Grand Challenges in Genomics for Public Health in Developing Countries:
Top 10 policy and research priorities to harness genomics for the greatest public health problems

Vision

To develop a list of the top 10 priorities ('Grand Challenges') for the effective development and application of genomics-based interventions for public health improvement in developing countries that WHO will take to Member States in 2012 to guide countries’ research and public health strategies on genomics to improve public health.

The priorities will be identified through a series of consultations with leading international scientific and public health experts. The consultations will identify the key Grand Challenges or bottlenecks to be overcome by developing countries to harness genomics for alleviating the greatest public health problems over the next 10 years. Grand Challenges comprise major problems and issues in public health in developing countries, the solutions or contributions to which genomics has an integrated, significant part.

Context

We live in a world in which the burden of disease and ill-health is a major barrier to the development and realization of every individual’s capabilities. Basic, clinical and population research can transform human well-being and has the potential to unite and empower countries and communities. Dramatic advances in our understanding of the molecular basis of human physiology and disease over the last decade have yielded enormous insights that may offer new and better ways to improve health and tackle disease.

Buoyed by the last decade's major advances in genomics, high expectations remain for genomic medicine and the translation of wider biomedical research into improved health. Novel discoveries are being reported daily, supported by the development of new and cheaper technologies. However, to date, much biomedical research has not translated into improvements in clinical outcomes in a commensurate manner. In the face of extensive and, thus far, largely unfulfilled media hype and societal expectations surrounding genomics, how can individuals – researchers, clinicians, policy-makers and the public – discern where the true benefits really lie and when they will be realized?

In 2001, the Science article "Harnessing Genomics and Biotechnology to Improve Global Health Equity" hypothesized a 2010 World Bank report on The Health Genomics Divide lamenting how an unfolding revolution in treatments and interventions based on genomics-related biotechnologies in rich countries has been denied to people in developing countries. No such revolution has been unfolding, and the World Bank has not published such a report. Truly, the last decade has however exposed a large gap between developed and developing countries in their capacity to carry out biomedical research, and with the vast majority of genomics research being carried out in the context of Western countries' genetic and environmental variation to address public health needs in these countries. If this trend continues, the health genomics divide is inevitable.

We therefore pose a simple question: what are the major Grand Challenges or bottlenecks to be overcome for genomics to be harnessed and used by developing countries to address the greatest public health problems over the next 10 years? The development of a list of priorities would help avoid the health genomics divide by focusing strategies and strengthening capacity in developing countries, stimulate debate and increase awareness internationally, but also ultimately shape the...
future through driving investment, research and development in priority areas in a manner closely tuned with global societal values, expectations and perceived needs.

WHO latest review of genomics and world health, the 2002 report "Genomics and World Health" prepared by WHO's Advisory Committee on Health Research, identified several concerns and many possibilities for the use of genomics knowledge in improving world health³. Our project to identify the Grand Challenges in Genomics for Public Health in Developing Countries can be considered an update to this report. The project is also an update with a broader capture of possible bottlenecks and solutions to the separate 2002 exercise "Top ten biotechnologies for improving health in developing countries"⁴, which was primarily focused on technologies. We have partly modeled our project after earlier complementary projects, including: "Grand Challenges in Global Health"⁵, "Grand Challenges in Chronic Non-communicable Diseases"⁶, and the ongoing "Grand Challenges in Global Mental Health"⁷. These Grand Challenge exercises have all used similar definitions of a Grand Challenge and similar methodology, but have focused primarily on scientific innovation to tackle infectious diseases, bottlenecks to fight major chronic non-communicable diseases, and mental health, respectively.

Definitions

We use the following definitions:

**Grand Challenge:**

A specific critical barrier that if removed would help to solve an important public health problem. The interventions(s) it could lead to might be innovative and, if successfully implemented, will have a high likelihood of impact and feasibility.

Note: a Grand Challenge is considered distinct from a simple statement of a problem, such as lack of resources, lack of access to medical care, lack of research capacity, malnutrition, or HIV / AIDS. Our Grand Challenge is meant to identify bottlenecks to be overcome by developing countries for them to harness genomics for the greatest public health problems over the next 10 years in their countries.

**Genomics:**

Genomics is the study of the total or part of the genetic or epigenetic sequence information of organisms, and attempts to understand the structure and function of these sequences and of downstream biological products. Genomics in health examines the molecular mechanisms and the interplay of this molecular information and health interventions and environmental factors in disease.

Note: human genomics is not the only part of genomics relevant to human health. Our genome interacts with those of a myriad other organisms, including plants, vectors and pathogens. For the project **Grand Challenges in Genomics for Public Health in Developing Countries**, we consider genomics across all organisms, as relevant to public health in human populations. In addition to genomics knowledge, the project also considers technologies that make use of genomics knowledge.

**Public Health:**

The science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals.

**Developing country:**

We use estimates of the UN Human Development Index from the Human Development Report 2010 to classify countries into developed and developing countries. The map below illustrates the Human
Development Index (HDI) for each country of the world. **Developed countries are countries with a HDI greater than 0.785 (blue in the map), and developing countries are those with HDI values of 0.785 or less.** HDI values for each country are listed in the Human Development Report 2010.

The geographic boundaries on this map does not imply official endorsement or acceptance by the United Nations.

**Methodology**

The WHO Initiative on Genomics & Public Health (IGPH) will lead project implementation through the Executive Committee, and a Scientific Board will oversee the process. Box 1 lists members of the Executive Committee and of the Scientific Board.

Over 300 international experts in science and public health will be invited to the Expert Panel. The Grand Challenges project will use two rounds of Expert Panel consultation to identify (Round I), and score and prioritize suggested Grand Challenges (Round II). Responses from the Expert Panel will be anonymous between experts, and also to the Executive Committee and Scientific Board at the analysis stage. Names of the Expert Panel will be made public as part of the dissemination of results.

Members of the Expert Panel have been identified primarily through nominations by the Scientific Board. The final list of members of Expert Panel were chosen to achieve a rational representation across: developing / developed countries; communicable / non-communicable diseases; and science or technology / clinical or public health experience. Communication with experts is expected to be done by email, but also by phone and fax as necessary.

In Round I of the Expert Panel consultation, each member of the Expert Panel is asked the open-ended Grand Challenge Question:

**What do you think are the grand challenges in genomics for public health in developing countries over the next 10 years?**

Note: these Grand Challenges should be interpreted broadly, and can include priorities which have the potential for improving all aspects of public health in the developing world in the next 10 years. They may include priorities which relate to: (1) application of existing genomics-based technologies; (2) research needs; (3) policy, communication and education challenges; (4) issues around inequity (e.g. the 'genomics divide'); (5) others. Depending on responses received, the challenges may be categorized and perhaps even expanded to a list of more than ten.
In Round II of the Expert Panel consultation, each member of the Expert Panel will score identified Grand Challenges from Round I against the following six criteria:

- **Answerability**: how likely is it that the Grand Challenge will be met given expected costs, public opinion, ethical concerns, and the current state of science and the size of the gap in knowledge?
- **Effectiveness**: how likely is it that the Grand Challenge, if overcome, will generate or improve truly effective health interventions?
- **Deliverability**: how likely is it that the Grand Challenge, if overcome, will improve the delivery of existing policies and programs?
- **Maximum potential for disease burden reduction**: how likely is the Grand Challenge, if overcome, to lead to significant improvement in disease burden reduction?
- **Effect on equity**: how likely is the Grand Challenge, if overcome, to benefit those who are most underprivileged?
- **Alternatives to genomics**: how likely is it that the expected outcome, if the Grand Challenge is overcome, is only achievable if genomics is used?

**Consensus building**

The project uses structures and elements from several consensus and priority setting methods to distil consensus among members of the Expert Panel. Our method is best seen as a hybrid of components from the Delphi method and the Child Health and Nutrition Research Initiative (CHNRI) approach to setting priorities.

The Delphi method has been used for consensus building in a wide variety of fields over the last six decades, for example to identify outcome measures in clinical trials, and to identify grand challenges in chronic non-communicable diseases. The standard Delphi method is a group communication method comprised of sequential rounds of questionnaires answered anonymously by a panel with relevant expertise. After each consultation round, responses to questionnaire are coalesced by the facilitators and then fed back to the panel members. Convergence in expert opinion is then expected after one or more rounds of expert consultation. The Delphi method was chosen primarily because of successful experiences in previous complementary exercises. There is little empirical research or theoretical justification for the various methodological considerations of the Delphi technique. Most published work on the Delphi method summarizes authors' experiences. Our implementation of the Delphi method was informed by a review of experiences from similar studies.

The CHNRI methodology was proposed in 2008 as a transparent, systematic, objective and repeatable approach to setting priorities in global health research investments, and has since been used to a wide range of topics, including birth asphyxia, childhood pneumonia, mental health, primary health care, and also country-level priority setting. There are four stages to the standard CHNRI methodology: (i) defining the context and criteria for priority setting; (ii) listing and scoring research investment options by technical experts using predetermined criteria; (iii) weighting criteria according to societal values with input from other stakeholders; and (iv) computation and discussion of scores and agreement between experts.

**Major steps and time line of the project**

**Step 1, by April 2011:**
The Scientific Board will establish the scope of the project, including: possible improvement of methodology suggested by the Executive Committee, agreement on criteria against which Grand Challenges will be judged, and the definition of genomics.

**Step 2, by May 2011:**
The Scientific Board guides the selection of a broad and representative Expert Panel.
Step 3, by July 2011 (CURRENT STAGE):
Round I of Expert Panel consultation. Each member of the Expert Panel is given two weeks to answer the Grand Challenge Question listed above using a web-based questionnaire.

The Executive Committee will synthesize responses from Round I and identify a list of mutually exclusive and collectively exhaustive Grand Challenges. The Scientific Board will validate the list to make sure identified Grand Challenges are distinct and within scope.

Step 4, by September 2011:
Round II of Expert Panel consultation. Each member of the Expert Panel (respondents and non-respondents from Round I) will be presented with the list of Grand Challenges identified in Round I and are asked to score each of the Grand Challenges from the list against each of the predetermined criteria. The scoring is comprised of answering three simple questions to each criterion, that is a total of 18 questions. For each criterion, questions are jointly used to assess the likelihood or collective optimism of panellists that the proposed Grand Challenge will satisfy each of the criteria. Box 2 outlines the questions to the criteria. To each question, answer options are: Yes / no; not informed enough to answer; informed, but neither agree nor disagree.

The Executive Committee will combine the responses and produce a point score for each Grand Challenge and produce a consolidated list of top 10 Grand Challenges based on the weighting and scoring of panellists.

Step 5, by October 2011:
The Scientific Board will be presented with the top 10 Grand Challenges from the previous step, and will be asked to classify the identified Grand Challenges into goals and to generate a list of specific research needed to address each goal.

Step 6, by April 2012:
Dissemination to WHO Member States, and wider dissemination that will include a peer-reviewed journal article, and which may also include conference presentations, and regional and country workshops.
Box 1. Members of the Executive Committee implementing the project, and of the Scientific Board overseeing the project.

**Executive Committee:**
- Tikki Pang (Switzerland, Director of the WHO Department of Research Policy & Cooperation).
- Mikkel Z Oestergaard (Switzerland, WHO Initiative on Genomics & Public Health).
- Other WHO staff, as required.

**Scientific Board:**
- Tikki Pang - Chair (Switzerland, World Health Organization).
- Josefina Coloma (USA, University of California, Berkeley).
- James Evans (USA, University of North Carolina).
- Eva Harris (USA, University of California, Berkeley).
- Gerardo Jimenez-Sanchez (Mexico, OECD).
- Leo ten Kate (Holland, VU University Amsterdam).
- Edison Liu (Singapore, Genome Institute of Singapore).
- Sangkot Marzuki (Indonesia, Indonesian Academy of Sciences & Eijkman Institute for Molecular Biology).
- Muin Khoury (USA, Center for Disease Control and Prevention).
- Vural Ozdemir (Canada, McGill University).
- Mark Perkins (Switzerland, Foundation for Innovative Diagnostics).
- Raj Ramesar (South Africa, MRC Human Genetics Unit).
- Charles Rotimi (USA, Center for Research on Genomics and Global Health, NIH)
- Igor Rudan (Croatia, University of Split).
- Magdalena Skipper (UK, Nature Publishing Group).
- David Weatherall (UK, University of Oxford).
- Henry Yang (China, BGI).
- Yongyuth Yuthavong (Thailand, National Center For Genetic Engineering and Biotechnology).
Box 2. Questions asked in Round II of the panel consultation to each proposed Grand Challenge.

**CRITERION 1: ANSWERABILITY**

1. Would you say the Grand Challenge is well framed and endpoints are well defined?

2. Based on: (i) the level of existing capacity and knowledge and (ii) the size of the gap from current level of capacity and knowledge to the proposed endpoints; would you say that a research and or public health strategy can be designed to reach the proposed endpoints?

3. Do you think that a research and or public health strategy designed to reach the proposed endpoints would be possible to implement given expected costs, public opinion, ethical concerns, and the current state of capacity and knowledge and the size of the gap in capacity and knowledge?

**CRITERION 2: EFFECTIVENESS**

1. Based on the best existing evidence and knowledge, would an intervention which could be developed/improved if the Grand Challenge was overcome be efficacious?

2. Based on the best existing evidence and knowledge, would the intervention which would be developed/improved if the Grand Challenge was overcome be effective?

3. If the answers to either of the previous two questions are positive, would you say that the evidence upon which these opinions are based is of high quality?

**CRITERION 3: DELIVERABILITY**

1. Taking into account the level of difficulty with intervention delivery from the perspective of the intervention itself (e.g., design, standardizability, safety), the infrastructure required (e.g., human resources, health facilities, communication and transport infrastructure) and users of the intervention (e.g., need for change of attitudes or beliefs, supervision, existing demand), would you say that the endpoints if the Grand Challenge was overcome would be deliverable within the context of interest?

2. Taking into account the resources available to implement the intervention, would you say that the endpoints if the Grand Challenge was overcome would be affordable within the context of interest?

3. Taking into account government capacity and partnership requirements (e.g., adequacy of government regulation, monitoring and enforcement; governmental intersectoral coordination, partnership with civil society and external donor agencies; favorable political climate to achieve high coverage), would you say that the endpoints if the Grand Challenge was overcome would be sustainable within the context of interest?

**CRITERION 4: MAXIMUM POTENTIAL FOR DISEASE BURDEN REDUCTION**

1. Taking into account the results of conducted intervention trials or for the new interventions the proportion of avertable burden under an ideal scenario, would you say that the successful reaching of endpoints if the Grand Challenge was overcome would have a capacity to remove 5% of disease burden or more?

2. To remove 10% of disease burden or more?

3. To remove 15% of disease burden or more?

**CRITERION 5: EFFECT ON EQUITY**

1. Would you say that the present distribution of the disease burden affects mainly the underprivileged in the population?

2. Would you say that the underprivileged would be the most likely to benefit from the results of the proposed research after its implementation?

3. Would you say that if the Grand Challenge is overcome this would have the overall potential to improve equity in disease burden distribution over the next 10 years?

**CRITERION 6: ALTERNATIVES TO GENOMICS**

1. Would you say that the expected endpoints if the Grand Challenge is overcome is only achievable if genomics is used?

2. Would you say that there is a simpler alternative / intervention not based on genomics (e.g. environmental, behavioral) that would lead to the same expected endpoints if the Grand Challenge is overcome?

3. If the answers to either of the previous two questions are positive, would you say that the evidence upon which these opinions are based is of high quality?
References
7. at http://grandchallengesgmh.nimh.nih.gov/