Values and Practices to Strengthen Genetic Research Partnerships with Indigenous Communities

RUNNING HEAD: Strengthening Genetic Research Partnerships

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ABSTRACT:

Genetic datasets lack diversity and include very few data from Indigenous populations. Research models based on equitable partnership have the potential to increase Indigenous participation and have led to successful collaborations. We report here on a meeting of participants in four Indigenous community-university partnerships pursuing research on precision medicine. The goal of the meeting was to define values and practices that strengthen opportunities for genetic research. The group accorded the highest priority to developing trusting relationships, ensuring respect for Indigenous community authority, and pursuing research that has the potential to lead to community benefit. Supporting priorities included incorporation of Indigenous expertise in research planning, transparent communication, and development of community capacity, including capacity to participate in formulating research questions, informing research methodology, and leading research projects. Participants also noted the importance of attention to social determinants of health so that genetic contributors to health are evaluated in the appropriate context.

KEYWORDS: Community health partnerships, Power sharing, Genetics, Native Americans, Ethics, Research

Introduction

Genetic datasets have been characterized by lack of diversity, with most data deriving from populations of European ancestry (1-5). In particular, data from Indigenous populations are notably scarce, reflecting both practical barriers and past research misconduct. Inclusion of small isolated populations poses scientific, ethical, legal and logistical barriers, but most importantly, research abuses have led to a mistrust of research in many Indigenous communities (6-9).

Initiatives to develop models for equitable research partnerships have sought to overcome this mistrust. These efforts have been informed by scholarship that acknowledges Tribal sovereignty and emphasizes community-based participatory research and related principles and practices (10-20). An important example is the ethical framework developed by Indigenous researchers and the Summer internship for INdigenous peoples in Genomics (SING) Consortium, which proposes six principles to govern genetic research with Indigenous communities: understanding Tribal sovereignty and research regulation, engaging and collaborating with Tribal communities, building cultural competency, improving transparency of research practices, building Tribal research capacity, and disseminating findings in community accessible formats (21). Dialogues among community members and academic researchers can support these principles and help to guide appropriate researcher conduct (22-24).

We report here on a meeting of participants from four research consortia: the Northwest-Alaska Pharmacogenomics Research Network (NWA-PGRN), the Center for the Ethics of Indigenous Genomic Research (CEIGR), the Stanford Precision Health for Ethnic and Racial Equality (SPHERE), and the Native BioData Consortium (NBDC) (Table 1). These consortia pursue unique goals but also include collaborative efforts and overlapping participation.

Partnership development has played a key role in designing relevant research projects (e.g., 12, 20, 24, 25, 26); research goals of these consortia include pharmacogenomics and other topics within the scope of precision medicine (27, 28) – defined as health care based on knowledge of a person's genetics, lifestyle, and environment (29) – including the ethical implications of such research and the views of community members about research priorities and related policy issues, such as return of research results, creation of biorepositories and data governance (12, 28, 30-35).

One of the SPHERE projects, The Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology (BRAICELET), is a partnership with American Indian (AI) communities from South Dakota that includes a Community Advisory Group (CAG), a Biobank lab, information technology infrastructure to support the Biobank, and educational initiatives related to health-science literacy, policy, genetics, and precision medicine. This work has led to the NBDC, which is a nonprofit organization to build a data repository run by Indigenous researchers and Tribal community members.

The goal of the meeting was to share perspectives from the experience of members of the different research consortia, including both community members and researchers. Working together in interactive small group and plenary sessions, meeting participants sought to identify and prioritize specific values and practices that can strengthen opportunities for genetic and precision medicine research in Indigenous communities.

Methods

Participants. The 40 meeting attendees included 14 Indigenous community members, many of whom had dual roles, including four university-based researchers, five researchers based in community organizations and five who held leadership roles in their respective communities. The non-Indigenous participants included principal investigators, co-investigators, graduate students and professional research staff, all participating in federally-funded community-university research partnerships. Most participants (29 of 40) were from the NWA-PGRN consortium, including five advisers from Indigenous communities. The remaining participants included eight members of the other research consortia (Table 1) and three scholars with ties to these research efforts; of these, six were members of Indigenous communities.

Structure of meeting. The one-day meeting, held on August 19, 2019, in Seattle, WA, was organized by a NWA-PGRN planning committee, based on deliberative and interactive approaches used successfully in previous NWA-PGRN meetings. The meeting started with presentations from participating centers, as well as invited speakers on Indigenous perspectives about genetic research. The meeting time was then structured to include two small group discussion sessions, two plenary discussions sessions, and a priority-setting exercise. Participants were preassigned to small group discussions to ensure that diverse perspectives would be represented at each discussion; there were 6-8 people in each of six groups. Discussions in small group and plenary sessions were moderated by designated NWA-PGRN members, with the goal of ensuring that all participants had the opportunity to present their views. Participants were not expected to serve as formal representatives of their organization. Designated note takers, who were also meeting participants, captured comments from plenary and small group sessions.

Two rounds of small group discussions addressed questions related to evaluation and governance of genetic research. In each round, half of the groups addressed Question A, and half addressed Question B (Table 1). After Round 1, each group presented the most important point emerging from their session for plenary discussion, with other relevant points captured in discussion notes. After Round 2, each group was asked to identify up to five relevant points or items from their discussion. These were posted on flip charts with additional detail captured in discussion notes. Participants were asked to use stickers to identify their highest and second highest priority points. This exercise was followed by a plenary discussion of these points.

Meeting follow-up. A draft meeting report was prepared by WB and revised by the writing group, based on summations from each small group, notes from plenary and small group discussions, and the in-meeting priority-setting exercise. This report described nine themes developed in the small group and plenary discussions. A draft was circulated to all meeting participants for review and correction. Based on feedback from meeting attendees, minor revisions were made. Meeting attendees were then offered the opportunity to complete a post-meeting survey concerning the priority of each theme and add additional comments. Themes were presented in alphabetical order, and participants were asked to rank the priority of each theme on a 3-point Likert scale (1= Less Important, 2= Important, 3=Very Important), and identify the three highest priorities among the nine themes. The survey also provided an opportunity for each respondent to indicate membership in an Indigenous community, if applicable. The survey represented an extension of the discussion that occurred at the meeting, and results are reported here by all participants. As such, it did not qualify as research requiring review by an Institutional Review Board (IRB). Participants were reminded, however, that completion of the survey was voluntary, and responses were collected anonymously. Surveys were assigned a 3-digit numeric code for analysis. Quotes reported in the Results were selected from notes taken from the discussion groups (Table 2) and from written comments in the returned surveys.

Results

Small Group Round 1: Identification of considerations for genetic research in AIAN communities

The first set of small group discussions considered issues related to participating in or evaluating genetic research proposals. Participants emphasized the importance of community authority (including authority vested in Tribal sovereignty and requirements for Tribal review and oversight), Indigenous expertise (including local knowledge that can inform research questions and study designs), and the development of sustainable and trusting relationships between communities and researchers. These relationships are “not just partnerships” one participant noted; another said researchers need to “think like a family” (Group 1F). Participants also emphasized that research should involve a pathway to community benefit – that is, research projects should have the potential to provide either direct benefit to the community (e.g., findings that could improve local health care delivery), a foundation for subsequent beneficial research (e.g., studies of disease biology that could ultimately inform therapy), or both. Participants identified two additional points that could weigh positively in the evaluation of research opportunities: whether a project has the potential to contribute to community capacity development, and whether it includes consideration of social determinants of health relevant to the community. While community benefit is the fundamental justification for research, “trade-offs always exist” and must be considered in the evaluation (Group 1D). For example, deciding whether or not to participate in a research project might include weighing the community resources required, the potential for community capacity development, and the focus of the research question, with no single factor necessarily determinative.

Small Group Round 2: Initial priority-setting

The second set of small group discussions identified principles, values, and rules of conduct for research and appropriate Tribal oversight or governance mechanisms. These were presented in a plenary session and subsequently categorized as higher, intermediate, and lower priorities in the priority-setting exercise (Table 3). These points included some redundancy, including points previously identified in Round 1 and similar points presented with varied wording, often referencing respect, trust and transparency. The importance of community authority was noted in several ways, for example, with the emphasis on involvement of the community in decision making, on Tribal protections and oversight, and on recognition of local knowledge and priorities (Table 3). Needs and priorities were noted to differ in different settings: "Local variation is huge; no one size fits all" (Group 2F). Some points accorded lower priority by the group often overlapped with similar points given higher priority. For example, "Both Tribal leadership and community members involved in research decision-making" was accorded highest priority, "Presence of Tribal protections and oversight" was accorded intermediate priority, and "Information and biospecimens governed by the tribe" was accorded lower priority (Table 2). The importance of oversight as an ongoing process, from design through implementation, was also noted: "[It's] one thing to get approval but another thing to follow through" (Group 2B).

Round 3: Consolidation of themes and post-meeting survey results

Many of the points identified by the successive small group discussions were closely related, emphasizing, in particular, issues of trust, transparency, community authority, and community benefit, and plenary discussion confirmed that these points often reflected different facets of a particular issue. Based on meeting notes, the writing team consolidated these points into nine themes (Table 4). The post-meeting survey offered participants an opportunity to prioritize the themes. Survey responses were obtained from 20 of 40 participants (50%). Of these participants, 16 completed the question on Indigenous group membership, with 5 (31%) indicating membership in an Indigenous group, similar to 35% for the participant group as a whole.

Results are shown in Table 5. The highest priorities were accorded to the creation of trusting and sustainable relationships, recognition of Tribal authority, and the importance of assessing potential research opportunities in terms of pathways to community benefit. The number of survey respondents was too small for a statistical comparison of Indigenous and non-Indigenous responses. However, 5 of 11 (45%) of non-Indigenous respondents accorded a high priority to transparency while none of the Indigenous respondents did so. Otherwise, both groups accorded highest priority to the same three themes.

Fourteen participants provided additional comments in the post-meeting survey. Respondents emphasized that recognition of community authority “is a given” (205) and “I don’t think there is a way to do research with Indigenous people without it” (211). Indeed, “researchers who don’t want to play by the community’s rules (or who can’t be bothered to find out what the rules are) simply don’t belong there” (208). Trust was similarly noted as “essential” (103) with requirements that may not be fully recognized. As one participant put it:

> I think the whole dynamic of trust in these contexts is often problematic, and that university researchers are often unaware of the fact. For a start, I think we need to be talking about trustworthiness instead of trust. I also think that trust should really be a two-

> way street, and/but researchers tend to think of it as a one-way thing: does the community trust me? I'd love to see more exploration of the flip side: do the researchers trust the community? When they say a research question is not important, or a plan needs adjusting, or there's relevant community knowledge that should be brought to bear, how do researchers respond? (208)

The importance of direct community input into the research process – as opposed to community participation limited to review and approval of research proposals - was also noted. "The idea is to have Indigenous people leading the research or functioning as peers with non-Indigenous partners in the research activity" (200).

> Individuals with deep knowledge of a community and its culture can contribute to scientific rigor by helping to design survey items that are interpreted by community members in the way intended by investigators. Scientific rigor is also promoted by involving community experts in the analysis and interpretation of interview transcripts and other qualitative data. (106)

In addition, a participant noted that "research often leads in unexpected directions. Thus, the goal should be dialogue and joint decision making rather than an *a priori* plan that is slavishly followed" (105). Similarly, "relationships are between people so these should be revisited especially as people come and go in a partnership" (101).

Explicit attention to community benefit was emphasized in some survey responses. One participant described the potential for community benefit as "critically important and currently lacking" (206). Another noted that "research should not be proposed without either long-term or short-term benefit" (106), and a third noted that "a mutually agreed upon pathway…should be revisited throughout the course of the project" (101). The issue of community benefit is not without problems, however. One participant noted that "'future beneficial work'… is a concept and term that has the potential for abuse. It would be helpful to give a 'range' to the future…

something less than 20 years" (203). This participant also commented on the inclusion of social determinants of health in precision medicine research:

> Omics data untethered to context is poor science at best and harmful at worst. In terms of cost-benefit analysis, Tribes need to know where to invest their time and money. This data is essential not only to contextualize research outcomes but also in determining whether a Tribe feels it's worth it to go down the path of genomic inquiry. (203)

Discussion

The meeting reported here sought to clarify values and practices that support responsible and productive genetic research in Indigenous communities. Of the nine themes identified in the discussion, the highest priorities were accorded to trusting relationships, community authority, and the potential for research opportunities to lead to community benefit. Among those themes assigned intermediate or lesser priority, several could be seen as corollaries to the highest priorities. For example, incorporation of Indigenous expertise, community investment and transparency are all measures that support and strengthen relationships between communities and researchers. Similarly, supporting materials, such as guidelines and information resources, and community liaisons who facilitate communication between researchers and the community, can help to support constructive partnership development. Although the numbers are limited, the survey data indicate that non-Indigenous respondents accorded a higher priority to transparency than Indigenous respondents. This difference may reflect the definition of the theme as an obligation of health researchers, thus receiving greater emphasis from participants who identified as health researchers.

Social determinants of health also emerged as an important underlying theme. As noted above, precision medicine is defined as individualized health care based on the contribution of genetics, lifestyle and environment to an individual's health (29). Although social determinants of health are rarely considered in genetic research, the impact of social disadvantage on health and health care has important implications for precision medicine interventions (38). In a Tribal health setting, for example, AIAN community members, health care leaders and providers identified the lifestyle and environmental components of precision medicine as a means to meaningfully address population health issues of concern to AIAN communities (32). From this perspective, the theme of social determinants of health underscores the value to research partnerships of Indigenous expertise and researcher willingness to understand community experience. It also emphasizes the need for meaningful dialogue as potential research projects are considered, so that community members and researchers can exchange views about the extent to which social determinants are relevant to the research, and how they can best be accounted for in study design.

The emphasis on recognition of community authority reflects the inherent right of Tribal communities to impose research oversight, ensure dissemination of research information, and create mechanisms to incorporate Indigenous knowledge into research planning and implementation on Tribal lands. Such oversight plays a key role in protecting research participants from harms and in management of tribal data (39,40). The theme also reflects awareness of the barriers Tribes may experience in executing oversight. The reach of Tribal oversight may depend on whether Tribes have a research regulatory code, research review processes or their own IRB (10). In addition, decisions of ethics committees or Tribal Councils may not be recognized by funders or partnering institutions; universities may be reluctant to cede oversight to Tribal IRBs; and memoranda of understanding may favor university partners, for example by privileging researchers' opportunity to publish research findings. Furthermore, the

United States' recognition of Tribal sovereignty is limited only to federally-recognized Tribal nations and excludes state-recognized or unrecognized Tribal nations.

Some limitations to this report should be noted. The discussion focused on evaluating research opportunities. Policy issues that arise in the implementation of innovative health care were not addressed, including challenges related to community uptake, patents for novel interventions, and alignment of federal and Tribal policy. In addition, participants' personal views as reported here should not be construed as representing those of Tribal governments, organizations, communities or other defined groups. Priorities might have differed among other individuals engaged in community-university research partnerships.

The meeting provided a broad view of community capacity development. This concept is often implemented as training of community members to participate as members of the research team (e.g., 41). In the discussions at this meeting, however, community capacity encompassed the potential to formulate research questions, inform research methodology, and lead research projects, in keeping with more recent commentaries (42-44). In addition, researchers' willingness to become knowledgeable about the communities in which they propose to work emerged as an important factor. The priority accorded to community authority suggests that researchers' lack of knowledge about or unwillingness to comply with Tribal requirements, including the development of community capacity, trustworthy partnerships and Tribal oversight, may represent a significant barrier to involving more Indigenous communities in genetic research.

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Table 1: Sponsoring Organizations

Organization	Partners	Areas of Research
Northwest-Alaska Pharmacogenomics Research Network (NWA-PGRN)	• Southcentral Foundation, Anchorage AK • Yukon-Kuskokwim Health Corporation, Bethel AK • Confederated Salish and Kootenai Tribes, Flathead Reservation MT • University of Washington, Seattle WA • University of Montana, Missoula MT • Oregon Health and Science University, Portland OR • University of Alaska, Anchorage AK	• Pharmacogenomics • Genetic and dietary contributors to Vitamin D and Vitamin K sufficiency and outcomes of anticoagulant, smoking cessation and mental health therapies • Community views about pharmacogenomics and clinical genetic testing
Center for the Ethics of Indigenous Genomic Research (CEIGR)	• Chickasaw Nation, Ada OK • Missouri Breaks Industries Research Inc., Eagle Butte SD • Southcentral Foundation, Anchorage AK • University of Oklahoma, Norman OK	• Tribal perspectives on precision medicine, return of genetic testing results, and biorepository policies • Normative and conceptual work on tribal data sovereignty and research partnerships
Stanford Precision Health for Ethnic and Racial Equality (SPHERE)	• Tribes of the U.S. Northern Plains • Stanford University, Palo Alto CA	• Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology • Understanding perspectives on precision health among underserved communities • Ethical guidelines for precision health research
Native BioData Consortium	• Stanford Precision Health for Ethnic and Racial Equality (SPHERE), Stanford University, Palo Alto CA • Center for the Ethics of Indigenous Genomic Research (CEIGR) University of Oklahoma, Norman OK • Summer Internship for Indigenous Peoples in Genomics (SING) University of Illinois	• Creation of a biological and data repository for Indigenous samples • Collaboration in the development of Tribal Public Health Departments • Collaboration in tribal research policy development, research on ethical implications of Omics technologies, and

		development of tailored machine learning and artificial intelligence (AI) for under-represented populations

Table 2: Questions for Small Group Discussions

Round 1

Question A (Groups 1A, 1C, 1E)

What are the unique considerations that researchers, AIAN community partners, and funders should think about when considering *whether to pursue genetic research* with US Indigenous communities?

Question B (Groups (1B, 1D, 1F)

What are the unique considerations that researchers, AIAN community partners, and funders should think about when *evaluating opportunities for genetic research* with US Indigenous communities?

Round 2

Question A (Groups 2A, 2C, 2E)

What *principles, values, and rules of conduct* should determine how researchers handle research information and biological samples?

Question B (Groups 2B, 2D, 2F)

What *oversight or governance mechanisms* are desirable in academic-community partnerships when planning and conducting genetic research with US Indigenous communities?

Table 3: Priorities emerging from initial priority-setting exercise

Highest priority

- Relationships between researchers and community members, incorporating trust, respect, and shared agency
- Respect throughout the partnership, with clear boundaries for responsibility
- Transparency and open communication
- Both Tribal leadership and community members involved in research decision-making

Intermediate priority

- Recognition of community autonomy and local knowledge
- Presence of Tribal protections and oversight
- Recognition of local variation - no one size fits all
- Community investment; research informed by community priorities
- Researcher should enter the community with empathy

Lower priority

- Capacity building: training opportunities; community groups to guide research process.
- Pre-negotiation of plans for data management
- Information and biospecimens governed by tribe
- Sharing of resources on terms of agreement/contracts and similar documents.
- Community liaisons to help explain/serve as liaison between researchers and community.
- Research decisions oriented toward community benefit, not research team's careers

Table 4: Definition of Themes for Responsible Genetic Research in Indigenous Communities

1. Community Investment

Investment in the community– rather than short-term funding to support university engagement in the study – should be provided, including training pipelines to increase the number of Indigenous investigators; resources to increase Indigenous community capacity to participate in implementation and management of genetic research; and training programs to increase community members' genetic knowledge, such as GENA (36). Mechanisms include material and financial compensation of individuals and Indigenous communities participating in research. The concept of moving "from leaky pipelines to irrigation systems" (37) was also noted; that is, the idea that exposure to community-based participatory research may promote further scientific training for some students, but for others who do not continue to graduate training, it may provide an important foundation for serving as community leaders in development of research partnerships.

2. Community Liaisons

Research collaborations should include community liaisons, that is, individuals who can serve as a link between health researchers and the Indigenous community. These individuals should have deep knowledge of both the community and the researcher's world – for example, a member of the Indigenous community who is a researcher, a health or social service provider, or a member of the local business community who has dealings with research institutions or other agencies.

3. Indigenous Expertise

Indigenous expertise should be integral to research planning, implementation, and dissemination. Expertise is provided through Indigenous investigators, joint planning by community members and researchers to shape study questions and research methods, and Indigenous community review of draft papers and other dissemination materials.

4. Pathway to Community Benefit

Planned research should be assessed with the pathway to Indigenous community health benefit in mind. Potential harms should be weighed against potential benefits. Some types of research, such as basic genetic science, may be unlikely to provide short-term benefit, but could provide a foundation for future beneficial work. Other short-term benefits (such as Indigenous investigator capacity-building or bringing resources into the community) may be part of the assessment of potential community benefit.

5. Recognition of Community Authority

Recognition of community authority should be built into the research process. Tribal rules and regulations must be respected. The Indigenous community should be involved from the outset in developing the rules and procedures that determine decision-making power within the collaboration.

6. Social Determinants of Health

Health research, including genetic research, should incorporate information about social determinants of health, such as where you live and the geographic impacts; poverty; and a history of western settlement, epidemic disease, cultural harms, and exposure to racism and discrimination.

7. Supporting Materials

Tools should be developed to support effective research collaborations between Indigenous communities and university-based researchers, including a central resource to provide examples of terms of agreement, memoranda of understanding (MOUs) and other documents supporting partnership, and guidelines and information sources for researchers interested in working with Indigenous communities, to assist them in complying with tribal requirements and understanding local history.

8. Sustainable and Trusting Relationships

Research should be built on sustainable and trusting relationships among community leaders, participants, and health researchers. Trust is built over time, through aligned goals, a track record of successful partnership, and ongoing, open communication.

9. Transparency

Health researchers should provide clarity about the intended research: what will happen, how it will be supported, how they expect the community will be involved. Open communication should occur throughout the research process, with ongoing dissemination of information back to the Indigenous community.

Table 5: Priorities emerging from post-meeting survey

Theme	Included in top three*	Mean score
Sustainable and trusting relationships	0.70	2.95
Recognition of community authority	0.55	2.95
Pathway to community benefit	0.55	2.70
Transparency	0.40	2.90
Indigenous expertise	0.35	2.80
Community investment	0.30	2.50
Community liaisons	0.10	2.35
Social determinants of health	0.05	2.15
Supporting materials	0.00	2.00

*Proportion of surveys in which theme was included as one of the three highest priorities