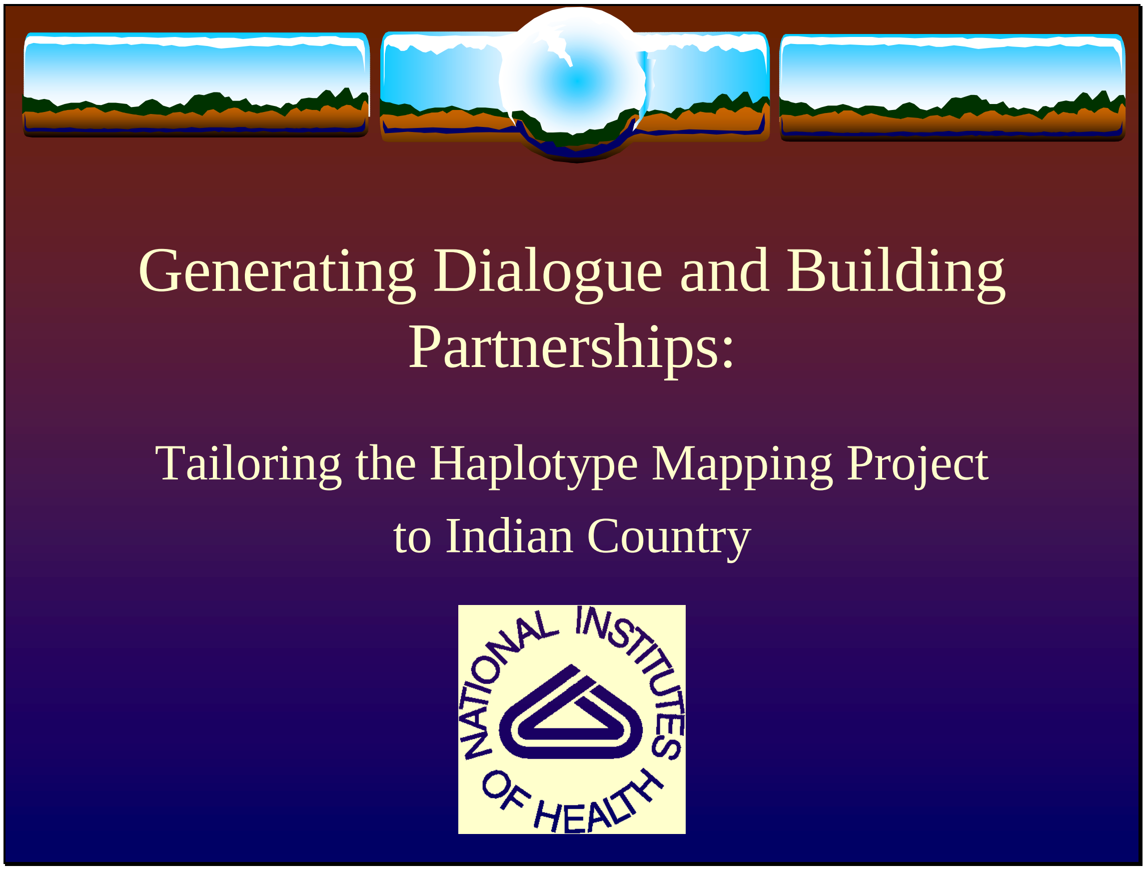

Generating Dialogue and Building Partnerships:

Tailoring the Haplotype Mapping Project to Indian Country

Prepared by Emily Robyn Van Dyke
Nation Building II
May 2003

HARVARD UNIVERSITY NATIVE AMERICAN PROGRAM
AN INTERFACULTY INITIATIVE OF HARVARD UNIVERSITY

Generating Dialogue and Building Partnerships:

Tailoring the Haplotype Mapping Project
to Indian Country

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Acknowledgements: Special thanks to Amy Besaw, Terrelene Gene, Jennifer Lincoln, Alyce Adams, Karen Diver, Jean McEwen, David Burgess, Joseph Kalt, and David Altshuler for their invaluable guidance and insight.

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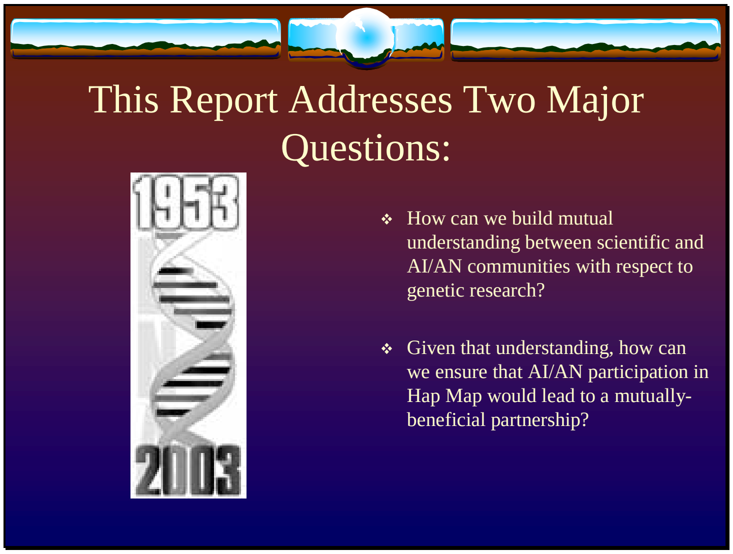

This Report Addresses Two Major Questions:

- How can we build mutual understanding between scientific and AI/AN communities with respect to genetic research?
- Given that understanding, how can we ensure that AI/AN participation in Hap Map would lead to a mutually-beneficial partnership?

This report seeks to equip Principal Investigators considering research in Indian Country and any associated researchers, sample collectors, repository technicians, and other associated members of the research team to make clear, comprehensive, and balanced presentations regarding the Haplotype Mapping Project to potential partners in Indian Country. In addition, it seeks to present a culturally aware and constructive framework through which such partnerships might be formed if and when a small-scale Haplotype Mapping Project is undertaken in Indian Country.

The following has been composed in the interests of promoting understanding, constructive dialogue, cooperation, and partnerships between the National Human Genome Research Institute (NHGRI), a division of the National Institutes of Health (NIH), and Indian Country. It seeks to compile much of the salient data available to date regarding the specific issues surrounding genetics research in Indian Country. Data collection efforts have centered on informal meetings in Bethesda, Maryland, which occurred on March 13th and 14th, and on online literature searches.

This report has been assembled due to concern that the original Haplotype Mapping Project (Hap Map) design preemptively excluded any American Indian or Alaska Native (henceforth to be abbreviated AI/AN) involvement. At a March 13th-14th meeting at NIH, the American Indian community leaders who attended the meeting made a strong recommendation that further efforts be made toward offering an opportunity for involvement in the Hap Map Project to AI/ANs.[1] There was concern that further exclusion from basic health research could result in AI/AN communities being left even further behind in terms of the standard of care available to them.

AI/AN involvement in the Hap Map Project would require extensive outreach efforts, long-term communication with AI/AN partners, and a respectful contractually binding equal partnership with the involved AI/AN communities. It should also be based on several fundamental precepts:

- Involvement should *promote* tribal sovereignty
- Involvement should be an exercise of AI/AN rights to self-determination
- Participation should initiate long-term cooperation between NHGRI, associated researchers, and the AI/AN partner

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[1] For a list of meeting participants, see Appendix F.

This report is organized into three main sections:

Organization of this Report

- Introducing the *challenge* of building communication and partnerships between Indian Country and scientific research institutions
- Offering an *analysis* of ways in which to bridge the divide between these divergent perspectives and cultures
- Proposing an *action plan* for implementing this involvement

Challenge

Analysis

Action Plan

NHGRI hopes to facilitate an understanding among researchers or technicians who may be involved in genetics research in Indian Country in the future that any research that has been or could be perceived as detrimental to indigenous nations does not and cannot benefit either NHGRI or the researchers' own scientific reputations. Genetic research done in partnership with indigenous nations must be done with full and informed consent of both the individuals and the communities involved and with an utmost respect for each indigenous nation's values, beliefs, and sovereignty before, during, and after this research is conducted. In addition to clarifying the background knowledge through which this project may be perceived in Indian Country, this report seeks to help equip researchers to provide an informative and culturally sensitive briefing for indigenous nations and for their community members. Because the sampling process involves drawing blood samples and creating immortal cell lines, participation in the project will be anathema to many AI/ANs. However, these aspects of the project are not anathema to all AI/ANs. Furthermore, participation in the HapMap Project could generate positive educational and skilled labor training opportunities for indigenous nations in addition to increased applicability of disease treatments over the long term. Partnership through the Hap Map Project is not the only means by which an AI/AN community could partner with NIH, however. NIH's Native American Research Centers for Health (NARCH) Program also has the capacity to offer opportunities for skills development and health research in AI/AN communities. However, especially due to the concern on the part of several indigenous leaders that American Indians were preemptively excluded from the Haplotype Mapping Project, and while bearing in mind that genetic research in Indian Country is a highly controversial and divisive issue, NHGRI is endeavoring to initiate dialogue that may lead to partnerships through the HapMap Project or through future initiatives.

This report concludes with Appendices that feature copious amounts of information including sample outreach materials, models that explore ways in which partnerships with interested indigenous nations may be formed; resolutions on genetics research ethics and procedures; details on the development of the Haplotype Map Project; Former President Clinton's applicable federal Executive Order and Memorandum on Government-to-Government relationships, scientific literature relating to the Hap Map Project, and the participant list for the March 13th-14th, 2003 Hap Map Meeting

To begin this exploration of the way in which the Hap Map Project may be adapted to suit the needs of Indian Country, here are some definitions of key terms that will be useful in subsequent sections.

Key Terms

A *community* is a group of people sharing a common interest – for example, cultural, social, political, health, and/or economic interests – but not necessarily a particular geographic association

Collaboration in participatory research is a partnership among equals with complementary knowledge or expertise

A *partnership* is a mutually respectful relationship based on sharing responsibilities, costs, and benefits leading to outcomes that are satisfactory to all partners

(Courtesy of Macaulay et al. "Participatory Research Maximizes Community and Lay Involvement. " *BMJ* 1999; 319:774-778)

THE CHALLENGE

Challenge

To develop mutual understanding and communication between scientific and indigenous communities regarding genetic research

- The perspectives and priorities of research scientists are often radically different from those of the AI/AN communities with which they may seek to work. This is by no means an insurmountable hurdle, but these different perspectives and priorities must be taken into account, and time and effort must be spent in order to help both parties understand each others' goals, plans, and concerns.

- Past failures to acknowledge and contend with these differences have lead to miscommunication, feelings of exploitation, and an unfortunate tendency to view AI/ANs as subjects to be studied rather than as partners with whom researchers should strive to work on equal terms. Some useful questions to ask are:

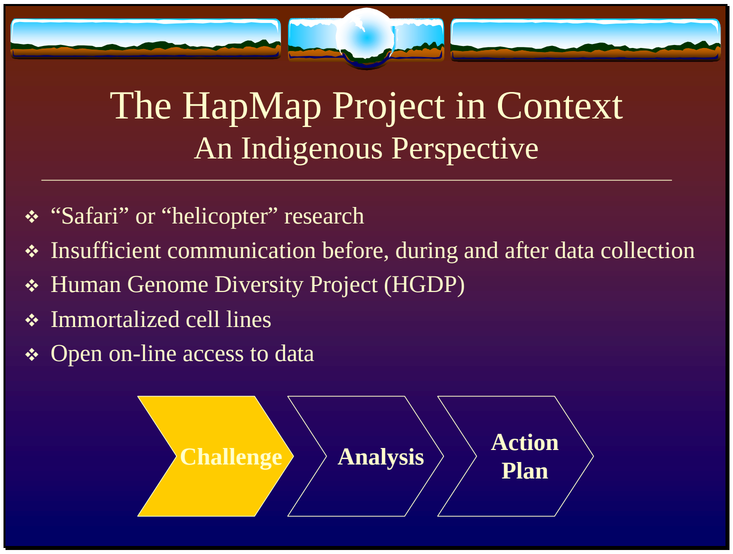
    1. What barriers are we currently facing as researchers working in the field of genetics research in Indian Country?
    2. What barriers are American Indian and Alaska Native organization and communities facing with respect to health research?

- Given this history, it is also especially important to recognize the commonalities between these disparate communities. Both potential partners probably have a shared goal of understanding human disease and accessing better ways to treat it.

If one were to ask:
Do you care about health?
The answer would be "yes" for both parties.

- When explaining the impetus behind the project, one might mention just how little is known about most human disease. The idea of the HapMap Project is that, with the genomic sequence information now available, we should use it to elucidate some of all that we *don't* know about human disease.

BACKGROUND



The HapMap Project in Context

An Indigenous Perspective

- “Safari” or “helicopter” research
- Insufficient communication before, during and after data collection
- Human Genome Diversity Project (HGDP)
- Immortalized cell lines
- Open on-line access to data

Challenge → Analysis → Action Plan

“Although native people may walk a different path, we are all walking through this life together. Even if our belief systems are different and one person believes in heaven while another believes in the spirit world, our spirits exist. Do not harm the spirits.”[2]

- Because AI/ANs have, at times, been regarded as subjects or specimens to be analyzed rather than intelligent and resourceful communities with which to partner, a significant amount of past research in Indian Country has involved a researcher dropping into a community, collecting whatever data he or she seeks, and then leaving with that data – never sharing research results with the community or engaging in a mutual exchange of expertise and resources. This mode of research is sometimes called “safari” or “helicopter” research.

- The Hap Map Project methodology may necessarily exclude some AI/AN nations from seriously considering participation in the Project. For instance, Navajo elders teach many illnesses are the result of the mishandling of body specimens once they are separated from the body and that genetics research can be a threat to Navajo health and wholeness because such research can involve compromising the sacred. For many Navajo, the bodily specimens that are currently used to extract DNA (e.g. blood, hair, and saliva) are sacred. Along a somewhat similar vein, “the Kanaka Maoli believe that every piece of an individual’s body contains a life force, *Mana*, that flows through the universe…. When a researcher fails to respect the Kanaka Maoli worldview, the researcher will cause disruption that may result in illness and injury to the Kanaka Maoli.[3]

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[2] Connie Garcia, Acoma Pueblo, Meeting Participant at the American Indian and Alaska Native Genetics Research Policy Formulation Meeting of February 7-9, 2001.

[3] Genetics Research Policy Formulation Meeting Summary Meeting Report. February 7-9, 2001.

The Human Genome Diversity Project

An "important resource for understanding contemporary problems and issues raised by proposals to study human genetic differences"[4]

Even though the Hap Map Project has very different goals from that of the Human Genome Diversity Project, the way in which Hap Map is perceived in Indian Country will reflect past experiences and debates regarding genetic research. The issues surrounding genetic research in Indian Country are inextricably linked with beliefs about self-identity, power relations between Indian Country and the "dominant society," issues of colonialism, intellectual property rights, and the origins of human diversity.

In 1991, population geneticists and evolutionary biologists proposed a worldwide project to sample and archive human genetic diversity. The project's goal was to "collect and preserve the genomes of 'isolated indigenous populations'," so the project could lead to "enormous leaps in our grasp of human origins, evolution, prehistory, and potential." They urged the Human Genome Project to "act swiftly before these isolated populations 'merged with their neighbors… destroying irrevocably the information needed to reconstruct our evolutionary history'".[5] Much to the surprise of the project's organizers, the Diversity Project aroused outrage and opposition from several indigenous groups and leaders. "In 1993, the World Council of Indigenous Peoples dubbed the project the 'Vampire Project.' In 1995, indigenous leaders from the USA, Canada, and Latin America issued a Declaration of Indigenous Organizations of the Western Hemisphere condemning the Project."

Tribal Sovereignty and Research
(Excerpted from the IHS informational document "The Role of Community in Research with Stored Tissue Samples")

Tribal sovereignty was recognized in the Constitution, and in the past 35 years has become stronger through Federal law, case law, and U.S. Supreme Court decisions. A major implication of Tribal sovereignty for research involving AI/AN people is that Tribal governments can legally prohibit or regulate research within their reservation, and even bar researchers from entering it.

The firestorm did not occur all at once, however, and it was not necessarily inevitable. The Diversity Project organizers are often portrayed as hopelessly naïve and obviously misguided individuals who were following a line of research that only naturally provoked controversy, yet the issues and problems that they faced are still very much applicable to the Hap Map Project. In the case of the Diversity Project, concern over the project design first came to light on April 6, 1993, when the Rural Advancement Foundation International (RAFI), an Ottawa-based international research organization that had been advocating on behalf of biodiversity and intellectual property rights since the 1970s, sent Diversity Project

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[4] Jenny Reardon. "The Human Genome Diversity Project: A Case Study in Coproduction" in *Social Studies in Science* 31/3: 357-88.

[5] Quotes taken from Jenny Reardon's "The Human Genome Diversity Project: A Case Study in Coproduction.".

organizers a letter expressing concern that the Project represented a serious threat to the livelihood and autonomy of indigenous groups. However, partly due to a lack of knowledge about past controversies regarding genetic research in Indian Country, the Project organizers were not equipped to structure the project or their responses to concerns about its implications such that constructive dialogue and the useful interchange of ideas could have resulted.

Lacking this background knowledge in what "genetic research" meant to many indigenous groups and without reflecting upon the challenge that the Project results might have made to many indigenous worldviews, the Project organizers were hopelessly handicapped in trying to respond to concerns about the Project. Partially due to preexisting mistrust of the motives of such projects and partially due to the inability of the organizers to communicate effectively with concerned organizations like RAFI, critiques and alarm spread about the Project, as did the suspicion that "the Project arose out of Western economic interests that sought to transform the genetic differences of indigenous peoples into dollars."[6] The use of terms such as "Isolates of Historical Interest" to mean modern-day vibrant and surviving indigenous communities only exacerbated the feeling that these genetic differences were going to be studied at the whimsy and for the profit of rich corporations and outside researchers with no interest in the preservation of current indigenous cultural and political autonomy. Issues also arose over who had been chosen to speak for indigenous interests at planning meetings and over the perceived preferential distribution of information on the project to scientists rather than to the communities that would potentially affect most directly. Rather than seriously addressing these concerns, project organizers tended to argue that the arguments of concerned parties were based on misinformation and argued that they were "factually incorrect and grossly misleading." Thus rather than capitalizing on the opportunity to engage in mutually instructive and useful dialogue with these concerned parties, they reacted in a somewhat defensive but uncommunicative manner. Furthermore, they failed to appreciate the underlying differences in perspectives and assumptions that were causing much of the rancor.

What caused the vehement response to a seemingly well-intentioned and inoffensive project? Perhaps if indigenous peoples had not been subjected to policies of annihilation and assimilation from many different governments for hundreds of years, then the response would not have been so negative. Perhaps if indigenous peoples had a secure power base and did not feel constantly under onslaught from the "dominant society" to disappear, assimilate, and quietly acquiesce to the loss of rights, lands, and personal identity, then the goals and methods of the project would not have seemed so threatening. However, as Jenny Reardon states, "what is at stake in understanding and ordering 'human genetic diversity research' is not merely the existence of a single truthful record of human diversity and history, but also constructions of identity and authority that have the potential to affect who will have a voice, rights, resources and authority in emerging governmental and legal orders around the globe. In an age where the connections between science, power and governing are harder to deny, especially in the field of human genetic research, scientists, ethicists and policy makers can only gain

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[6] Reardon, 370.

by reflecting on the causes of controversy and protest surrounding such projects." In addition, as Debra Harry points out, the project design prompts the compelling question of: "why the tremendous interest in saving the genes of Indigenous people and not the people themselves?"[7]

Yet notwithstanding the highly questionable objectives of the Diversity Project, the "Model Ethical Protocol for Collecting DNA Samples" generated for this project required individual and group consent, deliberations about appropriateness, and other checks and balances to try to make sure that the project would not be damaging to any communities involved. However, the *implementation* of the project fell abysmally short of the theoretical standards used in the project design. Especially given the rocky and rancorous history of genetics research in Indian Country, we cannot afford to allow this precedent of generating fairly enlightened theoretical models that are not actually *used* to continue.

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[7] Debra Harry. "The Human Genome Diversity Project: Implications for Indigenous Peoples." Available at www.hartford-hwp.com/archives/41/024.html

The HapMap Project in Context

A Research Perspective

- Pre WWII
  - Edward Jenner, Claude Bernard, Louis Pasteur, Walter Reed
- Post WWII
  - Nuremberg Code (voluntary consent, benefits should outweigh risk, ability of the subjects to terminate participation)
  - Willbrook, Jewish Chronic Disease Hospital, Migram, Humphries, USPHS Tuskegee Syphilis Study
  - The Belmont Report (respect for persons, beneficence, justice)

One starting point for researchers may be to review some of the key historical precedents for current ethical principles of human subject research (see above slide and Appendix B for major subjects for review).

Once discussions begin with AI/AN nations, a dialogue to help both parties understand each other's perspective would be expedient. Just as researchers may not have had access to the salient information regarding AI/AN perspectives on and experience with genetics research, AI/AN communities may not know a great deal about the research process. Therefore, it may be useful to simply describe the basics of the research process to potential partners:

- Identification of a potential topic can occur when a researcher sees a medical condition and wants to explore how it comes about. Alternatively, a researcher may choose to focus on a certain topic because it is part of a larger national research agenda, such as a set of NIH research initiatives. A researcher may also have a personal interest in a given topic.

- The best way to pursue a topic may be to draw on human subjects, animal models, computer simulations, or other techniques.

- Funding is also a necessary component of research, and researchers may have to write grant

Note: One way in which to promote collaboration and partnerships between researchers and indigenous communities could be for NIH to make research into the health concerns of nations with which it partners into a part of the national research agenda. In this manner, partnership with NIH could come to represent a mutual and meaningful gift giving rather than a one-way extraction of raw data and human products.

proposals to a number of funding agencies. Grant proposals are reviewed for scientific merit as well as human subjects protection. The will have to include a complete plan of the intended study, including its goals, hypotheses, details of the plan for data collection, the types of data that will be used, the methods of analysis, and the decision making process. The plan must be submitted to an IRB (Institutional Review Board) – sometimes several – and may need to undergo revisions. Throughout this process, the discourse between the tribe, the researcher(s) and the funding agency should be ongoing. The tribal council and health board will also need to review the proposal, and the tribe may also form focus groups to specifically to review a given research proposal.

- Data collection and analysis should be done in accord with the previously agreed-upon methods approved by the tribal health board and all applicable IRBs. If any changes to the methodology become necessary, then these boards must review the proposed changes.

- Analysis will include statistical methods to describe the data, and the results from the analysis are reported to the tribe, the IRB(s), and the scientific community.

It may also be useful to note to potential partners some of the difficulties and constraints inherent in the position of the researchers:

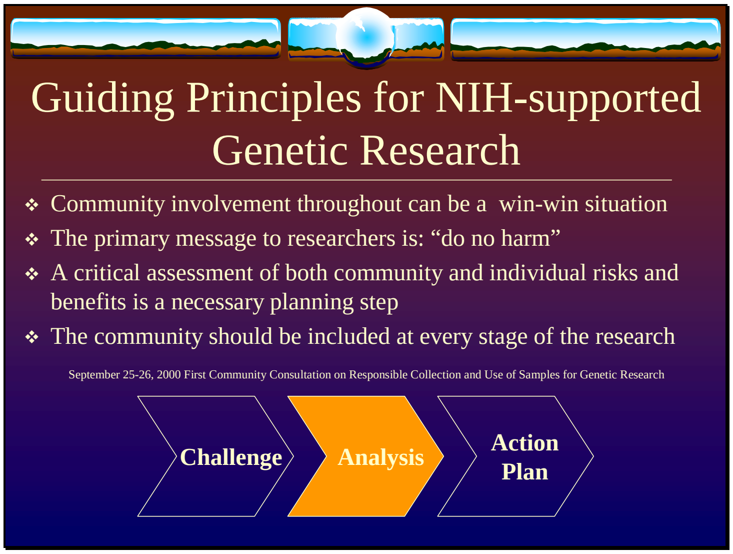
- Communities may confound geneticists interested in genetic variations with geneticists in human migration or human evolution studies.

- Because diabetes and alcoholism both have significant socioeconomic and lifestyle causation factors, and communities may not appreciate that genetics research truly is an important component of understanding these disorders.

- While very necessary, the many layers of bureaucracy involved in consulting IRBs, tribal health boards, and other authorities, cause time delays, funding challenges, and evoke the specter of intimidation in that the researcher must personally seek the permission of the tribal health board and the community at large to conduct the proposed research.

- Control over the process and the product, including sample taking, storage, maintenance, and location, as well as the publications that result from the research, is not always maintained in the hands of the particular researcher who took the samples.

- Taking on a research project in Indian Country is also intimidating because of the possibility of negative consequences if the project is not structured and carried out well or, even if the project itself is carried out well, if the research results lead to stigmatization because the general public does not understand the implications and limitations of the research.



Guiding Principles for NIH-supported Genetic Research

- Community involvement throughout can be a win-win situation
- The primary message to researchers is: “do no harm”
- A critical assessment of both community and individual risks and benefits is a necessary planning step
- The community should be included at every stage of the research

September 25-26, 2000 First Community Consultation on Responsible Collection and Use of Samples for Genetic Research

Challenge

Analysis

Action Plan

The complex and sometimes exploitative nature of past research conducted in Indian Country makes it especially crucial to design any Hap Map project in Indian Country with acute attention to respecting the rights and beliefs of the AI/AN partner community. Just as crucial are follow-ups with researchers to make sure that the high standards developed for the project design are upheld on the ground.

- The knowledge, expertise, and resources of the involved community are often key to successful research
- Three primary features of participatory research include collaboration, mutual education, and acting on results developed from research questions that are relevant to the community
- Participatory research is based on a mutually respectful partnership between researchers and communities
- Partnerships are strengthened by joint development of research agreements for the design, implementation, analysis, and dissemination of results
- Results of participatory research both have local applicability and are transferable to other communities

(Courtesy of Macaulay et al. “Participatory Research Maximizes Community and Lay Involvement. ” *BMJ* 1999; 319:774-778)

COMMUNICATION

Why is communication vital to success?

- A foundation upon which to base decisions and create ideas
- A means of focusing on where you want to be and what needs to be done to get there
- A tool for discovering opportunities, optimizing opportunities and initiating change
- Gain insights that would not otherwise come to light

Challenge → Analysis → Action Plan

Courtesy of Ontario's Ministry of Agriculture and Food Fact Sheet

Why develop a Communications Plan?

- A communications plan enables you to clearly and logically summarize what you want to say to your intended audience and to map out how you will deliver that message.

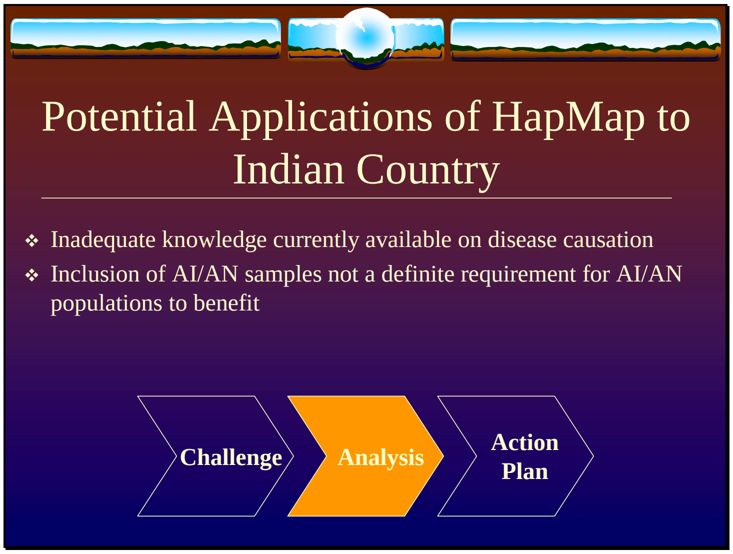
- Through dialogue with the community, weaknesses in the research plan may come to light. Insights about language barriers, beliefs, or specific concerns that could ultimately have threatened the feasibility of the research or undermined the validity of its results may come to light. These insights would probably not otherwise have been elucidated. Communication can also lead to a community-wide buy-in on the project, which may be helpful on a number of different levels.

A Communications Plan Can Serve Many Different Purposes:

To inform: You may need to let interested parties know who you are, what you can do for them, what they can do to help you, or even just how to get in touch.
To build understanding or change behavior: You may want to encourage others to think, act or feel a certain way; to stop smoking, for example. This can involve appealing to feelings, self-interest, or a person's imagination.
To prevent misunderstandings: Even a small misunderstanding can create large problems for your organization. You can ensure good communication by putting yourself in your audience's position, paying attention to their needs and getting to know them.
To present a point of view: Often, this is all you need to do to accomplish your goal.
To lower barriers between groups and individuals: These barriers may range from information overload to suspicion and prejudice.

Courtesy of Ontario Ministry for Agriculture and Food Fact Sheet on Communication Planning for Organizations, available at http://www.gov.on.ca/OMAFRA/english/rural/facts/93-045.htm

ANALYSIS



Potential Applications of HapMap to Indian Country

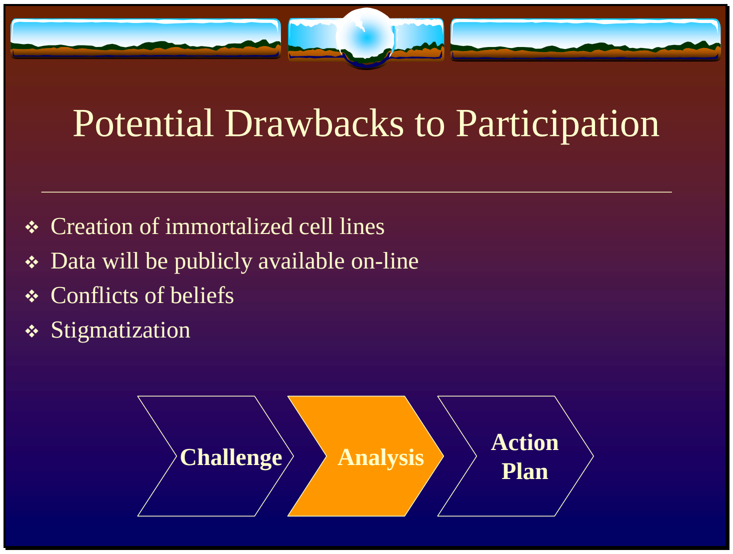
- Inadequate knowledge currently available on disease causation
- Inclusion of AI/AN samples not a definite requirement for AI/AN populations to benefit

Hap Map data may lead to much more effective treatments for future generations by providing the information necessary to create better treatments and a better understanding of disease and drug response.

- NHGRI recognizes the need to respect community rights, and it will not use any samples from a community that has decided against participation. As such, this is an opportunity – even if no indigenous group decides to participate – for the NHGRI to demonstrate its commitment to honoring the sovereignty of native nations.

- There is *so much* that we *do not* know about human disease. For instance, there is not a single effective treatment for obesity. You can try to tell people not to eat, but it’s not effective. Common diseases including cancer, obesity, diabetes, and hypertension affect all communities, and a better understanding of the genetic basis for these diseases could be invaluable in developing more effective prevention techniques and treatments in the long run.

- NHGRI does not *need* to include samples from AI/ANs in order for the HapMap to be useful in understanding diseases in AI/AN populations. The HapMap data *may* prove to be *more* useful in understanding some diseases in AI/ANs if it includes AI/AN samples. However, we cannot predict *how* much more useful the HapMap would be for AI/ANs if their samples are included *unless* we study those samples.



Potential Drawbacks to Participation

- Creation of immortalized cell lines
- Data will be publicly available on-line
- Conflicts of beliefs
- Stigmatization

Challenge **Analysis** **Action Plan**

- Both giving blood samples and allowing immortalized cell lines to be made using those samples is anathema to the beliefs and values of some native peoples.

- Yet the creation of cell lines is necessary for this project:

    1. Scientists cannot obtain sufficient genetic material for the project without generating cell lines from the samples taken.
    2. The Hap Map project represents a very coarse first exploration of the 400,000-1million SNPs of the genome. The project is limited by the technology that is currently available and will be able to do more with the data gathered once more technological advances occur.
    3. As researchers use the cell lines more, collective knowledge about successful methodologies will accumulate in the science community.

- In order to promote research into causes of disease, the HapMap data will be made publicly available as soon as it is generated. There is no foolproof way of confining the use of this data to investigations of genetic predispositions for disease and side effects to drug therapies. Given the widespread accessibility of a publicly available database, there is no way to guarantee that independent researchers will not use the data to investigate the very questions posed by the HGDP, including explorations of the "variation, selection, population structure, migration, mutation frequency, mechanisms of mutation, and other genetic events of our past." Thus while the project is not designed to study human evolutionary history, the database could still ultimately be used for this purpose, and resultant research may yield conclusions that are in conflict with the creation beliefs of the indigenous participants (or non-participants). This may or may not be an issue for AI/AN communities: one does not have to accept that the genetic analysis trumps the wisdom of oral tradition. However, some groups have expressed the fear that "a scientific theory of evolution and migration that is antithetical to an Indigenous group's common beliefs" might be used, at some point in the future, to challenge indigenous territorial land claims or to dispute indigenous rights to the lands that they now hold.[8]

- Stigmatization of specific communities, individual families, and native peoples in general are significant risks of an extension of the Hap Map project to include AI/AN samples. Due to incomplete public understanding of genetic predisposition for disease, AI/ANs could be labeled as the group with a predisposition for diabetes, for example. Furthermore, the decision of one nation to participate could affect other sovereign nations because assumptions may be made about all AI/ANs based on genetic information obtained from one or two groups during the HapMap project. If gene variants are found that predispose holders for disease, then the prevalence of that gene will probably fluctuate across populations. Due to these issues, NHGRI may want to consider a program of public education co-incident with outreach and negotiation efforts so that genetic research with respect to AI/AN communities and, indeed, all communities, may be better understood and may lead to less stigmatization.

BRCA1 and Ashkenazi Jews: The Ashkenazi Jewish population has been subjected to a certain amount of stigmatization because the BRCA1 gene, which predisposes people with mutations in this gene for a higher risk of developing breast cancer, is *known*. However, there may be *many* other genes that predispose people for breast cancer; these other genes just have not been isolated yet. Thus there is an association between breast cancer and Ashkenazi Jews even though science does not support this association.

Sickle cell anemia was also dubbed by some as an African American populational weakness. Yet this mutation, when heterozygous, conveys resistance to malaria.

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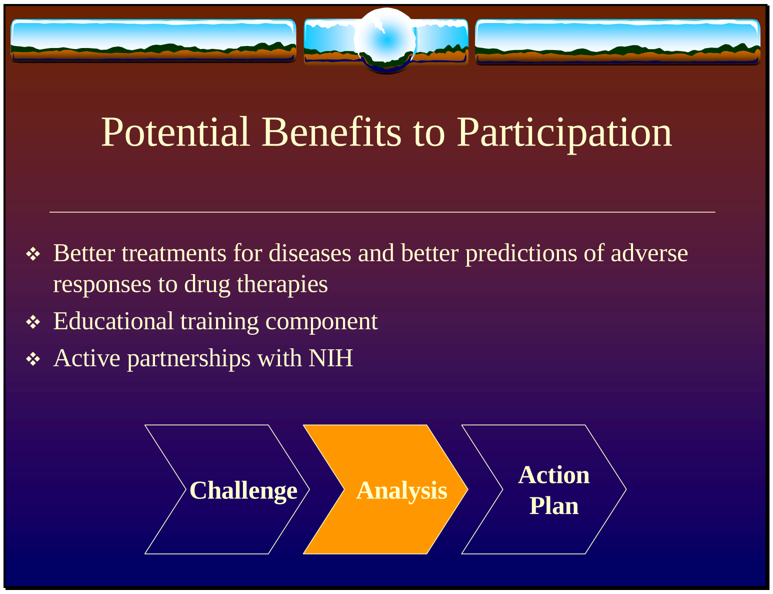
[8] Harry, 1.



Potential Benefits to Participation

- Better treatments for diseases and better predictions of adverse responses to drug therapies
- Educational training component
- Active partnerships with NIH

Challenge

Analysis

Action Plan

- The Hap Map Project may help to identify patterns of susceptibility genes for common diseases and to assess genetics risk/efficacy factors of various therapeutic drugs and their potential side effects. It could be considered yet another form of paternalism to try to *protect* potential AI/AN partners from all of the possible detrimental outcomes of participation in this research at the cost of presenting a balanced picture from which AI/AN communities can decide for themselves whether they want to participate. If we only point out the drawbacks, then AI/AN communities will justifiably ask why we are presenting the project as an option at all.

- In the outreach stage, AI/AN communities need the raw information that will help them to weigh the risks of participating against the risks of not participating. If the community decides to go forward with the project, then a continual dialogue must be maintained regarding ways in which to minimize drawbacks and maximize benefits.

- Storage of samples on-site could provide training opportunities and skilled labor development. This, in turn, could stimulate interest in further education in the sciences on the Reservation.

- An active partnership with NIH and NHGRI could blossom into future projects and further cooperation to combat health concerns on the Reservation. *However*, participation in HapMap is *not* the only means by which to build a partnership with NIH. Native American Research Centers for Health (NARCH) involvement is an alternate option. NARCH seeks to develop AI/AN scientists and health professionals engaged in research, to work in partnership with AI/AN organizations to reduce distrust by AI/AN communities toward research, to encourage research linked to the health priorities of the AI/AN tribal nations, and to reduce health disparities. NARCH partnerships might well involve much more direct and rapid dividends for AI/AN nations because they are specifically designed to address the health care needs of the nation involved.[9]

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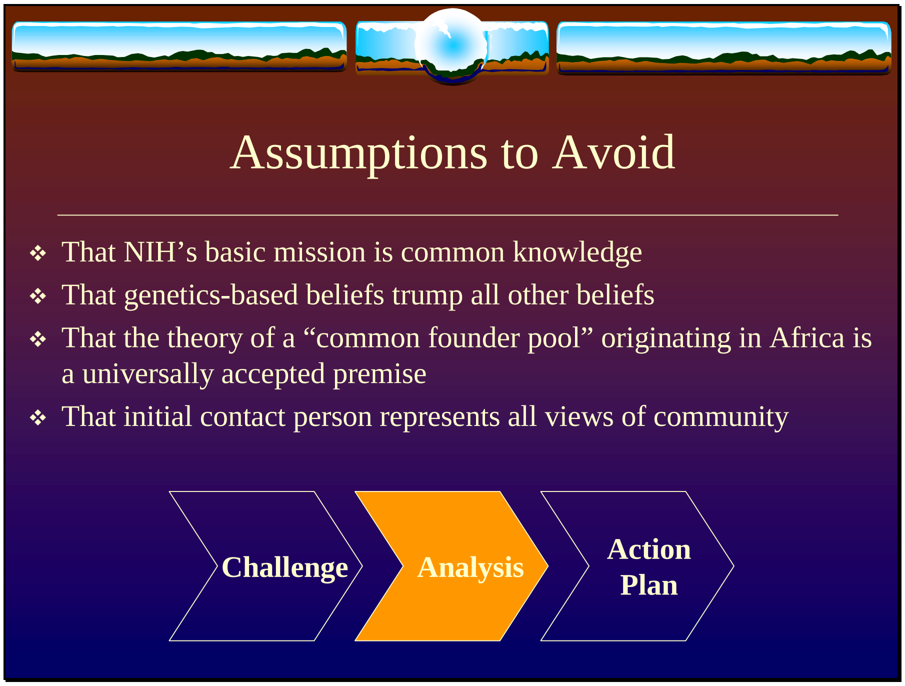
[9] See Appendix B for more information on NARCH.



Assumptions to Avoid

- That NIH's basic mission is common knowledge
- That genetics-based beliefs trump all other beliefs
- That the theory of a "common founder pool" originating in Africa is a universally accepted premise
- That initial contact person represents all views of community

Challenge

Analysis

Action Plan

Making the assumptions listed above may cause potential partners to stop listening and may cause an unnecessary barrier to communication. One may talk about the significant genetic commonalities between peoples without ranking one worldview over another and without assuming that genetic knowledge is *the* right answer.

A short description of NIH should be included in each pamphlet, video presentation, and other outreach materials, for instance:

- "Simply described, the NIH's goal is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold. The NIH works toward that goal by conducting research in its own laboratories in Bethesda, Maryland; supporting the research of nonfederal scientists throughout the country and abroad; helping to train research investigators; and fostering communication of medical information to the public."[10]

While it is important not to assume that the community has an active working knowledge of NIH and its initiatives, it is also important not to assume that its members have no knowledge of genetics or genetics research in Indian Country. Essentially, it is best to avoid assumptions as much as possible throughout the planning, implementation, and post-sampling stages.

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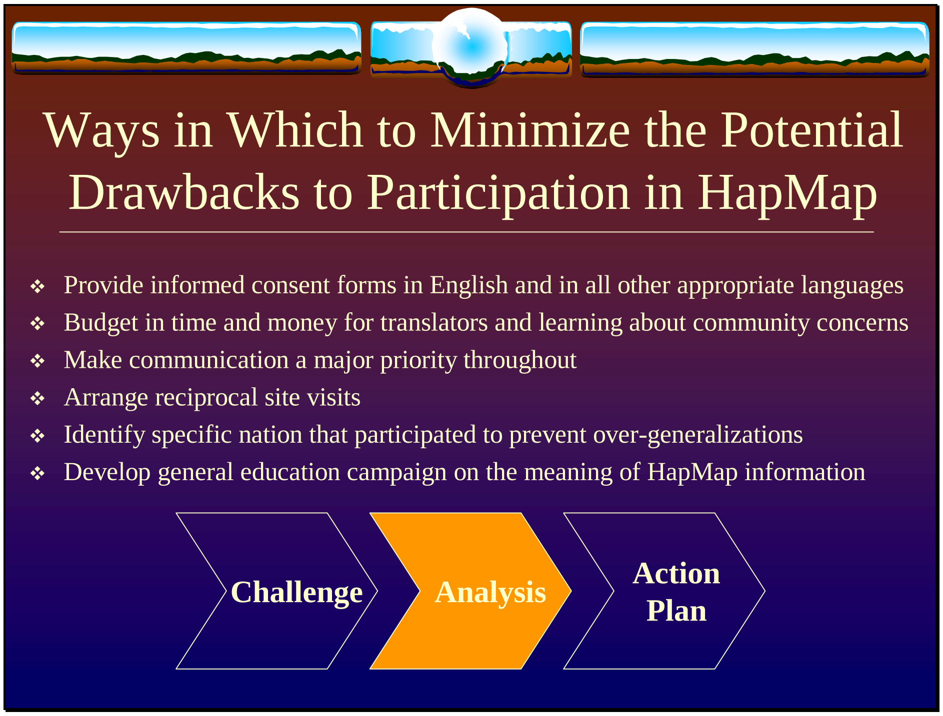
[10] Courtesy of the Human Genetic Variation teaching packet generated by NHGRI.

Speaking with anthropologists or other researchers who have worked with the community is one way to start the process of learning about an AI/AN community's perspectives and priorities, but it is only a beginning. Such consultations with people outside the community are no substitute for actually visiting the community. In addition, while it is best to do background research into the community, when researchers speak with members of that community, it would be ideal for them to be honest and straightforward: if researchers are willing to admit that they simply do not know a great deal about the AI/AN community's culture, history, political structure, or the day-to-day challenges it faces, then members of that community will probably be much more inclined to share this vital background knowledge with researchers. They will also be more inclined to collaborate meaningfully with researchers further regarding Hap Map discussions if they have already had constructive conversations with the visiting researcher. Furthermore, it is important to inquire about details of how a mutually beneficial partnership might be developed so that AI/AN involvement in the Hap Map Project would definitely not mean the further erosion of AI/AN sovereignty or belief in the potential of genetic research.

It is also very important to recognize the vast amount of diversity that exists between different AI/AN nations regarding economic and empowerment status, governmental structures, and perceptions of genetic research. For example:

- A researcher might be visiting a traditionally matrilineal society community in which the current government somewhat ignores the authority of the clan mothers. As in many other circumstances, the visiting researcher would need to be careful to consult all relevant parties and not to automatically assume that a given official leader represents the views of all community members.

While the post WWII inclination toward engaging in discourses of universal humanism, sameness, and unity -- rather than dividing the world into superior and inferior individuals based on race, ethnicity, and nationhood -- is widely considered a very positive development, it does not follow that the beliefs of indigenous peoples regarding the location of their origins should be denied or disrespected any more than researchers should categorically assume that all Christian participants in a study believe that all the world's flora and fauna evolved over millions of years rather than being created by God within the space of seven days.



Ways in Which to Minimize the Potential Drawbacks to Participation in HapMap

- Provide informed consent forms in English and in all other appropriate languages
- Budget in time and money for translators and learning about community concerns
- Make communication a major priority throughout
- Arrange reciprocal site visits
- Identify specific nation that participated to prevent over-generalizations
- Develop general education campaign on the meaning of HapMap information

Challenge
Analysis
Action Plan

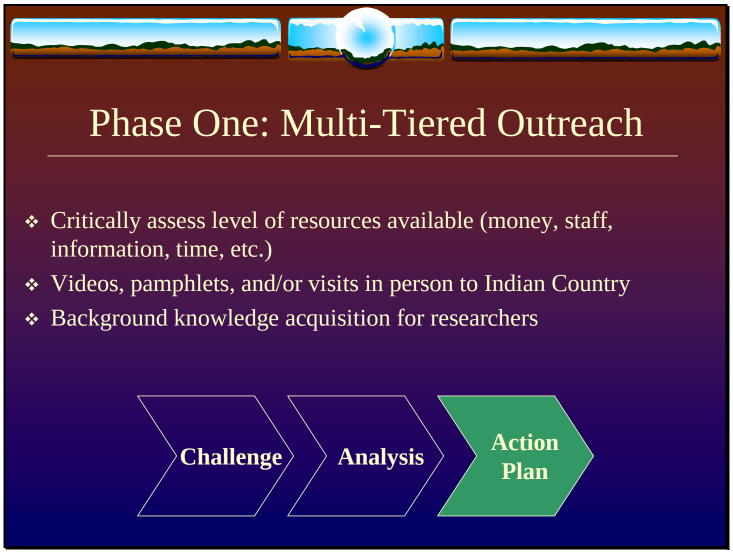
In addition to the steps suggested above, discussions should include discourse over the feasibility of and/or plans for having the partner AI/AN community review all papers related to their involvement in the Hap Map Project before publication.

In addition, the funding process should, by design, require a thoughtful, communicative, long-term process to be followed to ensure that each step will happen.

Tribal colleges can act as excellent intermediaries between the research community and the indigenous community because their faculties are likely to have some knowledge of the expectations, perspectives, and values of both communities. Thus the tribal college faculty may be able to help facilitate constructive interactions (see Appendix B for Whirling Thunder Wellness Program model, which successfully used just such a institutional collaboration).

NIH should consider initiating a general education campaign in which the HapMap Project coordinators will teach the general public that genetic variation does not represent “intrinsic unmodifiable defects” but rather risk factors that can be overcome and may never lead to disease. Such a campaign would also educate the public about the fact that the presence of a given mutation within a population does not mean that all or even a large percentage of that population has this mutation. It is utterly absurd to label that population as “defective” or “inferior” only because scientists have happened to discover a mutation present in a given population. Mutations with similar effects may be just as prevalent in other populations, but they may not have been found as yet (as in the case of BRCA1).

ACTION PLAN



Phase One: Multi-Tiered Outreach

- Critically assess level of resources available (money, staff, information, time, etc.)
- Videos, pamphlets, and/or visits in person to Indian Country
- Background knowledge acquisition for researchers

Phase One consists of a Public Information Campaign to get the word out:

1. Create a video of Francis Collins' Hap Map presentation.
2. Distribute video to nations who would not be clearly adverse to the protocol and goals of the project.[11]
3. Draft a press release for publication in journals such as Indian Country Today
4. Draft a pamphlet that explains basics of HapMap Project (and NIH) to laypeople and it distribute widely.
5. Send a representative to IHS and NCAI Conferences and to other appropriate meetings.
6. Collaborate with Genetics Education for Native Americans (GENA)[12] to generate educational materials that are tailored to the Hap Map Project.
7. Consider designing a NARCH or GENA project specifically directed toward genetics education and the applications of the Hap Map Project.
8. Initiate a general education campaign to teach that genetic variation does not represent "intrinsic unmodifiable defects" but rather that any given genetic "defect" generally has a very weak affect on any given population.

Meanwhile, the potential PI of the project may want to consider gathering background information on the specific nations that may be most inclined to consider participation (e.g. Sioux, White Mountain Apache, Hupa, Modoc, Salt River Pima). This would include research into the tribe's experiences with and conceptions of research, past and present tribal politics, and research interests/health care concerns.

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[11] The video, press release, and pamphlet should all summarize the research objectives, the perceived value of the research, research hypotheses, anticipated benefits and drawbacks of participation, background on research topic, and outcomes of previous research on similar topics.

[12] More information on the GENA project is available at http://members.aol.com/natamcan/gena.htm.

Developing a Collaborative Process for Community and Individual Informed Consent

Phase Two: Forging an Understanding

- Negotiable and non-negotiable components of project
- Taking, handling, and maintaining the samples
- Anonymity and confidentiality
- Risks and benefits
- Respecting privacy, dignity, culture, traditions, and rights
- Involving all clans and factions in dialogue

Challenge

Analysis

Action Plan

Ideally, the Public Information Campaign will yield responses from nations interested in learning more. If after an active, culturally cognizant effort to publicize this opportunity, there is no interest, then there should be no more pressure for AI/AN involvement in the Hap Map Project. All outreach materials should contain clear directions about whom to contact and when to insure that any interested communities are empowered to voice that interest.

However, if there *are* interested responses, then this is just the beginning of a long process. One must not assume that the initial contact speaks for all the members of the community. However, positive responses certainly merit the beginning of a lengthy discussion and negotiation process (if the community as a whole decides to move forward with initial talks). The researchers should have already begun to build contacts with and knowledge of the community with which they may be working (during the first phase). This knowledge acquisition should continue as the researchers visit the community and community representatives visit the potential repository and/or NIH.

Researchers should seek to inform themselves not just about the people, traditions, culture, and tribal government of the community with which they seek to partner, but also about when and where the best times and places to visit and to hold meetings are. The researcher would not want to arrive when much of the community is away nor would that researcher want to hear from a skewed cross-section of the community by meeting in a location or at a time accessible to only part of the population. The researcher should attempt to involve as much as is possible all the clans and factions of the community in dialogue. It may also be instructive to visit the local hospital and tribal museum to better understand the cultural background and health care status of the community. The researcher should also be prepared to discuss his or her background, family, training, and interests with interested community members.

It is also a gesture of respect and reciprocity to help arrange a site visit to NIH and to the potential repository.

It is also important to show respect for tribal sovereignty through respecting the dispute resolution mechanisms accepted and employed by and for the AI/AN nation in question. The site visit should serve to inform the researcher about the community and vice versa. With regard to presenting the details of the Hap Map Project to the nation, the researcher's job is to provide the information here discussed in as transparent and straightforward a manner as possible. The decision to move forward with negotiations rests with the AI/AN nation. It is the job of the tribal health board and later the Community Advisory Group to ensure that the community is behind whatever agreements are made. While researchers should actively keep abreast of all these dynamics so that they can continue to provide as much useful information as possible about the project status and so that they may promptly and knowledgeably respond to any concerns that arise, a respect for tribal sovereignty and self-government requires that neither NHGRI nor any affiliated researchers take it upon themselves to determine who is the legitimate spokesperson for the community and who is not. Furthermore, as upheld in court cases including *Santa Clara Pueblo v. Martinez,* tribes have the right to determine their own membership. Therefore, researchers are not in a position to determine who within the community qualifies as a tribal member for the purposes of Hap Map sampling (or for any other purposes).

Negotiations should explore the following topics:

- Research goals and objectives
- Methods and duration of the project
- Terms of the community-researcher partnership
- Degree and types of confidentiality
- Strategy and content of the evaluation
- Where the data are filed, current interpretation of data, and future control and use of data and human biological material
- Methods of resolving disagreements with the collaborators
- Incorporation of new collaborators into the research team
- Joint dissemination of results in lay and scientific terms to communities, clinicians, administrators, scientists, and funding agencies

(Courtesy of Macaulay et al., 1999)

At this stage, planning for a consent form that is specifically tailored for each nation and in cooperation with each nation should commence. Especially because "informed consent is a Western legal concept laden with Western assumptions about agency and autonomy, and sanctioned by Western conceptions of rights," it is particularly vital that the consent form be developed in active partnership with the community.[13] The

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[13] Reardon, 359.

community should be empowered to suggest terminology with which it is comfortable and to propose changes to the negotiable aspects of the project design. Negotiable aspects of the project design include setting up educational and job training opportunities, and establishing the option to withdraw samples from the project. Non-negotiable aspects of involvement would include the use of cell lines and the storage of Hap Map data in a public online database. Informed consent forms should not be full of dense text, but they do need to provide all the key details about the potential drawbacks and benefits of participation and other complex aspects of participation. Most of the information provided in this report should be summarized in each consent form.

While it is important to generate clear, complete, and accessible consent forms in cooperation with the AI/AN community partner, quality interpersonal communication during the process of obtaining consent is even *more* important.[14] Researchers, tribal government or personnel from the tribal health department, Health Boards, and IRBs can all collaborate on ways in which to create culturally sensitive and respectful consent processes.

In an ideal world, all of these stringent recommendations could be met. However, it is also important in the negotiations process to establish practical agreements that do not place an unreasonable burden on either the researchers or the AI/AN community involved. In order to implement these recommendations, additional personnel and financial resources within both the research and the AI/AN communities will be required. Thus funding agencies ought to recognize the need for more time and money in order to perform all of these recommended steps in the collaboration and partnership building process.

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[14] William L. Freeman. “Making Research Consent Forms Informative and Understandable: The Experience of the Indian Health Service.” *Cambridge Quarterly of Healthcare Ethics* 1994; 3:510-521.

An Example Model
For Initial Contact and Negotiation

Former Governor of Zuni Pueblo Malcolm Bowekaty proposed *one* possible model for negotiating partnerships – based on Zuni expectations – at the American Indian and Alaska Native Genetics Research Policy Formulation Meeting on February 7-9, 2001 (see Appendix D for Summary Meeting Report)

- Researchers should demonstrate respect *for* the community with which they seek to partner and ought to approach the community with an earnest intent to earn the respect *of* that community.

- Researchers who are ready and willing to share information about their background, training, interests, and family will help to create dialogue, trust, and a basis for mutual understanding.

- Initial communications regarding potential partnerships and research goals should discuss research objectives, the potential value of that research, current research hypotheses, possible benefits and drawbacks to the community should they choose to participate (and should they choose *not* to participate), background on the proposed research, and outcomes of previous work of a similar nature.

- The tribal government and community should be offered copies of relevant literature on the issues surrounding the research (both scientific and social).

- If interest within the community is continues throughout these steps, researchers should then allow time for a tribal subcommittee conduct an initial review, which can discuss ethical, medical, social, political, cultural, and other implications of potential participation.

- Provided that the subcommittee review supports further work toward a partnership, they may request a full proposal from the researcher (in the understanding that this proposal may be modified as negotiations continue – respecting the needs, concerns, and requirements placed upon both the researchers and the tribal government and community).

- The full proposal should include examples of any sample-taking instruments that may be used, and descriptions of the sampling and sample maintenance procedures should be submitted. The tribal health board can then review the full proposal, and the researchers ought also to submit their full proposal to the appropriate Institutional Review Board(s) (IRB), which may be a local tribal IRB, the National IHS IRB, or both.

- Researchers should attempt to make a site visit during which they may gain an increased understanding of local health resources available and taboos regarding the taking of bodily specimens. A site visit is a clear indication of the researcher's commitment to the project and to actively including the community in the planning of the project.

- If possible, NHGRI and/or the researchers should invite tribal representatives to visit NIH and/or the potential sampling and storage facilities.

- Storage, access, and ownership issues should be fully discussed during this review stage.

- The tribal review process can provide a forum through which to answer community questions and to facilitate discussion. This forum may improve the efficiency and applicability of the research that follows, so it is of interest to both parties to engage in this dialogue. Due to the past experiences of indigenous communities with respect to genetic research, these communities may have insightful and useful additions or modifications to make to the project design and implementation. Ideally, this dialogue will also include short- and long-term strategies through which to build scientific expertise and research capacity within the potential partner community. Negotiations should include ways in which the proposed project may advance these goals.

- If the partnership is established and sampling moves forward, then yearly status updates should be submitted to the subcommittee/community at large (as previously agreed during negotiations). Researchers should collaborate with tribal program staff to provide translations in all appropriate languages of the research outcomes.

Lisa Preston, a member of the National IHS IRB, outlined a modification for the model presented by Malcolm Bowekaty. She observed that the Tohono O'odham – and many other nations composed of multiple districts – have multiple districts, and each district has a district council that will need to review and approve research proposals before a formal partnership can be negotiated and approved.

- This may be a time-consuming process because the meeting schedules of each district council may not coincide with each other, which may require a long period of review at each stage.

- Researchers should be prepared to explain why genetics research might be an important priority for the community within the context of the health and economic concerns that it faces.

- Be prepared to explain why genetics research could, indeed, elucidate better treatments for predominantly behavioral conditions such as alcoholism and physical conditions partially caused by behaviors such as poor diet, including diabetes (see Appendix A for Sample Outreach Materials).

- Ask around about particular health concerns and priorities in order to alert community to possible benefits of participation in research

Taking informed consent seriously in research negotiations requires [researchers] to spend considerable time with prospective [members of the partner community]…. Investigators must go [to great lengths to explain] themselves and their intentions so that [community members] will know what is being asked of them. Respect for [the community members'] human rights dictates that [researchers] appreciate that the decision to participate in research entiails making a gift for the sake of others. – Jay Katz, "Ethics and Clinical Research." *Hastings Center Report* 1993; 23(5): 36.

Phase Three: Establishing a Formal Agreement

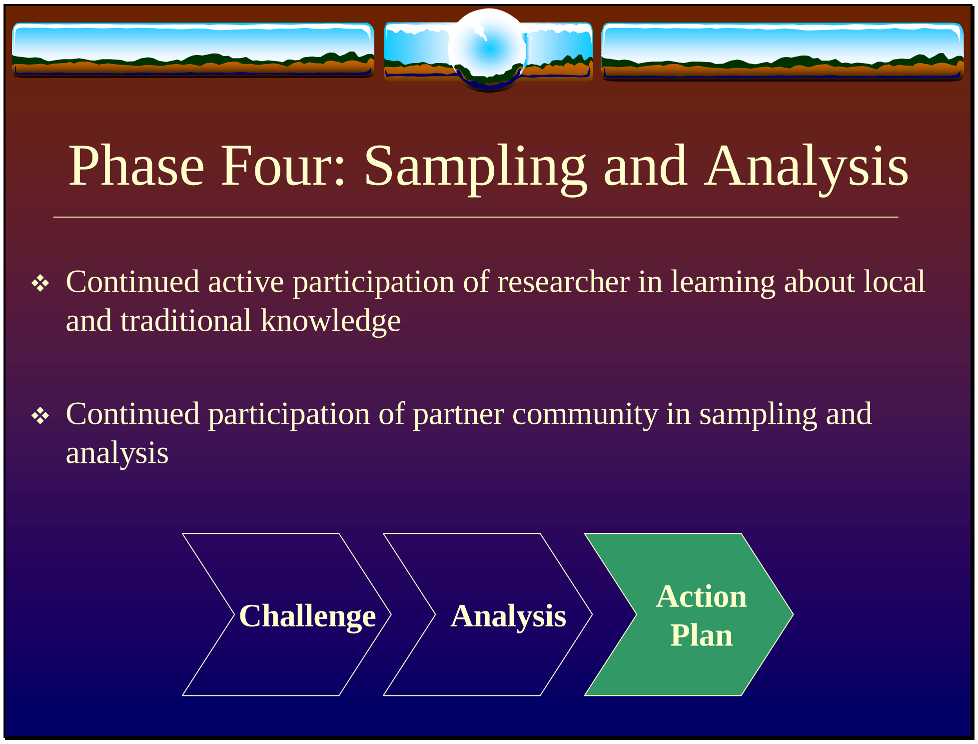
- Establish system of on-going dialogue
- Outline programs/initiatives through which NIH can contribute
- Establish ongoing community involvement in supervision of sample collection, storage, and management
- Include plans for meaningful skilled labor training
- Submit formalized agreement to appropriate IRB(s) and to tribal health review board

Challenge **Analysis** **Action Plan**

In transitioning between meetings and discussions about partnership to creating a formal written agreement regarding the specifics of the partnership, many of the same considerations apply in both phases. Both individuals and the support institution should continue to work with the tribal health review board or other appropriate groups to establish formal agreements regarding how and where the Repository will be run, whether and/or until when samples can be withdrawn (if the community subsequently decides to withdraw from the partnership), who will take the samples, how the samples will be maintained, and when, if ever, they will be scheduled to be destroyed.

Tribal health boards and IRBs are *resources* that can help to materially improve the project design. Thus they are not just bureaucratic hurdles to jump over or hassles to be avoided.

Once a negotiated formal agreement has been established, it is vital to install a plan that will ensure ongoing dialogue. A forum for dialogue will be necessary so that any problems that arise concerning research objectives, methods, findings, and interpretations may be aired and hopefully solved. Much of this communication will probably be mediated by the Community Advisory Group, but all researchers, supporting institutions, and community members should be encouraged to be actively involved in voicing ideas and concerns and in continuing constructive dialogue.



Phase Four: Sampling and Analysis

- Continued active participation of researcher in learning about local and traditional knowledge
- Continued participation of partner community in sampling and analysis

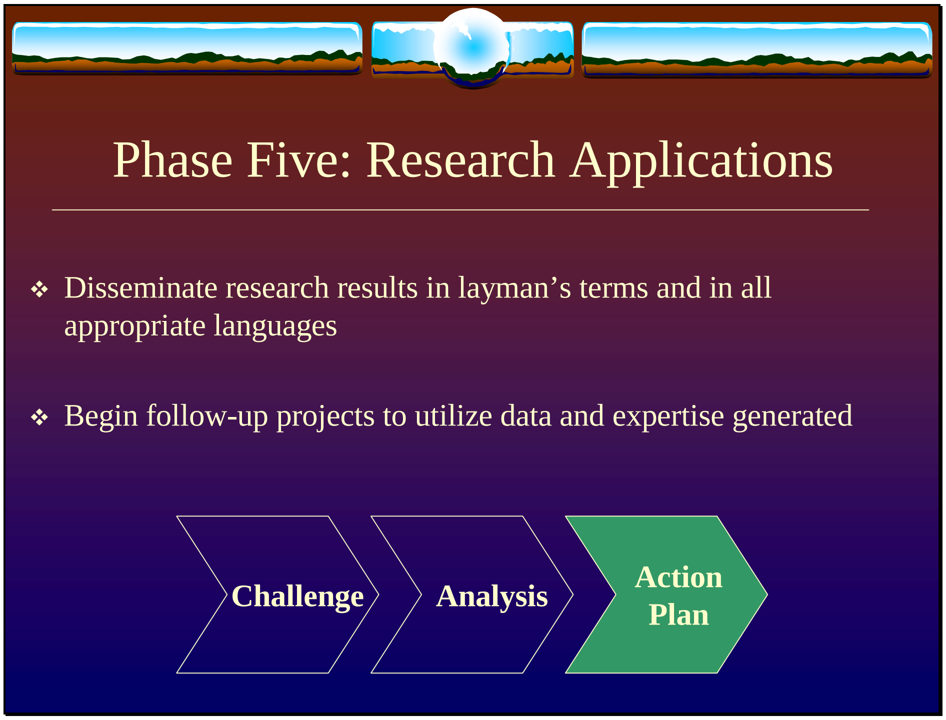
Challenge
Analysis
Action Plan

In addition to continued communication between the community, the researchers, and the sponsoring institutions, any changes to the project design and implementation at this stage need to be divulged to the Community Advisory Group and brought before the appropriate IRB(s).

Both tangible and dignitary collective harm must continue to be actively avoided through the sampling, analysis, and reporting stages. As Rae Mei-Ling Chang noted at the American Indian and Alaska Native Genetics Research Policy Formulation Meeting of February 7-9, 2001, it is crucial *never* to lose sight of the fact that “an individual is more than the sum of their genes.”

Education and skills training initiatives should be undertaken during this time if they have not already been initiated.

Important note: Funding for this phase should not be made available until evidence of extensive consultation and collaboration with community members is presenting to the funding body.



Phase Five: Research Applications

- Disseminate research results in layman’s terms and in all appropriate languages
- Begin follow-up projects to utilize data and expertise generated

Challenge
Analysis
Action Plan

Once all samples have been collected and analysis on those samples has been completed, a long-term partnership should still be maintained if it is feasible and desired by both parties. (Agreements regarding future collaboration will have been made during Phase Three.) Ideally, the Hap Map database enable researchers and the partner community to carry out research specifically related to the community’s health concerns.

APPENDICES

A: Sample Outreach Materials

1. Genetic Components of Disease
2. DNA Basics
3. What can DNA tell us?
4. Finding Mutations that May Increase Risk for Disease
5. Sampling Strategy
6. Project Design

B: Sample Agreements Involving Partnership Building

1. A Model Agreement for Genetic Research in Socially Identifiable Populations
2. Protocols and Principles for Conducting Research in an Indigenous Context
3. Indian Health Service Institutional Review Board
4. Native American Research Centers for Health
5. Kahnawake Schools Diabetes Prevention Project
6. Whirling Thunder Wellness Program

C: Applicable Federal Proclamations

1. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments
2. Memorandum for the Heads of Executive Departments and Agencies: Government-to-Government Relationships with Native American Tribal Governments

D: Policy and Model Code Documents

1. First Community Consultation on Responsible Collection for Genetic Research
2. American Indian and Alaska Native Genetics Research Policy Formulation Meeting
3. Policy for the Responsible Collection, Storage, and Research Use of Samples from Identified Populations for the NIGMS Human Genetic Cell Repository
4. Negotiating Collective Acceptability of Health Research
5. Model Tribal Research Code
6. The Role of Community Research with Stored Tissue Samples
7. The Role of Community Review in Evaluating the Risks of Human Genetic Variation Research
8. Indigenous Research Protection Act

E. Scientific Literature Exploring Linkage Disequilibrium and its Relevance in the Study of Human Disease

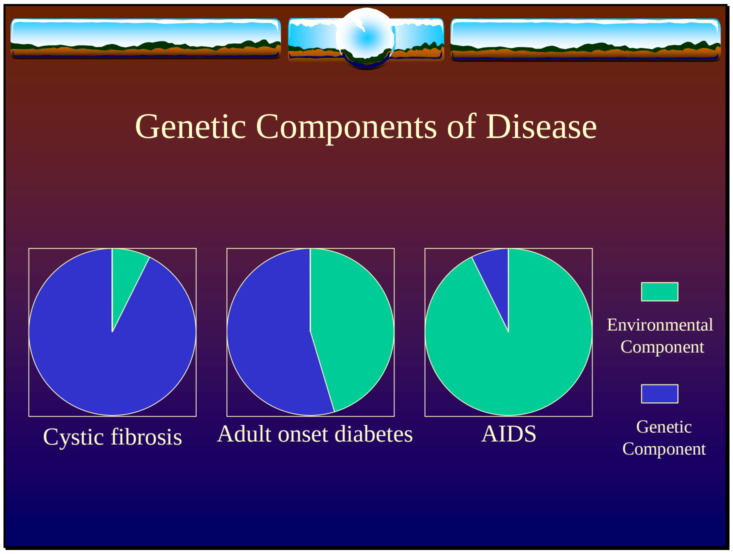
1. Sequence variation in the human angiotensin converting enzyme
2. High-resolution haplotype structure in the human genome
3. Linkage disequilibrium holds the key
4. The Structure of Haplotype Blocks in the Human Genome
5. Genome-Based Pharmacogenetics and the Pharmaceutical Industry

F. The Launch, Background, and Ethical Issues of the Hap Map Project

1. International Consortium Launches Genetic Variation Mapping Project
2. Developing a Haplotype Map of the Human Genome for Finding Genes Related to Health and Disease
3. International Hap Map Project Sample Collection
4. Background on Ethical and Sampling Issues Raised by the International Hap Map Project
5. Potential Hap Map Benefits for Native Americans

G. Participant Lists for the March 13th-14th, 2003 Hap Map Meeting

Appendix A: Sample Outreach Materials



Genetic Components of Disease

Talking Points

- Virtually all human diseases have a genetic component

- This genetic component is definitely not the only important aspect of disease for us to study; environmental factors may be at least as important if not more so

- Yet with the recent advances in genetic research, there is now an opportunity to learn more about many common diseases, which will *eventually* help doctors to treat these diseases more effectively

- HapMap will be a new tool to speed the discovery of genetic components of disease

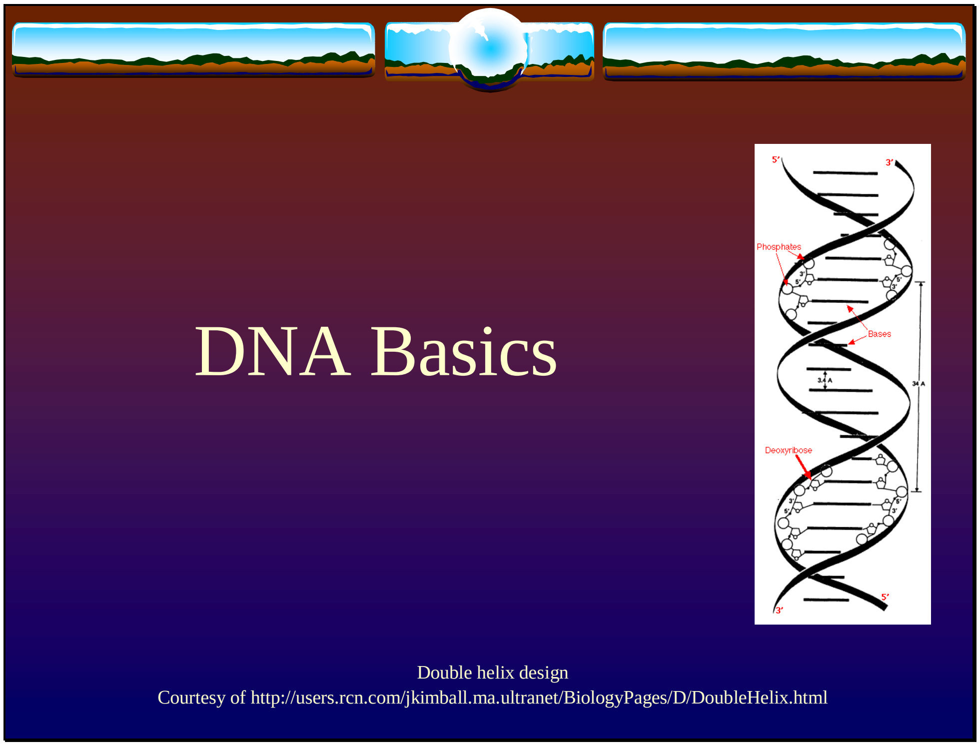
- Project will map out the common patterns of human genetic variation

- In future research, these maps will allow researchers to study the patterns in genetic variation (haplotypes)

- These future studies can compare the frequencies of a given set of variations in people who have a specific disease with the set of variations of people who do not have this disease

- Based on differences between these two groups, researchers will be better able to focus their search on regions in the genome where specific patterns of variation may contribute to the development of a specific disease

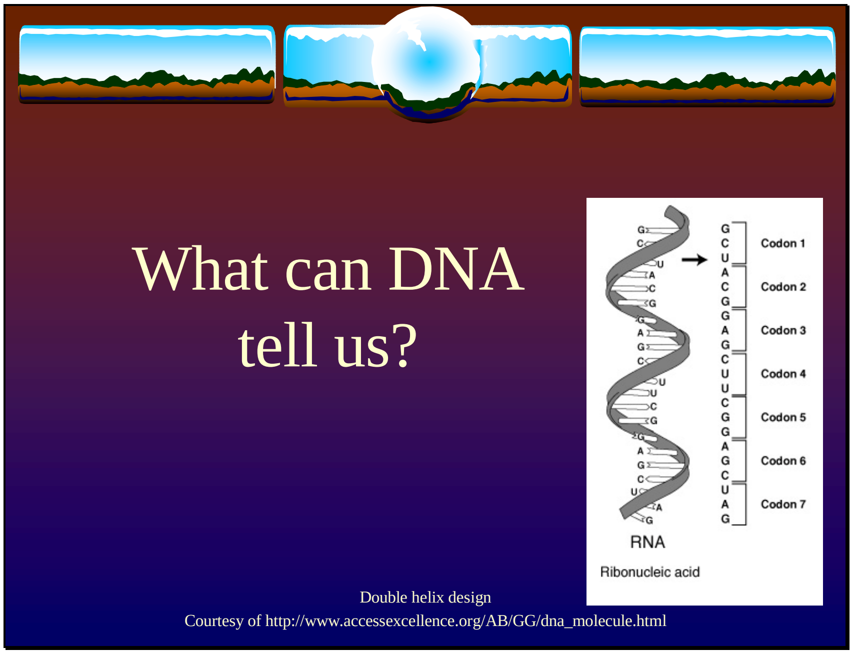
The “Talking Points” throughout this section are excerpted from the NIH News Advisory: Background on Ethical and Sampling Issues Raised by the International HapMap Project (October 2002)



DNA Basics

Double helix design
Courtesy of http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

- The human genome consists of 23 pairs of chromosomes
- The chromosomes contain the genetic information necessary to carry on life processes
- This information is stored in the form of nucleotides (also known as “bases” or, when talking about a bonded pair of nucleotides, as “base pairs”: adenine, cytosine, guanine, and tyrosine, which are abbreviated A, C, G, and T)
- Nucleotides tell the body how to assemble proteins



What can DNA tell us?

Double helix design

Courtesy of http://www.accessexcellence.org/AB/GG/dna_molecule.html

- As seen in this slide, sets of three nucleotides code for a given amino acid; these sets of three nucleotides are called "codons"

- A typical protein consists of thousands of amino acids

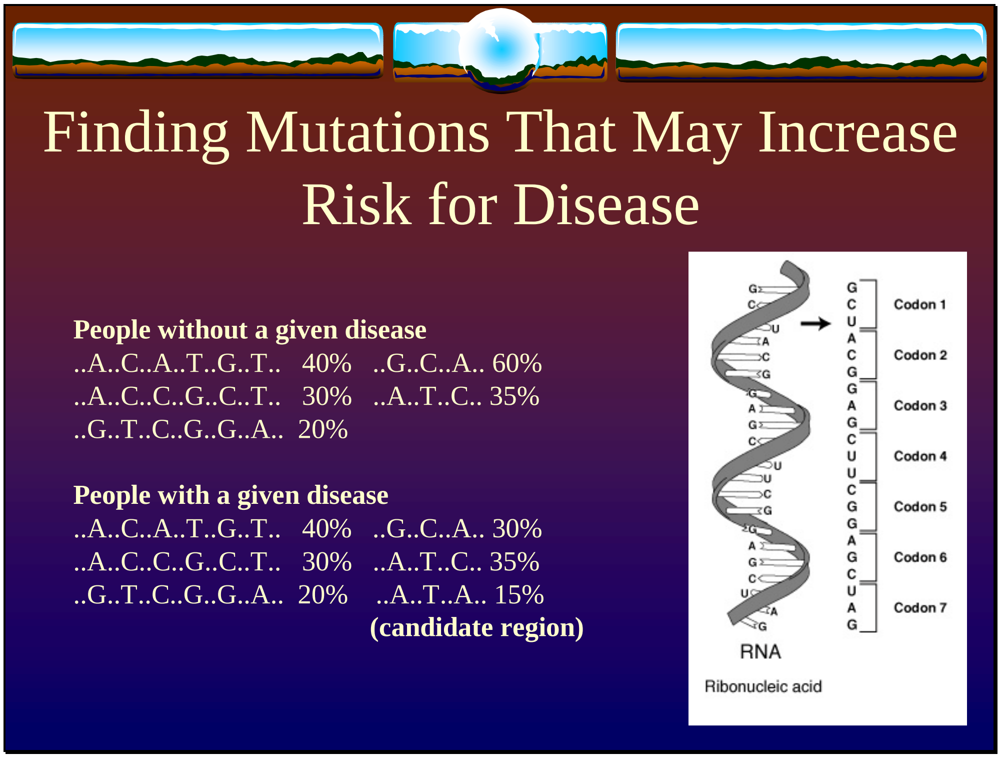
- A protein could become non-functional if one of the nucleotides in a codon that codes for an important amino acid in the protein is altered

- For instance, if Codon 1 (in the slide above) were mutated so that it read A-C-U rather than G-C-U, then it would tell each cell in the body to insert a Threonine amino acid into that spot in the protein rather than an Alanine amino acid

- This might or might not lead to a greater chance of developing a given disease; it might not affect the protein function very much or it could cause the protein to adopt a different shape than it should, which in turn could mean that the protein would not function properly and could lead to disease

- On the other hand, the three nucleotide sequence that makes up a codon can be altered without producing any changes in the amino acid sequence: for example, if Codon 1 (above) were mutated so that it was G-C-G rather than G-C-U, it would still tell the cell to put an alanine in that spot of the protein, so the protein would function in a completely normal way

- Both of these types of mutations are called "point mutations," and specific sets of point mutations in specific sites are sometimes more common in one population than in another

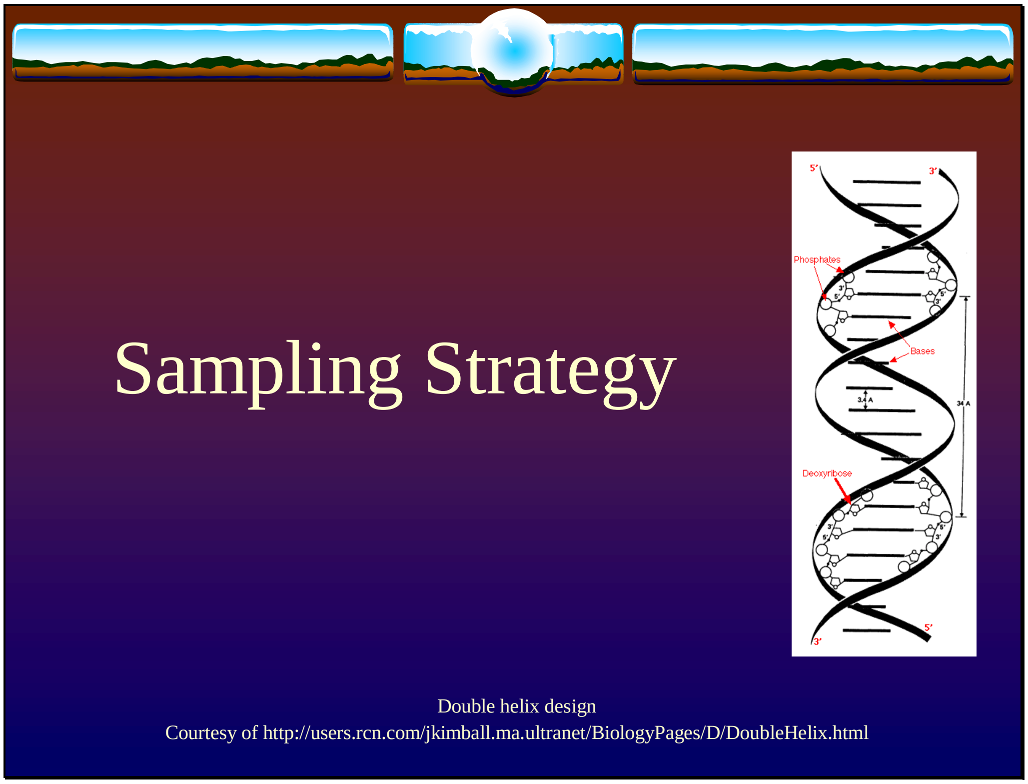


Finding Mutations That May Increase Risk for Disease

People without a given disease
..A..C..A..T..G..T..   40%   ..G..C..A.. 60%
..A..C..C..G..C..T..   30%   ..A..T..C.. 35%
..G..T..C..G..G..A.. 20%

People with a given disease
..A..C..A..T..G..T..   40%   ..G..C..A.. 30%
..A..C..C..G..C..T..   30%   ..A..T..C.. 35%
..G..T..C..G..G..A.. 20%   ..A..T..A.. 15%
(candidate region)

- Haplotypes are made up of these sets of point mutations
- If a haplotype is present to some extent in one group that has a given disease but that same haplotype is absent from a group that does not have that disease, then the haplotype may be a marker for a gene that is involved in causing the disease

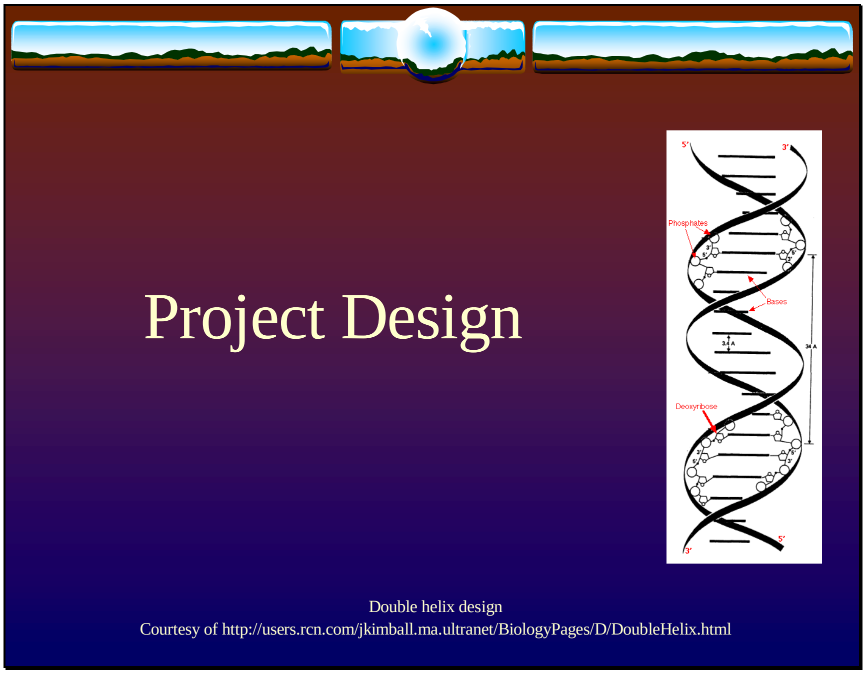


Sampling Strategy

Double helix design
Courtesy of http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

Talking Points

- The Large Scale project has already begun
- Through the Large Scale project, research groups will collect blood samples from four large and geographically distinct populations: the Yorubas of Nigeria, the Han Chinese, the Japanese, and U.S. residents with ancestry from Northern and Western Europe
- While the inclusion of AI/AN samples is not required for the Hap Map Project to be useful in understanding diseases in AI/AN populations, the Hap Map data *may* prove to be *more* useful in understanding *some* diseases in AI/ANs if it includes AI/AN samples
- We cannot predict *how* much more useful the Hap Map database would be for AI/ANs if their samples are included *unless* we study those samples



Project Design

Double helix design
Courtesy of http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

Talking Points

- Both the overall purpose and the specific sampling strategy are very different from the Human Genome Diversity Project (HGDP)

- The Diversity Project was proposed about a decade ago and was designed to study human population history and the degrees of separation between different populations

- The idea was to see if, for example, “the Irish are more closely related to the Spaniards or to the Swedes”

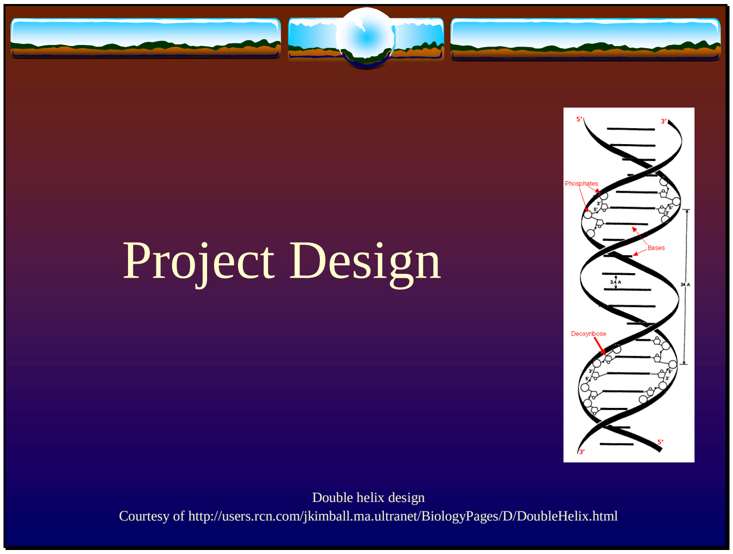
- The design and initial sample taking of this project caused a significant amount of uproar because of concern that the project was exploiting vulnerable individuals and populations; concern also arose because analyses of the data could have lead to a potential conflict with AI/AN origin beliefs

- The Diversity Project was never carried out

- In contrast to the Diversity Project, Hap Map’s goal is to find genes that contribute to complex diseases or to responses to drugs

- The HapMap project will generate a database that can be used in future studies of health and disease

- Unlike the Diversity Project, which would have focused on small and isolated populations, the HapMap Project seeks to study large and less vulnerable populations



Project Design

Double helix design
Courtesy of http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

Talking Points

- Donors will be asked to give consent for their samples to be used not just for the Hap Map Project but also for future medically-related genetic variation studies

- Future studies may explore how genes are regulated, the biology of DNA, how new variations arise, and the genetic history of human groups

- Hap Map-related benefits with respect to the level of medical knowledge and care available will probably not be forthcoming for some time

- A process of community engagement will be initiated before consent is ever requested from any individuals in the community

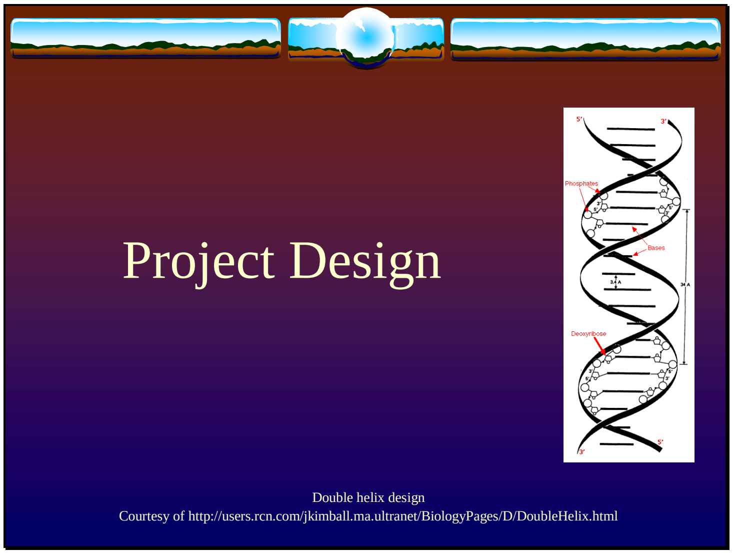
- Individual samples from your community will not be used if your community as a whole decides against participation

- The community engagement process will involve seeking advice and input about the informed consent process and about how samples from the community should be collected, described, and used

- If the community wants to proceed with negotiations regarding this potential partnership, then a Community Advisory Group will be appointed to serve as a liaison between the people of the community and the repository

- Samples will be collected and stored without medical or personally identifying information about the donors, and more samples will be collected than will be used to create the Hap Map database – as a result, not even the donors themselves will know exactly whose samples were used to create the database

- Discussions will also consider how skills development projects could be developed alongside participation



Project Design

Double helix design
Courtesy of http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DoubleHelix.html

Talking Points

- In future studies, some genetic variants will be identified that promote wellness and protect against disease while other variants will be identified that increase the risk for particular diseases

- When researchers use the Hap Map database and discover that a disease is associated with a genetic variant that is somewhat more common in one population than in another, some people may mistakenly generalize that all individuals in that population have an increased risk for the disease or even that the population as a whole is somehow genetically inferior

- A similar misconception is that genetic predisposition for disease means that people with particular genetic variants are “doomed” to get the disease

- Both of these incorrect assumptions ignore the strong contributions that environmental factors make in the development of disease *and* the fact that even if a person has an increased risk for a disease, there may be ways to reduce the risk of actually *getting* the disease – so many people who appear to be at risk from a genetic standpoint never actually get the disease

- Genetic discrimination and determinism are problems that can arise from any association study in which researchers relate genetic variation to disease risk, but the Hap Map group plans to make serious efforts to reduce the risk of Hap Map research causing such problems through two initiatives:

1. Education for both researchers and the public about the meaning of the Hap Map data -- the focus will be on the differences in genetic risk among individual people rather than among a population
2. Education for researchers so that they will design their studies and describe their results very carefully, including accurate descriptions of the population involved and how important both genetic and environmental factors are thought to be in causing a given disease. Uncertainty about these matters will be acknowledged.

Appendix B: Sample Agreements Involving Partnership Building

1. A Model Agreement for Genetic Research in Socially Identifiable Populations
2. Protocols and Principles for Conducting Research in an Indigenous Context
3. Indian Health Service Institutional Review Board
4. Native American Research Centers for Health
5. Kahnawake Schools Diabetes Prevention Project
6. Whirling Thunder Wellness Program

Model for Participatory Research in Indian Country

Kahnawake schools diabetes prevention project, Canada[1]

"This participatory research project is being conducted with a Mohawk community (population 7000) in Canada. The long term goal is primary prevention of type 2 diabetes, by promoting healthy eating and increased physical activity among 6-12 year old children. Kahnawake is represented through a community advisory board of 25 volunteers from the health, educational, political, recreational, social, spiritual, economic, and private sectors and the full time project staff.

The community is a full partner. It participated in *(a)* developing the goal and objectives, *(b)* planning and implementing the intervention and evaluation, *(c)* outlining the obligations of researchers and community in the code of research ethics, *(d)* collecting and interpreting data, *(e)* reviewing lay and scientific publications, and *(f)* disseminating results. Their collective wisdom adds a perspective that broadens interpretations, increases the project's effectiveness, helps to decrease harm and improves the credibility of oral and written results, which saves the community from potential stigmatization. The community had substantial influence by requesting that the project focus on children (which matched the scientific theory that lifestyles are learnt at an early age); by reaffirming to the funding agency that the two community schools should be analyzed together, because comparisons by schools would be contrary to community values; and by convincing researchers to postpone a food services intervention until there was greater community acceptance. The community was responsible for implementing and enforcing a schools healthy nutrition policy, increasing physical resources by building a recreation path, and expanding social resources with a dozen new yearly events. Finally board members ensure cultural relevance, promote the objectives, and are community role models for healthier lifestyles.

Early evaluation described baseline measures from Kahnawake and the comparison community. The board and researchers are currently analyzing data from the four year evaluation. This project, however, has demonstrated Kahnawake's self empowerment, increase of physical and social capacity, and how the participatory model improved the research to benefit the community. In turn, the community sustained the project with its own funds for one year, when grants were not available, and is using the newly acquired knowledge, skills, and experiences for continuing healthcare planning."

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[1] Case study excerpted from Ann C. Macaulay, Laura E. Commanda, William L. Freeman, Nancy Gibson, Melvina L. McCabe, Carolyn M. Robbins, Peter L. Twohig. "Participatory research maximizes community and lay involvement." *BMJ* 1999;319:774-778.

Model for partnerships between academic institutions and Indian Country

The Harvard Project on American Indian Economic Development: Honoring Nations 2002 Honoree

Whirling Thunder Wellness Program
Winnebago Tribal Health Department, Winnebago Tribe of Nebraska
Winnebago, Nebraska

To prevent and control the devastating effects of diabetes and substance abuse, in 1995, the Winnebago Tribe created the Whirling Thunder Wellness Program, which raises community awareness about diabetes and substance abuse, administers primary and secondary prevention services, and encourages healthy lifestyles that are consistent with traditional practices. Among the Program’s innovations are the “Team Up” diabetes patient retreat, “Kidz Café” which provides healthy summertime meals and snacks to community children, and after school programs that provide safe, adult-supervised cultural and physical activities for up to 50 children during peak “risk” hours.

Michele Smith
Certified Diabetes Educator/Coordinator
Winnebago Tribal Health Department
PO Box 687
Winnebago, NE 68071
Phone: (402) 878-3187
Email: upwellness@huntel.net

www.ksg.harvard.edu/hpaied/hn_main.htm

Appendix C: Applicable Federal Proclamations

While the following is not specifically directed at federally-funded research, it may be useful to note that not only will more productive, sustainable, and responsible research practices result from thorough consultation and collaboration with AI/AN communities, but also this type of interaction with tribal governments is mandated by Executive Order.

3. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

4. Memorandum for the Heads of Executive Departments and Agencies: Government-to-Government Relationships with Native American Tribal Governments

Appendix D: Policy and Model Code Documents

1. First Community Consultation on Responsible Collection for Genetic Research
2. American Indian and Alaska Native Genetics Research Policy Formulation Meeting Summary Report
3. Policy for the Responsible Collection, Storage, and Research Use of Samples from Identified Populations for the NIGMS Human Genetic Cell Repository
4. Negotiating Collective Acceptability of Health Research
5. Model Tribal Research Code
6. The Role of Community Research with Stored Tissue Samples
7. The Role of Community Review in Evaluating the Risks of Human Genetic Variation Research
8. Indigenous Research Protection Act

Appendix E. Scientific Literature Exploring Linkage Disequilibrium and its Relevance in the Study of Human Disease

1. Sequence variation in the human angiotensin converting enzyme
2. High-resolution haplotype structure in the human genome
3. Linkage disequilibrium holds the key
4. The Structure of Haplotype Blocks in the Human Genome
5. Genome-Based Pharmacogenetics and the Pharmaceutical Industry

Appendix F: The Launch, Background, and Ethical Issues of the Hap Map Project

1. International Consortium Launches Genetic Variation Mapping Project
2. Developing a Haplotype Map of the Human Genome for Finding Genes Related to Health and Disease
3. International Hap Map Project Sample Collection
4. Background on Ethical and Sampling Issues Raised by the International Hap Map Project
5. Potential Hap Map Benefits for Native Americans

Appendix G: Participant Lists for the March 13th-14th, 2003 Hap Map Meeting