THE EMERGENCE OF GENOMIC RESEARCH IN AFRICA AND NEW FRAMEWORKS FOR EQUITY IN BIOMEDICAL RESEARCH

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Individuals with African ancestry have the greatest genomic diversity in the world, yet they have been underrepresented in genomic research. To advance our understanding of human biology and our ability to trace human history, we must include more samples from Africans in genomic research. Additionally, inclusion of more samples from participants of recent African descent is imperative to provide equitable health care as genomics is increasingly used for diagnosis, treatment, and to understand disease risk. The Human Heredity and Health in Africa initiative (H3Africa) seeks to expand the number of Africans included in genomic research and to do so by expanding the research capacity on the continent. In this article, we discuss how H3Africa is endeavoring to achieve these goals while promoting equitable research collaborations. *Ethn Dis*. 2019;29(Suppl 1):179-186; doi:10.18865/ed.29.S1.179.

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INTRODUCTION

Scientists agree that increasing the diversity of participants and investigators in genomic research is both a scientific and an ethical imperative.[1] Despite this agreement, however, genomic diversity in research has lagged,[2,3] and it is widely recognized that "genomics is failing on diversity."[4] Ambitious efforts to rectify current research inequities have been set into motion, including the All of Us initiative in the US,[5] Trans-Omics for Precision Medicine (TOPmed) Program (https://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed); and the Population Architecture using Genomics and Epidemiology II (PAGE II) Consortium (https://www.genome.gov/27541456/population-architecture-using-genomics-and-epidemiology/).

Another effort, Human Heredity and Health in Africa (H3Africa), is a comprehensive initiative[6] with an investment of more than $170 million from the NIH and Wellcome Trust. H3Africa is poised to make a unique contribution to genomic research, and has already made considerable advances[7] (Table 1); geographical impact of H3Africa can be seen at https://h3africa.org/index.php/about/vision/. H3Africa endeavors to develop capacity and infrastructure, to promote an environment of collaboration and excellence, and to empower African scientists to take their place on the global stage. As the birthplace of modern humans and the home of the greatest genomic diversity, the African continent is a logical focus of efforts aimed at improving diversity, inclusion, and representation. Still, genomic research in Africa is emerging into a landscape fraught with historical missteps. In this article, we discuss the rationale for increasing representation of those with African ancestry in genomic research and how H3Africa is addressing the culture of exploitation that has pervaded health research in Africa.

WHY THOSE WITH AFRICAN ANCESTRY NEED TO BE INCLUDED IN GENOMIC RESEARCH

Africa has been described as the "most informative place on earth" to study the genomics of complex traits.[8] Nearly all of our evolutionary history as a species has occurred in Africa,[8] and studying only the genetic variation that exists outside of Africa curtails the potential insights that can come from genetic associations.[3] Within Africa may lie new discoveries for human biology and opportunities for a more complete mapping of human history.[2] Such discoveries are already being reported, as the inclusion of understudied African populations have led to new understanding of the evolution and complex regulation of skin pigmentation[9,10] and of population history.[11-13] Notably, exploration of African genomes has enabled the tracing of the sickle cell allele to a single ancestor,[14] and ancient African samples have facilitated new insights into ancient population structure[15-16] and the earliest known split between anatomically modern humans.[1]

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Beyond these reasons for including Africans in genomic research, there are also important reasons for inclusion related to equity for individuals with African ancestry.[17] For instance, inclusion can facilitate improved understanding of genetic contributions to health disparities, as discovery of the *APOL1* kidney disease risk variants were found to be associated with differences in kidney disease prevalence observed by ancestry.[2]

Within the context of pharmacogenomics, broad racial categories such as "Black" and "African" obscure relevant biomedical variation in drug response and have been proven to be inadequate.[18,19] Notably, the prevalence of a *CYP2D6* duplication that causes serious adverse outcomes with codeine use is very low in West Africa, but has a 30% occurrence among Ethiopians. As broad genotyping was not feasible, the use of codeine has been banned in Ethiopia.[20] Additional pharmacogenomic research of diverse populations is needed for better targeting of safe and effective treatments within population groups that appear to cluster together genetically.

Precision medicine efforts will be less well-targeted in individuals with African ancestry, as those with African ancestry are not well-represented in the data underlying these initiatives,[21-23] and polygenic risk scores, a new tool enabling researchers to identify individuals at increased disease risk, do not perform as well in those with African ancestry.[24] Similarly, individuals of African descent are more likely to face genetic misdiagnosis, as genomic representation in databases may be insufficient to characterize "normal" genetic variation.[25,26] In these instances, limited inclusion of individuals of African descent in genomic research could lead to inequalities in health care, race-based risk assessments, misdiagnosis, and drug prescriptions that are ineffective or unsafe.[2,17] As such, the goal of increasing inclusion of those with African ancestry in genomic research has important ramifications for equitable care for these individuals as well as for improved global scientific understanding.

African Leadership in Research and Governance

While greater inclusion of those of African descent in genomic research may seem straightforward, achieving this goal in an equitable way for participants and investigators is complex. Historically, international health researchers collaborated with African scientists chiefly for the collection of samples, while the expertise and decision-making remained with the non-African collaborator.[27] This exploitation of African samples and doctors/researchers without any true collaboration is an example of "parachute" research.[28] H3Africa has the objective and the promise of balanced relationships between scientists within and outside of Africa, requiring that all funded projects are led by African researchers.

As this initiative matures, scientists have shared their experiences on achieving equitable collaborations across economic, resource, and expertise gradients. African genomic researchers both within and outside of H3Africa have acknowledged the benefits of externally funded genomic research and biobanking that have fostered large scale collaborations with African scientists.[27] Despite this positive outlook, however, all of the interviewees remained concerned about exploitation from their non-African collaborators.[27] Setting up guidelines for equitable collaborations is seen as key to avoiding paternalism in these relationships.[27] Such guidelines (https://h3africa.org/wp-content/uploads/2018/05/Final-Framework-for-African-genomics-and-biobanking_SC-.pdf[29]) were recently developed as part of the H3Africa initiative highlighting key ethical values of reciprocity, consultation, and accountability for the African research context.[29]

To achieve fair treatment for African scientists, they should be central to the decision-making process. African scientists should not just be a part of the process, but leaders in the genomic research conducted on the continent.[29] As one African researcher stated, African ownership is important to avoid having "a stranger telling us our story."[27] Principal investigators for H3Africa research grants must be based at African institutions. Although co-investigators from outside Africa are permitted, H3Africa is designed to foster African leadership.[30] Maintaining this ownership over time will require concerted effort. Data and samples are being collected with an aim of long-term utility and re-use; yet, given the reality of infrastructure limitations (eg, less reliable power supply and Internet connections), the speed at which African researchers may be able to complete secondary analyses may be diminished compared with those in a setting with a better developed infrastructure. Thus, longer periods of time for protected use of samples/data by African researchers before they are made available to the larger research community may be necessary to ensure equitable access, though these decisions should thoughtfully balance the need for openness in genomic research.[6,29]

Table 1. H3Africa impact

Overall monetary investment by NIH/Wellcome Trust	$170 million
African nations involved	34
Consortium members	>500
Workshops/themed meetings (including H3ABioNet)	53
Projects supported	48
Trainees	382
BSc	61
MSc	127
PhD	193
Research participants recruited	54,000
Publications	197

Source: H3Africa.org, accessed 1/9/2019

H3Africa funding through the NIH Common Fund is limited to 10 years. With alternate sources of funding (eg, through African governments, specific NIH Institutes, or the Alliance for Accelerating Excellence in Science in Africa) far from guaranteed, there is considerable anxiety among researchers regarding sustainability of research efforts. Will African researchers or their international collaborators be more likely to maintain sustained research funding to use the data and samples that are being stored and generated?[27] Securing reliable funding is, perhaps, the key component in guaranteeing African ownership and leadership of genomic research conducted on the continent.

Capacity Building

Capacity building is one of the pillars of H3Africa. Research capacity building is a way to minimize the risks of exploitation,[27] develop sustainability of genomic research activities,[29] and promote H3Africa's primary goal of benefit sharing.[30] Unequal health research collaborations are a consequence of the fact that both human and physical resources for conducting research have been limited in Africa. Issues regarding the export of samples outside of Africa for analysis can demonstrate this complexity. Out of concern over historic exploitation and a perpetuation of inequalities by sending African samples to non-African laboratories, some African nations have strict guidelines regulating the export of samples.[31] However, retaining genomic samples in Africa for analysis depends on: 1) having researchers with sufficient genomic expertise to run analyses; 2) storage facilities with reliable power to store the samples; 3) necessary laboratory equipment to conduct assays; and 4) the infrastructure to maintain that equipment, each of which may be challenging in the African context.[3,27]

To achieve improvements in equitable collaborations, research capacity must be enhanced. The Framework for African Genomics and Biobanking recommends that sample export be accompanied by measures to improve the research capabilities of the region in which samples were collected and where there is a demonstrated focus on reducing global health inequality.[29] The potential impact of genomic infrastructure within Africa has already been demonstrated. For example, sequencing efforts within Africa were key to understanding the spread of the Ebola virus during the outbreak in West Africa in 2013-2016[32] and characterizing a surge in Lassa virus in Nigeria in 2018.[33]

To achieve sustainability, capacity building must occur across the breadth of research activities, from grant writing and administration to bioinformaticians and scientists to ethics committees, while involving both junior and senior scientists.[29] The Pan African Bioinformatics Network (H3ABioNet) supports H3Africa projects with training activities, standard operating procedures and workflows,[34] infrastructure development, and a help desk to facilitate interactions with H3ABioNet members with relevant expertise.[35] H3ABioNet trains bioinformaticians, scientists, and health care professionals in data management, analysis, interpretation, and infrastructure development.[7] H3ABioNet even provides the opportunity to complete comprehensive assessments of attained skills to ensure excellence in acquired skills, though this resource has, thus far, been underutilized.[36]

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Training of the next generation of genomic researchers is seen as one of the main benefits of the H3Africa initiative by African scientists within the H3Africa initiative.[27] A key concern among interviewed African scientists, however, is that these well-trained young scientists, sometimes trained outside of Africa, find an environment within their home country to support and foster their research and career, so that they do not choose to relocate off the continent.[27] This goal may be achieved by having faculty positions available upon completion of their degrees,[27] as is being planned for trainees at Makerere University and the University of Botswana.[37] In order to further support the successful establishment of trainees as genomic faculty in their institutions, the universities are developing genomic departments and improving laboratory infrastructure, and H3ABioNet is ensuring the availability of bioinformatics resources: a reminder of the multi-dimensional approaches needed to establish a new genomic researcher in this environment.[37] These trainees are expected not only to perform world-class science, but also to perform as advocates, lobbying local institutions and governments for investments in infrastructure improvements and stimulating interest and enthusiasm in the field of genomics.[37]

ETHICAL OVERSIGHT

Institutional review boards (IRBs) perform a critical role for all genomic research, and especially in

Table 2. Core principles of ethics and governance framework for best practice in genomic research and biobanking in Africa[29]

1. Research should be sensitive to and respectful of African values and cultures

2. Research should be for the benefit of African people recognizing that it likely also yields benefits of the global population

3. Research and dissemination of data in publications should take place with genuine and active intellectual participation of African investigators and other African stakeholders

4. Research should promote ways of relating typified by respect for individuals and communities, fairness, equity, and reciprocity

the context of research on the continent, where recruitment may take place in areas with limited access to health care, low incomes, high burden of disease, and lack of familiarity with genomic research. Limited research oversight creates an environment in which both participants and researchers are more vulnerable to exploitation.[27] Additionally, without ethical guidelines, there is greater risk that researchers and ethics committees may make decisions based on fear or misunderstandings.[31] In many African regions, IRBs have relatively little experience with reviewing protocols for genomic research,[38] and standard operating procedures for research ethics committees are still being developed in most countries.[31] As a result, unanticipated delays in the implementation of research projects could occur.[38] Guidelines regarding broad consent and data and sample sharing are important for ethics review committees as they receive increasing applications with a focus on genomic research.[31]

H3Africa has provided the Framework for African Genomics and Biobanking as a practical tool for IRBs to use when evaluating genomic research in Africa.[29] Table 2 lists the core principles defined in this framework. H3Africa meetings to train IRB members in concepts in genomics and biobanking have been observed to lead to improvements,[27] and the consortium regularly assembles members of ethics committees from across Africa to discuss appropriate and ethical consent processes.[7]

Appropriate informed consent is a key component to avoid exploitation of research participants. While ensuring voluntary agreement to participate in a study that is well-understood by the participant is not a unique challenge to genomic research conducted in Africa, some aspects of the consent process deserve careful consideration in the African context. In some regions, conveying complex genomic concepts adequately in languages for which related vocabulary is limited may be challenging.[38-40] There are cultures where family and community leaders have a role in the decision-making of an individual, making obtaining informed consent more complex and challenging.[38] As is the case globally, conversations regarding ways to improve informed consent methods for this situation are ongoing. Additional challenges may arise when individuals are poor, lack access to health care, and have low educational levels. Modest compensation for participation in a study or anticipation of otherwise inaccessible health care may constitute inducement in a low-resource environment. For example, an in-depth follow-up with research participants who served in the case and control arms of a genomic study of rheumatic heart disease in South Africa revealed a great deal of diagnostic misconception among those in control groups (the belief that they were participating in a screening program for heart disease) and therapeutic misconception among those in case groups (the expectation of personal benefit).[41] Some of the key factors that may have contributed to these misunderstandings included: conducting study activities in a van that resembled those used for screenings in the same region; the impression that study activities were free health care services; and language barriers that may have prevented full understanding. The authors concluded that further efforts were required to achieve genuine informed consent in these circumstances, including assessing potential participants' understanding.[41] A widespread misconception about an immediate return of results has also been reported,[38] consistent with the widespread belief that study activities were health care initiatives.

The H3Africa Working Group on Ethics and Regulatory Issues produced Guidelines for Informed Consent (https://h3africa.org/about/ethics-and-governance), highlighting the importance of engaging prospective participants and their communities in meaningful discussion on these issues. In addition, there have been efforts to train institutional review boards and members of research oversight and ethics committees on the ethical issues raised by genomic research conducted within an African context, including the issue of informed consent.[42] As the ethical concerns may be complex and specific to each region, it is necessary to have representation of local researchers and/or community leaders, such as in a community advisory board,[40] at the level of study design and implementation. African leadership in the design and interpretation of genomic research is also a safeguard against group harm or stigma, as local researchers are likely to be more sensitive to the issues and concerns of groups participating in research, and key to designing appropriate and meaningful community engagement strategies.[3,29,43]

CONCLUSIONS

The Human Heredity and Health in Africa initiative (H3Africa) has the goal of increasing the representation of Africans in genomic research. Yet, H3Africa demands that this goal be met with scientific endeavors rooted in equitable relationships. In order to distance this new emergence of genomics in Africa from the inequalities that pervaded previous health research on the continent, a comprehensive approach is needed. H3Africa is promoting African leadership and ownership of research projects, samples, and data by requiring that principal investigators be African researchers working in African institutions. Building research capacity, fundamental to developing equitable collaborations, is a cornerstone of H3Africa, including investments in infrastructure and training across the range of the research process. Considerable effort is also being expended in the development of guidance and education for ethical oversight of H3Africa projects. The comprehensive nature of the efforts of the H3Africa initiative to lift researchers on the continent to participate in world-class research are certain to change the trajectory of genomics in Africa and increase the independence of African researchers. In contrast to the riches of the continent historically taken from it to benefit other populations, the richness of the genomes found in Africa should be explored by African and global scientists for the benefit of African peoples and the larger global populations.

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CONFLICT OF INTEREST

No conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Research concept and design: Bentley, Callier, Rotimi; Acquisition of data: Bentley, Rotimi; Data analysis and interpretation: Bentley, Rotimi; Manuscript draft: Bentley, Callier, Rotimi; Administrative: Bentley, Callier; Supervision: Rotimi

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