Letter to the Editor: New Observation



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

Hugh J. McMillan¹, Hernan Gonorazky², Craig Campbell³, Nicolas Chrestian⁴, Megan Crone⁵, James J. Dowling², Kristina Joyal^{6,7}, Hanna Kolski⁸, Ed Leung⁶, Alex Mackenzie¹, Jean K. Mah⁵, Laura McAdam⁹, Elisa Nigro², Cam-Tu Nguyen¹¹, Maryam Oskoui^{10,12}, Chantal Poulin¹⁰, Jordan Sheriko¹³, Mark Tarnopolsky¹⁴, Jiri Vajsar², Amanda Yaworski¹ and Kathryn Selby¹⁵

¹Children's Hospital of Eastern Ontario Research Institute, Department of Pediatrics, University of Ottawa, Ottawa, ON, Canada, ²The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada, ³Department of Pediatrics, Epidemiology and Clinical Neurological Sciences, Schulich School of Medicine, Children's Hospital Western Ontario, University of Western, London, ON, Canada, ⁴Département de pédiatrie de l'Université Laval, Centre hospitalier Mère-Enfant-Soleil, Quebec, QC, Canada, ⁵Cumming School of Medicine, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada, ⁶Department of Pediatrics, Health Sciences Centre, Winnipeg, MB, Canada, ⁷Department of Pediatrics, Jim Pattison Children's Hospital, Saskatoon, SK, Canada, ⁸Department of Pediatrics, Stollery Children's Hospital and Glenrose Rehabilitation Hospital, University of Alberta, Edmonton, AB, Canada, ⁹Division of Developmental Pediatrics, Department of Pediatrics, Holland Bloorview Kids Rehabilitation Hospital, University of Toronto, Toronto, ON, Canada, ¹⁰Departments of Pediatrics and Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada, ¹¹Département de pédiatrie de l'Université de Montréal, Centre hospitalier Universitaire Sainte-Justine, Montréal, QC, Canada, ¹²Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montréal, QC, Canada, ¹³IWK Health, Department of Pediatrics and Medicine, Dalhousie University, Halifax, NS, Canada, ¹⁴McMaster Children's Hospital, McMaster University Medical Center, Hamilton, ON, Canada and ¹⁵Division of Neurology, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada

Keywords: spinal muscular atrophy; neonatal screening; survival motor neuron protein

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

Corresponding author: K. Selby; Email: kselby@cw.bc.ca

Cite this article: McMillan HJ, Gonorazky H, Campbell C, Chrestian N, Crone M, Dowling JJ, Joyal K, Kolski H, Leung E, Mackenzie A, Mah JK, McAdam L, Nigro E, Nguyen C-T, Oskoui M, Poulin C, Sheriko J, Tarnopolsky M, Vajsar J, Yaworski A, and Selby K. Equitable Access to Disease-Modifying Therapies for Canadian Children with SMA and Four SMN2 Copies. The Canadian Journal of Neurological Sciences, https://doi.org/10.1017/cjn.2024.319

[©] The Author(s), 2024. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

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.

Acknowledgments. We would thank Victoria Hodgkinson, PhD, for providing data from the CNDR regarding age of symptom onset for Canadian SMA patients with four copies of *SMN2*.

Author contributions. HJM, HG, KS – conceptualizing study, drafting and revising the manuscript.

CC, NC, MC, JJD, KJ, HK, EL, AM, JKM, LM, EN, CTN, MO, CP, JS, MT, JV, AY – critical review of the manuscript.

Competing interests. HJM received honoraria from Hoffman-La Roche and Novartis for consultancy work.

HG received honoraria from Biogen, Hoffman-La Roche and Novartis for consultancy work.

CC received travel support from Biogen, Hoffman-La Roche and Novartis to attend advisory meetings and honoraria from Hoffman-La Roche for consultancy work.

NC received honoraria from Biogen, Hoffman-La Roche and Novartis for advisory board participation.

MC received honoraria and travel reimbursement from Biogen and Hoffman-La Roche for advisory board participation.

JD received honoraria from Genzyme for expert testimony and is a member of Muscular Dystrophy Canada Scientific Advisory Board, NMD4C (Pediatric Lead), TREAT-NMD (Chair, Board of Directors), WMS (Executive Board) and Muscular Dystrophy Association RAC.

KJ received honoraria from Novartis, Hoffman-La Roche and Biogen for consultancy work.

HK, EL, AM, LM, CTN, CP and JV report no relevant disclosures.

JKM received research support from the Alberta Children's Hospital Foundation and research funds for clinical trials from Biogen and Hoffman-La Roche.

EN received honoraria from Novartis, Hoffman-La Roche and Biogen for presentations.

MO is a member of:] Muscular Dystrophy Canada Scientific Advisory Board.

JS received honoraria from Novartis and Biogen for advisory board participation (payments to the institution).

MT received honoraria from Aro Therapeutics and Sanofi-Genzyme. He received Canadian Institute of Health Research funding.

AY received honoraria from Novartis and Biogen for advisory board participation.

KS received honoraria from Biogen, Hoffman-La Roche and Novartis for consultancy work.

References

- Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a complication of 2834 reported cases. *Neuromuscul Disord*. 2018;28:208–15. DOI: 10.1016/j.nmd.2018.01.003.
- Ramos DM, d'Ydewalle C, Gabbeta V, et al. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. *J Clin Invest*. 2019;129:4817–31. DOI: 10.1172/JCI124120.
- Vill K, Tacke M, Konig A, et al. 5qSMA: standardized retrospective natural history assessment of 268 patients with four copies of SMN2. J Neurol. 2024;271:2787–2797. DOI: 10.1007/s00415-024-12188-5.
- Glascock J, Sampson J, Connolly AM et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn

screening who have 4 copies of SMN2. J Neuromuscul Dis. 2020;7:97–100. DOI: 10.3233/JND-190468.

- Blaschek A, Kölbel H, Köhler C, et al. Newborn screening for SMA can a wait-and-see strategy be responsibly justified in patients with four SMN2 copies? J Neuromuscul Dis. 2022;9:597–605. DOI: 10.3233/JND-221510.
- McMillan HJ, Kernohan KD, Yeh E, et al. Newborn screening for spinal muscular atrophy: Ontario testing and follow-up recommendations. *Can J Neurol Sci.* 2021;48:504–11. DOI: 10.1017/cjn/2020.229.
- Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis.* 2018;5:145–58. DOI: 10.3233/JND-180304.
- Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy number and outcome in spinal muscular atrophy types 0-4. J Neurol Neurosurg Psychiatry. 2017;88:365–7. DOI: 10.1136/jnnp-2016-314292.
- McMillan HJ, Gerber B, Cowling T, et al. Burden of spinal muscular atrophy (SMA) on patients and caregivers in Canada. J Neuromuscul Dis. 2021;8: 553–68. DOI: 10.3233/JND-200610.