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## Ethical Issues in Developing Pharmacogenetic Research Partnerships American Indigenous Communities

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### Abstract

Pharmacogenetic research offers the potential to improve the safety and efficacy of drug prescribing. Assuring that the benefits of this research reach indigenous and other medically underserved people is an important justice concern. First, however, a legacy of mistrust, derived from traditional research practices that disempower communities, must be overcome. Linking pharmacogenetic research to collaborative, power-sharing research partnerships provides a valuable opportunity to develop new and positive precedents for genetic research in indigenous communities.

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Rapid advances in genomic research, fueled in part by major investments from the National Institutes of Health, offer the promise of new insights and knowledge to improve health care. In particular, pharmacogenetic research offers the potential to improve the safety and efficacy of drug prescribing. But will the health benefits that flow from this public investment be distributed equitably? This question is particularly acute for indigenous people, who experience profound health disparities and often lack access to state of the art health care facilities. Assuring that the benefits of genomic research reach indigenous and other medically underserved people is therefore an important justice concern. However pursuing the necessary translational research requires overcoming a legacy of mistrust toward genetic studies.

Mistrust of researchers is part of a broader history of mistrust of US institutions among American Indian (AI), Alaska Native (AN) and other indigenous communities, linked to the historical roles of these institutions as colonizers, definers of identity and indigenous status,

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#### DISCLOSURE

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and appropriators of human remains, cultural knowledge, and cultural artifacts for display or study. Many indigenous communities are particularly wary of genetic research, because of past misuse of specimens in genetic studies, and because of its implications for identity and shared heritage [1,2]. There are also concerns about deterministic interpretations of genetic results, potentially leading to neglect of environmental or psychosocial determinants of health, and invalid, stigmatizing interpretations of genetic contributors to health disparity.

Traditional research practices have contributed to this mistrust because they are based on a differential power relationship, in which research questions, methods, study design, interpretation of results, and recommendations for policy or practice have been developed and controlled outside of the indigenous communities. Communities also typically lack control over whether results are returned or to whom they are returned. Results may not be shared in a culturally understandable manner, and may be used to the benefit of the researcher but not the community. The failure to return results or focus on community benefit has been characterized as “carpetbagger” or “helicopter” research: the researcher drops into the community, extracts data, and is never heard from again, or at best provides information about the study in technical language that is unfamiliar to most in the community.

In addition, two widely discussed examples of genetic research have generated a powerful backlash among indigenous people in North America. In both, samples collected for specific genetic research were shared among researchers for other studies, without community knowledge or approval. Samples collected from the Nuu-Chah-Nulth First Nation in British Columbia, Canada for studies of rheumatoid arthritis were subsequently shared with other investigators for a variety of research purposes; although these practices were common among researchers at the time, the Nuu-Chah-Nulth viewed them as a breach of faith and demanded that the samples be returned [3]. A more recent conflict involved the Havasupai Tribe in the Southwestern US. As with the Nuu-Chah-Nulth, samples were collected with tribal approval, in this case to study the genetics of diabetes [2]. When the Havasupai Tribe learned that samples were subsequently used for many purposes beyond diabetes research, including investigations of population evolution, schizophrenia, and inbreeding, they felt betrayed [2]. In 2004, lawsuits filed by the Havasupai Tribe and individual tribal members against Arizona State University (ASU) and the researchers alleged breach of fiduciary duty, lack of informed consent, fraud and misrepresentation, negligence, conversion and violation of civil rights, all arising from the use of research samples for purposes unrelated to what they believed were the original research goals [2]. All claims except for negligence and civil rights violations were dismissed by the District Court as either lacking merit or sufficient specificity. This ruling may reflect in part the fact that the researchers’ procedures in sharing the Havasupai samples were, like those for Nuu-Chah-Nulth, standard of practice and allowable under federal research regulations. In response, the Havasupai plaintiffs dismissed their federal case and refiled the remaining claims for relief in Arizona State Court. The refiled case recently settled with a monetary award and other concessions to the tribe [4]. The case has resonated among AI/AN communities. Many Southwest indigenous communities provided official tribal resolutions and correspondence supporting the Havasupai lawsuit and condemning the researchers’ actions. This effort culminated in 2006 with a resolution from the National Congress of American Indians supporting the Havasupai position and condemning the researchers’ actions. Similarly, in Canada, the Nuu-Chah-Nulth experience helped to promote the promulgation of new research guidelines from the Canadian Institutes of Health Research that preclude data-sharing without consent of the indigenous community.

Despite the negative history, some researchers have achieved mutually productive research partnerships with AI/AN communities that incorporate genetic research [e.g., 5]. These

researchers have used community-based participatory research (CBPR) methods, to determine collaborative research priorities and procedures. Developing partnerships of this nature offers a valuable framework for transforming research practice. CBPR values communities as partners in all aspects of the research process, and has the potential to establish trust and reorganize power relationships such that community members become co-researchers. In this respect, CBPR can be viewed as a well-developed model of relational research ethics, emphasizing respect for persons, reciprocity, and encouraging researchers to go beyond a contractual model to work collaboratively with participants and communities. Institutional Review Boards that understand these ethical concerns can assist researchers to pursue appropriately structured research partnerships with indigenous communities.

An important feature of CBPR practice is to ensure at the outset that the research addresses community priorities, utilizes appropriate research procedures, and helps to build local capacity. Health disparities are a major concern to most indigenous people, with a high priority placed on research that has potential to provide health benefit. Because pharmacogenetic research is focused on improving drug safety and efficacy, it offers a more immediate potential for benefit than most other genetic research and is likely to represent a much higher community priority for research than more abstract or basic genetic studies, such as those focused on inter-relatedness of indigenous communities or on basic questions of cell biology. Pharmacogenetics is also an area of health research where the inclusion of diverse populations is particularly important, to ensure that all relevant variants are identified, tests are designed based on prevalence of variants in different populations, and implementation of pharmacogenetic testing is appropriate in diverse populations.

Although pharmacogenetic tests offer potential health benefits, indigenous communities may differ in their judgment about its priority compared to other health research. Researchers interested in pursuing pharmacogenetic research with indigenous communities therefore need to commit first to the development of partnerships with community leadership and health care providers, and to discussions of health research priorities with communities. The process of partnership is time-consuming, but essential for the development of trust between communities and research institutions. Procedures may differ in different indigenous communities. Local means of garnering community approval must be identified and followed, and indigenous communities may assert ownership of data and samples gathered and have other stipulations such as return of the samples upon analysis and review of results prior to any form of dissemination.

CBPR and related community engagement procedures are a means to achieve mutually respectful research partnerships between academic institutions and communities [5], and in particular, are important methods for fostering research directed at understanding and eliminating health disparities. However, one of the core values implicit in CBPR is responsibility, whereby the researcher makes a long-term commitment to communities to collaboratively set research priorities, build local capacity to address health priorities, return results in a culturally understandable format, and re-visit communities to maintain a lasting partnership. When done well, CBPR also provides a laboratory for understanding and addressing challenges to effective communication between participants and researchers; the lessons learned in this context have potential applicability in all research settings in which trust and reciprocity are emphasized.

Linking pharmacogenetic research to these research practices provides a valuable opportunity to develop new and positive precedents for genetic research in indigenous communities. The commitment inherent in pharmacogenetic research is to generate new knowledge to improve the safety and efficacy of drug treatment. This commitment creates common ground with the goals of indigenous health leaders, and forms the basis for a new

research center within the Pharmacogenomics Research Network (PGRN), the Pacific Northwest-Alaska Center for Pharmacogenetic Research (NWA-PGRN). With research partnerships in Alaska, Washington, and Montana, the center seeks to provide indigenous communities in the Pacific Northwest with the information they need to utilize pharmacogenetic benefits. An important measure of the success of NWA-PGRN will be its capacity to sustain collaborative research focused on the health priorities of its partner communities.

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