



NEWBORN SCREENING FOR DUCHENNE MUSCULAR DYSTROPHY:

The Time to Start Is Now



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World Duchenne Organization

EXECUTIVE SUMMARY

Duchenne muscular dystrophy (DMD) is a rare, X-linked, recessive genetic disease and the most common type of muscular dystrophy affecting children. The incidence rate is estimated at 1 in 5000 live male births and the global prevalence rate is 4.8 per 100 000 (95% CI: 3.6-6.3 per 100 000).

The aim of this paper is to present the World Duchenne Organization's position on newborn screening (NBS) for DMD based on families' experiences and scientific developments. The World Duchenne Organization is an umbrella organization of national patient organizations for DMD and Becker MD (BMD) around the world. This organization aims to inform parents and people with DMD/BMD based on latest research, promote good standards of care, and actively participate in efforts develop safe and effective treatments for DMD/BMD and find a cure.

For more than 25 years, a steady majority of parents have been in favor of implementing NBS for DMD. Key reasons for this include the following:

- » avoiding the diagnostic delay, which interferes with “supportive parenting”, that is, parents' ability to provide their children with the support, care, and understanding they need
- » ensuring timely and appropriate early intervention for their infant, thereby maximizing the therapeutic window of opportunity
- » mitigating the challenges in therapy development for the early phase (e.g., 0- to 4-years of age)
- » understanding reproductive options and enabling families to make informed choices
- » being realistic that there is no such thing as a “carefree period” – parents' concerns arise long before a diagnosis of DMD is confirmed

Also, the discussion of implementing NBS programs for DMD has been ongoing around the world since the 1970s and different programs have been started and discontinued. Renewed interest to include DMD in NBS programs can be attributed to advancements in testing technology to minimize false-positive and false-negative cases, growing evidence that emerging therapies may be most effective in the early phase when muscle damage is still limited (e.g., early years between 0- to 4-years), and the evolving landscape of novel therapeutics in development. Indeed, DMD has been included in the NBS program in Taiwan since 2021 and universal NBS for DMD will begin the American states of New York, Ohio, and Minnesota in 2024.

In sum, there are combination of factors that indicate that the time to implement NBS for DMD is now: unacceptable risks associated with perpetuating diagnostic delays; modern perspectives on NBS policy criteria that recognize the importance of the patients' and parents' perspective; evidence for two-tiered testing and advanced testing technology to minimize false-positive and false-negative cases; international collaboration of stakeholders to develop and update practice guidelines; and a growing number of approved therapeutics and emerging therapies, including gene therapy. The recently published EURORDIS principles for NBS can help guide the policymaking, implementation, and evaluation processes.



1. PARENTS ARE ENTHUSIASTIC ABOUT NEWBORN SCREENING PROGRAMS

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy affecting children. It is a rare, X-linked, recessive genetic disease characterized by progressive and irreversible muscle damage and degeneration that leads to premature death. The incidence rate is estimated at 1 in 5000 live male births (Ellis et al., 2013; Mendell & Lloyd-Puryear, 2013; Mendell et al., 2012) and the global prevalence is around 4.8 per 100 000 (95% CI: 3.6-6.3 per 100 000) (Salari et al., 2022). An overview of the disease and its natural history is provided in Appendix 1.

For more than 25 years, a steady majority of parents have been in favor of newborn screening (NBS) for DMD. From the 67% of parents surveyed at the 1997 European Duchenne Meeting, findings from subsequent studies have indicated increasing rates of support among parents ranging from 87.5% to 100%. High rates of support are observed among parents of children with DMD who opted for NBS in pilot studies, parents whose sons were diagnosed later, and among expectant parents (Chung et al., 2016; Parsons et al., 2002; Plass et al, 2010; Wood et al., 2014). Reasons why parents strongly advocate the implementation of NBS programs for DMD are discussed in the next section.



2. REASONS THE TIME TO IMPLEMENT NBS FOR DMD IS NOW

2.1 To avoid the diagnostic delay, which interferes with supportive parenting (and more)

Despite the advances in multidisciplinary management of patients with DMD in preceding decades, diagnostic delay persists (see Box 1). The mean age of diagnosis remains around 4- to 5-years of age with an average delay of 1.1 to 2.2 years between the first signs of DMD and diagnostic confirmation (Crossnohere et al., 2022; Jackson, 2020; Thomas et al., 2022; Vry et al., 2016).

Box 1. Diagnostic delay in numbers

- » Delays range from 0 to 10 years with an average between 1.1 to 2.2 years.
- » Families seek help from an average of three health professionals before receiving a diagnosis.
- » Nearly 1 in 3 families seek help from four or more health professionals.

The protracted process leaves parents feeling stressed, frustrated, anxious, and guilty. They also experience feelings of anger with the health system, of having concerns being dismissed by others, and of self-doubt with their parenting ability (Wong et al., 2015). Delayed diagnosis can perpetuate parents' misunderstanding of their child's behavior (e.g., wanting to be carried), and prevent them from responding to and caring for their child in the best possible way (i.e., "supportive parenting"). Arguments against NBS that early diagnosis could disrupt parent-infant bonding or have a negative psychosocial impact are unfounded (Campbell & Ross, 2003; Chung et al., 2016; Parsons et al., 2002).

“Our son wasn’t diagnosed until he was 6 years old. We all babied him on one hand, but we often chastised him for being slow or clumsy. He masked everything, telling us he didn’t want to get dirty when really he knew he couldn’t do these things. His father was ashamed to watch him play soccer and only went to one match.”

Parent of a 14-year-old boy with DMD

“Go faster; climb the stairs, concentrate’... the remorse caused by misplaced demands is rarely discussed.”

Parent from France

2.2 Timely and appropriate early intervention for their child

Irreversible muscle damage and degeneration begins at birth. Also, other domains of child development can be affected in early life and observed as early as 2- to 3-months of age. These include communication, adaptive behavior (e.g., emotional/behavioral dysregulation), personal/social behavior (e.g., inattention/hyperactive; obsessive and compulsive features), intelligence (e.g., learning difficulties) (Connolly et al., 2014; Connolly et al., 2013; Darmahkasih et al., 2020; van Dommelen et al., 2020). There is higher prevalence for neuropsychiatric disorders such as autism spectrum disorder, attention-deficit hyperactivity disorder, and obsessive-compulsive disorder among children with DMD (Hendriksen & Vles, 2008; Pascual-Morena et al., 2022).

**“MUSCLES LOST
ARE LOST FOREVER.”**

“It’s more important than ever that parents are able to receive the diagnosis early and not go through a long diagnostic journey. Some of the new treatments, in fact, our gene therapy that was recently approved is only for 4- and 5-year-olds right now. So if you are diagnosed at 6 or 7 or even later, you miss your window of opportunity.”

Mother of a now 14-year-old boy (WTHR, 2024)

During the diagnostic journey, a child may inadvertently receive treatment that is harmful to their muscles and may accelerate loss of function. In addition, without NBS, young children between 0- to 4-years of age who are still undiagnosed miss the opportunity of starting treatments that can preserve their muscles and delay the loss of function. Examples of treatments include glucocorticosteroids (Connolly et al., 2019) and exon-skipping therapies (Mercuri et al., 2023). Furthermore, those with neuropsychiatric needs will miss out on early interventions, resulting in lower quality of life (Thangarajh et al., 2018). Delays in diagnosis also means that evaluations and resources are not in place when they start their school careers, further impeding their cognitive development.

Early intervention also comprises immediate monitoring of the infant and timely access to multidisciplinary care and emerging therapies. It also includes education and support for parents on how to care for their child and provide future perspective. With regards to emerging therapies, a handful of gene therapy products have been approved in the USA and a number are in the development pipeline (see Appendix 2; Tables A1 & A2). However, if the implementation of NBS for DMD is delayed, children may unnecessarily miss out on benefiting from these emerging therapies. Indeed, the time required to organize and launch NBS programs can be two years or longer (Bailey et al., 2021). This was unfortunately the situation experienced by the spinal muscular atrophy (SMA) community (European Alliance for Newborn Screening in SMA, 2021).

Findings from a recent survey of parents with siblings with DMD to gain insight into their lived experiences of early diagnosis indicate that their overall perception was positive. Benefits related to avoiding the diagnostic odyssey (younger siblings were diagnosed an average of 2 years earlier than older ones), support services, school preparedness, and treatment evaluation. A common downside was increased worry. Youngest siblings started DMD-approved therapies an average of a year earlier than older ones and a higher percentage of the youngest were still ambulatory at age 10 (62.3% versus 37.1% of oldest) (Bhattacharyya et al, 2024).

“It is never a good time to hear your child has Duchenne, but knowing allows you to prepare and make decisions and be a better parent.”

@FilippoBucella (Duchenne Parent Project Italy)

2.3 Mitigate the dilemma in drug development

One of the ongoing discussions related to implementing NBS for DMD is that therapeutics for the 0- to 4-years age group are not yet approved. However, a key obstacle to developing therapeutics for this age group is that young children are not being reliably diagnosed at this age and results in an insufficient pool of potential clinical trial participants. No participants result in no data, no drug development, no market approval, and no access to new drugs. This conundrum can only be solved by implementing NBS. Also, drug development for older children is hampered by the existing diagnostic delay, which shortens the time frame that children have for participating in clinical trials (Crossnohere et al., 2022; Farrar et al., 2023).

2.4 Reproductive choice

Timely diagnosis by NBS will mean parents have early access to genetic counseling and guidance and education about reproductive options for genetic carriers. Such support helps educate families about reproductive options, facilitate family planning, and enable families to make informed choices in full awareness (Campbell & Ross, 2003; Crossnohere et al., 2022; Jackson, 2020; Parsons et al., 2002).

2.5 No such thing as a “carefree period”

Another argument against NBS is the concern that early diagnosis takes away parents’ enjoyment of the first carefree years with their child before learning that their child is affected with DMD. However, survey findings indicate that parents with a child with DMD diagnosed later in life had significantly more worries during the first year of life than the general population. As such, a true carefree period does not exist and parents prefer early diagnosis as it would allow them to give their children the best possible care from the outset (Ellis et al., 2013). Indeed, early diagnosis would mean that parents would have time to come to terms with the diagnosis before their son was aware (Parsons et al., 2002). In addition, they would be able to plan other important life decisions such as where to live and work and best options for their child’s schooling (Crossnohere et al., 2022; Parsons et al., 2002).



“Our little boys know from a very early age that they are growing weaker and not stronger, they must be confused and sad and have feelings of inexplicable inadequacy because they are last at everything.”

“A lot of doctors patronize that it is nice for parents to be ignorant but if someone has cancer and not long to live, it would be reprehensible not to tell the patient of any age...our children’s muscles are dying from the beginning and there is a horrific mess under their skin.”

Perspectives of two parents from the Netherlands

3. MODERN PERSPECTIVES ON NBS FOR DMD

The discussion of implementing NBS programs for DMD has been ongoing since the 1970s and different programs have been started and discontinued in the past. There is a renewed interest to include DMD in NBS programs due to three factors. These include advancements in testing technology to minimize false-positive and false-negative cases, growing evidence that emerging therapies may be most effective when muscle damage is still limited (e.g., early years between 0- to 4-years), and the evolving landscape of novel therapeutics in development (Birnkrant et al., 2018a). Indeed, DMD has been included in the NBS program in Taiwan since 2021 (Chien et al., 2022) and universal NBS for DMD will begin the American states of Ohio, New York, and Minnesota in 2024 (Parent Project Muscular Dystrophy, 2023a, 2023b, 2024a). In this section, we discuss developments in NBS policy making such as the parents' perspective, healthcare professionals' perspective, and evolutions in the NBS screening process.

3.1 DMD is both actionable and treatable

Traditionally, public health policies on NBS have been based on 10 criteria proposed by Wilson & Jungner in 1968. At the time, the criteria were mainly developed with “chronic diseases of adults” in mind, and the authors did not intend for the criteria to serve as dogma nor remain unchanged over time (Wilson & Jungner, 1968; Andermann et al, 2008). The 10 principles are presented in Appendix 3.

Modern perspectives on NBS policy criteria recognize the importance of including the patients' and parents' perspectives, and that the focal point of assessing the benefits and risks should be the interest of the child (Cornel et al., 2014). These perspectives are expanding the original concept of a disease having to be treatable (Wilson & Jungner, 1968) to that of being actionable (EURORDIS Rare Diseases Europe, 2021; see Box 2). With this evolution, consideration is given to benefits beyond disease modification. These relate to the net health and psychosocial benefits of early detection (e.g., early surveillance and access to appropriate care; supportive parenting; psychosocial well-being of the family unit; restoring the reproductive options of genetic carriers), which potentially outweigh concerns related to receiving a diagnosis for a disorder without an approved medical intervention that modifies disease progression (Farrar et al., 2023; see Box 3).

Box 2. Three features of actionable diseases

- » Early intervention for the newborn leads to health gains.
- » A lengthy diagnostic odyssey can be avoided thanks to early diagnosis.
- » Reproductive options are available to parents with regards to subsequent pregnancies.

Indeed, the model of care for DMD has evolved to a holistic and proactive approach that addresses issues such as concerns within family unit, psychosocial care, life transitions, and disease modification. Multidisciplinary care guidelines were developed in 2012 and updated in 2018 by international DMD Care Considerations Work (Birnkrant et al., 2018a, 2018b, 2018c). Advancements have led to among others, longer life expectancy. An overview the management of DMD is provided in Appendix 1. This overview includes tables summarizing emerging therapies such as gene therapy that have been approved or are under development (Table A1 and A2).

“In progressive muscle wasting conditions [like DMD], lost muscle tissue cannot be recovered...Therapies are becoming available. In the US, Japan, and Israel, there are already antisense oligonucleotides (ASOs) that can be given in infancy, and there are many ongoing trials including next generation ASOs for which much greater clinical benefit is anticipated, and a rapid approval pathway. ASOs, but also AAV gene therapy which is likely to receive approval in 2024, can only work if there is muscle available for them to exert their actions.”

Prof. dr. Francesco Muntoni (University College London)

Box 3. Net health and psychosocial benefits of NBS for the infant with DMD, its family, and health care system

- » Timely knowledge enables parents to provide their child with the best possible care, fostering supportive parenting.
- » Parents have time to plan.
- » The diagnostic odyssey and associated negative psychosocial consequences can be prevented.
- » A child's inadvertent exposure to harmful treatment during the diagnostic journey, which can accelerate loss of function, can be prevented.
- » Early detection means infant can be immediately monitored and receive timely access to developmental assessments, multidisciplinary care including speech and/or autism therapies, glucocorticosteroids, and emerging therapies, and may be enrolled in innovative clinical trials.
- » The family has an increased time frame during which their infant's participation in clinical trials can be considered.
- » Parents gain control over their reproductive options and family planning since the recurrence risk of having another child with DMD are known.
- » Health care systems will benefit from avoiding resource waste from a protracted diagnostic process (e.g., unnecessary and irrelevant testing, consultations, referrals, and treatment).



3.2 The healthcare professionals' perspective

Perspectives on NBS for DMD among of physicians working at Certified Duchenne Care Centers across the USA were recently explored by survey. Results indicated that the vast majority (82%) of physicians saw benefit in NBS for DMD. With regards to follow-up after NBS, the majority recommended multiple interventions as follows (Armstrong et al., 2022):

- » early assessment of social and language development
- » testing maternal carriers and screening siblings
- » genetic counseling
- » referral to early intervention services
- » discussing clinical trials and potential participation
- » discussing exon skipping and other therapies
- » initiating approved therapies much earlier than the typical age of diagnosis

With regards to early intervention, 67% of clinicians would prescribe corticosteroids within the first two years of a child with symptoms and another 23% would initiate corticosteroids between 2- to 4-years of age. Also, more than half would prescribe a child diagnosed with DMD corticosteroids before the age of 2 years even if he was asymptomatic. In terms of exon-skipping therapy, 81% of clinicians would prescribe this therapy to children during their first year of life if they were symptomatic and had an amenable pathogenic variant (Armstrong et al., 2024).

“Newborn screening is important to identify patients [with Duchenne] early. This will allow timely care intervention and for some patients an opportunity to start treatment early. It also gives parents more time to plan and make decisions about trial participation and treatment options.”

Prof. dr. Annemieke Aartsma-Rus (Leiden University Medical Center)

3.3 Proof-of-concept for two-tiered testing

The proof-of-principle of NBS for DMD was established in 1975; it involved measuring creatine kinase (CK) levels from dried blood samples (DBSs) (Zellweger & Antonik, 1975). Building on this, proof-of-concept for two-tiered testing based on CK measurement followed by DMD gene testing was established in 2010 (Mendell & Lloyd-Puryear, 2013; Mendell et al., 2012). In general, this two-tiered approach begins with measuring the concentration of CK from a DBS collected from a heel prick. Thresholds for interpretation of CK concentrations are based on the timing of test in terms of days postpartum. Infants with an elevated CK level are referred for genetic testing to confirm diagnosis.

Recently, a pilot study evaluated the two-tier approach in the state of New York, USA (Tavakoli et al., 2023) and another is being planned in Australia (Farrar et al., 2023). During the 2-year study period of the New York study, close to 37 000 babies were screened. Of these, 42 babies (25 males, 17 females) were referred for second-tier gene testing. In the end, four males were found to have deletions or duplications consistent with DMD or BMD and one female was identified as a genetic carrier (Tavakoli et al., 2023). Subsequently, NBS was submitted to the Registered Uniform Screening Panel for review (Parent Project Muscular Dystrophy, 2024c). Universal two-tiered NBS for DMD will begin the American states of Ohio, New York, and Minnesota in 2024 (Parent Project Muscular Dystrophy, 2023a, 2023b, 2024a).

Reflecting the need for NBS programs to consider local healthcare system infrastructure, and economic, political, and cultural issues, the exact nature of the screening process can vary. For example, a three-step approach (i.e., initial DBS, repeat DBS if borderline or elevated CK level on initial DBS test, and genetic test if persistently elevated CK) has been included in the NBS program in Taiwan since 2021 (Chien et al., 2022). Also, a pilot study using this approach was recently completed in the province of Guangzhou, China (Jia et al., 2023).

The detection of other (genetic) conditions during NBS for DMD remains a possibility and a concern. An overview of the number of other diagnoses found in recent pilot studies and implemented programs is provided in Appendix 4. Care for these infants and their families are embedded in NBS programs built upon recommended principles such as that of EURORDIS: “The family of the newborn who has been diagnosed through NBS should be provided with psychological, social and economic support by the competent national health authorities” (principle 3; See Appendix 5 for all 11 EURORDIS principles).

3.4 Genetic testing process

Best practice guidelines on genetic testing recommend a stepwise approach. Initial confirmatory genetic testing should focus on determining the presence of dystrophin gene deletion and duplication. These mutations represent 70% of all those observed in patients with DMD. Multiplex ligation-dependent probe amplification (MLPA) or comparative genomic hybridization (CGH) array is preferred (Birnkrant et al., 2018a). If single- or multi-exon mutations are not detected, then genetic sequencing (Sanger sequencing) is recommended to screen for remaining small mutations. Finally, if results of these genetic tests are negative, then a muscle biopsy is taken to evaluate the localization, amount, and size of dystrophin protein using Western blot and immunohistochemistry (Birnkrant et al., 2018a; Duan et al., 2021). Ongoing development indicate that the use of genetic panels (e.g., exome sequencing, whole genome sequencing, massive parallel sequencing) may become possible in the future (Duan et al., 2021; Farrar et al., 2023). Next generation sequencing (NGS) for DMD is a potentially cost-effective alternative to the stepwise approach as NGS can identify all mutation types and can be upscaled to be used in screening procedures (Fratter et al, 2020).



3.5 NBS is not just a test but a program

NBS is a general term to describe tests used to identify various congenital health conditions in the neonatal period. The aim of NBS programs is to identify affected infants who would benefit from early diagnosis and treatment and management, thereby extending life expectancy and functional ability (Grosse et al., 2006; Scarpa et al., 2022; Therrell et al., 2015). It is critical to remember that NBS is not just about the test itself but also includes the follow-up care thereafter.

As with all NBS programs, proper governance, stakeholder involvement, and special attention for vulnerable groups (e.g., rural, indigenous, or minority communities) is essential (Farrar et al., 2023; Ke et al., 2017; Parsons et al., 2002). Various guidance documents exist to inform the policy making and screening process (Dobrow et al., 2018; EURORDIS Rare Diseases Europe, 2021). Relevant points for different stakeholders are as follows:

- » For parents: standard participation (with opt-out) versus voluntary (opt-in), informed consent, the way positive results and unintended findings are communicated, protection of privacy and rights, and the follow-up care
- » For public health systems: informing the public, adequate surveillance infrastructure, staff training, blood spot sampling and storage, laboratory procedures, confirming diagnosis and treatment, protection of privacy and rights, continuity of care with broader health care system and patient organizations, funding, quality assurance, program evaluation
- » For healthcare providers: communication of results, data sharing, continuity of care, protection of privacy and rights
- » For policy makers: continuity of care, evaluation of benefits and harms, health economic evidence, protection of privacy and rights, funding, quality assurance, program evaluation



4. OTHER CONSIDERATIONS

4.1 Health economic benefits of NBS for DMD

Evidence on the health economic benefits of NBS for DMD is limited. Nevertheless, results from a Canadian study indicate that costs of NBS for DMD are comparable to that for metabolic disorders (Rosenberg et al., 1993). Also, there will be benefits from avoiding resource waste and lost workdays for caregivers due to a protracted diagnostic process (e.g., unnecessary and irrelevant testing, consultations, and referrals) and irrelevant/inappropriate treatment. Indeed, a recent US study estimated that families accrue more than US \$211 000 in medical and productivity loss costs across the diagnostic odyssey (Every Life Foundation for Rare Diseases, 2023). Furthermore, prolonging a child's function with timely intervention has financial benefits for the family and society. That is, while the predicted loss of earnings of mothers with sons with DMD who were older than 4-years of age and non-ambulatory was nearly US \$24 000 annually, no loss of earnings was observed if boys were still ambulatory (Soelaeman et al., 2021).

4.2 Ethical issues

4.2.1 Risks of not implementing NBS for DMD

Bayley & Laing argue that permitting diagnostic delays to persist and placing families at risk to have multiple boys affected with DMD is not ethically justifiable (Bayley & Laing, 2012). In addition, with recently approved therapeutics and many under approval or clinical development, as well as therapeutic candidates receiving orphan drug designation, DMD is evolving into a treatable condition. Given this evolution and the fact that expanding NBS programs to include DMD will take time, decisions to delay the diagnosis of DMD and the risk of missed opportunities for appropriate and timely treatment, are unethical.

4.2.2 Participation in NBS programs for DMD

Past and current NBS programs for DMD differ in terms of how parental autonomy is protected. Procedures to ensure informed consent (e.g., providing education about NBS during prenatal check-ups and reviewing again before postnatal testing) and options to either opt-in or opt-out from participation can respect parental autonomy.

4.2.3 Health equity

While evidence supports the use of a two-tiered test, this testing approach is not feasible in all parts of the world. Factors that influence feasibility include how testing locations and storage are set up (e.g., does the DBS stay in the same testing location or it is transported to different locations), existing laboratory infrastructure, and available funding. In some countries, NBS using repeated CK assays without genetic testing or dystrophin protein analysis may be the only affordable and

“WITHOUT NBS, INFANTS AND CHILDREN WITH DMD BETWEEN 0- TO 4-YEARS OF AGE WILL CONTINUE TO MISS OUT ON THE BENEFITS OF EARLY INTERVENTION AND HAVE AN UNACCEPTABLE RISK OF BEING INADVERTENTLY HARMED BY INAPPROPRIATE TREATMENTS.”

feasible option. In others, the initial confirmatory genetic test is often limited to multiplex quantitative polymerase chain reaction (PCR) testing, which can only detect gene deletions and has poor accuracy (Duan et al., 2021; Fratter et al, 2020). These health inequities can further increase when gene panels, which have been identified as the future of NBS, are approved as not all public health systems may be able to afford them.

The inclusion or exclusion of screening newborn girls in NBS programs for DMD is an issue that each potential program needs to deliberate upon along with other public health considerations. Nevertheless, as there are health and reproductive consequences for female carriers, exclusion would contribute to the health inequity of these infants and their families. Recently, an algorithm for the screening, diagnosis, and follow-up management of female carriers has been published (Gruber et al., 2022).

5. CONCLUSION

The discussion of implementing NBS programs for DMD has been ongoing since the 1970s and for more than 25 years, a steady majority of parents have been in favor of NBS for DMD. Given the combination of 1) unacceptable risks associated with perpetuating diagnostic delays; 2) modern perspectives on NBS policy criteria that recognize the importance of patients' and parents' perspectives; 3) evidence for two-tiered testing and advanced testing technology to minimize false-positive and false-negative cases; 4) international collaboration of stakeholders to continually develop and update practice guidelines; and 5) a growing number of approved therapeutics and emerging therapies (e.g. gene therapy), the time to implement NBS for DMD is now.

APPENDIX I

Duchenne muscular dystrophy, the disease

DMD is caused by mutations in the dystrophin gene on the X-chromosome (Birnkrant et al., 2018a). A wide range of gene mutations exist. Approximately 60%-65% of the mutations are deletions, 5-10% duplications, and 25-35% small mutations (Farrar et al., 2023; Neri et al., 2020). In about two-thirds of patients with DMD, mothers are diagnosed as carriers of a DMD gene mutation; in the remaining one-third, spontaneous germ line mutation is the underlying cause (Caskey et al., 1980; Chen et al., 2013). If female carriers have another son, the son's chance of having DMD is 50%; if female carriers have a daughter, the daughter's chance of being a carrier is 50%. Female noncarriers with a son with DMD have a 4.3% to 8.6% chance of recurrence due to germ line mosaicism depending on the type of transmission (Helderman-van den Enden et al., 2009).

The dystrophin gene is responsible for the production of dystrophin. Dystrophin is a structural protein located underneath the membrane (i.e., sarcolemma) of skeletal, cardiac, and smooth muscle cells. Smaller amounts of dystrophin gene expression also occur in the brain (Falzarano et al., 2015; Farrar et al., 2023). Dystrophin combines with various other proteins to form structures known as dystrophin-associate protein complexes (DAPCs). DAPCs contribute to the structural stability, contractile activity, and signaling of muscle fibers (Duan et al., 2021).

Mutations in the dystrophin gene affect the production of functional dystrophin, and thus the formation of DAPCs (Birnkrant et al., 2018a; Duan et al., 2021). As a result, dystrophin-deficient muscle is mechanically unstable, vulnerable to tearing during contraction, and susceptible to muscle fiber necrosis (Duan et al., 2021). In addition, the ability of muscle cells to regenerate is impaired (Birnkrant et al., 2018a; Falzarano et al., 2015). As the amount of muscle fiber damage increases and accumulates, outward signs of diminishing muscle function become noticeable.

Natural history of DMD

DMD is characterized by progressive and irreversible muscle damage. Muscle degeneration begins at birth and leads to premature death. While clinical presentation may vary between persons with DMD, common signs and symptoms are muscular weakness, delays in motor development, loss of walking ability, difficulty breathing, and heart muscle disease (cardiomyopathy). Swallowing, gastric emptying, intestinal paresis, and bladder and urinary tract functioning may also be impaired (Birnkrant et al., 2018a, 2018b; Duan et al., 2021).

Other domains of child development that can be affected in early life and observed as early as 2- to 3-months of age. These include communication, adaptive behavior (e.g., emotional/behavioral dysregulation), personal/social behavior (e.g., inattention/hyperactive; obsessive and compulsive features), intelligence (e.g., learning difficulties) (Darmahkasih et al., 2020; van Dommelen et al., 2020). A recent systematic review has reported that there is higher prevalence for neuropsychiatric disorders such as autism spectrum disorder and attention-deficit hyperactivity disorder among children with DMD (Pascual-Morena et al., 2022).

Changes in gross motor function over time are summarized in Figure 1. Difficulty walking and climbing stairs, increased difficulty in keeping up with peers, compensatory postures, and frequent falls may be first observed around 2- to 3-years of age. Loss of ambulation may occur between 8- to 15-years of age with a mean around 10- to 12-years (Szabo et al., 2021; Vry et al., 2016). The average age of onset for scoliosis is around 14 years (Szabo et al., 2021).

Loss of arm function also occurs in the teenage years, resulting in the need for assistance with self-care activities such as bathing, toileting, dressing, and eating. Cardiac and respiratory symptoms can also emerge around this time with the need for ventilatory support occurring between 15- to 18-years of age (Szabo et al., 2021). Cardiac and respiratory failure account for the majority (approximately 80%) of deaths; the remaining 20% are attributable to noncardiopulmonary causes such as injury-related pulmonary embolism, stroke, gastrointestinal complications, and unnatural causes (Wahlgren et al., 2022). Median life expectancy with ventilatory support is between 29.9 to 31.8 years and without between 19.0 to 19.4 years (Landfeldt et al., 2020).

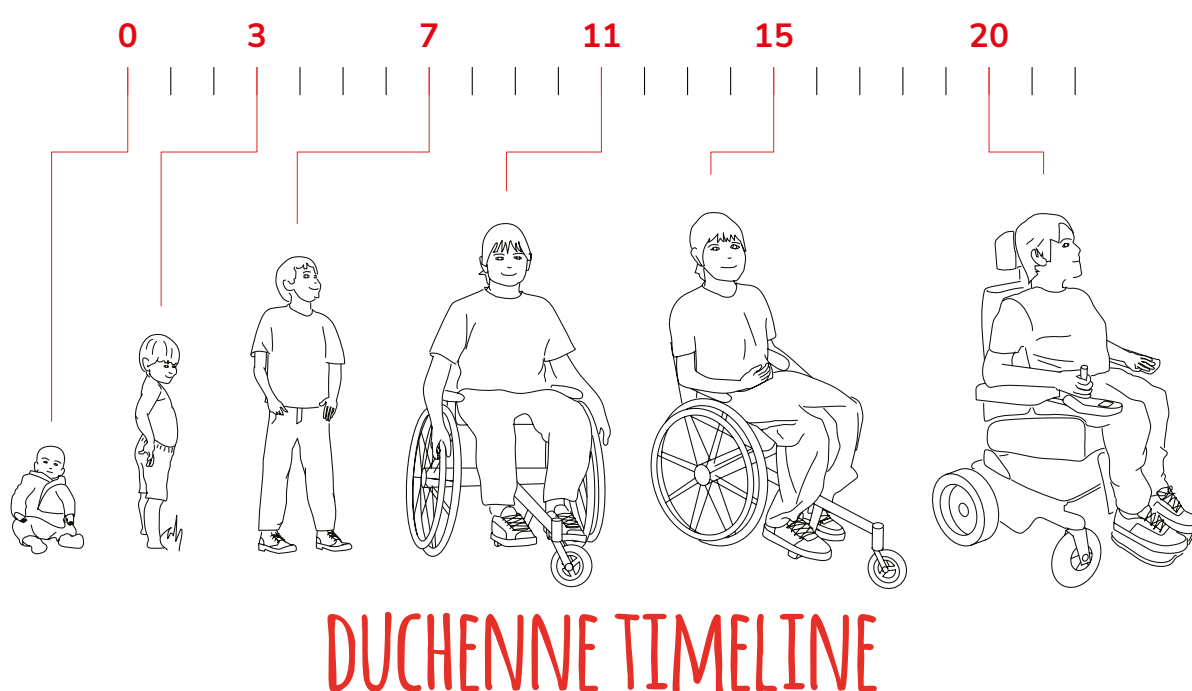


Figure 1. Changes in gross motor function over time in boys with Duchenne muscular dystrophy

Clinical presentation of female carriers

Female carriers may or may not become symptomatic. The age of symptom onset can vary widely (e.g., 1-50 years) as can the clinical presentation (Silva et al., 2020). Symptoms of female carriers may include a history of weakness and clumsiness in childhood, asymmetric muscle weakness and compensatory movements, enlargement of calf muscles (i.e., pseudohypertrophy), muscle cramps, myalgia, unexplained abdominal pain or chest pain, and rapid heart rate (i.e., tachycardia) of unknown origin (Gruber et al., 2022; Silva et al., 2020).

A recent review reported that the incidence of skeletal muscle damage among symptomatic and asymptomatic female carriers can range between 2.5% to 19% and that of dilated cardiomyopathy between 7.3% to 16.7% (Ishizaki et al., 2018). Myocardial fibrosis can develop in female carriers in a similar way to male patients with DMD (Florian et al., 2016). In addition, subclinical deterioration of systolic cardiac function has been observed in asymptomatic carriers (Kincl et al., 2020).

APPENDIX 2

Management of DMD

The diagnosis and treatment for patients with DMD is organized around multidisciplinary care. The multidisciplinary team includes medical specialists, allied health professionals (nurses, physiotherapists, occupational therapists, speech language pathologists, respiratory therapists), and genetic counselors. Best care guidelines exist, providing recommendations for managing neuromuscular, respiratory, cardiac, orthopedic, endocrinological, gastrointestinal, nutritional, urological, and neurodevelopmental and neuropsychological issues. Guidelines also address psychosocial concerns and challenges with transitioning into adulthood. Advancements during the past 30 years have led to gains in functional outcomes, quality of life, and life expectancy (Birnkrant et al., 2018a, 2018b, 2018c; Duan et al., 2021).

Specialized treatment centers for DMD exist around the world and they serve local, national, and international patients. In addition, patient organizations have a critical role in advocacy and providing a safety net of support to families who receive the unexpected news after NBS. Fellow parents can help educate new families, provide perspective that a good life is still possible, and share strategies for coping. The Duchenne patient community is an active partner in clinical research and a forerunner in developing digital infrastructure to ensure DMD-related data are findable, accessible, interoperable, and reusable (van Lin et al., 2021; Verhaart et al., 2019).

Management is patient-centered and is aligned to the stage of disease. Interventions aim to slow disease progression, prevent and manage symptoms, and address psychosocial issues to optimize a patient's participation in society and achievement of life goals. Nonpharmaceutical treatment include physiotherapy and assistive devices to prevent contractures and scoliosis, and surveillance of respiratory and cardiac function (Duan et al., 2021).

Standard pharmaceutical treatment include ACE-inhibitors and corticosteroids. ACE-inhibitors are prescribed as prophylactic cardiac treatment; nonprophylactic treatment is started once cardiomyopathy is diagnosed. Corticosteroids (prednisone or deflazacort) are effective in increasing muscle strength and delaying the loss of ambulation as well as pulmonary disease progression (McAdam et al., 2012; McDonald et al., 2018a; McDonald et al., 2018b; Merlini et al., 2020; Vry et al., 2016). Also, long-term corticosteroid use prevents the development of scoliosis and need for spinal surgery (Lebel et al., 2013; McAdam et al., 2012). Side effects of corticosteroids include weight gain and glucocorticoid-induced osteoporosis (Duan et al., 2021; Lamb et al., 2018; Mayo et al., 2012). Treatment regimens may vary to optimize the balance between benefits and risk.

A new development is vamorolone, a novel dissociative steroid that modifies the downstream activity of glucocorticoid receptors without customary side effects such as impaired bone metabolism (Guglieri et al., 2022). Vamorolone has recently received approval for use in patients 2 years and older by the Food & Drug Administration (FDA) and in patients aged 4 years and older by the European Medicines Agency (EMA) (Santhera Pharmaceuticals Holding AG, 2023).

The landscape of gene therapy for DMD to restore or replace dystrophin is evolving rapidly. So-called exon-skipping therapies are an emerging class of therapeutics. While exon-skipping therapies do not cure DMD, they may help delay the loss of muscle function in about 30% of the DMD population with certain exon mutations. Exon-skipping therapies correct the reading frame of the dystrophin gene in such a way to allow the production of a shortened piece of dystrophin (Duan et al., 2021).

In June 2023, the FDA approved the first gene therapy for DMD called Elevidys. An overview of approved therapeutics to restore or replace dystrophin is provided in Table A1. Therapeutics under development are summarized in Table A2.

Table A1. Summary of approved therapeutic approaches for restoring or replacing dystrophin as of January 31, 2024 in the USA, Europe, United Kingdom, and Japan¹⁻⁴

Therapeutic approach	Product (Manufacturer)	Approving regulatory agency	Indication in DMD
Exon skipping	Casimersen (Sarepta Therapeutics)	FDA	Amenable to exon 45 skipping
	Eteplirsen (Sarepta Therapeutics)	FDA	Amenable to exon 51 skipping
	Golodirsen (Sarepta Therapeutics)	FDA	Amenable to exon 53 skipping
	Viltolarsen (NS Pharma, Inc)	FDA, Japan	Amenable to exon 53 skipping
Nonsense mutation read-through	Ataluren (PTC Therapeutics, Inc.)	UK ^a	Ambulatory patients 2 years of age and older with a nonsense mutation in the dystrophin gene
Gene therapy (AAV-vector based)	Elevidys (Sarepta Therapeutics)	FDA	Patients 4-5 years of age with confirmed DMD gene mutation

^aConditional approval

Abbreviations: AAV, adeno-associated virus; FDA, Food & Drug Administration

¹Japan Agency for Medical Research and Development, 2020; ²Parent Project Muscular Dystrophy, 2024b; ³National Institute of Health Care and Excellence, 2023; ⁴World Duchenne Organization, 2024.



Table A2. Summary of clinical trials of therapeutics aiming to restore or replace dystrophin as of (January 31, 2024)¹⁻³

Therapeutic approach	Medication (Sponsor; trial number)	Phase of development	Indication in DMD
Exon skipping	SRP-5051 (Sarepta Therapeutics, NCT04004065; NCT03675126)	Phase II	Generation eteplirsen; amenable to exon 51 skipping
	NS-089/NCNP-02 (NS Pharma; NCT05996003)	Phase II	Amenable to exon 44 skipping
	DS-5141b (Daiichi Sankyo; NCT04433234)	Phase II	Amenable to exon 45 skipping
	DYNE-251 (Dyne Therapeutics; NCT05524883)	Phase I/II	Amenable to exon 51 skipping
	WVE-N531 (Wave Life Sciences; NCT04906460)	Phase I/II	Amenable to exon 53 skipping
	AOC 1044 (Avidity Biosciences; NCT05670730)	Phase I/II	Amenable to exon 44 skipping
	scAAV9.U7.ACCA (Audentes Therapeutics; NCT04240314)	Phase I/IIa	Amenable to exon 2 skipping
	PGN-EDO51 (Pepgen; NCT06079736)	Phase I	Amenable to exon 51 skipping
	BMN 351 (Biomarin)	Pre-clinical	Amenable to exon 51 skipping
Gene therapy (AAV-vector based)	PF-06939926 (Pfizer; NCT03362502)	Phase III	DMD confirmed by medical history and genetic testing
	rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) (Sarepta; NCT05096221, NCT05967351, NCT04626674)	Phase III/ open label	DMD confirmed by medical history and genetic testing; ambulatory and between 4-7 years of age
	SCAAV9.U7.ACCA (Nationwide Children's Hospital; NCT04240314)	Phase I/II	For patients with a duplication of exon 2 in the DMD gene
	RGX-202 (REGENXBIO; NCT05693142)	Phase I/II	DMD gene mutation in exons 18 and above, and a clinical picture consistent with typical DMD
	RAAVRH74.MCK.GALGT2 (Nationwide Children's Hospital; NCT03333590)	Phase I/II	Confirmed mutations 1,2
	SGT-003 (Solid Biosciences; NCT06138639)	Phase I/II	SGT-003 is designed to produce functional dystrophin protein containing the neuronal nitric oxide synthase (nNOS) domain in skeletal and cardiac muscles
	GNT-0004 (Généthon/Sarepta)	Phase I/II	DMD confirmed by medical history and genetic testing

¹Parent Project Muscular Dystrophy, 2024b; ²Genethon, 2021; ³World Duchenne Organization, 2024.

APPENDIX 3

Wilson & Jungner Public Health Criteria for Screening Programs (Wilson & Jungner, 1968)

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

APPENDIX 4

Table A3. Creatine kinase cut-off points on dried blood spot testing and the rate of diagnosing other neuromuscular conditions after further evaluation in recent pilot studies and currently implemented programs.

Author (Year)	Location of NBS pilot study or program	Number of infants screened	Creatine kinase-MM cut-offs		Referral cut-off for further evaluation	Number of infants diagnosed with DMD or as carriers	Other diagnoses (number)
			Age at collection ^a	Borderline cut-off (for rescreen)			
Mendell et al (2012)	Ohio, USA	37 649	NA	NA	Initially ≥ 600 U/L (3 SDs from the mean), then ≥ 750 U/L	DMD (n=6)	Limb-girdle MD (n=3)
Chien et al (2022)	Taiwan	50 572	48-72h	650 ng/mL ^b 750 ng/mL ^c	300 ng/mL	DMD (n=3)	Pompe disease (n=13); GAA deficiency (n=5); partial GAA deficiency (n=8)
Jia et al (2022)	Guangzhou, China	62 553	48h-7d	≥ 800 ng/mL	≥ 400 ng/mL	DMD (n=4)	Other muscular developmental disorder (n=1)
Tavakoli et al (2023)	New York, USA	36 781	0-47h 48-71h 72-167h ≥ 168 h	≥ 1990 ng/mL ≥ 1430 ng/mL ≥ 571 ng/mL NA	≥ 4000 ng/mL ≥ 4000 ng/mL ≥ 860 ng/mL ≥ 571 ng/mL	Diagnosed DMD/BMD (n=4) Carrier (n=1)	Alagille syndrome (n=1); carrier of LAMA2 MD (n=2); limb-girdle MD (n=1); carrier limb-girdle MD (n=2); carrier MD-dystroglycanopathy (n=1); cerebral palsy with neuromuscular respiratory weakness (n=1)

^aTime after birth; ^bCut-off values for babies born prematurely; ^cCut-off values for babies born at full term.

Abbreviations: BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; GAA, Acid alpha glucosidase; MD, muscular dystrophy; NA, not applicable; n, number of patients.

APPENDIX 5

EURORDIS Key Principles for Newborn Screening (EURORDIS Rare Diseases Europe, 2021)

1. Screening should identify opportunities to help the newborn and the family as broadly as possible. That is, screening should identify actionable diseases including treatable diseases.
2. NBS should be organised as a system with clearly defined roles, responsibilities, accountability and communication pathways that are embedded into the national health care system and recognised as a mechanism for earlier diagnosis of actionable conditions as part of the broader care pathway.
3. The family of the newborn who has been diagnosed through NBS should be provided with psychological, social and economic support by the competent national health authorities.
4. All stakeholders should be included in the different stages of the NBS process.
5. Transparent and robust governance for expanding NBS programmes is needed. Every country/region should have a clearly defined transparent, independent, impartial and evidence-based process for deciding which conditions are covered by the NBS programme that includes all stakeholders.



6. Governance of NBS programmes should be explicit, comprehensive, transparent and accountable to national authorities.
7. The evaluation process on the inclusion/exclusion of diseases in NBS programmes needs to be based on the best available evidence, reflecting health economic evidence but not determined only by health economics.
8. Information and education of all stakeholders on rare diseases and the whole NBS process is essential for a broad and fair implementation of NBS programmes.
9. European-wide standards addressing the timing, sample collection methods, follow-up, and information shared with parents are needed to guarantee uniformity and quality throughout the process.
10. Blood spot samples should be stored in national biobanks for research purposes while ensuring appropriate safeguards for data protection and data access are in place.
11. ERN affiliated centres should be integrated in the care pathways of the different Healthcare systems and should be considered as preferential partners in providing recommendations on NBS policies.



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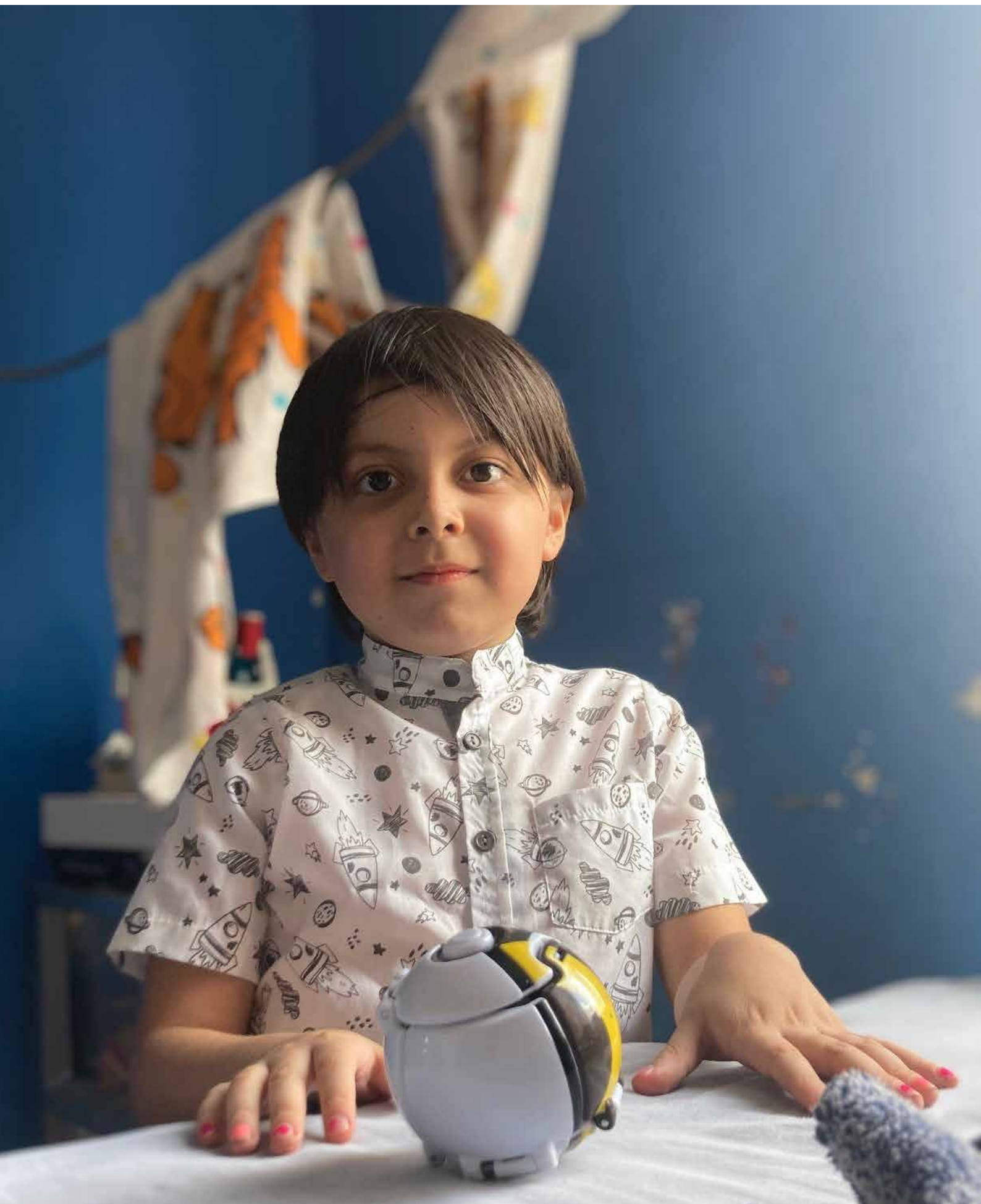
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About the World Duchenne Organization

The World Duchenne Organization is an umbrella organization of national patient organizations for DMD and Becker MD (BMD) around the world. This organization aims to inform parents and people with DMD/BMD based on latest research, promote good standards of care, and actively participate in efforts develop safe and effective treatments for DMD/BMD and find a cure.

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