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Current Therapeutic Landscape of Sickle Cell Anaemia in Nigeria: Focus on Gene Therapy

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ABSTRACT

Sickle cell anaemia (SCA) represents the most prevalent inherited haemoglobinopathy globally, with Nigeria bearing the disproportionate burden of approximately 150,000 annual births, roughly half of all infants born with the disorder worldwide. Despite the transformative potential of recently approved gene therapies, the Nigerian therapeutic landscape remains characterised by substantial infrastructure deficits, economic barriers, and ethical complexities that limit access to curative interventions. This narrative review examines the current state of SCA management in Nigeria, from conventional disease-modifying therapies to emerging gene editing technologies, while critically evaluating the feasibility of implementing advanced genetic interventions within Africa's most populous nation. We draw upon published clinical trials, real-world implementation studies, and health systems research to delineate pragmatic pathways toward equitable access to curative therapies. Our synthesis indicates that while allogeneic haematopoietic stem cell transplantation (HSCT) offers established curative potential with 90% disease-free survival in paediatric cohorts, autologous gene therapy exemplified by CRISPR-Cas9-mediated BCL11A enhancer disruption (exagamglogene autotemcel; Casgevy) and lentiviral β-globin gene addition (lovotibeglogene autotemcel; Lyfgenia) represents a paradigm shift that eliminates graft-versus-host disease risk. However, the estimated $2–3 million per-patient cost, requirement for myeloablative busulfan conditioning, and absence of local manufacturing capacity render these therapies currently inaccessible to the Nigerian population. We propose a phased implementation framework prioritising health system strengthening, local biomanufacturing development, and ethical governance structures to bridge the gap between genomic innovation and clinical reality in low- and middle-income settings.

Keywords: Sickle Cell Disease, Gene Therapy, CRISPR-Cas9, Nigeria, Health Equity, Haematopoietic Stem Cell Transplantation, Foetal Haemoglobin, Hydroxyurea.

INTRODUCTION

The global distribution of sickle cell disease (SCD) reflects one of the most striking disparities in modern medicine: while the condition affects approximately 100,000 individuals in the United States, sub-Saharan

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Africa harbours over 75% of the global birth cohort, with Nigeria alone accounting for an estimated 150,000 infants born annually with the disorder [1]. This epidemiological reality positions Nigeria not merely as a beneficiary of therapeutic innovation but as the epicentre where the success of any global SCD strategy will ultimately be measured.

The pathophysiology of sickle cell anaemia SCA (HbSS genotype), the focus of this review, centres on a single nucleotide substitution in the β-globin gene (*HBB*; Glu6Val), resulting in the production of haemoglobin S (HbS). Under deoxygenated conditions, HbS polymerises into rigid fibres that distort erythrocytes into the characteristic sickle morphology, precipitating vaso-occlusion, chronic haemolysis, and a cascade of inflammatory and thrombotic sequelae [2]. While SCA (HbSS) represents the most severe and common form, the broader SCD category encompasses compound heterozygous states including HbSC disease and HbSβ-thalassaemia, which exhibit variable clinical severity [3]. This review focuses primarily on SCA (HbSS), though reference to broader SCD literature is made where interventions apply across genotypes.

Until recently, therapeutic options in Nigeria have been confined to supportive measures: analgesia for vaso-occlusive crises (VOC), blood transfusion for acute complications, hydroxyurea for disease modification, and penicillin prophylaxis against encapsulated organisms [4]. The 2023–2024 US Food and Drug Administration (FDA) approvals of two autologous gene therapies, Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) have introduced the prospect of functional cure, yet their translation to the Nigerian system faces formidable obstacles [5,6].

This review provides a comprehensive analysis of the therapeutic continuum for SCA in Nigeria, examining conventional management, established curative approaches, and the horizon of gene editing technologies. We critically evaluate health system readiness, economic barriers, and ethical frameworks necessary to ensure that genomic medicine does not exacerbate existing health inequities.

METHODOLOGY

This narrative review was conducted through systematic searches of PubMed/MEDLINE, Scopus, and African Journals Online (AJOL) for literature published between January 2015 and December 2025. Search terms included combinations of "sickle cell anaemia," "sickle cell disease," "Nigeria," "gene therapy," "CRISPR," "haematopoietic stem cell transplantation," "hydroxyurea," "stroke prevention," and "health systems." Additional sources were identified through citation tracking of retrieved articles and review of conference proceedings from the American Society of Haematology and European Haematology Association. Priority was given to peer-reviewed original research, systematic reviews, and guideline documents; conference abstracts were cited only where peer-reviewed publications were unavailable. Studies were selected for inclusion based on relevance to SCA therapeutics in Nigeria or comparable low-resource settings, with particular emphasis on implementation science and health systems research.

Epidemiology and Disease Burden in Nigeria

The burden of SCA in Nigeria exceeds that of any other nation. A recent systematic review and meta-analysis of 211,938 Nigerian children and adolescents documented a pooled SCD prevalence of 4.0% (95% CI 3.0–6.0%), with significant regional heterogeneity: the northwestern geopolitical zone exhibited the highest prevalence (7.0%), while the southeastern region showed the lowest (2.0%) [7]. The pooled sickle cell trait (SCT) carrier frequency reached 21.0% (95% CI 20.0–23.0%), indicating that approximately one in five Nigerians harbours the HbS allele [7].

These figures translate to extraordinary mortality. Using sibling survival analysis from nationally representative survey data, researchers estimated that Nigerian children with SCA experience under-5 mortality rates of 490 per 1,000 live births four-fold higher than unaffected siblings contributing approximately 35,000 excess under-5 deaths annually and representing 4.2% of national under-5 mortalities [8]. Such statistics underscore the urgency of implementing effective therapeutic strategies at scale.

The clinical heterogeneity of SCA in Nigeria reflects complex interactions between the HbS mutation and genetic modifiers. Genome-wide association studies in African populations have identified *BCL11A, HBS1L-MYB*, and *KLF1* as principal regulators of foetal haemoglobin (HbF) expression, with recent meta-analyses revealing novel candidate loci including *FLT1* and *OPCML* in Cameroonian and Tanzanian cohorts [9]. In Nigerian populations specifically, Ojewunmi and colleagues demonstrated that genetic variants influencing HbF persistence significantly modify disease severity, with implications for stratified therapeutic approaches [9].

The high frequency of α-thalassaemia trait in Nigerian SCA patients further complicates phenotype prediction, as co-inheritance of α-globin deletions reduces mean corpuscular volume and may paradoxically ameliorate certain complications while exacerbating others [4]. Understanding these modifier effects becomes critical when selecting candidates for intensive therapies such as gene editing or transplantation.

Conventional Therapeutic Strategies

Hydroxyurea remains the most widely available disease-modifying therapy in Nigeria, functioning through multiple mechanisms including HbF induction, reduction of circulating leukocytes, and augmentation of nitric oxide bioavailability [10,11]. Despite WHO endorsement and extensive evidence from the BABY HUG and REACH trials, utilisation in Nigeria remains suboptimal due to cost constraints, fears of oncogenicity, and requirements for regular haematological monitoring that exceed local laboratory capacity [4,10].

Innovative implementation strategies have emerged to address these barriers. A prospective cohort study at Nnamdi Azikiwe University Teaching Hospital evaluated a simplified fixed-dose hydroxyurea regimen (20 mg/kg/day, capped at 500 mg) without routine laboratory monitoring in 100 paediatric patients [10]. Over 24 months, the regimen achieved 84.2% adherence and reduced emergency department visits for VOC to 1% of the cohort, demonstrating that pragmatic dosing protocols can overcome infrastructure limitations [10]. Notably, younger children exhibited superior adherence compared with adolescents (mean age 8.5 vs. 11.6 years; p=0.027), highlighting the need for age-specific adherence interventions [10].

The SPIN (Stroke Prevention in Nigeria) trial further established hydroxyurea's efficacy for primary stroke prevention in resource-limited settings. In children with elevated transcranial Doppler (TCD) velocities (≥200 cm/sec), moderate fixed-dose hydroxyurea (20 mg/kg/day) normalised TCD measurements in 80% of participants within three months a response rate exceeding that observed in the landmark STOP trial [12,13]. These findings have been extended in the ongoing SPRING trial, which randomises children to moderate versus low fixed-dose hydroxyurea for stroke prevention [13].

Chronic transfusion programmes for primary stroke prevention and secondary prevention of recurrent cerebrovascular events remain largely unavailable in Nigeria. The SPIN trial investigators documented that regular transfusion therapy was not feasible at Aminu Kano Teaching Hospital due to inadequate safe blood supply, cost, and caregiver reluctance [12]. This reality contrasts sharply with high-income countries where transfusion-dependent protocols form the backbone of stroke prevention.

When transfusions are administered, risks include alloimmunisation, iron overload, and transfusion-transmitted infections. Studies from Nigerian tertiary centres document HIV and hepatitis C transmission through unscreened blood products, while red cell alloimmunisation complicates subsequent transfusions in multi-transfused patients [2]. The absence of comprehensive transfusion registries impedes longitudinal tracking of iron burden; though emerging data suggest that hepatic iron overload develops rapidly in Nigerian children receiving intermittent transfusions without chelation [4].

The implementation of universal newborn screening (NBS) for SCD represents a critical unmet need in Nigeria. The Sickle Cell Support Society of Nigeria has advocated for mandatory NBS, citing evidence that early diagnosis coupled with penicillin prophylaxis and pneumococcal vaccination reduces childhood mortality by up to 70% [7]. However, coverage remains fragmented, with most diagnoses occurring only after the onset of symptomatic disease.

Pilot programmes in selected Nigerian institutions demonstrate feasibility. At the University College Hospital, Ibadan, point-of-care screening using dried blood spots achieved 94% sensitivity and 98% specificity for SCD detection, with results available within 72 hours [7]. Scale-up requires integration with existing immunisation programmes and community health worker networks, alongside educational initiatives to address stigma and misconceptions surrounding genetic disorders [4].

The management of acute complications in Nigerian SCA patients relies heavily on opioid analgesia for VOC, supplemented by oxygen therapy, hydration, and incentive spirometry for acute chest syndrome [4]. The opioid epidemic in North America has prompted cautious prescribing patterns globally, yet Nigerian patients frequently encounter inadequate pain control due to restricted access to morphine and pethidine at primary care facilities [4].

Pulmonary hypertension (PH) has emerged as a prevalent and under-recognised complication. Echocardiographic studies from Lagos and Kano document PH in 6–30% of SCA patients, with tricuspid regurgitant jet velocity ≥2.5 m/s serving as a surrogate marker [4]. The absence of right heart catheterisation facilities limits definitive diagnosis, while targeted therapies (sildenafil, bosentan) remain financially inaccessible for most Nigerian patients.

Curative Therapies: Allogeneic Haematopoietic Stem Cell Transplantation

Allogeneic HSCT from HLA-matched sibling donors remains the only established curative therapy for SCA, with disease-free survival exceeding 90% in paediatric recipients and stable engraftment documented beyond 15 years post-transplantation [14,15]. The European Society for Blood and Marrow Transplantation registry reports thalassaemia-free survival rates of 83% in children transplanted before age 14 years, with outcomes deteriorating significantly for adult recipients (overall survival ~80%, thalassaemia-free survival ~76%) [14].

In Nigeria, HSCT availability is severely constrained. The Benioff Children's Hospital at the University of California, San Francisco, has established partnerships with Nigerian institutions to facilitate transplantation for selected patients, though fewer than 50 Nigerian children have undergone HSCT internationally over the past decade [2]. Domestic transplantation programmes face challenges including inadequate conditioning regimen expertise, limited cryopreservation facilities, and insufficient donor registries for unrelated donor searches.

Given that only 15–20% of SCA patients have HLA-matched siblings, alternative donor approaches have gained traction. Haploidentical HSCT using TCRαβ+/CD19+-depleted grafts has demonstrated promising results in haemoglobinopathies, with reduced graft-versus-host disease (GVHD) risk and comparable survival to matched sibling transplants in experienced centres [16,17]. Unrelated donor transplantation with partial T-cell depletion has also shown safety and efficacy in paediatric SCA patients with ≥9/10 HLA-matched donors [18].

These advances hold particular relevance for Nigeria, where extended family structures increase the probability of identifying haploidentical donors. However, the sophisticated graft engineering required for T-cell depletion exceeds current domestic capabilities, necessitating international sample shipment and collaboration.

GENE THERAPY: MECHANISMS AND CLINICAL EVIDENCE

The approval of Casgevy and Lyfgenia in 2023–2024 represents a watershed moment in SCA therapeutics, introducing autologous strategies that circumvent the donor availability constraints of allogeneic HSCT while eliminating GVHD risk [5,6]. Both therapies require myeloablative busulfan conditioning and involve complex manufacturing processes, yet they offer the prospect of single-administration functional cure.

Exagamglogene autotemcel (Casgevy; CRISPR Therapeutics/Vertex Pharmaceuticals) employs CRISPR-Cas9 ribonucleoprotein complexes to disrupt the erythroid-specific enhancer of *BCL11A* in autologous CD34+ haematopoietic stem and progenitor cells (HSPCs) [5,19]. *BCL11A* functions as the principal transcriptional repressor of γ-globin gene expression; its downregulation reactivates fetal haemoglobin (HbF) production, compensating for defective adult haemoglobin in SCA [20,21]. Preclinical studies in humanised mouse models demonstrated that *BCL11A* knockdown ameliorates sickle cell disease phenotypes through robust HbF reactivation [22].

Lovotibeglogene autotemcel (Lyfgenia; bluebird bio) utilises a lentiviral vector (LentiGlobin BB305) to introduce a modified β-globin gene (β^A-T87Q^) encoding anti-sickling haemoglobin [6,23]. The T87Q amino acid substitution enhances the solubility of deoxygenated haemoglobin, reducing polymerisation propensity. This gene addition approach directly addresses the underlying HbS defect rather than compensating through HbF induction.

Table 1. Comparative characteristics of approved gene therapies for sickle cell disease

Characteristic	Casgevy (Exagamglogene autotemcel)	Lyfgenia (Lovotibeglogene autotemcel)
Manufacturer	CRISPR Therapeutics/Vertex Pharmaceuticals	bluebird bio
Mechanism of action	CRISPR-Cas9 gene editing targeting *BCL11A* erythroid enhancer	Lentiviral β-globin gene addition β^A-T87Q^
Therapeutic approach	Gene editing (HbF induction)	Gene addition (anti-sickling haemoglobin)
FDA approval	December 2023	December 2023
Age eligibility	≥12 years	≥12 years
Key trials	CLIMB SCD-121; CLIMB THAL-111	HGB-206; HGB-210; HGB-212
Primary efficacy	68.2% VOC-free ≥12 months	88% VOC resolution ≥12 months
Haemoglobin levels	HbF: 40–50%	Anti-sickling Hb: 30–40%
Neutrophil engraftment	Median 29 days (12–56)	Median 23–26 days
Platelet engraftment	Median 44 days (20–200)	Median 46–49.5 days
Malignancy risk	No reported cases; theoretical risk	AML (n=2), MDS (n=1); black box warning
Post-marketing surveillance	15 years	15 years
Estimated cost	~$2.2 million	~$3.1 million

Manufacturing time	4–6 months	4–6 months
Conditioning	Myeloablative busulfan	Myeloablative busulfan
Fertility considerations	Preservation recommended	Preservation recommended
Suitability (Nigeria)	Limited (cost, infrastructure)	Limited (cost, safety concerns)

Note: *Efficacy and safety data presented derive from separate clinical trials (CLIMB SCD-121 for Casgevy; HGB-206/HGB-210 for Lyfgenia) conducted in different patient populations and trial contexts. These data should not be interpreted as direct head-to-head comparative evidence.*

The CLIMB SCD-121 and CLIMB THAL-111 trials established the efficacy of Casgevy in transfusion-dependent β-thalassaemia and SCA, respectively [5,19]. In 44 evaluable SCA patients, 30 (68.2%) achieved the primary endpoint of freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period [5]. All 44 patients engrafted successfully, with median neutrophil recovery at 29 days (range 12–56) and platelet recovery at 44 days (range 20–200) [1]. Notably, HbF levels stabilised at 40–50% of total haemoglobin, with pancellular distribution evident on peripheral blood smears [5].

Long-term follow-up from the CLIMB-131 extension study (median 32.4 months, range 14.3–60.8) confirmed durable transfusion independence in 94.2% of β-thalassaemia patients and sustained VOC prevention in SCA cohorts [5]. No cases of malignancy or clonal expansion attributable to off-target CRISPR editing were observed, though the theoretical risk necessitates 15-year post-marketing surveillance [5,24].

Lyfgenia's efficacy was established through the HGB-206 and HGB-210 trials, with 28 of 32 (88%) evaluable patients achieving complete resolution of severe VOCs for at least 12 months [6]. The HGB-212 study in severe β-thalassaemia genotypes demonstrated 89% transfusion independence at median 48-month follow-up [25]. However, the HGB-206 trial reported two cases of acute myeloid leukaemia (AML) and one case of myelodysplastic syndrome (MDS) among 50 treated patients, prompting FDA-mandated warnings regarding insertional oncogenesis risk with lentiviral vectors [6,26].

The transition from clinical trials to clinical practice has revealed substantial logistical barriers. A real-world cohort of eight German patients with non-β^0^/β^0^ β-thalassaemia treated with betibeglogene autotemcel (the predecessor to Lyfgenia) demonstrated 100% transfusion independence at median 541 days follow-up, yet required 4–7 days of apheresis, 4–6 months of manufacturing time, and 6–7 weeks of hospitalisation for conditioning and engraftment [27]. Quality of life improvements were mixed, with one patient developing fatigue syndrome and another experiencing depression and panic attacks adverse events rarely captured in trial settings [27].

The manufacturing process for both therapies involve centralised facilities in the United States and Europe, with cells shipped internationally for modification, cryopreservation, and return [2,1]. This "hub-and-spoke" model imposes geographic constraints that effectively exclude Nigerian patients without substantial philanthropic or governmental subsidy.

Barriers to Gene Therapy Implementation in Nigeria

The estimated cost of gene therapy $2.2 million for Casgevy and $3.1 million for Lyfgenia exceeds Nigeria's annual health expenditure per capita by several orders of magnitude [28]. Even with manufacturer discounts or outcomes-based payment models, the absolute cost renders widespread access implausible without structural health financing reform [29].

Infrastructure deficits compound economic barriers. Myeloablative busulfan conditioning requires precise pharmacokinetic monitoring and therapeutic drug level management to prevent fatal toxicity or graft failure capabilities available only at Nigeria's premier tertiary institutions [2]. The 4–6-week hospitalisation for engraftment necessitates protected environment units with high-efficiency particulate air (HEPA) filtration, which are scarce outside Lagos and Abuja [2].

Current gene therapy manufacturing relies on Good Manufacturing Practice (GMP)-compliant facilities for lentiviral vector production or CRISPR ribonucleoprotein assembly, with capacity concentrated in North America and Europe [28]. The African continent lacks any operational GMP gene therapy manufacturing facility, necessitating international cell shipment with associated cold chain risks, regulatory delays, and substantial logistics costs [28].

Emerging initiatives aim to address this gap. The Global Gene Therapy Initiative (Ggti) has prioritised technology transfer to low- and middle-income countries, with preliminary discussions regarding lentiviral vector production in South Africa and Egypt [28]. However, Nigeria's biopharmaceutical ecosystem remains nascent, with limited capacity for even basic vaccine fill-finish operations.

The introduction of high-cost curative therapies in resource-constrained settings raises profound ethical questions. Discrete choice experiments in SCD populations reveal that patient willingness to pursue gene therapy varies inversely with perceived treatment-related mortality risk, with Nigerian patients potentially exhibiting greater risk aversion given the relative stability of chronic transfusion regimens [30,31].

Informed consent processes must navigate complex family dynamics and community decision-making structures distinct from Western individualistic frameworks. The requirement for fertility preservation counselling prior to gonadotoxic busulfan conditioning encounters cultural sensitivities regarding infertility, particularly in patriarchal contexts where childbearing carries significant social value [32,33]. Ovarian tissue cryopreservation remains experimental with unproven efficacy for future pregnancy, while sperm banking requires facilities that are virtually non-existent in Nigeria [33].

Long-term follow-up obligations 15 years for both approved therapies challenge existing clinical trial infrastructure and raise questions about sustainability of post-marketing surveillance when patients may relocate or disengage from healthcare systems [26].

FUTURE DIRECTIONS

Immediate priorities for Nigerian SCA care should focus on expanding access to established interventions rather than premature gene therapy introduction. The SPIN trial model demonstrating that fixed-dose hydroxyurea without intensive monitoring achieves stroke prevention comparable to high-resource protocols should be scaled nationally through task-shifting to community health workers [12,13]. Integration of TCD screening with routine immunisation visits could identify high-risk children for hydroxyurea initiation, creating a sustainable prevention infrastructure.

Blood transfusion safety requires urgent attention. Implementation of nucleic acid testing (NAT) for HIV and hepatitis C, alongside extended red cell phenotyping to reduce alloimmunisation, would reduce transfusion-related morbidity even without capacity for chronic transfusion programmes [2].

Nigerian research institutions must prioritise studies defining local disease modifiers and pharmacogenomic predictors of hydroxyurea response. The genetic diversity of African SCA populations encompassing *BCL11A, HBS1L-MYB*, and novel loci such as *KLF1* may influence gene therapy efficacy, as *BCL11A* enhancer editing relies on residual γ-globin gene capacity that varies across ethnic groups [9,20].

Clinical trial participation should be aggressively pursued. The ongoing CLIMB-151 paediatric trial of Casgevy (ages 2–11) and bluebird bio's studies in younger Lyfgenia cohorts offer opportunities for Nigerian site inclusion, provided ethical review boards and regulatory frameworks align with international standards [5]. Such participation would build local gene therapy expertise while ensuring that efficacy data reflect African genetic diversity.

Long-term strategies must address biomanufacturing capacity. The African Union's Pharmaceutical Manufacturing Plan for Africa (PMPA) provides a policy framework for local production, though gene therapy-specific GMP facilities require substantial investment and technical assistance [28]. Public-private partnerships with emerging manufacturers in South Africa, India, or Brazil may offer intermediate solutions for vector production while Nigerian capacity develops.

In vivo gene therapy approaches delivering CRISPR components directly to haematopoietic stem cells without ex vivo manipulation represent a potential paradigm shift that could eliminate the need for apheresis and centralised manufacturing [34]. Preclinical studies demonstrate feasibility in murine models, with human trials anticipated within 5–7 years. Such technologies may prove more adaptable to low-resource settings by circumventing the complex logistics of current autologous therapies. If proven safe and effective, such technologies may prove more adaptable to low-resource settings by circumventing the complex logistics of current autologous therapies, though this remains speculative at present.

Innovative payment models must be explored. Outcomes-based agreements, where manufacturers provide rebates for treatment failure, may align incentives but do not address absolute cost barriers [29]. Subscription models ("Netflix for gene therapy"), where health systems pay annual fees for unlimited treatment access, have been proposed for antibiotics and may be adapted for SCA therapies if pooled procurement across African Union member states achieves sufficient scale, though empirical evidence for this approach in gene therapy is currently lacking.

Philanthropic and development assistance will prove critical in the near term. The Bill & Melinda Gates Foundation's recent investments in SCA gene therapy manufacturing for Africa, while focused primarily on sickle cell trait carrier screening and hydroxyurea access, may expand to include curative therapy subsidies if cost-effectiveness thresholds are achieved [28]. However, the sustainability of such models beyond initial pilot phases remains uncertain.

CONCLUSION

The therapeutic landscape for sickle cell anaemia in Nigeria stands at an inflection point. While gene therapies offer unprecedented promise for functional cure, the immediate imperative remains strengthening foundational care: newborn screening, hydroxyurea access, transfusion safety, and complication management. The disparity between genomic innovation and health system reality in Nigeria reflects broader global inequities in access to advanced therapeutics.

The path forward requires pragmatic incrementalism rather than technological determinism. Allogeneic HSCT from haploidentical donors offers near-term curative potential that could be scaled with modest infrastructure investment and international technical assistance. Autologous gene therapy, while transformative, demands manufacturing capacity and health system capabilities that will require decade-long development.

Ultimately, the measure of success for SCA therapeutics in Nigeria will not be the number of patients receiving Casgevy or Lyfgenia, but the reduction in under-5 mortalities, the prevention of strokes in children who would otherwise suffer permanent disability, and the empowerment of patients to lead productive lives unhindered by chronic disease. Gene therapy must serve these ends not as an exclusive luxury for the privileged few, but as a catalyst for health system transformation that benefits the entire SCA population.

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