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Implementing health economics for pharmacogenomics research translation in Africa



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Pharmacogenomics studies how a person's inherited genes influence response to therapeutic drugs. Many drugs do not work in all patients and pharmacogenomics can assist in the identification of patients who are better suited to particular drugs or patients who need adjusted drug doses to reach better treatment outcomes. This stratification of patients could be beneficial in Africa as it would allow drugs that would ordinarily be discontinued due to toxicity on a proportion of the populations to be used in a directed manner in people for whom it is not toxic. However, there has been limited use of pharmacogenomics. One of the key issues has been the need to demonstrate the economic benefits of adopting pharmacogenomics implementation and the impact on healthcare cost drivers. Integration of pharmacogenomics into clinical practice has huge potential in Africa due to the large genetic diversity in African populations. This Perspective article explores the current pharmacogenomics landscape, the health economics associated with its implementation, and future directions for pharmacogenomics research translation in Africa.

Pharmacogenomics is the study of how inherited genetic variation affects a person's response to drugs. Pharmacogenomics leverages inherited genetics to deliver effective and safe therapeutics and thus has the potential to change medical practice. Many therapeutic drugs fail during development or post-marketing due to severe toxicities that are difficult to manage, and genetic variation is a major contributing factor to these failures¹. People in Africa are the most genetically diverse population globally. As few or no clinical studies are undertaken in Africa that lead to drug discovery, often drugs are identified to be toxic only after they have been approved and used in Africa. Thus, applying knowledge of pharmacogenomics in Africa could be more beneficial than in other populations because it would allow the stratification of patients and identification of those likely to experience toxicity, a proportion who are likely to require altered doses, and a proportion who are likely to benefit from a drug. This stratification allows the retention of drugs that would ordinarily be withdrawn due to toxicity. However, this requires pharmacogenomics genotyping tests to be developed and deployed alongside clinical decision-making. A recent study found that genetic testing for

just three specific genes (*CYP2C19*, *CYP2D6*, *SLCO1B1*) could help prevent up to 75% of ADRs prior to prescribing drugs². In addition, there is a high burden of infectious diseases in Africa that occurs in parallel with an increasing burden of noncommunicable diseases. Thus, people often have comorbidities that are not seen elsewhere in the world, which require complex polypharmacy. The economic impact of the disease burden, the underlying diverse genetics, and the need for combinatorial therapeutic drug treatment need to be analysed to enable a full understanding of the benefits of implementing pharmacogenomics in healthcare settings.

Africa's healthcare landscape is characterized by significant disparities in access to effective treatment, determined by various factors, including the availability of essential medicines and diagnostic services, lack of trained healthcare professionals, low health literacy and education level or poor leadership and management^{3,4}. For example, the United Nations Sustainable Development Goal to reduce maternal mortality rates in Sub-Saharan Africa has not yet been achieved⁵. Another example is access to cancer treatment, where significant inequities exist across and within countries⁶.

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Health economics and health technology assessment are disciplines facilitating evidence-based decision making to justify that healthcare resources are allocated efficiently. They promote explicit and transparent procedures to make better decisions related to patient access and reimbursement. Essentially, health economics strives to maximize health benefits to society using available resources⁷. Health economics in Africa presents profound challenges, as many healthcare systems face chronic underfunding, inefficient resource allocation, and fragmented health financing mechanisms⁸. For instance, out-of-pocket health expenditures remain high in many African nations, exacerbating economic hardship for patients⁶. In addition, the academic foundation for health economics in Africa is not as robust as in countries where the discipline is well-established. Moreover, the awareness of health economics varies greatly across the continent. Since the 1990s, health economics has received modest attention, especially evaluations focusing on communicable diseases⁸. Some African countries, such as Ghana or South Africa, were able to institutionalize the health technology assessment initiatives and procedures⁹, which is coupled with capacity building activities¹⁰. However, this is not true for most of the African continent.

In this Perspective article, we examine the current pharmacogenomics landscape in Africa, discuss the role of health economics in its clinical translation, and propose key strategies for implementation across African healthcare systems.

The need for pharmacogenomics research and translation in Africa

Africa has the most genetically diverse population across the world¹¹. Africa's healthcare landscape is marked by a high burden of infectious diseases intersecting with a rising prevalence of noncommunicable diseases. Additionally, Africa transcends different climatic conditions and offers a diverse environment. The combination of a diverse genome, a specific profile of disease, and expansive environmental exposure significantly influences the pharmacokinetics and pharmacodynamics of therapeutic drugs making the application of pharmacogenomics not only important, but essential, for effective treatment¹². Also, data generated from elsewhere across the world may not adequately represent the African context.

Humankind originated from Africa and for this reason Africa has the greatest genetic diversity in the world. This genetic diversity affects how individuals interact with infectious agents, present with susceptibility to diseases and respond to therapeutic treatment. Genetic interactions with therapeutic drugs can result in either beneficial or adverse outcomes. Typical examples of such outcomes include variations in treatment efficacy and adverse drug reactions in conditions such as HIV and malaria where therapeutic outcomes and drug safety profiles may be affected^{13–15}.

Case studies demonstrating the need for pharmacogenomics

HIV treatment

The variability in the response to antiretroviral therapy (ART) in African populations underscores the need for pharmacogenomics. For example, the antiretroviral drugs abacavir and efavirenz have been clearly shown to be affected by genetic variation in the human leukocyte antigen B, *HLA-B*5701* and cytochrome P450, *CYP2B6*6*, allele variants, respectively. Binding of abacavir to the variant *HLA-B*5701* alters the conformation of HLA-B, triggering a severe hypersensitivity reaction that can be life-threatening if not identified early¹⁶. The *CYP2B6*6* variant significantly affects plasma levels of efavirenz, impacting its efficacy and side effect profile¹⁷. These two variants further support the need for pharmacogenomics research translation in Africa, given that *HLA-B*5701* is prevalent among Europeans and is an important consideration for abacavir use, while *CYP2B6*6* is prominent in African populations, and its prevalence necessitates dose adjustments to optimise efavirenz therapy and minimise adverse effects¹⁸.

Malaria treatment

Pharmacogenomic studies on artemisinin-based combination therapies (ACTs) have shown that genetic variations can influence treatment

outcomes, highlighting the need for personalised approaches in malaria management. *CYP2C8* variants significantly impact the metabolism of amodiaquine, altering drug clearance, impacting toxicity and therapeutic efficacy. Given amodiaquine's widespread use in malaria-endemic regions of Africa, integrating *CYP2C8* genotyping into malaria treatment protocols could improve dosing precision and minimize adverse effects¹⁵. Implementing pharmacogenomic-guided malaria treatment in African populations aligns with global precision medicine initiatives, such as the pharmacogenomic trials in other diseases undertaken through the PREPARE study¹⁹. Specific polymorphisms in genes such as *CYP2A6* affect the metabolism of artemisinin derivatives, impacting their efficacy and safety²⁰. This necessitates pharmacogenomic-guided dosing strategies to improve therapeutic outcomes in malaria treatment. It is also important to take into account comorbidities, where coadministration of other therapeutic drugs could also impact the response to ACTs. The impact of these drugs could potentially be better understood by greater knowledge of the impact of pharmacogenomics.

Tuberculosis treatment

Tuberculosis (TB) remains a major public health concern across Africa, and pharmacogenomics offers an opportunity to improve treatment outcomes. Isoniazid, a first-line TB drug, is metabolized by the enzyme *NAT2*, whose genetic variants influence acetylation status. Slow acetylators are at increased risk of hepatotoxicity, while rapid acetylators may have subtherapeutic drug levels, compromising efficacy. A systematic review and meta-analysis confirmed that *NAT2* polymorphisms are significantly associated with isoniazid-induced liver injury²¹. Pharmacogenomic studies also implicate additional genes, including *CYP2E1*, *GSTM1*, and *GSTT1*, in modulating toxicity and variability in treatment response²². Data from a large cohort study further demonstrate that pharmacogenetic profiling can predict both treatment toxicity and effectiveness, reinforcing the clinical value of incorporating genotyping into routine TB care²³. In African settings, the integration of pharmacogenomics into TB programs has been proposed as a feasible strategy to reduce adverse events and enhance adherence, especially given the continent's high genetic diversity and historical underrepresentation in global studies²⁴. Despite growing global evidence, Africa remains underrepresented in prospective TB pharmacogenomic studies. The implementation of pharmacogenomic screening for high-risk genotypes could improve safety, reduce treatment interruptions, and contribute to more successful and sustainable TB control strategies.

Clinical outcomes and economic benefits of pharmacogenomics

Pharmacogenomics can provide several economic benefits as it enables optimized drug therapy, reduced ADRs and improved patient outcomes. This, in turn, can reduce healthcare costs and enhance workforce productivity by minimizing absenteeism and improving the overall well-being of employees. Findings from the PREPARE study demonstrate the economic value of pharmacogenomic-guided therapy across multiple disease areas. In psychiatry, *CYP2D6* and *CYP2C19* genotyping in patients on antidepressants and antipsychotics has led to a significant reduction in ADRs, treatment failures, and associated healthcare costs¹⁴. In cardiology, *CYP2C19* testing before initiating clopidogrel therapy has improved cardiovascular outcomes and shown cost-effectiveness in preventing major adverse events²⁵. The transferability of these results to African healthcare settings should be carefully investigated, as optimizing drug therapy is critical to reducing avoidable hospitalizations and improving treatment efficacy. Despite strong evidence supporting pharmacogenomics, implementation has been slow even in high-income countries such as the USA, Europe, and Asia, primarily due to cost concerns. For example, studies in Europe from the PREPARE trial demonstrated that preemptive pharmacogenetic testing improved patient outcomes but required substantial investment in healthcare infrastructure²⁶.

Reduction in adverse drug reactions

ADRs are a significant burden for healthcare systems, leading to increased hospitalizations and healthcare costs. Pharmacogenomics can help predict and prevent ADRs by identifying patients at risk based on their genetic profile. For example, screening for *HLA-B*5701* before prescribing abacavir can prevent hypersensitivity reactions, thus avoiding costly medical interventions²⁷. Implementing pharmacogenomic testing to predict and prevent ADRs can significantly reduce healthcare costs associated with managing these adverse events.

Improved drug efficacy and patient outcomes

Personalised medicine ensures that patients receive the most effective drugs at optimal doses, improving therapeutic outcomes and reducing the need for multiple treatment trials. This can lead to shorter hospital stays and lower overall treatment costs. Studies have demonstrated the cost-effectiveness of pharmacogenomic testing in improving drug efficacy for conditions such as cancer and cardiovascular diseases²⁸. For instance, pharmacogenomic-guided warfarin dosing has been shown to reduce the incidence of bleeding complications, leading to cost savings and better patient outcomes²⁹.

Decreased hospital stay and streamlined clinical decision-making

By avoiding potentially harmful medications, hospitals can reduce the number of patients requiring extended stays, additional treatments, or ICU admissions. The targeted therapy approach reduces trial and error prescribing, leading to shorter hospital stays and fewer resources spent on ineffective treatments. By optimising medication selection and dosing, pharmacogenomics can lead to faster patient recovery, reducing hospitalization duration and freeing up beds^{14,25}. Pharmacogenomics provides healthcare professionals with actionable genetic information, enabling more informed treatment decisions and reducing the time spent on medication adjustments²⁶.

Reduction in labour force time lost due to avoidable ADRs and increased productivity

ADRs are not only a burden to healthcare systems but also significantly impact workforce productivity. Pharmacogenomics helps optimize treatment by reducing ADRs, leading to healthier employees and fewer days lost to illness. Effective treatment enhances overall workforce well-being, reducing absenteeism and minimizing distractions caused by ongoing health issues^{28,29}. This improvement translates into increased productivity, higher job satisfaction, and reduced costs for employers due to lower healthcare expenditures for their workforce. The ripple effects of a healthier workforce benefit both the economy and the quality of life of employees and their families, making pharmacogenomics an essential tool for public and occupational health strategies³⁰.

Implementation challenges

Despite the potential benefits, there are several challenges to implementing pharmacogenomics in Africa, including pricing, evaluation, infrastructure, education, regulatory, and socio-economic barriers.

Education, training needs and uptake of pharmacogenomics

While some healthcare professionals in Africa have received training in pharmacogenomics, many still lack the necessary knowledge and resources to effectively interpret and apply pharmacogenomic data in clinical practice. Developing comprehensive educational programs and training modules is essential to equip healthcare providers with the necessary skills^{31,32}. The vast genetic diversity within African populations underscores the critical need for genomic sequencing across numerous ethnic groups to identify clinically relevant pharmacogenomic variants. However, in many parts of the continent, limited genomic data³³ availability makes it challenging to develop and implement population-specific pharmacogenomic tests. This underrepresentation in global pharmacogenomic research hampers efforts to understand how genetic differences influence drug response in African

populations. Genomic information is essential for guiding the safe and effective use of medications and for developing targeted therapies that reflect the genetic diversity of all populations. Without inclusive data, pharmacogenomic advances risk perpetuating health disparities and reducing the effectiveness of precision medicine in Africa. Integrating pharmacogenomics into medical and pharmacy curricula is essential for increasing the adoption of precision medicine. Early exposure to pharmacogenomics will equip future healthcare professionals with the ability to interpret genetic tests, incorporate pharmacogenomic data into clinical decision-making, and enhance patient safety through personalized medicine.

Pricing

Current healthcare pricing is another challenge for implementing pharmacogenomics. Clinical laboratory diagnostics are traditionally priced based on the cost of performing the test (cost-based pricing), whereas drug pricing is determined by the perceived therapeutic benefit and market demand (value-based pricing). In pharmacogenomics, where the diagnostic test and the subsequent therapy are combined, this discrepancy presents a challenge in integrating cost-effectiveness evaluations into healthcare systems. The traditional business model of molecular testing requires profound changes to determine the full value of targeted medicines. On the other hand, these value-based pricing strategies require a careful understanding of the methodology and how this will change market conditions³⁰.

Data requirements for evaluation

The evaluation of the impact of using pharmacogenomics for clinical decisions is an extra challenge due to the data requirements. The stratification of patients based on genetic data leads to smaller, more specific patient populations, making systematic data collection for pharmacoeconomic evaluations more complex. Conducting cost-effectiveness analyses in pharmacogenomics requires innovative study designs, such as adaptive trials and real-world evidence generation, to demonstrate clinical and economic value. In addition, the guidelines and practices for test-treatment combinations are frequently country-specific, which should be taken into account during evaluation³⁴.

Infrastructure and technological barriers

The lack of research laboratories, genetic testing facilities, and robust data management systems poses a significant challenge to the implementation of pharmacogenomics. Investments in infrastructure are crucial to support the necessary genetic testing and data analysis capabilities³⁵. Developing a network of laboratories equipped with modern genomic technologies is essential to facilitate pharmacogenomic research and clinical applications.

Regulatory and policy challenges

The absence of clear regulatory frameworks and policies for pharmacogenomics hinders its adoption. Establishing guidelines and standards for genetic testing and data privacy is necessary to ensure the ethical and effective implementation of pharmacogenomics²⁶. Policymakers need to develop regulations that promote the integration of pharmacogenomics into healthcare systems while safeguarding patient privacy and data security.

Establishing partnerships

There are obvious challenges to establishing successful partnerships, especially when both public and private institutions are involved, such as social and legal issues, political will, bureaucratic inertia, and competing interests. Privacy concerns and commercialization of health data have recently received more attention^{36–39}. Unfortunately, the disengagement between the public sector and industry creates additional hurdles preventing patient access to drugs, and less options for economic growth at the societal level⁴⁰.

Socio-economic and cultural barriers

Socio-economic disparities and cultural beliefs may also impact the acceptance and utilisation of pharmacogenomics. Efforts to increase public

awareness and engagement are crucial to addressing these barriers and promoting the benefits of personalised medicine⁴¹. Public education campaigns can help demystify pharmacogenomics and highlight its potential to improve healthcare outcomes.

Implementing pharmacogenomics

To implement pharmacogenomics effectively in Africa, an evidence-based and context-specific approach is essential. The PREPARE study offers a useful model for integrating pharmacogenomics into routine healthcare systems. One critical component is capacity building, which involves establishing reference laboratories and embedding pharmacogenomics into the training of healthcare professionals. The PREPARE study demonstrated how preemptive pharmacogenomic testing can be incorporated into clinical workflows, resulting in improved medication outcomes in psychiatry and cardiology^{14,25}. Equally important is policy development through collaboration with regulatory authorities to integrate pharmacogenomic testing into national treatment guidelines. Economic sustainability must also be addressed by conducting localized cost-effectiveness studies. Similar to the economic assessments carried out in the PREPARE study for cardiology and oncology, these evaluations can help determine the financial viability of implementing pharmacogenomics in African healthcare settings¹⁹. Finally, public engagement is crucial. Increasing awareness through targeted education programs for clinicians and patients will support the broader adoption of pharmacogenomics in everyday clinical practice.

In recent years, several international organizations, including the Clinical Pharmacogenetics Implementation Consortium (CPIC), PharmGKB, and the Dutch Pharmacogenomics Working Group, have developed structured guidelines to integrate pharmacogenomics into clinical practice^{42–44}. These guidelines provide clinicians with recommendations on gene–drug interactions to optimize drug therapy and ensure that genetic test results are used effectively in clinical decision-making. However, these frameworks have been primarily developed based on data from North American and European populations, raising concerns about their applicability in African contexts, where allele frequencies and disease burdens differ significantly⁴⁵.

For instance, genetic variants in drug-metabolizing enzymes such as *CYP2D6* and *NAT2* show distinct distributions among African populations, influencing drug efficacy and toxicity profiles in ways not captured by existing global guidelines⁴⁶. As such, African nations must invest in regionally tailored pharmacogenomics research to bridge this gap and adapt global recommendations to reflect the local genetic and clinical landscape. Developing Africa-specific pharmacogenomics guidelines is essential to ensure safe, equitable, and effective application of pharmacogenetics in healthcare systems across the continent^{42,45}. A critical next step toward implementation is the conduct of pragmatic clinical trials to evaluate the clinical and cost-effectiveness of pharmacogenetic testing in African settings. These trials should prioritize high-burden diseases such as HIV, malaria, and TB, where drug–gene interactions are already well-documented and could significantly improve treatment outcomes⁴⁷.

To harness the full potential of pharmacogenomics in Africa, a coordinated and context-specific implementation plan is essential. While scientific advancements offer promising opportunities for personalized medicine, realizing these benefits on the continent requires addressing infrastructural, educational, regulatory, and societal gaps. Below are key strategies that can guide the integration of pharmacogenomics into African healthcare systems.

Harmonization for evaluation

There is considerable variation in the methodology and reporting related to the evaluation of interventions using pharmacogenomics as national and international guidelines were not tailored for such cases. Although the concept of health economic evaluation is not inherently different, its execution can be complicated by several factors, leading to uncertainty or biases. More recently, international communities and initiatives provided lists of recommendations to measure the value of personalised medicine⁴⁸.

These help the preparation of high-quality studies in specific jurisdictions. An example of this is chronic lymphocytic leukemia, with studies from Australia⁴⁹ or United Kingdom⁵⁰. The Australian study provides a practical model for incorporating pharmacogenomic data into cost-effectiveness analyses, which can guide the design of similar frameworks in African health systems. The UK study highlights the feasibility of using genomic information to inform treatment decisions and optimize healthcare spending, offering a methodological example that could be adapted to local African contexts. Adapting and applying these international guidelines to African healthcare systems will be essential to ensure context-specific, evidence-based implementation of pharmacogenomics.

Building infrastructure and a community of practice

Investing in laboratories, genetic testing facilities, and data management systems is crucial. Collaborations with international organisations and leveraging public–private partnerships can help when building the necessary infrastructure³⁵. Establishing regional centers of excellence in genomics can facilitate the development of a robust pharmacogenomics network across Africa. An African Pharmacogenomics Network was launched (<https://www.aphgn.org/>) to utilise the limited expertise in pharmacogenomics on the continent, and provides a hub for sharing expertise and data.

Developing educational programs

Creating educational programs and training modules for healthcare professionals is essential. These programs should focus on the basics of pharmacogenomics, interpretation of genetic tests, and clinical application of pharmacogenomic data^{31,32}. Providing continuous professional development opportunities can keep healthcare providers updated on advances in pharmacogenomics.

Policy recommendations

Formulating policies and regulatory frameworks to support pharmacogenomics is vital. This includes establishing guidelines for genetic testing, ensuring data privacy, and promoting research and development in pharmacogenomics²⁶. Governments should collaborate with stakeholders to create policies that foster the integration of pharmacogenomics into national healthcare systems.

Public awareness and engagement

Engaging with communities and stakeholders through awareness campaigns can help address socio-economic and cultural barriers. Educating the public about the benefits of pharmacogenomics and personalised medicine can foster acceptance and utilization⁴¹. Community outreach programs can play a crucial role in building trust and promoting the adoption of pharmacogenomics.

Case studies of emerging success stories

Several African countries have started to implement pharmacogenomics with promising results. Highlighting these success stories can provide valuable insights and lessons for other regions.

South Africa

While pharmacogenomic research has provided valuable insights, its clinical implementation remains limited. For instance, South Africa has initiated pilot studies where pharmacogenomic-guided dosing of efavirenz in HIV treatment has reduced neuropsychiatric side effects and improved adherence rates, showing the feasibility of clinical integration⁵¹. South Africa has started to integrate pharmacogenomics into clinical practice, particularly in the treatment of HIV and cancer. For example, the South African Medical Research Council released a call for expression of interest in precision medicine. These initiatives have led to some incorporation of pharmacogenetics results in decision making for patients, with prospects of improved patient outcomes and cost savings⁵¹. The development of pharmacogenomic-guided treatment protocols for HIV has demonstrated

the potential of personalised medicine to enhance therapeutic efficacy and reduce adverse effects. However, most of this work is currently only undertaken during research and still needs to be translated into the clinics.

Mozambique

In Mozambique, pharmacogenomic studies of nevirapine have improved understanding of the genetic factors influencing drug response, leading to more effective HIV treatment strategies⁵². These studies have identified genetic variants associated with nevirapine-induced hepatotoxicity, informing safer prescribing practices and improving patient safety.

H3Africa initiative

The Human Heredity and Health in Africa (H3Africa) initiative has been instrumental in promoting genomic research and building capacity for pharmacogenomics in several African countries. This initiative has facilitated numerous studies that highlight the potential of pharmacogenomics to improve healthcare in Africa⁴⁷. The establishment of biorepositories and research consortia under H3Africa has provided a valuable resource for conducting pharmacogenomic research.

Future directions and recommendations

Given limited resources, the initial implementation of pharmacogenomics in Africa may need to prioritize key gene–drug interactions with high clinical relevance. Examples include ART (*CYP2B6* and efavirenz), TB treatment (*NAT2* and isoniazid metabolism), and malaria treatment (*CYP2C8* and amodiaquine metabolism). Targeting these specific areas can yield immediate benefits by improving treatment safety and efficacy for widespread diseases. However, from a research and policy perspective, it is equally important to adopt a broader view by exploring all available CPIC guidelines with necessary regional adaptations to establish a strong foundation for future clinical translation.

A critical next step involves integrating existing pharmacogenomic research findings into national healthcare frameworks while developing Africa-specific guidelines. These efforts will help create pharmacogenomics frameworks that reflect the genetic diversity and clinical realities of African populations. With the right strategic investments, capacity building, and regulatory support, the future of pharmacogenomics in Africa holds significant promise.

Research and development must be a cornerstone of this effort. Investing in identifying genetic markers relevant to African populations is crucial to support the creation of targeted therapies and improve patient outcomes⁵³. Collaborative research among African and global stakeholders can expand the understanding of genetic diversity and its influence on drug response, laying the groundwork for more equitable precision medicine initiatives across the continent.

A long-term vision for pharmacogenomics in Africa should include its integration into routine clinical care, backed by robust infrastructure, well-trained professionals, and supportive policy frameworks⁵⁴. Establishing national pharmacogenomics programs will help coordinate and sustain these initiatives over time. Partnerships will be vital in this process. Collaborating with international partners, academic institutions, and pharmaceutical companies can provide essential resources, facilitate knowledge transfer, and support capacity-building efforts⁵⁵.

Notably, successful global models offer valuable lessons for Africa. For example, Australia has launched an innovative multi-stakeholder public-private partnership model for sustainable precision oncology⁴⁰. Similar collaborative approaches in Africa, particularly when aligned with global genomic initiatives, can accelerate pharmacogenomic implementation by leveraging shared resources, expertise, and infrastructure.

Conclusions

Pharmacogenomics holds immense potential to transform healthcare in Africa by providing personalised treatment options, reducing healthcare costs, and improving patient outcomes. Despite the challenges, strategic

investments in infrastructure, education, policy, and public engagement can pave the way for the successful implementation of pharmacogenomics. Stakeholders must collaborate and invest in this promising field to realise its full potential and create a sustainable, cost-effective healthcare system in Africa.

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Author contributions

M.Z.A. conceptualized the paper with C.D. and G.D.O. M.Z.A. wrote the first draft of the paper. G.D.O., M.C., C.M., and C.D. provided inputs to improve

the content. All authors contributed to the final draft and approved the submitted version.

Competing interests

The authors declare no competing interests.

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