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Letter to the Editor: New Observation

Equitable Access to Disease-Modifying Therapies for Canadian Children with SMA and Four *SMN2* Copies

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As Canadian pediatric neurologists and neuromuscular specialists, we urge provincial payers to align and provide universal access to an appropriate disease-modifying therapy (DMT) for children with spinal muscular atrophy (SMA) with four *SMN2* copies identified through newborn screening (NBS). Failure to do so leads to preventable disability and widens inequity in care. Among comparable countries with public drug reimbursement programs, Canada is an outlier, with only Québec providing reimbursement for patients with SMA and four *SMN2* copies. It is not justifiable that patients must move across our country to access therapies.

SMA is an inherited disorder characterized by the irreversible loss of motor neurons and progressive muscle atrophy and weakness. SMA results from biallelic mutations in the survival motor neuron 1 (*SMN1*) gene. The paralogous *SMN2* gene shows copy number variability, with each *SMN2* copy producing about 10% of the survival motor neuron (SMN) protein ordinarily produced by a single, functional copy of *SMN1*.[1] *SMN2* copy number offers some predictive value regarding disease severity. The requirement for SMN protein is highest from late fetal life to early childhood when the structural connections of the neuromuscular system are developing.[2]

Prior to the emergence of effective treatments, individuals with SMA were classified into types based upon highest motor milestone achieved. Children with SMA type 3, the "mildest" form of childhood-onset disease, typically develop symptoms after 18 months of age, many before 3 years of age.[3] Although patients are initially able to walk independently, many will lose this ability without a DMT. Patients with SMA type 3 have either three (64%) or four (31%) *SMN2* copies.[1]

Health Canada has approved three DMTs for SMA: nusinersen (in June 2017), onasemnogene abeparvovec (in December 2020) and risdiplam (in April 2021). Clinical trials have demonstrated early, presymptomatic treatment to be associated with the greatest clinical benefit in infants with two and three copies of *SMN2*, which has prompted the inclusion of SMA into an increasing number of NBS programs. Infants with four *SMN2* copies are identified in most countries performing NBS, and the increased recognition of early childhood onset in the majority of these children has led to an increased number of jurisdictions treating patients with four *SMN2* copies.[4,5] As of August 2024, 100% of Canadian newborns are currently screened for SMA at birth, allowing for early and/or presymptomatic treatment.

Provincial NBS programs typically identify infants with biallelic *SMN1* deletions and four or fewer *SMN2* copies as a positive screen, referring them for counseling and confirmatory genetic testing. Ontario was the first province to include SMA in its' NBS program since January 2020.[6] The initial Ontario recommendations were to immediately treat infants with SMA who had three or

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fewer *SMN2* copies and to closely follow those with four *SMN2* copies. This recommendation was based upon the lack of inclusion of infants and children with four *SMN2* copies in clinical trials as well as uncertainty regarding natural history data for the four *SMN2* copies. While the Ontario recommendations were initially aligned with other expert opinions,[7] this has changed due to the emergence of increasing natural history data for patients with four *SMN2* copies. In a rapidly evolving field with new evidence, international expert opinion now recommends early and presymptomatic treatment of all patients with four *SMN2* copies[4,5]. There are several reasons for this recommendation. First, four *SMN2* copies can be associated with more severe, early-onset disease, with one cohort ($N = 52$) reporting 6% of patients with four *SMN2* copies to have severe, infantile SMA type 1 and 13% to have SMA type 2.[8] Second, 88%–92% of patients with four *SMN2* copies will show symptom onset in childhood,[1,8] with the median age of symptom onset at 3.0 years, and 55% of infants manifesting symptoms prior to that age.[3] A German cohort that followed some NBS-identified, four *SMN2* copy infants found that five out of seven (71%) of the untreated four *SMN2* cohort showed symptoms between 18 months and 4 years of age.[5] Unpublished data from the Canadian Neuromuscular Disease Registry (CNDR) for patients with SMA and four *SMN2* copies ($N = 42$), for whom symptom onset was reported ($N = 33$), demonstrated the median age of symptom onset to be 2.5 years old (range: 9 months to 24 years old).

In all subtypes of SMA, there is an irreversible loss of a large pool of motor neurons that occurs before the emergence of clinical symptoms. Without treatment, one-third (33%) of patients with four *SMN2* copies will lose the ability to walk, 43% will develop scoliosis and 6.3% will require noninvasive ventilation.[3] Although "milder" compared to the natural history of severe infantile SMA, severe proximal weakness with loss of independent ambulation and need for ventilatory support is a significant and avoidable burden of disease for patients, families and society. People with SMA type 3 and their caregivers report a considerable financial cost and burden. In the 12 months prior to completing an anonymous questionnaire, Canadians with SMA type 3 or their caregivers ($N = 283$) reported a mean expenditure of $16,360 Canadian dollars on assistive devices, $18,927 on home modifications and $14,103 on out-of-pocket expenses for SMA-related professional services.[9] Caregivers of people with SMA type 3 ($N = 241$) reported a high level of financial strain (59.5%), physical strain (55.5%) and sleep disruption (59.8%) and/or needed to adjust their own work schedule to accommodate their loved one's needs (80.9%).[9] Almost half of the caregivers (43.1%) reported "feeling completely overwhelmed," emphasizing the impact that this "milder" form of SMA has on Canadian families and society.[9]

In Canada, the Patented Medicine Prices Review Board (PMPRB) plays an important role to ensure that the pricing of patented medicines is not excessive and is aligned with key comparator countries (PMPRB-11) that provide public reimbursement of medication. Among the 11 comparator countries, Canada and Australia are two jurisdictions that do not extend DMT for all pediatric patients with four *SMN2* copies. In Canada, the treatment access for SMA patients with four *SMN2* copies highlights significant disparities due to varied provincial policies. While Québec's Institut national d'excellence en santé et en services sociaux (INESSS) recommends full reimbursement for these patients, other provinces follow the Canadian Drug Agency guidelines limiting coverage to presymptomatic patients with three or fewer SMN2 copies. This results in inconsistent treatment availability across the country. The PMPRB influences this landscape by regulating drug prices to ensure appropriate reimbursement. Consequently, this fragmented approach leads to unequal access to critical SMA therapies, leaving many Canadian patients without consistent support based solely on their geographic location.

Despite the implementation of NBS for SMA across Canada, which allows for the early detection of infants with four SMN2 copies or fewer, there is a significant gap in providing necessary therapies. Current policies often do not extend treatment to all detected cases, leaving families with babies identified with four *SMN2* copies in a distressing position, forced to wait for symptoms to manifest before any intervention can be considered. This delay in treatment exacerbates anxiety and uncertainty, highlighting a critical need for more comprehensive and equitable access to SMA therapies nationwide.

We urge provincial payers to provide universal access to an appropriate DMT for infant patients with SMA and four *SMN2* copies. It is neither ethical nor justifiable to delay treatment until a large proportion of motor neurons are lost and clinical symptoms manifest, typically in the toddler years. Canadians with SMA deserve reimbursement criteria that are aligned with those of comparator countries that share public drug reimbursement programs to allow for reduced disease burden and increased productivity.

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