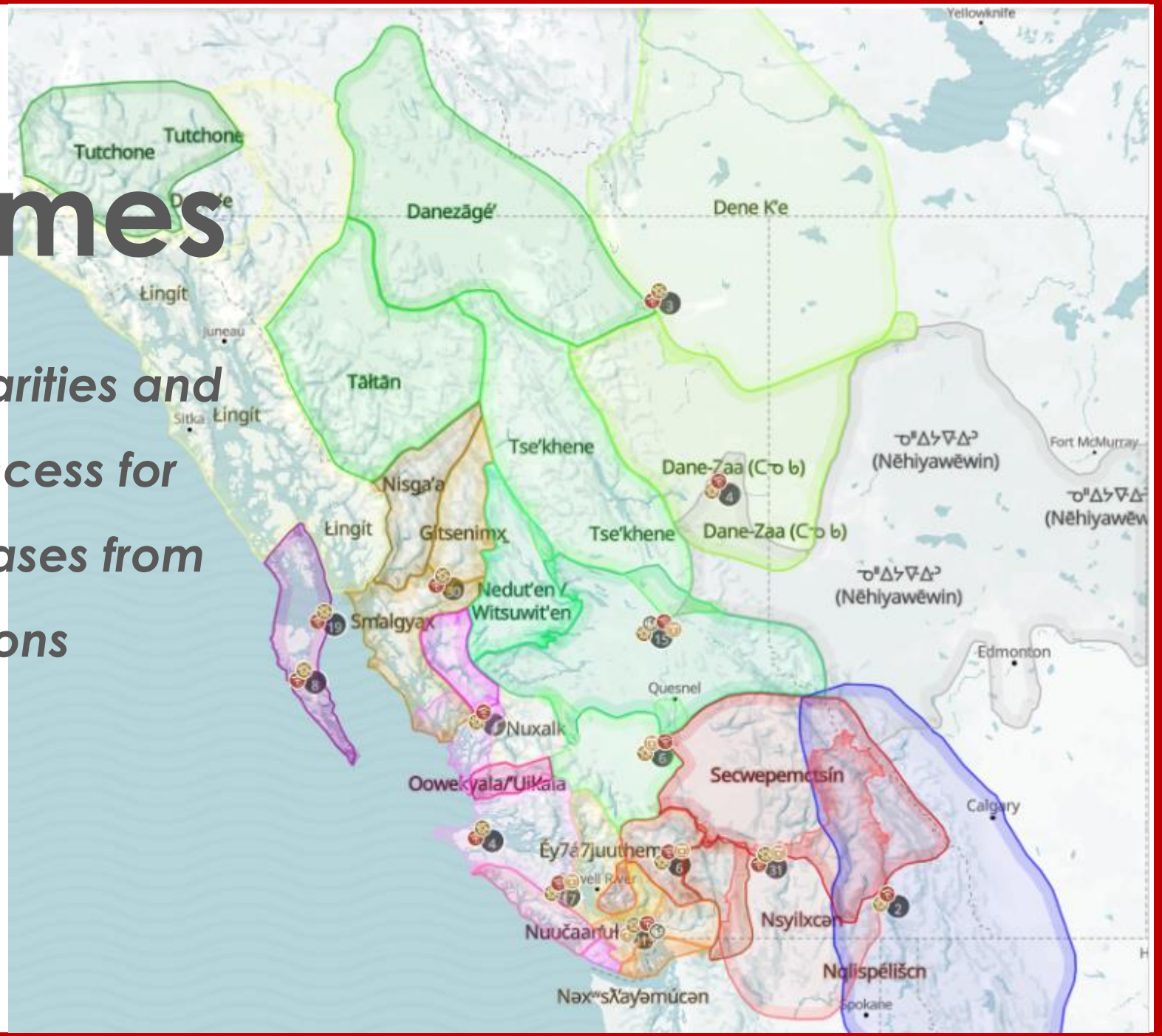
Silent Genomes

Reducing health care disparities and improving diagnostic success for children with genetic diseases from Indigenous populations



Overview Today

- What is the Silent Genomes Project?
- What needs to be done to ensure equity in genetic diagnosis for Indigenous people?
- Building an Indigenous Background (DNA) Variant Library
- How can First Nations people of BC get involved?

First Nations Health Authority
Health through wellness

ASSEMBLY OF FIRST NATIONS

MÉTIS NATIONAL COUNCIL
RALLIEMENT NATIONAL DES MÉTIS

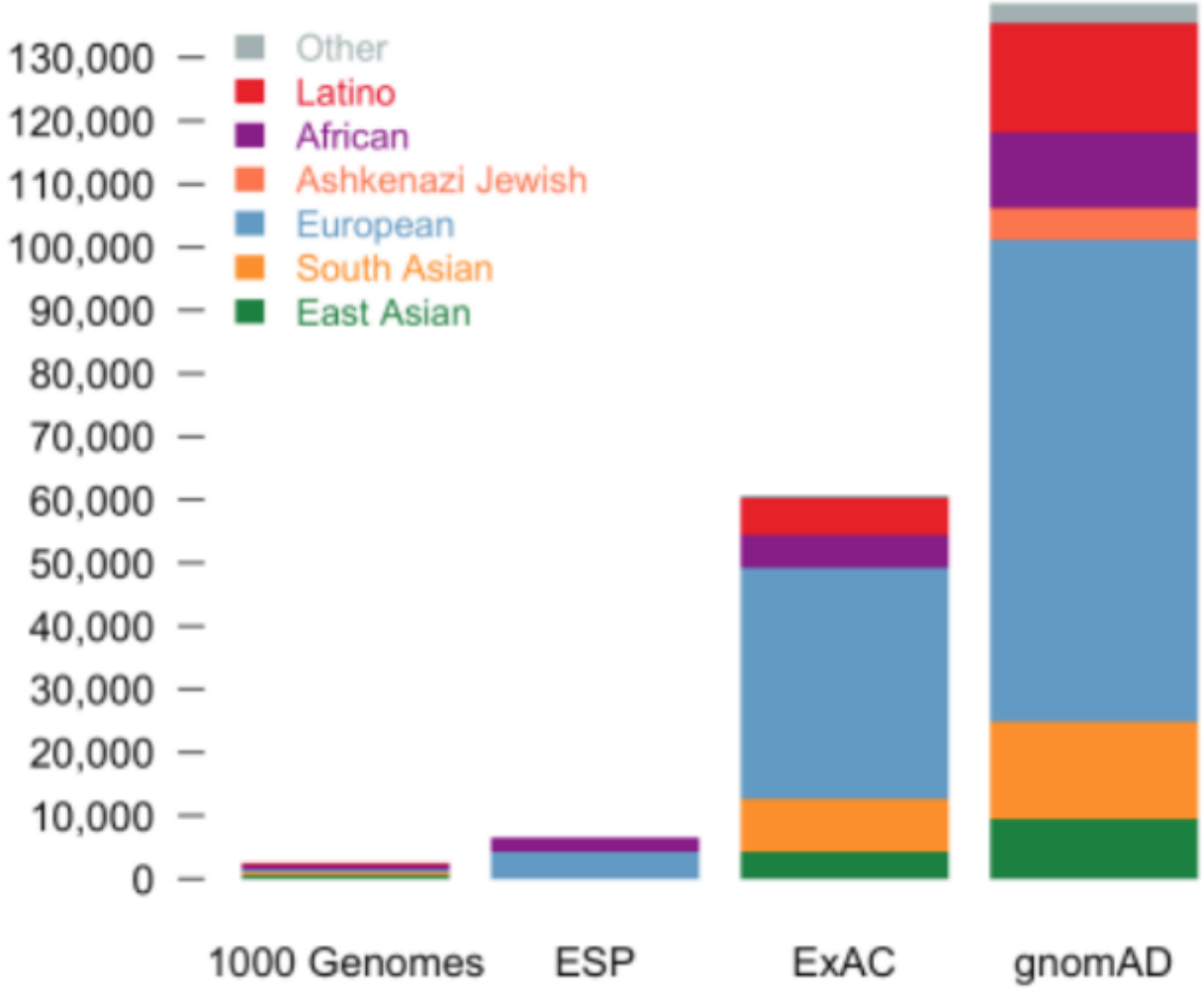
Equity

"The genomic health divide must be kept in check and ultimately bridged through equitable economic investment, clinical research, and provision and use of genomic services and technologies globally
http://www.who.int/genomics/healthdivide/en/

Current Inequity

Data from persons identified as Indigenous are starkly absent from reference databases used for genomic diagnosis.

Therefore access to precision diagnosis is limited - increasing health disparity



Access to Rare Disease Diagnosis In Indigenous Populations: Where do we start?

1 in 12 people have a rare disease, and a large proportion of those will have a genetic basis. Based on population estimates, >100,000 Indigenous people in Canada will be affected

Pedersen et al 2016

With Indigenous partners – nationally, regionally & on a community level - we are:

- **building** a governance model for genomics research;
- **offering genomic diagnosis** to Indigenous Children across Canada;
- **planning together,** the necessary steps for development of an Indigenous Background Variant Library (IBVL);
- **assess the effectiveness** of the IBVL and the cost to the system, with and without.

First Nations Health Authority
Health through wellness

ASSEMBLY OF FIRST NATIONS

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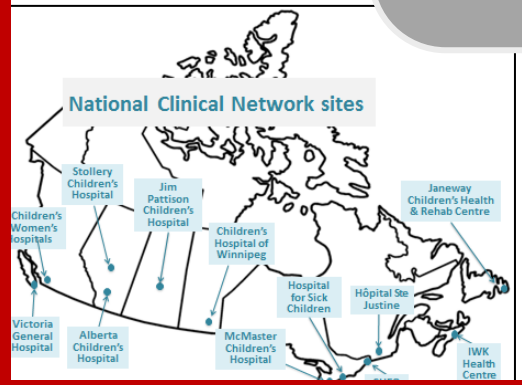
MÉTIS NATIONAL COUNCIL
RALLIEMENT NATIONAL DES MÉTIS

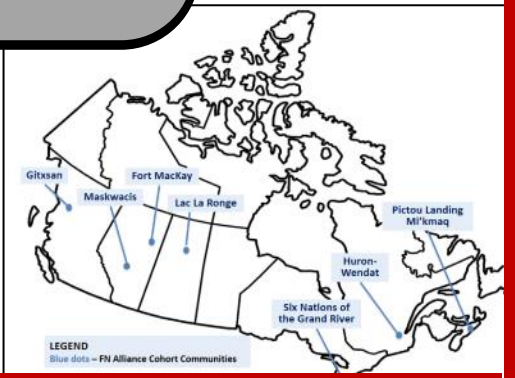
ACTIVITY 1:
First Nations, Inuit And Métis Engagement, Governance, and Capacity Building

ACTIVITY 2:
Precision Diagnosis of Indigenous Children with Genetic Disorders

ACTIVITY 3:
Build an Indigenous Background Variant Library

ACTIVITY 4:
Economics of Genomic Diagnosis in Indigenous Populations





RIGHTS AND SAFE GOVERNANCE TOOLS

- **Tri-council Policy Statement (TCPS2)- Chapter 9: Research Involving the First Nations, Inuit and Métis Peoples of Canada**
- **United Nations Declaration of the Rights of Indigenous Peoples (UNDRIP):**
  - Article 4, 18, 19, 24, 31 (focus on self- determination, decision making, and FPI consent)
- **Truth and Reconciliation Commission: Calls to Action (TRC-CTA):**
  - CTA 18-24 (specific to health)

- **Ownership, Control, Access, and Possession (OCAP):**
  - The First Nations principles of OCAP® are a set of standards that establish how First Nations' data should be collected, protected, used or shared.
- **DNA on Loan**
  - Considering DNA to be 'on loan' to the researcher for the purpose of the research for which consent was obtained


Community Genetics

Community Genet 2006;9:153–160
DOI: 10.1159/000092651

DNA on Loan: Issues to Consider when Carrying Out Genetic Research with Aboriginal Families and Communities

Laura Arbour[a] Doris Cook[b]

[a]University of British Columbia, Vancouver, and [b]Canadian Institutes of Health Research, Ottawa, Canada

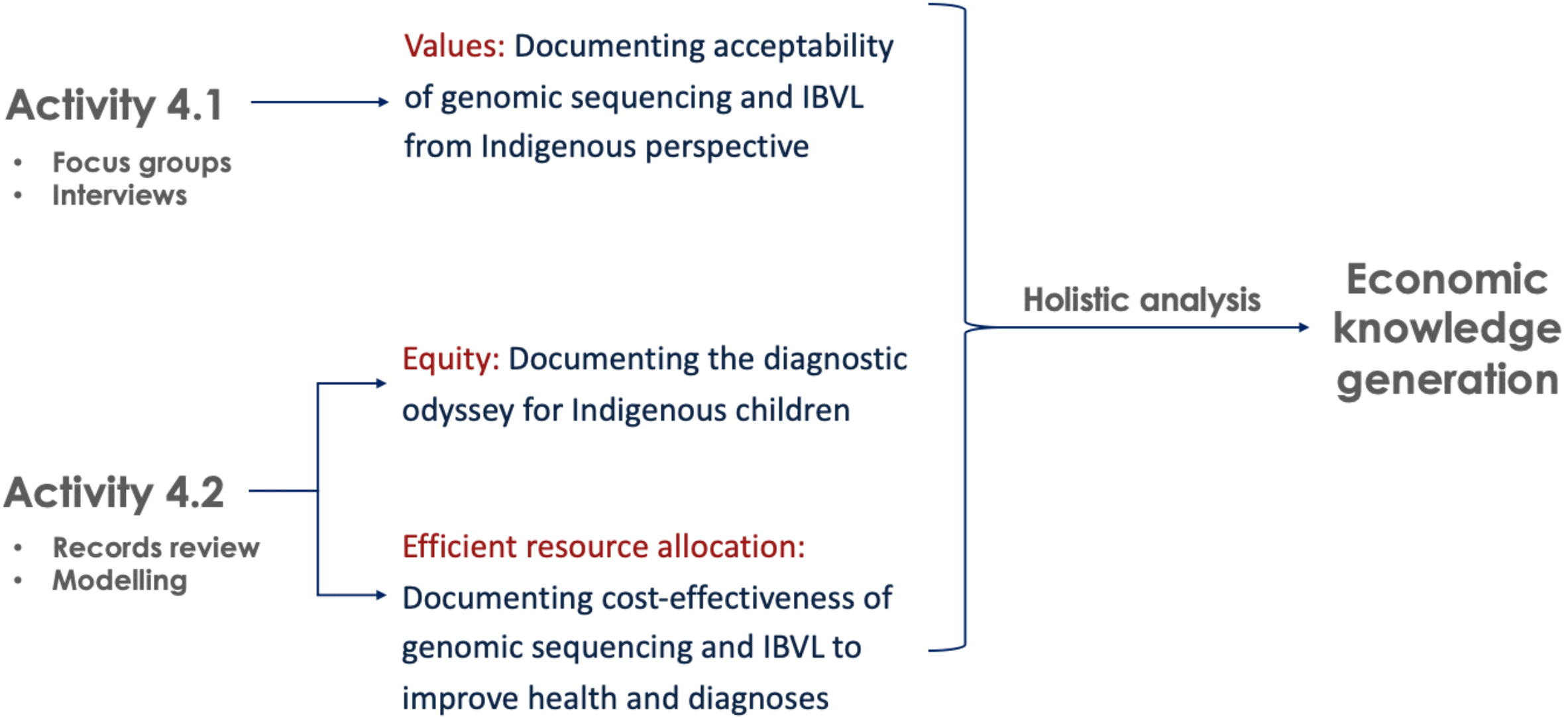
Guidance

"To us, any part of ourselves is sacred, it's not just DNA, it's part of a person, it is sacred, with deep religious significance. It is part of the essence of a person."

Frank Dukepoo, First Hopi Ph.D.

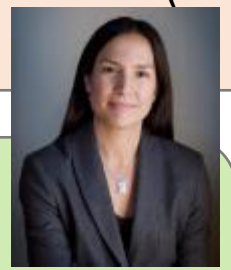
Interview, San Francisco Chronicle, 1998

Activity 4: ECONOMICS OF GENOMIC DIAGNOSIS IN INDIGENOUS POPULATIONS



END USERS / PARTNERS

Assembly of First Nations
Inuit Tapiriit Kanatami (ITK)
Métis National Council (MNC)
First Nations Health Authority (FNHA)
National FN Alliance Working Group
BC Ministry of Health
Nunavut Department of Health
National Clinical Network (NCN)




INDIGENOUS HEALTH

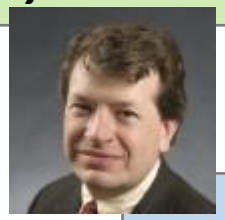
Nadine Caron (UBC/UNBC)
Jeff Reading (SFU)
Evan Adams (FNHA)
Sonia Isaac Mann (FNHA)
Nanibaa' Garrison (UW)
Laura Arbour (UBC/UVic)
Sonia Anand (McMaster)

MOLECULAR GENOMICS

Marco Marra (UBC)
Maja Tarailo-Graovac (UC)
Anna Lehman (UBC)

BIOINFORMATICS

Wyeth Wasserman (UBC)



COMMUNITY INFORMED ECONOMICS

Dean Regier (UBC/BCCA)
Morgan Ehman (UBC/BCCA)
Michael Burgess (UBC)
Nanibaa' Garrison
Anne-Marie Laberge (UM)

CLINICAL GENOMICS

Anna Lehman (UBC)
Maja Tarailo-Graovac (UC)
Laura Arbour (UBC/UVic)
Francois Bernier (UC)
National Clinical Network


COMMUNITY and PATIENT EDUCATION

Sarah McIntosh (GC)
Laurie Montour (CEC)
Brittany Morgan (CEC)
Karen Jacob (GC)

POPULATION GENOMICS

Ripan Malhi (UI)
Simon Gravel (McGill)

INTERNATIONAL INDIGENOUS GENOMICS ADVISORY

Nanibaa' Garrison (USA/Wash)
Kim Tallbear (Canada/AB)
Maui Hudson (New Zealand)
Phil Wilcox (New Zealand)
Ngiare Brown (Australia)
Keolu Fox (USA/Hawaii)
Maile Taualii-Chair
(USA/Hawaii)

Elders, Indigenous organization partners, Alliance members, IIGAC, staff & advisors

Silent Genomes Project team and our partners at the Gathering Ceremony, July 2018

International Indigenous Genomics Advisory Committee

Ngiare Brown M.D., Yuin Nation, Australia

Nanibaa' Garrison, Ph.D., Dine

Maui Hudson, Ph.D., Maori, New Zealand

Maile Tauali', Ph.D.
Chairperson
Native Hawaiian

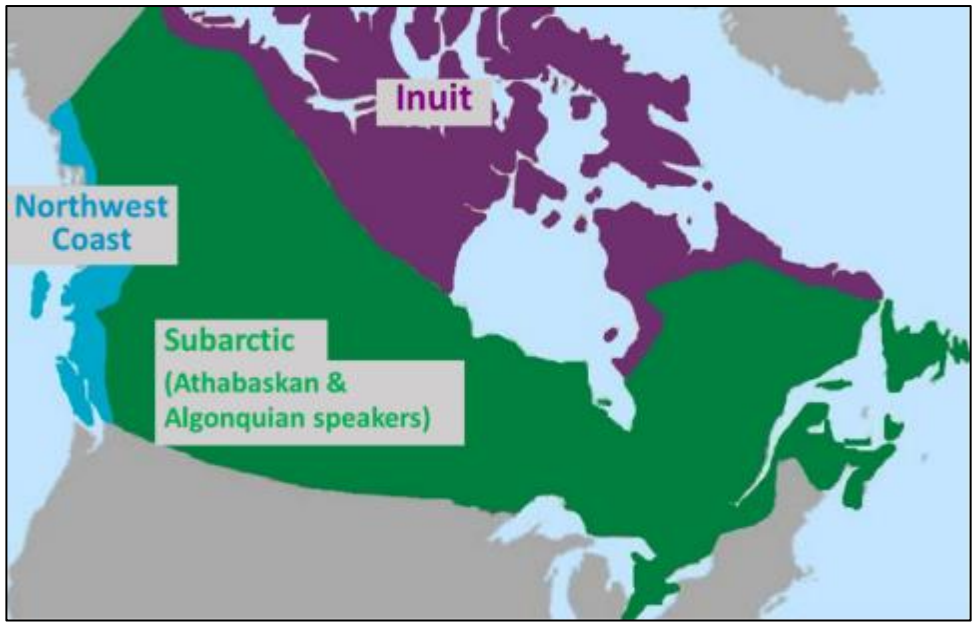
Phil Wilcox, Ph.D. Maori, New Zealand

Kim Tallbear, Ph.D. Sisseton-Wahpeton Oyate, SD

Keolu Fox, Ph.D., Kanaka Maoli, Hawaii

Activity 3 Planning together the necessary steps for development of an Indigenous Background Variant Library (IBVL)

Indigenous Background Variant Library Team

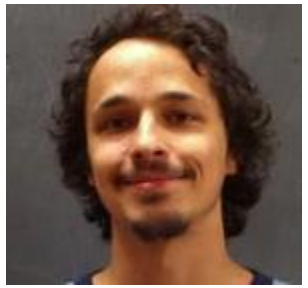


Alejandro Aguirre
(MSc student)

Solenne Correard
(Post-doctoral fellow)

Wyeth Wasserman

Ripan Malhi

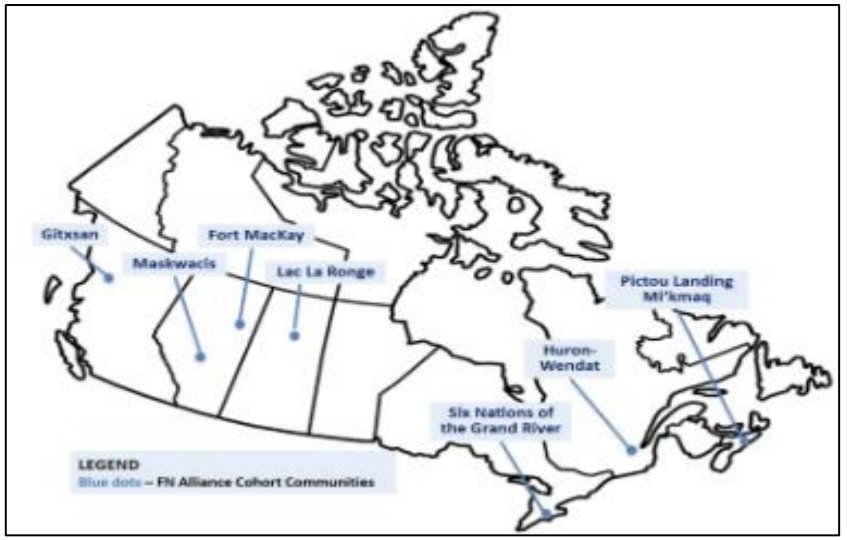


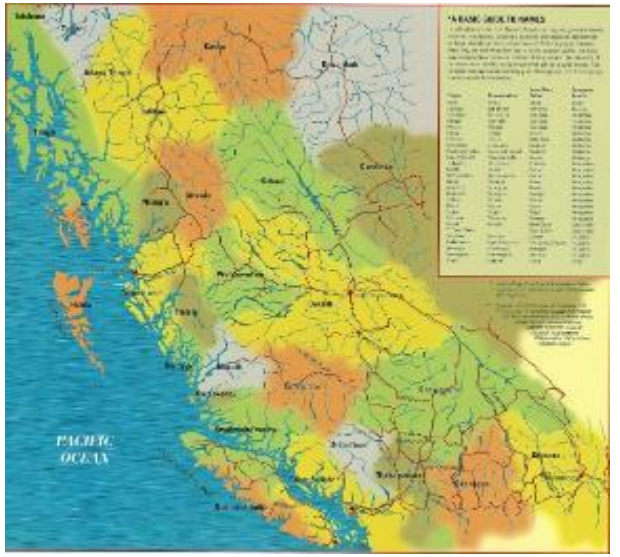
Simon Gravel

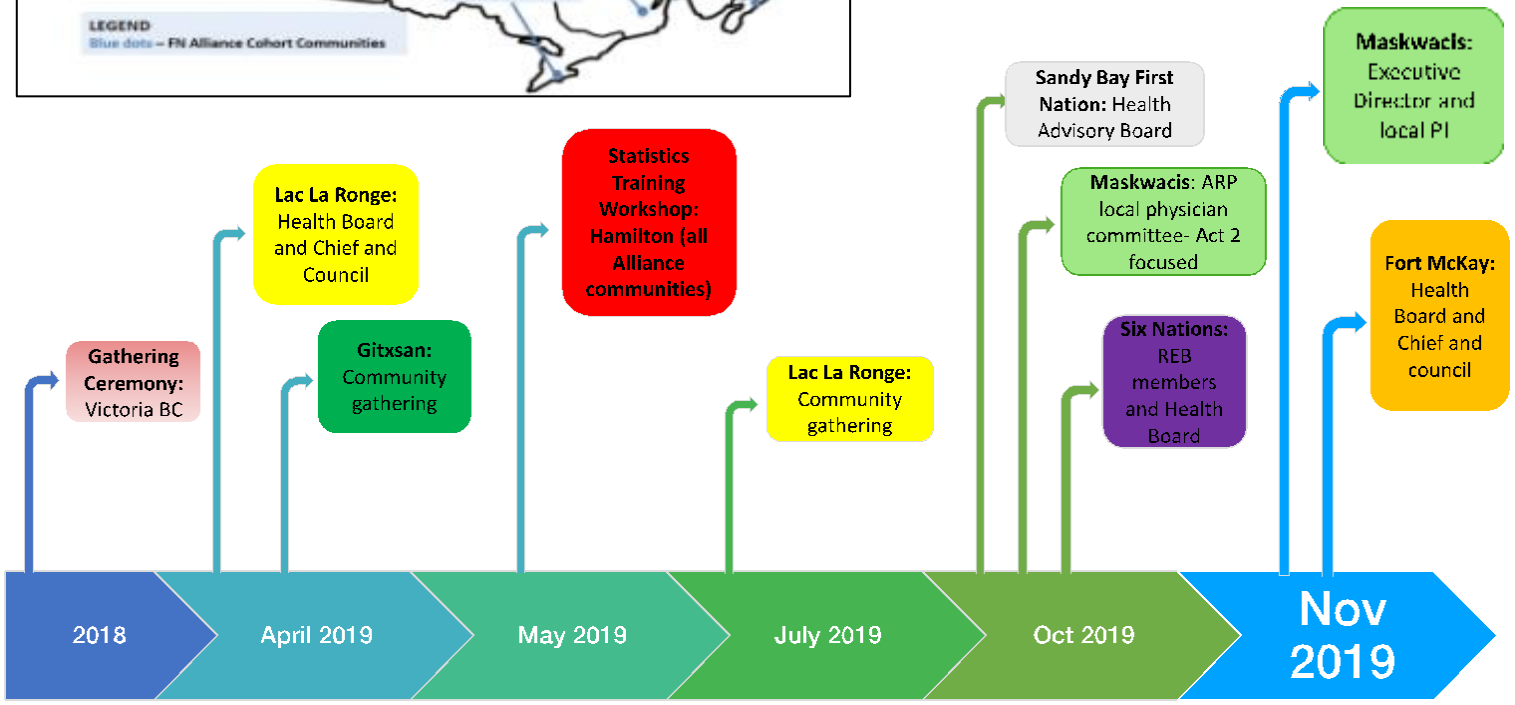
Proposed DNA Samples for the IBVL:

Origin	Number of Participants
Alliance – biobank	900
BC participants	200
Healthy relatives of Activity 2	400
TOTAL	1,500

Canadian ALLIANCE for Healthy Hearts & Minds







Imagine having a suspected rare disease

- ~72% of rare diseases are genetic, meaning their origins are in DNA
- 1 in 12 Canadians have rare disease, or ~ 100,000 Indigenous peoples
- 2/3 are children

- 30% of little ones won't reach their 5th birthday
- Rare diseases affect everyone
- Most genes do not cause health conditions

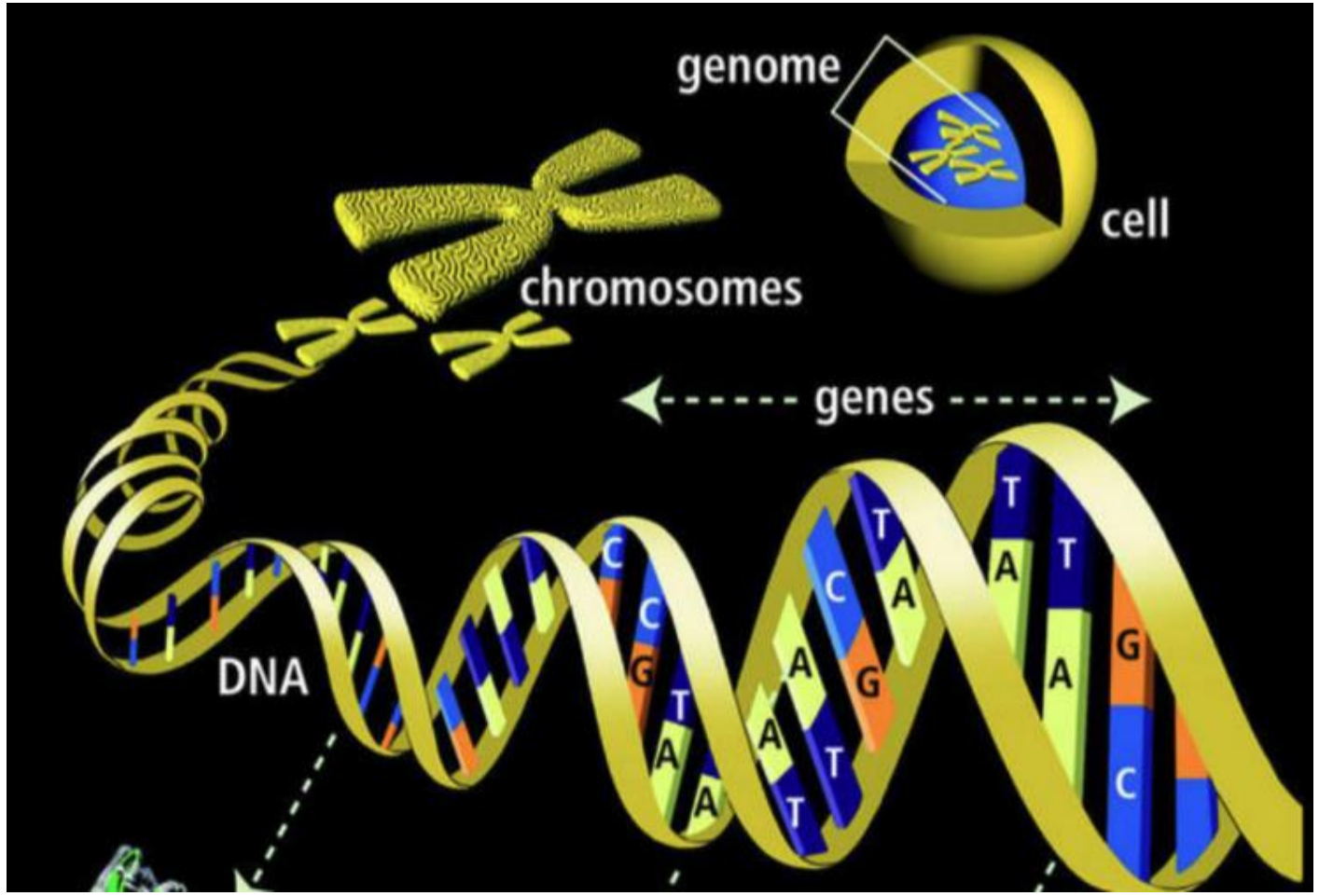
What if we could read your DNA to get a precise diagnosis of what may be causing a health condition?

Equity

This could mean the first step towards treatment or management of what are often complex health conditions.

Let's look at the biology

we will try to keep it simple…



- DNA is the ingredient for genes
- 20,000 genes
- ~ 3 billion individual nucleotides (A, T, G, C)

WHAT ARE VARIANTS?

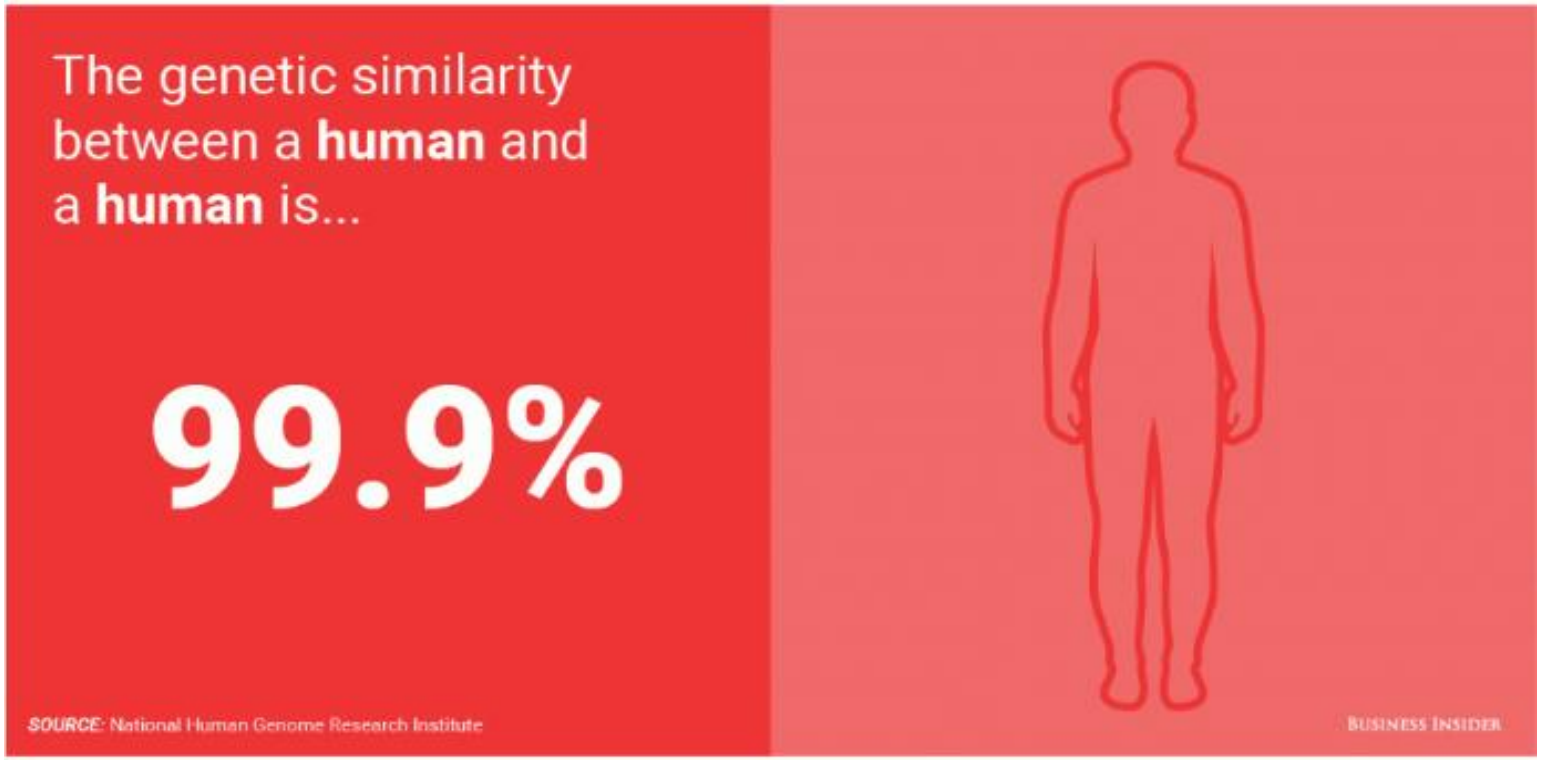
Variant: Variation (differences) in the DNA sequence

ATCGATCGAT

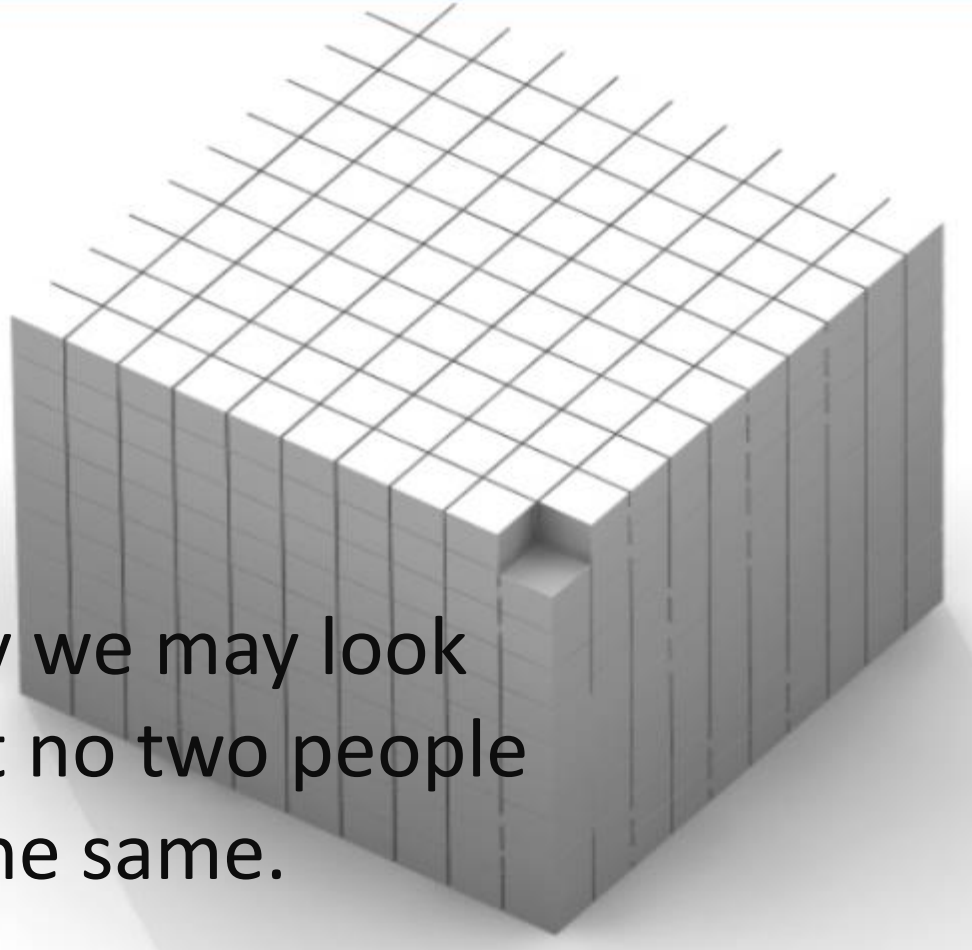
ATCGAACGAT

- Variations are natural
- Not all variations are disease causing (most do nothing at all)
- Variants may be more or less common in one population than another

How many DNA variations are we talking about?



0.1% does not seem like much difference



0.1% of 3,200,000,000 is…

3,200,000 total variants per person!

This is why we may look similar but no two people will look the same.

What is variant frequency?

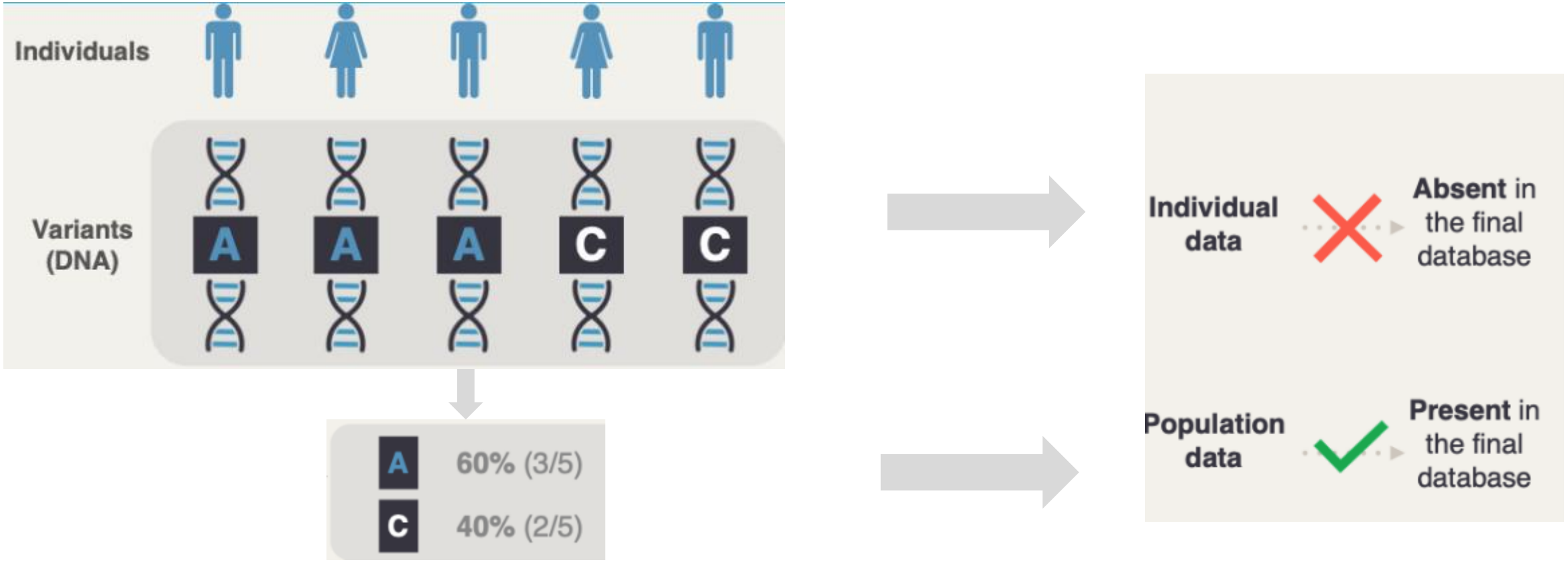
Common

- Seen more often in a healthy population
- Less likely to be associated with a significant health condition

Rare

- Seen less often (or not at all) in a healthy population
- More likely to be associated with a significant health condition

This is where the concept of a background variant library arises



It is DNA from people where the variants from each healthy person are identified and counted. Some variants are frequently found amongst a great amount of people, so will have a greater frequency. Other variants are rarely found, so, low frequency in the population.

Why do we need to know the variants?

Indigenous Peoples

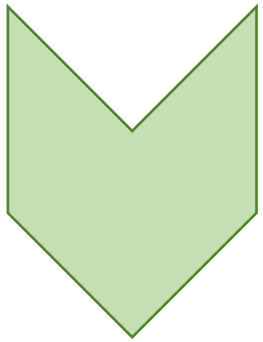
Non-Indigenous Peoples

- Variant(s) differ between populations

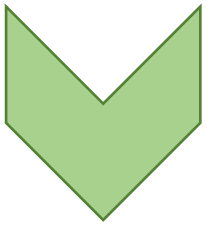
- Need to learn what are the ‘normal’ variants are for improved precise diagnosis

How does this help sick kids?

Geneticists need to screen through a lot of variants to arrive at the suspect variant thought to be the origin of the rare genetic disorder

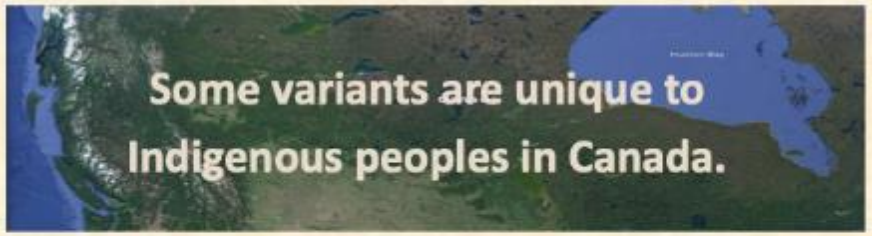


Which variants are common amongst healthy Indigenous peoples? If variants are common, they likely are not the cause of the health condition. If they were, more people would have it.



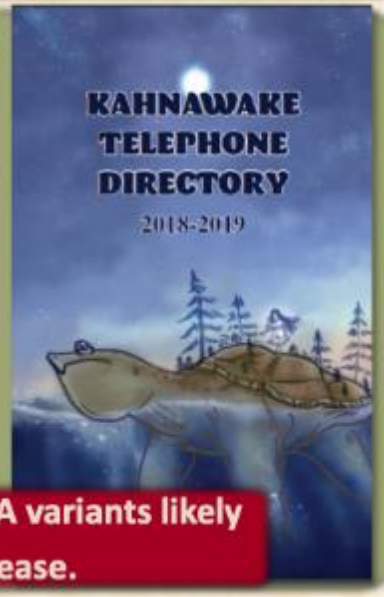
Which rare or unique variants of the child patient are remaining after eliminating the above? This reduces the search from 3.2 billion nucleotides to a handful. It becomes a precise diagnosis instead of a guessing game.

If we have our own IBVL……..



Imagine looking for the name of a relative in a pile of phone books. What are common and rare last names in your community?

If we have our own phone book with our own DNA names in it, it would be easier to focus on and eliminate healthy variants.



Matching DNA variants likely means no disease.

If we don't find what we are looking for, the search continues for a possible disease-causing DNA variant.

The more contributions of potential relatives' healthy variants, the greater the potential to eliminate those safe DNA variants & focus on what might be causing disease.

This is why a Background Variant Library is an effective tool that can increase the odds of an accurate diagnosis for a suspected genetic disorder. It is the first step towards proper management of a complex health condition.

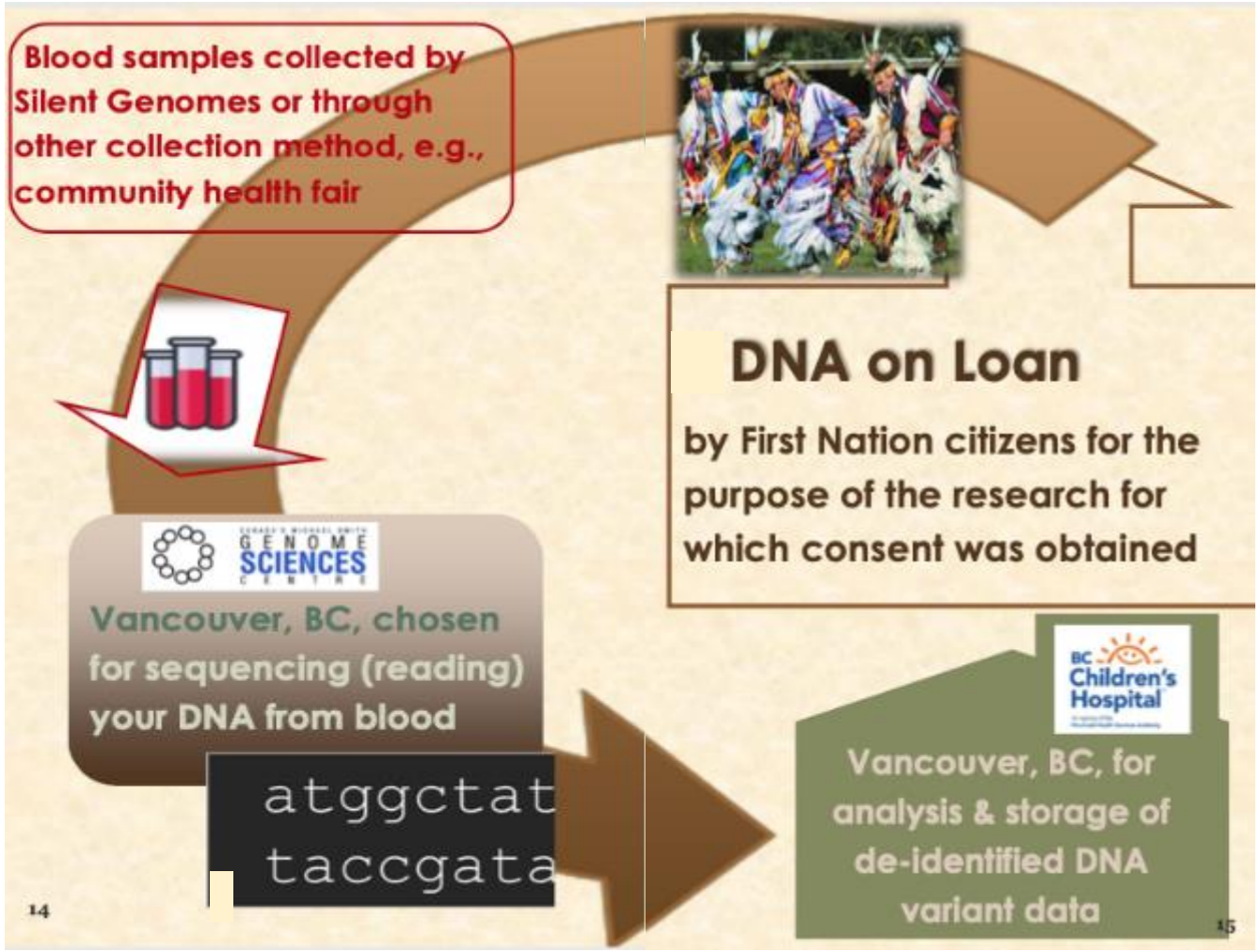
To conclude, a background variant library is basically an **elimination tool**. An IBVL would be the *first step* to filter out those common variants in Indigenous populations so that medical geneticists can focus on the remaining smaller amount of variants from the patient to find the one causing the health condition.

Haida master carver and hereditary chief 7idansuu (Edenshaw), James Hart.

AMANDA SIEBERT

(James Hart holding a tool as a first step for making magnificent totem poles)

Where do we get this DNA to help our kids?

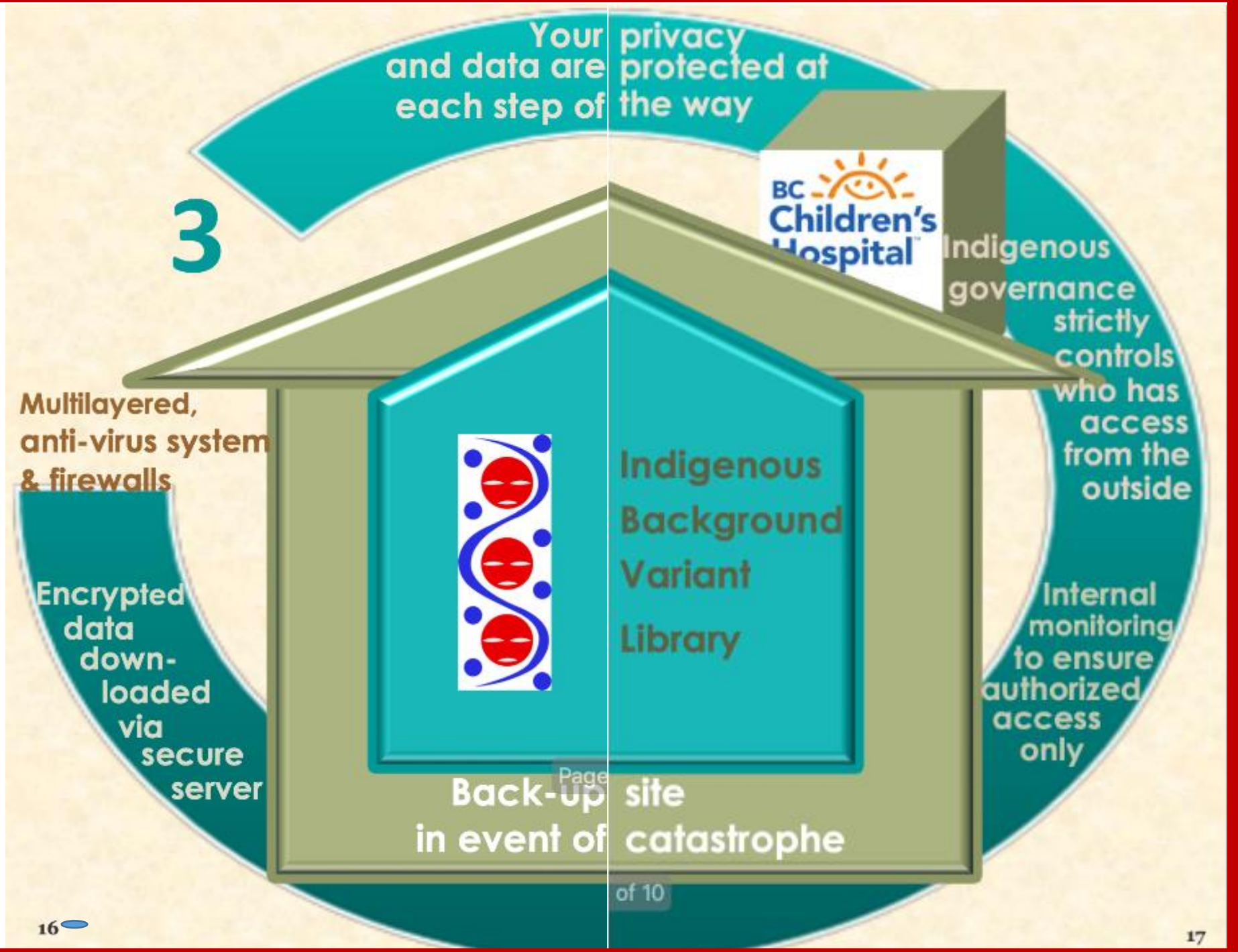


Individual data ✗ **Absent** in the final database

Population data ✓ **Present** in the final database

It can only come from us

How is our DNA protected?



How do we get this DNA to help our kids?

By building respectful relationships with individuals and communities. This is essential within our culture and in keeping with our values.

- This respect extends to the use of biological samples, including in the creation of the IBVL.
- The IBVL is not a biobank.

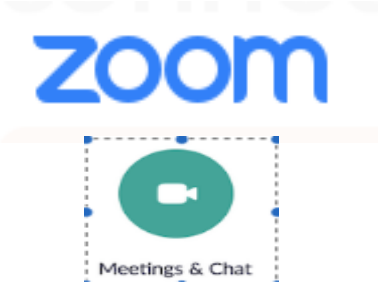
Sally Behn, Ft. Nelson First Nation

An IBVL is no guarantee that a diagnosis will be found. But it provides a much higher success rate when the inequity is addressed *by us* and *for us*.

Over time, the more participation in the IBVL, the closer we will be to equity in diagnosis

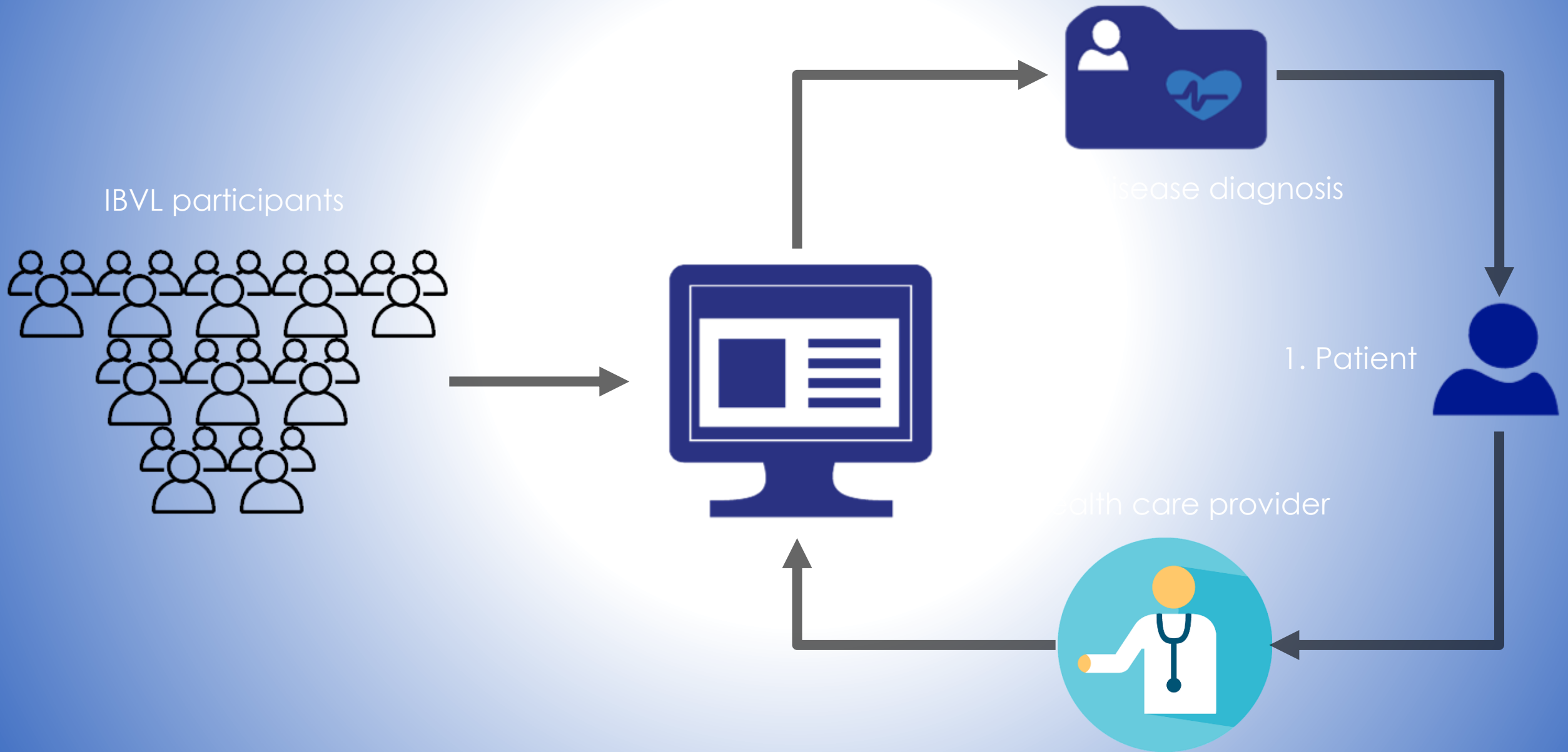
How Do We Start Building this Indigenous Background Variant Library?

It is up to you and your community if and how you want to be involved. We are working with the FNHA to introduce us to those who may be interested



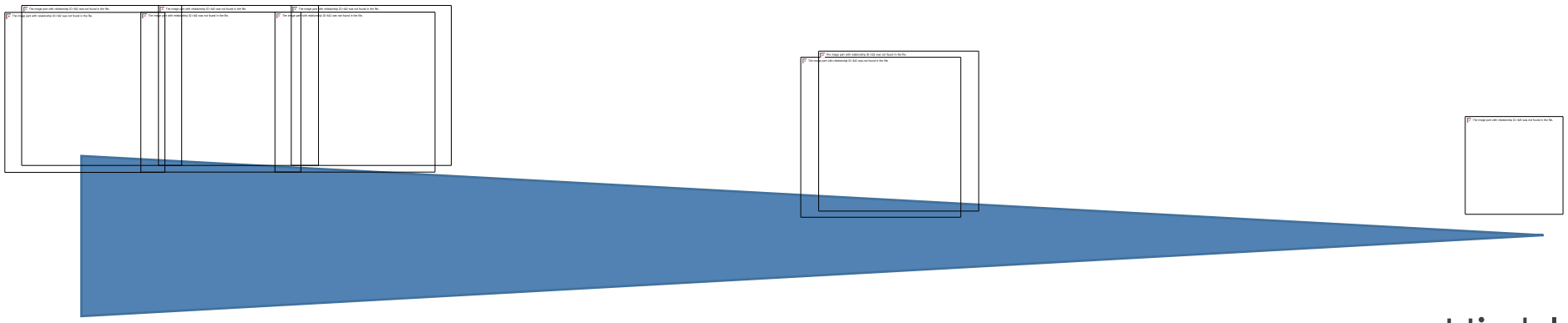
To conclude, the goal is to address inequity in order to improve diagnosis & healthcare for Indigenous children with genetic disorders

IBVL AS A CLINICAL TOOL



WHO CAN GET DATA FROM THE IBVL?

We will make the population-level data available to clinical end users within a unique data release/access model developed with our Indigenous data governance structure.



Unrestricted access

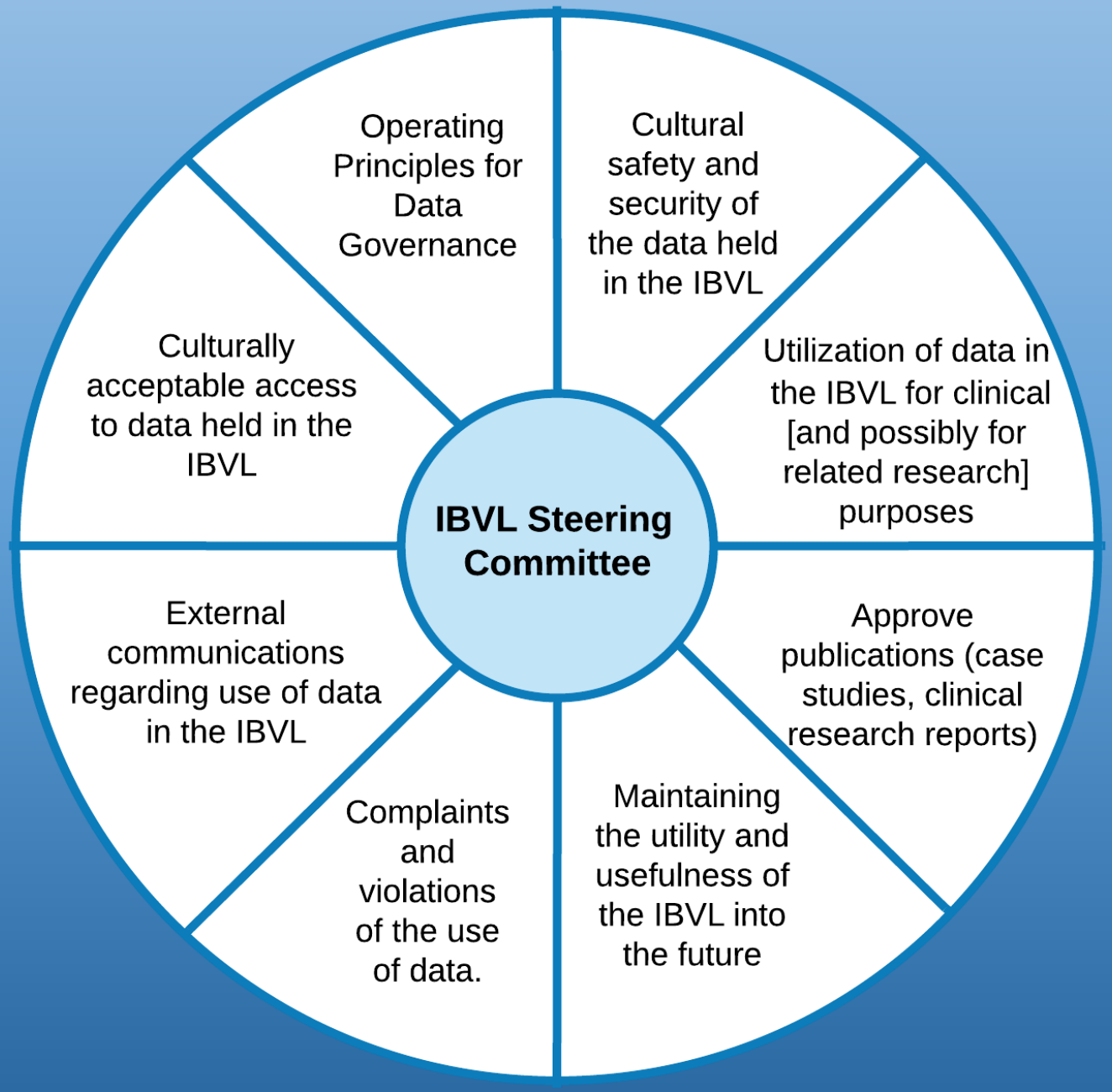
Intermediate

Highly restricted

- Continuous possibilities, not restricted to one of the 3 models
- For each model, we are addressing different questions:
  - Who can access?
  - What can be accessed?

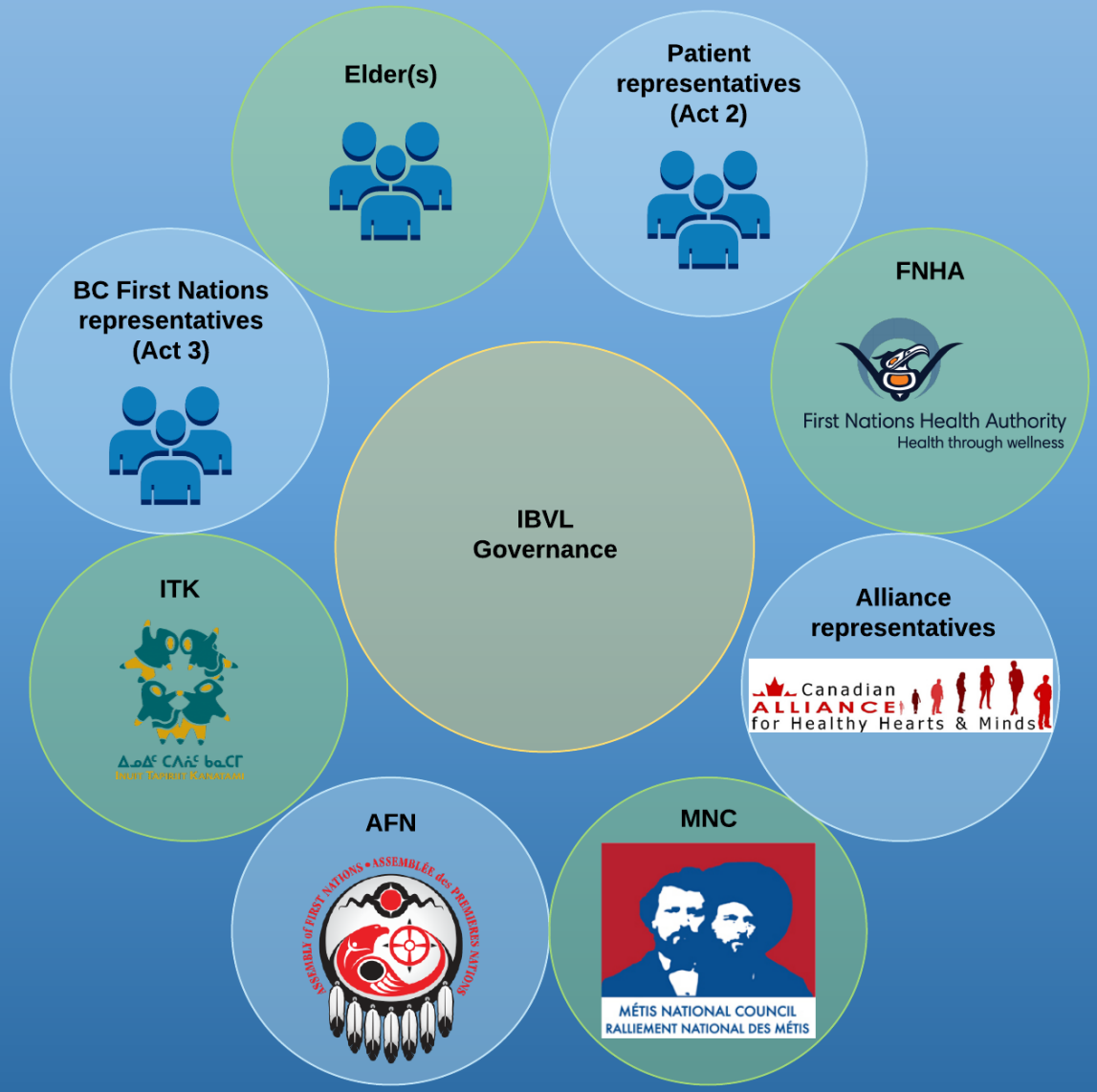
IBVL DEVELOPMENT STEERING COMMITTEE

Duties and Responsibilities of Steering Committee:



Resources and budget to operate the IBVL will be the responsibility of the BCCHRI

IBVL DEVELOPMENT STEERING COMMITTEE



WHAT WILL THE IBVL BE USED FOR:

- Clinical tool to improve diagnosis of genetic diseases
- [Potential] To be a long-term sustainable tool

THE IBVL IS NOT INTENDED TO BE USED FOR:

- As a Biobank
- Ancestry/Indigeneity determination
- To determine geographical origins (migration studies)
- To challenge cultural beliefs
- Commercialization and patenting interests
- 'Direct to consumer' genetic test results

Outline of IBVL Steering Committee So Far

- Being established to provide cultural oversight & strategic advice in support of the creation, implementation and utilization of culturally safe policies for clinical [and research] access to data held in the IBVL.

- Will be responsible for addressing issues highlighted through consultation & partnership building with Indigenous communities & leaders.

- TOR may evolve as the partnerships grow & transition is planned for when the Silent Genomes project ends.

- It is planned that the TOR for this Steering committee be reviewed, discussed & amended based on input from all our Indigenous partners (Inuit, Métis and First Nations).

CAPACITY BUILDING: STUDENTS

Summer Internship for INdigenous Genomics (SING)

SING USA (since 2011)
SING Aotearoa (New Zealand) (since 2016)
SING Canada (since 2018)
SING Canada (2020-deferred)

Dr. Kim Tallbear-lead for SING Canada

Acknowledgements


First Nations Health Authority
Health through wellness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Inuit Tapiriit Kanatami


ASSEMBLY OF FIRST NATIONS


MÉTIS NATIONAL COUNCIL
RALLIEMENT NATIONAL DES MÉTIS


GenomeCanada


Genome BritishColumbia


CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

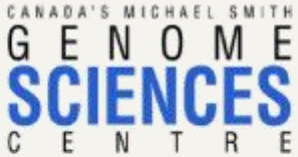

MICHAEL SMITH FOUNDATION FOR HEALTH RESEARCH
BC's health research funding agency


BC Children's Hospital
Research Institute


LifeLabs


illumina


Provincial Health Services Authority
Province-wide solutions. Better health.


CANADA'S MICHAEL SMITH GENOME SCIENCES CENTRE


University of Victoria


UNIVERSITY OF CALGARY


UNBC


THE UNIVERSITY OF BRITISH COLUMBIA

What are your thoughts?

Native American Women's Health Education Resource Centre