Genetic research and the vulnerability of Native Hawaiians

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VIEWPOINTS AND PERSPECTIVES

Abstract

Traditional research ethics are unable to provide adequate protections for human subjects involved in research—much less genetic research[1-3]. New principles need to be developed to change the paradigm and put human research subjects in a more equitable relationship with their researchers. In addition, new laws should be crafted to level the playing field for human research participants. Humans can no longer look at themselves as hereditary beings, but as stewards of intra- and inter-generational genetic material in need of protection. Recommendations are provided.

Introduction

Hui No Ke Ola Pono, the Native Hawaiian Health Care System on Maui, serves a population of Native Hawaiians who are striving to recover from injuries sustained when they were human subjects in an approved genetic research project. This experience—and its painful and long-lasting sequelae—has raised fresh concerns about the dangers surrounding glamorous new genetic research and what recourse participants have when harms occur. Genetic research is like exploring space; the inner universe is also vast, complex, uncharted, and unpredictable.

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This paper puts forth the following premises and conclusions: (a) there are foreseeable harms associated with genetic research[1-3], (b) traditional research ethics are unable to provide adequate protection for human subjects, and (c) new principles and laws need to be developed to change the paradigm and put human research subjects in a more equitable relationship with their researchers.

Foreseeable harms

What are the foreseeable harms for human genetic research subjects and their families? Data in genetic research may be used for purposes other than that of the original intent as well as by others not initially envisioned by the subjects. Conclusions and inferences made from the data may have deleterious psychological effects on the subjects, the subjects' families, and apparent members of the subjects' gene pool—present, past, and future. Social stigmatization, discrimination (e.g., in employment, social, and political status), and differential eligibility for marriage and insurance may follow the identification and classification of markers. These effects may transfer to more than the individual human genetic research subject[1] and may lead to a global caste system.

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Inadequacy of present protections

The responsibility for creating and maintaining an environment that protects the rights and welfare of people who are willing to be research subjects falls on the researchers, research institutions, and research sponsors[4]. In the United States, the *Code of Federal Regulations*, 45 CFR 46, expresses the extent of federal protection for human subjects in research projects funded by the federal government. The provisions are based on the venerable *Belmont Report*. The United States Department of Health and Human Services (DHHS) is the administering agency. The Office for Human Research Protection (OHRP; formerly the Office for Protection from Research Risks [OPRR]) is the division of the DHHS charged with overseeing all matters related to the implementation of the research regulations[5].

Institutional Review Boards (IRBs), mainly of colleges and universities, are supposed to follow the *Code* in an effort to

minimize harm and maximize benefits to research participants. Ideally, IRBs will use their authority to require researchers to structure their research in such a way that ensures that (1) the science is sound, culturally sensitive, and relevant, (2) the participants are aware of the risks involved and potential harms, and (3) if unexpected and harmful consequences related to the research occur, the research will be investigated in a timely manner and, when warranted, terminated. The main mechanism of IRBs for the protection of human subjects is the informed consent process and documentation. An informed consent represents an agreement between the researcher and human subject, where, in consideration for the human subject's participation, the researcher agrees[6]:

1. to identify the project as a study that involves research and provide an explanation of the purpose of the research,
2. to describe the protocols/procedures of the study and the expected duration of the subject's participation,
3. to describe any foreseeable risks/harms or discomforts to the subject, the subject's family, and the subject's community as well as the mechanisms to minimize those harms,
4. to disclose other alternative procedures or treatments available, if any, that might be advantageous to the subject,
5. to provide information as to policies and procedures designed to protect confidentiality and privacy,
6. to provide information about compensation, and a full explanation as to whether any medical treatments are available if injury occurs,
7. to provide information about who to contact for answers to pertinent questions about the research and research subject's rights,
8. to expressly state that participation is voluntary with no threat of penalty or loss of benefits to subjects who refuse to participate or choose at any time to discontinue their participation,
9. to assure that all of the above are understood by the research participant, and
10. to re-do the informed consent process and documentation with IRB notification and approval if any harm occurs or if any changes occur in the procedures.

How effective is the reliance on this overall mechanism? If not just based on a scan of daily newspapers, it would appear that such reliance on the system is inadequate, and at times, harm goes unchecked for years[7].

At the federal DHHS level, there are likely too many research protocols for the number of DHHS staff. As a result, heavy reliance is placed on Institutional Review Boards (IRBs), researchers' professional ethics, and complaints from individuals involved in research to prevent harm to participants and to stop protocols that are harmful to human subjects[8]. Unfortunately, many IRBs are burdened with more protocols than they can effectively review and monitor[9]. Conflicts of interests that occasionally arise between institutions and researchers can forestall the termination of failing protocols[7]. The DHHS Office of Inspector General Report (June 1998) called for IRB reform, citing trends that jeopardize the effectiveness of IRBs nationally, including[9]:

1. major changes in the research environment as a result of expansion of managed care, increased commercialization of research, new types of research, increased number of proposals and trials, including multi-site trials,
2. too many protocols to review resulting in hasty reviews with too little scientific expertise to reach informed judgments,
3. lack of meaningful continuing review of ongoing research projects, often resulting in limited information on the informed consent process and how well the research subjects are being protected,
4. conflicts that threaten the independence of IRBs when institutions expect their IRBs to support clinical research because it provides revenue and prestige to the institution, sometimes compromising IRBs' missions to protect human subjects,
5. insufficient training provided for investigators and IRB members, and
6. lack of attention on the part of IRBs and Department of Health and Human Service agencies to evaluating IRB effectiveness.

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An update Report by the Office of Inspector General two years later acknowledged that although several promising steps have been taken to address the deficiencies reported in 1998, overall, few of their recommendations for reform were enacted[9].

One of the main difficulties with the informed consent process is that there is no effective mechanism for enforcement[10]. This puts human subjects at a distinct disadvantage because, if the researcher fails to adhere to the assurances that were made to obtain the subjects' consent, the remedies available to the subjects are so cumbersome as to be almost nonexistent[11]. Informed consent documents are generally not perceived as contracts[11] and disappointed human subjects must look to tort law for resolution where opportunities for enforcement and restitution are questionable.

Research is driven, at its best, by the search for truth, knowledge, and betterment of humankind. At its worst,

research is driven by a relentless need to publish, make money, and gain personal and institutional recognition. It is contended that most research protocols represent a combination of these modes. The Nobel Prize sometimes looms like the Holy Grail. Research is an industry. It is composed of numerous competing institutions with highly organized internal bureaucracies supported by even more competitive groups such as health management organizations (HMOs), insurance companies, and pharmaceutical giants. Teams of scientists, experts, and administrators direct and manage the activities. Long-standing relationships among these players grease and keep the wheels of research turning unabated even in the face of egregious research wrong-doing[7,10]. It is contended that individual complaints are too often dismissed, ridiculed, and minimized[11,12].

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To compound the problem, these inadequate protections only apply to government-funded research. In the present atmosphere of genetic research excitement, privately funded research is unencumbered by these legal prescriptions when dealing with human subjects.

Research ethics reform

Minorities, native peoples, and parity

Groups or populations of individuals who share genetic markers are of special interest to genetic researchers. Indigenous populations are particularly vulnerable because they represent a homogeneous gene pool—the latter being a desirable sample for genetic study. Although native peoples may not actually benefit from genetic studies, they are vigorously recruited as human subjects. Native American Indian Tribes and Alaskan Natives have learned from past abuses and have taken steps to ensure that all research is now undertaken with explicit concern for and involvement of their people. Model agreements between tribes and researchers have been developed by the Navajo Nation, the American Indian Law Center, and others[13].

In Hawai'i, Native Hawaiians, the *Kanaka maoli*, are particularly at risk. *Kanaka maoli* have no distinct legal standing or power, have higher mortality rates, have lower socioeconomic and educational status, and have fewer resources (see other articles in this issue). They are left with the hope of IRB intervention, the over-burdened OHRP, and impractical private remedies.

Can potential research subjects, Native Hawaiians in particularly, achieve parity with the researchers, thus enabling Native Hawaiian subjects to better protect themselves from the potential harms of genetic research? How can parity be built into a David-and-Goliath relationship?

The research institutions created nearly all of the instruments of protection and compliance. The language, format, and implementation of the informed consent process and resulting documentation appear to be deficient and ineffective in protecting participants. Individuals are hard pressed to challenge the lawyers and activities of large institutions or multi-billion dollar complexes of people, disciplines, and businesses. Dr. John Pesandro, the "whistle blower" from the "Hutch,"—Fred Hutchinson Cancer Research Center, spent almost 20 years filing complaint after complaint to the Food and Drug Administration, the Office for Protection from Research Risks, the Secretary of Health and Human Services, other state and federal offices, and the media (e.g., *New York Times*) about the deadly risks, informed consent irregularities, and some of the researchers' conflicts of interest directly related to Protocol 126, the experimental procedure of the study. Each time, his complaints were circumvented, ignored, or minimized as the "Hutch" used its legal, political, and social muscle to justify the problems uncovered by the Office for Protection from Research Risks investigator. Meanwhile, some of the women who participated in Protocol 126 continued to die prematurely, despite the possibility that they may have lived longer if they were provided traditional cancer treatment. Finally, in 1998, the *Seattle Times* decided to investigate the issue and published its findings in a series of articles that began on March 11, 2001[7].

Legal contracts

Where is the protection for research participants? Perhaps the law of contracts provides a more viable model. Informed consent agreements with simple enforcement mechanisms, performance bonds, third-party beneficiaries, and stipulated minimum damages may be a more effective way of leveling the playing field.

Legislative protection

Legislation is needed to safeguard an individual's right to purchase and maintain life and medical insurance and to seek and maintain employment without being subject to discrimination on the basis of genetic predisposition.

Legislation is also needed to place strict controls on genetic tissue banks and on digitized genetic data (e.g., Proposed legislation: 45 CFR Parts 160 through 164, Standards for Privacy of Individually Identifiable Health Informa-

tion). Unfortunately, the proposed regulations are inadequate because they fail to sufficiently address tissue banks, digitized genetic data banks, military tissue and genetic data repositories, and genetic information collected and retained by state and federal law enforcement agencies. Without safeguards in these areas, efforts to preserve confidentiality in the area of genetic information may fail.

Summary

Traditional research standards of conduct and care appear skewed toward research institutions, researchers, and pharmaceutical companies. Raising the bar even higher, the dawn of the Human Genome Era places even greater social, legal, and ethical burdens upon an already faltering system. Native peoples, Hawaiians included, may be particularly vulnerable. Protecting humans involved in genetic research calls for a change in our self-perception from that of a "hereditary" entity to stewards of intra- and intergenerational genetic material. New laws should be created that recognize and protect this stewardship. Leveling the playing field means placing authority into the hands of the participants in an effort to truly attain the lofty ideals of the *Belmont Report*.

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Loa'a ke ola i Hālau-a-ola
Life is obtained in the House-of-life
One is happy, safe, well again