Submission for Rare Disease Consultation

March 26, 2021

We are writing to you on behalf of the national patient organizations and networks signatory to this submission regarding the open consultations on building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians.

We appreciate the opportunity to engage in this dialogue on behalf of oncology groups, some of which represent people living with rare cancers.

The issue of rare diseases is one that is of profound importance to people living in Canada as well as to people around the world. Between 6,000 and 8,000 rare diseases have been identified, most of genetic origin and with severe clinical manifestations. Due to insufficient knowledge on disease pathology, diagnosis is frequently delayed, often resulting in early and irreversible complications. Thirty percent of rare disease patients die before the age of five.[1]

Those affected by rare diseases are also more psychologically, socially, economically and culturally vulnerable. These difficulties could be overcome by appropriate policies that support patient health and wellness. Due to the lack of sufficient scientific and medical knowledge, many patients with rare diseases are not diagnosed and their disease remains unidentified. These are the people who suffer the most from difficulties in receiving appropriate support.[2]

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[1] Czech, Marcin, et al. "A review of rare disease policies and orphan drug reimbursement systems in 12 Eurasian countries." *Frontiers in public health* 7 (2020): 416.

[2] Orphanet: About rare diseases. https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN. Accessed March 19, 2021.

There is no question that research, clinical care and treatment access across the continuum for all diseases impacting small populations, be they for rare diseases that are genetically based, unlinked to each other, generally impacting young populations and life threatening such as Tourette Syndrome, Cystic Fibrosis, and narcolepsy or rare cancers including Multiple Myeloma, Chronic Myeloid Leukemia, Gastrointestinal Stromal Tumours, rare skin cancers , Uveal melanoma, Waldenstrom macroglobulinemia, Mycosis Fungoides Cutaneous T-Cell Lymphoma and pediatric cancers, do not fare well in the present Canadian public/private health research, health regulatory and reimbursement systems.

Not enough is spent on research in any of these areas and the present health technology assessment processes do not serve them well. As a result, reimbursement of rare disease drugs including those for cancer, in both the pediatric and adult settings, is often denied or limited. As a result, lifesaving, transformative, and quality of life-enhancing treatments are unavailable in practical terms except for the few who have access to a comprehensive private plan or can afford to pay for them out of pocket.

Treatments for these small population diseases require discrete, tailored policies and processes that recognize their distinct characteristics and needs, and taking into account the social determinants of health. Additionally, by nature of their rarity, small population diseases are likely to go undiagnosed for long periods of time due to lack of awareness and education by primary care providers. The number of specialists that diagnose and treat such diseases is limited.

We submit that rare cancers should indeed be considered as part of a national strategy for rare diseases. For the purpose of a national strategy for rare diseases, the proposed definition for a rare disease should include cancers that affect small populations, in both the pediatric and adult settings

We also submit that dedicated and equitable funding that is supported by robust risk-sharing models are important elements of such a national strategy.

In terms of infrastructure and supports, in the field of cancer, we have many foundational research and review bodies as well as strategies and agencies, including CADTH's pan-Canadian Oncology Drug Review (pCODR) process, the Canadian Strategy for Cancer Control under the auspices of the Canadian Partnership Against Cancer, provincial cancer agencies and networks such as Canadian Association of Provincial Cancer Agencies. We also have dedicated research bodies including the Canadian Clinical Trial Group (CCTG), Institute of Cancer Research (ICR) at the Canadian Institutes for Health Research (CIHR) Canadian Cancer Society, (CCS), BioCanRX, as well as hospital-based research initiatives. Their processes will require adaptation but are definitely amenable to accommodating the needs of rare cancers.

The treatment and management of cancers also have programmes and processes across Canada. Examples include the Odette Cancer Centre at Sunnybrook Hospital and the Princess Margaret Hospital in Toronto, Tom Baker Cancer Centre in Foothills Medical Centre in Calgary, the Segal Cancer Centre at the Jewish General Hospital in Montreal and the Nova Scotia Cancer Centre in Halifax.

In our submission, a dedicated stream for rare cancers within those bodies, programmes and agencies, supported by adequate resources is essential to supporting people impacted by these rare cancers. This ensures that the unique factors about rare cancers are built into these systems to provide them an equitable opportunity to be researched and for treatments for them to be developed, approved, reimbursed and made available to patients for whom traditional clinical trial methodologies and endpoints are challenging. Even in cases where clinical trials can be conducted in a small set of patients,

access may well still be unattainable through public reimbursement plans due to rigidity within current health technology assessment processes, inflexible pricing approaches and the lack of sufficient real-world evidence to support small clinical trials, even taking into account international data. A national strategy to improve patient access to rare disease drugs, including those that treat rare cancers, must provide adaptation for rare cancers that the limitations of the existing systems contain.

The first step is the recognition by all health stakeholders of the need for a dedicated stream for rare cancers along the translational continuum. Leadership at the political and bureaucratic levels, both federally and provincially, is required to ensure adequate dedicated funding for rare cancers and policy direction to create and implement dedicated streams across the cancer landscape within a specific timeframe.

Meaningful multistakeholder engagement, led by patients and their representatives, must be a pillar of the creation, implementation and monitoring and evaluation of this dedicated rare cancer stream within the present cancer system.

This dedicated programme would be cost-effective, efficient, sustainable, and patient-directed. It will require the agreement of all healthcare stakeholders but is eminently doable with the commitment of all our groups.

Overarching Recommendations

Recommendation 1

Meaningful engagement of patients and patient groups be undertaken to ensure the inclusion of patient voices, including those with limited access to the social determinants of health.

Recommendation 2

Consultations with Indigenous populations be undertaken to develop a national strategy for rare diseases that is led by them and meets the needs of these populations, aligning with OCAP, OCAS, QI and other relevant Indigenous principles.

Recommendation 3

The national strategy for rare diseases must take into account, and meaningfully engage with urban, rural and remote populations, to ensure that the strategy meets the needs of all rare disease patients living in Canada.

1. Strategy Scope and Definition

1.1. Rare Disease Definition Options

In considering an appropriate definition for rare disease in Canada, we reviewed definitions in selected countries and the processes by which they were chosen.

a) United States

The history of rare disease, also called orphan disease, drug policy in the U.S rose to prominence in the 1980s, although they had been aware of the problem for some time. The discussion began in earnest in the 1960s with concerns over pediatric drugs that were being approved for use in adults but not children, the reason for which was assessed to be the small sales potential for that population.

The U.S. *Orphan Drug Act* of 1983 has been considered by some to be one of the most successful pieces of health-related legislation passed in the U.S.[3] It is comprehensive including a definition of orphan drugs, provision of incentives for drug development as well as access opportunities for patients with rare diseases.

The definition of an orphan disease was difficult for the legislators to determine. Originally, *the Act* required the manufacturer to set out facts and circumstances that rendered the drug unprofitable, in order to qualify. Because the price of the product and the cost of its development were not available to regulators, the FDA recommended that a number be chosen to define an orphan drug. The original number was a prevalence of 100,000 patients in the U.S., but that number was increased to 200,000 because otherwise Tourette Syndrome, multiple sclerosis and narcolepsy would have been excluded.

Over time, orphan drugs became no longer drugs of limited commercial value but attractive business opportunities.

b) European Countries

In a review of rare disease drug policies in national plans in the EU, all EU countries have such plans. Implementation differs between countries, however, with nearly all Orphan Medicinal Products covered in the Netherlands, Germany, and France, but not in other EU countries. Reimbursement rules differ considerably regionally. A trend is being observed of reimbursement conditions getting stricter for expensive orphan drugs.

[3] Mikami, Koichi. "Orphans in the market: the history of orphan drug policy." *Social History of Medicine* 32.3 (2019): 609-630.

The EU defines a rare disease as that having a prevalence of fewer than 1 in 2000 people.[4] Some European countries, however, have add-on definitions. Examples follow.

Netherlands
In the Netherlands, the designation of an orphan drug also includes a drug that targets a disease with a prevalence of less than 1 in 150,000 and shows a clinically proven therapeutic benefit, and no other registered medicine exists.[1]

France
France introduced an extra definition of **rare cancer** if the cancer occurs in less than 6 in 100,000 per year or requires specialized treatment due to untypical tumour location or complex disease characteristics.[1]

c) United Kingdom

Early on, the UK government adopted a different approach than the U.S., considering that existing drug regulation could manage drugs for any size population. This changed, however, in the 1990s when European policy makers including the UK began to favour legislation similar to the U.S. model.[3]

The definition of rare disease in the UK is the same as the definition accepted by the EU, with the addition by the National Health Service (NHS) of all conditions that require specialized medical care as rare if they occur in fewer than 500 citizens yearly.[1]

Scotland
In addition, Scotland introduced a new definition for "ultra-orphan" drugs in October 2018 as "medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland," which is used to facilitate early access programs and reimbursement processes.[1]

1.2. How Do We Ensure the Strategy Includes Drugs for Multiple Therapeutic Areas?

This will depend on the definition of therapeutic area. Given that there are many different rare cancers, an overarching definition of oncology as a therapeutic area will not serve the needs of the rare cancer community.

[4] Building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians - Canada.ca. https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement/discussion-paper.html. Accessed March 19, 2021.

1.3. How to Ensure the Strategy Includes Different Types or Formats of Treatments?

Cancer is a complex and rapidly evolving field with accelerating developments in diagnostics, treatments, and novel research methodologies including basket trials. To ensure that the strategy includes different types and formats of treatment, the complexities around cancer diagnosis and treatment must be recognized and appreciated, and, therefore, decision-making must involve leading experts in the rare cancer field.

Recommendation 4

A multistakeholder group of leading experts in all relevant areas, including rare disease patients as well as those with rare cancers, both adult and pediatric, be convened with a Terms of Reference that include recommending the most appropriate definition for rare diseases in Canada that is inclusive, ensuring access for all rare diseases. In its deliberations, the group will take into consideration prevalence and incidence as well as other relevant factors, including best practices internationally. This group should also carefully consider drugs for conditions that span multiple therapeutic areas.

As a result of the dynamic landscape of cancers, including rare cancers, leading experts in the rare cancer community such as medical practitioners, researchers, patients, and patient representatives, must be included as an integral part of decision making about types and formats in rare cancers.

2. Funding and Risk-Sharing Models

In considering funding and risk-sharing models for rare cancers that are appropriate for Canada, we reviewed the development and implementation of such models in select countries.

a) European Countries

Compassionate Use

Most EU member countries have established a Compassionate Use Programme (CUP), that can be requested at the country level, or centrally via the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), when adequate clinical evidence exists on safety and efficacy. France uses CUPs extensively for rare diseases, with 70% of currently reimbursed orphan drugs having had early access prior to receiving market authorization.[1]

France has an additional legal framework for reimbursement, known as a Recommendation for Temporary Use (RTU), which provides early access to already registered drugs for which a new indication is still under assessment. RTUs provide a more flexible access approach than CUPs. In the Netherlands, CUPs are rigid and only allow access to non-registered drugs regardless of whether the orphan indication is approved or not.[1]

b) United Kingdom

Scotland has a two-tier program for access to drugs that are not normally available through the healthcare system called the Peer Reviewed Clinical System (PACS), with tier-1 reserved for ultra-orphan drugs and tier-2 for other non-routine drugs (not approved by the Scottish Medicine Consortium). Under PACS, cost-effectiveness is explicitly excluded from any argumentation for access.[1]

In addition to government programmes, the National Health Service (NHS) reached a specific agreement with Johnson and Johnson by which the company agreed to refund the NHS in either cash or product for Multiple Myeloma patients who do not respond after four cycles of treatment with Velcade, with responding patients receiving an additional 4 cycles for free.[5]

Recommendation 5

Under the umbrella of the multistakeholder group described in **Recommendation 4**, a committee be formed including all relevant health stakeholders, with Terms of Reference to analyze options for funding and risk-sharing models. The committee will develop a proof-of-concept in at least one rare cancer and one other rare disease area, and implement, monitor, and evaluate with a commitment to scale-up successful models.

3. Infrastructure and Supports

As discussed earlier, in the Canadian cancer landscape, we have many foundational research and review bodies as well as strategies and agencies including CADTH's pan-Canadian Oncology Drug Review (pCODR) process, the Canadian Strategy for Cancer Control under the auspices of the Canadian Partnership Against Cancer, provincial cancer agencies and networks such as Canadian Association of Provincial Cancer Agencies. We also have dedicated research bodies including the the Canadian Clinical Trial Group (CCTG), the Institute of Cancer Research (ICR) at the Canadian Institutes for Health Research (CIHR), BioCanRX, as well as hospital-based research initiatives.

As a result, we do not require the creation of new infrastructure. Presently, those infrastructures do not recognize the differences between generating and analyzing evidence regarding rare cancers and common cancers. For example, health technology assessment criteria that measure the value of treatments for common cancers cannot be applied in the rare cancer setting.

In considering infrastructures and support models for rare cancers appropriate for Canada, we reviewed innovative trial designs in select countries. Examples follow.

Novel Clinical Trial Methodologies in the EU

In the EU, programmes are being implemented to develop innovative scientific and methodological approaches to improve evidence generation and analysis for small populations including new trial

[5] Carlson, Josh J., et al. "Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers." *Health policy* 96.3 (2010): 179-190.

designs and clinical endpoints. Examples of these programmes include IDEAL (Integrated Design and AnaLysis of small population group trials), ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXellence).[1]

Novel methodologies such as Goal Attainment Scaling (GAS) and single-subject design allows for robust data collection on safety and efficacy of rare disease drugs and enables the adaptation of health technology assessment processes to rare diseases including rare cancers.[1]

Recommendation 6

The existing infrastructures and supports, both federally and provincially, be mandated to create a dedicated rare cancer stream aligned across provincial and federal jurisdictions to meet the discrete needs of rare cancer patients. Appropriate resourcing must be made available to support these mandates. To accomplish this, all relevant stakeholders must be meaningfully consulted.

International best practices in innovative clinical trial design for small populations must be evaluated and accepted as dedicated standards for rare cancers. The health technology assessment systems and other relevant reimbursement bodies must recognize and adopt these new dedicated standards in their assessments including value assessments.

Data Collection

Relevant evidence generation, data collection and data sharing, including real-world evidence, are key elements in rare disease infrastructures and supports.

Australian researchers strongly recommend the development of registries that collect accurate clinical data over time as critical for diseases with low prevalence, where there are large variations in treatments and outcomes. Rare disease registries can act as fundamental support structures for clinical trials and translational research that improves quality of care, quality of life and survival.[6]

Recommendation 7

Convene an expert group to conduct an environmental scan of repositories of data for rare diseases including rare cancers and ensure best practices in evidence generation, data collection and data sharing, including real-world evidence.

CanREvalue can potentially be the appropriate convenor for such a group given its work to date in developing a framework for the generation and use of real-world evidence for cancer drug funding decisions in Canada.

[6] Lacaze, Paul, et al. "Rare disease registries: a call to action." *Internal medicine journal* 47.9 (2017): 1075-1079.

4. Summary of Recommendations

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Working together, we can do better for rare cancer patients. We look forward to meeting with you to discuss specific considerations for rare cancer patients that would contribute to an effective, patient-oriented national strategy to improve cancer patients' access to rare disease drugs. Please do not hesitate to reach out if you have any questions or would like to discuss our submission. We will reach out to you in the coming days to schedule a meeting to continue this discussion.

On behalf of,

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CONECTed, a network of 7 National Cancer Groups including paediatric cancer
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