

## Canadian Institutes of Health Research Round Table

### A collaborative approach toward hereditary orphan diseases

November 19, 2013

#### Minutes

The round table begins with an introduction by Catherine Laprise who welcomes Stéphane Allaire, the Dean of Research and Creation at l'Université du Québec à Chicoutimi (UQAC), Étienne Richer, representative from the Canadian Institutes of Health Research (CIHR), conference attendees, and participants from outside of the region. She thanks the main participating institutions, including CIHR, UQAC, and the Cégep de Jonquière.

Stéphane Allaire takes the opportunity to underline his appreciation that this event is taking place in the region, as well as for the opportunity to participate. He emphasizes the importance of a collaborative approach that benefits actors from different domains, and reiterates the acknowledgments given by Catherine Laprise.

#### ***First set of presentations***

First speaker: **Hélène Vézina, PhD; Genetics and Population:** The BALSAC database, a unique resource for a better understanding of hereditary diseases in Quebec.

Hélène Vézina presents the population database BALSAC, developed at UQAC for over 40 years. The database is made up of marriage, birth and death certificates from Saguenay-Lac-Saint-Jean (SLSJ) and the rest of Quebec. Today the database contains more than 2.2 million marriage records and 550 000 baptism and burial records. All these records have been linked to provide information on five million individuals from 2.5 million families. For more than 30 years, many researchers interested in studying various hereditary diseases have employed data from BALSAC to reconstruct the family trees of affected individuals. These studies have focused on diseases with a higher frequency in the eastern regions of Quebec, particularly in the SLSJ population. This work has promoted a better understanding of the impact of demographic behaviour and settlement characteristics on the introduction and spread of these diseases in the studied populations. It has also helped to deconstruct some myths, such as the elevated consanguinity in the SLSJ region, thus removing the burden of social guilt. The BALSAC database is a unique resource that offers the potential for multidisciplinary research to both biomedical and social scientists. For example, a recent article published in *Science* (Nov 25, 2011; 334 (6059): 1148-50) and comprising over one million related individuals has shown the importance of the expansion process in the history of human evolution, demonstrating the possibilities of the database as a population laboratory.

Second speaker: **Nadine Arbour, M.Ed.**; ÉCOBES- Research and transfer, Development of novel strategies for knowledge translation for better prevention of hereditary diseases.

Nadine Arbour introduces the ÉCOBES group (Research centre on quality of life and population needs), an academic technology transfer centre in the area of novel social practices that is made up of stakeholders from 10 different disciplines. Ms. Arbour presents the results from a diversity of surveys, which include questions relating to: 1.) Knowledge and opinions concerning genetics, screening, the pilot project on test carriers of recessive diseases which occur frequently in Saguenay-Lac-Saint-Jean, and 2) The CORAMH organization. These questions have been integrated into the Health Agency population surveys and social services (ASSS) from 2002, 2007, and 2012. They have permitted better population targeting which hadn't yet been combined with these information methods, or those not yet referred to (in other words, those with a DES or DEP and under, couples with a healthy child, and men). The project follow-up allows for the selection of knowledge translation tools that will address these groups.

Third speaker: **Dr. Anne-Marie Laberge**; Population screening for recessive disease carriers: Factors predicting success and an example from the James Bay Cree.

Dr. Anne-Marie Laberge explains population screening by employing the James Bay Cree as an example. She explains the distinctiveness of a program with a healthy carrier population by explaining that, among other things, it does not target screening to those who have the disease (normally a recessive disease); rather, the goal is for individuals or couples to make informed reproductive decisions. Unlike a diagnostic test, the test does not search for a disease carrier. Different factors related to the disease (frequency and severity of the disease, populations at risk, etc.), and to the test (elevated sensitivity, interpretation of results, etc.) will add to the success of this kind of screening. She emphasizes the importance of adapting screening programs to target populations.

Fourth speaker: **Luigi Bouchard, PhD, MBA**; Genetics tests in Saguenay-Lac-Saint-Jean: A privileged connection to research.

Luigi Bouchard explains that several actors from the SLSJ region have worked on a pilot project to test genetic carriers for 4 frequent hereditary diseases in SLSJ (when combining the 4: 1 people in 5 in SLSJ is a carrier for one or more of these diseases compared to 1 in 20 on average in Quebec) which have been included in the action plan of the Health Minister and of Social Services (MSSS) from 2005-2008. One of the challenges of this project was the transfer of data from the research context to clinical diagnostics. In order to assure proper comprehension of the data, 30-minute training sessions were offered. Particular attention was placed on the cost of laboratory analysis, which was estimated to be \$28.50 per sample (for 5 mutations). Sample evaluations took place at the molecular biology clinic at the Centre de santé et de services

sociaux de Chicoutimi (CSSSC), and satisfied both rigorous validation criteria and cost criteria. Over a period of 2 years, 2,866 people took advantage of these carrier tests, and these were spread across the region. This allowed for the identification of 19 couples of which both parents were carriers of the same disease. The number of tests carried out per week was between 40-50, and the number of births in the region averaged 50. The accumulated carrier rate for 4 diseases was estimated at 1/5 and was validated. However, the needs of the population surpassed the services offered by the pilot project, and further related mutations could have been tested.

*Discussion after the first session of presentations:*

Before beginning the first round of discussions, Catherine Laprise emphasized that the goal of this round table is to **define the challenges and research opportunities** related to the support of hereditary orphan diseases, and to draw up key points for each round of discussions in order to send a clear message to the CIHR Institute of Genetics.

Dr. Charles Morin is a pediatrician practicing in the SLSJ region who has participated in defining certain orphan diseases in the region, such as lactic acidosis, Mucopolysaccharidosis type 2, and Zellweger syndrome. He mentions that 'in the field' people demonstrate that they accept screening, and ask relevant questions on the subject. Concerning screening, he says, "not doing it would be unethical". He confirms that it is often mothers who show the most interest. He mentions that it would be important to broaden screening in eastern Quebec to include other diseases.

Dr. Anne-Marie Laberge emphasizes that neonatal screening is lagging in Quebec and that neonatal screening should be sorted out to fix the minimum age of carrier screening (this decision is taken from the report on reproduction). Also, we should keep in mind that there is a need allocate resources at the screening, as well as for the lifespan of the individual (psychological follow-ups, consultations with family members, other kinds of care, etc.).

In terms of neonatal screening, Dr. Julie St. Pierre announces that she is participating in writing a screening recommendation for familial hypercholesterolemia, as it is practiced in other countries.

As mentioned by Dr. Luigi Bouchard, for many diseases, technology is no longer a restraint for disease screening. However, Catherine Laprise mentions that the limiting aspect is more at the level of support of screening, and that the criteria for the introduction of services must be established. Gail Ouellette mentions that there are many orphan diseases throughout Quebec, and that, for example, Cystic Fibrosis is present throughout. She also emphasizes that studies are helpful, but there is already a large number of screenings in other countries that we can use as examples, and that genetic counselors could be better employed as a resource. Luigi Bouchard emphasizes that screening should not be done exclusively in SLSJ, but that laboratories here could be a good example for putting this service into action elsewhere.

Social aspects are also very important. Indeed, Nadine Arbour and Dr. Anne-Marie Laberge mention that the message is not well communicated in families where someone has gone through screening. For example, sometimes the information does not get through to brothers and sisters of the screening candidate, and only 25% of people screened ask their spouse to take the test. In addition, concerning the carrier's screening, in comparison with neonatal, there is the possibility of information loss over time. Catherine Laprise mentions that despite all of the awareness in SLSJ, 60% of the population still believes that elevated hereditary disease in the region is due to consanguinity.

Dr. Damien Labuda raises a question about why genetics is considered a medicine apart from general medicine? Why not integrate it into an existing system?

Finally, Catherine Laprise ends this session by emphasizing that we should reflect on models and data before prioritizing the screening programs that will be put in place.

Here are some of the ideas that came out of this discussion:

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- Develop tools for groups for whom "messages are not getting through" (less-educated individuals, men, couples with a child who is not sick).
  - Expand screening for other diseases than the 4 already targeted; define criteria for the choice of diseases under consideration and develop models for original intervention in instances with a lack of resources (better use of genetic counselors and nurses for example).
  - Think of providing information about the importance of transmitting information to those concerned (reflect on information and awareness tools for the post-test screening reality of the carrier).
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## ***Second set of presentations***

First speaker: **Annie Plourde, PhD**; The challenges of knowledge translation with orphan diseases.

Annie Plourde explains that the first challenge is to find the means to expand access to knowledge for end users. The second challenge is to possess knowledge translation tools that fit the context of orphan diseases (for example, tools that doctors can use to promote knowledge to their patients). The third challenge is to disseminate developed knowledge translation products for orphan diseases. Finally, the fourth challenge is implement this knowledge into practice for orphan diseases. According to the results of their survey, experienced caregivers are the first source of information for patients, as well as the one considered the more reliable. To promote access to expertise of these experience caregivers, communities of practice constitute of the best tools according to Mme. Plourde.

Second speaker: **Dr. Jean Mathieu, neurologist;** Neuromuscular Clinic, A model innovation supporting rare diseases.

Founded in 1980, the Neuromuscular Clinic (CMNM), has been integrated into the Centre de réadaptation Le Parcours du CSSS de Jonquière since 1999. In 2000, the Groupe de Recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN) was formed. Their clientele is made up of 192 children and 1,373 adults (more than 1,000 patients are seen each year). The CMNM is an original practice, characterized by, among other things, the sharing of different tasks that gives nurses a major role, an efficient intra- and extra- regional network, and the integration of clinical goals, research, and education. The conceptual framework of the clinic equally favors a global approach (health of the person reached and their family, management of disease, and community integration).

Third speaker: **Annabelle Pratte, MSc;** Regional services in genetic counseling

Annabelle Pratte begins her presentation by defining what is a genetic counselor (master's in genetic counseling, employment title created by the MSSS in 2006) and its roles: helping to understand the essence, hereditary transmission, and the implications of genetic diseases, bringing support to people she meets, and coordinating the diagnostic steps and the follow-ups. The service for genetic counseling of the CSSSC was put in place in 1987, and aims to help a diverse clientele, i.e. prenatal, pediatric, and adult care, as well as different specialties such as metabolic and neuromuscular diseases, prenatal screening, etc. The pilot project in SLSJ has necessitated the implication of genetic counseling for its elaboration and implementation. One of its impacts has been to reorient some patients toward this area. The project allowed for counselors to contribute to the creation of a new mechanism for nurses: offering group information sessions in order to define targeted diseases, carrier tests, and to resume consent while the counselor is coming into action when a positive test result is obtained for a project participant.

*Discussion after the second set of presentations:*

Étienne Richer from CIHR asks if a study on the impact of the CMNM on the rest of the healthcare system has been carried out. Dr. Jean Mathieu mentions that it hasn't, since usually the performance indicators in the healthcare system are focused on hospitalizations and other similar criteria. However, he emphasizes that the clientele in their clinic is satisfied with the services, and that they are very comprehensive. However, these services do not decrease costs to the health system since this type of follow-up is expensive.

Next, a question from Bernard Brais concerns the cascade screening approach in genetic counseling in relation to how much it is offered and the fact that family history is no longer a prerequisite for consultation, Annabelle Pratte mentions that the approach is still in use, but is no longer a priority for diseases included in the pilot project. With the cascade screening approach, we rely on members of the family to transmit information (although, as we have seen in the first session, information does not always circulate within families). Dr. Luigi Bouchard asks what portion of the population not targeted by cascade screening were found to be carriers. Claude Prévost, the first genetic counselor in the region (now retired), indicates that the system is still efficient especially for dominant diseases. Dr. Anne-Marie Laberge also emphasizes the efficiency of this method for dominant diseases.

Dr. Julie St-Pierre mentions that cascade screening for familial hypercholesterolemia in The Netherlands over a 10-year period addressed 70% of the affected population. However, Charles Morin mentions that for many diseases, this method, which is easy to conceptualize, is not so useful for populations where certain rare mutations have an elevated frequency because this would target only families where there is a known history.

Dr. Jean Mathieu provides the example of myotonic dystrophy, a disease with dominant transmission for which we still see islets that have not yet been contacted. He emphasizes that we should use affected patients to transmit the information within the family, but that at times there is resistance to do this.

Catherine Laprise mentions that she assisted with a speech for minister Hébert in which he mentions that there are new medical developments in Quebec and Canada for medicines of a wider base (pediatrics and family medicine for example). These developments are aimed toward a community approach, and are based in realities. This framework is related to the example of the Clinique des maladies neuromusculaires, in which the patient and their family go to the same centre for access to health services (specialists doctors, nutritionists, physiotherapists, occupational therapists, and nurses are found in the same institution) for all life stages. The goal is to both better serve the patient (optimize follow-up, reduce anxiety, etc) while lessening pressure on the health care system. The Clinique des maladies métaboliques is another example from SLSJ. Dr. Bernard Brais emphasizes that the population is very informed and have access to different types of resources, and that we need to ask ourselves which tests should be offered and when.

Here are the main ideas that came out of the discussion:

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- Develop tools adapted to the context and to the users
- Optimize access to the tools through an efficient diffusion
- Translate knowledge into practice
- The neuromuscular clinic is multidisciplinary: the patient and the family are followed for the whole life of the patient. This clinic is a model in terms of patient approach, and

equally for the development of knowledge transfer tools (the clinic employs knowledge brokers). This model is exportable.

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### ***Third set of presentations***

First speaker: **Sophie Girard, MSc**; La corporation de recherche et d'actions sur les maladies héréditaires (CORAMH): A regional model for information and education

CORAMH started 30 years ago. Ms. Sophie Girard explains that its mission is to prevent hereditary diseases through sensitization, information, and education, and to transmit basic concepts to the population (genetics and heredity, the way that hereditary diseases are transmitted, description of frequent hereditary diseases in the SLSJ region). Certain diseases are more specific and frequent in SLSJ. The 5 most frequent recessive diseases grouped together occur at a rate of 1 in 4 of the SLSJ population. CORAMH sensitizes the population with information campaigns (television, radio, etc.). CORAMH has equally established a governing board of 11 members who are ambassadors of CORAMH and contribute financially to its mission. CORAMH has developed and maintains a travelling exposition on genetics, a book about this exposition, a documentary about rare diseases, informational flyers, a dissemination program, and workshops and exercises both for fund-raising and education. There are also activities concerning DNA and cells which are used for camps and elementary schools, and even experiments in Catherine Laprise's lab that the public can take part in. Over the past 30 years, it is estimated that the CORAMH activities have reached over 60 000 people, and have contributed to the acceptance of genetic testing in the region. CORAMH is a unique community organization in Quebec, adapted to the needs of the population, and has become a reference for developing information tools, sensitization, and education about hereditary diseases.

Second speaker: **Dr. Julie St. Pierre**; Elaboration of a partnership for a heritable diseases prevention program

Dr. Julie St. Pierre presents the PPPMH project (partnership for a heritable diseases prevention program). This project is connected to the mission – and is under the leadership - of CORAMH. The primary objective is to develop, realize, and evaluate an information program for those affected, their families, and health professionals and also to develop a more intensive sensitization program, and finally to offer a framework for reflection on the expansion of genetic testing. In order to achieve this, the PPPMH brings together actors from different environments such as CORAMH, l'ASSS, associations of affected individuals, different foundations and specialized clinics, researchers from UQAC, etc. This process will take place over two years and is presently in progress.

Third speaker: **Anne Vigneault, MSc**; The profile for hereditary orphan diseases in Quebec under the scrutiny of the Fondation du Grand défi Pierre Lavoie

Ms. Anne Vigneault presents the Fondation du Grand défi Pierre Lavoie, an organization that is interested in the development, support, and promotion of activities that contribute to the adoption of a more active lifestyle primarily among 6-13 year-olds. It is equally implicated in the cause of hereditary rare diseases via its support of research projects. From 2010-2013, 158 project proposals from students or researchers were submitted. In total, 68 projects were supported for a sum of \$1 095 000. The projects concerned 75 different hereditary orphan diseases (6 diseases were among those that were specific or frequent in SLSJ, 2 potentially of an more elevated frequency in SLSJ, and 67 were diseases that are present throughout Quebec). The supported projects allowed for the acquisition of better knowledge of these diseases (biological, social, etc), and the development of new approaches (technologies, models, therapies, etc). Ms. Anne Vigneault equally emphasized the importance of disease groups or associations, and the potential for partnering with larger granting agencies.

Fourth speaker: **Gail Ouellette, PhD**; Toward a Quebec strategy for rare diseases

The Regroupement québécois des maladies orphelines (RQMO) is an information service for people with rare diseases who would like to gather, share, and circulate information about rare diseases, sensitize the public, and foster exchanges among researchers of rare diseases. With the project Orphanet-Quebec, the RQMO lists all rare disease resources in Quebec that lead to Orphanet, an international portal. Upon the request of a patient or health professional, the RQMO can put together a complete file of a disease (what is known, existing associations, research projects, clinical trials, etc.). They can also initiate a research project by putting patients and researchers in contact with each other. Twenty-two patient organizations are part of RQMO, including CORAMH. Hundreds of people with rare diseases and without associations are also in contact with RQMO. According to a survey, patients would like doctors to be better informed and trained to promote and support research and to improve access to medicine and treatments. The RQMO is discussing an elaboration for a Quebec strategy toward rare diseases with the MSSS and INESSS. For research, new measures are proposed by RQMO: that rare diseases should be a specific research theme with FRQ-S, FRQ-SC, Genome Quebec, etc.; that there should be co-financing of projects by granting agencies with charities; indicative measures and help for therapies; active participation by research patients; patient registries and biobanks; coordination of ongoing research (networks, multidisciplinary clinics); research on non-diagnosed diseases, pan Canadian and international collaborations.

*Discussion after the third set of presentations:*

After a question by Dr. Charles Morin concerning the selection criteria for these projects, financed by the Grand défi Pierre Lavoie, Anne Vigneault mentions that the foundation is more sensitive to new initiatives, new researchers, as well as diseases that haven't been researched in years. Otherwise, the selection is based on scientific merit, and a committee of peers evaluates all the requests.

Étienne Richer emphasizes that support from foundations goes beyond the financial aspects, which amount may vary, but that they can play an important role by facilitating linkages among research and the needs of patients. He also mentions that there is already an ongoing discussion with the Grand défi Pierre Lavoie foundation for formalizing a structure for co-financing. He asks how CORAMH and the PPPMH see the influence and integration of their activities within international organizations (for example, IRDiRC). Dr. Julie St. Pierre emphasizes that the SLSJ population, Quebec, and Canada, have their own needs, but that they share expertise among groups. Dr. Bernard Brais mentions that the CIHR Institute of Genetics is well positioned to see international opportunities, and that concerning co-financing, a large part of research is supported by foundations. He also mentions that smaller foundations have contributed financially, demonstrating that their interest in Genome Quebec research projects even if their contribution is symbolic.

Gail Ouellette emphasizes that many foundations have amassed millions of dollars for research on rare diseases and asks that funding agencies do their part. Catherine Laprise cites the example of the Lactic Acidosis Consortium's first work following the identification of the causal gene. This was made possible by the Association de l'acidose lactique and allowed for the establishment of a biobank at the UQAC. These preliminary results lead to a CIHR team grant. She also highlights the difficulty to continue research efforts, as this grant is non-renewable. Participating researchers are now asking themselves how to continue their research at the end of this grant as the funding has been critical in obtaining deeper knowledge of this disease, and to create and characterize many models (cellular and murine). The RQMO have proposed to the Québec provincial government to allocate 5 million dollars within its National policy on research and innovation towards rare diseases by creating, as an example, specific programs for rare diseases at the FRQ-S, FRQ-SC, Genome Québec, etc.

Nadine Arbour mentions that there is a gap between the number of people who contribute to foundations and who wish to contribute financially, and the establishment of ways to transfer these funds to those in need (for example, for treatment, respite, or research needs). Catherine Laprise emphasizes that it is time to put partnerships in place, because it is impossible for each foundation or each group to put these structures in place on their own.

Here are the main ideas that came out of the discussion:

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- There is a limit to the feasibility of research on hereditary orphan diseases where finances are concerned.

- There is urgency for putting in place structures that permit financial partnerships among granting organizations and foundations. Foundations do not have the same structures as granting organizations for grant applications and funding decisions. In this regard, the Grand défi Pierre Lavoie Foundation is an exception (each foundation cannot provide a committee of researchers to evaluate applications or someone in charge of a program to support research).
  - It is necessary to insure the sustainability of successful research for front line services for affected patients and their families.
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### ***Conclusion***

Catherine Laprise emphasizes how difficult it is to have an overall vision of the situation of rare diseases. The issue requires bringing expertise together from several domains and targeting particular needs. Catherine Laprise ends by thanking all participants and gives the floor to Étienne Richer from CIHR.

Étienne Richer thanks the organizers of the round table (Catherine Laprise and Bernard Brais) and mentions that he now has many messages to transmit to CIHR, and that many discussions should be had among the different parties that are implicated. Round tables are essential in order to reinforce relationships and define priorities. He emphasizes the good relationship between CIHR and FQRS, and the possibilities for discussions about future funding opportunities.

CIHR round table report from November 19, 2013, drafted by Catherine Laprise and revised by Bernard Brais and Étienne Richer.