American Journal of Hematology

WILEY

CRITICAL REVIEW OPEN ACCESS

Genetics and Genomics in Sickle Cell Disease in Africa

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Received: 5 June 2025 | **Revised:** 14 January 2026 | **Accepted:** 20 January 2026

Keywords: Africa | benefits | challenges | genomics | molecular genetics | sickle cell anemia | sickle cell disease

ABSTRACT

Advanced genomic technologies are revolutionizing our ability to understand complex diseases. Large-scale population studies are needed to realize the potential of using individual genetic information to personalize treatments for better patient outcomes for chronic non-communicable diseases, such as sickle cell disease (SCD). SCD is recognized as a benchmark genetic disorder for study both in Africa and globally due to its unmet health burden and the potential utilization of genomic knowledge for improving the health outcomes for individuals living with the disease. Over the past two decades, groundbreaking genomic research in SCD has led to the discovery, fine mapping, and validation of genetic and epigenetic variants of importance for SCD. These include variants in genes such as *BCL11A*, *HBG*, *MYB*, *KLF1,* and *FLT1,* which are all associated with fetal hemoglobin expression, a major modifier of disease severity in SCD. There has also been increased genomic knowledge of other SCD modifiers, including the distribution of alpha- and beta-thalassemia variants in Africa, and infectious disease related markers such as *APOL1*. Pioneering pharmacogenomics studies for hydroxyurea are promising and have unveiled the importance of the implementation of such studies for all SCD therapeutics, including small molecules and recent gene-based therapies. Genomic research for the development of personalized medicine for SCD must involve countries in Africa due to the high prevalence of the disease in these countries, the high African genetic diversity that influences disease progression, and the potential to follow treatment outcomes in large cohorts of patients. These findings hold great promise to lead to a better understanding of SCD biology and treatment responses, the discovery of new therapies, and informing the design and execution of much needed clinical trials.

1 | Introduction

1.1 | Genomics for Health in Africa

The remarkable progress of genomic applications has ushered in a new era for understanding disease biology. The completion of the Human Genome Project (HGP) yielded valuable insights across various biological fields, particularly in understanding human diseases, both communicable and non-communicable [1, 2]. The emergence of advanced technologies, such as whole genome sequencing, whole exome sequencing, and single cell sequencing, has further accelerated the pace of genetic research [3, 4]. However, a significant challenge posed by these technological advancements is translating genomic medicine into tangible health benefits.

From a healthcare perspective, the key role of genetic research is to identify the gene–gene and gene–environment interactions that contribute to disease susceptibility. There are concerns that low- and middle-income countries (LMICs), particularly in Africa, may struggle to access and capitalize on these genomic advancements due to limitations in equipment, expertise, and financial resources [5]. This situation undermines the potential contributions of African populations to genomic research and may exacerbate the developmental and economic divide between high- and low-income countries.

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Nevertheless, initiatives have emerged to tackle these challenges, including the 1000 Genomes Project, the African Genome Variation Project, the Human Heredity and Health for Africa (H3A) initiative, H3Abionet, and most recently, the Data Science Initiative for Africa as well as the SickleInAfrica consortium (Table 1). The ongoing challenge lies in determining how LMICs can leverage these scientific advancements to enhance genetic research within Africa and ultimately improve health outcomes.

1.2 | Sickle Cell Disease Serves as a Model Disease for Genomics in Africa

Sickle cell disease (SCD) is a prevalent red blood cell disease, with approximately 260 000 children born with the condition in African countries each year. SCD is associated with a high mortality rate, where up to 50% of affected children in Africa do not survive past the age of 5 years [6–8]. Currently, there are limited interventions available for SCD. In higher-income countries, such as in the USA, early identification of newborns and infants with SCD followed by prompt infection management and comprehensive care has significantly reduced mortality rates, particularly among children under 3 years of age. Additionally, higher-income nations have made notable strides in leveraging genetic research to develop technologies and treatments that improve disease diagnosis, monitoring, and management, including revolutionary approaches like gene therapy. In contrast, countries in Africa bear the brunt of the disease and historically have lacked the resources to engage in transformative basic and translational research. However, with the research investments made on the African continent over the past two decades and advancements in technology, Africa is becoming well-positioned to actively participate in ongoing genetic and genomic research initiatives. This engagement can lead to improved diagnostic methods, the investigation of disease modifiers, studies on pharmacogenomics relevant to SCD treatments, and the development of innovative interventions, including pharmaceuticals and gene-based therapies [9, 10]. Sustained capacity building in sub-Saharan Africa will support optimal care for patients with

TABLE 1 | Major genomics and sickle cell disease research initiatives in Africa.

Major African genomics initiatives that include SCD genomics research activities			
#	**Name of initiative**	**Key deliverable**	**Role in SCD genomics**
1	H3Africa	Well established pan-African network of genomics laboratories and biorepositories	Available laboratories, biorepositories, and data to support SCD genomics research
2	H3Abionet	Developed bioinformatics capacity across African institutions	Available bioinformatics support for SCD genomics research
3	DSI Africa	Fosters data science and artificial intelligence research and innovation ecosystem across Africa	Available data science and artificial intelligence resources to support SCD genomics research
4	SickleInAfrica	Establishment of the registry for people living with SCD and implementation of large-scale research	Registry and data that can support SCD genomics research
5	INHERENT	Study of genetic modifiers for hemoglobinopathies through a large-scale genome-wide association study (GWAS)	Available data and resources for SCD genomics research
6	SCD Ontology	Developed a standardized vocabulary and framework for SCD data	Provides harmonized terminologies and standardized clinical phenotypes for SCD research
7	ASH-CONSA	Standardized newborn screening guidelines and patient outcomes.	Available data and framework for integration of SCD genomics in newborn and early infant diagnosis
8	PEN-PLUS	A strategy to integrate the management of severe non communicable diseases including SCD at peripheral hospitals	Platform and framework for SCD genomics research integration into primary health care
9	African Pharmacogenomics Network (APN)	Platform for African researchers working on pharmacogenomics in African populations	Platform and resources to support SCD pharmacogenomics research and initiatives
10	Africa Bioinformatics Institute	Provide bioinformatics training and research support in Africa	Bioinformatics support for SCD genomics research

Note: Ten collaborative initiatives are listed that were founded to provide more detail on the genomic diversity and health outcomes of people living in African countries. We highlight the intended purpose of each of these initiatives and how they provide a platform for future genomic endeavors in SCD research.

SCD, and the inclusion of research programs in these endeavors will accelerate new discoveries.

This review sketches the status of SCD genomic research across the sub-Saharan continent and emphasizes how collaborative efforts between countries in Africa to form large longitudinal population cohorts can power research and patient care. In particular, we focus on key findings from existing genomics studies and how future studies can address unanswered questions related to SCD biology (Figure 1).

2 | Genomics and Investigation of Disease Modifiers of SCD

SCD is regarded as an exemplary model for translating genomic medicine research into health advancements, both from public health and genomic research perspectives [11, 12]. SCD is a prevalent monogenic disorder caused by a mutation in the β-globin gene, but with considerable phenotypic heterogeneity of clinical outcomes that are influenced by genetic and environmental factors [12]. Individuals with SCD can suffer from a broad spectrum of clinical complications, including chronic anemia, pain episodes, recurrent infections, splenic sequestration, priapism, leg ulcers, acute chest syndrome, and end-organ damage such as nephropathy, avascular necrosis, and stroke. There is a high mortality rate associated with SCD without clinical intervention [6–8]. Many of the initiatives to establish sustainable research infrastructure and surveillance cohorts for SCD genomic research in Africa have been driven by the need to improve newborn screening and treatments for patients.

In addition, there are limited treatment options available for long-term care for individuals with SCD. These include blood transfusions, hydroxyurea (HU), L-glutamine, crizanlizumab, and voxelotor. Of these, HU is the only drug currently available for sub-Saharan African settings, and there are many difficulties in providing blood transfusions for patients in these countries. This lack of treatment options is spurring many studies of the mechanisms of disease pathophysiology to find alternative therapeutic targets to better help patients with the disease. However, few of these efforts have included individuals from African countries in their design. This limits the size of study cohorts available for study and diminishes the opportunity to identify treatments that will work for all patients with SCD worldwide. In addition, there have been very few genome-wide association studies (GWAS) performed in African populations looking for genetic modifiers of disease severity in SCD. There is an overarching need to dramatically enhance the genomic data from individuals of African ancestry [13]. As part of capacity building of biobanking and genomics expertise, it is imperative that a robust framework of governance is widely accepted, such as that developed by the Human Heredity and Health in Africa (H3Africa). The development and implementation of ethical guidelines should be directed by the research teams in Africa, particularly for the setting up of biobanking, the use of genomic data, and the sharing of research results with research participants and their communities [11, 14]. As highlighted in a recent review [15], there are opportunities to enhance SCD research by

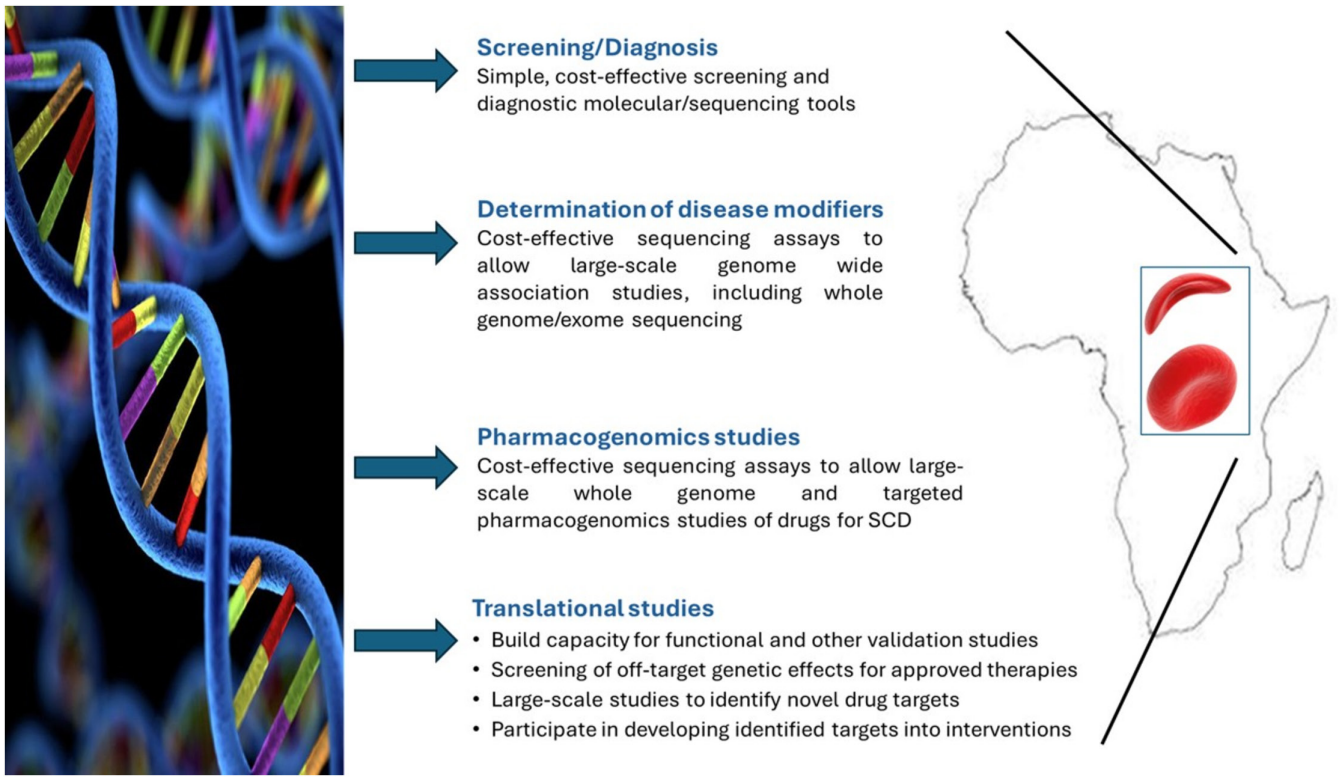

FIGURE 1 | Graphical illustration of review focus. Integration of genomic research can address critical research questions in Africa, including: (1) screening and diagnosis of SCD; (2) determination of modifiers that affect SCD manifestation; (3) identification of modifiers of treatment responses; and (4) power translational studies for the discovery of new treatments for SCD.

having African countries lead research efforts in two key areas: (1) genetic regulation of fetal hemoglobin (HbF); and (2) identifying genetic variants that impact clinical outcomes in SCD to generate risk models to personalize individual patient care.

2.1 | Fetal Hemoglobin in SCD

One of the most potent modifiers of SCD is HbF. HbF is highly expressed during fetal development, followed by a globin switch from HbF to adult hemoglobin shortly after birth. As the SCD mutation is in the adult beta-globin gene, patients with SCD will experience complications of SCD as their HbF levels decrease. HbF levels are higher in patients with SCD, ranging from about 3%–25% HbF compared to less than 1% in the general population. Higher HbF levels are associated with reduced morbidity and mortality in SCD across all populations with SCD [16–18]. Persistence of HbF expression is heritable, and several genetic loci have been found to impact HbF levels, including HBS*1L-MYB* and *BCL11A*. Naturally occurring variants located near the BCL11A gene are associated with higher levels of HbF, via their impact on basal BCL11A expression. However, most of these studies have been restricted to populations from Europe or from the African diaspora, which do not represent African populations where SCD is most common [19]. Variation in the genomic region surrounding the β-globin gene cluster has also been associated with clinical outcomes in SCD. There are four major SCD β-globin haplotypes, designated as the Benin (BEN); Central African Republic (CAR, also referred to as Bantu); Senegal (SEN); and Arab/India (AI) haplotypes [20]. SCD patients who inherit the sickle mutation on a SEN or AI β-globin haplotype tend to have milder disease, and with association of higher HbF levels in these haplotypes of 10% and 30% HbF respectively compared to 5%–6% HbF in patients with Benin and CAR haplotypes [21, 22]. There is a higher diversity of β-globin haplotypes in individuals with SCD from African countries [23], indicating that better definition of *BCL11A*, *HBS1L-MYB*, and β-globin genetic variation may be needed to deliver more tailored management of HbF in SCD [24, 25].

In 2013, the first large SCD GWAS was conducted in Africa [26]. In addition to replicating the known loci, this study identified eight novel loci associations (Figure 2A). Since then, there has been increased interest in conducting either independent GWAS studies or meta-analyses involving African datasets including the Cameroonian and Nigerian populations [30–32]. Recent HbF GWAS studies [27–29] reported a detailed dissection of the known loci as well as additional potential novel loci associated with HbF (Figure 2B,C). Using imputation to generate genome wide genotypes from existing single nucleotide polymorphism array data obtained from individuals with SCD from Cameroon and Tanzanian, there was a strong association of variants in BCL11A, *HBS1L-MYB* and the beta-globin loci with HbF levels [29]. In addition, this study identified novel variants primarily in the African cohorts in the *FLT1* gene associated with HbF, allowing for the cell-based assessment of FLT1 activity on hematopoiesis and HbF expression. These findings are an example of how detailed GWAS analyses in large cohorts of individuals with SCD from Africa can be leveraged to identify HbF-associated loci that are more common in African cohorts or require large cohort sizes for discovery and validation of GWAS results. In particular, large cohorts with greater than 1000 individuals with SCD will be essential for the identification of rare variants (allele frequencies below 0.01) that have strong effects on HbF expression. Further whole genome sequencing studies in additional African cohorts will lead to improved understanding of the loci that regulate HbF expression and the functional impact of genes such as FLT1 impact patient levels of HbF. These endeavors hold the promise of determining the biochemical pathways related to HbF synthesis that can be targeted for effective induction of HbF through pharmacologic intervention or gene therapy [33, 34].

2.2 | Genetic Modifiers of SCD Clinical Complications

Over the years, genetic polymorphisms in many genes have been linked with clinical outcomes of organ injury in SCD, including risk of kidney disease and ischemic stroke. Most of these variants were identified by targeted gene testing approaches in relatively small cohorts of individuals with SCD. There is ongoing need to validate suspected genes involved with specific outcomes in independent cohorts, such as the ongoing international initiative INHERENT [31, 32, 35]. Replicating and validating such findings has always been limited in SCD, and especially in cohorts from Africa. The

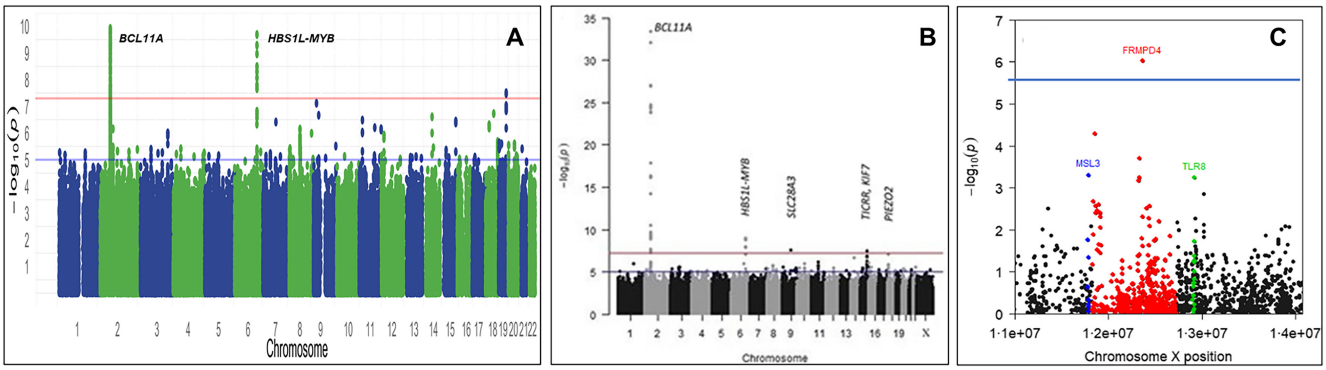

FIGURE 2 | Manhattan plots for normalized HbF genome-wide association results. For each plot, the significance of association (−log10 *p* value) is plotted against the chromosomal position of each genotyped variant. The red line indicates a genome-wide significance threshold at 5×10^{-8} *p* value. The blue line indicates genome-wide threshold for suggestive association at *p* value $<1\times10^{-5}$. Results are shown for HbF association in (A) a Tanzanian SCD population [26]; (B) a Nigerian population [27], and (C) a Tanzanian population reanalyzed for males and females separately [28, 29].

foundation of H3Africa has developed SNP array platforms to perform African-centric investigation of the association between genetic variants and clinical outcomes in SCD [15, 36]. The inclusion of sub-Saharan African countries in these endeavors will generate data that will be more representative of the genetic variation in these countries for people with this disease. Due to the prevalence of SCD in these countries, it is also expected that continued support of these programs will lead to significantly more individual data available for both discovery and validation efforts. Several genetic variants (Table 2) have already been investigated in African populations in association with key SCD phenotypes of stroke and renal dysfunction, respectively. Co-inheritance of alpha-thalassemia acts as a significant genetic modifier of risk of kidney disease and stroke in SCD. The most common type of alpha-thalassemia mutation in sub-Saharan Africa is the α3.7 deletion, where individuals inherit a 3.7 kb deletion in at least one of the four alpha globin genes. The prevalence of α3.7 alpha thalassemia has been recorded with the prevalence of 42% in Uganda and 12% in Senegal [42, 43]. Co-inheritance of alpha-thalassemia has repeatedly been shown to be associated with a decreased risk of stroke in individuals with SCD [44–46]. Genetic variants in both HMOX1 and APOL1 have been linked with risk of kidney disease [37–39], while single center studies have tested candidate genes associated with other SCD related phenotypes (Table 2). Availability of large SCD cohorts from African countries would provide an opportunity to verify the impact of other previously described loci (e.g., *BCL11A, TEK, ADCY9, ANXA2, HMOX1, SARA1A*) with specific clinical outcomes. More importantly, generating whole genome sequence data in these same African cohorts would enable unbiased GWAS analyses of genes associated with adverse clinical outcomes and organ injury. The discovery and promise of treatments involving *BCL11A* in HbF production show the value of using genomics to determine novel treatments for SCD [47, 48]. The integration of more sophisticated genome technologies in research efforts in Sub-Saharan Africa, such as whole genome sequencing and single cell sequencing will provide a more detailed view of the genetic variation associated with SCD clinical outcomes. Moving away from targeted candidate polymorphism testing to unbiased whole genome analyses in large cohorts will dramatically enhance the discovery of novel genomic modifiers of SCD. The maintenance of research consortia such as SickleInAfrica (Table 1) will enable validation of genomic findings in large independent cohorts to verify genetic variants that consistently affect SCD outcomes across diverse populations.

TABLE 2 | Genetic modifiers of SCD phenotypes in African ancestry populations.

Gene	Associated clinical phenotype in SCD	References
α-thalassemia (–α3.7 kb del)	Stroke, kidney disease	[31, 37]
APOL1 (G1, G2)	Renal (CKD, albuminuria) Renal (eGFR, albuminuria)	[37–39]
HMOX1	Renal (eGFR, albuminuria)	[37]
BCL11A	HbF expression Stroke risk	[26, 31, 40, 41]
FLT1	HbF expression	[29]
TEK, ADCY9, ANXA2	Stroke	[31]
A1CF, SYPL2, WNT7A, TMEM60	Renal (eGFR)	[38]
CRYL1, VWF, ADAMTS7	Renal (proteinuria, eGFR)	[35]

Note: Genes associated with complications of SCD are listed. Each gene has been associated with its relevant complication in at least two candidate gene association studies. We highlight where each gene has already been tested in an African population, indicating how future genomic studies in African cohorts can further validate these genes and identify new genetic modifiers via GWAS.

3 | Implementation of Genomics in SCD to Enhance Patient Care

For SCD, sub-Saharan populations represent the largest number of individuals with SCD and the greatest genetic diversity among all individuals with the disease. Building sustainable research infrastructure and surveillance cohorts linked with biorepositories would be a major boost for understanding the pathophysiology of SCD. The phenotypic and genomic data would help inform evidence-based policies and interventions to improve the future health of sub-Saharan Africa's diverse populations and impact global SCD populations. Integration and coordination of these efforts could make sub-Saharan Africa research a leader in the efforts to incorporate personalized medicine and pharmacogenomics across the life span of patients with SCD worldwide. We envision three major areas that genomics in Africa can benefit SCD research.

3.1 | Developing Genomic Risk Models to Personalize Individual Patient Care

The implementation of newborn screening programs and early-life interventions for babies with SCD leads to a dramatic decrease in childhood mortality. However, children born with SCD will face ongoing risks of developing severe clinical complications throughout their life, and many patients will still develop acute and chronic complications that require significant intervention. Unfortunately, there are limited means to identify which patients are at highest risk of developing specific complications and predicting which patients will benefit from which treatment options. A long-term goal for the genomic study of SCD would be to establish the spectrum of genes or genetic variants that modify risk of specific complications. This work would be reliant on having large cohorts of patients with robust longitudinal clinical data, access to biospecimen collection from individuals over time, and available resources to provide detailed genomic analyses. The involvement of countries in Africa is the most feasible approach

to achieve this goal of using genomics to personalize risk assessment and treatment approaches for specific adverse outcomes. There are known genes that affect clinical outcomes, including BCL11A, β-globin haplotypes, and co-inheritance of alpha-thalassemia. These can be included in making predictions of patient outcome risks and can be further refined by the results of large genomic studies of SCD cohorts with longitudinal clinical outcomes data. A key goal would be to introduce gene focused targeted screening that could help identify and monitor individuals with SCD at high risk for specific complications such as stroke and kidney disease. These efforts would mirror efforts to establish genetic modifiers of other diseases, such as Type II diabetes [49, 50] and Parkinsons disease [51]. Studying large cohorts of individuals with Type II diabetes has allowed polygenic scoring of risk of coronary artery disease, peripheral artery disease, and end-stage diabetic nephropathy across ancestry groups. There is an anticipated value in integrating multi-ancestry GWAS data with patient clinical data to optimize care of patients with diabetes [50], processes which would also benefit individuals with SCD.

3.2 | Pharmacogenomics in SCD

Pharmacogenomic studies, which focus on identifying genetic factors influencing drug responses, hold substantial promise in enhancing personalized medicine by: (1) improving drug efficacy and safety, (2) identifying severe adverse effects, and (3) predicting therapeutic outcomes, thereby advancing the field of genomic medicine [52]. The integration of pharmacogenomic testing into clinical practice has gained traction, notably with the US Food and Drug Administration (FDA) providing guidelines for such practices [53]. Despite the increasing prevalence of pharmacogenomic studies in high-income countries, their implementation and application remain limited in low- and middle-income countries [54]. This gap is particularly pronounced within the context of pharmacogenomic research related to treatments for SCD, such as HU. Pharmacogenomics has the potential to enhance therapeutic interventions in SCD; however, it must take into account variations within populations, ethical considerations, and socioeconomic factors to ensure effective clinical application [55].

HU has demonstrated significant benefits for patients with SCD, mainly through the induction of HbF and suppression of WBC and neutrophil levels. However, individual therapeutic response to HU is heterogeneous. While some patients may experience substantial increases in HbF, others exhibit minimal or no response [56, 57]. Factors such as the timing and dosage of HU administration, baseline HbF levels, white blood cell (WBC) counts, and absolute reticulocyte counts (ARC) have been identified as influencing the efficacy of HU treatment [57, 58]. Nonetheless, these parameters remain insufficient for accurately predicting individual responses to HU. The initial absorption and average absorption of HU is similar between SCD patients from higher-income countries and countries in Africa [59, 60], but there are substantial inter-patients differences associated with HU induced responses. Genetic factors have been implicated in modulating HU response [61, 62], prompting research efforts aimed at identifying specific genetic determinants of treatment efficacy [63, 64]. Determining HU treatment response via induction of HbF is often confounded by pre-treatment HbF levels. Availability of large SCD cohorts treated over time with HU will allow for a more robust examination of genetic factors that regulate HU response, particularly to distinguish between genes directly involved in HbF expression (e.g., *BCLL1A, HBS1L-MYB, HBB, NOS1, ARG2*, and *SAR1A*) versus genes associated with HU metabolism (e.g., *CYP2C9* and *CYP2E1*) [40, 65].

Recently, the SickleInAfrica consortium, which operates in seven countries, has embarked on conducting a multi-country cohort study to understand the pharmacogenomics of pain treatment responses in a diverse African SCD patient population (https://www.sickleinafrica.org/node/39553). Such studies are key in understanding the landscape of genetic factors associated with pain treatment in Africa. Pain management in SCD frequently falls short, as there is limited evidence backing the effectiveness of different analgesic treatments during acute pain crises [66]. Potential pharmacological strategies beyond HU include oral antioxidants such as L-glutamine and omega-3 fatty acids, as well as the intravenous anti-adhesive agent crizanlizumab [67]. Genetic polymorphisms in genes such as CYP2D6 and UGT2B7 significantly affect opioid metabolism and pain management outcomes in SCD patients [68]. More work is needed to evaluate how these genes and variants in other genes such as OPRM1, HMOX-1, GCH1, VEGFA, and COMT impact variable responses to pain and analgesics in SCD. Detailed study of the pharmacogenomics of specific drugs can reveal how to improve treatment outcomes for existing drug therapies by incorporating pharmacogenomic testing to reduce any associated toxicities or predicting patients who are likely not to respond to particular treatments. This would be similar to the discovery of the role of SLCO1B1 variants on statin-induced myotoxicity in individuals with African ancestry [69].

3.3 | Development of Personalized Interventions Using Genomics

The global rise in genomics medicine to inform precision medicine is not reflected by any major efforts in Africa. This disparity is mainly due to the expense and substantial infrastructure needed to implement genomic research and the current exploratory nature of potential treatments. Building sustainable research and surveillance cohorts linked with biorepositories would promote the discovery of new interventions that could improve the health of all patients with SCD. As described in the sections above, genomic research should be applied to identify the full spectrum of genes that affect clinical complications of SCD in African countries. Identifying these specific genes through genomic studies can establish molecular pathways that could be pharmacologically targeted to provide benefit for all patients with SCD, such as current efforts to target the HbF-modifying gene *BCL11A* [47, 48]. The potential discoveries from genomics research in SCD could also further our understanding of cardiovascular complications that are common in both SCD and the general population, such as stroke or kidney disease [38, 70]. For patients with SCD in Africa, it is also important to consider the relationship of gene-environmental interactions

that are related to endemic infectious diseases. Inflammation is common in SCD, and infectious agents that further trigger inflammation may exacerbate clinical events. Carefully curated patient histories would allow detailed analyses of which comorbidities impact both clinical outcomes and patient responses to current treatments such as HU [71].

A major advance in reducing the morbidity and mortality associated with SCD in sub-Saharan Africa would be to provide access to curative therapies. This would include the well-established procedure of allogenic hematopoietic stem-cell transplantation and the still largely experimental gene therapy options. These gene therapy methods use patient hematopoietic stem cells to introduce corrected HbA genes in patients with SCD (a complete cure) or stimulate HbF production (a functional cure) [72]. While these gene therapies can immediately provide a cure for some SCD patients, most patients will not be able to access these curative options. Both HCST and gene therapy curative options are expensive, require toxic conditioning regimens, and the collection of hematopoietic stem cells for transplant. Even with substantial capacity building, it would take significant investment for either HSCT or ex vivo gene therapy to be offered as standard of care for the millions of patients with SCD in African countries. The more practical approach for improving SCD patient care may be to develop drug and small molecule therapies that target specific pathways that are the cause of clinical complications in SCD.

The mortality associated with SCD is high in sub-Saharan African countries, especially for children [6–8]. There is a pressing need to provide cost-effective therapies for SCD that can complement current treatments such as HU. Small molecule therapies can be designed to target various aspects of SCD pathophysiology, such as reducing hemolysis [73], supplementing haptoglobin and hemopexin to reduce heme toxicity [74, 75], or stimulating HbF expression [76]. Developing additional molecular targets can be enhanced by genomic studies that are led by research collaboratives in African countries. The goal is to provide novel treatment options for managing SCD in diverse clinical settings, which can be scaled to care for the millions of individuals with SCD. A recent study that examined genetic risk loci associated with Parkinson's disease in Africa found that only African populations had causal variants in the *GBA1* gene that predisposed these individuals to Parkinson's disease [51]. While this finding provides an avenue to better understand the pathophysiology of the disease, there is also an opportunity to develop RNA-based and small-molecule therapies that target *GBA1* to reduce the risk of developing severe Parkinson's disease. This approach would also be of significant benefit to individuals with SCD in Africa and worldwide.

4 | Concluding Remarks

The majority of people with SCD live in countries in sub-Saharan Africa. Despite challenges that limit access for testing and treating patients with SCD, there is an opportunity to improve our broader understanding of SCD by including genomics as part of efforts to improve healthcare for patients (Figure 1). The implementation of affordable diagnostic tools, education campaigns, and establishing registries can significantly expand cohorts of patients with SCD and longitudinal clinical outcomes. There is an opportunity for patients in Africa to be included in clinical trials of novel treatments, and larger study cohort sizes will allow more robust study of the pharmacogenomics of drug treatments. The inclusion of genomic research would power efforts to understand the genetic modifiers of disease severity, individual response to specific drug treatments, and prediction of patient outcomes to allow for more intensive interventions. These efforts will provide the framework to develop and refine the urgently needed new therapies to care for all patients with SCD worldwide.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data represented in this review are available from previous publications. Data for Figure 2 are adapted from references [26–29].

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