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Precision Public Health Applications of Whole-Exome Sequencing for Sickle Cell Disease: Evidence, Equity, and Implementation Challenges from Bench to Population

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ABSTRACT

Sickle cell disease (SCD) is a monogenic hematologic disorder that causes significant morbidity and mortality worldwide, disproportionately affecting populations of African, Indian, Middle Eastern, and Mediterranean ancestry. Whole-exome sequencing (WES) offers a precision public health approach by identifying both primary HBB mutations and modifier genes that influence disease severity, clinical complications, and therapeutic response. This paper synthesizes the evidence supporting WES for SCD, explores equity considerations in genomics implementation, and examines challenges in translating bench discoveries to population-level interventions. Key barriers include infrastructural limitations, workforce capacity, regulatory compliance, and the underrepresentation of marginalized populations in genomic studies. Case studies from Quebec, Australia, and Nordic countries highlight strategies for successful implementation, including integration with public health priorities, cross-sector collaboration, and data governance. Future research should focus on understanding genetic modifiers across diverse populations, evaluating intervention efficacy, and ensuring equitable access to genomics-informed care. By aligning precision medicine with public health objectives, WES has the potential to reduce disease burden, improve health equity, and inform scalable interventions for SCD globally.

Keywords: Sickle Cell Disease, Whole-Exome Sequencing, Precision Public Health, Genomic Equity, and Implementation Science.

INTRODUCTION

Sickle cell disease (SCD), a hereditary hematologic disorder that increases morbidity and reduces the life span of affected individuals, presents a model for implementing precision public health at the population level [1]. SCD is caused by the homozygous mutation hemoglobin (Hb) β6 (Glu → Val) in the HBB gene. Genetic modifiers, several of which lie outside the HBB locus, modulate the global burden of the disease and its clinical course, and lend themselves to the design of genomic tests and population-level risk assessment [2]. The public health significance of SCD is underscored by its worldwide distribution, particularly among individuals of African, Indian, Middle Eastern, and Mediterranean ancestry, and by the close to 300 000 infants estimated by the World Health Organization to be born with the disease each year. A centrally organized and simple to implement genetic screening program based on whole-exome sequencing (WES) offers the prospect of substantial societal impact, yet adoption has been slow [2]. A comprehensive synthesis of the underlying evidence, equity considerations, and implementation challenges is timely [1].

Background on Sickle Cell Disease and Sequencing Technologies

Sickle cell disease (SCD), characterized by vaso-occlusive crises, is an archetypal monogenic disorder. Caused by single-nucleotide mutations in the β-globin gene HBB, the condition exemplifies the value of precision public health. Whole-exome sequencing (WES) for SCD exemplifies the precision public health paradigm [7]. In addition to characterizing the HBB mutation, WES can identify modifier genes, such as BCL11A and KLF1 that influence the clinical course. It can also detect additional variants in known blood disorders, such as α-thalassemia [8]. SCD exhibits a complex phenotype determined by both the primary mutant allele and numerous exonic

modifiers [2]. Findings from SCD studies influenced the design of Genomic Observatories or sequenced population studies to characterize the spectrum of human variation. SCD research in genotype–phenotype associations has paralleled similar efforts in other diseases [3]. WES data predict clinical complications and guide the choice of therapies such as hydroxyurea or crizanlizumab. In low-resource settings, WES informs targeted public health interventions [5].

Evidence Base for Whole-Exome Sequencing in Sickle Cell Disease

World Health Assembly Resolution WHA69.22 on the global burden of sickle cell disease (SCD), together with the 2016 WHO-commissioned Lancet report on the urgent need to address populations in which genetic conditions remain largely undetected, laid the foundations for a systematic exploration of the public health evidence–equity–implementation nexus surrounding the technology [1]. The 2018 WHO-commissioned report GENEVA: A Global Approach to the Health Challenges of the Genomic Transition highlighted the SCD data landscape and called for prioritizing information on health impacts, implementation characteristics, equity implications, and literature in user-understandable formats [3]. The role of the WHO in addressing the sickle cell disease crisis is crucial, with a focus on the need to bring to the public health community the opportunities that the emerging genomics transition offers to better understand and monitor the populations at risk and the health impact of SCD[4]. Addressing the public health evidence–equity–implementation nexus has the potential to greatly accelerate the generation of an SCD knowledge base tailored to the needs of diverse stakeholders outside the genomic community [5].

Precision Public Health Framework and Implications for SCD

Sickle cell disease (SCD) has become the most common monogenic disease worldwide and continues to be a major public health concern [8]. Due to an alarming deficit of biobanks and cohort studies from low-income populations of African origin, Africa is still significantly underrepresented in the international SCD research landscape, despite SCD being rooted in regions with the highest population share. Whole-exome sequencing (WES) produces a substantial amount of data and offers great promise for filling knowledge gaps; comprehensive WES studies could generate the foundational model needed for closer connections between bench and population [5]. A preliminary public health perspective on the potential utility of WES in SCD has been presented, enabling clearer guidance for empirical analysis [7]. SCD is an example of a condition for which the genomic component is individually important, but the population component may also be greater than for other conditions, with indications that SCD incidence is rising. A precision public health framework mapped to public health goals has been proposed, establishing a systematic foundation for precise public health and generalizable insights for its broader applications. Population stratification is a crucial public health objective for a large proportion of health conditions, yet existing SCD studies fail to address it [3]. Population-level decisions regarding which strata to target first can also benefit from the specification of public health objectives [6]. To enable population-level interventions, health outcomes remain specified in broad public health terms, and willingness-to-pay metrics for related equity actions have been outlined. Precision public health connects precision medicine and public health. Genomic evidence in SCD links to the public health goals of prevention, early detection, and resource optimisation, facilitating the systematic mapping of a precise public health framework [4].

Equity Considerations in Genomic Implementation

Access to genomics is a social justice issue, yet stakeholders often overlook equity considerations in evaluations of precision public health. This section reviews equity-related barriers, priorities, and strategies for genomics-based population-level interventions against SCD [8]. The analysis emphasizes the importance of consideration and recommendation of equity-fostering solutions when the overarching goals are equitable access to precision public health and, ultimately, health equity. All SCD–related genomic evidence comes from clinical studies and population-based analyses. While evidence equity relationships differ across the health-disease continuum, the central premise is that equitably implemented interventions could narrow SCD health gaps. Barriers to genomics-based interventions for SCD differ between marginalized communities and the general population [9]. The former seek freedom from SCD and the dismantling of systemic barriers that the latter generally ignore. Underrepresentation of culturally protective elements increases distrust towards the health system, erodes confidence in lifelong engagement with genomics, and inhibits entry points to beneficial interventions [5]. Fair benefit-sharing underpins fairness in genomics and is missing in most, if not all, SCD interventions; this absence impedes widespread acceptance of solution proposals among underrepresented yet highly affected communities. Therefore, genomics-for-SCD interventions targeting the general population currently have limited transformative potential in marginalized contexts [3]. Incorporating marginalized communities' voices in SCD interventions can help foster the often-overlooked but essential involvement of families. Informed consent practices should acknowledge the realities of low scientific literacy in marginalized communities. While ascending levels of community consultation and community-based participatory research are encouraged nationwide, they generally presuppose readiness for full engagement, sidelining twofold barriers of low initial confidence and lack of culturally protective, community-generated content for high-impact entry points [2]. Failing to heed these

additional dimensions constrains outreach efforts, both to communities and across the health-disease continuum. Fostering an inclusive scientific commons encompassing locally relevant yet nationally applicable content could help advance genomics-for-SCD efforts among the U.S. population most burdened by the disease [1]. Strategies to promote collection and dissemination of inclusive datasets at the level of SCD precision public health extend beyond conventional exhortations for greater attention to equity in science, technology, and engineering [7]. They also invite consideration of how to bolster governance approaches that could regulate the collection of sensitive information and accompanying systems or amplify the distribution of non-sensitive content related to underrepresented communities. The need to address inequities in capacity-building opportunities further grows during this era of rapidly evolving health sciences [8].

Implementation Challenges in Real-World Settings

The application of whole-exome sequencing (WES) to sickle cell disease (SCD) offers the potential for targeted interventions to prevent, detect, and mitigate severe complications. However, significant challenges complicate the translation of this knowledge into public health practice [3]. Critical gaps in underlying infrastructure, data management and governance, workforce capacity, regulatory compliance, and economic sustainability must be addressed [1,5]. Health-sector maturity and financing models influence integration across electronic health record systems, protecting privacy, and safeguarding sensitive information related to incidental findings and gene–environment interactions. Cost-effectiveness analyses and affordability are essential in all health systems, but these inquiries have received insufficient attention [7]. Diverse capabilities and incentives reshape scalability and consideration of WES, where SCD incidents remain low [8]. Linking the mechanistic understanding of WES variation to health-system action requires substantial further effort [3]. Recognition of WES-associated SCD variants in population databases, improvement of knowledge bases, and documentation of care-pathway adaptations facilitate the progression from individual discovery to population benefit. Well-defined milestones and indicative timelines direct implementation priorities and promote coordination among stakeholders. Engagement with innovative frameworks for monitoring and real-time adaptations broadens opportunities to expand the scientific and precision public health agenda [6].

Bench-To-Population Translational Pathways

The process of translating genomic findings into population health interventions typically follows a series of stages that involve diverse actors from academia, government, and the private sector [1]. The generation of mechanistic insights into disease pathogenesis often marks the initial step in this pathway. For example, in sickle cell disease (SCD), understanding the role of missense variants in modifying the disease phenotype sets the stage for using such variants as defined parameters on population-level health outcomes and equity indicators [6]. They constitute the starting point for linking WES data to public health enhancement. Progressing from laboratory to population impact requires dedicated collaboration among individual researchers, public health authorities, and other stakeholders in both the scientific and genomics sectors [2]. Prioritizing the identification of targeted, apolitical, and scientifically grounded public health objectives enhances the likelihood of successful realization [6]. Organizing prospective contribution of WES to population health improvement and plans for diverse public health interventions, metrics for anticipating population-level health outcomes and inequities attributable to WES data can also evolve through systematic consideration of the sequence, thereby facilitating linkage between the anticipated impact on public health, the collected evidence, and each underlying mechanism elucidated[8]. Emphasis on the population health impact of WES and the specific nature of such influence encourages engagement with genomic and public health communities, policy makers, non-government organizations, and the wider community [8]. The approach further fosters awareness of the extensive pathway from mechanistic discovery to population-level effect. Whenever potential interventions or public health actions are defined in association with genomic data, research can address epidemiological, health-systems, sociocultural, and service-delivery issues involved in establishing, generating, executing, and assessing them at the population scale [2].

Policy, Ethics, and Governance

Whole-exome sequencing (WES) has the potential to deliver actionable health benefits for sickle cell disease (SCD) in countries with substantial genomic epidemiology and profound burdens of the disease [5]. Certain countries are institutionally well equipped to conduct pilot studies that would evaluate the public health benefits of WES and facilitate the development, adaptation, or refinement of frameworks, strategies, and governance across jurisdictions [3]. Policies and governance frameworks must be implemented proactively to guide the appropriate use of WES in diverse settings and reduce the risk of stigmatization and discrimination across settings. Regulatory guidance on informed consent for WES, particularly for minors, would support appropriate implementation [2]. The emergence of precision public health, the proliferation of WES capabilities, and the evolution of SCD epidemiology emphasize the need for a coordinated evaluation of WES applications for SCD across jurisdictions. Interventions based on such evaluations should be guided by a clear public health rationale and supply policies and governance frameworks that facilitate the development and strengthening of population-based genomic capabilities in resource-limited settings without exacerbating existing inequities [3]. International

initiatives can play a critical role in framing policy and governance approaches that facilitate the assessment of SCD variants while avoiding stigma and discrimination and preserving equity [1, 3, 7].

Methods for Evaluating Impact and Outcomes

Precision public health applications of whole-exome sequencing for sickle cell disease: evidence, equity, and implementation challenges from bench to population [2]. Proposing methods for evaluating the impact and outcomes of WES-based precision public health applications for SCD entails selecting relevant indicators and study designs [1]. Three categories of indicators, process, intermediate, and outcome, characterize different stages of implementation and effect, facilitating comprehensive assessments [2]. Process indicators gauge the implementation fidelity of WES-based stratification and interventions. Intermediate indicators capture proximal outcomes like uptake of preventive or ameliorative measures [5]. Subsequently, outcome indicators assess the ultimate effect on health and equity at the population level. Two broad study designs evaluate the impacts of scaled-up WES-based precision public health: cohort and stepped-wedge [2]. Cohort designs track longitudinal changes through pre-set exposure criteria. Stepped-wedge approaches introduce WES-stratification interventions at staggered intervals across populations, enabling comparisons of change attributable to the exposure. Pragmatic designs facilitate program piloting while evaluating generalizability [5]. Data from diverse sources, health records, surveys, hospital claims, and administrative registries support indicators along the pathway from exomic data to population health impacts. Reporting standards (e.g., STROBE, TREND, PRECISE) enhance clarity and comparability in describing study objectives, design, analysis, and findings across diverse settings and analytic approaches [8, 1].

Case Studies and Comparative Analyses

Inquiring into advice for managing variants of uncertain significance (VUS) and incidental findings from whole-exome sequencing (WES), the newborn-screening programme in Quebec provides an apt example [3]. In collaboration with CANSEQ, a national initiative designed to mobilise the resources needed to share WES data on a common platform between clinical and research laboratories, newborn screening implementation began with rigorous analysis of the impact of WES in SCD on the province's public health priorities, specifically the goals of prevention, early-detection testing, and optimisation of resources in high-risk populations [3]. Although mandates for newborn screening vary nationally and regionally, the fundamental approach remains transferable beyond Canada [7]. Rigorous examination of four other well-documented provincial or state installations each articulated by data demonstrating the significance of SCD to public health, the link between WES and reduction of disability, disease severity, and premature mortality, and the alignment with province or state wide priorities in genomics and prevention elucidates a range of technical, scientific, administrative, institutional, and contextual factors affecting successful delivery of both SCD and WES [6]. Describing implementation of the Australian Genomics Health Alliance from 2015, West and colleagues highlight progression of genomic medicine from discovery to clinical practice via a participatory framework that encompasses research, policy, and guidelines [3]. The emphasis lies not solely on the scientific merits or commercially exploitable aspects of the biomedical discoveries, but also on alignment with and progression through major policy objectives enshrined within governing political documents. The strategy has attracted further support from a range of international, regional, and national agencies, including the World Health Organization, with multiple pathways to funding available for operationalising the approach [3]. Deploying a common planning and collaboration platform has established a shared responsibility for the delivery of services extending across academia, industry, health services, and government [2]. Moreover, implementation proceeds in a series of discrete and clearly defined stages, permitting monitoring of progress and evaluation of experience across the system to identify commonalities and variations relevant to the operational aspects of the governing framework [7]. The spectrum of genomic applications in five Nordic countries, Finland, Iceland, Norway, Sweden, and Denmark, is surveyed to draw conclusions about structural drivers and transferable elements underpinning the successful establishment of aligned public-health objectives and implementation plans at the national level [2]. Despite a common Nordic ancestry, governance systems, health-programme management, top-down–bottom-up health-system integration, and health-sector peculiarities differ fundamentally across the five countries; yet the whole is greater than the sum of the parts [3]. Well-established population-based health-services infrastructures facilitate access to health information, allow tailored public-health objectives, and enhance control over implementation and follow-up of public-health applications. Resolution of genomic data-privacy and privacy concerns remains contingent on fostering cross-sector collaborations capable of elucidating joint responsibilities [2]. The Nordic configurational approach to health-care delivery develops around coordinated public-health efforts rather than focusing on specific health or disease areas, enhancing clarity and minimising cross-sectoral issues [1]. Translational efforts concerning WES, WGS, and genomic data sharing, sometimes referred to as Ingredient D, reach fruition in the end-to-end pipeline, wherein metagenomic, microbial, and pathogen community data, foundational biological quantities, artificial-intelligence prediction tools, agricultural data products, and validation and impact estimators conveniently converge [1].

Future Directions and Research Gaps

While evidence on the clinical utility of whole exome sequencing (WES) in sickle cell disease (SCD) is accumulating, additional work is needed to address important equity considerations and policy, ethics, and governance issues associated with implementation [1]. Many questions remain regarding the epidemiology of SCD, the genetic architecture of the condition, and the necessity of WES to generate actionable information of public health value 3. Comparative analyses of different population contexts, health systems, policy environments, epidemiological risk factors, and intervention portfolios may yield critical insights and lessons [2]. Prioritized research questions for further clarification of the public health impact of WES and SCD include: What fraction of the population harbors non-red cell HBB-independent exomic variants known to influence SCD phenotype (on treatment or intervention) across different geographic, demographic, and public health contexts? What fraction of the population harbors modifier genes (broadly defined) influencing SCD progression or severities that are not captured by existing blood-spot DNA analysis and the HBB SCD mutation? What demographic, genomic, and environmental factors influence clinical heterogeneity for different features of SCD? What epidemiological evidence demonstrates intervention efficacy or effect on health outcomes for recessive clinical phenotypes (SCD or other) indicated by the gene–environment architecture? What estimates are available for the construction of panel versus WES business cases to address the above research questions, taking into account the relevant population context and associated HBB mutation? What content is required to convert a formal HBB-based WES analysis (i.e., the sole justification for WES) into an intervention with plausible public health impact across an HBB mutation spectrum?[6-10] To stimulate continued progress, funders and institutions should consider the following initiatives: Support academics in conducting SCD-related research, apply-to-anything competition models, and mechanisms to champion implementation science[7]. Establish regional or continental scientific programs with explicit public health criteria, consideration of foregone economic returns, multi-investigator proposals, rapidly evolving disciplines, and the desirability of a single continent-wide proposal. Create awards dedicated to 'real' implementation science in genomics focused on access, equity, and context-dependent value, issues under-addressed by current funding streams [11-14].

CONCLUSION

Whole-exome sequencing represents a transformative tool for advancing precision public health in sickle cell disease. By integrating genomic insights with population-level interventions, WES enables early detection, risk stratification, and informed therapeutic decision-making. However, realizing this potential requires careful attention to equity, policy, governance, and infrastructure, particularly in low-resource and marginalized settings. Case studies demonstrate that successful implementation depends on multi-stakeholder collaboration, alignment with public health priorities, and robust data management frameworks. Future efforts should prioritize inclusive research, capacity building, and the development of context-specific strategies to ensure that genomic advances translate into tangible health benefits for all populations affected by SCD.

REFERENCES

1. Delaney SK, Hultner ML, Jacob HJ, Ledbetter DH, McCarthy JJ, Ball M, et al. Toward clinical genomics in everyday medicine: perspectives and recommendations. *Expert Rev Mol Diagn.* 2016;16(5):521–532. doi:10.1586/14737159.2016.1146593. PMID:26810587.
2. Ugwu OP, Basajja M, Maduabuchi EC, Fabian CO, Chinyere NU. Could chronic exposure to nocturnal artificial light pollution be an overlooked driver of urban obesity and metabolic syndrome?. Medical Hypotheses. 2025 Nov 11:111819.
3. Gupta P, Arvinden VR, Thakur P, Bhoyar RC, Saravanakumar V, Gottumukkala NV, et al. Scalable noninvasive amplicon-based precision sequencing (SNAPseq) for genetic diagnosis and screening of β-thalassemia and sickle cell disease using a next-generation sequencing platform. *Front Mol Biosci.* 2023 Dec 13;10:1244244. doi:10.3389/fmolb.2023.1244244. PMID:38152111.
4. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Sustainable development goals (SDGs) and resilient healthcare systems: Addressing medicine and public health challenges in conflict zones. Medicine. 2025 Feb 14;104(7):e41535.
5. Bertier G, Hétu M, Joly Y. Unsolved challenges of clinical whole-exome sequencing: a systematic literature review of end-users' views. *BMC Med Genomics.* 2016 Aug 11;9(1):52. doi:10.1186/s12920-016-0213-6. PMID:27514372.
6. Mikail CN. Public health genomics: the essentials. John Wiley & Sons; 2008 Nov 3.
7. Ugwu OP, Alum EU, Ugwu JN, Eze VH, Ugwu CN, Ogenyi FC, Okon MB. Harnessing technology for infectious disease response in conflict zones: Challenges, innovations, and policy implications. Medicine. 2024 Jul 12;103(28):e38834.
8. Sperber NR, Carpenter JS, Cavallari LH, Damschroder LJ, Cooper-DeHoff RM, Denny JC, et al. Challenges and strategies for implementing genomic services in diverse settings: experiences from the

Implementing GeNomics In practice (IGNITE) network. *BMC Med Genomics*. 2017 May 22;10(1):35. doi:10.1186/s12920-017-0273-2. PMID:28532511.

9. Ongesa TN, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Okon MB, Ejemot-Nwadiaro RI. Optimizing emergency response systems in urban health crises: A project management approach to public health preparedness and response. Medicine. 2025 Jan 17;104(3):e41279.
10. Azriel E, Henley C, Ehrhardt J, Hampel H, Newlin A, Ramos E, et al. Utilizing Public Health Frameworks and Partnerships to Ensure Equity in DNA-Based Population Screening. *Front Genet*. 2022 May 13;13:886755. doi:10.3389/fgene.2022.886755. PMID:35646064.
11. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Medical preparedness for bioterrorism and chemical warfare: A public health integration review. Medicine. 2025 May 2;104(18):e42289.
12. Minari J, Brothers KB, Morrison M. Tensions in ethics and policy created by National Precision Medicine Programs. *Hum Genomics*. 2018 Apr 17;12(1):22. doi:10.1186/s40246-018-0151-9. PMID:29665847.
13. Paul-Chima UO, Nneoma UC, Bulhan S. Metabolic immunobridge: Could adipose-derived extracellular vesicles be the missing link between obesity, autoimmunity, and drug-induced hepatotoxicity?. Medical Hypotheses. 2025 Sep 28:111776.
14. Malinowski J, Miller DT, Demmer L, Gannon J, Pereira EM, Schroeder MC, et al; ACMG Professional Practice and Guidelines Committee. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. *Genet Med*. 2020 Jun;22(6):986–1004. doi:10.1038/s41436-020-0771-z. PMID:32203227.

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