Human Genome Diversity Project

Model Ethical Protocol for Collecting DNA Samples North American Regional Committee Human Genome Diversity Project

The guidelines have subsequently been published in the *Houston Law Review* 33(5): 1431-1473 (1997, with the addition of the first title word "Proposed")

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Introduction

How to Use This Document

This document is a Model Ethical Protocol for collecting DNA samples for the Human Genome Diversity Project (HGD Project). The HGD Project is an international effort to collect, preserve, analyze, and make available genetic and ethnographic information from people all around the world. The Project expects that its work will lead to advances in understanding the biological development and the history of our species and, ultimately, in understanding and treating many diseases with genetic components. The Project will collect DNA samples and ethnographic information from communities throughout the world, thus correcting the current bias in research in human genetics toward people of European descent. The Project expects that the samples will be preserved in repositories where they will be available to all qualified researchers. The samples will be analyzed, and the results of these analyses will be widely available through computerized databases. The Project is currently in its early stages and is still largely being planned.{1}

The Project is organized into different regional committees, coordinated by an international executive committee. This Model Protocol has been produced under the auspices of the North American Regional Committee of the Project and is intended to guide HGD Project sampling done in the North American region or sponsored by institutions within that region. That Committee hopes that the Protocol will also be helpful to HGD Project researchers and institutions in other parts of the world and even to researchers not involved in the HGD Project.

This document is intended as a guide to the ethical issues that will be encountered in collecting samples for the Project. The issues that the

Protocol discusses are numerous and complex, but they are not new. They necessarily have been confronted in various contexts in anthropology, medicine, genetics, and many other fields.

In preparing this document, the North American Regional Committee has relied heavily on the work of others who have examined these issues. The Council for International Organizations of Medical Sciences has prepared two documents that were particularly useful: INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1993) and INTERNATIONAL GUIDELINES FOR ETHICAL REVIEW OF EPIDEMIOLOGICAL STUDIES (1991). The Committee has also taken into consideration the 1982 Proposed International Guidelines for the Conduct of Biomedical Research by the CIOMS; the fourth edition of the Declaration of Helsinki of the World Medical Association; the Nuremberg Code; and United States regulations for the Protection of Human Subjects, among other sources.{2} We intend the Model Protocol to be consistent with those authorities.

At the same time, none of those authorities provides a direct discussion for the unique combination of ethical issues faced by the Project. This Model Protocol is intended to fill that gap, by applying the ethical principles set forth in those documents to the HGD Project's concrete challenges. We expect it to be useful to at least four different constituencies.

First, the Model Protocol is intended to provide detailed and specific advice to researchers involved in the HGD Project. We want it to state important principles and rules, to show researchers non-obvious issues that may arise, and to discuss usefully the complexities that may confront them in the field.

Second, the Model Protocol should be useful to populations that are participating or considering participating in the HGD Project, or other similar research projects. It may help them understand better some of the possible implications of participating in the Project and may serve as a way to test the good faith and sophistication of the researchers that approach them. Populations may learn of the Model Protocol directly or through the assistance of non-governmental or governmental organizations.

Third, the Model Protocol should be useful to Institutional Review Boards or other groups that review human subjects research. We have written the Model Protocol with those kinds of organizations in mind. We hope that they will use the Model Protocol to judge whether proposed research projects have given sufficient consideration to the ethical issues their work may raise and whether their plans for informed consent are appropriate. Similarly, sources for research funding, public or private, should find the Model Protocol useful in assessing applications for financial support.

Finally, the Model Protocol will guide the work of the North American Regional Committee of the HGD Project. Activities within North America or sponsored by North American institutions will not be accepted as part of the HGD Project unless they comply with these guidelines. The North American Regional Committee will provide no endorsement or support, including funding support it that becomes available, to researchers who violate the Protocol's principles. The Project may refuse to accept into its repositories any samples collected in violation of this Protocol or refuse to include in its databases any analyses of samples so collected. (The North American Regional Committee may apply similar penalties to failure to comply with other HGD Project protocols, such as those on the collection of ethnographic information.) We expect this Protocol to be the main guide for the North American Regional Committee in ensuring that its part of the Project is carried out in an ethical manner.

Notes {1} More-detailed information about the Project is available from its North American Regional Committee, c/o Morrison Institute for Population and Resource Studies, Stanford University, Stanford, CA 94305-5020; by electronic mail to morrison@forsythe.stanford.edu [since 2003, morrinst@stanford.edu]. {2} A particularly good discussion of many of the issue involved can be found in a symposium issue of *Law, Medicine, and Health Care* devoted to the CIOMS epidemiological guidelines. The articles by Barnard M. Dickens, A. M. Capron, Larry Gostin, Robert J. Levine, Nicholas A. Christakis and Morris J. Panner, and Charles R. McCarthy and Joan P. Porter are particularly helpful, as is its collection of original sources. *Law, Medicine, and Health Care* 19, #3-4 (1991).

I. An Overview of the Ethical Issues and the Collecting Process

Three principles have guided our consideration of the ethical issues raised by this Project:

informed consent,
respect for the participating population's culture, and
adherence to international standards of human rights.

These principles combine to help us ensure that the Project not only does no harm to the participating communities, but, where possible, brings it benefits.

We have looked to these principles in assessing what constitutes ethical behavior in the diverse situations that researchers will face. Different field situations will necessarily produce different answers in applying ethical principles and rules. Researchers may be sampling populations with high

levels of scientific knowledge and education or communities with almost no knowledge of Western science. The precise form of the interaction should and must vary with the circumstances, but any researchers who want to participate in this Project in North America must accept the principles and rules discussed below. This section will summarize those principles briefly, while describing how we expect the sampling process to proceed.

First, sampling must be planned and prepared well in advance. Researchers must first learn about a population they wish to sample. Consultation with anthropologists or others knowledgeable about the population will usually be essential. Once informed, the researchers can approach the population to determine whether it is interested in participating in the Project. Researchers need to build time and funding into their proposals for the possibly lengthy discussions with the population, through its members or through culturally and legally appropriate leadership groups. Final funding and final Institutional Review Board approval for sampling is better granted only after the *population* gives the researchers permission to pursue the Project among its members.

At the time of the sampling, as well as earlier, researchers will need to explain the sampling process and the Project thoroughly to the population and to individual population members who agree to participate. Researchers must completely explain what they plan to do in the field and why. Although conveying a *complete* understanding of human genetics and molecular biology will often prove impossible, researchers must make full efforts to explain the nature and goals of the Project, in the language appropriate for the population and in terms that are relevant to its culture.

The North American Regional Committee expects participating researchers to obtain several different kinds of consent. Along with permission of the relevant governments, researchers must obtain both the informed consent of the population *and* the informed consent of the individuals who give samples. Although this requirement goes beyond the strictures of existing law and ethical commentary, we believe it flows necessarily from the nature of the research, which is, by definition, research aimed at understanding human populations and not individuals.

In addition, the researchers must seek to collect the ethnographic information sought by the Project's standard ethnographic protocols. Researchers must carefully consider the immediate benefits they plan to provide to the sampled population, including particularly medical benefits. The researchers must abide by culturally appropriate standards of privacy and confidentiality designed to protect individuals and their populations from harm. The researchers must plan to serve as educators, where appropriate, about human genetics. The researchers must accept and implement the

Project's efforts to protect the population's rights in commercial uses, if any, of their samples. And, most important, researchers must seek, wherever possible, to engage participating populations as *partners* in planning and carrying out the research and not just as research subjects.

The Institutional Review Boards, or other bodies that determine the propriety of research on human subjects, need to examine all these factors carefully. As the CIOMS recommends, these bodies should themselves contain or seek out independent expertise on the cultures involved. Institutional Review Boards should approve only research protocols that cover all the areas discussed above in ways appropriate for the culture of the participating populations.

The Project categorically rejects the idea of "bleed and run" collecting, done by researchers who appear and disappear without a trace. Collecting must be done only with the full consent, cooperation, and engagement of those sampled. Although this will require close and expert knowledge about the populations and may take a long time, respect for the populations as partners in the scientific enterprise -- rather than as objects of it -- requires no less.

II. Before Contacting the Population

Populations may be considered for participation in the Project vin several ways. Some populations may approach the Project itself, seeking inclusion. In other cases, individual scientists or groups of scientists may wish to study a particular population. Sometimes a government or non-governmental organization may want to sample the population. We envision that the sampling will often be undertaken by scientists who have been working for a long time with a population and who decide to add another, genetic, aspect to their investigations. To the extent that the researchers have worked closely with the population before, many of the steps outlined below may be fairly easy. For those new to working with a given population, they may prove quite difficult, but all the more essential.

Once a population has selected itself or has been selected for *consideration* for inclusion in the Project, a great deal of work and preparation must take place before the group is asked whether it wants to participate. This is a matter of ethics, not just prudence. Not only is approaching a population without proper preparation a waste of the researchers' time, money, and effort; it wastes the population's time and shows a lack of respect for them.

It is absolutely essential that the researchers learn as much as possible about the population. The researchers will want to read, to consult academics, to approach organizations, churches, health care workers, and

others who know the population, including, of course, individual members of that population. The researchers may want to make informal trips to the population, to get a better sense of its culture before ever approaching the population about the Project. This preliminary work is essential to determine whether a population's participation seems even feasible.

Researchers will need to make these kinds of investigations in order to understand basic aspects of the population's culture and politics. Researchers need to learn how the population is organized and what groups, governmental or cultural, can best speak with authority for the population. They also may learn important information about how collecting should be proposed. In many societies around the world, hair is secretly collected from intended victims to harm them through witchcraft. Consequently, people collect their own loose hair, fingernail parings, and other body products and bury them to avoid this danger. Researchers who asked such a population for hair might be seen as intending to perform witchcraft. Blood is often intended as a sacrifice, sometimes through special rituals. Donation of blood in such cultures is a serious matter that would require discussion and perhaps a neutralizing ritual. Before approaching the population, researchers need to know as much as possible about its likely concerns about and reaction to their collecting plans.

The researchers must then begin to consider seriously the details of any proposed sampling. They need to determine what language or languages would be appropriate for communication with the population. Researchers cannot assume that all populations speak the most common language in their countries, nor, for that matter, that a population speaks its traditional language instead of the national language. The next step is to find interpreters and translators who can help them communicate with the population. Finding interpreters or translators with some scientific training or education may be both extremely important and extremely difficult.

The researchers also have to consider the logistical problems that might be encountered in sampling a population. These concerns not only affect the cost and ease of collecting samples but may even make some kinds of sampling impossible. As a general matter, for blood samples to be transformed into cell lines, existing technology requires that they reach a laboratory within about 72 hours of collection. Many of the populations sampled by the Project will live in major urban areas, with easy access and with no problems in transporting the samples to laboratories quickly enough. Other populations, however, may be several days' journey from such a laboratory.{3}

If, after learning more about a population, the researchers decide to continue, they must determine which national governments need to be

consulted. Often, that will be the national government within whose boundaries the population is located. In some cases, other governments may have to be consulted because their territory will have to be used to reach the population or because they have some important connection to the population. In all these circumstances, permission from the national governments may be required. Researchers should try to discover very early whether it is likely that such permission would be granted in order to avoid wasting their time and that of the population. In some cases, it may be useful or even necessary to get such permission before even exploring the possibility of sampling a population or making first contact with it.

Note {3} We hope that this constraint will not turn out to be important. Newer methods of preserving DNA samples are currently under development that hold great promise for dispensing with the need for cell lines or for allowing the creation of good samples from frozen blood.

III. Making Contact with the Population

If the inquiries described above yield favorable signs, direct contact with the population about the Project may begin. This first contact should rarely include sampling. The first contact should *begin* the process of informing the population about the Project and determining whether its members want to participate. Usually, researchers should only seek final approval from their own authorities for the research after the details of the collecting have been discussed with the population and the population has agreed to participate.{4}

This several-stage process is important. It gives the population an opportunity to make a considered decision about its participation, without the time pressure of a sampling process ready to begin. It allows the researchers and the population to discuss how sampling should be done in their community, perhaps leading to important changes in the methodology. And it removes an incentive for the researchers to cut corners with the informed-consent process. Researchers who have received funding and Institutional Review Board approval for a collecting project and arrive at the community for the first time with equipment and personnel in hand may feel tremendous pressure to get the population to participate, pressure that could undercut the process of true informed consent. Instead, researchers need to find out whether the population is interested in participating before *they* has become committed to sampling them. And researchers, and funding agencies, must take into account that the time and the costs required for such contacts are essential parts of the research, not unnecessary frills.{5}

The nature of the first contact will be very important. It should always be

handled in a manner appropriate to the culture of the sampled population. If the traditional culture requires that outsiders must establish contact by observing certain etiquette, rituals, protocols, or procedures, these must be rigidly observed. For example, custom may dictate that the initial entry into a population is through a chief or council of elders, then this should be how contact is initiated. In other circumstances, if the population has an established health care clinic, hospital, or other health facility, it might provide an appropriate way to contact the population. Certainly, if members of the population have scientific or medical training, the researchers should try to meet with them as part of the initial contact.

Obviously, advice from other researchers who have studied or worked with the population will be extremely useful. The North American Regional Committee will be happy to try to help well-prepared researchers get advice from fieldworkers and knowledgeable members of the traditional community about how to approach the population in a respectful and open manner. The researchers must always remember that they are asking the community to help them and that the community's past experiences with outsiders, including scientists, will often have been unhappy. This process of asking for help is part of the process of informed consent.

Notes {4} Thus, funding may be provided in separate parts, with funding for discussions approved immediately and funding for sampling contingent on evidence of population approval. Institutional Review Board approvals might be similarly staged. {5} In some instances, logistical difficulties may make it prohibitively expensive or difficult to make separate trips. Even in those cases, we recommend that researchers explore the likelihood of group consent extensively before seeking samples. They might be able to do so through local collaborators, other outside experts on the population, local government authorities, or otherwise.

IV. Informed Consent

The Council of International Organizations for Medical Sciences defines informed consent as follows:

Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires a person to do and to risk, and what benefits are intended to result from the study.{6}

The discussion of informed consent that follows is the longest part of the protocol -- not just because of its undoubted complexity, but because of its importance. Truly informed consent is both the greatest protection against exploitation of the sampled population and the strongest way to

demonstrate respect for its culture. The informed-consent process, even in the best of situations, with the most technically sophisticated audiences, is rarely perfect. The HGD Project, particularly when it collects from populations with little scientific knowledge, will not face the best of situations for informed consent. The North American Regional Committee does not hold up an unattainable perfection as the standard that must be met before any research can proceed, but it does insist that the best practical informed-consent process be used.

This section describes the informed-consent process that the Project demands. To the extent researchers want any assistance from the North American Regional Committee of the HGD Project, they will have to show that they have followed this process. We strongly urge Institutional Review Boards, funding sources, and contacted populations to insist on it as well.

This section discusses two different aspects of informed consent: the consent of the sampled population and the consent of the individual donors. It looks at those two issues through four questions: from whom to seek informed consent, when to seek informed consent, what information should be included in informed consent, and how to approach and formalize the informed consent.

A. From Whom Should Consent Be Sought?

1. Individual Consent

Discussions of biomedical ethics have, by and large, focused on individual consent. Consent from the individual participant is generally required by the Nuremberg Principles, the Helsinki Declaration, the CIOMS, and U.S. and Canadian law. The HGD Project fully accepts the ethical necessity of generally sampling only from those individuals who have given personal, informed consent. Such consent requires a full discussion of the methods, goals, risks, and benefits of the Project.

Two complications with individual informed consent must be noted, although neither seems likely to be important for this Project. The CIOMS guidelines recognize that sometimes truly informed consent will not be possible. In those circumstances, it allows a carefully circumscribed use of community consent or "permission," if the potential benefits are sufficiently great and particular ethical care is taken. Some U.S. regulations allow something short of individual informed consent under limited circumstances. We expect that individual informed consent will rarely, if ever, be impossible in this Project, and strongly discourage researchers from seeking to circumvent it.

The second issue concerns informed consent by and for particularly vulnerable subjects. These clearly include juveniles and the mentally incapacitated. For purposes of the HGD Project, we believe it will never, or almost never, be necessary to sample such individuals. Their participation in the Project should be avoided because of the serious ethical problems it could raise. If such sampling is absolutely necessary in particular circumstances, it should be done only after the explicit review and approval by an Institutional Review Board of both the need for such sampling and the consent process adopted. Juveniles{7} and the mentally incapable should never be routinely sampled as part of the Project.

In other contexts, certain subgroups may have such subordinated positions in the culture that consent from their members may be suspect. Such groups may include, in some cultures, low class or caste individuals, prisoners, particular minority groups, or women, among others. The extremely low risks to individuals associated with the HGD Project may limit the consequences of "false" consent from such subordinated groups; nonetheless, researchers, and Institutional Review Boards, must be particularly careful in such cultures to ensure, as far as possible, that the consent is truly voluntary. Securing the collective permission of the subordinated group may provide some extra assurance.

2. Group Consent

In addition to individual informed consent, the North American Regional Committee believes that a further consent process is required. The Project intends to study populations, not individuals. As a result, we believe that the populations, as well as the individuals, must give their free consent to participate. This is particularly true because the effort to include samples from throughout the human species means that many of the populations sampled will not be part of the industrialized world, where genetic studies to date have concentrated. Many of the populations that might participate in the Project are politically or economically marginal in their countries. They have faced discrimination, oppression, and even genocide. Under such circumstances, it cannot be ethically appropriate to sample some members of a group when the group itself has not agreed to participate in the Project. Such methods would themselves be another form of attack on the autonomy of the population.

Specifically then, the HGD Project requires that researchers participating in the Project show that they have obtained the informed consent of the population, through its culturally appropriate authorities where such authorities exist, before they begin sampling. If, for example, the Navajo nation decided that it would not participate in the Project, the Project would not accept samples taken from members of that population. We recognize

that this may be a controversial position. Some may argue that this violates the rights of an individual who wants to participate, even if their group's organization does not. We believe, however, that the population-based nature of this research requires population-based consent and we will insist on it.

Of course, this position requires one to determine both what the relevant "population" is and what are its "culturally appropriate governing authorities." Both questions can be complicated. Each can be answered, by researchers and Institutional Review Boards, only in the detailed factual context of a population, but we will offer some general advice.

First, consent must *always* be sought from the local community affected. If the researchers are sampling members of a town, a village, or a religious unit, they need to explain the Project to the members of that community and obtain its permission to seek willing individual participants. If the researchers intend to sample only a particular part of such a unit, the group from whom consent must be sought is defined by the researchers' sampling criteria. For example, if researchers wanted to sample all members of a village who spoke a particular language, that portion of the village would be the relevant community.

This community consent can only be given after the researchers have fully explained their proposed activities. That explanation can be provided to, and consent sought from, culturally appropriate authorities within the community, where such exist, or through a consensus of the entire community, where there are no relevant authorities (or where a consensus is the culturally appropriate authority).

In cases where communities do not have a "culturally appropriate authority," there still may be institutions that provide a useful focus for community discussions and consensus. For example, in a Catholic parish in Seattle that served a largely Irish-American population, the parish priest would certainly not be a "culturally appropriate authority" to give permission to work with that population. But the priest would be a useful and knowledgeable figure with whom to discuss the community's participation and the parish may provide the best focus for the community and through its auspices the researcher may be able to present information and seek approval from the active members of the community.

When does one have to move beyond the immediate community and get consent from some larger group? That depends necessarily on two things: the population's view of its identity and the existence for the larger group of entities that the population itself recognizes as culturally appropriate authorities.

The existence of such a larger identity among the population will depend on the circumstances. Indigenous populations, for example, may almost always view themselves as, and be viewed as, distinct cultural entities that are part of a group sharing a language and culture. On the other hand, it is much less clear that Irish-Americans are, culturally, a "population," as opposed to a group of Americans with some common ancestry, some of whom share some aspects of a common cultural heritage.

Even if Irish-Americans were viewed as a population of national scope, they would fail the second test: they have no culturally appropriate authority with the recognized power to give, or withhold, permission for all Irish-Americans. Researchers can only seek consent from a broader representative of a population if such a representative exists.

Thus, ultimately, the question of the levels at which consent should be sought is a question that only the population can answer. Consent must be sought at higher levels if the populations believes it is meaningfully part of such a higher level grouping and if there are entities operating at that level whose decisions on the population's participation in the research would be accepted by the local population as authoritative. Three examples may be useful.

A large group of Native American peoples speak languages that belong in the Na Dene group. Na Dene speakers are found largely in Alaska, northern and western Canada, and the American Southwest. The Navajo are one large population that speaks a Na Dene language. Although they may have some sense of some kinship with groups that speak other Na Dene languages, the Navajo consider themselves a separate people and culture. There is a Navajo tribal government, with a President and tribal council. Researchers seeking permission to sample a Navajo village would have to obtain the consent at the levels of both the village, through consensus or its culturally appropriate authorities, and the Navajo tribe. They would not have to obtain permission from a Na Dene authority, both because the people identify as Navajo, not as Na Dene, and because there is no overarching Na Dene organization that the Navajo would accept as having authority over them.

Another example is presented by peoples speaking Cree languages, who are spread throughout much of northern North America. They are organized into a number of different bands, each with governmental authority and most with relatively small populations. There is no overarching organization, in Canada or in the United States, that the bands recognize as having authority over them. Members of the individual bands may recognize themselves as part of a larger Cree population, but without some accepted authority at that higher level, consent can only be sought at the level of the individual band.

Other populations are more complicated. In New Zealand, the Maori, or Tangata Whenua, are organized into units called "iwi," roughly equivalent to a tribe. The entire Maori population historically shared a largely common language and culture. Both Maori and non-Maori in New Zealand recognize the Tanata Whenua, as a whole, as a distinctive population. There are organizations that purport to speak for all Maori, in all iwis. Whether such pan-Maori organizations would believe they were culturally appropriate authorities with respect to an iwi's participation in this Project, and whether the iwi would accept such a claim, is not clear. Researchers would need to have a very sophisticated knowledge of Maori culture and politics before proceeding.

Determining the appropriate levels at which to seek consent occasionally will be complex, but, as a practical matter, it will usually be easy in the United States and Canada. Most Native American populations have their own recognized governments and identification. Most other ethnic groups in those two countries do not have those kinds of cultural identities or group-wide culturally appropriate authorities.

Once researchers have identified the levels for seeking group consent, they still may have difficulty identifying all the culturally relevant authorities. Certainly, recognized Native American tribal governments will always be at least one appropriate authority. But many cultures also have non-governmental authorities of importance. These may be elders, religious leaders, traditional leading families or clans, or other people recognized within the culture as having authority. For populations without formal governments, such informal authorities will have to be consulted. Even for populations with formal governments, the "informal authorities" will often be of such cultural significance that their permission should also be obtained.

Thus, for example, among the Cheyenne Indians, the permission of the Council of Chiefs should also be sought, even though the formal *legal* authority to approve such research rests in the official Business Committee. If researchers wanted to sample a religious community without an official governmental status, such as Lubavitcher Jews, Coptic Christians, or Hutterites, the group's religious authorities would likely be the culturally appropriate authority.

The process of identifying the culturally appropriate authorities will be easy in some cases and extremely difficult in others. The appropriate chain of consent must be sought by consultation with traditional leaders of the community and with appropriately experienced fieldworkers who have worked with the population. The North American Regional Committee will be happy to recommend experts on particular populations and, when it can, provide advice on what the culturally appropriate authorities might be. It will

insist, however, that researchers who want to be part of the Project must both explain why they concluded consent was appropriate at the levels they chose and why any particular entity was considered a culturally appropriate authority. We encourage Institutional Review Boards to demand discussion and explanation of the same choices.

B. When Should Consent Be Sought?

We believe that normally the group consent should be obtained before a trip is made to do sampling.{8} This consent may not come quickly or easily. A year or more of contact, explanation, and service to the community may be necessary before sufficient mutual trust can be established to conduct the research. This additional time and expense *must* be incorporated into the research design and understood, by the researchers and funding agencies, as an essential part of the research.

The individual informed consent, in contrast, should be obtained shortly before or at the time of sampling. If individuals have given informed consent before the sampling, their consent should be reconfirmed at that time.

C. What Information Should Be Provided and How?

This section focuses on two related questions: what should sampled populations and their individual members be told about the sampling, and in what way should they be told. The short answers are that they should be told, in summary form, almost everything about the Project and that it should be explained in the way the population can best understand.

The CIOMS defines the scope of informed consent as "any and all information that a reasonable person would consider material to making a decision about whether to consent. . . ."{9} This includes, among other things, information about the purpose and nature of the study, the nature and risks of the individual's participation, the benefits that are expected from the study, and procedural aspects of his or her participation.

Before a population agrees to participate in the Project, it must be given that information, through whatever methods and authorities are appropriate, as well as a real opportunity to ask questions and seek further information. Individuals, before they choose to participate, should be given much the same information and opportunity to ask questions. The individuals should be given information about all the issues the general population has been told, although not necessarily at the same level of detail.

The first category of information concerns the Project itself. The population needs to be told about the nature, the goals, and the methods of the

Project. The researchers should inform them that this is an international scientific project, not directed by any one country. The researchers should tell them that the Project is designed to collect samples from people all over the world, to add to the samples already being analyzed. The samples may be used for many different purposes, but that the two that seem most important are tracing human history and helping to understand some diseases.{10} Samples will be taken to one or more locations to be stored, analyzed, and shared with other researchers from around the world. As part of this last disclosure, the researchers must make clear that the samples may be used for a variety of different projects in the future, including projects that are not currently anticipated.{11}

Obviously, this category of information can only be well understood by a population that has some understanding of genetics. Often, that will not be the case, and the researchers will have to educate the population about genetics. This does not require that the population receive college-level courses in biochemistry and classical genetics. It is the core ideas that are important, that humans inherit some of their characteristics from each of their parents and the kind of information that can follow from that fact, including information about the relationship between groups and its implications for human history.

Researchers must search rigorously for the best ways to convey that kind of information. This may include explaining it in terms that are not entirely correct but that serve as useful analogies within the population's conceptual framework. For example, if the community understands the mechanism of biological inheritance in terms of blood rather than genes, it is not essential, or necessarily appropriate, to try to destroy that understanding and replace it with deoxyribonucleic acid contained within eggs and sperm. Populations that herd animals may have a very sophisticated understanding of the realities of inheritance among their stock animals, without knowing scientific explanations. Researchers could use that local knowledge as one way to convey information about human genetics. The idea of elementary units of inheritance that can be perceived and analyzed is the important point, not the names we have given those units.

The Mvskoke Creek people of Oklahoma provide a useful example of the importance of culturally appropriate explanations. The Mvskoke Creeks have matrilineal clans. They believe that their substance and spirit are derived entirely through the female line. Nevertheless, the clans sometimes adopt people whose fathers are members of the clan, but whose mothers are not Mvskoke Creeks, and it is recognized that many children resemble their fathers. These facts should be emphasized in explaining why geneticists consider both parents to be important, while respecting the traditional

Mvskoke Creek emphasis on the maternal line. This example further demonstrates the importance of early learning about and contact with the population; researchers unaware of this aspect of Mvskoke Creek culture might seriously damage their relationship with the population by the way in which they described the process of genetic inheritance.

Of course, if the population's language is different from the researchers' languages, researchers must employ experienced bilingual interpreters, preferably those with enough technical knowledge to ease the translation of the scientific concepts. While it will often be difficult to communicate the science of the Project across barriers of language and culture, an honest and persistent attempt must be made. Researchers who have done this kind of work before have, of course, confronted these problems. The North American Regional Committee will be happy to provide specific advice to researchers and Institutional Review Boards on ways of explaining genetics that have proven effective in the past.

The second category of information concerns the participation by, and risks to, the participants. This includes a discussion of the collecting methods themselves -- what physically will be involved in giving blood samples, hair samples, cheek scrapings, or other samples; what the risks are, if any, of those sampling techniques; and how many, and what kind of, ethnographic questions participants will be expected to answer. These issues should be straightforward.

The third category of information deals with the benefits of the research. The researchers must tell the population exactly what benefits, if any, the Project will bring to the community, through supplies, medical services, or otherwise. They must explain, along the lines discussed in Section IX below, the possibility, however faint, of commercial value being derived from the samples and the protections set up for the population in that event.

Finally, some procedural points need to be covered. The researchers need to tell the population of the precautions to be taken to preserve the information's confidentiality. The researchers must give the population information about how to contact them -- and how much follow-up contact to expect from them. And, most important, the researchers must stress that participation is entirely voluntary. Both individuals and groups need to know that they are under no obligation to participate or, having once agreed, to continue their participation.{12} Depending on the circumstances, additional items of disclosure may be required by local law, the laws of the researchers' nations, or otherwise. Thus, for example, research funded by the governments of Canada or the United States would have to comply fully with those nations' requirements.

The absolute core requirement in providing all of this information is honesty. The researchers have an obligation to provide the population with as honest and meaningful information as possible, both in their presentation to the population and in their answers to their questions. That information must be *both* honest and meaningful. Answering a question about what is going to be done with the samples by detailed discussion of the restriction enzymes that will be applied to it may be honest but not meaningful. Saying that they will be used "to cure diabetes" may be meaningful but not honest.

The researchers must neither hide behind jargon nor overpromise. The task of providing possible participants with a full understanding of proposed research is difficult, if not impossible, in the best of circumstances. Researchers collecting samples for the HGD Project will often find it extraordinarily challenging. But this is not a problem unique to the HGD Project. Researchers confront it every day, whenever they need to explain complicated science to populations, industrialized or otherwise, that are not very familiar with science. All research, whether biomedical or anthropological, with populations that are not scientifically sophisticated faces the same challenge. Confronting that challenge is a basic ethical imperative. We encourage IRBs to question researchers in detail about their plans for providing information about the Project. The North American Regional Committee will be happy to suggest specific ways, in particular situations, to make the information as meaningful as possible.

D. What Form Should Consent Take?

Consent should be formalized in a way that is appropriate for an individual culture. For some cultures, that will be individual signed consent forms, written in a language in which the participants are literate, as well as a group consent form or agreement signed by the population's authorities. In other cultures, however, written documents may not be culturally appropriate. Some populations may strongly distrust any document that calls for their signatures, viewing it through the prism of their historical experience as perhaps a deed to their land. In still others, limited literacy may make such documents meaningless. The precise form of the consent must take these differences into account.

It is important that some formal record of the information given the population be kept within the population, for its future reference. This may be a written account, in their language, if possible, or in a language reasonably accessible to them. It might be audio cassettes or videotapes if those technologies are used in their area. It could be a commitment to have a knowledgeable person nearby and accessible to the population for some time. Fairness to the participating population demands that they not be made to rely solely on their memories of what was said.

There is a possible conflict between this advice and the law of some sponsoring countries. The United States, for example, generally requires signed consent forms from all individuals participating in federally funded research who are subjected to a risky procedure. Researchers using funds from the U.S. government would, of course, have to comply with those rules. This example is only illustrative, as the methods of sampling individual DNA used by the Project will not involve risky procedures. If, however, there is a direct conflict between the requirements of American or Canadian law and what is feasible in the field, the researchers may have to abandon plans to work with that community. Affected researchers should feel an obligation to inform the governmental authorities of the conflict and, when appropriate, lobby them for changes in the relevant regulations.

Notes {6} *CIOMS International Guidelines for Ethical Review of Epidemiological Studies* (1991). {7} Even if a particular research project needs two or more generations from a single family, it should be possible to use adult children and grandchildren. {8} We recognize, of course, that some funding may be needed for the researchers to seek the population's consent, but we believe funding for the actual *collection* should not normally be made available until such consent has been received. {9} CIOMS, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993). {10} We envision that often researchers will collect samples for the HGD Project as part of some other research. In that case, of course, the more specific goals of the other research -- to look for markers linked to susceptibility to disease, to check for relationships to a particular distant population with a similar language -- need to be disclosed. {11} This disclosure of unanticipated future uses is necessary to avoid the kinds of questions about undisclosed uses of samples that have arisen with materials collected in the past. See NIH and CDC Working Group on Regulations for the Protection of Human Subjects, *Informed Consent for Genetic Research on Stored Tissue Samples* (1995). {12} See the discussion on withdrawal in Section IX(B), below.

V. Providing Benefits to Participating Populations

For many reasons, researchers should and will want to provide some tangible benefits to participating communities. Researchers should feel an obligation, based on justice, to help the communities that help them. Many times this impulse will be reinforced by the community itself, whose culture may demand something of value from researchers in return for the community's participation in the research. The provision of benefits to the

participating community in connection with collection of samples is an important part of any ethical research design, but it raises complex issues. For example, at the extreme, providing benefits in return for participation can vitiate the community's informed consent, by "bribing" it into agreement. The line between an appropriate return for the community's participation and inappropriate bribery cannot be drawn in the abstract and will necessarily vary with each population and each researcher.

This is not a new issue -- any researcher, in any discipline, working with human subjects faces these questions today. We believe the issue needs to be discussed openly and that the distribution of any benefits to the participating population needs to be raised before, and considered by, the Institutional Review Board considering the ethical aspects of a research proposal.

This section discusses some of the concerns that researchers, funding groups, Institutional Review Boards, and populations need to consider with respect to promises of benefits to participating communities. Three basic principles should govern researchers in this connection: honesty, legality, and appropriateness. Two issues that might be viewed as providing benefits -- medical services and financial interests in the samples and their use -- raise special problems and are specifically discussed in Sections VI and IX below, respectively.

A. Honesty

The first principle that must be followed with respect to all dealings with the population, including any benefits, is rigorous honesty. Any benefits that are promised must be both deliverable and delivered. For researchers to promise help to a community without delivering it is fundamentally unethical and an abuse of the population.

The area where this may be most dangerous in the HGD Project is in the discussion of research on disease. Many diseases are thought to have significant genetic components. Some of those diseases will be particular burdens on certain communities, such as diabetes among many Native Americans, hemoglobin variants in many populations in areas of endemic malaria, Tay-Sachs disease in Ashkenazic Jews, and others. It may well be that samples from a Native American community may help contribute to a better understanding of genetic contributions to diabetes. That better understanding might lead to better treatments or even a "cure." But it is fundamentally unfair to tell a community that this research will "cure" their diabetes, or even to couch an explanation of the research in a way that allows the community to believe a cure will result. Vague disclaimers are not enough, particularly when health problems are concerned. The community

must understand the very tenuous connection between the sampling and any treatments for any disease; to play on a people's hopes, for themselves and their families, in order to get permission to collect samples would be unconscionable.

If the sampling is a part of research aimed at studying a disease, the community must be told so, but it should also be warned, quite clearly, that the research may not lead to any useful knowledge and that even useful knowledge may not lead to treatments. Even if treatments do ultimately result, they might not appear for decades. If the sampling is not part of research aimed directly at studying a disease, the most researchers can honestly say is that the samples may help other researchers study that disease. Again, researchers must ensure that the population understands both the limits of disease-related research and the limits of their own work.

B. Legality

A second principle is compliance with the applicable laws. A substantial "gift" to the mayor of an American city in return for allowing research in the city would be quickly spotted by researchers as an illegal bribe; national and local laws in the areas where research is being conducted must be consulted to see what kinds of benefits may legally be given to whom. The researchers' national laws, or the conditions of any financial support for their specific project, may also affect what benefits can be legally given.

C. Appropriateness

The range of possible benefits that researchers might confer on a community is vast and could include products, supplies, training, or services. The third principle the researchers must follow is that the benefit be appropriate: in its nature, in its scale, and in its distribution within the community.

1. Appropriate in Nature

It would make no sense to provide medical supplies to a population that does not know how to use them or to give a videocassette recorder to a community that has no electricity. Benefits may also be inappropriate in the context of the community's culture. Sometimes the benefits might conflict with deep cultural or religious beliefs. Providing alcohol to a devout Muslim community or canned beef to a Hindu one would obviously be inappropriate. At other times, the problem may be one of taste or familiarity. The consequences of an inappropriate benefit may be minor or major; researchers planning to provide a benefit must consult with those knowledgeable about the population's culture *before* arriving bearing gifts.

Money is one kind of benefit that demands particular mention. Paying a community in cash for participating may raise special concerns about legality (both under the population's laws and those of the researchers' governments). If the payments are excessive, they may raise concerns, discussed below, about coercion. And if the payments are distributed in a manner inappropriate to the community's culture, they may raise issues of disruption, also discussed below. Subject to those qualifications, however, there is no inherent reason why researchers cannot make an appropriate payment to the community or to individual donors for their participation in the Project, as compensation for the time and effort that participation has taken.

Still another kind of benefit may be particularly useful in some contexts. The HGD Project can serve to help transfer scientific technology to communities around the world. In some contexts such technology transfer will fail the test of appropriateness. In other cases, the populations being sampled will be part of cultures that have universities, research institutes, scientists, and others who could use some parts of the technology used by the researchers. Schools may be particularly appropriate recipients of such benefits; for example, high school students across the United States are already experimenting with polymerase chain reaction, one of the most powerful of the new genetic technologies. Providing primers, reagents, equipment, or education about these technologies will often be a useful and particularly appropriate benefit for the researchers to provide a participating population.

2. Appropriate in Scale

The scale of the benefit is also a crucial concern. If an offered benefit -- whether money, goods, or services -- is too large, it risks being coercive. An enormous benefit may make the process of informed consent meaningless by making it effectively impossible for the community to say no. Consider a hypothetical situation where a researcher said to the leader of a community, "I can save your sick child's life, but I will only do so if you participate in the Project." That kind of coercive use of an offered benefit is grossly unethical. Other, less dramatic, kinds of benefits can also be offensive. It is fundamentally disrespectful of the autonomy of the community to "make it an offer it can't refuse."

One might argue that it is disrespectful of the autonomy of the community to treat it paternalistically by "protecting it" from "too large" a benefit. This debate may or may not ultimately have a definitive answer; for purposes of the HGD Project, however, the North American Regional Committee has chosen the side of avoiding coercion, even coercive "benefits."

How much is too much? That question cannot be answered in the abstract.

The core issue is whether the population, in its cultural setting, retains a real opportunity to say "no" in face of the offered benefit.{13}

3. Appropriate in Distribution

The third aspect of determining appropriateness concerns the distribution of any benefits. It also can be deeply disruptive to a community, and even dangerous, to give benefits to the "wrong" people, as defined *by* the community, within that community. Thus, giving an important gift to a person of low status within the community might upset the community's social system and could even result in harm to the "beneficiary." In North America, the Lewis and Clark Expedition, for example, distributed Jefferson Peace Medals to low-ranking chiefs. This created consternation and confusion among many of the Indian nations they met. More ominously, European agents in North America often cultivated relationships with low-ranking collaborators in various tribes, pretending that these collaborators were, in fact, legitimate political leaders in order to get access to lands and resources owned by Indian people. Because of this history, researchers must be especially careful about properly identifying legitimate leaders and distributing benefits in a respectful and traditional manner. Often, this will require that any benefits go to the group's leaders, who will redistribute them to the community in a structured and traditional manner.

Researchers are obligated to do no harm to the participating population. This includes doing no harm through a careless distribution of benefits within the community. Here again, researchers must become knowledgeable about the population before beginning sampling.

Note {13} This may well turn out to be a moot point. Given the funding levels we expect for the HGD Project, it seems unlikely that any researchers will be in a position to offer a community "too much" for its participation. Nonetheless, the issue needs to be considered, by researchers and Institutional Review Boards, in designing research in specific communities.

VI. Medical Services

Researchers may well want to provide some medical services to members of the participating community. This form of benefit is likely to be appealing for several reasons. The researchers themselves may well have medical training and they may be accompanied by physicians or nurses. Medical services may *seem* an almost uniquely good benefit, welcomed by almost anyone. In

some cases, medical services may otherwise be unavailable to the sampled population. Researchers might be able to do more good for the population at less cost through providing medical services than through any other method.

Nevertheless, providing medical services creates challenges as well as opportunities. This section explores some of the issues that must be considered before undertaking, or approving, the provision of medical services in connection with collecting samples for the HGD Project. It will discuss providing medical treatment, medical capabilities, and medical screening.

A. Medical Treatment

Researchers may be able to provide great benefits through medical treatments. For example, when Dr. Cavalli-Sforza first worked with populations in central Africa, they found that some of them suffered from a high incidence of yaws, an infectious skin disease. On subsequent trips, they brought antibiotics, which quickly cured the illness among the people they treated.

Before deciding to provide medical treatments to the participating population, researchers must consider several issues.{14} First, the research group must have the knowledge and skill necessary to provide those treatments. Second, the medical personnel involved must be able to provide the medical treatment legally in the sampled population's community. American states, for example, usually make it a criminal offense for someone without a license in the appropriate jurisdiction to practice medicine or nursing. Canada has similar restrictions. Third, providing the treatment must be culturally appropriate for the population. And fourth, the kind of medical treatment must be both useful and feasible.

One good source for the last kind of information is the community itself. The researchers considering providing medical treatment should investigate that possibility during their early contacts with the group, long before sampling begins.

The medical treatment must also be appropriate to the circumstances. Treatments for tuberculosis, for example, often require the patient to take medication for a year or more. Providing two weeks of drug treatment to such a patient would be useless, if not counterproductive. The researchers must choose treatments that are either self-contained or amenable, realistically, to being continued once the researchers leave.

The researchers must also be realistic about their abilities, and those of their project's budget. They cannot go into a community and offer rationed

medical services. They will have to be able to offer treatment to the entire community, not just those who participate in the Project. It is the *community* that participates in the HGD Project, not just those whose DNA is sampled. The *community* should receive the benefits. To limit medical benefits to those who donate samples not only contravenes that principle, but also risks coercing individuals to participate. And it is unrealistic. Are the researchers going to refuse services to a participant's children, spouse, or extended family? Researchers must be prepared to provide services to far more people than those who provide samples.

B. Medical Capabilities

Instead of providing treatment for a few days, researchers might seek to improve the community's long-term medical situation. Funding from the HGD Project almost certainly will not be sufficient to create, supply, and staff a medical clinic, but researchers who are part of the Project may be able make some less dramatic but lasting contributions in at least two major respects.{15}

First, researchers may be able to provide equipment or supplies for a pre-existing community clinic or group of medical practitioners. This could range from durable medical equipment to pharmaceuticals to first-aid supplies. The researchers would need to determine in advance what supplies the community needs and could use. It would do little good, and possibly much harm, to supply potentially dangerous drugs if the community does not have access to someone who can dispense them properly. If those conditions are met, however, researchers may well be able to get donations of supplies from manufacturers and others to be used for this purpose.

Second, researchers may be able to provide training to members of the community. Teaching ten members of a community the basics of first aid, or how to provide rehydration therapy for infant diarrhea, might save many lives. The researchers must determine in advance that the training is needed and must ensure that their group has the expertise to provide such training, but this seems a particularly promising way to help at least some participating communities.

C. Medical Screening

Ethically, medical screening is the most complicated of the medical services researchers could provide. It could come about through on-site screening for diseases common in a particular population, such as tuberculosis, hypertension, or diabetes. It could also result from an analysis of the samples donated by the community. The value of screening depends enormously on the context: the medical context, the social context, and the

personalities of those involved. Screening can also raise particularly difficult issues of privacy and confidentiality. Screening may be appropriate in some situations, but it needs to be thought through with particular care by researchers and Institutional Review Boards. It is *not* to be undertaken lightly.

1. On-Site Screening

Researchers may be able to screen populations easily for some diseases, but the ability to do such screening does not mean that it should be done. Researchers must consider carefully the consequences of the screening. Those consequences present such great potential difficulties that screening will usually not be an appropriate medical service to offer.

First, the researchers must consider the medical consequences of the screening. Will the screening lead to any useful end? For some conditions, there may be effective treatments, but even in such cases the researchers need to consider, realistically, whether the treatments will be available in the population. Some screened conditions can be treated quickly and easily by the research party. Others, such as tuberculosis, can be treated only over a long period of time. Still others may have no treatment at all. In some situations, the group might benefit from screening by taking steps to limit transmission of an infectious disease. Those steps might be quite negative to the screened individual identified as contagious.

That leads to the second point, that the researchers must consider the social consequences of screening individual participants. A diagnosis of a disease may affects individual within different cultures in very different ways. In many cultures, including those with highly developed medical services, many people, consciously or not, equate disease with evil. Diagnosis of a disease may lead to discrimination and shunning, as has often been the case with HIV-infected people in the United States. It could lead to understanding and support. It could lead, particularly with dangerous infectious diseases, to banishment or murder. What would happen depends enormously on the culture and the condition. Nor can one assume, in any culture, that the social implications of screening can be avoided by disclosing the results only to the individual concerned. Protection of this kind of confidentiality within a community cannot be assumed. Anyone considering providing medical screening as a benefit to a community participating in the HGD Project must ascertain in advance what the social consequences of the screening test would be.

Finally, the researchers would have to consider the effects of screening on the individual. Some people may want to know about a condition, whether they can do anything about it or not. Others may find such knowledge an

unbearable burden. Research on people at risk for Huntington's disease, for example, has shown that a large percentage of those offered a screening test, with full counseling about its implications, turn it down. These kinds of considerations will apply with even more force to some kinds of screening tests in sampled populations. It may be difficult, if not impossible, for the researchers to be sure that those screened will truly understand the purpose of the test and its possible effects.

Unless the researchers can be confident -- from a deep knowledge of the culture, the circumstances, and the condition that is the subject of the screening -- that the screening will not do any significant harm, they should avoid providing screening as a medical service. Researchers who want to retain the possibility of doing such medical screening must discuss it thoroughly in their initial proposals so that it can be thoroughly considered by any ethical-review panel.

2. Screening of Samples

The second screening context is more complicated. Rather than screening individuals in the field, it may be that the samples provided by donors will, as a result of their handling and analysis, lead to information about the individual donor's health. This could be a result of genetic analysis of the samples; it could be the result of screening the samples for non-genetic disease; it could be a chance discovery. Samples might be analyzed for non-genetic diseases for a variety of reasons, ranging from scientific purposes or to determining and limiting safety risks to personnel who handle them.

The medical information that might result from subsequent analysis of samples poses a knotty ethical problem. What should be done if researchers analyzing a sample determine, some time after collection, that the donor was infected with HIV? Was infected with the parasite that causes malaria? Carried the gene for Huntington's disease? Once that information is known, is there an ethical obligation to do anything with it to protect the donor? To protect a laboratory worker? Does the answer to those questions depend on the characteristics of the medical problem? And, if some intervention is ethically compelled, how does that affect ethical obligations of confidentiality?

We have no firm answers to these questions, which should be of concern with all sample collecting activities, particularly collection done for purposes of genetic analysis. Much would seem to depend on the circumstances, notably the consequences for the donor of knowing about the health problem. The complexity of the issue should counsel researchers against easy screening of samples for medical information. Before any such screening is done, the researchers analyzing the samples must think through

carefully the consequences for the donors.

Researchers collecting the samples should also consider whether to raise this issue as part of the informed consent. They may want to ask the population or individual donors whether individuals should be informed of health risks that ultimately appear through analysis of the samples. Of course, that kind of "informed consent" loses much meaning because it is not really in context - can an individual, at the time of donation, really give an answer to that question when the health risk might be as different as HIV infection, malaria, or Huntington's disease?

At this point, the North American Regional Committee has no definitive advice on this issue, other than that careful consideration is needed if it arises. As discussed in the next section, the confidentiality provisions will allow the possibility of identifying an individual donor for the purpose of conveying health information when appropriate, but whether it is appropriate will depend entirely on the individual circumstances.

Notes {14} The people actually providing the medical services will also be entering into a physician-patient or nurse-patient relationship, which entails its own set of separate ethical obligations. This document does not discuss those issues, but researchers must bear them in mind. {15} There is at least one more possible way to provide longer-lasting benefits. Researchers may be able to contribute to the long-term health of the community by providing an avenue of contact between the community and the medical personnel at the researchers' institutions. The existence of a contact person at a medical school, for example, could be useful to some participating groups, although this will obviously vary with the circumstances.

VII. Privacy and Confidentiality

Privacy issues can be divided into four important areas of potential concern: activities in the field, post-collection protection of individual identity, post-collection protection of group identity, and confidentiality control. Each seems to be subject to some general guidelines, although, as always, individual populations must be dealt with in ways that respect their culture and are consistent with their situation.

A. Privacy in the Field

In the field, the privacy with which collecting activities are pursued must be ruled by the cultural norms of the populations being sampled. In much of the United States, it would be appropriate to determine someone's willingness to participate in a research project in private. It also will often be appropriate to take the samples in private. These cultural norms concerning privacy in

the collection process are not universal. In some cultures, it may be viewed as rude or suspicious to talk with people in private or to take samples from them outside the view of their neighbors or family. The appropriate ethical norm is respect for the sampled population's culture, whatever perspective that culture may take on privacy. The extent to which imposition of outside norms of ethical behavior is appropriate in any circumstance may be controversial, but in this case there seem to be no strong reasons to protect individual privacy in the field if the individual has a different preference. Similarly, at the time of the sampling, disclosure of whether any individual has actually participated or not should be governed by the local norms.

After collection, the issues shift from privacy in the collecting process to confidentiality of the results of the collection. These issues operate at two levels: the individual and the group.

B. Individual Confidentiality

The HGD Project's standard ethnographic protocols call for the collection of some cultural and ethnographic information from individual donors, including names and other information that could be used to identify a donor. One might argue that no personally identifying information should be collected, thereby making breaches of confidentiality impossible. Such a draconian rule would make impossible a number of scientifically useful analyses that could depend on cultural characteristics of individual donors and, in some cases, even on the ability to re-contact a particular donor. The basic rule must be protection of the confidentiality of all individual donors, but we believe that it should be done through control over personally identifying information, not its total exclusion.

The idea of individual confidentiality, and the uncertainty about why anyone should want to know the identity of individual donors, makes this a powerful underlying rule. It might, of course, be waived by a fully informed donor, but such waivers should be rare.

The donor's name will, of course, usually be the most powerful identifier, but it will not be the only one. For example, if one donor from a particular village had a mother with one native language, a father with another, and was born in a neighboring village, that information might make the donor identifiable, at least to people in the village. On the other hand, some of the work that can be done with the DNA samples may require knowledge about a donor's individual characteristics, either in terms of background or in terms of biological relationship (parent, sibling, child, etc.) to other donors.

As a result, a nuanced approach to confidentiality is probably the best. Information disclosed generally through the HGD Project database should

not include any information that could be used to identify individuals. If particular researchers can demonstrate that they need further detail for scientific work and can guarantee appropriate protection of individual confidentiality in their actions, such data could be revealed to them. If they could show a very strong need to contact an individual donor, that might be allowed, acting through a culturally sophisticated and appropriate intermediary. Who should make these determinations, and on what grounds, are obviously crucial questions and are addressed in the discussion of control of confidentiality, below.

C. Group Confidentiality

Just as individuals may want to remain unidentifiable, so may larger populations. At the extreme, of course, this runs counter to the goals of the HGD Project. It cannot study the history and diseases of individual populations without knowing what populations provided the DNA samples.

On the other hand, it will usually not be necessary to provide sufficient information to define the exact group of people from whom the samples were taken. For example, rather than identify samples as coming from a particular settlement among the Navajo nation, the samples could be identified as coming from a population located in the northern portion of the reservation. Geographic coordinates about the sample site could be given with only limited precision, to the degree rather than the minute or second of longitute or latitude. The individual samples will contain other information about the individuals, but, except in the case of very small populations, that information should not allow researchers to identify the precise settlement from which the samples were taken.

Some communities may want their precise location protected; others may not care. The issue of disclosure of community location should be discussed with the group before beginning sampling. After a full discussion of the possible consequences, the group should choose between complete disclosure and confidentiality, along with a variety of intermediate positions.

We do not believe that researchers should normally encourage populations to seek complete confidentiality. As with individual confidentiality, however, there may be circumstances under which later researchers have good reasons for needing to know the identity of the sampled populations. Normally, even when communities choose to protect their identity, a reasonable degree of protection would be to allow disclosure of that identity to other researchers upon demonstration, to the HGD Project and, where possible, to the community, of such a good reason. That disclosure would, of course, have to be coupled with guarantees that the new set of researchers will keep the information appropriately confidential. Of course, if the

community finally chooses absolute confidentiality, the researchers must either abide by that wish or abandon the effort to study samples from this community.

D. Control of Confidentiality

The discussion above of both individual and population confidentiality noted circumstances where disclosure may be appropriate, but who should have the information that is to be protected or disclosed and who should make that decision?

The researchers who sampled a population will normally have complete records of the sampling process, including the identities of individual donors. That information should also be kept in a central location, probably associated with the proposed HGD database, in case the researchers' records become lost or otherwise unusable. Neither the central repository nor the particular researchers should normally be empowered to make a decision to release additional identifying information. Instead, the information should be released only if both the researchers and the HGD Project, acting perhaps through a regional HGD ethics committee, agree that it should be released. In addition, if the community or individuals can be contacted, their views should also be sought. The decision should be made only after full discussion of the circumstances of the request, the circumstances of sampling in that population, and guarantees from the recipients of the information that they will appropriately protect the confidentiality of the sampled individual or populations.

VIII. Education and Racism

Researchers involved in the HGD Project have an opportunity to provide important information to the communities they sample, and the communities in which they work. Seizing this opportunity may itself be ethically compelled.

The revolution in molecular biology and genetics of the past several decades has far outstripped the public's understanding of this science. The film *Jurassic Park* has probably done more to educate, or miseducate, people around the world about DNA than all the efforts of the scientific community. As a result of this public ignorance, misunderstandings of genetics, and of the human species, flourish.

Researchers involved in the Project have a unique opportunity to provide useful information about human genetics. The human species is, genetically, quite homogeneous. The genome of humans appears to differ, on the average, by about 1 base pair in a thousand. In coding regions of the

genome, the differences are closer to one in 10,000. Variation in the species, though of some scientific and medical value, is just not very great. And genetic variation within almost any human population is substantially greater than variation between any two populations. Some people, and greater and lesser percentages of some populations, have genetic traits that, in some contexts, convey advantages or disadvantages. The ability of adults to digest milk products is an advantage in an area where dairy products are common; hemoglobin variants that confer some protection against malaria can be beneficial where malaria is common. But there is no evidence that any populations have any general (or any very important specific) genetic advantages or disadvantages. In all but the most literally superficial ways, humans are just not very different genetically.

It is important that these points be more widely understood. The study of human genetics did not create hatreds between different populations, whether based on "race," ethnicity, religion, or other grounds. It is unlikely to end it. But it can defeat efforts by racists to enlist "science" in their causes.

Researchers are not usually preachers or public educators. But the researchers participating in the HGD Project will have a unique chance to make these important points about our species known. Researchers should affirmatively seek ways to inform their own populations and communities of this information. Researchers should consider using lectures, seminars, interviews, popular articles, and other methods to use their knowledge against the scourge of group hatreds. Institutional Review Boards and funding agencies should count such proposed public-education efforts positively in reviewing proposals for research in this area.

IX. Questions of Ownership and Control

The issue of "property rights" in the samples collected for the Project has provoked a great deal of discussion, much of it poorly informed. These issues are important, both for reasons of possible commercialization and for other purposes.

A. Patenting and Commercial Use

The issue of property arises primarily because of the possibility that DNA samples taken for the Project could have some commercial value. Searching for such value is *not* one of the purposes of the Project. And, in fact, it seems unlikely that any one sample or set of samples would lead to a commercially relevant breakthrough or a commercial product, but the possibility cannot be ruled out.

The issue of property rights in human tissues or in information derived from human tissues has a long and heated history. It currently is most controversial in connection with the patentability of "inventions" derived from the scientific analysis of human material. The patentability of human genes, of human proteins, of other human molecules, or of medications derived from them remains hotly contested in various nations and within particular groups.

The HGD Project has no position on questions of patentability, although individuals participating in the Project hold a variety of positions. The HGD Project does, however, hold clear positions about the commercial use of its samples and of the information derived from them.

First, it has resolved that it will not profit from any commercial uses of samples it gathers or knowledge derived from those samples. Second, it has vowed that to ensure that, should commercial products be developed as a result of the Project's collections, a fair share of the financial rewards shall return to the sampled populations. Any researchers who take part in the Project must accept these two points.

The implementation of these resolutions therefore affects this Protocol in two respects. First, it sets out the rules by which vvresearchers collecting samples for the Project, along with the rest of the Project, should be bound. Second, those rules must be disclosed as part of the process of obtaining informed consent from populations that may be sampled.

At this point, the Project has not reached a conclusion about the manner in which these resolutions shall be implemented. The North American Regional Committee believes the most promising alternative is contractual: anyone seeking access to the Project's samples or data would have to agree to be bound by contract to a set of rules concerning the rights of the sampled populations. The precise nature of those rules may vary among participating populations.

Three different approaches seem most plausible. Under the first approach, no one could make use of the Project's samples or data in a patent application or a commercial product without the express written permission of the sampled populations involved, and subject to whatever conditions they impose for that permission. Under vvthe second, anyone making commercial use of the Project's samples or data would pay a set percentage royalty to a designated body, to be used for the benefit of the sampled populations. Under the third, anyone making commercial use of the Project's samples or data would have to negotiate a reasonable financial payment with a trustee for the sampled populations, with the proceeds to be used for the populations' benefit. In both the second and third scenarios, a respected

international body, such as UNESCO, could be the fund-holder or trustee.

Which, if any, of these three plausible mechanisms the Project will adopt to implement its resolutions depends in large part on the preferences of sampled populations, national governments, and other interested parties. It may be that sampled populations should be offered a choice among the options.

We assume that the Project's international executive committee will adopt a policy before collecting begins for the Project under the auspices of the North American Regional Committee. If no formal position has been taken by the overall Project at that time, the North American Regional Committee intends to require researchers participating in the Project to give participating populations their choice among the three contractual options described above, with the third, trustee, option as a default position. We urge Institutional Review Boards similarly to require evidence of the arrangement accepted by the population before approving this kind of research.

The financial arrangements must therefore be part of the informed consent at the group level. This clearly could introduce a great deal of complexity and possible discord into the informed-consent process, but the issue cannot be ignored. Failure to discuss the financial arrangements may lead to disillusionment and distrust among the sampled population in the long run.

It is important, however, that the discussions not go too far in the other direction. No population should be enticed to participate in the Project in the hopes of reaping a financial bonanza from commercialization of their genes. Both commercialization and any resulting bonanza would be extremely unlikely in any particular case.

It does not seem necessary to discuss the arrangements concerning possible products as part of the individual informed consent, unless, of course, the donor asks about it. The arrangement would be with the population as a whole, through the appropriate legal or cultural leadership group. This seems appropriate as the commercial value of the data, if any, will come from its context within one or more sets of population data.{16}

In summary, the rules to govern the commercial use of the Project's samples must be accepted by the researchers and fully explained to the participating population. Barring other decisions by the HGD Project or other relevant authorities, the North American Regional Committee intends to establish a system of contractual protection of the population's interest, through the population's choice of its own control, control by a charitable third party (such as UNESCO), or a fixed-percentage royalty.

B. Other Issues

Although patenting and commercial use have received the most attention, two other related issues of control also must be discussed: the right to withdraw samples, and the right to order them destroyed.

As in other research, the HGD Project must allow participants to withdraw from the research. In one sense, that means deciding, at the last minute, not to donate a sample. But it should have a deeper meaning as well. If an individual, or a population, chooses to withdraw its participation in the Project, the samples collected from it should be returned (or destroyed) and the data derived from those samples should be eliminated from the Project's database. Withdrawal from the Project may necessarily be somewhat limited. If data has been published, it cannot be withdrawn. If samples have been distributed widely, it may not be possible to retrieve all of them, even though the samples remaining in the repositories could be returned or destroyed. The Project, however, must respect a legitimate decision to terminate participation as far as possible.

In addition to the right to withdraw from the Project, some individuals and populations may be unsettled by the possibility that their samples will be kept indefinitely. Researchers may want to raise with populations and individuals the possibility of a "sunset" date for storage of their samples. If the date chosen provides a reasonable amount of time -- perhaps 25 or 30 years -- the scientific value of the samples should have been largely or entirely extracted. The physical samples themselves at that point would have little value to science and their return or destruction may have great value to some populations. Whether this option is important will depend on the communities involved and their cultures.

Note {16} In addition, the only case law that exists on the subject, the *Moore v. Board of Regents* case from California, implies that individuals have very limited property interests in their cells.

X. Partnerships with Participating Populations

This section discusses the overall relationship that researchers should strive to create between themselves and the communities that they study. It is, in some respects, less concrete than other sections of this document. Although it contains some specific recommendations, it is more about a state of mind in working with communities.

The key word is "with." We believe that, ideally, researchers involved in collecting samples for the HGD Project should be closely connected with the populations that provide those samples, connected not as "scientist" and

"subject" but as partners. They might even be the same people, as communities may undertake to sample themselves in order to participate in the Project. That kind of direct scientific activity by the sampled population may prove rare, but it is the ultimate partnership in the research and the firmest guarantee that the community's interests and concerns are truly considered in the Project. Even when the collection is done by scientists from outside the community, opportunities for partnership exist and should be pursued with enthusiasm.

A. Involvement of the Population in Planning the Research

As discussed above, the researchers must have extensive contact with the population before beginning sampling. This period of contact is crucial to the process of informed consent, but it can also be used to create a working partnership between the researchers and the community. The best place to start is by involving the population in planning the research.

The community's participation may be particularly helpful in planning at least two aspects of the research: its goals and its methods. The goals of the research in this context include the questions that the research will seek to answer. Those questions include issues that may be very important to communities, ranging from their genetic relationships to other populations to their genetic susceptibilities to disease. The community may have specific question they find interesting. They may want to know how closely they are related to various neighboring groups or whether a particular disease that they think runs in some of their families has genetic links. Researchers need to look for these questions for several reasons.

First, the community's questions are entitled to respect because the community is interested in them. It is allowing the researchers to take information important to its identity and fairness dictates the use of that information, where possible, to answer the community's questions. And second, the community's questions may be questions that the researchers would find interesting. A community necessarily knows things about its history and health that no outsider, no matter how expert, can know. That knowledge may lead to questions of substantial scientific issues, questions the researchers would never know to ask.

Of course, the sampled population is unlikely to present researchers with fully worked out, scientifically testable hypotheses. The process will be a complex one, with the community explaining its interests, the researchers explaining what is possible, and then both sides starting again on the basis of that discussion.

The community also may help the researchers use the best methods of

sampling. It will know, better than the researchers, what days, times, and places are convenient. It may be able to point the researchers to individuals or families of particular interest.

Community involvement thus can improve the science. It can lead to the return of useful information to the community. And, perhaps most important, it can establish a relationship of trust and partnership between the scientist and the community, a relationship that can eliminate both the possibility and the perception that the researchers are exploiting the community. The community should be involved in planning the collecting, before anyone arrives to take samples. This could often be done as part of the initial process of seeking the informed consent of the community. Bodies charged with reviewing requests for funding or ethical issues in proposals should look to see the extent to which the researchers have established these early connections with the relevant population.

B. Involvement of the Population in Conducting the Research

Sampling for the HGD Project will involve numerous tasks. In most cases, some blood samples will be drawn. In all cases, numerous other DNA samples will be taken, from hair roots, cheek scrapings, or phlegm. The process must also include the collection of substantial ethnographic information, from the community at large and from individual participants.

We recommend that, whenever possible, the researchers use local people in performing these tasks. These activities will allow the local population to be more engaged in the research. Their involvement in the collection process, like their involvement in planning, should also prevent the reality or perception that the researchers are exploiting or abusing the population. And, in some cases, their participation may contribute usefully to the education or training of members of the population.

Obviously, the nature and degree of community involvement in the process will vary dramatically between communities. One researcher has told of contacting a genealogical society in Great Britain for help in locating residents whose families had long lived in that area. The society became excited by the Project, used doctors and nurses who were part of the society to draw blood, and had it delivered to the researchers. Many of the populations that participate in the Project will include physicians, nurses, scientists, anthropologists, and others with relevant skills. Where those skills are found in the population, researchers would be foolish not to try to use them. Even in populations that lack people with those skills, some of the tasks can surely be performed by local people, often after a little training.

As a matter of scientific ethics, when a scientific community exists in or

around the population, the researchers should make every effort to involve it in the research. In many parts of the world, researchers are making valiant efforts to participate in science while sorely lacking funds, equipment, colleagues, and communication. Whenever possible, researchers in the HGD Project should seek out scientists in the regions where they are sampling and engage them as equal collaborators in all aspects of the work, including authorship of reports of the work.

Participating communities are likely to differ in more ways than their levels of skills. Some may be willing to participate but eager to have as little to do with the researchers as possible; others may be enthusiastic about learning more about and participating in the research. The community's culture will have an influence on how it reacts; so will personalities, the time of year, individual work loads, and a host of other factors. Each population must be approached on its own terms, but in every case the researchers should try to create an appropriate role for the community in doing the work.

C. Involvement of the Population in the Results of the Research

Too often, participants in research projects have no ongoing involvement after donating their samples and time. This might generate resentment; it will inevitably waste an opportunity to get the public more involved in, and knowledgeable about, science. In the case of the HGD Project, this problem seems intense. The very point of the Project, after all, is to collect information about communities that can be useful in improving understanding of the history and health of that community. In those circumstances, it is absolutely imperative that the community be kept informed of the results.

Of course, "results" usually take much longer and are much less informative than the research participants expect. The researchers must make sure that the community has a realistic understanding of what results can be expected and in how many years. But the researchers also must make sure that those results are communicated to the community and that a path of communication is kept open for questions from the community to the researchers.

We believe that researchers should make, and keep, a commitment to the community to report to it on the research results at specified times and in specified manners. For example, a researcher might make a commitment to mail the community a report on the progress of the research at 18 months and to return in person to the community to give a report in two years.

The community must also know one or more ways to contact the researchers. The exact manner will vary enormously with the situation of the

participating population. Electronic-mail addresses will be useful to some populations, as will telephone or fax numbers. For others, the communication may have to be by mail or through an intermediary in the local area. The existence of such a usable link, in whatever form, is crucial to sustaining the role of the population as a partner in the research.

The population should also have access to other sources of information about the Project and the progress of analysis of their samples. To that end, we encourage researchers to provide participating communities with the means of contacting the relevant regional committee or committees of the HGD Project.

Conclusion

The Human Genome Diversity Project is an exciting effort to increase our knowledge of the human family: its evolution, history, diversity, and essential unity. Its breadth may be unique among major scientific endeavors -- it seeks to study our entire species in ways that will engage the attention of tens of millions of people. This scientific project intrigues people who are interested in origins, history, languages, cultures, medicine, and a host of other topics. In particular, anthropology, genetics, and molecular biology combine in the Project to reach out to an enormous audience, throughout the world.

This breadth of the Project is one of the things that makes it even more crucial that it be conducted according to the highest ethical standards. There may be no other scientific project that has the capacity to touch so many lives and minds. At the beginning of this document, we set out its guiding principles:

informed consent,
respect for the sampled population's culture, and
adherence to international standards of human rights.

If the Project is conducted according to these principles, it should enhance not only humanity's knowledge of itself, but also humanity's interest in, knowledge of, and confidence in science. If conducted poorly, without respect for and protection of the rights of those who participate, it may prove a disaster -- not for humanity, but for science. Researchers participating in this Project, and those who review their proposals for funding or ethical compliance, bear an enormous responsibility both to participating communities and to science. This document is an effort to help them discharge those responsibilities well.