Roundtable Discussion:
Precision Public Health in Africa

October 7th 2016, Sheraton, Addis Ababa, Ethiopia

Bill & Melinda Gates *foundation*

AESA AN INITIATIVE OF AAS & NEPAD AGENCY

Meeting Summary Notes:

Present:

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Michele Ramsay, University of the Witwatersrand
Peter Waiswa, Makerere University
Eunice Nduati, KEMRI Wellcome Trust Research Programme
Guida Landoure, University of Bamako
Collen Masimirembwa, African Institute of Biomedical Science and Technology
Rizwana Mia, South African Medical Research Council
Gabriel Anabwani, Botswana-Baylor Children's Clinical Center of Excellence
Mark Nicol, University of Cape Town
Lulu Muhe, Addis Ababa University
Taye Balcha, Armauer Hansen Research Institute
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Haddis Tadesse, Bill & Melinda Gates Foundation, Africa
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Introduction

To achieve the ambitious Sustainable Development Goals (SDGs) set out for maternal, newborn, and child health (MNCH), countries in Africa must take full advantage of potentially transformative new health and development technologies. While some may argue that high mortality rates in LMICs have more to do with geography and poverty than genetics, there is a budding wealth of evidence on the African continent that understanding genomics and environmental determinants of common diseases will help reduce preterm mortality rates and improve neonatal outcomes. However, studies of human genetics, particularly genome-wide association studies (GWAS), have concentrated heavily on European populations, with individuals of African ancestry rarely represented.

While precision medicine at a personalized level may not be achieved in Africa, strategies that may be employed to address public health issues need to be explored to ensure that healthcare disparities are not further driven by precision medicine.

To explore challenges and opportunities for precision medicine specifically for Africa, the Bill & Melinda Gates Foundation and the Alliance for Accelerating Excellence in Science in Africa (AESA) organized a roundtable with the aim of defining what is useful and relevant for precision medicine in public health in Africa. The roundtable brought together African researchers from across the continent to explore how precision medicine can help alleviate the double burden of infectious and non-communicable diseases by ensuring that the right medicine reaches the right patients at the right time.

At the start of the roundtable, Gates Foundation CEO, Sue Desmond-Hellman reflected on her personal journey working with targeted therapies for breast cancer, and how there has been some disappointment within the health community that a decade after the human genome was announced, there has been no significant progress in using precision medicine to address the world's most pressing health needs.

She emphasized that precision medicine is about being more effective and efficient in enhancing health and well-being. New tools and approaches (such as self-monitoring, mobile technology and geospatial monitoring) offer exciting prospects for global health, but they must not increase the inequity in health (there is a risk of this due to the differences in the right access to tools).

As an example of what precision medicine for public health could mean, Sue mentioned the approach of testing and treating pregnant women to bring mother-to-child transmission of HIV down. This is a great example of considering specific populations and targeting approaches rather than just considering the individual. Sue also referred to the Gates Foundation-supported CHAMPS (Child Health and Mortality Prevention Surveillance) Network as a specific area where we can help ensure the right interventions are delivered to the right children in order to save lives.

Presentation Highlights

Michele Ramsay: The Burden of Non-Communicable Diseases

The focus in Africa has always been on infectious disease, but there is a dramatic increase on the continent of the non-communicable disease (NCD) burden. Precision medicine implies that there will be an element of genetic predisposition that will need to be considered when making a diagnosis or prescribing a treatment most appropriate for an individual, or, in the case of public health, a large component of the population. However, it is important to understand that we can't think of Africa as one people, as there is great genetic diversity across multiple ethnolinguistic groups – and yet the continent's people are very understudied.

In light of this, collaborative efforts like H3Africa and the INDEPTH Network serve as important opportunities to conduct meta-analyses of the data available. The different studies could act as replication cohorts for one another. For example, since cardiovascular disease (CVD) has a multifactorial etiology, it is necessary to examine genomic, epigenomic, phenotypic, social and environmental data to uncover the drivers of the CVD epidemic across the continent, and to build and test hypotheses that could lead to feasible interventions.

The NCD-related projects in H3Africa study kidney disease, cardiometabolic disease, cervical cancer, strokes, diabetes and rheumatic heart disease. There DNA biorepositories in three different parts of the continent and H3ABioNet supports the building of capacity for data management and analysis. The AWI-Gen Collaborative Center under H3Africa is a partnership between Wits University and the INDEPTH Network to understand the interplay between genetic, epigenetic and environmental risk factors for obesity and associated cardiometabolic disease and to enable the application of genomics in addressing questions of biomedical importance.

Peter Waiswa: Measuring Maternal and Newborn Health

Precision public health above all requires data. The INDEPTH Network, which is led by the global South, is positioned to do that through prospective monitoring of 3.8-million individuals in 20 countries and 52 Health and Demographic Surveillance System (HDSS) sites. As all INDEPTH HDSS member centers currently track pregnancies, newborn births and deaths, the network provides an excellent platform for tracking newborn health interventions, as well as morbidity and mortality trends on a longitudinal basis.

The network sites also capture episodes or illness, pregnancy birth, hospital episodes and cause of death (via verbal and social autopsy), as well as recent efforts to use minimally invasive autopsy to collect tissue samples for more precise COD.

While HDSS sites have been used to track population trends, migration and infectious diseases, they have been used less for maternal and newborn health. The INDEPTH Network Maternal and Newborn Working Group was created to improve pregnancy and pregnancy-outcome tracking, in order to provide a better platform for testing precision public health approaches across the research pipeline, from description, discovery and development to delivery science.

There are currently 20 member sites of the group, and the data being collected provide an interesting insight into the intergenerational effects of pregnancy through to death.

Eunice Nduati: Precision HIV Immunology

HIV infection remains a key health burden in sub-Saharan Africa. The main current challenges facing HIV control include a highly mutating virus; host immune responses that are not totally protective and lag behind a rapidly mutating virus; and latent infection, which is a persisting reservoir. Immune response to HIV infection at an individual level differs with patients, affecting progression of the disease. However, there are a number of aspects that would need to be considered and addressed for applying precision medicine in a public health context to HIV in Africa. These would include host immune response, host genetics, virus mutability, environmental influence, and the cost-versus-benefit analysis to assess feasibility in resource-challenged environments and systems.

It would also be prudent to target interventions for the key drivers of the HIV epidemic in Africa. This would include men who have sex with men, female sex workers, heterosexual discordant couples, and mother to child transmission. Interventions could include applying pharmacogenomic approaches to ensure optimal therapy; monitoring viral mutability and drug-resistant strains; early antiretroviral therapy; and pre-exposure prophylaxis, among others.

Guida Landoure: Neurological Disorders in Mali

Hereditary neurological disorders display a high clinical and genetic heterogeneity that translates into differences in clinical presentation and natural history, but also in population-specific genetic entities. They bear a high burden because they can start early in life, are often incurable, are debilitating and can cause premature death.

There are a number of challenges regarding neurological disorders that are specific to Africa. The burden of these diseases is higher in Africa because of the low literacy rate, social factors leading to stigmatization and the lack of infrastructure and specialists that limits genetic studies. There is much to be done by way of needing to understand neurological disorders on the continent as there has been a dearth of cohort and longitudinal data available. The high consanguinity rate increases the number of recessive disorders that are more severe, and the high fertility rate increases the number of affected per family. These last two characteristics, however, offer a unique opportunity to find new genes that can be studied in other populations.

In terms of an approach, the low detection rate of some mutations and differences seen in types of mutation for several diseases in Africa should govern a population or ethnic-specific investigation and treatment of disease.

Pilot studies in Mali have found favorable attitudes towards genetic testing and counselling, but there is still a need to educate the general population on the basics of genetic diseases, and to strengthen the skills of geneticists and molecular biologists.

Studies by Dr Landoure and colleagues have found a genetic diversity (that could be extended to the entire African population) translating into new disease genes with new entities, other genetic diversities as lower carrier frequencies of diseases such as spinal muscular atrophy (1/209 compared with 1/25-50 for Eurasians); and families negative for all clinically relevant genetic testing – all suggesting that current diagnosis panels or tools are not suited for African populations.

The decreasing cost of sequencing and production and the availability of large-scale data provide an opportunity for rapid advances to be made on the continent, but they need to be facilitated by collaborations within and beyond Africa, and supported by more favorable policies for data access and sharing. The cultural context in Africa should also not be overlooked when considering the pursuit and application of precision medicine. For example, Africans deal with their problems in a community or family-based way, and too much confidentiality may lead to stigmatization in some cases.



Collen Masimirembwa: A Pharmacogenomics Perspective

The driving principle of a pharmacogenomics perspective is to give medicines only to populations that will respond to them, and at doses that will be efficacious. Differentiating patient populations is very important for this reason, for both health providers and industry partners. Currently, more than 30 drugs have pharmacogenetics guidelines for their use/dosing in clinical practice. While the FDA and EMA have issued guidelines on pharmacogenomics/genetics, there is still much that needs to be done in the regulatory arena, particularly in Africa where there has been a late but promising entry into genomics research.

The genetic diversity of African populations has been demonstrated through various studies. The African Pharmacogenomics Research Consortium has shown that while there is distinct clustering of Caucasians, Asians, and African populations, there is more dense clustering of the first two groups and there are more genetic differences within African populations. The implications of this diversity for precision public health for populations in Africa are that:
i) there is differential susceptibility to disease and disease progression, and
ii) there are differential responses in terms of drug safety and efficacy.

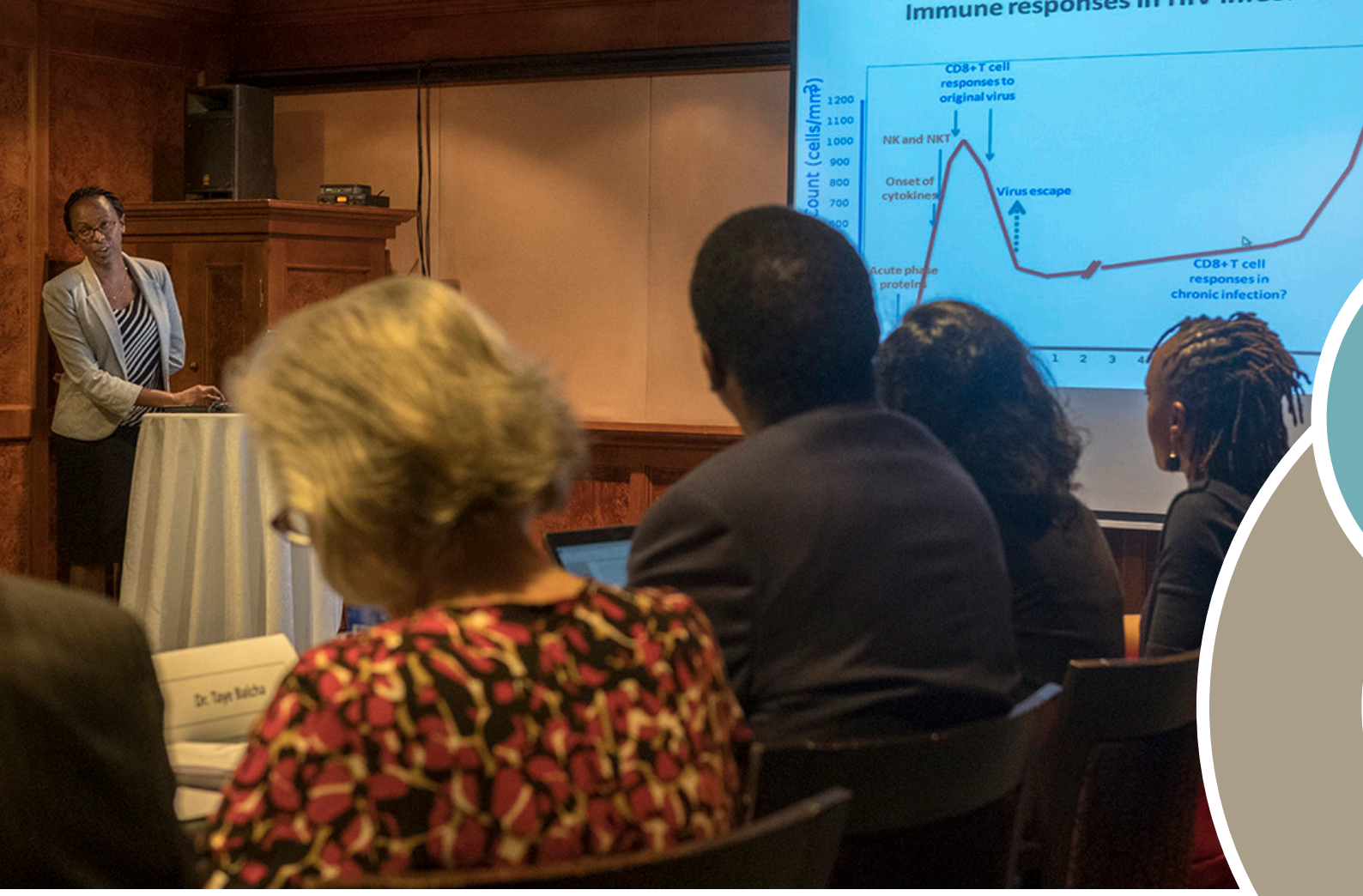
Drugs optimized in one population might not work in African populations; population data highlights major population differences in CYP450s (drug-metabolizing enzymes), which apply to approximately 90% of drugs on the market. This suggests that there are possible population differences in drug response and efficacy.

A study by Collen Masimirembwa and team found that 83% of patients on HIV and/or TB treatment in a case-control study exhibited one of four adverse drug reactions (ADRs). Their study also demonstrated that patients in Zimbabwe might better benefit from different doses of HIV treatment then standard guidelines advise: 20% of Zimbabwean patients would require only 200mg of the given 600mg Efavirenz. Building on this, they have been developing a genetic test kit for individualised use of Efavirenz in the safe treatment of HIV/AIDS.

The implications of administering doses of drugs that cause ADRs are poor compliance and resulting risk of drug resistance; high cost of the treatment program; and poor quality of life and low economic productivity for the patient.

Key recommended priorities for pharmacogenomics in sub-Saharan Africa:

- Strengthen genomics research capacity for biomarker of treatment responses
- Collaborate with R&D pharmaceutical companies in evaluating the pharmacogenetics of their new chemical entities in African populations
- Evaluate the role of pharmacogenetics in the safety and efficacy of drugs already on the market
- Integrate pharmacogenetics in pharmacovigilance programs
- Ensure cost-effective analysis for public health settings in HIV/AIDS



Rizwana Mia: South African Precision Medicine Program

Acknowledging that a "one-size fits all" approach does not work in Africa, a precision medicine program in South Africa was conceptualized and proposed to the Minister of Science and Technology, who initiated a Precision Medicine Think Tank. The mandate is to drive the innovation pipeline to develop cost-effective precision medicine tools that can be used in transforming healthcare towards the adoption of precision medicine.

Given limited public resources, a product development partnership model is used to leverage funding through partnerships with a wide range of stakeholders. This then allows for a business case to be made for the adoption of precision medicine, and serves as a bridge to link the gap between public and private healthcare. The incentives for private investment include opportunities to seek innovative, cost-effective genetic diagnostics and to repurpose existing drugs, as well as access to the African market.

Lulu Muhe: Ethiopia Study of Illness in Preterms Project

The main causes of preterm mortality are well known in developed countries but are not precisely defined in low-resource countries. While advances have been made in Ethiopia in under-five mortality reduction, the same is not true for neonatal mortality. Preterm complications are the direct causes of neonatal deaths in 35% of all newborn deaths, contributing to 40% to 60% of all neonatal deaths.

The objective of the Ethiopia Study of Illness in Preterms is to determine the major causes of illness and mortality in preterm hospitalised infants in Ethiopia based on standardised diagnostic protocols. It is a multicentered clinical study of admitted pre-term babies in four hostpitals in Addis Ababa, Gondar, and Jimma University hospitals. Using a range of data (socioeconomic, clinical, imaging, microbiological, minimally invasive tissue samples and verbal autopsy), it is hoped that the major causes of preterm mortality are elucidated, in order to inform the development of an appropriate package of management protocols and to scale up strategy with costed interventions for implementation.

Discussion Highlights:

Key priorities and opportunities:

- **Need for a clear definition:** It was felt that clarity is needed on what exactly is meant by precision medicine to maintain focus and not represent a "catch-all" term for clinically relevant research. The group agreed the following elements of a definition for precision medicine:
  - It is about genomic and environmental variability (in host and pathogen) and how this impacts on disease and interventions
  - It allows us to provide more focused interventions in a way we were not able to do before
  - It is about targeting the right population in the right geography at the right time with the right intervention

- **Potential to improve TB treatment in Africa:** In Europe, precision medicine approaches have helped very successfully to treat MDR and XDR TB, and yet in Africa generic approaches persist, which we know are failing large proportions of patients due to widespread drug resistance. Geospatial mapping and the use of sequencing and information technology have valuable roles to play.

- **The importance of cross-cutting efforts of collaborative networks like H3Africa:** The H3A consortium agreed there is a need for a genotype chip designed for African population studies, as most of the sequencing efforts to date have been done on genotype chips on European males. African populations have a higher number of average variant SNP sites compared to European and Asian individuals. An H3A chip-design working group was formed, and analysis and design were driven by the H3ABioNet with collaborators at the Wellcome Trust Sanger Institute. This African chip is in development and will be launched in March 2017, and offers great potential for the precision medicine research agenda in coming years.

- **Supporting capacity development and access to technologies:** Much of the analysis is felt to still be happening outside of the continent by those who have access to the relevant technologies (example: high throughput sequencing) and possess the skill set and manpower.
  - Access to technology: There could be an opportunity to establish centres of excellence with the requisite technological capacity on the continent. In the case of sequencing, there would need to be an economic imperative to make it the preferred option (i.e. subsidised costs could be an option). This would also help to provide opportunities for careers and help mitigate brain drain
  - Capacity: A key level of capacity-strenghtening is at the institutional level. This would include alleviating the teaching load for researchers, and ensuring access to resources and reagents. Postdoctoral opportunities were identified as a key gap on the continent. Research groups grow around the PIs, and support is also needed to help researchers with writing, and acquiring their own grant funds. So many postdocs who are PI material who just might not be competitive enough for WT funding schemes. A new initiative called the Alliance for Research Universities in Africa is looking to bring together universities to stimulate how to become research intensive

- **Ethical issues:** There are many fears about exploitation, which has happened in the past, that need to be addressed today. We need to engage more appropriately with communities that provide the samples, as many communities appreciate the opportunity to contribute to universal knowledge.

- **South-South collaboration:** There are many opportunities to collaborate with other countries/regions such as India, which have similar health challenges and resource profiles, but have been able to develop strong health technologies and supportive regulatory frameworks.

Next Steps

- **A publication and White Paper on what precision public health means for Africa:**
  - The approach must prioritize Africa's major health burdens and demonstrate an economic benefit and case
  - It will be important to identify some "use cases" for this, particularly when the public and policymakers get engaged. These could include key priority areas of adverse drug resistance, emerging neglected NCDs and prevention approaches particularly given Africa's increasingly young population. In the UK, an example of a "use case" is gene-based diagnosis as part of the UK's precision-based medicine program. This involves cost-effective panel tests and could form the basis of a similar approach on the African continent. For lay audiences, a good, simple example is blood type
  - A sustainability funding strategy/public-private partnership model could be proposed to enable a mind-shift about how to not just rely on university or government funding
  - The aim would be to have either/both produced in draft by December 2016

- **Regulatory issues:** There is a lot of room in the area of precision medicine to have a conversation with regulatory agencies on the continent to appreciate the need for sharing samples. Often regulatory agencies are national, and/or are supposed to represent specific communities but they are not always directly engaged with them. It was agreed African ministers could be engaged with on a framework for data and sample sharing within the continent.

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