

# Population Genomic Screening for Indigenous Communities and People: Key Considerations

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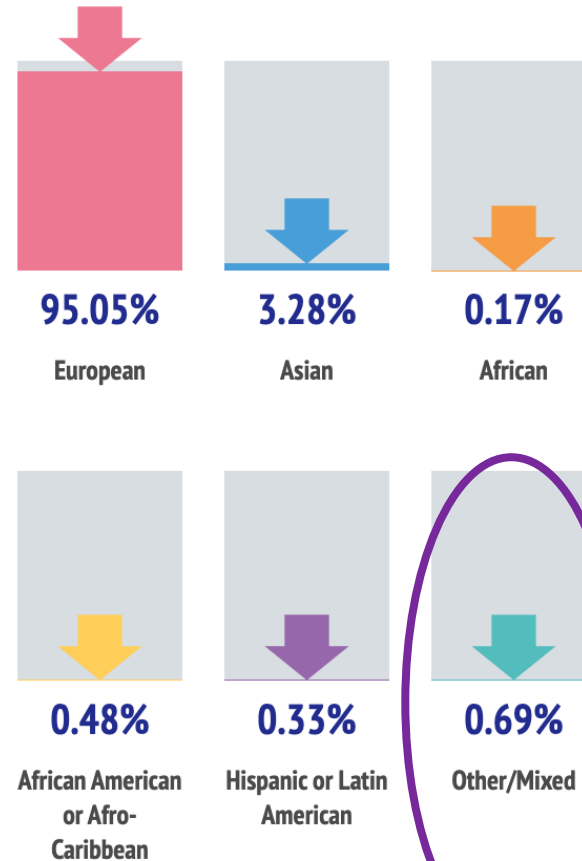
Even with the expanded ACMG panel, only **5 medically actionable genes** have variant information specific to Indigenous peoples

How does this affect **clinical utility** and **equity**?



### Total GWAS participants diversity

Version 1.0.0. Last check for data: 2023-07-15 00:17:39.



Despite efforts to increase diversity in genomic studies, **Indigenous people still constitute <1% of research participants**

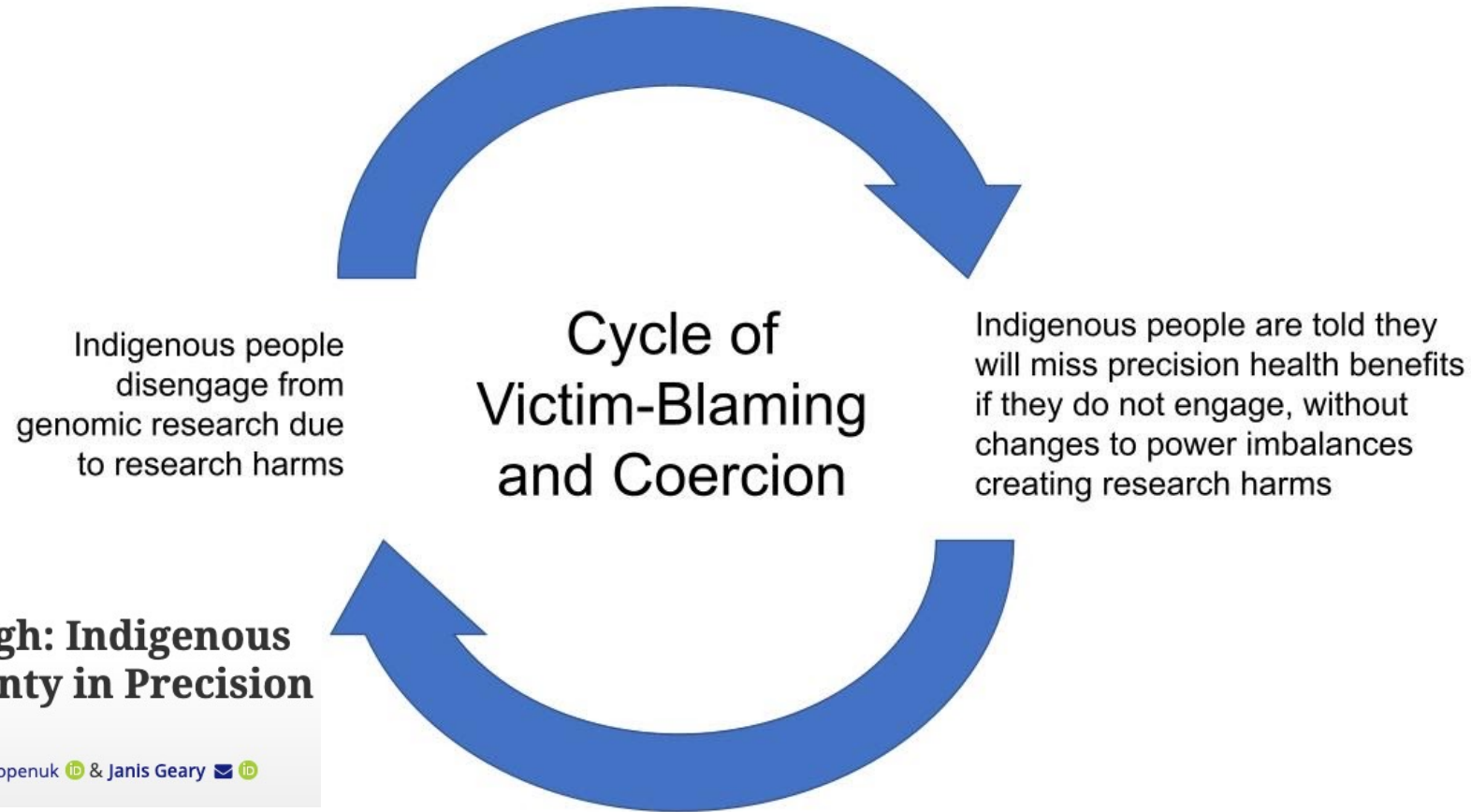
This is not a matter of engagement via recruitment nor selling the benefits of genomics and precision medicine.

It's a matter of overcoming mistrust, thinking more proximally about health, and empowering data-decision equity.

# Thinking Structurally About Health Inequities

"In 2018, Indian Health Services spent an average of \$3,779 per patient. The national spending per capita that same year was \$9,409"

National Indian Health Board



Open Peer Commentaries

## We Have “Gifted” Enough: Indigenous Genomic Data Sovereignty in Precision Medicine

Krystal S. Tsosie , Joseph M. Yracheta , Jessica A. Kolopenuk  & Janis Geary  

Pages 72-75 | Published online: 07 Apr 2021

**Merely making clinical genetic tests available is not going to solve the equity problem.**

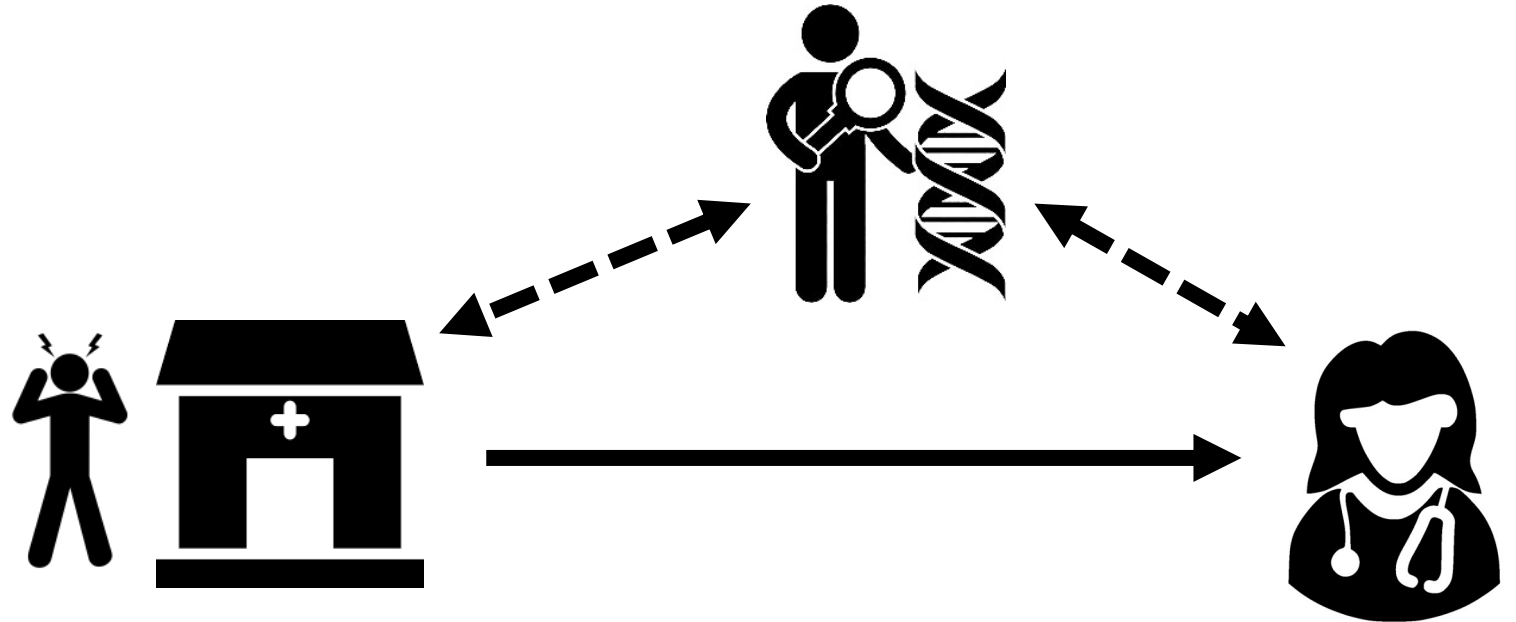
# Clinical Pathway of Care for Rural, Tribal Patients Seeking Genetic Testing

Indigenous patient may need to be referred out by their Indian Health Service primary care provider to a specialist, often located 100+ miles away



# Clinical Pathway of Care for Rural, Tribal Patients Seeking Genetic Testing

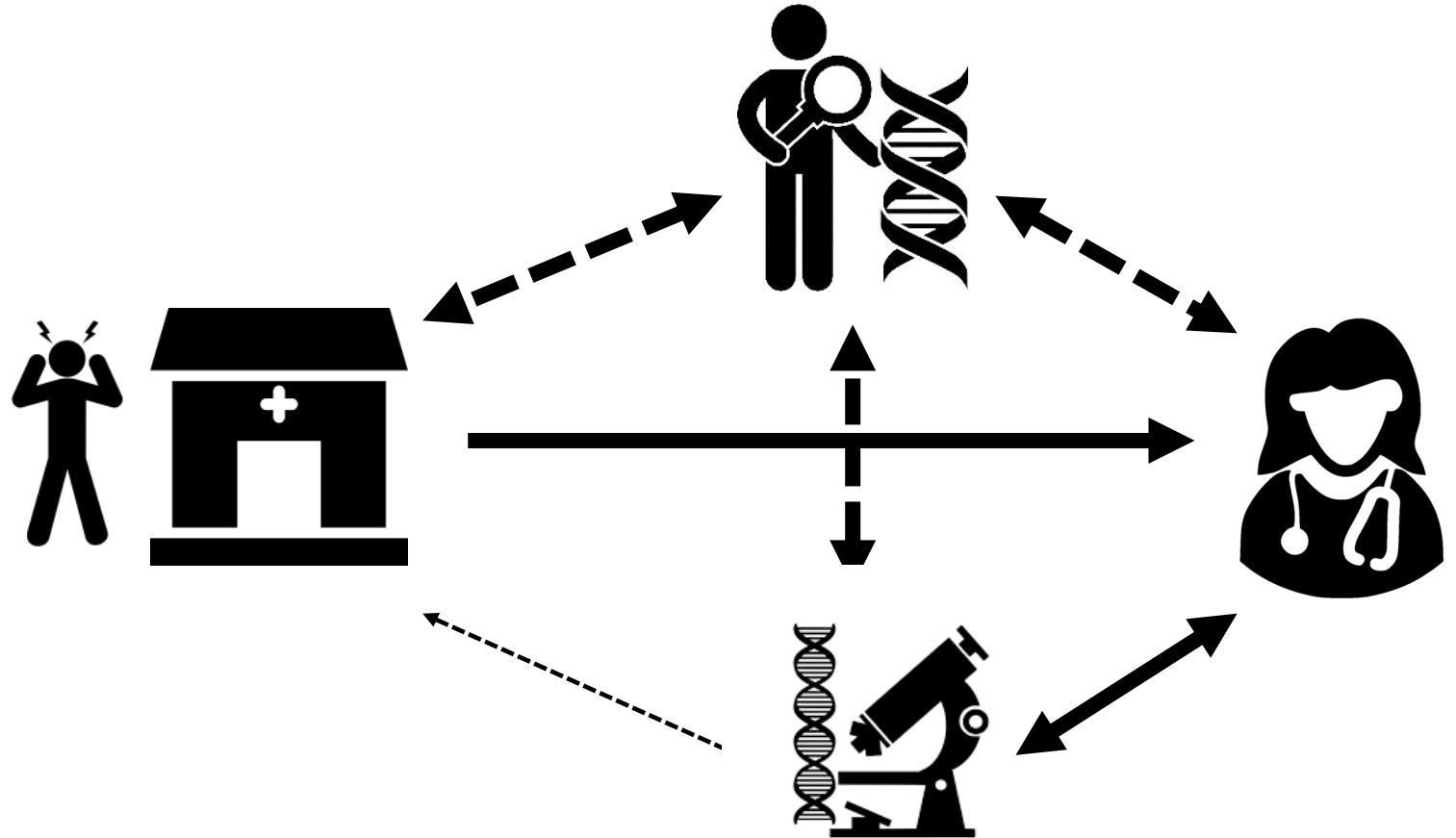
Of question is whether a genetic counselor is available to contextualize clinical genetic testing results



# Clinical Pathway of Care for Rural, Tribal Patients Seeking Genetic Testing

Are the clinical genetic test results interpreted against the relative lack of information on Indigenous-specific genetic variation?

What is the potential impact due to false negative results?

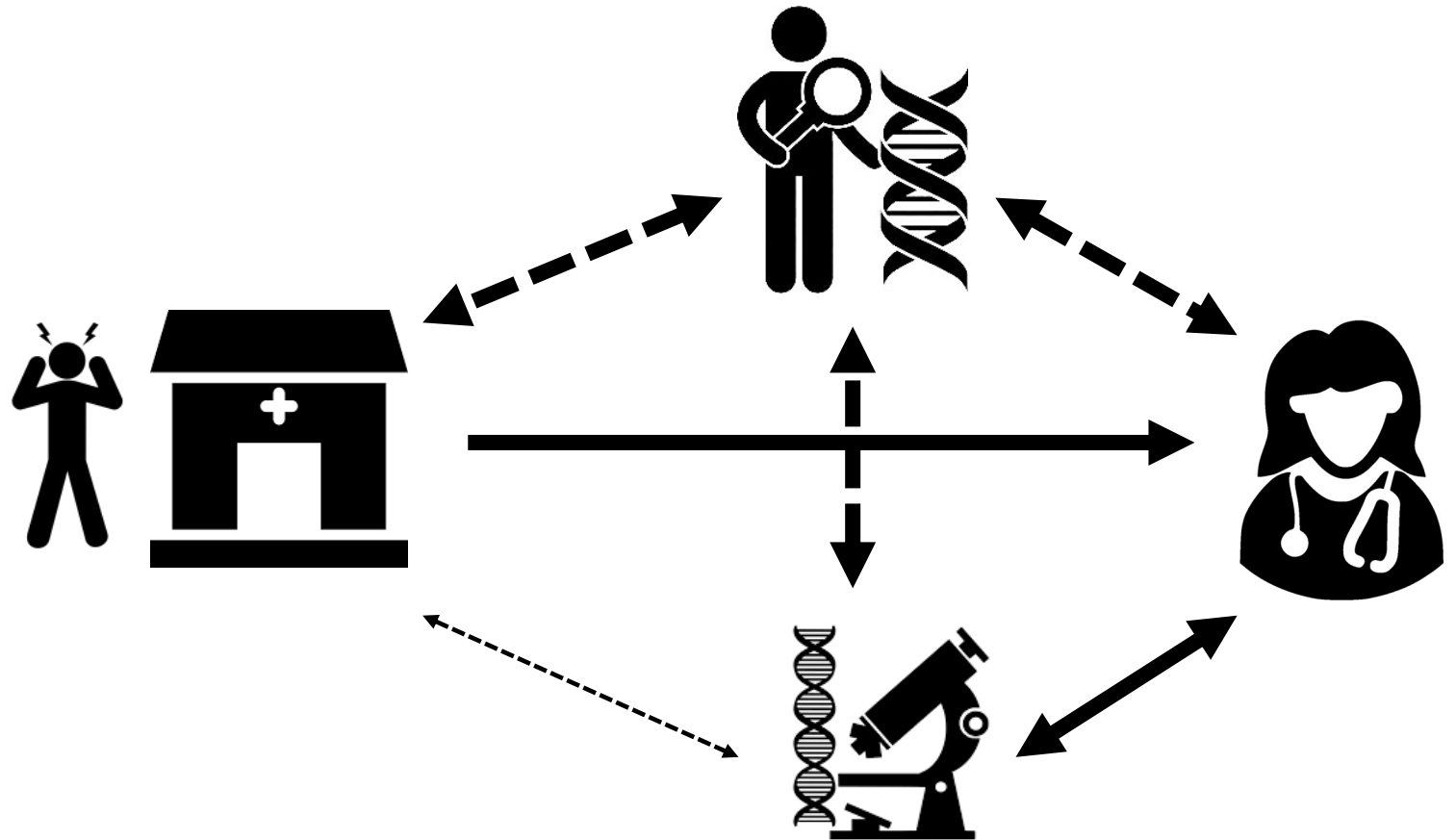


# Clinical Pathway of Care for Rural, Tribal Patients Seeking Genetic Testing

What training is available to deliver culturally-specific care to Indigenous genetic test users?

Are patients being fully informed about default data sharing?

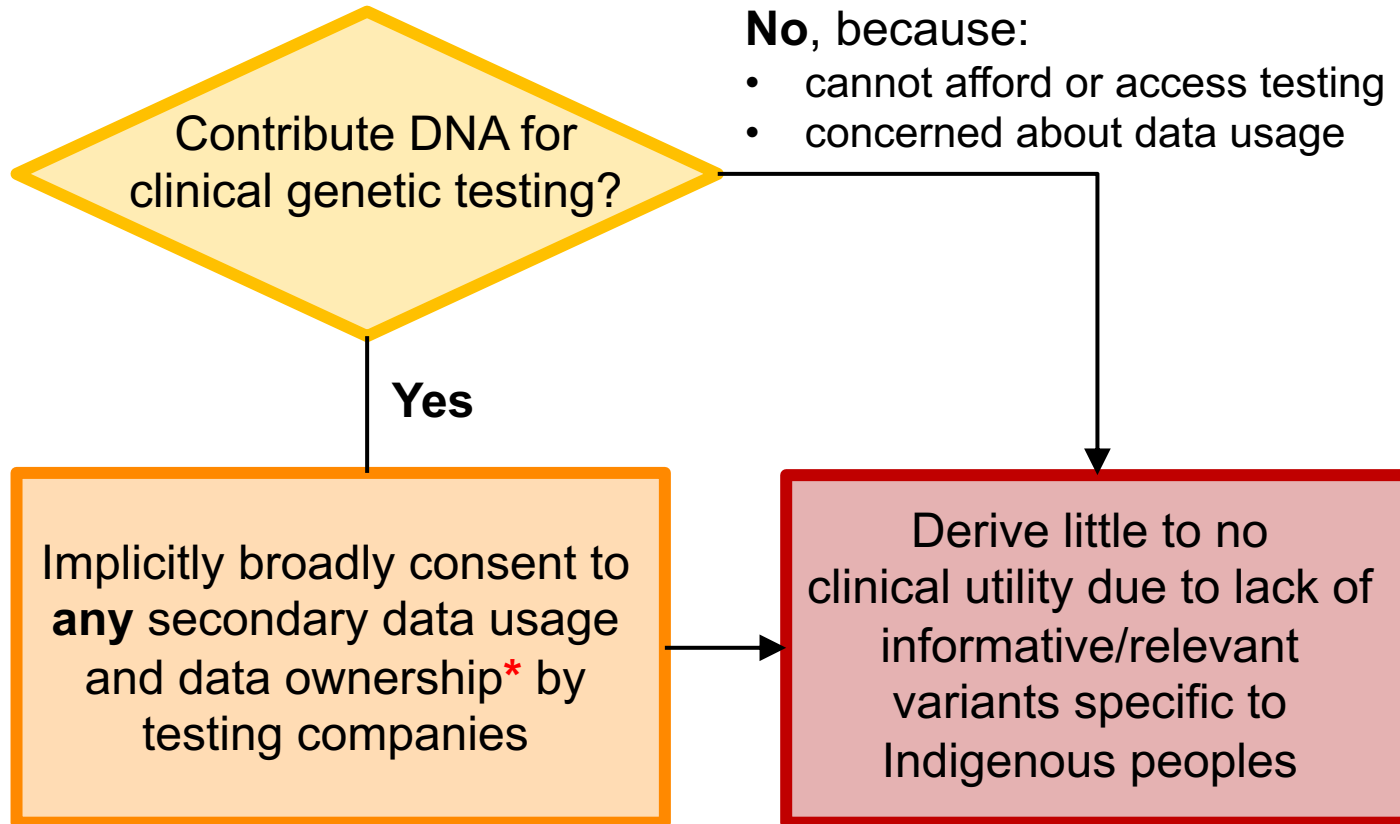
What are risks for Indigenous patients who are not protected by federal privacy laws (GINA)?





# CATCH-22

## Decision Tree for Indigenous Patients



\* This is outside the consideration of many providers who are focused on patient care, but simply using a clinical genetic test

- means that commercial genetic testing companies can co-opt and claim ownership of Indigenous peoples' genomic data
- that this data will be deposited into public databases like ClinVar, even if patients know to ask to opt-out of data sharing
- urban tertiary care centers that see Indigenous cancer patients may also be biobanking samples and data for research under broad consent **without** Tribal Nation approval
  - raises ethical questions about the conflation of research consent versus consent to care for minoritized communities

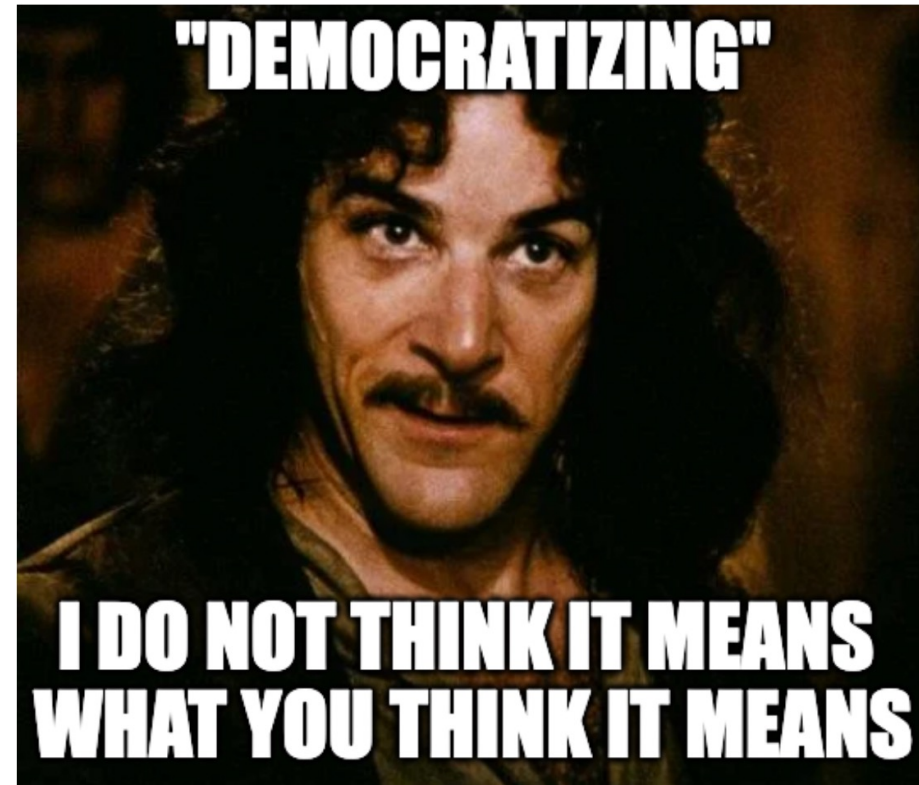


**It is not “profit-generative” to use Indigenous peoples’ DNA to create therapeutics that specifically impact Indigenous peoples.**

What pharmaceutical companies told Indigenous scientists

Recruiting more Indigenous peoples into datasets is not going to solve the health inequity problem.

Dropping genetic tests into our communities is not going to solve the health inequity problem.



# ISSUES USING INDIGENOUS GENETIC ANCESTRY

## COLONIALITY OF POPULATION DESCRIPTORS

- Like all processes of gene flow and drift, Indigenous peoples had systems of kinship and relationality that were not mediated by blood; e.g. expansion with people from neighboring Tribal Nations
- Our clanship systems acknowledged our heterogeneous genetic backgrounds under a unified identity. But these were always sociological in distinction

Under the **Indian Reorganization Act** (1934) or the Wheeler–Howard Act, US federal legislation that “dealt with” the status of Indigenous peoples, the US established:

**Blood quantum laws** to define Native American status by fractions of Native American ancestry.

These laws were enacted to establish *legally defined racial population groups*, but which are inconsistent with how we define ourselves and indeterminate means of tracking gene flow.



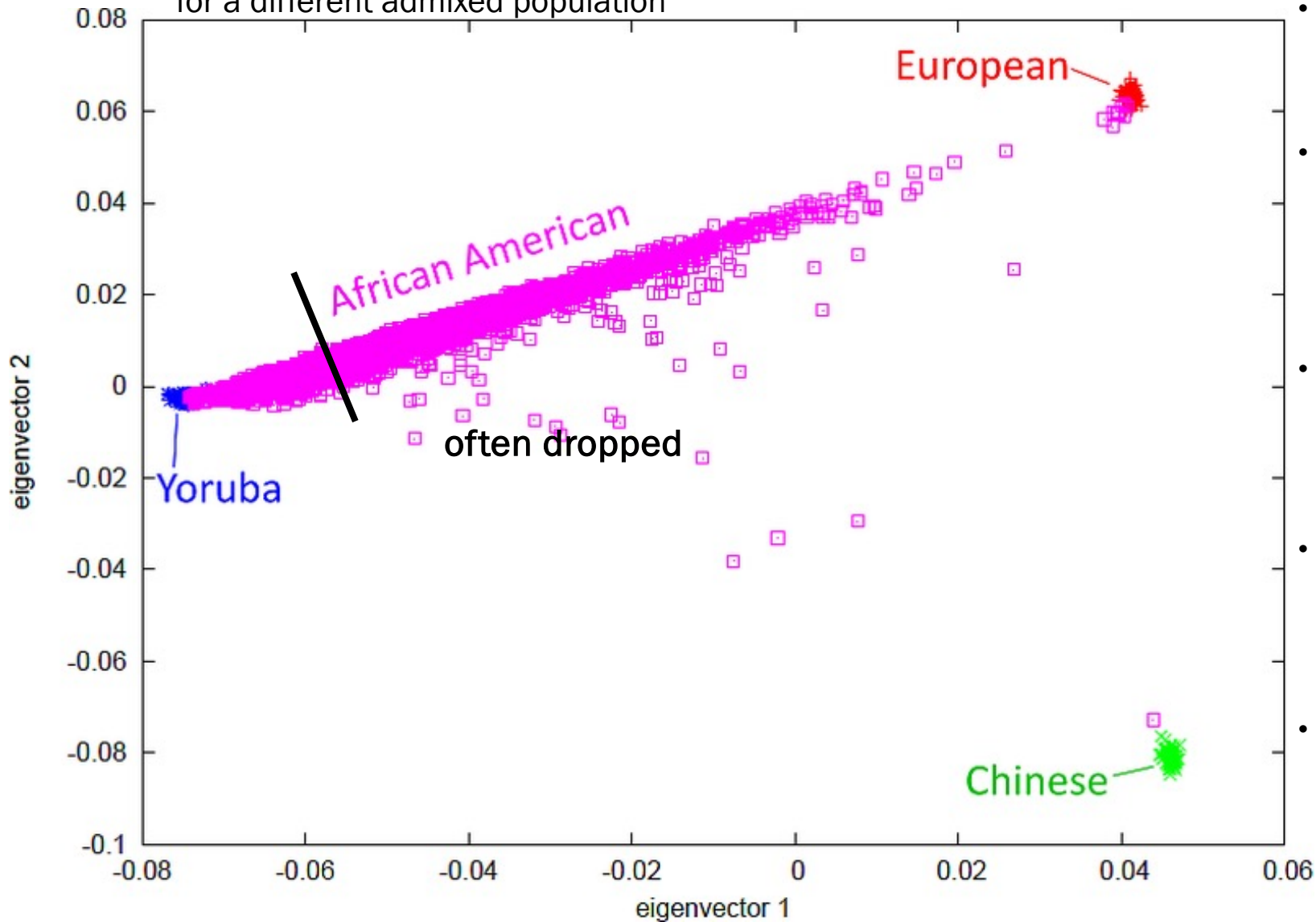
We also draw from public reference datasets, including the [Human Genome Diversity Project](#), [HapMap](#), and the [1000 Genomes Project](#). Finally, we incorporate data from 23andMe-sponsored projects, which are typically collaborations with academic researchers. We perform the same filtering on public and collaboration reference data that we do on 23andMe customer data.

**Datasets for imputation have relatively few Indigenous individuals (N~30), specific to peoples in Central and South America.**

**Yet, these data used to infer genetic ancestry for all US Indigenous peoples.**

**It also promotes problematic conflated narratives of Indigeneity as rooted in biology thought to be validated by genomic science.**

A simplified example of a Principal Components Analysis for a different admixed population



- In most gen-epi studies, the focus is on imputed SNP data and information found in the EHR
- For "Native Americans", we are often left out because analyses on our small datasets necessitate other statistical protocols outside the standard QA/QC pipeline
- OR "Native Americans" are pooled together in the same stratum, leading to mixed-effects issues and poor conclusions
- But the standard QA/QC pipeline **reifies assumptions of biological purity against inappropriate reference populations**
- **Ignores real contributions of inequities due to social and structural determinants of health**

Pasaniuc B et al. (2011) Enhanced Statistical Tests for GWAS in Admixed Populations: Assessment using African Americans from CARE and a Breast Cancer Consortium. PLoS Genet 7(4): e1001371.

# RE-THINKING “ONE PERSON – ONE TRIBE”

- Too often, Indigenous peoples (and others) are categorized as one Tribal affiliation
- However, populations are not stagnant. Drift and gene flow are recurrent
- **We do a disservice** when we:
  - Default to colonial definitions of Indigeneity
  - Do not acknowledge multiple Tribal identities, especially due to political disempowerment
- **We do poor science** when we reify Indigeneity as a biological construct
  - Use Indigenous biomarkers from groups with distinct genetic histories: “pan-Indigeneity”
  - Focus on “biological pure” or “least admixed” Indigenous peoples ignores the lived experience of many Indigenous peoples

1

**Population descriptor ≠ group label.**

A population descriptor is a way to classify individuals according to perceived differences among groups; a group label is a specific name used to describe a population.



2

**Researchers often use population descriptors inconsistently and/or inappropriately.**

Race, for example, should not be used for analysis in most genomics studies. It may be used for some health disparities studies.



4

**Genetic ancestry** refers to the lines or paths through an individual's family tree by which they inherited DNA from specific ancestors. It can be useful when studying human evolutionary history.

**Genetic similarity**, a measure of genetic resemblance among individuals, is preferred in many other contexts because it moves away from race and the misconception that humans can be grouped into discrete categories.



3

Sometimes funders require collection of Office of Management and Budget (OMB) Standards categories to report demographic information of research participants, but **use of OMB categories is not required for scientific analysis.**



**Key Considerations for Using Population Descriptors**

The National Academies' "Using Population Descriptors in Genetics and Genomics Research" report provides guiding principles and best practices for researchers. Below are four key concepts to keep in mind for using population descriptors

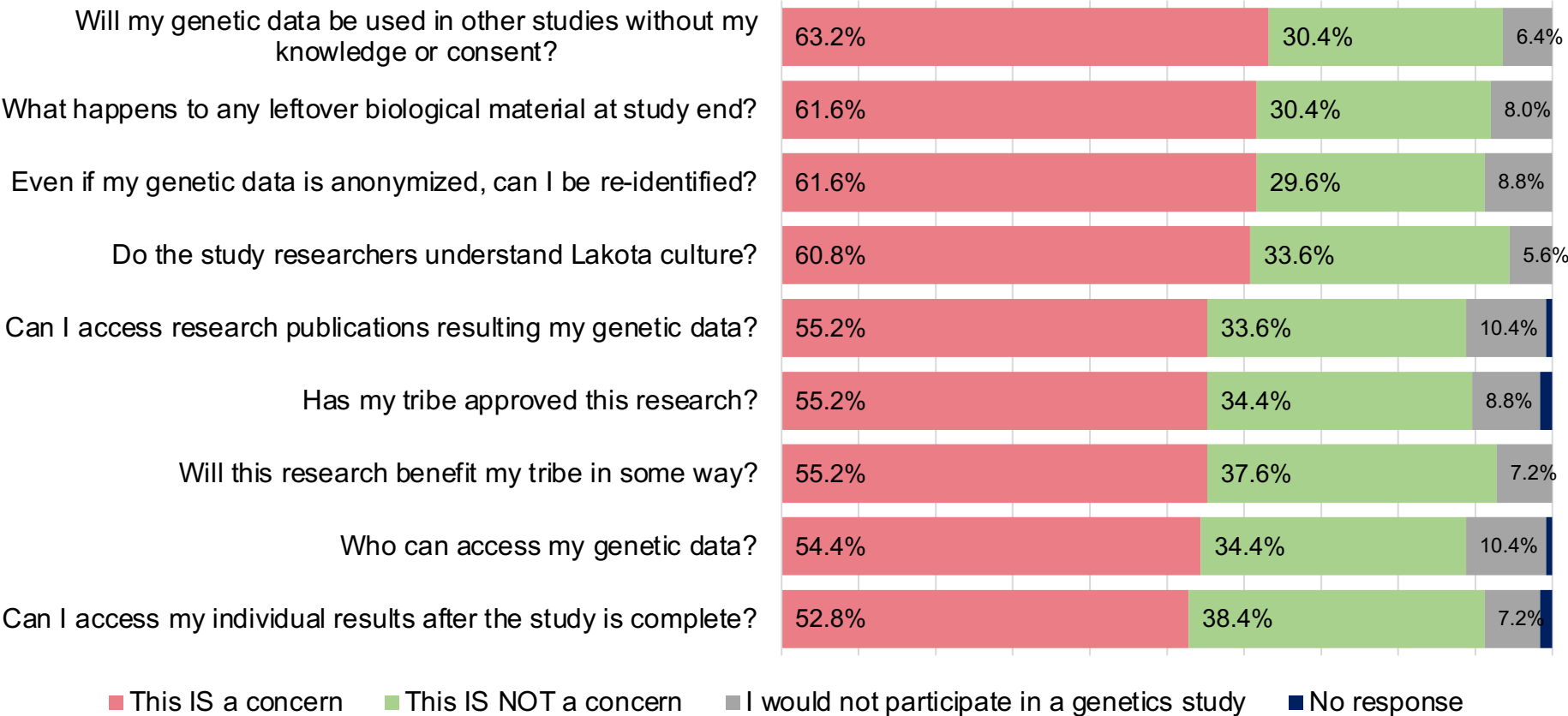
Using Population Descriptors in Genetics and Genomics Research

A New Framework for an Evolving Field

In a mixed-methods assessment of Tribal community members' perspectives of genomics research and data sharing, Indigenous people were most concerned about the unconsented use of their data in other studies

Tsosie et al 2022

### Concerns About Participating in Genetics Research



“I want to know who’s looking at my DNA and our genes”

“We should at least be able to reserve the right of who is going to use it [genetic data] and what they’re going to use it on.”

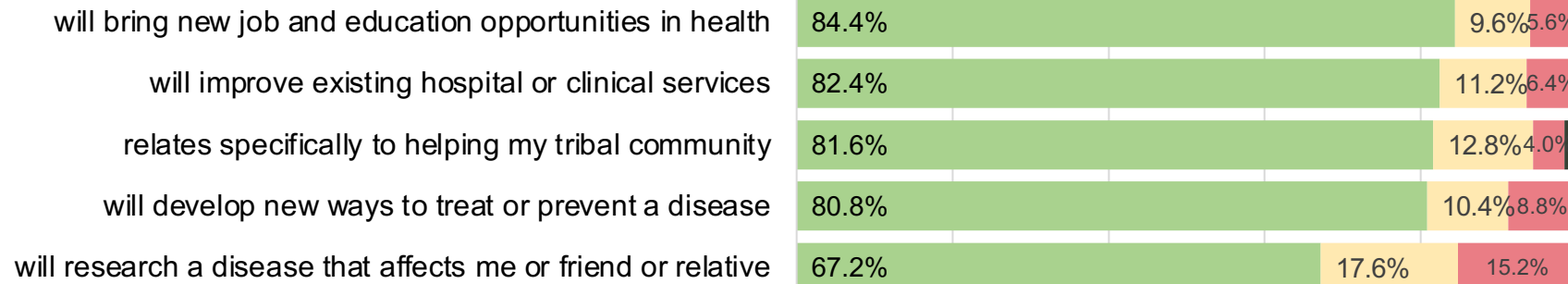


- Tribal community member rated job and education opportunities created by health research higher than benefits from researching a disease or condition.
- Pharmaceutical companies and federal biomedical institutions were rated last in terms of trustworthiness.

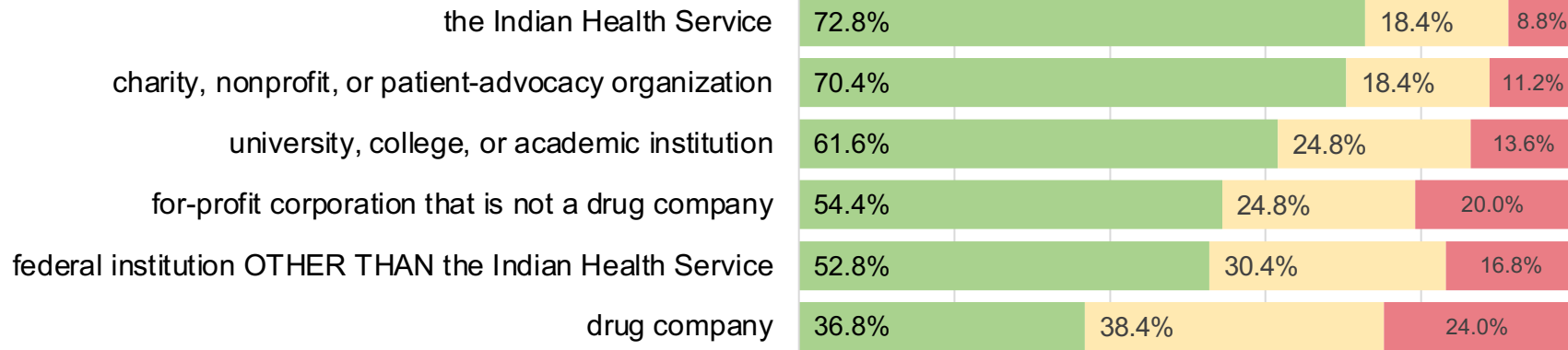
## Factors Considered when Deciding Whether to Participate in Health Research

Tsosie et al 2022

### The study



### The study is led or partnered by



■ More willing to participate 
 ■ Less willing to participate 
 ■ I would not participate in such a study 
 ■ No response



# Toward Equitable Innovation in Health and Medicine

A Framework

Consensus Study Report

## IMPERATIVES

Broadening participation and sharing responsibility to empower a wider range of stakeholders

Aligning incentives to encourage equitable decision making

Determining how inequities develop along technology innovation life cycles and taking responsibility for mitigating them

Crafting timely guidance for pursuing equitable ends

Sharpening ongoing, iterative oversight and evaluation along innovation life cycles

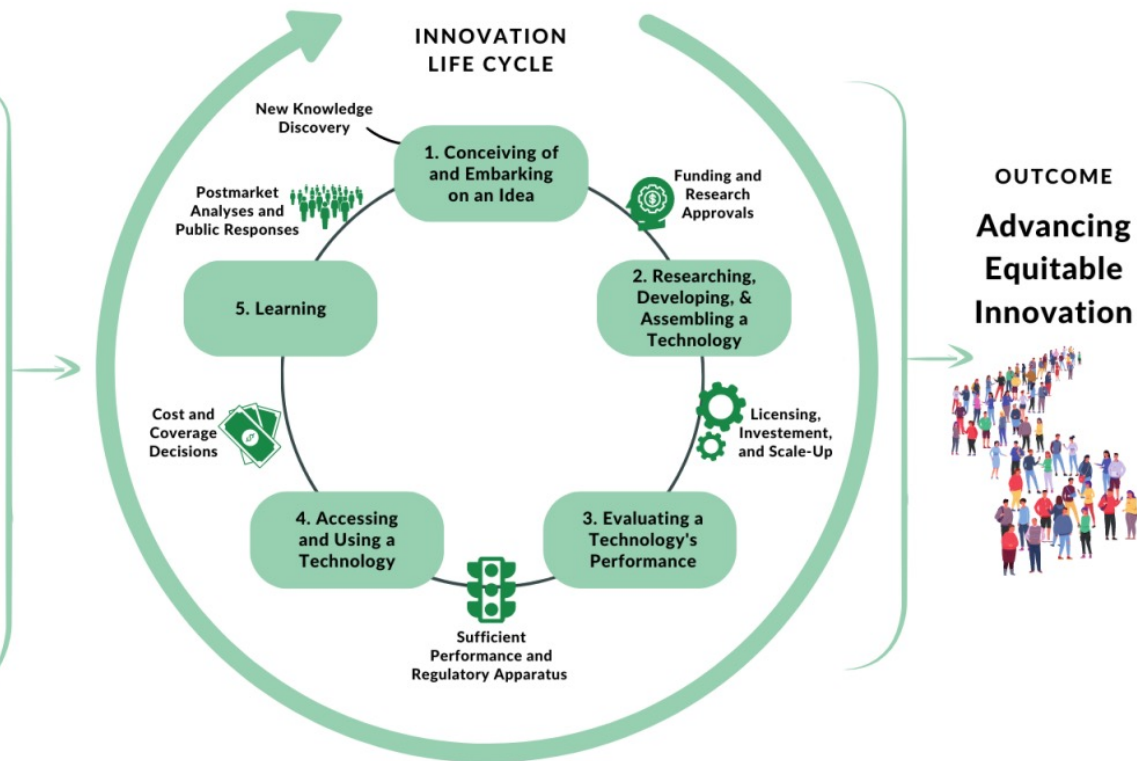


FIGURE 1 The governance framework for aligning emerging science, technology, and innovation in health and medicine with ethical principles, emphasizing alignment with equity.

# Digital Data Tools

## Facilitate Data Sharing

## Respect Indigenous

## Genomic Data Sovereignty

**Cell**

Volume 185, Issue 15, 21 July 2022, Pages 2626-2631

Establishing a blockchain-enabled  
Indigenous data sovereignty framework  
for genomic data

Tim K. Mackey<sup>1 2 3 4</sup>, Alec J. Calac<sup>3 5 6</sup>, B S Chenna Keshava<sup>7</sup>, Joseph Yracheta<sup>8</sup>,  
Krystal S. Tsosie<sup>8</sup>, Keolu Fox<sup>1 8 9</sup>  

nature machine intelligence

<https://doi.org/10.1038/s42256-022-00551-y>

## Federated learning and Indigenous genomic data sovereignty

- ✓ **Blockchain.** A distributed ledger system that tracks sharing via transactions, can fine-tune user access, attribute provenance, and facilitate data governance.
- ✓ **Federated learning.** To facilitate secure and community-consented data sharing.
- ✓ **Dynamic Consent Portal.** In Indigenous-led data repository to house Tribally-consented genomic sequence data and manage access and attribution.
- ✓ **Traditional Knowledge (TK) Labels.** Digital markers that define attribution, access, and use rights for Indigenous cultural heritage
- ✓ **Biocultural (BC) Labels.** Digital markers for provenance, transparency and integrity in research engagements related to community expectations and consent for use of collections and data.

# Indigenous Data Economies

Indigenous  
Cloud Solutions

Digital Data Tools

Indigenous Data Infrastructure

Indigenous Data Repositories

Indigenous Data Governance

Indigenous Data Policy & Law

Indigenous Data Leaders

**Indigenous Digital Sovereignty**

- ASU American Indian Policy Institute

**Indigenous Data Sovereignty**

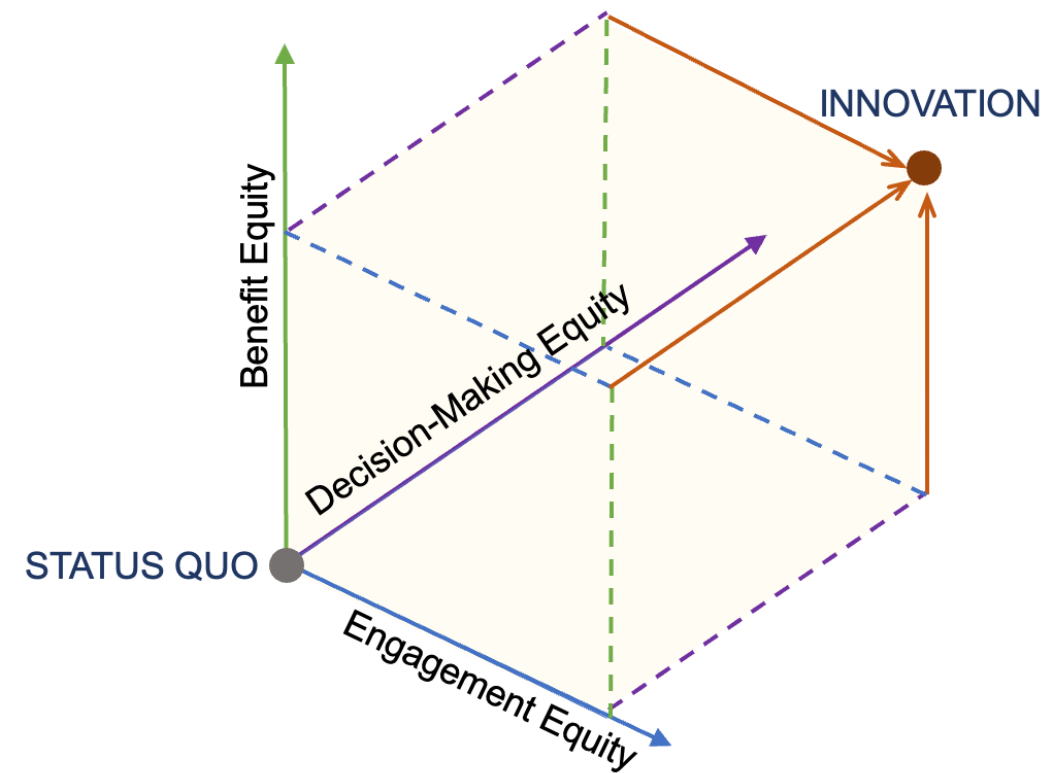
- UA Native Nations Institute

# **INDIGENOUS DATA SOVEREIGNTY**

U.S. recognizes the sovereign authority of 574 Tribal nations to self-govern. This is further recognized by the 2017 changes to the Common Rule (45 CFR 46)

**What happens to Indigenous people who reside outside of U.S. Tribal jurisdictions?**

- Native Hawaiians
- Indigenous peoples from unrecognized or state-recognized Tribes
- Indigenous migrants from outside U.S.
- Urban Indigenous peoples

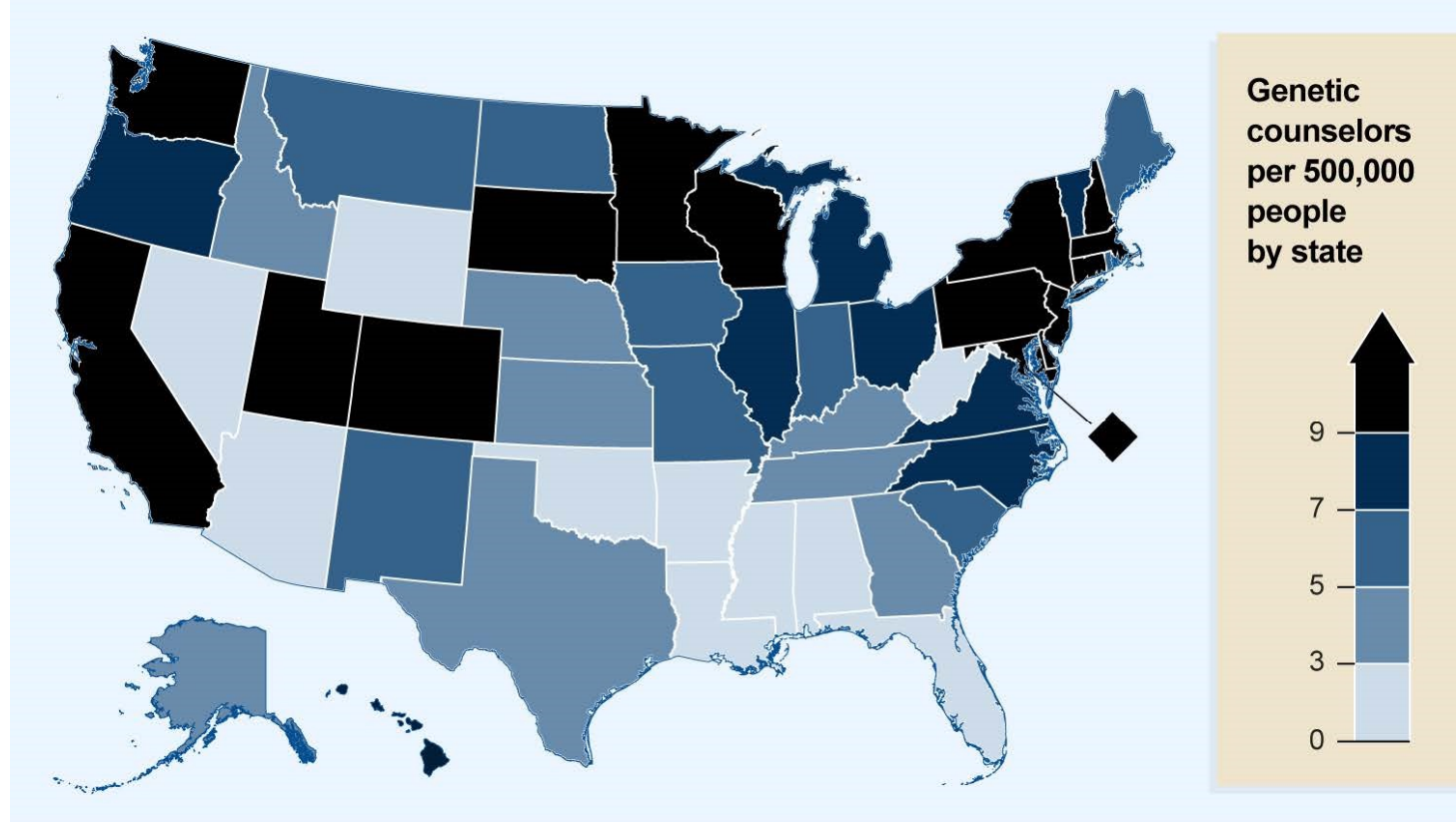


Tsosie (unpublished)

- ✓ **Consider Benefit Sharing.** Ensure benefits of research more proximally go to Indigenous partners.
- ✓ **Re-Think “Informed Consent”.** Use dynamic consent as opposed to broad consent; acknowledge group consent.
- ✓ **Acknowledge Indigenous Data Sovereignty.** Build equitable data partnerships and agreements, and acknowledge that not all Tribal Nations use IRBs.
- ✓ **Re-think Data “Ownership”.** Think instead of stewardship and responsibility to society and building trust with colonized peoples.
- ✓ **Ensure Innovation is Aligned with Equity.** Galvanize national leadership for aligning emerging science, technology, and innovation in health and medicine with principles of equity. Empower communities to participate in the innovation system.
- ✓ **Think Globally about Health.** Contextualize whether the study or treatment is meaningful for underserved communities.



# Improving Care, and Genetic Counseling for Indigenous Patients



Source: GAO analysis of data from the American Board of Genetic Counseling and Census Bureau; Map Resources. | GAO-20-593

Our goal is to work with Indigenous patients, genetic counselors, and stakeholders across the entire pathway of care to improve education about these gaps in clinical care.

One way forward is to train more Indigenous genetic counselors.





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Tsosie Lab for Indigenous Genomic Justice