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# Ethical and practical challenges surrounding genetic and genomic research in developing countries

Aceme Nyika*

*African Malaria Network Trust (AMANET), P.O. Box 33207, Dar es Salaam, Tanzania*

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ABSTRACT

The nature of some potential benefits and risks associated with genetic research is different from the types of potential benefits and risks associated with other types of health research such as clinical trials and biomedical research involving humans. Whereas most potential risks associated with biomedical research or clinical trials are mainly biological in nature, potential risks associated with genetic research are mainly of socioeconomic nature. Although the peculiarity of some of the aspects of genetic research and the complexity of the science involved are acknowledged, the extent to which these characteristics hinder firstly disclosure of information to participants and their communities and secondly comprehension of the disclosed information is a practical challenge that tends to be exaggerated in some cases.

In this article, a brief overview of the various types of genetic research will be given in order to set the scene for some ethical and practical issues surrounding the research in developing countries that will be discussed subsequently. Case studies that illustrate some of the ethical and practical issues flagged will be given, followed by suggestions on possible ways of tackling some of the challenges in developing country settings. Nevertheless, genetic and genomic research could go a long way in providing knowledge that could be useful in the development of drugs and vaccines for many diseases affecting the developing countries.



## 1. Introduction

For people who are not specialized in such fields as Genetics, Molecular Biology, Biochemistry and others it may be helpful to first understand what a gene is in order to understand what genetic or genomic research is all about. Examples of living things around us and how they remain existent could help to explain the term gene and genetic information. A mango tree bears mango fruits, and if the seed contained in the mango fruit gets the right conditions such as water and nutrients it germinates and grows to become a mango tree. It does not become an orange tree, or any other type of tree for that matter, because the seed contains instructions that ensure that it grows into a mango tree. Such information in the seed is contained in cells in structures called 'genes' and the information is referred to as 'genetic information'. A gene is basically a part of a chemical molecule called Deoxyribonucleic Acid (DNA) that contains some complete set of genetic instructions for the synthesis of a particular functional protein.

Genetic research is generally aimed at understanding the way information contained in biological cells affect the functioning of organisms and the way the organisms interact with the environment. This includes developmental processes, disease pathogenesis, response to medicinal products and many more. Although the functional units of the cellular genetic material are mainly genes, other parts of the genetic material may affect the way the genes work and they may also be the focus of genetic studies. Examples include such sequences as promoters that are critical for the functioning of genes. Indeed it should be acknowledged that overall, there are various potential benefits of genetic research.

Ethical issues surrounding genetic research have been shaped to a large extent by the impact of technological development in that field and the tendency of researchers and funders to engage in collaborative research projects which inevitably cut across geographical, political, socioeconomic and cultural boundaries. In the past few decades there has been an increase in genetic epidemiological research focusing on Mendelian, single gene disorders such as cystic fibrosis, haemophilia, Huntington's disease, myotic dystrophy and neurofibromatosis as well as on complex diseases. Genetic epidemiological studies may be based on data of diseases or traits derived from families, ethnic groups, communities or populations.

The advent of new high throughput genotyping technology in general and the Human Genome Project in particular has made genome-wide analyses feasible, thus facilitating genomic research on multi-gene, multi-factorial diseases such as cancer, malaria, dia-

* Tel.: +255 22 2700018; fax: +255 22 2700380.
*E-mail address:* anyika@amanet-trust.org.

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betes mellitus, heart disease, stroke, hypertension, schizophrenia, depression, congenital abnormalities and asthma. These complex diseases are influenced by both genes and some environmental factors. Genetic epidemiological research aimed at investigating causal pathways for diseases that result from interactions between genetic and environmental factors usually involves use of DNA samples from large populations and may generate databases with genetic, phenotypic, clinical and/or sociodemographic data. Although people who participate in genetic research might give informed consent in their own individual capacities, their participation and or the data generated from such research could affect their families, communities, ethnic groups, and or populations in one way or another. Thus the potential risks and benefits of genetic research could therefore be to do more with families, communities, ethnic groups or populations than individual sample donors.

In the case of international collaborative genetic research projects focusing on diseases that are prevalent in developing countries, there is usually South-to-North shipment of samples to high-tech laboratories in developed countries. DNA samples for genetic research are either collected prospectively or the DNA is extracted from stored samples. However, the use of stored human samples is a challenge that has sparked debate globally (Hansson et al., 2006; Wendler and Emanuel, 2002). The stored samples could have accumulated from routine diagnostic and treatment activities of health institutions or from health research conducted years ago. In light of the ethical, legal and socioeconomic issues surrounding genetic research and the use of stored samples, most developed countries have come up with legislative and regulatory frameworks aimed at addressing the pertinent issues (NIH Office of Protection from Research Risks, 1993; Data protection Act, 1998; CCNE, 2003; Genetic Information Nondiscrimination Act (GINA), 2008). Although in some international collaborative research projects focusing on diseases of the poor the bulk of samples for genetic research, either newly collected or from archives, originates from developing countries, development of the necessary frameworks for genetic research and use of archived samples is still in the infancy stages in most developing countries.

## 2. Genetic and genomic research

In general, any research involving studying of gene(s) is referred to as 'genetic research'. However, it is important to differentiate between 'genetic research' and 'genomic research' because the ethical issues surrounding the two types of research are not necessarily the same. Genetic research focuses on certain genes, whereas genomic research focuses on the whole set of genes, the genome. For instance, a study may look at some aspect of the gene that causes Sickle Cell Disease, in which case only that part of the DNA that constitutes the Sickle Cell Disease gene would be analysed.

In contrast, in genomic research other parts of the whole genome are also analysed, which means that the researchers obtain a lot more genetic information than what their study may be focusing on. Thus if a genomic study aimed at understanding the genetic factors associated with malaria is conducted, other genetic information related to other diseases and conditions as well as paternity may be available to the researchers. Genetic or genomic research could be further divided into different types based on the use of the genetic information obtainable. The specialized areas of genetic or genomic research are particularly important in the field of drug and vaccine development, which is a field that raises the issue of availability and affordability of research products to the majority of developing countries. However, the term 'genetic research' is generally used in its broad sense, encompassing both genetic and genomic research.

### 2.1. Pharmacogenetics

In simple terms, this is the study of genes which influence people's responses to drugs. Different people respond differently to the same drug partially due to differences in the genetic information contained in specific genes. Such genetic variation generally affects the biochemical functioning of drug metabolising enzymes which play a critical role in the safety and efficacy of drugs.

An example that illustrates the practical importance of pharmacogenetics is the gene that codes for an enzyme called thiopurine methyltransferase (TPMT), which metabolises the drugs azathioprine and 6-mercaptopurine that are used to treat childhood leukaemia (Lennard, 2002; Schaeffeler et al., 2003). People with the genetic variation that causes a deficiency in TPMT use an alternative biochemical pathway to metabolise the two drugs, but the alternative pathway produces a product (a metabolite) that is toxic to bone marrow. Thus people deficient in TPMT are at risk of potentially fatal bone marrow suppression. Pharmacogenetic tests for TPMT can therefore minimize the potential risk of bone marrow suppression as a serious adverse drug reaction. In other words, azathioprine and 6-mercatopurine should not be prescribed to patients shown by the TPMT test to be deficient in the enzyme.

Although such tests may not be available or affordable to the majority of populations in most developing countries, a few developing countries that have been experiencing some economic growth are making progress in terms of translating research findings into products. Examples are Brazil, Indonesia, India, Vietnam and South Africa. Such development could be attributed to policies and regulations that promote benefit sharing through technology transfer and channelling of a proportion of proceeds arising from knowledge derived from genetic or genomic research back to the communities that participated in the research.

### 2.2. Pharmacogenomics

Unlike pharmacogenetics which focuses on a few genes, pharmacogenomics is based on analysis of the whole genome, and is aimed at optimising a patient's drug therapy in light of the patient's genetic information obtained from the whole genome. This approach of optimising drug therapy on the basis of a person's overall genetic information is called 'personalised medicine', and has become more promising after the completion of the Human Genome Project. It should be pointed out that the majority of the populations in the developing world may not benefit from such high-tech approaches due to prevailing socioeconomic factors, and stakeholders should always make concerted collective efforts to ensure availability and affordability. The need to pay attention to the interests of communities has been highlighted (Weijer and Miller, 2004).

### 2.3. Genomic epidemiological research

Complex diseases are caused by a combination of environmental and genetic factors. Examples of such complex diseases are cancer, asthma, heart disease, diabetes, Alzheimer's disease, schizophrenia and atherosclerosis. Interactions of multiple genes across the whole genome, together with various environmental factors, cause these illnesses. In order to gather as much knowledge about the multifactorial genetic and environmental causes of the complex diseases as possible, clinical, sociodemographic and genomic data of large samples of people have to be collected in population-based genomic epidemiological studies.

Findings from genetic or genomic epidemiological studies could generate data useful in the development of drugs or vaccines for diseases such as malaria, HIV/AIDS and tuberculosis that negatively affect most developing countries. Since large sample sizes

are required for such epidemiological research, the tendency has been to use whatever stored samples for which the corresponding clinical and sociodemographic data are available in addition to newly collected samples and other relevant data. Although on one hand this approach prevents destruction of human samples that could be useful in health research, on the other hand there are some pertinent ethical and practical issues that arise.

### 2.4. Genetic or genomic research on pathogens

Knowledge about the genetics of pathogens and how they interact with their hosts may help researchers to design effective vaccines or drugs for various bacterial, viral, fungal or parasitic diseases. However, genetic or genomic research on pathogens uses samples from the pathogens and not human samples. Although in some cases the pathogens may be obtained from humans, most ethical issues such as privacy and confidentiality, potential stigmatization of people, potential abuse of data generated from the research and others may not apply because the findings will be pertaining to the pathogens or their interaction with their hosts and not to humans per se. However, genetically modified organisms, which may be derived from research that involves pathogens and other non-human organisms, may have ethical implications by virtue of them interacting or sharing the same environment with humans.

## 3. Other related types of research

Although the volume of some types of research related to genetic or genomic research may not be relatively huge in the developing world, one major concern is the lack of appropriate guidelines or laws that clarify which of these related types of research, which generally tend to be controversial, are permissible and which types are prohibited out rightly. One of the major criticisms is that these types of research tamper with the moral integrity of humanity. Some specialized types of research such as those outlined below may raise more or less similar ethical issues to those raised by genetic or genomic research.

### 3.1. Cloning research

In simple terms, cloning is a scientific process of creating an identical copy of something. Cloning can be at the molecular or cellular level, and 'cloned' organisms can be derived from the cloned cells. Cloning can be broadly divided into therapeutic cloning, which is generally widely acceptable and reproductive cloning, which is very controversial because some opponents argue that it basically devalues the worth of a human being.

### 3.2. Research on genetically modified foods

The advent of biotechnology has led to the intensification of research on genetically modified organisms (GMOs). Although such genetically modified organisms may have some beneficial properties, they raise quite a number of ethical and socioeconomic questions. In general, the GMOs are said to be the solution for the problems of developing countries that face perpetual food shortages because of various factors. Microbial genetic or genomic research has the potential to indirectly benefit human beings by alleviating some of the environmental problems that the world faces today. However, there are fears that some GMOs may not be safe to human beings and the environment. It has also been argued that GMOs could actually perpetuate the dependency of the developing world on the developed countries that are in control of the technology and the relevant resources. Thus there are opposing schools of thought regarding research aimed at developing GMOs for the world in general and for developing countries in particular.

## 4. Possible sources of samples for genetic or genomic research

Human samples include a range of human biological materials from sub-cellular molecules like DNA and cytoplasmic organelles (e.g. mitochondria, enzymes), to cells and tissues (such as blood, muscle and skin), gametes (sperms and ova), embryos, fetuses, organs (such as heart, kidney, liver, bladder, placenta), secretions (such as saliva) and waste material (such as urine, feces, hair, nail clippings and sweat). DNA samples can be extracted from these materials for research purposes, and lack of appropriate informed consent (where possible) and relevant approvals could violate the rights of sample donors and their communities. In addition, researchers should be sensitive to cultural or traditional norms and practices when collecting samples. Various possible sources of such human materials are outlined below.

### 4.1. Samples collected prospectively with informed consent from participants

Samples for genetic studies may be collected prospectively, ideally after obtaining ethical approval from relevant Ethics Review Committee(s) and informed consent from the participants. It is important for researchers to ensure that the informed consent captures all issues that are of concern to the participants and their communities. Such concerns could be found out by engaging with the target communities in advance of the genetic research. The 'let-sleeping dogs lie' approach may backfire in future when issues that had not been addressed or clarified adequately crop up. Thus prospective collection of samples for genetic research is an appropriate opportunity to deal with pertinent ethical and practical issues, rather than as and when the issues manifest as roadblocks for the research.

### 4.2. Archived samples stored in health institutions

When people present to hospitals with various illnesses, samples of human tissues or fluids are sometimes collected for diagnostic purposes. In addition, some samples may be collected to monitor effectiveness of treatment. For instance, if a patient is showing symptoms of HIV infection, a blood sample may be taken for HIV tests. If the tests confirm that the patient is HIV positive, blood samples will be collected at specified intervals to monitor the CD4 count and to determine the point in the progression of the disease when it is necessary to start antiretroviral treatment. Consequently, some blood samples collected are kept frozen for future reference. This process of collecting samples from patients is routine procedure for a variety of diseases globally. It follows therefore that health centers accumulate samples from patients.

### 4.3. Archived samples from previous research projects

Some stored samples are derived from previous research projects. Such stored samples are common at teaching hospitals where some of the clinicians undertake research in addition to practicing medicine. Thus over periods of time, stored samples build up at the teaching hospitals, and they may be used for research purposes.

### 4.4. Samples stored in national or private commercial biobanks

Some countries, especially developed countries, have developed national frameworks for systematic development and management

of national biobanks. In addition, there are private companies that are developing biobanks for commercial purposes, either currently or for the future. Although various control mechanisms have been put in place and are continuously being reviewed in most developed countries, not much has been done in the developing world. Thus it is generally easy to collect large quantities of human samples in developing countries relative to the developed countries where usually there are stringent regulations or laws. However, limited resources and other factors may hinder the ability of some developing countries to maintain biobanks, and 'off-shore' storage in developed countries may be preferred. For instance, a private cord blood bank in South Africa is a branch of a European company, Cryo-Save, and all samples collected in South Africa have to be shipped to Mechelen in Belgium for storage in an internationally accredited laboratory (http://www.cryo-save.co.za/).

### 4.5. Samples stored in police biobanks

In some countries, especially developed ones, police have powers based on Acts of Parliament to take and retain specimens from suspects and criminals. For instance, in England the Criminal Justice Act of 2003 gave the police the power to take and retain indefinitely biological specimens and fingerprints from all people arrested for recordable offences, even if the arrestees are subsequently acquitted. This is due to the fact that the technology of DNA profiling is quite advanced and is becoming increasingly robust and reliable. Consequently, large biobanks have been developed, and huge forensic DNA databases have been created.

## 5. Some ways of handling samples for research

The way samples are handled could have ethical implications. Some ways of handling samples could compromise the privacy and confidentiality of sample donors and in the case of genetic research the repercussions may go beyond the donors to affect their families, ethnic groups, communities or populations. There are a number of ways of handling samples some of which are explained below.

### 5.1. Samples with personal identifiers

Personal identifiers include such information as the name of participant, address of participant, telephone number, birth certificate number, national identification number and hospital admission number. Other information such as full date of birth, DNA, ethnic or racial group and sex might be used in combination with other personal identifiers to determine the identity of a particular person. At community/population level, such information as location (e.g. name of village, suburb, town, province, and country), name of ethnic or racial group and mother language could lead to the identification of a particular community or population.

### 5.2. Anonymized samples

These are samples that do not have any personal identifiers. Thus it is not possible to link any sample to the particular person who donated it. However, some anonymous samples may still be traced back to the community or population that donated the samples through such information as recruitment location, name of race, name of ethnic group, or mother language of the sample donors if such information is available.

### 5.3. Reversibly de-linked samples: linking code kept

If personal identifiers are removed, and the samples are given new codes, then the samples become anonymized. However if the linking code is kept, it means that the new codes can be reverted to the original sample numbers that have personal identifiers. In other words, the samples are reversibly made anonymous.

### 5.4. Irreversibly de-linked samples: linking code destroyed

Unlike reversibly de-linked samples, irreversibly de-linked samples are given new codes but the linking code is not kept but is disposed of. Thus the samples are permanently made anonymous.

## 6. Some ethical and practical issues surrounding genetic or genomic research

### 6.1. Informed consent issues

#### 6.1.1. Practicalities of disclosure of information by researchers and comprehension by participants and their communities

In order for participants to give truly informed consent to take part in research, firstly the researchers have to disclose all the critical information about the study, and secondly the prospective participants should understand the information in terms of potential risks, potential benefits and what participation will entail. In most developing countries lower levels of literacy could make it difficult to explain research, be it genetic research, biomedical research, clinical trials or any other types of research. In addition, there may not be appropriate corresponding terms for some of the scientific jargon that may need to be explained to participants. Such practical challenges could compromise comprehension of the disclosed information by the participants if researchers do not take appropriate measures and make extra efforts to address the challenges. It is important for researchers to disclose information that is critical for determining potential risks of the study versus potential benefits. Provision of both verbal and visual information may help to enhance comprehension as well as retention of the disclosed information.

#### 6.1.2. Exaggeration of impact of illiteracy on comprehension of disclosed information

Low literacy levels of the majority of the developing world populations complicates the process of obtaining informed consent and engaging with communities to some extent; information has to be explained to the prospective participants orally. Thus it requires more effort on the part of researchers than when dealing with highly literate people who may read and understand on their own instead of depending entirely on oral explanations. However, there is a tendency to exaggerate the extent to which illiteracy hinders comprehension of information that is relevant to determining the potential risks or benefits of genetic or genomic research, or any type of research for that matter.

The scientific jargon that is used in genetic or genomic research has been cited as one of the problems that negatively affect disclosure and comprehension of information. However, one does not necessarily have to understand the scientific jargon or the ATCGs that make up genes in order to understand the nature of potential risks or benefits associated with genetic or genomic research. For instance, comprehension of the fact that information obtained from a sample from a participant may reveal some information about family members or even the whole ethnic group of the participant does not necessarily require understanding of structure of genes and genomes and such processes as transcription, translation, mutations and others that are associated with expression of genes. This point is analogous to medical treatment because a patient does not necessarily have to understand the chemical structure and mode of action of the prescribed medicine in order to understand the potential side effects and contraindications which are to be explained by the medical personnel.

*6.1.3. Obtaining voluntary informed consent: socioeconomic and cultural factors*

For poor populations in most developing countries, participation in research may be the only way to access health care due to prevailing socioeconomic factors. Consequently, voluntariness in the informed consent process may be compromised, especially in genetic or genomic research projects conducted in hospital settings. This challenge is captured in case study 2; Jayaguru and his family went through the informed consent process and agreed to participate in the genetic study yet he later went to the hospital to ask the researchers for the cause of his child's ambiguous genitalia which was not the focus of the study at all. If they had resources they would have taken their child for the appropriate medical intervention without having to try and take advantage of participation in a study. Thus the family may not have voluntarily joined the study but may have been compelled by their predicament and poverty to take part. It is worth noting that Jayaguru suggested to the researchers that his other wife should also donate a sample for the study and she agreed. In most cultures of developing countries, a husband is the head of the family and makes decisions on behalf of the family. It may be difficult for the researchers to know whether or not the wife voluntarily accepted to donate the blood sample. In addition, a participatory decision-making process that involves other family members is typical of many cultures in developing countries (DeCosta et al., 2004; Nyika et al., 2009), especially for such studies as genetic or genomic research that may have implications for the whole family or clan.

*6.1.4. Use of archived samples for genetic or genomic research*

For archived samples that were collected long time ago, there may be no informed consent at all given by the sample donors in the first place or if informed consent was obtained, it may not cover the new studies that would be conducted in future. Thus, in general, either archived samples are used without any informed consent from the sample donors, ideally after an ethical approval has been obtained, or the consent given previously may not explicitly allow future use of the samples.

*6.1.5. Consent for samples to be stored for future research*

Nowadays the informed consent used by researchers in some genetic or genomic studies includes a statement to the effect that samples will be stored for future genetic or genomic studies, and in some cases the future use of samples is not disease-specific. Thus participants give an open-ended consent, analogous to issuing a blank signed cheque which has no payee, no amount and no date. In light of this practice, how should Ethics Review Committees in developing countries deal with the informed consent for genetic/genomic studies?

Unlike some developed countries like the USA where attempts to know the views of sample donors on use of stored samples in future genetic or genomic research have been made (Wendler and Emanuel, 2002), there are no reports in the public domain pertaining to views of at least some sample donors in developing countries. Such views should be factored into the informed consent as well as relevant ethical and legal frameworks that may be developed for genetic or genomic research.

*6.1.6. Pseudo-community engagement*

Due to the nature of genetic or genomic research, community engagement helps to ensure that there is awareness about the research at community level and not just at the individual level. The communities from which samples are collected should know about the genetic or genomic studies being conducted. However, there are activities that are generally considered to be 'community engagement activities' when in actual fact they do not involve dealing with the ordinary members of the targeted communities. Such 'pseudo-community engagement' activities could be favored by researchers because they are relatively less demanding in terms of time required and resources. The first example is the establishment of some 'Advisory Committee' or 'Advisory Board' whose mandate is to give advice to the researchers on ethical and community-related issues. The members of such committees or boards are usually renowned, influential professionals from the countries or communities where the samples originate from. Although such professionals may advise the researchers on best ways of approaching the targeted communities, engaging with them should not substitute engagement with the ordinary target communities. In some cases the members of such committees or boards, who are generally from the elite and educated class and are out of touch with the poor people in the villages or high-density townships, are too busy to interact with the ordinary members of communities so as to know the issues that matter to the communities of interest.

The second example of pseudo-community engagement activity is the engagement of research team members from the target countries or communities from which samples are drawn; consultative meetings with such local research team members are not community engagement activities, although ideas on how real community engagement could be done may come from such consultations. A third involves provision of scholarships by the researchers to enable postgraduate studies focusing on community related issues or other ethical issues surrounding genetic or genomic research. Although findings from such postgraduate studies could inform the researchers as to what the issues to be addressed are, the postgraduate studies and scholarships do not constitute community engagement. These examples are covered in case study 1.

**Case study 1: Open-ended informed consent and ethical approval for storage of samples for possible future research**

A proposal for a 4-year international collaborative genetic study to investigate the genetic basis of 'natural resistance' to a certain infectious disease was approved by the relevant Ethics Review Committees in participating countries in the developed and developing countries. The informed consent document contained all the relevant information about the study such as (i) the purpose of the study, (ii) the procedures involved, (iii) the details of local collaborators in the developing countries where the disease was prevalent and samples were to be collected, and (iv) collaborators in a developed country where genome-wide analysis of the samples was to be done. There was a clause in the informed consent document to the effect that DNA samples collected would be stored for possible future studies on the same disease and 'other related diseases'. Required samples were collected within a shorter period than anticipated and shipped to the high-tech laboratory in the developed country for analysis. The study was completed successfully and three papers were published in very reputable journals with all the collaborators as co-authors.

Three years after the successful completion of the consortial research project, the researchers in the developed country successfully applied for a big collaborative research grant firstly to conduct further genetic studies on the same disease investigated in the previous consortial project using the stored samples and secondly to investigate other related diseases using the same samples. The collaboration was with another group of researchers in the same developed country who had decades of experience in some of the diseases that were the focus of the new collaborative project. Since the samples were already collected and were in the custody of the researchers in the developed country, it was deemed unnecessary to form any consortium with researchers from the developing countries. In the grant application the researchers indicated that

they already had informed consent for all the samples that were to be used, and that they had ethical approval from the relevant Ethics Review Committees in the developing countries from which the samples were collected which permitted them to store the samples for possible future research.
When asked by their institutions if the communities in the developing countries from which sample donors were drawn had been adequately engaged and informed about the previous plus the new studies, the researchers assured their institutions that all necessary measures had been taken to ensure that the studies were ethical. The measures included (i) approval from Ethics Review Committees in the developing countries that were part of the consortium, (ii) an advisory group made up of internationally renowned African professionals that was set up to ensure that the study was ethical and scientifically sound, (iii) engagement of the communities from which sample donors were drawn was done through workshops organized for participating researchers based in the African countries from which samples were collected, and (iv) five post-graduate students from the participating developing countries had been sponsored by the previous consortial project to conduct studies on informed consent in genetic studies and community perceptions of genetic studies. However, some critics argued that the activities implemented by the researchers could be regarded as 'pseudo-community engagement' which although addressing the issue of capacity building, sidelined the ordinary community members or were merely community-related research activities for academic purposes.

### 6.2. Peculiarity of some potential risks

#### 6.2.1. Information about others may be deduced from participants

Although the issue of privacy and confidentiality is important in all health research studies, it is more critical in genetic or genomic research since information about other people, such as family members, ethnic groups, communities or populations who may not be participating in the research may be deduced from the findings from those who participated. This type of risk may not be dealt with by the researchers and participants alone but may require engagement of other stakeholders who may be affected by findings of the research. In addition, divulgence of genetic information, knowingly or inadvertently, may reveal personal or family secrets like false paternity, which could destroy relationships and cause social problems. It is therefore critical that researchers handle genetic information responsibly.

**Case study 2: Some unusual potential risks and practicalities in genetic studies**

Researchers obtained ethical approval to conduct a genomic epidemiological study on genetic factors associated with severe malaria. Samples for the study were to be obtained from children with severe malaria as well as from the biological mothers and fathers of the sick children, while controls were to be from matched participants not suffering from severe malaria. Jaya, a two and half-year old boy from Zuva village suffering from severe malaria and referred to Chipatara referral hospital by a local clinic in Zuva, was brought to the hospital in an ambulance accompanied by Sarah, a woman in her mid-30s. Sarah reported that she was the mother of Jaya, and the child was hospitalised. In addition to treating Zuva, the nurses explained to Sarah about the genomic study that was going on and asked her if she would like Jaya to participate. Sarah said she wanted Jaya to participate, and the nurses went through the informed consent process, explaining everything about the study and giving Sarah time to ask questions. Sarah said she understood and she gave proxy consent by putting her thumb print on the informed consent form since she was illiterate and could not sign. Another nurse who was present during the informed consent process signed the proxy consent form as a witness.
When Jaya recovered, the research team offered Sarah transport to her village, which was 60 km away, in order for blood sample to be collected from Jaya's father, Jayaguru. Upon arrival at Sarah's home, Jayaguru happily gave informed consent after explanations by the researchers and donated a blood sample. He even suggested that Jaya's other mother, Vahosi, could also be asked to donate a sample. This confused the researchers, and it later turned out that Vahosi was the biological mother of Jaya and Sarah was the third and youngest wife of Jayaguru. Vahosi had a 6-week old baby hence could not accompany Jaya to hospital. Vahosi gave informed consent and donated a sample.
After about two months, Jayaguru went to Chipatara hospital to ask what caused Jaya to have both male and female genitalia, and whether the doctors were going to make the child a boy or girl. He also wanted to know why Jaya had fallen sick while Tafu, his sibling of more or less the same age and a son of the second wife, did not fall sick yet they were almost always together. The research team explained to him that the study was focused on severe malaria, and not the issue of ambiguous genitalia, and that the issue of susceptibility to severe malaria might be answered only after all the data from many countries are analysed. A heated argument ensued, and Jayaguru requested to withdraw from the study and he wanted the researchers to give him back the 4 blood samples from his family. The researchers checked their records and found out that 3 of the 4 samples had been sent to the high-tech lab in the collaborating developed country for genotyping. However, the 3 samples had been destroyed because the lab discovered that Jayaguru was not the true biological father of Jaya, hence the set of 3 samples could not be used in the study. The researchers were then not sure how to handle the matter.

#### 6.2.2. Distress if some predisposition is discovered and disclosed

If participation in a genetic or genomic study reveals predisposition to some disease and the participant is informed, such information could cause distress. If a proven intervention for the condition discovered exists, then the participant may benefit from the early detection provided the intervention is accessible. However, if the proven intervention is not accessible to the participant and the researchers are not able to assist, or if no proven intervention exists, then such disclosure of the findings may cause severe harm in terms of distress. Thus genetic testing should not be done willy-nilly; a plan to deal with test outcomes should be in place upfront otherwise the genetic tests should not be done.

#### 6.2.3. Potential stigmatization: perceived or real

Findings from population-based studies may apply to the whole population, community or ethnic group from which the individual participants were drawn. Thus participation of some members of the target group will affect, positively or negatively, members of the same group who did not participate. Efforts to minimize the risk of stigmatization should always be made and should be planned upfront so as to be included in the timeframe and budgets. Community engagement is one useful method of minimizing the potential risk of stigmatization. Case study 3 illustrates an example of potential stigmatization of a community.

**Case study 3: Genetic studies on Ashkenazi Jews and fears of stigmatization**

In the early 1990s genetic studies were conducted on the Ashkenazi Jews aimed at determining genetic factors associated with breast cancer. The studies showed that the breast cancer gene 1(BRCA1) and breast cancer gene 2 (BRCA2) mutations, which are associated with predisposition to breast cancer, occurred at significantly higher rates in Ashkenazi Jews than the general population (Rothenberg, 1997). Prior to the publication of these findings, the Jewish people were generally comfortable participating in subsequent confirmatory studies. However, when another predisposition to colorectal cancer due to higher prevalence of the APCI1307k allele in the Ashkenazi Jews was reported, some Jewish community leaders started to discourage Jews from participating in further genetic studies because they feared stigmatization of Jews (Woodage et al., 1998; Rothenberg and Rutkin, 1998).

Although no harm may have been intentionally caused by the researchers, the findings may have caused negative societal effects inadvertently. Thus precautions should be taken when dealing with genetic research because firstly socioeconomic risks may be at the family or community level and not at the level of the individual who may have given consent to participate in the research and secondly the risks may materialize long after the genetic research projects have been completed.

*6.2.4. Therapeutic misconception*

Case study 2 shows how therapeutic misconception may lead to misunderstandings between researchers and their institutions on one hand and research participants and their families and communities on the other. It seems that Sarah and her husband thought that the genomic epidemiological research that was being conducted was going to immediately answer questions about the two conditions affecting their child, namely severe illness and ambiguous genitalia. In cases where recruitment of participants for genetic research is done in hospital settings and by medical personnel who also provide health care services, the chance of participants mistakenly considering proposed research to be part of treatment is arguably higher than when recruitment is not in clinical settings.

*6.2.5. Genetic discrimination: health insurance and employment*

Whereas in most developed countries the fear of potential discrimination mainly by health insurance companies and by employers due to divulgence of information about genetic predisposition to some disorder is a major consideration when prospective participants decide whether or not to take part in genetic research (Clayton, 2003; Hamvas et al., 2004), that fear is relatively less in developing world settings. The main reason for the difference is that the majority of people who participate in the genetic research in developing countries are not formally employed and do not have any health insurance in the first place. Thus although it may be a major risk that participants in developed countries may worry about, it is a relatively remote risk in most developing countries.

*6.3. Nature of potential benefits*

*6.3.1. Generation of knowledge as opposed to direct benefits*

Whereas other types of research such as clinical trials may benefit the participants directly in one way or the other, genetic or genomic research tends to generate knowledge which may or may not lead to some intervention or policy. For instance, at the time the early studies on phenylketonuria were conducted, the immediate benefits that would have been foreseen could have been nothing more than knowledge. As explained in case study 4, the knowledge generated from genetic research on PKU was translated into diagnostic methods decades after the studies.

**Case study 4: Nature of some potential benefits of genetic studies**

Phenylketonuria (PKU), which is due to defective phenylalanine 4-hydroxylase, causes severe mental retardation, often with fair skin, eczema and epilepsy. Genetic studies on PKU started as long ago as 1953, involving some samples taken from patients suffering from PKU. However, it was not until decades later that some of the cumulative knowledge generated from the genetic studies on PKU was translated into diagnostic tools or interventions that now benefit people with the defective enzyme in some countries especially developed countries. For instance, nowadays diagnostic tests such as the Guthrie test and the Fluorometric assay have been developed and are in use. In addition, preventive interventions such as dietary modifications have been shown to prevent mental retardation from PKU (Burke et al., 2002).

Nowadays, routine screening of newborns in some countries enables early detection of PKU and proper care. PKU patients who participated in early studies may not have benefited from the diagnostic tests eventually developed. Thus some potential benefits of genetic research may not be at individual level and may not be immediate. In some cases the genetic research may yield knowledge that may or may not eventually lead to general improvement of the health of mankind.

*6.3.2. Interventions may not be immediate and may not be to the participants of the research*

The benefits derived from knowledge generated from genetic or genomic research may come decades after the research was done, and may not be to the participants who participated in the research. This is unlike some studies such as clinical trials in which participants may benefit to some extent from the investigational product or the active control product. In addition, although the research to be conducted in future using stored samples could generate generalizable knowledge that could benefit mankind, in some cases the future research is driven by pharmaceutical companies who benefit commercially while the donors may not have access to the commercial products derived from the research on their samples. For instance some of the participants who were involved in the early genetic studies on phenylketonuria may not have lived long enough to see the interventions derived from the knowledge generated from the studies. Even for those who were still alive when the diagnostic tests were eventually developed, they may never have become aware of the eventual translation of the knowledge generated from the studies into diagnostic tests.

*6.3.3. Sharing of samples and data by researchers and their institutions*

Due to the nature of some genetic/genomic epidemiological studies focusing on diseases of the poor countries, researchers from the North and from the South tend to form consortia of many institutions so as to be able to achieve the required large sample sizes within reasonable period of time. Local collaborators in the participating developing countries are usually the ones who provide the clinical data, the sociodemographic data and the samples from the populations in the developing countries for analysis.

The collaborators from the developed countries usually are the PIs of the research grants, have the technology in their laboratories for the genetic/genomic analyses, and may be in control of all the collected data at the end of a given project. Thus although the

local collaborating researchers may benefit during the course of the project from such activities as capacity building, when future research that may have been referred to in the informed consent happens to start, they may not necessarily be part of it.

### 6.4. Some practical challenges

#### 6.4.1. Disclosure of sensitive findings

One major challenge is how to handle findings that may cause some form of harm to participants, their families or community. One example is discovery of genetic predispositions for health conditions that are not the focus of the current genetic or genomic study. If a proven intervention is available and accessible to the participants concerned or their relatives, then there may not be a big challenge. However, if there is no proven intervention, or if a proven intervention exists but is not accessible to the participants concerned, then an ethical dilemma as to whether to disclose the findings or not arises. Another example is a discovery of false paternity which could cause social problems if not handled properly. There is also the issue of ancillary care for conditions that may not be the focus of the study; absence of proven treatment, or if proven treatment exists, issues of sustainability of ancillary care that may be provided by researchers may be a practical challenge.

#### 6.4.2. Inadequate capacity to store samples and to carry out high-tech analyses

Currently, most developing countries do not have the capacity to store large quantities of samples for genetic or genomic research on a long term basis; hence samples are shipped to developed countries for storage. The other reason for the shipment of the samples is that most developing countries do not have high-tech laboratories capable of doing high-tech analyses. Consequently, most developing countries play the role of 'sample collection ground'. Although the benefits derived from research may eventually spread to all parts of the world, the developing countries could probably realize more immediate as well as long-term benefits if they were capable of storing and analysing samples locally than when those activities are done off-shore.

#### 6.4.3. Inadequate capacity to make optimal use of the data generated globally

Various types of data generated from many genetic and genomic research projects conducted worldwide are being made available in the public domain. For instance, the human genome is almost completely sequenced, with only parts of centromeres, telomeres and some loci containing multigene families still outstanding due to technological constraints (Venter et al., 2001; International Human Genome Sequencing Consortium, 2004). Another example is the human genome haplotype map which shows over a million single nucleotide polymorphisms (SNPs) derived from 269 DNA samples from people drawn from 4 different countries, namely Nigeria, China, Japan and United States of America (International HapMap Consortium, 2005). In addition, various sequencing projects focusing on pathogens and other organisms have been completed or are in progress and information is freely available (http://www.sanger.ac.uk/Projects/Pathogens/). However, most developing countries may have limited capacity in terms of resources and expertise to make maximum use of the information in their own priority research. Thus although most of the developing countries may be involved in the genetic or genomic research in one way or another, they may face challenges when it comes to utilization of the findings and translation of the findings into commercializable products or policies that would contribute towards the reduction of the disease burden of their populations.

#### 6.4.4. Intellectual property rights (IPR) issues

Another potential challenge is the issue of intellectual property rights for inventions based on findings from genetic or genomic studies. For instance, suppose a certain ethnic group is observed to be resistant to some disease and scientists investigate the genetic factors associated with the resistance. If such studies were to provide leads for the development of vaccine or therapeutic drug for the disease, the scientists who invented the vaccine or drug would patent their invention. However, the ethnic group from which the genetic factor was discovered may feel that they should benefit in one way or another. The challenge could be exacerbated if the research involved international collaborative research involving researchers, institutions and sample donors from developing and developed countries. One real life example is the controversy sparked by alleged efforts to patent findings from international collaborative genomic research that involved some DNA samples collected from various countries including Tanzania, Kenya, Sudan, South Africa and USA and researchers from African and American institutions (Jordan, 2009; Tishkoff et al., 2009). It is therefore imperative that the issues of IPR and patents be discussed and agreed on upfront. In addition, efforts should be made to explore feasible mechanisms of ensuring that participants and their communities who participated in the research that led to commercializable findings benefit in one way or another. There may be need to involve various stakeholders in such mechanisms.

## 7. Possible ways of addressing some of the ethical issues

### 7.1. Having explicit informed consent for samples used in genetic research

The informed consent should explicitly explain all the pertinent issues upfront, minimizing use of such vague terms as "your sample will be stored for possible future research". It should be made clear that storage of samples for possible future research per se is not unethical, but the point is that all issues pertaining to the future research should be dealt with as much as possible upfront. Thus it should be clear why there is need to store the samples in the first place, for how long the samples will be stored, who will be conducting the possible future research and whether the research will be on particular disease(s) or it will be any disease. The informed consent should also draw the attention of the participants to the peculiar nature of genetic research in terms of potential risks and potential benefits.

### 7.2. Effective review and monitoring of genetic research by ERCs/IRBs

There is need for well-trained Ethics Review Committees (ERCs) capable of teasing out the pertinent issues during review. After approval, the committees should be able to monitor the research; the monitoring should go beyond the life span of the approved project. The risks and benefits peculiar to genetic research should be adequately weighed, bearing in mind that they may be at the level of families, communities or populations rather than the individual participant. ERCs should be on the lookout for future research that may be inappropriately based on stored samples and ethical approval given for previous studies.

### 7.3. Development of national regulatory and/or legal frameworks for genetic research

Existing regulations were developed from a developed world perspective and may not address some of the issues prevailing in the developing world settings. For instance, whereas it may be very important for guidelines developed in the developed world to

address the potential risk of insurance companies discriminating against insurance policy holders on the basis of some genetic predisposition, the majority of sample donors in the developing world are drawn from poor communities who may not even know what health insurance is, let alone having such health insurance policies. Thus the issue of potential discrimination by health insurance companies may not be as important a risk for developing countries as it probably is for the developed countries.

### 7.4. Material transfer agreements

In cases that involve transfer of samples for genetic or genomic research from one research institution to another, be they in the same country or different countries, it is critical to have a material transfer agreement (MTA) that explicitly states all the details pertaining to the use of the samples. The MTA should state such details as the number of the samples to be transferred, the purpose for which they should be used, the researchers or institutions permitted to use the samples, whether or not they may be stored for possible future research and the details of such future research. It may also be necessary to state whether or not personal identifiers should be removed before transfer.

### 7.5. Community engagement

Since findings from genetic or genomic research may affect families as well as communities of the participants, it is critical to engage the ordinary communities from which participants are drawn. Although the individual participants would give their informed consent, informing the whole community about the purpose of the study and the potential use of the findings could go a long way in minimizing the risk of angering the community if it has to 'discover' one way or the other that research which could affect them was conducted without their knowledge. There are various models of community engagement (Tindana et al., 2007) and researchers have to find out the model or models that would be acceptable in the particular communities where the study is to be conducted. It should be emphasized that community engagement should be planned upfront so that it is included in the budget and in the project timeframe just like other project activities. The HapMap project, an international consortium that conducted genetic research in Japan, China, Canada, United Kingdom and Nigeria, demonstrated how advance planning and practical commitment could help to minimize potential challenges that hinder community engagement (International HapMap Consortium, 2003, 2004).

### 7.6. Genetic counseling

It is critical for researchers and medical personnel to be continuously trained in genetic counseling as recent findings from genetic research lead to new interventions. The factors that have to be considered and discussed include the availability of effective proven interventions in the case of genetic predisposition to certain diseases. However, due to socioeconomic problems prevailing in most developing countries, some interventions may not be accessible even if they are available in the rich countries.

It should also be acknowledged that for certain diseases accumulated knowledge generated from genetic research may not necessarily lead to effective interventions that could help patients suffering from the particular diseases. One good example is sickle cell disease (SCD), research on which has revealed the SCD gene and the mutations that cause malfunctioning of the encoded protein, yet there is not yet a proven corrective intervention although management of the disease through treatment helps the patients. A major point to be explained is that detection of genetic predisposition to a certain disease in pre-symptomatic people gives the probability of developing the disease but does not necessarily mean that one will certainly develop the disease. Consequently, it is critical for laboratory genetic testing to be done and interpreted in light of family medical history.

In the case of antenatal counseling a major challenge in the developing countries is the issue of availability and accessibility of necessary interventions. For instance, whereas simple methods of antenatal detection of abnormal haemoglobin are relatively easily accessible in developed countries, in most developing countries such procedures may not be available at all. This also raises another controversial issue related to possible need for safe termination of pregnancy when abnormalities are detected. Another challenge in developing countries is that a big proportion of women may not use antenatal clinics, thus reducing the possibility of them benefiting from genetic interventions that may be available.

### 7.7. Technology transfer and capacity building

Whenever possible, efforts should be made to transfer relevant modern technology from the developed countries to the developing countries to enable industrial development that could reduce dependency on products from developed countries. Capacity building in terms of human resources and infrastructure in specialized fields would enable sustainable utilization of the available data and technology. Complementary efforts by various players such as governments, private sector, non-governmental organizations and philanthropic organizations could make such an endeavour successful. It is hoped that the noticeable development of biotechnology industries in such developing countries as South Africa, Brazil and India will not only intensify in those few countries but also spread to other developing countries.

## 8. Discussion

Genetic research has been the major driving force behind the emergence and development of 'Molecular Medicine', which is a specialized field in clinical medicine that covers diagnostic methods for detecting genetic predisposition to diseases, drug and vaccine design, gene therapy and customised drugs (pharmacogenomics). In light of such diseases as inheritable colon cancer, familial breast cancer, neurofibromatosis types 1 and 2, Huntington disease, myotonic dystrophy, Alzheimer's disease and fragile X syndrome, genetic research is critical to find out genetic factors associated with the diseases.

For some hereditary conditions such as breast or ovarian cancer, research has led to the development of effective pre-symptomatic interventions; for instance, removal of fallopian tubes and ovaries after childbearing in women with BRCA mutations has been shown to reduce the risk of developing ovarian or breast cancer by at least 75% (Kauff et al., 2002; Scheuer et al., 2002). There is also research focusing on the feasibility of incorporating edible vaccines into food products. The advancement in genetic research and development of diagnostic and therapeutic methods for some of the diseases is accompanied by a series of ethical and practical challenges that range from informed consent issues, through privacy and confidentiality concerns, to potential negative impact on families or communities (Hansson et al., 2006; Nedal et al., 2005; Offit et al., 2004). It is also critical for developing countries to have research agendas that address diseases such as malaria, HIV/AIDS, TB, and other tropical diseases most of which are causing high rates of mortality and morbidity in the developing countries compared with the so called 'lifestyle diseases' or 'diseases of longevity'.

In addition, microbial genomic research has the potential to contribute sustainable solutions to energy and environmental

problems by creating biofuels as new energy sources, safe and efficient methods of environmental remediation and development of environmental markers for early detection of pollutants. Additional potential benefits could be in the fields of agriculture where such phenotypes as resistance to disease, pests and drought as well as increased yields may be incorporated into crops through genetic techniques. As for livestock breeding, disease-resistance and productivity could be improved through genetic research.

In spite of all the potential benefits, there are ethical and practical challenges that stakeholders should be aware of and should make efforts to address. One such major challenge is simply to do with perceptions of the ordinary people in the street who are supposed to eventually appreciate and accept the benefits, some of which may not be conventional and may seem to go against value systems of the communities. Thus community views should be known in order to address any concerns that may be prevailing.

It is worth noting that community views and concerns regarding genetic studies have been explored in various developed countries. In the UK, a Wellcome Trust and MRC qualitative study on public perceptions of collection of human samples and human genetic research revealed that some participants in the study perceived genetic research as not being purpose-driven, but only for the benefit and interests of researchers and not for the good of the general society (Wellcome Trust & MRC Report, 2000). The Wellcome Trust & MRC study was conducted ahead of recruitment of a population cohort, which was to be linked to individual participants' medical information and to NHS records to facilitate follow-up.

Another study conducted in the UK by the UK Human Genetics Commission indicated that four in five respondents wanted specific informed consent for any new studies on existing samples (Human Genetics Commission, 2001). A national survey in the USA by the National Health and Nutrition Examination Survey (NHANES) showed that in 2000 there was wide acceptance of storage of human samples for future genetic research across many sociodemographic variables (McQuillan et al., 2003). In Sweden, a survey indicated that 66% of respondents were happy to waive their right to informed consent and to let ethics review committees make surrogate decisions on their behalf, but 48% of respondents felt respected if they were notified each time their sample in a biobank was used in a genetic study (Hoeyer et al., 2004).

Whereas the burden of infectious diseases is such that the majority of potential sample donors for international collaborative genetic research focusing on diseases of poverty live in developing countries, not many efforts have been made to engage with the ordinary populations in developing countries in order to find out their views on genetic or genomic research. Furthermore, unlike most developed countries that have national guidelines and or legislation focusing specifically on issues surrounding genetic research to help protect the interests of DNA sample donors, most developing countries operate without such specific guidance. Thus in most cases samples for international genetic or genomic research on some major diseases originate from communities in regions where ethical, regulatory, legal and technological frameworks specific for such human genetic studies may still be in their early developmental stages. Although the participating populations could eventually benefit from the results of the research, efforts should be made to inform and consult them about current and future research on their samples and sharing of data generated from the samples.

At the level of the individual participants, the issue of 'open-ended' consent has been debated in the context of biobanks which are common in developed countries (Hansson et al., 2006; Hoeyer et al., 2004) and for genetic research in general (McQuillan et al., 2003). In developing countries the issue of informed consent for genetic research is of major concern because there may not be effective mechanisms of protecting the interests and welfare of participants in genetic research. The potential risk of discrimination by insurance companies and employers is also a major concern in developed countries (Hamvas et al., 2004), but is not so important in the developing world where accessibility of insurance and employment to the ordinary people is limited. Indeed some developed countries such as the USA have put in place appropriate laws to protect participants in genetic research against such potential discrimination (Genetic Information Nondiscrimination Act (GINA), of 2008).

## 9. Concluding remarks

There are several specialized research fields that fall under genetic or genomic research. The term genetic research is generally used in its broad sense to cover studies focusing on specific genes as well as studies covering the whole genome. The main characteristic of the various specialized fields is that the fundamental basis is genetic information which may be obtained from various types of samples ranging from cells, through tissues and organs, to whole organisms. When the samples are collected prospectively, the issues of disclosure of information and comprehension of the disclosed information during the informed consent process arise. Since findings from genetic research may have implications on the families or communities of the participants, community engagement is critical in genetic research. In the context of developing countries, literacy levels have been observed to complicate the processes of informed consent and community engagement, but the impact of illiteracy is sometimes exaggerated since the nature of most of the potential risks of genetic research is such that high literacy levels may not necessarily be a pre-requisite for comprehension of the risks.

Utilization of available data by researchers as well as accessibility of interventions derived from genetic or genomic research may be compromised by the socioeconomic factors prevailing in the developing world. Thus although genetic research required for the development of personalised medicine is important, that may not be the immediate priority for developing countries that are experiencing huge disease burdens that may need to be tackled at population levels. Consequently, it is hoped that genetic or genomic studies that could yield findings relevant to the development of vaccines or drugs for tropical diseases will be intensified.

In addition, pre-symptomatic detection of genetic predispositions to certain diseases raises ethical and practical issues that are related not only to availability and accessibility of proven interventions, but also to cultural acceptability of the interventions. For instance, the chances of a recommendation for safe termination of pregnancy due to antenatal detection of severe abnormalities not being acceptable in developing world cultural and socioeconomic settings are arguably higher than in developed world settings. In general, community engagement and complementary efforts by such stakeholders as researchers, the public sector, the private sector, non-governmental organizations and philanthropic organizations could go a long way in enabling genetic and genomic research to effectively contribute towards addressing some of the socioeconomic problems prevailing in most developing countries.

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