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Harnessing Genomic Technologies Toward Improving Health in Africa:

OPPORTUNITIES AND CHALLENGES

Recommendations for the
Human Heredity and Health in Africa (H3Africa) Initiative to the
Wellcome Trust and the National Institutes of Health

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January 2011

This white paper is a community-generated document outlining the opportunities and challenges for the National Institutes of Health (NIH) and the Wellcome Trust (WT) in creating a genomics-focused, population-based research initiative in Africa. This document discusses problems and solutions for the Human Heredity and Health in Africa (H3Africa) Initiative identified by senior African scientists and others that have worked extensively on the continent. The document was prepared by the H3Africa Working Group, with editing and composition provided by Emmanuel K. Peprah, Ph.D., and Charles N. Rotimi, Ph.D., M.P.H., both of the Center for Research on Genomics and Global Health, National Human Genome Research Institute, NIH.

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I. EXECUTIVE SUMMARY

Background

The peoples of Africa suffer a disproportionate burden of avoidable illness. This disease burden results primarily from widespread poverty, compounded by very limited access to modern health care. Although communicable diseases are the major causes of morbidity and mortality among African peoples, noncommunicable diseases are assuming growing importance. The World Health Organization's (WHO) Millennium Development Goals have brought welcomed attention to Africa's ongoing health crisis and mainly emphasize basic poor health indicators related to women and children; the WHO Global Burden of Disease Study has demonstrated high mortality rates across the age and gender spectra. Differences in disease prevalence between countries, geographic regions within a country, and ethnic groups in the same geographic region are the result of a combination of human genomic and environmental factors. Recent advances in the capacity to link genetic variation to disease predisposition are providing important clues to disease pathogenesis and, over the coming decade, are expected to assume an important role in informing the prediction, diagnosis, monitoring, and treatment of many conditions. However, African researchers and populations are substantially underrepresented within this increasingly global research endeavor. The failure to adequately engage Africa and African researchers and scientists in genetics and genomics research limits overall scientific progress, scientific and economic development on the continent, and the capacity for the research to address health questions of particular importance to African and African diaspora populations.

If we are to understand the basis of disease, there is much to be gained by the development and integration of genomic, epidemiologic, and clinical research in Africa and elsewhere. The genetic diversity of African populations, from which modern human populations originate, makes a strong argument for substantial scientific investment to study genetics and health in Africa on the basis that this will contribute to improvement in the health prospects of humans across the globe.

The Role of H3Africa

The Human Heredity and Health in Africa (H3Africa) Initiative was born out of a partnership among the African Society of Human Genetics (AfSHG), the Wellcome Trust (WT) (United Kingdom), and the National Institutes of Health (NIH) (United States). In conjunction with the AfSHG meeting in Yaounde, Cameroon, in March 2009, scientific experts of diverse backgrounds met with the goal of identifying the major scientific, ethical, and practical issues pertaining to the development of a large-scale genomics research program in Africa. The H3Africa Communicable and Noncommunicable Diseases Working Groups, which were established following this meeting, have formulated this white paper to support the mission of creating and sustaining a

network of African centers that will provide training, research, and clinical services that are based on the implementation of state-of-the-art genomics approaches. By supporting infrastructure development, training, and specific research projects, H3Africa will catalyze genomics research concerning human diversity and disease biology that will be of particular relevance and benefit to African populations and societies. Further development of this agenda and preparation of this white paper were pursued at a meeting in Oxford, United Kingdom, in August 2010.

The importance of genomics and biotechnology to Africa's development was highlighted in the 2007 report by the New Partnership for Africa's Development (NEPAD) and the African Union (AU),[1] which states that "Development for any nation or region needs minimum capacity in at least three areas: (I) Infrastructure to support science, technology and innovation; (II) Human resources, training and education in science and technology; and (III) Public awareness of—and engagement in—science and technology."

The two H3Africa Working Groups have diligently conceived specific recommendations that heed these principles espoused by the NEPAD, the AU, and other organizations with extensive experience in Africa. Below are aspirations for H3Africa articulated in synopses of the ethos and vision as well as abbreviated versions of the recommendations that the H3Africa Working

Groups discussed and confirmed during the Oxford meeting.

Ethos and Vision for H3Africa

Ethos

The central ethos of the H3Africa Initiative is the development of a sustainable, collaborative African research enterprise that will generate improvements in health. Through the resourcing, training, and networking of African scientists, high-quality research in human genomics will be designed to address questions of particular medical and scientific importance to Africans.

Vision

H3Africa's vision is the establishment of a viable, productive clinical and research infrastructure, through combined leveraging of capacity, expertise, and infrastructure within existing institutions and investing in new centers of excellence. This new infrastructure will require investment in capacity development (i.e., training of clinicians and researchers). Sustainability should be ensured through strong links with European, U.S., and other international collaborators and institutions. The "hub and spoke model" will enable the codevelopment of specialist regional "nodes" within a wider network of participation.

Recommendations for H3Africa

Resource Development

The development of resources (including human capital) for H3Africa should focus on (but not be limited to) clinical phenotyping; sample collection and biobanking; genomic analysis (genotyping, sequencing); bioinformatics; statistics; functional analysis; and ethical, legal, and social issues (ELSI) research. The organizational structures required for each of these are likely to differ (e.g., sample collection and phenotyping will inevitably be more widely distributed than large-scale genomic analysis).

Infrastructure

H3Africa should develop an infrastructure and programs that support epidemiologically and ethically sound project designs resulting in large-scale ascertainment and recruitment of individuals and the collection of biological samples and related phenotypic data. Currently, few centers in Africa are equipped to take care of patients and undertake large-scale sample collection. Existing centers have limited capacities for sample storage, and H3Africa will need to establish biorepositories for the storage, retrieval, distribution, and management of large sample collections. Transportation limitations within Africa suggest that these biorepositories should be established at the regional level. This infrastructure also should include a shared resource environment of clinical standard operating procedures for phenotypic consistency, research protocols, and high-throughput technology platforms. Access to finite samples will need to be managed so as to ensure equipoise between the interests of collectors and the wider research community. H3Africa should provide a technological infrastructure (units/centers of excellence) for genetic and genomic data generation and analysis that enables investigators to accomplish clinical research in the African context and to foster collaborations within the African scientific community.

Education and Training

H3Africa should support the training of Africans in the fields of genetic epidemiology, bioinformatics, statistical analysis, high-throughput technologies, genomic data analysis, clinical research, and ELSI research to address current disparities in expertise and enable African researchers to participate fully in the generation, interpretation, and utilization of data and discoveries from the samples donated. Given that effort in modern genomics is increasingly computational (i.e., manipulation, interpretation, and analysis of data), the development of capacity in these areas is of paramount importance. Training should be developed in close collaboration with non-African institutions to leverage existing non-African expertise and transfer it to African researchers in a consistent and sustainable manner. Non-African institutions and laboratories (in particular those of African diaspora scientists) should be able to work with H3Africa to build capacity by hosting training visits for African researchers and clinicians and by supporting genomics research and practice within Africa through mentorship and training linked to existing and new educational programs. H3Africa should maintain a database of African graduates from pertinent disciplines and support collaborations to develop African scientists, with a view to achieving long-term sustainability in Africa.

Population/Health/Disease Foci

H3Africa should provide sufficient support for focused research projects that address major areas of scientific and medical importance. These are likely to include studies of comprehensive human genetic diversity in Africa, as well as studies to understand patterns of predisposition to selected communicable and noncommunicable diseases. It seems likely that maximal efficiency for H3Africa investment will require some degree of integration and coordination of infrastructure development and specific research projects. We suggest that the NIH and the WT consider a Funding Opportunity Announcement structure to solicit collaborative proposals for specific research projects and/or infrastructure development that are consistent with H3Africa principles.

Ethical, Legal, and Social Issues

H3Africa should ensure not only that the projects performed meet the highest ethical, legal, and socially appropriate standards for research but also that explicit support is provided for the training of African researchers and that research addresses the particular challenges of genomics research in Africa (and in low- to middle-income countries in general). H3Africa must invest in improving the general knowledge of genomics among African communities, identifying traditional knowledge and cultural practices around which new concepts in genomics can be built for integration into the understanding of African populations, supporting the development of guidelines for the regulatory aspects of genomics research and its use, and developing tools to enhance the understanding and use of new products of genomics research by the population. One key issue that must be addressed is the extent to which H3Africa projects should support the provision of clinical care for research participants (particularly where those projects involve case discovery). With regard to the ongoing issue of inequities in collaborative efforts, H3Africa should seek to develop models for ethical collaboration and data sharing that overcome current limitations to collaboration between researchers and to support equitable access to the data generated by H3Africa (and other) projects. Policies for data release and publication need to be developed so that African researchers gain full credit for their endeavors and are able to play leading roles in the analysis of the data generated and in the followup of the findings.

The Future of H3Africa

The model proposed for H3Africa seeks to position Africa not only as a vital resource for genetic and genomic data collection but also as the recognized scientific hub for the initiation and full implementation of modern genetic and genomics research in African populations. The success of H3Africa depends largely on the provision of adequate resources and infrastructure for African scientists to lead scientific inquiries to improve the health of African populations. In this endeavor, African scientists will be empowered to determine the circumstances of investigations, including sample transport and analysis within Africa, or to establish collaborations for external analysis. This emphasizes a preference for samples and other resources to remain within Africa for analysis, given suitable sustainable infrastructure. However, this model not only does not exclude but also encourages collaborations for continual analysis outside of Africa, with the expectation that these collaborations should be at the discretion of African scientists and complement the infrastructure developments that H3Africa will achieve. Although this is a bold step, which if executed properly will be significantly favorable to the development of genomics research in Africa, the vision is that the powerful instrument of genomics will prime human health-related research in Africa in a large and well-organized way. It is envisioned that this investment will attract the support of researchers in all areas of biodiversity, other international agencies, and African governments. In due course, the impact will be more far reaching than human health and disease, perhaps most notably in biotechnology. ❖

II. SUMMARY RECOMMENDATIONS OF THE H3AFRICA WORKING GROUPS

Resources (Internet)

Develop a comprehensive database of biomedical research, with special attention to genetics/genomics projects in Africa with Geographical Information System database maps that include several layers of information.

Infrastructure

1. Develop a fully functional biorepository that will house all the biological specimens to be collected under the H3Africa research umbrella. This infrastructure will ensure that biological specimens remain on the continent and will encourage large-scale collaboration between African scientists while fostering collaborations between African and international scientists. With sufficient capacity, the H3Africa biorepository can support other biomedical research on the continent.
2. Develop regional centers of excellence that will house modern genotyping/sequencing and phenotyping laboratories. The centers will serve as core training facilities for African scientists.
3. Develop a network of clinical centers that will collect demographic, epidemiologic, and clinical data on all H3Africa participants. The centers will develop standard operating procedures that will be employed for patient enrollment and examination.
4. Develop a continent-wide bioinformatics network that will provide the necessary foundation for the large-scale genomic data sets that will be generated by H3Africa investigators. This network will be primarily responsible for the training of African scientists in bioinformatics.

Education and Training

1. Develop a comprehensive educational and training program that will be situated within the H3Africa research initiatives. This strategy will ensure that trained scientists have a "home" to come to after training and will facilitate the building of an extensive skills base in Africa. Support should be provided toward the training of Africans scientists in multiple disciplines, including in genomics (high-throughput technologies), genetics, epidemiology, bioinformatics, statistical genetics, and Ethical Legal and Social Issues (ELSI). Educational and training materials should be developed that can be shared among researchers in African countries. Scientists from the African diaspora should be involved and should be encouraged to work with those on the ground in Africa in a mentorship role. An extensive mentorship program also should be developed.
2. Hold annual scientific meetings for H3Africa investigators on the continent. These meetings will enhance opportunities for collaborations.

Disease Research

The following diseases and programs (list not final) were suggested for consideration:

- Communicable diseases
  - Tuberculosis
  - Human African trypanosomiasis (HAT)
  - Cancer due to infectious agents
- Noncommunicable diseases
  - Sickle cell disease
  - Hypertension/stroke
  - Type 2 diabetes mellitus
  - Cancer
- Pharmacogenomics
- New and innovative ideas

Ethical, Legal, and Social Issues

ELSI programs should be incorporated into all aspects of H3Africa disease research programs.

Governance

Policies for the establishment of principles of governance should employ a system of committees. ❖

III. HARNESSING GENOMIC TECHNOLOGIES TOWARD IMPROVING HEALTH IN AFRICA: OPPORTUNITIES AND CHALLENGES

1. The Opportunity of Genomics and Health Research for African Populations

1.1. The Health Burden in Africa

The impact of the burden of disease in Africa is still very poorly characterized. Vital health statistics have not been recorded for many geographic populations, with the exception of a few countries such as the Republic of South Africa (RSA).[2] Although direct census data exist for most countries, large sections of the population—perhaps the majority—die without access to modern medical care, making it difficult to determine the cause of death and to gather proper health statistics. Age estimates for elderly Africans, who account for most deaths, until recently have also been problematic. In addition, there have been no systematic prevalence studies that cover the broad range of chronic diseases and that include poor persons in either urban areas or isolated rural communities. High-visibility reports, sponsored initially by the World Bank and the World Health Organization (WHO), and now supported by the Bill & Melinda Gates Foundation, have generated detailed estimates for mortality rates and disability-adjusted life years (DALYs), giving the impression of greater understanding of the burden of chronic diseases in Africa.[3] However, the reality of the situation in Africa was underestimated since, as stated in the report published by Murray and Lopez in 1996, all of the data for sub-Saharan Africa (SSA) were mere extrapolations from local regions within the RSA, and many anomalies such as very high homicide rates in rural populations were apparent.[4] The most recent Global Burden of Disease Study incorporated data from demographic surveillance systems and sibling survival surveys and appears to present a more realistic landscape for Africa, even though the mortality statistics were restricted to people between the ages of 15 and 59 years.[3] Adult mortality risk—referred to in demographic terms as "45Q14"—averages between 350 and 400 for men in SSA and between 250 and 300 for women.[3] In contrast, similar statistics for Europe are approximately 100 for men and 50 for women. The uncertainty limits are often half as large as the total rate, and on the surface, the estimates for some of the countries continue to appear to be implausible. For example, it is difficult to reconcile the large variations among countries—from 733 in Zambia to 282 in Niger.[3] Thus, even these new estimates are too crude to provide the basis for any policy decisions.

In light of the problems highlighted above when assessing mortality in Africa, it follows that any attempt to gauge the prevalence of chronic conditions and other disease-specific rates would be problematic and therefore not known. Again, the RSA remains the exception; Mayosi and colleagues provide a thorough review of the current public health situation with regard to chronic diseases in the RSA.[5] Another potential exception is the island nation of the Seychelles, where excellent vital statistics and survey data are available.[6] However, the data from both of these countries do not encompass the diversity within SSA and the population-specific issues that may be linked with geography, climate, and other confounding problems. In the absence of a coordinated process of estimating disease prevalence, information gleaned from available specialized surveys, a small set of prospective studies, and hospital experiences has highlighted a substantial burden from hypertension, particularly in urban areas, and a high mortality from stroke in SSA.[7] In addition, a broad range of evidence from surveys and hospital reports documents the rapidly growing threat from diabetes. Clinical and epidemiologic research on these conditions has been conducted all over the continent, and clinical expertise can be found in virtually all hospital and tertiary care settings related to these conditions.

In contrast to research on chronic conditions, historically significant attention has been given to infectious diseases. Recently, genomics research has occurred that utilizes African populations to understand the genetics of infectious diseases, including tuberculosis and malaria.[8,9] In addition to infectious diseases and population genetics, genetics and genomics research also has focused on assessing the evolutionary history of African populations.[10,11] Of the two areas, the evolutionary history of African populations has brought significant information to light about human adaptation and migration out of Africa. Recent work on lactase persistence demonstrates the scientific rewards gained from studies of the diverse ancestry and environments in Africa.[12,13] Tishkoff and colleagues identified new genotype-phenotype relationships among pastoral groups in East Africa,[13] illuminating how selection shaped the genome. However, several groups have reiterated that essential research to address diseases

within African populations is not always the focus of funding from international organizations.[10,14]

Despite these recent studies, Africa is clearly underrepresented in the field of molecular, clinical, and genetics research. A recent review documented that, worldwide, the majority of the thousands of studies completed to date (about 75%) were conducted exclusively in populations of European descent.[15] The paradox of limited genomics research conducted in Africa and the centrality of contemporary African populations for our understanding of human evolution and population genetics have now been widely noted.[12,11,15] As a consequence of greater allelic diversity within Africa and the associated reduction in linkage disequilibrium, African populations harbor informative alleles, and studies in these populations can facilitate the fine mapping of genetic elements predisposing to disease. Therefore, any effort to obtain a complete survey of the genetic architecture of common human traits will require the substantial involvement of populations from Africa. The potential value of African and African-origin populations has been demonstrated in several collaborative analyses.[16,17] One international collaboration, the original HapMap Project, included Nigerians of Ibadan, insured high visibility for West Africans, and brought a broad appreciation of the value and importance of including Africans in the current generation of research studies.[18,15]

2. Resource Utilization and Development

The development of resources for a population-based genomics research agenda for Africa that is funded under the H3Africa Initiative should focus on infrastructure development, research (i.e., clinical phenotyping, sample collection, biobanking); training and education; analytical issues (i.e., genomic analysis, bioinformatics, statistics, functional analysis); and ethical, legal and social issues (ELSI). The organizational structures required for each of these are likely to differ (e.g., sample collection and phenotyping inevitably will be more distributed than large-scale genomic analysis). However, for resource utilization and development, several principles should be considered before allocation of capital for resources. These general principles are outlined below.

First, there are substantial benefits in working with established networks to harness scientific strengths and linkages. In utilizing existing resources within Africa for the development of a population-based genomics research initiative, funding agencies should critically engage with established networks and assess whether these networks will assist in advancing the vision and mission of equipping the African continent with centers that are open to all well-designed, genomics-related scientific endeavors. In engaging with existing networks, it will be necessary to ascertain the networks' future sustainability and, more importantly, to gauge the previous record of training African scientists. Due diligence will be critical in assessing the impact that previous and existing resources will have on the mission of developing this population-based genomics research initiative.

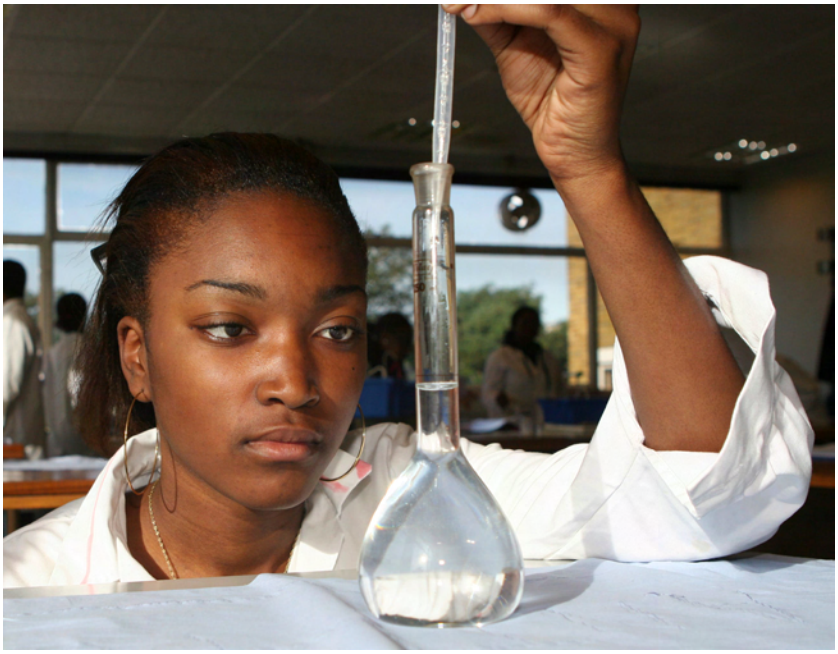
Second, many such centers in Africa arose from initial investments in research infrastructure and are currently maintained by funders via a variety of mechanisms. This approach demonstrates that sites created to facilitate research are successful in Africa when proper governance and knowledge are created, sustained, and utilized. These centers should be encouraged to assist with capacity development by engaging actively with other research institutions within the countries where they exist as well as with other countries. In addition, the success of these centers provides impetus for the establishment of new centers through H3Africa that will complement and expand the efforts of existing centers.

Third, other components of infrastructure development also will require an investment in personnel, training, and sustainable joint responsibility between European and U.S. collaborators with researchers at these sites on the African continent. The design of such a network should emphasize a tiered node capacity to include other African institutions. The tiered node system acknowledges that within Africa, as in other parts of the world, various institutions have differing levels of infrastructure, governance structure, institutional culture, and leadership; however, these properties should not be a barrier to involvement under the H3Africa research umbrella if the institution can meet the requirements for inclusion as a node in this network.

H3Africa is a unique opportunity that will be attractive for previously established centers. Unfortunately, although there are several examples of centers and individuals on the African continent that have catalogs of computer/sequencing/genotyping equipment, in too many cases these vast amounts of equipment do not come with the necessary level of expertise to promote skills transfer or capacity development. To achieve a sustainable research infrastructure, the ability to transfer the expertise and data analysis skills to the broader community on the African continent is paramount.

2.1. Specific Recommendations for Database Development as a Resource for African Scientists

Africa hosts more than 200 universities and other scientific institutions. Because the majority of these are in the public sector,



most researchers are supported by external funding. Simultaneously, limitations of human resources, qualified personnel, and technical capacity and restrictions in the scope of funding—particularly in genomics research and training—have created significant problems for collaborations within Africa.

To help overcome limitations in the ability to establish collaborations among African researchers, the AfSHG aims to develop a database of all universities, other scientific institutions, and researchers in the field of human genetics in Africa. This database will be an invaluable resource for African scientists and funding organizations because it will help foster the broader representation of African human genetics research networks in international forums and activities, while encompassing a wide array of researchers. The project will consist of two parts:

Part A: Database of African Human Genetics Research, including:

- A survey to identify all universities, other scientific institutions, and researchers involved in human genetics research in Africa, thereby creating a database of "African Human Genetics"
- A directory of resources housed at each institution, such as public databases, biobanks, technologies, and special skills and knowledge
- A networking service for institutions, groups, and individuals with common research interests

Part B: Geographic Information System database maps with the following layers:

- African human genetics research centers
- African populations sampled for human genetics studies
- Research focus areas (infectious diseases, pharmacogenetics, etc.)
- General country information plus disease epidemiologic data

The proposed databases are specific examples of the infrastructure development that can be accessed by the greater scientific community.

3. Infrastructure Development

The African continent lacks significant infrastructure for genomics research in some regions but has significant infrastructure, which maintains a robust research agenda, in other areas. Thomson Reuters has reported information about the infrastructure capabilities, publication output, and general research development of several leading African countries.[19] Nwaka and colleagues highlighted the uneven distribution of the capacity for research and development (R&D) of novel therapeutics in Africa. They also acknowledged that the R&D situation could be greatly advanced by a multifaceted, collaborative approach, which the African Network for Drugs and Diagnostics Innovation will utilize to develop capacity for novel health therapeutics via several concurrent mechanisms.[14] Daar and colleagues have discussed the development of North-South and South-South collaborations that have increased capacity through the development of private/public enterprises.[20,21,22] Overall, such reports place the RSA, Kenya, Egypt, Nigeria, Tunisia, and Algeria (no specific order) among the leading African countries in which genomics research exists and where it may be enhanced due to their existing infrastructure capacities and collaborative partnerships within and outside Africa. Thus, the creation of specific centers devoted to genomics research and the support of existing genomics networks offer several advantages for building genomics capacity in Africa.

It is recommended that the NIH and the WT conduct a comprehensive review of non-African organizations with successful research networks in Africa. Second, the NIH and the WT also should examine their agencies to identify those with successful research portfolios in Africa and to combine the two sets of data to determine the essential elements for building a successful research infrastructure in Africa. As demonstrated previously, considerable infrastructure exists within several African countries that could allow a population-based African genomics initiative to (1) capitalize on existing infrastructures and

networks and recruit new partner institutions to participate in the genomics research umbrella and (2) develop new capacities through training and the technology transfer of genomics and other related technology that are required for genomics infrastructure creation.

The aforementioned countries represent four foci of research in Africa that are located both in Francophone and Anglophone countries. Several of these centers arose from investments in research infrastructure. This approach has demonstrated that, with proper governance, the creation of sites in Africa that facilitate research can be successful and sustainable.

Finally, the development of a network structure for a population-based genomics initiative should emphasize a tiered node capacity to include other African institutions. Below are specific recommendations for research networks using the African Bioinformatics Network as a prototype for other disease-focused networks. This general hub and spoke model should be utilized for research networks in which a specific disease (i.e., infectious or chronic) can be explored.

3.1. Research Network (Hub and Spoke Model)

Bioinformatics as a discipline is gaining momentum in African universities and institutes through initiatives such as the establishment of an African Regional Training Center for Bioinformatics and Applied Genomics in Cape Town, South Africa, and the Malaria Research and Training Center in Bamako, Mali. These and other bioinformatics workshops in Africa were funded by the United Nations, the NIH, and other international organizations. The same institutions—in collaboration with the Southwest Biotechnology Center of Excellence, the National Biotechnology Development Agency/Federal Ministry of Science and Technology in Abuja, Nigeria, and the West African Biotechnology Workshop Series—sponsored a workshop held in Abuja in April 2008 to establish a strategy for the subsequent development of an African Bioinformatics Network (ABN) (described in section 3.1.1. below) that develops capacity and improves human health in Africa through the leveraging of biological information. The workshop brought together researchers from various African countries that are currently involved in bioinformatics research and training.

Workshop discussions proposed the formation of the ABN, with the mission of increasing research output in biological information translation from Africa. The aims of the ABN would be achieved through the following activities: (1) capacity building, including (a) human resources training at all levels for molecular biologists and bioinformaticians and career and leadership development for staff members (e.g., system administrators) and (b) infrastructure development, including identifying the needs, challenges, and solutions related to equipment and the Internet; (2) data gathering and access and data management, storage, and sharing; (3) establishment of training and hosting facilities; and (4) the fostering of translational biological research, including developing collaborations, establishing links between various research groups and institutions, generating data, and providing services to build capacity and provide training and sourcing/facilitation of funds.

3.1.1. African Bioinformatics Network

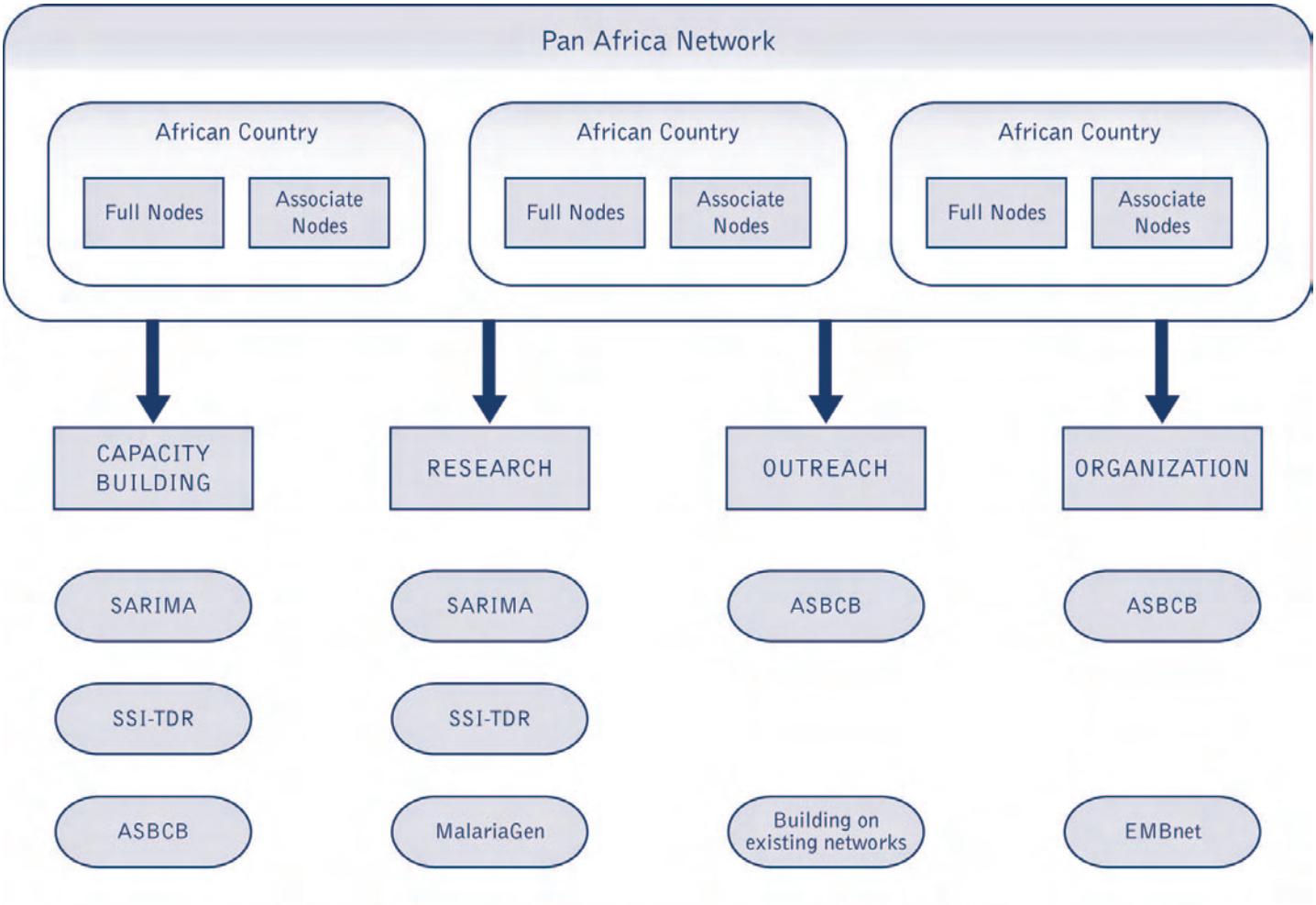
The Network should be organized around the concept of full and associate nodes from different countries as outlined in Figure 1 below. A node is defined as an established or newly developed center of expertise in bioinformatics that pursues the mission of the ABN. Its activities should include internationally recognized research programs and training and education to develop human capacity in bioinformatics. The research should be supported through access to biological data generated locally or obtained from public data sources. A node can be hosted only by an academic institution involved in the teaching of accredited undergraduate and postgraduate degree programs. Nonacademic institutions such as research organizations, service organizations, or research councils may be a part of another node that is located within an academic institution. Therefore, programs based at nonacademic institutions will function under the umbrella of a node hosted by an academic institution. This is a necessary provision to ensure that the nodes are able to provide for the training of students and scientists skilled in bioinformatics.

The full or associate status of nodes will be decided on the basis of the criteria outlined below, but the aim for all nodes should be to achieve full node status. The Network and its full nodes should work toward helping associate nodes build capacity in bioinformatics and strive for full node status. The various components of the ABN should identify and work with existing networks to avoid duplication of effort.

3.1.2. Incentives for ABN Membership

1. Training and access to training expertise
2. Building research networks
3. Peer review and scientific opportunities
4. Access to funding
5. Exchanging and sharing expertise
6. Building leadership

Figure 1. Pan Africa Network



KEY: SARIMA = Southern African Research and Innovation Management Association, ASBCB = African Society for Bioinformatics and Computational Biology, SSI-TDR = South-South Initiative for Tropical Disease Research, EMBnet = European Molecular Biology Network, MalariaGen = Malaria Genomic Epidemiology Network

3.1.3. Criteria for a Full Node

1. Hosting capability to handle at least one guest, including trainees, trainers, and other visitors
2. Recognition as a bioinformatics expert by having relevant publications, invitations to bioinformatics meetings, and/or a particular academic or institutional position that includes research training
3. Internet access
4. Computing resources or access to them
5. Altruistic attitude
6. Capacity to host training courses
7. Evidence of time and resources to devote to capacity building and training
8. Record of obtaining funding to provide local support
9. Statement of motivation and potential contributions and benefits from Network membership
10. Letter of institutional support for proposed activities and training (e.g., hosting, courses, signing off on grants, etc.)

3.1.4. Criteria for an Associate Node

1. Internet access
2. Computing resources or access to them
3. Appropriate credentials and a plan and desire to learn or build capacity (must state why bioinformatics is needed for research)
4. Letter of institutional support

5. Motivation to obtain and receive training
6. Altruistic attitude

3.1.5. Defining Target Health-Related Areas Where Bioinformatics Can Make an Impact

Health-related areas where bioinformatics can make an impact should include building and maintaining databases of pathogens, which will provide African bioinformaticians with the long-term ability to take advantage of available clinical data for a large diversity of human diseases (infectious and genetic diseases) and to integrate them with functional genomics data for a better understanding of the diseases, thereby promoting the diagnostics, drug, and vaccine design processes.

3.2. Clinical Centers

For large-scale, population-based research to occur, knowledgeable clinicians need clinical centers, which will allow clinicians to assist in management strategies, sample collection, and the identification of the phenotype specific to the research agenda for large-scale population studies. The clinical centers that are involved in such studies should be organized along the lines of the hub and spoke model as recommended for the establishment of the African Bioinformatics Network.

The participating institutions and clinical centers must have the infrastructure, expertise, and resources needed for phenotyping the selected condition, either chronic or infectious. The selection of clinical sites should be based on criteria established by a panel of scientists and also should require that each site has adequately addressed (1) ELSI for research design and recruitment of populations, (2) sustainable funding after the initial phase of investment by H3Africa, (3) geographic proximity to infrastructure allowing for sample collection and delivery and/or suitable storage capability, and (4) current expertise to address issues related to patient health.

3.3. Biological Laboratories for Phenotyping, Genotyping, and Sequencing

Large-scale, population-based genomics initiatives require laboratories that can perform a variety of tasks, including, but not limited to, sample processing, temporary specimen storage, and phenotyping/characterizing samples with molecular and genomics techniques (e.g., the capacity to perform large-scale, accurate genotyping and sequencing). Essentially, the utilization of genomics technologies in population-based genomics research requires establishing genomics "core" facilities or retrofitting facilities with new genomics technologies by expanding existing capacities.

The need for these infrastructures is critical because, currently, there are few centers that can undertake population-based genomics studies. Existing centers have limited capacities for samples and specimen storage. For the H3Africa Initiative to fulfill its mission, it either should establish core genomics facilities or should partner with research institutions with sufficient infrastructure to house genomics research (i.e., Tier 1 institutions) and the ability to make that infrastructure available to the general scientific community. Many scientists favor the latter approach because it allows distribution of H3Africa resources among institutions. Several models could be utilized because of the infrastructure that exists in many parts of Africa. A designated core facility/center of excellence could be created where a genomics laboratory could be established, or an existing center could be retrofitted with new technologies. A hybrid model also could be utilized, with some centers retrofitted while a core center also is established. In the hybrid model, a division of labor would allow each center to specialize in a specific set of molecular and genomics techniques. Regardless of which model is utilized, for all biological laboratories to perform each specific task, standard operating procedures must be established to provide consistency for each research center.

3.4. Biorepositories

To achieve the population-based research aims of the H3Africa Initiative, the appropriate samples (i.e., blood, sera, tissues) must be collected, processed properly, and stored for use by the research community. The samples also must have been collected with the appropriate Institutional Review Board (IRB) approval for use of the material for multiple purposes. The processing and storage of samples for large-scale studies require the development of the appropriate infrastructure, including facilities that can store, retrieve, distribute, and manage large collections of biological materials. The research agenda (see Section 5. Population Health and Disease Research below) will include large-scale, population-based studies, which will require the creation of biorepositories for the storage of these samples. Although genomic technologies evolve, there is an ongoing need for biorepositories for the storage of biological materials as an essential component in population-based research. The creation of adequate biorepository facilities to house and manage distributions of DNA samples would benefit from a preexisting infrastructure similar to those required to set up the core genomics facilities. Currently, however, there are no such biorepositories available that have the storage capability to facilitate and advance the population studies envisioned in Section 5. It is recommended that H3Africa have one biorepository for the initial phase that would be

centrally located to the core genomics facilities, with clearly outlined rules of governance agreed to by all participating stakeholders.

4. Education and Training

For genomics-centered, population-based research to be conducted successfully in Africa, considerable attention must be paid to education and training and the mechanisms of technology and knowledge transfer that help create a critical mass of appropriately trained individuals. For example, the Stanford-South Africa Biomedical Informatics Program (SSABIP) has demonstrated that effective communication between the RSA and U.S. institutions of higher education allows Africans to produce leaders who can begin to have an impact on the public health of African populations.

4.1. Retention of African Scientists

In the past 5 years, the SSABIP model for genomics training in bioinformatics has been successful and has been shown to be scalable. Using this model, individuals have been trained who, in turn, have established training efforts in a growing number of regional and international training centers, which has led to a coherent network of experts with shared training responsibilities. Several important aspects of the SSABIP (funded by the John E. Fogarty International Center at the NIH) are:

- Development of a graduate curriculum that expands existing bioinformatics and genomics graduate training to include short, intensive 3- to 5-day sessions on biomedical informatics, ethics, genomics, statistical genetics, and associated areas
- Financial support for postdoctoral and predoctoral trainees in Africa
- Financial support for graduate students, postdoctoral fellows, and junior faculty members for focused 3- to 6-month research visits to study at U.S. and U.K. partner institutions
- Oversight of student/trainee development by an international committee that mentors students regularly in addition to formal and informal oversight through existing training mechanisms
- Trainee oversight by joint African-U.S. partner institution principal investigators

The SSABIP model provides training in bioinformatics. Similar to this model, H3Africa also should include building a solid foundation of expertise in genomics (and associated disciplines such as ethics) and informatics leadership development in Africa.

Within the initial 5-year timeframe, H3Africa should lay a solid foundation for the establishment of a vibrant, internationally competitive set of African sites for performing high-impact genomics and informatics research across Africa. The centers should be populated by scientists who understand the effective approaches to training in human genetic variation (HGV), genomics, bioinformatics, and key issues in public health, similar to the SSABIP training model. Export of this model as a robust training mechanism for African scientists also should involve linkage with partners in other programs that exist on the African continent. Linkage among successful models of training for African scientists will enable the development of well-connected regional and international consortia to drive discoveries pertinent to local public health and will provide the biomedical information necessary to promote research.

To address current disparities, support for the training of African scientists should include genetic epidemiology, bioinformatics, statistical analysis, high-throughput technologies, genomic data analysis, clinical research, and ELSI research. With regard to training and education, H3Africa should have a long-term impact by funding a few programs and providing funding to fellows who train with scientists in both African and non-African institutions and laboratories (in particular, those of African diaspora scientists). Applications for funding from H3Africa should be accepted only if the application clearly outlines a method for meeting the criteria for H3Africa funding and ensures a long-term impact.

4.2. Specific Recommendations

4.2.1. Build an Extensive Skills Base in Africa for the Disciplines Needed for Research Projects

- Develop education and training that can be shared among researchers in African countries. Offer training in a modular manner to make it more accessible.
- Involve scientists from the African diaspora and encourage them to work with those on the ground in Africa (e.g., in a mentorship role with potential communication through the African Institute of Science and Technology and the African Renaissance Institute of Science and Technology).
- Develop an extensive mentorship program.

4.2.2. Hold Annual H3Africa Meetings on the Continent

- Use the annual meeting as an opportunity to bring together different disciplines and to foster interdisciplinary engagement (cross-pollination between disciplines).

- Use workshop formats for training and teaching.
- Create a sense of belonging to the H3Africa Initiative.

5. Population Health and Disease Research

The advances in genomics within the past few years have been considerable. With these advances, has come an increasing focus on the medical care and health benefits of genomics. Although the medical implications are important, genomics has not yet improved medical treatment to the extent that some had suggested it would have by now. Genomics likely will be very helpful, but it is only beginning to contribute such benefits. Until now, the primary success of genomics has been in adding to the greater knowledge of biological understanding, including principles and phenomena that have been instrumental in understanding some disease processes. It is expected however, that genomics will help address the questions facing many diseases, including HGV among populations, allowing observations of differences in disease progression, such as those observed in sickle cell disease, or susceptibility to infectious diseases.[8,9]

It is suggested that the NIH and the WT consider a request for proposals to support a number of focused research projects that could address questions of significant scientific and medical importance to African populations. Because of the nature of HGV within African populations noted above, considerable attention will need to be paid to African genetic diversity; thus, it is also suggested that any genomic study in African populations also include characterization of the comprehensive human genetic diversity in African populations.

5.1. Comprehensive Evaluation of Human Genetic Variation in African Populations

The original goal of the H3Africa Initiative was to design a stand-alone project to facilitate the development of the most comprehensive database of HGV across the continent of Africa. Although major international projects such as the HapMap Project and the 1000 Genomes Project were designed to capture the distribution of HGV across world populations, these populations are not representative of the genetic complexity of African populations. In this regard, it is proposed to collect and sequence, after appropriate community engagement, the DNA from 100 unrelated individuals (50 males and 50 females) from 100 ethnic African populations, for a total of 10,000 individuals. A secondary goal of this project was to establish one of the world's leading biorepositories of African samples that will be housed on the continent of Africa. It was anticipated that this resource would facilitate multiple important scientific and capacity development activities, including (1) intra-Africa scientific collaboration, (2) global collaboration between African scientists and their international partners, (3) training of African scientists, and (4) development of regional research capacity on the continent of Africa.

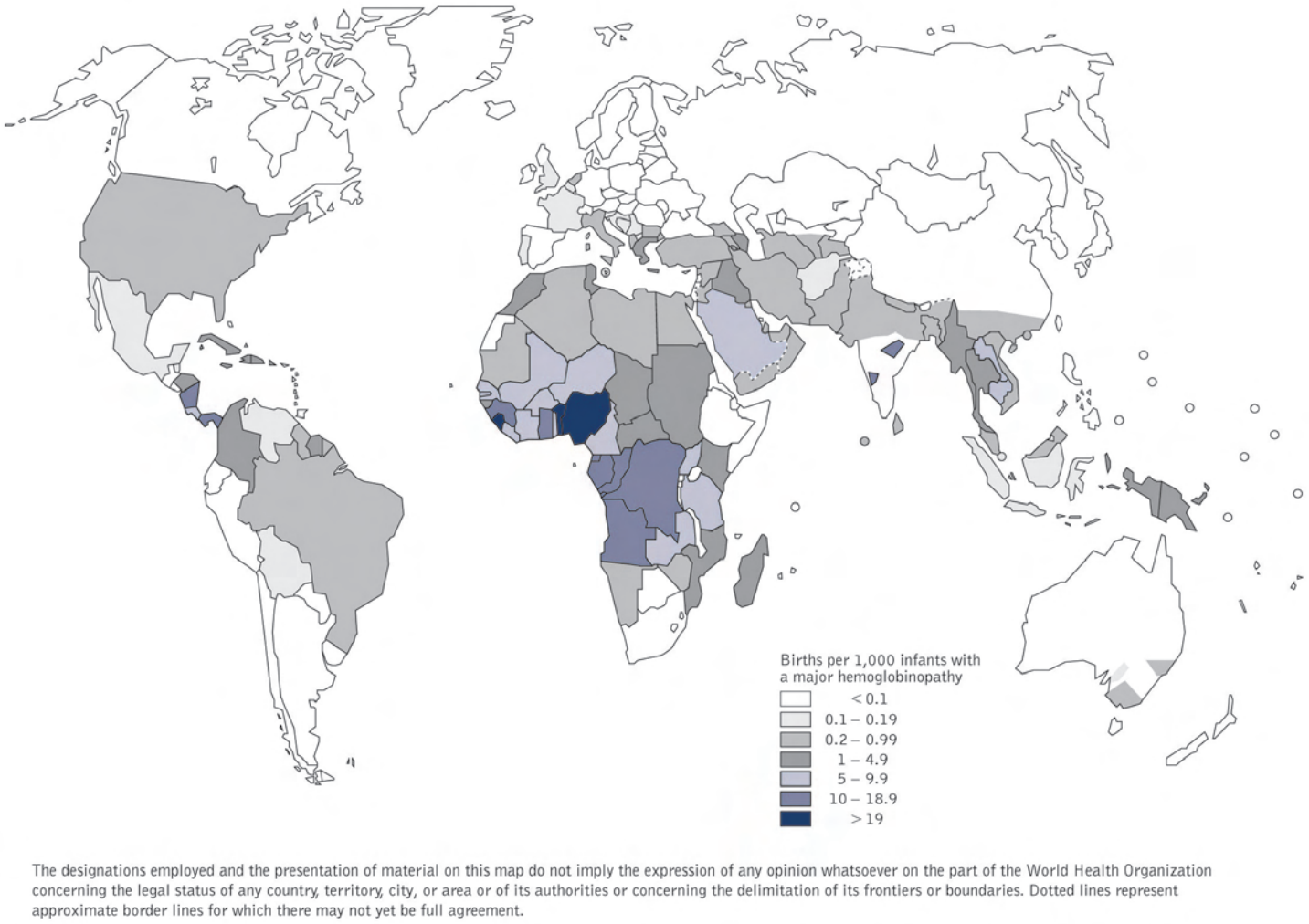
However, following meetings of the H3Africa Communicable Diseases and Noncommunicable Diseases Working Groups in Oxford in August 2010, an alternative strategy for a comprehensive understanding of HGV in African populations was discussed. It was suggested that the documentation of HGV should be tied to specific disease research activities. The primary reason for this recommendation was that H3Africa should be about solving the health problems of African people by understanding the complex interactions between genetic and nongenetic factors and not just about documenting HGV. However, this recommendation was made with the clear understanding that the successful elucidation of the genetic basis of human diseases requires a detailed documentation of HGV in the populations being studied. This alternative strategy calls for the use of samples collected during disease research activity to form the basis of the HGV project. The advantages and disadvantages of this strategy need to be discussed further.

5.2. Noncommunicable Diseases

A recent comprehensive review by a working group associated with the AfSHG provides complete summaries of research occurring in Africa.[10] The majority of genomic research in Africa has been conducted on infectious diseases and population genetics.[10,8,11] For chronic conditions, the Africa America Diabetes Mellitus Study has served as the basis for numerous analyses of genetic factors influencing glucose metabolism, obesity, and serum lipids.[23] Linkage, candidate gene, and genome-wide association studies (GWASs) have been completed and have served to identify potential new loci and replicate findings from other large collaborations.[24,25,26] Other research that includes hypertension and obesity has been ongoing among the Yoruba people in Nigeria since 1995, leading to linkage, candidate gene, and GWASs.[27,28,29,30] Similar research has been conducted in Ghana, including a candidate gene study of the hemostatic factors plasminogen activator inhibitor-1 and tissue plasminogen activator.[31,32] Other chronic conditions, including common cancers (e.g., breast, prostate, esophageal), have been the subjects of candidate gene studies in Africa.[10]

If chronic metabolic disorders are to be studied, particularly those related to the cardiovascular system, an important design consideration is the relative advantage of a cohort study or a design that relies on

Figure 2. Global Distribution of Hemoglobin Disorders in Terms of Births of Affected Infants per 1,000 Births



The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.

SOURCE: Modell B and Darlison M. *Bulletin of the World Health Organization. Global Epidemiology of Haemoglobin Disorders and Derived Service Indicators.* 86(6):June 2008.

recruitment of cases from hospitals and clinics. Since genotype is fixed, prospective epidemiologic studies are not required to define genotype-phenotype relationships. Nonetheless, to appropriately characterize environmental factors, longitudinal followup offers important advantages. These advantages, however, must be balanced against the cost and time required to accumulate an appropriate number of cases. Even for relatively common events, such as incident hypertension, a large cohort and/or moderate followup would be required. Therefore, a mixed design, including elements of both approaches, most likely would be necessary.

5.2.1. Sickle Cell Disease

It is estimated that approximately 300,000 children are born each year with sickle cell disease (SCD), with 75% of these births occurring in Africa.[33] SCD is the most common single-gene disorder in the world. Several observations indicate that SCD prevalence is increasing due to several factors, including reduction in childhood mortality from infectious diseases and improvement in health care (see Figure 2 above).[32] When left untreated, up to 90% of SCD patients die in childhood. With increased survival, the burdens to individuals, the health system, and the country are significant, since SCD individuals require medical care, have a poor quality of life, and are disabled.

SCD is also characterized by significant clinical heterogeneity in the affected population. Although some patients suffer life-threatening complications at a young age, including stroke and pulmonary complications, others live into the fifth and sixth decades of life with few major vascular episodes. Understanding the genetic basis of variability in severity is important in the process of predicting the clinical course of SCD and selecting treatments with appropriate

risk-benefit profiles for SCD patients. Over the past 50 years, anecdotal reports have suggested that some SCD patients have few clinical complications; this variability cannot be accounted for by environmental or hematologic variables.[34] Recent genetic evidence demonstrates that HGV associated with fetal hemoglobin (HbF) levels also influences clinical severity in SCD patients.[35]

At birth, a developmentally regulated gene expression switch leads to the replacement of HbF with adult Hb. This developmental switch is not complete, because residual amounts of HbF are produced throughout adulthood. Across healthy individuals, a 20-fold variation in HbF level can be observed.[36] In addition, HbF is the strongest modifier of clinical severity in SCD: SCD patients with elevated production of HbF have less severe complications and live longer.[37,38] Substantial progress has been made toward the identification of genes that modify HbF expression.[39,40,35,41,42,43,44] These include the β-globin locus itself, the HBS1L-MYB intergenic region on chromosome 6q23, and the BCL11A gene on chromosome 2p15.[45,46,39,47,40] A recent GWAS showed that the minor allele of the single nucleotide polymorphism (SNP) rs4671393 in the BCL11A locus is additively associated with increased HbF levels among African-American and Brazilian SCD patients.[35] BCL11A is also a direct negative regulator of HbF production.[48] Together with other known modifiers at the loci, it is estimated that these variants can account for 20-50% of the variations observed in the expression of HbF found in many SCD patients.[36] Although the relationship is not as well described as with malaria, initial observations suggest that the mutation might be protective against human immunodeficiency virus (HIV) and tuberculosis infections. Understanding the protective mechanisms of this mutation against malaria and HIV and characterization of its variants associated with SCD will contribute to the knowledge required for successful vaccine development. These important new developments in SCD will at some point need to be pursued in Africa given the high burden of SCD and the substantial challenge of infections that vary greatly from those found in the Americas.

In addition, much of the current knowledge about SCD comes from studies conducted in America and Europe. However, a difference is observed in Africa, where a significant proportion of the population has SCD. Differences among African populations that influence SCD progression and outcome include bacterial infections (e.g., *Streptococcus pneumoniae*), malaria, poor nutrition (insufficient iron, folic acid, vitamins B12 and A), low socioeconomic and educational status, and limited access to health care. Furthermore, genotype-phenotype studies are needed to determine the relationships among these factors in determining disease progression.

5.2.2. Monogenic Disorders

In addition to SCD, African populations have other uncharacterized monogenic disorders for which a genomics approach would be informative. For example, local founder effects and the cultural practice of consanguineous marriages in many communities in Africa have resulted in the increased prevalence of monogenic traits in some communities across the continent. Unlike complex multifactorial traits, monogenic or Mendelian traits have a direct genotype-phenotype correlation and are usually highly penetrant. Although individually relatively rare, with the exception of high prevalence rates in specific populations, together monogenic and Mendelian traits contribute significantly to the burden of disease yet also provide insight into pathways involved in more common complex disorders (e.g., Mendelian susceptibility to mycobacterial infection and tuberculosis, single-gene hypertension disorders, essential hypertension). Monogenic traits are tractable to genetic investigation with relatively modest resources and are amenable to participation by clinicians and researchers across Africa who have limited access to genetic laboratory and clinical resources. By forming partnerships, this could lead to increased capacity development in several regions and the forging of networks based on mutual support and local requirements for service provision. The outcomes of such studies have the potential for implementation in a clinical setting through the introduction of mutation detection tests for families and

founder communities. Imperatives for success are adherence to universal ethical processes and tenets, clinical utility of the tests that are developed, and laboratory quality control to ensure appropriate and accurate testing. Such a project can start as a modest initiative with a small number of participants but would have the potential to grow into a continent-wide network on which other initiatives could be built over time.

A specific example of a specific project is the genomic characterization of nonsyndromic deafness in a population from the Limpopo Province in the RSA. The etiologic diagnosis of nonsyndromic hearing loss (NSHL) poses a challenge owing to its marked genetic heterogeneity and lack of clinical features that allow for grouping into separate nosocomial entities. The high frequency of *GJB2* mutations identified among Caucasians within the RSA opened the way for diagnostic testing for congenital NSHL in Europe and North America. Despite the paucity of deafness research from SSA, diverse results have emerged regarding *GJB2*: a low prevalence of *GJB2* variations among Kenyans, a high prevalence of the R143W mutation among Ghanaians, and the presence of the 35delG mutation among the Sudanese. When considered together with the findings from other populations outside of Africa, these results suggest that *GJB2* may not be a significant deafness gene among SSA Africans, pointing to other unidentified genes as being responsible for NSHL among these African populations (unpublished data).

5.2.3. Stroke

Population-based genomics studies of stroke in African populations are limited. The limited data available suggest that the age-standardized mortality, case fatality, and prevalence of disabling stroke in Africa may be similar to or higher than that observed in most high-income regions.[49] However, the overall prevalence of stroke is less than half that found in high-income regions. Data from a large verbal autopsy study in Tanzania indicated that stroke was responsible for 5.5% of adult deaths.[50] Despite its importance, stroke would require extensive case finding and diagnosis of the stroke subtype, which would be difficult due to the limited availability of radiodiagnostic facilities on the African continent. Moreover, cerebrovascular infarctions are gaining prominence in SSA.[51,52] Subclinical cerebrovascular vascular disease may be inferred from a number of noninvasive tests, including carotid artery intima-media thickness (CIMT) on ultrasound. As a surrogate for atherosclerotic cardiovascular disease, CIMT provides a noninvasive, accurate, and portable imaging modality for both population- and band clinic-based studies for estimating the risk of stroke and global vascular disease burden.[53] CIMT is associated with increased risk for stroke,[54] and changes in CIMT have been used as surrogate endpoints for the diagnosis of atherosclerotic vascular disease and for long-term prospective cohort studies.[55] However, equipment for determining CIMT is relatively expensive and not readily available. Other chronic conditions offer a less problematic diagnosis and treatment potential that do not require expensive technology. These chronic conditions are outlined below.

5.2.4. Cardiovascular Disease

Limited infrastructure could limit a comprehensive genomic analysis of stroke in African populations; hypertension, stroke, and heart failure have emerged as the dominant forms of cardiovascular disease (CVD) in SSA.[56] Data from 2001 indicate that CVD was the leading cause of death worldwide, with the exception of SSA, where HIV/acquired immunodeficiency syndrome (AIDS) (HIV/AIDS) was the leading cause of death, with CVD being the second most common cause of mortality in this region.[57] The emergence of heart failure as an important form of CVD in SSA holds great public health relevance because of its high prevalence and impact on young, economically active individuals, resulting in significant disability, premature death, and loss of economic productivity.[58,59]

Recent studies reveal intriguing insights into the unique epidemiology of heart failure in Africa.[60] First, heart failure in Africa is largely due to nonischemic causes, with hypertensive heart disease, rheumatic heart disease, and cardiomyopathy accounting for at least two-thirds of cases. The observation that the diagnosis of myocardial infarction was made in only 3-10% of cases admitted to African hospitals for heart failure confirms that ischemic heart disease remains uncommon in Africa.[61] Second, common causes of heart failure in Africa, such as rheumatic heart disease, peripartum cardiomyopathy, and endomyocardial fibrosis, present in children and young adults. This is in contrast to industrial nations where heart failure is a disease of elderly persons, with a mean age of onset of 76 years. Third, infections remain a significant cause of heart failure in Africans. Pulmonary heart disease and pericarditis, largely due to tuberculosis, account for approximately 10% of causes of heart failure in Africa. HIV-related CVD includes tuberculous pericarditis and HIV cardiomyopathy, both of which are important causes of heart failure in SSA.

Rheumatic heart disease and the endemic cardiomyopathies are enigmatic conditions that are neglected, are common in Africa, affect the young, and are likely to be fruitfully investigated through a molecular genetic approach. For example, twin studies show that there is a high

degree of genetic influence in the development of rheumatic fever, the antecedent of rheumatic heart disease.[62] Significant familial aggregation has been shown in the case of endomyocardial fibrosis,[63] whereas genetic factors are being reported in those with apparently idiopathic and peripartum cardiomyopathies.[64,65]

Registries of large numbers (i.e., several thousand) of well-characterized cases of rheumatic heart disease and the endemic cardiomyopathies are needed to identify the genetic factors that underlie these conditions, through case-control studies and family-based studies. It will be necessary to establish clinical and genetic infrastructures for the phenotyping and genotyping of these CVD cases.

5.2.5. Hypertension

Hypertension is highly prevalent and widespread in Africa and is of immense economic importance due to associated premature disability and morbidity from its varied complications. The WHO estimates that more than 30 million people in Africa have hypertension. It is projected that by 2020 three-quarters of all deaths in Africa may be attributable to hypertension. Stroke deaths and disability attributable to hypertension in SSA cause 73,000 deaths in men and 107,000 deaths in women and a total disability of 2.6 million DALYs.[66] Hypertension is also the strongest risk factor for myocardial infarction in black Africans, with an odds ratio of 6.99.[67] Other major complications of hypertension in Africans include heart failure[68] and end-stage renal disease.[69] The diagnosis of hypertension is relatively straightforward but requires adherence to correct procedures. In contrast, the etiologic diagnosis is relatively more challenging in most parts of Africa. The great majority of causes result from essential hypertension, with only about 5% having secondary causes.

5.2.6. Type 2 Diabetes Mellitus and Obesity

The prevalence rates of type 2 diabetes mellitus (T2D) and obesity are rising across Africa, especially in urban settings where changes in lifestyle and diet are most marked. Detailed epidemiologic data are lacking, but risk factor profiles are likely to involve factors that are similar to those influencing non-African populations (e.g., age, obesity), with possible additional contributions from infections such as hepatitis C.[70] The rise in T2D has been attributed to several factors, including aging of the population, increasing rates of obesity, physical inactivity, and greater longevity in patients with diabetes due to improved diabetes care. It has been estimated that care of T2D and its complications consumes between 2.5% and 15% of health care budgets in SSA countries.

According to current estimates, 10 million Africans have diabetes in Africa; this is projected to rise to 19 million by 2030. The number of patients with T2D is likely to be even higher than current estimates[71] since a substantial proportion of patients with T2D are undiagnosed. In this regard, up to 70-80% of T2D may be undiagnosed in Africa.[72,73,71] Diabetes represents a potent risk factor for coronary artery disease and imposes additional morbidity and mortality through microvascular complications.[74,75]

Up to 6% of deaths in adults ages 20-70 years is attributable to diabetes.[71] Population-based diabetes morbidity and mortality data are limited in Africa. Available data on morbidity and mortality are largely hospital based. Thus, hospital-based diabetes clinics in major urban areas provide the most obvious source of cases for genetic studies, and controls can be identified from the local community (ideally from the same ethnic and linguistic groups as the cases) through the usual range of options (e.g., spouses, other patient samples, cohort studies). Validation of the diagnosis is relatively straightforward (especially if initially supported by the appropriate diagnostic measures), and exclusion of disease in controls can be achieved using either fasting or untimed samples (given rates of hemoglobinopathies, glucose levels are likely to be preferable to glycated Hb). Studies in West Africa (Nigeria and Ghana) have shown that this approach can work,[23,24] and groups in the United Kingdom are currently supporting studies elsewhere on the continent (particularly Malawi, Uganda, the RSA, Cameroon) that have identified approximately 15,000 clinical cases of diabetes (along with suitable controls) that are available for potential recruitment. Several recent community-based studies in parts of SSA report diabetes prevalence in excess of 4%.[76,77] Moreover, there are relatively large clinic cohorts of T2D in many parts of Africa.[78]

Studies of diabetes-related quantitative traits (including obesity) are most easily supported through epidemiologic surveys, which often capture a wider range of phenotypes. Several large surveys that are scattered across the continent (e.g., in Gambia, Kenya, Uganda, Malawi) provide access to approximately 40,000 subjects that could be recruited to such a study.[79] Body mass index and glycemic traits are amenable to relatively straightforward measurement using readily available and well-established procedures. A key issue for any study that involves "case-finding" (e.g., screening for diabetes) is the requirement that local infrastructure exists that can support sustained health care delivery for diagnosed individuals. These infrastructures are already in place for a number of centers within Africa (including those described above), often in association with existing infrastructure investment from external

funders (e.g., the WT in Kenya, the Medical Research Council [MRC] in the United Kingdom, Uganda, and Gambia).

Diabetes, hypertension, and obesity are also risk factors for stroke and are linked together in the metabolic syndrome. The relatively large population burdens of these conditions, their projected increases, and the relative ease of ascertainment make them suitable candidates for consideration for study in Africa. Patients with hypertension and diabetes tend to vary with respect to their susceptibility to complications. It has been postulated that genetics may be important in this respect.

Finally, other neglected conditions that are prevalent in Africa or unique to the region could benefit from a genetic approach. Prominent among these are rheumatic valvular heart disease, Mseleni joint disease, diffuse gastrointestinal leiomyomatosis, and head nodding disease of Tanzania and Sudan. Interestingly, many Mendelian conditions have not been fully characterized in African populations. Moreover, several chronic conditions, including stroke, hypertension, CVD, and T2D, present significant opportunities that could generate data beneficial to populations outside of Africa.

5.3. Communicable Diseases

A combination of population variation factors, environmental diversity, and economic disparity makes Africa an endemic focus for various infectious diseases, including malaria, leishmaniasis, trypanosomiasis, and schistosomiasis. From the various regions in Africa, these diseases prevail with variable intensities. The burden of infection is exacerbated by extreme poverty, malnutrition, limited access to essential drugs, drug resistance or resistance of disease vectors to insecticide, and lack of effective vaccines against these deadly diseases.

The leading causes of morbidity and mortality in Africa are malaria, acute respiratory infection (pneumonia), diarrheal diseases, HIV/AIDS, and tuberculosis,[80] which cause approximately 90% of deaths.[81] An estimated 300-500 million Africans are infected with malaria each year, causing 1.5 million to 2.7 million deaths.[79] In 2007, 22.5 million adults and children in SSA were living with HIV out of 33.2 million worldwide.[82] Acute respiratory infection (mainly pneumonia) contributes annually to the deaths of more than 2 million children younger than age 5 years, more than half of them in Africa and Southeast Asia.[83,84] About 30% of people living in SSA are latently infected with *Mycobacterium tuberculosis* (*M. tuberculosis*), which causes 2.4 million tuberculosis cases and 540,000 tuberculosis deaths annually.[85] Epidemics such as meningococcal diseases in the meningitis belt of Africa,[86,87] cholera, Ebola, and Lassa fever[88,89,90] are also found in Africa and strike down adults and children alike.

Several other diseases (often neglected) can cause chronic conditions resulting in long-term disability, including lymphatic filariasis, schistosomiasis, and cancers caused by other infectious disease agents. Lymphatic filariasis, a mosquito-borne disease affecting about 120 million people, can cause grotesque enlargement of the limbs and genitals and damage to internal organs. More than 12 million people are infected with leishmaniasis, another vector-borne disease that can cause internal organ damage, skin lesions, and mutilation of the nose and mouth. Sleeping sickness transmitted by the tsetse fly threatens 55 million people in 36 countries in SSA[81] and causes long-term debilitating illness and mental suffering. Other infectious disease agents include human papillomavirus, which is associated with cervical cancer, the most prevalent cancer among women in many African countries.[91,92] Schistosomiasis, a widespread parasitic worm disease, causes chronic urinary tract disease and often results in cirrhosis of the liver and bladder cancer.[93] Liver cancer, the number one cause of cancer deaths in males in many African countries, is associated with chronic hepatitis B and C infections.[94] *Helicobacter pylori* has been found to be directly responsible for most peptic ulcer disease and for gastric carcinoma.[95] These associations have potentially important implications for the development of vaccines to prevent microbe-associated cancers and for genomic research on both infectious diseases and cancer.

Despite the widespread nature of infectious diseases and the high rates of infection in populations living in similar environmental conditions, there is considerable interindividual phenotypic variability, ranging from asymptomatic to lethal infections (e.g., despite the high prevalence of malaria in children, only 1% develop life-threatening cerebral malaria). Genetic studies aim to determine the genetic variations accounting for this interindividual variability in the course of human infections. The genetic contribution to infectious diseases in human populations has been supported by many epidemiologic studies that are based on ethnic differences,[96,97,98] familial aggregation, and segregation analysis.[99,100,101] Candidate gene studies and genome-wide linkage analyses have shown evidence of variation in susceptibility to infection among different ethnic groups and have implicated various chromosomal regions, including SLC11A1, 5q31, and 6q27.[102,103,104,105,106] Some well-established, population-based mutations show clear effects on disease and include defective alleles of CCR5, a known receptor of HIV that is associated with resistance to HIV infection[107] and the presence of potential genetic factors that play a role in susceptibility to trypanosome infection.[108,109,110]

Finally, some studies indicate that certain human genes exert an almost pathogen-specific effect in protective immunity.[111]

Research on infectious diseases requires the study of the pathogens (e.g., parasite, virus, bacterium), the hosts, and the disease vectors (e.g., Anopheles mosquito, sand fly, tsetse fly) or of the interactions among the three (i.e., human pathogen, human vector, vector-pathogen). The completion of a number of genome sequences for both human pathogens and for various insect disease vectors will enable the development of tools to query genetic variation in each of these organisms and will provide substantial clues to mechanisms that may potentially be rendered to translation in vaccination or therapy. The discovery of biologically important loci may allow conversion of these loci into biomarkers for the monitoring, surveillance, and diagnosis of infectious diseases. The ability to examine, across the entire human genome, the expression of the full menu of host factors involved in the response to a microbial pathogen will provide unprecedented opportunities to understand disease pathogenesis and the cascade of gene expressions involved in the response of the innate and the adaptive immune systems to an invading microbe. Currently, data generated after the sequencing of the human genome have identified millions of SNPs that facilitate the implementation of GWASs. Using the GWAS approach to infectious disease, many more genetic loci can be expected to be revealed, molecular pathways to disease described, and therapeutic targets identified, with the hope that these can be translated quickly into treatments. The GWASs being applied to tuberculosis, malaria, HIV infection, dengue fever, and other diseases[112,113,114,8] will have implications for population-based treatment and prognosis strategies.

5.3.1. Tuberculosis

It is estimated that 2 billion people are infected with *M. tuberculosis*, the cause of tuberculosis (TB). TB is the leading infectious disease cause of adult mortality globally, accounting for more than 2 million deaths each year. The prevalence of TB in African countries varies and shows close correlation with the burden of HIV, given the role of HIV-driven immunodeficiency in activating latent TB. Demographics indicate that rates vary widely, but in 2008 the prevalence across the continent was 473/100,000 population, and the incidence was 385/100,000 population (see Table 1 and Figure 3 below) compared with 333/100,000 and 162/100,000, respectively, in 1990. This translated into 3.8 million prevalent cases and 2.83 million incident cases total in 2008 and accounted for 30% of the global TB burden in Africa—11% of the world's population. TB accounted for 56 deaths per 100,000 population in HIV-negative individuals (caused specific mortality) and for 46 deaths per 100,000 population in HIV-positive individuals in the WHO Africa region.[80] TB kills more women annually than all the causes of maternal mortality combined. As shown in Table 1 below, although the absolute numbers of TB cases in the WHO Africa region are not the highest, the incidence and prevalence rates are more than double that of Southeast Asia (which harbors the highest number of cases), and the morality rate is also the highest globally.

There is an increasing problem with multidrug-resistant TB (MDRTB) and extensively drug-resistant TB (XDRTB). Both of these

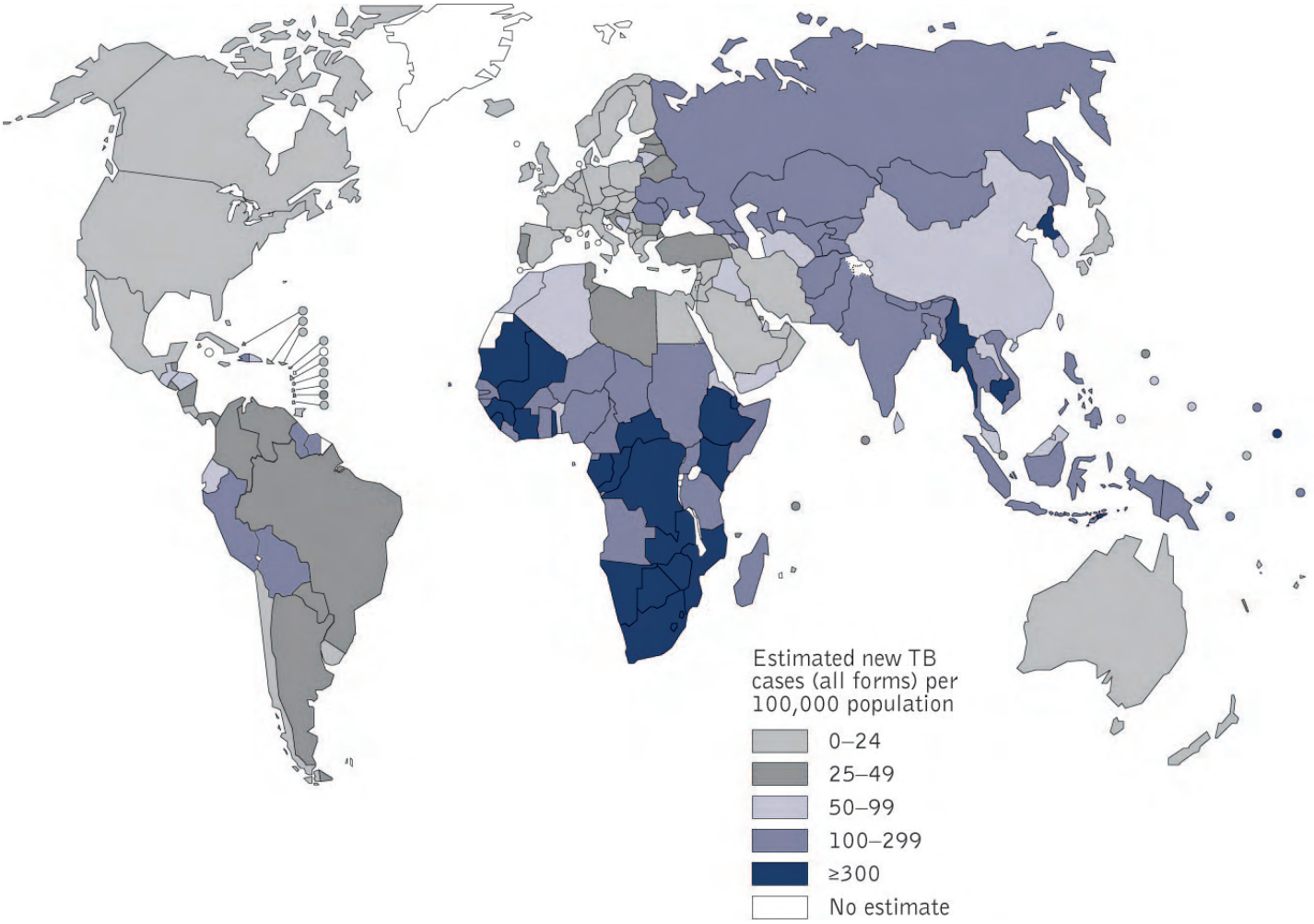
Table 1. Estimated Tuberculosis Incidence, Prevalence, and Mortality, 2008

	Incidence[1]			Prevalence[2]		Mortality	
WHO Region	Number (in thousands)	Percentage of global total	Rate per 100,000 pop[3]	Number (in thousands)	Rate per 100,000 pop[3]	Number (in thousands)	Rate per 100,000 pop[3]
Africa	2,828	30%	351	3,809	473	385	48
The Americas	282	3%	31	221	24	29	3
Eastern Mediterranean	675	7%	115	929	159	115	20
Europe	425	5%	48	322	36	55	6
Southeast Asia	3,213	34%	183	3,805	216	477	27
Western Pacific	1,946	21%	109	2,007	112	261	15
Global Total	9,369	100%	139	11,093	164	1,322	20

[1]Incidence is the number of new cases arising during a defined period.
[2]Prevalence indicates the numbers of cases (new and previously occurring) that exist at a given point in time.
[3]Pop = population.

SOURCE: Adapted from World Health Organization (2009). *Global Tuberculosis Control: A Short Update to the 2009 Report.* Geneva, Switzerland: World Health Organization. ISBN 978-92-4-159886-6.

Figure 3. Estimated Tuberculosis (TB) Incidence Rates by Country, 2009



SOURCE: Adapted from World Health Organization (2009). *Global Tuberculosis Control: A Short Update to the 2009 Report.* Geneva, Switzerland: World Health Organization. ISBN 978-92-4-159886-6.

situations create special problems in low-resource settings since drug regimens to treat MDRTB are expensive and involve drugs that are not easily available; XDRTB is usually fatal in this setting. Some 95% of the 8 million new cases of TB and 98% of deaths from TB worldwide are in developing countries. Of the 15 countries with the highest estimated TB incidence rates per capita, 12 are in Africa, and the regional variation in incidence is best represented as shown in Figure 3 above. The variation correlates with HIV prevalence, and in inner-city areas, TB incidence rates are as high as 1,000/100,000 population.

Only 10% of the 2 billion people estimated to be infected with *M. tuberculosis* develop clinical disease. Epidemiology studies, including twin studies, indicate that up to 40% of phenotypic variation in TB is genetic in origin. However, attempts to identify specific genes have to date been disappointing, and conflicting data have been published. One published GWAS for TB was conducted in West Africa populations,[9] which identified a locus on chromosome 8. The lack of success most likely reflects the diverse clinical phenotypes represented in TB: Even pulmonary TB has numerous clinical manifestations (i.e., cavitating, pneumonia, etc.), and disease may disseminate to extrapulmonary sites, requiring more meticulous clinical phenotyping for success using genetics research. In addition, case-control studies have reported different genetic variants in association with the different clinical phenotypes, which could be addressed further in larger studies. However, larger studies have not been addressed to date. Whether host genotypes influence response to treatment beyond pharmacogenetics factors is an area that needs significant attention.

Basic research components include identification of host genetic variants that predispose to disease and that modify clinical presentation (e.g., localized versus disseminated

disease) and response to treatment. Studies on host-pathogen interactions also are required. Translational returns are potentially high; there has not been a new TB drug for 40 years, yet MDRTB and XDRTB are on the increase. There is also an urgent need for new vaccines; BCG, the current vaccine for TB, does not protect against common forms of TB in endemic countries. Given the high rates of coinfection, it would be difficult to study TB without including studies on HIV as well.

Because TB is a significant public health issue for all populations, it offers an opportunity to use a strong, multicenter approach. Also, resources exist that can help mitigate the cause of this disease, which represents actionable patient care and a research framework that, given appropriate resources, can be beneficial to African populations while also demonstrating a research structure that can be very successful within the short term.

5.3.2. Human African Trypanosomiasis

Sleeping sickness (human African trypanosomiasis [HAT]) and visceral leishmaniasis (VL) (also called kala-azar) are two diseases caused by different parasites of the order Trypanosomatidae. HAT is caused by *Trypanosoma brucei gambiense* (*T.b. gambiense*), which occurs in West and Central Africa, and *Trypanosoma brucei rhodesiense*, which occurs only in East Africa; VL, which occurs mainly in East Africa, is caused by the *Leishmania* species *L. donovani* and *L. infantum*.[115] Approximately two-thirds of reported *T.b. gambiense* cases occur in the Democratic Republic of Congo (DRC), and most of the VL cases reported in Africa occur in Sudan.[115,116] Until recently, both were considered tropical diseases, but the spread of HIV/AIDS has expanded the domain of VL north, including southern Europe.[116] Both HAT and VL have multiple clinical forms in which the causative organisms can be distinguished only through molecular methods. Tsetse flies (*Diptera glossinidae*), which are the vectors of trypanosomes, are found exclusively in Africa.

HAT and VL have reemerged after a period of being under control in the 1960s. The WHO estimates that 300,000-500,000 people are affected by HAT and that approximately 55 million people in 36 countries in SSA[80] are at risk. VL is estimated to affect 200 million people worldwide, with 500,000 new cases occurring annually.

Although VL and HAT cause significant mortality and morbidity in Africa, they remain largely neglected due to underreporting in the affected poor and marginalized populations. In southern Sudan, VL caused the deaths of 100,000 persons in the western area of Upper Nile State between 1984 and 1994, a loss of nearly one-third of the population.[117] More than 80,000 patients have been treated in Sudan and Ethiopia.[118] However, these treatments have had significant limitations, including unresponsiveness, relapse, and specific toxicities.

The elucidation of genetic factors that influence susceptibility to trypanosome infection has been explored.[108,109] Among the effectors of immune response that could be strongly involved in susceptibility/resistance to HAT are cytokines such as interleukins (ILs) (e.g., IL-6, IL-8, IL-10), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ).[119,120,121,122,123,124] However, little is known about the role of human genetic polymorphisms in HAT. Association studies conducted in DRC and Ivory Coast on the influence of human genetic polymorphisms showed a significant association between SNPs located on the IL-6 and IL-10 genes and decreased susceptibility to HAT. However, polymorphisms located on IL-α and TNF-α increased the risk of developing the disease.[123,124] Previous studies using either the candidate gene approach or genome-wide scan in Sudan have shown evidence of variation in susceptibility to infection among different ethnic groups.[102,103,104,105,106] In both HAT and VL, genomics has not been readily used compared to other diseases.[110] Thus, there is a significant opportunity for the conduct of large-scale, population-based genomics studies for these populations and for further molecular investigation of host factors and genetics associated with VL and HAT.

5.4. Pharmacogenomics

Pharmacogenomics research seeks to identify genetic factors that are responsible for individual differences in drug efficacy and susceptibility to adverse drug reactions (ADRs). Knowledge of which individuals are most likely to suffer an ADR and, conversely, those most likely to benefit from a medication would allow both safety and efficacy to be maximized in the medical treatment of disease. ADRs rank as one of the leading causes of morbidity and mortality, with direct medical costs estimated to exceed $100 billion annually in the United States. In Africa ADRs may have an even more profound effect. In the face of minimal social support, disability caused by an ADR can lead to the greater poverty of families and communities.

African populations have been underrepresented in pharmacogenomics research. Yet these populations show the highest levels of genetic diversity among human populations, frequently placing them at greater risk of ADRs or therapeutic failures. Although pharmacogenomics can be applied to numerous illnesses that plague the African continent (e.g., nevirapine- and abacavir-induced hypersensitivity reactions for the treatment of HIV, amodiaquine-induced agranulocytosis and hepatotoxicity for the treatment of malaria), the potential for

pharmacogenomics to impact the treatment of noncommunicable diseases such as cancer is particularly great.

Cancer is a growing and largely silent epidemic in low- and middle-income countries. Currently, cancer deaths worldwide exceed those from HIV/AIDS, TB, and malaria combined. Astonishingly, by 2020 more than 70% of new cancer diagnoses will be in developing countries.[125] As cancer treatment guidelines are being developed for these countries, there are opportunities to incorporate pharmacogenomics data to maximize drug safety. This is particularly relevant to the African context, where cancer treatment will likely take place primarily in outpatient settings and the ability to monitor for ADRs may be limited. A child who develops irreversible deafness, for instance, as a complication of chemotherapy may be subject to social stigmatization and a life of profound hardship and disability.

Genetic variants have been discovered that are predictive of an increased risk of severe ADRs for two major classes of chemotherapeutic agents, cisplatin and anthracycline.[126] Both of these agents are likely to be important parts of chemotherapeutic protocols in Africa, since they are manufactured as generics, are low in cost, and have highly effective antitumor activity. Yet both are associated with severe, potentially life-threatening toxicity—deafness in the case of cisplatin and cardiomyopathy in the case of anthracycline.

Another area in which pharmacogenomics could have a major impact on African populations is pain medication. Genetic markers have been discovered in opioid metabolism and in the action pathway affecting opioid response and toxicity. Specifically, genetic variation was discovered to be associated with potentially life-threatening central nervous system depression induced by codeine, globally one of the most widely used opioid analgesics for the treatment of mild to moderate pain.[127] Interestingly, extremely high frequencies of these risk markers have been characterized in preliminary studies in African populations.

Major scientific and political obstacles exist in the application of this knowledge to health care delivery in Africa. The frequency of these key pharmacogenetic polymorphisms must be ascertained in different African populations. This is a central scientific question, since African populations are known to harbor far greater genetic diversity than European or Asian populations, yet they are systematically underrepresented in genetic studies. Studying African populations may yield important new rare or common genetic polymorphisms that have not been observed in other ethnic groups and that exert substantial influence on drug response. There are also great challenges in establishing the infrastructure to carry out this research and in determining who would order a pharmacogenomic test, how and where the information would be stored and shared in ways that respect the patient's genetic privacy, and what type of public education would be required regarding the basic principles of genetics.

In spite of these obstacles, the implementation of pharmacogenomics in Africa also offers an incredible opportunity. It may be possible, for instance, for pharmacogenomics technology in Africa to have advanced effects beyond those available to Western nations. In the same way that cellular technology has exploded in Africa in the absence of preexisting physical landlines, the developing regulatory and scientific environment in Africa may be amenable to early adoption of pharmacogenomics in ways that are not possible in more developed countries with more complex regulatory frameworks that were created in the prepharmacogenomics era.

A grand challenge for H3Africa is to prevent morbidity and mortality in communities that are under heavy burden of disease and that have limited resources. The importance of including pharmacogenomics in the H3Africa Initiative is clear: It is feasible and practical, and the results can be applied to improve the health care and well-being of Africans. In addition, there is a scientific and moral imperative to extend treatment for both chronic and acute illnesses in Africa. Pharmacogenomics provides a powerful tool to accomplish this in a way that is safe, efficacious, and ultimately cost-effective.

5.5. Longitudinal Cohort Studies

Prospective longitudinal cohort studies (LCSs) are the most scientifically rigorous survey methods

in observational epidemiology, and their value in contributing to the understanding of disease etiology, risk factors, research methodology, health and disease outcomes, and training in epidemiology, biostatistics, and public policy has been amply demonstrated. Examples include the Framingham Heart Study, the Nurses Health Study, and the European Prospective Investigation into Cancer and Nutrition. However, despite their acknowledged value, LCSs are rarely conducted, largely because of their high cost and the required, long followup before adequate events occur for adequately powered studies. The closest alternatives to prospective LCSs are case-control studies, which are severely limited by different types of bias that often make their results unreliable. Moreover, they are not useful for studying multiple outcomes.

There are many unique reasons to conduct LCSs in Africa. Modern humans originated from Africa between 6 and 8 million years ago, and the dispersal of *Homo sapiens* to other continents is thought to have started about 60 to 100,000 years ago. One outcome of the "out of Africa" migration is that African ancestry populations are the most genetically heterogeneous population in the world.[128] This high level of genetic diversity makes African populations particularly informative and required study in any analysis of disease etiology, population history, and pharmacogenomics (aforementioned).[129] Although there has been some detailed characterization of the genome of selected African populations,[130,131,132] findings from these studies show evidence of convergent adaptation, which emphasizes the need for broader and deeper studies of the genomics of different African populations.[13,133]

The prevalence of environmental risk factors related to complex diseases is relatively low in Africa, but this is rapidly changing.[134,12] For example, the prevalence of smoking among adults in the United States is 21% and is 9% in Nigeria. In contrast, the prevalence of smoking in the United States fell by 20% between 1981 and 1991, and yet it rose by slightly less than 10% over the same period in Nigeria.[135,136,137] Another instance where variation in environmental exposure may be a major determinant of risk is the marked variation in the incidence of prostate cancer, which is much higher among African-Americans compared with Africans despite similarities in genetic background.[138] Such findings suggest that studying African populations can contribute substantially to efforts to differentiate genetic from environmental attributable risk fractions.[12,139,140,133,141]

Epigenetics has emerged as an exciting and potentially important area of research that can clarify how environmental factors affect gene expression, potentially allowing such genomic imprinting by environmental factors to become heritable and transmissible.[142] Unlike genes that are largely fixed throughout life, epigenetic changes vary from tissue to tissue, differ with age, and are influenced by environmental factors. Studies of monozygotic twins, for example, have shown that although they have similar amounts of DNA methylation while young, these amounts differ considerably as they age.[143,144] It is increasingly clear that environmental factors that are known to be important risk factors for noncommmunicable diseases (e.g., diet, alcohol, smoking and other environmental pollution) cause epigenetic changes.[145] Therefore, analysis of epigenetic factors is emerging as an important component of the study of disease etiology, progression, and outcome.[146] Despite these early developments, much clarification remains as to which epigenetic changes are most important, which are causal, and whether the same environmental factors lead to similar "causal" epigenetic changes.[147,148,149] To date, more than 35,000 papers have been published in PubMed on epigenetics, yet none of these relates to studies in Africa.

The mixture of highly informative genomic data, the plethora and variety of environmental and infectious exposures, and the epidemiologic transition occurring in Africa combine to make an LCS a hugely important opportunity to contribute science in unique and specific ways. There are many opportunities for African researchers and educational institutions to develop an LCS as part of H3Africa or to engender collaborations between existing LCSs in Africa and H3Africa. An appropriately worded Funding Opportunity Announcement (preferably using a U01 or P01 mechanism) should invite investigators associated with existing LCSs or those who consider themselves capable of developing such an LCS to compete for funding for studies that integrate their cohorts, provide data and genomic samples, share platforms, or provide other avenues of collaboration through which H3Africa can have access to well-characterized phenotypes, data, and biological materials. Such cohorts also should be able to demonstrate a multicountry capacity for enrollment of participants, infrastructure to manage high-quality data and biological sampling, quality assurance and quality control, integrated training programs, and equitable and just management that empowers African scientists and allows them to receive the necessary training to assume scientific and administrative leadership of the LCS and collaborations within a reasonable period of time.

Study designs within such an LCS can be cross-sectional, nested case-control, or prospective studies. The flexibility afforded by an LCS is unparalleled and cannot be replicated by any other study design. Clear and measurable training and research deliverables, with evidence that the collaborating teams have experience and a track record in Africa, should

be required. Given that H3Africa should be an engine for further growth of scientific research in Africa, such collaborations will synergistically extend the impact of H3Africa and the LCS.

5.6. New and Innovative Ideas

Within the field of genomics, considerable attention is focused on the variants that predispose individuals to disease. However, there are additional opportunities to contribute to the health benefits of studying human disease. These opportunities are best characterized as innovative ideas and should be carefully considered for a population-based genomics research agenda. One such example follows.

5.6.1. Ouabain and Blood Pressure

Ouabain is a digitalis glycoside that was originally identified as the main active ingredient in African arrow poison, which is derived from the ripe seeds of *Strophanthus gratus* and the barks of the *Acokanthera ouabaio* and *Acokanthera schimperi* trees. The latter tree also contains substantive amounts of acolongifloroside K. Historically, because the chemical structure of ouabain was similar to digitalis glycosides, it was administered in small doses to patients with coronary artery disease in whom it proved extremely efficacious. From these initial observations, ouabain was widely used for the intravenous treatment of congestive heart failure and both atrial and ventricular arrhythmias for more than 100 years. Although ouabain use has decreased in the United States, the glycoside is still widely used in many European countries, such as France and Germany, where many physicians continue to advocate its administration, both intravenously and orally, in the therapy of angina pectoris, myocardial infarction, and cardiac arrhythmias, including atrial fibrillation. Data are difficult to obtain; yet, over the past 100 years, the use of ouabain could have saved millions of lives of patients afflicted with coronary artery disease and cardiac arrhythmias.

There are increasing reports of a high incidence of hypertension, especially in urban areas, in much of SSA. Given the high incidence of essential hypertension among African-Americans, it might be argued that its prevalence in SSA is similar. A proposal to study the levels of ouabain as well as rennin and other factors in newly diagnosed, untreated patient populations using a pharmacogenomics or population-based genomics approach would be informative because correlations of hypertension to ouabain levels might have therapeutic implications.

6. Ethical, Legal, and Social Issues

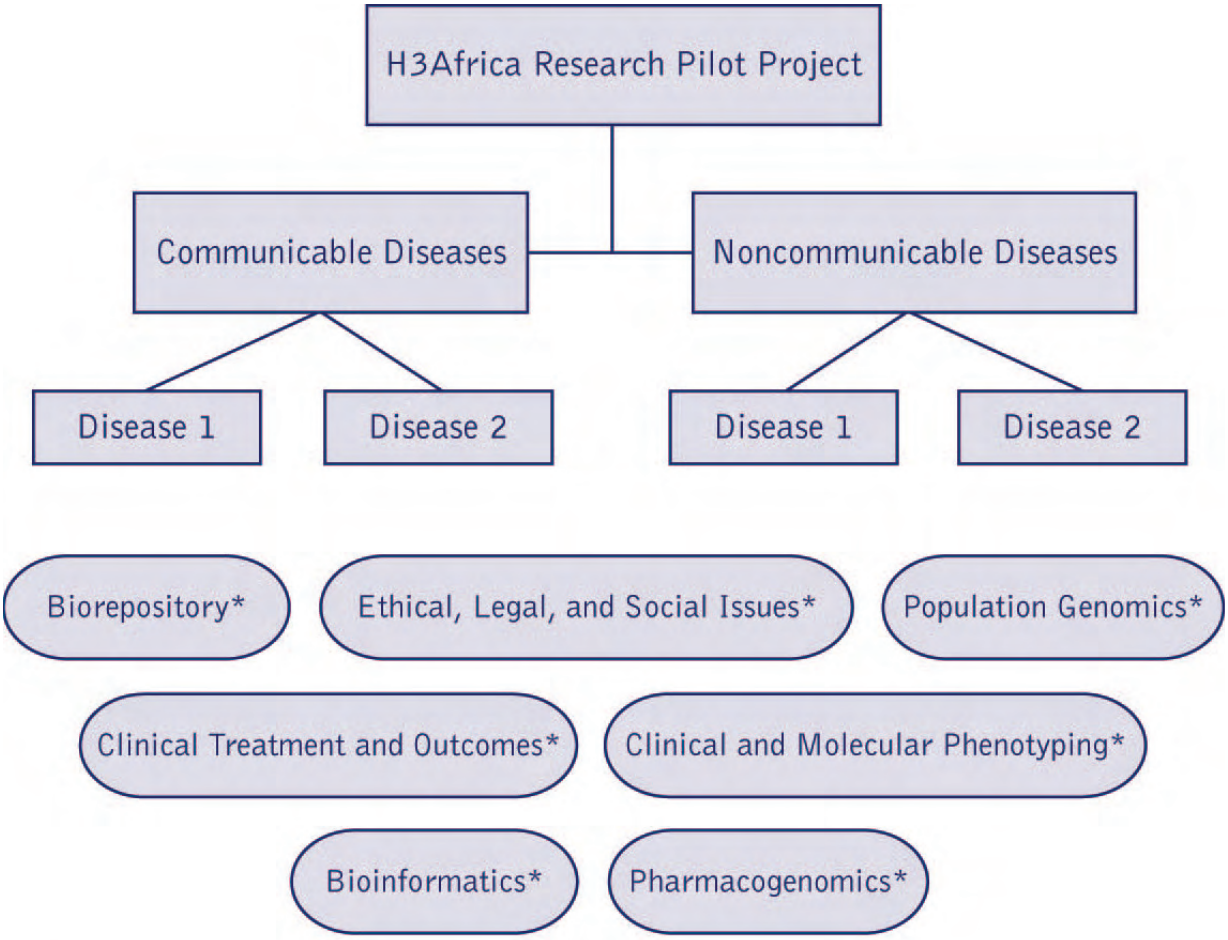
For a population-based genomics initiative such as H3Africa to advance ELSI research on the African continent, it is generally acknowledged that African scholars and researchers in bioethics, the social sciences, and other relevant disciplines must be involved. Some large-scale projects such as MalariaGEN have developed strategies to address many of the ELSI that will occur in H3Africa. It would be beneficial to learn from and build on the experiences of these studies in refining and implementing the ELSI research agenda for H3Africa. ELSI researchers should be embedded within the H3Africa framework to develop and support the stated goals of H3Africa.

6.1. Attending to ELSI

Several complex ELSI matters are associated with executing a research endeavor such as H3Africa. These center around respecting and protecting the interests of the research participants, communities, and researchers involved in the project; developing collaborative partnerships; and building capacity. Some key activities in the ELSI agenda for H3Africa will include the following:

- Developing culturally appropriate means of engaging with research participants and communities prior to, during, and after sample and data collection about issues related to sample collection and the creation and governance of databases and biobanks
- Building capacity to support the appropriate identification and resolution of ELSI matters raised by specific studies in specific contexts and the ethical review of such studies

Figure 4. Suggested Model for H3Africa Pilot Projects



*Each pilot project should address specific questions relevant to a particular disease in each of these categories.

- Addressing issues related to the appropriate storage of samples and data generated by the project
- Developing mechanisms for equitable and ethical sample sharing and data sharing and release, including addressing ownership issues
- Depending on the outcomes of the research, addressing issues related to benefit sharing and intellectual property
- Addressing issues related to the governance and conduct of large-scale collaborative research projects
- Identifying and assessing national and international ethical guidelines and policies relevant to the conduct of genomic research and the establishment of biorepositories in African countries, including guidelines for DNA data sharing and sample sharing
- Assessing current mechanisms for the regulatory oversight and ethical review of genetic and genomic research protocols within African countries
- Identifying mechanisms for the oversight and ethical review of protocols for genomic research at governmental agencies (e.g., ministries of health), universities, medical centers, hospitals, and other relevant institutions
- Reviewing and contributing to the literature on empirical research and normative, philosophical approaches relevant to ethical, legal, social, and cultural issues in genetic research and in the practice of clinical genetics in African countries

6.2. Elements of an ELSI Infrastructure (see Figure 4 above)

- Collaboration with existing institutions within and outside Africa with expertise in genomics and associated ELSI to draw on existing expertise and develop capacity.
- Support from senior academics from multiple institutions with relevant expertise to support infrastructure activities.
- Creation of a program for about five African Ph.D. students to address ELSI related to genomic research in Africa such as those identified in the section above. These Ph.D.s are likely to be based at different academic institutions, and it is likely that supervisors in multiple disciplines from multiple institutions will be required for each student.
- Creation of a program to develop and deliver training initiatives for research ethics committees to strengthen and build capacity for the ethical review of genomics research protocols, the establishment of biorepositories, and DNA data sharing and sample sharing.
- Design and implementation of training and educational initiatives for professionals, including genetics and genomics investigators, public health and social science researchers, and scholars in the humanities.
- Development of ELSI policies for H3 Africa on ELSI topics of general relevance, such as seeking consent, community engagement, and sample and data collection, release, and sharing.
- Support for ethics coordinators (see Section 6.3.1. Staffing below) in the development of relevant policies for individual research projects.
- Provision of ad hoc ELSI support as required by H3Africa staff members involved in infrastructure or disease proposals.
- Development and conduct of empirical research (in addition to the Ph.D. students' projects) to support the above activities if necessary. Examples of potential empirical studies include the following:
    - A multisite study of public beliefs and opinions regarding the collection of DNA samples for biorepositories to promote research on HGV and genetic factors in disease and the potential influence of genomic research on reducing health inequities in Africa
    - A multisite, mixed-methods study of approaches to informed consent for donating DNA samples to biorepositories for research on HGV and on genetic factors in disease

6.3. Resources

6.3.1. Staffing

- The H3Africa infrastructure is likely to require at least one full-time senior postdoctoral staff member and one full-time junior postdoctoral/senior administrator to manage the above activities.
- It is desirable that an ELSI coordinator position be created and embedded within each disease project, or if a larger number of smaller projects are funded, a coordinator could provide support for more than one project. The person(s) in such a position should work closely (and preferably be colocated with) the H3Africa research teams and also would work closely with the ELSI infrastructure team.
- The costs of the percentages of time provided by senior academics from a number of institutions also should be covered to enable them to provide support to the staff for the ELSI activities outlined above.

6.3.2. Training

- Funding for approximately five residential, 3- to 5-day training programs for about 30 participants
- Funding for about five fully funded Ph.D. scholarships
- Funding for annual meetings for all H3Africa ELSI staff members

6.3.3. Other Related Costs

- Costs of empirical research required to address various H3Africa-wide or site-specific ELSI matters
- A travel budget allowing the ELSI staff to visit and support sites as appropriate

7. Governance Structure

7.1. Principles for Sample/Data Collection

The H3Africa Initiative will lead to the generation of samples and data. Therefore, a policy is needed that clearly describes the goals, mechanisms, and safeguards for sharing samples and data. For example, MalariaGEN has dealt with some of these issues in a sensitive and effective way and is viewed as an excellent model on which to base some of the broader H3Africa principles.

Such a policy should be developed and implemented before any data collection takes place to ensure that investigators, research participants,

African governments, local communities, and other stakeholders have clear guidance on how data and samples will be shared. This would facilitate the processes of the following:

- Obtaining appropriate informed consent at the point of data collection
- Getting support and buy-in from governments, communities, and other stakeholders
- Informing participating African investigators who generate data and samples about how their priority access to these resources will be protected
- Informing the broader scientific community about when and which data and sample resources will be made available for investigator-initiated research

A mechanism for managing data and sample sharing is needed. It is suggested that a Data Access Committee (DAC) be established with oversight activities for sample and data sharing. The work of this oversight group would overlap with and involve coordination with several other committees, especially the ELSI and biorepository committees.

7.2. Principles for Data Sharing and Release of Data

It is suggested that the methods of data sharing and data release be incremental processes in which protocol may change over time (as with NIH and WT policy development), albeit within the parameters of agreed-on general procedures. The DAC should serve as a standing ethical advisory board to maintain continuity and harmonization of data sharing/release and related issues, including the following:

- Distinguishing between data designed to be shared openly (i.e., publicly accessible through a Web site) versus data accessible on request through the DAC versus data accessible only through collaboration.
- Classification of data samples.
- Creation and monitoring of rules of access based on the classification and definition of each type of sample.
- Consideration of both summary-level (e.g., population-level descriptions, summary disease association statistics) and individual-level data (e.g., phenotype, genotype, actual sample).
- Development of realistic and appropriate policies regarding data sharing and distribution (e.g., current practices). Deposition of data in the database of Genotypes and Phenotypes (dbGAP) prior to sharing may disenfranchise African investigators, given the obstacles to retrieval from dbGAP such as needing local IRB approval to be registered by the Office for Human Research Protections, U.S. Department of Health and Human Services. ❖

IV. CONCLUSIONS

The choice of a research topic and the specific designs of large-scale genomics research projects that encompass many countries as envisioned by H3Africa should reflect the interests of the African investigators and the resources that are available. First, there must be a match between the focus of the project and the interest and expertise of the African investigators who are to be the principal actors. These investigators may not require current expertise in genomics, but certainly they must have expertise in the characterization and treatment of the health condition.

Second, resources (i.e., infrastructure; physicians, nurses, phlebotomists, other health care personal; proper specimen storage equipment) either must be available at the site, or at a minimum, infrastructure must be in place that can be enhanced to create the necessary resources. Local support and political will at the site also will be crucial, including the need to develop infrastructure where such support and will are lacking or limited. Most of the successful research endeavors in West and East Africa (e.g., Noguchi Memorial Institute for Medical Research in Ghana, the MRC in Gambia, NIH-related centers in Kenya and Mali) involve the provision of substantial infrastructure. Existing infrastructure can be built on to provide necessary elements and assistance to underresourced regions in Africa.

Third, and perhaps the most challenging, is the requirement for a plausible basis for the assertion that a contribution will be made to the health of Africans and, by extension, to non-Africans. As all members of the H3Africa Communicable and Noncommunicable Diseases Working Groups are acutely aware, translation has been the greatest challenge for molecular genomics. As Harold E. Varmus, M.D., former NIH Director, recently noted in the first of two articles in *The New York Times* on "The Genome at 10," "genomics is a way to do science, not medicine".[150] Although much has been learned about population genetics and many specific genetic traits, progress toward useful knowledge about common diseases and clinical application of that knowledge is still limited. The rapid development of genomic technology has led to the availability of ever more powerful and expensive methods of analyses. In recognizing the limitations of GWASs, most of the cutting-edge science is now focused on sequencing. Simultaneously, conventional wisdom has moved from the "common disease-common variant" hypothesis to a concentration on rare variants.[151,152] The technical challenges of finding rare or unique variants for many conditions and translating those findings into medical practice seem overwhelming at this point. Each transition from candidate genes, to linkage, to genome-wide associations, to whole-genome (or exome) sequence raises the complexity and cost of the research endeavor by several orders of magnitude. At the same time, in moving away from the cutting-edge science that focuses on the discovery of new genetic mechanisms, there is a vast landscape of research on biological mechanisms and the consequences of known variants. On the other hand, many observers have looked to pharmacogenomics for the most relevant first-generation applications. Although potential clinically important examples of drugs that have a gene-drug effect have been identified (e.g., warfarin, clopidogrel, abacavir), so far they have been shown to be relevant only in very small niches.

The issues raised in this white paper are intended to draw attention to the dual nature of the challenge faced: developing excellent science that keeps pace with the field on an international scale and making that science useful in Africa. Genomics is under increasing pressure to demonstrate the value of the enormous investment being made or at least proof of principle in support of ambitious past claims made to justify the large investments that have been made. Genomics soon will be asked to accept a direct comparison to epidemiology and public health as weapons in efforts to improve human health and reduce the disease burden. Nowhere will this competition be more difficult than in Africa. ❖

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APPENDIX A. LISTS OF INVOLVED INDIVIDUALS AND PARTIES

1. Contributors to This White Paper

Sonia Abdelhak, Ph.D., Sc.D., M.S.
Principal Biologist and Head
Research Unit on Genetic Orphan Diseases
Institut Pasteur de Tunis
13 Place Pasteur
Tunis 1002
Tunisia
216 71849110
216 71791833 Fax
sonia.abdelhak@pasteur.rns.tn

Clement Adebamowo, M.D., Sc.D.
Director
Office of Strategic Information, Research, and Training
Institute of Human Virology
252 Herbert Macaulay Way
Abuja 900000
Nigeria
234 8033520571
cadebamo@yahoo.com

Adebowale Adeyemo, M.D.
Deputy Director
Center for Research on Genomics and Global Health
National Human Genome Research Institute
National Institutes of Health
Building 12-A, Room 4047
MSC 5635
12 South Drive
Bethesda, MD 20892-5635
United States
(301) 594-7501
adeyemoa@mail.nih.gov

Albert G.B. Amoah, M.D., Ph.D.
Professor of Medicine
Head
Cardiovascular Research Laboratory
Director
National Diabetes Management and Research Center
Consultant Physician
Diabetes and Chronic Disease Research Laboratory
Department of Medicine
Korle Bu Teaching Hospital
College of Health Sciences
University of Ghana Medical School
Medical Block, Room 26/28
Guggisberg Avenue
Accra
Ghana
233 202012224
agbamoah@chs.edu.gh

Susan Bull, Ph.D., L.L.B., M.A.
Senior Researcher, Ethics of Genomics and Global Health
Department of Public Health and Primary Care
The Ethox Center
University of Oxford
Badenoch Building
Old Road Campus
Headington
Oxford OX3 7LF
United Kingdom
44 1865287878
susan.bull@well.ox.ac.uk

Alan Christoffels, Ph.D.
Associate Professor
South African National Bioinformatics Institute
University of the Western Cape
Private Bag X17
Modderdam Road
Bellville
Cape Town 7535
South Africa
27 219593645
27 219592512 Fax
alan@sanbi.ac.za

Richard Cooper, M.D.
Professor and Chair
Department of Preventive Medicine and Epidemiology
Stritch School of Medicine
Loyola University Chicago
3722 North Lowell Avenue
Chicago, IL 60641
United States
(708) 327-9010
rcooper@lumc.edu

Seydou Doumbia, M.D., Ph.D.
Professor of Epidemiology
Department of Public Health
Deputy Scientific Director
Malaria Research and Training Center
Faculty of Medicine, Pharmacy and Odontostomatology
University of Bamako
BP 1805
Bamako
Mali
223 20231318
223 20224987 Fax
sdoumbi@icermali.org

Michael Hayden, M.D., Ph.D.
Director and Senior Scientist
Canada Research Chair in Human Genetics and Molecular Medicine
University Killam Professor
Department of Medical Genetics
Center for Molecular Medicine and Therapeutics
Child and Family Research Institute
Faculty of Medicine
University of British Columbia
3025-950 West 28th Avenue
Vancouver, BC V5Z 4H4
Canada
(604) 875-3535
(604) 875-3819 Fax
mrh@cmmt.ubc.ca

Winston Hide, Ph.D., M.A.
Associate Professor of Computational Biology and Bioinformatics
Extraordinary Visiting Professor
South African National Bioinformatics Institute
Biostatistics Department
Harvard School of Public Health
Affiliate Faculty
Harvard Stem Cell Institute
Associate
Ludwig Institute for Cancer Research
Building 2, Fourth Floor
655 Huntington Avenue
Boston, MA 02115
United States
(617) 432-2681
whide@hsph.harvard.edu

Muntasar Ibrahim, Ph.D., M.Sc.
Professor
Department of Molecular Biology
Institute of Endemic Diseases
Medical Campus
University of Khartoum
Qasser Street
Khartoum
Sudan
249 183793263
249 183779712 Fax
mibrahim@iend.org

Bernard David Keavney, M.D.
British Heart Foundation Professor of Cardiology
Institute of Human Genetics
Newcastle University
Central Parkway
Newcastle NE3 4DS
United Kingdom
44 1912418615
b.d.keavney@ncl.ac.uk

Dominic P. Kwiatkowski, F.Med.Sci., M.B.B.S.
Director
MRC Center for Genomics and Global Health
Wellcome Trust Sanger Institute
University of Oxford
Henry Wellcome Building for Genomic Medicine
Roosevelt Drive
Oxford OX3 7BN
United Kingdom
44 1865287654
dominic@well.ox.ac.uk

Rose Gana Fomban Leke, Ph.D.
Professor
Department of Microbiology, Immunology and Hematology
Faculty of Medicine and Biomedical Sciences
Head
Biotechnology Center
University of Yaounde I
Yaounde
Cameroon
237 22237429
237 22225955 Fax
roseleke@yahoo.com

Julie Makani, M.D.
Research Fellow
University of Oxford
Senior Lecturer
Department of Hematology and Blood Transfusion
Muhimbili University of Health and Allied Sciences
P.O. Box 65001
Dar-es-Salaam
Tanzania
255 754381551
juliemakani@yahoo.com

Patricia Marshall, Ph.D.
Professor of Bioethics
Co-Director
Center for Genetic Research Ethics and Law
Department of Bioethics
School of Medicine
Case Western Reserve University
10900 Euclid Avenue
Cleveland Heights, OH 44106-4976
United States
(216) 368-6196
(216) 368-8713 Fax
pam20@cwru.edu; bioethics@case.edu

Bongani M. Mayosi, D.Phil.
Chief Specialist
Groote Schuur Hospital
Professor and Head
Department of Medicine
Faculty of Health Sciences
University of Cape Town
Private Bag X3
Anzio Road
Observatory 7925
Cape Town
South Africa
27 214066200
27 214486815 Fax
bongani.mayosi@uct.ac.za

Mark McCarthy, M.D., M.B.
Robert Turner Professor of Diabetes
Oxford Center for Diabetes, Endocrinology and Metabolism
University of Oxford
Center for Human Genetics
Wellcome Trust
Churchill Hospital
Old Road
Headington
Oxford OX5 2UQ
United Kingdom
44 1865857298
mark.mccarthy@drl.ox.ac.uk

Hiba Salah-EIDin Mohamed, Ph.D.
Assistant Professor
Department of Molecular Biology
Institute of Endemic Diseases
University of Khartoum
P.O. Box 102
Khartoum
Sudan
249 183793263
249 183779712 Fax

Olugbenga A. Mokuolu, M.D.
Associate Professor of Pediatrics
Department of Pediatrics and Child Health
University of Ilorin
Private Mail Bag 1515
Ilorin 240001
Nigeria
234 8037137407
mokuolu@hotmail.com

Melanie J. Newport, M.D., Ph.D.
Professor in Infectious Diseases and Global Health
Department of Medicine
Brighton and Sussex Medical School
Medical Research Building
University of Sussex
Brighton
Falmer BN1 9PS
United Kingdom
44 1273877882
44 1273877884 Fax
m.j.newport@bsms.ac.uk

Onesmo Ole-MoiYoi, M.D.
Senior Visiting Scientist
International Center of Insect Physiology and Ecology
Senior Consultant
Faculty of Arts and Sciences
Aga Khan University and Medical School
Chairman
Kenya Agricultural Research Institute
P.O. Box 30772
Nairobi 00100
Kenya
254 722473711
moiyoioo@gmail.com

Olufunmilayo Olopade, M.D.
Associate Dean, Global Health
Walter L. Palmer Professor of Medicine and Human Genetics
Director
Center for Clinical Cancer Genetics and Global Health
Section of Hematology/Oncology
Department of Medicine
The University of Chicago Medical Center
Mail Code 2121
5841 South Maryland Avenue
Chicago, IL 60637
United States
(773) 702-1632
folopade@medicine.bsd.uchicago.edu

Emmanuel K. Peprah, Ph.D.
Research Fellow
Center for Research on Genomics and Global Health
National Human Genome Research Institute
National Institutes of Health
Building 12-A, Room 4047
MSC 5635
12 South Drive
Bethesda, MD 20892-5635
United States
(301) 402-6560
(301) 451-5426 Fax
peprahek@mail.nih.gov

Rajkumas Ramesar, Ph.D.
Professor
Division of Human Genetics
Department of Clinical Laboratory Sciences
Institute of Infectious Diseases and Molecular Medicine
Faculty of Health Sciences
University of Cape Town
Anzio Road
Observatory 7925
Cape Town
South Africa
27 214066297
27 214066286 Fax
raj.ramesar@uct.ac.za

Michele Ramsay, Ph.D.
Professor
Division of Human Genetics
National Health Laboratory Service
Sydney Brenner Institute for Molecular Bioscience
University of the Witwatersrand
P.O. Box 1038
Johannesburg 2000
South Africa
27 114899214
27 114899226 Fax
michele.ramsay@nhls.ac.za

Charles Rotimi, Ph.D., M.P.H.
Director
Center for Research on Genomics and Global Health
National Human Genome Research Institute
National Institutes of Health
Building 12-A, Room 4047
MSC 5635
12 South Drive
Bethesda, MD 20892-5635
United States
(301) 451-2302
(301) 451-5426 Fax
rotimic@mail.nih.gov

Charmaine Royal, Ph.D., M.S.
Associate Research Professor
Duke Institute for Genome Sciences & Policy
Duke University
Campus Box 90141
North Building, Room 230
450 Research Drive
Durham, NC 27708-0141
United States
(919) 668-6515
(919) 613-6448 Fax
charmaine.royal@duke.edu

Himla Soodyall, Ph.D.
Medical Scientist and Professor
Division of Human Genetics
National Health Laboratory Service and University of the Witwatersrand
P.O. Box 1038
Johannesburg 2000
South Africa
27 114899208
27 114899226 Fax
hxsood@global.co.za

Bamidele O. Tayo, Ph.D.
Assistant Professor
Department of Preventive Medicine and Epidemiology
Stritch School of Medicine
Loyola University Medical Center
Loyola University Chicago
Building 105
2160 South First Avenue
Maywood, IL 60153
United States
(708) 327-9013
btayo@lumc.edu

Sekou F. Traore, Ph.D.
Director
Entomology Department
Malaria Research and Training Center
Professor
Faculty of Medicine, Pharmacy and Dentistry
University of Bamako
BP 1805
Bamako 223
Mali
223 66753394, ext. 223
223 6620224987 Fax
cheick@icermali.org

2. Members of the H3Africa Communicable Diseases and Noncommunicable Diseases Working Groups

Communicable Diseases Working Group

Chair

Sekou F. Traore, Ph.D.
Director
Entomology Department
Malaria Research and Training Center
Professor
Faculty of Medicine, Pharmacy and Dentistry
University of Bamako
BP 1805
Bamako 223
Mali
223 66753394, ext. 223
223 6620224987 Fax
cheick@icermali.org

Deputy Chair

Dominic P. Kwiatkowski, F.Med.Sci., M.B.B.S.
Director
MRC Center for Genomics and Global Health
Wellcome Trust Sanger Institute
University of Oxford
Henry Wellcome Building for Genomic Medicine
Roosevelt Drive
Oxford OX3 7BN
United Kingdom
44 1865287654
dominic@well.ox.ac.uk

Susan Bull, Ph.D., L.L.B., M.A.
Senior Researcher, Ethics of Genomics and Global Health
Department of Public Health and Primary Care
The Ethox Center
University of Oxford
Badenoch Building
Old Road Campus
Headington
Oxford OX3 7LF
United Kingdom
44 1865287878
susan.bull@well.ox.ac.uk

Alan Christoffels, Ph.D.
Associate Professor
South African National Bioinformatics Institute
University of the Western Cape
Private Bag X17
Modderdam Road
Bellville
Cape Town 7535
South Africa
27 219593645
27 219592512 Fax
alan@sanbi.ac.za

Seydou Doumbia, M.D., Ph.D.
Professor of Epidemiology
Department of Public Health
Deputy Scientific Director
Malaria Research and Training Center
Faculty of Medicine, Pharmacy and Odontostomatology
University of Bamako
BP 1805
Bamako
Mali
223 20231318
223 20224987 Fax
sdoumbi@icermali.org

Muntasar Ibrahim, Ph.D., M.Sc.
Professor
Department of Molecular Biology
Institute of Endemic Diseases
Medical Campus
University of Khartoum
Qasser Street
Khartoum
Sudan
249 183793263
249 183779712 Fax
mibrahim@iend.org

Julie Makani, M.D.
Research Fellow
University of Oxford
Senior Lecturer
Department of Hematology and Blood Transfusion
Muhimbili University of Health and Allied Sciences
P.O. Box 65001
Dar-es-Salaam
Tanzania
255 754381551
juliemakani@yahoo.com

Olugbenga A. Mokuolu, M.D.
Associate Professor of Pediatrics
Department of Pediatrics and Child Health
University of Ilorin
Private Mail Bag 1515
Ilorin 240001
Nigeria
234 8037137407
mokuolu@hotmail.com

Melanie J. Newport, M.D., Ph.D.
Professor in Infectious Diseases and Global Health
Department of Medicine
Brighton and Sussex Medical School
Medical Research Building
University of Sussex
Brighton
Falmer BN1 9PS
United Kingdom
44 1273877882
44 1273877884 Fax
m.j.newport@bsms.ac.uk

Onesmo Ole-MoiYoi, M.D.
Senior Visiting Scientist
International Center of Insect Physiology and Ecology
Senior Consultant
Faculty of Arts and Sciences
Aga Khan University and Medical School
Chairman
Kenya Agricultural Research Institute
P.O. Box 30772
Nairobi 00100
Kenya
254 722473711
moiyoioo@gmail.com

Charmaine Royal, Ph.D., M.S.
Associate Research Professor
Duke Institute for Genome Sciences & Policy
Duke University
Campus Box 90141
North Building, Room 230
450 Research Drive
Durham, NC 27708-0141
United States
(919) 668-6515
(919) 613-6448 Fax
charmaine.royal@duke.edu

Himla Soodyall, Ph.D.
Medical Scientist and Professor
Division of Human Genetics
National Health Laboratory Service and University of the Witwatersrand
P.O. Box 1038
Johannesburg 2000
South Africa
27 114899208
27 114899226 Fax
hxsood@global.co.za

Noncommunicable Diseases Working Group

Chair

Bongani M. Mayosi, D.Phil.
Chief Specialist
Groote Schuur Hospital
Professor and Head
Department of Medicine
Faculty of Health Sciences
University of Cape Town
Private Bag X3
Anzio Road
Observatory 7925
Cape Town
South Africa
27 214066200
27 214486815 Fax
bongani.mayosi@uct.ac.za

Deputy Chair

Albert G.B. Amoah, M.D., Ph.D.
Professor of Medicine
Head
Cardiovascular Research Laboratory
Director
National Diabetes Management and Research Center
Consultant Physician
Diabetes and Chronic Disease Research Laboratory
Department of Medicine
Korle Bu Teaching Hospital
College of Health Sciences
University of Ghana Medical School
Medical Block, Room 26/28
Guggisberg Avenue
Accra
Ghana
233 202012224
agbamoah@chs.edu.gh

Sonia Abdelhak, Ph.D., Sc.D., M.S.
Principal Biologist and Head
Research Unit on Genetic Orphan Diseases
Institut Pasteur de Tunis
13 Place Pasteur
Tunis 1002
Tunisia
216 71849110
216 71791833 Fax
sonia.abdelhak@pasteur.rns.tn

Clement Adebamowo, M.D., Sc.D.
Director
Office of Strategic Information, Research, and Training
Institute of Human Virology
252 Herbert Macaulay Way
Abuja 900000
Nigeria
234 8033520571
cadebamo@yahoo.com

Adebowale Adeyemo, M.D.
Deputy Director
Center for Research on Genomics and Global Health
National Human Genome Research Institute
National Institutes of Health
Building 12-A, Room 4047
MSC 5635
12 South Drive
Bethesda, MD 20892-5635
United States
(301) 594-7501
adeyemoa@mail.nih.gov

Richard Cooper, M.D.
Professor and Chair
Department of Preventive Medicine and Epidemiology
Stritch School of Medicine
Loyola University Chicago
3722 North Lowell Avenue
Chicago, IL 60641
United States
(708) 327-9010
rcooper@lumc.edu

Michael Hayden, M.D., Ph.D.
Director and Senior Scientist
Canada Research Chair in Human Genetics and Molecular Medicine
University Killam Professor
Department of Medical Genetics
Center for Molecular Medicine and Therapeutics
Child and Family Research Institute
Faculty of Medicine
University of British Columbia
3025-950 West 28th Avenue
Vancouver, BC V5Z 4H4
Canada
(604) 875-3535
(604) 875-3819 Fax
mrh@cmmt.ubc.ca

Winston Hide, Ph.D., M.A.
Associate Professor of Computational Biology and Bioinformatics
Extraordinary Visiting Professor
South African National Bioinformatics Institute
Biostatistics Department
Harvard School of Public Health
Affiliate Faculty
Harvard Stem Cell Institute
Associate
Ludwig Institute for Cancer Research
Building 2, Fourth Floor
655 Huntington Avenue
Boston, MA 02115
United States
(617) 432-2681
whide@hsph.harvard.edu

Bernard David Keavney, M.D.
British Heart Foundation Professor of Cardiology
Institute of Human Genetics
Newcastle University
Central Parkway
Newcastle NE3 4DS
United Kingdom
44 1912418615
b.d.keavney@ncl.ac.uk

Patricia Marshall, Ph.D.
Professor of Bioethics
Co-Director
Center for Genetic Research Ethics and Law
Department of Bioethics
School of Medicine
Case Western Reserve University
10900 Euclid Avenue
Cleveland Heights, OH 44106-4976
United States
(216) 368-6196
(216) 368-8713 Fax
pam20@cwru.edu; bioethics@case.edu

Mark McCarthy, M.D., M.B.
Robert Turner Professor of Diabetes
Oxford Center for Diabetes, Endocrinology and Metabolism
University of Oxford
Center for Human Genetics
Wellcome Trust
Churchill Hospital
Old Road
Headington
Oxford OX5 2UQ
United Kingdom
44 1865857298
mark.mccarthy@drl.ox.ac.uk

Olufunmilayo Olopade, M.D.
Associate Dean, Global Health
Walter L. Palmer Professor of Medicine and Human Genetics
Director
Center for Clinical Cancer Genetics and Global Health
Section of Hematology/Oncology
Department of Medicine
The University of Chicago Medical Center
Mail Code 2121
5841 South Maryland Avenue
Chicago, IL 60637
United States
(773) 702-1632
folopade@medicine.bsd.uchicago.edu

Rajkumas Ramesar, Ph.D.
Professor
Division of Human Genetics
Department of Clinical Laboratory Sciences
Institute of Infectious Diseases and Molecular Medicine
Faculty of Health Sciences
University of Cape Town
Anzio Road
Observatory 7925
Cape Town
South Africa
27 214066297
27 214066286 Fax
raj.ramesar@uct.ac.za

Michele Ramsay, Ph.D.
Professor
Division of Human Genetics
National Health Laboratory Service
Sydney Brenner Institute for Molecular Bioscience
University of the Witwatersrand
P.O. Box 1038
Johannesburg 2000
South Africa
27 114899214
27 114899226 Fax
michele.ramsay@nhls.ac.za

APPENDIX B. LIST OF ABBREVIATIONS AND ACRONYMS USED IN THIS WHITE PAPER

ABN	African Bioinformatics Network
ADR	adverse drug reaction
AfSHG	African Society of Human Genetics
AIDS	acquired immunodeficiency syndrome
ASBCB	African Society for Bioinformatics and Computational Biology
AU	African Union
CIMT	carotid artery intima-media thickness
CVD	cardiovascular disease
DAC	Data Access Committee
DALY	disability-adjusted life year
dbGAP	database of Genotypes and Phenotypes
DRC	Democratic Republic of Congo
ELSI	Ethical, Legal, and Social Issues
EMBnet	European Molecular Biology Network
GWAS	genome-wide association study
H3Africa	Human Heredity and Health in Africa
HAT	human African trypanosomiasis
Hb	hemoglobin
HbF	fetal hemoglobin
HGV	human genetic variation
HIV	human immunodeficiency virus
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
IFN-γ	interferon gamma
IL	interleukin
IL-α	interleukin alpha
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IRB	Institutional Review Board
LCS	longitudinal cohort study
M. tuberculosis	*Mycobacterium tuberculosis*
MalariaGEN	Malaria Genomic Epidemiology Network
MDRTB	multidrug-resistant tuberculosis
MRC	Medical Research Council (United Kingdom)
NEPAD	New Partnership for Africa's Development
NIH	National Institutes of Health (United States)
NSHL	nonsyndromic hearing loss

R&D	research and development
RSA	Republic of South Africa
SARIMA	Southern African Research and Innovation Management Association
SCD	sickle cell disease
SNP	single nucleotide polymorphism
SSA	sub-Saharan Africa
SSABIP	Stanford-South Africa Biomedical Informatics Program
SSI-TDR	South-South Initiative for Tropical Disease Research
T2D	type 2 diabetes mellitus
TB	tuberculosis
T.b. gambiense	*Trypanosoma brucei gambiense*
TNF-α	tumor necrosis factor alpha
VL	visceral leishmaniasis
WHO	World Health Organization
WT	Wellcome Trust (United Kingdom)
XDRTB	extensively drug-resistant tuberculosis