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Building a Platform to Enable NCD Research to Address Population Health in Africa:

CVD Working Group Discussion at the Sixth H3Africa Consortium Meeting in Zambia

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The establishment of the Human Heredity and Health in Africa (H3Africa) cardiovascular disease (CVD) working group and subsequent meeting during the Fourth annual H3Africa Consortium meeting in Cape Town, South Africa, provided opportunities for new collaborations as well as avenues to develop a road map for harmonizing efforts to address CVD within the continent [1]. One of the outcomes of this collaboration was a journal special issue publication comprising a series of articles describing the epidemiology of CVD, stroke, end-stage kidney disease, rheumatic heart disease, sickle cell disease, and other infectious and noncommunicable diseases related to CVD conditions [2–11].

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This collaboration was further enhanced at the Sixth H3Africa Consortium meeting in Livingstone, Zambia. The H3Africa CVD working group discussed the aggregation and specialized harmonization of the phenotypic and genomic data being collected by its members. When completed, the working group will have genome-wide association data that consist of comparable genomic data for over 50,000 phenotyped individuals. This aggregate dataset will contain diverse samples from individuals across various African regions/countries, ethnic groups, disease phenotypes, and non-disease-specific control subjects. Table 1 highlights the diversity of phenotypes of the various H3Africa projects. This accumulated dataset captures major elements of the cardiovascular disease spectrum (Figure 1) and will be one of the largest collections of population data containing both disease and non-disease-related measures obtained from transcontinental African groups that are not fully represented within existing genomic studies.

This joint research platform is similar to large population cohorts such as the CARTaGENE Study in Canada [12,13], CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) study [14] and also the 100,000 Genome Project in the United Kingdom [15], which is expected to be completed by 2017. These large-scale cohort studies will be critical to identifying CVD-associated variants and translating those genetic variants to clinical applications and disease-specific interventions that will ultimately affect population health. Furthermore, the translation of hundreds of thousands of genetic variants to evidence-based applications for medicine and public health requires multidisciplinary research enterprises [16]. For genomics research to impact public health, discoveries must traverse the continuum of translation research that can be differentiated by boundaries or types. These various phases of the research spectrum have been adapted to genomics by Khoury et al. [16,17]. Currently, this continuum starts with translation phase 0 (translation of basic research, or biomedical and social science research), moves to translation phase 1 (translation to humans and also phase I clinical trials), translation phase 2 (translation to phase II and phase III clinical trials), translation phase 3 (translation to phase IV clinical trials, comparative effectiveness research), and finally, translation phase 4 application to real-world settings (translation to populations and population-level evaluation of health via implementation and dissemination research).

H3Africa projects have the potential to answer diverse questions in the translation phase 0 or T0 research domain [18]. T0 research encompasses fundamental discovery science and includes the discovery and internal and external validation of variants associated with disease states or phenotypes. It also includes determining which variants are pathogenic, protective, and/or clinically actionable [19–21]. Next steps involve utilizing the genomics data to inform health and will require an enhanced translational genomics research agenda firmly rooted in the population sciences [16,22]. Ultimately, the aggregated dataset generated from the H3Africa studies will facilitate further understanding of genetic correlates of health in all populations. In the near term, the expanded H3Africa dataset could augment individual studies by providing control cohorts, both as population control subjects from different regions and ethnolinguistic groups and as disease-free control subjects for case-control studies. This resource could also be used for replication studies because the datasets will have common measures and phenotypic data related to multiple African populations and could provide additional resources for ongoing or future studies. The

availability of these large accurately phenotyped cohorts will enormously enhance the statistical power for discovery and validation of new genetic associations and could be used to examine unique and cross-cutting questions. Moreover, it would stimulate functional studies on genomic associations and trigger research into animal models and the development of in vitro, or in vivo systems to unravel the molecular framework and mechanisms of genotype and phenotype correlations.

Although H3Africa projects have focused on understanding the most fundamental aspects of disease including identifying genetic variants associated with specific diseases in African populations, there are also future opportunities to improve the health of African populations by translating these findings into clinical practice, policies, tailored guidelines, and evidence-based intervention strategies that can positively affect population health. During the H3Africa CVD working group meeting, members enthusiastically supported the need to undertake research within the late stage of translation research or T4 research—research that takes evidence-based interventions and studies how to increase uptake with a focus on affecting population health [23–25]. Although T2 to T4 research is ongoing for infectious diseases [26,27], research for noncommunicable diseases such as CVD in low-resource settings is minimal. The noncommunicable disease burden in Africa provides an opportunity to address the implementation barriers for CV and CV-associated diseases that exist in low-resource settings [28]. Understanding these barriers and how to overcome them could lead to changes in practice that will have a positive impact on populations in Africa and other parts of the globe.

Late-stage T4 implementation research has been used to successfully address noncommunicable disease in Africa. For example, the use of penicillin prophylaxis and therapy with hydroxyurea for treatment of children and adults with sickle cell disease has resulted in decreased mortality [29–31]. Although the aforementioned examples do not involve the utilization of genomic knowledge, tailoring of these interventions might benefit from a pharmacogenomics approach in the future. Moreover, there are potential opportunities to build on the genomic-based research for sickle cell disease in Africa to transform the health outcomes of patients [3], especially in the area of vascular complications such as stroke, progressive proliferative systemic vasculopathy, pulmonary hypertension, and left ventricular diastolic dysfunction [32,33]. It is important to investigate whether these conditions could be mitigated by tailoring effective evidence-based interventions to low-resource settings [34–36]. Similarly, there are evidence-based interventions available for hypertension and stroke that may be adaptable to low-resource settings [4,5].

Stroke, the leading cause of CV death and disability in Africans, presents disproportionately with relatively higher hemorrhagic type and worse outcomes among Africans [5,37]. Understanding the genomic and environmental underpinnings of these disparities could result in interventions tailored toward reducing the overall burden and complications of stroke in Africans and possibly African Americans [38]. Such interventions can then be tested in randomized clinical trials—an example being the THRIVES (Tailored Hospital-based Risk Reduction to Impede Vascular Events After Stroke) study in Nigeria [39].

The CVD working group discussed opportunities to support longitudinal cohort studies and randomized clinical trials, and how their combined resources could further support research into the health needs of Africans. There is good evidence that the clinical manifestation and disease progression for several complex diseases are different in African populations. Chronic kidney disease, for example, has greater prevalence, severity, and more rapid progression in African populations than in individuals of European ancestry [40–43]. There are few data about the efficacy of current chronic kidney disease therapeutic approaches in African populations, especially in patients with comorbid conditions such as sickle cell trait or human immunodeficiency virus infection. Thus, some randomized clinical trials may need to focus on unique research questions that will be indispensable in deciphering the treatments that will be most appropriate and effective for African populations with kidney disease.

With the harmonized high-quality phenotype and genomic database that will be developed as part of the mandate of the CVD working group, unifying compelling cross-cutting questions and hypotheses on determinants of the escalating burden of CVD in Africans can be explored. Similarly, overlaps in genomic and environmental determinants of the various cardiovascular phenotypes can be unraveled. Consequently, the emerging common risk factors could be targeted for intervention to reduce the overall disease burden.

In conclusion, the H3Africa program is propelling genomics research in African populations to a higher level. One of the great strengths is the creation of an integrated genomics and disease research program to facilitate clinical and genetic cardiovascular epidemiology research in Africa. This platform will be useful to build a translational research program focused on some of the most significant diseases affecting African populations.

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FIGURE 1. The CV spectrum indicating stages of progression from CV health to established CVD and mortality

The stages of progression from a nondisease state to the development of single or multiple cardiovascular (CV) risk factors to intermediate phenotype of cardiovascular disease (CVD) and finally to established CVD is indicated by the gray arrows illustrating a stepwise progression from a nondisease to a disease state. Examples of CV risk factors include hypertension, dyslipidemia, diabetes mellitus, and smoking. Intermediate phenotype includes atherosclerosis/endothelial injury, which can be assessed with carotid intima media thickness or microalbuminuria. Factors underpinning this progression from nondisease to disease phenotypes are genetics and exposures of individuals that represent environment (i.e., Africa). Mortality can occur at any stage in this scheme as indicated by red arrows. H3Africa projects that are collecting participant samples across the spectrum are indicated in the light orange section. Essentially, the Human Heredity and Health in Africa (H3Africa) CVD data span the spectrum (e.g., risk factors including modifiable and nonmodifiable) to established CVD phenotypes including stroke, chronic kidney disease, and myocardial infarction. The H3Africa projects represent an opportunity to examine unique phenotypes for CVD in African populations and explore the genetic and environmental contributions to CV health and disease in many diverse African populations. ACCME, African Collaborative Center for Genomics and Microbiome Research CVD Project; AWI-Gen, Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans; DM, burden, spectrum, and etiology of type 2 diabetes in sub-Saharan Africa; RHDGen, Genetics of rheumatic heart disease Research Network; SIREN, Stroke Investigative Research & Educational Network.

TABLE 1

H3Africa CVD Working Group projects

Project	Countries Where Participants Were Recruited	Type of Study	Recruitment Strategy	Cases (Inclusion Criteria)	Control Subjects (Inclusion Criteria)
Burden, spectrum, and etiology of type 2 diabetes in sub-Saharan Africa (DM group)	Cameroon Guinea The Gambia Malawi Nigeria South Africa Tanzania Uganda	Cross-sectional	Health facility-based recruitment of cases and community recruitment of control subjects	Male and female >25 yrs Diabetes: Fasting plasma glucose >126mg/dl, or RPG >11.1 mmol or 12-h plasma glucose >11.1 mmol Oral/insulin treatment	Population-based control subjects >18 yrs
Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans (AWI-Gen)	Burkina Faso Ghana Kenya South Africa	Cross-sectional and population-based cohort	Community-based (randomized by household and unrelated participants)	Male and female 40–60 yrs Population cross section (no phenotype selection) (Retrospective nested cases and control subjects for diabetes, hypertension, stroke)	
Stroke Investigative Research and Educational Network (SIREN)	Ghana Nigeria	Prospective and population-based cohort	Hospital-based cases, community- and hospital-based control subjects	Male and female >18 and up to 100 yrs Stroke: Cranial CT/MRI-confirmed first stroke episode	Male and female >18 yrs Unrelated subjects No history of stroke, with or without CVD risk factors Sex, age, and ethnicity matched
Genetics of Rheumatic Heart Disease Research Network (RHDGen)	Kenya Mozambique Namibia Nigeria South Africa Sudan Uganda Zambia	Case-control cohort	Hospital-based recruitment of cases and community-based control subjects with no valvular heart disease by echocardiography	Male and female Echocardiographically confirmed cases of rheumatic heart disease Pediatric and adult cases	Male and female >18 yrs With no valvular heart disease by ECG
H3Africa Kidney Disease Network	Nigeria Ghana Kenya Ethiopia	Prospective and population-based cohort	Cases: outpatient clinics and patient admissions Control subjects: outpatient clinics in the community	Male and female 0–74 yrs Diabetic CKD Hypertensive CKD Biopsy-proven FSGS Biopsy-proven minimal-change disease Biopsy-proven membranous nephropathy Childhood/adolescent-onset steroid-resistant nephrotic syndrome HIV CKD Sickle cell disease CKD CKD of unknown etiology	Healthy individuals and individuals attending ambulatory clinics or hospitalized patients with no evidence of kidney disease and no systemic condition known to be a common cause of kidney disease and eGFR >60 ml/min/1.73 m ² and random ACR mg/mmol of <3.5 mg/mmol in a female; <2.5 mg/mmol in a male Diabetes control subjects Hypertension control subjects HIV control subjects Sickle cell disease control subjects CKD of unknown etiology General population control subjects

Project	Countries Where Participants Were Recruited	Type of Study	Recruitment Strategy	Cases (Inclusion Criteria)	Control Subjects (Inclusion Criteria)
African Collaborative Center for Genomics and Microbiome Research (ACCCME)	Nigeria Zambia	Prospective cohort study (with planned nested case-control analyses)	Recruit at cervical cancer screening clinic	Female only >18 yrs Recruited from among 10,000 women screened in Nigeria; there will be cases with the following conditions: Diabetes: random blood sugar is conducted on all participants, participants with 10% above the normal upper limit (125 mg/dl) and risk factors for diabetes will be invited for further testing when funding is available Hypertension: defined by WHO criteria Obesity: defined by WHO criteria Kidney disease: urinalysis with dip stick tests has been done on all participants, Participants with abnormal parameters will be invited for further testing when funding is available Stroke: National Survey of Stroke Criteria used MI: defined by WHO criteria Cancers: defined by WHO criteria Control subjects free of these traits can be retrospectively assigned	

ACR, albumin creatinine ratio; CVD, cardiovascular disease; CT, computed tomography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; H3Africa, Human Heredity and Health in Africa; HIV, human immunodeficiency virus; MI, myocardial infarction; MRI, magnetic resonance imaging; RPG, random plasma glucose; WHO, World Health Organization.