INOSR APPLIED SCIENCES 14(2):13-21, 2026 ©INOSR PUBLICATIONS

International Network Organization for Scientific Research ISSN: 2705-165X
https://doi.org/10.59298/INOSRAS/2025/14.2.1321 INOSR14.2.00.000

Population Genomics for Sickle Cell Disease: Return of Results, Cascade Testing, and Health System Readiness, Implementation and Equity Considerations

Kibibi Wairimu H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Population genomics is increasingly positioned as a transformative approach for identifying and managing monogenic disorders at scale through systematic analysis of genomic variation within populations. Sickle cell disease (SCD), a globally prevalent hemoglobinopathy with well-defined genetic etiology and significant public health burden, represents a strong candidate for population-based genomic screening programs. This paper examines the implementation of population genomics for SCD with emphasis on three core components: return of results, cascade testing, and health system readiness, while critically engaging with equity, ethical, legal, and social implications.The return of genomic results raises challenges related to timing, communication strategies, and health literacy, particularly in settings with limited genetic counseling infrastructure. Cascade testing emerges as a cost-effective and preventive strategy for identifying at-risk relatives, but its success depends on effective family communication pathways and culturally sensitive consent processes. Health system readiness is essential for sustainable implementation and requires robust infrastructure, workforce capacity, data governance systems, and integration with clinical workflows and electronic health records. Equity considerations remain central, as disparities in access to testing, interpretation, and follow-up care may exacerbate existing health inequalities if not carefully addressed. Community engagement, trust-building, and participatory governance are essential for ethical implementation and long-term sustainability. Ultimately, population genomics for SCD offers significant promise for precision public health, but its success depends on balancing technological capability with ethical responsibility, system capacity, and equitable access.

Keywords: Population genomics, Sickle cell disease, Cascade testing, Health system readiness and Health equity.

INTRODUCTION

Population genomics refers to the analysis of genomic variation among individuals in a population. When coupled with data regarding publicly known variation and genotype phenotype relationships, population genomics enables direct-screening strategies aimed at facilitating high-impact, preemptive intervention for common, monogenic disorders[1]. Sickle cell disease (SCD), which features a precisely delineated genomic etiology and diverse, population-specific distributions of common carrier variants, constitutes a candidate condition [2]. SCD ranks among the sickle cell anemia (hemoglobin S disease) over 330,000 annual births worldwide [3]. Population genomics for SCD encompasses three focal activities: return of results, cascade testing, and preparation of the health system for implementation [4]. Population genomics aims to study genomic variation within and between populations to derive insights into evolutionary dynamics historical and recent as well as to estimate mutation and recombination rates [5]. Returning genomic information illustrates the potential for using population-genomic data for preemptive intervention. Sickle cell disease is of public health interest across the globe. Sickle cell screening programs based on population-genomic principles can serve as models for the implementation of

genomic health initiatives aimed at common, Mendelian disorders [6]. Population attention to SCD in the context of health equity, agenda-setting, and sustainability still remains limited [7].

Background on Population Genomics and Sickle Cell Disease

Population genomics provides a novel opportunity for informing individuals about genetic conditions before symptom onset, and sickle cell disease is an ideal candidate because of its burden and the availability of preventive interventions [1, 2]. Population screening for sickle cell disease is now conducted in many countries, but the implementation of genomics is complex and raises questions about return of results, cascade testing and health system readiness [1, 2].

Return of Results in Population Genomics for Sickle Cell Disease

The potential for new population-scale genomic analyzes, termed population genomics, has been promoted as a strategy for understanding the genetic risk factors contributing to diseases or the development of adverse effects following treatment [3]. Much emphasis has been placed on population screening programs to investigate genetic risk for a particular cohort that is informative at the population level [4]. Given the definition of sickle-cell disease (SCD), the basic idea is that SCD occurs in those who are either homozygous or compound heterozygous for mutations that alter the β-globin gene and that SCD is prevalent in highly ancestral regions [5]. Therefore, population sequencing projects, in which an entire community is sequenced, could clearly indicate how genomic variants are distributed among the population pre-screening at epidemic frames [6]. Population-scale whole-exome or whole-genome sequencing studies have already been conducted on large African, African-American, and African-Indigenous cohorts. Population-scale RNA-sequencing has characterized high-volume data in patients with different types of cancer [7]. Ranges of transcriptomic dataset are available across distinct human tissues, documented variation at single-nucleotide variants between tissues, populations, and subpopulations among the human population worldwide [8]. Taking advantage of emerging technologies in sequencing and computational analysis, in conjunction with available publicly and ethically accessible genomic data on SCD, a concurrent announcement regarding the concept of population genomics for SCD is proposed [2].

Ethical, Legal, and Social Implications

Information systems are organized systems for the collection, organization, storage and communication of information. Management information systems is a sub-discipline of information systems, focusing on the systems applied in business environments [2].Population genomics has the potential to enhance population health by identifying individuals in need of healthcare resources, unraveling the molecular mechanisms underlying phenotypic heterogeneity, and improving the understanding of population history and dynamics [3]. The ability to link genomic information with health data and rapidly and cost-effectively sequence DNA has propelled the interest in large-scale population genomics initiatives [3]. The objectives of these projects are to extract information from population-wide genomic data and to facilitate discovery across multiple disciplines [4]. Sickle cell disease was selected as a disease focus for a conceptual framework to facilitate the process of planning and decision-making toward the design and implementation of population genomics projects, because it has diverse population contact, demonstrated affordability, manageable ethical-legal-social implications and obvious health-system readiness [5]. Many communities around the world are involved in a systematic process to identify population health priorities. One priority for larger and smaller communities alike is the genetic conditions affecting their population. Sickle cell disease remains an indelible legacy of human migration from Africa within the world(s) population(s)[6].

Modes and Timing of Disclosure

Early results from a sickle cell disease (SCD) study in Ghana raised questions about tracking in-country transmission. Of 855 participants who received results, a third remained uncontacted 6 to 12 months after initial reporting [3]. The rich set of feedback on the timing and methods of results disclosure helps inform population genomics initiatives in Caribbean and Pacific Asia nations with greater population structure than the Africa SCD project [4]. Low overall health literacy levels compounded the challenge of communicating detailed risk information. Informed by these insights, SCD stakeholders have privileged the development of materials that facilitate patient-centered exchange [5]. Population genomics studies in Caribbean and Pacific Asia nations with significant population structure and other genomic epidemiology settings have generated input on results return. Most respondent populations in these studies have received their entire genome or exome sequenced, and findings have predominately been conveyed through healthcare professionals [6]. The dissemination of drafts, however, elicited mixed responses, highlighting ongoing uncertainties about preferred methods of result sharing within the sector. Participation in genome sequencing efforts has also raised queries about tracking in-country transmission and the challenges of recontacting patients who have received outreach messages [7].

Health Literacy and Patient Autonomy

Broadly speaking, "health literacy" refers to the ability to read, comprehend, and communicate about health concepts [4]. Directly relevant to reporting primary findings and cascade testing, a range of health literacy

frameworks exist and can be applied to both individual and population levels. General population studies indicate that at least a third of adults struggle to understand medical information [5]. Although these estimates vary considerably across demographic groups and test modalities, they remain pertinent to genomic precision medicine, where the idea of the "informed patient" is paramount. Health-system readiness therefore encompasses the information formats, decision-support tools, and approaches needed to facilitate patient-supported interpretation, understanding, and decision-making around clinical-research reporting [6]. Individual self-determination is compromised for individuals who cannot understand clearly articulated results or who lack access to appropriate additional support, and these dimensions of health literacy are thus relevant to patient-centered frameworks and individual autonomy [5]. In the case of cascade testing, a parallel assessment of literacy levels and conditions needed to support the accurate understanding of testing, status, and implications for dependents remains equally relevant to preparedness frameworks [6]. Many families will rely on the original recipient to communicate these additional dimensions of testing and support and making assessment attention to these channels will influence both the appropriate timing of disclosures and the range of support and resources necessary to facilitate understanding both at the level of the test recipient and the dependents across the family[7]. Population-level estimates of literacy and comprehension directly influence the extent to which individuals equitably can benefit from patient-centered reporting of genomic insights and options [8]. The presentation of supporting materials designed to address the anticipated comprehension levels of recipients and their dependents remains underconstraining with respect to the broad array of potential results available for the full spectrum of genomic conditions expressed selectively at various tiers across these conditions [9].

Equity Considerations in Result Reporting

Equity considerations in result reporting can help identify disparities in access to testing, interpretation, and follow-up care [4]. A targeted, cascade-based approach can increase equity in resource-constrained settings by prioritising individuals most likely to benefit, but this may risk reinforcing existing inequities if access to cascade testing remains limited [3]. Community engagement can build trust, establish partnerships, and involve stakeholders with insight into local needs and perspectives [5]. Gender-based interventions that engage men, community-based testing, and culturally appropriate communication materials can promote equity in access to testing. Monitoring for bias during implementation, evaluation of equity in outcomes, and mechanisms for accountability can support equitable implementation and inform revisions where needed [6].

Cascade Testing: Strategies, Benefits, and Challenges

The analysis of sickle cell disease (SCD) is a high priority, since it causes significant suffering and necessitates preventive measures such as cascade testing, which is crucial for identifying additional at-risk individuals in the family [6]. When information from a sickle cell disease case emerges in a family, sickle cell carrier analysis can be performed on other relatives [7]. Different referral models (family-based, index-based) can be used either centrally or through the patient's care team. A family-centered approach, in which patients are informed after birth, allows for family testing without stigmatization [8]. Coordination of a sustainable and transparent referral response and return of results through care-networking among patients in the same family contextualizes sickle cell [9]. Sickle cell cascade testing relies on systematic integration of follow-up care, description of inter-institutional referral practices, and broad accessibility of sickle cell community programmes. In the family-referral model, infant results are communicated to the sickle cell care provider, who can coordinate follow-up at the family level [7, 10].

Conceptual Framework for Cascade Testing

Cascade testing is defined as the process of extending genetic testing to at-risk biological relatives of an affected individual [2]. In autosomal dominant disorders, for example, an individual with a pathogenic variant has a 50% chance of passing it on to their biological children and a 50% chance of transmitting the variant to a sibling. Because of this characteristic, cascade testing also contributes to disease prevention [3]. Sickle cell disease is a global health concern, especially for centralized countries where infants are routinely screened for this condition. Despite this fact, genetic testing for other disorders such as hereditary cancer syndromes seldom extends to unaffected family members, even though it could benefit them. Sickle cell disease usually emerges in infancy [4]. Therefore, the offspring of an affected person remain at risk of exhibiting the disorder unless their spouse is tested at the same time [5]. Cascade testing implemented in the context of sickle cell disease can both help the original patient's partner acquire knowledge about their carrier status and involve the patient's biological children early on in the screening process at a future stage of their lives [6]. Family members of a sickle cell disease patient are particularly relevant as candidates for cascade testing; therefore, after the primary patient goes for genetic testing, the biological relatives are usually considered the next-best candidates to undergo cascade testing [7, 8].

Operational Models and Referral Pathways

Population-level demographic and clinical last-mile SCD disclosure pathways are emerging fetal to adult transparent bioinformatics protocols for preschool genotype-phenotype testing centres or laboratories [10]. The family-centered approach incorporates lay and age-appropriate illustrations of the interrelationship of genomic

variants, red cell rheological biophysical properties, below capacity frontier disease risks transmissions, clinical events, proteomic, and microscopy-based erbios analysis [9]. Milestones align with the normal development of health thematic illiteracy along paediatric-gynaecological-urological surgeons to adults including oocyte or sperm, foetal-to-infants, sex, sickle cell trait, professional and employment predisposition, non-cancer, onward transmission objectives, and precluded informational biosecurity disclosures [8]. Emergent health literacy adults educational needs addressed include fundamental genomics-bioinformatics-health risks-genecity-care frameworks via professionally-sourced publicly-available web-delivered illustrative materials [7]. These consider a GCSQ analogue-similar work practising rapidly expanding early screening-phase interventions [8].

Family Communication Dynamics and Consent

Family communication dynamics and consent are crucial in population genomics for sickle cell disease, as varied cultural practices can influence dissemination of results [5]. Here, ethical dilemmas include disclosure of return-of-results information, management of parental carrier-status information, and engagement of minors. Community consultations in coastal Kenya revealed a desire for appropriate and timely feedback from researchers, with recommendations for a high-level disclosure summary alongside detailed reports [6, 7]. Involving communities from the research-design stage engenders respect for local traditions and protective measures, thereby enhancing compliance and the ethical conduct of research in uncertain environments [9].

Counseling and Support Services

Access to genetic information is widely regarded as an essential factor for individuals seeking to make informed decisions regarding their own health [3]. In circumstances where the primary reason for testing has passed or testing for the same condition becomes relevant, the appropriateness and timing of result reporting must be reconsidered. Health literacy also varies individually and across populations, exercising a significant influence on effective interpretation [4]. Preconditioned approaches or reliance on preconceptions from widespread health messages may not align with the nature or nuances of specific genomic screening results. Competing priorities prevent the equal distribution of attention across multiple significant prevention options, particularly when they take different forms [5]. Evaluation of specific challenges and obstacles must prioritize a balance between aiming to avoid disregarding more serious diseases and recognizing that non-lethal conditions also may not indicate a lack of importance. These parameters naturally fluctuate among members of a given population, thereby complicating direct extrapolation of conclusions drawn from a universal perspective [3, 8].

Health System Readiness for Implementation

Population level genomic testing linked to actionability, even if an individual is not tested, necessitates consideration of population health issues, including cascade testing of family members affected by sickle cell disease. Seeking testing without that information could generate distress and unnecessary steps [1]. Testing systems with extensive responsibility matrix documentation of responsibilities offer a safer approach [1]. Health systems may be involved at different levels. At the highest level, broccoli would be clearly linked to population-level clarity on responsibility connected with actionability [2]. Individual health systems and the national health system are responsible for ensuring readiness. An analysis of major components that support readiness follows.

Commonly referred to as structural and enabling considerations [8], several key components or infrastructure elements need to be in place for successful implementation. Readiness is situational, demanding adaptation to the setting and circumstances, such as the number of individuals and families affected by sickle cell disease, what other genomic analysis is part of standard care, and the role each health system plays in the national genomic landscape [3]. The following summarises main infrastructure, governance, and sustainability themes relevant to that national landscape [4]. A resilient health system resource is needed to manage genomic data responsibly over the lifespan of individuals tested and any affected family members [5]. The accompanying study identifies core infrastructure considerations when seeking to embed sickle cell genomic population screening within the national referential genomic programme. Such a system addresses complex data management, privacy, governance, and other requirements directly [6]. Competencies are needed to enable individuals and families to make informed decisions about access and, subsequently, to interact safely and effectively with any service. Availability of selected genome-derived data in anonymised but still useable form for analysis of national conditions warrants careful consideration by governance bodies, including the overall national genomic programme, related health systems, or genomic centres of excellence [7]. The transition towards establishing sickle cell genomic population screening may prompt a series of key considerations on business case structuring for standardisation and sustainable financing [10]. Implementation and longer-term sustainability considerations become crucial. An associated prioritisation of long-term sustainability is adoption of a population screening model with a low distinctive cost or repetition of testing compared with market alternatives, thus already encouraging financial support [11].

Infrastructure and Workforce Requirements

The health system infrastructure for implementation must address laboratory, bioinformatics, data management, information technology (IT), and workforce capacity requirements [7]. Such capacities underpin the safe and

effective provision of genomic services in population-based sickle cell disease screening [8]. Population-level screening for sickle cell disease and carrier status entails return-of-results options that require distinct infrastructure [9]. Return of sickle cell disease carrier status information does not necessitate clinical risk communication and support, individuals identified as carriers are not expected to require follow-up care. Water-tight infrastructure and management systems enable the return of sickle cell carrier information in decoupled facility and private-sector models [10]. Cascade testing relies on a logic framework and operational models tailored to testing for sickle cell disease carrier status. The specificity with which cascade testing is undertaken, alongside accompanying referral networks, determines the particulars of infrastructure and services required to support implementation [8].

Data Management, Privacy, and Governance

Despite features of genomic variation that are well-characterized, testing capabilities that address those features are inaccessible to most people who could benefit. A general expectation of genomic and health system evolution is that clarity or richness of information conveyed will grow over time, whether by state or process [10]. Defining timing and style of return therefore entails weighing additional information against the health-situation benefit associated with earlier receipt of results. A supporting argument is that particular components of benefit do not depend strictly on their anchoring to immediate health interventions or circumstance [11], suggesting a greater temporal allowance. Health-situation characteristics for imposing additional delay toward clearer information or richer interpretative models must also be articulated in effect, tipping points or red flags that would halt return altogether until further development [3]. The phrasing of these questions highlights values reflected in the initial nature of proposed return-pathway arrangements, notably the ethos of primary care as an original anchor shaping their formulation. A complementary framing focuses instead on routes or content for return, exploring whether any prioritization explicitly tied to the pandemic might shape the degree or manner of consideration, and if so, how [4]. A health-situation lens capable of accommodating those alternative aspects becomes necessary, further complementing delineation of current priorities.

Integration with Clinical Workflows and Electronic Health Records

Guidelines establish that returning genomic variants should ordinarily occur in a clinical context and that all results must be linked to relevant health conditions [12]. A close relationship is thus expected between genomic tests and standard-of-care interventions. To facilitate a structured, consistent approach to the return of results, various frameworks have been developed. The one used in the current analysis hinges on two axes: mode and timing of disclosure. Mode encompasses the methods used to communicate results, whereas timing addresses when communication of the findings occurs [13]. The following sections delineate a patient-centered framework for the return of results related to the risk of sickle cell disease. The focus is on the possibility of providing results to parents for newborns with normal screening tests whose sickle cell trait status has not been previously disclosed. The framework encompasses tests undertaken on newborns and adults screening cards, but results of tests performed on older children require a separate conceptualization [13].

Cost, Reimbursement, and Sustainability

Sickle cell disease (SCD) represents a significant health burden; globally, it affects millions of individuals, particularly in low-resource regions, and can result in early morbidity and mortality [5]. Accessible, objective tools to identify at-risk populations are imperative for the establishment of evidence-based intervention programs. Genomic testing has begun to be proposed for conditions such as SCD; however, significant uncertainties remain regarding the integration of population-level genomic screening programs [6]. Considerations associated with cascade testing for SCD, pathways to health system readiness, and an evaluation of equity implications form the basis of the ongoing systemic analysis within the health governance framework [7]. Genomic technologies are rapidly expanding the understanding of the links between genetic variants and disease phenotype. These technologies hold the promise of enhancing risk assessment and informing preventative health strategies, potentially improving population health outcomes and equality of access to care [8]. Nevertheless, the large-scale collection of sequence data poses substantial social, ethical, and technical challenges regarding the transparency of data ownership and use, particularly when data are excluded from the ownership of the original collector [7]. Real-world examples highlight how the secondary use of population-level genomic screening data may impact family members of tested individuals, including the dissemination of potentially sensitive medical information without consent and the collection of identifiers that could enhance the sharing of sensitive health information. Risk assessment and the establishment of regional risk registrations may offer feasible avenues for mitigating some of these issues [8]. Health governance defines access to public health programs that are considered legitimate and beneficial from a societal perspective [9]. Formulated by the United Nations, the health governance framework comprises five fundamental principles: equity, public benefit, salience, transparency, and accountability. The inclusion of variations in prevalence and therefore risk of disease causation across diverse populations and auxiliary language, literacy, and socioeconomic factors, aligns with the equity dimension of health

governance. The shift from passive to active strategies for, and expansion and prioritization of, public health genomics in SCD can therefore be integrated into the pre-existing health governance framework [8]. Recent decisions taken at the European region of the World Health Organisation also emphasize the key trinity of equity, health promotion, and cost-effectiveness dimensions [9]. Furthermore, health governance specifies attendance to the means, methods, and choices available to citizens when programs are invoked and defines the advantage of active over passive participation and therefore when pre-testing information and pro-active measures become available to citizens [10].

Equity Considerations in Implementation

In population genomics for sickle cell disease, equity considerations arise when evaluating the implementation of return of results and cascade testing as strategies tailored to specific populations, needs, and existing capacities[10]. Differential access to screening technologies, interpretation services, and follow-up care could reinforce existing inequities and deepen health disparities [10]. Furthermore, population screening entails large-scale testing of diverse individuals, which carries the risk of unanticipated inequitable access to services in territories where certain populations rather than the general populationare prioritized. Information equity may also be affected, as approaches oriented towards specific populations may restrict access to relevant information for others outside those populations [11]. A desire to promote equity across populations subsequently motivates the exploration of universal implementations alongside targeted strategies, guiding engagement with partners and stakeholders [3]. Targeted implementation strategies could widen social disparities if marginalized populations disproportionately lack access to testing, interpretation, and care [11]. Cascade testing within affected families holds promise as a strategy that could greatly benefit, rather than further disadvantage, families already impacted by the disease. Implementing cascade models in a manner that intentionally safeguards equity across diverse cultural, linguistic, and geographic contexts may yet be advantageous [12]. A central commitment to monitoring, surveillance, and accountability further strengthens these considerations; policies centred on universal population access, proposals like community-based implementation, or preference for family-focused avenues may complement cascade testing in equitable fashion. Monitoring emergence of bias and ongoing recording of outcome equity across dimensions such as geography, culture, population, and language could provide multiple avenues for safeguarding equitable systems [13].

Access and Inclusion across Populations

Sickle cell disease disproportionately affects diverse populations particularly those with ancestral ties to malaria-endemic regions and genomic studies often focus on majority groups [12]. Genetics also influences disease pathophysiology, variable clinical presentation, and associated health burdens [13]. Population interventions targeting trans-ethnic carriers without adequate safeguards could exacerbate differences in screening access, counseling, and follow-up, hindering rather than enhancing health equity [14]. In the United States, incidental findings from newborn sequencing report actionable variant classes affecting numerous conditions in up to one-quarter of the population. Incorporating equitable population considerations before seeking public engagement or policy endorsement is therefore essential [13].

Targeted versus Universal Strategies

Targeted strategies aim to maximize utility in high-incidence populations, whereas universal strategies strive for equitable access irrespective of carrier status and genotype frequency [1]. Through carrier-selective return of results, targeted approaches seek to avert wasted educator effort and limit counselling to those most likely to benefit 10. Population genomics has the potential to reframe sickle cell access, expanding the debate beyond questions of free or paid testing to encompass issues of even more fundamental equity [12].

Community Engagement and Trust-building

Population genomics for sickle cell disease: return of results, cascade testing, and health system readiness—implementation and equity considerations [13]. Community engagement and trust-building are essential to conduct ethically responsible research on population genomics and sickle cell disease and to facilitate implementation of relevant population-level initiatives. Review of practices from other contexts suggests that meaningful partnerships with affected communities can build understanding and acceptance of new health initiatives [9]. Involving communities at the outset can enhance the design of informed consent processes and support broader participation, especially in under-resourced settings where compliance with regulatory frameworks is sometimes minimal [13]. Ongoing relationships are also fundamental to ensuring that communities continue to feel involved and respected throughout the research process, and trust is further strengthened by transparent communication about research results and by addressing ethical, legal, and social implications thoughtfully [14]. Consulting communities about the return of results and the conduct of cascade testing can strengthen research ethics and enhance implementation, because the Scientific Community already possesses information about areas of concern in addition to potentially sensitive findings [15].

Monitoring, Evaluation, and Accountability

In monitoring and evaluation, it is vital to define metrics that reflect the extent to which sickle cell population genomics implementation aligns with established equity principles and its specific community aspirations [14]. This requires identifying key populations affected by sickle cell disease, clarifying their priorities concerning population genomics, and determining metrics to assess whether these priorities are being realized. Existing programs can serve as valuable references in this regard [15]. Careful framing of the equity framework to assess population genomics allows for consideration of aspects that matter to communities themselves rather than imposing external frameworks that may not resonate. The Framework for Equity in Development and the Framework for Enabling, Fostering, and Sustaining Equitable Access to Health Products offer widely recognized insights for this task [16]. These frameworks, which extend conventional access considerations to include rights, social justice, empowerment, engagement, social and political capital, trust, and awareness, support the development of questions and indicators that cover these broader equity dimensions. They can also be employed in different contexts where equity is a concern and associated questions and indicators are required [15].

Case examples and Lessons from Existing Programs

Cascade testing allows for targeted testing of family members after the identification of an affected individual, potentially averting unnecessary tests and enhancing access to timely, accurate results [1]. Cascade testing for genetic conditions has gained traction globally, emerging as a preventative initiative that capitalizes on the genetic links within families [2]. The underlying concept is straightforward: once an individual has been diagnosed with a heritable condition or identified as a carrier, relatives of that individual are presented with an opportunity to learn about their own genetic status [14]. Cascade testing is notably beneficial for conditions with age-related or variable penetrance, such as hereditary breast and ovarian cancer syndrome, sickle cell disease, and Huntington disease, wherein examination of prior family history may not yield sufficient information for a full risk assessment [15]. In sickle cell disease (SCD) cascade testing, a timely opportunity arises to avert needless worry about sickle cell trait (SCT) following a newborn-screened positive diagnosis of SCD [14]. Families with potential SCD risk may not have undergone proper characterization of identifying variant, potentially missing relevant information that could preclude them from presenting a prior family history to the newborn-testing cycle of events. Cascade testing directly informs about family members who are eligible for population testing, allowing for referrals based on positions within the pedigree and providing timely access to answers within families with SCD [15]. The availability of automatic cascade testing downstream of population-testing systems streamlines both operational and administrative logistics, widening access by reducing the need for renewed general population engagement processes to inform at-risk families about the potential value of testing[15].

Research Gaps and Methodological Considerations

Genomic information holds potential to benefit individuals beyond testing recipients, yet the conditions under which this occurs, and the implications for delivery and prioritization remain poorly understood [16]. The intervention proceeds through tiered testing of relatives of individuals diagnosed with sickle cell disease, with implications for follow-up care shaped by the genetic status of secondary and tertiary contacts [13]. Ensemble and composite modelling approaches representing various population or policy scenarios would capture the multiplicity of options, together with determination of the relative impact on tested individuals, deployment setting, and associated trajectories. Attention to return of results would then inform the design of programming relevant for sickle cell disease that respects the diversity of stakeholder values and aspirations across settings [16].

CONCLUSION

Population genomics presents a powerful framework for advancing the prevention and early management of sickle cell disease through large-scale identification of genetic risk and structured return of results. Its integration into health systems enables proactive identification of affected individuals and carriers, while cascade testing extends benefits to families by facilitating early diagnosis and preventive care. However, the successful implementation of these approaches depends not only on technological advancement but also on the readiness and resilience of health systems. Infrastructure, workforce capacity, data governance, and clinical integration must be sufficiently developed to support sustainable genomic services. Without these, the potential benefits of population genomics risk being undermined by inefficiencies and inequitable access. Equity remains a defining concern throughout all stages of implementation. Differences in literacy, access to healthcare, cultural norms, and socioeconomic conditions can significantly influence who benefits from genomic interventions. As such, community engagement, culturally sensitive communication, and transparent governance structures are essential to ensuring fairness and trust. Ultimately, population genomics for sickle cell disease offers a model for integrating precision medicine into public health. Its success will depend on a balanced approach that aligns scientific innovation with ethical responsibility, health system capacity, and a strong commitment to equity and inclusiveness.

REFERENCES

1. Foss, K. S., O'Daniel, J. M., Berg, J. S., Powell, S. N., Cadigan, R. J., Kuczynski, K. J., Milko, L. V., Saylor, K. W., Roberts, M. C., Weck, K. E., & Henderson, G. E. (2022). The rise of population genomic screening: Characteristics of current programs and the need for evidence regarding optimal implementation. *Journal of Personalized Medicine*, *12*(5), 692. https://doi.org/10.3390/jpm12050692
2. Blumling, A. A., Prows, C. A., Harr, M. H., Chung, W. K., Clayton, E. W., Holm, I. A., Wiesner, G. L., Connolly, J. J., Harley, J. B., Hakonarson, H., McGowan, M. L., Miller, E. M., & Myers, M. F. (2022). Outcomes of returning medically actionable genomic results in pediatric research. *Journal of Personalized Medicine*, *12*(11), 1910. https://doi.org/10.3390/jpm12111910
3. Suckiel, S. A., O'Daniel, J. M., Donohue, K. E., Gallagher, K. M., Gilmore, M. J., Hendon, L. G., Joseph, G., Lianoglou, B. R., Mathews, J. M., Norton, M. E., Odgis, J. A., Poss, A. F., Rego, S., Scollon, S., Yip, T., & Amendola, L. M. (2021). Genomic sequencing results disclosure in diverse and medically underserved populations: Themes, challenges, and strategies from the CSER Consortium. *Journal of Personalized Medicine*, *11*(3), 202. https://doi.org/10.3390/jpm11030202
4. Blizinsky, K. D., & Bonham, V. L. (2018). Leveraging the learning health care model to improve equity in the age of genomic medicine. *Learning Health Systems*, *2*(1), e10046. https://doi.org/10.1002/lrh2.10046
5. Sabatello, M., Bakken, S., Chung, W. K., Cohn, E., Crew, K. D., Kiryluk, K., Kukafka, R., Weng, C., & Appelbaum, P. S. (2024). Return of polygenic risk scores in research: Stakeholders' views on the eMERGE-IV study. *Human Genetics and Genomics Advances*, *5*(2), 100281. https://doi.org/10.1016/j.xhgg.2024.100281
6. Cernat, A., Hayeems, R. Z., Prosser, L. A., & Ungar, W. J. (2021). Incorporating cascade effects of genetic testing in economic evaluation: A scoping review of methodological challenges. *Children*, *8*(5), 346. https://doi.org/10.3390/children8050346
7. Chiang, J., Chua, Z., Chan, J. Y., Sule, A. A., Loke, W. H., Lum, E., Ong, M. E. H., Graves, N., & Ngeow, J. (2024). Strategies to improve implementation of cascade testing in hereditary cancer syndromes: A systematic review. *npj Genomic Medicine*, *9*, 26. https://doi.org/10.1038/s41525-024-00412-0
8. Wildin, R. S., Giummo, C. A., Reiter, A. W., Peterson, T. C., & Leonard, D. G. B. (2022). Primary care implementation of genomic population health screening using a large gene sequencing panel. *Frontiers in Genetics*, *13*, 867334. https://doi.org/10.3389/fgene.2022.867334
9. Marsh, V., Kombe, F., Fitzpatrick, R., Williams, T. N., Parker, M., & Molyneux, S. (2013). Consulting communities on feedback of genetic findings in international health research: Sharing sickle cell disease and carrier information in coastal Kenya. *BMC Medical Ethics*, *14*, 41. https://doi.org/10.1186/1472-6939-14-41
10. Kingsmore, S. F., Lantos, J. D., Dinwiddie, D. L., Miller, N. A., Soden, S. E., Farrow, E. G., & Saunders, C. J. (2012). Next-generation community genetics for low- and middle-income countries. *Genome Medicine*, *4*, 25. https://doi.org/10.1186/gm324
11. Tiffin, N. (2019). Potential risks and solutions for sharing genome summary data from African populations. *BMC Medical Genomics*, *12*(1), 152. https://doi.org/10.1186/s12920-019-0604-6
12. Williams, M. S., Taylor, C. O., Walton, N. A., Goehringer, S. R., Aronson, S., Freimuth, R. R., Rasmussen, L. V., Hall, E. S., Prows, C. A., Chung, W. K., Fedotov, A., Nestor, J., Weng, C., Rowley, R. K., Wiesner, G. L., Jarvik, G. P., & Fiol, G. D. (2019). Genomic information for clinicians in the electronic health record: Lessons learned from the Clinical Genome Resource Project and the Electronic Medical Records and Genomics Network. *Frontiers in Genetics*, *10*, 1059. https://doi.org/10.3389/fgene.2019.01059
13. Azriel, E., Henley, C., Ehrhardt, J., Hampel, H., Newlin, A., Ramos, E., Wicklund, C., & Duquette, D. (2022). Utilizing public health frameworks and partnerships to ensure equity in DNA-based population screening. *Frontiers in Genetics*, *13*, 886755. https://doi.org/10.3389/fgene.2022.886755
14. Mathew, S. S., Barwell, J., Khan, N., Lynch, E., Parker, M., & Qureshi, N. (2017). Inclusion of diverse populations in genomic research and health services: Genomix workshop report. *Journal of Community Genetics*, *8*(4), 267–273. https://doi.org/10.1007/s12687-017-0317-5
15. Inusa, B. P. D., Anie, K. A., Lamont, A., Dogara, L. G., Ojo, B., Ijei, I., Atoyebi, W., Gwani, L., Gani, E., & Hsu, L. (2018). Utilising the 'Getting to Outcomes®' framework in community engagement for development and implementation of sickle cell disease newborn screening in Kaduna State, Nigeria. *International Journal of Neonatal Screening*, *4*(4), 33. https://doi.org/10.3390/ijns4040033
16. Fullerton, S. M., Knerr, S., & Burke, W. (2012). Finding a place for genomics in health disparities research. *Public Health Genomics*, *15*(3–4), 156–163. https://doi.org/10.1159/000334717

CITE AS: Kibibi Wairimu H. (2026). Population Genomics for Sickle Cell Disease: Return of Results, Cascade Testing, and Health System Readiness, Implementation and Equity Considerations. INOSR APPLIED SCIENCES 14(2):13-21. https://doi.org/10.59298/INOSRAS/2025/14.2.1321