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Health equality, race and pharmacogenomics

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Abstract

Pharmacogenomics is increasingly moving into mainstream clinical practice. Careful consideration must be paid to inclusion of diverse populations in research, translation and implementation, in the historical and social context of population stratification, to ensure that this leads to improvements in healthcare for all rather than increased health disparities. This review takes a broad and critical approach to the current role of diversity in pharmacogenomics and addresses potential pitfalls in order to raise awareness for prescribers. It also emphasizes evidence gaps and suggests approaches that may minimize negative consequences and promote health equality.

Keywords

bioethics; pharmacogenomics; pharmacotherapy; therapeutics

1 | INTRODUCTION

Pharmacogenomics (PGx), the use of genetic information to guide therapeutic prescription with the goals of increasing efficacy and decreasing toxicity, is entering clinical practice to varying degrees. However, there remains uncertainty about application of variants across diverse populations, and the impact of implementing PGx on health equality is not yet clear.

Established PGx success stories based on well validated data include testing for thiopurine methyltransferase (TPMT) genetic mutations in patients starting azathioprine for immune suppression and testing for HLA-B*5701 in patients with human immunodeficiency virus who may benefit from abacavir. Reduced function variants of the TPMT gene, which codes for the TPMT enzyme responsible for clearing active metabolites of thiopurines such as azathioprine, result in an increased risk of toxic side effects, including bone marrow

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COMPETING INTERSETS

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suppression, which can result in death.[1] Patients with HLA-B*5701 are likewise prone to potentially severe hypersensitivity reactions in response to abacavir exposure.[2] On the other end of the spectrum, much exploration into PGx in heart failure and hypertension has resulted in identification of many variants, but no clinically significant outcomes, while therapy in heart failure and hypertension remains stratified by racial algorithms. Uptake of PGx testing has been highest for a few drugs across various specialities, some of which are listed below. Table 1 is not meant to be an exhaustive list, but merely represents some of the most commonly available and accepted PGx drug/gene pairs.

Meanwhile, PGx has been further propelled into public consciousness via direct-to-consumer testing, even before being taken up by larger health systems. However, there is a well-described problem of inclusion in the research, which forms the foundation of PGx.[3] Therefore, any bias in the earliest stages of evidence may manifest in unpredictable and harmful ways downstream in clinical implementation. This may result in increasingly unequal health outcomes stratified by race and conflated with socioeconomic background.

A fractured society with 2-tiered health outcomes along racial and economic lines is already clearly visible in the USA.[4] A recent letter from Congress describing systemic racially based clinical care algorithms and requesting inquiry into this practice highlights some ways in which the unfounded narrative of race as a biological construct has bled into clinical practice, to the detriment of patients.[5]

It is no surprise that BiDil (isosorbide dinitrate/hydralazine), the only drug tested and approved for use solely in African Americans, and motivated by commercial interest, sparked distrust and has become a cautionary tale.[6–8] There is evidence of physician concern that racial categories used to determine treatment strategy in heart failure could prevent patients from receiving medication that would in fact benefit them.[9] Race is currently deeply entrenched in clinical practice, with differences in therapeutic algorithms for example in treating hypertension or heart failure, as well as diagnostic thresholds such as renal or lung function parameters.[5]

How then can the scientific and medical community go about extricating discussions of race from genetically derived ancestry? Particularly when the latter is an integral part of genomic studies, to ensure validation of PGx work in people from diverse ancestral regions. It is important both to have data representative of the whole population spectrum, and to avoid assumptions that racial construct can be held as a proxy for genetic variation. The way forward is thus to end discussion of race in PGx and replace it with genetically determined ancestry. This is challenging as research to date has used racial and or self-reported ethnic categories. There is an inherent dilemma in using existing work highlighting novel rare variants from geographically diverse populations in a call for diversity while arguing against the continued use of racial stratification from such studies going forward and emphasizing that there is still agreed to be more genetic diversity within a population than between populations. There also needs to be some standardization of ancestry terms used in PGx studies, as currently there is much heterogeneity.[10,11] Furthermore, the aim would be to represent highly genetically heterogenous populations in PGx research and clinical trials.

PGx is already on the scene, whether we are equipped to manage it or not. It is visible in the direct-to-consumer context, as well as in specialist centres in developed nations. As more validated examples increasingly become mainstream, it is anticipated that PGx is soon to be part of wider medical practice within nationalized health systems. Therefore, it is imperative to explore possible biases within the context of social equality, and to thereby open discourse. While PGx holds much promise, acknowledging potential weaknesses will facilitate a critical understanding of the evidence base for prescribers, and highlight potential effects on health equality.

2 | HOW DIVERSITY MAY AFFECT DATA ROBUSTNESS

Pharmacogenomic profiles can differ across ancestral groups, with clinically significant impacts on drug efficacy and safety. A better understanding of PGx across diverse populations would allow more precise dosing and monitoring. Genetic variation can influence drug response through differences in pharmacokinetics, and pharmacodynamics across different populations. For example, the genetic variants in the *CYP2C9* and *VKORC1* regions predisposing to warfarin-related adverse events differ among people of African, European and Asian ancestries.[12] Algorithms that optimize warfarin dosing, therefore, incorporate ancestry information.[12] Efficacy can also differ across different population groups. Variation in how these groups are described reflects a slippage in language between ancestry, ethnicity and race. For example, clinical trials suggest that African Americans are at higher risk of treatment failure with combination therapies for asthma compared to White Americans.[13] Idiosyncratic side effects can also vary across populations. For example, Asian patients harbouring the HLA-B*1502 variant are at significantly greater risk for carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis, and genetic testing is recommended prior to dosing among Asian patients.[14]

Despite these differences, much of PGx research and its translation into genomic medicine has focused predominantly on individuals of European ancestry.[15,16] European heritage populations are genetically more homogenous than African heritage populations due to a historical population bottleneck that substantially reduced genomic diversity during the out-of-Africa migration 50 000–70 000 years ago.[17,18] By contrast, African populations show high levels of genetic diversity due to population sizes, and rapid population growth which has resulted in a higher proportion of rare and population-specific variants.[19,20] Modern genetic diversity in humans is a product of mass migrations across the globe, with most populations today being a product of extensive complex admixture between different ancestral groups.[20,21] Given the lack of large-scale genomic research across these populations, it is likely that much of the variation associated with complex traits, including drug responses in these groups, remains undiscovered. Inclusion of multiethnic groups in genomic studies can substantially enhance the power to detect low frequency or rare variants associated with traits.[19,22] Equally, population-specific variants associated with drug response would remain undiscovered even in genomic studies of millions of Europeans, highlighting the vital importance of large-scale genomic research in a global context. The lack of PGx research in African and other non-European populations has also limited the utility and generalizability of PGx research to many population groups across the globe.[23]

Underrepresentation of certain global groups in research may stem from the lack of investment in research in more diverse contexts, lack of investment in capacity building, and poor engagement with communities.[16] Lack of representation of indigenous populations in genomics research may also arise from distrust among communities due to perceived exploitation of these groups in previous genomics research, as in the case of the Havasupai tribe.[24] Members of the indigenous tribe in Arizona found that genetic samples understood to be donated for research in diabetes were being used for other, non-related, studies into stigmatized subject matter such as mental illness and inbreeding, as well as migration pattern studies.[25,26] Stakeholder engagement with an emphasis on community-based participatory research may help to overcome such barriers.

Our limited understanding of PGx in more diverse populations has a domino effect on application in the clinical context. Ascertainment of genetic markers primarily based on populations of European ancestry can bias panels, and reduce performance in more diverse understudied population groups, worsening inequities in translation of genomic research into clinical practice.

Additionally, race has often been used as a proxy for genetic background or ancestry in clinical practice.[11] Race is a social, rather than a biological, construct.[10] Racial categories do not capture complex genetic diversity across groups, given extensive migrations, and mixing across large swathes of global populations over many centuries. The notion of race as indicative of biological differences is rooted in eugenics, which has been used historically to legitimize racial discrimination, with devastating impacts on already marginalized population groups. Broad categories of race, geographical proximity or cultural context are not good proxies for biological differences, adhering to Lewontin's assertion from nearly 50 years ago.[20,27]

Recent efforts to characterize the use of race, ethnicity and ancestry in research and clinical practice have found substantial heterogeneity in the way these constructs are perceived, defined and measured.[10,11] The lack of standardized definitions of race and ethnicity across precision medicine research and practice has contributed to inconsistencies in data collection, interpretation of results and clinical applications.[10,11] The conflation of race with genetic background has also likely disproportionately disadvantaged groups underrepresented in genomic research, as well as people from multiple ancestral backgrounds whose genetic background is incongruous with discrete race categories.[11]

3 | HOW DIVERSITY MAY INTERFACE WITH DRUG DEVELOPMENT AND REGULATORY APPROVAL

A narrow ancestorial spectrum in PGx studies may limit the breadth of knowledge acquired. An example is the discovery of *PCSK9*, a lipid-lowering target that was discovered because of a higher prevalence of nonfunctioning variants, with resultant reductions in low-density lipoprotein cholesterol, in populations self-identified as Black.[28] This emphasizes how diversity in genetic studies can highlight mechanisms applicable to clinical translation and implementation across all populations.

The recruitment of ethnically diverse populations into private databases has recently been a priority for companies such as 23&Me and 54Gene. Considering the 23&Me and GSK alliance, and the quantity of data held by the direct-to-consumer company, this could drive increased inclusion in data used for drug development, which would be a step forward. However, data sharing and commercialization of the genetic data of marginalized populations may set off alarm bells in the context of prior notorious ethical breaches such as in the case of Henrietta Lacks, whose cells were shared for research purposes, and with financial gain, without her knowledge or consent.[29]

Genomic based design of drugs and recruitment to trials holds promise for improved efficiency of drug development, but BiDil's trajectory should discourage from the race-based targeting of therapeutics. While genetically selected clinical trial populations may enhance success in therapeutic development, it leaves the question of who will be genotyped and targeted by this therapy, and on what basis, unclear.[30]

We can look to existing clinical trial data to more fully appreciate possible scenarios. In the negative US COAG trial, participants who were identified as black had significantly less time in the therapeutic range when genotype was added to the clinical algorithm, as compared with their clinically dose guided counterparts. It was noted that only the *CYP2C9* alleles common to participants identified as nonblack were included in the genetic dosing algorithms.[31] Allele frequency may differ in diverse ancestry populations. In this case, application of an algorithm targeted at populations who were identified as nonblack could conceivably worsen clinical outcomes for population identifying as black. This emphasizes the need to include all associated genetic variants ascertained across diverse populations in dosing algorithms. Such an approach implies both inclusive panel testing (i.e. more variants) and inclusive population testing (i.e. a uniform algorithm for all with no racial eligibility for testing). The cost implied could therefore be more if applied at population level.

Homogenous recruitment to clinical trials has long been a source of concern in generating population level externally valid data for licensing therapeutics. There are obvious financial incentives to target large and wealthy populations in drug development. What happens when a drug with efficacy and/or adverse events linked to particular genetic polymorphisms is developed and moves to the phase of regulatory approval? Regulatory bodies routinely accept evidence from largely white middle-aged male nonpolymorbid clinical trial populations. How can this be harmonized with recommendations for PGx implementation and in which population? How can we define the population–by genetic ancestry or everyone? Will the answer depend on the payment system and who carries the fiscal burden of testing and actioning results? While licensing bodies consider safety and efficacy of therapy, organizations responsible for advocating use within a single payer system, such as the National Institute for Health and Care Excellence, look at cost-efficacy. This shifts the focus from individual health benefit to population level benefit on balance with cost, and therefore weighed against other possible uses of funding, or consideration of opportunity cost. This may mean that answers vary widely from private insurance driven systems to single payer national health systems.

There is currently a lack of consensus between academic consortium PGx guidance and regulatory agency recommendations included in summary of product characteristics regarding PGx actionability, as well as between regulatory agencies internationally (e.g. USA vs. Europe).[32] There is only 18% agreement between both generally cited consortia guidelines (The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group) and the European Medicines Agency and the US Food and Drug Administration, with only 54% agreement between the last 2 of these.[32] This demonstrates a need for a unified approach with respect to PGx implementation. Such a unified approach would require regulators to take a joint stand regarding standard of evidence to recommend testing and actionability. This requires a decisive approach to questions of external population validity and the management of evidence of genetic stratification within PGx research and trial evidence-base. The heterogeneity identified in racial and ethnic categories used in PGx studies and poor ability of such constructs to predict genotype suggest that this problem may only be solved by a 2-pronged approach of widely inclusive research and pre-emptive genotyping without incorporation of self-declared race and ethnicity into eligibility or action algorithms.[10]

In summary, genetic diversity may soon be further explored in the context of therapeutics and is likely to pose ongoing challenges to regulatory bodies presented with PGx data, as well as to various models of health care systems seeking to implement personalized medicine. Regardless, economics will continue to have a strong role in driving decisions regarding which population to target in drug development and subsequent trials, and cost-efficacy thresholds for implementation would probably be higher in nationalized health systems. As sequencing improves, and costs decrease, routine pre-emptive genotyping may make reliance on self-declared race and ethnicity obsolete.

4 | HOW DIVERSITY MAY INTERFACE WITH DEPLOYMENT

The importance of diversity cannot be underestimated in the deployment of PGx as a medical service. This relates to the clinical care delivery as well as the evidence-base. The evidence-base is necessary to, but not sufficient for, deployment. Clinical support tools that can be applied to all patients must be developed.

Current PGx studies, representative of genomic studies more widely, are concentrated in wealthy European and North American countries. As of 2016, only 19% of genome-wide association study (GWAS) participants were from non-European ancestries. The large proportion of this relates to the rapid increase in GWAS studies based in east, south and southeast Asian populations.[33] However, many traditionally underserved populations within wealthy nations, including persons of African, Hispanic and Latin American ancestry, seem to be left behind. Notably, only 1% of those enrolled in GWAS studies self-identify as having multiple ancestries; by contrast self-defined multiple ethnicities accounted for 2.2% of the UK population in 2011 and 2.8% of the US population in 2019.[34–36]

Many different factors require careful consideration at the point of delivery to reduce unequal access across socioeconomic classes. This may include the impact of language barriers, perceptions of the testing, as well as fiscal accessibility.

While there are limited studies in the context of PGx, genetic counselling is complex. There are gaps in effective communication both in absence of language barriers, due to literacy and cultural variation, and when utilising medical interpretation to bridge a language barrier.[37] These factors may contribute to widening health inequalities. In the UK, 7.7% of the population did not have English or Welsh as main language, and 1.6% were not proficient in English.[38] In the USA, 8.6% of the population reports their ability to speak English as less than "very well".[39] Those who were nonproficient in English tended to report poorer health, and the trend was exacerbated by advancing age.

While minority populations are underrepresented in studies, there is some evidence that this is not due to a lower effective recruitment rate. One study showed that African Americans can be successfully recruited to PGx trials, and in fact were less likely to decline then their non-Hispanic White counterparts.[40] The reasons provided when deciding not to participate were similar to their counterparts. This suggests that there should be increased recruitment efforts for all underserved populations. It highlights that participation could be boosted by raising awareness and decreasing perceived inconveniences.[40] Strategies that may improve the uptake of PGx testing include providing thorough information about testing, including the benefits of testing to predict treatment efficacy and improve clinical outcomes, and discussing any perceived negatives consequences. Clear explanations that bolster the patients' trust in their providers to make correct genotype-guided prescribing decisions are also important. Important barriers that will need to be overcome are concerns regarding privacy of the test results, as well as insurance coverage and test affordability. Notably, in 1 survey-based study, 44% of people were not willing to pay for a PGx test.[41]

As the willingness of the individual to pay appears to be an important factor in the uptake of PGx testing, it is important to consider system-wide health economics. A modelling study examining the cost-effectiveness of a multigene panel following acute coronary syndrome with percutaneous coronary intervention suggests that this approach may meet the willingness-to-pay threshold for Medicare in terms of cost per quality-adjusted life year gained. This multigene panel aimed to support decision-making regarding antiplatelets, statins and anticoagulant therapy.[42] While this supports economic PGx panel viability at a population level, treatment guidelines and costs can vary with time and between diverse national healthcare systems. Furthermore, there is variation in insurance coverage within countries and across different healthcare systems, which may potentially exacerbate existing health inequalities.[43] As clinical application of PGx is increasingly established it is important that uptake across all sections of the population is continually reviewed, aiming to remove any barriers identified.

5 | POTENTIAL LONG-TERM EFFECTS WITHIN THE CURRENT CONTEXT

While there has been much discussion of PGx as a tool to improve health outcome disparities there is no evidence that this has transpired. Others have made the argument that pinning hopes of health equality on genomics is misplaced, and indeed risks trivializing the detrimental impact of social injustice and feeding into racial typing.[44] PGx may further personalize medicine for white male patients of European descent, improving health care for this already advantaged demographic, while further racially stratifying,

therefore depersonalizing and further degrading the level of health care available to minority/indigenous or financially disadvantaged populations. If PGx costs are high or only insurance subsidized for those fortunate enough to have more comprehensive health insurance, then those with higher deprivation, already disadvantaged in health outcomes, will be further disadvantaged. Considering the already gaping health outcomes between socio-economic groups in North America and western Europe, this is worrying.

The above discussed biases in data currently underpinning PGx must be considered as part of implementation, and mechanisms put in place to address these gaps. For example, policies could be put in place to advise against any racial qualifiers for PGx testing and actioning, as well as against the use of race in PGx research.

The stakes around PGx being deployed uncritically in the context discussed is of immediate clinical concern in terms of patient outcomes, but also of long-term concern in facilitating trust between the medical and scientific establishments and disenfranchised population demographics already suffering from health inequality. At present there is no clear conclusion, as demonstrated by the systematic review by Martin et al., regarding the role PGx will play in health equality.[45] The authors discovered only 5 studies examining effects of PGx on health equality, 3 finding that PGx may exacerbate inequity and 2 finding that it may reduce inequality. The most significant conclusion, however, is that the dearth of data is problematic and represents a key area for further research. Going forward, therefore, the focus must be on ensuring that advances result in improved patient safety, therapeutic efficacy and access to care for all strata of society, detracting from rather than leading to further potential differences in health outcomes.

6 | WHAT CAN WE DO ABOUT IT WITHIN CLINICAL PHARMACOLOGY?

There is an urgent need for genomics research across globally representative populations, to ensure that benefits of PGx and precision medicine are realized in a global context, and do not worsen existing healthcare disparities by excluding already marginalized groups.[45] Further research into the impact of PGx on health disparities is needed, as well as raising awareness within the scientific and clinical communities.[45] These considerations should be central to discussions of genomic medicine rather than an afterthought.

Representative and inclusive genomic research requires rebuilding trust with communities, where this has been broken, with an acknowledgement of the historical context. Community engagement with local leaders and trusted representatives must be central to such endeavours. Researchers must listen to concerns about use of samples and data, and involve communities in development of regulatory frameworks, including ethical and data sharing guidelines. Several communities such as an indigenous population of South Africa, the San community, have been active in this area and have developed their own code of ethics.[46] This provides a useful model for partnering with and empowering communities to play a key role in managing research arising from their participation. Such research must also involve multidisciplinary teams, including researchers from bioethics and sociology backgrounds, underpinned by local capacity building to benefit the community and create a sustainable framework for genomic research.[3]

Several efforts across the globe, including those led by academic and commercial organizations, have emerged to ensure better representation of diverse ancestral groups in genomic resources and PGx panels. These include genomics research and capacity building initiatives such as Human Heredity and Health in Africa (H3Africa) consortium and the African Pharmacogenomics Research Consortium, which aims to consolidate PGx research in Sub-Saharan Africa and accelerate translation into clinical application.[47,48] Private companies are also actively working to increase representativeness of more diverse populations in genomic data. However, given the commercial nature of these endeavours, and the historical exploitation of indigenous populations for research and commercial gain, benefit-sharing models must be considered in consultation with communities to ensure that these projects benefit the participating communities.

The clinical genetics community has called for definitions of race, ethnicity and ancestry in clinical genetics to be standardized, evidence based, and justified, in order for the implementation of genomic medicine to be consistent, scientifically valid, and ethically responsible.[11] Individually targeted treatments based on a more complex understanding of ancestry and its distinction from race, and more diverse PGx panels, where available, should be used rather than basing treatment on race. This will require far more research across underrepresented groups, and translation of this research into precision medicine tools. Regulatory bodies can also contribute to these efforts through necessitating research, and validation of tools across diverse ethnic groups prior to approval.

Finally, although PGx is the study of the interaction between genes and drugs, the impact of treatments at an individual level is substantively determined by socio-economic, behavioural and environmental factors, which may influence access to treatment and compliance. Contextualising precision medicine initiatives within an understanding of social determinants of health disparities is key the successful translation of PGx into clinical practice. The promise of PGx must be realised in this context, ensuring that applications of PGx in clinical medicine reduce rather than exacerbate existing healthcare disparities across different communities.

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TABLE 1

Commonly recognized drug/gene pairs

Genetic test	Drug	Relevant clinical areas
TPMT	Mercaptopurine/azathioprine	Gastroenterology, oncology, rheumatology
HLA-B*5701	Abacavir	Infectious disease
HLA-B*1502	Carbamazepine	Neurology, psychiatry
DPYD	Fluoropyrimidines	Oncology