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Forward Look: Tenth Anniversary of the Human Genome Sequence and 21st Century Postgenomics Global Health — A Close Up on Africa and Women's Health

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CONFLICT OF INTERESTS
None declared/applicable.

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"I want my leadership to be judged by the impact of our work on the health of two populations: women and the people of Africa."

Margaret Chan Director-General World Health Organization [1]

"My hope is that my genetic code may provide a voice for the region and serve as the starting point for a map of DNA variation significant for Southern African peoples, to be used for medical research efforts and effective design of medicines."

Desmond Tutu Archbishop Emeritus of Cape Town, South Africa [2]

"The crisis in global health is not a crisis of disease, it is a crisis of governance."

Ilona Kickbusch Global Health Program, The Graduate Institute of International and Development Studies, Switzerland [3, 4]

1. TEN YEARS AFTER THE HUMAN GENOME SEQUENCE

1.1. Where Now for Postgenomics Global Health and Personalized Medicine?

February 2011 witnessed the celebration of the 10th anniversary of the first publication of the human genome sequence. As "data enabled sciences" such as pharmacogenomics have emerged over the past decade in this postgenomics era [5], we have more data available than ever before while the global reach of genomics and personalized medicine has extended to resource limited settings in developing countries [6–8]. The practice of postgenomics personalized medicine is transforming with current attempts to creatively mine such large

genomics and postgenomics (e.g., proteomics) data sets [5, 9]. CPPM was launched in 2008 as a transdisciplinary, integrated, peer reviewed postgenomics forum, addressing both pharmacogenomics and personalized medicine [10]. The Journal targets three cross-linked knowledge domains that have not been addressed in personalized medicine in an integrated manner hitherto: (1) genomics and postgenomics biotechnologies that enable personalized medicine (e.g., pharmacogenomics nutrigenomics, pharmacoproteomics); (2) personalization of health interventions across the continuum of drug therapy, nutrition, vaccines, and emerging cell-based therapies that collectively contribute to healthcare; and (3) integration of molecular and clinical investigation with social, ethical, public policy and global health impacts that together shape the innovation trajectory in pharmacogenomics and personalized medicine. Importantly, CPPM reports advances in personalized medicine from both developed and developing countries through a lens of global public health genomics [8, 11–14].

Despite the undeniable potential of postgenomics personalized medicine, vast inequities in global health continue to exist. Poor health outcomes are firmly linked with poverty; it is worst in South Asia and Sub-Saharan Africa [15, 16]. An estimated 82% of maternal, newborn, and child deaths occur in Sub-Saharan Africa and South Asia [15]. High prevalence of disease burden in Africa stems from both communicable (e.g., HIV/AIDS and tuberculosis) and non-communicable (e.g., diabetes and cardiovascular) diseases. Alarmingly, South Africa, which represents 0.7% of the world's population, carries 17% of the global HIV/AIDS burden and 5% of the global tuberculosis burden [12].

In North Africa, specifically in Egypt, hepatitis C is the most common cause of chronic liver disease, cirrhosis and liver cancer, and hence, represents a serious public health problem and a socio-economic burden. Moreover, Egypt has the highest prevalence of hepatitis C in the world, affecting 14% of the population, equating to an estimated 12 million anti-HCV-positive persons [17].

Such astounding disease burdens across the African continent stand to benefit from novel diagnostics and targeted health interventions enabled by genomics and postgenomics technologies such as proteomics [6, 12]. The current issue of the CPPM features a lead expert review article by Warnich *et al.* [12] that examines how best to approach to new genomics biotechnologies in a manner that carefully considers the public health needs and extant disease burden in South Africa. Equally important, Warnich *et al.* [12] evaluate the strategic direction that future pharmacogenomics research should take in South Africa. This is timely and important as locally situated knowledge can vastly influence global development of postgenomics personalized medicine in resource limited settings. Additionally, in the current issue of the Journal, Oonagh Corrigan examines personalized medicine in the consumer age [18]. Drawing on the UK Nuffield Council of Bioethics' recently published report, *Medical Profiling and Online Medicine: The Ethics of Personalized Healthcare in a Consumer Age*, she provides a detailed account of the ways the concept of the "consumer" has been built into the technologies that enable personalized medicine and suggests that despite the push from the diagnostic sector and the often uncritical acceptance of this by governments, the commercialization of personalized medicine will not succeed unless the benefits are considered as beneficial by those who use

it. Of course, the latter ought to include the users of genomics/postgenomics biotechnologies in Africa and other resource limited settings. Thus, the contributions made by Warnich *et al.* and Corrigan, together with other comprehensive papers and editorials in the September issue collectively attest to the rapidly expanding boundaries of pharmacogenomics and personalized medicine in this postgenomics era, not only geographically but also in terms of the attendant definitions that increasingly describe this highly fluid and dynamic field.

Of the current global population, 4.8 billion people live in developing countries while 2.7 billion live on less than two U.S. dollars a day [19]. The global health predicaments noted above are not however solely attributable to economic factors or inadequate access to biotechnology. They also require analyses through the lens of political science, and notably, the ways in which extant power imbalances in global health impact R&D and innovation in the postgenomics era. Among the important queries: who decides which global innovations should be created, and under what motivations are these decisions made? How is R&D aid coordinated among various stakeholders in global health [20]? Additionally, gender-based inequities face the same cross-cutting issues that impact global health and are exacerbated by the limited extent to which women are represented in key leadership positions or in any decision-making process in either developed or developing countries. As discussed recently by Tikki Pang [16], women and girls disproportionately represent 70% of the world's poor and 80% of the world's refugees. Gender violence against women aged 15–44 is responsible for more deaths and disability than cancer, malaria, traffic accidents and war [21]. Indeed, Dr. Margaret Chan, the current Director-General of the World Health Organization (WHO), has defined her leadership mission to focus on the health of women and the people of Africa [1].

Such intertwined and inseparable effects of biological, social and political determinants of health cannot be studied in isolation from each other. Nor are health inequities neatly confined to developing countries. These cross-linked health determinants are also in effect in various less developed regions of the industrialized countries of the North [22]. In an age of governance for health, with many explicit and implicit interdependencies among human populations, it is impossible to view health in isolation from other sectors [3, 4, 23]. Indeed, both the problems of, and the solutions to, global health are systemic in nature. As a complement to the article on pharmacogenomics in South Africa by Warnich *et al.* [12], this editorial analysis provides a forward look on postgenomics personalized medicine with a focus on Africa and women's health, two priority global health topics that have been firmly endorsed as noted above [1].

2. GLOBAL SOUTH AND GENOMICS BASED HEALTH INNOVATIONS

The Global South refers to the technologically developing nations in Africa, Asia and Latin America, where health innovations often face the challenge of fragile or under-resourced research infrastructures, as well as a lack of innovative governance of health innovations. A common misconception in the field of global health innovation is that genomics and personalized medicine has little to offer developing countries with scarce resources. However, genomics/postgenomics technologies, when considered under a sound public health genomics framework, can offer innovative and potentially cost-effective solutions to

major public health burdens "whether via 'leapfrog' technologies, or new ways of using existing genomics knowledge in a different environment" [24]. Moreover, as noted by Burton *et al.*, it is essential to bear in mind the wealth of opportunities for improved population health achievable today through implementation of our current knowledge of congenital disorders and single gene defects [13].

In an analysis of the Global Health Initiatives (GHIs), the alignment of donor assistance and needs of Cambodia during the 2003–05 period was found to be largely mismatched [25]. GHIs such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and the Global Alliance for Vaccines and Immunization (GAVI) illustrate the cross-sectoral involvement of the private sector, philanthropic trusts and civil society in global health. Yet, eliminating the endemic poverty that quietly runs beneath many of the health challenges demands innovative ways of tackling the political determinants of global health. The perception that development aid is invariably beneficial for recipient countries or that the aid contents reflect the *actual* needs of the recipient countries is an outdated mode of international development for global health. Top-down aid can result in a waste of precious resources or remain ineffective at the local level if the knowledge of local health systems is ignored by the donor countries. Instead, GHIs need to be closely aligned with target countries' health systems and their local public health priorities as genomics research and applications permeate into public health practice in the Global South.

3. FROM SOUTH TO NORTH AFRICA

3.1. Hepatitis C Virus Infection in Egypt: Another Model Genomics Application for Global Health

Hepatitis C virus (HCV) infection represents a major public health, societal and economic burden in Egypt. The HCV prevalence rates reach 14%, while the incidence ranges from 2.01 to 25.47 HCV cases per 1000 person-years [26], with the predominance of the relatively less therapeutically responsive genotype 4 [27] and the prevalence of HCV and *Schistosoma mansoni* co-infection that is characterized by accelerated hepatic fibrosis with development of cirrhosis within 8–10 years [28]. The standard therapy for HCV is both difficult and expensive, particularly with the huge burden of disease in Egypt. Stigma also exists for people who are infected with HCV, resulting in inequities in employment opportunities.

These public health burdens in Egypt stand to benefit from the applications of personalized medicine and pharmacogenomics. Identification of individuals at higher risk of accelerated liver fibrosis progression who are likely to benefit from anti-viral therapy will not only maximize the efficacy and cost-effectiveness of therapy but will also reduce the rates of HCV transmission.

3.2. HIV Resistance in Africa: The Role of CCR5 and CXCR4 Co-Receptor Polymorphism and Development of Targeted Inhibitors

In addition to the CD4 receptor on T cells, two co-receptors are required for HIV to enter human cells: the chemokine (C-C motif) receptor 5 (CCR5) or chemokine (C-X-C motif)

receptor 4 (CXCR4) [29]. In the 1990s, it was identified that individuals who were either homozygous or heterozygous for a 32-bp deletion (Δ32) of the CCR5 receptor exhibit no expression or reduced expression of this receptor protein, respectively, at the cell surface [29]. It was also observed that the Δ32 polymorphism was associated with modest resistance to HIV infection in that variant individuals showed a delayed onset of immunological failure and had a slower progression to developing the full blown AIDS [30]. More recently, based on these initial molecular observations, a CCR5 receptor inhibitor, maraviroc, has been developed and has shown efficacy in the treatment of HIV through inhibition of cell entry [31]. Global health priorities in Africa would be well served through personalized medicine research on resistance to HIV infection which may inform the design of future targeted therapeutics.

3.3. Non-communicable Chronic Diseases

In addition to infectious diseases, common chronic diseases disproportionately affecting the African populations across the continent warrant future attention in the context of postgenomics personalized medicine. For example, uterine leiomyomas are the most common tumors of the female genital tract, and affect nearly 80% of the female population [32]. Uterine leiomyomas are more common in Black women than White women. Population differences in polymorphism of genes involved in estrogen synthesis and/or metabolism, estrogen and progesterone receptors or retinoic acid nuclear receptors or aberrant expression of micro-RNAs are some of the conceivable molecular genetic mechanisms that may offer insights on this tumor highly prevalent among African women [32].

4. A PAN-AFRICAN GENOMICS RESEARCH NETWORK – A ROLE FOR NEPAD?

To date, the utilization of genomic research to address the public health priorities in Africa has been largely restricted by limited facilities, financial support and human resources. However, it is envisaged that the establishment of a Pan-African genomics research network, supported by key international collaborations, will allow large prospective longitudinal cohort studies that are needed to elucidate the gene-environment interactions that underlie the complex disease burden in Africa [33]. Not only can such studies contribute to training and capacity building, but evidence-based findings can also stimulate innovation and economic growth and influence policies to enhance genomics applications for public health [34, 35]. Although established research centers in the south and north of the continent will be the key partners in such a network, as many African countries as possible should be included to ensure that the current global north-south genomics divide is not repeated on a continental scale.

Interestingly, a number of existing regional programs share the same ethos for an equitable development in Africa but have not hitherto incorporated, explicitly or implicitly, genomics medicine within their strategic agenda. For example, The New Partnership for Africa’s Development (NEPAD) is a program of the African Union adopted in Lusaka, Zambia in 2001 [36]. NEPAD is led by African leaders to develop new approaches for socio-economic

transformation of Africa. Conceivably, NEPAD and other programs with deep knowledge of the local and regional public health priorities can play a significant role as boundary organizations to form effective bridges across the local, national, supranational and global health divides.

5. NUTRIGENOMICS APPLICATIONS IN AFRICA

In parallel with pharmacogenomics, the science of nutrigenomics considers the ways in which genetic variations among individuals influence dietary requirements, and modify responses to different nutrients and phytochemicals [37]. This is not only highly relevant to malnutrition, but also to the increasing incidence of communicable and noncommunicable diseases in Africa. For example, Mbikay *et al.* [38] described possible survival benefits of a loss-of-function mutation for a key enzyme in cholesterol homeostasis (Proprotein convertase subtilisin/kexin type 9; PCSK9), in the context of parasitic infections that are still common in Sub-Saharan Africa. The 1000 Genomes Project is an international collaboration that is sequencing the whole genomes of approximately 2,000 individuals from different ethnic groups. As well as enabling prediction of disease susceptibility and drug response, it will augment our understanding of the genetic basis of responses, not only to dietary deprivation, but also to the excesses that are becoming increasingly common in some parts of Africa. Hence, nutrigenomics is a pivotal postgenomics field with substantial relevance for Africa and global public health.

6. BIOBANKS AND AFRICA – WHAT NEXT?

6.1. Current Status

Political, social, economic and organizational factors largely explain the limited number of biobank initiatives in Africa compared to other continents [39]. Nevertheless two interesting projects in Africa deserve mention, together with another population genomics resource in Israel closely situated to Africa. These could serve as models for future initiatives. Of the African biobank initiatives, the largest and most advanced has been set up in Gambia in collaboration with the United Kingdom Medical Research Council [40]. It hosts approximately 57,000 samples of the West African populations. A multi-national, but smaller initiative, The Biobank and Pharmacogenetics Databasing Project of African Populations, includes around 1,500 samples originating from nine ethnic groups from five African countries (Nigeria, Kenya, Tanzania, Zimbabwe and South Africa) [41].

There are a number of concrete opportunities for building new consortia across the African continent. Situated on the bridge between Asia and Africa, Israel is home to Jewish communities who immigrated there from Europe, the Near East, North Africa and Ethiopia during the previous century, after being geographically and genetically isolated from one another for two millennia. These populations are represented by nearly 2000 unrelated donors whose blood samples were used for preparing immortalized lymphoblastoid cell lines and DNA samples reposited by the National Laboratory for the Genetics of Israeli Populations at Tel-Aviv University (NLGIP; http://nlgip.tau.ac.il). A genome-wide study on the variation of the Jewish ethnic groups indicated a Middle-Eastern genetic signature closely similar to Cypriots and Druze, although gene flow from non-Jewish communities is

evident, while the Ethiopian Jews show closer similarity with other Ethiopian populations [42]. The Israeli biobank with its donors from communities originating in Algeria, Ethiopia, Libya, Morocco and Tunisia is therefore a novel resource for pharmacogenomics-oriented research collaborations on the large genetic diversity of the African populations.

6.2. Proteomics and African Biobanks

During the last decade proteomics research activities at the Council for Scientific and Industrial Research, University of Pretoria, the Centre for Proteomic and Genomic Research, University of Cape Town, and the Proteomics Research Group, University of Western Cape as well as development of Proteomics Association of South Africa, are positive initiatives to accelerate proteomics research in Africa [43]. Pharmacoproteomics deals with the applications of proteomics in the field of drug discovery and personalized medicine. It offers tremendous promise to accelerate clinical research in Africa and provide novel information related to biobanks [44]. Pharmacoproteomics and ultrasensitive “nanoproteomic” approaches will be crucial to study several challenging health issues in Africa such as infectious diseases and developing resistance against pathogens (e.g., Plasmodium, Mycobacterium and Leishmania); cancers associated with virus infection; and understanding structural and biological properties of HIV-related proteins. Functional proteomics will aid these studies further by providing expression profile changes at transcriptome and proteome levels. The future of African pharmacoproteomics and biobanks initiatives will be determined in part by the development of research infrastructure, including a data and bioresource commons [45] and skilled scientists who can bridge the regional health and research nuances with international outreach.

7. GENOMICS AND ESSENTIAL MEDICINES

7.1. Has the Time Come for “Essential Diagnostics Model List”?

The notion of essential medicines is founded on precepts of public health and equal access. The WHO Model List of Essential Medicines is an important resource for global public health. Genomics can potentially promote these objectives in two ways: by appropriately targeting medical interventions at the level of subpopulations wherein they display greater efficacy and safety; and by making available a greater number of interventions as genomic studies reveal which subpopulations can be safely administered medicines otherwise unavailable to them due to toxicity among the general population. Just as the WHO’s Model List of Essential Medicines is based on objective measures of efficacy, safety, and comparative cost-effectiveness, an *Essential Diagnostics Library* [10] could conceivably catalogue field-tested diagnostics that facilitate targeted health interventions in global public health.

Implementing such a library, however, is not without obstacles. Human disease and pharmacological phenotypes are highly heterogeneous even within the same clinically defined disorder or drug class. Moreover, the story of antiretroviral treatments and the lack of “clocks, running water, and refrigerators” in developing nations raises the specter of regional capacity. Prior to rolling out genetic/genomics diagnostic testing, there should be adequate infrastructure to support both the tests and the individuals who must interpret them.

The case of essential medicines is marked by the abject neglect for global R&D for diseases such as TB, malaria, sleeping sickness and other acute respiratory infections that, although accounting for nearly a fifth of global mortality, primarily afflict developing countries. Market mechanisms associated with the extant drug development frameworks do not always generate socially adequate solutions for developing countries. This necessitates a more collective orientation to develop new models for the integration of genomics with the concepts and practical delivery of essential medicines in resource-limited settings [14].

At this critical juncture when genomics and postgenomics diagnostics are edging into applications for generic drugs and essential medicines, evidence-based policy innovations such as the creation of a United Nations (UN) led Essential Diagnostics Model List could potentially contribute towards affordable and equitable access to diagnostics, especially in resource limited settings [10]. For health, there should be access not only to essential medicines but also to evidence-based companion essential diagnostics that can address the pressing global public health priorities. As a policy innovation, for example, a WHO Essential Diagnostics Model List, could accelerate transition of novel diagnostics (e.g., genomics, proteomics, metabolomics) into primary health care, instead of provision solely through tertiary health care or ad hoc direct-to-consumer testing without a strong public health framework. Such an Essential Diagnostics Model List would be consistent with the ethos of the Alma-Ata Declaration (September 1978) on Primary Health Care and may particularly serve well developing countries or resource-limited rural societies.

8. BEST PRACTICES FOR RESEARCH IN MATERNAL HEALTH

Maternal death is disproportionately high in developing countries and health statistics consistently reveal great disparities between the developing and the developed countries. An often overlooked question is whether pregnant women have access to the latest scientific discoveries. While women have increasingly been included in research, pregnant women have often been left behind. This reluctance to include pregnant women in research probably reflects in part the thalidomide episode and presumably, the perceptions of physicians as if every drug is a potential thalidomide. Few medications have been approved for use during pregnancy. The exclusion of pregnant women from clinical trials must be challenged, considering that nearly half of all pregnancies are unplanned. Women are in need of effective and safe treatment during pregnancy because many chronic conditions like diabetes, hypertension, cancer, psychiatric illness, malaria, and HIV infection, or common conditions such as pre-eclampsia and extreme nausea complicate their pregnancy. Similarly, scant information is available about the effects of vaccination during pregnancy. While research is a key tool to tackle these challenges, the decision to include pregnant women in drug trials in developing countries is a complex issue. While more and more clinical trials are carried out in developing countries, ethics restrictions are less widespread. For example, regarding such matters as the use of placebos for the control group, there is a lack of research ethics infrastructure and research might be undertaken in these locations primarily because it is less costly for the drug developers. However, despite these challenges, collaborative international research networks, such as the one coordinated by the Department of Reproductive Health and Research at WHO [46], will provide much needed support to overcome some of these impediments.

9. BEYOND BIOTECHNOLOGY

9.1. Recognizing Political Determinants of Health and Politics of Gender

The challenge in global health is not only a challenge of disease, but also a challenge of governance [4, 47]. One dimension of governance for global health that is particularly relevant to Africa is the politics of gender and the politics of knowledge based innovations. Gender inequities in health outcomes are deeply political, reflecting traditional power differentials between men and women, and the historical exclusion of women from positions where they can participate in, and have an influence on, knowledge production and thus help set health and research agendas. In turn, while pharmacogenomics and personalized medicine promise to improve health outcomes in Africa, a narrowly framed biological or technological approach to health will not alone combat the health inequities that characterize much of the African continent. Gender inequities in health outcomes such as access to health care, quality of care within the health system, and overall health indicators, are the result of complex social systems. To effectively address gender inequities in health outcomes will require not only science and technology specific to women's distinct needs, but also a new form of governance for health that reflects the multiple determinants of health both inside and outside the health sector [3, 4]. Donors and policy makers should thus strive to balance disease-specific or *vertical* initiatives that focus on isolated aspects of health with comprehensive and *horizontal* initiatives that aim to strengthen health systems and services, keeping in mind that health is multi-faceted and interactive with the wider socio-political context. In fact, horizontal global health initiatives are most crucial to ensure lasting impacts in global public health especially in resource limited settings. As part of such horizontal initiatives, the international community has recognized the importance of addressing gender inequities, as evidenced by the inclusion of women in the UN Millennium Development Goals. The challenge moving forward will be to link incoming R&D and other forms of aid with local leadership and input to create holistic health policies that will combat the root causes, or the "causes of causes" [48] of gender and population health disparities.

CONCLUSIONS: A TRI-PARTITE VISION FOR GLOBAL PUBLIC HEALTH GENOMICS

This editorial analysis has asserted that public health (and its pharmacogenomics and personalized medicine derivatives) embodies explicit and implicit interdependencies among human populations and that it cannot be viewed in isolation from sectors that are traditionally placed outside health. The biological, social and political are *co-constructed* domains that work in tandem to foster human flourishing, health and well-being. As the original WHO definition of health makes clear, *health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* [49]. Hence, this view not only broadens the concept of health beyond absence or presence of disease but also illustrates that global health is more than an intrinsic value. It holds an instrumental, political value as well. Indeed, health and international development aid must not "bracket out" the political determinants of health. Global health is both a *cause* and *effect* of national and supranational governance and international political systems. Just as research aid can be

formulated under various, latent political motivations and consequently impact health outcomes, so too can public health impact governance systems.

Hasty conclusions on the meaning of the human genome might miss the mark: a decade is not enough to assess the social and moral impacts of publication of the human genome sequence in February 2001 [50]. At a practical and technical level, personalized genomics will require a sound genomics infrastructure science, detailed clinical histories, deep phenotyping and extended data sharing for the purposes of clinical research translation and implementation [51, 52]. It also needs considerations for genomics in developing countries and other resource limited settings. As such, in these early days of pharmacogenomics applications in developing countries, we advocate a new global public health genomics vision that illuminates these dynamic, bi-directional and *tri-partite* (biological, including genomics, social and political) determinants. Global public health is important because its absence impairs our ability both to live as autonomous individuals and actively participate as members in civil society. Explicating this important recognition of the political and social connection to health allows us to view Africa and women's health as a microcosm of the larger personalized medicine picture in the postgenomics era. Improving the health of women and the people of Africa is critical not only because it improves the physical, mental and social well-being of traditionally under-represented individuals and communities, but also because it promotes participation in social life and political decision-making processes. Such participation, in turn, reflects each person's innate desire for self-realization together with the need to be part of a community.

Health can therefore be viewed both as an intrinsic and instrumental value, dependent on and determinative of values that drive human or institutional behaviour. Most critically, health can be viewed as a keystone to human flourishing in a 21st century inter-connected biological, social and political world. Ignoring any one of these three domains of health is not an option. That would add to inherent uncertainties of knowledge-based health innovations [53, 54] and turn novel postgenomics biotechnologies against us before we can turn to them to benefit our health and well-being.

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ABBREVIATIONS

HCV	Hepatitis C Virus
NEPAD	The New Partnership for Africa's Development

NLGIP	National Laboratory for the Genetics of Israeli Populations
UN	United Nations
WHO	World Health Organization

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