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Early diagnosis of Duchenne muscular dystrophy - A Treat-NMD international workshop ☆

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ABSTRACT

The diagnosis of Duchenne muscular dystrophy (DMD) is significant at any stage, however an early diagnosis in a presymptomatic or very early phase of DMD, offers unique opportunities and challenges for families and health care providers. Currently, there is limited evidence as to the optimal models of care during this stage of the condition.. To address this, in 2023, Treat-NMD facilitated the Early Diagnosis for DMD project; bringing together 42 experts from across Europe, the US and Australasia, including health care professionals, researchers, and people with lived experience to discuss the complexities of an early or newborn diagnosis of DMD, and provide recommendations regarding approaches to multidisciplinary care. A series of virtual meetings followed by a hybrid workshop resulted in broad recommendations to support clinicians in caring for children and families following an early diagnosis of DMD. The workshop did not define a cut-off for early diagnosis, however much of the discussion focused on diagnoses that occurred prior to 2 years. There is recognition that boys may first present with non-motor symptoms, such as speech delay or neurodevelopmental issues that are secondary to their dystrophinopathy, and therefore this report refers reflects that infants with DMD may be presymptomatic or early symptomatic.

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy, affecting 1 in 5000 boys. This genetic condition, results in progressive muscle weakness and is life limiting. In 2023, gene transfer therapy for DMD was conditionally approved by the FDA for boys with DMD aged 4–5 years and in June 2024 the FDA expanded the label to all DMD patients ages 4 years and older. Approval of other pharmacotherapies including vamorolone in the US and EU, and antisense oligonucleotides that allow exon skipping and givinostat also in the US [1], have increased the options for DMD pharmacotherapy in certain jurisdictions. This shifting landscape, along with the aims to promote equity in early-stage care that allows for early assessment and intervention for developmental and behavioural manifestations, and to empower families with information for family planning [2], have prompted a reconsideration of the validity and benefit of newborn screening (NBS) in DMD [3]. In addition, utilisation of chromosomal microarray testing in general paediatrics has increased the likelihood of diagnosing DMD in the setting of any developmental delay.

Newborn screening programs for DMD have previously been trialled in pilots in multiple countries including the USA [4,5], Taiwan [6], China [7], Wales [8], France [9], Germany [10] and Canada [11] and Newborn Screening Programs have been approved across a number of US states including Ohio, New York and Minnesota. The *Lancet* guidelines for the care of DMD are regarded as tenets of best practice [12,13], however, minimal guidance exists as to the most effective approach regarding a model of care following an early pre-symptomatic or early symptomatic diagnosis. One USA group led by Kwon et al., published broad recommendations developed by a US Taskforce in 2016 [14]; however, given the advances in clinical trials and

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the varying approaches to clinical practice internationally, TREAT-NMD identified a need to convene an up-to-date discussion with diverse stakeholders across the European, American and Asia-Pacific regions, and this led to the *Early Diagnosis for DMD Project*. The aim of this project was to unite patients, clinicians, advocates, and researchers in considering the impact of an early DMD diagnosis on this increasing patient subset and to create a flexible framework to ensure the best model of care to support children and families following an early diagnosis of DMD.

Between July and October 2023, 42 stakeholders participated in 5 online meetings and 1 hybrid workshop hosted by TREAT-NMD to gain perspectives regarding the needs and priorities for recommendations related to an early diagnosis of DMD. The fundamental question we sought to answer was: how does an early diagnosis of DMD do more good than harm?

The 42 participants who accepted the invitation and/or have contributed to the project to date represent 26 different institutions and organisations across three continents, and we continue to hear from individuals who are keen to join and help achieve the project objectives.

2. Workshop method

An introductory meeting was held in July 2023 where global experts (patients, families, clinicians, patient organisations, researchers, genetic counsellors, allied health providers and policy makers) were invited to consider, more broadly, the impact of an early diagnosis on patients, families, and clinical practice. Stakeholders met initially so project leads could outline the project's context and objectives and facilitate early discussion around the topic.

During the introductory meeting, Dr. Michelle Lorentzos (Paediatric Neurologist at The Sydney Children's Hospitals Network, Sydney, Australia) presented the changing landscape of clinical trials and diagnosis for DMD. Dr. Lorentzos discussed 3 clinical contexts that had necessitated an approach to early diagnosis of DMD; the first being an infant that had undergone chromosomal microarray testing for global delay, the second was a neonate who was found to have elevated creatine kinase (CK) following investigations for persistent neonatal jaundice, and the third being a pilot project for a two-tier NBS of DMD in New South Wales, Australia. Each of these exemplar cases resulted in a need to convey diagnosis and commence care in a pre-symptomatic or early symptomatic phase, highlighting the need for an effective model.

Dr. Julie Parsons (Paediatric Neurologist at Children's Hospital Colorado, USA) presented an overview of newborn screening programs that have been previously utilised including pilots in New York [5], North Carolina [15] and Massachusetts [16]. Dr. Parsons presented alternative screening scenarios from primary carers to evaluating CK for any male child presenting any form of delay, as well as the possibility of routinely checking CK at a set point in time, such as 6 months.

Professor Laurent Servais (Professor of Paediatric Neuromuscular Disease, University of Oxford, UK) presented an overview of treatments utilised in DMD, emphasising that evidence is sparse regarding children under the age of 2 years. Prof. Servais outlined the few examples of research in infants and children, including the study of eteplirsen in children 6–48 months [17] and weekend steroids in boys as young as 4 months [18], both of which were focused on tolerability and safety. He described the lack of efficacy data in children younger than 2 years and outlined limiting factors to research in this younger cohort, with specific focus on the lack of validated outcome measurements. He emphasised the need to gather data efficiently to inform practice and to potentiate improved outcomes in DMD.

At the conclusion of these plenary presentations, discussions were held in small breakout groups and covered issues such as the multidisciplinary needs of DMD, and the importance and challenge of non-motor developmental surveillance. There was anecdotal acknowledgement that clinicians were diagnosing more younger patients, even in areas without NBS, often due to the integration of first line chromosomal arrays in the assessment of infants with developmental delay. Parents generously shared personal experiences of diagnosis and emphasised the impact of language in conveying a new diagnosis of DMD to families. There was recognition that adequately responding to early diagnosis, especially in the context of a NBS, required resourcing for genetic counselling, nursing and timely medical review.

At the end of the initial meeting, participants were invited to join four distinct working groups where recommendations for the care and treatment of patients would be established. Four working groups were established: Working Group 1: Medical treatment pathway; Working Group 2: Family genetic counselling / psychosocial / education; Working Group 3: Allied health, nursing and functional assessment; and Working Group 4: Newborn screening integration of screen positive babies into therapy.

3. Working group discussions

As expected, the discussion of the working groups overlapped significantly. The medical management working group, convened by Prof. Servais, focused on the importance of providing accurate information at the point of diagnosis, including the genetic counselling necessary to enable decision-making regarding future reproductive planning. There was recognition that the limited evidence-base for medical interventions in the early pre-symptomatic phase of DMD prevented prescriptive guidelines regarding therapeutics such as corticosteroid or exon skipping interventions in infancy.

The psychosocial care and education working group facilitated by Dr. Lorentzos, and the allied health group facilitated by Dr Julie Parsons, reflected similar concerns and priorities. A focal point was the impact of non-motor aspects of DMD, including emotional, behavioural, and social development, and the experiences for families that these were under-recognised and undertreated. As such, there was hope that an earlier diagnosis would provide a window of time before motor deficits were significant, to assess and arrange interventions across these non-motor areas. There was also extensive discussion about the grief and adjustment experienced by families and potential mechanisms to address these aspects were presented.

The fourth working group, embedding newborn screening into the clinical care pathway, was facilitated by Dr. Lorentzos and provided opportunity to discuss previous and emerging NBS models including the Welsh and Ohio experiences. Prof. Angus Clarke presented insights gained from Wales, a screening pilot that offered opt-in screening for DMD, in contrast to the mandated model of screening in Ohio. It was evident that appetites for, and expectations of, NBS in DMD varied significantly across international jurisdictions, however, there were several principles pertaining to essential considerations in designing NBS programs that were broadly agreed upon. Approaches for newborn screening are rapidly changing and may include combinations of CK and/or genetic testing and nature of false positives and false negatives will vary depending on the approach and technology. A model of care applicable to newly diagnosed DMD patients, as well as false negatives and positives, should be considered prospectively.

In keeping with the disease stage-based sections of the Lancet guidelines, a model of care was drafted that outlines the important interventions over 3 timepoints: (1) at the time of an early diagnosis, (2) in the infancy stage of a DMD diagnosis, and (3)

in the very early ambulatory stage of DMD. This model was then presented and debated at the four working group meetings and the edited version was then presented at a hybrid meeting in Charleston, South Carolina in October 2023. Modifications were achieved based on the perspectives of participants in the meeting and agreement regarding a first draft framework was reached.

4. Thematic summaries

4.1. Newborn screening

Recommendations for models of NBS programs were outside the scope of this discussion, however, the context was enriched by the perspectives of stakeholders who had been involved in the Wales and Ohio programs. Based on these experiences it was recommended that NBS programs for DMD robustly consider the ethics of consent (i.e. voluntary opt-in and opt-out or mandated screening). The approach to consent will vary significantly depending on the aim, context, and model of the NBS screening program (for example, research pilots of NBS versus state-mandated public programs) in each jurisdiction and requires careful consideration depending on aim, context, and community experiences related to NBS. A clear pathway for managing false positives should be outlined prospectively, relating to patients found positive due to an incorrect blood sample being processed, or false positive results for reasons such a transient hyperCKaemia or alternative diagnosis [19].

It was acknowledged that NBS provides one means of earlier diagnosis, in addition to increased medical education for earlier diagnostic testing and reproductive genetic carrier screening.

Based on previous experiences, the process surrounding the conduct of NBS, particularly in relation to informing a family of a positive screen, is likely to impact their adjustment to the diagnosis. The timing of the communication of the positive result to the family may need to consider both the readiness of the medical model to review and support the family, and the optimal time for the family to receive the diagnosis.

4.2. The power of language

One father generously shared his lived experience of his son with DMD and informed that whilst it is helpful to receive comprehensive information about the serious and life-limiting aspect of this condition, it is not necessary to apply words such as ‘fatal.’ He acknowledged that “life itself was fatal” and that such catastrophic terms could overwhelm or traumatise families during a vulnerable period of adjustment.

There was explicit feedback from families affected by DMD that the language used by clinician to communicate the diagnosis of DMD should balance the severity of the condition without catastrophising. Words such as ‘lethal’ and ‘fatal’ do not acknowledge that boys with DMD are now living until an average of 30 years.

DMD is a life-limiting disease; a disease that boys not only die from, but also live with, many for 3 decades or more. It was suggested that scripts of examples of phrasing, co-designed with partners with lived experience, may be a useful resource for future development.

4.3. Partnership

There was agreement that the initial appointment required building rapport and orientating a family to the clinic. This is a time to communicate the basis of inheritance, considering cascade screening of family members, and introduce the family to the genetic counsellor. Representatives from patient advocacy groups, and family members, recommended that a specific person be nominated as a primary point of contact or ‘face of the neuromuscular clinic’. Depending on the clinic structure, this may be a medical specialist, specialist nurse, clinic manager or social worker. If the diagnosis has been made following NBS, there may also be initial explanation required as to the process of NBS, as, depending on the details of the screening process, parents may not recall consenting or receiving information regarding these programs. The Wales experience involved changing the timing of positive screening disclosure from 2 to 3 weeks (or as soon as the result was available) to 6 weeks due to the experience of one family that appeared to result in significant trauma from the diagnosis [20,21].

The research around this program also developed an approach to consent that emphasized the difference between screening for Duchenne and screening for the other disorders included in the screening panel.

Participants discussed that a multidisciplinary team featuring medical, nursing and allied health, was valuable in delivering holistic care for patients with DMD. At tertiary and quaternary centres, it may be possible to facilitate such teams within the hospital setting as a ‘one-stop shop’; however, in some settings the treating clinician may be linking with providers from local or remote locations.

4.4. Psychological support and counselling

There was robust agreement that psychological support for families and patients was integral to the care of patients with DMD, but that resources and expertise were limited in most centres. Clinicians and families agreed that a diagnosis of DMD was lifechanging for a patient and their family, and that psychological and community support were essential, although the pathways for such support would vary across different health systems. Screening for pre-existent and new psychological concerns in parents and siblings, and accessing social work or psychology where available, were regarded as important. Liaising with primary carers and connecting families to support organisations was also recommended. Drs. Parsons and Clarke, in their psychosocial analysis of the Wales NBS program, found that mothers whose boys were diagnosed with DMD following NBS experienced elevated levels of anxiety; however, this was comparable to the anxiety experienced by mothers whose boys were diagnosed later through the traditional diagnostic pathway [22].

4.5. Medical management

There was discussion as to whether recommendations should be provided regarding commencement of exon skipping drugs and corticosteroids, however, there is insufficient evidence to support a single approach, and access to pharmacotherapies varies across regions according to the FDA, EMA or other regulatory authorities. Evidence to guide decision making in this young cohort was identified as an area of need moving forward. The holistic approach for medical care was promoted with acknowledgement that monitoring growth, nutrition and vitamin D should be commenced in infancy.

An important aspect of medical management was clinical trial readiness. There were strong opinions from individual participants in the workshop that clinical trial recruitment should not alone justify the commencement of NBS, however there was agreement, that clinical trial awareness and the potential to participate in a clinical trial were important aspects of providing support to families and best care to children. This perspective is not new, with Dr. Scheuerbrandt’s account of newborn screening from the 1970s describing letters from families requesting information on scientific

advancements in the field of DMD immediately following a child's positive screen [23].

4.6. Developmental monitoring

Patient advocates and clinicians reported that non-motor aspects of DMD, especially the cognitive, psychological, and behavioural components, have been under-recognized, under-communicated, and under-treated in proportion to the impact of these difficulties. There was extensive discussion as to the role of developmental monitoring and interventions in the early phases of DMD. It was acknowledged that not all boys with DMD will experience developmental problems and the value and feasibility of screening was raised, with recognition that this is resource intensive and there is scarce evidence as to the most appropriate tools for assessments. Parents of young men with DMD commented that the behavioural, emotional, and cognitive aspects of DMD had not been adequately communicated with them. Participants outlined the need to proactively assess for vulnerabilities in terms of emotional, behavioural, and cognitive difficulties, however, the selection of specific assessment tools should be decided by a specialist (developmental paediatrician, neuropsychologist, occupational therapist or physiotherapist) until there are validated forms of assessment specific to DMD in the early stages. It was also acknowledged that the selection of assessment tools benefitted from expertise of the clinician involved such as the neuropsychologist, developmental paediatrician or occupational therapists, who would select tools based on the clinical and cultural context. This is in keeping with previous recommendations from Colvin et al. [24].

The key factor was to ensure consideration of the non-motor comorbidities as a core aspect of the multidisciplinary clinics in a similar way to surveillance of respiratory and orthopaedic complications seen in later years. Early diagnosis provides an opportunity, before the motor deficits become prominent, to address the non-motor aspects of DMD.

5. Recommendations

The following broad recommendations were established as an initial version of a flexible framework to ensure the best model of care to support children and families following early diagnosis of DMD

5.1. Recommendations for the time of diagnosis

Recommended discussion points between the neuromuscular clinician and the family at the time of diagnosis:

Introduce the role of the neuromuscular clinic and establish a partnership.

Nominate a primary person who is the point of contact for the family moving forward (neuromuscular nurse, social-worker, genetic counsellor, clinic nurse, medical practitioner), and create pathways for asking questions or making contact.

Discuss the nature of the diagnosis and the therapeutic landscape (tailored to the specific family and their response to the diagnosis) including the state of research in DMD.

Introduce the family to support groups and useful resources.

Conduct a transparent discussion regarding the seriousness of the condition avoiding catastrophic language such as 'fatal', 'lethal' and 'incurable' as well as focusing on the treatment options of this condition.

Discuss genetic counselling including initiating testing for the family members (consider family's well-being - this can be delayed until the next visit if needed).

Introduce the family to support groups and useful resources, including avenues for seeking psychological support during this period of adjustment

Recommended action points for the clinician at the time of diagnosis:

Review variant and comorbidities, in terms of risk and potential clinical trials and therapies

Carry out initial review of motor, language, social and cognitive development, including considerations based on age, presentation, and feedback from parents.

Arrange another appointment for 3 months later (or earlier if required.) Centers may also offer a phone call within 2 weeks of the initial appointment from social worker, genetic counsellor, clinic nurse or doctor.

Liaise with professionals known to the family and community health care supports (GP, obstetrician, community nurse, psychologist) if required.

5.2. Recommendations for the infancy stage of DMD (prior to 1 year)

Recommended discussion points between the neuromuscular clinician and the family at each appointment for the infancy stage of DMD:

Explain the value of registries and facilitate connection.

Discuss the management of carriers (including referral to cardiac or genetic services).

Discuss indications for developmental assessment and referral.

Introduce options for financial support (i.e. social security, government reimbursement programs) as required.

Recommended action points for the clinician at each appointment for the infancy stage of DMD :

Review familial screening initiated at diagnosis.

Monitor growth, nutrition, and vitamin D.

Consider medical treatment options (including steroids, Ataluren, exon skipping or gene transfer therapy).

Consider clinical trial readiness (i.e. genetic variant, comorbidities, geography, and possibly AAV Ab if applicable).

If there are concerns, arrange for a standardized, holistic developmental assessment if resources are available.

Review the family's psychosocial health following diagnosis. Liaise with the general practitioner or other relevant community practitioners in relation to parental or sibling health; highlight any other psychosocial care pathways that may be available locally/nationally.

5.3. Recommendations the very early ambulatory stage (1–4 years) at each appointment

Recommended discussion points between the neuromuscular clinician and the family at each appointment for the very early ambulatory stage of DMD:

Discuss steroids and other disease modifying treatments with family and observe for indications to commence.

Check-in with the family as to their understanding of the disease and the clinical trials landscape, both generally and specific to their mutation and local regulatory factors

Encourage balanced nutrition and exercise and discuss the importance of this in relation to introduction of steroids.

Encourage families to connect with local therapists (physiotherapist, occupational therapist, speech therapist) as required.

Recommended action points for the clinician at each appointment for for the very early ambulatory stage of DMD:

Review the child and family's psychosocial health regularly. Liaise with GP in relation to parental or sibling health.

Schedule neuromuscular appointments every 3 months until 1 year of age (utilizing telemedicine when appropriate) then every 6 months thereafter.

Monitor growth, nutrition, and vitamin D levels.

Ensure ongoing consideration of clinical trial and therapy readiness (i.e. genetic variant, comorbidities, geography, and possibly AAV Ab if applicable).

Ensure immunizations are up to date.

Review any developmental concerns and refer for assessments as required.

Assess children for psychological or behavioural comorbidities and make appropriate referrals for further evaluation as required.

Arrange regular social work input as required. Provide support to family and assess for social and psychological risk factors.

6. Future directions

An integral aspect to the care following an early diagnosis is effective communication. A strong theme from the workshop was the impact of communication at, and following, diagnosis in the family's adjustment and patient experience. It was recommended that TREAT-NMD collaborate with clinicians and patient organisations to create and implement educational material for this purpose.

Discussions outlined the need for natural history data for young boys with DMD in the early or presymptomatic phases. As we aim to diagnose boys earlier and implement early interventions, natural history data is essential in allowing for evaluation of these interventions. Options to expand existing registries and collaborate with Industry to collect natural history datasets, were raised.

Tools that assess outcomes and severity in DMD, such as the North Star Ambulatory Assessment are not validated or clinically useful in infants and tools that are developmental tools that are validated in infants, are not validated as robust tools for DMD. As clinical trials move to recruit very young cohorts, it is essential that we have ability to measure benefit, or lack of, effectively and efficiently. Measurement tools are not only required across the gross motor domains, but across other parameters that are meaningful to parents, such as behaviour and social development. Work to establish validated, meaningful outcome measurement tools that would be valued by industry and regulatory authorities was regarded as a possible next direction. SV95C- the top velocity of patients in their home environment measured by a wearable device that has been qualified by the EMA as a primary endpoints for infants younger than 4 years- has shown very promising results in terms of reliability and discrimination with healthy controls in ambulant DMD patients as young as 20 months [21].

This workshop initiated important international discussion and recommendations related to a model of care in early DMD, however, more focused recommendations would require a formal consensus process and a Delphi study, with multidisciplinary input including lived experience, would be valuable and informative.

Workshop participants

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Declaration of competing interest

There are no direct conflicts of interest related to this manuscript, however full disclosures are listed below:

Michelle Lorentzos has been an investigator on clinical trials sponsored by Pfizer Sarepta, PTC, Antisense and Dyne and engaged in advisory work by way of participation in Medical Advisory Boards for Roche.

Laurent Servais has given consultancy/is member of the board for Dyne, Entrada, Wave, Pfizer, Santhera, Italfarmaco, Sysnav, RegenexBio & Solid.

Julie Parsons has been an investigator for clinical trials sponsored by Novartis, Biogen, Biohaven, Scholar Rock, PTC Therapeutics and has engaged in advisory work with Novartis, Biogen, Scholar Rock, Pfizer and Genentech.

Kristi Jones has been an investigatory on clinical trials sponsored by PTC, Sarepta, Pfizer

GSK/Biomarin/Prosensa, Dyne, NS Pharma, Wave Life Sciences, Roche and Antisense Therapeutics and has engaged in work by way of speaking engagements to government on behalf of, and advisory boards for Roche, Precision Biosciences, Pfizer Novartis, Wave Life Sciences, Biomarin/Prosensa Biogen and PTC Therapeutics.

CRediT authorship contribution statement

M. Lorentzos: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **JA. Parsons:** Investigation, Methodology, Writing – review & editing. **KJ. Jones:** Investigation, Methodology, Writing – review & editing. **L. Servais:** Investigation, Methodology, Writing – review & editing.

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