Journal of Neuromuscular Diseases 11 (2024) 253–274
DOI 10.3233/JND-230189
IOS Press

Review

The Importance of Early Treatment of Inherited Neuromuscular Conditions

Laurane Mackels[a,b] and Laurent Servais[c,d,*]
[a]*MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK*
[b]*Adult Neurology Department, Citadelle Hospital, Liège, Belgium*
[c]*Neuromuscular Centre, Division of Paediatrics, University and University Hospital of Liège, Liège, Belgium*
[d]*MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford & NIHR Oxford Biomedical Research Centre, Oxford, UK*

Accepted 28 November 2023
Pre-press 30 January 2024
Published 5 March 2024

Abstract. There has been tremendous progress in treatment of neuromuscular diseases over the last 20 years, which has transformed the natural history of these severely debilitating conditions. Although the factors that determine the response to therapy are many and in some instance remain to be fully elucidated, early treatment clearly has a major impact on patient outcomes across a number of inherited neuromuscular conditions. To improve patient care and outcomes, clinicians should be aware of neuromuscular conditions that require prompt treatment initiation. This review describes data that underscore the importance of early treatment of children with inherited neuromuscular conditions with an emphasis on data resulting from newborn screening efforts.

Keywords: Inherited neuromuscular conditions, children, timely treatment, early treatment, newborn screening

ABBREVIATIONS

CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMS	congenital myasthenic syndromes
DMD	Duchenne muscular dystrophy
EAP	expanded access program
ERT	enzyme replacement therapy
GAA	acid α-glucosidase
Gb3	globotriaosylceramide
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE-2	Hammersmith Infant Neurological Examination – Part 2
IOPD	infantile-onset Pompe disease
LOPD	late-onset Pompe disease
LysoGb3	globotriaosylsphingosin
NBS	newborn screening
rhGAA	recombinant human acid alpha-glucosidase
RULM	Revised Upper Limb Module
SMA	spinal muscular atrophy

INTRODUCTION

Until recently, there were very few therapeutic options for patients with inherited neuromuscular diseases, but over the last twenty years, discoveries related to the mechanisms underlying neuromuscular conditions have led to the development of varied

*Correspondence to: Laurent Servais, E-mail: laurent.servais@paediatrics.ox.ac.uk.

therapeutic approaches that have drastically changed clinical practice and patient outcomes [1]. Evidence indicates that greater benefit derives when disease-modifying and symptomatic treatments are administered early in life, emphasizing the need for prompt diagnosis. These data support the importance of implementation of newborn screening (NBS) programs that allow diagnosis of various inherited diseases within the first few days of life. To improve patient care and outcomes, clinicians should be mindful of neuromuscular conditions that require urgent treatment initiation. This review aims to assist neurologists and neurogeneticists in their clinical practice by providing an overview of evidence supporting the value of early treatment of various neuromuscular conditions. Additionally, we outline validated treatments for such use in clinical practice, the optimal timeframes for treatment initiation, and address key challenges in initiating early treatment.

It should be noted that for certain neuromuscular diseases, potential therapies are currently in development or undergoing clinical trials, but they have not yet received approval for clinical use. These diseases include X-linked myotubular myopathy, centronuclear myopathy [2], nemaline myopathy [3], limb-girdle dystrophy [4, 5], thymidine kinase 2 deficiency [6] and various other neuropathies [7]. Moreover, the significance of timely treatment has not been adequately addressed for certain drugs already available in clinical practice. Furthermore, some therapeutic options are approved for use in adults but have not been studied in children. These aspects are beyond the scope of this paper.

METHODOLOGY

The two authors prepared a list of neuromuscular and neuromuscular conditions encountered in clinical practice using a strategy described in a previous review [8] and extended based on the expertise of the authors. Appendix A provides the list of terms included in our search strategy. Three different databases (Medline (Ovid, Pubmed), Scopus, and Embase) were searched for research articles, reviews, and grey literature published since 2000. Key papers describing initial clinical trials published prior to this date were included for completeness. The two authors successively and independently screened titles and abstracts for eligibility. When the abstract was considered relevant to this review, the authors reviewed the article in detail to confirm inclusion. To be included, studies had to meet the following criteria: (1) the study was performed on human patients, (2) patients were less than 18 years old and had been diagnosed with one of the diseases included in our list, (3) a pharmacological treatment or diet was evaluated, (4) results were presented, and (5) time to treatment was clearly stated. Therapeutics that have been discontinued or withdrawn from clinical use were not considered. Publications and/or clinical trial reports that discuss therapeutics for which time to treatment was not addressed or that are used exclusively in adults were excluded. The two reviewers compared their findings and potential disagreements were resolved by consensus. Data extraction was carried out by LM and reviewed by LS.

NEUROMUSCULAR DISEASES WITH EVIDENCE SUPPORTING BENEFITS OF EARLY INTERVENTION

Conditions requiring early drug-modifying treatment

Spinal muscular atrophy

Background and therapeutics approved for treatment of spinal muscle atrophy: Spinal muscular atrophy (SMA) is a serious inherited neuromuscular condition caused by heterozygous mutations in the *SMN1* gene, which has an average incidence of 1 in 14,848 births [9]. Mutations in *SMN1* that result in loss of function of the survival motor neuron protein (SMN) cause premature motoneuron degeneration. This condition affects both the peripheral and central nervous system resulting in proximal muscle weakness, hypotonia, and muscle atrophy [10]. In the most severe form of the disease, affected children typically present soon after birth with severe motor impairment, and premature death usually occurs within their first year of life due to respiratory failure. The severity of the phenotype is mainly modulated by the number of copies of *SMN2* [11, 12], a paralogue gene that is alternatively spliced. Little functional SMN is produced from this gene, but patients with more copies of *SMN2* have better clinical outcome [13, 14].

SMA patients were historically distributed into five types depending on age at symptom onset and motor milestones acquisition [10]. Type 0 occurs before birth, is rare, and fatal within 6 months. Types 1, 2, and 3 typically manifest in infancy but, in some cases, in adolescence. Type 4 is adult-onset. Before treatments were available, SMA was either fatal or responsible for significant and progressive disability

[15–19]. With the development of disease-modifying therapies, the clinical journey of patients has been transformed, and NBS allows patients to be diagnosed prior the appearance of symptoms in many cases. Three drugs are currently approved for clinical use in SMA, nusinersen (Spinraza®) [20–32], onasemnogene abeparvovec-xioi (Zolgesma®)[33, 34], and risdiplam (Evrysdi®)[35–38] (Table 1). All have been assessed in asymptomatic patients [39–45].

Early treatment in symptomatic patients diagnosed by symptoms: Initial evidence for the benefits of early SMA treatment emerged from clinical trials and expanded access programs (EAP) in patients with SMA types 1 and 2. In patients with SMA type 1, the ENDEAR study showed that early treatment with nusinersen (within the first 13.1 weeks of disease duration) led to better outcomes, with lower ventilation needs (23% required ventilation if treated before 13.1 weeks vs. 54% if after) and improved motor development on the Hammersmith Infant Neurological Examination – Part 2 (HINE-2) scale (93% vs. 45%) compared to later treatment [32]. In the subsequent SHINE study, SMA 1 patients treated before 5.42 months achieved higher Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores, with a larger proportion achieving independent sitting (60% vs. 38%), and assisted walking (10% vs. 0%) [46, 47]. Data from EAPs in Italy and Germany showed that treatment before 7 months resulted in significantly higher CHOP-INTEND scores compared to later treatment [24, 25]. The FIREFISH study demonstrated that a higher proportion of SMA 1 patients were able to sit unassisted at 8 months follow-up when treated with risdiplam before 5 month of age (75% vs. 30%) [48]. Initiation of onasemnogene abeparvovec-xioi treatment prior 3 month of age resulted in earlier achievement of a CHOP INTEND score above 40 (median 11.9 months) [33, 49] and the ability to sit [34, 49] when compared to later start in treatment. Of note, initial findings from the clinical evaluation of the oral therapy branaplam (NCT02268552) in infants with SMA 1 who have two copies of *SMN2* also indicate greater improvement in patients treated before 4 months of age compared to those treated after 4 months [50]. However, clinical development of this molecule was halted in 2021.s

In SMA type 2, a placebo-controlled study assessing nusinersen in 66 patients (aged 2 to 12 years) showed better response rates in those treated before age 6 (64% vs. 14%) and those with shorter disease duration [51]. Similar correlations between the age at treatment initiation and the average improvement achieved on various motor scales (e.g., Hammersmith Functional Motor Scale – Expanded (HFMSE) and Revised Upper Limb Module (RULM)) was confirmed in subsequent studies with nusinersen [23] and risdiplam [52–54]. Thus, outcomes and survival are enhanced when initiated at younger age. This prompted further study assessing treatment in pre-symptomatic patients and the development and implementation of NBS programs [55–64] to accelerate diagnosis and treatment initiation.

Early treatment in pre-symptomatic patients: The rationale for initiating treatment in asymptomatic patients was supported by evidence discussed above and by findings that indicate that rapid motor neuron degeneration occurs during the first weeks of life and even during fetal development in patients with SMA [65]. Additionally, electrophysiological studies showed reduced compound muscle action potentials in otherwise asymptomatic patients, reflecting ongoing axonal loss [60]. Three main clinical trials, NURTURE, SPR1NT, and Rainbowfish, focused on pre-symptomatic patients treated with nusinersen ($n = 25$) [66–69], onasemnogene abeparvovec ($n = 29$) [44, 70], and risdiplam ($n = 7$) [71, 72], respectively, in patients with one to three copies of *SMN2*. Pre-existing symptoms were an exclusion criterion, limiting the study to strictly asymptomatic patients. These trials showed that patients with three *SMN2* copies who were treated prior to symptom onset achieved independent ambulation before the age of two. Roughly half of patients with two copies of *SMN2* achieved typical motor milestones, whereas the other half experienced mild-to-moderate motor delay indicating significant variation in treatment response [9]. Although there is no precise equivalence between *SMN2* copy number and SMA type [73], these data clearly contrast with evolution observed in SMA2 patients from the SHINE study. Long-lasting benefits of early intervention were also evident in the five-year follow-up of subjects treated through the NURTURE trial [68]. Emerging evidence indicates potential benefits on swallowing functions due to treatment prior to symptom onset [41], but the effects on neurocognitive development require further thorough assessment.

Early treatment in patients diagnosed via newborn screening: Evaluation of SMA patients identified through NBS programs revealed that a considerable

Table 1
Summary of validated disease-modifying treatments

Disease	Molecule	Category	Mechanism	Physiological effect	Route	Dosing and Frequency	Approval	Minimum age at administration across studies	Clinical trial in PSP	Real-world data in PSP
SMA	Nusinersen	ASO	Enhances *SMN2* mRNA exon 7 inclusion	Enhances production of functional SMN protein	IT	4 loading doses (2 mg, 5 mL) First 3 at 14-day intervals. 4th 30 days after the 3rd dose. Maintenance dose every 4 months.	FDA: Dec 2016 EMA: Jun 2017	Newborn	Yes	Yes
SMA	Onasemnogene abeparvovec-xioi	AAV9- based gene therapy	Delivers a copy of SMN in a scAAV9	Permits sustained expression of the SMN protein	IV	One administration of 1.1 × 1014 vg/kg	FDA: May 2019 EMA: May 2020	Full term newborn < 13.5 kg	Yes	Yes
SMA	Risdiplam	Small molecule	Promotes *SMN2* splicing	Enhances production of functional SMN protein	Oral	0.15 mg/kg to 5 mg depending on age	FDA: Aug 2020 EMA: March 2021	Newborn	Yes	Yes
IOPD LOPD	Alglucosidase alfa	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen	IV	20 mg/kg every 2 weeks	FDA: Aug 2006/2010 EMA: Apr 2006	Newborn	No	Yes
LOPD	Cipaglucosidase alfa + miglustat	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen	IV	20 mg/kg every 2 weeks 1 h after taking oral 65 mg miglustat	FDA: Under regulatory review EMA: Mar 2023	Newborn	No	No

IOPD LOPD	Avalglucosidase	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen		20 mg/kg eow	FDA: 2021 (LOPD only) EMA: 2022 (LOPD and IOPD)	> 6 months of age	No	No
DMD	Deflazocort	Anti-inflammatory treatment	Pleiotropic effects	NA	Oral	0.9 mg/kg/day 0.6 mg/kg/d for the first 20 days of each month	FDA: Feb 2017 EMA: Oct 1993	≥ 4 years	No	No
DMD	Prednisone/ prednisolone	Anti-inflammatory treatments	Pleiotropic effects	NA	Oral	0.75 mg/kg/day	FDA: Feb 2017 EMA: Oct 1993	≥ 2 years	No	No
DMD	Ataluren	Stop codon readthrough	Ribosome readthrough of stop codons (for non-sense mutation)	Enables translation of full-length dystrophin	Oral	10 mg/kg tid	FDA: Not approved EMA: July 2014	≥ 2 years	No	No
DMD	Eteplirsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Sep 2016 EMA: Sep 2018	≥ 6 months	No	No
DMD	Golodirsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Aug 2019; EMA: Dec 2019	> 6 years	No	No
DMD	Viltolarsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	40 mg/kg/week 80 mg/kg/week	FDA: Jul 2020 EMA: Not approved	≥ 4 years	No	No
DMD	Casimersen	Exon skipping	Promotes exon 45 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Feb 2021 EMA: Feb 2021	> 6 years	No	No
DMD	Delandistro-gene moxeparvo-vec-rokl	AAV9-based gene therapy	Delivers a gene encoding a shortened 138-kDA micro-dystrophin protein to muscles	Reestablishes truncated dystrophin expression to attenuate the phenotype	IV		FDA: Jun 2023 EMA: Not approved	4-5 years	No	No

(*Continued*)

Table 1
(*Continued*)

Disease	Molecule	Category	Mechanism	Physiological effect	Route	Dosing and Frequency	Approval	Minimum age at administration across studies	Clinical trial in PSP	Real-world data in PSP
Fabry	Agalsidase beta	ERT	Replaces deficient α-GAL endogenous enzyme	Decreases accumulation of Gb3	IV	1 mg/kg eow	FDA: 2001 EMA: 2003	≥ 2 years (USA) ≥ 8 years in other countries (other countries)	No	No
Fabry	Agalsidase alfa	ERT	Replaces deficient α-GAL endogenous enzyme	Decreases accumulation of Gb3	IV	0.2 mg/kg eow	FDA: Not approved EMA: Aug 2001	≥ 7 years	No	No
Fabry	Migalastat	Chaperone therapy	Increases α-GAL enzyme availability inside lysosomes by correcting the misfolding of α-GAL (for amenable mutations)	Increases α-GAL activity, decreases accumulation of Gb3	Oral	123 mg eod	FDA: August 2018 EMA: May 2016	≥ 12 years	No	No

Abbreviations: AAV9-GT, AAV9-based gene therapy; ASO, antisense oligonucleotide; CT, clinical trial; DMD, Duchenne muscular dystrophy; eow, every other week; eod, every other day; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IT, intrathecal; IV, intravenous; LOPD, late-onset Pompe disease; NA, not applicable; NS, not specified; PSP, pre-symptomatic patients; scAAV9, self-complementary adeno-associated viral serotype 9; SMA, spinal muscular atrophy; tid, three times a day; vg, vector genome.

proportion of patients have symptoms at diagnosis [56, 74], indicating that not all patients identified through NBS can be classified as pre-symptomatic. Since 2021, evidence from real-world screening programs has increasingly demonstrated benefits of early treatment [59, 62, 63, 75–85]. A recent systematic review focused on outcomes in SMA patients who have two or three copies of *SMN2* identified via NBS provides a summary of prognosis of these patients and provides an overview of the global population not restricted to pre-symptomatic patients [9]. The authors identified 77 patients with two *SMN2* copies; of these, 73 were treated at a median age of 23 days. Of the 41 identified patients with three copies of *SMN2*, 38 were treated at a median age of 52 days. Also identified were 24 subjects with four copies of *SMN2*; of these, 18 were treated at a median age of 2019 days. Of the patients with two copies of *SMN2* copies, 37% had symptoms prior to treatment, whereas 1% of those with three *SMN2* copies and 6% of those with four *SMN2* copies had symptoms. The authors concluded that patients with three *SMN2* copies and no symptoms at treatment initiation had excellent functional prognosis, achieving normal development in over 90% of cases. Patients with two *SMN2* copies had more variable outcomes [9], although their outcomes were significantly better than those identified by symptoms [83]. Due to the very small sample size, clear conclusions could not be drawn for patients with four copies of *SMN2*. The most recent recommendations, published in 2021, suggest that treatment should be initiated early for patients with four copies of *SMN2*, although there is still limited data available to support this approach [86].

Pompe disease

Background and approved therapeutics for Pompe disease: Pompe disease is an autosomal-recessive neuromuscular condition caused by mutations in the gene that encodes acid α-glucosidase (GAA). The enzyme is normally responsible for breaking down lysosomal glycogen. In Pompe disease, deficiency of GAA [87, 88] leads to glycogen accumulation, cellular dysfunction and progressive damage of smooth, cardiac and skeletal muscles [89]. As in SMA, symptom onset spans from early childhood to adulthood. Those with infantile-onset Pompe disease (IOPD) are characterized by a severe or complete GAA deficiency (<1% residual activity) [87]. Late-onset Pompe disease (LOPD) [90] is associated with a partial GAA deficiency (<30% residual activity) [91] and is usually more insidious [92–95]. In patients with IOPD, symptoms may manifest within the first days of life up to 12 months of age and can occasionally be noted *in utero* [96]. Affected children experience significant motor delay and die of cardiorespiratory failure within the first year of life [94, 97].

Treatments available to date (Table 1) include enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA). ERT reverses cardiomyopathy, improves motor development, and enhances overall survival [98–100]. Alglucosidase alfa (Myozyme®) has been used the longest and has mainly been studied in patients with IOPD. Although IOPD patients can show great improvement when treated with ERT, they often plateau and clinical decline may be observed around 20–24 months of treatment duration. Moreover, residual long-term sequelae have been observed in surviving patients, especially in those with IOPD who do not have cross-reactive immunological material (CRIM) [101–106].

A more recent version of rhGAA, avalglucosidase alfa (Nexviazyme®), was specifically engineered to increase glycogen clearance [107]. Cipalglucosidase alfa (Pombiliti®) is another ERT, used in combination with miglustat [108]. Avalglucosidase alfa was shown to be a safe and efficient alternative to alglucosidase alfa in LOPD [109–111] and has received marketing authorization in several countries for LOPD and/or IOPD, whereas cipaglucosidase alfa has received recent approval for adult LOPD [145]. Results from the mini-COMET trial suggest that avalglucosidase alfa is beneficial in IOPD patients who are less than 18 years of age who were declining on alglucosidase alfa [112], but the timing of treatment was not specifically evaluated. Currently, there are two ongoing open-label phase III trials assessing the safety and efficacy of cipaglucosidase alfa in pediatric patients (< 18 years old) with IOPD (NCT04808505) and LOPD (NCT03911505). Overall, data on IOPD patients treated with ERTs other than alglucosidase alfa remain very limited, and the impact of age at treatment has not yet been addressed. Several factors have shown to impact patient outcome and response to treatment including CRIM status [94, 97, 101, 113–118], the development of anti-rhGAA immunoglobulin G (IgG) antibodies [119], ERT dosage and dosing regimen [99, 100, 106, 120–122], the severity of muscle involvement at treatment onset [123], and failure thrive at baseline [123]. Age at treatment has also been shown influence response as summarized below.

Early treatment in infantile-onset Pompe disease: The use of the terms "pre-symptomatic" or "asymptomatic" in published works can be ambiguous in distinguishing between LOPD patients without symptoms at diagnosis and IOPD patients identified through NBS who may have mild symptoms (Table 2). Clinical manifestations like increased left ventricular mass index and/or Glc4 levels have been described in most IOPD cases [124, 125], which has contributed to the ambiguity of these terms. To avoid misunderstandings across articles, it is important to provide a clear definition of these terms, similar to what has been done in SMA. As we move forward, we will discuss IOPD as a whole, using the term pre-symptomatic specifically for LOPD patients who have no clinical or sub-clinical symptoms at screening.

Alglucosidase alfa, the FDA-approved rhGAA form, was initially shown to be safe and efficient in four patients with IOPD at starting doses of 15 mg/kg or 20 mg/kg and later increased at 40 mg/kg [98]. The two patients treated before 3 months of age were ventilation-free after 36 weeks of treatment, whereas the two patients who began treatment at the ages of 7 and 8 months required ventilator support [98]. The two younger patients had no significant respiratory problems during the first 2 years of life and showed greater motor progress than the older subjects [99]. A phase I/II clinical trial confirmed cardiac and skeletal muscle function improvement in three patients with IOPD who began treatment at dose 5 mg/kg at 2.5, 4, and 4 months of age. The youngest patient exhibited significant clinical improvement, achieving normal clinical status by 16 months of age. The two other patients developed high anti-rhGAA antibody titers, declined in motor development and pulmonary function, and required ventilator support [115].

Early initiation of ERT yielded to sustained motor and cardiac improvement at 48 weeks of treatment and beyond in two patients treated at age 3.1 and 5.9 months [126, 127]. An open-label study in eight patients with IOPD treated between 2.7 and 14.6 months of age demonstrated enhanced ventilator-free and prolonged overall survival compared to historical cohort of untreated patients. Patients who received treatment before reaching six months of age had better motor outcomes and prolonged survival [128, 129], suggesting that earlier intervention yields greater advantages. Even greater motor advancements were subsequently observed after 52 weeks of treatment in a cohort of 18 patients with IOPD who received treatment before the age of 6 months [100]. A follow-up study of 16 of these patients who had been treated for up to 3 years with ERT showed extended survival, improved ventilation-free survival, and improved cardiomyopathy compared to untreated patients [130]. Another study of 15 patients with IOPD who were treated at a median age of 13 months (3–43 months) demonstrated similar benefits [131]. Patients treated after 12 months of age had higher survival rates (90.9%) than those treated earlier (50.1%), but this reflected the high risk of death in the first year of life for patients with IOPD [131]. In addition to these studies, the value of early treatment on cardiac, biological (e.g., CK levels) and motor outcomes was further supported by case reports and small case series [125, 132]. Additionally, the correlation found between cognitive and motor development in an IOPD cohort treated before 6 months of age suggests early treatment's impact on neurocognitive development [133].

Data from NBS programs collected since 2005 further supports the value of early intervention in infants with IOPD [134]. Most patients identified by NBS were treated within the first month of life [135–142]. Improved long-term prognosis was observed in Taiwanese CRIM-positive IOPD patients diagnosed via NBS and treated within 34 days of life, with enhanced survival and independence in ambulation after 2 years of treatment compared to natural history [102]. Patients identified through NBS who began ERT at a very young age (mean age 11.92 days; range 6–23) had superior biological, physical, and developmental outcomes and lower levels of anti-rhGAA antibodies after 2 years of treatment in comparison to a group that started ERT only 10 days later [143, 144]. Of the Taiwanese CRIM-positive IOPD cohort, 26 patients were followed for an average of 6.18 ± 3.14 years. All patients included in the study had normal heart sizes, achieved typical motor milestones, demonstrated intact cognitive function, and displayed pulmonary function that ranged from near-normal to normal [145]. Long-term study in one of the largest cohort of IOPD in France recently showed fewer benefits of ERT, with only temporary improvements followed by muscle and respiratory function deterioration; however, the impact of the age of ERT initiation was not explicitly assessed [146].

Real-world data in patients who were either pre-symptomatic or lacked clinical or chemical signs of deterioration demonstrate the benefit of higher doses of ERT (e.g., 40 mg/kg every other week and

Table 2
Publications reporting data from real-world NBS identification and treatment of IOPD

Country	Publication date	Population	IOPD (*n*)	CRIM +	CRIM –	Treated IOPD (*n*)	Pre- or asymptomatic[1] (n)	Pre-ERT cardiac abnormalities[2]	Pre-ERT laboratory abnormalities[2]	Median age at diagnosis/referral*	Median age at treatment (range)	Outcomes reported	Follow-up duration (range)
Taiwan	Feb 2016	669,797	14	14	0	14	0	Y (13/14)	Y (NS)	3.02 ± 0.38*	11.92 days (6–23 days)	Yes	NS (6-year-long study)
Taiwan	Apr 2015	470,000	10	10	0	10	10	Y (10/10)(*)	Y (NS)	9 (0–33 days)	16 days (6–34 days)	Yes	6.18 years (±3.14)
Italy	Dec 2022	206,741	3	1	2	3	1/3	Y (3/3)	Y (3/3)	(3–14 day)	(5–19 days)	Yes	(1.5 –3.5 years)
Italy	Nov 2017	44,411	2	NS	NS	2	0	Y (2/2)	Y(2/2)	NA	Promptly	No	NA
Japan	Jun 2022	296,759	1	1	NS	1	0	Y 1/1	Y (1/1)	NS	58 days	Yes	14 months
USA (California)	Feb 2020	453,152	2	NS	NS	2	2*	Y (2/2)	Y (2/2)	NS	2 months, NA	No	NA
USA (Missouri)	Feb 2020	467,000	10	9	1	10	0	Y (7/8)	Y (10/10)	NS	4 days– month	Yes	NS
USA (Illinois)	Dec 2019	684,290	3	3	0	3	0	Y (3/3)	Y (3/3)	NS	10 days–6 weeks	Yes	(Several months to 4 years)
USA (Pennsylvania)	Dec 2019	531,139	2	2	0	1	1	Y (2/2)	Y (2/2)	19 days NS	21 days 10 days	Yes	31 months 6 months
Austria	Nov 2011	34,736	1	NS	NS	NS	0	NS	NS	NS	NS	No	NS

[1]As labeled by authors. [2]When available, the number of patients with abnormalities is shown in brackets relative to those tested. Abbreviations: IOPD, infantile-onset Pompe disease; NA, not applicable; NS, not specified; Y: yes.

20 mg/kg weekly) early in life [147, 148]. Early initiation of higher-dose ERT led to a delay in motor decline, whereas motor decline was significantly higher in patients with late ERT initiation ($p = 0.006$) or late increase in ERT dosage ($p = 0.044$) [147]. Of five patients who received 40 mg/kg every other week, the four who were walkers at analysis began treatment at 5, 6, 13, and 33 days of life; the non-sitter was first treated at 3.3 months of age [147].

To date, evidence supporting the benefits of early intervention in CRIM-negative IOPD patients remains limited [98, 100, 149]. A retrospective study gathered data from 20 CRIM-negative patients treated with ERT and immune tolerance induction at median ages of 2.1 weeks (0.3–3.4 weeks), 7.6 weeks (4.4–13.3 weeks), or 17.9 weeks (15.4–28.3 weeks) [149]. Clinical outcomes including invasive ventilation-free survival, left ventricular mass index, and motor and feeding status tended to be significantly better in the group treated at a median age of 2.1 weeks [149], whereas CRIM-negative patients from an historical cohort treated at median age of 13 weeks were all deceased or invasive ventilator–dependent by 27.1 months of age [114]. Due to the small number of patients, more research is needed to establish a clear understanding of the advantages in this population.

It should be noted that treatment outcomes in IOPD can be influenced by multiple factors that contribute to the complexity of comparing outcomes across studies and even within the same study. These factors will need to be carefully considered in order to understand the variations in treatment response among IOPD patients. In summary, collective evidence from clinical trial cohort studies, case series, and expert consensus [150, 151] supports the early management of IOPD patients with immunomodulation and a low-dose ERT (20 mg/kg/EOW). Additionally, the potential benefits of earlier and higher regimens have been suggested and require further investigation.

Early treatment in symptomatic and asymptomatic late-onset Pompe disease: Differentiating between IOPD and LOPD in NBS is challenging due to the limitations of enzyme assays. About 75% of Pompe disease cases are LOPD [152], and to date, there is not clear consensus regarding therapeutic strategies for treatment of pre-symptomatic LOPD and guidelines addressing this topic are sparse [153, 154]. However, evidence suggests that initiating ERT prior to the occurrence of irreversible muscle damage could yield to improved treatment outcomes [124, 155–157]. Expert consensus is that ERT should be initiated upon the earliest onset of objective signs of Pompe disease, with pre-symptomatic LOPD patients being monitored every 6 months [158–160].

Duchenne muscular dystrophy

Background and approved therapeutics in Duchenne muscular dystrophy: Duchenne muscular dystrophy (DMD) is a progressive X-linked recessive disorder resulting from out-of-frame mutations in the gene that encodes dystrophin. Dystrophin deficiency or absence leads to progressive muscle weakness, loss of independent ambulation, and serious multisystem complications, including cardiomyopathy and respiratory muscle dysfunction, that culminates in premature death. With the advancement in multidisciplinary management and glucocorticoid therapy, patients can now live into their thirties. Although standard of care has improved life expectancy, glucocorticoids (prednisolone and deflazacort) remain the only clinically proven treatments that slow disease progression [161–163]. A variety of therapeutic strategies are being explored, and six compounds (i.e., ataluren (Translarna®), eteplirsen (Exondys 51®), golodirsen (Vyondys 53®), viltolarsen (Viltepso®), casimersen (Amondys 45®), and delandistrogene moxeparvovec-rokl(Elevidys®) have received conditional regulatory approval in some jurisdictions [161, 164, 165] (Table 1).

Early treatment in Duchenne muscular dystrophy: In 2022, a systematic review explored the importance of timing of clinical interventions in DMD [166]. Of the 12 studies the authors included, six examined glucocorticoid timing [167–172] and one focused on ataluren [173]. There is low-quality evidence that earlier initiation of glucocorticoids prolongs ambulation in patients with DMD, but these agents may also decrease cardiac and respiratory health. The evidence suggesting that early initiation of ataluren improves lower extremity and motor function was graded as being of very low quality. Given the limitations of the studies reviewed, such as confounding by indication, small sample size, and lack of longitudinal follow-up, the authors concluded that the optimal timing of clinical interventions, including glucocorticoids and ataluren, in DMD is still unknown and that further research is needed [166]. Expert recommendations slightly differ, yet generally lean toward advocating steroid trials for children aged 2 to 5 [174–177]. Notably, in June this year, delandistrogene moxeparvovec-rokl (SRP-9001) gained FDA approval to treat ambulatory pediatric patients aged

4 to 5 with certain DMD gene mutations. Approval was based on a double-blind placebo controlled phase 2 trial, including 43 patients, of whom 41 subjects received study treatment (20 subjects in the SRP-9001 group and 21 subjects in the placebo group) [164].

Fabry disease

Background and approved therapeutics in Fabry disease: Fabry disease is a life-limiting X-linked inherited lysosomal disorder caused by pathogenic *GLA* variants [178–180]. These mutations result in inadequate activity of α-galactosidase A, leading to the accumulation globotriaosylceramide (Gb3), and its deacylated form, globotriaosylsphingosine (lysoGb3) within lysosomes in various tissues. As in Pompe disease, accumulation of metabolites causes cellular damage and dysfunction and structural damage to organs [181–184]. Clinical manifestations are numerous and include small fiber neuropathy, renal failure, cutaneous rash, neuropathy, stroke, and cardiomyopathy [180].

GLA variants associated with minimal or no α-galactosidase A activity occur in males and lead to the classic Fabry phenotype with early onset of symptoms and progressive multisystemic involvement. Patients experience acroparesthesia during childhood, but renal, cardiac, and cerebral involvement is typically not detectable at that stage [185, 186]. Cardiac left ventricular mass increases and albuminuria develop during adolescence. Subsequently, ECG changes, cerebral white matter lesions, stroke, and myocardial and glomerular sclerosis ensue, resulting in cardiac complications, renal failure, severe morbidity, and death by the age of 60 [187, 188]. In classic Fabry disease, the variant Gb3 is thought to accumulate *in utero* [189, 190] so that organ damage manifests early in life [191, 192]. In females, the clinical severity of Fabry disease varies considerably [193, 194] due to the presence of residual α-galactosidase A activity and X-chromosome inactivation patterns [179, 195, 196]. Although symptoms in woman often manifest during childhood, they usually appear at later stages than in males [197, 198].

Agalsidase beta and agalsidase alfa are the two ERTs approved for treatment of Fabry disease that have been available since 2001 [199–201] (Table 1). Both drugs are approved in adults and adolescents; agalsidase beta is approved for use in children aged 8 years and above, and agalsidase alfa is approved for use in children aged 7 years and above. Migalastat, a pharmacologic chaperone, is another oral treatment approved for Fabry disease patients aged 12 years and above with amenable GLA variants (Table 1). Migalastat stabilizes renal function and reduces cardiac mass [202, 203], offering an alternative to ERT in adult patients [204]. Data regarding the impact of treatment timing are not available at the time of this review.

Early treatment with enzyme replacement therapy in Fabry disease: The safety and effectiveness of managing Fabry disease with both agalsidase alfa and agalsidase beta were demonstrated in pivotal trials and related open-label extension studies. Agalsidase alfa and beta initially induce a clear biochemical response in adults, reducing Gb3 levels in plasma and urine [200, 201, 205, 206] and clearing storage material from endothelial cells and various renal cell types [207]. From a clinical perspective, although the response was highly variable, ERT improved neuropathic pain [201, 208], renal function [201, 209], cardiac function [201, 210–213], gastrointestinal symptoms [214, 215], and quality of life [216]. These benefits were confirmed by real-world data and follow-up studies [217–220], some of which also demonstrated a delay of clinical events in treated patients [214, 218].

Agalsidase beta (1 mg/kg) was well tolerated and efficacious in a 48-week open-label study of patients aged 8 to 16 years [199]. The treatment resulted in clearance of Gb3 from dermal capillary endothelial cells and reduction in gastrointestinal symptoms [199]. Agalsidase alfa also had good safety and tolerability profiles in pediatric populations [221, 222]. An open-label follow-up study in young patients (age range: 8.6 to 17.3 years; 90.9% males) treated with agalsidase alfa for 6.5 years showed that the ERT was tolerated long term and that reductions in plasma and urinary Gb3 levels were maintained, that left ventricular mass and eGFR were normal, and that heart rate variations were reduced [223].

Multiple prospective, follow-up, and retrospective studies mostly in adults have indicated that initiating treatment at an early stage of disease prior to irreversible organ damage leads to improved clinical and biological outcomes [224–230]. Despite the encouraging evidence supporting early treatment, the optimal timing for initiating treatment remains uncertain. In a study of 12 patients with classical Fabry disease, the greatest clearance of podocyte Gb3 inclusions at 65 weeks of treatment was observed in the youngest patient, aged 7 years old [231]. In a retrospective cohort study, initiation of ERT at less than

25 years of age in men with classical Fabry disease led to a better biochemical response, with higher odds of achieving a plasma lysoGb3 levels below 20 nmol/L and significantly lower lysoGb3 levels one year after ERT initiation compared to those who started treatment later in life [232]. In a retrospective study of seven males with classical Fabry disease who received agalsidase beta treatment during childhood [213], evaluation after 10 years (median age 24 years, range 14–26) showed reduced albuminuria, lower left ventricular mass, absence of myocardial fibrosis, and normal eGFR compared to untreated patients [217]. The authors suggested that initiating ERT before age 16 may decrease renal and cardiac manifestations of Fabry disease [217].

Pre-symptomatic patients can now be identified with NBS [233], but limited genotype-phenotype correlations and the abundance of unique *GLA* mutations make it nearly impossible to accurately predict disease severity or to determine the appropriate timing for ERT initiation [234]. Further, patients identified prior to symptom onset have been rarely studied [235].

In 2015, the European Fabry Working Group recommended starting ERT in patients with classic and non-classic Fabry disease immediately after early clinical signs of Fabry disease-related involvement appear; it was also recommended that treatment be considered in asymptomatic male patients older than 16 years (Class IIB recommendation) [236]. The US expert panel recommended considering treatment for boys with classic Fabry disease mutations as early as 8–10 years of age, irrespective of whether symptoms are present [237]. In 2019, experts suggested consideration of ERT initiation in asymptomatic boys with classical Fabry disease and for girls aged 7 and above who are Fabry disease heterozygotes, although no data are available for these population sub-groups [238].

Conditions requiring early symptomatic treatment

Congenital myasthenic syndromes

Congenital myasthenic syndromes (CMSs) are a group of rare inherited neuromuscular disorders resulting from mutations in genes that regulate the neuromuscular junction function [239]. The clinical presentation of CMS is diverse, encompassing varying degrees of axial and limb-girdle muscle weakness and muscle fatiguability [240]. Notably, symptoms may include weakness in ocular, facial, and bulbar muscles leading to ptosis, ophthalmoplegia, and feeding difficulties [240, 241]. Respiratory issues such as episodic apnea, and joint contractures may also be present. The onset of symptoms can occur from infancy to adulthood [242–244], although the majority of cases manifest within the first year of life [245]. Genetic diagnosis is essential for confirming CMS and over 35 genes have been identified that are associated with CMS, with pathogenic variants in the gene encoding the acetylcholine receptor subunit epsilon being the most prevalent [246]. Due to the heterogeneity of CMS, specific phenotypic manifestations and disease progression vary significantly between subtypes and even among individuals with the same genetic mutation.

There are no approved curative therapies for CMS. The choice of symptomatic therapeutic agents is determined by the underlying genetic defect. Treatment options may include acetylcholinesterase inhibitors, 3,4-diaminopyridine [247], adrenergic agonists (such as salbutamol [248], albuterol [249], and ephedrine [250]), long-lived open-channel blockers of the acetylcholine ion channel (fluoxetine and quinidine) [245], and acetazolamide. The evidence supporting symptomatic treatment in CMS primarily relies on prospective and retrospective case series [251–254], individual and familial case reports, literature reviews [245, 250, 255, 256], and practice-based consensus expert reviews and recommendations [239, 246, 257–259]. Interventional studies involving albuterol (NCT01203592) and expanded access programs for 3,4-diaminopyridine (NCT00872950, NCT03062631, NCT02189720, NCT01765140) have also been conducted. There have been recent reviews of drug efficacy in CMS patients [245, 257], but to our knowledge there have been no studies assessing the impact of treatment timing on the outcomes of CMS. It should be mentioned that initiating treatment early may be critical in certain cases, such as during life-threatening respiratory episodes or when intensive care treatment is required [259]. Genes that are associated with episodic apnea notably include *CHAT* [260, 261], *RAPSN* [262], *SCN4A* [263], *SLC5A7* [264], *CHRNE, CHRND, MYO9A, SLC18A3,* and *COLQ* [251]. Since symptomatic treatment may improve functional ability, quality of life, and life expectancy, avoiding treatment delay is crucial, especially considering that some of these treatments are sometimes low-cost.

Metabolic diseases

Patients with various metabolic conditions can significantly benefit from appropriate symptomatic management early in the disease course. Timely initiation of treatment is essential, as it can be life-saving in certain cases [265, 266]. Management approaches often involve supplementation with essential cofactors or specific dietary adjustments to counterbalance the underlying enzyme deficiency. These conditions include multiple acyl-CoA dehydrogenase deficiency (managed with riboflavin and coenzyme Q) [267], primary carnitine deficiency (managed with carnitine) [268], and Brown-Vialetto-Van Laere and Fazio-Londe syndromes (managed with riboflavin) [265, 269]. Some benefit, mainly due to improving effort intolerance, is obtained in carnitine palmitoyltransferase II deficiency with a high-carbohydrate diet [266, 270].

DISCUSSION

Double-blind, randomized, placebo-controlled trials, open-label studies, systematic reviews, case reports, and expert consensus all provide evidence emphasizing the importance of early treatment in neuromuscular diseases. Nevertheless, the quality of evidence differs across diseases, and the age range recommended for initiating treatment also varies depending on the specific condition. The most compelling evidence for the benefits of early treatment exists for SMA. Treatment of pre-symptomatic SMA patients has shown remarkable and long-lasting effects on motor function in certain patient subgroups, transforming the disease from condition fatal before the age of 2 to nearly or completely normal development. Early treatment provides substantial benefits for IOPD patients as well; however, deterioration after the initial improvement remains prevalent. The ideal treatment window remains less clear for LOPD [271, 272]. Notably, due to the variability of phenotype, even within the same family, and the lack of well-defined genotype-phenotype correlations, determining the optimal treatment window is quite challenging. In Fabry disease, treatment is generally advised upon the appearance of symptoms, and initiating treatment in pre-symptomatic patients remains a debated topic, as disease course is influenced considerably by factors such as sex and age. It is important to note that the natural history of this condition involves symptoms that develop during childhood, not necessarily at birth, and that treatments are only approved for patients aged 7 and above. Currently, the therapeutic window appears to be later than what is considered in SMA and Pompe disease. However, as expert recommendations shift toward early treatment initiation in patients with known later onset of symptoms, including SMA patients with four copies of *SMN2* and LOPD, it may be that early treatment will also be recommended for patients with Fabry disease. There is limited evidence supporting early intervention in DMD and CMS due to the clinical and genetic heterogeneity. However, in CMS and several metabolic conditions, early initiation of symptomatic treatment can be life-saving, and the benefits and drawbacks of early treatment should be further evaluated. Similar to SMA [15, 16], Pompe [94] and Fabry Disease [187], which have multiple robust historical cohorts as references, initiating natural history studies for these condition on a larger scale is imperative, as they are essential for enabling more accurate comparisons with treated patients and design informative clinical trials.

Initiating treatment early in infants and children has various challenges and certain considerations must be acknowledged. Firstly, early diagnosis can lead to situations where the ideal treatment strategy is unclear. In SMA, expert-based consensus updated in 2019 guides therapeutic decisions in infants diagnosed through NBS [273], but evidence supporting prompt drug administration in newborns with four copies of *SMN2* remains limited [63, 86, 274]. In LOPD, although there is evidence to support treatment upon symptom appearance, the management of pre-symptomatic patients remains contentious due to the significant costs (both economic and social), antibody development concerns, and the requirement for life-long intravenous infusions [271]. In IOPD, there is uncertainty about the optimal dose and frequency of treatment, with some evidence suggesting more favorable outcomes with higher doses or more frequent treatment [120, 122, 147]. In Fabry disease, the precise definition of what "early" means is disputed, particularly for very young patients with a wide range of possible organ involvement and for non-classic variants or variants of unknown significance with uncertain natural history.

Secondly, it is essential to recognize the significant variability in treatment response occurs and that early initiation of treatment does not guarantee notable or lasting improvement or even any response at all. As examples, classic Pompe disease remains a serious life-limiting disease despite the therapeutic options [146], and outcomes in SMA patients with one copy

of *SMN2* remain poor despite early treatment initiation.

Thirdly, therapeutic advancements are giving rise to new phenotypes. Certain disease aspects may not be adequately addressed in clinical trials. For example, in SMA, drug-modifying treatments have positively impacted survival and motor function, but concerns are emerging about bulbar, speech, and cognitive function [275], especially in SMA1 patients [276, 277]. In Pompe disease, ERT improves survival and early-life ambulation, but later manifestations may include skeletal muscle decline, cardiac arrhythmias, hearing loss, speech dysfunction, cognitive impairment, and gastrointestinal and respiratory issues [101, 278–280]. Additionally, considering that these treatments are relatively recent, the long-term effectiveness remains unclear. Close patient monitoring is vital for developing a comprehensive understanding of treatment implications and their long-term effects.

Lastly, NBS holds tremendous potential for facilitating early diagnosis and timely treatment, but screening has some caveats that should be acknowledged. For instance, NBS accuracy is well-established in SMA; however, in Pompe disease, distinguishing between IOPD and pseudodeficiency poses challenges [136], resulting in variable positive predictive values of NBS across countries [281]. Conditions characterized by genetic diversity and the continual emergence of new variants, as seen in CMS, may present challenges. This underscores the importance of comprehensive genetic testing, incorporating approaches such as whole-exome sequencing.

CONCLUSION

Early treatment in neuromuscular diseases can prevent severe complications and can be live-saving. Acting in the early stages, before extensive function loss, is clearly beneficial in SMA for example. Delaying treatment can significantly reduce its efficacy, making timing crucial for optimal results in conditions like SMA and IOPD. The ideal therapeutic window for Fabry disease requires further investigation, and the impact of early treatment in DMD is still being evaluated due to clinical heterogeneity. CMS patients can benefit from life-saving symptomatic treatment, emphasizing the importance of raising awareness about these rare conditions and the need for broad genetic testing. When considering early treatment, aspects such as response variability, cost, and safety must be taken into account. Stronger evidence is needed to support early intervention in several conditions, but the low incidence of rare diseases poses challenges to obtaining reliable data. Systematic reviews and meta-analyses can help summarize evidence, but they have limitations and biases. Finally, NBS is a powerful tool that has the potential to revolutionize the course of diseases where early intervention is crucial.

REFERENCES

[1] Wirth B, Garbes L, Riessland M. How genetic modifiers influence the phenotype of spinal muscular atrophy and suggest future therapeutic approaches. Current opinion in genetics & development. 2013;23(3):330-8.

[2] Tasfaout H, et al. Antisense oligonucleotide-mediated Dnm2 knockdown prevents and reverts myotubular myopathy in mice. Nat Commun. 2017;8(1):15661-15661.

[3] Fisher G, et al. Early clinical and pre-clinical therapy development in Nemaline myopathy. Expert Opinion On Therapeutic Targets. 2022;26(10):853-67.

[4] Estepan I, Sarepta Therapeutics Announces Positive Functional Results from the SRP-9003 (MYO-101) Gene Therapy Trial to Treat Limb-Girdle Muscular Dystrophy Type 2E, or Beta-Sarcoglycanopathy| Sarepta Therapeutics. Inc. Investorrelations, 2019.

[5] Mendell JR, et al. Limb-girdle muscular dystrophy type 2D gene therapy restores α-sarcoglycan and associated proteins. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2009;66(3):290-7.

[6] Berardo A, et al. Advances in thymidine kinase 2 deficiency: Clinical aspects, translational progress, and emerging therapies. Journal of Neuromuscular Diseases. 2022;9(2):225-35.

[7] Hustinx M, Shorrocks A.-M, Servais L. Novel Therapeutic Approaches in Inherited Neuropathies: A Systematic Review. Pharmaceutics. 2023;15(6):1626.

[8] Dangouloff T, Boemer F, Servais L. Newborn screening of neuromuscular diseases. Neuromuscular Disorders. 2021;31(10):1070-80.

[9] Aragon-Gawinska K, et al. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening—A Systematic Review. Genes. 2023;14(7):1377.

[10] Munsat T. Meeting report: International SMA consortium meeting. Neuromusc Dis. 1992;2:423-8.

[11] Calucho M, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular Disorders. 2018;28(3):208-15.

[12] Czech C, et al. Biomarker for spinal muscular atrophy: Expression of SMN in peripheral blood of SMA patients and healthy controls. PloS one. 2015;10(10):e0139950.

[13] Lefebvre S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155-65.

[14] Coovert DD, et al. The survival motor neuron protein in spinal muscular atrophy. Human molecular genetics. 1997;6(8):1205-14.

[15] Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy: Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Archives of neurology. 1995;52(5):518-23.
[16] Annoussamy M, et al. Natural history of Type 2 and 3 spinal muscular atrophy: 2-year NatHis-SMA study. Ann Clin Transl Neurol. 2021;8(2):359-73.
[17] Russman B, et al. Function changes in spinal muscular atrophy II and III. Neurology. 1996;47(4):973-6.
[18] Chabanon A, et al. Prospective and longitudinal natural history study of patients with type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. PLoS One. 2018;13(7):e0201004.
[19] Mazzone E, et al. Six minute walk test in type III spinal muscular atrophy: A 12 month longitudinal study. Neuromuscular Disorders. 2013;23(8):624-8.
[20] Finkel RSD, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: A phase 2, open-label, dose-escalation study. Lancet. 2016;388(10063):3017-26.
[21] Haché M, et al. Intrathecal injections in children with spinal muscular atrophy: Nusinersen clinical trial experience. Journal of child neurology. 2016;31(7):899-906.
[22] Chiriboga CA, et al. Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology. 2016;86(10):890-7.
[23] Darras BT, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology. 2019;92(21):e2492-e2506.
[24] Pechmann A, et al. Evaluation of children with SMA type 1 under treatment with nusinersen within the expanded access program in Germany. Journal of neuromuscular diseases. 2018;5(2):135-43.
[25] Pane M, et al. Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data. Annals of Neurology. 2019;86(3):443-51.
[26] Artemieva SB, et al. The efficacy and safety of nusinersen within the expanded access program in Russia. Nervno-Myshechnye Bolezni. 2021;10(3):35-41.
[27] Birsak T, et al. P.366 Nusinersen improves motor function in ambulatory SMA III patients. Neuromuscular Disorders. 2019;29:S188.
[28] Day JW, et al. Longer-term experience with nusinersen in teenagers and young adults with spinal muscular atrophy: Results from the CS2/CS12 and shine studies. Neurology. 2020;94(15).
[29] Deconinck N, et al. Nusinersen experience in teenagers and young adults with spinal muscular atrophy (SMA): Results from CS2/CS12 and SHINE. European Journal of Neurology. 2019;26:143-4.
[30] Aragon-Gawinska K, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: A cohort study. Neurology. 2018;91(14):e1312-e1318.
[31] Tiongson E, et al. Effect of aggressive therapies on spinal muscular atrophy type 1 patients receiving nusinersen. Neurology. 2019;92(15).
[32] Finkel RS, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. 2017.
[33] Mendell JR, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. New England Journal of Medicine. 2017;377(18):1713-22.
[34] Lowes L, et al. AVXS-101 phase 1 gene therapy clinical trial in SMA Type 1: Patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age. Neuromuscular Disorders. 2017;27:S208-S209.
[35] Masson R, et al. Safety and efficacy of risdiplam in patients with type 1 spinal muscular atrophy (FIREFISH part 2): Secondary analyses from an open-label trial. Lancet Neurol. 2022;21(12):1110-9.
[36] Darras BT, et al. Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls. The New England journal of medicine. 2021;385(5):427-35.
[37] Baranello G, et al. Risdiplam in Type 1 Spinal Muscular Atrophy. N Engl J Med. 2021;384(10):915-23.
[38] Chiriboga CA, et al. Risdiplam in patients previously treated with other therapies for spinal muscular atrophy: An interim analysis from the JEWELFISH study. Neurology and therapy. 2023;12(2):543-557.
[39] Darras BT, et al. Safety profile of nusinersen in presymptomatic and infantile-onset spinal muscular atrophy (SMA): Interim results from the nurture and endear-shine studies. Neurology. 2020;94(15).
[40] Alvarez Molinero M, et al. EP.110Clinical and neurophysiological outcome of a patient with predicted type 1 SMA presymptomatically treated with nusinersen. Neuromuscular Disorders. 2019;29:S200.
[41] Baranello G, et al. Preserved swallowing function in Infants who initiated nusinersen treatment in the presymptomatic stage of SMA: Results from the NURTURE study. Developmental Medicine and Child Neurology. 2022;64(SUPPL 1):67-68.
[42] Bertini E, et al. Efficacy and safety of nusinersen in infants with presymptomatic spinal muscular atrophy (SMA): Interim results from the NURTURE study. European Journal of Paediatric Neurology. 2017;21:e14.
[43] De Vivo DC, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-56.
[44] Strauss KA, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: The phase III SPR1NT trial. Nature medicine. 2022;28(7):1381-9.
[45] Finkel RS, et al. RAINBOWFISH: A study of risdiplam in newborns with presymptomatic spinal muscular atrophy (SMA). Neurology. 2021;96(15 SUPPL 1).
[46] Finkel RS, et al. Interim Report on the Safety and Efficacy of Longer-Term Treatment With Nusinersen in Infantile-Onset Spinal Muscular Atrophy (SMA): Updated Results From the SHINE Study (S25. 004). 2019, AAN Enterprises.
[47] Dangouloff T, Servais L. Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives. Ther Clin Risk Manag. 2019;15:1153-61.
[48] Seabrook T, et al. FIREFISH part 1: Early clinical results following an increase of SMN protein in infants with type 1 spinal muscular atrophy (SMA) treated with risdiplam (RG7916). in MDA Clinical & Scientific Conference. 2019.
[49] Lowes LP, et al. Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy. Pediatr Neurol. 2019;98:39-45.
[50] Jevtic S, Carr D, Dobrzycka-Ambrozevicz A. Branaplam in type 1 spinal muscular atrophy: Second part of a phase I/II study. in Communication presented at 23rd SMA researcher meeting, Cure SMA. 2019.

[51] Mercuri E, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. JAMA : The journal of the American Medical Association. 2018;319(5):625.
[52] Mercuri E, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): A phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2022;21(1):42-52.
[53] Mercuri E, et al. SUNFISH Part 2: Efficacy and Safety of Risdiplam (RG7916) in Patients with Type 2 or Non-Ambulant Type 3 Spinal Muscular Atrophy (SMA) (1260). Neurology. 2020;94(15 Supplement):1260.
[54] Oskoui M, et al. SUNFISH Part 2:24-month Efficacy and Safety of Risdiplam in Patients with Type 2 or Non-ambulant Type 3 Spinal Muscular Atrophy (SMA) (2240). Neurology. 2021;96(15 Supplement):2240.
[55] Kimizu T, et al. Spinal Muscular Atrophy: Diagnosis, Incidence, and Newborn Screening in Japan. Int J Neonatal Screen. 2021;7(3).
[56] Boemer F, et al. Newborn screening for SMA in Southern Belgium. Neuromuscular Disorders. 2019;29(5):343-9.
[57] Vill K, et al. One Year of Newborn Screening for SMA - Results of a German Pilot Project. J Neuromuscul Dis. 2019;6(4):503-15.
[58] Gailite L, et al. New-Born Screening for Spinal Muscular Atrophy: Results of a Latvian Pilot Study. Int J Neonatal Screen. 2022;8(1).
[59] Hale JE, et al. Massachusetts' Findings from Statewide Newborn Screening for Spinal Muscular Atrophy. Int J Neonatal Screen. 2021;7(2).
[60] Kariyawasam DST, et al. The implementation of newborn screening for spinal muscular atrophy: The Australian experience. Genet Med. 2020;22(3):557-65.
[61] Mikhalchuk K, et al. Pilot Program of Newborn Screening for 5q Spinal Muscular Atrophy in the Russian Federation. International Journal of Neonatal Screening. 2023;9(2):29.
[62] Kucera KS, et al. A voluntary statewide newborn screening pilot for spinal muscular atrophy: Results from early check. International Journal of Neonatal Screening. 2021;7(1):20.
[63] Boemer F, et al. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. Scientific reports. 2021;11(1):19922.
[64] Dangouloff T, et al. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. Neuromuscul Disord. 2021;31(6):574-82.
[65] Soler-Botija C, et al. Neuronal death is enhanced and begins during foetal development in type I spinal muscular atrophy spinal cord. Brain. 2002;125(7):1624-34.
[66] De Vivo DC, et al. Interim efficacy and safety results from the Phase 2 NURTURE study evaluating nusinersen in presymptomatic infants with spinal muscular atrophy. Neurology. 2017;88(16).
[67] Crawford T, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim efficacy and safety results from the phase 2 nurture study. Annals of Neurology. 2018;84:S392.
[68] Crawford TO, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle & Nerve, 2023.
[69] Finkel RS, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the phase 2 nurture study. Neurology. 2020;94(15).
[70] Strauss KA, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: The Phase III SPR1NT trial. Nature medicine. 2022;28(7):1390-7.
[71] Finkel RS, et al. RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA (P17-5.003). 2022, AAN Enterprises.
[72] Bertini E, et al. RAINBOWFISH: A study of risdiplam in infants with presymptomatic SMA. European Journal of Neurology. 2021;28(SUPPL 1):396.
[73] Calucho M, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular Disorders. 2018;28(3):208-15.
[74] Pane M, et al. Neurological assessment of newborns with spinal muscular atrophy identified through neonatal screening. European Journal of Pediatrics. 2022;181(7):2821-9.
[75] Butterfield RJ, Spinal Muscular Atrophy Treatments, Newborn Screening, and the Creation of a Neurogenetics Urgency. Semin Pediatr Neurol. 2021;38:100899.
[76] Vill K, et al. Newborn screening for spinal muscular atrophy in Germany: Clinical results after 2 years. Orphanet J Rare Dis. 2021;16(1):153.
[77] Elkins K, et al. Georgia State SMA Newborn Screening (NBS) Program: A Two Year Follow-up Study. Annals of Neurology. 2021;90(SUPPL 26):S89-S90.
[78] Elkins K, et al. Georgia state spinal muscular atrophy newborn screening experience: Screening assay performance and early clinical outcomes. in American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2022. Wiley Online Library.
[79] Lee BH, et al. Newborn screening for spinal muscular atrophy in New York state: Clinical outcomes from the first 3 years. Neurology. 2022;99(14):e1527-e1537.
[80] Noguchi Y, et al. PCR-based screening of spinal muscular atrophy for newborn infants in hyogo prefecture, Japan. Genes. 2022;13(11):2110.
[81] Matteson J, et al. California's experience with SMA newborn screening: A successful path to early intervention. Journal of Neuromuscular Diseases, 2022(Preprint): 1-9.
[82] Blaschek A, et al. Newborn Screening for SMA–Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies? Journal of Neuromuscular Diseases, 2022(Preprint):1-9.
[83] Schwartz O, et al. Spinal Muscular Atrophy -Is Newborn Screening Too Late for Children with Two SMN2 Copies? J Neuromuscul Dis, 2022.
[84] Sawada T, et al. Newborn screening for spinal muscular atrophy in Japan: One year of experience. Molecular Genetics and Metabolism Reports. 2022;32:100908.
[85] Kariyawasam DS, et al. Newborn screening for spinal muscular atrophy in Australia: A non-randomised cohort study. The Lancet Child & Adolescent Health. 2023;7(3):159-70.
[86] Glascock J, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. Journal of neuromuscular diseases. 2020;7(2):97.
[87] Pompe J, Concerning idiopathic hypertrophy of the heart. Ned Tijdschr Geneeskd. 1932;76:304-11.

[88] Kishnani PS, Howell RR. Pompe disease in infants and children. The Journal of pediatrics. 2004;144(5):S35-S43.
[89] van der Ploeg AT, Reuser AJ. Pompe's disease. The lancet. 2008;372(9646):1342-53.
[90] Engel AG. Acid maltase deficiency in adults: Studies in four cases of a syndrome which may mimic muscular dystrophy or other myopathies. Brain. 1970;93(3):599-616.
[91] Lim J-A, Li L, Raben N. Pompe disease: From pathophysiology to therapy and back again. Frontiers in aging neuroscience. 2014;6:177.
[92] Lin C.-Y, Shieh J.-J. Molecular study on the infantile form of Pompe disease in Chinese in Taiwan. Zhonghua Minguo Xiao er ke yi xue hui za zhi [Journal]. Zhonghua Minguo Xiao er ke yi xue hui. 1996;37(2):115-21.
[93] Yang C.-F, et al. Late-onset Pompe disease with left-sided bronchomalacia. Respiratory Care. 2015;60(2):e26-e29.
[94] Kishnani PS, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. The Journal of pediatrics. 2006;148(5):671-676. e2.
[95] Hers H, α-Glucosidase deficiency in generalized glycogen-storage disease (Pompe's disease). Biochemical Journal. 1963;86(1):11.
[96] Hamdan MA, et al. Antenatal diagnosis of pompe disease by fetal echocardiography: Impact on outcome after early initiation of enzyme replacement therapy. Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism. 2010;33: 333-9.
[97] van den Hout HM, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics. 2003;112(2):332-40.
[98] Van den Hout H, et al. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. Lancet. 2000;356(9227):397-8.
[99] Van den Hout JM, et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. Pediatrics. 2004;113(5):e448-457.
[100] Kishnani P, et al. Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease. Neurology. 2007;68(2):99-109.
[101] Prater SN, et al. The emerging phenotype of long-term survivors with infantile Pompe disease. Genetics in medicine. 2012;14(9):800-10.
[102] Chien Y-H, et al. Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth. The Journal of pediatrics. 2015;166(4):985-91. e2.
[103] Peng SS-F, et al. Slow, progressive myopathy in neonatally treated patients with infantile-onset Pompe disease: A muscle magnetic resonance imaging study. Orphanet journal of rare diseases. 2016;11:1-10.
[104] Kumamoto S, et al. High frequency of acid α-glucosidase pseudodeficiency complicates newborn screening for glycogen storage disease type II in the Japanese population. Molecular genetics and metabolism. 2009;97(3):190-5.
[105] Hahn A, et al. Outcome of patients with classical infantile pompe disease receiving enzyme replacement therapy in Germany. JIMD Reports, Volume 20, 2015:65-75.
[106] Case LE, et al. Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease. Neuromuscular Disorders. 2015;25(4):321-32.
[107] Zhu Y, et al. Glycoengineered acid α-glucosidase with improved efficacy at correcting the metabolic aberrations and motor function deficits in a mouse model of Pompe disease. Molecular Therapy. 2009;17(6):954-63.
[108] Blair HA, Cipaglucosidase Alfa: First Approval. Drugs. 2023:1-7.
[109] Pena LD, et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscular Disorders. 2019;29(3):167-86.
[110] Dimachkie M, et al. NEO1 and NEO-EXT Studies: Long-Term Safety and Exploratory Efficacy of Repeat Avalglucosidase Alfa Dosing for 5.5 Years in Late-Onset Pompe Disease Patients (695). 2020, AAN Enterprises.
[111] Diaz-Manera J, et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): A phase 3, randomised, multicentre trial. The Lancet Neurology. 2021;20(12):1012-26.
[112] Kishnani PS, et al. Safety and efficacy of avalglucosidase alfa in individuals with infantile-onset Pompe disease enrolled in the phase 2, open-label Mini-COMET study: The 6-month primary analysis report. Genetics in Medicine. 2023;25(2):100328.
[113] Gupta N, et al. Clinical and Molecular Disease Spectrum and Outcomes in Patients with Infantile-Onset Pompe Disease. Journal of Pediatrics. 2020;216:44-50.e5.
[114] Kishnani PS, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Molecular genetics and metabolism. 2010;99(1):26-33.
[115] Amalfitano A, et al. Recombinant human acid α-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial. Genetics in Medicine. 2001;3(2):132-8.
[116] Parini R, et al. Long term clinical history of an Italian cohort of infantile onset Pompe disease treated with enzyme replacement therapy. Orphanet journal of rare diseases. 2018;13:1-12.
[117] van Gelder CM, et al. Enzyme therapy and immune response in relation to CRIM status: The Dutch experience in classic infantile Pompe disease. Journal of inherited metabolic disease. 2015;38:305-14.
[118] Berrier KL, et al. CRIM-negative infantile Pompe disease: Characterization of immune responses in patients treated with ERT monotherapy. Genetics in Medicine. 2015;17(11):912-8.
[119] Banugaria SG, et al. The role of anti-rhGAA antibody titers and clinical outcomes in infantile pompe disease patients. Molecular Genetics and Metabolism. 2010;99(3): 199.
[120] Khan AA, et al. Higher dosing of alglucosidase alfa improves outcomes in children with Pompe disease: A clinical study and review of the literature. Genetics in Medicine. 2020;22(5):898-907.
[121] Landis JL, et al. Pompe disease treatment with twice a week high dose alglucoside alfa in a patient with severe dilated cardiomyopathy. Molecular Genetics and Metabolism Reports. 2018;16:1-4.
[122] Van Gelder C, et al. Effects of a higher dose of alglucosidase alfa on ventilator-free survival and motor outcome in classic infantile Pompe disease: An open-label single-center study. Journal of inherited metabolic disease. 2016;39:383-90.

[123] Broomfield A, et al. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism. 2016;39(2):261-71.
[124] Gragnaniello V, et al. Newborn screening for Pompe disease in Italy: Long-term results and future challenges. Mol Genet Metab Rep. 2022;33:100929.
[125] Matsuoka T, et al. Divergent clinical outcomes of alpha-glucosidase enzyme replacement therapy in two siblings with infantile-onset Pompe disease treated in the symptomatic or pre-symptomatic state. Molecular genetics and metabolism reports. 2016;9:98-105.
[126] Klinge L, et al. Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: Results of a phase II clinical trial. Neuromuscular Disorders. 2005;15(1):24-31.
[127] Klinge L, et al. Enzyme replacement therapy in classical infantile pompe disease: Results of a ten-month follow-up study. Neuropediatrics. 2005;36(01):6-11.
[128] Kishnani PS, et al. Chinese hamster ovary cell-derived recombinant human acid α-glucosidase in infantile-onset Pompe disease. The Journal of pediatrics. 2006;149(1):89-97.
[129] Kemper AR, et al. Newborn screening for pompe disease: Synthesis of the evidence and development of screening recommendations. Pediatrics. 2007;120(5): e1327-e1334.
[130] Kishnani PS, et al. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res. 2009;66(3):329-35.
[131] Nicolino M, et al. Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genetics in medicine. 2009;11(3):210-9.
[132] de las Heras J, et al. Importance of timely treatment initiation in infantile-onset pompe disease, a single-centre experience. Children. 2021;8(11).
[133] Spiridigliozzi GA, et al. Early cognitive development in children with infantile Pompe disease. Molecular genetics and metabolism. 2012;105(3):428-32.
[134] Chien YH, et al. Early detection of pompe disease by newborn screening is feasible: Results from the Taiwan screening program. Pediatrics. 2008;122(1): e39-e45.
[135] Klug TL, et al. Lessons learned from Pompe disease newborn screening and follow-up. International journal of neonatal screening. 2020;6(1):11.
[136] Sawada T, Kido J, Nakamura K, Newborn screening for pompe disease. International Journal of Neonatal Screening. 2020;6(2).
[137] Sawada T, et al. Current status of newborn screening for Pompe disease in Japan. Orphanet Journal of Rare Diseases. 2021;16(1):1-14.
[138] Tang H, et al. The First Year Experience of Newborn Screening for Pompe Disease in California. Int J Neonatal Screen. 2020;6(1):9.
[139] Ficicioglu C, et al. Newborn screening for Pompe disease: Pennsylvania experience. International Journal of Neonatal Screening. 2020;6(4):89.
[140] Burton BK, et al. Newborn Screening for Pompe Disease in Illinois: Experience with 684,290 Infants. International Journal of Neonatal Screening. 2020;6(1):4.
[141] Hall PL, et al. Two-Tiered Newborn Screening with Post-Analytical Tools for Pompe Disease and Mucopolysaccharidosis Type I Results in Performance Improvement and Future Direction. Int J Neonatal Screen. 2020;6(1).
[142] Burlina AB, et al. Implementation of Second-Tier Tests in Newborn Screening for Lysosomal Disorders in North Eastern Italy. Int J Neonatal Screen. 2019;5(2):24.
[143] Chia-Feng Yang CFY, et al. Very early treatment for Pompe disease contributes to better out-comes: 10-years of experience in Taiwan. Journal of Inherited Metabolic Disease. 2018;41:S183-S184.
[144] Yang CF, et al. Very Early Treatment for Infantile-Onset Pompe Disease Contributes to Better Outcomes. J Pediatr. 2016;169:174-80.e1.
[145] Yang, C.-F., et al. Long-term outcomes of very early treated infantile-onset Pompe disease with short-term steroid premedication: Experiences from a nationwide newborn screening programme. Journal of Medical Genetics. 2023;60(5):430-9.
[146] Tardieu M, et al. Long-term follow-up of 64 children with classical infantile-onset Pompe disease since 2004: A French real-life observational study. European Journal of Neurology. 2023.
[147] Chien YH, et al. Earlier and higher dosing of alglucosidase alfa improve outcomes in patients with infantile-onset Pompe disease: Evidence from real-world experiences. Mol Genet Metab Rep. 2020;23:100591.
[148] Spada M, et al. Early higher dosage of alglucosidase alpha in classic Pompe disease. J Pediatr Endocrinol Metab. 2018;31(12):1343-7.
[149] Li C, et al. Transforming the clinical outcome in CRIM-negative infantile Pompe disease identified via newborn screening: The benefits of early treatment with enzyme replacement therapy and immune tolerance induction. Genet Med. 2021;23(5):845-55.
[150] Hassnan ZA, et al. Expert Group Consensus on early diagnosis and management of infantile-onset pompe disease in the Gulf Region. Orphanet Journal of Rare Diseases. 2022;17(1):388.
[151] Fatehi F, et al. Recommendations for infantile-onset and late-onset Pompe disease: An Iranian consensus. Frontiers in Neurology. 2021;12:739931.
[152] Stevens D, Milani-Nejad S, Mozaffar T. Pompe disease: A clinical, diagnostic, and therapeutic overview. Current treatment options in neurology. 2022;24(11):573-88.
[153] Kronn DF, et al. Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum. Pediatrics. 2017;140(Suppl 1):S24-s45.
[154] Echaniz-Laguna A, et al. Should patients with asymptomatic pompe disease be treated? A nationwide study in France. Muscle and Nerve. 2015;51(6):884-9.
[155] Van der Ploeg AT, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. New England Journal of Medicine. 2010;362(15):1396-406.
[156] Lee N-C, et al. Outcome of later-onset Pompe disease identified through newborn screening. The Journal of Pediatrics. 2022;244:139-147. e2.
[157] Huggins E, et al. Early clinical phenotype of late-onset Pompe disease: Lessons learned from newborn screening. Molecular Genetics and Metabolism. 2022;135(2):S57.
[158] Erdem Ozdamar S, et al. Expert opinion on the diagnostic odyssey and management of late-onset Pompe disease: A neurologist's perspective. Frontiers in Neurology. 2023;14:1095134.
[159] Cupler EJ, et al. Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve. 2012;45(3):319-33.

[160] van der Ploeg AT, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: A 10-year experience. European journal of neurology. 2017;24(6):768-e31.
[161] Markati T, et al. Emerging therapies for Duchenne muscular dystrophy. The Lancet Neurology. 2022;21(9):pp814-829.
[162] Mendell JR, et al. Randomized, Double-Blind Six-Month Trial of Prednisone in Duchenne's Muscular Dystrophy. New England Journal of Medicine. 1989;320(24): 1592-7.
[163] Szabo SM, et al. The clinical course of Duchenne muscular dystrophy in the corticosteroid treatment era: A systematic literature review. Orphanet Journal of Rare Diseases. 2021;16(1):237.
[164] [cited 2023 30 August]; Available from: https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-fda-approval-elevidys-first-gene.
[165] Hoy SM, Delandistrogene Moxeparvovec: First Approval. Drugs, 2023.
[166] Landfeldt E, Ferizovic N, Buesch K, Timing of Clinical Interventions in Patients With Duchenne Muscular Dystrophy: A Systematic Review and Grading of Evidence. Journal of neuromuscular diseases. 2022;13:13.
[167] Bonifati DM, et al. The glucocorticoid receptor N363S polymorphism and steroid response in Duchenne dystrophy. Journal of Neurology, Neurosurgery & Psychiatry. 2006;77(10):1177-9.
[168] Davidson Z, et al. GP 77 Deletions in the dystrophin gene predict loss of ambulation before 10 years of age in boys with Duchenne muscular dystrophy. Neuromuscular Disorders. 2012;22(9):835.
[169] Kim S, et al. Corticosteroid treatments in males with Duchenne muscular dystrophy: Treatment duration and time to loss of ambulation. Journal of child neurology. 2015;30(10):1275-80.
[170] Kim S, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Neuromuscular Disorders. 2017;27(8):730-7.
[171] Lamb MM, et al. Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. The Journal of pediatrics. 2016;173:207-213. e3.
[172] Ricotti V, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. Journal of Neurology, Neurosurgery & Psychiatry. 2013;84(6):698-705.
[173] Ruggiero L, et al. One-year follow up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: Is earlier better? Therapeutic Advances in Neurological Disorders. 2018;11:1756286418809588.
[174] Araujo APdQC, et al. Update of the Brazilian consensus recommendations on Duchenne muscular dystrophy. Arquivos de Neuro-psiquiatria. 2023;81:81-94.
[175] Armstrong N, et al. Duchenne expert physician perspectives on Duchenne newborn screening and early Duchenne care. in American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2022. Wiley Online Library.
[176] Yoon JA, et al. Corticosteroid use and bone health management for Duchenne muscular dystrophy in South Korea. Scientific Reports. 2022;12(1):11300.
[177] Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Respiratory, cardiac, bone health, and orthopaedic management. The Lancet Neurology. 2018;17(4):347-61.
[178] Germain DP, Fabry disease. Orphanet journal of rare diseases. 2010;5(1):1-49.
[179] Arends M, et al. Characterization of classical and nonclassical Fabry disease: A multicenter study. Journal of the American Society of Nephrology: JASN. 2017;28(5):1631.
[180] Desnick RJ, et al. Fabry disease, an under-recognized multisystemic disorder: Expert recommendations for diagnosis, management, and enzyme replacement therapy. Annals of internal medicine. 2003;138(4):338-46.
[181] Weidemann F, et al. Fibrosis: A key feature of Fabry disease with potential therapeutic implications. Orphanet journal of rare diseases. 2013;8(1):1-12.
[182] Godel T, et al. Human dorsal root ganglion *in vivo* morphometry and perfusion in Fabry painful neuropathy. Neurology. 2017;89(12):1274-82.
[183] Hofmann L, et al. Characterization of small fiber pathology in a mouse model of Fabry disease. Elife. 2018;7:e39300.
[184] Waltz TB, et al. Sensory-specific peripheral nerve pathology in a rat model of Fabry disease. Neurobiology of Pain. 2021;10:100074.
[185] Ramaswami U, Children with fabry disease. Clinical Therapeutics. 2012;34(4):e18.
[186] Ramaswami U, et al. Clinical manifestations of Fabry disease in children: Data from the Fabry Outcome Survey. Acta paediatrica. 2006;95(1):86-92.
[187] Mehta A, Widmer U. Natural history of Fabry disease. Fabry disease: Perspectives from 5 years of FOS. 2006.
[188] Sims K, et al. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: Natural history data from the Fabry Registry. Stroke. 2009;40(3):788-94.
[189] Thurberg BL, Politei JM. Histologic abnormalities of placental tissues in Fabry disease: A case report and review of the literature. Human pathology. 2012;43(4):610-4.
[190] Tsutsumi O, et al. Early prenatal diagnosis of inborn error of metabolism: A case report of a fetus affected with Fabry's disease. Asia-Oceania Journal of Obstetrics and Gynaecology. 1985;11(1):39-45.
[191] Tøndel C, et al. Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. Nephron. 2015;129(1):16-21.
[192] Laney DA, et al. Fabry disease in infancy and early childhood: A systematic literature review. Genetics in Medicine. 2015;17(5):323-30.
[193] Wang RY, et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genetics in Medicine. 2007;9(1):34-45.
[194] Eng CM, et al. Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. Journal of Inherited Metabolic Disease. 2007;30(2):184-92.
[195] Echevarria L, et al. X-chromosome inactivation in female patients with Fabry disease. Clinical genetics. 2016;89(1):44-54.
[196] Wilcox WR, et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. Molecular genetics and metabolism. 2008;93(2):112-8.

[197] Hopkin RJ, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. Pediatric research. 2008;64(5):550-5.
[198] Ramaswami U, et al. Fabry disease in children and response to enzyme replacement therapy: Results from the Fabry Outcome Survey. Clinical genetics. 2012;81(5):485-90.
[199] Wraith JE, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: An international, open-label study in pediatric patients with Fabry disease. J Pediatr. 2008;152(4):563-70, 570.e1.
[200] Eng CM, et al. Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. New England Journal of Medicine. 2001;345(1):9-16.
[201] Schiffmann R, et al. Enzyme replacement therapy in Fabry disease: A randomized controlled trial. Jama. 2001;285(21):2743-9.
[202] Germain DP, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. New England Journal of Medicine. 2016;375(6):545-55.
[203] Schiffmann R, et al. Migalastat improves diarrhea in patients with Fabry disease: Clinical-biomarker correlations from the phase 3 FACETS trial. Orphanet journal of rare diseases. 2018;13(1):1-7.
[204] Müntze J, et al. Oral chaperone therapy migalastat for treating Fabry disease: Enzymatic response and serum biomarker changes after 1 year. Clinical Pharmacology & Therapeutics. 2019;105(5):1224-33.
[205] Eng CM, et al. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: Pharmacokinetic, substrate clearance, and safety studies. The American Journal of Human Genetics. 2001;68(3):711-22.
[206] Schiffmann R, et al. Infusion of α-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. Proceedings of the National Academy of Sciences. 2000;97(1):365-70.
[207] Thurberg BL, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney international. 2002;62(6):1933-46.
[208] Guffon, N. and Fouilhoux A, Clinical benefit in Fabry patients given enzyme replacement therapy—a case series. Journal of inherited metabolic disease. 2004;27(2):221-7.
[209] Wilcox WR, et al. Long-term safety and efficacy of enzyme replacement therapyfor fabry disease. The American Journal of Human Genetics. 2004;75(1):65-74.
[210] Hughes DA, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson–Fabry disease: A randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008;94(2):153-8.
[211] Waldek S, PR interval and the response to enzyme-replacement therapy for Fabry's disease. New England Journal of Medicine. 2003;348(12):1186-7.
[212] Weidemann F, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study. Circulation. 2003;108(11):1299-301.
[213] Spinelli L, et al. Enzyme replacement therapy with agalsidase β improves cardiac involvement in Fabry's disease. Clinical genetics. 2004;66(2):158-65.
[214] Banikazemi M, et al. Agalsidase-beta therapy for advanced Fabry disease: A randomized trial. Annals of internal medicine. 2007;146(2):77-86.
[215] Breunig F, et al. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney international. 2006;69(7):1216-21.
[216] Watt T, et al. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: Findings from the Fabry Registry. Genetics in Medicine. 2010;12(11):703-12.
[217] Van der Veen S, et al. Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression. Molecular Genetics and Metabolism. 2022;135(2):163-9.
[218] El Dib R, et al. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. PloS one. 2017;12(3):e0173358.
[219] Feriozzi S, et al. Agalsidase alfa slows the decline in renal function in patients with Fabry disease. American journal of nephrology. 2009;29(5):353-61.
[220] Feriozzi S, et al. The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy. Clinical Journal of the American Society of Nephrology: CJASN. 2012;7(1):60.
[221] Ramaswami U, et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. Acta paediatrica. 2007;96(1):122-7.
[222] Schiffmann R, et al. Four-year prospective clinical trial of agalsidase alfa in children with Fabry disease. The Journal of pediatrics. 2010;156(5):832-837. e1.
[223] Schiffmann R, et al. Agalsidase alfa in pediatric patients with Fabry disease: A 6.5-year open-label follow-up study. Orphanet J Rare Dis. 2014;9:169.
[224] Arends M, et al. Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: Analysis of prognostic factors. PloS one. 2017;12(8):e0182379.
[225] Weidemann F, et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: Evidence for a better outcome with early treatment. Circulation. 2009;119(4):524-9.
[226] Hopkin RJ, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: Data from the Fabry Registry. Molecular genetics and metabolism. 2016;119(1-2):151-9.
[227] Warnock DG, et al. Renal outcomes of agalsidase beta treatment for Fabry disease: Role of proteinuria and timing of treatment initiation. Nephrology Dialysis Transplantation. 2012;27(3):1042-9.
[228] Fellgiebel A, et al. Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis. 2014;38(6):448-56.
[229] Germain DP, et al. Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: Data from the Fabry Registry. Genetics in medicine. 2013;15(12):958-65.
[230] Ortiz A, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: Data from the Fabry Registry. Journal of Medical Genetics. 2016;53(7):495-502.
[231] Tøndel C, et al. Agalsidase benefits renal histology in young patients with Fabry disease. Journal of the American Society of Nephrology: JASN. 2012;24(1):137.

[232] Arends M, et al. Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease. Mol Genet Metab. 2017;121(2):157-61.
[233] Wasserstein MP, et al. The New York pilot newborn screening program for lysosomal storage diseases: Report of the First 65,000 Infants. Genetics in Medicine. 2019;21(3):631-40.
[234] Wang RY, et al. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011;13(5):457-84.
[235] Kritzer A, et al. Early initiation of enzyme replacement therapy in classical Fabry disease normalizes biomarkers in clinically asymptomatic pediatric patients. Molecular Genetics and Metabolism Reports. 2019;21:100530.
[236] Biegstraaten M, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: The European Fabry Working Group consensus document. Orphanet journal of rare diseases. 2015;10(1):1-10.
[237] Hopkin RJ, et al. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016;117(2):104-13.
[238] Germain DP, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clinical Genetics. 2019;96(2): 107-17.
[239] Engel AG, et al. Congenital myasthenic syndromes: Pathogenesis, diagnosis, and treatment. The Lancet Neurology. 2015;14(4):420-34.
[240] Eymard B, D. Hantaï, Estournet B, Chapter 151 - Congenital myasthenic syndromes, in Handbook of Clinical Neurology, O. Dulac, M. Lassonde, and H.B. Sarnat, Editors. 2013, Elsevier. p. 1469-80.
[241] Engel AG, Chapter 37 - Genetic basis and phenotypic features of congenital myasthenic syndromes, in Handbook of Clinical Neurology, D.H. Geschwind, H.L. Paulson, and C. Klein, Editors. 2018, Elsevier. p. 565-589.
[242] Kinali M, et al. Congenital Myasthenic Syndromes in childhood: Diagnostic and management challenges. Journal of Neuroimmunology. 2008;201-202:6-12.
[243] Garg N, et al. Late presentations of congenital myasthenic syndromes: How many do we miss? Muscle Nerve. 2016;54(4):721-7.
[244] Ben Ammar A, et al. Phenotype genotype analysis in 15 patients presenting a congenital myasthenic syndrome due to mutations in DOK7. Journal of Neurology. 2010;257(5):754-66.
[245] Thompson R, et al. Targeted therapies for congenital myasthenic syndromes: Systematic review and steps towards a treatabolome. Emerging Topics in Life Sciences. 2019;3(1):19-37.
[246] Rodríguez Cruz PM, Palace J, Beeson D, The Neuromuscular Junction and Wide Heterogeneity of Congenital Myasthenic Syndromes. International Journal of Molecular Sciences. 2018;19(6):1677.
[247] Palace J, Wiles CM, J. Newsom-Davis, 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. J Neurol Neurosurg Psychiatry. 1991;54(12):1069-72.
[248] Lorenzoni PJ, et al. Salbutamol therapy in congenital myasthenic syndrome due to DOK7 mutation. Journal of the Neurological Sciences. 2013;331(1):155-7.
[249] Liewluck T, Selcen D, Engel AG, Beneficial effects of albuterol in congenital endplate acetylcholinesterase deficiency and Dok-7 myasthenia. Muscle Nerve. 2011;44(5):789-94.
[250] Vrinten C, et al. Ephedrine for myasthenia gravis, neonatal myasthenia and the congenital myasthenic syndromes. Cochrane Database of Systematic Reviews. 2014(12).
[251] McMacken G, et al. Congenital myasthenic syndrome with episodic apnoea: Clinical, neurophysiological and genetic features in the long-term follow-up of 19 patients. Journal of Neurology. 2018;265(1):194-203.
[252] Bauché S, et al. Mutations in GFPT1-related congenital myasthenic syndromes are associated with synaptic morphological defects and underlie a tubular aggregate myopathy with synaptopathy. Journal of Neurology. 2017;264(8):1791-803.
[253] Estephan EdP, et al. A common CHRNE mutation in Brazilian patients with congenital myasthenic syndrome. Journal of Neurology. 2018;265(3):708-13.
[254] Chaouch A, et al. A retrospective clinical study of the treatment of slow-channel congenital myasthenic syndrome. Journal of Neurology. 2012;259(3):474-81.
[255] Witting, N. and Vissing J, Pharmacologic Treatment of Downstream of Tyrosine Kinase 7 Congenital Myasthenic Syndrome. JAMA Neurology. 2014;71(3):350-4.
[256] Shao S, et al. Pharmacological Treatments for Congenital Myasthenic Syndromes Caused by COLQ Mutations. Curr Neuropharmacol. 2023;21(7):1594-605.
[257] Lee M, Beeson D, Palace J, Therapeutic strategies for congenital myasthenic syndromes. Ann N Y Acad Sci. 2018;1412(1):129-36.
[258] Farmakidis C, et al. Congenital Myasthenic Syndromes: A Clinical and Treatment Approach. Curr Treat Options Neurol. 2018;20(9):36.
[259] Maggi L, et al. Italian recommendations for diagnosis and management of congenital myasthenic syndromes. Neurological sciences : Official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2019;40(3):457-68.
[260] Ohno K, et al. Choline acetyltransferase mutations cause myasthenic syndrome associated with episodic apnea in humans. Proceedings of the National Academy of Sciences. 2001;98(4):2017-22.
[261] Byring R, et al. Congenital myasthenic syndrome associated with episodic apnea and sudden infant death. Neuromuscular Disorders. 2002;12(6):548-53.
[262] Burke G, et al. Rapsyn mutations in hereditary myasthenia. Distinct early- and late-onset phenotypes. 2003;61(6):826-8.
[263] Tsujino A, et al. Myasthenic syndrome caused by mutation of the SCN4A sodium channel. Proceedings of the National Academy of Sciences. 2003;100(12): 7377-82.
[264] Bauché S, et al. Impaired presynaptic high-affinity choline transporter causes a congenital myasthenic syndrome with episodic apnea. The American Journal of Human Genetics. 2016;99(3):753-61.
[265] Bosch AM, et al. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: Natural history, genetics, treatment and future perspectives. Orphanet Journal Of Rare Diseases. 2012;7:83.

[266] Orngreen MC, Vissing J. Treatment Opportunities in Patients With Metabolic Myopathies. Current Treatment Options in Neurology. 2017;19(11):37.
[267] Olsen RK, et al. ETFDH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. Brain. 2007;130(8):2045-54.
[268] Lamhonwah AM, et al. Novel OCTN2 mutations: No genotype–phenotype correlations: Early carnitine therapy prevents cardiomyopathy. American journal of medical genetics. 2002;111(3):271-84.
[269] Anand G, et al. Early use of high-dose riboflavin in a case of Brown-Vialetto-Van Laere syndrome. Dev Med Child Neurol. 2012;54(2):187-9.
[270] Ørngreen MC, Ejstrup R, Vissing J, Effect of diet on exercise tolerance in carnitine palmitoyltransferase II deficiency. Neurology. 2003;61(4):559-61.
[271] Faraguna MC, et al. Treatment Dilemma in Children with Late-Onset Pompe Disease. Genes. 2023;14(2): 362.
[272] Montagnese F, et al. Clinical and molecular aspects of 30 patients with late-onset Pompe disease (LOPD): Unusual features and response to treatment. J Neurol. 2015;262(4):968-78.
[273] Glascock J, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis. 2018;5(2):145-58.
[274] Markati T, et al. Risdiplam: An investigational survival motor neuron 2 (SMN2) splicing modifier for spinal muscular atrophy (SMA). Expert Opinion on Investigational Drugs. 2022;31(5):451-61.
[275] Varnet M, Castro D, Goodspeed K, Advances in SMA treatment, a Consideration. Journal of Clinical Neuromuscular Disease. 2022;23(1 SUPPL):S13-S14.
[276] Weststrate H, et al. Evolution of bulbar function in spinal muscular atrophy type 1 treated with nusinersen. Dev Med Child Neurol. 2022;64(7):907-14.
[277] Masson R, et al. Brain, cognition, and language development in spinal muscular atrophy type 1: A scoping review. Dev Med Child Neurol. 2021;63(5):527-36.
[278] Hahn A, Schänzer A. Long-term outcome and unmet needs in infantile-onset Pompe disease. Annals of Translational Medicine. 2019;7(13).
[279] Harlaar L, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. Neurology. 2019;93(19):e1756-e1767.
[280] Papadimas GK, et al. Effect of long term enzyme replacement therapy in late onset Pompe disease: A single-centre experience. Neuromuscular Disorders. 2021;31(2):91-100.
[281] Jalal K, et al. A Roadmap for Potential Improvement of Newborn Screening for Inherited Metabolic Diseases Following Recent Developments and Successful Applications of Bivariate Normal Limits for Pre-Symptomatic Detection of MPS I, Pompe Disease, and Krabbe Disease. International Journal of Neonatal Screening. 2022;8(4):61.