Special Report

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Personalized Medicine

Recommendations to researchers for aiding in increasing American Indian representation in genetic research and personalized medicine

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Increasing American Indian/Alaska Native (AI/AN) representation in genetic research is critical to ensuring that personalized medicine discoveries do not widen AI/AN health disparities by only benefiting well-represented populations. One reason for the under-representation of AIs/ANs in research is warranted research distrust due to abuse of some AI/AN communities in research. An approach to easing the tension between protecting AI/AN communities and increasing the representation of AI/AN persons in genetic research is community-based participatory research. This approach was used in a collaboration between a tribe and academic researchers in efforts to increase AI/AN participation in genetic research. From the lessons learned, the authors propose recommendations to researchers that may aid in conducting collaborative and respectful research with AI/AN tribes/communities and ultimately assist in increasing representation of AIs/ANs in personalized medicine discoveries.

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Background

The era of genetic research and personalized medicine has arrived. In 2015, US President Barack Obama launched the Precision Medicine Initiative to collect and analyze genetic data from a million Americans (i.e., the NIH All of Us Research Program) and generate new understandings of how genetics, environment and lifestyle contribute to disease [1]. Extensive research efforts are now ongoing to understand the role of genetics in behavior and health outcomes and to develop treatment strategies tailored to an individual's unique genetic makeup [2]. Such research is leading to transformations in the prevention, diagnosis and treatment of disease.

A concern related to this transformative research is the under-representation and under-study of racial and ethnic minority populations, including American Indians/Alaska Natives (AIs/ANs). AIs/ANs experience some of the greatest health disparities documented in a variety of diseases [3,4]. Increasing AI/AN representation in genetic research is critical to ensuring that personalized medicine discoveries do not widen AI/AN health disparities by only benefiting well-represented populations (e.g., persons of European ancestry).

One reason for the under-representation of AIs/ANs in genetic research is warranted research distrust due to historical abuse and exploitation of AI/AN communities in research. Genetic data can provide individualized and sensitive information about health predisposition, disease carrier status, wellness, physical traits and ancestry and thus rightly invoke data privacy questions such as who will be using the data? And for what purposes will the data be used? In an AI/AN community where there is shared heritage and culture, not only must an individual's interests

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be considered, but the tribal community's interests must be considered as well. Thus, it is vitally important that the tribe owns the data and is involved in all decisions regarding the data because of historical practices conducted by the dominant culture that involved breaking promises and the exploitation of AI/AN communities in genetic research. For example, in the 1990s, researchers at Arizona State University used genetic data collected from the Havasupai Tribe for purposes other than what was agreed upon by the tribe [5]. The tribe was told their genetic data would be used solely for studying genetic susceptibility to diabetes, but researchers later used their data to examine other medical disorders, such as schizophrenia, without seeking consent from the tribe or the research participants [5]. In 2010, a settlement was agreed upon whereby Arizona State University provided the Havasupai Tribe US$700,000 in compensation, resources for securing a tribal clinic and school and return of the tribe's DNA samples [5]. This widely publicized incident along with other unpublicized negative experiences, such as researchers developing studies that were not relevant, feasible or culturally appropriate and researchers collecting data from communities without communicating the results, have contributed to distrust and hesitation by AI/AN communities to participate in genetic research.

There is clear tension between protecting AI/AN communities and increasing the representation of AI/AN persons in genetic research. An approach to relieving this tension is community-based participatory research (CBPR). CBPR has been defined as a "collaborative, action-oriented research approach that seeks to address health disparities through aligning community members' insider knowledge of their community's needs with academic researchers' methodological expertise" [6]. CBPR has been described as providing a "win-win" relationship for academic institutions and AI/AN communities [7–9]. Ongoing efforts are embracing CBPR to increase genetic and personalized medicine discoveries with AI/AN communities, including those of the Northwest-Alaska Pharmacogenomics Research Network and the University of New Mexico Health Sciences Center's cooperative agreement with the National Cancer Institute.

Another example is a recent collaboration between a tribe in Minnesota and academic researchers at the Masonic Cancer Center, University of Minnesota, who used a CBPR approach to implement a research study within the tribe's rurally located health system that involved the collection of genetic data related to smoking behavior, toxicant exposure and cessation among tribal members. From the lessons learned working together on this project, the authors describe herein multiple recommendations that may be helpful to other academic researchers who are interested in or already embarking upon collaborations with AI/AN communities that involve collection of genetic data and personalized medicine efforts. Importantly, these recommendations are based on the experiences and perspectives of both tribal and academic collaborators, and both parties contributed to writing and reviewing this article. The authors' recommendations corroborate prior recommendations for conducting research with AI/AN communities [9–13], yet extend the body of recommendations by integrating specific considerations for a collaboration that involves collection of genetic data from a single tribe. Collectively, these recommendations may aid in making the research process more transparent for academic researchers and more respectful of AI/AN culture and may ultimately help increase AI/AN representation in genetic research and personalized medicine and decrease overall health disparities among AIs/ANs.

Background of the research collaboration, study rationale & utilization of CBPR principles

To contextualize the recommendations, the authors first provide a brief overview of the collaboration and rationale for the study that used a CBPR approach. The tribe is located within the northern plains region of the US, where it is estimated that more than half of AI/AN adults smoke commercial cigarettes daily or some days [14]. As a result, smoking-related diseases like lung cancer are the highest among AIs/ANs residing in this region versus AIs/ANs residing elsewhere [15,16]. Witnessing the grave burden of smoking among tribal members, community stakeholders, who included tribal leaders as well as health professionals employed by the tribe, and academic researchers convened in 2015 to discuss the potential for a research study on genetic susceptibility to smoking and lung cancer.

The academic researchers' expertise included how racial/ethnic differences in the rate of nicotine metabolism, which is largely influenced by genetic variation, is associated with racial/ethnic differences in smoking intensity, carcinogen exposure from cigarettes, and lung cancer risk [17–23]. Also, a growing body of evidence in predominantly Caucasian and African American smokers indicates that genetic variation in nicotine metabolism may inform the type of US FDA-approved smoking cessation treatment (e.g., varenicline vs nicotine replacement therapy) that would maximize quitting success while minimizing side effects for each smoker [24–26]. Thus, information on nicotine metabolism has potential clinical utility through personalizing cessation treatment options for smokers. Through regular in-person meetings, the community stakeholders and academic researchers jointly decided to pursue study of genetic variation in nicotine metabolism pathways among smokers to inform future personalized smoking cessation treatment. The site for study recruitment and participation was the tribe's primary health clinic. Recruitment commenced in 2018 and finished in 2020. Participants were daily commercial cigarette smokers who provided biological samples, including a saliva sample, for assessment of variation in nicotine metabolism genes. At present, enrollment is completed and data analysis and interpretation are ongoing.

Principles of CBPR were utilized to empower the tribe to be the primary driver of the research, to enhance the tribal clinic's capacity to conduct the research and to facilitate a collaborative balance between the tribe and the academic researchers throughout the research process. A collaborative approach is critical for AI/AN communities given their history of exploitation and abuse in some research. For the researchers, the CBPR approach encourages commitment to a sustained process of relationship building and to listening to the community's needs and requests for making the research relevant, feasible and culturally appropriate. For example, the community stakeholders expressed to the researchers a major concern about the high smoking prevalence observed among members and an interest in the role of genetic susceptibility but raised concerns regarding genetic data ownership, privacy and storage. Thus, the collaboration jointly decided to focus on assessing the role of genetic factors in smoking susceptibility, and, as described later in this article, numerous safeguards were introduced to respect the community stakeholders' wishes around data ownership and privacy. Ultimately, the CBPR approach helped to promote the conduction of research with or alongside versus on the tribe. Many of the lessons learned intrinsically highlight principles of a CBPR approach and showcase the immense benefit of a CBPR approach for AI/AN community and academic collaborations.

Recommendations for researchers

Although the community stakeholders and academic researchers are involved in building and sustaining a research relationship, the authors provide recommendations specifically for researchers in the hopes of mitigating the legacy of researchers abusing and exploiting AI/AN communities in research.

Researchers must familiarize themselves with tribal governance & federal law, which gives federally recognized tribes the legal right to self-govern

As there are now 574 federally recognized tribes, it is important to understand how culturally distinct each tribe is and to understand the uniqueness of doing research with tribal governments. As sovereign nations, tribes are responsible for the overall health and well-being of their populations, which includes controlling research activities and entering into formal collaborations. Included in tribal responsibilities is the ability to develop and maintain policies to protect the integrity of operations and guard against predatory and harmful use of data from the populations they serve. This is an absolute and non-negotiable function of a tribe to ensure present and continued viability of all future generations. Each tribe has their own constitution and government, which is led by elected members. Researchers should familiarize themselves with the tribe's leadership structure and order of command for decision-making. One way to do this is to engage in conversations with the community stakeholders to understand how decisions are made and by whom. Another resource is the tribe's website, as most tribes have their own website that describes their governmental structure and elected leadership, Researchers should also be aware that elected leaders can change throughout a collaboration through sanctioned tribal constitutional elections. These elections may be every year or every two or three years as guided by their constitution. Therefore, depending on the length of the research project, the collaborative relationship may need to be built in time for newly elected leadership to review, ask questions and provide advice.

Build trust with the AI/AN community

Distrust of researchers is justified based on prior research experiences of some AI/AN tribes as well as the broader history of distrust of US institutions. Trust cannot be built overnight; however, there are steps and promising practices that will help work toward building trust with tribal governments and their communities, which can in turn help bolster participation of AIs/ANs in genetic research and personalized medicine.

Researchers should familiarize themselves with the tribe's history of involvement in research

The AI/AN population is a heterogeneous group of tribes representing different cultures and histories. Tribes are diverse with respect to their experiences and comfort level with research, let alone research involving genetic data. Understanding the history of the community's research involvement, if any, and views on research can provide critical insight into the community's openness to research participation and ways to work together to mitigate concerns and build trust. Therefore, do literature reviews, check tribal websites and newspapers and facilitate discussions with community stakeholders on prior research experiences and lessons learned.

Plan to spend time in the community (with tribal permission & guidance)

In the authors' experience, after permission from the tribe and community stakeholders, there is no better way to build trust with the community than by spending ample time with community members in person. Researchers should therefore plan to spend time traveling to and visiting with the community. Attending community events, if invited, such as health fairs, pow wows and crafting events is one way to benefit the relationship by showing that the researcher has genuine interest in and respect for the community's cultural practices and traditions. Additionally, in-person meetings with community stakeholders can aid in building trust over time because trust is not implicit and is not earned in one meeting.

Engage community stakeholders throughout the entirety of the research process

Central to building trust, and a core principle of the CBPR approach, is ensuring the community is a lead player in all decisions made for the collaboration and the research study [27]. Distrust may be a result of perceived authority imbalances when researchers fail to engage the community from the beginning of the proposed project and discount the value of the indigenous knowledge of the community. Although it is not often realistic to assume that community stakeholders will contribute as much time and effort to the study as the researchers, all decisions for the study should be driven by the community stakeholders and mutually agreed upon prior to implementation.

Exercise the lifelong pursuit of becoming culturally attuned by practicing cultural humility

Although inherently embedded in the trust building strategies previously discussed, the pursuit of cultural attunement was viewed as essential to our tribal–academic collaboration and therefore warrants its own discussion. Cultural attunement is a term that has evolved to represent an action that is more sensitive than cultural competency and humility. Cultural competency is defined as becoming educated regarding another person's or group's experience, culture and identity [28]. Cultural humility is the next step toward cultural attunement and involves not only education but also engagement with the community and their culture. Cultural attunement is a continual, endless process of practicing cultural humility. It has been depicted as "to walk beside or with an other" [29] and to "bow to another person" [30]. Cultural attunement has also been described as a "lifelong pursuit" [29]. This practice can assist academic researchers in adapting their research styles, approaches, resource allocations, decision-making processes and measures of success to be accepted, effective and valued by the AI community. The practice of cultural attunement was first described by Hoskins [29], and because the authors perceive it as critical to the success of our collaboration, its components are briefly highlighted in the following sections.

Acknowledge the presence & pain of oppression

Hoskins suggests that those who belong to a dominant culture must recognize, acknowledge and self-evaluate their oppression of others, whether explicit or implicit [29]. Hoskins further states that "without acknowledging these dark places, it is difficult to take responsibility for and to change our own oppressive tendencies." This continual process of self-awareness among academics is essential to ensuring that community stakeholders' culture and traditional values are understood and respected throughout the research process.

Practice humility & mutuality

As stated by Hoskins, "Those who are part of the dominant culture have to constrain their own inclination to constantly privilege their own perspective" [29]. Humility is carried out by making sure the relationship and decisions are not centered solely on the academic's perspective or input. Further, restraint, modesty, understanding one's own culture and being humble in the presence of other cultures are necessary for any research project to ensure that the attributes of the community stakeholders are realized. This is furthered by the practice of mutuality, which means allowing for voices and perspectives of the community to be heard and incorporated into the research process.

Act with reverence

Reverence is defined as having deep admiration for someone and their differences and implies kindness and compassion. It may be depicted by the act of bowing to another person's culture and differences. As discussed by

Hoskins, it requires a person to listen, think, act and respond from the heart [29]. The practice of listening with reverence was such a cornerstone to the success of the authors' collaboration that it requires further discussion. The goal is to listen to learn, not to just be polite – a practice commonly referred to as active listening. Active listening is an advanced communication skill that requires concentration, patience and empathy. Active listening has been described as "requiring the listener to empty themselves of personal concerns, distractions and preconceptions" [31] and "to place all of one's attention and awareness at the disposal of another person, listening with interest and appreciating without interrupting" [32]. Active listening can be an uncommon practice for many academics since academic settings tend to involve discussions that entail competition to speak and share one's expertise [33]. Robertson describes multiple roadblocks to active listening common to those in the medical field, including judging, suggesting solutions and avoiding the other's concerns, and strategies to overcome these roadblocks [33]. A resource on active listening skills within the context of CBPR can be found in Community and Faculty Training Curricula to Prepare Partners for Community-based Participatory Research Collaborations (specifically slides 26–30 of the training curriculum, under Academic Faculty Training Materials) [34].

Practice coming from a place of not being the expert

The practice of cultural humility requires the academic collaborator to practice being open to the expertise of the community and learning from the community. This can be uncomfortable for academics because academics have historically been valued for being experts.

Be straightforward with expectations & ideal communication strategies

Another recommendation based on the authors' experiences is the need to be clear on the expected study timeline, which likely differs between the community stakeholders and academic researchers. Although it is common for academics to devote as much as 50–75% of their time to research efforts, community stakeholders juggle multiple responsibilities and may have limited time and effort for research. In addition, although meeting grant and publication timelines is common currency for academics, AI/AN communities will often have other metrics of success and value. Being aware of this time and effort discrepancy and discussing its potential implications can help with setting expectations and reducing disappointment. When collaborating with other academics, a grant deadline may be reason enough to expedite some activities, but this may not be as meaningful to community stakeholders. Expect collaborations, especially in the beginning, to take more time than you might estimate. Another recommended practice is discussing how best to problem solve, communicate with one another (e.g., in person, email, over the phone) and determine who is held accountable for which aspects of the research. A recommended guide for facilitating discussions on these issues is the Research Partnership (Collaboration) Checklist developed by the University of Minnesota Program in Health Disparities [35]. Finally, it is important that researchers are clear about the potential results from a study. Researchers should make it known that research is based on a hypothesis and not overpromise the potential value of the findings and their implications to the community.

Develop a research agreement to define study goals, intended outcomes, responsibilities of key personnel & plan for using & sharing genetic data

Research agreements, such as a written memorandum of understanding or agreement and data use and sharing agreements, can be useful for formalizing the research collaboration and are a transparent way to describe the mutual goals, responsibilities and intended research benefits. For research involving biological samples and genetic data, research agreements are particularly helpful for ensuring the tribe has full regulation of the collection, storage, analysis and dissemination of data. The authors recommend that the following be clearly depicted in a research agreement/contract: overall study goals and mutually agreed upon timeline; roles and responsibilities, as approved by the tribal government of the community leaders and the academic collaborators; order of authority for decision-making and who directs the work, creates the work plan and supervises the key research personnel; plans for study review and approval, such as review by tribal governance and tribal and university institutional review board (IRB); and a data use and sharing agreement that describes data ownership and sharing, location of where biological samples will be stored and for how long, the process for analysis and destruction of leftover samples and the approval process for disseminating results, including how the tribe will be referred to in publications and presentations. The data use agreement should explicitly outline plans for securing funding and how funds will be used and distributed. Because the relationship between the community and academic collaborators is continually evolving, research agreements/contracts should be revisited frequently and updated as needed under guidance and the terms of the agreement/contract. Example templates and considerations for research agreements/contracts are available through several online resources, including the National Indian Health Board (www.nihb.org) and National Congress of American Indians (www.ncai.org) and the School of Public Health at the University of Minnesota (www.sph.umn.edu/resources).

Ensure the study receives appropriate review by the tribe for ethical & cultural considerations

Many tribes have used the Indian Health Service's national IRB, and others may have their own tribal IRB that guides research requirements such as the cultural appropriateness and feasibility of the study and the study-related risks versus benefits to participants and the tribe. However, many tribes do not have access to a formal IRB, which was the case in the authors' collaboration. For this reason, the community stakeholders organized an informal review of all study procedures by members of the community, including tribal officials, health professionals and elders. Research and data agreements, as described in the prior section, also serve as a tool to improve the likelihood that the study and data being collected have been scrutinized by the stakeholders, tribal government and their respective communities to increase the ability of researchers and policy makers to analyze and translate data into meaningful reports and knowledge.

Provide the tribe with resources & personnel to support the research study

Academic collaborators should expect to financially support the research, as tribal governments' limited budgets seldom have funds for such projects. Additionally, tribal employees are often assigned multiple responsibilities to address the acute needs of their population and therefore may be limited in the time and effort they have available to assist with the study. For the authors' collaboration, an elder of the tribe was hired as the study coordinator. Hiring a community member was advantageous for several reasons, including their ability to identify helpful solutions for maximizing recruitment and participation; trust and respect by the community members, which helped with study buy-in by participants; and ability to facilitate communication between the community stakeholders and academic researchers due to being in person in the community and in proximity to the tribe's leadership and governing members. In addition, being on site ameliorated issues regarding traveling long distances from the university to the AI community.

In the authors' case, the academic researchers obtained financial support through the Minnesota Cancer Clinical Trials Network. A freezer was purchased for the tribe, which honored the tribe's ability to maintain ownership and storage of samples on tribal land, as well as basic research materials, such as a laptop, desk, cabinets, office supplies and study phone. Resources for the tribe can also include educational opportunities for the tribe's health professionals and leadership to learn about genetics and personalized medicine. For example, a health professional from the tribal clinic joined, free of charge, a semester-long, two-credit online class on pharmacogenetics offered at the University of Minnesota. A final resource to consider introducing is broad educational opportunities for the tribe's community members, such as on the topic of genetic data and how they may be useful for tailoring treatment and training opportunities for youth with an interest in research or health-related careers.

Strike a balance between gaining scientific knowledge & providing tangible benefits to the community

In the authors' experience, the AI community is not opposed to genetic research when the resulting data have the potential to be used to educate the community and inform the community's clinical practice and are directly related to the health concerns raised by the community. For the authors' study, nicotine metabolism genes were selected for examination because of their role in identifying smokers who are at greater risk of tobacco-related disease and their potential for personalizing treatment medications for smoking cessation. Thus, the authors' collaboration may provide important insight into why the tribe experiences such high rates of lung cancer and how the tribe can develop more effective ways to help their members quit smoking. Another benefit that should be considered is that a community's positive experience with a research study may foster a culture of research in the community and therefore ignite an interest in further participation in genetic research and personalized medicine.

Conclusion

Based on the authors' experience, AI/AN communities and academic researchers can collaborate together on genetic research if the research is guided by the community's stakeholders, has the tribal government's approval, addresses a clear community need, includes safeguards around the use and protection of genetic data and has tangible benefits for the community. Researchers must make a commitment to building and sustaining trust, listening, practicing cultural humility and ensuring that the community has the capacity and appropriate safeguards in place throughout all phases of the research process.

Future perspective

Although the authors' recommendations are based on our single experience collaborating together and have not been formally evaluated, we foresee that these recommendations will aid in making the research process more transparent for academic researchers and more respectful of AI/AN culture and will ultimately help increase AI/AN representation in genetic research and personalized medicine discoveries.

Executive summary

- There is tension between protecting American Indian/Alaska Native (AI/AN) communities and increasing the representation of AI/AN persons in genetic research. An approach to relieving this tension is community-based participatory research.
- Based on the authors' experiences with a tribal/academic collaboration that utilized a community-based participatory research approach to collect genetic data from members of the tribe, we offer recommendations for researchers to aid in conducting collaborative and respectful research with AI/AN communities. These recommendations include:
  - Becoming familiar with tribal governance and its structure.
  - Building trust with the AI/AN community.
  - Exercising the lifelong pursuit of becoming culturally attuned.
  - Being straightforward with expectations and ideal communication strategies.
  - Developing a research agreement and a plan for using and sharing genetic data.
  - Ensuring the study receives appropriate review by the tribe for ethical and cultural considerations.
  - Providing the tribe with resources and personnel to support the research study.
  - Striking a balance between gaining scientific knowledge and providing tangible benefits to the community.
- These recommendations will likely aid in making the research process more transparent for academic researchers and more respectful of AI/AN culture and will ultimately help increase AI/AN representation in genetic research and personalized medicine discoveries.

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