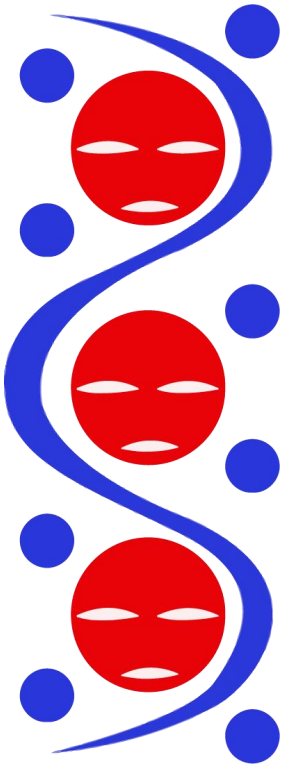
Silent Genomes
IBVL Resource Document



Written in collaboration with the Silent Genomes Indigenous Rare Disease Diagnosis (S-GIRDD) Steering Committee members

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SUMMARY

SILENT GENOMES PROJECT

The **Silent Genomes Project (SGP)** is a national research project that aims to increase access to genomic testing technologies and improve diagnostic success for Indigenous Peoples with genetic diseases (www.bcchr.ca/silent-genomes-project). It is supported by the Assembly of First Nations, the Métis National Council, and Inuit Tapiriit Kanatami.

The SGP is being carried out in partnership with the First Nations Health Authority (FNHA) in British Columbia and the First Nations communities participating in the Canadian Alliance for Healthy Hearts and Minds (CAHHM; 'Alliance Study').

The SGP team is committed to taking the advice of the Silent Genomes Indigenous Rare Disease Diagnosis Steering Committee (S-GIRDD) and the International Indigenous Genomics Advisory Committee (IIGAC) to help make decisions to best serve First Nations, Inuit and Métis people.

SGP includes four key activities:

- Activity 1: Integrating Indigenous-led governance, community engagement, community education, and student capacity building across all activities.
- Activity 2: Precision Genomic Diagnosis for Indigenous Patients with Genetic Diseases.
- Activity 3: Developing an Indigenous Background Variant Library (IBVL).
- Activity 4: Assessing the socio-economic impact of the IBVL and the SGP in general.

This document serves as a resource to those who will be accessing the IBVL (additional materials to learn more about the IBVL or the SGP can be found here). The development and implementation of an IBVL containing reference genomic data from Indigenous participants is key to improving access to the benefits of genomic diagnosis.

THE SILENT GENOMES INDIGENOUS RARE DISEASE DIAGNOSIS STEERING COMMITTEE (S-GIRDD)

The Silent Genomes Indigenous Rare Disease Diagnosis (S-GIRDD) Steering Committee is comprised of 8 to 12 Indigenous members, including Elders, community members, and representatives from Indigenous organizations (link to the terms of reference (TOR) on the website). The S-GIRDD Steering Committee was established to provide cultural oversight and strategic advice in support of the collaborative creation, implementation, and utilization of the IBVL including respectful, culturally safe policies regarding access to data and clinical diagnoses [and related research]. The S-GIRDD steering committee is responsible for the following:

1. Guiding the development of the IBVL Operating Principles for Data Governance.
2. Advising on the protocols to ensure the cultural safety of the data held in the IBVL.
3. Informing on the protocols for culturally and ethically acceptable access to data held in the IBVL.
4. Reviewing and providing feedback on the utilization of data in the IBVL for clinical use and approved related research purposes.
5. Providing input for external communications regarding use of data in the IBVL including reports to Indigenous partners.
6. Advising on the process for review of all publications (case studies, clinical research reports) generated from the SGP. This will take into consideration other relevant parties and stakeholders who have in place their own review processes (such as the Alliance Study or National Clinical Network sites).
7. Providing strategic guidance to the SGP team and the leadership of the BC Children's Hospital Research Institute [BCCHR] about maintaining the utility and usefulness of the IBVL into the future.
8. Providing guidance in the situation of complaints involving creation and use of the IBVL.
9. Providing guidance in conflict resolution as needed during the development of the IBVL.

Consultation and partnership building with Indigenous communities and leaders highlight issues the S-GIRDD Steering Committee addresses with the SGP team. Transition to an Indigenous governance group, that will sustainably provide oversight of the IBVL, is planned for when the SGP ends.

INDIGENOUS BACKGROUND VARIANT LIBRARY

INTENTION

The proposed **Indigenous Background Variant Library** (IBVL) is a database showing the frequency of each DNA variant found in a population of Indigenous people who have not been diagnosed with a severe genetic condition. Given the importance of background variant libraries (BVLs) in diagnosis, they have been created for many human populations, although mostly emphasizing individuals of European descent. It is crucial to have as many populations as possible be represented in BVLs, since variants not seen in one group of people may be more common in another. More information about DNA variants and BVLs can be found here.

To date, **Indigenous peoples have little representation in the BVLs** that are currently available. For example, people of European, Asian, African, and Ashkenazi Jewish backgrounds are represented in the most widely used background variant library, the gnomAD library, but data identified from Indigenous Peoples is absent (Figure 1).

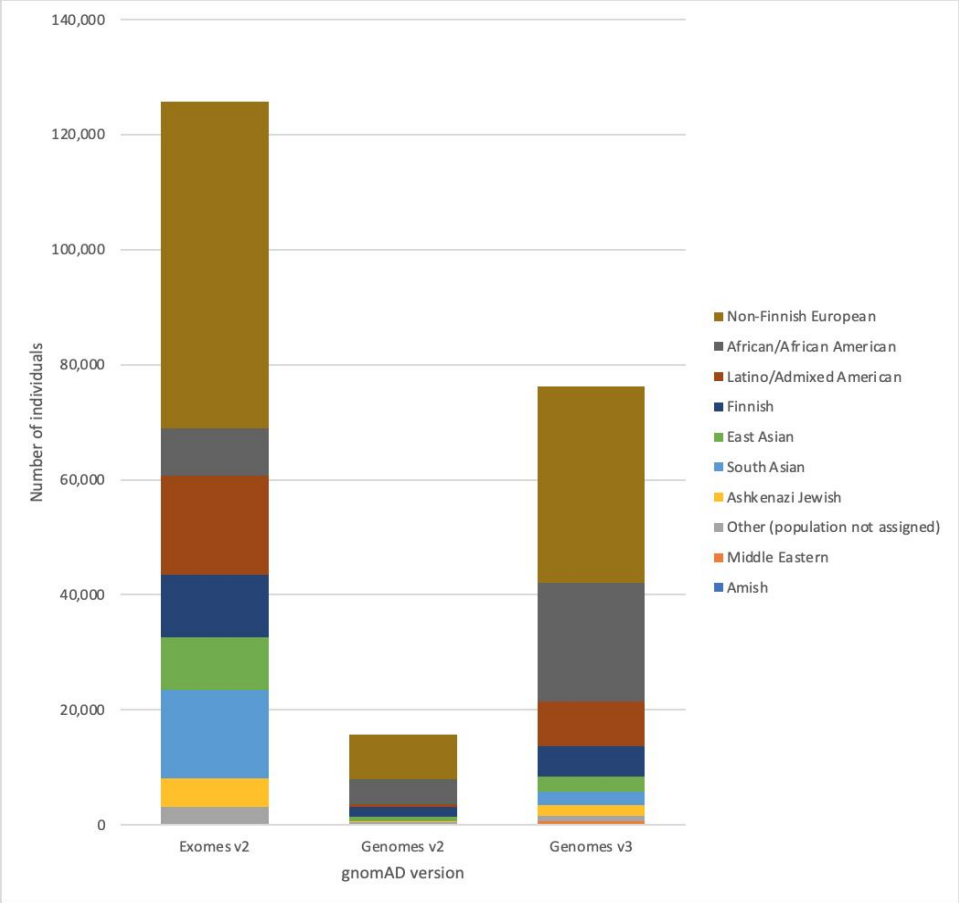

Figure 1: Number of individuals by population and subpopulation in different DNA variant databases. Several databases were produced over time, with an increasing number of individuals. gnomAD is currently the most used database for variant interpretation. However, Indigenous peoples are under-represented within these databases; therefore, it is more difficult for genetic specialists and doctors to differentiate normal variation from potential disease-causing variants in Indigenous patients. | Source: MacArthur Lab et.al |Updated by Dr. Solenne Correard (2022)

The IBVL is a clinical tool to improve the diagnosis of genetic diseases. It is NOT a biobank containing human samples. Nor will it be used to determine the level of Indigenous ancestry, geographical origins, or to challenge cultural beliefs. It will NOT be used for commercialization, patenting interests, or to provide 'direct to consumer' genetic test results to SGP participants. The purpose is to provide access to the benefits of genomic medicine for Indigenous people.

In conclusion, each population worldwide has genetic variants that are unique to them and are not present in the DNA of other populations or are found more or less frequently. The lack of an IBVL means that genetic specialists and doctors do not know which DNA variants are common and therefore less likely to be causing severe genetic disease in Indigenous peoples. This makes diagnosing genetic conditions in Indigenous patients much more difficult and less efficient than many other patients because doctors cannot quickly rule out the common variants seen in the general population as they seek to find the real 'suspect' variants that cause a patient's rare disease. This, unfortunately can result in delayed diagnosis, potentially less effective health management and treatment for patients, and ongoing stress for families due to unanswered questions. The SGP strives to fight inequity in genetic diagnoses for Indigenous patients.

DEVELOPMENT

All the SGP activities are integrated, and teams work in close collaboration. For example, as part of Activity 1 (First Nations, Inuit and Métis Engagement, Governance and Capacity Building), an Indigenous Steering Committee (the S-GIRDD, see above) was established.

Participants in the IBVL:

The IBVL will initially be composed of about 600 stored blood samples from First Nations across Canada. Some First Nation communities who are participating in the First Nations arm Canadian Alliance for Healthy Hearts and Minds (CAHHM) ['Alliance Study'] are participating in the IBVL. Extensive engagement took place (over a period of 5 years) to determine whether their stored samples could be utilized for the IBVL. For those interested in proceeding, community approval was necessary for transfer. The goal is to engage with other Indigenous communities, and perhaps patients and their families to allow expansion and robust genomic reference data coverage for all Indigenous people residing in Canada.

Sample Management:

There will be no biobanking as part of the IBVL. Samples will only be used to determine the DNA sequences required to build the IBVL.

Sample Processing / Sequencing:

Genomic DNA sequence data were generated at Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer Agency. The genomic data was transferred to the BC Children's Hospital Research Institute to be processed and variant frequencies are being stored in the IBVL database.

Confidentiality of Patients' and Communities' Identities

There is no personal or health information associated with the samples or data generated through genome sequencing. All samples used in the creation of the IBVL are anonymized before arrival at the GSC for genome sequencing. No personal or identifiable community information is included in the IBVL. A code for geographic region is included for the purpose of understanding geographical distribution of frequency of variants but that level of information would be provided on an approved case-by-case basis. Variant information will be released to health professionals providing diagnoses to patients as per the access and registration requirements suggested by the S-GIRDD.

GOVERNANCE

As previously discussed, the S-GIRDD Steering Committee will transition to an *Indigenous governance group* that will sustainably provide oversight of the IBVL once the project ends. The S-GIRDD Steering Committee was established to provide cultural oversight and strategic advice in support of the collaborative creation, implementation, and utilization of the IBVL including respectful, culturally safe policies.

The S-GIRDD and the Indigenous governance group guide the development and operations of the IBVL which includes

- Creating policies during the SGP and after the project ends
- Overseeing IBVL User approval and usage
- Ensuring the IBVL is culturally safe and accessible
- Providing input on security measures of the IBVL.

Updates on the governance of the IBVL will be provided once the Indigenous governance group is developed.

IBVL MODEL

BENEFITS

The IBVL will benefit mainly those with genetic diseases (for example inherited heart disease, cancer, and severe genetic disease in children and adults) and their family members. Benefits are expected to include:

- Help healthcare providers understand the common DNA variants in Indigenous peoples in Canada and in their patients in particular;
    - The more common a variant is, the less likely it is to be a rare disease-causing variant
- Indigenous peoples are helping Indigenous peoples for generations to come,
- Increased diagnoses of rare genetic diseases within the Indigenous community in Canada and potentially around the world.
- Increased equity and reduction of health disparities through more efficient and accurate diagnoses, which can lead to more accurate treatment plans, reduced wait time for diagnosis, and/or more information for patients and families

Overall, the IBVL will address inequity and will provide better opportunities for genetic diagnoses aiming to improve overall medical care and well-being for families.

SECURITY

The IBVL will only include de-identified data, which means that no name or other identifier will be associated with the genomic data. It will be hosted at BC Children's Hospital Research Institute, where it will be protected by multiple safeguards, including restricted access, monitoring of use, and other high-security features. The staff working with the IBVL will be required to take relevant cultural safety training.

Data stored at the BC Children's Hospital Research Institute meets a high standard of security required for health information. This includes a firewall-protected network (with a commitment to continuous upgrades of the firewall), restricted access to data to those with approved accounts, and computer server rooms with monitored access within buildings requiring pass-card entry. The SGP contracted an independent, external security audit of the BC Children's Hospital Research Institute, which confirmed the high standard of data protection.

The IBVL data is held within a database providing an audit trail, which means it records which users are accessing which data.

<u>Access Model</u>

The access to the IBVL will be restricted and will require a registration step. This means that potential users will have to request access before using the IBVL and will be prompted to fill out an online form before receiving approval.

Once a user submits all the required information, SGP staff will review and approve or decline the request. The approval is based on users with a need to access data in accordance with the IBVL guidelines. Once granted access, the user will further need to state their reasoning as to why they are accessing each variant within the IBVL. No approved user may access more than a small amount of data in a 24-hour time period, providing further protection to the information in the IBVL.

REGISTERED RELEASE OF VARIANTS

Before accessing variants, the interested user will fill out an online form. The form will ask for the user's information such as:

- Full name
- Work email
- Profession
- Full name, email, and profession of those responsible for staff person accessing IBVL on that professional's behalf
- Urgency of use
    - Whether a user needs immediate access to the IBVL (e.g., a patient in a neonatal intensive care unit (NICU))
- How the IBVL will be used
- Licensing number (if applicable)
- Institutional information
    - Name
    - Address
    - Affiliation
- Phone number
- Username
- Password

Before submitting the required information, potential users must affirm that they have read and understood the purpose of the IBVL and include their initials to show that they have read each point in the statement of context. In terms of the statement of context, the users need to agree that the IBVL's purpose is for diagnosis, and users will NOT use the IBVL for other reasons.

After they fill out that information, they wait to be approved by a staff professional.

Once registered, a user will sign in and again will need to review and agree to the statement of context and provide the reason for use. At this point, the search for a variant can be performed.

REGISTRANT ACCOUNTABILITY

Users must understand and agree with each of the points within the statement of context. For questions on any of the points made in the statement of context, please feel free to reach out to the SGP at 1 (888) 853-8924. The user agrees to the statement of context by checking the boxes.

Each time someone uses the IBVL, they will be prompted to sign that they understand the statement of context which includes the following points:

- I agree that this IBVL has been developed specifically for the purpose of diagnosis.
- I agree that this information will not be used for other purposes.
- I agree that this information will not be used for publication(s).
- I understand that this is a monitored registration, and the use of the database will be periodically reviewed.
- I have read and agree to the terms of the intended use stated in the IBVL resource document including respecting Indigenous data sovereignty (defined in the appendices of this document).
- I understand that failure to comply with this statement will result in access being revoked and other potential consequences.

As noted above, the IBVL database provides an audit trail – a record of when and which data is accessed by each user. The system is monitored for patterns that are inconsistent with appropriate use, and accounts will be immediately suspended if such behavior is detected.

If users abuse the IBVL, they will be held accountable through sanctions and legal actions by the British Columbia Provincial Health Services Authority (PHSA) as the Health Services Authority is legally responsible for the BC Children's Hospital Research Institute. This can result in rescinding access to the IBVL, reporting the behavior to professional organizations, employers, and/or communities, and other potential sanctions as appropriate.

APPENDICES

These resources guide the SGP to ensure that we are consistent, respectful, and culturally safe when conducting research. For more principles, guidelines, and policies please refer to our *Best Practices* webpage: https://www.bcchr.ca/silent-genomes-project/research-communities

DEFINITIONS

- **Background Variant Library (BVL):** a list or collection of all the DNA variants in a group of people without severe genetic conditions, which helps to determine variants that are common or rare in the general population (*More information about BVLs can be found here)*

- **Cultural Safety**: is an outcome based on respectful engagement that recognizes and strives to address power imbalances inherent in the health care system. It results in an environment free of racism and discrimination, where people feel safe when receiving health care. (*Definition from Creating A Climate For Change on the FNHA website*).

- **Indigenous Data Sovereignty**: is at minimum, about the ownership and control of samples, records, information, and the data derived from it (United Nations, 2007), as defined by, and benefiting Indigenous peoples; and in particular, human and genetic resources (Native BioData, 2021). This is part of the inherent rights held by individuals and as citizens of distinct societies and nations, and includes but is not limited to the right to repatriate, maintain, protect and develop their biological and intellectual property (British Columbia First Nations' Data Governance Initiative, n.d.).

CARE PRINCIPLES FOR INDIGENOUS DATA GOVERNANCE

The CARE Principles were written in response to the FAIR Principles published in ***Scientific Data*** in 2016. Supporting open access to data, the FAIR Principles are defined by F: Findability, A: Accessibility, I: Interoperability, and R: Re-use of digital assets. Indigenous scholars (International Indigenous Data Sovereignty Interest Group) responded to the FAIR Principles with the slogan Be FAIR and CARE, CARE being defined by C: Collective Benefit, A: Authority to Control R: Responsibility E: Ethics (CARE principles for Indigenous Data Governance) reflecting concerns about secondary use of data and limited opportunities for benefit-sharing.

C: Collective Benefit

- Research being done with Indigenous Peoples must benefit the community for equitable outcomes and contribute to well-being. This is done by governments actively supporting use and reuse of data, community engagement when planning, implementing, evaluating, and decision-making.

A: Authority to Control

- Indigenous Peoples have the right and control over their own data for their own interests which is protected by their own Indigenous governance.

R: Responsibility

- Those working with Indigenous data have the responsibility to maintain positive relationships with Indigenous Peoples which include providing resources for Indigenous language and world views and to enhance data literacy within Indigenous communities to expand capability and capacity.

E: Ethics

- Indigenous People's rights should be the primary concern at all times in order to minimize harm and maximize benefit by addressing power imbalances and fighting for justice as well as take everything learned about data governance to improve ethics for future usage.

THE FIRST NATIONS PRINCIPLES OF OWNERSHIP, CONTROL, ACCESS, AND POSSESSION (COMMONLY KNOWN AS OCAP)

Established in 1998 during a meeting of the National Steering Committee (NSC) of the First Nations and Inuit Regional Longitudinal Health Survey, the First Nations Principles of Ownership, Control, Access, and Possession (OCAP) were created to address the lack of laws or concepts to protect community rights, interests, and information. This means that First Nations have control over data collection processes, ownership of their data, and control over how their data can be used, stored, interpreted, and shared. OCAP is further defined as:

O: Ownership

- Refers to when a community or group has ownership over their information or data just like it is their own personal data.

C: Control

- First Nations can have the right to control all aspects of research from start to finish. This extends to having control over resources, review processes, planning processes, and information management.

A: Access

- First Nations have access to information and data about themselves and their communities wherever it is stored. In addition, First Nations' Communities are also to manage and make decisions regarding the access of their information through standard or formal protocols.

P: Possession

- While ownership refers to the relationship between people and their information, possession is more concrete. It is the mechanism by which ownership can be asserted and protected.

IBVL VIDEO

The video was developed in response to a request by one of the Alliance members to provide a short, easy-to-understand educational tool for community members. It was subsequently translated into French for one francophone Alliance community in Quebec.

FUNDING INFORMATION

The Silent Genomes Project has generously been supported by

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