

GENETIC RESEARCH IN THE GLOBAL COMMUNITY GLOBALIZATION AND HUMAN RIGHTS: BIOETHICS

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In today's world, genetics conjures up an array of images. At one extreme is the notion of genetic determinism, that genes 'Rus, with the corollary that the differences among us will be biologized. The nightmare that often follows from this line of thinking is that discrimination —treating some people worse than others— is inevitable, even though these social consequences do not necessarily follow. At the other extreme, we imagine engineering ourselves, our children, and each other, perhaps to create super people, or perhaps —one hopes inadvertently— to create monsters. In my comments today, I do not plan to address the issues of engineering although we can perhaps talk about them in the discussion session. What I do plan to focus on is difference —in genetic makeup, in power, in assets, in culture— and less frequently discussed similarity and their impact on the conduct of genetic research.

One oft overlooked truth is that we share 99.9% of our DNA sequence. This fact has often been cited to support the solidarity of humanity. At the same time, of course, all individuals, except identical twins, differ from each other and are genetically unique. A primary goal of genetics research is to understand how these differences among individuals contribute to health and disease.

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We are only beginning to understand these differences, but some of the things we have learned so far about the distribution of genetic variation potentially have tremendous impact on how we conduct research. It would be easier to design research if one of two things were true. If all variation were equally distributed in all populations, it would not matter where one conducted research, which would allow one to avoid many ethical dilemmas. But we know that this is not true. Hemoglobinopathies such as sickle cell anemia and the thalassemias are more common in people with ancestry from areas in which malaria was historically endemic. Cystic fibrosis is more common in people of northern European ancestry.

Designing research would also be easier if genetic variation correlated closely with current notions of race and ethnicity. This is not true either. The diseases I just mentioned can be found in virtually all populations, and most functional variants are distributed quite broadly. A good example can be seen in the recent paper by Wilson, et al, in which they examined the distribution of variations in cytochrome p450, a molecule critical to the metabolism of a wide array of drugs as well as many hormones. Some variants differ rather widely, while others are more similar, but no clear patterns can be seen and no bright lines can be drawn.

Variations in the organization of the human genome—the total DNA complement—also correlate poorly with race and ethnicity. Because humans are such a young species, our DNA tends to be inherited as blocks, and not completely randomly. Efforts are underway to try to identify these blocks, and the evidence so far suggests that these blocks are largely but not completely shared among all population groups. This slide adapted from a paper last year by Gabriel et al is just one example of what has been observed. So far, the evidence is limited but a major international effort is underway to map these blocks or haplotypes. That race and ethnicity are not powerful predictors of genetic variation is not particularly surprising, es-

pecially if one recognizes how much these notions change over time and depending on perspective.

The fact that humanity is in the middle —neither genetically homogeneous nor genetically divided along current social and geopolitical lines— poses enormous challenges for genetics research. It means that it is necessary to conduct research throughout the world – looking only in one or a few countries, even a melting pot like the United States, will not reveal all there is to know about genetic variation. Indeed, many argue that justice demands that all peoples be included in genetics research. This point has been powerfully made by the World Health Organization in its recent report on genomics and world health. But conducting research throughout the world has enormous consequences. Countries vary enormously in the cultural beliefs and practices, assets, and power. Efforts are underway to develop norms of international research, which requires identifying international human rights and trying to balance them with local values. This endeavor poses enormous challenges and is by no means complete. In the discussion that follows, I will identify areas on which consensus seems to exist. The most challenging issues surround the distribution of the burdens and benefits of research.

And there are some real burdens of genetic research, mostly having to do with the implications of genetic information. At the most immediate level, learning about one's genetic makeup may affect how one feels about oneself. We all have harmful genetic traits, but the ones we know about can make us feel worse and can affect how we feel about our life plans for our work and our family lives. We share genetic information with our relatives. You will not be surprised, for example, to know that my children are blond and fair skinned. They also are both color blind as was my father, a trait I passed on. These traits are trivial, at least in the world in which my family lives, but other traits are less desirable, raising all kinds of questions for families and for the clinicians who care for them.

Genetic information about an individual can also affect the social group or groups of which he is a part, even though as we have already seen there is often little biological basis for such generalizations. In the United States, for example, members of the Ashkenazi Jewish community have often enrolled in genetics research, in part because of their belief in the value of science and in part because there are a number of mutations that are more common among them as a result of founder effects. In the late 1990's, however, some of their members became concerned that the very success of the science was causing them to be seen as unusually unhealthy, a perception that was empirically unfounded. The fear of discrimination, of being treated less well than others, has pervaded the debate about the impact of genetic information. Some have argued that genetic discrimination rarely occurs, but there is plenty of evidence over millennia that human beings often see themselves as intrinsically (read biologically) better than others. There is no reason to think that people will not try to exploit real or perceived genetic differences for their own benefit.

Discrimination is not the only adverse impact that people worry will come from genetics research and the knowledge that results. Many individuals and groups have been very concerned that their biological heritage and even their very selves are being stolen for the benefit of others. The sources of these fears are myriad, and include efforts by international pharmaceutical companies to learn about the practices of indigenous health care providers and beliefs by some that taking a body part steals part of the soul or prevents rest after death. One of the most important influences is the failed Human Genome Diversity Project, in which it was perceived that researchers from well-to-do countries were "helicoptering" in to isolated populations and collecting DNA from these people before they disappeared or were admixed with the outside world with no prospect of benefit in return. These perceptions were unfounded at least in part and did not reflect the true intentions of the organizers of the

HGDP, but the suspicion of genetics research that resulted from this experience has to be addressed in designing any current project.

So what steps need to be taken? The first is a commitment to education about genetics, focused on two fundamental issues. One is what genetics does and, perhaps more important, does not mean for human health and function. Genes probably affect every aspect of our lives, but rarely are they the only influence. The impact of any particular gene can be influenced by other genes in the person's genetic makeup, the genes of other organisms with which we interact, and the environment very broadly understood. Many examples come to mind, but the fact that even so-called simple single gene disorders such as sickle cell anemia affect each person differently is enough to make the point. The second issue is that understanding what genes do does not necessarily lead directly to effective therapy. Here as well, sickle cell anemia is a good illustration – the exact biochemical and genetic defects have been known for this disorder for a half century, but this knowledge has not allowed physicians either to cure this disease or even markedly improved its outcome. I do not want to be pessimistic here – there have been some spectacular successes, of which Gleevec is currently the most famous – but realism is essential.

This education needs to be directed broadly. The first audience is the public so they can make informed decisions about their own participation in research and in testing and about public policy. This is an enormous hurdle, particularly for groups who lack even the words for genetics and DNA. On the other hand, I suspect that all cultures have concepts of inheritance, of traits being handed down from one generation, concepts that can form the foundation for discussion. Clinicians and investigators also need to know more about genetics and its implications.

A number of steps need to be taken in the research process as well. To begin with, protocols need to be designed in a way that minimizes the risk that genetic information obtained in the

research context will be disclosed inappropriately. Two critical concepts here are the least *necessary* and the least *identified* data set. It is important to limit the ability of the investigator to identify individual research participants. I focus on investigators here because they are the ones who most often tend to try to recontact research participants either to obtain more information, or more problematically, to disclose research results that the participants may not want to have. A critical step in this process is limiting the amount of information the investigator has to that necessary to conduct the research because it is sometimes quite remarkable how few pieces of information can identify a person. For example, the data set of female pediatricians and lawyers in Tennessee is one – me. Attention also needs to be paid to the security of the data. Two easy steps are keeping data only on computers that are not linked to the internet and limiting access to a small number of people.

After much discussion around the world, there is now general agreement that informed consent is needed for current efforts to collect DNA and medical information for research. Critical issues that must be addressed include possible future uses of samples and information, policies of providing (or usually not providing) individualized research results, and privacy protections. Greater debate surrounds the need or appropriateness of seeking consent to use already existing records and tissue. Obtaining informed consent, while often critical, in no way vitiates the need for rigorous research design and adequate information security.

One of the most challenging issues is the increasing importance of engaging with the communities from which research participants come, a notion that arose in no small part out of the recognition of the risk of group harms. It is important to acknowledge that this is an evolving area so that neither the ethical justification nor the procedural requirements are fully defined. Thus, it is not entirely clear what is meant by community, particularly when you move beyond groups that either are isolated

or have a clear governance structure. It nonetheless seems appropriate to consider the impact on people who may be viewed differently because of research conducted on others with whom they are grouped. Similarly, it is not clear what is meant by engagement or involvement. Does it mean deferring entirely to the political process in which the decision of the leadership, whether despots or democratically elected officials, or is there room for individual decision making, a position that seems to be required by international human rights? These fundamental issues are not yet resolved, but some goals have nonetheless emerged. These include learning about the concerns of *all* members of the group, not just the leaders. Typically, this requires determining how the group is structured and then trying to develop strategies to give a voice to those who tend to silent. It also means developing responses to the concerns that are expressed, preferably working with the group to ensure that the solutions are truly their own. Finally, it requires creating a mechanism for ongoing feedback to and oversight by the group so that they know what is being learned and have a hand in shaping its use. This notion of ongoing engagement is scary because taking this process seriously inevitably requires a lot of time and effort and means that the investigator must give up some control over the research process. One major advantage of well-done community engagement is that it avoids much of the specter of “helicopter genetics”.

All protocols need to reviewed by an ethics review committee or institutional review board (IRB), which must be independent of the investigator. In international research, oversight must occur at both the local level as well as the home of researcher. These committees are responsible for assessing the soundness of the research design including weighing risks and benefits, the qualifications of the investigator to conduct the research, the adequacy of procedural and security provisions, and the appropriateness of the informed consent process. They also must conduct ongoing oversight of the research. This

broad array of obligations is challenging to even the best-constituted and energetic IRB. As a result, the Institute of Medicine in the United States recently recommended the creation of separate committees to assess the soundness of the research design and to manage conflicts of interest. Their recommendations can then inform the deliberations of the IRB. Here as well, further changes in the process of ethical review will surely evolve with the increasing scrutiny of research, particularly in the international context.

Even with all this attention to consent, engagement, and oversight, international genetics research must also address the question of distribution of benefits. A very real concern is that only rich countries will reap the benefits of the genomics revolution, probably increasing already existing disparities between rich and poor. One area in which this has emerged is in the debate about patenting genetic information. Many people characterize patenting DNA sequences as “biopiracy.” The 1998 UNESCO Declaration on the Human Genome and Human Rights, which is currently being revised, states that “the human genome in its natural state shall not give rise to financial gain.” Others, however, argue that patents are necessary if the fruits of genomic research are to be made available. Interestingly, many investigators around the world involved in the human genome project and the international haplotype map project have taken the strong position that human DNA sequence data should be in the public domain. Even the US Patent and Trade Office in recent years has imposed more stringent requirements before it will grant patents on DNA sequences. At the same time, recent efforts to standardize patent protection around the world, most recently embodied in the TRIPS (Trade-related Aspects of Intellectual Property Rights) Agreement, appears to require more rigorous enforcement of patents, no matter where obtained. While the outcome of this struggle over the patenting of genes and their products is uncertain, it seems quite likely that substantial patenting will occur.

This fact, which inevitably will increase the price of products developed with these patents, coupled with the already existing inequities in access to new technologies and concerns about exploitation, gives even greater urgency to addressing research in resource poor countries. A number of international bodies have addressed this issue and have generally agreed on at least the following principles. One is the importance of attending to cultural and language differences, a concept deeply embodied in the practice of community engagement. It is worth mentioning again the great difficulties of bridging these differences. Another is that the research should address a local health issue. In many countries, this may mean focusing on genetic factors that contribute to susceptibility to infectious diseases. The relative immunity to HIV/AIDS conferred by the CCR5 mutation is a good example. The goal of such research is not necessarily to figure out how to confer genetic immunity to these diseases but to give insights into potential targets for therapeutic drugs.

A critical issue is the need for local benefit from research participation. This can occur in a variety of ways. Efforts to create local research capacity can increase the likelihood that local health concerns will be addressed. Local investigators will be more knowledgeable and can act as a counterweight to the interests of multinational corporations, which may be focused on problems in other parts of the world. But capacity building need not be limited to enhancing local research. In many instances, more critical needs may include the development of basic infrastructure. One of the most contentious issues is whether local research participants and their communities are entitled to benefit from the particular research project itself. Some have urged, for example, that research participants should be entitled to receive drugs that are found in protocols to be efficacious, perhaps at reduced or no cost and for varying periods of time. The Ethics Committee of the Human Genome Organization boldly recommended that “profit-making entities dedicate

a percentage (e.g. 1%-3%) of their annual net profit to healthcare infrastructure and/or to humanitarian efforts.”

The notions of benefit sharing are embodied in the Declaration of Helsinki (2000), which states that

- Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. (paragraph 19)
- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (paragraph 30)

Similar language is contained in guideline 10 in the most recent International Ethical Guidelines for Biomedical Research Involving Human Subjects.

This survey reveals that delivering the benefits of genetics research to all people will require truly collaborative efforts that are attentive to local and international concerns.

In closing, let me say why I am particularly pleased to be taking part in this conference. In my research, I found little evidence of the voice of Latin America. Moreover, it seems that relatively little genetics research is being conducted in this part of the world. It is notable that no populations indigenous to the Western Hemisphere are included in the International Haplotype Map project. (The CEPH, from Utah, are intended to represent northern Europe.) These disparities, perceived and real, need to be rectified, and you, with the expertise in law, ethics, and genetics that exists in Mexico as well as in Chile and Argentina, with your new genomics institute, and in a country with enormous cultural and political diversity, are uniquely poised to close these gaps.

Useful Resources:

HumGen, (www.humgen.umontreal.ca) a very useful resource for ethical and legal documents

UNESCO, *Declaration on the Human Genome and Human Rights* 1998 and currently under revision.

World Health Organization, *Genomics and World Health*, HUGO Ethics Committee.

CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects.

Nuffield Council on Bioethics.

Indigenous Peoples Opposition to the HGDP,

http://www.ipcb.org/resolutions/htmls/summary_indig_opp.html (6/15/03).