

Inclusion of Indigenous Peoples in Genetic and Genomics Research



Ethical and Regulatory Aspects of Clinical Research

NIH Department of Bioethics

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University of Colorado
Anschutz Medical Campus



The traditional homelands of the Apache, Ute, Cheyenne, Comanche, and Arapahoe tribes, and is now home to many other Indigenous peoples today

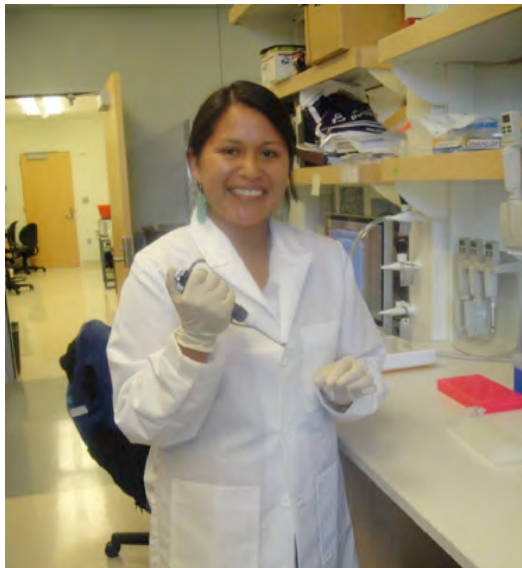
Talk Overview

- My journey in academia and motivations
- Indigenous ways of knowing
- Precision pharmacogenomics and CYP450 enzymes
- Moving toward Community-based research
- Conclusion & Future directions

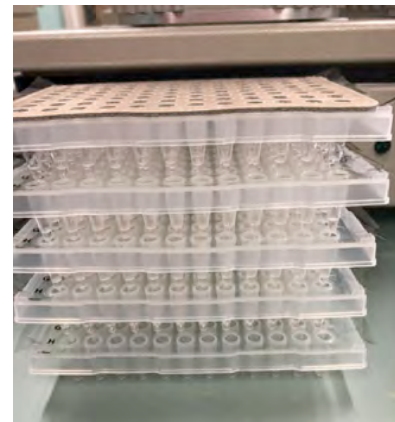
From the Rez to a PhD and beyond



Finding my passion in research



```
R - toyQNorm.R (/Programs/R) - VIM - vim - 80x29
1 # http://www.johndcook.com/normals_cdf_inverse.html
2 #
3 toyQNorm <- function(p){
4   if (class(p)!="numeric"){
5     stop("Input must be numeric or numeric vector")
6   }
7   if (p[1] < 0 || p[1] > 1){
8     stop("Input must be between 0 and 1")
9   }
10
11   rationalApprox <- function(t){
12     c <- c(2.53237, .000001, .000000)
13     d <- c(1.432780, .109209, .001300)
14     return(1 - (c[1] + (c[2] + c[3]*t*log(t))/
15               (1 + (d[1] + (d[2] + d[3]*t*log(t))))))
16   }
17
18   getInvNorm <- function(p){
19     if (p[1] < 1){
20       return(rationalApprox(sqrt(1-2*log(p))))
21     } else {
22       return(rationalApprox(sqrt(-2*log(1-p))))
23     }
24   }
25
26   return(sapply(p, getInvNorm))
27 }
toyQNorm.R
```



Disconnect between 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.

Inbreeding Coefficients of the Ramah Navaho Population

J.N. SPUHLER¹ AND CLYDE KLUCKHOHN²

A STUDY OF THE BLOOD GROUPS AMONG THE AMERICAN INDIANS¹

CLARA NIGG *J. Immunol.* 11

From the Department of Bacteriology, University of Kansas, Lawrence

Received for publication August 1, 1925

In 1923 Coca and Deibert (1) studied the percentage distribution of the four Landy blood groups among the four American Indian races. The Navajo Indian is of Mongolian type, and the percentage of group I blood is 86.2 per cent, group II 12.1 per cent, group III 2.1 per cent, group IV 0.0 per cent.

Hereditary Nonpolyposis Colorectal Cancer in a Navajo Indian Family

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



Concerns about participation in research

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

Focusing on questions that matter to my communities

- Focus on pharmacogenomics, bioethics, and community engagement
- PGx is the foundation of precision medicine
- Drew to research area because of traditional medicines and herbal remedies



Navigating an unequal playing field in STEM

- Great sacrifices despite privileged experiences
 - Being away from home and family
 - Language/culture/traditions
- Emotional distress
 - Self-doubt and uncertainty
 - Imposter Syndrome
 - Pressure, stress, loneliness
- Unequal networks, training, and expectations



<http://www.thebigidea.co.uk/cost-gender-inequality/>

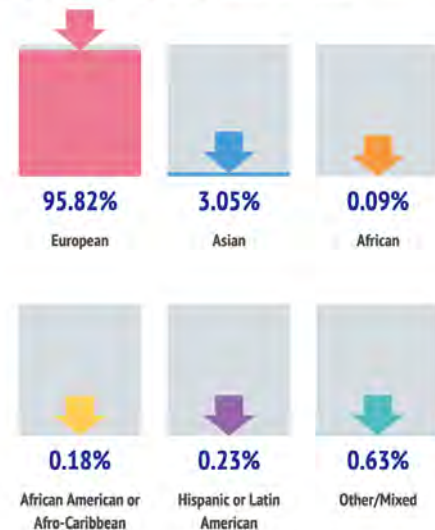
Changing the academy

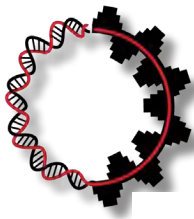
My research program is broadly motivated by:

- 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

Version 1.0.0. Last check for data: 2022-01-18 09:34:08 .





Claw Indigenous Genomics and Ethics Laboratory

Pharmacogenomics research in diverse populations

1. Nicotine metabolism personalized medicine



Strong Heart Study



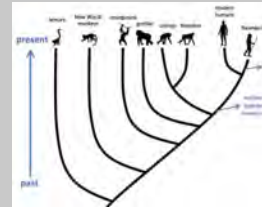
Southcentral
Foundation



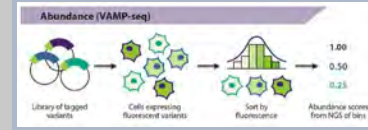
2. Cytochrome P450 Diversity



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



7. Impacts and mentorship of Indigenous trainees



Bringing my culture into the laboratory



Home > News > Blessing Ceremony Opens New Genomics and Health Research Lab

Blessing Ceremony Opens New Genomics and Health Research Lab

Researcher wants to ensure she shows respect for the Native Americans with whom she plans to collaborate

February 18, 2020: <https://news.cuanschutz.edu/>



Home > News > CU Professor Draws on Indigenous Roots in Approach to Research and Mentoring

CU Professor Draws on Indigenous Roots in Approach to Research and Mentoring

November 21, 2022:
<https://news.cuanschutz.edu/dbmi/>

Indigenous people have always been scientists



<https://www.yesmagazine.org/>



<https://www.iied.org>

There are multiple ways of knowing

- Traditional knowledge, Traditional Ecological Knowledge, Indigenous knowledge
- These are passed on through oral and written knowledge, ceremonial practices, beliefs, and general knowledge from our ancestors
- Indigenous Science

91-3 | SUMMER 2019 | INDIGENOUS SCIENCE



HUMAN BIOLOGY

THE OFFICIAL PUBLICATION OF THE AMERICAN ASSOCIATION OF ANTHROPOLOGICAL GENETICS

[illegible]

- 2010 U.S. Census Bureau Map of American Indians and Alaska Natives in the United States

Personalized Medicine - Pharmacogenetics

Personalized or Precision Medicine is an emerging field that uses an individual's genetic profile, environment, and lifestyle to aid in the diagnosis, prevention, and treatment of diseases.

BioMe™ BioBank Program

Your History Is Our Future™



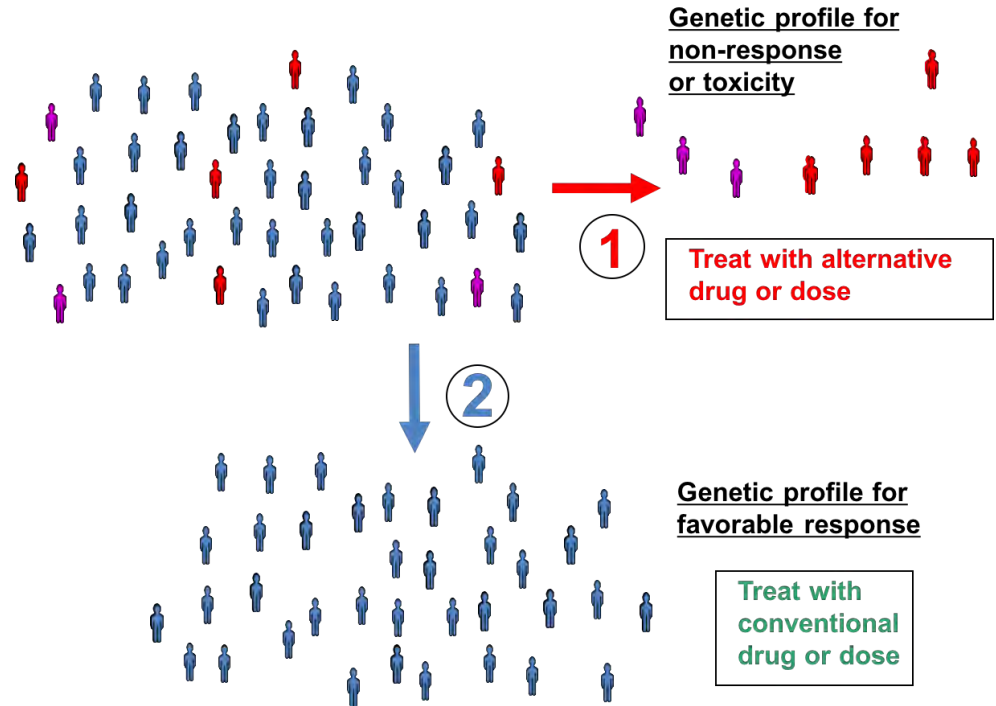
Colorado Center for Personalized Medicine

Biobank

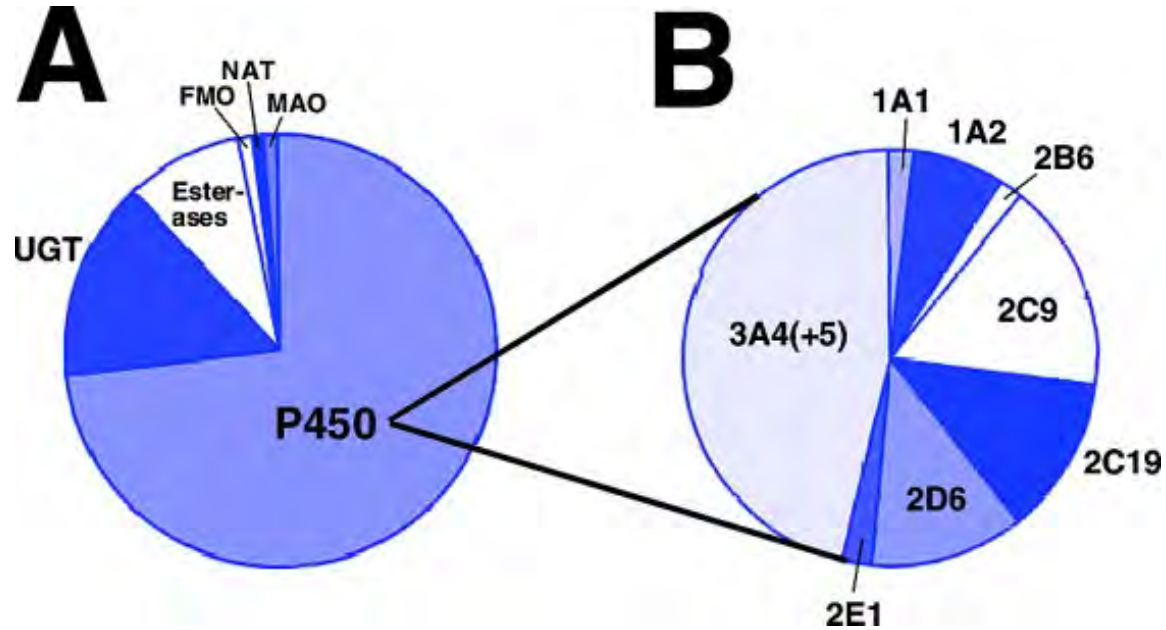
Pharmacogenomics is the foundation for personalized medicine.

Diverse Populations and Promise of Pharmacogenomics

- 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



Cytochrome P450 Enzymes and Drug Metabolism



Human Genetic Variation

Single Nucleotide Variants (SNVs)

...AG**C**G... → ...AG**T**G

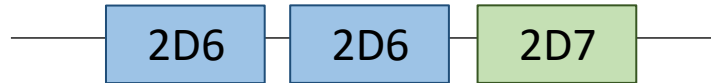
Insertions and Deletions (Indels)

...AGCG... → ...AGC**A**G...

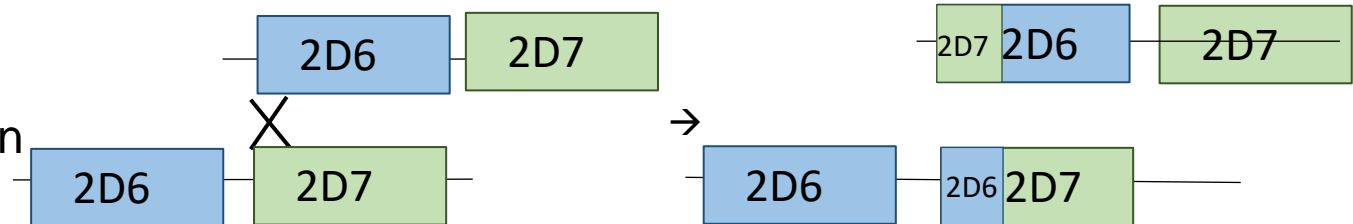
...AGCG... → ...AG-**G**...

Structural Variations

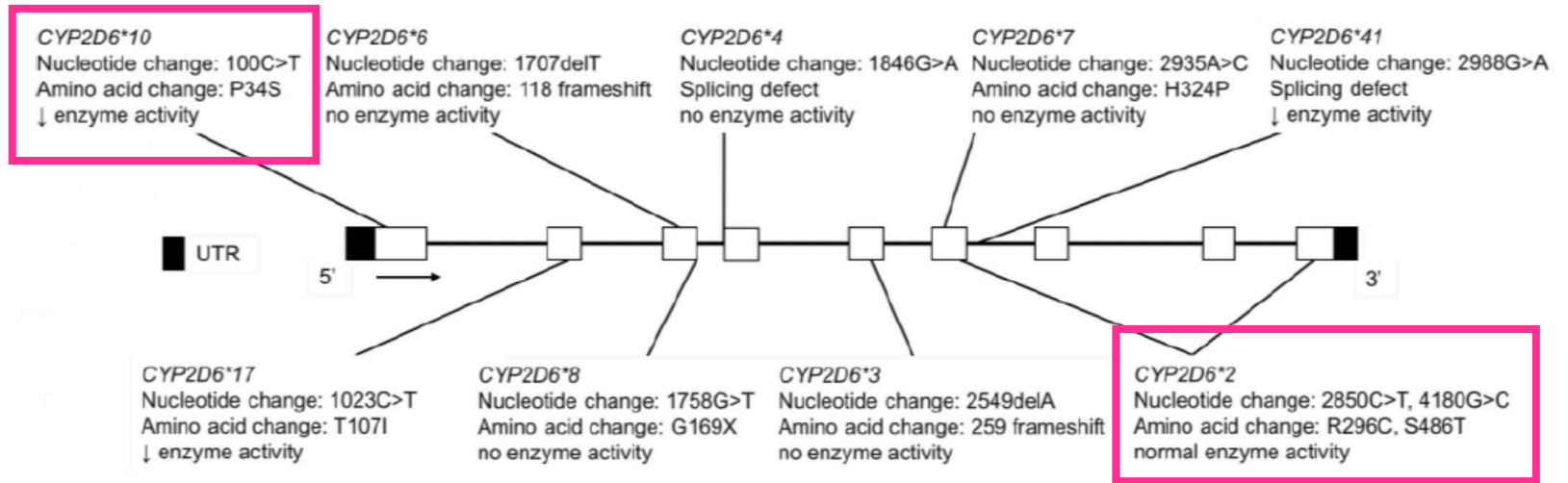
- Copy Number Variation



- Non-Allelic Homologous Recombination



Pharmacogenetics Star Alleles



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

Genomic variation in Isolated Human Populations

| Geographical Region/Ethnicity | Frequency CYP2C19 PM (%) |
|---------------------------------------|--------------------------|
| Papua New Guinea | 44 |
| Vanuatu | 71 |
| Aboriginal Australians | 26 |
| Melanesia Average | 50 |
| Samoan, Tongan, Cook Islander, Niuean | 13 |
| Samoan, Tongan, Fijian, Cook Islander | 4 |
| Maori | 7 |
| Polynesia Average | 8 |



- Founder effect
- Selective pressures
- Genetic drift

A Call to Action

- There is a bias in who is represented in genomic and pharmacogenomic research
- The lack of Indigenous PhDs and PIs in biomedical sciences is shocking
- Increasing the number of Indigenous scholars into the genomic workforce represents powerful and sustained way of affecting changes
- Working with communities as partners is one way to move forward

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

Moving toward Community-based Genomic Research

**“IF YOU’RE GOING TO
WORK WITH INDIGENOUS
COMMUNITIES ON
GENETICS, YOU HAVE
TO BE WILLING TO MAKE
LIFELONG RELATIONS.”**

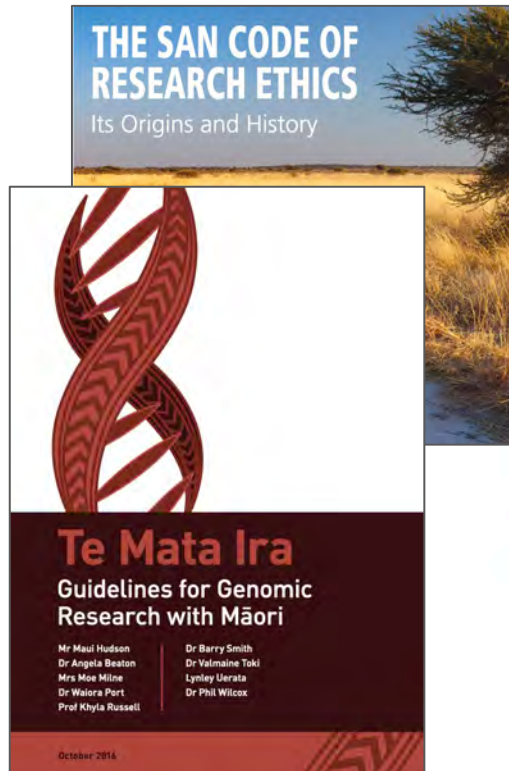
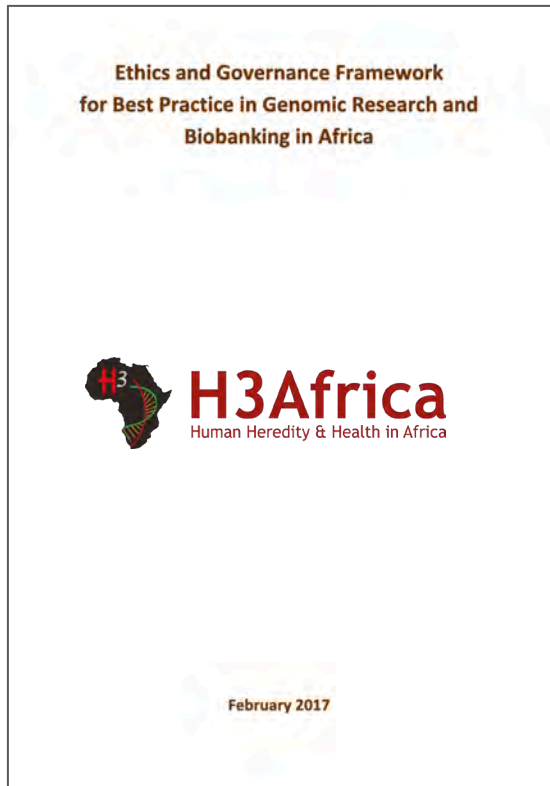
—Kim TallBear,
University of Alberta



**CBPR: A
collaborative
approach to
research**

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

Recent advancement of community-specific research ethics guidelines

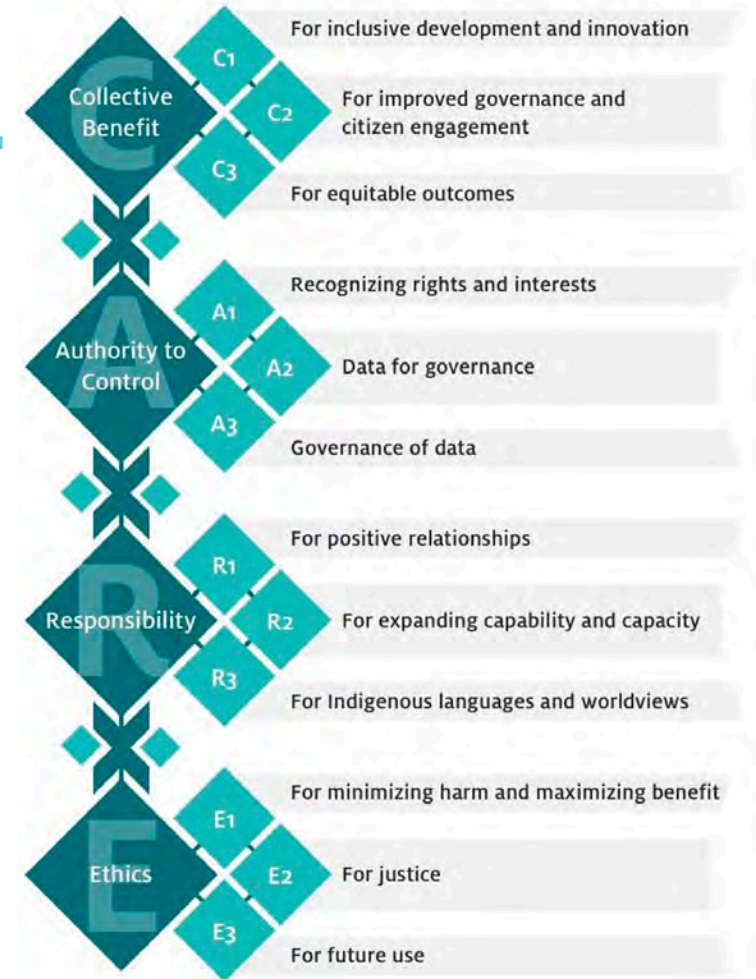


Enhancing ethical genomic research with Indigenous



Indigenous genomic data sovereignty and governance in precision medicine

- 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

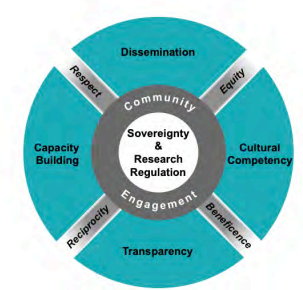
Enhancing ethical genomic research with Indigenous communities

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



Sovereignty and Research Regulations

- The study acknowledges tribal sovereignty
- Both individuals and tribal groups must consent
- Integration of urban and rural AIANs

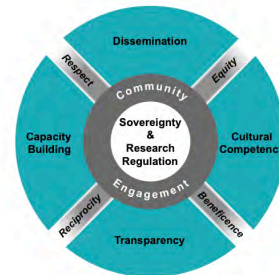


Pharmacogenetic Research in Partnership With AIAN Communities (NWA-PGRN)

| NWA-PGRN Community partner | Oversight and approval process |
|--|--|
| Southcentral Foundation (SCF) | SCF Oversight Committee and Alaska Area IRB |
| Yukon-Kuskokwim Health Corporation (YKHC) | UA-Fairbanks IRB, YKHC Medical Director, YKHC Human Studies Committee, Exec. Board |
| Confederated Salish and Kootenai Tribes (CSKT) | UM IRB, CSKT Tribal Health, CSKT Tribal Council |

Community Engagement

- Build long-term relationships
- Engagement plans or community advisory groups



Partnership with the Confederated Salish and Kootenai Tribes:

Establishing an Advisory Committee for Pharmacogenetic Research

Chelsea T. Morales, LeeAnna I. Muzquiz, Kevin Howlett, Bernie Azure, Brenda Bodnar, Vernon Finley, Tony Incashola, Cheryl Mathias, Cindi Laukes, Patrick Beatty, Wylie Burke, Mark A. Pershouse, Elizabeth A. Putnam, Susan Brown Trinidad, Rosalina James, and Erica L. Woodahl

Enhancing ethical genomic research with Indigenous communities

Cultural Competency

- Integration of cultural and traditional knowledge
 - Views and perspectives of tribal members taken into consideration in study goal and design
 - Review by tribal IRB and community researchers



Exploring stakeholder perceptions before embarking on a genetic project

- **Qualitative study** of patients, providers, and healthcare system leaders' perceptions regarding pharmacogenetics use to guide tobacco cessation treatment at SCF.
- **Results:** Supported tobacco research, should collaborate with existing tribal programs, return of results

Enhancing ethical genomic research with Indigenous communities

Transparency

- Consent and process shared in detail
- Storage of data and samples
- Future use of data and samples



Example of language in an informed consent.

USE AND OWNERSHIP OF SAMPLES: Your DNA and blood samples belong to you. Your blood and DNA will be used in this study of conditions related to blood clotting and stroke. Samples will be stored for the duration of this study at the University of Tribal Nations. Samples will be sent to the Indigenous Peoples' University for analyses without any identifying information. All of your samples are stored with only an identification number, and your name does not appear on your samples. This research does not involve giving treatment or other medical procedures as a part of the study. It only involves using information and samples obtained from the participants to explore factors related to blood clotting among indigenous people. At the end of the study, you may choose to have your left over blood samples stored at the International Indigenous Biobank, which has a long history of storing samples and managing them for health research for the benefit of indigenous people

Enhancing ethical genomic research with Indigenous communities

Capacity building

- Diversifying the workforce
- Collaborative analysis
- Co-authorship with researchers and communities



Summer internship for Indigenous peoples in Genomics (SING)

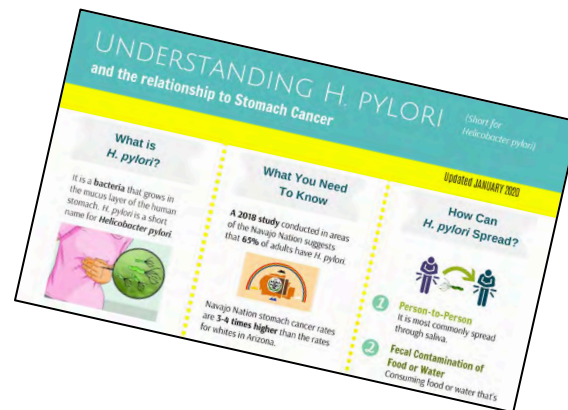
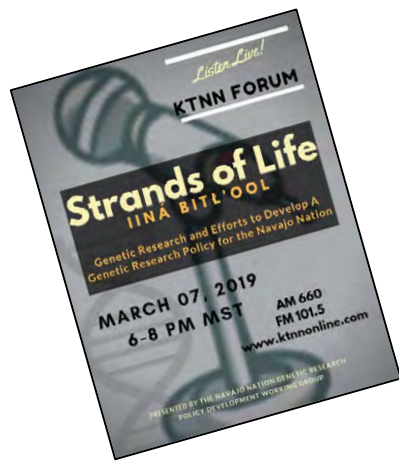
- Hands-on training in genomics
- ELSI discussions
- Decolonizing Science
- Indigenous Knowledge



Enhancing ethical genomic research with Indigenous communities

Distribution of findings and knowledge

- Publish only aggregate data and use geographical locations, no tribal identification
- Make pamphlets, newsletters, and presentations in addition to peer-reviewed publications



Future of pharmacogenomics research for Indigenous People

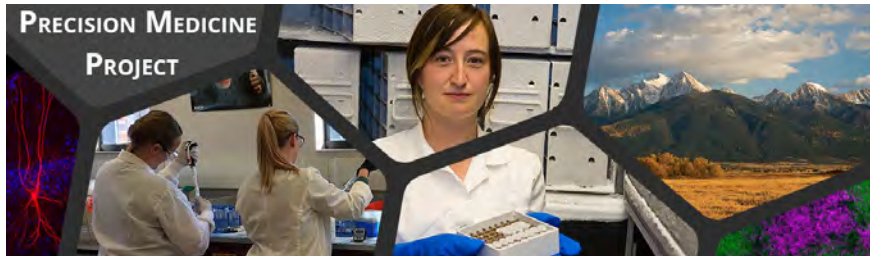


How Indigenous Scientists Are Taking Control of Their Data

Next-generation sequencing is helping Native nations with sovereignty and genetic research



Native BioData Consortium (NBDC) is the first nonprofit research institute led and staffed by Indigenous scientists and tribal community members in the US.



Dorfman et al., *Pharmacogenomics*, 2014; <http://umt.edu/pmp>

Genomic Innovator Awards



Katrina Claw, Ph.D.
University of Colorado, Denver

Focus on understanding individual variation in drug response and provide guidelines for applying personalized medicine in American Indian and Alaska Native (AIAN) communities.

#Clawlab
#IndigenousGenomics
@drkatclaw

Implementing community-engaged pharmacogenomics in Indigenous communities

[Katrina G. Claw](#) , [Casey R. Dorr](#) & [Erica L. Woodahl](#)

[Nature Communications](#) **15**, Article number: 920 (2024) | [Cite this article](#)

1224 Accesses | 9 Altmetric | [Metrics](#)

Innovative pharmacogenomic approaches (genetic variation related to medication response) are needed to reduce disease and disparities in Indigenous communities. We support community-based pharmacogenomics research, inclusive of Indigenous values and priorities, to improve the health and well-being of Indigenous peoples.



Pharmacogenomics in American Indian and Alaska Native Communities

- Holistic and community-based approach

It is important “for researchers to understand there is an intersection between health, research, and spirituality” in AIAN health”

-Traditional Medicine Summit Report, THRO

Summary & Future Directions

- Knowledge processes can come in many forms
- The inclusion of an Indigenous perspective is important in research
- A shift toward Community-based Genomic Research and Holistic healing is needed
- We must ensure that Indigenous communities govern and benefit from genetic and genomic research

Ahéhee' (Thank you)

Claw lab members: Carissa Sherman, Crystal Musser, Kendra Ferrier, Shalom Guitierrez, Jack Staples, Matthew Blake

Past lab members: Leah Nez, Amber Nashoba, Kaja Aagaard, Tadeusz Wroblewski, Suzanna Garcia-Mota

Tribal partnerships:

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

CU Boulder

Fernando Villanea
Luke Evans

UCLA

Nanibaa' Garrison
Luke Nez

U. Illinois

Ripan Mahli

U. Montana

Erica Woodahl
Shayna Killam

PrIME

SING

NWA-PGRN

Claw Indigenous
Genomics and Ethics
Laboratory



at the University of Colorado Anschutz Medical Campus

