

# Review of Studies of African Genome in the Rare Diseases Causes: Disease Burden, Barrier and Challenges, Current Practice and Future Approaches.

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## ABSTRACT:

People living with rare diseases face significant challenges during their lifetimes. These challenges include delayed diagnosis, unavailable treatments and the poor quality of life associated with the chronic illnesses. These health inequalities are more common in Africa. Most diseases are genetic in origin. The hereditary nature of the rare diseases makes them cluster in families thereby intensifying the burden for those affected. The study of genetics can help come up with solutions for people living with rare diseases. Genomics can help reduce the time taken for diagnosis, identify new rare diseases and pave the way for new treatments through genetic manipulation. This literature review noted the burden and challenges of rare diseases in Africa and available resources and funding models. It was noted that the African genome was unique and diverse. The challenges noted were paucity of data, financial constraints, cultural barriers, historical exploitation, poor infrastructure and limited expertise. Significant progress has been made in addressing the health inequalities with the formation of patient advocacy groups and genomic programs such as national genomic reference databases.

**Keywords:** *Rare diseases, African Genome, Health inequalities, Disease burden*

## 1. INTRODUCTION:

### 1.1 Background:

A disease that affects on average 1 in 2,500 people is referred to as a rare disease. As much as rare diseases individually affect a few persons, known rare diseases (more than 6000 identified) aggregated affect a significant proportion of the world population (Repetto and Rebolledo-Jaramillo, 2020). In the United States, 9% to 12% of the population is affected by rare diseases ('The Challenge of Rare Diseases', 2018). Globally, the number of persons is estimated to be 473 million (Ferreira, 2019). People with rare diseases experience many burdens and challenges more than those with common diseases. These are inequitable access to diagnosis and treatment. They also face social and isolation, discrimination and hopelessness (D'Angelo *et al.*, 2020) (Palmer *et al.*, 2024).

The rarity of these diseases poses many challenges. Timely and accurate diagnosis is one major challenge. In developed countries, it takes at least 5 years for a diagnosis to be made. The time frame is longer in developing nations (Marwaha, Knowles and Ashley,

2022) (D'Angelo *et al.*, 2020) (Palmer *et al.*, 2024). Treatment is usually unavailable due to it being non-existent or expensive. This is because the few numbers do not attract support for clinical research or reasonable funding for subsidization.

Most of the diseases are debilitating and chronic with high rates of admission into healthcare facilities. This leaves people living with rare diseases (PLWRD) being neglected, discriminated and socially disadvantaged. The burden of rare diseases puts the patients and their caregivers at a higher risk of mental ill health (Ferreira, 2019) (D'Angelo *et al.*, 2020). The clinicians and researchers are equally frustrated by the absence of expert guidelines, treatment options and reasonable funding ('The Challenge of Rare Diseases', 2018). Fortunately, these challenges and neglect (unmet needs) of PLWRD have been recognized by many organizations including the World Health Organization. Nations are following the mantra "leave no one behind" (UNSDG | Leave No One Behind, no date), (D'Angelo *et al.*, 2020). The recognition has led to the creation of many international organizations and government initiatives

dedicated to the management of rare diseases. A significant number of these organizations are led by patient advocacy groups. The advocacy groups have made significant collaborations with clinicians, scientists, funders, governments, drug companies and regulators (D'Angelo *et al.*, 2020) ('The Challenge of Rare Diseases', 2018). As a result, developed nations have made huge strides towards tackling the inequalities experienced by PLWRD. Similarly, developing nations have also begun to focus their attention and resources on meeting the needs of PLWRD ('The Challenge of Rare Diseases', 2018). One of the most important steps in the management of rare diseases is identifying the cause and identifying new rare diseases (Product Development, Field and Boat, 2010).

### **Genetic disorders are the most common causes of rare diseases (Product:**

Development, Field and Boat, 2010). Other causes are cancers, infections and autoimmune disorders. Generally, interest in genomics has risen globally as aberrations in genes are now a significant cause of diseases following successful control of infectious and nutritional etiologies. Gene therapies are the future for the prevention and therapy of rare diseases (Braga *et al.*, 2022).

There are five categories of genomic testing which are tumor testing, diagnostic, pharmacogenomics, clinical predictive and direct-to-consumer (Jackson *et al.*, 2023). Genomics play a crucial role in understanding the pathology of disease. It enables early detection and rational drug use. The development of cost-effective, next-generation sequencing (NGS) which analyses multiple genes simultaneously and advances in genomics has led to widespread interest in the study of genomics. The study is now beyond diagnostics to including therapeutic, ancestry and migration studies (De Oliveira *et al.*, 2023) (Phillips *et al.*, 2021) (Omotoso *et al.*, 2022).

With the human genome mapped in 2010, this diagnostic and therapeutic potential of genomics in the rare disease space will solve the major challenges faced by PLWRD (Braga, Conte Filho and Mota, 2022) (De Oliveira *et al.*, 2023). This has been demonstrated in the successful treatment of inherited retinal diseases using gene therapy Luxturna ("Precision ophthalmology n.d.).

Genomics are also an essential component of precision medicine (Jackson *et al.*, 2023). Precision medicine is a promising practice that will enable individually specific therapies based on an individual's lifestyle, environment and genetics. It entails pharmacogenomics in which drug response and dosing are determined from the genome (Scherr *et al.*, 2019) ("Egypt Genome," 2024) (Ilori *et*

*al.*, 2023). This is a promising future for the treatment of rare diseases.

High-income countries have made significant progress in genomics. The results are informing daily clinical practice (Phillips *et al.*, 2021). Unfortunately, Africa is lagging behind in the study of genomics as well as in the care of PLWRD. Several reasons account for this gap. These are lack of awareness of the burden of PLWD, limited resources for genomics and the absence of structures supporting PLWD programs. These challenges are slowly being overcome with the pricing of whole genomic testing having been reduced from several thousand American dollars to less than one thousand, with the formation of African organizations dedicated to rare diseases and increased international support (Genomics and Fletcher, 2024) (Snelling, n.d.).

In addition, the African genome has been noted to be diverse and unique. Studying it will provide valuable information that will inform clinical practices globally (Ramsay, 2022). As an illustration, the study of only 400 Africans detected new 3 million undocumented variants (Hanchard, n.d.).

This study aimed to aid the progress of reducing the challenges of rare diseases by evaluating the work done to date on the African genome in the rare disease space. There is a need to explore funding opportunities for genomics in rare diseases in Africa.

Funding is a challenge to genomics globally and is more so in low-income countries (Phillips *et al.*, 2021). Three funding models have been described in high-income countries. In the United Kingdom, Belgium, Denmark, Australia and the Netherlands, there is public funding availed by the government at the national level. In Canada, there is also public funding which is approved at the provincial level after some consideration. Thirdly, in countries such as the United States of America, there is mixed private and public funding with variable contributions from both the government and private insurers (Phillips *et al.*, 2021). In South Africa funding is mostly private (Mudau, n.d.).

Government-funded programs are successful as noted in the United Kingdom where the government funded Genomics England 100 000 Genomes Project which successfully sequenced 100 000 patients. This project showed the feasibility and clinical utility of genomic testing in improving the management of patients. This is a step further in realizing health for all (Phillips *et al.*, 2021).

### **1.2 Statement of the problem:**

People living with rare diseases in Africa face challenges in diagnosis and treatment of their ailments.

### 1.3 Significance of Research:

The work in rare diseases in Africa is at the infancy stage. Information needs to be generated to convince relevant stakeholders to create structures that offer optimal care and research for the local populations. Africa needs to identify rare diseases prevalent in their populations as founder mutations may make certain rare diseases more prevalent in certain areas (Ferreira, 2019) (D'Angelo *et al.*, 2020) (Bouzidi *et al.*, 2022). Since the African genome has been noted to be unique and diverse, studying it may help understand or offer solutions to hereditary conditions (Gomez, Hirbo and Tishkoff, 2014).

To coordinate the efforts in Africa, the many organizations afflicted with rare diseases, need to unite. Progressive rare disease management requires enhanced collaboration between communities, governments and all stakeholders ('The Challenge of Rare Diseases', 2018) (Munung *et al.*, 2018). This collaboration will enable the identification of available resources (for example disease-specific organizations), prevent duplication of efforts and garner enough patient numbers to support research. To assist in creating these collaborations, this study will note and document all relevant organizations and funders ('The Challenge of Rare Diseases', 2018). In Canada, there is a collaboration called the Genomic Application Partnership Program which aims to address the limited infrastructure and equity for genetic testing for people with rare diseases. This collaboration has various crucial stakeholders namely patient advocacy, regulators, institutions and researchers and is making headway progress in translating genomics into clinical practice for patients with rare diseases (Phillips *et al.*, 2021). Such a collaboration can help Africa improve services for PLWRD.

In some developed nations, the clinical utility of genomic tests has been appreciated by health insurers. This follows their noting that genomic testing is providing previously elusive diagnoses. Patients are therefore getting timely and appropriate management. This reduces the financial burden of other unnecessary and unyielding tests (Phillips *et al.*, 2021) and avoids unnecessary side effects of drugs (Baine-Savanhu *et al.*, 2023). Precision medicine via genetic guidance is projected to reduce healthcare expenditure (CooperDavid *et al.*, 2017). It is therefore crucial to promote precision medicine for PLWRD in Africa.

### 1.4 Aims and objectives:

- To note the burden, and distribution of rare diseases in Africa.
- To determine the barriers and challenges in the study of genomics in African patients with rare diseases.

- To note the extent of the study of genomics in rare disease patients in Africa.
- To determine if the uniqueness of African genomes is reflected in the genomics of rare diseases.
- To determine the funding models and available resources (organizations) for genomics in rare disease patients in Africa.

## 2. METHODOLOGY AND ANALYSIS:

### 2.1 Study design:

#### 2.1.1 Review scope determination:

A comprehensive and exhaustive literature search in several databases including EBSCO, Google Scholar, PubMed, EMBASE, MEDLINE, Cochrane and Science Direct was done. Grey literature was also sought from the databases.

#### 2.1.2. Review technique:

Medical Subject Headings (MeSH), free text terms and adapted text terms were used in the search with the use of Boolean operators, truncation and wildcards. Search terms used were 'burden of rare disease in Africa', 'causes of rare diseases', organizations funding genomics in low-income countries', 'rare disease organizations in Africa', 'people living with rare disease in Africa', 'barriers and 'challenges in the study of genomics for people with rare diseases in Africa'. An additional search for relevant articles was done by manually searching the reference list of the chosen articles. The search was done up to November 2024.

The researcher screened for eligibility through the process of initially reviewing the study titles, then the abstract followed by a full text review. A conservative approach in the exclusion of studies was used. Those that were uncertain were retained. The Rayyan application was used to check duplicates ("Rayyan | Full-Text Screening," n.d.).

### 2.2 Inclusion and exclusion criteria:

All types of articles that discuss rare diseases and genomics in Africa or people of African descent were included in the review. The included studies should have been published in the last 10 years. The articles were classified into their different types for example but not limited to original articles, case reports or review articles. Cited references within the selected articles were also evaluated. The review was limited to English articles. Abstracts were excluded.

### 2.3 Ethical consideration:

This study was considered low risk by the ethical board as no subjects were involved.

2.4 Data analysis and management:

2.4.1 Data analysis:

For analysis, the researcher extrapolated information that included the study design, sample size, population setting and sample. Relevance of these articles was screened for by the authoring researcher. Zotero reference manager was used for referencing. Ryann's application was used to check for duplication(“Rayyan | Full Text Screening,” n.d.). A review matrix was used to tabulate the author, title, journal, methodology and findings for the selected articles. Articles pertinent to the study but not qualifying for the review were put in the appendix.

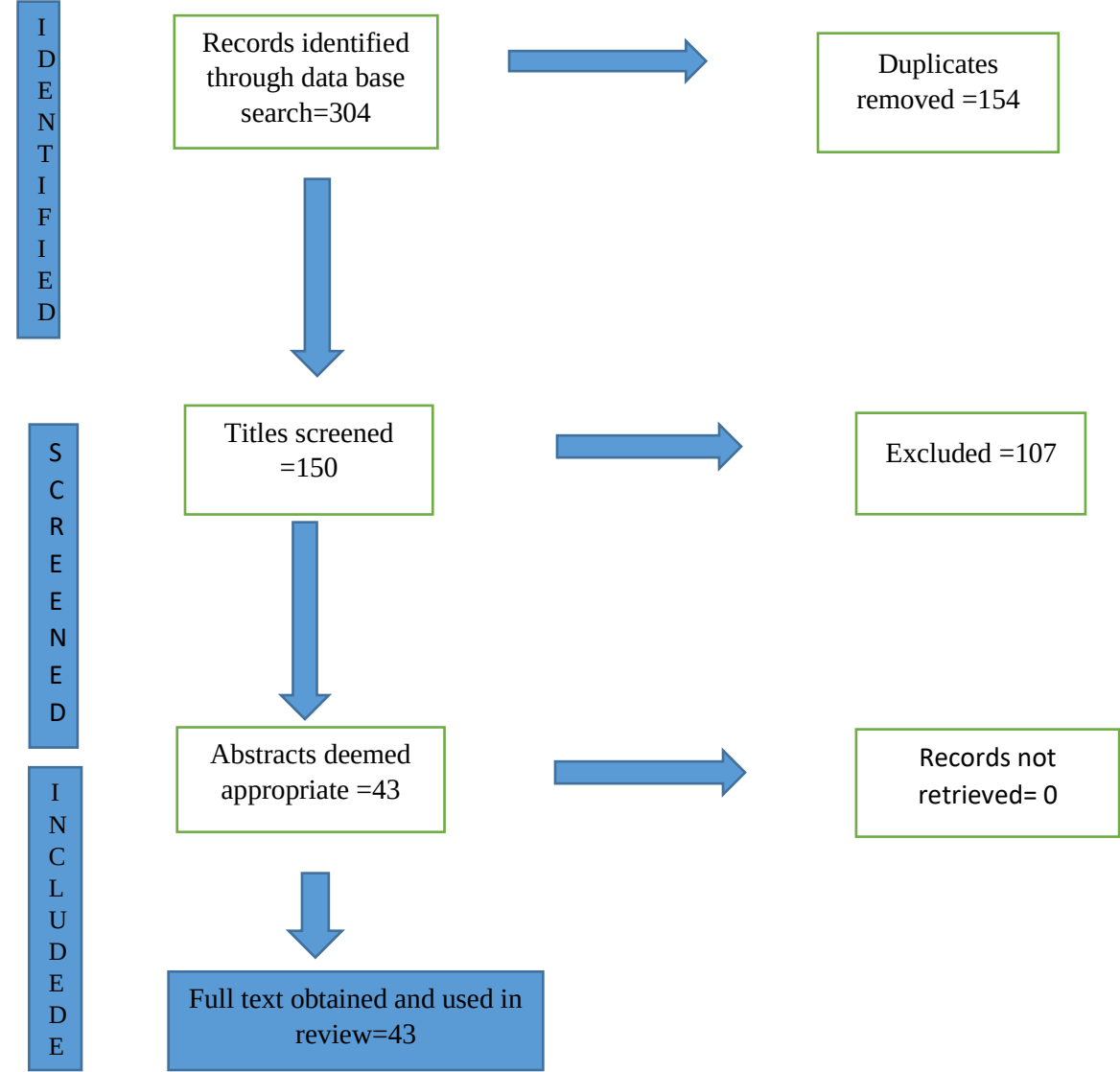
2.4.2 Data quality control:

To ensure relevance and trustworthiness of the results, a critical appraisal tool was used (“Critical Appraisal Tools,” n.d.).

3. RESULTS:

A search of the database yielded 304 articles. After checking for duplication, 154 were removed. Screening for relevance using titles, removed 106 articles. An additional search for relevant articles was done by manually searching the reference list of the chosen articles. This yielded an additional 3 articles. The resultant total articles was 43 (Figure 1). Forty-one of the articles were from journals and two were book chapters. The majority (31) of the articles were reviews, 2 descriptive studies, expert opinions 7, 2 book chapters, 2 qualitative research and 1 experimental study (Fig 2).

Figure 1: PRISMA flow chart for the review



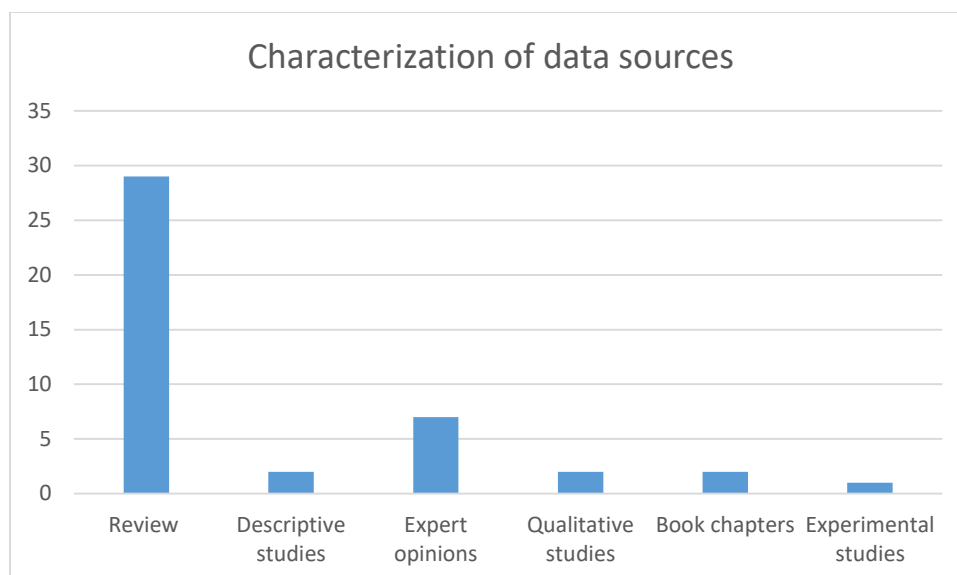


**Figure 2: Characterization of data sources**

Almost half of the first authors/ origin of papers were from developed nations (Europe, America and Australia). From Africa, South Africa had a significant number of articles (8) followed by Tunisia and Egypt which had 2 articles. Other contributory African countries were Morocco, Tanzania and the Democratic Republic of Congo. Most of the articles had Africans who resided in the African continent, 3 were of African Americans from both North and South America.

The challenges noted were mainly paucity of data, lack of knowledge, poor infrastructures, poor governance, financial incapacitation, and cultural and historical barriers. Significant progress has been made to fund genomic services, especially in South Africa, Tunisia, Egypt and Nigeria. Eight of the studies were disease-specific (systemic lupus erythematosus, inherited myopathies, intellectual disability, hereditary eye disease, chronic kidney disease, inherited retinal dystrophy, neuromuscular diseases, RASopathies, Cornelia de Lange, Treacher Collins Syndrome, CHARGE) (Mudau *et al.*, 2024) (Scherr *et al.*, 2019) (De Oliveira *et al.*, 2023) (“Egypt Genome,” 2024) (Mahungu *et al.*, 2022) (Todt, 2021) (Ramsay, 2022) (Snelling, n.d.) (Ilori *et al.*, 2023) (Louw *et al.*, 2023) (Ju *et al.*, 2022) (Owolabi *et al.*, 2023) (Ateia *et al.*, 2023). Data of Africans and Latin Americans represent merely 4% (D’Angelo *et al.*, 2020) (Omotoso *et al.*, 2022) (Bope *et al.*, 2019) (Baine-Savanhu *et al.*, 2023) (Swart *et al.*, 2020).

#### **4. DISCUSSION:**

The 43 articles describe similar barriers which are paucity of data, lack of knowledge, poor infrastructure, governance issues, financial incapacitation, and cultural and historical barriers. Moves to apply genomics to

diagnosis and therapy for PLWRD have been set in Africa, especially in the Northern part. There has been the creation of African reference databases, African genomic consortia, governance frameworks, and international collaborations. Several funding models have also been set in place (Mudau *et al.*, 2024) (Scherr *et al.*, 2019) (De Oliveira *et al.*, 2023) (“Egypt Genome,” 2024) (Mahungu *et al.*, 2022) (Todt, 2021) (Ramsay, 2022) (Snelling, n.d.) (Ilori *et al.*, 2023) (Louw *et al.*, 2023) (Ju *et al.*, 2022) (Owolabi *et al.*, 2023) (Ateia *et al.*, 2023). Data of Africans and Latin Americans represent merely 4% (D’Angelo *et al.*, 2020) (Omotoso *et al.*, 2022) (Bope *et al.*, 2019) (Baine-Savanhu *et al.*, 2023) (Swart *et al.*, 2020).

#### **4.1 Challenges:**

##### **4.1.1 Paucity of data and poor representation:**

A major challenge being faced in African genomics is a paucity of data with poor representation in reference databases (Mudau *et al.*, 2024) (Scherr *et al.*, 2019) (De Oliveira *et al.*, 2023) (“Egypt Genome,” 2024) (Mahungu *et al.*, 2022) (Todt, 2021) (Ramsay, 2022) (Snelling, n.d.) (Ilori *et al.*, 2023) (Louw *et al.*, 2023) (Ju *et al.*, 2022) (Owolabi *et al.*, 2023) (Ateia *et al.*, 2023). Data of Africans and Latin Americans represent merely 4% (D’Angelo *et al.*, 2020) (Omotoso *et al.*, 2022) (Bope *et al.*, 2019) (Baine-Savanhu *et al.*, 2023) (Swart *et al.*, 2020). To fully characterize the African genome, it has been suggested that 3 million individuals from all areas in Africa need to be studied (Wonkam, 2021). The limited availability of African genomic data on reference panels does not only affect clinical practice and disease prevention in Africa but also globally. It results in a knowledge gap of disease etiology, inheritance, pathogenesis and

pharmacogenomics (Snelling, n.d.) (D'Angelo *et al.*, 2020) and ascertainment bias (Jackson *et al.*, 2023).

To make a diagnosis of a rare disease, information from several sources is used. These sources are reference databases, inheritance data, computational predictions and phenotypic overlap (Lumaka *et al.*, 2022). Therefore, absence of African genomics in databases hinders diagnosis. This makes NGS useless for the underrepresented populations (Lumaka *et al.*, 2022). In a study of kidney disease genetics, it was noted that 75% of Eurocentric data could not be extrapolated to Africans due to the lack of similarities between Europeans and Africans (Ilori *et al.*, 2023).

Every so often, African data is extrapolated from research done on Africans or those of African ancestry in the diaspora. Unfortunately, even in the diaspora, the data on people of African descent is also poor.

As an illustration, the largest database for European Americans has 100,000 people whilst that of African Americans has 8000 (Jackson *et al.*, 2023) (Bope *et al.*, 2019). When it is available, the data may not be representative due to the confounding effect of differing geographical locations and social determinants on health outcomes (Hwang, 2024). Black people in the diaspora are also not a true representation of all regions of Africa as some communities in Africa are not migratory. Additionally, the genetics of persons of African ancestry in the diaspora has been modified by high degrees of admixture (Ramsay, 2022) (Omotoso *et al.*, 2022) (Jackson *et al.*, 2023) (Bope *et al.*, 2019) (Lumaka *et al.*, 2022). Africa has the most diverse genetics (Omotoso *et al.*, 2022). The reference panels in NGS for Africans are not representative of this diverse population (Bope *et al.*, 2019). This affects the diagnostic and therapeutic potential of NGS for PLWRD in various ways. Firstly, the paucity of data makes it impossible to correctly assign rare or pathogenic or incidental labels to detected variants. This leads to misdiagnosis with lethal consequences (Bope *et al.*, 2019) (Ilori *et al.*, 2023) (Diallo *et al.*, 2017) (Swart *et al.*, 2020) (Owolabi *et al.*, 2023) (Jackson *et al.*, 2023) (Lumaka *et al.*, 2022) (De Oliveira *et al.*, 2023) (Owete *et al.*, 2024) (Hwang, 2024). Secondly, it results in misinterpretation of the effects of genomic variants in Africans (Ilori *et al.*, 2023). Thirdly, incomprehensive databases hamper the production of efficacious drugs as pharmacogenomics on certain populations cannot readily be generalized especially in this era of precision medicine (Ju *et al.*, 2022). Tragically, formulations tested on a limited sample (usually European) are used on a diverse global population undermining safety. Disastrous effects have occurred as in the case of Efavirenz (an antiretroviral drug) in Zimbabwe. Efavirenz was introduced into the national program as a

first-line treatment for Acquired Immunodeficiency Syndrome. Unknowingly, 20 % of the population have two variant genes that interfere with the metabolism of the drug. This resulted in disastrous effects and attendant public health crisis due to drug defaulting and resistance. Such adverse effects occur in certain ethnic groups can lead to mistrust and vaccine hesitance (Nordling, 2017). Fourthly, the poor representation creates gaps in the epidemiology of diseases and what is not known cannot be actioned (Bope *et al.*, 2019) (Jackson *et al.*, 2023). For example, Systemic Lupus Erythematosus was believed to be rare in Africa until a genomic study in Nigeria described significant prevalence (Hwang, 2024). Fifthly, in this era of precision medicine in rare diseases, the generalization of polygenic risk scores that are Eurocentric to African populations is incorrect (Cooper David *et al.*, 2017) (Owete *et al.*, 2024) (Ilori *et al.*, 2023) (Wonkam, 2021) (Ju *et al.*, 2022). Sixthly, limiting studies to certain populations limits the discovery of new variants. This creates a genomic gap which widens health disparities (Swart *et al.*, 2020) (Hetu *et al.*, 2017) (“A call for global action for rare diseases in Africa - PubMed,” n.d.). (Jackson *et al.*, 2023) (Ilori *et al.*, 2023) (Lumaka *et al.*, 2022). Uncharacterized genetic variants can derail disease eradication or even create a reservoir of lethal strains putting global health at risk (Omotoso *et al.*, 2022).

The poor representation in genetic studies of African is due to lack of infrastructure, limited support for research, exploitation, mistrust, lack of knowledge, few collaborative opportunities due to political, geographical and economic reasons and logistical challenges (Cooper David *et al.*, 2017) (Omotoso *et al.*, 2022) (Jackson *et al.*, 2023) (Ilori *et al.*, 2023) (Lumaka *et al.*, 2022) (Munung *et al.*, 2018). The poor representation is also due to poorly documented data in Africa with very few publications coming out of the continent. The publication of African research in high-impact journals is mostly by non-Africans with unbalanced authorship being common (Kpokiri *et al.*, 2021). Baines-Savanhlu *et al.* noted that some publications on African cohorts actually had no African authors and if the African author was there, they rarely were the first author (Baine-Savanhlu *et al.*, 2023).

Poor data sharing (Ramsay, 2022) and poor coordination (Ateia *et al.*, 2023) efforts throughout the continent and within nations (Alimohamed *et al.*, 2021) are also other challenges facing African nations in the management of PLWRD.

#### **4.1.2 Lack of knowledge:**

Genomics illiteracy occurs at the levels of health professionals, community, patients and even policymakers (Ju *et al.*, 2022) (Owolabi *et al.*, 2023)

(CooperDavid *et al.*, 2017) (Munung *et al.*, 2018). A scoping review by Walters *et al* which focused on the genomic knowledge base of primary healthcare practitioners (PHCPs) noted that they lack knowledge in genomics despite their appreciation of the importance of genetic services. (Walters *et al.*, 2023). PHCPs are usually the first point of call for PLWRD such that there is a need to strengthen their knowledge base so as to improve the care of persons with genetic diseases. Barriers cited were limited resources, cultures, religious beliefs and finances as well as the fact that the field of genomics is rapidly evolving (Walters *et al.*, 2024) (Munung *et al.*, 2018).

#### 4.1.3 Financial constraints:

Genomics is expensive and more so for rare diseases that have limited sample sizes. The limited sample sizes make testing expensive and time-consuming (Mudau *et al.*, 2024). Less than 3% of clinical trials in gene therapy are done in Africa in spite of Africa having 90% of the global disease burden. The low number is due to poor infrastructure, poor profit returns, politics and logistical challenges (Doxzen *et al.*, 2024). Generally, the costs of genome sequencing in Africa are higher than in developed nations (Ramsay, 2022) (Snelling, n.d.) (Louw *et al.*, 2023) (Munung *et al.*, 2018) (Ateia *et al.*, 2023). This is because of high import taxes, low competition and monopolized supply. Similarly, funds for data storage, integration and reuse are limited or not prioritized (Ramsay, 2022).

The inhibitive costs of genomics make African researchers perpetually dependent on international collaborators for access to consumables, equipment and technical support. This dependence trades off independence and control of projects (Snelling, n.d.) (Ramsay, 2022) (Omotoso *et al.*, 2022) (Kpokiri *et al.*, 2021) (Jackson *et al.*, 2023). Often, African samples are shipped to developed nations for analysis (Snelling, n.d.) (Walters *et al.*, 2024).

Sending away human tissue samples for evaluation and analysis in foreign lands is at the expense of local institutions' autonomy. It takes away control of data generated or future studies which may have not been consented to at the initial study (Snelling, n.d). It allows unchecked predatory research which exploits local populations (Jackson *et al.*, 2023). The shipping of samples causes delays in diagnosis and has logistical challenges (Palmer *et al.*, 2024) (Walters *et al.*, 2024) (Doxzen *et al.*, 2024).

It is reported that a mere 1% of global investment in genomics research has been awarded to Africa (Jackson *et al.*, 2023). Generally, LMICs do not easily access global funding for research in genomics for various reasons including structural racism and having fewer established researchers who are competitive at the

international level (Baine-Savanhu *et al.*, 2023) (Jackson *et al.*, 2023). Most research in Africa is led by international investigators (Baine-Savanhu *et al.*, 2023). In as much as international donors can assist in African genomic research for PLWRD, there is a disadvantage in that they can push their agenda while disregarding the local needs or safety (Kpokiri *et al.*, 2021) (Sturdy, 2020) (Ju *et al.*, 2022). These agendas include advances in academic careers and testing of treatment options for developed nations (Wonkam, 2021) (Sturdy, 2020). Dependence on foreign grants causes research regression when terminated, which can be as per schedule or unexpected. The latter has more serious consequences (Omotoso *et al.*, 2022).

In Africa, most governments do not have funding for genomic services as the limited health budget is directed towards other life-threatening priorities such as nutrition, safe water, civil unrest and communicable diseases (D'Angelo *et al.*, 2020) (Wonkam, 2021) (Alimohamed *et al.*, 2021) (Ju *et al.*, 2022). The cost of gene therapy for one patient can save lives from dying from common conditions (Doxzen *et al.*, 2024). However, there is a moral obligation to perform genomics in Africa to reduce health disparity for PLWRD. ("Precision ophthalmology: a call for Africa not to be left in the dark | Gene Therapy," n.d.) ("A call for global action for rare diseases in Africa - PubMed," n.d.). The available genomic services are paid out of pocket or donor-funded. Reimbursement from insurers is not yet clear due to pricing differences and unproved benefits (CooperDavid *et al.*, 2017).

#### 4.1.4 Historical Background:

One of the barriers to genomics in rare diseases noted by Scherr *et al.*, 2019 is poor recruitment. For example, in America where genomic sequencing is available and health services are advanced, fewer African- Americans are recruited into the studies. Many factors were cited for this poor recruitment. The poor recruitment is partly due to mistrust and fear of research, research institutions and health professionals. This is worsened by existing mistreatment in health institutions. There are many negative views on the intention and conduct of studies (Scherr *et al.*, 2019).

On the intention of studies, there is fear of gene manipulation for elimination of the inferior race (eugenics and even genocide) and fear of the study findings being used for discriminatory purposes whereby persons with certain genotype can be excluded from certain services, for possible criminal investigations, for surreptitious surveillance or for cloning purposes. There is also fear of exploitation with the results believed to be used to better lives of whites and perceived uselessness of research in which results of research may not benefit them due to existing health inequities (Scherr *et al.*,

2019) (Snelling, n.d.) (Jackson *et al.*, 2023) (D'Angelo *et al.*, 2020). The inhibitive fear and mistrust have a historical background in which Africans have been violated in research. The most popular is the case of Tuskegee syphilis in which a controversial study was done on over 400 male African American patients. The study aimed to note the effects of untreated syphilis. Patients were therefore observed with no treatment despite it being available during the course of study. The consequences were fatal (Gamble, 1997). In Zimbabwe, a discriminatory practice was practiced during colonial times. The colonialists studied human blood for sickle cell for a presumption of purity and used the information to settle land disputes (Fullwiley and Gibbon, 2018).

In the conduct of research, there is mistrust of data privacy and fear of the safety of interventions. This is due to previous unethical practices (Jackson *et al.*, 2023) (Doxzen *et al.*, 2024). These unethical practices go unchecked due to African countries not having effective ethics committees. At times, local ethical committees are created by foreign researchers resulting in questionable independence of review processes. Some committees are even formed without consulting local research centers (De Oliveira *et al.*, 2023). The absence of local representatives on these boards means there is limited advocacy, limited evaluation and monitoring of ethical practices. However, even with sought and well-documented ethical approval from the level of researchers to the editorial level, ethical practices and meaningful engagements with communities in Africa fall short according to Ramsay (Ramsay, 2022). There continues exploitation and limited benefit of the study participants. Other unethical practices in LMICs are populations used in clinical trials failing to access the drug when on the market, bribery and bad data sharing (De Oliveira *et al.*, 2023) (Ramsay, 2022) (Doxzen *et al.*, 2024).

In the places where there is access to genomic testing, there are also healthcare pathway challenges. Vulnerable communities face non-referrals due to bias or discrimination (Baine-Savanhu *et al.*, 2023). The uptake of the services is also affected by cultural appropriateness (Scherr *et al.*, 2019) (Baine-Savanhu *et al.*, 2023).

#### 4.1.5 Cultural background:

Cultural appropriateness refers to methods and teachings that resonate with people's languages, gender roles, beliefs, daily practices, gender roles, society hierarchy, and decision-making pathways among other considerations (D'Angelo *et al.*, 2020) (Scherr *et al.*, 2019) (Ilori *et al.*, 2023) (Hetu *et al.*, 2017). It has a strong bearing on the uptake of services (Baine-Savanhu *et al.*, 2023) (Scherr *et al.*, 2019).

Differing language pose a significant barrier to genomics for PLWRD. The process of communication is particularly challenging. People fail to understand each other. This can be due to medical jargon or failure to correctly translate to local languages as there are no words for genetic terms (Diallo *et al.*, 2017) (Scherr *et al.*, 2019) (D'Angelo *et al.*, 2020). Incorrect translation can lead to the loss of key points and can even lead to the introduction of fallacies/ misconceptions. Ineffective communication can also be by not involving families in decision-making in societies which practice shared decision-making. An anecdotal study at a genetic clinic in Zimbabwe revealed that the absence of fathers at hospital visits delayed genetics testing as the mothers would need to go first seek paternal approval. This also led to stigmatization as poorly informed relatives blame the “womb” that carried the child. Communication of results is also a challenge as frequently the results are vague, have incidental findings or affect other family members (El-Attar *et al.*, 2022). This is made worse by the shortage of genetic counsellors with poor cultural diversity in those available (D'Angelo *et al.*, 2020) (Bope *et al.*, 2019) (Ilori *et al.*, 2023) (Cooper David *et al.*, 2017). Language barriers necessitate multilingual support for data management as well as the need to standardize computational pipelines (Snelling, n.d).

A cultural issue to consider is the action after genetic testing. The results have a bearing on future pregnancies and bring about the issue of termination of pregnancies. Cultural beliefs in most African countries are against termination of pregnancy. This brings futility to the use of genomics in rare disease diagnosis and management (Walters *et al.*, 2024) (El-Attar *et al.*, 2022). There is the stigma of having a genetic disease and the consequences for other relatives in cases of inherited disorders. There is also the revealing of unanticipated diseases or risk factors which can be stressful. This also a reason for the low uptake of genetic services in developed nations. Detected risk factors or diseases can lead to discrimination in insurance, employment and education (Scherr *et al.*, 2019), (Hetu *et al.*, 2017), (El-Attar *et al.*, 2022).

Culture influences the clustering of rare diseases and their management. North Africa (Morocco, Algeria, Tunisia, Egypt) has done considerable research in the genomics in the rare disease space (“Egypt Genome,” 2024), (Mahungu *et al.*, 2022), (Romdhane *et al.*, 2024), (“Inherited myopathies in the Middle East and North Africa,” 2022), (Baine-Savanhu *et al.*, 2023) (El-Attar *et al.*, 2022). In these closely knit communities, the practice of consanguinity and endogamy is a major cause of the clustering of rare diseases (Bouzidi *et al.*, 2022) (“Inherited myopathies in the Middle East and North Africa,” 2022), (Zayed, 2016), (Romdhane *et al.*, 2024), (Baine-Savanhu *et al.*, 2023), (Ateia *et al.*, 2023). In a

review of 413 North African families with eye diseases, more than 75% of family studies were consanguineous. The consanguinity causes recessive transmitted disorders to be more common (Bouzidi *et al.*, 2022) (“Inherited myopathies in the Middle East and North Africa,” 2022). Consanguinity is more practiced in the North of Africa than in the South with reported rates ranging from 20% to as high as 60% in the former. This high rate of consanguinity is also high in similar populations residing in the diaspora (Bouzidi *et al.*, 2022) (Mahungu *et al.*, 2022) (Romdhane *et al.*, 2024).

The high burden of rare diseases in North Africa may be a big driver to genomic research as well as the fact that the North have comparatively robust health systems. The consanguinity with the presence of many affected generations provides learning opportunities for characterizing phenotypes and genotypes of rare diseases (Omotoso *et al.*, 2022) (Sturdy, 2020).

#### **4.1.6 Resources:**

Lack of expertise (especially bioinformatics) hampers genomic practice in PLWRD in Africa (Ju *et al.*, 2022). Genomics requires significant expertise in complex data analysis which is generated by high throughput computational software (Snelling, n.d.). The genomic illiteracy is due to few training centers in the continent (“A call for global action for rare diseases in Africa - PubMed,” n.d.). In institutions, there is a stagnant hierarchy that discourages potential researchers. There are no opportunities (research posts), programs (degrees) or incentives to train researchers in genomics. There is also no motivation, rewarding salaries or job opportunities for people to study degrees in genetics (El-Attar *et al.*, 2022).

Professionals in the study of genomics for rare disease patients in Africa face the challenge of limited time due to teaching and other clinical commitments (Ramsay, 2022) (Omotoso *et al.*, 2022) (Alimohamed *et al.*, 2021) (Ju *et al.*, 2022). These manpower challenges are worsened by brain drain. Even Tunisia which has one of the best genomic researchers in Africa, suffers from brain drain (Hamdi *et al.*, 2024). Brain drain leads to the loss of trainer experts making planning long-term projects difficult. Many genomic projects therefore source experts out of the continent (Snelling, n.d.) (Ramsay, 2022) (Omotoso *et al.*, 2022) (Kpokiri *et al.*, 2021) (Jackson *et al.*, 2023).

The dependence on foreign researchers who come from different geographical and psychosocial backgrounds has many challenges, especially in communication and work ethics. It also increases the time taken for projects (Snelling, n.d.).

Genomics requires complex, high throughput secure computational software which is not available in most African centers that help PLWRD. To further compound

these computational challenges are suboptimal internet connectivity, unreliable power, inability to use advanced software and limited local storage or cloud-based data storage facilities. These challenges also impede interoperability between geographically distant institutions which is a prerequisite for most collaborations (Snelling, n.d.) (Bope *et al.*, 2019) (Lumaka *et al.*, 2022). In South Africa, where comparatively significant genomics in Africa is being done, it is noted that these facilities are only available in urban cities. This limited accessibility worsens health disparities across socioeconomic groups. (Mudau *et al.*, 2024) (Snelling, n.d.) (Ilori *et al.*, 2023) (Walters *et al.*, 2024) (Munung *et al.*, 2018).

Genomic material and its reagents require the cold chain (- 80 degrees Celsius). There is an inability to maintain this cold chain due to unreliable electrical power supplies and inadequate cold chain equipment. There is also a lack of technical staff to maintain and repair the expensive genomic machines (Snelling, n.d.).

#### **4.1.7 Governance:**

There is a lack of frameworks to govern research in terms of ethics, safeguarding and other legalities. These are needed to guide data sharing, intellectual property, commercialization and translational research (Ju *et al.*, 2022). These also have cost implications. The developing nations are therefore unable to translate research findings into clinical practice. Developed nations then benefit from research that would have been done in LMICs (Ju *et al.*, 2022) (Munung *et al.*, 2018).

African research institutions lack guidelines on the authorship of publications done in their institutions. Measures to prevent exploitative research are not set or followed (Fullwiley and Gibbon, 2018). This occurs in the background of corruption, political mismanagement, and abuse of research funds (Omotoso *et al.*, 2022).

There is absence of policies to instruct foreign researchers to report findings to investigated communities (Bope *et al.*, 2019). There is also absence of clear guidelines on the management of incidental findings (Bope *et al.*, 2019).

#### **4.2 Genomic diversity:**

Africa is believed to be the origin of the modern human race. It has been noted to have the greatest diversity of genome with other continents having a subset of the African genome (De Oliveira *et al.*, 2023) (Todt, 2021) (Jackson *et al.*, 2023) (Bope *et al.*, 2019) (Palmer *et al.*, 2024) (Wonkam, 2021) (Wonkam, 2021) (Alimohamed *et al.*, 2021) (Diallo *et al.*, 2017) (Ju *et al.*, 2022) (Fullwiley and Gibbon, 2018) (Owolabi *et al.*, 2023).. This greater variation has also been observed in those of African ancestry in the diaspora (Mudau *et al.*, 2024) (De Oliveira *et al.*, 2023) (Scherr *et al.*, 2019) (Mahungu

*et al.*, 2022). According to Swart *et al.*, Africa has approximately 3 million DNA (Swart *et al.*, 2020). The diversity is greatest in the Sub-Sahara region (Romdhane *et al.*, 2024). This genomic diversity is increased by miscegenation (De Oliveira *et al.*, 2023). African countries like Tunisia with high rates of endogamy (98%) and consanguinity (38%) have the narrowest diversity in genomics (Romdhane *et al.*, 2024). The diversity of the African genome contributes to disease phenotypes, response to pathogens, ancestry-specific risk of disease and response to treatment (Swart *et al.*, 2020). In an experimental study in South Africa, to evaluate the feasibility of custom-designed targeted next-generation sequencing, they noted a lower detection rate due to the diversity of the African genome and the current poor representation (Mudau *et al.*, 2024). With Africa being projected to be the most populous by 2050, and it having the world's youngest population, and there being poor representation in genomic studies, a wide genomic gap is being created (Omotoso *et al.*, 2022) (Jackson *et al.*, 2023) (Scherr *et al.*, 2019) (Ju *et al.*, 2022). A genomic gap is defined as “the (intentional or unintentional) omission of genomic data of a group or subset of a population by researchers in a scientific effort or research, which requires inclusive genomic data” (Omotoso *et al.*, 2022).

The importance of the uniqueness of the African genomes has the potential to provide diagnostic solutions for human disease. For example, the African genetic structure has a low linkage of variants which makes the identification of pathogenic variants easier (Alimohamed *et al.*, 2021). The benefits of adding African data to the reference database were demonstrated by just adding 426 African genomes to the Human Heredity and Health in Africa (H3A). It led to reclassifications of pathogenic variants to benign due to their prevalence in the African community (Baine-Savanhu *et al.*, 2023).

### 4.3 Progress to date:

A multidisciplinary approach has been used to address the genomic gap. The efforts have been to generate African genomic data to improve data availability, promote precision medicine, avail funding, overcome cultural barriers, perform ethical research and capacitate African institutions in research of genomics in rare diseases (Omotoso *et al.*, 2022). Progress has been made easier by cheaper genomic sequencing (Snelling, n.d.).

#### 4.3.1 To address data paucity:

##### 4.3.1.1 Data generation:

Significant research on rare diseases using genomics has been done mostly in North Africa (Mahungu *et al.*, 2022). In Sub-Saharan Africa, there is comparable research in South Africa (Mahungu *et al.*, 2022) (Mudau

*et al.*, 2024) (Omotoso *et al.*, 2022) (Lumaka *et al.*, 2022). To address the paucity of the African genome, the Human Heredity and Health in Africa (H3A) consortia was assembled. H3A aims at closing the genomic gap on African genomes (Mahungu *et al.*, 2022) (De Oliveira *et al.*, 2023). Other initiatives to address the disparity in gene diagnostics and therapies are disease-specific with organizations such as the International Centre for Genomic Medicine in Neuromuscular Disease (Mahungu *et al.*, 2022).

To tackle the diagnosis odyssey of patients with rare diseases, the National Institutes of Health (NIH), instituted the Undiagnosed Disease Program (UDP) and the Undiagnosed Disease Network. The UDP brings together researchers, clinicians, counsellors and patient organizations. It has more than 161 (5 are from Africa) members which share biological material and analytical skills (Sturdy, 2020). These programs promote the use of genomics in clinical practice to facilitate early and accurate diagnosis. The experts meet regularly to discuss referred undiagnosed cases. In the UDP, each collaborator has a significant role to play. Of particular mention, is the patient area where patients share their information virtually for clinicians to diagnose. The sharing of data and samples in the UDP is done after seeking appropriate consent and standardized data-collecting tools. To promote timely access to diagnosis and capacity building, well-resourced members are connected to new or poorly resourced ones (Palmer *et al.*, 2024). The International Rare Disease Research Consortium set timely diagnosis at 1 year (D'Angelo *et al.*, 2020) (Palmer *et al.*, 2024). In addition to making a diagnosis, UDP also provides family-centered information on rare diseases which can be used for counselling by local UDPs. They ensure that the information is easy to translate and understand (Palmer *et al.*, 2024). Regionally, South Africa has an Nngwe initiative whose aim is to reduce the number of undiagnosed cases (Doxzen *et al.*, 2024).

Pushed by the high burden of genetic diseases, secondary to consanguinity and old maternal age, Egypt has been active in genetic studies arena since the 1960s. They have studied more than 21000 families with rare diseases. In 2002, they established a national genetic counselling program and comprehensive referral pathway from primary to tertiary health care. Some genetic tests are available for free with newer technologies not so readily available or are paid out of pocket. In 2020, to safeguard its people, it passed the data protection law and the clinical research law. They also increased funding for research (El-Attar *et al.*, 2022).

A measure to address the paucity of data is the purposeful increase in the number of publications from Africa (Baine-Savanhu *et al.*, 2023) (Walters *et al.*,

2024) (Owolabi *et al.*, 2023). Northern Africa has spearheaded this move as noted in a systemic review by Baine-Savanhu *et al.* The authorship of most publications from Northern Africa is predominated by investigators from the region (Baine-Savanhu *et al.*, 2023) (Hetu *et al.*, 2017). To shift the imbalance in authorship, the Senegalese recently protested against unfair authorship practices. This has led to the development of fairer practices. Similarly, researchers from South Africa clearly stated on international forums, the need to end exploitative research (Fullwiley and Gibbon, 2018).

To enhance African research in rare disease genomics, Mahungu suggested collaborations with African researchers in genomics. This will help pool funds together, reduce unnecessary duplications and also increase the number of cases (Mahungu *et al.*, 2022).

Besides research on genomics variants on African people, there is a need to research their perceptions of genetic studies in terms of appropriateness, confidentiality and handling of biological specimens (Wonkam, 2021). This is crucial to improve the uptake of services. It also ensures that genomic research in Africa is designed to meet the needs of the continent (Munung *et al.*, 2018). To fill the knowledge gap in rare diseases in Africa by characterizing rare diseases clinically, Snell *et al.* in their review article, propose the development of globally inclusive atlases of single-cell RNA. These atlases will inform future research and guide precision medicine (Snelling, n.d.)

#### **4.3.1.2 Data availability:**

Available data on the African genome should be made accessible. H3A has done significant work in setting up programs to generate data. There is the creation of the African Genome Variation Data Base by H3A (Todt, 2021). Within the H3A, there is a Rare Disease Work Group that meets monthly. Bope *et al.* created an inventory of African Whole Genome (Bope *et al.*, 2019). On national levels countries such as Nigeria have made huge strides in generating genomic data (Omotoso *et al.*, 2022). In Nigeria, the creation of dedicated funding helped shift from passive capture of Systemic Lupus Erythematosus cases to active searches with creation of registry specific. The identification of new cases increased significantly from detecting 5 cases to 746 cases per annum (Hwang, 2024). Health institutions should be encouraged to create disease-specific rare disease registries and provide dedicated funding to sustain them (Hwang, 2024) (Snelling, n.d.).

Similarly, Tunisia did a situational analysis using a specifically created data analysis team. The work of the team was to catalogue available bioinformatics infrastructure, wet labs and expertise. They created detailed patient-centered pathways from tests to results

with clearly defined roles of involved clinicians. For effective communication, a detailed plan was developed which involved a dedicated website, press releases and project logos (Hamdi *et al.*, 2024). South Africa and Egypt have also set up their genomic reference database (“Egypt Genome,” 2024) (Lumaka *et al.*, 2022).

The quality and quantity of African data can be improved by data sharing (Lumaka *et al.*, 2022). For data to qualify for sharing, African researchers need to put in place standards that ensure that data is findable, accessible interoperable, reproducible and unidentifiable according to the FAIR principles (“Operationalizing the CARE and FAIR Principles for Indigenous data futures | Scientific Data,” n.d.). This involves use of electronic health records, using standardized documentation of research processes, seeking the reuse of data in the informed consent process and setting up governance frameworks that prioritize standard ethical practices (Ramsay, 2022) (Omotoso *et al.*, 2022).

Measures to increase African data availability include raising awareness of the importance of data sharing, by having consent to large-scale data sharing being part of research methodologies and by encouraging data sharing in public resources such as DECIPHER, ClinVar, and MatchMaker Exchange. The University of Kinshasa is currently using the latter two (Lumaka *et al.*, 2022). Sharing of data enables extrapolation of African research findings to those of African descent in the diaspora as in the case of Canada requesting information on variants from the H3A following detecting a peculiar illness in 3 Africans (Lumaka *et al.*, 2022).

To match genotypic data to phenotypic data, there has been improved access to phenotypic data repositories such as Orphanet and Genetic and Rare Disease Information Centre. However, there is need to fully characterize African phenotypes as they are not exact to those of other ethnicities (“A call for global action for rare diseases in Africa - PubMed,” n.d.). To encourage data sharing, researchers need to be aware of measures used to safeguard the data (Snelling, n.d.).

To safeguard data, the Tunisian genome project adapted guidelines from the H3Africa project. Their data is stored in a national portal with controlled access by a specialized multidisciplinary team (legislators, ethics, data analysis, patient advocates, anthropologists, and bio bankers). To ensure cost-effectiveness, they created a health economic task force for guidance. For capacity building and strengthening, they are collaborating with regional and international initiatives such as the Assessing Genomic Diversity in Africa project and Personalized Medicine in North Africa (Hamdi *et al.*, 2024).

To address the genomic gap, there is the Genomic Medicine Alliance which collaborates with main partners among which is the DRIFT (Discovery

Research Investigating Founder Population Traits (Hwang, 2024). Other organizations related to genomics in developing nations are the Global Alliance for Genomics and Health the Human Genome Organization) (Cooper David *et al.*, 2017). There is also the Human Variome Project which gathers information on genetic variation and its effect on human health at the international level. The information is curated and interpreted. This information is shared freely to inform clinical practice (Cooper David *et al.*, 2017).

#### 4.3.2 Precision medicine:

Precision medicine is the future of comprehensive care for PLWRD. The progress in Africa to achieve this has begun in South Africa with the South African Precision Medicine Initiative (CooperDavid *et al.*, 2017). Similarly, Egypt is setting up its precision medicine program (Ateia *et al.*, 2023). The use of genomic modifiers in the treatment of Sickle cell disease, a rare disease that affects Africans, is underway with some positive results (Doxzen *et al.*, 2024).

To pave the way for precision medicine, a fast-second winner strategy has been suggested by CooperDavid *et al* to help low-income countries design their precision medicine programs. This is done by those in poorly resourced nations beginning their research midstream from discoveries and mistakes made by others (CooperDavid *et al.*, 2017).

#### 4.3 To address finances:

To overcome the cost associated with running tests for a few samples, grouping is a solution for poorly resourced nations (Louw *et al.*, 2023) (Mudau *et al.*, 2024). The feasibility of a multi-disease NGS-targeted gene sequencing by Mudau in South Africa, demonstrated a cost reduction of 1000%. Samples of patients with different diseases of monogenic etiology were batched together in a single run using next-generation sequencing. The multi-disease sequencing also reduced turnaround time.

However, for some conditions, they had low detection rates. They suggested that accuracy could be improved by grouping phenotypically similar diseases (Mudau *et al.*, 2024).

Egypt has established a well-coordinated genomic project at the national level as a result of government support. The government provided funding and has set favorable policies. Many government-supported projects succeed (El-Attar *et al.*, 2022) (Phillips *et al.*, 2021). Sickle cell disease has a significant prevalence of 3.9% in Tanzania. The Tanzanian government recognized this and has prioritized genomic research for Sickle Cell Therapy. It pledged funds towards the project and collaborated with the Bill and Melinda Gates

Foundation. The local universities took up the task and potential is being realized (Doxzen *et al.*, 2024). The role of the government as an enabler is recognized in this case.

So, there should be consistent advocacy for local governments to prioritize funding for research in genomics for PLWRD (Snelling, n.d.).

To reduce reliance on foreign funds for research, African institutions should consider commercialization of their research findings. This is done by translation of findings into medical products and clinical processes. This needs assurance of ownership of research and intellectual properties from the commencement of the study (Omotoso *et al*). Lower-income countries should also consider crowdfunding. This is getting small contributions from the members of communities. This has many benefits as it will: 1. create local partnerships 2. create a sense of ownership 3. ensure that priorities of the communities are met and 4. enable sustainability. Crowdfunding is done through public engagement (Kpokiri *et al.*, 2021) (Doxzen *et al.*, 2024). Other fundraising initiatives include the engagement of private insurers for reimbursement considerations (CooperDavid *et al.*, 2017) and the use of tax and market incentives to the private sector to encourage their funding of genomic research (Wonkam, 2021).

#### 4.3.4 Solutions to cultural barriers:

Community-based approach can provide solutions to cultural barriers. The approach can tackle the problem of poor recruitment as it builds trust and a sense of ownership. Community-based approach entails involving the community from the beginning of the study so that they fully understand the purpose and benefits of the study. It allows them to make any necessary adjustments. This also provides an opportunity for the investigators to know what communities collectively value. To ensure a community-based approach, the researchers need to avail all necessary resources. Throughout the study, there should be continuous communication and engagement. At the end of the research, there has to be an acknowledgement of the community contribution and meaningful feedback on results. The communication should be culturally appropriate and in meaningful language (Scherr *et al.*, 2019) (De Oliveira *et al.*, 2023) (Jackson *et al.*, 2023). Trust is built by care, genuine engagement and communication. It is also a product of shared experiences and shared expectations (Jackson *et al.*, 2023) such that one way of improving engagement is using persons trusted by the communities. It is stated that African Americans are more likely to participate in studies led by Historically Black Colleges. This is more so when local physicians take key roles in the study (Jackson *et al.*, 2023). A successful community-based

approach has been facilitated by the African Genomic Medicine Training Initiative by upskilling local health professionals via workshops (Nembaware *et al.*, 2019). The shared background ensures that belief systems and perceptions are matched (Scherr *et al.*, 2019) (Jackson *et al.*, 2023).

It has a positive long-term impact on the capacitation of native populations (D'Angelo *et al.*, 2020). In the study of Indigenous people, the Australian researchers engineered a 'bicultural method' in which for projects in the community a non-Aboriginal health worker is paired with an Aboriginal health care worker to avert cultural misconduct and also for linguistic purposes (D'Angelo *et al.*, 2020).

To foster a positive attitude to genomic research, appropriate educational material should be availed to improve the knowledge base. Knowledgeable people are more likely to participate in research. A group of African American women who had extensive knowledge of ethical research conduct expressed willingness to participate in genomic research (Scherr *et al.*, 2019). However, of paramount importance, is appreciating that attitude to genomic research is influenced by values and beliefs as well (Scherr *et al.*, 2019).

Governments should enact legislation that supports genetic research and actions that safeguard its people. Patient advocacy groups have been key in the formulation of these ("Precision ophthalmology: a call for Africa not to be left in the dark | Gene Therapy," n.d.) (Ju *et al.*, 2022). South Africa has successfully set national policies for genetic services with however limited implementation (Walters *et al.*, 2024).

#### **4.3.5 Ethical research:**

To ensure proper ethical processes, research in vulnerable communities (descendants of sub-Saharan) in the Latin American Caribbean) now require consent at the level of the community so as to respect the politics, linguistics cultures and religious beliefs (De Oliveira *et al.*, 2023) (Jackson *et al.*, 2023). Some nations are safeguarding vulnerable communities at the national level. In Brazil, research on isolated vulnerable communities is not permitted unless it is of direct benefit to them (Walters *et al.*, 2023). To reduce exploitation, several authors emphasized the need for African researchers to be custodians of their data and act by all means to protect the local study participants. They should also make cognizant plans for ensuring benefit to the local populations. This can be done by promoting translational science (Jackson *et al.*, 2023) (Ramsay, 2022) (D'Angelo *et al.*, 2020) (Omotoso *et al.*, 2022) (Ilori *et al.*, 2023) (Hetu *et al.*, 2017). Regardless of funding, research should be led by local investigators (Ilori *et al.*, 2023).

Transparency on study protocols and data sharing are reported to improve participation (Scherr *et al.*, 2019) (Jackson *et al.*, 2023). However, a compromise has to be reached on data sharing and data protection. Limited sharing can increase disparities whilst broad sharing can impinge on the rights of tissue donors (D'Angelo *et al.*, 2020). Fortunately, research institutions can follow the internationally approved CARE and FAIR principles for the ethical use of data.

The CARE principles are "Collective benefit, Authority to control, Responsibility Ethics". The FAIR principles are "Findable, Accessible, Interoperable, Reusable" ("Operationalizing the CARE and FAIR Principles for Indigenous data futures | Scientific Data," n.d.). Governments should be urged to craft policies that help self-guard data and govern bio specimen storage (Jackson *et al.*, 2023) (D'Angelo *et al.*, 2020) (Snelling, n.d.).

By investing in research infrastructures, African research communities are empowered to negotiate favorable and mutually beneficial terms with international collaborators. The mutual benefits are equal access to data, co-authorships, funds allocation and rightful ownership of patents (Snelling, n.d.). The successful recall of possibly abused samples from the Wellcome Sanger Institute by the University of Pretoria is a good example of stewardship of African Researchers ("Major U.K. genetics lab accused of misusing African DNA | Science | AAAS," n.d.).

To address the ethical challenges in genomic research, there has been significant progress in establishing ethical boards and research ethics committees in Africa. The H3A, with the African Society of Genetics, the Wellcome Trust and the National Institute has done significant work in promoting research protocols that are ethical, legal and socially appropriate. Awareness has been raised through workshops, research and international collaborations (Snelling, n.d.).

To reduce the misalignment of values of foreign researchers and local study participants, the former before commencing the study should be educated on cultural humility and cultural competence. These should be spelt out in the rules of engagement. The concept of cultural humility is acknowledging that cultures are different and that one should be able to put aside own cultural biases to learn about other cultures. This is important when dealing with bio specimens. Several communities consider bio specimens sacred and need special handling (Snelling, n.d.) (D'Angelo *et al.*, 2020) (Omotoso *et al.*, 2022). Evaluation of the cultural competence of researchers should be done periodically. Countries are urged to come up with culturally sensitive protocols (Hetu *et al.*, 2017). Similarly, material to improve genetic literacy should be made available to the communities so as to improve their knowledge and

subsequently their cooperation (D'Angelo *et al.*, 2020). To ensure, culturally sensitive practices, IRDiRC has a specific task force that will focus on cultural safety, linguistics, and ontology among many others (“A call for global action for rare diseases in Africa - PubMed,” n.d.). The need to acknowledge and appreciate research participants' sovereignty and rights cannot be overemphasized (D'Angelo *et al.*, 2020) (De Oliveira *et al.*, 2023) (Omotoso *et al.*, 2022).

#### 4.3.6 Capacity building:

Since 3 million individuals are needed to fully characterize the African genome, a Three Million African Genome project is being launched (Wonkam, 2021). The Human Pangenome Project which is an extension of the Human Genomic Project aims to note and address the gaps in the current human reference genome framework. The ‘pan’ in pangenome emphasizes inclusivity (Snelling, n.d.).

Research in Africa can be strengthened by investing in research infrastructure and creating local training programs. Research development training programs should be part of undergraduate training through to postdoctoral levels (“Precision ophthalmology: a call for Africa not to be left in the dark | Gene Therapy,” n.d.) (Snelling, n.d.) (Wonkam, 2021) (Ju *et al.*, 2022) (Owolabi *et al.*, 2023) (Diallo *et al.*, 2017), (Jackson *et al.*, 2023). In America, the study of genomics begins in primary schools (CooperDavid *et al.*, 2017). In sub-Saharan, South Africa has formal training in genetics (clinical geneticists, genetic counsellors (Walters *et al.*, 2024). It has been undertaking initiatives to reduce the translational gap in gene therapies by undertaking clinical trials in hemophilia. To enable this, South Africa has research and regulatory frameworks that meet international standards (Doxzen *et al.*, 2024). In Tunisia and other countries, there are plans to revise broad academic curriculum and education programs to promote genomics and bioinformatics (“Precision ophthalmology: a call for Africa not to be left in the dark | Gene Therapy,” n.d.) (Walters *et al.*, 2024). African young researchers are being trained in scientific writing and bioinformatics by specific educational grants.

There are also young researchers' forums at conferences to strengthen data dissemination skills (“AFREhealth - The African Forum for Research and Education in Health,” n.d.). As most high-powered conferences are out of reach for African researchers, there is a need to increase the quality and quantity of regional conferences in genomics for rare diseases. For these conferences to be successful, recognized African researchers in genomics should be invited as they attract sponsorship (CooperDavid *et al.*, 2017).

Various programs are available for the continuous education of educated health professionals. H3ABioNet project offers online courses in genomics (Munung *et al.*, 2018). Research culture can be promoted by making allowances for dedicated time for clinicians (Ramsay, 2022) (Omotoso *et al.*, 2022). The failure of health professionals to recognize phenotypes that need genetic evaluation can be reduced by increasing the number of African facial dysmorphology in phenotypes databases (Baine-Savanhu *et al.*, 2023) and creating phenotypic atlases with matching genotypes for African regions (Swart *et al.*, 2020).

To foster more community engagement and mutual empowerment, the communities need to appreciate research and suggest priority areas. Several engagement models can be employed to achieve this (Snelling, n.d.). The World Health Organization has a health promotion guide for community engagement. The five key actions of this guide are “(i) developing personal skills, (ii) strengthening community action,

(iii) creating supportive environments, (iv) building healthy public policy, and (v) reorienting health systems” (Community Engagement, 2020).

The shortage of genetics counsellors can be dealt by educating all medical personnel in all disciplines in genetic counselling. This has been successful in some parts of Africa. It has created a diverse workforce (“A call for global action for rare diseases in Africa - PubMed,” n.d.). It is crucial to ensure that all ethnic groups are trained in genetic counselling to enhance cultural appropriateness. (D'Angelo *et al.*, 2020). Next Steps Roadmap is a toolkit available for individualized electronic counselling that can strengthen genetic counselling (“A call for global action for rare diseases in Africa - PubMed,” n.d.). There is African Genomic Medicine Training Initiative which provides virtual genetic courses to upscale competencies in African health professionals (El-Attar *et al.*, 2022). To reduce the failure to recognize rare diseases due to the limited clinical expertise of health practitioners, the European Commission established the European Reference Networks which is a readily available source of information on rare diseases. Such databases can be created for specific populations with high incidences of rare diseases. An example is the consanguineous Irish Traveler community with a high incidence of rare diseases. A catalogue of these has been created and is accessible to clinicians to ensure that diagnoses are not missed (D'Angelo *et al.*, 2020). Similarly, Morocco has established a nation-specific database referred to as the Moroccan Genetic Disorders Database for similar purposes. Ethnic or national-specific databases are crucial as rare diseases can be more prevalent in certain geographical areas or certain persons such that data from

elsewhere may not be useful. Other such establishments have been reported in Africa (De Oliveira *et al.*, 2023). Tanzania inaugurated the Tanzania Society of Human Genetics in 2019. There is also Ugandan 2000 Genomes project for genomic characterization of the nation (Swart *et al.*, 2020). Other countries that have such societies are Cameroon, Rwanda, Mali, Senegal, Egypt, the Democratic Republic of the Congo, Ghana and South Africa (Alimohamed *et al.*, 2021). Together they make the African Society of Human Genetics whose main aim is networking and collaborations of genomic researchers in Africa. These efforts will strengthen human genomics research in Africa (Diallo *et al.*, 2017) (Owolabi *et al.*, 2023).

An interplay between the government and academic institutions is crucial for successful genomic projects. Institutions advise the government. The government monitor and supports institutions. The Egyptian genomic project has collaborations with main Egyptian universities and international institutions (“Egypt Genome,” 2024). This formation of strategic partnerships enhances research capacity (CooperDavid *et al.*, 2017). A healthy and supportive relationship between the two can prevent brain drain (Doxzen *et al.*, 2024).

To counteract the brain drain, governments should put efforts to attract their established researchers from foreign lands and reintegrate them into research systems (Hamdi *et al.*, 2024) (Owolabi *et al.*, 2023). Collaborations of African nations can also strengthen African research in genomics for PLWRD (El-Attar *et al.*, 2022). In recent years Egypt and South Africa have collaborated in genomic research to promote innovations for the continent (El-Attar *et al.*, 2022). These partnerships within Africa are more likely to address the needs of the continent and offer sustainable solutions. The benefit of collaboration is access to diverse expertise encompassing the knowledge of the local population and local politics to the knowledge of competitive research (Ateia *et al.*, 2023). Doxzen *et al* mentions the African Medicine Agency (AMA) in which nations collaborate to improve drug accessibility through regional marketing, pharmacovigilance and surveillance (Doxzen *et al.*, 2024).

For motivation, Hetu *et al.*, suggest that the success of genomic research should not be measured by the commercialization achieved but by various indicators

that reflect on LMIC engagement in the research such as the amount of LMICs data collected, the number of African scientists’ researchers in the programs, the priorities of Africa that have been achieved, the infrastructure developed among many other indicators (Hetu *et al.*, 2017).

To overcome the challenges brought about by the need for high throughput complex computation, there has been the development of user-friendly interfaces, less complex hardware and cloud-based analysis (Snelling, n.d.) (Owolabi *et al.*, 2023). Investment in sustainable solar energy can resolve the challenges faced by erratic power supplies and the inability to maintain cold chains (Snelling, n.d.).

Hwang *et al* to improve care for patients with SLE suggest that Africa needs to 1. perform epidemiological studies that will evaluate prevalence and incidence and the relationships of the rare diseases to social determinants of health. 2 create physician and patient support groups to improve access to care. In Ghana, there is a successful partnership called the Rheumatology Initiative which has community participation 3. improve access to testing and medication (use of cheaper generic formulations and community cost-sharing through international collaborations and use of telemedicine). 4 improve training to reduce misdiagnosis and enable early diagnosis 5. improve community awareness through collaborative endeavors for example faith-based educational models (Hwang, 2024) (D’Angelo *et al.*, 2020) (Omotoso *et al.*, 2022).

To improve communication by enabling correct and standardized translation of medical jargon into local languages there has been the creation of translating platforms such as the Lyfe Languages. This has been extended to African languages in Ghana (D’Angelo *et al.*, 2020) (“A call for global action for rare diseases in Africa - PubMed,” n.d.).

**4.4 Organizations and Funders of Genomic Research in Africa:**

Most successful projects are government funded as shown in Egypt, Tunisia and Nigeria (El-Attar *et al.*, 2022) (Hamdi *et al.*, 2024) (Phillips *et al.*, 2021) (Romdhane *et al.*, 2024).

Several organizations involved in genomics in PLWRD in Africa are listed in Table 1 below:

| Organization                                     | Description                                                         |
|--------------------------------------------------|---------------------------------------------------------------------|
| 54 gene, Nigeria                                 | Characterizing Nigerian genome and precision medicine               |
| The Nigerian bioinformatics and genomics network | Collaborative research to improve bioinformatics within the country |

|                                                                                                                      |                                                                        |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Ingaba Biotech, South Africa                                                                                         | Offers genetic services                                                |
| Human Heredity and Health in Africa (H3Africa)                                                                       | Collaborative genetics research led by African scientists              |
| H3ABioNet is a Pan African Bioinformatics Network for the Human Heredity and Health in Africa (H3Africa) consortium. | To improve bioinformatics expertise                                    |
| International Haplotype Mapping                                                                                      | Determined 1 million sequences worldwide                               |
| The Human Pangenome Project                                                                                          | Aimed to create a diverse genome database                              |
| The African Genome Variation Project                                                                                 | sub-Sahara collaborative research for genetic diversity                |
| Genome Aggregation Database (gnomAD) consortium                                                                      | Reference database for rare diseases                                   |
| Deciphering Developmental Disorders in Africa (DDD-Africa, South Africa and the Democratic Republic of Congo)        | Research projects using NGS                                            |
| Trans-Omics for Precision Medicine (TOPMed)                                                                          | Precision medicine for 47,020 participants of African ancestry         |
| Hearing Impairment Genetics Studies in Africa (HI-GENES Africa, South Africa, Cameroun, Ghana, Mali)                 | Research projects for rare diseases using NGS                          |
| Three Million African Genomes                                                                                        | Initiative to sequence 3 million African people                        |
| The Human Genomic project                                                                                            | Rare disease studies                                                   |
| Genome Aggregation Database (gnomAD)                                                                                 | Genomic data curation for 20,744 African/African American participants |

(Snelling, n.d.). (Omotoso *et al.*, 2022) (Lumaka *et al.*, 2022) (Jackson *et al.*, 2023)

**Table 1: Organizations involved in genomics in Africa**

Frequent sponsor for African research are the National Genome Research Institute National Research Foundation and Medical Research Council in South Africa, the U.K. Department for International Development, Centers for Mendelian Genomics (CMG The Bill & Melinda Gates Foundation, the German research-funding organization DFG, the WHO, the World Bank, USAID, NZAID, AUSAID, NIH, Wellcome Trust and iHope foundation (Lumaka *et al.*, 2022)(Omotoso *et al.*, 2022) (Jackson *et al.*, 2023) (Omotoso *et al.*, 2022).

#### 4.5 Limitations of the study:

Some studies may have been omitted due limitations posed by term selection and exclusion criteria. Publication bias is also a source of error as grey literature was not readily available. Considering that

Africa is multilingual, exclusion of non-English articles excludes relevant and informative articles.

#### 4.6 Recommendations:

To improve the genomics study for rare diseases, African nations need to strengthen their capacity. This include infrastructure, local expertise, governing frameworks and funding models.

African nations are urged to form regional collaborations to maximize on resource utilization, data sharing and prevention of duplication. International support should be sought and monitored to ensure mutual benefit.

#### CONCLUSION:

Rare diseases are common in Africa with certain recessive disorders clustered in consanguineous communities. Work in genomics is at infancy stage and

Africa is plunged with many challenges. These challenges include paucity of data, poor infrastructure, low expertise, cultural barriers and poor governance. Many initiatives have been undertaken to overcome these challenges. These include dedicated funding for rare diseases, collaborations, training programs and targeted next generation sequencing.

## REFERENCES:

1. A call for global action for rare diseases in Africa - PubMed [WWW Document], n.d. URL <https://pubmed.ncbi.nlm.nih.gov/31873296/> (accessed 11.18.24).
2. AFREhealth - The African Forum for Research and Education in Health [WWW Document], n.d. URL <https://afrehealth.org/> (accessed 12.1.24).
3. Alimohamed, M.Z., Mwakilili, A.D., Mbwanji, K., Manji, Z.K., Kaywanga, F., Mwaikono, K.S., Adolf, I., Makani, J., Hamel, B., Masimirembwa, C., 2021. Inauguration of the Tanzania Society of Human Genetics: biomedical research in Tanzania with emphasis on human genetics and genomics. *Am. J. Trop. Med. Hyg.* 104, 474.
4. Ateia, H., Ogrodzki, P., Wilson, H.V., Ganesan, S., Halwani, R., Koshy, A., Zaher, W.A., 2023. Population Genome Programs across the Middle East and North Africa: Successes, Challenges, and Future Directions. *Biomed. Hub* 8, 60–71. <https://doi.org/10.1159/000530619>
5. Baine-Savanh, F., Macaulay, S., Louw, N., Bollweg, A., Flynn, K., Molatoli, M., Nevondwe, P., Seymour, H., Carstens, N., Krause, A., Lombard, Z., 2023. Identifying the genetic causes of developmental disorders and intellectual disability in Africa: a systematic literature review. *Front. Genet.* 14, 1137922. <https://doi.org/10.3389/fgene.2023.1137922>
6. Bope, C.D., Chimusa, E.R., Nembaware, V., Mazandu, G.K., de Vries, J., Wonkam, A., 2019. Dissecting in silico Mutation Prediction of Variants in African Genomes: Challenges and Perspectives. *Front. Genet.* 10. <https://doi.org/10.3389/fgene.2019.00601>
7. Bouzidi, A., Charoute, H., Charif, M., Amalou, G., Kandil, M., Barakat, A., Lenaers, G., 2022. Clinical and genetic spectrums of 413 North African families with inherited retinal dystrophies and optic neuropathies. *Orphanet J. Rare Dis.* 17, 1–21.
8. Braga, L.A.M., Conte Filho, C.G., Mota, F.B., 2022. Future of genetic therapies for rare genetic diseases: what to expect for the next 15 years? *Ther. Adv. Rare Dis.* 3, 26330040221100840. <https://doi.org/10.1177/26330040221100840>
9. Community Engagement: A Health Promotion Guide for Universal Health Coverage in the Hands of the People, 1st ed. ed, 2020. World Health Organization, Geneva.
10. CooperDavid, N., ReichardtJürgen, K.V., AliBassam, R., PatrinosGeorge, P., 2017. Genomic medicine without borders: which strategies should developing countries employ to invest in precision medicine? A new “fast-second winner” strategy. *OMICS J. Integr. Biol.*
11. D’Angelo, C.S., Hermes, A., McMaster, C.R., Prichep, E., Richer, É., van der Westhuizen, F.H., Repetto, G.M., Mengchun, G., Malherbe, H., Reichardt, J.K.V., Arbour, L., Hudson, M., du Plessis, K., Haendel, M., Wilcox, P., Lynch, S.A., Rind, S., Easteal, S., Estivill, X., Thomas, Y., Baynam, G., 2020. Barriers and Considerations for Diagnosing Rare Diseases in Indigenous Populations. *Front. Pediatr.* 8, 579924. <https://doi.org/10.3389/fped.2020.579924>
12. De Oliveira, T.C., Secolin, R., Lopes-Cendes, I., 2023. A review of ancestrality and admixture in Latin America and the Caribbean focusing on native American and African descendant populations. *Front. Genet.* 14, 1091269. <https://doi.org/10.3389/fgene.2023.1091269>
13. Diallo, R.N., Gadji, M., Hennig, B.J., Guèye, M.V., Gaye, A., Diop, J.P.D., Niang, M.S., Lopez Sall, P., Guèye, P.M., Dem, A., Faye, O., Dieye, A., Cisse, A., Sembene, M., Ka, S., Diop, N., Williams, S.M., Matovu, E., Ramesar, R.S., Wonkam, A., 2017. Strengthening human genetics research in Africa: report of the 9th meeting of the African Society of Human Genetics in Dakar in May 2016., in: *Global Health, Epidemiology & Genomics*. Presented at the Global Health, Epidemiology & Genomics, Hindawi Limited, pp. 1–5.
14. Doxzen, K.W., Adair, J.E., Fonseca Bazzo, Y.M., Bukini, D., Cornetta, K., Dalal, V., Guerino-Cunha, R.L., Hongeng, S., Jotwani, G., Kityo-Mutuluzza, C., Lakshmanan, K., Mahlangu, J., Makani, J., Mathews, V., Ozelo, M.C., Rangarajan, S., Scholefield, J., Batista

- Silva Júnior, J., McCune, J.M., 2024. The translational gap for gene therapies in low- and middle-income countries. *Sci. Transl. Med.* 16, eadn1902. <https://doi.org/10.1126/scitranslmed.adn1902>
15. Egypt Genome: Towards an African new genomic era, 2024. *J. Adv. Res.* <https://doi.org/10.1016/j.jare.2024.06.003>
  16. El-Attar, E.A., Elkaffas, R.M.H., Aglan, S.A., Naga, I.S., Nabil, A., Abdallah, H.Y., 2022. Genomics in Egypt: Current Status and Future Aspects. *Front. Genet.* 13, 797465. <https://doi.org/10.3389/fgene.2022.797465>
  17. Fullwiley, D., Gibbon, S., 2018. Genomics in emerging and developing economies. *Routledge Handb. Genomics Health Soc.* 228–237.
  18. Gamble, V.N., 1997. Under the shadow of Tuskegee: African Americans and health care. *Am. J. Public Health* 87, 1773. <https://doi.org/10.2105/ajph.87.11.1773>
  19. Genomics, F.L., Fletcher, L., 2024. The \$100 Genome: Where's the Limit? *Front Line Genomics*. URL <https://frontlinegenomics.com/the-100-genome-wheres-the-limit/> (accessed 7.16.24).
  20. Hamdi, Y., Trabelsi, M., Ghedira, K., Boujemaa, M., Ben Ayed, I., Charfeddine, C., Souissi, A., Rejeb, I., Kammoun Rebai, W., Hkimi, C., Neifar, F., Jandoubi, N., Mkaouer, R., Chaouch, M., Bennour, A., Kamoun, S., Chaker Masmoudi, H., Abid, N., Mezghani Khemakhem, M., Achour, A., 2024. Genome Tunisia Project: paving the way for precision medicine in North Africa. *Genome Med.* 16, 1–19.
  21. Hanchard, C., n.d. High-depth African genomes inform human migration and health | Nature [WWW Document]. URL <https://www.nature.com/articles/s41586-020-2859-7> (accessed 10.25.24).
  22. Hetu, M., Joly, Y., Koutouki, K., 2017. Measuring the performance of international genomics research projects in fostering genomic capacity in the developing world. *New Genet. Soc.* 36, 315–335.
  23. Hwang, B.A., 2024. Addressing the research gap: access to care hinders genetic discovery in systemic lupus erythematosus patients throughout the African diaspora - PMC [WWW Document]. URL <https://pmc.ncbi.nlm.nih.gov/articles/PMC11358083/> (accessed 10.25.24).
  24. Ilori, T., Watanabe, A., Ng, K.-H., Solarin, A., Sinha, A., Gbadegesin, R., 2023. Genetics of chronic kidney disease in low resources setting. *Semin. Nephrol.* 42, 151314. <https://doi.org/10.1016/j.semnephrol.2023.151314>
  25. Jackson, F., Clinton, C., Caldwell, J., 2023. Core issues, case studies, and the need for expanded Legacy African American genomics. *Front. Genet.* 14, 843209. <https://doi.org/10.3389/fgene.2023.843209>
  26. Ju, D., Hui, D., Hammond, D.A., Wonkam, A., Tishkoff, S.A., 2022. Importance of Including Non-European Populations in Large Human Genetic Studies to Enhance Precision Medicine. *Annu. Rev. Biomed. Data Sci.* 5, 321. <https://doi.org/10.1146/annurev-biodatasci-122220-112550>
  27. Kpokiri, E.E., Sri-Pathmanathan, C., Shrestha, P., Navaid, S., Wiwatpanit, T., Wijegunawardana, A., Umar, M.A., Jackson, D., Alger, J., Bohren, M.A., 2021. Crowdfunding for health research: A global systematic review, qualitative evidence synthesis and TDR pilot for LMIC researchers. *medRxiv* 2021–11.
  28. Louw, N., Carstens, N., Lombard, Z., Consortium, for D.-A. as members of the H., 2023. Incorporating CNV analysis improves the yield of exome sequencing for rare monogenic disorders—an important consideration for resource-constrained settings. *Front. Genet.* 14, 1277784. <https://doi.org/10.3389/fgene.2023.1277784>
  29. Lumaka, A., Carstens, N., Devriendt, K., Krause, A., Kulohoma, B., Kumuthini, J., Mubungu, G., Mukisa, J., Nel, M., Olanrewaju, T.O., Lombard, Z., Landouré, G., as members of the Rare Disease Working Group of the H3Africa Consortium, 2022. Increasing African genomic data generation and sharing to resolve rare and undiagnosed diseases in Africa: a call-to-action by the H3Africa rare diseases working group. *Orphanet J. Rare Dis.* 17, 230. <https://doi.org/10.1186/s13023-022-02391-w>
  30. Mahungu, A.C., Monnakgotla, N., Nel, M., Heckmann, J.M., 2022. A review of the genetic spectrum of hereditary spastic paraplegias inherited neuropathies and spinal muscular

- atrophies in Africans. *Orphanet J. Rare Dis.* 17, 133. <https://doi.org/10.1186/s13023-022-02280-2>
31. Major U.K. genetics lab accused of misusing African DNA | Science | AAAS [WWW Document], n.d. URL <https://www.science.org/content/article/major-uk-genetics-lab-accused-misusing-african-dna> (accessed 11.6.24).
  32. Mudau, M.M., Seymour, H., Nevondwe, P., Kerr, R., Spencer, C., Feben, C., Lombard, Z., Honey, E., Krause, A., Carstens, N., 2024. A feasible molecular diagnostic strategy for rare genetic disorders within resource-constrained environments. *J. Community Genet.* 15, 39–48. <https://doi.org/10.1007/s12687-023-00674-8>
  33. Munung, N.S., Mayosi, B.M., de Vries, J., 2018. Genomics research in Africa and its impact on global health: insights from African researchers. *Glob. Health Epidemiol. Genomics* 3, 1–8.
  34. Nembaware, V., African Genomic Medicine Training Initiative, Mulder, N., Abidi, O., Akanle, M.B., Ali, S.A., Aliga, C.A., Chauke, P., Cotzee, M., Dandara, C., Fadlilmola, F.M., Fawale, M.B., Fernandes, P.L., Ghansah, K., Kashim, Z.A., Kassim, S.K., Komolafe, M.A., Landouré, G., Leisegang, C., Madden, E.B., Majada, K., Malope, M., Kaba, M., Mathuba, K., Matimba, A., Mochamah, G., Morgan, S.L., Mulder, N., Oyekanmi, N., Munung, N.S., Nembaware, V., Owoeeye, T.E., Pepper, M.S., Pienaar, L., Pietersen, E., Radouani, F., S Ramesar, R., Skelton, M., Mpoloka, S.W., Misaki, W., Wonkam, A., Adesina, A.S., Wessels, T.-M., 2019. The African Genomic Medicine Training Initiative (AGMT): Showcasing a Community and Framework Driven Genomic Medicine Training for Nurses in Africa. *Front. Genet.* 10. <https://doi.org/10.3389/fgene.2019.01209>
  35. Nordling, L., 2017. How the genomics revolution could finally help Africa. *Nature* 544.
  36. Omotoso, O.E., Teibo, J.O., Atiba, F.A., Oladimeji, T., Adebessin, A.O., Babalghith, A.O., 2022. Bridging the genomic data gap in Africa: implications for global disease burdens. *Glob. Health* 18, 1–8.
  37. Operationalizing the CARE and FAIR Principles for Indigenous Data Futures | Scientific Data [WWW Document], n.d. URL <https://www.nature.com/articles/s41597-021-00892-0> (accessed 11.1.24).
  38. Owete, A.C., Ionin, R., Huryn, L.A., Cukras, C.A., Blain, D., Agather, A.R., Hufnagel, R.B., Brooks, B.P., Nwanyanwu, K., Zein, W.M., 2024. Seeing in Color: Inclusion and Characterization of Hereditary Eye Disease in African Americans. *Transl. Vis. Sci. Technol.* 13, 4. <https://doi.org/10.1167/tvst.13.9.4>
  39. Owolabi, P., Adam, Y., Adebisi, E., 2023. Personalizing medicine in Africa: current state, progress and challenges. *Front. Genet.* 14. <https://doi.org/10.3389/fgene.2023.1233338>
  40. Palmer, E.E., Cederroth, H., Cederroth, M., Delgado-Vega, A.M., Roberts, N., Taylan, F., Nordgren, A., Botto, L.D., 2024. Equity in action: The Diagnostic Working Group of The Undiagnosed Diseases Network International. *Npj Genomic Med.* 9, 1–7. <https://doi.org/10.1038/s41525-024-00422-y>
  41. Phillips, K.A., Douglas, M.P., Wordsworth, S., Buchanan, J., Marshall, D.A., 2021. Availability and funding of clinical genomic sequencing globally. *BMJ Glob. Health* 6, e004415. <https://doi.org/10.1136/bmjgh-2020-004415>
  42. Precision ophthalmology: a call for Africa not to be left in the dark | Gene Therapy [WWW Document], n.d. URL <https://www.nature.com/articles/s41434-024-00448-y> (accessed 11.10.24).
  43. Ramsay, M., 2022. African genomic data sharing and the struggle for equitable benefit. *Patterns* 3, 100412. <https://doi.org/10.1016/j.patter.2021.100412>
  44. Rayyan | Full Text Screening [WWW Document], n.d. URL <https://new.rayyan.ai/reviews/1183263/fulltext> (accessed 10.21.24).
  45. Romdhane, L., Kefi, S., Mezzi, N., Abassi, N., Jmel, H., Romdhane, S., Shan, J., Chouchane, L., Abdelhak, S., 2024. Ethnic and functional differentiation of copy number polymorphisms in Tunisian and HapMap population unveils insights on genome organizational plasticity. *Sci. Rep.* 14, 1–17.
  46. Scherr, C.L., Ramesh, S., Marshall-Fricker, C., Perera, M.A., 2019. A review of African Americans' beliefs and attitudes about genomic studies: opportunities for message design. *Front. Genet.* 10, 548.

47. Snelling, S., n.d. Overcoming barriers to single-cell RNA sequencing adoption in low- and middle-income countries | European Journal of Human Genetics [WWW Document]. URL <https://www.nature.com/articles/s41431-024-01564-4> (accessed 10.28.24).
48. Sturdy, S., 2020. Finding the global in the local: constructing population in the search for disease genes. *Glob. Health New World Order*.
49. Swart, Y., van Eeden, G., Sparks, A., Uren, C., Möller, M., 2020. Prospective avenues for human population genomics and disease mapping in southern Africa. *Mol. Genet. Genomics* 295, 1079–1089.
50. Todt, D., 2021. An African Genome Variation Database and its applications in human diversity and health.
51. Walters, S., Aldous, C., Malherbe, H., 2024. Knowledge, attitudes, and practices of primary healthcare practitioners in low- and middle-income countries: a scoping review on genetics. *J. Community Genet.* <https://doi.org/10.1007/s12687-024-00721-y>
52. Wonkam, A., 2021. Sequence three million genomes across Africa. *Nature* 590, 209–211. <https://doi.org/10.1038/d41586-021-00313-7>