

Inclusion of Indigenous Peoples in Genetic/Genomics Research



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**Ethical and Regulatory Aspects of
Clinical Research**

NIH Department of Bioethics

October 11, 2023

From the Rez to a PhD and beyond

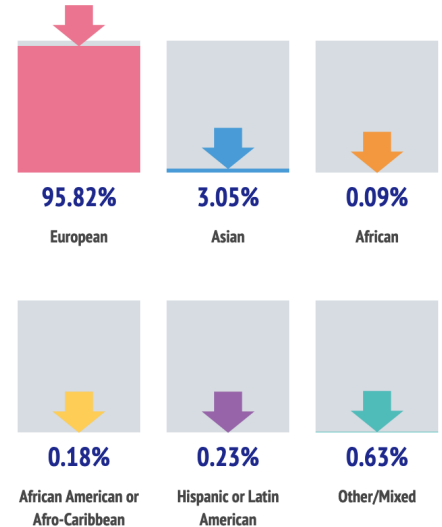


My research program is broadly motivated by:

- Supporting equity and inclusion of diverse populations in genomic research
- Addressing disparities in health and health care
- Enhancing ethical research with Indigenous and other historically underrepresented communities

Total GWAS participants diversity

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Claw Indigenous Genomics and Ethics Laboratory

Pharmacogenomics research in diverse populations

1. Nicotine metabolism personalized medicine



Strong Heart Study



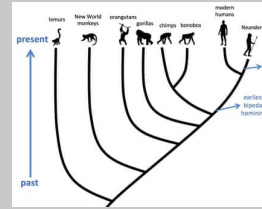
Southcentral
Foundation



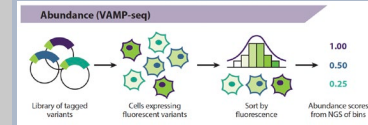
2. Cytochrome P450 Diversity



3. Evolution of Pharmacogenes



4. Understanding variants with multiplex assays



Cultural and bioethical research with Indigenous populations

5. Navajo Perspectives on genetic research



6. Ancient DNA ethics



NATIVE AMERICAN DNA

7. Impacts and mentorship of Indigenous trainees



Ethical research approaches

- What does it mean to be an ethical researcher?



Research with contemporary Indigenous peoples

- Precision medicine-pharmacogenomics research with tribal communities

Research involving Ancestors

- Fostering responsible research with Ancestors and ethical guidance

There is a disconnect between genetic and genomic research and Indigenous communities



Members of the Havasupai Tribe, shown in 2010 looking at blood samples previously taken from them, had to fight for access to their samples.

A moratorium on Genetic Research conducted within the Navajo Nation was approved in April 2002.

A STUDY OF THE BLOOD GROUPS AMONG THE AMERICAN INDIANS

CLARA NIGG

From the Department of Bacteriology, University of Kansas, Lawrence

Received for publication August 1, 1925

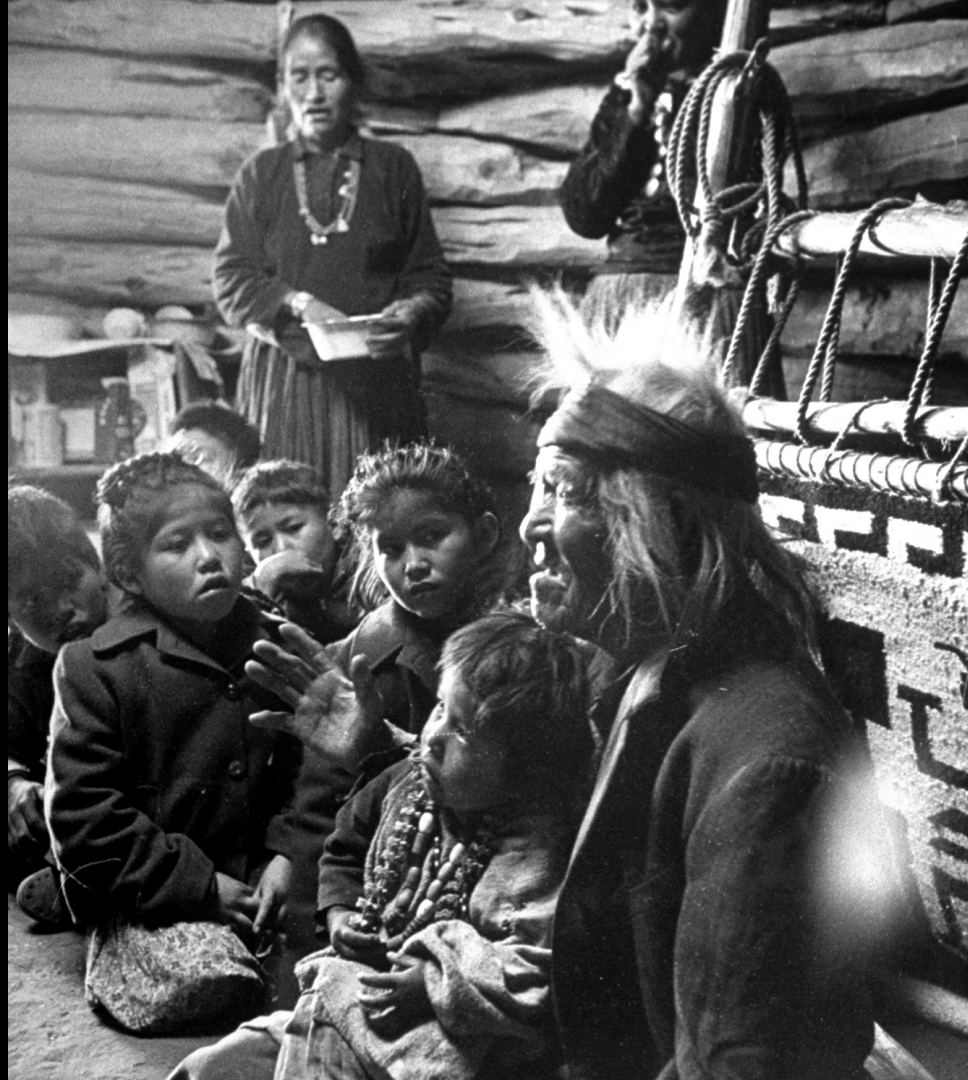
In 1923 Coon and Deibert (1) studied the percentage distribution of the four Landsteiner blood groups in the North American Indians in order to investigate the question of the relation of the American Indian race to the northeastern Asiatic races (Chinese, Japanese, Koreans), since it has been thought that the American Indian is of Mongolian origin. Their results in comprising 862 full-blooded Indians showed the following occurrence: group I 77.7 per cent, group II 20.2 III 2.1 per cent, group IV one individual.

Inbreeding Coefficients of the Ramah Navaho Population

J.N. SPUHLER¹ AND CLYDE KLUCKHOHN²

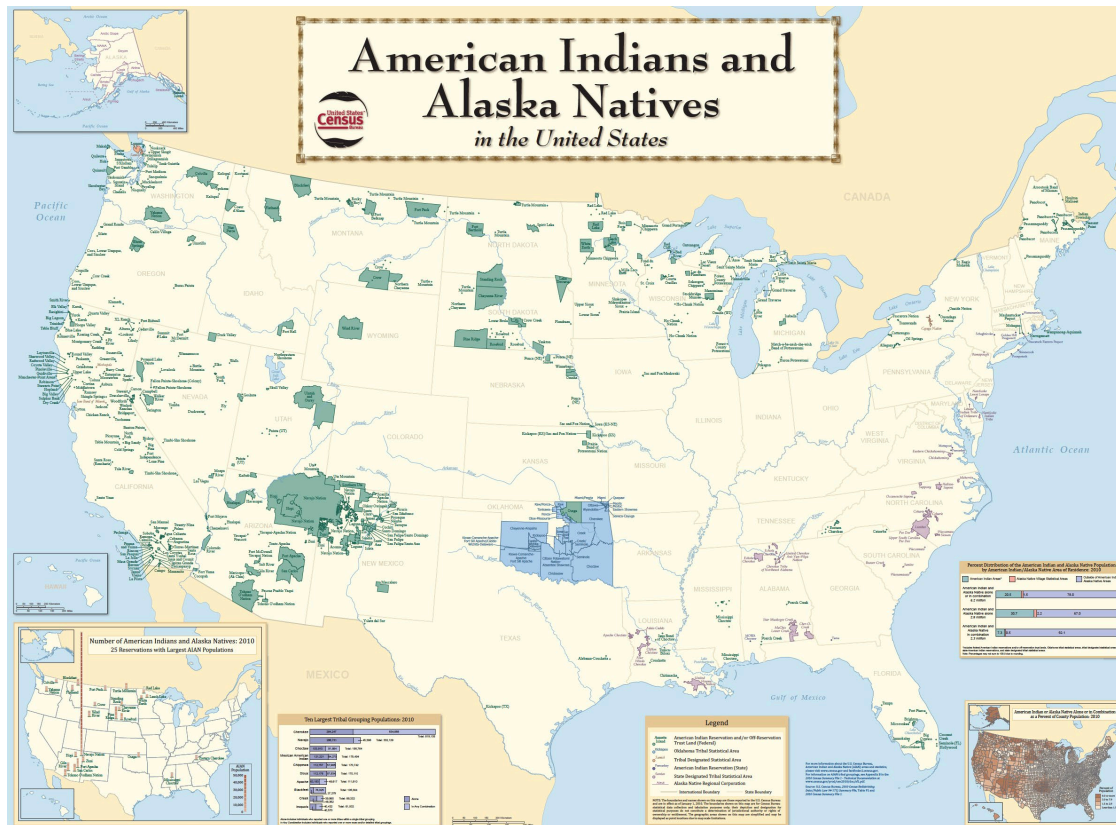
Hereditary Nonpolyposis Colorectal Cancer in a Navajo Indian Family

Henry T. Lynch, Thomas J. Drouhard, Guy S. Schuelke, Karen A. Biscione, Jane F. Lynch, and B. Shannon Danes



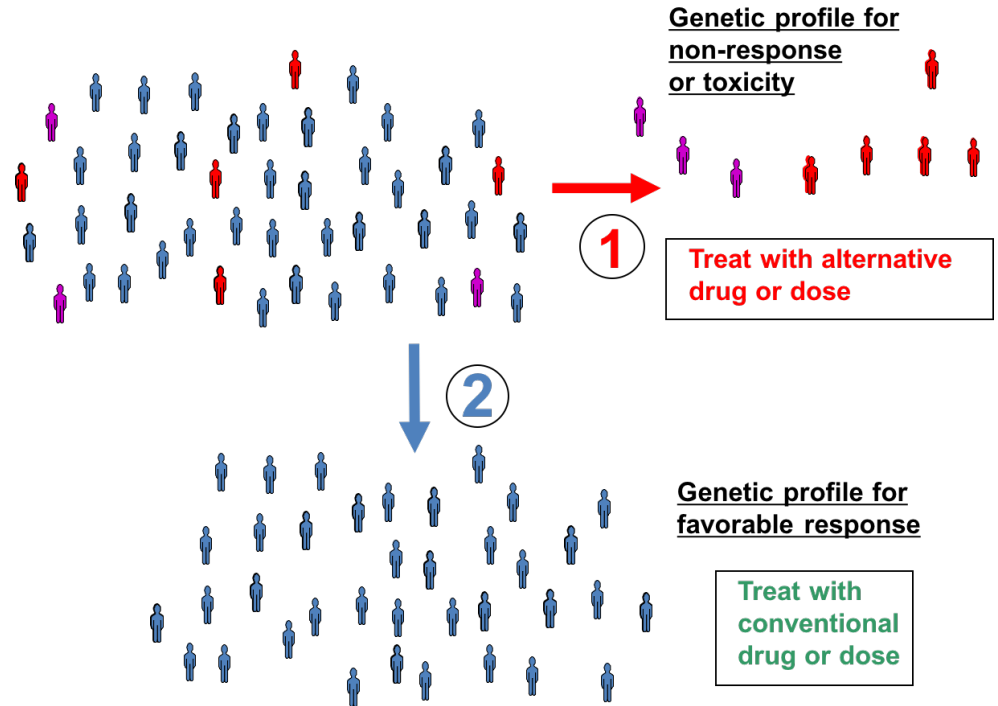
Indigenous tribes in the US

- 574 federally recognized American Indian and Alaska Native tribes
- 70% of tribal members and descendants live in cities.
- The Common Rule upholds tribal sovereignty.



Diverse Populations and Promise of PM & PGx

- Promote personalized medicine to optimize the quality of patient care
- Guide selection of best drug and dose for an individual
- Minimize adverse drug reactions
- Potential to improve health outcomes and reduce the cost of care



Genomic medicine for underserved communities

As more genomic studies are pursued,

- How can research be done in a respectful and culturally appropriate way with Native communities?
- How can we, as researchers, institutions, and funders, engage Native communities and tribes in genomic research?

As health applications are developed from genomic research,

- How can we assure that everyone benefits?
- How can we assure that disadvantaged populations are not harmed?

Precision Medicine may widen, not reduce, health disparities.

Past history

Benefits

Tribal sovereignty

Data-sharing policies



Consent

Intellectual property

Structural barriers

Social and racial barriers

COVID-19 Further Strains Care Disparities Among Native Americans

Community-based Genomic Research Approach

Applicability of Pharmacogenetic Information

Pharmacogenetic Algorithm based on VKORC1 and CYP2C9 genotype status Vs. Standard Clinical Care	
EU-PACT European Pharmacogenetics of Anticoagulant Therapy	Benefit for genotype-guided warfarin dosing
COAG Clarification of Optimal Anticoagulation through Genetics	No significant difference between the 2 groups

- Why conflicting results?

Applicability of Pharmacogenetic Information

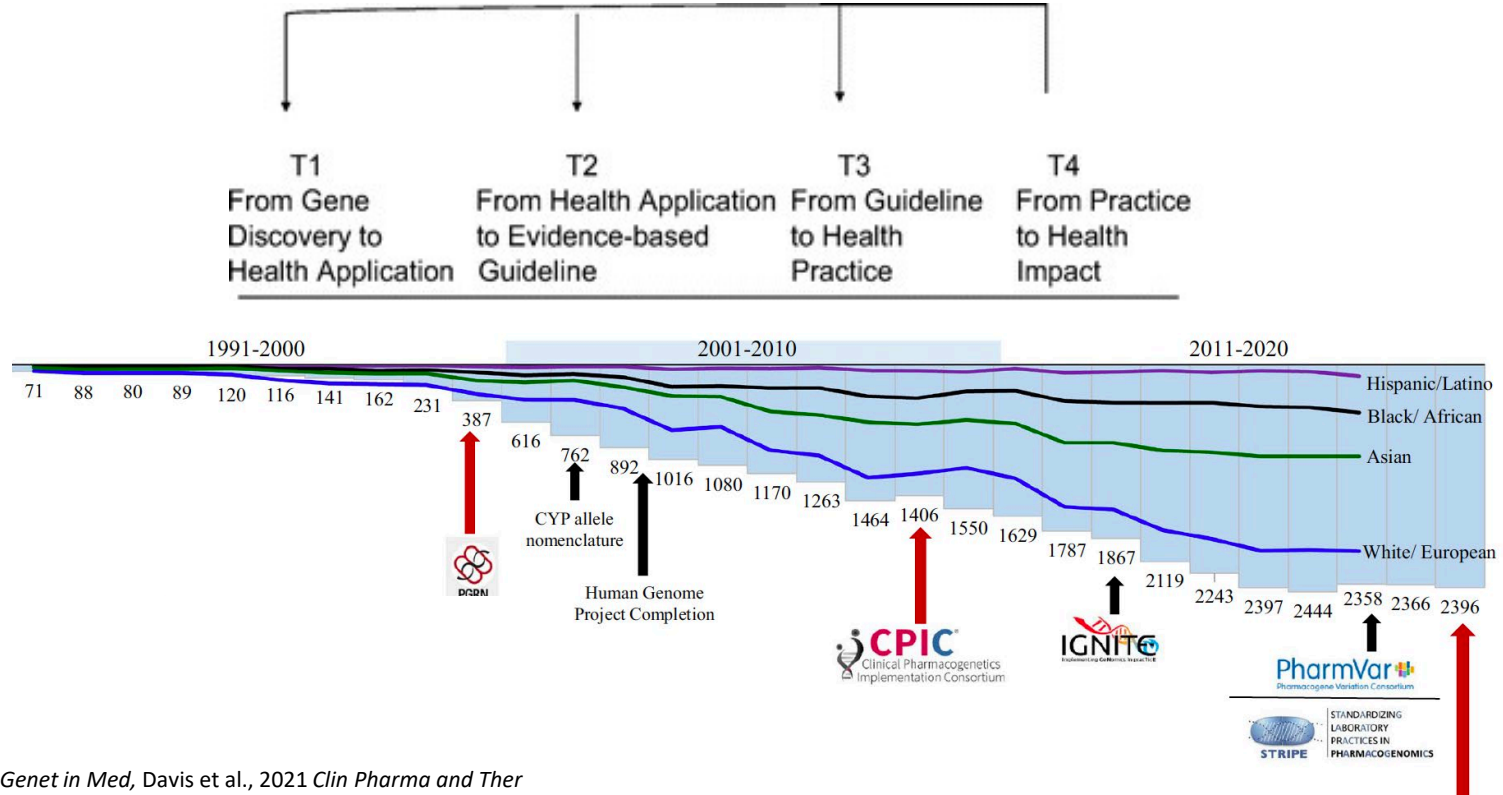
Pharmacogenetic Algorithm based on VKORC1 and CYP2C9 genotype status Vs. Standard Clinical Care	
EU-PACT Primarily European descent	Benefit for genotype-guided warfarin dosing
COAG 27% African American	No significant difference between the 2 groups

- African Americans have lower frequencies of CYP2C9*2 and *3, the only CYP2C9 variant alleles considered in the pharmacogenetic algorithm

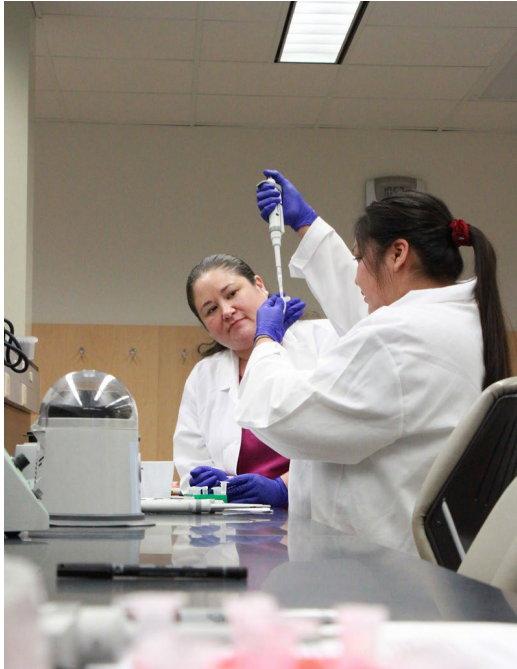
Clinical Implications of Uncharacterized Variation

- Potential for phenotypic misclassification
- Contribute to health care disparities
- Missed opportunities for optimizing care
 - PGx test implementation
 - Formulary selection

Translational Pharmacogenomics



Moving toward Community-based Genomic Research



The Summer Internship for Indigenous Peoples (SING) Consortium hosts workshops to engage students and tribal members in genomics.



A collaborative approach to research

Question:

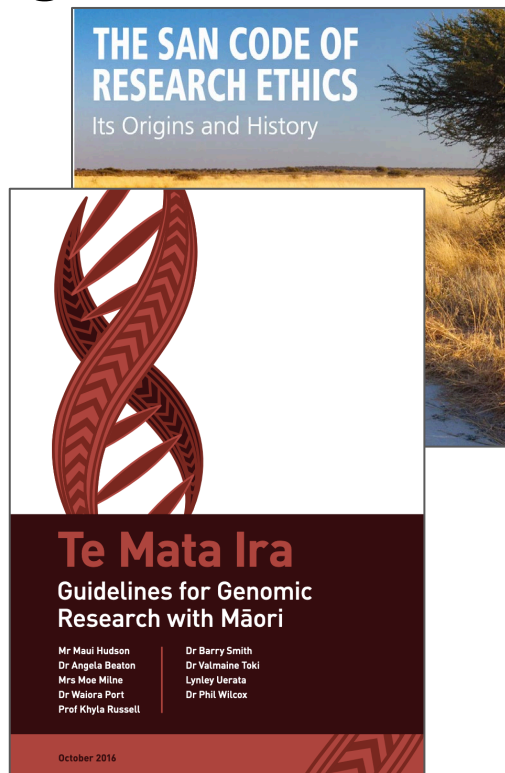
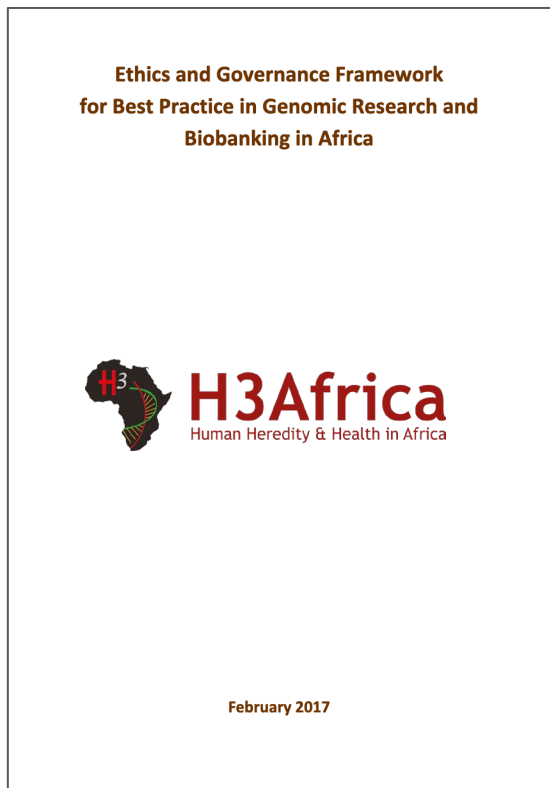
What would/does your study look like when community is involved?



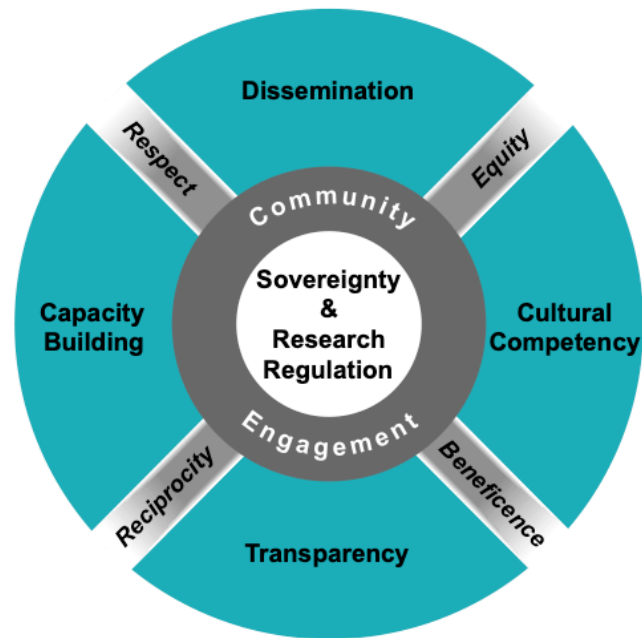
"IF YOU'RE GOING TO WORK WITH INDIGENOUS COMMUNITIES ON GENETICS, YOU HAVE TO BE WILLING TO MAKE LIFELONG RELATIONS."

—Kim TallBear,
University of Alberta

Recent advancement of community-specific research ethics guidelines

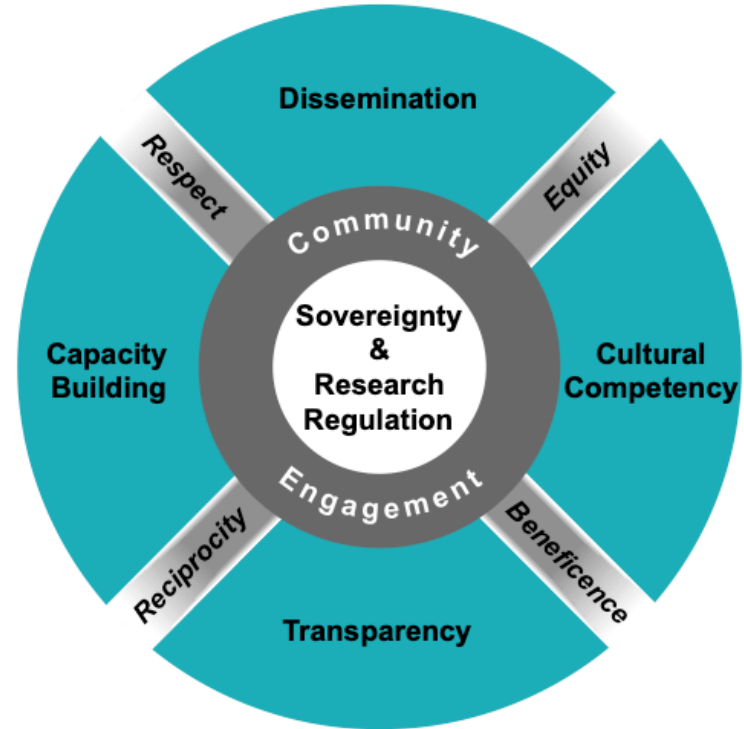


**Enhancing ethical genomic research
with Indigenous communities**



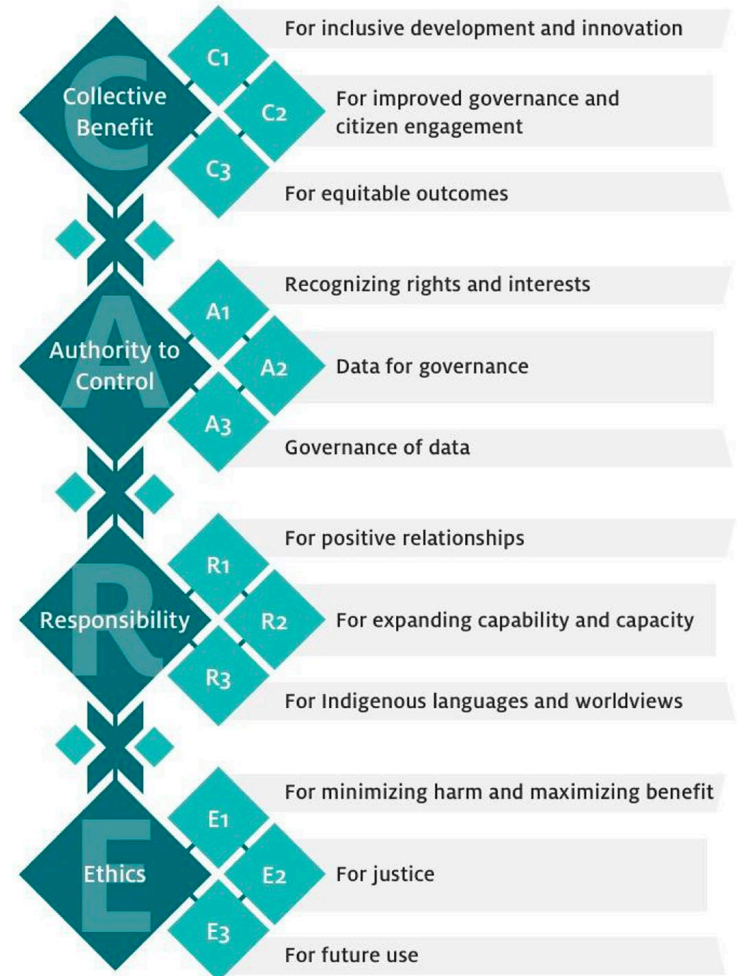
Enhancing ethical genomic research with Indigenous communities

1. Understand existing regulations
2. Foster collaboration
3. Build cultural competency
4. Improve transparency
5. Support capacity
6. Disseminate research findings



Indigenous genomic data sovereignty and governance in PM

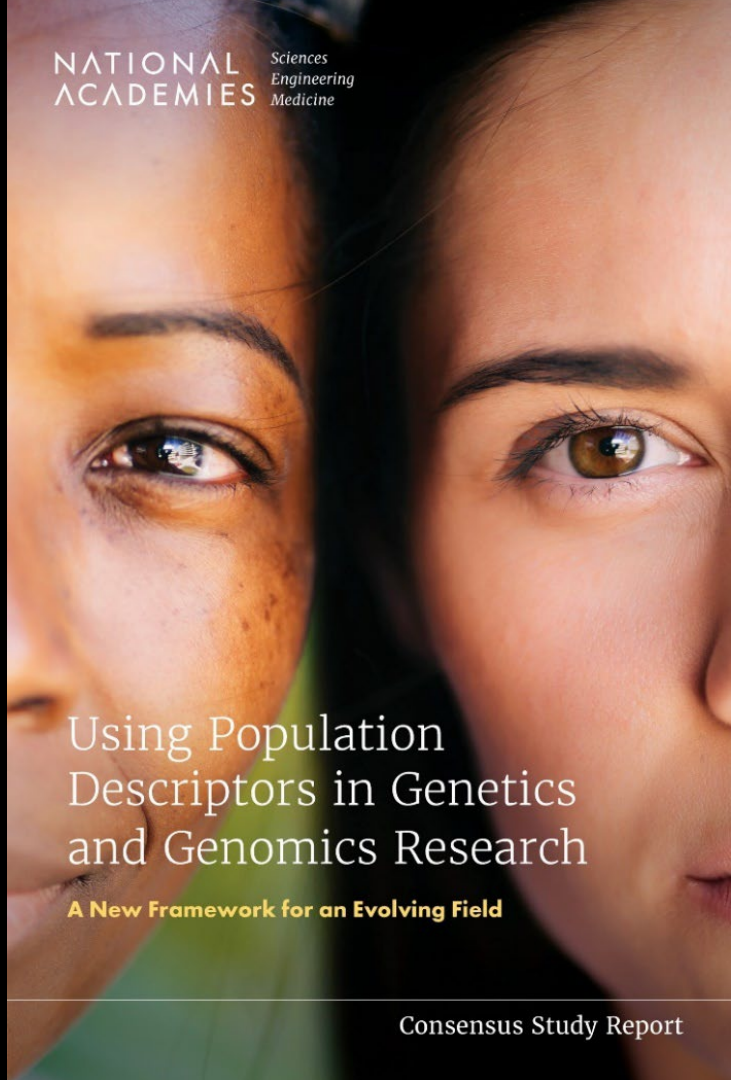
- Collection, ownership and application of data and specimens
- Consider data *stewardship* rather than *ownership*
- DNA on Loan concept



The CARE Principles for Indigenous Data Governance

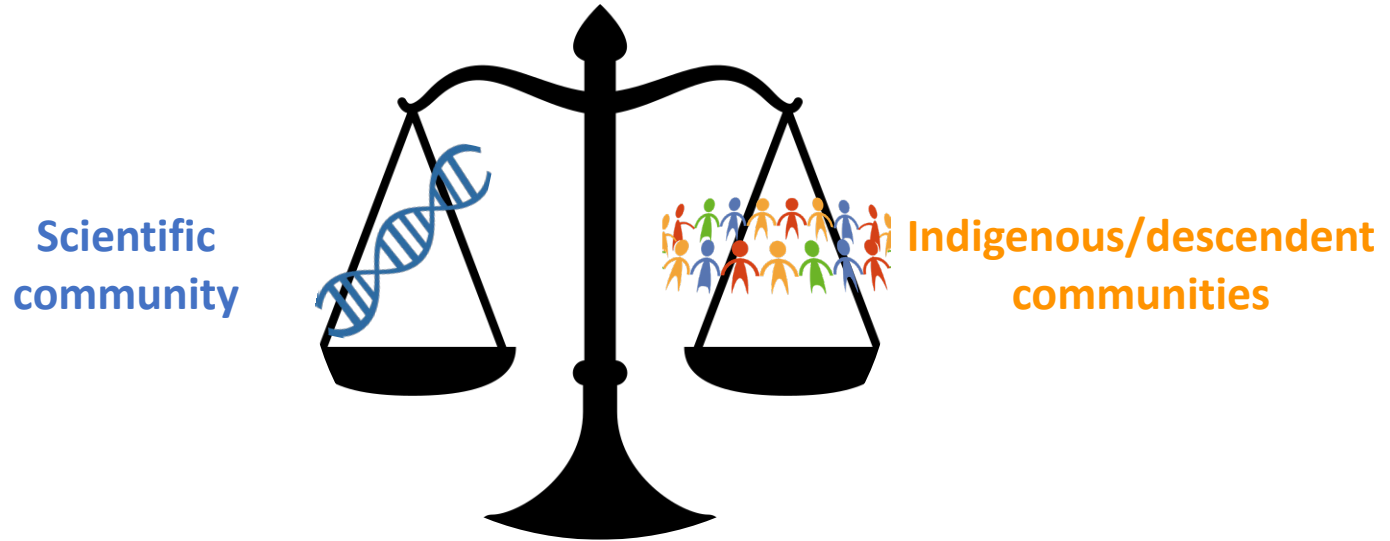
Using population descriptors in genetics and genomic research

An ad hoc committee to review and assess existing methodologies, benefits, and challenges in the use of race and ethnicity and other population descriptors in genomics research.



Using Population Descriptors in Genetics and Genomics Research

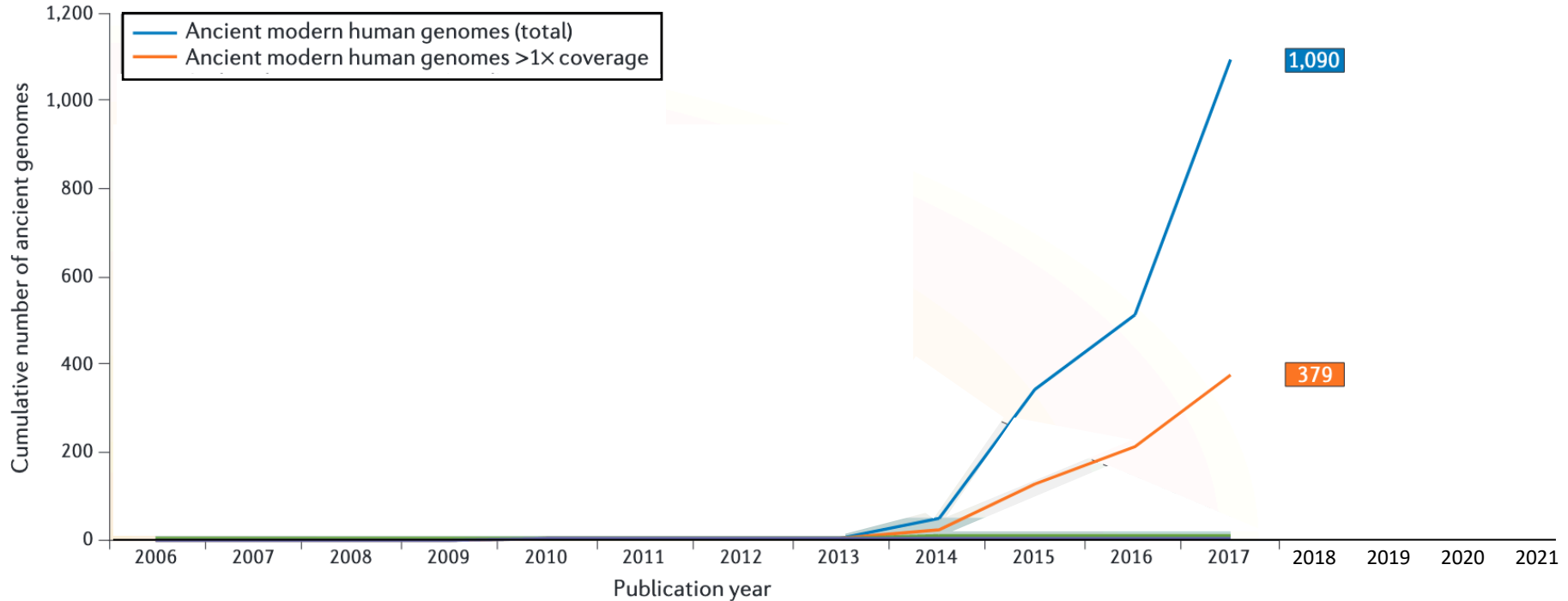
A New Framework for an Evolving Field



*“There cannot be a single standard when it comes to the ethics of anthropological research, or even of aDNA research in anthropology. Because aDNA research generally falls outside the domain of institutional review boards, **we must regulate ourselves...**”*
-Kaestle & Horsburgh, 2002

ANCESTORS and ANCIENT ONES are excluded from biomedical ethics regulatory oversight

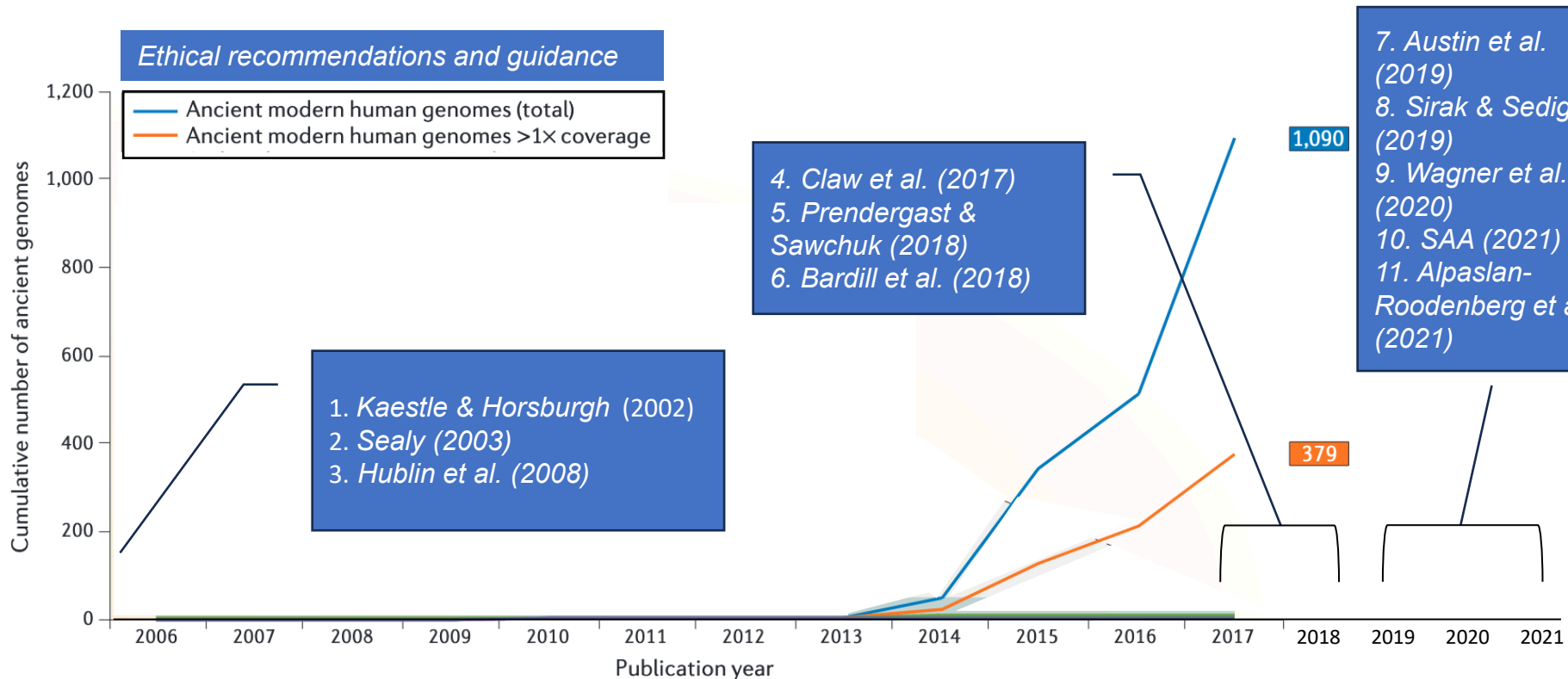
Ongoing ancient DNA explosion



Indigenous concerns about Ancestors in Research

- *Cultural and ethical concerns*
- *Adequate community consultation*
- *Appropriate research directions*
- *Acceptable risk*
- *Research outcomes*
- *Long-term data storage*
- *Biological sample stewardship*

Ongoing ancient DNA explosion



Guidance on ethics in ancient DNA research

1	Kaestle & Horsburgh (2002)
2	Sealy (2003)
3	Hublin et al. (2008)
4	Claw et al. (2017)
5	Prendergast & Sawchuk (2018)
6	Bardill et al. (2018)
7	Austin et al. (2019)
8	Sirak & Sedig (2019)
9	Wagner et al. (2020)
10	Society for American Archaeology (2021)
11	Alpaslan-Roodenberg et al. (2021)

The ethical, legal, and social concerns within human paleogenomics are “likely to become more, rather than less, important or complicated”

- O’Rourke et al., 2000

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Tensions between stakeholder
groups

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Professional organization sponsorship

American Society of Human Genetics

Society for American Archaeology

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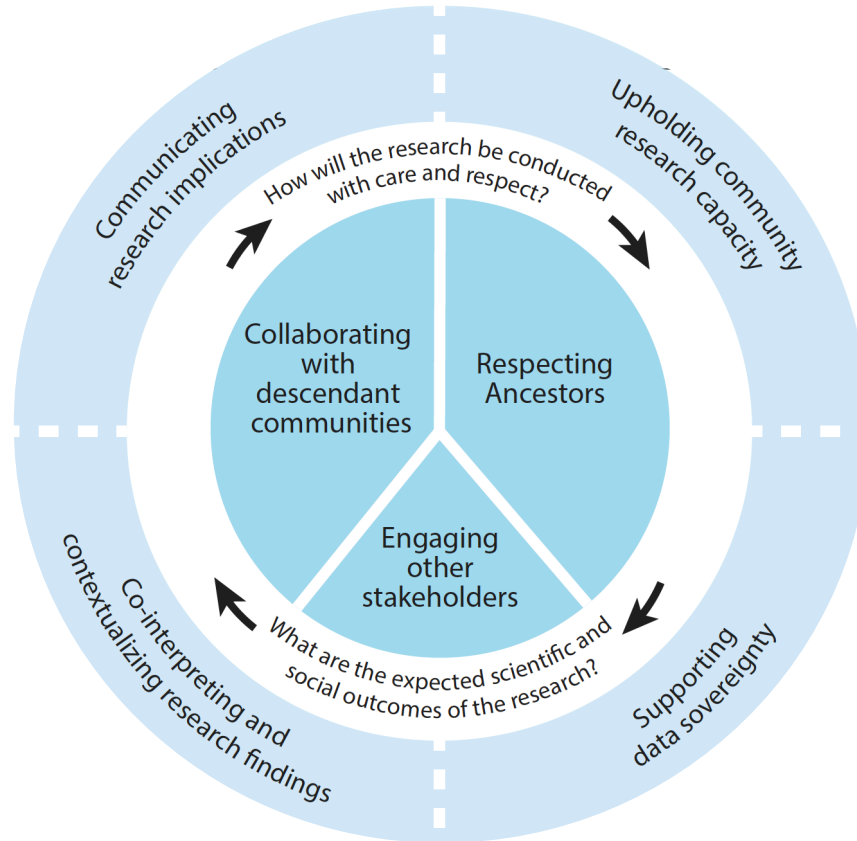


Guidance on ethics in ancient DNA research

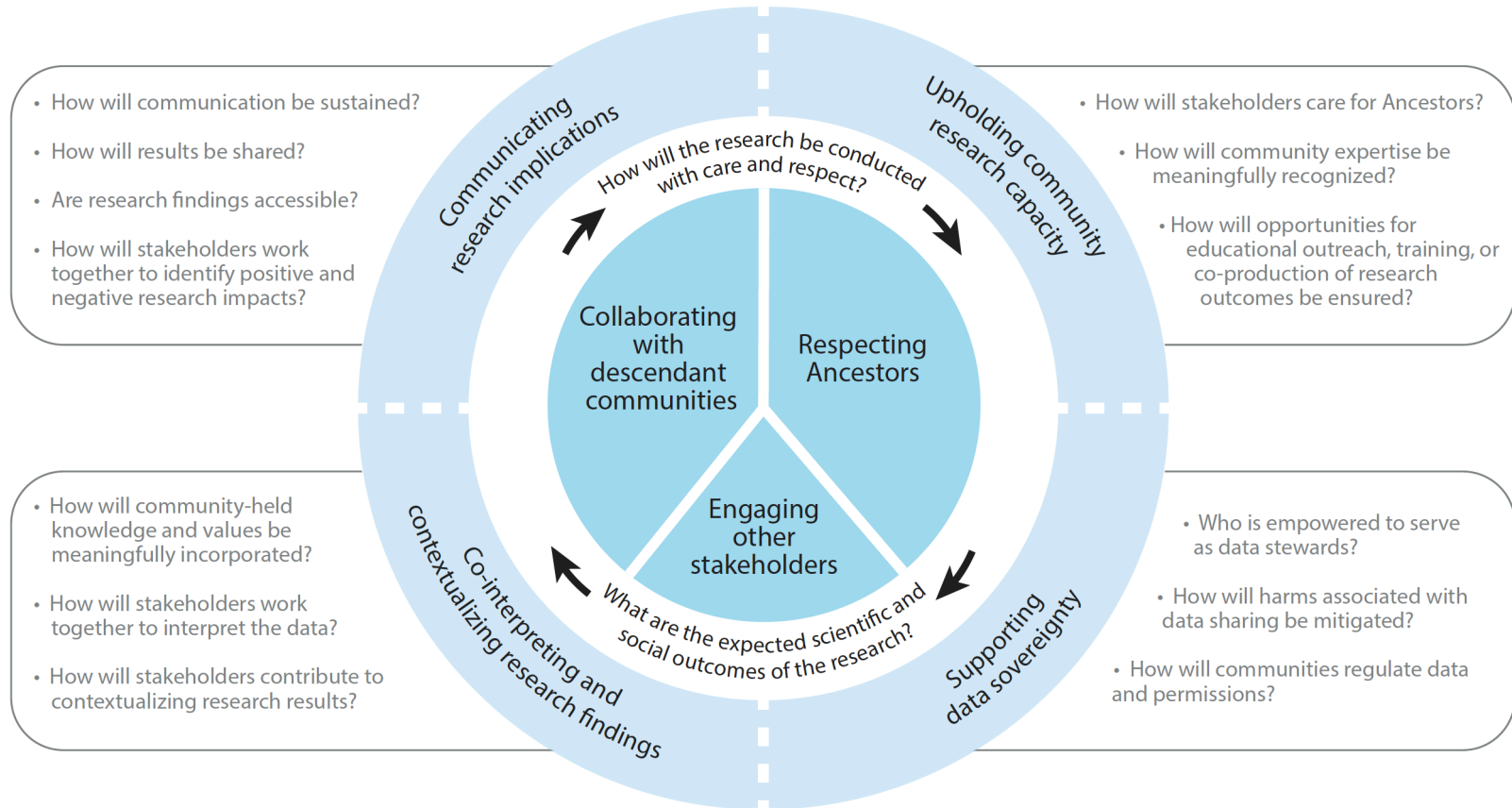
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Ethical ethos for paleogenomic research

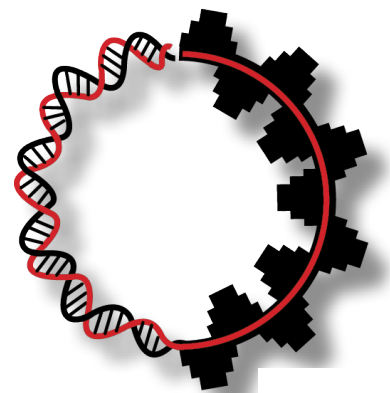


Ethical ethos for paleogenomic research



Ethics and Best Practices

- We must ensure that genomics/paleogenomics is not used to further disenfranchise any Peoples
- Instead, it can be used to empower and support Indigenous communities to govern and benefit.
- A shift toward Community-based Genomic Research is needed
- As with living humans, one should prioritize respect, beneficence, and justice for Ancestors.
- Guidelines and best practices are becoming more sophisticated and complex, and need to be considered in every situation



Ahéhee' (Thank you)

Claw lab members: Carissa Sherman, Leah Nez, Amber Nashoba, Kaja Aagaard, Crystal Musser, William Moreno

Tribal partners:

Southcentral Foundation, Strong Heart Study, Confederated Salish and Kootenai tribes, Navajo Nation, Metlakatla First Nations, individual tribal members

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Fernando Villanea

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Ripan Mahli

SING Consortium

NWA-PGRN

UCLA

Nanibaa' Garrison

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