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REVIEW

The dawn of a cure for sickle cell disease through CRISPR-based treatment: A critical test of equity in public health genomics

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Abstract

Equity in access to genomic technologies, resources, and products remains a great challenge. This was evident especially during the coronavirus disease 2019 (COVID-19) pandemic when the majority of lower middle-income countries were unable to achieve at least 10% population vaccination coverage during initial COVID-19 vaccine rollouts, despite the rapid development of those vaccines. Sickle cell disease (SCD) is an inherited monogenic red blood cell disorder that affects hemoglobin, the protein that carries oxygen through the body. Globally, the African continent carries the highest burden of SCD with at least 240,000 children born each year with the disease. SCD has evolved from a treatable to a curable disease. Recently, the UK medical regulator approved its cure through clustered regularly interspaced short palindromic repeat (CRISPR)-based treatment, whereas the US Food and Drug Administration has equally approved two SCD gene therapies. This presents a remarkable opportunity to demonstrate equity in public health genomics. This CRISPR-based treatment is expensive and therefore, a need for an ambitious action to ensure that they are affordable and accessible where they are needed most and stand to save millions of lives.

KEYWORDS

Africa, clustered regularly interspaced short palindromic repeat treatment, equity, public health genomics, sickle cell disease

1 | INTRODUCTION

Genomic applications in health and disease are transforming medical practice, especially prenatal, newborn, and disease carrier screening. Elsewhere, gene therapy is redefining the management of both infectious and genetic diseases. The speed at which these advances are being adopted is relatively faster in the developed world compared to lower and middle-income settings. In the United States, the National Human Genome Research Institute (NHGRI) anticipates that progress in technology, biological insights, and clinical applications will lead to more extensive integration of genomics into almost all areas of biomedical research, as well as routine medical and public health practices. In 2020, the NHGRI made 10 Bold Predictions for Human Genomics with the hope that they would

Gerald Mboowa and Benson Kidenya have equal contributions.

be attained by 2030 and two of these included (i) breakthrough discoveries to lead to curative therapies involving genomic modifications for dozens of genetic diseases and (ii) people from ancestrally diverse backgrounds benefit equitably from advances in human genomics (Green et al., 2020). These two critical predictions are in tandem with the core guiding principles and values for human genomics which aim to maximize the usability of genomics for all members of the public, including the ability to access genomics in healthcare, engagement, inclusion, and understanding of the needs of diverse and medically underserved groups (Green et al., 2020). This was similarly echoed by the International Summit on Human Genome Editing which encourages gene-editing equity and access for underserved populations.

The coronavirus disease 2019 pandemic catapulted genomics to the forefront of effective infectious disease testing, characterization, response, and surveillance globally. Similarly, clustered regularly interspaced short palindromic repeats (CRISPR)-based Sickle cell disease (SCD) treatment presents a unique window of opportunity to demonstrate equity in access to therapeutic advances in human genomics for public health. A blueprint with the potential to define how genetic diseases in diverse populations globally could benefit from this CRISPR technology in future. Essentially, this requires unprecedented investment in genomic capacity, infrastructure, human resources, and coordination at national, regional, and continental levels. Here, we discuss prospects for CRISPR-based SCD treatment in Africa.

2 | SICKLE CELL DISEASE (SCD)

SCD, although described as the first molecular disease in 1910 (Frenette & Atweh, 2007), the development of its effective therapies has lagged behind that of many other similar known disease conditions. SCD results from the substitution of a valine for a glutamate amino acid affecting the hemoglobin conformation as a result of a substitution of A to T in the β-globin gene located on human chromosome 11p15.5 (Husain et al., 2017). SCD is an inherited monogenic, autosomal recessive red blood cell disorder that is characterized by flawed hemoglobin which interferes with the amount of oxygen delivered to essential organs causing anemia, increased risk of stroke, and substantial pain (Zhou & Travassos, 2022). Individuals affected with this disorder produce deoxygenated hemoglobin molecules, which cause the red blood cells to distort and form a rigid, crescent (sickle) shape. The affected red blood cells have a reduced lifespan in the body, resulting in critical shortages of red blood cells.

Although SCD occurs worldwide, sub-Saharan Africa (SSA) has the highest prevalence (Adigwe et al., 2023). More than 66% of the 120 million people affected globally by SCD live in Africa, making it the most prevalent genetically acquired disease in the continent. In Africa, at least 240,000 children are born each year with SCD (Williams, 2016). It is a neglected disease, where an estimated 50%–90% of those born with the condition eventually die undiagnosed before their fifth birthday (Uyoga et al., 2019). In the United States, by contrast, people with SCD often live into their forties or beyond (Zhou & Travassos, 2022). The high burden of the disease stems from low investment in several proven interventions. Hydroxyurea has been used to reduce the frequency of SCD crises and prolong survival thereby becoming the standard of care for SCD in many countries. It costs about USD 0.27 per 500 mg capsule (Costa et al., 2021) though vastly underutilized in the SSA (Zhou & Travassos, 2022) due to limited access. Many public health facilities across this region lack the services for early detection and care for SCD. Inadequate medical personnel and lack of supportive services at community-level health facilities also hamper effective responses to the disease. In 2022, African health ministers launched a campaign to ramp up awareness and bolster prevention and care to curb the toll of SCD. Importantly, they acknowledged that it is one of the most common illness in the region but received inadequate attention. This new campaign was supported by the World Health Organization (WHO), World Bank, the US Department of Human and Health Services, Novartis Foundation, Global Blood Therapeutics, and Sickle in Africa (World Health Organization (WHO) | Regional office for Africa, 2023).

With the dawn of a cure for SCD through CRISPR-based treatment, access to this novel cure may remain unavailable to many infected individuals for several years to come because of the prohibitive cost of roughly USD 2.0 million per patient (Wong, 2023). This treatment even by Western world standards is high (Subica, 2023). In many African countries, SCD services remain a low priority for governments (Grosse et al., 2011). Therefore, this may only be accessible through medical insurance coverage which is also largely underutilized due to unaffordable costs. A recent study examining the level and inequality in health insurance coverage in 36 SSA countries revealed that the coverage of health insurance was very low and largely pro-rich (Barasa et al., 2021). Besides, an assessment of the continent's readiness for translational genomics suggests that genetic service delivery remains limited and extremely fragile (Kamp et al., 2021).

3 | SICKLE CELL DISEASE AND CRISPR-BASED TREATMENT: THE ROAD AHEAD

3.1 | Sickle cell disease and CRISPR-based treatment

CRISPR/Cas9, a revolutionary genome editing technology that allows for precise, directed changes to genomic DNA is promising to provide cures for a number of diseases such as hemoglobinopathies, human immunodeficiency virus (HIV), cystic fibrosis, muscular dystrophy, and Huntington's disease. SCD is caused by a genetic mutation. It is a picture-perfect candidate for CRISPR-based gene therapy. Treating sickle cell gene with CRISPR involves an ex vivo method, where hematopoietic stem cells are extracted from the infected individual, corrected, and then returned into the infected patient. Before CRISPR-based treatment of SCD, the cure has been achieved through the transplantation of bone marrow from a matched healthy donor. This method is marred with challenges, such as identifying a suitable consenting donor for the bone marrow, immune rejection of the transplant, and graft-versus-host disease. It is also typically restricted to children and young people because the associated risks increase with the age of the recipient. Ex vivo engineering of autologous hematopoietic stem and progenitor cells followed by the transplantation of genetically modified cells potentially provides a permanent cure applicable to all SCD patients (Park & Bao, 2021). Treating SCD with CRISPR involves an ex vivo procedure known as gene-edited cell therapy, where hematopoietic stem cells are extracted from the patient, corrected through a gene knockout, switching off the gene that suppresses fetal hemoglobin and then returned into the patient. This leads to fetal hemoglobin (hemoglobin F) being expressed, replacing the mutated adult hemoglobin. This CRISPR-Cas9 sickle cell therapy is now in clinical application than β-globin gene editing.

SCD is a monogenic disease caused by a distinct point mutation in the β-globin gene unlike β-thalassemia, whose mutations are far more heterogeneous. Instead of developing genome editing approaches to correct each of these mutations separately, an ideal alternative is to reactivate the expression of fetal globin genes, which offers the prospect of a single genome editing therapy for a diverse array of hemoglobinopathies, including SCD (Schambach et al., 2023). A prime target of this approach is the transcription factor BCL11A, which is responsible for the decline of fetal globin levels after birth and subsequent increased β-globin levels. Genome editing-based disruption of the erythroid enhancer controlling the BCL11A gene has been used, resulting in fetal globin expression in patients with SCD and transfusion-dependent β-thalassemia due to inactivation of the BCL11A transcription factor (Demirci et al., 2018; Schambach et al., 2023). This approach was developed after it was found that sickle cell patients with a natural mutation in their *BCL11A* gene were resistant to disease symptoms. Briefly, bone marrow stem cells are extracted from infected patients and CRISPR-edited to inactivate *BCL11A*, a repressor of fetal hemoglobin production. The edited stem cells are introduced back into the patient with the hope that the new red blood cells produced by the edited stem cells would express fetal hemoglobin (Smith et al., 2006).

Markedly, the United Kingdom approved the application of CRISPR to cure SCD and β-thalassemia (Wilkinson, 2023; Wong, 2023). However, the majority of the world's SCD cases occur in SSA (Adigwe et al., 2023). There is a moral need to work toward ensuring access to affordable CRISPR-based SCD cures in places where this disease occurs most. Certain populations have remained underrepresented in genomics health research as most participants in genomic studies are of European ancestry suggesting a future pattern in which non-Caucasian populations will fail to benefit equally from CRISPR advances for improving public health (Subica, 2023). Though SCD affects at least 100,000 people in the United States who are primarily of African ancestry or Central and South American descent, it has historically received limited research and clinical funding compared with genetic conditions that are more prevalent in European ancestry populations (Subica, 2023). For instance, despite hemophilia and cystic fibrosis being less prevalent than SCD, large US networks of hemophilia and cystic fibrosis treatment centers provide high-quality specialty care to most individuals with these disorders, whereas only a minority of individuals with SCD receive specialty care (Bulgin et al., 2018).

3.2 | Sickle cell disease and CRISPR-based treatment accessibility challenges to Africans

Lessons can be learned from the HIV/acquired immunodeficiency syndrome (AIDS) epidemic. Following the approval of zidovudine in March of 1987 by the US Food and Drug Administration as the first HIV antiretroviral therapy (ART) (Commissioner, 2021), it took more than a decade to make these drugs accessible in low-income settings like Africa, yet this is where the majority of HIV infections occurred causing thousands of deaths. To address this inequity, an ambitious initiative aimed to increase large-scale access to ART in resources-limited settings began in 2003 led by the US President's Emergency Plan for AIDS Relief (PEPFAR) (Bendavid & Bhattacharya, 2009). PEPFAR combated the HIV epidemic by supplying

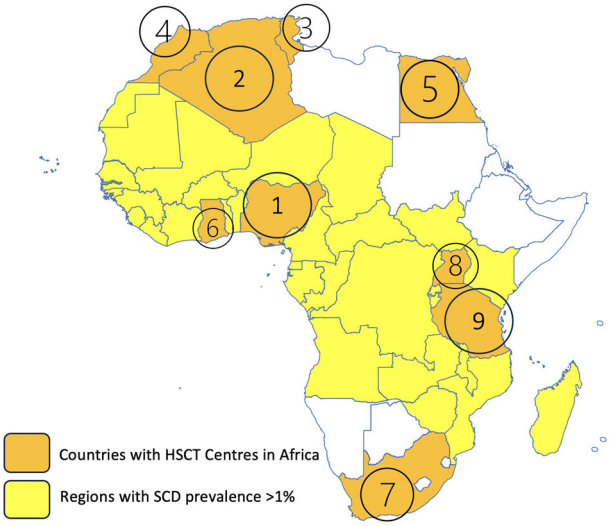

FIGURE 1 Annotated map of Africa showing the locations of bone marrow transplantation centers and countries with prevalence of sickle cell disease >1%.

and negotiating the prices of essential antiretroviral medications and establishing basic medical and social support services. The program significantly expanded resources for capacity building by funding medical institutions in Africa to train the healthcare workforce and investing in infrastructure for laboratory HIV testing and viral load monitoring (Fauci & Eisinger, 2018). Others have also envisioned PEPFAR as the preferred program to bring the novel SCD treatment in SSA based on their extensive role in effectively responding to the HIV epidemic in Africa and their experience in brokering dramatic price reductions for antiretrovirals for low- and middle-income countries (Zhou & Travassos, 2022). A similar program can work with pharmaceutical companies to establish ultramodern SCD CRISPR treatment centers strategically across Africa driving down the price of the treatment and saving millions of lives. Additionally, other players such as the WHO and United Nations Children's Fund (UNICEF) could also play a major role by encouraging pharmaceutical companies to make more CRISPR lifesaving treatments available at reasonable prices in resource-limited settings.

3.3 | Strategies to increase accessibility of sickle cell CRISPR treatment in Africa

In Africa, bone marrow transplant or hematopoietic stem cell transplantation centers (HPSCT) are located in Nigeria, South Africa, Ghana (Mtenga et al., 2021), Uganda (Bone Marrow Transplant in Uganda | Find Cost & Reviews, 2023), Tanzania, Tunisia, Algeria, Egypt, and Morocco (Figure 1). HPSCT involves administering healthy hematopoietic stem cells to patients with SCD, aplastic anemia, and several other hematological malignancies (Khaddour et al., 2023). There is increasing demand for HSCT centers in low- and middle-income countries and established HSCT centers in Africa can work as entry points for CRISPR-based treatment for SCD. Through technology transfer, infrastructure improvement, and training, these centers can be upgraded to provide SCD CRISPR-based treatment services with plans to establish more centers.

Large-scale application of CRISPR-based treatment will demand a thorough understanding of the landscape of African SCD patients' genomes. African populations inherently have high genetic diversity and so the genomic architecture of SCD remains poorly understood, with only a few highly heritable traits associated with SCD having been identified. Phenotypic heterogeneity in the clinical expression of SCD is problematic for follow-up, management, and treatment of patients (Quinlan et al., 2014). A study on SCD patients in SSA identified several genes associated with disease severity and longevity (Wonkam et al., 2020). It should be noted that therapeutic advances in non-African populations may not easily be generalized to African populations due to the high genetic diversity. As CRISPR systems rely on Watson–Crick nucleotide base pairing to ultimately mediate genomic cleavage; genetic variations affect CRISPR targeting by increasing or decreasing sequence homology at on-target and off-target sites or by altering protospacer adjacent motifs (Canver et al., 2018). Human genetic variation has been shown to alter CRISPR-Cas9 on- and off-targeting specificity at therapeutically implicated loci (Lessard et al., 2017). A major aspect of attention is unintended mutations, caused by CRISPR-Cas9, at locations in the genome other than the targeted site. Such off-target mutations can have serious consequences as they might disrupt the function or regulation of non-targeted genes. In addition, larger structural changes in the genome sequence, occurring at the intended on-target editing site, are another cause of concern (Höijer et al., 2022). A study assessing the impact of ethnic origin on CRISPR/Cas off-target in the different ethnic groups concluded that the highest number of events was found in African-ancestry populations (Coe Torres et al., 2021).

Studies assessing CRISPR gene editing have revealed that it induces complex on-target outcomes in human cells including unwanted on-target mutations that occur after CRISPR-Cas9 cleavage that requires comprehensive assessment of on-target outcomes and safety concerns (Wen & Zhang, 2022). Hence, genome sequencing for off-target activity and structural variants using patient material is advisable in clinical applications to reduce the risk of unanticipated effects with potentially large

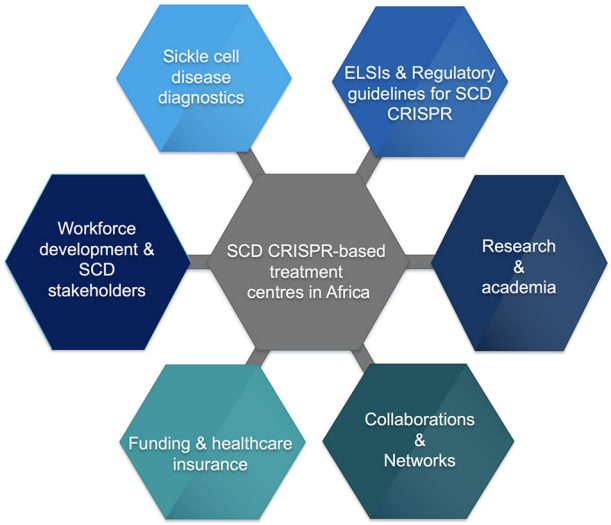

FIGURE 2 Essential requirements for the establishment of clustered regularly interspaced short palindromic repeat (CRISPR)-based treatment services.

implications as off-target mutations can have serious consequences as they might disrupt the function or regulation of non-targeted genes (Höijer et al., 2022). There will eventually be a great need to support SCD CRISPR treatment centers with expertise to generate evidence on the safety and efficacy of CRISPR-based treatment in genetically diverse populations. We believe that SCD can be eradicated through increased testing of the disease in populations at risk, SCD carrier screening programs, improved awareness, and SCD CRISPR-based treatment. These centers will require a substantial investment that will involve engagement and advocacy with several players including national governments through their health ministries, the WHO, HSCT centers, African Medicines Agency, pharmaceutical companies, specialized hospitals, academic and research communities, bioethics, SCD interest groups, local community leaders, philanthropies, funding agencies, and policy makers at different levels among others (Figure 2). To ensure that the treatment centers are self-sustaining, they will need to provide effective, safe, and affordable services.

With millions of individuals suffering from SCD and more children being born each day with SCD in Africa, the treatment centers will need to establish an ethically and scientifically sound approach to identify who to prioritize for SCD CRISPR-based treatment. Lessons can be learned from the early years of HIV/AIDS treatment with antiretroviral drugs, the WHO first provided guidelines that prioritized antiretroviral treatment for those in the late stage of HIV infection using patients' CD4 count. SCD is designated by the WHO and the United Nations General Assembly as a major global health burden, and therefore, it is imperative to promote equity in therapeutic approaches to cure SCD. These agencies could work with health organizations and networks such as the Sickle Cell Disease Genomics of Africa (SickleGenAfrica) Network within the Human Heredity and Health in Africa (H3Africa) (Anie et al., 2021) to promote access to affordable CRISPR-based SCD treatment in Africa.

Knowledge of genomic applications remains scanty even among healthcare professionals, and researchers in Africa. The promotion of SCD CRISPR-based therapy in Africa must address this challenge. It is also important to cultivate trust in gene editing services through transparent communication, making information accessible, relatable, and culturally relevant for all. More challenging is the fact that the African continent has the lowest literacy levels and over 2000 languages being spoken. There is a need to translate these complex terminologies and applications to reach wider audiences.

Because CRISPR therapies operate at the individual rather than population level, there is an urgent need to scale up population-level genome sequencing projects among diverse populations to understand the impact of human genetic variation on SCD. This is because there remains a lot of undiscovered genetic variation in diverse SCD-affected populations in Africa that may influence the success of the treatment. With some genome sequencing companies promising a human genome to be sequenced at $200 in the near future, one of the bold predictions of the NHGRI of having an individual's complete genome sequence along with informative annotations will, if desired, be securely and readily accessible on their smartphone. As seen elsewhere with emerging genomic technologies such as mRNA vaccines, campaigns to overcome CRISPR hesitancy, misinformation (e.g., CRISPR treatment causes infertility and human chimerism) as well as stigma, are anticipated to be triggered by SCD CRISPR-based treatment from anti-CRISPR groups. If not handled well may affect acceptance, therefore, stakeholders must be well prepared to address such complex expressions. Furthermore, quality assurance ensures that the therapy is free from any unintended DNA contamination of the patients' genetically modified stem cells and enables an auditable process in case of future legal challenges mounted by patients.

Guidance on prospective recipients of SCD CRISPR treatment, such as individuals with underlying comorbidities like Cancer and HIV or special groups like pregnant women, is essential. Programs must be established to study and monitor the long-term safety risks associated with SCD CRISPR-based treatment, classify or document treatment effectiveness, track severe adverse events, and address incidental results. Failure to address these aspects may undermine or impede the progress made in curing

SCD using this technology. Importantly, Ethical, Legal, and Societal Issues in CRISPR-based therapy for SCD are complex but can be effectively addressed through a comprehensive approach involving various stakeholders and SCD initiatives (Munung et al., 2023).

4 | CONCLUSION

Africa has the lowest life expectancy worldwide largely due to the high burden of both genetic and infectious diseases; however, genomic applications are changing mainstream medical and public health practices with a promise to cure several diseases. The dawn of SCD CRISPR-based cure presents hope for so many curative possibilities in both genetic and infectious diseases such as HIV. There is a need for urgent action to ensure that this technology is affordable and accessible where it is needed most and stands to save millions of lives. As PEPFAR transformed the management of the HIV/AIDS epidemic especially in Africa through increasing large-scale access to HIV ART, training the healthcare workforce, and equipping laboratories, we envision that the establishment of affordable SCD CRISPR-based treatment services and programs in Africa could save millions of people living with SCD on the continent, improve their livelihoods and quality of life.

AUTHOR CONTRIBUTIONS

Gerald Mboowa conceived the study and finalized the data extraction methodology. Ivan Sserwadda, Stephen Kanyerezi, Stephen Tukwasibwe, and Benson Kidenya examined the data and reviewed the article. All the authors read and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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