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Review

Newborn screening of neuromuscular diseases

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Abstract

Neuromuscular diseases represent an heterogenous group of more than 400 diseases, with a very broad phenotypic spectrum. Given their rarity and complexity, neuromuscular diseases are often diagnosed with a very significant delay after which irreversible muscle damage may limit the efficacy of treatments when available. In this context, neonatal screening could constitute a solution for early detection and treatment. A systematic review of the literature in PubMed up to May 1, 2021, was conducted according to PRISMA guidelines, including classical neuromuscular diseases and diseases with a clear peripheral nervous system involvement (including central nervous system disease with severe neuropathy). We found seven diseases for which newborn screening data were reported: spinal muscular atrophy (9), Duchenne muscular dystrophy (9), Pompe disease (8), X-linked adrenoleukodystrophy (5), Krabbe disease (4), myotonic dystrophy type 1 (1), metachromatic leukodystrophy (1). The future of newborn screening for neuromuscular disorders pass through a global technological switch, from a biochemical to a genetic-based approach. The rapid development of therapy also requires the possibility to quickly adapt the list of treated conditions, to allow innovative therapies to achieve their best efficacy.

Keywords: Newborn screening; Neuromuscular disorder; Pompe disease; Spinal muscular atrophy; Duchenne muscular dystrophy.

This paper is an invited review for the special issue of Neuromuscular Disorders to celebrate Professor Victor Dubowitz's 90th birthday.

1. Introduction and context

Forty-five years ago, a *stricto sensu* mid-career 45-year-old myologist proposed Creatine Kinase (CK) dosage as a valid approach for Duchenne muscular dystrophy (DMD) and introduced the concept of screening newborns for neuromuscular disorders [1]. At that time, phenylketonuria newborn screening (NBS) had only been recently implemented in most developed countries. This paper is a tribute to this former mid-career myologist who celebrates today his 90th birthday.

Forty-five years later, the Dubowitz disease (not to be confounded with Dubowitz syndrome...) [2], also inappropriately called 'spinal muscular atrophy type 2′ by a very limited number of physicians, has become the stereotype of the perfect indication for NBS in the neuromuscular field.

Neuromuscular diseases represent an heterogenous group of more than 400 diseases, with a very broad phenotypic spectrum. Until very recently, few disease-modifying treatments were available for most of them. However, with a growing understanding of pathophysiology and preclinical research, several transformative treatments have had dramatic effects on not only inflammatory diseases, but also genetic diseases such as congenital myasthenia (CMS), spinal muscular atrophy (SMA), Pompe disease, or Brown-Vialetto-Van Laere syndrome (BVVL). Promising preliminary data have also been reported in limb girdle muscular dystrophy, X-linked myotubular myopathy or in DMD, for which five drugs have so far reached regulatory approval.

Given their rarity and complexity, neuromuscular diseases are often diagnosed after a very significant delay [3–6] during

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which irreversible muscle damage may limit the dramatic efficacy of early treatment administered patients [7,8]. Even in the absence of a muscle destruction process, such as in some form of CMS, the long diagnostic journey can cause decades of limitation in quality of life [9] before a correct diagnosis is established and the appropriate treatment is prescribed.

Neonatal screening is generally governed worldwide by the modified criteria proposed by Wilson and Jungner [10] which are widely used to determine whether screening for a disease should be included in an NBS panel. This list consists of the following ten items:

1 The condition sought should be an important health problem.
2 There should be an accepted treatment for patients with recognized disease.
3 Facilities for diagnosis and treatment should be available.
4 There should be a recognizable latent or early symptomatic stage.
5 There should be a suitable test or examination.
6 The test should be acceptable to the population.
7 The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8 There should be an agreed policy on whom to treat as patients.
9 The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10 Case-finding should be a continuing process and not a "once and for all" project.

These criteria are broadly applied across the world, with a much more conservative approach in European Union (EU) and UK in comparison with the US. As a consequence, the number of diseases screened in different countries, or even in different regions of a same country, varies significantly [11]. In line with these criteria, our mid-career myologist had already noticed in 1976 that "*the stage does not yet seem set for a [UK] nationwide program of screening for preclinical Duchenne muscular dystrophy, but when the time is ripe for it the techniques will hopefully be sufficiently standardized for immediate application.*"[1]

NBS has been organized for the last 60 years as a metabolic and endocrine screening process, but many treatable genetic neuromuscular diseases in children, such as BVVL, CMS or SMA have no metabolic or endocrine marker, which causes additional challenges in implementation of screening.

Nevertheless, the dramatic difference observed between pre-symptomatic and post-symptomatic treated patients with SMA, the successful implementation of NBS for SMA across the world, and the pipeline of potential therapy, all suggest that several neuromuscular diseases could be targeted by NBS before our previous mid-career myologist celebrate his 100th birthday. In this context, we conducted a review of the existing pilot or official NBS programs in the area of neuromuscular disease.

2. Methods

2.1. Literature search

A literature search was conducted using Medline (PubMed) following the PRISMA checklist [12]. We searched for original, full-text articles reporting NBS program in neuromuscular disease published after the 70th birthday of Prof. Victor Dubowitz (i.e., August 06th 2001). To identify relevant articles, key terms related to NBS (e.g., 'neonatal screening', 'dried blood spot testing', 'dried blood', and 'guthrie') were combined with key terms for neuromuscular disease. The detailed search strategy is shown schematically in Supplementary file 1. The literature search was conducted until May 1, 2021.

2.2. Selection of studies

Two researchers (TD, LS) first screened titles and abstracts independently for eligibility and then evaluated the full text. To be included, the articles had to be published original research, in English or French, and had to report NBS program for at least one neuromuscular disease, or a disease with a clear peripheral nervous system involvement (mostly peripheral neuropathy). The two reviewers compared their findings, and a list of studies for full-text screening was created. Reasons for article exclusion were recorded, and potential disagreements were specified to be resolved by consensus.

2.3. Data extraction and presentation

Studies were classified by disease screened: SMA, DMD, myotonic dystrophy type 1 (MD1), Pompe disease, X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD) and Krabbe disease.

Study characteristics related to publication (e.g., authors, year of publication, journal name) and study design (e.g., country, sample size…) were extracted.

3. Results

3.1. Study selection process

The initial searches identified 405 articles that describe NBS for neuromuscular diseases. After removing 108 duplicates, and screening by title and abstract, 84 articles were identified for full-text screening; 36 full-text studies were validated as eligible and 8 identified by bibliography were added. Supplementary file 2 shows the flowchart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines used for the identification of these studies.

Articles concerning the same pilot project were disregarded and only the most recent update was considered. We retained studies demonstrating the efficacy of NBS on deidentified

Guthries cards only if pilot projects with identified patients had not taken place.

3.2. Spinal muscular atrophy

SMA is a recessive disorder caused by a homozygous loss of function mutation (mostly a deletion of exon 7) of *SMN1*. There are three drugs approved for treatment [13] (nusinersen [14], onasemnogene abeparvovec [15] and risdiplam [16]), and three pre-symptomatic trials published or ongoing (Nurture: NCT02386553, SPR1NT: NCT03505099, Rainbowfish: NCT03779334). Several other drugs are in pre-clinical or early clinical development [17].

NBS for SMA has been reported in nine countries / subnational regions [18–25]. The first pilots were implemented in 2014 in Taiwan [18], and in New-York in 2016 [19]. Interestingly, these pilots were implemented prior to the approval of any medications, and some of the patients identified through these pilots could be included in pre-symptomatic studies [26]. The incidence found in these screening programs ranges from 1 in 5,000 in Italy to 1 in 28,000 in Ontario [27]. One of the lowest rates of incidence was found in New York [28], which may be explained by an increase in the use of preconception screening as a result of increased communication about the disease [29]. An additional reason of variability from study to study resides in the small number of cases in some reports, which over-weight the influence of a single case on the prevalence.

In most programs, the first tier of screening is done by quantitative real-time polymerase chain reaction (qPCR), while the second is done by MLPA. In the USA and Italy, qPCR is also used for the second tier.

Even if this remains to be confirmed in the next few years for SMA with later onset, no false negatives have yet been found in countries that have developed NBS programs. False positives were only encountered at the beginning of the pilot programs [27].

A recent survey has demonstrated that several countries anticipate to initiate a NBS program in the coming months and years, so that the number of newborn screened for SMA, today approximately 2% of the world population, should progressively climb to 24% of the total world population and 88% of the population of countries where a disease modifying treatment is available [27].

The characteristics of NBS programs in SMA are reported in Table 1.

3.3. Pompe disease

Pompe disease, also known as glycogenosis type 2, is an autosomal recessive inherited lysosomal storage disease caused by a deficiency of acid alpha-glucosidase.

Pompe disease has a wide clinical spectrum ranging from the infantile form, beginning in the first months of life, to adult forms. In the absence of treatment, the infantile form always leads to early death by cardiorespiratory failure or respiratory infection, usually before the age of one year. Symptoms can appear at any age in the later forms and are related to progressive skeletal muscle dysfunction.

Enzyme replacement therapy (ERT) using alglucosidase alfa (Myozyme) was approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2006. Early treatment has been associated with better outcome [30,31].

The first NBS pilot was initiated in Taiwan in 2005 and has been regularly documented since then [31–35]. In the USA, since 2015, Pompe Disease is part of the Recommended Uniformed Screening Panel (RUSP) program and is implemented in almost half of the states [36–39]. Other projects were conducted in Mexico [40], Japan [41] and Brazil [42]. The rate of incidence reported across all screening program was extremely variable: 1 in 10,600 in Brazil, 1 in 20,000 in Mexico, Taiwan and in the US, and 1 in 38,000 in Japan.

The characteristics of NBS programs in Pompe disease are reported in Table 2.

3.4. Duchenne muscular dystrophy

DMD is the most common inherited muscular dystrophy in childhood and is characterized by progressive muscle weakness. It is caused by an out-of-frame mutation of the *Dystrophin* gene located on the X chromosome. The incidence is around 1 in 4,700 [43] of young males. The first symptoms most commonly appear at as early as two years of age; the disease manifests as a proximal weakness leading to a rapid loss of walking between the ages of seven and fifteen. The delay between the appearance of symptoms and diagnosis is on average two years [3]; this diagnostic errancy, which causes parental distress, can also create a delay in the child's care.

Five drugs have achieved US FDA approval: Deflazacort, a corticosteroid; and Eteplirsen, Casimersen and Golodirsen for exon skipping 51, 45 and 53, respectively. Vitolarsen has also been approved for exon 53 skipping. In the EU, only Ataluren has been conditionally approved [44]. The clinical efficacy of these different drugs remains modest.

We found nine pilot projects or official implementations for DMD [45–54] between 1974 and 2017. The aim of these screening programs, as there was no treatment approved when they were initiated, was most often to establish recommendations for the following-up of patients. An early follow-up seemed preferable, not only to avoid diagnostic delay, but also to prevent a recurrence in the family through genetic counselling.

The characteristics of NBS programs in DMD are reported in Table 3.

3.5. Myotonic dystrophy 1

MD1 is an autosomal dominant disorder characterized by muscle weakness, myotonia, early onset cataracts, and systemic manifestations (cerebral, endocrine, cardiac, gastrointestinal tract, uterus, skin, and immunologic involvement) that vary depending on the age of onset.

Table 1
Newborn screening programs in SMA.

	Country [ref]	Date	Pop	Total number	Scr First-tier	Scr 2nd-tier	Conf	Cons	First result	N° cases	Prev	Aim of study
SMA	Taiwan [18]	2014–2016	NB	419,102	qPCR	ddPCR	MLPA	Opt-in	28	20	1/21,000	Explore NBS SMA feasibility
	USA [19,20]	2016–2017	NB	2,395,718	qPCR	ddPCR	MLPA	Opt-out	190	180	1/13,300	Report on NBS SMA
	Germany [21]	2018–2019	NB	297,163	qPCR	/	MLPA	Opt-in	43	43	1/7,000	Report on 2 years pilot
	Belgium (FWB) [22]	2018–2021	NB	153,728	qPCR	MLPA	MLPA	Opt-out	12	12	1/12,800	Explain start of NBS SMA
	Australia (NSW, ACT) [23]	2018–2019	NB	202,388	qPCR	ddPCR	ddPCR	Opt-out	19	19	1/10,600	Evaluate implementation
	Italy (Tuscany, Lazio)	2019–2021	NB	58,558	qPCR	qPCR	qPCR	Opt-in	12	12	1/5,000	Evaluate NBS
	Russia (Moscow)	2019–2021	NB	12,000	qPCR	MLPA	MLPA	Opt-in	0	0		Evaluate NBS
	Canada (Ontario) [24]	2020–2021	NB	139,810	Mass Array	MLPA	/	Opt-out	5	5	1/28,000	Report on beginning of NBS
	Japan [25]	2020–2021	NB	22,209	qPCR	MLPA	MLPA	Opt-in	0	0		Evaluate NBS
	Total World [27]		**NB**	**3,674,277**					**307**	**288**		**NBS SMA in the world**

List of abbreviations: Conf: Confirmatory assay; Cons: parents' method of consent; ddPCR: digital droplet PCR; First result: Positive first result or inconclusive; FWB: Federation Wallonia-Brussels (Region of Belgium); MLPA: multiplex ligation-dependent probe amplification; NB: Newborn; N° cases: Number of confirmed cases; NSW/ACT: New South Wales and Australian Capital Territory (region of Australia); Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

Table 2
Newborn screening programs in Pompe disease.

	Country [ref]	Date	Pop	Total number	Scr First-tier	Scr 2nd-tier	Conf	Cons	First result	N° cases	Prev	Aim of study
Pompe disease	Taiwan [31,32]	2005-2014	NB	669,797	Fluor assay	/	Leukocytes Enzymatic assay	Opt-in	4184	13 IOPD >19 LOPD	IOPD: 1/51,500 LOPD: 1/35,300 All: 1/21,000	Demonstrate advantage of early treatment, even for LOPD
	Mexico [40]	2012-2016	NB	20,018	LC-MS-MS	/	Enzymatic + Molecular testing	Opt-in	19	1	1/20,000	Evaluate the results of a lysosomal NBS
	USA (MO) [36]	2013-2018	NB	467,000	Fluor Digital Micro-fluidics	/	Enzymatic + Molecular testing + Urinary GAGs analysis + CK	Opt-out	274	10 IOPD 36 LOPD	IOPD: 1/46,700 LOPD: 1/13,000 All: 1/10,200	Report on 6-year NBS
	Japan [41]	2013-2016	NB	103,204	Fluor assay	/	Molecular testing	Opt-in	225	0 IOPD 3 LOPD	LOPD: 1/34,000 All: 1/34,000	Summary of NBS program + results
	USA (IL) [37]	2015-2019	NB	684,290	LC-MS-MS	2-tiered cutoff system	Enzymatic + Molecular testing + Urinary GAGs analysis	Opt-out	397	3 IOPD 26 LOPD	IOPD: 1/228,100 LOPD: 1/26,300 All: 1/23,600	Description of experience of NBS
	USA (PA) [38]	2016-2019	NB	531,139	FIA-MS-MS	/	Enzymatic + Molecular testing	Opt-out	115	2 IOPD 31 LOPD	IOPD: 1/265,500 LOPD: 1/17,100 All: 1/16,100	Evaluation of benefits + challenges of NBS
	USA (CA) [39]	2018-2019	NB	453,152	FIA-MS-MS	Molecular testing	Molecular testing	Opt-out	88	2 IOPD 16 LOPD	IOPD: 1/226,600 LOPD: 1/28,300 All: 1/25,200	Report on 1-year NBS program
	Brazil [42]	2016	NB	10,567	Fluor assays		Enzymatic + Molecular testing + Urinary GAGs analysis	Opt-out	4	1	1/10,600	Evaluation of challenges of NBS

List of abbreviations: CA: California; Conf: Confirmatory assay; Cons: parents' method of consent; FIA-MS-MS: flow-injection mass spectrometry; First result: Positive first result or inconclusive; Fluor: Fluorometric; IL: Illinois; IOPD: infantile onset Pompe disease; LC-MS-MS: liquid-chromatography mass spectrometry; LOPD: late onset Pompe disease; MO: Missouri; NB: Newborn; N° cases: Number of confirmed cases; PA: Pennsylvania; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

Table 3
Newborn screening programs in DMD and MD1.

	Country [ref]	Date	Pop	Total number	Scr First-tier	Scr 2nd-tier	Conf	Cons	First result	N° cases	Prev	Aim of study
DMD	Germany [51,54]	1974-2011	NB (M)	537,000	CK assay	/		Opt-in		155	1/3,500	Evaluation of opportunity of NBS for DMD
	France [53]	1975-1986	NB (M)	218,851	CK assay	/	Clinical assessment	?		48	1/4,600	Report on course of NBS
	New Zealand [52]	1979	NB (M)	10,000	CK assay	/	Clinical assessment	?		2	1/5,000	Report on course of NBS
	Canada (Man) [50,51]	1986-2007	NB (M)	172,860	CK assay	/	DMD molecular testing	Opt-out		18	1/9,600	Reduction of the number of 2nd^{s} DMD children born. Observation of development.
	USA (PA) [49]	1987-1995	NB (M)	403,576	CK assay	CK isozyme	DMD molecular testing / muscle biopsy	Opt-out, verbal consent		39	1/10,300	Description of attitude of patients + parents diagnosed with or without NBS toward NBS
	UK (Wales) [48]	1990-2011	NB (M)	369,780	CK assay	/	DMD molecular testing / plasma CK	Opt-in	145	56	1/6,600	Report on 21-year NBS pilot program
	Cyprus [47]	1992-1997	NB (M)	30,014	CK assay	/	DMD molecular testing / muscle biopsy	Opt-out	43	5	1/6,000	Evaluation of the method + implementation of NBS pilot
	USA (OH) [46]	2007-2010	NB (M)	17,865	CK assay	/	DMD molecular testing	Opt-in	168	3	1/6,000	Evaluate of method + feasibility of NBS
	China (Zhejiang) [45]	2017	NB (M)	18,424	CK-MM assay	/	DMD molecular testing	Opt-in	13	4	1/4,600	Recommendations for follow-up care
MD1	USA (NY) [57]	2013	DBS	51,341	triplet primed-PCR + melt curve analysis		Molecular testing	no	143	24	1/2,100	Determination of prevalence

List of abbreviations: CK-MM: Creatine kinase muscle; Conf: Confirmatory assay; Cons: parents' method of consent; DBS: DBS deidentified; First result: Positive first result or inconclusive; M: Male; Man: Manitoba; NB: Newborn; N° cases: Number of confirmed cases; NY: New York state; OH: Ohio; PCR: polymerase chain reaction; PA: Pennsylvania; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

MD1 is caused by a pathological (>50) CTG repeat in the *DMPK* gene. Anticipation, a phenomenon in which the age of onset of an autosomal dominant disease becomes earlier with each successive generation, typically occurs in maternal transmission of the disease. The most severe form is the congenital form (15% of cases) which includes severe generalized weakness at birth with respiratory distress, hypotonia and feeding difficulties. Patients subsequently develop delayed cognitive and motor milestones, intellectual disability, and autism spectrum disorder with the physical symptoms taking a potentially fatal course. The incidence is extremely variable from 0.5 to 1.8 per 100,000 [55].

Despite several pre-clinical developments [56], no specific disease-modifying therapy is currently available. Management consists primarily of monitoring for complications and standard of care (assistive devices, hormone therapy, pain medication).

We found one pilot project for MD1 in 2013, in the USA, using deidentified dried blood spot (DBS), with the aim of determining prevalence [57]. This was found to be 1 in 21,100.

The characteristics of NBS program in MD1 are reported in Table 3.

3.6. Krabbe disease

Krabbe disease is an autosomal recessive lysosomal disease affecting the white matter of the central and peripheral nervous systems, characterized by neurodegeneration whose severity depends on the age of onset. Krabbe disease is caused by a loss of function mutation in both alleles of the *GALC* gene leading to a deficit in galactosylceramidase.

Historically, 85–90% of patients were diagnosed with the infantile form, which is the most severe and manifests in the first six years of life. In those in whom the disease begins in the first year, a rapid neurological deterioration is observed, leading to death before the age of two years. Late-onset Krabbe disease is much more variable in its presentation and

course [58]. The incidence of both forms of Krabbe disease is estimated to 1 in 100,000 [59].

The low incidence of the disease is an obstacle for the observation of the effectiveness of a pre-symptomatic treatment. Post-symptomatic treatment, presently limited to hematopoietic stem cell transplantation, slows disease progression. However, this is far from being transformative [60]. Pre-symptomatic treatment was initially presented as being much more efficient, but a recent report has demonstrated that only 1 of 18 patients treated before the onset of symptoms presented with mild disability; 13 of the other patients presented with severe disability, and four died [60–62].

We found four pilot projects for Krabbe disease as part of the introduction of NBS for a range of lysosomal diseases. The five-year NBS program in Mexico [40], with 20,000 newborn babies screened, found zero cases. The first US program in New York States screened more than two millions newborns and identified five case [63], the second, in Kentucky with 55,000 newborns, identified one case [64], and the third in Illinois, with almost 500,000 babies, identified eight cases: two infantile Krabbe disease and six probable late-onset Krabbe infants [65]. This NBS is a recommended disease in the RUSP but is now implemented in seven states in the USA. Recent publications have questioned the ethical basis of such screening [66].

The characteristics of NBS programs in Krabbe disease are reported in Table 4.

3.7. X-linked adrenoleukodystrophy

X-ALD is a peroxisomal genetic disease caused by a loss of function mutation in *ABCD1* gene. It is a devastating metabolic disorder affecting the adrenal glands, brain, and spinal cord. X-ALD affects hemizygous boys more severely than heterozygous girls (60%). If untreated, X-ALD is most often fatal.

Corticosteroid treatment for adrenal insufficiency, hematopoietic stem cell transplantation, and gene therapy for neurologically devastating brain adrenoleukodystrophy administered at the very beginning of brain inflammation, have been associated with improved survival and functional outcomes [67].

The RUSP included X-ALD as a secondary condition in 2016. Only eight states in the US were conducting X-ALD NBS in 2019, rising to twenty in 2021 [68,69]. Several articles reported on the implementation of X-ALD NBS in their states [69–71]. The Ministry of Health of the Netherlands added ALD in the NBS panel in 2015, but only for males [72]. A prospective pilot study was first implemented to assess feasibility and establish the algorithm that identifies only males. Broad implementation began on January 1, 2021.

Another NBS pilot project is currently underway in Taiwan for X-ALD. Started in 2016, it has already screened 45,796 newborns. Results have not yet been published (NCT02952482) [73].

The characteristics of NBS programs in X-ALD are reported in Table 4.

3.8. Metachromatic leukodystrophy

MLD is an autosomal recessively-inherited metabolic disease characterized by accumulation of sulfatides in the central and peripheral nervous system due to deficiency of the enzyme arylsulfatase A, which leads to demyelination. The main characteristics of the disease are a deterioration of motor or cognitive functions, depending on the subtype, leading to severe disability and death after a very variable evolution and duration of the disease.

Gene therapy has recently been approved in the US and the EU (OTL-200). Pre-symptomatic patients have presented much better outcome [74,75].

To our knowledge, only one pilot project aimed at demonstrating the feasibility of MLD NBS took place in the USA in 2020, screening 27,335 de-identified DBS [76].

The characteristics of NBS program in MLD are reported in Table 4.

4. Discussion

We identified seven diseases with a clear peripheral neurologic system component that have been targeted by NBS over the last twenty years. SMA is certainly the disease for which NBS has the greatest consensus, given the importance of early intervention demonstrated or suggested in all clinical developments, and the dramatic efficacy of pre-symptomatic treatments [26,77]. Interestingly, SMA NBS programs were initiated before the approval of disease modifying treatments but have contributed to demonstrating the dramatic efficacy of early treatment. The low cost of screening [78] which contrasts with the very high societal cost of untreated disease, or post-symptomatic diseases [79] also suggests that the NBS program is highly cost-effective, even if this remains to be formally demonstrated. The treatment algorithm, including the difficult question of patients with symptoms at birth and on the other hand of the spectrum patients with four copies of *SMN2* remains to be established [80,81]. Although an agreement was revised in favour of early treatment of patients with four copies, there is no clear and unanimous attitude today towards the choice of the treatment of these patients.

NBS of Pompe disease brings different technical and prognostic consideration, the most significant of which is the proportion at birth of late onset forms, for which there is today no indication of early treatment, compared to the infantile form, for which a treatment certainly should be initiated. A recent study in Pennsylvania has illustrated that the earlier form is less prevalent than later forms with a ratio of 1:15 [38]; this situation is completely different to that of SMA in which the more severe form represents about 60% of all forms [82]. As it is the case for other the other neuromuscular diseases with metabolic origin (i.e., Krabbe,

Table 4
Newborn screening programs in Krabbe disease, X-ALD and MLD.

	Country [ref]	Date	Pop	Total number	Scr First-tier	Scr 2nd-tier	Conf	Cons	First result	N° cases	Prev	Aim of study
Krabbe	USA (NY) [63]	2006-2014	NB	2,090,910	LC-MS-MS	Molecular testing	Enzymatic testing	Opt-out	620	5	1/418,000	Report on experience of NBS
	Mexico [40]	2012-2016	NB	20,018	LC-MS-MS	/	Enzymatic and Molecular testing	Opt-in	38	0		Evaluation of the results of a lysosomal NBS
	USA (KY) [64]	2016-2017	NB	55,161	FIA-MS-MS	CLIR tools		Opt-out	181	1	1/55,000	Report on experience of NBS
	USA (IL) [65]	2017-2020	NB	494,147	LC-MS-MS	Molecular testing + psychosine levels	Follow-up	Opt-out	288	2 IOKD 6 LOKD	IOKD: 1/250,000 LOKD: 1/82,400 All: 1/61,800	Report on experience of NBS and role of psychosine in disease diagnosis
X-ALD	USA (NY) [69]	2013-2019	NB	1,039,000	NA	NA	NA	Opt-out			1/18,783	Update on NBS, explanation of diagnosis and treatment
	USA (MN) [70]	2017-2018	NB	67,836	FIA-MS-MS	/	Molecular testing + Very-Long Chain Fatty Acids analysis	Opt-out	56	14 (9 M, 5F)	All: 1/4,845 Male: 1/3,878	Report on experience of NBS
	USA (NC) [71]	2018(6 m)	NB	52,301	FIA-MS-MS	Molecular testing	/	Opt-out	12	6	1/18,717	Evaluation of the performance of a single-tier NBS assay
	Taiwan [73]	2016-2018	NB	45,796	FIA-MS-MS	/	/	Opt-in				Evaluation of routine NBS method
	The Nether-lands [72]	2015/2020	DBS (M)	250	FIA-MS-MS	LC-MS-MS and Molecular testing	/	Opt-out				Assessment of feasibility of NBS only for male
MLD	USA (WA) [76]		DBS	27,335	LC-MS-MS	Enzymatic assay	Molecular testing	no	195	2		Assessment of feasibility

List of abbreviations: Conf: Confirmatory assay; Cons: parents' method of consent; DBS: DBS deidentified; FIA-MS-MS: flow-injection mass spectrometry; F: Female; First result: Positive first result or inconclusive; IL: Illinois; IOKD: infantile onset Krabbe disease; KY: Kentucky; LC-MS-MS: liquid-chromatography mass spectrometry; LOKD: late onset Krabbe disease; M: Male; m: months; NA: not available; MN: Minnesota; NB: Newborn; NY: New York state; NC: North Carolina; N° cases: Number of confirmed cases; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay; WA: Washington.

X-ALD and MLD), the setup of specific and laborious assays tends to hamper the implementation of corresponding NBS programs.

Aside from deflazacort, which is usually not prescribed before the age of three years, all approved treatments for DMD are mutation-specific, which raises questions as to the utility of broadly screening for CK or CK-MM levels at birth. Indeed, only about 30% of patients could potentially benefit from early detection, however this remains hypothetical as it has not yet been demonstrated. Recently, an assay has been proposed for identifying only the patients with a mutation eligible for exon [83]. The lack of specificity of CK level also makes the use of this test difficult to use at a population level.

As discussed in the present review, some neuromuscular diseases are currently amenable to NBS as they are identifiable either by a sensitive biochemical assay or by a specific hotspot mutation (e.g., deletion of SMN1 exon 7 in SMA). However, most NMDs have neither a specific biomarker nor a prevalent molecular defect. Screening for these disorders is therefore not suitable for current technological NBS platforms, which are biochemically driven. Two clear examples can be found in CMS and BVVL. To date, 34 genes are described as being involved in CMS [84]. Low-cost treatments such as salbutamol or pyridostigmine can avoid sudden death or disability in the course of a long diagnostic journey. BVVL, a recessive disorder caused by a loss of function mutation in one of

the three different intestinal riboflavin transporter genes, can be managed with a high dose of riboflavin [85], and leads to severe bulbospinal atrophy in absence of treatment. Unfortunately, neither CMS not BVVL can be identified by any sensitive biomarker and are thus not amenable to NBS; identification of such disorders at birth should therefore be carried out through whole exome or targeted sequencing.

The same will apply for conditions for which transformative clinical or pre-clinical results have been reported recently. One example is X-linked myotubular myopathy, a rare congenital myopathy caused by a loss of function mutation in the X chromosome located *myotubularin* protein, which leads to early death in the most severe form and to severe disability in the milder forms [86,87]. X-linked myotubular myopathy patients treated with gene therapy have initially demonstrated dramatic improvement [88] and although severe safety concerns have been raised [89], it is very likely that a drug will be approved for the condition, as several other therapeutic approaches are in development [90].

Taken as a whole, we should expect the future for NBS for neuromuscular disorders globally to pass through a technological paradigm shift, from a biochemical to a genetic-based approach. The rapid development of therapies also requires the prospect of promptly adapting the list of treated conditions in order to allow innovative therapies to achieve utmost efficacy.

NBS and carrier screening (explored in another review of this issue), should be simultaneously implemented. Carrier screening has the potential to decrease the incidence of diseases in a population, but fails to address the whole population, and is obviously socially oriented. It fails to identify neo-mutations, a situation in which both variants are on the same allele (which is not rare in SMA) and of course cannot fully cover babies with an unknown father or with one or both parents absent. NBS is universal, addresses all children regardless of parents' conditions, and allows both patient and society to obtain the maximal benefit of innovative medications.

Let's hope that in 45 years, our 135-year-old dear myologist, wherever his rambling of child neurologist has led him, could list 90 diseases that we have happily blown out as we wish him to happily blow out his 90 candles today.

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Supplementary materials

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