Considerations for Meaningful Collaboration with Tribal Populations

The Tribal Collaboration Working Group Report
to the *All of Us* Research Program Advisory Panel

April 4, 2018

All of Us
RESEARCH PROGRAM
The Precision Medicine Initiative

Roster

Lynn Malerba, D.N.P., M.P.A. (co-chair)
Mohegan Tribe
National Institutes of Health (NIH) Tribal Advisory Committee

Spero Manson, Ph.D. (co-chair)
University of Colorado Anschutz Medical Campus

Murray Brilliant, Ph.D.
Marshfield Clinic Research Institute

Denise Dillard, Ph.D.
Southcentral Foundation
NIH Tribal Advisory Committee

Abigail Echo-Hawk, M.A.
Seattle Indian Health Board
Urban Indian Health Institute

Kevin English, Dr.P.H.
Albuquerque Area Southwest Tribal Epidemiology Center

Karen Maschke, Ph.D.
The Hastings Center

John Molina, M.D., J.D., L.H.D.
Native Health

Kelly Moore, M.D., FAAP
University of Colorado Anschutz Medical Campus

Marcia O'Leary, RN
Missouri Breaks Industries Research, Inc.

Liana Onnen
Prairie Band Potawatomi Nation
NIH Tribal Advisory Committee

Dara Richardson-Heron, M.D.
All of Us Research Program

Bobby Saunkeah, RN, MSHCE, CIP
Chickasaw Nation Department of Health
NIH Tribal Advisory Committee

Rachael Tracy, M.P.H.
Indian Health Service

Malia Villegas, Ed.M.

David Wilson, Ph.D.
NIH Tribal Health Research Office

Table of Contents

Executive Summary

The Tribal Collaboration Working Group (TCWG) of the *All of Us* Research Program Advisory Panel was charged with providing guidance to the *All of Us* senior leadership on how to develop meaningful, culturally sensitive collaborations with American Indian and Alaska Native (AI/AN) populations. The information and options presented by the TCWG, along with additional input that will be collected from listening sessions with tribal organizations and consultation with tribal leaders, will be reviewed by the *All of Us* consortium and may lead to changes to the program's protocol or policies.

To develop this report, the two co-chairs and 14 members of the TCWG met by phone and in-person between October 2017 and February 2018. The TCWG included tribal leaders, providers, researchers, and other community members, as well as *All of Us* staff and consortium representatives. The group was diverse in terms of geographic representation, size of tribes, area of expertise, etc. The group considered the potential benefits of the *All of Us* Research Program, barriers to AI/AN participation in the program, and best practices, strategies, or potential protocol changes needed to overcome these barriers.

This report outlines several overarching principals for engagement with tribal communities—including respect for tribal sovereignty, acknowledgement of historical transgressions, importance of engagement with Urban Indian leaders, and need for continued bi-directional engagement. Additionally, the report focuses on four specific topic areas:

- Governance
- Tribal sovereignty and consent
- Ethics, including institutional review boards, biospecimen storage and access, and protection and benefits
- Engagement and partnerships

The options outlined in this report are not consensus opinions of the TCWG, but rather options raised by one or more of the TCWG members. In some instances, the TCWG offered multiple, even contradictory, options for a specific topic, representing the disparate needs and opinions of different tribal nations and individuals. This is to be expected, as the AI/AN population is highly heterogeneous, and different tribes or individuals may have different views on biomedical research and the *All of Us* Research Program.

The TCWG recognizes that the *All of Us* Research Program could offer potential benefits to the health of tribal nations and individuals and has appreciated this opportunity to engage with the *All of Us* team on how to develop meaningful collaborations. The TCWG recognizes this is just the beginning and supports continued thoughtful, respectful, bi-directional engagement between *All of Us* and tribal communities.

Purpose and Activities of the Tribal Collaboration Working Group

Purpose

The Tribal Collaboration Working Group (TCWG) is a working group of the *All of Us* Research Program Advisory Panel. On October 27, 2017, *All of Us* Research Program Director Eric Dishman charged this working group with providing guidance to *All of Us* senior leadership on how to develop meaningful, culturally sensitive collaborations with American Indian and Alaska Native (AI/AN) populations. The TCWG was asked to describe:

- Strategies for collaborating with tribal nations, clinics, and organizations to enable AI/AN participation in the program.
- Unique considerations, such as tribal sovereignty, cultural beliefs and traditions, and historical trauma, that the program should be aware of as they seek to engage tribal populations.
- Potential modifications that could be made to current *All of Us* Research Program protocol to facilitate AI/AN participation in the program.
- Ethical, legal, and social issues that should be considered prior to enrollment of AI/AN individuals.
- Major research questions that might be of interest or return value to tribal nations and AI/AN individuals.

The information provided by the TCWG will inform subsequent work by the *All of Us* Research Program consortium's committees and task forces as the program considers potential changes to the protocol or policies.

About the* All of Us *Research Program

Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in environment, lifestyle, and biological makeup. Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through careful measurement of molecular, environmental, and behavioral factors that contribute to health and disease. Such understanding may lead to more accurate and earlier diagnoses, more rational wellness and disease-prevention strategies, better treatment selection, and the development of novel therapies. Coincident with advancing the science of health and medicine is a changing culture of practice and research that engages individuals not just as patients or research subjects but as active partners. *All of Us* believes the combination of a highly engaged population and rich biological, health, behavioral, and environmental data has the potential to usher in a new and more effective era of health and health care in the United States.

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all. The overall objective of the program is to build a robust research resource to facilitate the exploration of biological, clinical, social, and environmental contributors to health and disease. The program will collect and curate health-related data and biospecimens from individuals who reflect the diversity of the United States; these data and biospecimens will then be made broadly available to the research community.

The program seeks to achieve this mission through building relationships with one million or more participant partners, delivering the largest, richest biomedical dataset ever, and catalyzing a robust ecosystem of researchers and funders eager to use and support the dataset. By combining health-related information from a large pool of diverse participants, the *All of Us* Research Program will reach the scale and scope necessary to enable research on a wide range of diseases and health topics.

Activities

Prior to the formation of the TCWG and in preparation for engaging Native peoples in the *All of Us* Research Program, staff conducted an informal literature review to understand the issues related to research involving AI/AN individuals. Program staff spoke with tribal leaders and researchers to gather input and feedback and to build relationships, attended and spoke at the National Institutes of Health (NIH) Tribal Advisory Committee (TAC) meetings, and presented at events organized by tribal organizations. The *All of Us* team also conferred with U.S. Department of Health and Human Services (HHS) and NIH colleagues who are experienced in engaging with tribal nations. The University of Arizona, an *All of Us* Research Program consortium health care provider organization, organized a conference to engage with tribal nations in their region, which was attended by program leadership.

Many of the individuals and organizations the team engaged with recommended that the program form an advisory group to give formal and thorough input on the inclusion of AI/AN individuals in *All of Us*, which led the program to form the TCWG. With input from a team of NIH and external advisors, the program identified tribal leaders, providers, researchers, and other community members to invite to serve on the working group. The program was careful to seek a diverse group in terms of geographic representation, size of tribes, area of expertise, etc. Since the *All of Us* leadership is committed to taking the time to thoughtfully engage tribal nations, the program has promised it will not actively recruit tribal participants until the TCWG has delivered its report and the program has a chance to review the input.

The two co-chairs and 14 members of the TCWG met eight times by phone and once in person between October 2017 and March 2018. To assist with their work, the TCWG members received copies of the *All of Us* Research Program protocol, consent form, and September 2015 Precision Medicine Initiative Working Group Report to the Advisory Committee to the Director. *All of Us* staff also gave presentations about all aspects of the program including the program governance, consent form, and policies on the return of results, data and biospecimen storage, and data access.

The TCWG considered nine potential topic areas to discuss and address in this report. Using the Delphi method, the TCWG members identified four priority areas to consider when recruiting and retaining AI/AN individuals:

- Governance
- Tribal sovereignty and consent
- Ethics, including institutional review boards (IRBs), biospecimen storage and access, and protection and benefits
- Engagement and partnerships

The TCWG will sunset after finalizing this report. However, the group will be reconvened in the future as needed to continue to provide advice on the engagement and retention of Native peoples.

Tribal Consultation

The *All of Us* Research Program recognizes that tribes are sovereign nations and has committed to consultation with tribal leaders to ensure they have an opportunity to provide meaningful and timely input. This report is not intended to replace consultation; however, the input from a group of tribal leaders and researchers who have dedicated many hours to considering and discussing how *All of Us* can successfully engage tribal populations will serve as an important resource for the program as it seeks to overcome the barriers of historical transgressions and mistrust and successfully include AI/AN individuals in the program. This report will be shared with tribal leaders as a starting point for further feedback and input when *All of Us* is ready to request consultation.

Rationale for the Tribal Collaboration Working Group and Report

AI/AN individuals make up approximately 1.7% of the U.S. population, with more than 5 million people reporting at least some AI/AN ancestry, according to the 2010 U.S. census.[1] This is a highly heterogeneous group, with 573 federally recognized tribes and more than 100 state-recognized tribes in the United States today.[2] There are approximately 326 tribal reservations on 56.2 million acres of land. Some tribes, including most in Alaska, may have tribal communities but do not have reservations.[3] More than three-quarters of Native peoples live outside of tribal lands, including 71% who live in cities.[4]

Tribal Sovereignty

Tribal sovereignty refers to tribes' right to ongoing self-government on their own lands and within their jurisdictions and communities. The U.S. Constitution recognizes that tribal nations are sovereign governments—that is, they possess nationhood status and retain inherent powers of self-government—and the U.S. Supreme Court has repeatedly upheld tribal sovereignty in court decisions.[5] Tribal sovereignty has further been affirmed over the past 150 years by hundreds of treaties, the U.S. President, and Congress.[6] The relationship between federally recognized tribes and the U.S. government is that of one between sovereign nations, i.e., a "government-to-government" relationship. Tribal sovereignty ensures that any decisions regarding tribal members and tribal property are made with their participation and consent.[7]

According to the National Congress of American Indians (NCAI), "Tribal nations ceded millions of acres of land that made the United States what it is today and, in return, received the guarantee of ongoing self-government on their own lands. The treaties and laws create what is known as the federal 'trust responsibility,' to protect both tribal lands and tribal self-government, and to provide for federal assistance to ensure the success of tribal communities.

"Today, tribal governments maintain the power to determine their own governance structures, pass laws, and enforce laws through police departments and tribal courts.

"Tribal governments provide multiple programs and services, including, but not limited to, social programs, first-responder services, education, workforce development, and energy and land management. They also build and maintain a variety of infrastructure, including roads, bridges, and public buildings.

“The governmental status of tribal nations is at the heart of nearly every issue that touches Indian Country. Self-government is essential if tribal communities are to continue to protect their unique cultures and identities.”

This sovereign status, which is a political designation, gives tribes legal rights and privileges that are distinct from racial and ethnic groups. Research partnerships with AI/AN populations require unique considerations, including greater input and oversight by tribal communities on data and biospecimen policies, beyond those for other groups.

American Indian/Alaska Native Health Care System

The U.S. government has a trust obligation to provide health care for enrolled members of federally recognized tribes. The Indian Health Service (IHS), part of HHS, is the federal agency charged with fulfilling this responsibility.[8] As of 2016, the IHS provided services to 2.2 million AI/AN individuals via the I/T/U system of care. This system represents IHS–operated facilities (I), Tribally operated facilities (T), and Urban Indian Health organizations (U).[9] These services included ambulatory primary health services; dental, mental health, and vision care; inpatient care; and substance abuse treatment programs.

Raven Ross et al.[10] describe the Indian health care system in a 2015 paper: “The IHS is divided into 12 areas and provides a variety of health care services through a comprehensive network in 35 states that includes hospitals, health centers, Alaska Village clinics, and health stations. These facilities receive 45,907 inpatient admissions and 13,280,745 outpatient visits annually. However, the Agency provides these services in a significantly under-funded environment. For example, in Fiscal-Year (FY) 2014, the IHS has a budget appropriation of 4.4 billion, which resulted in an IHS expenditure on user population of $2,849 compared with the total U.S. population expenditure of $7,713….

“Over the past few decades, tribes have moved towards taking control of their health care delivery system. This is often referred to as the *638 process*, after Public Law 93–638, which regulates self-determination contracts and self-governance compacts. Through this process, a tribe operates health care service sites that are supported by funds allocated from the federal government which are distributed through the IHS and are subject to IHS funding. Both the IHS and tribal system strive to be culturally appropriate and community driven. Currently, over 50% of the mental health programs and over 80% of the alcohol and substance abuse programs that service AI/ANs are tribally operated.

“Urban Indian Health Programs (UIHPs) provide services to AI/AN individuals residing off reservations [or outside of tribal jurisdictional territories] through 34 urban-centered nonprofit organizations at 57 locations. The services provided vary by UIHP and range from ambulatory health care to outreach and referral services, and may include some behavioral health services. Funding for these organizations come from the IHS (Title V of IHCIA) and other federal, state, local, and private sources. Approximately 45% of the UIHPs receive Medicaid reimbursement as Federally Qualified Health Centers (FQHC).”

In FY 2017, the IHS received $5.98 billion in funding, of which $48 million was dedicated to UIHPs.[11]

Historical Transgressions: A Barrier to Participation

Many tribal nations and individuals are hesitant to participate in biomedical research due to historical transgressions by both the federal government and researchers. The history of the government's mistreatment of tribal nations includes forcible removal of tribes from their lands and attempts to eliminate their way of life, their social structure, and their culture. This history, both distant and more recent, has left tribal nations mistrustful of the federal government and federally sponsored research.

Additionally, some research has stigmatized or harmed AI/AN tribes. For example, in 1979, a study of the Inupiat community in Utqiaġvik, Alaska[12] resulted in widespread negative publicity about the use of alcohol in the community.

Some researchers have also engaged in practices that violate tribal beliefs. For example, in 1989, the Havasupai tribe in Arizona approved collection of blood specimens from tribal members for a study on diabetes. After the researchers completed the study, they allowed other researchers access to the remaining specimens without the tribe's knowledge. The tribe sued, arguing that the tribe and its members did not give permission for further use of the specimens, that the research conducted was on subjects the tribe considered taboo, and that the remaining specimens should be returned to the tribe.[13]

Tribes have also reported that researchers who have conducted studies on tribal lands failed to report to the tribe on their results. This has left tribal members feeling that they were used for the researcher's own professional advancement and that they received no benefits in return.[14] Tribes are also aware that there is a great deal of research occurring, including through the military and prison systems, that has not gone through any tribal approvals.

Tribal members are reluctant to participate in research after those types of experiences and the reluctance extends beyond tribal lands. One study found that urban AI/AN individuals were less likely to participate in a research study conducted by the federal government or a state university compared to a study conducted by a health care provider.[15]

Additionally, tribes have concerns about participating in programs that may collect genetic data, since the federal government has in the past used genetics, blood quantum, and intermarriage as tools to eliminate tribal nations. Using genetic information for ancestry studies is an especially sensitive topic for tribal communities, because tribal membership and the exercise of tribal sovereignty is a decision to be made by tribal governments and not to be determined by biomarkers.

Finally, AI/AN communities are among the most economically disadvantaged in the United States.[16] Almost 30% of AI/AN individuals were living in poverty according to 2014 census data,[17] and 7.5% of AI/AN homes still lacked safe drinking water in 2013, though these numbers have been decreasing in recent years.[18] Due to these resource limitations, tribal governments prioritize basic services, and some have not had the interest or the opportunity to build tribal research capacity. As a result, some tribes require capacity-building assistance before they are able to engage with researchers or implement the new knowledge gained from biomedical research that can benefit the tribe.

Key Considerations for the Inclusion of American Indian and Alaska Native Populations

Overview

AI/AN populations demonstrate many cultural strengths and are highly resilient, but they also experience a multitude of health disparities relative to other population groups. For example, compared to white Americans, AI/AN individuals have a shorter life expectancy and die at a higher rate from chronic liver disease and cirrhosis, diabetes, unintentional injuries, and suicide.[19] The AI/AN infant mortality rate is 60% higher than for non-Hispanic whites.[20] In addition, the AI/AN population experiences socioeconomic and other inequities compared to the overall U.S. population.[21] These health disparities have been linked to historical trauma,[22] inequities in health care access,[23] and higher exposures to environmental contaminants.[24]

These health disparities represent a loss of individual and societal potential that could be reduced through inclusion in research. Unfortunately, AI/AN individuals have been severely underrepresented in clinical trials and often are not included in sufficient numbers in national research studies.[25] A research program on the scale of *All of Us*, with its focus on environmental and lifestyle factors in addition to biological makeup, could be of potential benefit to tribal nations and individuals.

AI/AN culture greatly values activities or programs that will benefit their communities and future generations. AI/AN communities have always been researchers, so tribal communities recognize the potential benefit of precision medicine in the long term and want to be involved to lay the groundwork to improve the health of their children and grandchildren. Tribal communities recognize that we currently have gaps in our understanding of specific risk factors, medication responses, and optimal treatment strategies for AI/AN individuals in part because AI/AN individuals have often been left out of biomedical research. New and important aspects of risk and resilience may be discovered—for both tribal communities and the general population—if AI/AN individuals are willing to participate in this type of research program.

However, AI/AN people also fear that their participation in research programs, including *All of Us*, will result in benefits for others, but not for AI/AN communities. Some may be hesitant to participate because they worry that the improved prevention and treatment methods that come out of the program, especially ones that may be based on an individual's genetic makeup, will be prohibitively expensive or not available for a health care system that is already under-resourced. Currently, even many AI/AN individuals who live near leading research centers may not receive access to the newest advances in health care. *All of Us* will need to partner with tribal communities to work toward equity goals and ensure that the program is beneficial and does not actually increase health disparities.

The TCWG recognizes the game-changing potential of the *All of Us* Research Program as well as the barriers that may prevent tribal nations and individuals from participating. The goal of this report is to provide input to help *All of Us* overcome some of these challenges to successfully partner with AI/AN populations. It's important to note that the options outlined in this report are not consensus opinions of the TCWG, but rather options raised by one or more of the TCWG members. In some cases, the TCWG offers multiple, even contradictory, options on a specific topic, representing the disparate needs and opinions of different tribal nations and individuals.

In addition to the specific options outlined below, there were a few themes that arose consistently throughout the TCWG discussions:

1. Start from a position of attention to and respect for tribal sovereignty. Researchers who wish to use tribal data must also respect tribal sovereignty.
2. Acknowledge that tribes, and not genetics, determine an individual's tribal membership.
3. Acknowledge the history that American Indians and Alaska Native individuals and communities have experienced with the government and keep in mind how that shapes AI/AN perceptions about participating in government research. Special approaches will be necessary to overcome the mistrust and fear. Also, if the program makes any mistakes or missteps, they should be acknowledged as well.
4. Since many of the participants will be Urban Indian individuals, in addition to reaching out to tribal leaders, engage with the organizations that represent Urban Indian individuals.
5. Remain responsive to the AI/AN community as the program evolves.

The TCWG has appreciated the opportunity to have these discussions, but this should just be the beginning to *All of Us's* engagement with tribal nations. We encourage the *All of Us* team to continue conversations with tribal communities and to solicit input from tribal leaders through consultation. We realize this process will take time. *All of Us* should not rush its engagement with tribal nations and also should not delay national launch for other communities while these tribal engagement efforts continue.

Tribal nations have long advocated for thoughtful, respectful, bi-directional engagement when researchers seek to establish research collaborations involving AI/AN participants. The bi-directional engagement that *All of Us* is undertaking shows promise so far. We hope it continues successfully, as we believe it could serve as an important engagement model for other research programs.

Governance: Involvement at Every Level

The *All of Us* Research Program is an incredibly complex research effort. Not only does it aim to gather a multitude of data types over many years, but it will also make this data available to interested researchers, including industry researchers and citizen scientists. While *All of Us* has put protections in place—including de-identifying participant data and developing data access policies and a researcher code of conduct—tribes remain concerned about the potential for inappropriate use and mistreatment of their data and loss of their collective privacy. Therefore, it is important to make sure AI/AN individuals are involved in the program's governance and tribal input is solicited as the program develops its policies and processes, especially around data access and the types of research that may be conducted with AI/AN data.

In order to ensure that a multitude of tribal voices can be heard, it is important to solicit tribal input through both the inclusion of tribal representatives directly in the *All of Us* governance structure and additional engagement with tribal nations and organizations. AI/AN engagement in governance should include tribal participants in the program, tribal leaders, and other tribal members.

AI/AN individuals can be included in the following *All of Us* governance areas:

- At least one representative from the AI/AN community should be appointed to the *All of Us* Research Program Advisory Panel. The Advisory Panel is composed of outside experts who provide oversight and advice on the vision, scientific goals, and operations of the *All of Us* Research Program. Among other duties, the Advisory Panel conducts an ongoing assessment of the projects and programs supported by *All of Us*.
- A representative of tribal nations should be appointed to the *All of Us* Research Program IRB to ensure that tribal interests and beliefs are represented on the board that is charged with protecting uniformly the rights and welfare of research participants. The *All of Us* IRB reviews the protocol, informed consent, and other participant-facing materials for the program. Given the heterogeneity of tribal nations, the program should also consider appointing additional tribal representatives as ad hoc advisors who can be called upon to provide additional perspective and input on aspects of the program that especially impact AI/AN populations.
- One or more AI/AN representative(s) should be invited to serve on the *All of Us* Research Program Research Access Board. The Research Access Board is the group that oversees operationalizing the program's data access policies and procedures. Given the concerns of tribal nations about inappropriate use and mistreatment of their data, tribal membership on the Research Access Board is essential.
    - *All of Us* should also create a subcommittee consisting mostly of native individuals to review applications for data or research projects focusing on AI/AN peoples. This subcommittee needs to have decision-making power.
- *All of Us* is working to include participants in their governance committees, boards, and task forces. The program should ensure that AI/AN individuals who are enrolled in the program are included in these governance opportunities.
- Additionally, the program should consider including individuals who have expertise in small population measurement in the governance structure. These individuals do not necessarily need to be AI/AN.

All of Us can also gather additional input from the tribes and tribal members through the following channels:

- The program should periodically reconvene the TCWG to evaluate the program as it evolves and ensure that the program continues to be responsive to Native peoples.
- *All of Us* should provide updates to the NIH TAC during the TAC's twice-yearly in-person meetings. Ideally, updates from *All of Us* can become a standing item on the TAC agenda. Since the TAC was established to help ensure that tribes and AI/AN people have meaningful and timely input in the development of NIH policies, programs, and priorities, *All of Us* should seek the TAC's assistance to help share information about the program with tribal nations and address any issues that may arise as the program enrolls AI/AN members. This will also support ongoing engagement between TAC and NIH leadership on important tribal considerations, particularly tribal sovereignty.
- *All of Us* should also provide updates to major AI/AN organizations such as the IHS, the Tribal Epidemiology Centers, the NCAI, the National Indian Health Board, the National Council on Urban Indian Health, the Urban Indian Health Institute, and regional tribal organizations (such as

the United South & Eastern Tribes, Inc.). The program could provide updates at the organizations' regular meetings.

AI/AN input into the program should be continually re-evaluated to ensure a high level of meaningful input from tribal nations. The program should plan touchpoints over time to reassess tribal involvement in governance.

Tribal Sovereignty and Consent

Tribal Sovereignty

It is important for NIH leadership to have a clear understanding of tribal sovereignty as the program works to partner with tribal nations. NIH and *All of Us* leadership may consider arranging a training session by a Native lawyer who specializes in this area.

The balance of tribal sovereignty with individual sovereignty and decision-making ability is an incredibly complex issue. Some tribal leaders and TCWG members believe that individuals' rights take precedence over tribal rights when it comes to research participation. Others believe that an individual's participation could impact the tribe and therefore tribal consent is required. Some believe an individual can enroll in tribal research, but they must obtain the tribe's permission if they wish to provide their tribal affiliation. If the tribe denies their permission or the individual does not seek tribal approval, then the individual can only identify as AI/AN—and not as a member of a specific tribe—when they participate in the research study.

A further bioethics consideration is that many Urban Indian individuals, though they reside outside of federally defined tribal lands, still receive health care through tribal funding. Their participation in research studies may have an impact on their health care system. For this reason, tribes may believe that these individuals still fall under tribal purview.

All of Us may wish to follow the practices of most NIH research studies when evaluating the need for tribal consent:

- Tribal consent is required if the program wishes to recruit and enroll participants on tribal lands.
    - Tribes vary in their expressions of sovereignty and self-determination over research and in the resources or processes they have in place to review and approve research requests. Because of this variation, the program will need to discover and follow the policies and procedures for each specific tribe with whom they wish to partner.
    - Tribal jurisdiction is also a complex matter. Some tribes may have jurisdiction over lands near their reservations. *All of Us* should be sensitive to these complexities.
- Tribal consent may not be required if the program is enrolling individuals who permanently reside outside of federally defined tribal lands.
    - However, in order to build trust with tribal nations, *All of Us* may consider sending courtesy letters to all tribal leaders in the region, including leaders of Urban Indian organizations, to inform them of the program.

    - *All of Us* may consider going even a step further by getting tribal buy-in, in the form of a letter or resolution of support from the relevant tribal council, before engaging with Native individuals, even if those individuals are not living on tribal lands.
    - Tribal consent is necessary to obtain access to electronic health records (EHRs) stored at I/T/U facilities. This could be a significant consideration for the program because many AI/AN individuals may have received care at an IHS or tribal facility at some point, even if they are receiving care at nontribal clinics now.

Given the complexities around tribal sovereignty and jurisdiction, especially of individuals who live away from tribal reservations, *All of Us* may wish to seek additional input on this topic through consultation.

In order to ensure that Urban Indian individuals make informed decisions about participation in the program, *All of Us* should:

- Produce educational videos featuring tribal leaders, providers, researchers, and community members or potential participants discussing their opinions about the program. The videos should also include higher-level administrators to discuss accountability. The videos should note that the AI/AN individuals who are featured are not endorsing the program. Since different tribes may have different concerns, videos that can be targeted to specific tribes would be valuable.
    - Since these videos will take a while to produce, start this project as soon as possible.
    - Ask the TCWG to help shape the questions and provide guidance on who to include in the videos.
    - Include tribal leaders from a diverse set of tribes—e.g., urban and rural, large land-based tribes, small land-based tribes, landless tribes.
    - Ask the TCWG and/or the TAC to advise on the dissemination of these videos, including when they should be rolled out and where they should be shown. Partnering with TAC will decrease the perception that these videos are intended as recruitment materials or endorsements of the program. The TCWG or TAC may want to consider sharing these videos through IHS Good Health TV programming in clinic waiting rooms.
- Alternatively, the program could leverage available video resources, such as the videos in the Association of American Medical Colleges Native Health Equity Toolkit.
- The program could also encourage AI/AN individuals to check with their tribes before determining whether to participate in the program.

Tribal Affiliation

Whether *All of Us* should collect tribal affiliation information is another important and controversial topic. On the one hand, data from individual participants who identify as tribal members could potentially be used to make generalizations about an entire tribe, possibly without the tribe's consent. Also, if the individual comes from a small tribe, the participant may be at higher risk of re-identification.

On the other hand, some tribes may be interested in and benefit from aggregate results and learnings from research involving their members. Previous research studies have shown there are significant differences among Native individuals when it comes to pharmacogenomics, so tribal affiliation data could lead to valuable research results. Tribal members also appreciate the opportunity to recognize and acknowledge their tribal affiliation and address the perception that the AI/AN community is one homogenous group. However, because the tribal affiliation data the program collects may be self-reported and tribes have varying enrollment criteria, some believe the information may be of limited utility for studies seeking to identify biomarkers or tribe-level risk factors.

The *All of Us* Research Program can consider several different approaches:

- Do not ask participants for their tribal affiliation.
- Allow participants to provide their tribal affiliation if they so choose. However, do not make the information available to researchers except in instances where the tribe has agreed to partner with *All of Us* and wishes to allow researchers access to this information.
- Allow participants to provide their tribal affiliation if they so choose. However, do not make this information available to researchers unless the sample size for that particular tribe is large enough to protect individual confidentiality.
- Allow participants to provide their tribal affiliation if they so choose. However, consider the tribe's policies regarding research before determining whether to make the information available to researchers.
- Allow participants to provide their tribal affiliation if they so choose. Allow researchers to have access to this information so they can run analyses based on tribal affiliation and share any learnings with the tribes. However, all publications should only note the number of individuals and tribes in the sample. The specific tribes should not be identified.
- If the tribal affiliation is self-reported data, append the data to note this.
- Only collect tribal affiliation when partnering with a tribe, since the tribes can verify tribal enrollment.
- If a researcher wants to name a tribe in their study in a paper, presentation, etc., require that they get permission in the form of a resolution or letter of support before they can name the tribe. This is not necessary if they intend to study the AI/AN community as a whole. However, even when conducting generalized research, it could be beneficial for the researcher to consult a tribal organization, such as the NCAI, for comment or review.
    - Also require researchers allow the tribal IRB—or their council if they do not have an IRB—to review and approve any papers or presentations to make sure the research is not stigmatizing.
    - It should be clearly stated in a paper or presentation if the research used self-reported tribal affiliation data.

All of Us may wish to refer to the Urban Indian Health Institute's policies for guidance as they develop their policies in this area. The program should also be aware that tribal affiliation and blood quantum information may be included in an individual's EHR. However, the information may not be complete as many individuals may have multiple tribal affiliations but only one may be listed in the record. Any use of tribal affiliation or blood quantum information from EHR would require tribal approval.

Consent

All of Us should make sure that the consent document includes information about genetics research, with a clear explanation about what that means. The document should also address specific risks for vulnerable populations.

Since some individuals may only be willing to participate in certain types of studies, the program may want to consider offering tiered consent so participants can specify what types of research they would be willing or unwilling to allow their data to be used for.

Ethics, Including Institutional Review Board, Biospecimen Storage and Access, and Protection and Benefits

Though the *All of Us* Research Program is not seeking to enroll AI/AN individuals while they are still carrying out this engagement process, a limited number of self-reported AI/AN participants have enrolled in the program during the beta phase after seeing general marketing materials (such as program flyers in a nontribal health clinic). The TCWG members had conflicting opinions about what the program should do with this data. The majority suggested treating the AI/AN participants as they do other participants and allowing their data and biospecimens to be included in the general dataset.

A few raised the option of sequestering the data of all AI/AN individuals who enroll prior to the release of the TCWG report. This means AI/AN participants' data cannot be accessed by researchers, but any return of information by the program would be allowable. Once the engagement process is complete, *All of Us* should provide information about the engagement activities and outcomes to these AI/AN participants.

Researchers currently do not have access to any participant data. *All of Us* anticipates the researcher portal will not open until 2019, so these considerations may be moot.

Institutional Review Board

The *All of Us* Research Program has a single IRB that serves as the IRB of record for the program. The *All of Us* IRB follows the regulations and guidance of the Office for Human Research Protections for all studies, ensuring that the rights and welfare of research participants are overseen and protected uniformly. While a single IRB may be sufficient for other populations, because of tribal sovereignty, NIH's single IRB requirement does not apply to tribal nations. Therefore, *All of Us* must also obtain approval from a tribal and/or IHS IRB, as applicable, when recruiting on tribal lands or at a tribal facility. When a tribe has an IRB, they have jurisdiction first, before the IHS IRB.

When recruitment for research takes place on tribal lands, the tribe and the tribal IRB have jurisdiction. The IHS IRB has jurisdiction when research is conducted with IHS staff or resources, or within IHS facilities.[26] Human participant research conducted in IHS facilities or with IHS staff or resources must be approved by the IHS IRB. This includes research done in Tribal or Urban facilities since I/T/U sites fall under the IHS federal-wide assurance (FWA) #00008894.[27] While tribal consent may not be required if the program is enrolling individuals who permanently reside outside of federally defined tribal lands, this should not be seen as a way to circumvent tribal oversight.

It is important to note that even if a tribal IRB approves the *All of Us* protocol, the program still needs to obtain approval from the tribal council in the form of a resolution or letter of support. Some tribes or tribal clinics may not have an IRB, a clear understanding of the role of an IRB, or what it would mean to defer to the *All of Us* IRB. *All of Us* should reach out to these tribes and tribal clinics with information about the role and processes of an IRB and should work with the tribe or tribal clinic to determine who needs to review the protocol to authorize a partnership.

In Alaska, in addition to IRB review, studies must also go through tribal research review. The process "involves a multi-level process of administrative, scientific, and tribal review" and is "designed to allow… customer-owners, clinical providers, health system and tribal leaders, and administrative staff to work as partners with researchers in developing a balance between expected immediate and long-term benefits of the proposed research to participants and AN/AI people and risks associated with the research."[28] *All of Us* should review the Southcentral Foundation and other's tribal research review processes for additional information.

Since it can be confusing to determine who to approach first, which IRB is the IRB of record, etc., *All of Us* may need to provide educational resources for researchers who want to use tribal data for their projects.

All of Us would benefit from respectful, bi-directional discussion with tribal IRBs to learn from their best practices. The program should ask tribal and IHS IRBs to read the protocol and suggest changes that may allay some of the tribes' concerns, to ensure that the research is not conducted in ways that are antithetical to tribal values.[29] Trust-building and frequent contacts between the program and tribal IRBs will enhance the ability to address any challenges that arise.[30]

In addition to including tribal representatives on the *All of Us* IRB and Resource Access Board, as outlined in the governance section, the program should ask IHS and tribal IRB representatives to provide cultural sensitivity training for the other IRB and Research Access Board members. The training should include background information, best practices, and cultural and ethical issues to be aware of and respect.

Biospecimen Storage and Access

The *All of Us* Research Program intends to allow researchers to request access to biospecimen samples donated by participants for use in their research studies, though the specific policies and procedures governing biospecimen access are currently still under development. In some tribal cultures, everything that comes from the body, including blood and hair, is sacred, so donation of a biospecimen is a significant act, as it may feel like the researcher is taking a piece of the individual's spirit and soul. Due to these cultural beliefs, AI/AN individuals will be especially interested in knowing how their biospecimens will be used, where they will be stored, and how they will be disposed of upon the donor's death.[31] The program should ensure that these details are clearly explained to AI/AN individuals using the following best practices:

- Use a framework in all communications that emphasizes the care and respectful treatment of biospecimens. Clearly communicate safeguards in place to protect these biospecimens. De-emphasize the robots or technology involved in processing biospecimens.
- Develop a flow chart to illustrate what happens to the biospecimens after collection.
- Clearly communicate the withdrawal options for AI/AN individuals when they enroll. Note that AI/AN participants will have the option to request that their samples be blessed by a tribal healer or medicine man in a ceremony arranged by the program before the biospecimen is withdrawn.

All of Us needs to develop clear data access policies for all participants, not just AI/AN individuals. These policies should:

- Clearly address who will be able to access biospecimens and data, the types of research the biospecimens can be used for, and how ancillary studies will be reviewed and approved.
- Include clear guidelines on pharmaceutical companies' and industry's access to biospecimens and data.
- Include a clear description about who the program will recognize as a "citizen scientist" who can be granted access to the data. Also include clear policies around data access by these recognized citizen scientists.
- Explain the labels that will be attached to biospecimens and data. In order to understand community-level risk factors, there must be some labels attached to the data; however, this can increase re-identification risks, especially for individuals who are from small tribes.
- Report back to the TCWG once the data access policies are finalized.

All of Us should also review IHS data access policies to guide the development of the program's policies, though given the unique nature of the *All of Us* Research Program, some of the IHS policies may not necessarily translate well. Tribal policies and processes regarding data access as well as secondary use of data and biospecimens should be respected.

As the program is developing its data access policies, it is important to balance privacy protections with the burden for researchers. The policies should not be so restrictive that AI/AN principal investigators struggle to meet the requirements to access the data, with the ultimate result that only non-Native researchers are able to carry out studies using AI/AN data. We believe in the concept of "research for our people by our people." We encourage the program to think creatively about activities that build capacity to support young tribal investigators or facilitate partnerships between senior investigators and junior tribal researchers.

Protection and Benefits

As mentioned in the governance section, it is essential that *All of Us* invite one or more AI/AN representative(s) to serve on the *All of Us* Research Program Research Access Board. The program may also consider creating a subcommittee with decision-making power, that consists mostly of Native individuals, to review applications for data or research projects focusing on AI/AN peoples.

All of Us should develop a process to identify organizations and individuals who have breached ethics policies and have a way to bar them from the program.

To ensure AI/AN communities benefit from participation in *All of Us*, the program should ask tribal nations to share research questions that would be of interest to their communities. These may include research into the top causes of mortality for AI/AN populations, the health impact of environmental exposures and strategies to mitigate the effects of these exposures, and pharmacogenetics.

Engagement and Partnerships

Sustained engagement with tribal nations and organizations is key if *All of Us* wishes to successfully include AI/AN individuals in the program. Even when recruiting off tribal lands, it is best practice to inform and have a conversation with tribal leaders in the area if the program is planning to recruit AI/AN individuals. Since *All of Us* currently has health care provider organizations in Arizona and Wisconsin, where there are high AI/AN populations, the program should prioritize meeting with tribal leaders in those two states.

All of Us may benefit from having a dedicated tribal liaison to continually build relationships with tribal nations, answer questions from tribal leaders and individuals, and help guide researchers through tribal engagement and best practices for research involving AI/AN populations. Ideally this would be a Native individual who has a deep understanding of AI/AN culture.

All of Us should also ask TCWG and NIH TAC members to allow the program to post their contact information so tribal leaders and organizations can have a regional contact person whom they may be more comfortable approaching with questions about the program. The tribal liaison can work closely with these members to make sure they have the information and resources needed to answer any questions they receive.

To support these engagement activities, the program should develop a well-written one-page document that summarizes the purpose and value of the program. The document should also convey the open-ended nature of the Research Program. To help vet these materials, *All of Us* should work with many different tribal groups to get feedback so the program can understand what is interesting and helpful.

With this information in hand, *All of Us* should engage with tribal leaders and councils on an ongoing basis through a variety of venues:

- Enlist AI/AN organizations to help disseminate materials through their contacts and listservs.
- Create an interactive webpage where tribal leaders can access information and updates about the program. Launch a blog or email address where questions and comments from tribal leaders can be sent. Post all the questions and answers to the webpage.
- Hold a series of webinars with Native peoples following the national launch and on an ongoing basis to answer questions and address concerns that have been expressed in Indian country.
- Ask national and regional tribal organizations to post a link to joinallofus.org on their websites. Some tribes may not have fast or reliable internet connections, so it is also important to have printed materials that can be provided to the regional organizations to help disseminate information about the program.
- Reach out to Tribal Epidemiology Centers or known entities already conducting research in tribal communities to establish talking sessions.
- Organize a symposium with tribal leaders and researchers, making sure to invite both those who are firmly opposed to biomedical research as well as those who believe this program will be very helpful. For efficiency, the program may consider holding the symposium as part of an established tribal conference, rather than creating a new convening. Make sure to schedule with plenty of lead time so the convening does not conflict with other consultations or listening sessions. An ideal time may be the day before or after the established tribal conference, because tribal leaders often expect to stay for those extended days to attend convenings. The program should coordinate with TCWG members and ask them to speak about *All of Us* or answer questions from their perspective as a TCWG member.

- Conduct periodic visits and two-way conversations with the communities or tribes that tribal participants come from, potentially on tribal lands.
- Hold consultation with tribal nations.

After getting input from these tribal nations and organizations, *All of Us* must go back to the nations and organizations to close the loop by sharing what the program has done as a result of the input provided, including what input the program has decided not to adopt.

The program can also build trust with AI/AN populations by returning information both to the individuals and, in cases where a tribe has agreed to partner with *All of Us*, in the aggregate to the tribe. In one study, Alaska Native individuals said that researchers often fail to report any results to them, which leaves the impression that the community did not benefit from the research, making it less likely that they would participate in future studies.[32] *All of Us* must be careful to avoid this misstep through the following best practices:

- Use many different venues and formats for returning the information, including videos, handouts, presentations, etc.
- Require researchers to develop laymen's summaries of their research question, methods, and results. Require researchers to explain what their results will look like when translated into clinical practice or clearly state that the results currently have no implications for clinical practice.
- If the researcher would like to study a specific tribe and name the tribe in their paper, require the researcher to return information to the tribe, get tribal permission for all publications, and organize "meet the investigator" nights, when tribal members can ask questions.
- Engage the Native researcher community. NIH's BUILD program offers a potential model and/or partner.
- Support efforts that promote the next generation of researchers. *All of Us* can consider partnering with the American Indian Science and Engineering Society (AISES) and the Society for the Advancement of Chicanos/Hispanics and Native Americans in Science (SACNAS) on such efforts.
- Many tribes now require that researchers engage in a community-based participatory research process. Since researchers will need time in order to build these relationships, *All of Us* should consider methods to facilitate such engagement.

Finally, the program would benefit from including tribal members in all levels of the research project by enhancing the diversity of awardee site staff, who may guide participants through the informed consent process, in regions where AI/AN individuals will be recruited.[33]

References

[1] U.S. Census Bureau. The American Indian and Alaska Native Population: 2010. 2010 Census Briefs. Retrieved February 2018 from https://www.census.gov/prod/cen2010/briefs/c2010br-10.pdf.
[2] US Department of Health and Human Services. Profile: American Indian/Alaska Native. Office of Minority Health. Retrieved February 2018 from https://www.minorityhealth.hhs.gov/omh/browse.aspx?lvl=3&lvlid=62.
[3] Bureau of Indian Affairs. Frequently Asked Questions. Retrieved March 2018 from https://www.bia.gov/frequently-asked-questions.
[4] U.S. Census Bureau. 2010 Census redistricting data (Public Law 94-171) summary file, Table P1. Washington, DC: US Bureau of the Census; 2010.
[5] Native American Caucus of the California Democratic Party. Tribal Sovereignty: History and the Law. Retrieved March 2018 from http://www.nativeamericancaucus.org/content/tribal-sovereignty-history-and-law.
[6] National Congress of American Indians. Tribal Governance. Retrieved March 2018 from http://www.ncai.org/policy-issues/tribal-governance.
[7] Bureau of Indian Affairs. Frequently Asked Questions. Retrieved March 2018 from https://www.bia.gov/frequently-asked-questions.
[8] Indian Health Service. Agency Overview. Retrieved March 2018 from https://www.ihs.gov/aboutihs/overview/.
[9] Indian Health Service. IHS 2016 Profile. Retrieved March 2018 from https://www.ihs.gov/newsroom/factsheets/ihsprofile/.
[10] Ross RE, Garfield LD, Brown DS, & Raghavan R. The Affordable Care Act and implications for health care services for American Indian and Alaska Native individuals. J Health Care Poor Underserved. Author manuscript; available in PMC 2016 Apr 7. Published in final edited form as: J Health Care Poor Underserved. 2015 Nov; 26(4): 1081–1088.
[11] Department of Health and Human Services. HHS FY 2017 Budget in Brief—IHS. Retrieved March 2018 from https://www.hhs.gov/about/budget/fy2017/budget-in-brief/ihs/index.html.
[12] Norton IM, Manson SM. Research in American Indian and Alaska Native Communities: Navigating the Cultural Universe of Values and Process. J Consult Clin Psychol. 1996;64(5):856–860.
[13] Whitener RJ. Research in Native American communities in the genetics age: Can the federal data sharing statute of general applicability and tribal control of research be reconciled? J Technol Law Policy. 2010;15:217–274.
[14] Hiratsuka VY, Beans JA, Robinson RF, Shaw JL, Sylvester I, & Dillard DA. Self-determination in health research: An Alaska Native example of tribal ownership and research regulation. Int J Environ Res Public Health. 2017;14(11): 1324.
[15] Buchwald D, Mendoza-Jenkins V, Croy C, McGough H, Bezdek M, & Spicer P. Attitudes of urban American Indians and Alaska Natives regarding participation in research. J Gen Intern Med. 2006;21(6): 648–651.
[16] Krogstad, JM. One-in-four Native Americans and Alaska Natives are living in poverty. Pew Research Center Fact Tank. 2014. Retrieved March 2018 from http://www.pewresearch.org/fact-tank/2014/06/13/1-in-4-native-americans-and-alaska-natives-are-living-in-poverty/.
[17] U.S. Census Bureau. Facts for Features: American Indian and Alaska Native Heritage Month: November 2015. Retrieved March 2018 from https://www.census.gov/newsroom/facts-for-features/2015/cb15-ff22.html.
[18] Indian Health Service. Press Release: IHS signs pact for sanitation development in tribal communities. Retrieved March 2018 from https://www.ihs.gov/newsroom/index.cfm/pressreleases/2013pressreleases/ihssignspactforsanitationdevelopmentintribalcommunities/.
[19] Indian Health Service. Fact Sheets: Disparities. Retrieved February 2018 from https://www.ihs.gov/newsroom/factsheets/disparities/.
[20] Department of Health and Human Services. Office of Minority Health. Infant Mortality and American Indians/Alaska Natives. Retrieved February 2018 from https://www.minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlID=38.
[21] Indian Health Service. Fact Sheets: Disparities. Retrieved February 2018 from https://www.ihs.gov/newsroom/factsheets/disparities/.
[22] Walters KL, Simoni JM, & Evans-Campbell T. Substance use among American Indians and Alaska Natives: Incorporating culture in an "indigenist" stress-coping paradigm. Public Health Reports, 2002;117(1), 104–117.

[23] Centers for Disease Control and Prevention. Health, United States, 2015. Retrieved March 2018 from https://www.cdc.gov/nchs/data/hus/hus15.pdf.

[24] McOliver CA, Camper AK, Doyle JT, Eggers MJ, Ford TE, Lila MA, Berner J, Campbell L, & Donatuto J. Community-based research as a mechanism to reduce environmental health disparities in American Indian and Alaska Native communities. Int J Environ Res Public Health. 2015;12(4):4076–4100.

[25] Guadagnolo B, Petereit DG, Helbig P, Koop D, Kussman P, Dunn EF, & Patnaik A. Involving American Indians and medically underserved rural populations in cancer clinical trials. Clin Trials. 2009;6(6):610–617.

[26] Yuan NP, Bartgis J, & Demers D. Promoting Ethical Research with American Indian and Alaska Native People Living in Urban Areas. Am J Public Health. 2014;104(11):2085–2091.

[27] Indian Health Service. Human Subjects Research Protections. Retrieved February 2018 from https://www.ihs.gov/dper/research/hsrp/.

[28] Hiratsuka VY, Beans JA, Robinson RF, Shaw JL, Sylvester I, and Dillard DA. Self-determination in health research: An Alaska Native example of tribal ownership and research regulation. Int J Environ Res Public Health. 2017;14(11): 1324.

[29] Palosaari N. Intellectual property rights and informed consent in American Indian Communities: legal and ethical issues. Am Indian L Rev. 2016;41(1):125–165. Retrieved February 2018 from http://digitalcommons.law.ou.edu/ailr/vol41/iss1/4?utm_source=digitalcommons.law.ou.edu%2Failr%2Fvol41%2Fiss1%2F4&utm_medium=PDF&utm_campaign=PDFCoverPages.

[30] Bruhn J. Identifying Useful Approaches to the Governance of Indigenous Data. International Indigenous Policy Journal. 2014;5(2). Retrieved March 2018 from http://ir.lib.uwo.ca/iipj/vol5/iss2/5.

[31] Hiratsuka VY, Brown JK, Hoeft TJ, & Dillard DA. Alaska Native people’s perceptions, understandings, and expectations for research involving biological specimens. Int J Circumpolar Health. 2012;71:18642. Retrieved February 2018 from https://doi.org/10.3402/ijch.v71i0.18642.

[32] Hiratsuka VY, Brown JK, Hoeft TJ, & Dillard DA. Alaska Native people’s perceptions, understandings, and expectations for research involving biological specimens. Int J Circumpolar Health. 2012;71:18642. Retrieved February 2018 from https://doi.org/10.3402/ijch.v71i0.18642.

[33] Norton IM, Manson SM. Research in American Indian and Alaska Native Communities: Navigating the Cultural Universe of Values and Process. J Consult Clin Psychol. 1996;64(5):856–860.