RARE DISEASES

COMMITTED STAKEHOLDERS, DETERMINED TO WORK WITH THE GOVERNMENT TOWARDS A QUEBEC **POLICY FOR RARE DISEASES**

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Montréal InVivo's Project Committee on Rare Diseases

MONTRÉAL INVIVO

Note to the reader

This brief is the result of work conducted since 2019 by Montréal InVivo and its Rare Disease Project Committee. This working group brings together several stakeholders including patient groups, clinicians, researchers, representatives of para-governmental organizations and industry representatives.

The purpose of this strategic plan is to **inform** and **inspire** the Quebec government to act quickly and seize the opportunity to be a pioneer in Canada in the field of rare diseases. Our guiding principles were to make the patient and Quebec's economic development central to our thinking. Inspired by **international best practices**, the concrete **recommendations** proposed complement and aim to be consistent with the future *Quebec Policy on Rare Diseases*, while aligning with the *Quebec Life Sciences Strategy (QLSS) and the Quebec Research and Innovation Strategy (QRIS)*.

Communauté métropolitaine de Montréal

Québec

Développement économique Canada pour les régions du Québec

Canada Economic Development for Quebec Regions

EXECUTIVE SUMMARY

A disease is said to be “rare” or “orphan” if, by definition, it affects only a very small portion of a population. However, this rarity is frequently associated with great complexity: these diseases often pose several challenges in terms of diagnosis, management and treatment when one exists, while requiring niche medical expertise and increasingly personalized multidisciplinary care. Individually, a rare disease seems isolated, but when rare diseases are counted as a whole, their weight in our society far exceeds the notion of scarcity.

- In the United States, a rare disease is a disease that affects fewer than 200,000 people. In the EU, a disease is defined as rare when it affects less than one person in 2,000.
- Globally, there are ~ 7,000 are diseases with 250 new ones identified each year, affecting 350 million people worldwide. Eighty percent of rare diseases are due to a genetic abnormality, and 75% of rare diseases affect children, 35% to 50% of rare diseases have a neurological component.
- In Quebec, there are approximately 690,000 people living with a rare disease on a daily basis.

Although Quebec does not yet have a policy or action plan specific to rare diseases, the life sciences community and Quebec families affected by one of these diseases have proactively led several initiatives to raise awareness among the general public and the various governments to take action. In early 2019, the **Quebec Working Group on Rare Diseases** was mandated by the MSSS to issue recommendations on the organization of services for the management of rare diseases. In complementarity, Montréal InVivo (MIV) has created a **Specialized Project Committee on Rare Diseases** representing the entire ecosystem, to propose a national plan with the following objectives: **1)** To allow Quebec patients suffering from a rare disease to have rapid and optimal access to therapeutic and diagnostic innovations; and **2)** To improve the competitiveness of Quebec’s innovation ecosystem to attract investment and develop our skills by drawing inspiration from international best practices.

This strategic plan first identifies important issues to address its two objectives. Then, Strategic recommendations are then based on seven action themes aimed at addressing four major issues in the context of rare diseases:

ISSUES

1) Sub-optimal and complex provision of patient care; **2)** The level of funding limits the competitiveness of research and development activities; **3)** Significantly less competitive business environment; **4)** Concerns about the ability to pay for new value-added innovations. These themes bring together recommendations for the development of a Quebec and national policy on rare diseases.

RECOMMENDATIONS

The seven themes in the strategic plan are as follows:

1. Speeding up diagnosis to limit diagnostic delays;
2. Improving patient health care;
3. Aggregate health data to optimize care pathways and research opportunities;
4. Supporting the development of innovations in Quebec;
5. Leveraging clinical trials to improve patient care and create economic wealth;
6. Improving access to approved treatments so that Quebec patients can benefit quickly from innovations;
7. Creating a public-private fund dedicated to rare diseases.

All of these recommendations are presented and broken down into a three-year action plan. This timeline also identifies a few project leaders who are most strategically positioned and equipped to carry out the implementation. Montréal InVivo and its specialized project committee on rare diseases believe that Quebec must capitalize on the skills and experience of the stakeholders identified as the bearers of solutions arising from the seven (7) major recommendations proposed. We firmly believe that the active and collegial participation of these key stakeholders would ensure a precise and effective collective deployment of the actions necessary to improve the situation of Quebec families affected by rare diseases. Quebec would therefore be considered a leader in Canada thanks to many short-term gains while carrying a long-term vision of excellence, collaboration and innovation in the support and care of affected families as well as in the investment and promotion of innovation in rare diseases.

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THÉRÈSE
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Chair, Montréal InVivo Rare Disease Project Committee

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WORD OF ACKNOWLEDGEMENT

Message from the Chair of the Rare Disease Project Committee

It is estimated that between 6% and 8% of the population are patients with rare diseases[1], which represents up to 690,000 Quebecers[2]. The impact at the pediatric level is significant since 75% of rare diseases begin in childhood and nearly one hospital bed out of 4 is occupied by a child with a rare disease[3]. Furthermore, it is estimated that approximately 1 in 15 children are born with a rare disease. In comparison, pediatric cancers have an incidence of 1 in 1,500, which means that pediatric rare diseases are 100 times more common[4]. Finally, it is unfortunately estimated that nearly 30% of affected children will die before the age of 5[4].

Although the diseases they suffer from are different, these patients, their loved ones and the care teams share common challenges for which it is imperative to implement solutions, knowing that these diseases are often complex, chronic, degenerative and incapacitating. Moreover, Quebec's ecosystem is rich in expertise and opportunities that Quebec should build on in order to position itself as a leader in the field.

The rare disease community is active and motivated to improve the lives of the 690,000 Quebec families affected. The Rare Disease Project Committee set up by Montréal InVivo brings together several stakeholders including patient groups, clinicians, researchers and representatives from the pharmaceutical and biotechnology industries. During its mandate, the committee generated data to inform its work, including the development of this strategic plan. For example, it conducted a comparative study of public policies in the most competitive regions of the world in rare diseases.

It should be noted that Canada is the only G20 country without a rare disease strategy. On the other hand, France recognized rare diseases as a public health priority in 1995, published its first national plan for rare diseases in 2004 and is currently in its third edition[5].

Based on the results of the committee's work and the expertise of its members, a strategic plan was developed to inform and inspire the Quebec government to act quickly. Our guiding principles were to place the patient and the economic development of Quebec at the heart of our reflection. Moreover, the concrete recommendations proposed are inspired by international best practices. This strategic plan is intended to complement the future Quebec Policy on Rare Diseases and to be in line with the Quebec Life Sciences and Research and Innovation Strategies.

I would like to thank all those who have been involved in the development of this strategic plan. Together, we can find innovative solutions for the rare disease community!

Message from the Chief Executive Officer of Montreal InVivo

FRANK BÉRAUD, B.SC. MBA

CEO

Montréal InVivo

Quebec has a unique opportunity to take and assert a leadership role in the field of rare diseases in Canada.

The upcoming announcement of the Quebec Policy on Rare Diseases, supported by the implementation of the concrete recommendations in this report, will allow the province to position itself as a leader in the sector in Canada and to leverage the major investments in rare diseases announced in 2021 by the federal government.

Montréal InVivo is an economic development organization specialized in the life sciences field that has no intention of interfering in the responsibilities of the Ministère de la santé et des services sociaux in terms of the organization of care in Quebec. The approach proposed here is complementary to that of the Ministère and is intended to be very holistic and inclusive in order to address the needs of the various stakeholders in the rare disease ecosystem, including first and foremost patients and their families, but also researchers, clinicians and companies working in this field.

We believe that the success of any action plan on rare diseases depends on a real willingness to engage in a dialogue and promote collaboration with the other provinces and the federal government, on the implementation of a predictable and coherent regulatory framework inspired by international best practices, and on innovation that will improve the competitiveness of our entire ecosystem. In return, Quebec will be able to benefit from important and concrete economic spin-offs by attracting private investment, but also from the health of patients suffering from rare diseases by attracting a greater number of clinical studies and the increased availability of therapeutic and diagnostic options.

I would like to recognize the colossal work carried out by the Montréal InVivo Project Committee on Rare Diseases, led by Nathalie Ouimet and Thérèse Gagnon-Kugler, a duo of exceptional and passionate women. For your involvement, I would like to congratulate and thank you.

It is now up to all of us to bring these recommendations to life and to implement them as soon as possible for the benefit of patients and their families.

INTRODUCTION

The advancement of knowledge, particularly in genetics, has made it possible to identify and characterize more than 7,000 rare diseases, nearly 75% of which begin in childhood[3]. Rare diseases are often complex, chronic, degenerative and incapacitating and affect a significant proportion of the Quebec population. The Ministère de la Santé et des Services sociaux (MSSS) du Quebec recently estimated that 6 to 8% of Quebecers are affected by a rare disease, which represents up to 690,000 families in the province! The following statistics also highlight the need for prompt action!

- Nearly **1 in 4 pediatric hospital beds** is occupied by a child with a rare disease;
- **1 in 15 children** are born with a rare disease. In comparison, pediatric cancers have an incidence of 1 in 1,500; thus, pediatric rare diseases are, taken together, 100 times more prevalent[3];
- Close to **30% of affected children will die before the age of 5**[4];
- Approximately **80%** of rare diseases are caused by a genetic disorder, **552,000 Quebecers** have a genetic disorder leading to serious and complex health conditions;
- **Up to 7 years to obtain a diagnosis** and sometimes, still today, patients with a rare disease are referred to psychiatry.
- Approximately **95% of rare diseases are orphan diseases**, that is, without approved/marketed treatments.

We all know someone affected by a rare disease… it's time to take action!

Quebec and Quebecers are changemakers and take action. For years, Quebec has been initiating projects to improve the competitiveness of its health innovations and to accelerate and optimize access to health care for its citizens. In the rare disease niche, Quebec's stakeholders wish to offer the best care to patients and a competitive environment to life sciences players. By positioning itself as a leader in this field, Quebec could influence the other provinces and the federal government to take action to develop policies on rare diseases, while respecting their respective jurisdictions.

This is not the first time that Quebec has mentioned its desire to put in place a policy for rare diseases. In October 2010, the MSSS had already expressed its intention to establish a strategy for the management of rare diseases. The same year, the Institut national d'excellence en santé et en services sociaux (INESSS) was mandated to conduct an international review of the situation and to propose a definition of a rare and/or orphan disease. The INESSS subsequently published its report in 2011, entitled Prise en charge des maladies rares : expériences étrangères. In this report, the INESSS recommends the implementation of a process of analysis of what is already being done in Quebec as well as the needs concerning rare diseases. It also recommends the creation of a committee to develop a management plan composed of stakeholders from the field.

Between this INESSS report and future rare disease policy initiatives, Health Canada (Office of Legislative and Regulatory Modernization) had developed, in 2012, "A Canadian Orphan Drug Regulatory Framework," but this framework never came to be.

While she was Minister of Health and Social Services, Ms. Danielle McCann announced in the winter of 2019 the creation of the Groupe de travail québécois sur les maladies rares (GTQMR). This group, composed of clinicians, researchers and MSSS officials, was mandated to identify initiatives to optimize the care of patients with rare diseases. In July 2020, the GTQMR published a report which includes, among other things, recommendations concerning the creation of provincial and supra-regional reference centres, the realization of diagnostic tests in Quebec, optimized neonatal screening, improved access to approved treatments, an integrated partnership approach to care with patients and their families, as well as the implementation of strategies to promote research on rare diseases.

At the same time, the federal government invited Canadians to share their vision for a national policy on access to treatments for rare diseases. Six hundred and fifty (650) individuals and organizations contributed to this consultation to identify the key elements needed in a national policy to help patients get better access to the medications they need. A report entitled: Building a National Strategy for Drugs for Rare Diseases - What We Heard from Canadians was published in July 2021 and presents the results of this consultation highlighting the importance of improving access to treatments for rare diseases and standardizing access across Canada, better cost sharing and risk pooling, the need for a responsive review process, and the need for international collaboration to host more clinical trials (see Appendix C for the report summary).

The strong mobilization of stakeholders demonstrates the importance and urgency of having rare disease policies that will include concrete actions to improve the lives of patients and their families and create value for the life sciences ecosystem!

Studies, organizations and groups inform the Quebec government of the urgency to act!

The majority of stakeholders involved in rare diseases in Quebec agree on the **urgency to act**. The Quebec government has demonstrated its leadership by putting forward initiatives to obtain data and recommendations to fuel its reflection. These facts are in addition to reports published by the federal government and leading organizations (Regroupement québécois des maladies orphelines (RQMO), Canadian Organization for Rare Diseases (CORD), the European Union, France's new strategy, Best Medicine Coalition, etc.). The strategic plan presented in this document aims to inform and support the government in its reflection and in the implementation of recommendations inspired by international best practices.

It is now imperative that the Quebec government develop and implement a policy for rare diseases that will allow concrete solutions to be applied in the coming years.

Montréal InVivo's approach

In March 2020, Montréal InVivo, the Greater Montréal Life Sciences and Health Technologies (LSHT) Industry Cluster, established a specialized Project Committee on Rare Diseases. This committee is composed of clinicians, researchers, representatives of large and small companies as well as patient groups and associations, including RQMO. In keeping with its mission to create a business environment conducive to innovation, growth and competitiveness of public and private organizations in the rare disease sector, the Project Committee has been examining the current issues of rare diseases in the Quebec health system and the development of initiatives to improve the competitiveness of the Quebec rare disease innovation ecosystem. Regular discussions with the **CORD** and other stakeholders have also fuelled the Project Committee's reflection.

Since the Project Committee was created, Montréal InVivo has conducted three studies to better understand Quebec's rare disease environment and to support the work of the Project Committee.

— Directory of companies developing a treatment or diagnostic solution for rare diseases (2020).

- In the fall of 2020, 67 companies were active in the rare disease niche, 63% of which were small companies headquartered in Quebec. Most of the companies are in the biotechnology, pharmaceutical and research services sectors, and finally, 3 of them commercialize a health technology. Although some companies are active in several therapeutic areas, neuroscience and oncology dominate with 54% of the companies involved.

— Comparative bibliometric study of public research in rare diseases in Quebec and Canada (2020), which evaluated the competitiveness of research activities.

- Canada contributed to the publication of 42,000 (3.8%) articles. It ranks 9th out of 25 countries in this respect. Canadian public research production on rare diseases is less abundant than the world average.

Benchmarking study on public policies for rare diseases, funded by the CanExport Community Investments program[1] and several pharmaceutical companies[2] (2021)

- Canada is the only G20 country that does not have a rare disease policy. The majority of industrialized countries have legislation, plans or strategies for rare diseases: Twenty-six of the twenty-eight (26/28) countries in the European Union have a rare disease plan or strategy. France, for example, established its first National Plan for Rare Diseases in 2004 and is now in its third. The United Kingdom has just published a framework for rare diseases (The UK Rare Diseases Framework - GOV.UK). The United States established the Orphan Drug Act in 1983 and the Office of Rare Disease Research at NIH in 1993. The most inspiring models for Canada would be those of France and Germany.

- Best practices and experiences from Australia, European countries and the United States offer concrete solutions to be implemented in the development of a global policy for rare diseases, including:
  - Accelerated approval and access to orphan drugs prior to market authorization
  - Marketing exclusivity of at least 10 years
  - Grants and/or tax credits for research on rare diseases (50% tax credit applicable to costs associated with clinical research on orphan drugs in the United States)
  - Creation of a national registry of rare diseases, centres of excellence and centres of reference (Successful models in France and Germany)
  - Raising public awareness and educating health professionals about rare diseases

These three studies are available upon request from Montréal InVivo.

Main issues identified by the project committee

Discussions at the Montréal InVivo Committee as well as consultations with Quebec SMEs have identified (or confirmed) the main issues affecting Quebec and Canada's competitiveness when it comes to rare diseases. The challenges faced by Quebec patients, as expressed in a survey conducted by the RQMO, are similar to those described by the European Organisation for Rare Diseases (EURODIS), based on a survey of 12,000 patients afflicted with rare diseases.

1. Sub-optimal and complex provision of patient care

Every Quebecer with a rare disease, no matter where they live, must have access to the same quality care and services as other Quebecers with more common diseases[6]. This is currently not the case. This inequity can be explained by several factors: clinicians' lack of knowledge about rare diseases, the absence of rare diseases in the training curriculum of health professionals, and the absence of practice guidelines on rare diseases. The GTQMR report presents the challenges in the organization of care, some of which are highlighted here.

Patients suffering from rare diseases need to be managed by multidisciplinary teams since the health issues are numerous and varied. This adequate management begins with early diagnosis, access to genetic/genomic testing and more complete neonatal screening. However, new generation genetic/genomic tests are still rarely prescribed, or are prescribed based on a clinician's more advanced knowledge, which results in inequitable access.

Diagnostic delays are also well documented for rare diseases since 27% of patients wait more than five years before obtaining a diagnosis, which delays the adequate management of their health. On average, patients consult three to four doctors before obtaining a diagnosis[6]. This diagnostic delay has a significant impact on the person with the disease and those around them. By not finding the answers to their problems or not being believed, they can become aggressive,

lose confidence in the health care system and sink into depression. Patients with rare diseases are still sometimes referred to psychiatry when their symptoms cannot be explained by a confirmed diagnosis. A 2010 RQMO survey of 300 respondents highlighted the issues experienced by patients during what is often called the diagnostic odyssey. When asked what they considered to be priorities for action, respondents identified the need to better inform the public and educate health care professionals about rare diseases, promote and support research, and improve access to medications and other treatments.

The issue of newborn screening is also well known. Early detection of a rare disease is important in order to quickly initiate management and/or treatment and to avoid complications, particularly in children. Quebec lags behind the other Canadian provinces because even today, some diseases that are screened in Canada are not yet screened in Quebec (e.g. congenital adrenal hyperplasia, severe combined immune deficiency, spinal muscular atrophy).

A large proportion of rare disease patients have a severe progressive form of the disease that requires treatment within a limited therapeutic window. Time can be an issue as the health records assessment process can delay patient care and have a significant and irreversible impact on patient health.

CASANDRA POITRAS'S TESTIMONIAL

"I spent several years under major investigation with many departments and hospitals in order to get a diagnosis because I had several symptoms and atypical reactions. I was seen in rheumatology, allergology, dermatology, gastroenterology and endocrinology. I had several pre-diagnoses over the years, but each time tests were done to confirm the diagnosis, they came back negative and we found ourselves back to square one. I was treated according to my symptoms, with no diagnosis for several years. From time to time, I would have persistent atypical seizures that were not controlled by medication and the specialists were unable to identify the cause. These seizures got worse every year and increasingly frequent. This inevitably had significant personal repercussions.

In the late spring of 2020, for no reason, I experienced four anaphylactic shocks within 24 hours of idiopathic causes in addition to complications that were partially controlled in the emergency room.

During the time I was hospitalized, I experienced various complications that really made me feel like my life was was in the balance during my stay in the trauma unit.

That was the turning point for me. I wanted answers. With a medical book in hand, I spent an entire summer reading and learning about the various mechanisms of the human body as well as rare and orphan diseases in an effort to find answers to my questions. I also compiled personal information as well as important data on my health such as blood results and various tests that I had done over the years.

After several months of research, I finally found a rare disease that matched some of my symptoms. I presented the file I had compiled to one of my specialists. He took the time to analyze the file carefully and recognized a match. Afterwards, my file was transferred to another department and I began a series of tests to eliminate other possible illnesses. In the end, it turned out that my suspicions were well founded.

To this day, I am still waiting for a diagnosis that can explain all my symptoms." - CASANDRA POITRAS, PATIENT-PARTNER

2. The level of funding limits the competitiveness of research and development activities

Since 95% of rare diseases remain without approved treatments today, it is important to foster research in this field to develop knowledge of these diseases in order to identify potential treatments. However, research on rare diseases is proportionally less well funded than other areas. In addition, research expertise is dispersed, making knowledge transfer more difficult. All of these elements present challenges for the next generation of researchers and exacerbate the lack of expertise. The conduct of clinical trials for rare diseases is complex given the small number of patients affected by them. These patients are scattered over a large area in Quebec and Canada, which makes recruitment difficult and increases costs. Canada hosts proportionally few clinical trials on rare diseases. Some patients have participated in clinical trials in the United States, others wanted to but could not afford the necessary transportation and accommodation expenses. In addition, rare diseases are not taught to health professionals, which does not encourage the next generation to take an interest in them.

Due to Quebec's reduced competitiveness on certain parts of the business environment compared to other regions of the world (see next category of issues), Quebec struggles to attract a portion of the international clinical studies on rare diseases. For an orphan disease, participating in a clinical study is the best way to obtain faster access to a treatment that represents the only potential therapeutic option. Some patients choose to invest significant amounts of money in transportation and accommodation to participate in a clinical study in the United States. This option is not a solution.

The absence of a centralized and accessible registry of health data on rare diseases in Quebec and of a classification system for rare diseases in the diagnostic directory of the Régie d'assurance maladie du Quebec (RAMQ), slows down basic research and limits the recruitment of patients for clinical trials in Quebec and Canada. Moreover, the lack of centralization and access to genetic and genomic data does not allow for a good epidemiological picture (including the founder effect) of rare genetic diseases in Quebec.

3. Significantly less competitive business environment

The business environment in the rare disease niche is not very competitive in Canada and Quebec, because these regions are lagging behind in terms of legislation, health and economic policies. On the one hand, the rare disease niche is globally a small market and Canada is a small regional market within this small market. Among the few companies in this niche, a minority is specialized in the development of products for rare diseases in Quebec. Moreover, the lack of specific incentives for companies operating in this niche encourages few Quebec SMEs to take an interest in rare diseases.

On the other hand, Canadian approval and reimbursement systems are lengthy and complex, and are divided among different players in different jurisdictions, for example, HealthCanada, health technology assessment agencies (INESSS and Canada's Drug and Health Technology Agency - CADTH), public and private payers, Patented Medicine Prices Review Board (PMPRB), pan-Canadian Pharmaceutical Alliance (pCPA). While Health Canada's ability to review cases quickly has been widely demonstrated for COVID-19 products, approval times for rare disease treatments are very long. Finally, the most significant delays in access are often caused by price negotiations and agreements between public payers and drug manufacturers (12-18 months). It should be noted that Canada is second to last among the countries of the Organisation for Economic Co-operation and Development (OECD) in terms of the time it takes eligible patients to be able to access a drug.

The uncertainty that has existed for several years regarding price controls for patented medicines in Canada represents a significant barrier to access to new treatments. PMPRB reform is of particular concern for rare and orphan diseases and has been identified as a significant barrier to the introduction of new treatments in Canada.

4. Concerns about the ability to pay for new value-added innovations

Governments' ability to pay and the sustainability of the health care system are major concerns. In addition, the traditional reimbursement model is not adapted to new innovations such as gene therapies. Public payers are concerned about the budgetary impact as well as the long-term effectiveness and safety of treatments. In addition, the burden of a worker with a rare disease sometimes puts private insurance out of balance for employers who tend not to cover them or to increase premiums.

Quebecers are fortunate to be able to rely on public drug coverage, i.e. the Basic prescription drug insurance plan (RGAM), which allows them to limit their contribution to the annual maximum as defined by the RAMQ, which is currently $1,161 / year / drug. When a drug is not reimbursed by the RGAM, Quebecers whose private insurance does not reimburse the drug have no support, even if the treatment is their only therapeutic option.

To access a drug for a rare disease that is not covered by the RGAM, Quebecers can sometimes count on RAMQ's Patient d'exception (exceptional patient) program. A physician who is aware of this program and whose patient meets the criteria can apply by completing a complex administrative process. While this program does in fact help many patients, it is an exceptional reimbursement mechanism. Inequity is also an issue as access is dependent on the clinician's knowledge of this program. In addition, this mechanism creates delays and the need to renew every six months, which is of concern to physicians, patients and their families.

RECOMMENDATIONS

It is time to act. The opportunity is now.

All of these issues were also mentioned, among others, by the GTQMR, the RQMO, and the CORD. They identify critical needs in the LSHT sector that must be prioritized by the Quebec government. These issues are important, growing and affect patients, but also the competitiveness of Quebec in rare diseases, particularly for orphan diseases.

Canadian provinces have universal public health care systems and it is time to implement concrete actions so that patients with rare diseases can benefit from a quality health care offer, equivalent to the care provided for common diseases. Among other things, diagnostic delays should be addressed and diagnosed patients should be taken care of quickly. Furthermore, today's scientific knowledge allows for the development of therapies that could improve the health of eligible patients. International best practices should be adopted to significantly accelerate access to these innovations. For more than 10 years, Canadian interest groups have been proposing elements that would enable a policy for rare diseases to be developed.

Recently, the federal government reaffirmed its commitment to invest $1 billion over two years, starting in 2022-2023, to ensure that patients with rare diseases have better access to treatment. Since Quebec has its own drug evaluation process for listing on the RAMQ formulary *via* the INESSS and has already implemented a public drug insurance plan, it would be important for the provincial government to propose to the federal government a Quebec policy on rare diseases that would include an action plan, in order to benefit from its fair share of federal funds proportional to what the federal government could provide to the other Canadian provinces as part of its national policy for rare diseases.

In order to act now for the development and implementation of a Quebec Policy for Rare Diseases, organizations such as Montréal InVivo and RQMO wish to work together with the Quebec government. The 2020 report of the GTQMR proposes several interesting avenues, supported by best practices, that could be part of this Quebec Policy. The international practices already in place could also be a source of inspiration to make Quebec attractive thanks to a strong innovation ecosystem in rare diseases.

Towards a Quebec Policy for Rare Diseases — possible concrete actions

The strategic plan developed by the Montréal InVivo project committee and presented in this document is based on the expertise and experience of its members and draws on international best practices. Recommendations from organizations such as the GTQMR and the RQMO are also included. The strategic plan is positioned to support the Quebec government in the development and implementation of the Quebec Policy for Rare Diseases. The implementation of the various actions could be carried out by both the government (among others, MSSS and MEI), as well as by other stakeholders, such as Montréal InVivo, CATALIS Quebec and the RQMO, in accordance with the scope of their respective missions and their value-added contribution to these actions.

> Furthermore, the members of the project committee firmly believe that regular communication between all stakeholders, allowing for constructive discussions in a spirit of openness, collaboration and transparency, is an essential success factor for any future policy. Together we can succeed!

To facilitate the reading, recommendations are presented by theme, but it should be noted that these categories are not exclusive; some recommendations will have an impact on more than one theme because they are interrelated.

THEME 1

Accelerate diagnosis in order to limit diagnostic delays

Recommendation 1.1: Facilitate access to genetic testing to speed up diagnosis

The Government of Quebec, through Génome Quebec and Genome Canada created and supports the Centre Québécois de Génomique Clinique (CQGC). The MSSS has chosen to centralize high-throughput genome sequencing (exome, transcriptome or whole human genome sequencing) for clinical purposes at the CQGC, which requires state-of-the-art equipment and highly specialized technical expertise. Since interpretation will be decentralized, institutions will be able to maintain and develop their clinical expertise. For rare diseases, the acceleration of diagnosis must be supported by the easier availability of genome sequencing tests. One solution will be to inform the clinical community of the availability of these tests (see Recommendation 1.2) and to increase genetic resources.

Health care professionals should be better informed about the availability of genome sequencing tests and the importance of referring a patient to the genetics clinic, or prescribing them when appropriate, when a specific diagnosis cannot be made. A best practices guide should be developed to help clinicians identify when to refer/prescribe such tests. In addition to offering training sessions, artificial intelligence tools could analyze clinical records, identify patients who have received an abnormally high number of diagnostic tests or seen multiple specialists over a defined interval to identify people with undiagnosed rare diseases.

Recommendation 1.2: Offer whole genome sequencing tests to all individuals without a diagnosis

The Integrated Centre for Pediatric Clinical Genomics, the first in Canada, offers targeted next-generation sequencing (NGS) of the coding portion of the genome (exome) for children, allowing for the identification of known genetic disorders. The whole genome sequencing (WGS) option allows for the identification of the whole genome sequence in a single run, allowing to stimulate

research and characterize new rare diseases.

Through the All for one initiative, Genome Canada funds six (6) projects in different provinces. Collectively, these projects will create a cohort of nearly 3,400 patients (650 in Quebec). The projects will demonstrate the clinical utility of whole genome sequencing as a standard of care for individuals suspected of having a severe genetic disease (80% of rare diseases).

Access to whole genome sequencing should be made available in a timely manner to children and adults suspected of carrying or having a rare disease. Specific testing could be offered to family members and newborns when a family diagnosis is confirmed. This practice would reduce the period of diagnostic delay and improve prevention and early management of patients and carriers.

Recommendation 1.3: Be proactive in updating the Quebec neonatal screening program and in immediately adding rare diseases for which a treatment is available

The Programme québécois de dépistage néonatal sanguin et urinaire (Quebec newborn blood and urine screening program) aims to detect certain rare diseases before the onset of symptoms to avoid serious and permanent consequences. Mandated by the MSSS, the INESSS regularly evaluates the list of diseases to be included in the Programme de dépistage néonatal. The MSSS then adds them to the program based on the recommendations of the INESSS. The program should be improved without delay by including the rare diseases recommended by INESSS in addition to those included by the programs of other Canadian provinces. In addition, it would be important that when a new treatment for a rare disease is evaluated, the INESSS assesses in parallel the relevance of adding this disease to the Quebec newborn screening program and that an immediate addition to the program be made following a positive recommendation from the INESSS to this effect. It is important to note that, for several rare diseases, rapid management (pharmacological or clinical) following birth is recommended in order to limit the progression of the disease.

THEME 2

Improving the care of *patients'* health

Recommendation 2.1: Create specialized care centres and regional centres of expertise that include multidisciplinary expertise

As proposed by the GTQMR, the international experience has demonstrated the benefits of pooling care expertise in specialized centres. The proposed specialized care centres (Centres de soins spécialisés) and regional centres of expertise (Centres d'expertise en région) will bring together clinical and research expertise, promote the sharing of knowledge and equipment to improve public and private research on rare diseases. These centres must also include research teams, young innovative companies, and provide access to health data and registries on rare diseases. While patients are scattered throughout Quebec, the leading-edge multidisciplinary expertise on rare diseases is generally found in urban areas such as the university hospital centres (Centres hospitaliers universitaires or "CHU"). The project committee also recommends that these centres be grouped together in a connected network to facilitate the exchange of knowledge (see section support of innovation, theme 4).

A few specialized centres have been created in Quebec and Canada, and should be supported; for example:

- The CIUSSS Saguenay Lac-Saint-Jean has developed a genetic health program offering specialized clinical genetic services for rare diseases specific to the founding population of this region;
- Cystic Fibrosis Canada supports a Canada-wide network of specialized clinics where the full range of patient care is available. These clinics also conduct research and collect data within a recognized registry;
- The Montreal Clinical Research Institute (**IRCM**) established the Research Centre on Rare and Genetic Diseases in Adults with three areas of specialization: genetic dyslipidemias, primary immunology and rare kidney diseases;
- The mother and child university hospital centres of CHU Sainte-Justine and of the Montreal Children's Hospital also bring together forces for the diagnosis, treatment and care of children with a rare disease;

- ERADICATE is a consortium of Canadian experts in clinical research on neurodegenerative diseases (some of which are rare diseases) that shares best practices to improve the capacity and attraction of clinical studies; NEURO provides leadership.

Recommendation 2.2: a) Develop the necessary expertise and b) increase resources to manage patients' health

It is essential to offer more diagnostic testing to patients more quickly, but it is also necessary to ensure that the health and social services network can manage the patient once diagnosed. In order for the specialized care centres and centres of regional expertise to meet the demand, it will be necessary to intensify efforts to train and recruit health professionals such as genetic counsellors, nutritionists, psychologists, physiotherapists, etc., and to ensure that all regions of Quebec have access to these multidisciplinary resources. The use of telemedicine could also be encouraged, when appropriate, in order to limit unnecessary travel by patients and health specialists from the regions to the major centres.

A variety of health care professionals must be available to manage patients' health once a diagnosis has been made. When treatment is not available, the multidisciplinary care team must help the patient, and his or her family caregivers, to better manage the consequences of the disease. However, a lack of resources often limits this essential management. It is therefore necessary to ensure that the number of health care professionals will be able to meet the growing needs.

To stimulate the development of expertise, these measures could be put in place, without any real impact on existing budgets:

- Enhance training curricula and provide continuing education for health care professionals to raise awareness and teach about rare diseases;
- Promote interdisciplinary knowledge transfer within the specialized care centres and the regional centres of expertise;
- Promote health care professions such as genetic counselors, nutritionists, psychologists, bachelor-level nurses, general practitioners and specialists, hospital pharmacists, etc.;
- Make existing practice guidelines (national or adapted from international guidelines) for the diagnosis, management and treatment of specific rare diseases easily accessible to health care professionals (e.g. Orphanet documents, GeneReviews, etc.);
- Relaunch and promote the Orphanet-Quebec project.

Recommendation 2.3: Increase resources to improve the quality of life of people with rare diseases and ensure equity in medical and paramedical care

People with rare diseases will need not only qualified and specialized personnel, but also support services to ensure their safety, health maintenance, independence and active participation in society.

Technical aids, accessible housing options, funding for home adaptations, vehicle adaptations, home support services, as well as funding to ensure access to an accessible and inclusive education and employment system are all services that will need to be considered for a holistic approach to health for people with rare diseases.

Recommendation 2.4: Develop and regularly update a directory of expertise in rare diseases

As RQMO and other patient associations have been recommending for several years, this leading-edge expertise on rare diseases and their management should be presented in a directory that is easily accessible to health professionals. Such a directory would help, among other things, family physicians and other specialists to direct patients to a specialized service. A Quebec directory would be the first step, but a Canadian directory would then allow Quebec patients/physicians to identify experts in Ontario, for example. RQMO has developed such a directory, but its internal resources must be enhanced to complete it and funded on a long-term basis to ensure it is regularly updated.

Rare disease patient organizations play an important role in supporting patients and their caregivers. They are complementary and essential stakeholders to the services offered in the RSSS and some of them are important research funders. As resources for both patients and health professionals, associations should also be included in the rare disease expertise directory. The GTQMR recommended the establishment of a rare disease information center. RQMO, with its iRARE Centre (Centre d'information et de soutien en maladies rares), has played this role for many years with patients and health professionals. In the past, RQMO has been a representative of the Orphanet-Quebec project and could reintegrate this project into its centre in order to continue to list and promote expertise in rare diseases in Quebec if these resources were increased. Finally, patient associations and RQMO can be important partners for research on rare diseases, which is reflected, among other things, in the new trends in patient-oriented research strategies (SPOR of the CIHR, participatory research, patient engagement, etc.).

THEME 3

Aggregating health data to optimize care pathways and research opportunities

Recommendation 3.1: Create a registry that consolidates health data on rare diseases and facilitates access to it

Following the findings of the analysis of the most internationally competitive countries, there is no doubt that access to quality health data is key to better understanding rare diseases and supporting the development of innovations. All groups that have proposed strategies or plans to better support rare-disease patients have emphasized this. Biological, healthcare, or connected object data enrich knowledge, enable the development of artificial intelligence (AI) algorithms to support medical decision-making, identify patients most likely to have a rare disease or to participate in a clinical study, and to characterize more rare diseases. The generation and aggregation of real-world evidence (RWE) and home health data would allow both treatment value and care trajectories to be measured to support decision-making and optimize health outcomes (see next section).

Bill 19, tabled in December by the MSSS, is essential to facilitate the pooling of health data on rare diseases. The new modalities will eliminate obstacles that currently slow down the judicious use of this data. Rare diseases should be identified as a priority and the introduction of the internationally recognized classification for rare diseases (ORPHA Coding - RD-CODE) should be considered for implementation at the RAMQ. This would make it possible to build a de facto Quebec registry for all rare diseases.

A few initiatives are already in place to facilitate access to health data and promote Quebec's competitiveness on the international scene. These recent advances now allow us to plan the consolidation of data for rare diseases in Quebec.

The majority of Quebec's CHUs group patient data generated in their institutions in internal warehouses. However, the nomenclature used does not allow for rare diseases to be grouped together and would require the intervention of specialized researchers to identify patients. Similar to what the CODA -19 project[7] was able to achieve, health data for rare diseases could be grouped within several institutions, then analyzed in a decentralized manner before being grouped together to create a specialized Quebec registry.

In 2021, several Quebec institutions created, with funding from Génome Quebec and the federal government, the Centre québécois de données génomiques (CQDG), a platform for the harmonization and dissemination of genomic data generated by research and clinical studies in Quebec, in adults and children. The CQDG is the platform used by the MSSS to consolidate the data generated by the CQGC into care trajectories. It is important to note that the CQDG adheres to the GA4GH international standards to facilitate collaboration and secure data sharing with other genomic data centres around the world. Experts are currently working to connect the CQDG's genomics data to hospital clinical data lakes.

The CQDG infrastructure will also be used to host Quebec data through the *All for One* Pan-Canadian Health Data Ecosystem (see above) launched this year. The ecosystem will allow data to be shared between institutions, across provincial or territorial boundaries, and between the clinical and research communities.

Ideally, this genomic data would also be matched with other clinical data available for each patient, such as the Dossier de santé du Quebec (DSQ). This step is not planned at this time. The Interdisciplinary Research Group in Health Informatics (GRIIS) in the Sherbrooke area is proposing to connect genomic data to family medicine data via the PARS3 platform, as the group has done for other types of data.

Registries initiated and managed by patient groups

In recent years, patient organizations have been developing registries for their rare diseases. In consultation with their communities, they are building the registries to include relevant data related to the disease and the patient-reported outcomes. Those using these registries are the patients and caregivers, and they can contribute their medical, genetic, etc. information. Researchers (and the associations themselves) can have access to anonymous data. These registries are based on digital platforms that ensure transparency, confidentiality and security, developed largely by the American groups, NORD and Genetic Alliance, in collaboration with the NIH and the FDA. These registries are also useful for recruiting patients for research projects and clinical trials. RQMO promotes the 150 or so existing international disease-specific registries to patients and researchers and is working to establish such a global registry for rare-disease patients in Quebec.

Recommendation 3.2: Develop the Quebec reference genome and multi-omics profile

The GenoRefQ initiative will allow for the development of Quebec's reference genome. The objective is to create a catalog of genetic variants present in the Quebec population, and to provide clinical geneticists with a tool that will enable them to interpret the results of genetic tests and thus improve diagnosis. This catalog will be available through the CQDG and its portal should be launched in spring 2022.

To better support pediatric rare diseases, which constitute 75% of rare diseases, and in a manner similar to the GenoRefQ initiative, it would be very useful to develop tools (such as proteomics, metabolomics or other *omics analyses) that would enable environmental and genetic factors that participate in the clinical expression of rare diseases to be better understood. This pediatric database could also be used as a control arm for clinical studies. It could also be useful to evaluate the relevance of having a pediatric population cohort from CARTaGENE (children or grandchildren of current CARTaGENE participants) which could provide exceptional family depth to understand genetic disorders of rare diseases.

DR. VINCENT MOOSER'S TESTIMONIAL

> *"In order to optimize its investments and allocation of resources, to boost research and to attract external public and private funding, while capitalizing on the unique structure of its population and its exceptional capacities, Quebec definitely needs a detailed mapping of its rare diseases, with in-depth epidemiological studies that cover clinical, molecular and genomic, administrative and financial data."*
>
> DR VINCENT MOOSER, MD, CANADA EXCELLENCE RESEARCH CHAIR IN GENOMIC MEDICINE, DIRECTOR OF QUEBEC'S COVID-19 BIOBANK, DEPARTMENT OF HUMAN GENETICS, FACULTY OF MEDICINE, MCGILL UNIVERSITY

THEME 4

Supporting the development of innovations in quebec

Recommendation 4.1: Stimulate collaboration to increase innovation development and investment attraction

Specialized Care Centres and Centres of Expertise have access to the aggregated health data of the provincial/national registry for rare diseases. It would be appropriate for these Centres to network to optimize knowledge-sharing. The creation of a network of Specialized Care Centres and Centres of Expertise for rare diseases in Quebec represents an opportunity to be explored, notably with the Fonds de la recherche du Quebec - Santé (FRQS). The “Network” (Réseau) designation by the FRQS for Rare Diseases would make it possible for core funding to be secured for this network’s required infrastructure.

The network of Specialized Centres represents a significant asset for stimulating the development of innovations, both in academic research and in Quebec SMEs. To achieve this, an environment open to collaborations and partnerships with companies, large and small, academic research, health professionals and patients, their caregivers and their patient advocacy associations will need to be put in place.

Recommendation 4.2: Increase funding for rare disease research and provide incentives to attract new talent

The study conducted by Montreal InVivo, as well as discussions at the Project Committee, showed that few academic researchers study rare diseases, it is a complex field of research and funding in this area is less abundant. A number of researchers will soon be retiring and there is no succession to transfer their knowledge. It is therefore necessary to stimulate the development of expertise in order to improve Quebec’s competitiveness in rare diseases.

Existing programs would better support the development of leading-edge expertise in public research, such as:

- Providing more research funding (through the CIHR, the FRQS Network for Rare Diseases and Génome Quebec, for example), ensuring that at least 8% of available funds (the proportion of Canadians living with a rare disease) are allocated to rare disease projects;
- Reserving a portion of the FRQ's research scholars' program and start-up grants for young researchers, for rare diseases.

Recommendation 4.3: Support expertise on rare diseases more specific to Quebec to develop distinctive niches of excellence

The Quebec founding population is studied by several research groups locally, but also internationally. Some rare diseases are proportionally more frequent in Quebec than elsewhere. This "Franco-Quebecois Heritage" is a distinctive source of knowledge on which Quebec can rely to attract investments. In addition, the cultural diversity of Greater Montréal is a distinctive asset to attract investment in clinical research. To benefit from these spin-offs, investments must be made to better characterize the Quebec founding population and to rely on Quebec's advanced genomics expertise to achieve this.

Recommendation 4.4: Support the development of innovations by SMEs in the field of rare diseases

Few Quebec SMEs are developing a product for rare diseases. To stimulate the development of innovations in companies, countries that have implemented plans and strategies for rare diseases propose a few measures that have shown their relevance. Quebec, and Canada, must join these leaders by offering conditions that are at least equivalent and whose positive impact has been demonstrated.

Here are the essential elements to improve Quebec's attractiveness in terms of rare diseases for SMEs:

- Offer 10 years of market exclusivity as in the EU and two additional years for a pediatric indication, for a total of 12 years of exclusivity;
- Co-finance preclinical, clinical and RWE studies conducted in Quebec, whether by international or Canadian companies (e.g. France, United States);

- Provide an enhanced tax credit for the development of a product for rare diseases in Canada. In the United States, a 50% tax credit is applicable to the costs associated with clinical research on orphan drugs;
- Set up a specifically dedicated support program, e.g. Biomed Propulsion for rare diseases.

In Quebec, the venture capital sector is proportionally more interested in the field of rare diseases, which is an asset. However, this field is considered more risky by many funding stakeholders. The most successful entrepreneurs have sometimes used great creativity to finance their R&D programs, notably by combining grants, loans, foundation funding and venture capital.

THEME 5

Leveraging clinical trials to improve patient care and create economic wealth

Recommendation 5.1: Position clinical research in the care trajectories for rare diseases

Specifically for rare diseases, patient health care must also be supported by better integration of clinical trials into care pathways. Communities of practice must break down the silos between "research" and "clinical" as clinical trials are implemented according to best practices of care. Clinical trials allow patients to have faster access to innovative therapies. For Quebecers suffering from an orphan disease (95% of rare diseases have no approved treatment), clinical research often represents the only option for access to innovative treatments. Moreover, for therapeutic areas where patients may progressively become refractory to the first lines of reimbursed treatments, clinical research becomes a matter of survival.

In addition to providing early access to innovations, clinical studies also allow clinicians and researchers to gain international recognition through their publications, to create revenue in their research centres and to improve their expertise on rare diseases in Quebec by learning about new innovative treatments earlier.

Recommendation 5.2: Attract more clinical studies in rare diseases by providing incentives

The *Quebec life sciences strategy (2017-2027 SQSV)* aims, among other things, to make Quebec the Canadian province that attracts the most investment in clinical research, thereby recognizing the importance of optimizing the clinical research environment in Quebec. The operational progress made within the framework of the SQSV is already significant[8], and covers all medical conditions, including rare diseases. These advances currently allow Quebec to aspire to be substantially more competitive, both in Canada and internationally. However, it would be important to think about additional initiatives that could specifically target rare and orphan diseases, as is done in the best positioned countries in this market.

Despite optimized operational activities and a distinctive population profile with a high prevalence of certain rare diseases, Quebec remains in competition with other high-performing countries, which offer several financial, fiscal and commercial incentives to stimulate and support the conduct of clinical studies on their territory. These incentives would increase the attraction of clinical trials in Quebec and at the same time promote the retention of Quebec investigators and the loyalty of the resulting foreign investments.

Legislation, regulations and policies in Europe and the United States developed to encourage research of all kinds focus on four broad categories of incentives: tax credits, research grants, priority drug reviews by regulatory agencies (see theme 6) and market exclusivity.

In order to maximize Quebec's competitiveness and attract a growing share of global clinical trials, we recommend offering incentives that are minimally equivalent to competitive countries. Experience in the United States and Europe shows financial incentives to be effective and allow innovative companies to recover a certain return on their investment, otherwise impossible with the simple marketing and sale of drugs for rare diseases. For example, in the United States, a 50% tax credit is applicable to the costs associated with clinical research on orphan drugs, while in Japan, 12% of the expenses incurred are exempt from all taxes.

THEME 6

Improving access to approved treatments so that Quebec patients can benefit quickly from innovations

Recommendation 6.1: Make representations to the Canadian government to optimize Health Canada's evaluation processes

The Quebec government and its counterparts in other provinces should work together to make changes to Health Canada's processes. These changes will speed up the process of assessing a technology and ultimately may lead to faster treatment for a patient in need. This would include:

- Decreasing the time for approval of new products to reach the average time of leading countries in rare diseases;
- Beginning evaluation at the same time as agencies elsewhere in the world, such as the FDA, or building on the FDA's report to accelerate its work. The example of Projet ORBIS in oncology has demonstrated the feasibility of this approach. The Orbis partners (United States, Australia, Brazil, **Canada**, Singapore, Switzerland, United Kingdom) work together on the review of cancer drug applications under a confidentiality agreement. A similar approach for rare diseases would be very relevant;
- Providing fast-track access to promising treatments for rare and orphan diseases, even if clinical research data is not complete, by offering conditional access (*Notice of compliance with conditions - NOCC*) with follow-up measurement of value in the real-world setting of care, when relevant;
- After Health Canada's Notice of Compliance, offering ten years of effective market exclusivity, as is done in all countries with a rare disease strategy. Often, a twelve-year exclusivity is proposed for a pediatric indication.

Recommendation 6.2: Support INESSS assessment improvement processes for access to treatment

The Project Committee recommends continuing to improve the processes undertaken by the INESSS, as proposed in its 2021-2024 strategic plan (in French only), Appuyer la création de valeur pour la collectivité. The INESSS is an organization at the forefront of science and best practices, which is an asset for Quebec's competitiveness in rare diseases. Here are two excerpts:

[TRANSLATION] SUPPORTING INNOVATION MANAGEMENT IN A CLIMATE OF UNCERTAINTY

> In particular, INESSS is called upon to evaluate increasingly complex innovations, earlier in their life cycle, in the presence of a high degree of uncertainty regarding their value added. In fact, various regulatory provisions encourage the marketing of health technologies and drugs on the basis of early data. The INESSS must therefore adapt its evaluation approaches and methods to new constraints: often limited number of patients, insufficient quantity of reliable clinical data, lack of comparable studies, high level of uncertainty regarding the proof of clinical value and long-term safety, etc.
>
> ...
>
> The INESSS will be called upon on several levels: monitoring and identification, prioritization, management of uncertainty, development of evidence in a real context, conditional introduction strategies, adapted recommendations, determination of conditions for implementation and scaling up, etc.

Adjustments can still be made to improve the evaluation processes to speed up and facilitate access to new treatments for rare diseases. Here are some of the measures that should be put in place:

- Avoiding delays in the initiation of treatment evaluations, diagnostic tools and assessments to be added to the Quebec Newborn Screening Program for Rare and

Orphan Diseases (Programme québécois de dépistage néonatal pour les maladies rares et orphelines);

- Adding a feedback process and allowing for interaction with manufacturers during the evaluation to, among other things, discuss uncertainty management;
- As the National Institute for Health and Care Excellence (**NICE**) in Great Britian does, assisting the health care system in implementing studies to measure the value of innovations in real care settings, or real life, when recommendations for reimbursement with conditions are proposed, in collaboration with the manufacturer;
- Proposing research topics arising from the elements of uncertainty noted during the evaluations by the experts consulted during the evaluation work, to advance knowledge on rare diseases. (SQRI – Quebec research and innovation strategy white paper – of the INESSS, solution 2).

Recommendation 6.3: Make innovations accessible as soon as their therapeutic value is recognized by the INESSS for orphan diseases and rare diseases with unmet health needs

The pan-Canadian Pharmaceutical Alliance (pCPA) negotiates the Canadian price with the manufacturers. This negotiation period can take up to three years. Canadian provinces have little influence over the negotiation process with the pCPA, therefore products should be available upon confirmation of therapeutic value by the INESSS and prices should be adjusted *a posteriori*.

In addition, Canada's proximity to the largest market in the pharmaceutical industry, the United States, inevitably influences its business environment and this element cannot be ignored in the development of Canadian and Quebec policies. A company risks harming the marketing of its products in the United States if it markets its product in Canada at a significantly lower price. It would therefore be wiser for Canada to post a price proportionally comparable to that of the United States and leading countries, while negotiating significant benefits for Canadians on a confidential basis.

Recommendation 6.4: Implement innovative reimbursement mechanisms

Other reimbursement methods could be adopted in Quebec, and in Canada, to mitigate risks while optimizing and accelerating the treatments offered to patients suffering from a rare disease, in a fair and equitable manner within the framework of Quebec public insurance. The adoption

of these new reimbursement methods in the field of rare diseases is most relevant since many of the new treatments are based on new scientific advances, highly targeted therapies. The population treated is smaller than for other more common diseases, so the overall impact on the health care budget is relatively small, which would allow the different methods to be tested.

Thus, the Quebec government, in collaboration with stakeholders, could analyze the criteria for which different reimbursement methods could be put in place and support the health network in implementing such agreements. Several methods are currently used elsewhere in the world, such as:

- Pay-for-performance where the price paid is adjusted to measured health outcomes;
- A form of “Mortgage”, to spread the costs over several years;
- Adjusting prices according to the specific conditions of each therapeutic application of a product;
- Investing a portion of confidentially negotiated rebates in the public-private fund dedicated to rare diseases, to support research projects, patient organizations or treatments for which the promise of value and risk are high.

THEME 7

Creating a public-private fund dedicated to rare diseases

Recommendation 7.1: Make representations to the Canadian government so that the Quebec government receives its share of the future federal program on rare diseases

The most competitive countries have all set aside public funds to support the special needs of rare disease patients. Canada is the only industrialized country that does not yet have a national rare disease policy in place, but the federal government has pledged to invest $1 billion over 2 years, starting in 2022-2023, to facilitate access to treatments. Based on current discussions with other provinces, this investment could be allocated to the implementation of a national drug plan for rare diseases (*National Pharma Care*). The federal government would also consider offering a surcharge when a patient's annual cost level exceeds a threshold at which the national insurance would cover the cost of treatment.

Given that Quebec already has a public group drug plan in place, the $1-billion federal investment could be allocated to the components of the strategic plan proposed here, through a federal health transfer. Quebec would have to recover approximately 25% of the federal government's investment, which corresponds to approximately $120 million/year. Quebec must seize this opportunity to leverage this investment and address the needs of patients and the innovation ecosystem.

Recommendation 7.2: Evaluate current Quebec government support for rare diseases

It would be important for the Quebec government to document the amount of money that is currently allocated to rare diseases. This evaluation would establish the basis from which improvements can be measured in the coming years.

Recommendation 7.3: Create a public-private support fund dedicated to rare diseases to leverage federal investment

The creation of a public-private investment fund dedicated to rare diseases would help develop a competitive innovation ecosystem and assist rare disease patients in obtaining the best available health care and enable the life sciences ecosystem to be more competitive. This fund could finance or co-finance concrete measures that have been agreed upon by the Montréal InVivo committee and the rare disease community.

The public-private rare disease fund could be established with contributions from all stakeholders to collectively drive and collaborate in its success. Each stakeholder could include their current or planned investments, but also enhance their support through existing or new programs.

- Federal government: health transfer dedicated to rare diseases associated with Quebec's portion of the $1 billion over 2 years, evaluated at $120 million/year, PLUS, enhancement of SR&ED tax credits for innovations in rare diseases and clinical research, increased investment in research via CIHR (competition dedicated to rare diseases each year);
- Quebec government: Current investments in health for rare diseases and for the support of research infrastructure (see 7.2) PLUS, implementation of the network of Centres of Expertise and Regional Centres, increased investments in research on rare diseases (target of 8% of the total budget), recruitment and training of health professionals for the management of patients' health, start-up grants to young researchers, directory of expertise for rare diseases and creation of a data registry for rare diseases;
- Pharmaceutical companies: confidentially negotiated rebates in rare disease drug reimbursement agreements directed to the fund, PLUS project funding to support rare disease innovation and improve patient care;
- Charities and patient associations: Evaluation of current support for charities, PLUS, funding for innovation projects and clinical studies driven by patients and their associations, funding for patient association registries, funding for the rare disease expertise directory and the RQMO iRARE Centre.

The needs are not one-time and isolated, but rather growing. Quebec must put in place a business model that will ensure the fund is sustainable so that the investment income generated can cover part of the fund's renewal. Models here and elsewhere have proven successful.

Our strategic plan proposes a series of measures that would enhance the investment of the governments of Quebec, Canada and other stakeholders to make Quebec at least as competitive as the world's leading countries in the field of rare diseases. These improvements could be financed by the public-private fund put in place.

If the key stakeholders were to invest a portion equivalent to the federal investment in Quebec, Quebec could have $360 million annually to improve patient care and stimulate innovation in the field of rare diseases. We do not have the data to determine the investments that would be required to implement the proposed recommendations. However, some of them would be low-cost (e.g., training of health care professionals) and should therefore be prioritized.

TIMELINE

The following diagram presents our proposed timeline for implementing our recommendations and identifying champions since responsibilities are sometimes associated with one party, such as the Quebec government or one of its departments. However, it is essential that all actions be supported by all stakeholders.

Figure 1: Timeline for strategic plan recommendations

2022 · 2023	2023 · 2024	2024 · 2025
Launch of activities of the rare disease consultation table (MIV, stakeholders) **1.3** Enhancing the newborn screening program (Quebec govt, INESSS, RSSS) **2.2 a** Training more health care professionals to optimize patient care (RQMO, MIV, universities, govt) **2.3** Developing and regularly updating a directory of expertise (RQMO) **5.2** Attracting more private investment in clinical research through competitive incentives (Govt, stakeholders) **6.1** Making representations to the federal government to accelerate Health Canada's processes (Govt and stakeholders) **7.1** Making representations to the federal government to recover Quebec's share of the federal program on rare diseases (Quebec govt, stakeholders) **7.2** Assessing the value of current Quebec support for rare diseases (Govt)	**2.2 b** Recruiting more health care professionals to optimize patient care (Govt) **3.1** Creating a Quebec health data registry for rare diseases (Govt, stakeholders) **4.4** Implementing a series of competitive incentives to support SME innovation (Ministère de l'Économie et de l'Innovation) **5.1** Positioning clinical research in the care trajectories for rare diseases (Govt, Catalis and stakeholders) **6.3** Making innovations accessible as soon as the therapeutic value is recognized by the INESSS and adjusting prices afterwards (Quebec govt and manufacturers) **6.4** Implementing innovative reimbursement arrangements (Govt and manufacturers)	**2.1** Creating specialized care centres and centres of expertise in the regions that include multidisciplinary expertise (Govt) **1.1** Facilitating access to genetic testing to speed up diagnosis (Govt) **1.2** Whole genome sequencing tests to all persons suspected of having a rare disease and their families (Govt) **3.2** Developing the Quebec pediatric reference genome (Govt, FRQ-S, GQ, CIHR, universities, stakeholders) **4.2** Increasing funding for research into rare diseases (Govt, FRQ-S, GQ, CIHR, universities, stakeholders) **4.3** Developing distinctive niches of excellence in rare diseases more common in Quebec (Govt, FRQ-S, GQ, CIHR, universities, stakeholders) **7.3** Creating a public-private support fund dedicated to rare diseases (All stakeholders)
Maintaining and reinforcing the achievements: **4.1** Stimulating collaboration between stakeholders **6.2** Supporting the improvement of INESSS evaluation processes		

Furthermore, the creation of a round table which brings together stakeholders will be essential to develop a global vision, mobilize the ecosystem, strengthen collaboration between all stakeholders and ensure a rapid and optimal deployment of the action plan resulting from the future Quebec policy on rare diseases and other initiatives of the rare disease community.

CONCLUSION

This Strategic Plan proposes seven major practical recommendations to the Quebec government to improve the competitiveness of its health innovations and to accelerate and optimize access to health care for its citizens. With a timeline spread over the next three years, the Montréal InVivo Rare Disease Project Committee is proposing concrete actions to certain project leaders in the sector. This timeline may seem aggressive and ambitious, but it reflects the committee members' sense of urgency to act and the great mobilization of the stakeholders in the ecosystem who were involved in developing this plan. Quebec patients and their families need more than a simple policy; what they need is an integrated action plan that is well articulated around the issues that affect them.

These recommendations are also the result of a consultation between several life sciences ecosystem stakeholders who would like to see the needs in the field of rare diseases met and significant scientific advances in diagnosis and treatment become more accessible to patients who could benefit from them.

In Canada

This Strategic Plan is inspired by the approach used in some European countries, notably Germany, France and the United Kingdom, where major axes have made it possible to articulate national strategies for rare diseases. Moreover, these national strategies make these countries internationally competitive in the development of innovations for the diagnosis and treatment of rare diseases. What Canada needs is not just a strategy, but a national plan, as in these countries, for rare diseases that is articulated around major axes. It must encompass several strategic areas, particularly support for research and development through innovation, national and international sharing of rare disease data, and appropriate patient support and management. The national plan for rare diseases must therefore be developed with the main goal of encouraging the emergence of therapeutic innovations in Canada, reducing delays in obtaining a diagnosis, rapid access to care and treatment, and better management of people affected by rare diseases.

Quebec's momentum

Without this national plan, Canada is behind other international players. Montréal InVivo and its specialized Rare Disease Project Committee believe that Quebec must rely on the skills and experience of the stakeholders identified as the bearers of solutions arising from the seven (7) major recommendations proposed. We firmly believe that the active and collegial participation of these key stakeholders would ensure a precise and effective collective deployment of the actions necessary to improve the lot of Quebec families affected by rare diseases. Quebec would thus be a leader in Canada as a result of the numerous short-term gains while carrying a long-term vision of excellence and innovation in the support and care of affected families as well as in the investment and promotion of innovation in rare diseases.

Finally, the measures proposed for rare diseases would be equally relevant for rare cancers and complex therapies. These broader applications demonstrate the need to look at the big picture across government departments, to foster decompartmentalisation, and to support open and transparent collaboration between government, policy, industry, medical, research and community stakeholders.

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APPENDIX A

List of the members in the Rare Diseases Project Committee

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Coordination of the Rare Diseases Project Committee
(until January 2022):

Nathalie Ouimet
Vice-President
Montréal InVivo

A multi-disciplinary committee representing the entire ecosystem
We also thank all the external contributors of this Committee for their involvement in the project.

*Members of the Working Committee

APPENDIX B

Developing a national drug strategy for rare diseases - what we have heard from Canadians, Health Canada consultation report

EXECUTIVE SUMMARY

Canadians with rare diseases want access to medications that can help them manage and treat their disease. However, these drugs can be extremely costly: in 2019, there were 93 rare disease drugs approved in Canada that cost more than $100,000 per patient per year, with more than half costing more than $200,000.

The question of how to ensure equitable access to medications for the treatment of rare diseases while supporting the sustainability of the health care system was raised during the 2018 consultations of the Advisory Council on the Implementation of National Pharmacare. In its final report, the Council recommended the creation of a national strategy to provide patients with equitable, consistent and evidence-based access to these specialty drugs. In response, the Government of Canada has committed to working with the provinces, territories and other partners to create a national strategy on drugs for rare diseases.

In January 2021, Health Canada launched a national online engagement process to allow Canadians - particularly rare disease patients, their families and other stakeholders - to provide their views and ideas for a national strategy. This report summarizes the responses to the national public and stakeholder engagement, which took place from January 27 to March 26, 2021.

Participants were invited to respond to the document entitled: Building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians, which raises three main issues:

How to improve patient access to high-cost drugs for rare diseases and ensure that access is consistent across the country.

How to ensure decisions on covering high-cost drugs for rare diseases are informed by the best evidence available.

How to ensure spending on high-cost drugs for rare diseases does not put pressure on the sustainability of the Canadian health care system.

Engagement was conducted through five virtual town hall meetings, 16 virtual stakeholder meetings, an online questionnaire, and email and mail submissions. The engagement captured diverse perspectives and participation from more than 650 individuals and organizations, including patients and family members with lived experience. Here is a summary of what we have heard.

What we heard... about improving access to treatments for rare diseases and standardizing access across Canada

Where a person lives should not affect their access to treatment. People told us that the "postal code lottery" exists because each jurisdiction (i.e., the provinces and territories) decides which drugs it will cover (commonly referred to as the "list of insured medications"). In addition, jurisdictions may have different criteria that must be met before drug coverage is considered. People noted that similar issues arise when an individual's drug coverage is part of a private insurance plan (i.e., a drug plan offered to employees by their employer). This creates gaps in treatment according to the place of residence.

Participants felt that a single national framework for rare disease treatments would make access more fair and would be the most important element of a national strategy. However, participants cautioned that a national strategy should not eliminate access for those who already have access through public programs. They also called for a transparent coordinating body and greater system alignment, and for patients and clinicians to have a greater say in all aspects of the strategy.

What we have heard... about getting the best possible evidence for decisions on drugs for the treatment of rare diseases

Because of the small number of people with rare diseases, it is rarely possible to meet the usual standards of evidence for drug approval. Many participants stated that drugs for rare diseases must be evaluated differently than drugs for common diseases. There was a call for patients and their caregivers to be engaged in defining what constitutes a "benefit" or "improvement" when evaluating treatment outcomes.

The vast majority of respondents ranked innovative approval and coverage models, such as payment for performance, early access and managed access, as the most important option for building a better evidence base. Some of the alternative options suggested included accelerating the approval of drugs already approved in other countries, evaluation of evidence by expert panels using international and Canadian data, and membership in international evidence-sharing networks. Participants emphasized that patients and clinicians must be included in any expert panel that reviews the potential benefits of a drug.

What we have heard... about the balance between spending on drugs for rare diseases and the overall sustainability of the Canadian health care system

Many people felt that the focus on the high cost of medicines overlooked their value to patients, the health care system, and society as a whole. In general, participants felt that there was a need for more transparency in the way drug prices are set and suggested that governments work together to bring prices down. In considering the options, most felt that more cost sharing and risk pooling was the best approach. Some participants thought that the federal government could reinsure drug plans, covering the costs of drugs exceeding a certain threshold.

Other ideas included payment for performance (where governments fund drugs based on the effectiveness of the product), but others cautioned that this approach does not result in lower costs or more effective treatments. Some people thought that investing in open science and in Canadian drug research, development and manufacturing would produce cost-effective treatments over time. We saw overwhelming support for international collaboration and many people wanted to see more done to bring clinical trials to Canada, as they allow patients to try new and promising treatments.

What we have heard... from Aboriginal partners

Aboriginal Canadians carry a higher burden of illness and have poorer health outcomes than non-Aboriginal Canadians, and face a different reality when accessing health services. First Nations, Inuit and Métis experiences with the system can differ significantly, making it important for the national strategy to recognize and consider a distinctions-based approach to improving health outcomes.

Building trust and combating racism in the health care system is key. Aboriginal participants and many other stakeholder groups want to see transparency in decisions about an individual patient's eligibility for funding for drugs for rare diseases, and an appeal process so that patients who are denied funding have the opportunity to challenge the decision.

Aboriginal peoples are increasingly providing their own health services. Participants expressed concern about the impact of the national strategy on existing Aboriginal health programs, as there are existing agreements between Aboriginal governments and other governments on the funding and provision of health services. The strategy must respect these existing agreements, maintain an ongoing dialogue with Aboriginal partners at the decision-making tables and ensure that care is maintained.

APPENDIX C

Summary of the results of the bibliometric study on public research in rare diseases

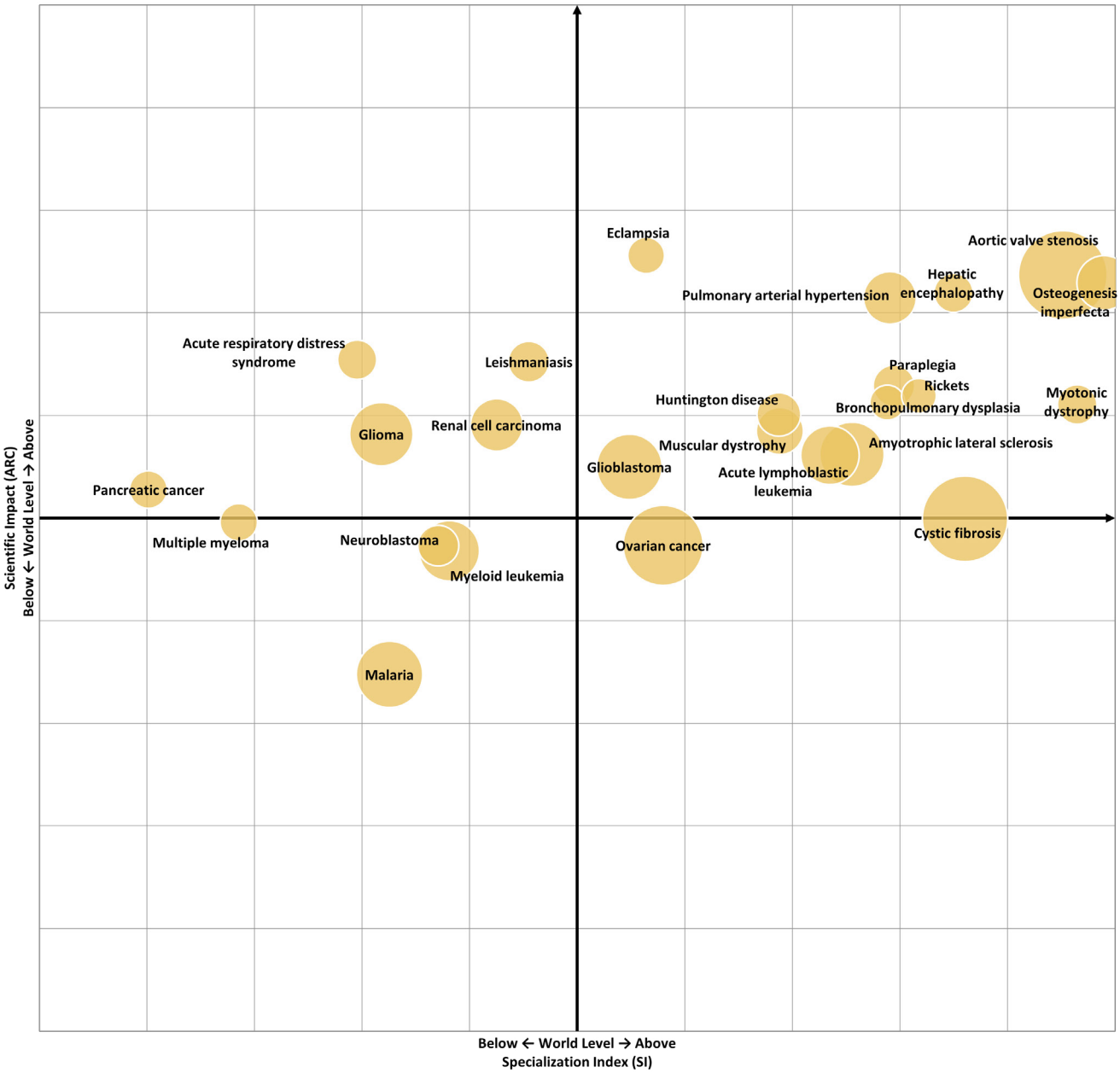
From a set of 1.1 million articles published between 2010 and 2019 on rare diseases, Canada contributed 42,000 (3.8%) of these articles, in 9th place. Quebec contributed 10,000 articles (24.7% of the Canadian total and 0.9% of the global total). Ontario published half of the Canadian publications on rare diseases with 21,600 articles. 59.3% of the articles published by Canada were international collaborations (8th highest). It is also noted that the trend of publication on rare diseases is increasing worldwide, particularly in China and Russia.

The medical subject headings (MeSH) in MEDLINE were used to determine whether the articles were on rare disease diagnoses or therapies. Quebec contributed 2,000 articles on rare disease diagnoses (23.5% of the Canadian total) and 3,700 articles on rare disease therapies (23.6% of the Canadian total).

Specialization is measured by comparing the proportion of the number of articles published in the field of rare diseases in a country, compared to the global proportion. Turkey, Japan and Italy were the countries most specialized in rare diseases. Canada does not specialize in rare diseases, so public research output in rare diseases is less than the world average for publication in this area. None of the provinces are specialized, with Ontario and Manitoba being the most specialized. The analysis of specialization by disease shows that Quebec research is specialized in osteogenesis imperfecta, aortic stenosis and cystic fibrosis.

The impact of publications is measured by comparing the number of relative citations an article received to the number of citations received by all articles published in the same year and in the same field. We also analyze the proportion of publications in the top 10% of most cited publications, based on the number of relative citations. Publications from the United States, the Netherlands and the United Kingdom had the highest impact in the field of rare diseases. Canada had the highest impact worldwide (5th out of 25 countries). It should be noted that scientific articles published by Canadian researchers are always among those with the highest impact. This is also the case for the field of rare diseases.

Figure 2: Quebec's performance by disease

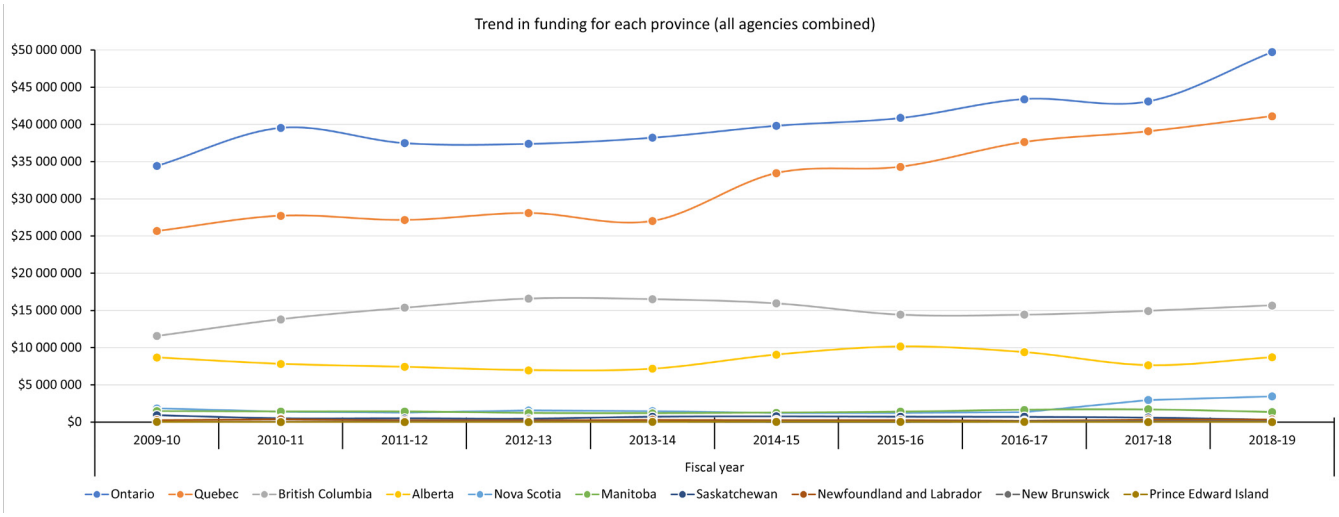


Legend: Right side: specialization above the world average; Top side: impact above the world average.

Finally, research funding was determined by analyzing the amount of funding for rare disease research in each province from the databases of the three granting councils: Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC) and the Social Sciences and Humanities Research Council (SSHRC). The CIHR, the NSERC and the SSHRC granted $1 billion in research funding for rare diseases in Canada between fiscal years 2009-10 and 2018-19. Ontario received 40.2% of this funding, Quebec 32.5% (above its population weight), British Columbia 14.9% and Alberta 8.3%.

Funding increased in Ontario and Quebec, but remained stable in the other provinces. The gap between Ontario and Quebec has narrowed in recent years. Note that the funding data does not include funding received by foundations, which are important sources of funding in the field of rare diseases.

Figure 3: Funding for research on rare diseases



APPENDIX D

Comparative study on public policies for rare diseases - summary provided by Synergyx Consulting

Canada is lagging far behind in the area of rare diseases, both in terms of legislation and health and economic policies to encourage research and access to treatments for those affected.

Most industrialized countries have legislation, plans or strategies for rare diseases: the United States adopted the *Orphan Drug Act*, other countries have followed or been inspired by the American model, notably Japan (1993), Australia (1998) and the European Union (2000). France is already in its third French National Plan for Rare Diseases (2018-2022). Germany is currently working on its second *National Action Plan for People with Rare Diseases*. In fact, 26 of the 28 European Union member states have their own national plans for rare diseases.

The Canadian government initially rejected the idea of an orphan drug policy in 1997. Then in 2012, Health Canada announced its intention to develop a strategic framework. Almost a decade later, Canadians with rare diseases continue to wait for a comprehensive plan to be implemented. In January 2021, Health Canada announced a consultation with rare disease patient organizations in connection with the *National Strategy for Drugs for Rare Diseases Online Engagement*.

In Quebec, the provincial government had established the Groupe de travail québécois sur les maladies rares (Quebec working group on rare diseases) (GTQMR) in July 2018. The GTQMR presented the results of its work in a report published in July 2020 with general recommendations at the strategic level concerning the organization of care and services for the care of people affected by rare diseases.

Although the actions initiated by the Canadian and Quebec governments represent the first steps in the right direction, there are still many steps to be taken before we arrive at a national plan or strategy that addresses the complex needs of people living with rare diseases.

Health and economic policies

Business incentives have been the cornerstone of policies to stimulate research and development of so-called orphan drugs for the treatment of rare diseases. These incentives have had the desired effect of stimulating research into treatments for rare diseases.

Legislation, regulations and policies in Europe and the United States have been developed to encourage research and development of drugs for the treatment of rare diseases. Essentially, five broad categories of incentives have been created: tax credits, priority drug reviews by regulatory agencies, research grants, scientific support in clinical research protocol development and market exclusivity.

These financial and structural advantages in support of research and development of treatments for rare diseases have had a significant impact on the expansion of the pharmaceutical industry and the marketing of drugs for rare diseases.

Access to treatment

The current Canadian policy on drug development and marketing is not specifically adapted for orphan drugs. As for Quebec's drug reimbursement policy, it does not, in its current state, address the issue of access to drugs for rare diseases.

While there is no national program to cover drugs considered expensive for rare diseases, most Canadians have some protection against the cost of these drugs through provincial, territorial, federal or private insurance programs.

In sum, Canada currently does not have a national drug plan for rare diseases like France and Germany, but rather a patchwork of public and private drug plans. As a result, this results in inequities in drug coverage for rare diseases from province to province.

Need to develop an integrated national plan

Canada should follow the model of developing national plans for rare diseases in France and Germany. The central framework of the national plan should be developed with the priority objectives of improving diagnosis and screening for rare diseases, providing better coordination of care and tailored support for patients. In addition, the plan should put in place measures for more efficient and equitable access to treatments, as well as foster the emergence of innovation and research for rare diseases.

It is essential that Canada put in place a legislative and regulatory framework specifically developed for rare diseases. Through this process, Canada should also consult with rare disease patients and families, specialized clinicians, researchers in the field and representatives of the pharmaceutical industry. Canadians need an orphan drug framework to ensure timely access to safe and effective treatments.

Moreover, patient groups for rare diseases, such as the *Canadian Organization for Rare Disorders* (CORD) and the Regroupement québécois des maladies orphelines (RQMO), had each developed rare disease strategies, policies promoting innovative research, action plans and numerous proposals, mainly aimed at reducing screening and delays in diagnosis, improving patient management and optimizing access to treatments. The federal and provincial governments could adopt and implement the strategies developed by CORD and RQMO, since these strategic frameworks have been developed and validated by scientific and clinical experts in rare diseases.

Possible solutions

There are many sources of inspiration in the development and reimbursement of drugs for rare diseases. The majority of the 30 member countries of the Organisation for Economic Co-operation and Development (**OECD**) have orphan drug policies, programs or legislation in the form of designations, market exclusivity, research grants, pre-market access to drugs, tax credits, research grants and fee waivers from regulatory agencies.

First, while respecting the sharing of provincial health jurisdictions, the Government of Canada should create a federal bill including a national strategy for rare diseases. A detailed action plan with specific timelines and funding to support the actions and implementation of the plan across the provinces. The efficiency of this approach has been demonstrated in France and Germany. Moreover, in 2017 Ontario developed its strategic framework aligned with the one proposed by CORD, including an action plan, a work schedule and grants from public funds.

Second, the federal government should amend the Food and Drug Regulations to provide additional intellectual property protection for drugs for rare diseases. Given that the time required to research and develop these drugs can be inordinately long, providing additional time for patent protection could be an important strategic incentive for pharmaceutical companies. This would make Canada more competitive in the international market and more attractive to foreign investment.

Another incentive for the federal government to consider is the possibility of granting market exclusivity to pharmaceutical companies developing drugs for rare diseases. Studies in the United States and Europe show that this has been one of the best incentives for research and innovation in rare diseases, as it provides certainty for pharmaceutical companies to gain a tangible commercial advantage. The period of market exclusivity is seven years in the United States, five years in Australia, ten years in Japan and in the European Union (with an additional two years for a pediatric indication, for a total of twelve years of exclusivity in Europe).

Another interesting intervention would be to provide tax credits, grants or funding to encourage research and development of therapies for rare diseases. Experience in the United States and Europe shows that these financial incentives allow pharmaceutical companies to recoup a certain return on their investment, otherwise impossible with the simple marketing and sale of drugs. In the United States, a 50% tax credit is applicable to the costs associated with clinical research on orphan drugs. In Canada, the *Scientific Research and Experimental Development Program* (**SR&ED**) exists to obtain tax credits. However, this program is not specifically designed for research in rare diseases.

Second, concrete accessibility legislation, such as drug reimbursement policies, should be enacted at the provincial level. A pan-Canadian initiative to harmonize provincial reimbursement policies would make access to treatment faster, more efficient and more equitable.

An often overlooked initiative is public awareness and education of health professionals about rare diseases. Very few Canadians understand exactly what a rare disease is. It is therefore important to address this issue quickly in order to obtain a network of specialized clinical experts across Canada. Moreover, one of the recommendations of the GTQMR in its July 2020 report is to develop a training plan for front-line professionals to recognize rare diseases and to quickly refer patients to an expert for a diagnosis to be made.

Finally, the proposals of CORD and RQMO concerning the creation of a registry for the collection of data on rare diseases would be relevant in the Canadian and Quebec context. This would make it possible to count the number of people suffering from rare diseases, to follow them throughout their illness,
to have access to a bank of patients in order to facilitate recruitment in clinical trials, to accumulate data on the real clinical situation, the costs of treating rare diseases and the insurance coverage of drugs. This real-life data will contribute to the development of evidence-based bills.