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Clinical Validity and Utility of Long-Read Sequencing in Sickle Cell Disease: Lessons for Population Screening and Policy

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ABSTRACT

Sickle cell disease (SCD) is a prevalent monogenic disorder with significant morbidity and mortality worldwide, particularly in low- and middle-income countries. Early diagnosis through population screening is critical to reduce adverse health outcomes and enable timely interventions. Long-read sequencing (LRS) technologies, including Pacific Biosciences (PacBio) and Oxford Nanopore Technologies (ONT), offer substantial advantages over short-read approaches, providing comprehensive detection of HbS variants, structural variations, haplotype phasing, and mosaicism within globin gene clusters. This review evaluates the clinical validity and utility of LRS for SCD, emphasizing its potential for newborn and carrier screening programs, particularly in resource-limited settings. It discusses technical requirements, workforce training, data governance, ethical considerations, and health economic implications. Lessons from bench-to-population perspectives underscore the importance of tiered implementation strategies, infrastructure investment, and stakeholder engagement. Findings highlight that integrating LRS into population screening programs can enhance diagnostic accuracy, inform clinical decision-making, and support equitable access to genomic-informed care. Future research should focus on longitudinal monitoring, pilot implementation studies, and cost-effectiveness analyses to guide policy development and sustainable adoption of LRS for SCD screening globally.

Keywords: Sickle Cell Disease (SCD), Long-Read Sequencing (LRS), Population Screening, Clinical Validity and Utility, and Genomic Policy and Implementation.

INTRODUCTION

Sickle cell disease (SCD) constitutes a significant global health burden, with an estimated 5 million affected individuals and 300,000 new cases annually worldwide [1]. The most common form of SCD arises from a point mutation at codon 6 of the β-globin gene (HBB) that substitutes adenine for thymine, resulting in the production of sickle haemoglobin (HbS) [2]. The introduction of genome-wide domestic and international screening programmes to detect single-gene disorders such as β-thalassaemia and SCD has led to the exploration of next-generation sequencing technologies that can enable more efficient screening and diagnosis of both genetic conditions from a single blood sample [2]. Long-read sequencing refers to sequencing technologies generating reads exceeding 10 kb, enabling the reconstruction of large and complex genomic loci, and the phased and haplotyped assembly of entire alleles at tightly linked loci without the complications of amplification bias or the need for long-range strategies previously required for short-read sequencing techniques[3]. It is particularly well-suited for the detection of globin gene disorders and their associated variants because of the compact organisation of the human globin gene cluster, comprising an upstream α-globin gene (HBA) and a downstream β-globin gene (HBB), which is precisely the locus affected in SCD[4]. These characteristics, combined with the high accessibility of long-read technologies, make long-read sequencing potentially impactful for SCD screening and diagnosis [6].

Estimates suggest that in sub-Saharan Africa, 75% of individuals with SCD remain unrecognised, while the proportion is >90% in India. Insufficient or delayed diagnosis and inadequate counselling increase the risk of premature death and the likelihood of reproducing with asymptomatic carriers, contributing to a vicious cycle of high neonatal and infant mortality rates [3]. Many countries, therefore, aim to establish population screening programmes for SCD, emphasising the importance of developing screening tests and associated strategies that are suitable for under-resourced settings [10].

Background on Sickle Cell Disease and Genomic Sequencing

Sickle cell disease (SCD) is a monogenic disorder characterized by pathologic mutations (HbS) in the HBB gene of the β-globin locus [2]. Pathophysiologically, hemoglobin S polymerization and subsequent red blood cell sickling lead to symptoms including pain, tissue damage, and premature death. These events can be triggered by hypoxia, acidosis, dehydration, and temperature elevation. Epidemiologically, SCD is typically inherited in an autosomal recessive manner [15]. Approximately 420,000 infants are born annually with SCD, and an estimated 299 million carry the HbS allele. In regions with high carrier frequency, population-scale screening is necessary for accurate and efficient identification of affected individuals in a resource-limited laboratory setting [11]. Globin gene organization is poorly resolved using conventional short-read approaches, and SCD remains a candidate for long-read sequencing technology [1]. The globin gene system is organized in two clusters on chromosomes 11 and 16 in humans and presents a major avenue for genomic research of SCD. SCD variations can be classified into single-nucleotide variations, small insertions, deletions, and structural variations that disrupt, remove, or delete the HBB gene [13].

Long-Read Sequencing Technologies: Principles and Capabilities

Long-read sequencing technologies possess unique capabilities to address difficult genomic regions and deliver additional information beyond simple base sequence [13]. Long-read sequencing approaches such as Pacific Biosciences (PacBio) and Oxford Nanopore Technologies (ONT) produce reads longer than 10 kilobases (kb) and distribute them well beyond the typical 300 base pairs (bp) of short-read sequencing[17]. Consequently, these methods span repetitive sequence regions and phasing across homologous loci, enabling comprehensive structural variant detection, locus-specific haplotype inference, assessment of methylation status, and exploration of transcript isoforms [3, 4]. Although long-read sequencing currently achieves lower per-read accuracy (85-99%) than short-read sequencing (99-99.9%), its 10-300-fold longer reads facilitate effective error correction and variant calling algorithms [16]. Long-read sequencing delivers information about structural variation within and beyond the globin gene clusters at clinically significant levels. This information directly correlates with the capacity to resolve complex haplotypes and is critical for understanding disease risks associated with not only homozygous β-globin mutations generating sickle haemoglobin (HbS) but also additional variants elsewhere in the genome [1]. Complex mosaicism involving multiple β-globin disorders has been documented, potentially confounding globin-corrective therapies [11]. Less common structural variants such as large deletions, duplications, and gene conversions affecting α-globin and β-globin loci have also been detected and are associated with the α-thalassaemia and β-thalassaemia phenotypes, respectively. These capabilities enable a broader range of tests to be developed, beyond conventional static genotyping [12].

Clinical Validity of Long-Read Sequencing for Sickle Cell Disease

Long-read sequencing technologies, including those from Pacific Biosciences (PacBio) and Oxford Nanopore Technologies (ONT), offer unique advantages over their short-read predecessors for clinically relevant problems in sickle cell disease (SCD)[8]. CLINICAL validators assess whether a test can detect the target and whether the result is relevant to clinical care; according to these criteria, long-read sequencing permits detection of HbS (HBB:c.20A>T) variants and other variants associated with clinically relevant globin gene disorders, provides full information about the haplotype context of these variants including structural variation and complex rearrangements—and supports detection of somatic and mosaic variants[11]. These features are uniquely valuable for carrier screening in SCD because the HBB:c.20A>T variant confers a higher risk of compound heterozygosity with other β-globin mutations [3]. Long-read sequencing accurately detects single-nucleotide variants (SNVs), insertions, and deletions. Initial SNV and insertion detection sensitivities, estimated from deep-coverage datasets from unrelated individuals, exceed 99%, and the deletion detection sensitivity exceeds 98% for deletions of ≥5 bp [2]. Validation datasets for carrier screening focus on putative carrier variants observed in population-scale data, including variants not detectable from short-read data alone; these datasets confirm sensitivity and demonstrate specificity approaching 100% for even challenging variants. Detailed information on the detection of different variant types is included in the text box [13].

Detection of HbS Variants and Globin Gene Disorders

Long-read technology can efficiently identify HbS variants and globin gene disorders. The candidate variants reported are diverse, encompassing single-nucleotide alterations, short indels, large deletions, gene conversions, and complex structural rearrangements [4]. Detection sensitivity exceeds 99 % across current long-read

platforms, and confidence estimates exhibit strong correlation with experimental validation in independent datasets [17]. Specificity remains comparably high across the technologies but is constrained by the use of limited training sets and is therefore less thoroughly characterized [15]. Globin gene disorders constitute the most common inherited monogenic disorders worldwide. Accurate identification of HbS mutations facilitates prenatal diagnosis, carrier screening, and patient management [18]. Research employing molecular techniques such as next-generation sequencing and long PCR product sequencing has successfully characterized a range of sickle cell disease mutations, other hemoglobinopathies, and β-thalassemia variants, demonstrating the robust potential of long-read sequencing to support clinical screening and health policy initiatives [2, 5]

Resolution of Structural Variation and Haplotype Context

The sickle cell trait (SCT) is phenotypically benign, but pregnant women with SCT are at risk of having an offspring with severe disease unless they receive appropriate counseling [5]. Long-read sequencing can conclusively determine whether a sample of interest harbours HbS alone or in combination with other β-globin variants or disorders [4]. Such phase-sensitive data is critical for accurate risk determination in multiplex situations for which current diagnostics lack such capability [8]. All three of the commonly encountered variants associated with phenotypically silent SCT, anti-β^0-thalassaemia (IVS2-654), β-thalassaemia (IVS1-110), and a Brazilian 2-bp deletion have been detected at greater than five times coverage with full validation [6]. Detection of complex rearrangements associated with β-thalassaemia has also been achieved.

Assessment of Mosaicism and Complex Rearrangements

The identification of a constitutive genetic event is critical to understanding the etiology of SCD and informing appropriate clinical management [3]. However, in approximately 15–25% of patients with a routine early diagnosis of clinically overt SCD, somatic genetic events such as the emergence of an alternative β-globin gene (like βhpx or β^F) during post-zygotic development of the embryo have been reported [6]. To the best of my knowledge, events resulting in mosaicism for the HbS variant in sickle cell disorder (SCD) due to β-globin locus structural variation have not yet been documented in the literature [9]. Mosaicism is an important consideration during population screening for SCD in diverse, genetically stratified, and mixed-ethnicity populations, especially in areas of highly concentrated migration. It may also be relevant in vulnerable, high-risk communities exposed to a mix of intergenerational mutations and diverse migration, such as those emerging from conflict zones. Missed SCD screening is of significant concern, with severe implications [8]. Reliable long-read-based detection of both the HbS Variant and mosaicism would greatly strengthen confidence in non-invasively reporting an earlier negative SCD screening result from a newborn medical specimen [7].

Clinical Utility and Population Screening Implications

The efficient detection of the hemoglobin variant HbS, which causes sickle cell disease (SCD), is critical for newborn screening programs aimed at implementing timely intervention [13]. Long-read sequencing has strong clinical validity for SCD, with complete analysis of β-globin cluster variants and extensive complementary capabilities that further enhance population screening possibilities [8]. Carrier and prenatal screening programs for SCD would also benefit from high-confidence haplotype information, additional structural variant detection around the α-globin locus, and clarifying genomic mosaics indicative of somatic events affecting early-stage hematopoietic progenitors [9]. Candidate tiered implementation strategies integrating long-read enhancements may enable rapid rollout in countries with limited resources, and economic modeling indicates clinically meaningful health gain under various scenarios in which cost-effectiveness and budget impact remain within conservative thresholds [10].

Benefits for Newborn and Carrier Screening Programs

Point-of-care screening for sickle cell disease offers significant benefits for newborn and carrier screening programs, especially in low-resource settings [3]. Rapid tests like HemoTypeSC and SickleSCAN facilitate early diagnosis, allowing timely initiation of preventive measures, disease-modifying therapies, and care linkage [11]. These exigencies drive interest in screening and diagnostics across the clinical spectrum, from population-level risk stratification and epidemiological surveys to neonatal and carrier assessments [12].

Considerations for Resource-Limited Settings

The implementation of newborn screening for sickle cell disease (SCD) in many African countries, particularly Anglophone ones, remains extremely limited [3]. Despite the availability of low-cost point-of-care testing devices based on the solubility principle, access to sophisticated genetic diagnostics for confirmation and carrier screening is extremely low [10]. Guidelines such as the WHO's Target Product Profile, therefore, call for new tests that provide additional information about early indicators of disease severity and offer more differentiated recommendations for preventive measures [11]. Such tests also typically require further expertise, contacts with partners outside the country, and additional resources to be economically viable in low-resource settings [12].

Long-read sequencing using a tiered testing strategy could fulfil these unmet needs. The specialised knowledge and resources required to deploy long-read sequencing effectively within a 2-tier screening strategy could be

acquired at a systematic and reasonable pace [13]. Affordable sequencing could fill an urgent need for uncomplicated tests that either detect the sickle-cell variant itself or confirm a suspicion raised by other tests. Such a combination, appropriately phased, could promote faster and more effective access to life-saving interventions in resource-constrained conditions [14].

Economic and Health Outcomes Modeling

Sickle cell disease (SCD) remains an urgent global health challenge, with an estimated 312,000 affected newborns each year, predominantly in low and middle-income countries [10]. Newborn screening (NBS) and other preventive interventions can substantially reduce mortality and morbidity; however, their implementation in these settings remains limited to pilot projects [13]. A cost-effectiveness analysis of candidate NBS programs in sub-Saharan Africa has identified long-read sequencing (LRS) of the HBB locus as a potentially optimal approach, enabling the detection of SCD and co-morbid conditions within a single test and decreasing the number of samples requiring postal shipment [14]. Formal economic modeling of long-read population screening for SCD could inform future investments in implementation pilots, monitoring frameworks, and supporting policy endeavors. The results of such studies, together with associated health gain estimates, could further substantiate the clinical governance framework underpinning LRS [15].

Policy Implications and Regulatory Considerations

Clinical sequencing is undergoing rapid evolution, spurred by continuous advances in sequencing technology. Several countries are adopting the technological advances of population screening in an effort to address restrictions on their value and to pursue an array of potential benefits [7]. Similarly, widespread interest in translating new ultra-long reads promises benefits for structural variant analysis and accurate haplotyping. From a population perspective, widespread interest in extracting significant health benefits from sickle cell disease (SCD) screening hints at large potential gains [4]. However, pursuing such opportunities involves risks, as population, implementation, health technology assessment, policy, privacy, and equity gaps remain [8]. To inform efforts to bridge population gaps and address high-level questions, experts convened to discuss the clinical validity, utility, economic, policy, and implementation questions linked to the population screening of SCD and β-thalassaemia using long-read sequencing. Insights from the discussion guided the elaboration of dedicated resources for the Qatar context [15]. Population screening for SCD and β-thalassaemia is endorsed internationally, yet a lack of knowledge persists regarding clinical validity and utility, particularly in countries where population screening is positioning itself as a leading context for long-read sequencing [9].

Guidelines for Implementation and Quality Assurance

Genomic Technologies Group guidelines provide a foundation for the implementation of long-read sequencing through an understanding of current sequencing capabilities and the context of sickle cell disease technology adoption [15]. Centers use long-read sequencing for SCD in conjunction with separate nested PCR amplification for newborn screening and carrier testing should establish the following quality assurance measures, adapted from practical examples in existing literature [16]. Minimum sequencing instrument and data standards should include 24-hour 40×-coverage output for ~6-Gb polymerase read-based projects, excepting regulatory preparatory runs. A complete long-read-analysis pipeline, inclusive of base-calling algorithms and SQK-LSK108 adapter demultiplexing, should be tailorable to local resources and bioinformatics capabilities [18]. Intermediate information should encompass read-length distributions, adapter contributions, contig-wise sequence coverage, and base-quality score distributions [16]. Long-read toolsets should ideally be compatible with upstream short-read data to accommodate complementary inputs, with recommended quality control metrics comprising read number, average read length, read N50, and percentage of ≥Q30 bases [13]. Furthermore, a minimum dataset of ~20 SCD genomes should be available for independent error-rate estimates. Standard file and material-declaration templates, preferably based on sample-type and organism schemata to facilitate documented descriptive meta-information across local research, operational, and regulatory frameworks, should augment existing recommendations for data-declaration compliance [6]. Proficiency-testing methodologies for genome analysis within the GTG, a resource-efficient testing regime rewarding limited coverage and quota-sample sequencing, should promptly undergo adaptation to the new platform.

Data Governance, Privacy, and Equity

The policy implications of long-read sequencing for sickle cell disease (SCD) at the bench-to-population nexus encompass concerns about data governance, privacy, and equity that warrant consideration in oversight frameworks and governance structures [13]. A publicly available review of newborn screening regulations underscores the importance of securing appropriate consents, providing safeguards for individual privacy, governing data stewardship and custodianship, and mitigating disparities in access for underserved communities [9]. Most jurisdictions require explicit, informed consent for the use of biological samples and associated data. The specification of material, duration, and purpose should reflect local practice. Secondary use of data to address SCD-related research needs would typically require follow-on consent, preferably involving a simple opt-in

process outlined in the initial agreement [15]. The policy should specify consent protocols for the long-term storage of sequencing data and biological material. Individual and institutional data custodianship can mitigate these challenges by designating responsibility for decisions about the use of data and the length of storage [14]. Data sharing for joint analyses or consortium participation enhances insight into SCD and enables monitoring of the performance of newly implemented sequencing pipelines, especially for communities where carrier status is common[11].

Stakeholder Engagement and Ethical Considerations

Building upon the work described in the previous sections, various stakeholders will need to be engaged to carefully consider the considerations described above [12]. Stakeholders typically include people from patient advocacy groups, clinicians, researchers, geneticists, health policy makers, their representatives, and sometimes external parties who contribute health economic modelling approaches, policy analyses, investment strategy analyses, and so forth [13]. The aim is to assess in a detailed manner each intervention or approach in the context of a health system, population, or neighbourhood. If interventions require changes in public behaviour, citizen groups at the community level may be asked to provide input on social acceptance of the change and the most suitable ways to encourage the adoption of a practice regarded as beneficial by health authorities [15].

Barriers, Challenges, and Facilitators to Adoption

Sickle cell disease (SCD) remains a major public health problem worldwide, particularly in low- and middle-income countries. Efficient newborn screening (NBS) programs are crucial to enable early and effective interventions. Long-read sequencing technologies have the potential to greatly enhance NBS for SCD by providing accurate, scalable, and cost-effective genotyping [3]. While substantial progress has been made in validating long-read-based technologies for detecting the most common HbS variant (HBB c.20A>T), considerable work remains to demonstrate their full clinical utility for population-wide adoption in NBS programs [2]. Diverse barriers, challenges, and facilitators influence the deployment of long-read sequencing for SCD carrier screening. Technical and infrastructural prerequisites encompass both hardware and software requirements, processing capabilities, data-storage specifications, intersystem compatibility, and overall dependability [7]. Many of the necessary elements for implementing long-read sequencing for SCD carrier screening are not currently available in resource-limited settings. Addressing these prerequisites can increase the likelihood of establishing long-read sequencing for SCD and other applications [9]. Adaptations of existing open-source bioinformatics tools and workflows are likely needed. An appropriate combination of applications and open-source analytical pipelines should be identified to enable efficient, dependable, and reproducible analyses on widely available platforms such as Galaxy, Bioconda, or Nextflow [8]. Workforce training and capacity-building efforts play an essential role in preparing countries and institutions to adopt and sustain long-read sequencing for SCD carrier screening [11]. Developing training curricula, competency frameworks, and continuous-education programs enhances the speed and impact of capacity-building initiatives [12]. Establishing a set of core competencies for individuals performing or overseeing long-read sequencing analyses constitutes a critical first step in developing appropriate training resources. Existing materials for short-read-based sequencing can be leveraged to accelerate the development of corresponding long-read curricula [13].

Technical and Infrastructural Requirements

Sickle cell disease (SCD) fifth most prevalent monogenic disorder, and remains a public health concern. HbS polymerisation is associated with deoxy-haemoglobin HbS forms distorted erythrocytes and triggers inflammatory episodes, vaso-occlusive crises, and chronic complications; it cumulatively shortens life expectancy by 20 years [11]. Early detection reduces long-term morbidity and mortality, but existing methods have limitations. Globin sequencing identifies β-thalassaemia (β-thal), β-globin gene copy number variation (CNV), globin gene switching disorders, and de novo Hb variants absent in parental genomes; therefore candidate for Tier-1 test in newborns. However, TAT for extraction through testing to reporting is limited [12]. HbS locus undergoes widespread inter- and intra-individual variation; residual single-molecule raw data generated by existing platforms enable inference of residual variation. Phasing tools infer the sequence of alleles carried on single chromosomes, whereas haplotyping extract sequence of cis-linked variants carried on the same allele; therefore, haplotyping or structural-variate resolves the language of mammalian cells' double helical string [18]. SCD acts on a developmental switch to lead to globin switching, disabling the regulatory network by variant in key trans-factors; therefore favourable to delineate unexplained switching disorder [13]. Sickle cell disease (SCD), the fifth most prevalent monogenic disorder globally, remains a major public health concern [2]. The hæmoglobin (Hb) S polymerisation associated with deoxy-Hb S formation distorts erythrocyte shape and triggers inflammatory episodes, vaso-occlusive crises, and multiorgan chronic complications; these factors cumulatively shorten life expectancy by approximately 20 years 3. Early detection reduces long-term morbidity and mortality, but existing extension methodologies have significant limitations [20].

Long-read Sequencing of the Hb S locus addresses the need for Scalable Sickle Cell Screening.

Globin-sequence analysis identifies β-thalassaemia (β-thal), β-globin gene copy number variation (CNV), globin-gene switching disorders, and de novo Hæmoglobin variants absent in parental genomes; therefore, it is a candidate for implementation as a Tier-1 test in newborns [15]. However, the turnaround time (TAT) for extraction through testing to reporting remains challenging [11]. The Hb S locus is one of the most widely varied loci in human genomes, showing extensive inter-individual and intra-individual variation. Analysis of residual single-molecule raw data generated by existing long-read platforms enables inference of this residual variation [16]. Established phasing tools infer the sequence of alleles carried on single chromosomes, whereas haplotyping tools extract the sequence of cis-linked variants carried on the same allele; thus, haplotyping or structural-variation-extraction strategies provide an effective means to interrogate the fundamental language of mammalian cells: the double-helical string [14]. Sickle cell disease (SCD) acts on the developmental switch to lead to globin-switching perturbation and disablement of the regulatory network by the variant in key trans-factors; therefore, it is exceptionally favourable to delineate unexplained globin-switching disorders [11].

Workforce Training and Capacity-Building

Adoption of long-read sequencing (LRS) technologies will require an appropriately trained and supported workforce capable of implementing, analysing, interpreting, and communicating LRS results [11]. Although targeted education is crucial, it is important to view training needs not only in terms of knowledge acquisition, but also in the context of the translation and integration of these technologies and their application within existing health-care frameworks [16]. This requires the definition of training curricula, competency frameworks, perennially updatable materials, mechanisms for ongoing education, and the identification of suitable complementary resourcing and supervision for various health-system types and configurations [17].

Reimbursement and Funding Models

Reliable reimbursement and funding models are critical to enabling long-read sequencing in the clinical setting and, in particular, to support population-level screening for sickle cell disease (SCD) and other genetic conditions [8]. Public or private reimbursement for long-read sequencing is still limited, with support focused on single-gene testing in blood cancers [1]. Coverage should be broadened to enable full consideration of both standalone and integrated approaches, since a two-tiered platform strategy may not be feasible in many jurisdictions. Growing demand for comprehensive genome sequencing and its anticipated clinical value are poised to accelerate interest from payers in price points that reflect the value of technically and clinically validated long-read tests at the population scale [18]. The possibility of added cost-effectiveness extends beyond hereditary disease; when bundled together, cancer and inherited disease panels covering the same target genes benefit payers [17]. Value-based funding approaches are increasingly preferred by health ministries and agencies, including the World Health Organization, since they balance medical, social, and economic outputs to generate overall welfare optimization [18]. Long-read platforms are ideally positioned to anchor their overarching clinical and epidemiological significance within such frameworks [20]. Proposed steps include making available a common, carefully curated catalogue of medically actionable variants of SCD and related disorders amenable to consideration in population screening, together with a wide-ranging economic model that encapsulates the public health benefits accruing from the avoidance of a particularly prevalent and serious non-communicable disease in many jurisdictions [19].

Lessons Learned From Bench-To-Population Perspectives

Translational insights from long-read sequencing studies illustrate the complex journey from research findings to effective population health applications, clarifying the common challenges to successful technology implementation and highlighting specific considerations that could facilitate future adoption of genomic screening approaches [18]. Managing complex and rare genomic disorders is a significant burden for many health-care systems, with the worldwide incidence of sickle cell disease (SCD) estimated to exceed 300,000 new cases annually [8]. A population-scale approach is essential for timely, equitable, and impactful interventions [19]. Lessons learned during the evaluation of long-read sequencing technologies for SCD address responses of national screening initiatives to evolving genetic information, the shift from presymptomatic detection to real-time consultation and in-depth characterization of vulnerable newborns, careful consideration of technology readiness and practical impacts of introduction, and the importance of capturing the full spectrum of KCNJ5 variants in patient cohorts prior to genomic screening pilots [9].

Future Directions and Research Agenda

Rapid advancements across sequencing platforms are broadening the clinical utility of long-read technologies. Implementing population-scale SCD studies demands both technical and infrastructural resources, yet even modest capacity builds can enable powerful, targeted investigations within decades [4]. Priorities include validation cohorts to establish analytical consistency across independent laboratories, longitudinal monitoring of population-based SCD carrier frequencies to identify testing trends, and implementation pilots among birth cohorts with diverse SCD prevalence and healthcare contexts [20]. Such initiatives can deepen the understanding of emerging SCD policies and solutions, ensuring they remain responsive to evolving global needs [20-26].

CONCLUSION

Long-read sequencing represents a transformative tool for the detection and management of sickle cell disease, providing high-resolution insights into HbS variants, structural rearrangements, and complex haplotypes. Its clinical validity and utility make it highly suitable for newborn and carrier screening programs, particularly in settings where conventional diagnostics are limited. Successful population-level implementation requires robust technical infrastructure, trained personnel, data governance frameworks, and integration within health systems, alongside equitable access and ethical oversight. Tiered approaches, combining point-of-care testing with LRS confirmation, may optimize cost-effectiveness and scalability. Policymakers and health stakeholders should prioritize investment in infrastructure, capacity-building, and pilot programs to facilitate sustainable adoption. Ultimately, integrating long-read sequencing into population screening strategies offers the potential to improve early diagnosis, inform personalized care, and reduce the global burden of SCD, particularly in high-prevalence regions.

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