Activity 2 of the Silent Genomes Project:
Precision Diagnosis Study for Indigenous Families with Genetic Conditions

Background

The goal of the Precision Diagnosis Study is to increase access to genetic technologies and diagnoses for Indigenous families with undiagnosed rare genetic conditions by offering state-of-the-art genomic testing in a culturally safe way. Whole genome sequencing (WGS) will be offered to at least 200 Indigenous families across Canada with a suspected rare single-gene condition that has not been diagnosed by standard tests available through the medical system. WGS is a new technology that can search through all of one's genetic material at once to try and find DNA variants that might explain the cause of their health condition. WGS is not widely available through the Canadian health care system, which is why this study is so unique.

National Clinical Network (NCN) Updates

Recruitment and enrollment into the Precision Diagnosis Study is coordinated through a network of sites at genetic health centres across Canada, referred to as the *National Clinical Network* (NCN). Last year 8 NCN sites had fully completed all the steps required to open for recruitment, and this year 3 additional sites (Montreal-CHU Sainte-Justine, Kingston, and London) opened. The NCN is comprised of a dedicated team of genetic counselors, principal investigators, research assistants, research nurses, and research coordinators. We have seen many new faces at the Vancouver, London, Ottawa, Toronto, and Kingston sites this past year. With the help of our NCN, we have had a total of 117 families referred, and 62 families enrolled into the Precision Diagnosis Study to date. Each NCN team member directly engaging with study participants is required to complete Indigenous Cultural Safety (ICS) training. To date, 28 NCN team members across Canada have had ICS training. Only 2 of these individuals had already taken ICS training prior to joining the study team, and training for 26/28 (93%) was initiated by the Silent Genomes Project. Given that NCN personnel only work part-time on this study and have additional clinical and research roles at health centres across the country, the education and ICS training provided through the Silent Genomes Project will help facilitate cultural safety more broadly within the healthcare system.

Findings from Whole Genome Sequencing (WGS)

WGS is a state-of-the-art genetic test that can look at virtually all of a person's DNA at once. When an individual or family enrolls in the study, a sample of their DNA will go through WGS, and genome analysts will interpret and prioritize the DNA variants that could play a role in their condition. The results are then reviewed at our variant committee meetings which include the clinical team that enrolled the individual/family as well as the lead geneticists, genetic counsellors, and genome analysts on the Silent Genomes team.

We have currently discussed 35 of the families who have undergone WGS, and have reported 34/35 (97%) of the results back to the NCN site for disclosure to the referring physician. To date, 23% of families have received negative results, and 31% have received at least 1 diagnostically helpful finding (probable or definite). However, 46% of families have had one or more uncertain finding returned. We hope that the Indigenous Background Variant Library (IBVL) being developed as part of 'Activity 3' of the Silent Genomes Project will help resolve the uncertainty in some of these cases and facilitate diagnoses for more families.

Families who did not receive an answer from our preliminary ('level 1') WGS analysis undergo 'level 2' analysis to assess more complex and difficult to detect genomic causes for the condition. So far, for those eligible for level 2 analysis, 10 analyses have been completed.