmacogenomics. *Front. Pharmacol.* 13:866058

44. Sever P, Gouni-Berthold I, Keech A, Giugliano R, Pedersen TR, et al. 2021. LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial. *Eur. J. Prev. Cardiol.* 28(8):805–12
45. Planelles B, Margarit C, Inda M-D-M, Ballester P, Muriel J, et al. 2020. Gender based differences, pharmacogenetics and adverse events in chronic pain management. *Pharmacogenom. J.* 20(2):320–28
46. Knadler MP, Lobo E, Chappell J, Bergstrom R. 2011. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin. Pharmacokinet.* 50(5):281–94
47. Dawed AY, Mari A, Brown A, McDonald TJ, Li L, et al. 2023. Pharmacogenomics of GLP-1 receptor agonists: a genome-wide analysis of observational data and large randomised controlled trials. *Lancet Diabetes Endocrinol.* 11(1):33–41
48. Pinho-Gomes A-C, Carcel C, Woodward M, Hockham C. 2023. Women's representation in clinical trials of patients with chronic kidney disease. *Clin. Kidney J.* In press. **https://doi.org/10.1093/ckj/sfad018**
49. Lakoski SG, Lagace TA, Cohen JC, Horton JD, Hobbs HH. 2009. Genetic and metabolic determinants of plasma PCSK9 levels. *J. Clin. Endocrinol. Metab.* 94(7):2537–43
50. Cui Q, Ju X, Yang T, Zhang M, Tang W, et al. 2010. Serum PCSK9 is associated with multiple metabolic factors in a large Han Chinese population. *Atherosclerosis* 213(2):632–36
51. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, et al. 2017. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Engl. J. Med.* 376(18):1713–22
52. Cordero A, Fernández Del Olmo MR, Cortez Quiroga GA, Romero-Menor C, Fácila L, et al. 2022. Sex differences in low-density lipoprotein cholesterol reduction with PCSK9 inhibitors in real-world patients: the LIPID-REAL registry. *J. Cardiovasc. Pharmacol.* 79(4):523–29
53. Myasoedova VA, Rimbert A, Camera M, Le May C, Capoulade R, et al. 2023. LDL lowering effect of PCSK9 inhibition is reduced in women. *Eur. Heart J. Cardiovasc. Pharmacother.* In press. **https://doi.org/10.1093/ehjcvp/pvad009**
54. Zucker I, Prendergast BJ. 2020. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol. Sex Differ.* 11(1):32
55. Pilote L, Raparelli V. 2018. Participation of women in clinical trials: not yet time to rest on our laurels. *J. Am. Coll. Cardiol.* 71(18):1970–72
56. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero J-J, et al. 2020. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 396(10250):565–82
57. Sarton E, Olofsen E, Romberg R, den Hartigh J, Kest B, et al. 2000. Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 93(5):1245–54
58. Dahan A, Sarton E, Teppema L, Olievier C. 1998. Sex-related differences in the influence of morphine on ventilatory control in humans. *Anesthesiology* 88(4):903–13
59. Zun LS, Downey LVA, Gossman W, Rosenbaumdagger J, Sussman G. 2002. Gender differences in narcotic-induced emesis in the ED. *Am. J. Emerg. Med.* 20(3):151–54
60. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL. 2003. Side effects of opioids during short-term administration: effect of age, gender, and race. *Clin. Pharmacol. Ther.* 74(2):102–12
61. Anthony M, Berg MJ. 2002. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: part I. *J. Women's Health Gend.-Based Med.* 11(7):601–15
62. Anthony M, Berg MJ. 2002. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part II. *J. Women's Health Gend.-Based Med.* 11(7):617–29
63. Bansal S, Mahendiratta S, Prakash A, Medhi B. 2021. Social pharmacology and its impact on clinics. *Indian J. Pharmacol.* 53(6):437–39
64. Zarin DA, Tse T. 2008. Moving toward transparency of clinical trials. *Science* 319(5868):1340–42