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# Risk, Reward, and the Double-Edged Sword: Perspectives on Pharmacogenetic Research and Clinical Testing Among Alaska Native People

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## Abstract

**Objectives—**Pharmacogenetic research and clinical testing raise important concerns for individuals and communities, especially where past medical research and practice has perpetrated harm and cultivated distrust of health care systems and clinicians. We investigated perceptions of pharmacogenetics among Alaska Native (AN) people.

**Methods—**We held four focus groups for 32 ANs in south central Alaska to elicit views about pharmacogenetics in general and for treatment of cardiovascular disease, breast cancer, depression, and nicotine addiction. We analyzed data for perceived risks and rewards of pharmacogenetics.

**Results—**Potential risks of pharmacogenetics included health care rationing, misuse of information, and stigma to individuals and the AN community. Potential rewards included decreased care costs, improved outcomes, and community development. Participants also

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**Contributors**

W. Burke and D. A. Dillard have been involved with the study since its conceptual beginning and have participated as leaders in all phases of the research from design to data collection and dissemination. H. Starks was also involved in the design of the study and participated substantially in data analysis and writing and revision of the article. R. Robinson led the study operations at SCF and organized all study activities, including data collection and approvals from the Alaska Area Institutional Review Board and tribal health organization, as well as participated with H. Starks and J. L. Shaw in data analysis and writing the article. J. L. Shaw led the data analysis phase of the project, completed the analysis with H. Starks and R. Robinson, and led the writing team, which included the active participation and critical discussion among all listed contributors.

**Human Participant Protection**

Approval for this research was received from the Alaska Area Institutional Review Board and University of Washington Institutional Review Board, as well as tribal approval from the Southcentral Foundation and Alaska Native Tribal Health Consortium.

discussed 8 contingent conditions that could mitigate risks and increase pharmacogenetic acceptability.

**Conclusions—**Alaska Natives perceive pharmacogenetics as potentially benefitting and harming individuals, communities, and health systems, depending on methods and oversight. Researchers, clinicians, and administrators, especially in community-based clinic and health care systems serving minority populations, must address this "double-edged sword" to effectively conduct pharmacogenetics.

References to "personalized" and "individualized" medicine are now frequently made in popular and professional health media, with particular emphasis on the potential of pharmacogenetic research and clinical testing to ensure safer and more effective drug therapy. Such benefits could have an important impact; adverse effects from pharmacologic agents and drug reactions result in more than 100 000 deaths annually in the United States[1,2] and contribute significantly to health care costs.[3–6]

Accurate use of pharmacogenetics requires knowledge of genetic variation from diverse populations because genetic differences across groups can affect both dosing requirements and likelihood of adverse drug reactions for a number of drugs.[1,4,7] However, most pharmacogenetic research has been done in populations of European descent.[7] Scant data exist for American Indian and Alaska Native (AI/AN) populations, making it difficult to assess the clinical utility of pharmacogenetics for AI/AN individuals.[8] In addition, the cost of pharmacogenetic testing may remain out of reach of underresourced health systems such as Medicaid, the Indian Health Service, or other tribal health systems. Under this scenario, the net effect of pharmacogenetics could increase, rather than decrease, health disparities.

For the AN people, considerations about participation in pharmacogenetics must be understood in the context of a documented history of unethical, even harmful, research conducted in their communities and the accumulation of associated distrust of outside researchers. Examples include the Barrow Alaska Alcohol study, research with the Havasupai Tribe in Arizona, and related concerns of the Navajo Nation that led to a moratorium on genetic research that continues today.[9–12] Mistrust of medical care endures because of negative experiences with the Indian Health Service and the lack of cultural knowledge of clinicians. These concerns raise timely and relevant questions for medical and tribal communities regarding the potential value and consequences of pharmacogenetics in indigenous communities across North America.[13–15]

We aimed to understand the key concerns and priorities of the AN people regarding the use of pharmacogenetics in Alaska's tribal health care system. We conducted research in a tribally owned and managed health care organization to engage AN community perspectives and to inform administrative and clinical decisions regarding use of pharmacogenetics in 4 clinical and 2 research scenarios.[16] This community-based participatory research approach offered a model for investigating the acceptability of pharmacogenetics in other AN and American Indian health systems, and in systems serving other populations with histories of negative experiences with medical research and care.[17,18]

## METHODS

The Southcentral Foundation (SCF) is an AN-owned, nonprofit health corporation providing primary care for 60 000 AI/AN people living throughout south central Alaska. In partnership with the Alaska Native Tribal Health Consortium, SCF also co-owns and co-manages the Alaska Native Medical Center, which serves 120 000 AI/AN people state-wide. SCF serves a highly diverse population of AI/AN people, representing more than 229 of the 565 federally recognized tribes in the United States. The Southcentral Foundation's AI/AN patients are both customers and owners of the health care system. As such, they play an essential role in shaping it, through participation in customer surveys, scientific research, and program evaluation, as well as governance and oversight. These characteristics make SCF an ideal setting for research that engages lay perspectives on pharmacogenetic use in diverse AN communities.

### Participants, Recruitment, and Incentives

We recruited a sample of 32 individuals, representing elders and younger SCF customer-owners, through flyers posted in SCF's Alaska Native Primary Care Center (ANPCC) clinics and lobby. Prospective participants contacted the researchers and were screened for eligibility criteria (at least 18 years of age, AI/AN heritage, English-speaking, and eligible to receive ANPCC services). Institutional review board considerations limited demographic characteristic data collection to categorical gender and age to protect privacy and anonymity. There were 12 men (38%) and 20 women (62%); 15 (47%) of the participants were 18 to 39 years old, and 17 (53%) were 40 years old or older. Participants received a $50 gift card, which is common practice for research at SCF.

Four focus groups were held at the ANPCC between November 2010 and January 2011. The groups were stratified by age (younger than 40 years or 40 years old or older; 2 groups each) to encourage discussion by all participants, in recognition of AN social norms that encourage deference to elders. All groups were audio recorded, and the recordings were transcribed. An experienced AN researcher who was not associated with the research team moderated each discussion with the same interview guide (data available as a supplement to the online version of this article at http://www.ajph.org).

After providing written informed consent, participants in each focus group received a brief, verbal explanation of pharmacogenetic research and clinical testing (data available as a supplement to the online version of this article at http://www.ajph.org). Discussions focused on eliciting a full range of participant views of using pharmacogenetic clinical testing for 4 conditions that could be considered both genetically and behaviorally influenced. The moderator read aloud descriptions of the scenarios, which included cardiovascular disease (warfarin), breast cancer (tamoxifen), depression (no specific medication), and nicotine addiction (no specific medication). Discussions of each health condition concluded with a question about additional factors that ought to be considered for the use of pharmacogenetic clinical testing. Participants were then asked about the acceptability and utility of pharmacogenetic research under 2 scenarios: (1) in AN populations, and (2) linking research samples to health information in the medical record. All research activities were approved

by the Alaska Area institutional review board and tribal leadership of SCF and Alaska Native Tribal Health Consortium.

### Data Analysis

We conducted a thematic analysis of the focus group data through an iterative and inductive process.[19] All focus group transcripts were reviewed by 3 members of the research team (J. L. S., R. R., H. S.). Each researcher independently coded the same 2 transcripts to generate an initial list of codes that were used to develop a coding framework, which was then applied to all the transcripts by 2 coders. The coders met to compare the transcripts, resolve any discrepancies, and revise and expand the definitions for the codes. We defined a set of primary and secondary codes through this process. Primary codes included perceived risks, perceived rewards, and contingencies. Secondary codes corresponded to the individual, community, and institutional levels where the risks and rewards of pharmacogenetics were identified.

We generated reports of the primary and secondary codes and analyzed them for salient patterns in the risks and rewards regarding the use of pharmacogenetics. We examined the reports by focus group, and within and across gender and age categories to identify how perceived risks and rewards varied across these characteristics.[20]

## RESULTS

Across the 4 focus groups, participants perceived both risks and rewards of pharmacogenetics in both clinical and research applications, often speaking of these as a "double-edge sword." Participants generally saw the rewards of pharmacogenetics as outweighing the risks, but articulated several conditions considered essential for pharmacogenetics to occur. Although the scenarios were meant to differentiate between clinical practice and research, some participants responded to the clinical scenarios with research concerns, given their understanding of historical events; for example, when clinical information was perceived as something that was used in research without explicit consent. The main themes are presented in the box on the next page and described briefly in the following.

### Perceived Risks

Participants' concerns centered on 3 themes that focused equally on individual- and community-level concerns across the clinical and research scenarios. First, they noted the importance of adequate protection of AI/AN people, focusing on issues of confidentiality, consent, and justice. An underlying concern was the potential that genetic test information from either clinical practice or research could be misused or result in stigma. This was reflected in a conversation about linking genetic information to medical records in the context of pharmacogenetic research:

> How far into your medical records do they dig and what information are they recording? … why (are we) doing a focus group on genetic testing at a Native hospital and not [another hospital] where they have all races? Just the fact that that's happening makes me concerned about them wanting to find more out about

> Native genes and how Natives are affected by different medication. – Woman, younger than 40 years

Second, participants expressed concern that clinical use of pharmacogenetics could result in reduced health care access for ANs by diverting funds from other health care needs, such as primary care. Participants stated that even if pharmacogenetics benefitted some community members, the value would be limited if other effective, less-expensive treatments are available.

Finally, participants had doubts about pharmacogenetic testing in the context of nicotine cessation, because this was perceived to be a personal choice. For example, 1 participant worried that to save health system costs, testing could become mandatory and override individuals' preferences to continue tobacco use.

## Perceived Rewards

Participants generally endorsed the use of pharmacogenetics in the AI/AN community when it could improve health care. Participants viewed pharmacogenetics as potentially yielding faster, safer, and more effective diagnoses and treatments of cardiovascular disease and breast cancer, although they were less optimistic about its utility for nicotine cessation or as depression treatment. Some suggested that pharmacogenetics could potentially maximize health care resources by reducing the time and money spent achieving effective treatments, and thus expand overall access for the entire community. Participants also endorsed pharmacogenetics as a potential opportunity for AI/AN community development through direct participation of AI/AN people in pharmacogenetics as researchers, clinicians, and administrators.

Participants articulated 8 contingencies pointing to factors that could mitigate the risks of pharmacogenetics enough to realize the potential rewards. These "if/then" statements indicated a view of pharmacogenetics as potentially useful and acceptable in the tribal health system as long as specific conditions are met (box on the next page).

**Health care value—**Younger and older participants indicated that acceptability of pharmacogenetics in their communities depends on both efficacy and cost. The primary factor for participants in deciding to use pharmacogenetics in clinical settings was the potential for improved treatment efficacy, particularly when there is substantial individual variability in response to treatment, such as in tamoxifen treatment of estrogen receptor-positive breast cancer. For these participants, improved efficacy meant reducing (1) time to diagnosis and cure, (2) side effects and complications, and (3) mortality:

> If it's causing a lot of deaths …. it's worth researching.—Woman, older than 40 years The consequences of the (tamoxifen) not working is a chance of the cancer coming back. (That) should be weighed.—Man, younger than 40 years

Participants also expressed concerns about cost, suggesting that health risks in certain conditions are too great to not test, provided that testing is cost-effective and timely. Participants showed concern about equitable distribution of health care dollars and

suggested pharmacogenetics would be advantageous if the whole system could sustain the cost burden:

> As long as it's cost-effective and time effective too, especially in (warfarin's) case, time is of great importance so if the patient has enough time to undergo the testing. —Man, older than 40 years

> In a perfect world with unlimited amount of resources, it makes sense to test everyone to make sure that they're getting the right treatments. … I'd say if Southcentral Foundation was investing in that … it'd be a really good idea because prescribing someone the wrong medication, that costs time and themedication itself … it could lead to really adverse side effects.—Woman, older than 40 years

**Protection of individuals—**Pharmacogenetics was generally viewed as incurring more reward than risk if participation is strictly voluntary and confidential. Younger participants in particular viewed these protections as necessary to protect privacy at the individual level, especially when health care is perceived to involve behavioral issues:

> Yes, but only with patient consent because obviously not everyone that smokes wants to quit. –Woman, younger than 40 years

Some participants worried about whether adequate safeguards are in place to assure voluntariness, confidentiality, and guarantees against harmful uses of data; for example, the inappropriate release of information, rationing of health care, or coercion:

> Could they use the information … from the genetic testing and from that blood work—could they use it and manipulate it in a way that harms the care that you receive?—Woman, younger than 40 years I worry … because … a lot of people … don't have a choice to say, "I'm going to go to another hospital that's going to let me do what I want to do." –Woman, younger than 40 years

Study participants in both age groups indicated that oversight and assuring that tests were used for specific purposes could help mitigate these risks.

> It needs to be really watched on, again, with the privacy thing. … We don't know, then who would be watching the people that are supposedly watching us … what is it used for? Is it used correctly?—Woman, older than 40 years

Another subtheme of protection was culturally competent consent. Younger participants endorsed the view that for pharmacogenetics to be acceptable, consent procedures must be in accordance with locally relevant communication patterns, as well as generational differences.

> Lots of people (would participate in pharmacogenetic research), as long as it is approached in a respectful and appropriate manner and people understand what it is.—Woman, younger than 40 years

> I don't feel comfortable with my grandmother coming in here and being informed about what she's signing up for. —Man, younger than 40 years

In response to concerns about culturally and intergenerationally competent consent, another related theme of self-determination was particularly evident among younger participants.

### Self-Determination

Self-determination was seen as an important factor for ensuring a net benefit from pharmacogenetics. Several younger participants suggested this could occur by developing capacity in the community to conduct pharmacogenetic research and clinical testing:

> It'd be really tough to convey all that information to the Elder population. Now if it were, say, 10 or 15 years down the road, and we have the youth of this generation actually educated in this type of genetic testing and everything, then it might be a different story.—Man, younger than 40 years

Participants also indicated that AN people should be directly involved in developing, overseeing, and leading pharmacogenetic efforts in their communities:

> We need to start being the leader. … Genetics opens a whole new ball game of medicine … to not take advantage of it … it's a sad thing. … Imagine a cure for diabetes and cancer, and our people are the ones leading the cure.—Man, younger than 40 years

Thus, participants suggested that pharmacogenetics represent not only an opportunity for individualized medicine, but also an opportunity for AN community development and capacity building.

## DISCUSSION

Participants in this study had a sophisticated understanding of the potential value of pharmacogenetics. They identified risks and rewards of this testing approach and the conditions under which pharmacogenetics would be more promising than perilous for themselves, their families, and their communities. Their concerns related to the confidentiality of pharmacogenetic information and the potential for misuse. Their comments that reflected distrust of research and medical care were consistent with previous findings from indigenous and other minority communities.[21–24] Concerns about misuse of genetic data have led many tribes and indigenous groups to implement data sharing agreements and other regulations of the research process to protect their communities.[25,26] However, more work is needed to guide protections in the clinical setting if pharmacogenetic testing is introduced.

Participants' views on pharmacogenetics, especially as a potential contributor to safer, more efficient diagnosis and treatment of chronic and life-threatening health conditions, such as cardiovascular disease and cancer, were consistent with previous studies.[26,27] Their concerns about unacceptable increases in health care costs accurately reflected the current uncertainties about the scope of benefits pharmacogenetics could deliver.[28,29] This pointed to the need for tools to assess the real fiscal effects of pharmacogenetics for individuals, communities, and health care systems. Such assessments might be particularly important in resource-limited situations in which significant opportunity costs could occur as a result of introducing new technology that provides only incremental improvement in health care.

Our participants were also concerned that testing be voluntary, and identified culturally competent consent processes as a means to accomplish this goal. They saw the need for mechanisms to assure that pharmacogenetics is limited to approved uses. Additionally, our participants saw potential for AI/AN involvement in pharmacogenetics as a source of capacity development and a further way to exert appropriate oversight over this technology and increase the value of pharmacogenetics. These findings resonated with the emerging body of research related to responsive justice, incorporating recognition of community views, and response to past injustices, as well as fair distribution of benefits.[30] They also saw the importance of self-determination in communities historically underrepresented in research that have persistent socioeconomic disparities.[31–36]

### Limitations

These findings might have limited generalizability because they were drawn from a small sample at a single AN institution. Although fewer men than women volunteered, the male-to-female ratio reflected ANPCC service use, suggesting our sample represented the gender distribution of urban SCF health care users.

These data also did not allow us to fully explain why participants endorsed the use of pharmacogenetics for cardiovascular conditions and breast cancer more strongly than for nicotine cessation and depression. More research is needed on variability in participants' explanatory models and their associated relationships to perceived utility of pharmacogenetics.

These findings might be relevant in population-based health care systems in which limited and often dwindling resources require complex and challenging cost-benefit analyses among consumers, clinicians, and administrators to maximize health care access, and where there are concerns about stigma and misuse of genetic information. These findings, therefore, should be considered in other underserved populations and minority populations.

### Conclusions

The growing number of complex health concerns in the AI/AN community are expanding the need for health research within the native community.[37–41] AI/AN people are not opposed to research, as evidenced by the Strong Heart Study and numerous other examples.[37,38,40–46] However, tribal people, tribal governments, and tribal health organizations are increasingly taking an active role in research, developing policies and procedures to regulate and protect AI/AN research participants.[9,12] In this community-based study, pharmacogenetics was recognized as a "double-edged sword"—a cutting-edge science with the power to provide both benefit and harm. The participants' recognition of the dual potential of pharmacogenetics tells a cautionary tale for anyone working in communities where medical practice and research has perpetrated harm or cultivated distrust. Pharmacogenetic research must be undertaken with respect for these histories, restoration of trust, and responsiveness to the communities in which we work.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Note.** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Sample Quotes on Perceived Risks and Rewards of Pharmacogenetics: Perspectives on Pharmacogenetic Research Among Alaska Native People, 2010–2011

| | |
|---|---|
| **Risks** | |
| Importance of adequate protection of individual participants in pharmacogenetic research | "I think it (participation in pharmacogenetic research) should be voluntary, but the first thing I start thinking of is exactly who would be trying to look at in your health record, who is watching, who is looking at, if they're doing genetic testing only on certain areas or certain people and not leaving it up to other people–just like I've heard about Natives being just tested in (other regions of Alaska). People working at that hospital know they're doing this right now. And whether it's voluntary or not, sometimes it's just done anyway, in my opinion. And there's, for me, a lot of privacy (concerns) on what else are they looking at … who would be watching the people that are supposedly watching us? Or, what is it used for? Is it used correctly?" |
| Increased costs/decreased access to primary care | "It sounds very expensive, and I think that it (clinical pharmacogenetic testing) is very expensive. And I know that we're funding our own health care here with a limited amount of money. And we have people who have–and we have high rates of almost every disease and a lot of social ills. It sounds like testing that could help a few people when maybe that money could be spent to help a lot more people." |
| Limited utility of testing for behavioral health conditions | "So genetic coding, you want a piece of my blood to understand how … I work mentally. That just doesn't add up for me." |
| **Rewards** | |
| Improved health | "I think it (clinical pharmacogenetic testing) would be very beneficial for patients with warfarin because the dosage varies widely with that specific medicine, and with the trial-and-error dosing you have constant monitoring of the medicine. But then, if you're able to do genetic testing and you can narrow down the variability, that could help to decrease unwanted effects." |
| Decreased costs/increased access | "I'd say if Southcentral Foundation was investing in that, if they had enough money to invest in a program like that, like pharmacogenetic research and genetic testing, I'd say it'd be a really good idea because prescribing someone the wrong medication, that costs time and the medication itself—like a lot of people were saying, it could lead to really adverse side effects." |
| Community development | "Genetics is a lot of doors to be opened, to have that kind of research there is a very good thing I believe the hospital should really look into. I'd like to see something like that. I'm tired of seeing all this space age stuff happen in the Lower 48 and all over. Why don't we lead the way, you know? Alaska leading the way in this genetic thing would be a good door to open for a hospital." |

Conditions Under Which Pharmacogenetics Were Deemed Acceptable by American Indian and Alaska Native People: Perspectives on Pharmacogenetic Research Among Alaska Native People, 2010–2011

| Theme | Condition(s)—Pharmacogenetic Acceptability |
|---|---|
| Health care value | Is more clinically effective than extant treatment options, especially if the particular condition or disease is life threatening or affects a small population. |
| Health care access | Does not result in rationing of health services and reducing health care access for AI/AN people. |
| Moral economy of scale | Benefits the majority of patients with a particular condition and conserves resources. |
| Worldview | Does not conflict with individually- or collectively held spiritual values or religious beliefs. |
| Self-determination | Directly involves AI/AN community members as drivers of PGR/X education, research, and practice. |
| Effects of racism | Do not perpetrate prejudicial views of AI/AN people (e.g., as “entitled” or receiving “special benefits”). |
| Negative health effects | Avoid increasing health disparities, as occurred with some previously introduced technologies (e.g., processed food). |
| Protection of people | Is voluntary and confidential. |
| | Develops and follows culturally appropriate informed consent procedures. |
| | Assures that AI/AN community standards of oversight are in place and followed to mitigate misuse of genetic data. |

*Note*. AI/AN = American Indian/Alaska Native; PGR/X = pharmacogenomics/pharmacogenetics.