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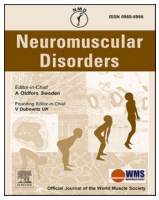

283rd ENMC international workshop: Establishing expert care recommendations for LAMA2-RD: A prototype for the development of congenital muscular dystrophy subtype-specific care guidelines. Hoofddorp, The Netherlands, January 17th-19th 2025

Alberto Andrea Zambon [a], Andrea Klein [b], Anna Sarkozy [c], A. Reghan Foley [d,*], on behalf of the Workshop participants

[a] IRCCS San Raffaele Scientific Institute, Unit of Neurology and Neurophysiology, Milan, Italy
[b] Division of Neuropaediatrics, Development and Rehabilitation, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
[c] Dubowitz Neuromuscular Centre Great Ormond Street Hospital, Institute of Child Health, London, UK
[d] Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

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ABSTRACT

LAMA2-related dystrophies (LAMA2-RDs) are among the most frequent congenital muscular dystrophies, caused by pathogenic variants in the *LAMA2* gene. They typically present in infancy with severe muscle weakness but span a wide clinical spectrum, from neonatal onset to milder, later-onset forms. Complications include respiratory insufficiency, nutritional difficulties, joint contractures, scoliosis, and central nervous system involvement. No specific internationally agreed standards of care (SoC) exist, leading to variability in diagnosis, monitoring, and access to multidisciplinary management and care. The 283rd ENMC International Workshop gathered international stakeholders to review current evidence, suggest expert care recommendations and reach an agreement on the best methods to develop diagnostic and care guidelines for LAMA2-RD. Key outcomes included consensus care recommendations across major clinical domains, strategies for dissemination through a dynamic, open-access resource, and a framework to guide development of SoC for other genetic forms of congenital muscular dystrophies.

1. Introduction and overview of the workshop

On January 17th-19th 2025, a group of 21 scientists and clinicians, along with two patient advocates, and one individual affected by LAMA2-related dystrophy (LAMA2-RD) from 10 different countries, convened in Hoofddorp, The Netherlands. Two patient representatives also contributed remotely.

The aim of this workshop was to define the core elements of expert care recommendations for LAMA2-RD and establish the process for developing clinical care guidelines for the disease, as there are currently no specific clinical guidelines for the care of patients affected by LAMA2-RD or other congenital muscular dystrophies (CMDs).

Care guidelines for CMDs published in 2010 [1] and 2015 [2] covered the CMDs as a disease group, and thus features specific to LAMA2-RD were not addressed. Given promising therapies in preclinical development for LAMA2-RD that may translate into clinical trials within the next few years, there is an urgency to improve clinical trial readiness for this patient population, which relies on: a) an understanding of the disease's natural history, b) the identification and validation of outcome measures and c) the standardisation and optimisation of clinical care.

The first objective of this workshop was to consolidate existing evidence and expertise on the clinical care of individuals affected by LAMA2-RD. Throughout the workshop, care recommendations and suggestions were formulated based on the level of available evidence across various discussed topics. Additionally, gaps in current knowledge were identified, along with potential measures to address them.

A second key objective was to discuss and possibly decide a methodology for establishing clinical guidelines for rare neuromuscular

* Corresponding author at: Dr. A. Reghan Foley, Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
E-mail address: reghan.foley@nih.gov (A.R. Foley).

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conditions such as CMDs in a broader international and global context, serving as a prototype for the development of clinical care guidelines for the other CMD subtypes (e.g., COL6-RDs, LMNA-related CMD, SELENON-RD and α-dystroglycanopathies). In preparation for the workshop, various methodologies were evaluated, with the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach being prioritized. GRADE, adopted by the European Academy of Neurology (EAN) in 2015 for its guidelines, [3] has also been successfully applied to other rare disorders [4–6].

Prior to the workshop, each presenter was instructed to provide an overview of a specific aspect of LAMA2-RD, summarize the existing evidence and strength of current recommendations, share personal expertise, and highlight key gaps in knowledge for each topic, wherever applicable. On the final day of the workshop, in line with the GRADE system, the group collectively outlined potential PICO (Patient/Population, Intervention, Comparison, Outcome) questions, categorized under "diagnosis and prognostication" and "treatment and intervention", and areas for future research. We summarise below the main topics where consensus was reached for each aspect of LAMA2-RD, while others were marked for further investigation and discussion (Supplementary material).

2. Disease overview and diagnosis

Following a welcome from Patricia van Dongen, ENMC representative and director, and the chairpersons of the workshop, Andrea Klein (CHE) gave an overview of LAMA2-RD. The disease, resulting from biallelic pathogenic variants in the *LAMA2* gene, is among the most common CMD, with an estimated prevalence of 8.3 per million. Patients typically present congenitally with facial, axial and proximal upper limb predominant weakness, along with early-onset contractures, scoliosis, and hyperlordosis; less than 10 % of individuals with "CMD" phenotype achieve the ability to walk independently. Milder phenotypes consistent with limb girdle muscular dystrophies (LGMDs) have been observed in childhood and adulthood. Respiratory involvement and difficulties in feeding are important disease-related complications, particularly at the most severe end of the spectrum. Additional features include tongue hypertrophy and ophthalmoplegia. Central nervous system involvement (CNS) is present, including white matter abnormalities (WMA), cortical malformations and pontine hypoplasia, with 30-40 % of patients developing seizures [7].

Although there is ongoing discussion regarding the most appropriate nomenclature to define different subtypes of LAMA2-RD related to their severity (e.g., using maximal motor milestones of sitting vs independent ambulation) or based on muscle biopsy immunohistochemical studies of merosin expression (complete deficiency vs partial deficiency), etc., here we use the pragmatic definition of CMD vs LGMD subtypes of LAMA2-RD. We acknowledge that further discussion regarding the need for harmonisation of nomenclature is needed in view of ongoing natural history studies as well as future clinical trials (Fig. 1).

2.1. The caregiver perspective in LAMA2-RD

Bram Verbrugge (NLD), father of a child with LAMA2-RD and founder of Voor Sara foundation, shared his personal experience, highlighting the challenges faced by caregivers. He described the difficult journey to obtaining a diagnosis, emphasizing the emotional and logistical struggles families encounter due to the rarity of the condition and a lack of immediate clinical expertise. Daily life presents significant obstacles, from managing medical needs to navigating accessibility barriers. Despite these difficulties, he underscored the importance of motivation and resilience, advocating for physical exercise as a key factor in maintaining mobility and well-being in affected individuals. He highlighted that raising awareness and fostering a supportive community are essential for improving care, access to resources, and research efforts. He called for greater collaboration between caregivers, researchers, and medical professionals to enhance the quality of life for individuals with LAMA2-RD and their families. The preliminary results of a survey circulated between the community of patients and caregivers, and workshop participants, were also presented.

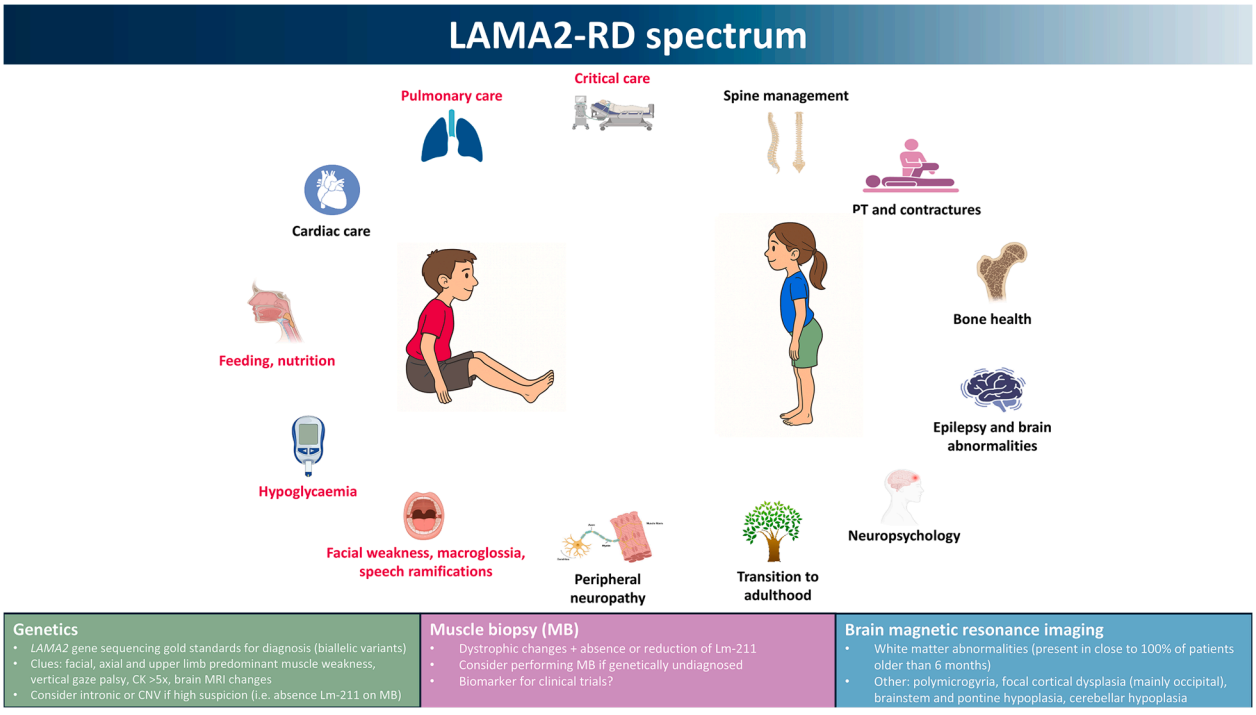

Fig. 1. Infographic illustrating the need for multidisciplinary management across the spectrum of LAMA2-RD. Aspects highlighted in red are particularly relevant for patients presenting at the most severe end of the spectrum.

2.2. Patho-mechanisms, preclinical research and its implications for care management

Stefano Previtali (ITA) introduced the clinical aspects of the LAMA2-RD, emphasizing its multi-organ nature with primary effects on skeletal muscle, peripheral nerves and brain. *LAMA2* mutations disrupt the α2 subunit of the heterotrimeric protein Laminin-211 (Lm-211) which is primarily located in the basal lamina and interacts with various proteins, including α-dystroglycan and integrin α7β1 in muscles, as well as α-dystroglycan, integrin α6β1, and GPR126 in nerves [8,9]. The most commonly used animal models for LAMA2-RD were discussed, highlighting the advantages and limitations of zebrafish and mouse models. The multiple available lama2 deficiency mouse strains represent the range of human disease severities [10], and replicate key findings in muscle, nerve, and brain pathology. In the context of skeletal muscle, the primary cellular and molecular dysfunctions observed in mutant mice include altered regulation of the cell cycle and cell survival, inflammation, extracellular matrix remodelling, and fibrosis [11–14]. Current preclinical therapeutic strategies aimed at reversing these dysfunctions and ameliorating the disease were reviewed [15–19]. Prof. Previtali outlined the major defects in peripheral nerves of lama2 mutants, focusing on impaired axonal sorting and myelination [8,20]. He discussed how these defects can be partially rescued in preclinical models using linker molecules that reconnect Lm-211 receptors to the basal lamina [21], and potentially by normalizing cell cycle progression (Previtali, unpublished results). Finally, he reviewed the brain abnormalities in lama2 mutant mouse models, including blood-brain barrier leakage, dysregulation of aquaporin-4 receptors, microglial activation, and impaired oligodendrocyte precursor survival and maturation. He also highlighted reduced myelination and loss of nerve fibers in the brain [22,23].

2.3. Natural history data of LAMA2-RD

Francina Munell (ESP) provided an overview of current and recently completed natural history studies for LAMA2-RD, [7] which are key to assessing phenotype variability, validating outcome measures, collecting biomarkers, and laying the groundwork for future clinical trials. Additionally, these studies help to develop and disseminate care recommendations. Several retrospective natural history studies have been conducted worldwide, [24–28] with at least six ongoing prospective studies (Switzerland, Netherlands, USA, France, Spain, Italy) [29–32]. All require a confirmed LAMA2-RD diagnosis, typically through two biallelic pathogenic variants in the *LAMA2* gene, or one variant plus supportive evidence [muscle biopsy (MB), brain magnetic resonance imaging (MRI), or compatible phenotype]. Age eligibility varies among studies.

Common outcome measures include changes in motor and pulmonary function. Motor function is assessed using different age-specific scales timed functional tests, dynamometric strength evaluations in some. Pulmonary function is monitored through respiratory tests, ventilatory support data, polysomnography and capnography. Some studies also include muscle imaging (ultrasound and/or quantitative MRI). Additional collected data include nutritional status (feeding mode, growth, swallowing issues), range of motion (goniometry), spinal deformities, bone density (DEXA scan), and plasma/serum samples for biomarker analysis. Some studies incorporate echocardiography, ECG, EMG, brain MRI, EEG, and CK level assessments.

2.3.1. Key agreements

Key priorities include selecting the most informative outcome measures, defining the minimal clinically important difference for each, and promoting data sharing (data federation). Integrating a standard of care questionnaire into natural history studies could further enhance awareness and understanding of LAMA2-RD.

2.4. Diagnostic approach and challenges

Anna Sarkozy (GBR) presented previous national and international recommendations for the diagnosis of LAMA2-RD. It is generally agreed that genetic diagnosis, with identification of pathogenic *LAMA2* gene variant/s, is the gold standard diagnosis for LAMA2-RD, and this should be achieved for all patients, wherever possible. In 2014, a consensus statement summarized international diagnostic recommendations for CMDs, [33] with key clinical features of LAMA2-RD being hypotonia and muscle weakness in early age, raised CK (>5x upper limit of normal), typical brain MRI findings, seizures and deficiency of Lm-211 protein in the muscle fibres and nerves. In 2015, evidence-based guidelines emphasized that MB and brain MRI were recommended (and should be performed in expert centres) if the risks of sedation or anaesthesia were acceptable [2]. With the wider availability of next-generation sequencing (NGS), gene panels, whole-exome (WES), and whole-genome sequencing (WGS) have become first-tier tests for suspected CMD, including LAMA2-RD, often preceding MB [34]. Current multicentric consensus guidelines also recommend prompt genetic testing in hypotonic infants, with additional investigations, including MB, considered if no molecular diagnosis is found [35]. Most LAMA2-RD patients carry coding sequence variants, while copy number variants (CNVs) and deep intronic variants are less common. For patients with proven Lm-211 deficiency, but negative coding sequence results, further *LAMA2* dosage and intronic region analysis is recommended. Improved variant classification and advanced genetic approaches—such as RNA sequencing and long-read (LR) WGS—are expected to increase diagnostic yield, particularly for variants of unknown significance (VUS) [36,37]. However, to date applications of such more advanced molecular techniques remain mainly limited to research settings. RT-PCR on peripheral blood RNA has limited success in assessing *LAMA2* VUS' impact on splicing and may not be a reliable substitute for skeletal muscle analysis [38]. The prevalence of LAMA2-RD in patients with atypical or milder presentations, such as neuropathy, brain malformations, cognitive impairment, or seizures, remains unknown, complicating diagnostic strategies. Agreement on classification and reporting in particular of rare missense variants may help to improve diagnostic ability. Development of international variants' repositories, further implementation of patients' registries and natural history studies will also support better understanding of genotype-phenotype correlations, guide prognostication and help to define a new and more accurate nomenclature for LAMA2-RD.

2.4.1. Key agreements

Genetic testing is the gold standard for diagnosing LAMA2-RD. *LAMA2* full gene sequencing (Sanger or NGS) is the recommended first-tier test, with single-gene sequencing, gene panels, WES, (rapid) WGS all considered valid testing options. Diagnostic testing should be offered in severe/early-onset patients typically presenting with hypotonia, muscle weakness, CK levels >5x the upper limit of normal, brain MRI changes, and ± absence or reduction of Lm-211 on MB, or in mild/later-onset patients with muscle weakness, raised CK levels, brain MRI abnormalities, or with absence or reduction of Lm-211 on MB. Further research is needed to define a stepwise approach in case of negative first-tier testing. Brain MRI and/or MB may also help categorize patients and guide management and outcome. As outlined above, there is an unmet need to agree and harmonise nomenclature to define different subtypes of LAMA2-RD related to disease severity.

3. Cardiac care

Denis Duboc (FRA) provided an overview of cardiac involvement in LAMA2-RD, highlighting its unclear clinical significance compared to other neuromuscular disorders (NMDs). A study of 16 LAMA2-RD patients reported an average ejection fraction (EF) of 43 %, with two of these with EF 40 % [39]. Seven out of 20 patients in one series, [40], and

7/42 in another, [24], had ECG or echocardiogram abnormalities, including right bundle branch block, dilated cardiomyopathy and borderline cardiac function changes. Importantly, cardiac involvement might be more prominent after the third decade [41–44]. While Q-wave abnormalities and QRS fragmentation resemble patterns in other muscular dystrophies, they do not necessarily indicate cardiac involvement, underscoring the need for systematic monitoring and tailored management [45,46]. Existing recommendations provide a strong foundation but require refinement for LAMA2-RD [1]. While routine ECG and echocardiography are recommended, they may not be sufficient for prognosis. Strain rate evaluation via echocardiography or MRI was proposed for detecting early myocardial degeneration, though variability remains a challenge. Prof. Duboc emphasized the importance of early detection and preventive treatment to improve outcomes. However, individualized decisions are necessary, as no universal protocol exists for LAMA2-RD. Pharmacological approaches include in particular beta-blockers and ACE inhibitors, but aldosterone inhibitors (e.g., eplerenone) and sodium-glucose cotransporter-2 (SGLT2) inhibitors can also be considered as potential therapeutic options, although further evaluation is needed. Several critical gaps in knowledge regarding cardiac involvement in LAMA2-RD include the timing, methods and rationale for cardiac screening and treatment.

3.1. Key agreements

The group agreed that annual cardiac assessment, including ECG, echocardiography, and Holter ECG, should be standard practice for LAMA2-RD patients. Further research is needed to establish the frequency of investigations according to individual risk, and the need for 2nd tier tests, such as cardiac MRI. Early pharmacological intervention with ACE inhibitors, beta-blockers, and potentially aldosterone inhibitors may be considered to help manage cardiac involvement in LAMA2-RD. There is no current evidence to justify preventive treatment. Longitudinal studies are needed to optimize screening, refine treatment strategies, and assess advanced cardiac interventions in LAMA2-RD, as well as to define the long-term effect of treatments. In view of concerns over reports of sudden unexplained deaths in LAMA2-RD patients, the participants agreed to perform a multicenter data collection to clarify possible risk factors and inform future guidelines.

4. Pulmonary care

4.1. Overview of respiratory care in LAMA2-RD

Hemant Sawnani (USA) provided an overview of the respiratory care in LAMA2-RD. Respiratory status in the LAMA2-RD can be complicated by failure to thrive, dysphagia, and scoliosis, usually in, but not exclusive of, CMD patients. Repeated respiratory infections, irritability, tachypnoea or paradoxical respiration may be the primary presentation of respiratory involvement in this subgroup [47,48]. The 2010 CMD consensus statement focused on the primary goals of secretion-clearance and assisted ventilation [1]. The statement supports the use of assisted cough techniques to promote secretion clearance, listed sleep-related polysomnography (PSG) findings that could support initiation of non-invasive ventilation (NIV), and tracheostomy considerations. The 2015 evidence-based guideline summary recommended the use of pulmonary function tests (PFTs) and oxygen saturation monitoring while awake and asleep, and supported referrals to local aerodigestive teams for additional evaluations [2]. Specific features to LAMA2-RD are the development of global contractures that drive the restrictive chest wall physiology in older children and adolescents. PFTs can be difficult to perform due to open bite and macroglossia, both prevalent in LAMA2-RD. Cough strength is weaker, and patients are at risk for aspiration and atelectasis. Finally, the combination of macroglossia, neck rigidity and mid-face hypoplasia presents the need for fibreoptic endotracheal intubation in the setting of elective procedures.

Federica Trucco (ITA) reviewed sleep disordered breathing (SDB) in LAMA2-RD. Restrictive thoracic defect shows high variability in PFTs, and its severity correlates with scoliosis and motor function impairments. While intercostal respiratory muscles are impaired, the diaphragm remains relatively spared, as indicated by the absence of significant drop in % predicted forced vital capacity (FVC %) from upright to supine, diaphragmatic ultrasound and dynamic breathing MRI (personal data from Dr. A. R. Foley). Natural history studies have described respiratory progression, [24], with respiratory symptoms present at disease onset in 10–20 % of LAMA2-CMD patients. Two critical periods of respiratory decline have been identified: the first, mainly in LAMA2-CMD, at around 24 months, often requiring NIV support during respiratory infections. The second involves a gradual progression of respiratory impairment over time. NIV use was reported in 30–48 % of patients at a median age of ~12 years, although details on the specific indications for initiation of NIV were lacking. In addition to the generic CMD guidelines cited above, recommendations on the respiratory and sleep care, as well as indications for NIV, are provided in two main reports [1,49]. In young children with LAMA2-RD the presence of failure to thrive and recurrent respiratory infections should prompt respiratory evaluation. Respiratory and sleep assessment should be conducted at the time of disease diagnosis and at least annually, and more frequently if SDB is suspected. Irrespective of the type of sleep assessment, the monitoring of CO_2 should be included. Dr. Trucco also presented the results of a survey conducted across Italian centres involved in a multicentre LAMA2-RD study, highlighting high heterogeneity in the diagnosis of SDB and in the criteria for initiating and monitoring NIV.

Susana Quijano-Roy (FRA) presented the rationale of daily hyperinsufflation as a technique to enhance lung volume recruitment and to promote thoracic growth in patients with LAMA2-RD. In CMDs, limb and axial joint contractures develop early due to weakness in paraspinal and intercostal muscles, leading to reduced spine and chest wall mobility and growth, and reduced lung compliance. In LAMA2-RD, diffuse respiratory muscle involvement increases the risk of respiratory failure due to fatigue, particularly during REM sleep, or metabolic stress. The first eight years of life are crucial for pulmonary development, [50], and impaired lung and thoracic volume growth contributes to progressive restrictive respiratory insufficiency. Additionally, spinal deformities (notably thoracic lordosis) are common in LAMA2-RD and further exacerbate respiratory dysfunction. Positive pressure devices, including intermittent positive pressure breathing, insufflators, cough assist devices, and BiPAP, may help counteract chest wall stiffness, promote thoraco-pulmonary growth, and improve perioperative and brace tolerance, although supporting evidence is limited. The 2010 consensus recommended early NIV and in-exsufflators for airway clearance and chest growth [6], but a 2020 study with in-exsufflators reported low adherence rates and uncertain long-term efficacy in CMDs, including LAMA2-RD [51]. Recent studies from France suggest that insufflators improve lung volumes and chest wall compliance more effectively than in-exsufflators [52,53]. Insufflators are the preferred technique to manage respiratory health promotion in early onset NMDs among paediatric pulmonologists in France, [54], yet standardized protocols and clinical studies defining their indications and efficacy in LAMA2-RD are lacking [55]. In sharing her experience, Prof. Quijano-Roy observed that daily hyperinsufflation treatment in LAMA2-RD patients was associated with preserving vital capacity and reducing the need for invasive ventilation. A rapid FVC decline with obstructive pattern on PFTs may indicate airway compression from lordotic thoracic spine deformity, warranting serial X-rays (lateral views) and tomography to monitor onset and progression, and indicate spinal surgery in case of airway compression by vertebral bodies.

Gaps in respiratory knowledge include particularly how pulmonary function evolves with growth, and the identification of surrogate markers of respiratory health to guide interventions. There is limited data on the prevalence and characteristics of SDB and nocturnal

hypoventilation, as well as how LAMA2-RD-specific comorbidities—such as thoracic restriction, macroglossia, and facial weakness—affect NIV strategies, initiation, and monitoring. Further research is needed to define clear criteria for initiating NIV, establish ventilator support titration principles, and evaluate the feasibility of diaphragmatic and intercostal muscle ultrasound for assessing muscle function and fibroadipose replacement.

4.1.1. Key agreements

The group reached consensus on the importance of early assessment of restrictive chest wall deformities and hypoventilation. Timely NIV initiation is recommended, and previous guidelines suggest PSG evaluation at diagnosis and then every 12–18 months, with PFTs conducted at least annually. Sleep and ventilation assessments should be performed more frequently in case of clinical symptoms, and restrictive (stiff) chest wall physiology should lower the threshold to do so. As spinal deformities may contribute to airway compression, comprehensive presurgical preparation and management (including NIV initiation) is recommended to minimize procedural risks. Despite limited but positive data, the benefits of lung volume recruitment and daily hyperinsufflation therapy should be emphasized. In-exsufflators are recommended for secretion clearance, while intrapulmonary percussive devices should not be used routinely. Universal immunization against pneumococcal, influenza, and COVID-19 infections is strongly recommended, with monoclonal RSV antibody treatment being made available for eligible patients. There was general agreement on the need for pulmonary care guidelines, particularly for surgery preparation and extubation protocols. The group emphasized the urgent need to better characterize SDB in LAMA2-RD, including its prevalence, onset, severity, and nocturnal hypoventilation, and to establish a minimum core set of assessments for determining NIV requirements [56]. When considering NIV, ventilator support may be set to either volume or pressure-targeted modes, yet there is no clear consensus on the incorporation of a physiologic respiratory rate and inspiratory time, an area where further clarification is needed. Mouthpiece ventilation can be introduced when mask ventilation extends from overnight to daytime use.

5. Critical care

Fabrizio Chiusolo (ITA) presented on the topic of critical care, tracheostomy and perioperative management. Respiratory failure is the leading cause of morbidity and mortality in LAMA2-RD, in particular within the first two years of life in the CMD form. Patients frequently require hospitalization due to dysphagia, malnutrition, and breathing-swallowing coordination difficulties, increasing the risk of critical care admission and mortality [24,25,57]. NIV is the first-line treatment for respiratory distress, with BiPAP as the preferred mode, particularly in the LAMA2-RD phenotype of a maximal motor milestone of sitting. While new-generation interfaces have improved patient tolerance and skin protection, challenges such as facial distortion and maxillary hypoplasia remain. Invasive mechanical ventilation (IMV) is necessary when secretion clearance fails and airway protection is lost. IMV should be minimized to prevent ventilator-induced lung injury and diaphragm dysfunction, as preserving diaphragm function is critical. Planned post-extubation NIV is widely recommended to reduce extubation failure. Prolonged invasive ventilation and tracheostomy are rarely indicated, with tracheostomy being performed when facial abnormalities do not allow for correct NIV management, when the patient develops intolerance to NIV, or at the request of caregivers or parents [1,7,24]. Despite these measures, perioperative complications such as respiratory instability, prolonged recovery, and difficulties with pain management are common. A multidisciplinary (MDT) perioperative approach, incorporating pre- and post-operative NIV, secretion clearance, and nutritional optimization, has been shown to reduce PICU stays and improve outcomes. Current CMD guidelines emphasize secretion clearance and assisted ventilation as primary goals. Continuous monitoring of SpO2, CO2 levels, arterial blood gases, and diaphragm dynamics is essential to track disease progression and guide interventions [1]. Despite the severity of respiratory involvement in LAMA2-RD, data on emergency and PICU management are scarce. IMV and tracheostomy are infrequent but significant interventions and best practices for acute respiratory care remain unclear.

5.1. Key agreements

The group agreed that NIV should be the first-line respiratory intervention and BiPAP the preferred mode in acute/critical care setting. IMV should be minimized and, when needed, used for the shortest duration feasible, with planned post-extubation NIV to reduce weaning failure [58,59]. An MDT perioperative approach integrating pre/post-operative NIV, secretion clearance, and nutritional support is crucial for optimizing recovery and reducing PICU stays. Experts recommended proactive home and acute care strategies, including a 24-hour on-call system and patient-specific identification cards to facilitate timely interventions, avoid high-flow nasal therapy, and prioritize early NIV in emergencies. Significant research gaps remain in acute and perioperative care, requiring observational studies to improve respiratory failure management and establish evidence-based guidelines for LAMA2-RD.

6. Orthopaedic, physical therapy (PT) and motor assessments

6.1. Management of scoliosis

Mr. Athanasios I. Tsirikos (GBR) presented on the natural history of spinal deformity in patients with NMDs and in particular in CMDs, including LAMA2-RD. He highlighted the prognosis of spinal deformity in these conditions and the principles of conservative and surgical therapies. Recommendations for spine management and monitoring in CMDs are mentioned in Wang et al. [1]. The 2015 statement review identified one Class III study of spinal fusion that demonstrated correction and prevention of progression of scoliosis and pelvic obliquity over 2 years, with unclear effects on respiratory function [2]. Mr. Tsirikos provided further recommendations based on his experience. Early spinal care is essential to preserve mobility and prevent contractures and this should include active movement, hydrotherapy and passive stretching. Postural management through customized spinal braces and wheelchair adaptations can improve seating balance, but respiratory function must be monitored to ensure braces do not restrict breathing. Children with LAMA2-RD are at high risk for scoliosis, often with increased lordosis that can extend from the lumbar spine to the thoracic and occasionally the cervical spine. Of note, thoracic lordosis causing airway compression and obstructive lung disease could further complicate the restrictive lung disease frequently observed in LAMA2-RD [60]. Initially, spine deformity is flexible and postural, but progressively becomes rigid and structural.

Spinal surgery should be delayed when possible until puberty to preserve growth of the spine and chest development, allowing for a single-stage posterior correction and fusion, while reducing the need for multiple high-risk procedures. If early surgical intervention is required due to early onset rapidly progressing deformity, growth-preserving techniques such as traditional growing rods or the bipolar technique can be considered, though these carry risks of implant failure, infections, and repeat surgeries. Surgical decisions should be individualized, weighing risks against functional benefits rather than relying solely on radiographic progression. Considerations include pain, respiratory compromise, and mobility limitations.

Preoperative preparation involves an MDT to assess and optimize nutrition, respiratory function, and overall stability [61]. Gastrostomy or nasogastric/nasojejunal feeding tubes may be needed for nutritional support, while NIV initiation can help facilitate postoperative

extubation. Anaesthetic precautions include fibreoptic intubation, central IV access, and blood product availability to manage anticipated high intraoperative blood loss. Surgical techniques should minimize blood loss and operative time, ideally performed by two attending surgeons for safety. Segmental spinal instrumentation ensures stability, while fusion typically extends from the upper thoracic to the lower lumbar spine, sparing the sacrum when possible to maintain distal spinal flexibility. Postoperatively, early extubation to NIV, mobilization, respiratory therapy, and nutritional support are essential for recovery. Close monitoring is necessary due to high risks of wound infection, non-union, and reoperation. Surgical success should be evaluated based on patient-reported functional and quality-of-life improvements, rather than radiographic curve correction alone. There are no studies comparing the effectiveness of different surgical procedures, investigating the potential for hip contractures release to prevent the development of lordosis, and studying the consequences of neck hyper lordosis observed in LAMA2-CMD patients. Moreover, there is limited data regarding the management of bone-related treatments (i.e. bisphosphonates) in the months preceding and following surgery, particularly in osteoporotic patients.

6.1.1. Key agreements

The participants agreed that spinal deformity is a key feature of LAMA2-RD, particularly in the CMD phenotype, although it can also affect milder forms as well. Rapid progression is possible within the first decade of life, often leading to respiratory complications [24]. Lumbar and neck hyperlordosis are important features of LAMA2-RD. While postural management can enhance quality of life, its effectiveness in preventing scoliosis progression is limited. MDT involvement is essential for surgical planning, with a consensus that surgery should be delayed whenever feasible. Based on personal experience, Mr. Tsirikos does not recommend magnetic rods for NMDs, whereas growing rods are considered a more suitable option.

6.2. Physical therapy and functional outcome measures in LAMA2-RD

Lindsay Alfano (USA) presented on the topics of physical therapy (PT) care and motor assessments in the context of LAMA2-RD. Dr. Alfano summarised evidence of PT care available in the literature for NMD patients, that it should be supportive, goal-oriented and meaningful to the patient and family. PT intervention, bracing, specialized equipment prescription, and other recommendations can be made to optimize patient's independence and participation; however, these recommendations should be individualized to the patient and family needs in specific age ranges or stages of disease. Children and adults with LAMA2-RD can present with a wide-range of abilities and needs, and thus generalized recommendations will reduce applicability to individual patients. These differences underline the need for tailored therapeutic approaches. Available research on motor outcome assessments in patients with LAMA2-RD was presented, including previous prospective studies that explored strength, range of motion, patient-reported outcomes, and the motor assessments in patients 5 years and older. Dr Alfano examined the utility of types of outcomes including uses for diagnostic decision-making versus ongoing measurement to proactively inform clinical care recommendations.

Knowledge gaps in this field include LAMA2-RD-specific PT, exercise/activity, and contractures management. While early natural history studies have begun to critically evaluate available outcomes for use to quantify meaningful function in patients with LAMA2-RD, a thorough comparison of the validity, reliability, sensitivity, and meaningful change in optimal clinical outcome assessment and/or development of novel tools is warranted to achieve clinical trial readiness.

6.2.1. Key agreements

The goal of PT and rehabilitation in LAMA2-RD is to optimize functional independence and participation across all ages. Recommendations should align with the International Classification of Functioning, Disability and Health (ICF) framework, be goal-oriented, and reflect patient and family priorities. While PT and rehabilitation provide supportive benefits, there is no clear evidence of improvement in function or range of motion (ROM), including scoliosis progression. Key questions remain about which clinical measures should guide care, such as strength, ROM, gross and fine motor function, or patient-reported outcomes (pain, fatigue, activity levels, etc.). Further research is needed to determine when, how, and in which subpopulations PT should be recommended. This includes early intervention for development, targeted exercise to maintain or enhance function, active/passive stretching, bracing, serial casting, or standers to preserve ROM and bone health. Additionally, guidance is needed on seating, wheelchair use, and adaptive equipment to support mobility and independence.

6.3. Bone strength in LAMA2-RD

Nicol Voermans (NLD) presented on bone health in LAMA2-RD, a critical management aspect for paediatric and adult NMD patients, as it can be compromised by various pathophysiological mechanisms. These include impaired bone-muscle "cross-talk," reduced biomechanical loading, nutritional deficiencies, insufficient weight-bearing physical activity, muscle weakness or immobility, and the effects of drug treatments. Furthermore, long bone fractures (LBFs) can negatively influence functional prognosis, quality of life and survival [62].

The consensus statement on standard of care for CMDs (2010) underscored the importance of nutritional status and physical activity for optimal bone care, but did not include specific recommendations [1], and the evidence-based guideline summary for CMDs (2015) did not include any recommendations on bone health [2].

The 274th ENMC (2024) workshop focused on optimizing bone strength in NMDs in general [63]. Apart from Duchenne muscular dystrophy, guidelines for the evaluation and management of bone strength in other hereditary NMDs is limited, supporting the need for greater understanding of the factors influencing the development and maintenance of bone strength in these conditions as well.

A recent scoping review on bone health in congenital myopathies identified 37 % (93/244) of patients with reduced bone health, with 24 % with congenital LBFs and (fragility) and 10 % with LBFs later in life [64]. The ongoing prospective Dutch national history study has assessed bone health in 21 patients with LAMA2-RD, looking at fracture history and bone quality assessment through dual energy Xray absorptiometry scan (DEXA-scan) and/or bone health index. Seventy percent (children) and 100 % (adults) showed low bone density of the femur, and 14 % (children) and 33 % (adults) of the lumbar spine. Eight (38 %) patients had a history of fragility LBFs. During the one-year follow-up period, one patient (female, age 3 years) experienced a fragility LBF. No difference was found in bone mineral density between baseline and one-year follow-up [62]. Management to enhance bone health was initiated in collaboration with (paediatric) endocrinologists.

6.3.1. Key agreements

Participants agreed that until more evidence is available, the 274th ENMC workshop provides useful recommendations on bone health for LAMA2-RD [63]. The patient's clinical context and disease milestones (particularly ambulatory status) are key for bone health promotion. Longitudinal skeletal phenotyping is also helpful to understand the individual's bone health trajectory. Time to initiate bone health monitoring, indication and type of therapy, and duration of clinical follow-up are not defined for most NMDs, including LAMA2-RD. It was recommended to initiate bone health monitoring at least when patients become non-ambulant. Bisphosphonates seem efficacious as first-line therapy in bone fragility treatment in NMDs, but further research is needed. A bone endocrinologist should be involved in the care of patients.

7. Mouth, facial weakness, enlarged tongue, speech ramifications

Two affected individuals with LAMA2-RD shared (via pre-recorded videos) how tongue enlargement and facial weakness have impacted their quality of life and ability to communicate, and how this particular disease aspect has the potential to create stigma. Ilse de Laat (NLD) then presented on mouth/facial weakness/enlarged tongue/speech ramifications in the context of LAMA2-RD.

Facial weakness in patients with LAMA2-RD is common and can significantly impact oral function, such as speaking and swallowing. Macroglossia [65], observed in patients with LAMA2- CMD phenotype, further affects a patient's ability to speak and swallow. Both facial weakness and macroglossia can contribute to articulation difficulties and limited facial expression. Articulation difficulties may also result from oral motor muscle weakness, hypophonia, hypernasality, abnormal oral structures, mid facial hypoplasia due to prolonged NIV use, breath control difficulties, and presence of tracheostomy. Taken together, facial weakness and macroglossia can severely impact not only physical function including breathing and feeding, but social interaction as well, [66], leading to communication difficulties. Early interventions with speech therapy are therefore important [67].

The CMD consensus statements lack recommendations on this topic, while the congenital myopathies consensus [68] suggested referral to a speech and language therapist for compensatory strategies (articulation and breath training, oral motor therapy), alternative communication methods, and consultation with an oral surgeon or ENT specialist if needed. No consensus has been reached on macroglossia treatment, and available data in LAMA2-RD is limited to a case report [69]. Treatment options include speech therapy, surgery (considered in <10 % of cases typically when there is a significant mandibular protrusion and/or open bite) [65], and orthodontics.

7.1. Key agreements

Participants agreed on the importance of an MDT approach involving speech therapists, oral surgeons, ENT specialists, dentists, and psychologists, and recommended speech therapy for LAMA2-RD patients. Surgery for macroglossia is not currently advised due to high risks and insufficient available evidence. More research is needed on speech impairments, macroglossia treatment, and their impact, and natural history studies should include speech impairment and macroglossia assessments with standardized methods in particular for tongue size.

8. Feeding and nutrition

8.1. Feeding/nutrition in LAMA2-RD

Reghan Foley (USA) presented on the topic of feeding and nutrition in LAMA2-RDs. Nutritional management is crucial at all stages of LAMA2-RD, yet optimal strategies remain unclear. Studies from the UK, Switzerland, China, and Qatar highlight significant weight concerns among patients with the LAMA2-CMD phenotype, with over 50 % experiencing low weight (below the 5th percentile for age) and chewing difficulties. Indications for enteral feeding (nasogastric or gastrostomy tubes) vary internationally, underscoring the need for standardized guidelines [24,25,28,29,70]. A key objective of clinical recommendations is to optimize nutritional status across all ages and disease stages. However, the ideal timing for gastrostomy tube placement remains uncertain.

The 2010 consensus statement on CMD standards of care indicates that in the setting of poor feeding "If symptomatic management is insufficient, the use of tube feeding has to be considered" [1]. This consensus statement also highlights that in general, patients with CMDs typically have a growth curve below what is expected for their age and that evidence of stagnation in growth would prompt evaluation for an intervention. The 2015 evidence-based guidelines summary for CMDs [2] outlines that given the absence of guidelines specific to CMD that recommendations are based on evidence from other NMDs, including the overall general recommendation that an MDT "should recommend gastrostomy placement with or without fundoplication in the appropriate circumstances."

While malocclusion, macroglossia and slow chewing contribute to decreased caloric intake and thus poor weight gain, low appetite and early satiety may be important factors which are not fully recognized and understood. For many LAMA2-CMD patients, the decision about gastrostomy tube placement is prompted by plans for an upcoming scoliosis surgery and the goal of maximizing nutritional status for optimizing recovery. Anecdotally, episodes of hypoglycemia, which can be frequent and severe in young LAMA2-RD patients with the CMD subtype, seem to improve following gastrostomy tube placement.

Dr. Foley highlighted that gaps in knowledge include whether the underlying disease process in LAMA2-RD affects metabolism and whether these effects are dynamic/change during different stages of disease. Furthermore, it remains unclear which measurement may best reflect overall nutritional status in patients with LAMA2-RD. Body mass index (BMI) cannot be reliably estimated given that the calculation of BMI relies on an accurate height measurement, which is challenging in the LAMA2-RD due to joint contractures. For patients older than age 5 years, ulnar length can be measured and used to estimate standing height. Equations for estimating height for children less than 5 years of age are complex and are more typically used in intensive care units [71]. Lean body mass can be estimated from DEXA scanning; however, the frequency of its use is more limited given patient contractures as well as radiation exposure [72].

8.1.1. Key agreements

The group agreed that nutritional management must be prioritized in LAMA2-RD, with early gastrostomy placement considered when growth stagnation and hypoglycaemia episodes occur, or to support perioperative recovery. While mechanical difficulties contribute to poor caloric intake, metabolic factors remain poorly understood and require further study. The standardization of nutritional assessment tools is essential. Future research should explore metabolic changes in LAMA2-RD and their impact on disease progression and treatment strategies.

8.2. Hypoglycaemia in LAMA2-RD

Clara Gontijo Camelo (BRA) presented on hypoglycaemia in the context of LAMA2-RD. Two key studies highlighted the higher risk of developing hypoglycaemia in the LAMA2-RD, particularly those younger than 10 years, with low body weight, inability to walk independently and dysphagia [73,74]. The underlying cause of hypoglycaemia is still unknown, but appears to be linked to reduced muscle mass and atrophy, which limit glycogen storage. As a result, fasting periods and situations of increased metabolic demand (e.g., during illness or after major surgery) pose an increased risk of hypoglycaemia [75].

There is no existing consensus regarding the care of hypoglycaemia, as signs and symptoms (such as lethargy/sleepiness, nausea/vomiting, and symptomatic epileptic seizures) are nonspecific and must be actively assessed during medical consultations. It is also crucial to differentiate hypoglycaemia from epileptic seizures. Risk factors include severe motor impairment, dependence on NIV, lower Neuromuscular Disease Swallowing Status Scale (NDSSS) scores, and presence of two loss-of-function *LAMA2* gene variants.

8.2.1. Key agreements

The working group identified several knowledge gaps, including need to identify specific risk factors for hypoglycaemia episodes, effective treatments to prevent these episodes, and the underlying pathophysiological mechanisms that make hypoglycaemia more prominent in

LAMA2-RD [76,77]. The group agreed that LAMA2-RD patients, particularly those who are non-ambulant, younger, without gastrostomy tubes, or with lower weight, are at an increased risk of hypoglycaemic episodes. Testing for hypoglycaemia is recommended when symptoms such as lethargy, vomiting, or nausea occur, especially after fasting, during illness, or following major surgery. In cases of hypoglycaemia, management should include nutritional guidance with recommendations on meal frequency and strategies to prevent prolonged fasting. Specific protocols should be in place to address hypoglycaemia during periods of illness, metabolic stress, or surgery, ensuring that patients receive appropriate intervention. A thorough evaluation by a nutritionist and an endocrinologist is advised to tailor management to individual needs. When necessary, the use of nasogastric tubes or gastrostomy should be considered to provide adequate nutritional support and help to prevent further hypoglycaemic episodes.

9. Central and peripheral nervous systems involvement

9.1. Brain/seizures in LAMA2-RD

Daniel Natera-de Benito (ESP) presented on the neurological manifestations, epilepsy, and cognitive impairment in LAMA2-RD. Neurological complications in LAMA2-RD extend beyond motor impairment, with cortical malformations, epilepsy, and cognitive difficulties reported, which do not correlate with muscular phenotype. An abnormal appearance of the white matter is the most common brain MRI finding, detectable from six months of age, sometimes as early as one month. Some patients present with polymicrogyria, focal cortical dysplasia (mainly occipital), brainstem hypoplasia, or cerebellar hypoplasia [22,29]. Although prevalence estimates range from 9.5 % to 36 %, epilepsy likely occurs in around one-third of patients across the lifespan, with variable presentations, including absence, generalized, and focal seizures (e.g., visual and autonomic symptoms with vomiting). EEGs often reveal occipital and temporo-occipital epileptiform abnormalities, correlating with seizure localization. Focal-onset seizures (with or without impaired awareness) are most frequent, although bilateral tonic-clonic seizures, atypical absences, and epileptic spasms also occur. Some generalized seizures described in past literature may actually be secondarily generalized focal seizures [78]. While cortical malformations increase epilepsy risk, they are not clearly linked to motor severity or Lm-211 expression. Their causes and reason for posterior localization remain unknown.

While existing CMD guidelines address brain malformations and associated challenges such as intellectual disability, seizures, and behavioural issues, they lack specificity for LAMA2-RD [1].

In a Spanish cohort (Hospital Sant Joan de Déu, Barcelona) using 3T MRI scanners and epilepsy protocols, over 50 % of LAMA2-RD patients exhibited polymicrogyria-like malformations, particularly in occipital and mesial temporal regions. Similar findings were reported in Switzerland (58 %) [29], but lower frequencies were noted in British, Brazilian, and Chinese cohorts (20 %) [24,25,27].

Despite a lack of standardized guidelines, Dr. Natera showed that in a series of individuals with LAMA2-RD and epilepsy, more than half were responsive to antiepileptic drugs, while some were drug-resistant. In this cohort, valproic acid was frequently used as a first-line treatment; however, it remains unclear whether other medications could be equally or more effective [78].

The true prevalence of cortical malformations in LAMA2-RD remains uncertain due to variability across studies. Similarly, epilepsy prevalence is inconsistently reported, complicating estimates. Additionally, the mechanisms driving cortical malformations and their posterior localization remain unclear, as does their potential impact on cognitive function and seizure risk.

9.1.1. Key agreements

The group emphasized the need for 3T brain MRIs in LAMA2-RD to better assess cortical malformations and epilepsy risk, when available. Long-term studies should clarify epilepsy prevalence, seizure types, and treatment responses. Developing consensus guidelines for epilepsy and cognitive management, including early diagnosis and tailored interventions, is a priority. Further research should explore cortical malformation mechanisms and clinical impact.

9.2. Neuropsychology in LAMA2-RD

Andrea Klein (CHE) presented on cognitive function in LAMA2-RD. Studies investigating cognitive function of patients with LAMA2-RD are limited, and there is a lack of longitudinal data to illustrate the trajectory of cognitive development. A large range of cognitive function is reported in LAMA2 [29,79], larger than in other NMDs. While correlation of cognitive function with cortical malformation, cerebellum or brainstem involvement is unclear, cognitive issues seem to be more prevalent in patients with epilepsy and brain malformations [24,27,80]. Difficulties in subdomains with normal IQ have also been described [81].

The goal of neuropsychological testing is to define the cognitive profile, with strengths and weaknesses, including attention deficits and executive function to understand and manage cognitive potential and guide individualized educational and vocational plans. Neurocognitive examinations should have predefined aims. For patients in mainstream schools, the aim should be to avoid over challenging, adapt mainstream school material to the individual patient's needs and cognitive profile. For children in special needs schools, the aim should be to avoid under challenging and to tailor cognitive therapies to the cognitive potential.

Previous consensus, also in light of the high prevalence of cognitive impairment and/or learning issues in CMDs [2], generically recommended cognitive testing when cognitive issues were present. Additionally, psychologist referral is warranted in case of concerns regarding mood, behaviour, or other psychiatric issues [1]. Prof. Klein's experience is that neuropsychological testing should be arranged before or at school entry, as difficulties may not be reported by parents or teachers in questionnaires. Neuropsychological tests may show reduced attention span and executive dysfunction, which may result in an underestimation of cognitive abilities. For children in mainstream schools, special awareness should be placed on attention difficulties.

There is limited knowledge about the range of cognitive abilities in LAMA2-RD and their relationship with brain malformations, as well as epilepsy, seizure control, and medication effects, which should be further explored in larger cohorts. In the literature, screening tests are commonly used to diagnose intellectual disabilities, but these should be followed by full neuropsychological assessments. Additionally, cognitive profiles of patients with normal intelligence remain poorly documented. Another key area is illness perception and coping, which should be investigated across the spectrum of LAMA2-RD to better understand psychosocial adaptation.

9.2.1. Key agreements

Workshop participants agreed that a neurocognitive assessment is necessary in case of concerns regarding school performance or at onset of seizures. A neuropsychological test before starting school is suggested to avoid over or under stimulation. Special attention should be given to attention and to executive functions. Multidisciplinary teams of neurologists, neuropsychologists, and educators should ensure comprehensive medical, educational, and social support.

9.3. Peripheral neuropathy in LAMA2-RD

Alberto A. Zambon (ITA) presented on the topic of peripheral neuropathy in LAMA2-RD. Laminins, including Lm-211, play a crucial role in Schwann cell-axon interactions, influencing myelin formation, axonal sorting, and nerve regeneration. In LAMA2-RD, defects in Lm-211 may impair myelination and axonal support, contributing to the development of peripheral neuropathy [20,82]. Neuropathy can be detected as

early as 1–6 months of age and is not related to muscular phenotype. Electroneurography (ENG) and electromyography (EMG) usually indicate mild-to-moderate sensory-motor demyelinating neuropathy, with reduced conduction velocity and lower compound muscle action potential amplitudes, suggesting both demyelinating and axonal components. Histological studies show reduced myelinated fiber count, focal myelin thickening, thinner and uncompacted myelin, shorter internodes, and wider nodes of Ranvier. However, demyelination and onion bulb formations have been observed only in proximal nerve roots. Unlike in LAMA2-RD animal models, where defective axonal sorting is a key feature, no direct evidence of axonal sorting defects has been observed in human patients, maybe due to limited nerve biopsy data. Of note, experimental studies provide evidence that neuropathy can become clinically meaningful in mice when skeletal muscle are selectively targeted by new treatments [18,21].

Previous consensus guidelines do not cover this topic, and the true prevalence of peripheral neuropathy in LAMA2-RD remains unknown, as this has been variably reported in large case series [24,82–84]. It is also unclear whether neuropathy significantly impacts the overall disease phenotype or if its contribution to morbidity increases over time. The lack of systematic studies limits understanding of whether autonomic nervous system involvement occurs in LAMA2-RD.

9.3.1. Key agreements

The group agreed that peripheral nerve involvement in LAMA2-RD requires further study and that routine ENG/EMG is not justified for all patients at this stage. Research should clarify neuropathy prevalence, progression, and impact, especially in milder or later-onset cases. While mild-to-moderate sensory-motor neuropathy is documented, its clinical significance remains unclear.

10. Transition to adulthood

Ulrike Schara-Schmidt (GER) presented on the topic of transitioning of care from paediatric to adult care teams, a critical phase for individuals with chronic illnesses, including LAMA2-RD. The term “transition” defines the purposeful, planned transition of adolescents and young adults with chronic disabilities from child-centered to adult-centered health care systems, with the goal of ensuring coordinated, uninterrupted healthcare. Transition represents a challenge primarily for young people with special healthcare needs, especially with chronic illnesses. However, it is important, especially in this phase of life, since healthcare is subject to complex changes and often fails. Transition may be neglected for various reasons, with frequent negative impact on the further course of the disease and poorer health outcomes. The term “transfer” refers to the one-time event moving a patient from paediatrics to adult medicine. LAMA2-RD patients enter adulthood with varying care needs, from severe CMD to milder LGMD phenotypes. A structured transition from adolescence to adulthood is essential and should begin early, with written guidance and joint paediatric-adult neurology visits in the final year before transfer.

Current guidelines on transition include:

- The S3 guideline from the Society of Transition Medicine and two German transition models
- The Berliner Transitionsmodel (https://www.btp-ev.de/)
- The Essener Transitionsmodel: a "transition day" introduced in 2018, promotes collaboration between paediatric and adult care teams. Electronic patient records allow for data sharing, fostering long-term follow-up and shared decision-making [85]

Despite the availability of transition models, challenges remain. The transition process is not systematically funded, creating inconsistencies in care. There are no standardized general recommendations for transition of care in LAMA2-RD. Local adaptations vary, and access to structured programs depends on healthcare resources and legal frameworks.

10.1. Key agreements

The group agreed on the need for a structured transition plan that ensures multidisciplinary, patient-centered care from adolescence to adulthood. Early involvement of paediatric and adult teams, joint consultations, and written transition plans should be incorporated. Future recommendations must consider local healthcare systems and legal constraints to improve long-term continuity of care.

11. Care guidelines methodology

11.1. Establishing a template/process for further CMD subtype-specific care guidelines

Carsten Bönnemann (USA) presented on the different methodologies that can be used to establish guidelines for rare disorders, including Consensus Building, Delphi Methods, GRADE, and Post-Guideline Validation (AGREE II), incorporating patient and caregivers’ input as well.

Consensus Building and Evidence Review involve a structured assessment of existing clinical research, followed by the assembly of a panel of experts, and panel discussions to weigh benefits and limitations of treatments or recommendations. Draft guidelines subsequently undergo public review before final approval.

The Delphi Method, with multiple variations including the Basic, Modified, Policy, Real-Time and Argumentative Delphi, is commonly used in rare diseases and employs iterative surveys with anonymous expert input, progressively refining statements until consensus is reached. It ensures anonymity, preventing bias from dominant voices while allowing geographically dispersed specialists to contribute. It is flexible for the choice of statistical analysis, can rapidly identify important issues and lead to conclusions, and can gather a large range of opinions and synthesize knowledge. However, it is time-intensive, requires multiple iterative rounds, and the consensus does not always guarantee accuracy, as it reflects expert opinion rather than definitive evidence. Moreover, there is no universally accepted standard for conducting a Delphi study, and there is a lack of methodological rigor and inconsistent reporting.

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology provides instead a systematic and transparent approach to assessing the strength of clinical recommendations. It evaluates study quality, the consistency of results, applicability to real-world settings, and the balance of benefits versus harms while considering patient values and preferences. GRADE ensures structured decision-making, integrating both scientific data and expert clinical experience, which is particularly valuable for rare disease guideline development where high-level evidence is often scarce. GRADE uses Evidence to Decision (EtD) Frameworks to present evidence and facilitate decisions, by clearly stating how this was assessed and how recommendations were formulated [86].

Once guidelines are developed, they must be validated to ensure they meet international standards. The AGREE II framework is a tool used to assess the rigor, clarity, and applicability of guidelines in clinical practice. It evaluates aspects such as scope and purpose, stakeholder involvement, and editorial independence, ensuring that guidelines are both evidence-based and practical for implementation.

11.1.1. Key agreements

Regardless of the chosen methodology, care guidelines should be informed by disease-specific data but also draw from comparable clinical situations. Given the limited empirical evidence in rare diseases, expert experience plays a central role. Guidelines must identify critical care issues while also highlighting gaps requiring further research.

Carsten Bönnemann also discussed possible steps to allow continued development of these guidelines, in the form of a “living document”.

This document would be hosted virtually and be accessible via link from a number of stakeholder sites as well as professional organizations. It would be updated as new evidence and experience (from caregivers and patients) pertinent to its content becomes available. A Curation Committee may need to oversee guideline revisions, supported by administrative resources. Similarly, lay guidelines should be uniform in various languages and updated with the main guidelines, similar to what is being developed for other complex NMDs like Duchenne muscular dystrophy (https://dmdcareuk.org/clinical-recommendations). A way to measure use and impact of the guidelines needs to be developed.

11.2. Methodology for care guidelines consensus

Göknur Haliloğlu (TUR) provided an overview of existing care management guidelines and introduced the GRADE system in more detail, drawing from experience in developing guidelines for methylmalonic and propionic acidaemia [87].

The GRADE framework evaluates evidence not only based on study design, but also by assessing factors such as study limitations, the balance of benefits and harms, and clinical relevance. This is built into EtD Frameworks to present the evidence and facilitate decision. This evidence ideally is based on published peer reviewed data that is weighted by quality and importance by a panel of experts. For use with LAMA2-RDs and other CMDs, the evidence permissible in the EtD framework will have to be modified to allow for clinical experience, and also to allow for importance weighing based on clinical importance and impact. The published evidence to be included in the EtD framework can be broadened by including literature pertinent to clinical scenarios and problems that are fairly directly applicable to those posed by LAMA2-RDs, but will need careful curation before inclusion. Recommendations are then formulated through a structured process, incorporating PICO questions. The ultimate goal is to produce guidelines that impact clinical care, with external review required before publication [86, 88–93].

Finally, the AGREE instrument does not establish specific standards for guideline development, but it serves as a valuable tool for assessing the quality of the process. Several major health organizations, including the U.S. Institute of Medicine, WHO, NICE, and the Guidelines International Network, have outlined principles for ensuring high-quality, evidence-based recommendations. To maintain consistency, working groups must clearly document their methodology, covering aspects such as group composition, decision-making, conflict of interest management, evidence review, recommendation grading, stakeholder consultation, and update mechanisms.

To develop subtype-specific clinical guidelines, the ENMC working group on expert care recommendations for LAMA2-RDs and other CMD subtypes must first determine the most appropriate methodology [94]. The previous CMD guidelines acknowledged the need for subtype-specific recommendations, but none have been established to date. The process to develop the previous guidelines involved expert and family surveys, presentations by topic leaders, and consensus-building among participants [1]. Subsequent guidelines incorporated systematic literature reviews and classified evidence using the American Academy of Neurology's evidence rating system [2,95]. Recommendations were linked to strength of evidence, other related literature, and general principles of care.

While core elements in care may be shared, specific factors affecting care, survival, and quality of life will vary. Early respiratory insufficiency is a topic shared with other types of CMD; however, whether the diaphragm is predominantly involved or not and if there is an additional stiffness to the chest wall are important consideration for disease-specific care recommendations [96].

Organizations like Cure CMD and TREAT-NMD have published family-oriented guides and condition-specific protocols, including the CMD Pulmonary Guide, Hypoglycemia Fact Sheet, and Proactive Cardiac Care in LMNA-CMD [97,98]. (https://www.curecmd.org/care-guidelines and https://www.treat-nmd.org/resourcesand-support/care-guides/cmd-care/). In parallel, several ENMC workshops have addressed related topics, including natural history and trial readiness for skeletal muscle laminopathies and dystroglycanopathies, overlapping with the objectives of this workshop [99].

11.2.1. Key agreements

Key action points include addressing the needs of newly diagnosed patients and families, ensuring genetic counselling not only at diagnosis but also at transition to adult care, defining best practices for primary and acute care management, and incorporating the ICF framework for functional classification [100].

Developing common data elements (CDEs) for each CMD subtype is essential to meet expectations while accommodating differences in primary disease manifestations. While core outcome measures may be shared, specific factors affecting care, survival, and quality of life will vary. For example, respiratory involvement, spinal deformities, contractures, and pain management are key concerns in COL6-RDs, whereas cardiac surveillance is critical in LMNA-CMD, early respiratory insufficiency in SELENON-RD, and intellectual disability, epilepsy, and sensory impairments in α-dystroglycanopathies [96]

Finally, there is a pressing need to harmonize clinical care guidelines across different medical societies. Increased collaboration between specialties will facilitate knowledge exchange and promote adherence to guidelines across disciplines, ensuring that primary care and acute care physicians—both in paediatric and adult settings—are equipped to provide comprehensive care for individuals with CMDs.

12. Patients' perspective and registries

12.1. Affected individual perspective

Justin Moy presented on his perspective as an affected individual. As a 24-year-old bioinformatics PhD candidate living with LAMA2-CMD, Justin discussed his life story in the context of his disease management and two surgical interventions. Justin emphasized the importance of building a community of care through early integration of family members and turning symptom management into exciting activities. For instance, his grandmother encouraged him to sing which helped his respiratory health. Justin also talked about the joint surgeries he underwent (hip flexor and knee release surgery), and discussed reasons why he did not undergo spinal fusion surgery. Justin recommended that clinicians should aim to address their questions guided by patients' activities of daily living. He also recommended that clinical guidelines should be specified by age ranges, so that affected individuals and their families know to anticipate upcoming care needs.

12.2. Congenital muscle disease international registry (CMDIR) data in LAMA2-RD – clinical care guidance important to patients and families

The patient advocacy organization Cure CMD (https://curecmd.org), represented by Scientific Director Gustavo Dziewczapolski and Executive Director Rachel Alvarez, compiled insights from the LAMA2-RD community, emphasizing the urgent need for updated Clinical Care Guidelines, which have remained unchanged for over a decade. These guidelines are essential for individuals with LAMA2-RD and other CMD subtypes, particularly in ensuring proper care by non-specialist clinicians.

Due to the rarity of LAMA2-RDs, many affected individuals receive care from clinicians with little experience in NMDs. Cure CMD is frequently asked to support and advocate for appropriate care, not only in acute/emergent situations but also in basic preventative care like pulmonary function surveillance and timely interventions related to feeding and nutrition, surgical interventions, and obtaining authorization for durable medical equipment such as BiPAP/NIV, Cough Assist machine, and mobility devices. These guidelines will help non-expert

providers manage care more effectively, allow families to recognize early symptoms, and support early interventions to prevent complications including prolonged hospitalizations.

Cure CMD believes standardized clinical care guidelines will help reduce disease burden, morbidity and mortality, while also improving clinical trial readiness. Published recommendations will ensure proactive, consistent care worldwide, regardless of access to expert clinicians.

Dr. Dziewczapolski also presented the Congenital Muscle Disease International Registry (CMDIR) (https://cmdir.org), the largest patient-reported database for congenital muscle diseases, with over 4000 participants from over 90 countries.

The CMDIR provides de-identified data to researchers and clinicians and is structured into sub-registries for CMDs (COL6-RDs, LAMA2-RDs, LMNA-related CMD, SELENON-related CMD and α-dystroglycanopathies), as well as nemaline myopathy and titinopathy, with other subtypes included in a general registry. This structure enables targeted data collection for each condition. The registry also serves as an ideal platform for disseminating new care guidelines, ensuring broad access, adoption, and ongoing updates, with Cure CMD committed to hosting and promoting them through its website and communication channels.

13. Conclusions and workshop deliverables

In order to fulfil the objectives of the workshop, participants summarized key questions for each subtopic before the final workshop day, which were then discussed in a plenary session. These discussions formed the basis for defining questions and first recommendations to guide the establishment of expert care recommendations, as outlined in each previous section and in the supplementary material.

Throughout the workshop, presenters pooled evidence and expertise to improve clinical care and monitoring strategies for individuals with LAMA2-RD. However, several important topics were not covered due to limited time during the workshop, although relevant for purpose of establishing clinical care guidelines. These include (but not exclusive of) palliative care, monitoring of fatigue, pain and quality of life, orthopaedic management of contractures and hip dislocation, and drug repurposing. The timing and approach to G-tube placement, including the need for fundoplication, also requires further discussion. Family planning and genetic counselling should address the needs of both parents and patients, particularly concerning pregnancy and parenting. While social aspects such as schooling, employment, accessibility, and social life were partially explored in the survey completed by the patient community and the clinicians caring for patients with LAMA2-RD, they require deeper analysis. The management of aids and orthoses would also benefit from information from the shared experiences among families and patients.

Developing comprehensive clinical care guidelines for the LAMA2-RDs will require a multidisciplinary team approach, including nutritionists, speech and language therapists, endocrinologists, psychologists, orthopaedic surgeons, gastroenterologists and general surgeons. Additional expertise from maxillofacial and ENT surgeons (for management of macroglossia and craniofacial abnormalities) will be useful. Specialist nurses and care coordinators will also play a key role in implementing expert care recommendations.

Importantly, all workshop participants agreed that these recommendations should be equitable and applicable to different settings, hence regional differences in organizational models should be accounted for.

Participants agreed that while the GRADE system could be applied in areas with existing evidence, such as respiratory care, it may not be easily applicable for all areas of clinical care. Regardless of the chosen methodology, the approach should be clearly defined, topics prioritized based on clinical relevance, and the strength of recommendations transparently communicated. The evidence to decision (EtD) framework could allow for the inclusion of evidence from related conditions, provided it is carefully evaluated before application to LAMA2-RD.

There was a consensus that a methodologist should be involved in the process of creating clinical care guidelines and that the outcome should be a "white paper" working as a living document, which would be available online and thus accessible to clinicians as well as the general public and regularly updated for usability and clinical relevance. Increasing awareness among non-neuromuscular specialists of these recommendations is critical, particularly concerning acute presentations and emergency hospital admissions.

To fill the remaining gaps in knowledge, it is important to differentiate whether the gap is to inform care recommendations and in turn clinical trial readiness or gaps in pathophysiologic knowledge. The gaps can be addressed by registries that pool data on specific subtopics as well as pilot studies, such as defining protocols for peripheral nerve involvement or definition of sleep disordered breathing.

To ensure consistency across research efforts, natural history studies should be harmonized in data coding, definitions, and outcome measurement methods. Patient Advocacy Organizations could take the lead in coordinating an umbrella initiative to unify existing natural history data.

Lastly, participants will evaluate common topics across CMD subtypes. Collaboration between working groups from different neuromuscular conditions could strengthen methodological validation and ensure broader applicability of the findings beyond LAMA2-RD.

14. Organizers and participants

Lindsay Alfano: *Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA.*

Carstenn Bönnemann: *National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA.*

Clara Gontijo Camelo: *Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil.*

Gianpaolo Cicala: *Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*

Fabrizio Chiusolo: *Bambino Gesù Hospital, Rome, Italy.*

Ilse de Laat: *Radboud university medical center, Nijmegen, The Netherlands.*

Denis Duboc: *Hôpital Cochin, Paris, France*

Gustavo Dziewczapolski: *patient representative, Cure CMD, USA*

A. Reghan Foley: *National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA.*

Göknur Haliloğlu: *Hacettepe University Faculty of Medicine, Ankara, Turkey.*

Andrea Klein: *Bern University Hospital, University of Bern, Switzerland*

Justin Moy: *patient representative, Boston University, USA*

Francina Munell: *Vall d'Hebron University Hospital, Barcelona, Spain.*

Daniel Natera De Benito: *SJD Barcelona Children's Hospital and Institut de Recerca Sant Joan de Déu, Barcelona, Spain.*

Stefano Carlo Previtali: *IRCCS San Raffaele Scientific Institute and Università Vita-Salute San Raffaele, Milan, Italy*

Susanna Quijano-Roy: *Raymond Poincaré University Hospital, Garches, France.*

Anna Sarkozy: *Dubowitz Neuromuscular Centre Great Ormond Street Hospital, Institute of Child Health, London, UK.*

Ulrike Schara-Schmidt: *University Hospital Essen, Essen, Germany.*

Hemant Sawnani: *Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.*

Federica Trucco: *IRCCS Istituto Giannina Gaslini and University of Genoa, Genova, Italy.*

Athanasios I. Tsirikos: *Royal Hospital for Children and Young People, Edinburgh, UK.*

Bram Verbrugge: *patient representative, Voor Sara, The Netherlands.*

Nicol Voermans: *Radboud university medical center, Nijmegen, The Netherlands.*

Alberto Andrea Zambon: *IRCCS San Raffaele Scientific Institute, Milan, Italy*

CRediT authorship contribution statement

Alberto Andrea Zambon: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Andrea Klein:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Anna Sarkozy:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **A. Reghan Foley:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alberto Andrea Zambon reports administrative support and travel were provided by European Neuromuscular Centre. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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