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Original Article

Variability in Newborn Screening Across Canada: Spinal Muscular Atrophy and Beyond

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ABSTRACT: ***Background:*** Newborn screening (NBS) identifies infants with severe, early-onset diseases, enabling early diagnosis and treatment. In Canada, decisions regarding disease inclusion in NBS programs occur at the provincial level, which leads to variability in patient care. We aimed to determine whether important differences exist in NBS programs across provinces and territories. Given that spinal muscular atrophy (SMA) is the most recent disease added to NBS programs, we hypothesized that its inclusion would show interprovincial variability and be more likely in provinces already screening for a greater number of diseases. ***Methods:*** We conducted a cross-sectional survey of all NBS labs in Canada to understand: 1) what conditions were included in their program; 2) what genetic-based testing was performed and; 3) if SMA was included. ***Results:*** All NBS programs ($N = 8$) responded to this survey by June 2022. There was a 2.5-fold difference in the number of conditions screened ($N = 14$ vs $N = 36$) and a 9-fold difference in the number of conditions screened by gene-based testing. Only nine conditions were common to all provincial NBS programs. NBS for SMA was performed in four provinces at the time of our survey, with BC recently becoming the fifth province to add SMA to their NBS on October 1, 2022. Currently, 72% of Canadian newborns are screened for SMA at birth. ***Conclusion:*** Although healthcare in Canada is universal, its decentralization gives rise to regional differences in NBS programs which creates inequity in the treatment, care, and potential outcomes of affected children across provincial jurisdictions.

RÉSUMÉ : ***Variabilité du dépistage néonatal au Canada dans le cas de l'amyotrophie spinale et d'autres affections. Contexte :*** Le dépistage néonatal (DNN) permet d'identifier les nourrissons atteints d'affections graves et précoces, ce qui permet d'établir un diagnostic et un traitement de manière précoce. Au Canada, les décisions concernant l'inclusion d'affections dans les programmes de DNN sont prises au niveau des provinces, ce qui entraîne une variabilité dans les soins destinés aux patients. Nous avons ainsi cherché à déterminer s'il existe des différences marquées dans les programmes de DNN parmi les provinces et les territoires. Étant donné que l'amyotrophie spinale (AS) est la maladie la plus récemment ajoutée aux programmes de DNN, nous avons émis l'hypothèse que son inclusion donnerait à voir une variabilité interprovinciale et serait plus probable dans les provinces qui dépistent déjà un plus grand nombre d'affections. ***Méthodes :*** Nous avons mené une enquête transversale auprès de tous les laboratoires de DNN au Canada afin de mieux comprendre : 1) les conditions rattachées aux programmes de DNN ; 2) les tests génétiques qui sont effectués ; 3) si l'AS était incluse. ***Résultats :*** Tous les programmes de DNN ($n = 8$) ont répondu à cette enquête avant juin 2022. On a noté une différence de l'ordre de 2,5 dans le nombre d'affections dépistées ($n = 14$ contre $n = 36$) et une différence de l'ordre de 9 dans le nombre d'affections dépistées par des tests génétiques. À noter que seulement neuf affections étaient communes à tous les programmes provinciaux de DNN. Le programme de DNN pour l'AS était en vigueur dans quatre provinces au moment de notre enquête, la Colombie-Britannique étant devenue la cinquième province à ajouter l'AS à son DNN le 1er octobre 2022. À l'heure actuelle, 72 % des nouveau-nés canadiens font l'objet d'un dépistage de l'AS à la naissance. ***Conclusion :*** Bien que les soins de santé au Canada soient universels, leur décentralisation donne lieu à des différences régionales en ce qui regarde les programmes de DNN, ce qui entraîne presque certainement, d'une juridiction provinciale à l'autre, une inégalité significative sur le plan des traitements, des soins et de l'évolution de l'état de santé des enfants atteints.

Keywords: Spinal muscular atrophy; Neonatal screening; Mass screening; Genetics

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Introduction

The goal of newborn screening (NBS) is to identify newborns with potentially disabling conditions for which early detection may allow for treatment initiation to reduce or eliminate disease symptoms. Diseases selected for inclusion in NBS programs share several characteristics including: 1) well-known natural history with the majority of affected patients showing severe and early-onset disease; 2) screening tests that are robust and reliable; 3) treatment that is effective, acceptable, and uniformly accessible to all patients; 4) societal acceptance that the benefits of early diagnosis outweigh risks associated with potential harm from false diagnosis, premature diagnosis, and/or over-treatment and; 5) evidence that screening is cost-effective.[1]

Spinal muscular atrophy (SMA) has been included in an increasing number of NBS programs. It is an autosomal recessive disorder characterized by irreversible loss of motor neurons causing progressive muscle atrophy and weakness.[2] Estimated to affect 1 in 10,000 live born infants,[3] SMA is one of the leading genetic conditions contributing to infant mortality.[4] SMA results from pathogenic variants affecting both *SMN1* alleles, although a paralogous gene, *SMN2,* has a disease-modifying effect where a lower number of *SMN2* copies is predictive of a more severe and earlier-onset phenotype.[1] While 95% of affected individuals have the more common homozygous deletion of *SMN1* exon 7, 5% are compound heterozygotes with an *SMN1* deletion and *SMN1* point mutation affecting each allele.[3] Three therapies for SMA have been approved by Health Canada including nusinersen (approved in June 2017), onasemnogene abeparvovec (in December 2020), and risdiplam (in April 2021). Public reimbursement or coverage for at least one of these therapies is currently available in all Canadian provinces. Clinical trials for all disease-modifying therapies have demonstrated that presymptomatic treatment is associated with the greatest improvement in survival and motor milestone acquisition.[5–8] Accordingly, several NBS programs for SMA are emerging around the world to allow for earlier diagnosis and treatment initiation.[9]

Canada does not have a nationally accepted screening panel for hereditary disorders, and all decisions pertaining to disease inclusion in NBS programs are made at the provincial level. Consequently, there is a potential for variability to arise among provinces. In the USA, there had been similar concerns regarding lack of uniformity among states which led to the creation of a Recommended Uniform Screening Panel (RUSP). An expert committee in the US Department of Health and Human Services provides evidence-based recommendations regarding which conditions are recommended for inclusion in each state's NBS program.[10] Their proceedings and decisions are published in an open and transparent manner with the goal of encouraging states to use evidence and work toward uniformity in their NBS programs.

Our goal was to determine the total number and specific conditions that are part of NBS programs in each Canadian province and territory to understand similarities and differences. We identified which provincial NBS programs used gene-based testing, as this is required for an increasing number of childhood-onset diseases for which therapies are emerging including SMA. In view of provincial approvals and access to disease-modifying therapies for SMA, we also sought to more specifically explore which provinces included or planned to include SMA into their NBS program.

Methods

Study Design and Data Collection

We conducted a cross-sectional study of all provincial and territorial NBS programs in Canada. Each medical or laboratory director was sent an online survey that was composed of 22 questions designed to obtain information regarding: 1) all conditions included in NBS for each province at this time; 2) conditions screened using genetic-based testing; and 3) if the province included SMA in their NBS program. The survey required approximately 10–15 minutes to complete and remained open for 22 days. All surveys were completed by June 10, 2022. REB review was not required as this study met deferral criteria as a quality assurance study.

Conditions that were included in each province's NBS were categorized as either primary, secondary, or additional as per their classification by the RUSP as of May 2022.[11,12] Since there is no equivalent to the RUSP in Canada, we sought an objective tool to not arbitrarily select one Canadian province as a "gold standard" over others.

Results

Responses were obtained from 8/8 (100%) medical or laboratory directors ($N = 7$) or geneticists ($N = 1$) representing all provincial NBS programs in Canada. One respondent was contacted representing the three Maritime Provinces (Nova Scotia, New Brunswick, and Prince Edward Island). NBS for the three Canadian territories proceed as follows: Nunavut Territory NBS samples are sent on a regional basis to Ontario, Manitoba, or Alberta; Northwest Territories NBS are sent to Alberta and; Yukon Territory NBS are sent to British Columbia. As such, the conditions included in each territorial NBS program were inferred from the province(s) where testing was carried out.

NBS Programs

Although all Canadian provinces perform NBS, the number of conditions screened ranged from 14 to 36, which represents a 2.5-fold difference between the provinces screening the fewest to the largest number of infant-onset conditions (Table 1).

Among the RUSP primary diseases ($N = 36$), the number of conditions included in provincial NBS programs ranged from 14 to 30. Only nine ($N = 9$) conditions were common across all provincial NBS programs in Canada and included cystic fibrosis (CF), congenital hypothyroidism (CH), glutaric aciduria type 1 (GA1), long-chain-3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, maple syrup urine disease (MSUD), medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, mitochondrial trifunctional protein deficiency, phenylketonuria (PKU), and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. Regional differences exist for all remaining disorders, which are included in some but not all programs. Among RUSP secondary diseases ($N = 25$), Canadian NBS programs included 0 to 3 of these conditions.

NBS Using Genetic Testing

Testing for some infant-onset disorders cannot be performed using biochemical or other phenotypic testing, and a form of genetic testing is required to identify the presence or absence

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Table 1: Diseases included in newborn screening by Canadian provinces organized by the RUSP

Province: Total diseases in NBS:	AB *n* = 25	BC *n* = 26	MB *n* = 31	NB *n* = 24	NS *n* = 24	NL *n* = 18	ON *n* = 31	PE *n* = 24	QC *n* = 14	SK *n* = 36
Primary diseases										
Argininosuccinic aciduria		X	X	X	X	X	X	X	X	X
Beta-ketothiolase deficiency			X							X
Biotinidase deficiency	X		X	X	X		X	X		X
Congenital adrenal hyperplasia	X	X	X				X			X
Critical congenital heart disease							X			
Cystic fibrosis	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Congenital hypothyroidism	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Citrullinemia[$]	X	X	X	X	X	X	X	X		X
Carnitine uptake/transport deficiency	X	X	X	X	X	X	X	X		X
Glutaric aciduria, type 1	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Galactosemia	X	X	X	X	X		X	X		X
Glycogen storage disease, type 2 (Pompe)										
Guanidinoacetate methyltransferase def		X								X
Hemoglobinopathy: SC disease	X	X		X	X		X	X	X	X
Hemoglobinopathy: SS, sickle cell disease	X	X		X	X		X	X	X	X
Hemoglobinopathy: S-ß-thal disease	X	X		X	X		X	X	X	X
Holocarboxylase synthetase deficiency			X							
Homocystinuria		X	X			X	X			X
3-hydroxy-3-methyl-CoA lyase deficiency	X		X							X
Isovaleric acidemia	X	X	X	X	X	X	X	X		X
LCHAD deficiency	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
MCAD deficiency	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Mitochondrial trifunctional protein def.	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
MMA: cobalamin A or B disorder	X	X	X	X	X	X	X	X		X
MMA: methylmalonyl-CoA mutase	X	X	X	X	X	X	X	X		X
3-MCC-carboxylase deficiency										X
Propionic acidemia	X	X	X	X	X	X	X	X		X
Mucopolysaccharidosis, type 1							X			
Mucopolysaccharidosis, type 2										
Maple sugar urine disease	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Phenoketonuria	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Severe combined immunodeficiency	X	New	X[†]	X	X		X	X		X
Spinal muscular atrophy	X	New	X				X			X
Tyrosinemia, type 1	X	X	X			X	X		X	X
VLCAD deficiency	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
X-linked adrenoleukodystrophy										
Secondary diseases*										
Carnitine acylcarnitine translocase def.			X							X
Carnitine palmitoyltransferase type 1			X	X	X		X	X		X
Carnitine palmitoyltransferase type 2			X	X	X			X		X
Additional diseases^										
Congenital cytomegalovirus (CMV)			X[&]				X			X

(*Continued*)

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Table 1: (*Continued*)

Province: Total diseases in NBS:	AB *n* = 25	BC *n* = 26	MB *n* = 31	NB *n* = 24	NS *n* = 24	NL *n* = 18	ON *n* = 31	PE *n* = 24	QC *n* = 14	SK *n* = 36
Hearing loss (common mutations panel)							X			X
HHH			X[&]							X[&]

AB = Alberta, BC = British Columbia; MB = Manitoba; NB = New Brunswick; NS = Nova Scotia; NL = Newfoundland; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; def.=deficiency; ß-thal.=ß-thalassemia; LCHAD = long-chain-3-hydroxyacyl-CoA dehydrogenase; MCAD = medium-chain-acyl-CoA dehydrogenase; MMA = methylmalonic acid; 3MCC = 3-methylcrotonyl-CoA carboxylate; VLCAD = very-long-chain acylCoA dehydrogenase; HHH = hyperornithinemia-hyperammonemia-homocitrullinuria; RT-PCR = reverse transcriptase polymerase chain reaction; TREC = T-cell receptor excision circle.

Diseases included in provincial and territorial newborn screening (NBS) programs were grouped as core primary, secondary, or additional diseases as outlined in the Recommended Uniform Screening Panel (RUSP) as described in text. Data is correct as of June 2022. NBS is performed in Canadian territories as follows: Nunavut Territory NBS samples are sent on a regional basis to either ON, MB or AB; Northwest Territory NBS samples are sent to AB; and Yukon Territory is sent to BC. The RUSP lists include primary diseases (N = 36) and secondary disease (N = 25). Bold rows reflect the nine (N = 9) disorders that are screened in all Canadian provinces and territories.

British Columbia (BC) added spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID) to its NBS panel on October 1, 2022.

[$]Citrullinemia was not differentiated between type 1 and/or type 2 on our survey;

[&]For targeted populations and; [†]Allele-specific RT-PCR for non-TREC-deficient *ZAP-70* and *IKBKB* founder mutations.

*Secondary diseases on RUSP that are not included in provincial NBS program include: malonic academia; medium- and short-chain L-3-hydroxyacyl-CoA-dehydrogenase deficiency; medium-chain ketoacyl-CoA thiolase deficiency; arginemia; galactoepimerase deficiency; galactokinase deficiency; benign hyperphenylalinemia; biopterin co-factor defects; glutaric aciduria type 2; isobutyrlglycinuria; hypermethioninemia; short-chain acyl CoA dehydrogenase deficiency; tyrosinemia type 2 and 3; 2-methylbutyrylglycinuria; 2-methyl-3-OH-butyric academia; 3-methyl-glutaconic aciduria; lymphocyte deficiencies; and other hemoglobinopathies.

^Additional diseases are those not included in RUSP such as: ethylmalonic encephalopathy; multiple carboxylase deficiency; non-ketotic hyperglycinemia; ornithine transcarbamylase deficiency; pyruvate carboxylase deficiency; and S-adenoslyhomocyteine hydroxylase deficiency.

of predicted disease. Genetic-based testing in NBS also showed variability among provinces with some provinces only performing gene-based testing for CF (Quebec, Newfoundland), while others used gene-based testing platforms to screen for up to nine childhood-onset disorders (Ontario). Table 2 provides an overview of genetic-based testing including platforms used for each condition in provincial NBS programs, based on the information provided by the respondents.

NBS for SMA

As of June 2022, NBS for SMA was performed in four Canadian provinces: Alberta, Manitoba, Ontario, and Saskatchewan, as well as two Canadian territories: Nunavut and the Northwest Territories (Figure 1). Based on 2021 birth estimates from Statistics Canada,[13] 60% of Canadian newborns were screened at birth for SMA (Supplemental Table 1). Those four provinces that screened for SMA were also the four provinces with the greatest number of conditions included in their NBS program.

Ontario was the first Canadian province to begin screening for SMA in January 2020,[14] initially as a 6-month pilot funded by Biogen, before being accepted into the list of conditions screened in its NBS program. Alberta began screening as a 1-year pilot study and Manitoba as a 2-year pilot study, both funded by Muscular Dystrophy Canada, before each province accepted SMA into its provincial NBS program. In contrast, Saskatchewan implemented NBS for SMA immediately without a preceding pilot phase. British Columbia (BC) added SMA to their NBS program on October 1, 2022, after the completion of our survey and after the manuscript was submitted for peer review. Since BC also performs NBS for the Yukon, this new implementation increased the number of Canadian provinces screening for SMA to 5 and the number of territories to 3. It also increased the proportion of Canadian infants screened for SMA at birth to 72% (Supplemental Table 1). For the other provinces not screening for SMA, their respective provincial governments and/or responsible decision-making committees have committed to including SMA in their NBS programs in the near future.

There are numerous techniques used in NBS for SMA including quantitative polymerase chain reaction (qPCR), multiplex ligation-dependent probe amplification (MLPA), MassArray, and droplet digital polymerase chain reaction (ddPCR), all of which can potentially be used to determine *SMN1* deletion status and *SMN2* copy number. The testing platform(s) used for NBS for SMA varied among provinces. In Ontario, MassArray is used as the first tier of screening with MLPA used as a second tier.[10] In contrast, Alberta, Manitoba, and Saskatchewan use qPCR is as a first-tier test. BC, the most recent province to initiate testing, uses MLPA as a first-tier test. Confirmatory testing in commercial laboratories utilizes MLPA testing to detect the *SMN1* deletion.

Similar to other jurisdictions, the testing platforms used in Canadian provinces screen for the common exon 7 deletion and will not detect *SMN1* point mutations which are seen in a small proportion of patients with SMA.

Differences also exist in what constitutes a positive screening test among Canadian provinces. The Saskatchewan NBS program reports all biallelic *SMN1* deletions, whereas Alberta, Manitoba, Ontario, and more recently BC only report newborns with biallelic *SMN1* deletions who also have ≤4 copies of *SMN2*. With regard to obtaining parental consent for NBS for SMA, Alberta currently uses an opt-out process, whereas most provinces perform SMA screening alongside other standard NBS tests and do not require any SMA-specific consent.

When asked the reason(s) for not including SMA in NBS programs, the lack of or delayed governmental funding for its inclusion was the most commonly identified obstacle, followed by a lack of financial and human resources.

Among provinces actively screening for SMA, the target time to obtain the results of the initial screen ranged from 4 to 10 days, while the target time for the initiation of disease-modifying therapy ranged from 10 to 30 days from the initial blood sampling. In Saskatchewan, an application for disease-modifying treatment coverage can be submitted to the provincial health insurance plan after a positive NBS test for SMA. By comparison, most Canadian provinces require a positive confirmatory genetic test prior to application submission, which can result in an additional 1–2 week(s) delay in initiating treatment for children with a rapidly progressive disease characterized by the irreversible loss of motor neurons.

All four provinces that included SMA in their NBS also performed other gene-based screening for severe combined

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Table 2: Genetic-based newborn screening testing in Canadian provinces

Province	List of diseases screened by gene-based testing	Platform(s) used
Alberta	Cystic fibrosis	xTAG Cystic Fibrosis 39 Kit v2 (Luminex)
	Severe combined immunodeficiency	qPCR
	Spinal muscular atrophy	qPCR (first tier)
British Columbia	Cystic fibrosis	IRT-DNA-IRT
	GAMT	Full gene sequencing (third tier)
	Severe combined immunodeficiency*	MLPA (first tier)
	Spinal muscular atrophy*	MLPA (first tier)
Manitoba	Congenital CMV^	RT-PCR
	Cystic fibrosis	IRT-DNA-IRT
	HHH^	PCR, capillary electrophoresis
	Severe combined immunodeficiency†	RT-PCR
	Spinal muscular atrophy	RT-PCR (first tier)
New Brunswick, Nova Scotia & Prince Edward Island	Cystic fibrosis	RT-PCR (second tier)
	Severe combined immunodeficiency	RT-PCR
Newfoundland & Labrador	Cystic fibrosis	xTAG Cystic Fibrosis 39 Kit v2 (Luminex)
Ontario	Congenital CMV	qPCR
	Cystic fibrosis	MassArray, NGS
	Carnitine palmitoyltransferase, type 1	qPCR (second/third tier)
	Hearing loss: (common mutations panel)	MLPA
	Methylmalonic acidemia	qPCR
	Mucopolysaccharidosis 1H (Hurler)	NGS/Sanger sequencing
	Proprionic acidemia	qPCR
	Severe combined immunodeficiency	RT-PCR (first tier), MassArray
	Spinal muscular atrophy	MassArray (first tier), MLPA (second tier)
Quebec	Cystic fibrosis	qPCR
Saskatchewan	Congenital CMV	RT-PCR
	Cystic fibrosis	IRT-DNA-IRT
	HHH^	PCR, capillary electrophoresis
	Severe combined immunodeficiency	RT-PCR
	Spinal muscular atrophy	RT-PCR (first tier)

GAMT = guanidinoacetate methyltransferase deficiency; HHH = hyperornithinemia-hyperammonemia-homocitrullinuria; IKBKB = inhibitor of nuclear factor kappa B kinase subunit beta; IRT-DNA-IRT = immunoreactive trypsinogen-deoxyribonucleic acid-immunoreactive trypsinogen; MLPA = multiplex ligation-dependent probe amplification; MMA = methylmalonic academia; NGS = next-generation sequencing; PCR = polymerase chain reaction; qPCR=quantitative polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction; TREC = T-cell receptor excision circle; ZAP-70 = zeta-chain-associated protein kinase-70.
*British Columbia began testing for spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID) using MLPA (first tier) on Oct 1, 2022.
^For targeted populations.
†Includes allele-specific RT-PCR for non-TREC deficient *ZAP-70* and *IKBKB* founder mutations.

immunodeficiency (SCID) using reverse-transcriptase polymerase chain reaction (RT-PCR) among other genetic tests (Table 2). BC began testing for both SMA and SCID at the same time, using MLPA testing.

Discussion

Regional differences exist with regard to NBS within Canada with some provinces including 2.5-fold more conditions in their NBS program compared to others. In addition, the use of genetic-based NBS shows an even greater degree of variability with as much as a 9-fold difference in the number of conditions included in provincial NBS programs. This creates inequity in the prevention and treatment of disease in Canadian born children. Infants born with a treatable, rare disease in one Canadian province or territory with a more comprehensive NBS program benefit from early diagnosis and presymptomatic treatment. By comparison, Canadian children born in another province may only be identified with the same rare disease after an acute life-threatening event or irreversible loss of tissue, thus reducing the potential benefit of otherwise effective disease-modifying therapies. Moreover, there may be a lesser potential for long-term survival or attaining neurodevelopmental milestones with delayed treatment initiation.

Long delays between symptom onset and diagnosis have been well described for some rare diseases. Children who are symptomatic with the most severe, infant-onset form of SMA (i.e., type

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Figure 1: Newborn screening programs for SMA presently include 72% of Canadian newborns. **Legend**: Solid green = provinces and territories screening for SMA as of June 2022. Hatched green = BC and YT that began screening for SMA as of October 1, 2022. Grey = provinces that do not currently include SMA as part of their NBS panel. SMA = spinal muscular atrophy; YT = Yukon; NT = Northwest Territories; NU = Nunavut; BC = British Columbia; AB = Alberta; SK = Saskatchewan; MB = Manitoba; ON = Ontario; QC = Quebec; NL = Newfoundland and Labrador; NB = New Brunswick, PE = Prince Edward Island; NS = Nova Scotia. NB, NS, PE, NL, and QC have announced plans to initiate NBS screening for SMA, but no formal start date has been set at the time of publication. Provincial and territorial birth rates from Statistics Canada.[13] Figure was designed using MapChart.[24]

I) experience a mean delay in the time from symptom onset to diagnosis of 2.5 months.[15] The mean delay to diagnosis for SMA type II, where symptom onset occurs between 6 and 18 months old, is over 12 months.[15] Delays to diagnosis were primarily attributed to patients having to visit multiple healthcare professionals to exclude other diagnoses prior to undergoing genetic testing for SMA.[15] Such delays in diagnosis represent a lost opportunity, particularly given the rapid and irreversible progression of SMA where the life expectancy ranges from a median of 8 months[16] to a mean of 10-1/2 months[17] for infants with SMA type I (typically 2x*SMN2* copies) unless given continuous ventilator support and/or receiving disease-modifying therapy.

As of January 2023, approximately 72% of Canadian newborns are screened for SMA at birth. This stands in contrast to the USA where NBS for SMA is performed in 48 of 50 states, ensuring that 98% of American newborns are tested at birth.[18] Globally, nine countries or jurisdictions had already included SMA into their NBS programs as of December 2020.[9] Overall, very low rates of false positives have been reported around the world, and the opt-out consent process was found to have higher rates of acceptability relative to opt-in.[9] To date, there have been no reported cases of false positives in Ontario. However, the NBS programs for SMA in other Canadian provinces have not been in place for a sufficient amount of time to gather reliable data on false-positive rates. In the USA, state NBS programs received financial and educational support from the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) to facilitate the implementation of screening for SMA.[19] The mean time required to fully implement statewide screening for SMA was 24 months, which is considerably shorter than what was reported for other conditions including Pompe and mucopolysaccharidosis type I.[19]

As more provinces begin to include SMA in their NBS program, it will be important to document the time from sample acquisition (typically on blood spot paper) to when confirmatory diagnosis is made, and disease-modifying treatment is initiated. Over 40% of SMA patients identified in an Australian NBS program showed clear onset of clinical symptoms within the first weeks of life,[20] underscoring the need for efficiency even after the NBS specimen is acquired. Allowing applications for disease-modifying therapies to be submitted for review after a positive screen, and for other testing (e.g., AAV9 antibody status for potential gene therapy, baseline CHOP-INTEND motor scales) to be done in tandem with application review, can help streamline this process so that eventual approval occurs more quickly once diagnosis is confirmed. Physicians will need to understand interprovincial variability regarding the availability of NBS, as well as variability in the provincial definitions of a "positive" versus a "negative" NBS test for SMA, since this has the potential to create confusion and further delay for yet-diagnosed children moving from one province to another.

Lastly, cost efficacy analysis has demonstrated an economic value for universal NBS for SMA in countries and jurisdictions where disease-modifying therapy is available.[4,21] Australian data have also reported NBS, coupled with early gene therapy, to be cost-effective and to improve the quality and length of life for children with SMA.[22]

Conclusion

NBS represents an opportunity for the early identification of infants with a range of severe or potentially fatal diseases,

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facilitating diagnosis even prior to the onset of symptoms. Although healthcare in Canada is universal, its decentralization gives rise to regional differences in the provision of care. NBS is an example where regional variations exist, with the number of diseases included in NBS programs ranging from 14 to 36. SMA is currently included in NBS programs screening Canadian children born in five provinces and all three territories. As of January 2023, 72% of Canadian newborns benefit from early or presymptomatic diagnosis of SMA. This discrepancy leads to significant differences in survival and motor outcomes including the higher probability to have sufficient strength to walk compared to those diagnosed after symptoms have appeared. Learning from the USA experience, Canadian provinces must work to standardize NBS panels across the country to reduce the existing inequities that can have life-altering consequences for children born in some but not other areas within our country. These results emphasize the importance of the key guiding principle of Canadian healthcare: universality and equity, regardless of which Canadian province or territory a child is born in.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2023.34.

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Abbreviations.
CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
ddPCR = digital droplet polymerase chain reaction
MLPA = multiplex ligation-dependent probe amplification
NBS = newborn screening
qPCR = quantitative polymerase chain reaction
RT-PCR = reverse transcriptase polymerase chain reaction
RUSP = Recommended Uniform Screening Panel
SMA = spinal muscular atrophy
SMN1 = survival motor neuron 1 gene

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