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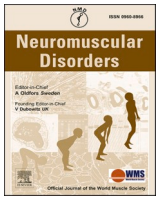

277th ENMC international workshop: Congenital myopathies: revising and revisiting nomenclature and diagnostic guidelines, 21–23 June 2024, Hoofddorp, The Netherlands

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ABSTRACT

The 277th ENMC workshop on Congenital Myopathies was held in Amsterdam, The Netherlands, on 21–23 June, with 26 clinical, research, and curation experts and patient representatives from five continents. The workshop aimed to 1) establish an updated nomenclature and 2) update recommendations for their diagnostic evaluation. It was agreed that the preferred acronym for congenital myopathies is CMYO. Consensus defined CMYOs as a heterogeneous group of genetic muscle disorders typically presenting perinatally or in infancy with hypotonia and muscle weakness, usually non- or slowly progressive, with distinctive structural, non-dystrophic histopathological features. A nomenclature framework integrating gene, mode of inheritance, and histopathology was proposed, exemplified by "autosomal recessive RYR1-congenital myopathy with cores." Diagnostic consensus emphasized a genetics-first approach, using targeted massively parallel sequencing panels, exome, or genome sequencing, complemented by electromyography, muscle imaging, and biopsy when indicated and available. The workshop highlighted the need for harmonized classification across databases, patient engagement, and global representation to support precise diagnosis, genotype–phenotype correlation, and equitable access to care and research.

1. Introduction: Background and historical perspective

The 277th ENMC International workshop was held in Hoofddorp, The Netherlands, from 21–23 June 2024 and included 26 participants representing 8 countries from 5 continents. Clinicians, basic scientists, researchers, and patient representatives were amongst the attendees. The aim of the workshop was to update the nomenclature and diagnostic guidelines for congenital myopathies (CMYO), inherited muscle disorders which typically present with hypotonia, skeletal muscle weakness and amyotrophy from the first months of life.

Ana Ferreiro (AF) introduced the rationale and goals of the workshop. CMYOs have been traditionally classified and named based on the predominant abnormalities in muscle fiber structure identified on muscle biopsies [1]. However, there is significant overlap and variability

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among the supposedly distinctive CMYO histopathologic abnormalities, and muscle biopsies are not being performed on all patients. Thus, the CMYO definition has gradually evolved to encompass, in addition to the clinical phenotype and histological profile, the causative gene(s) [2–4]. The identification of numerous disease-causing genes (> 40, including the exceptionally large *TTN, NEB* and *RYR1* genes), in addition to the continued presence of cases without genetic diagnoses (up to 40 %), pose challenges for both patients, clinicians and academic experts [5–7]. As a result, the current nomenclature is considered outdated and insufficiently descriptive/accurate [8,9]. This is particularly true given that the current diagnostic standard for other genetic muscle conditions involves (where available) a "gene first" approach, reflecting the need to consider prioritizing the causative gene (if known) in the nomenclature, and additionally highlighting the need to update existing diagnostic standards of care.

2. Part 1 : Definition of congenital myopathies

2.1. Overview of congenital myopathies and the current nomenclature

Jim Dowling (JD) provided an overview of presenting clinical features of CMYO. He first discussed existing definitions as a starting point for the workshop's goal of providing an accurate definition of this heterogeneous group of disorders. JD also presented a summary of the existing nomenclatures and classifications for CMYO. He highlighted that there are several terms and names used, and that there is a lack of uniformity in nomenclature across the wider literature. For example, in OMIM there are 5 entries for *ACTA1* CMYO, including acronyms (NEM and MYOP) that are not used in current practice. He also summarized the work that was performed before the ENMC workshop by a TREAT-NMD CMYO taskforce, and described a draft nomenclature developed by this group. This draft nomenclature was circulated prior to the meeting and was used at the workshop to inform the development of a new classification and nomenclature.

He next discussed the most common CMYO clinical presentation, i.e., neonatal onset hypotonia and weakness. There is a broad differential diagnosis for neonatal hypotonia; CMYO make up < 10 % of all cases [10] and can often be difficult to discriminate from other causes [11]. Some additional clinical features that are preferentially present in infants and young children with CMYO include ptosis, facial and bulbar weakness, ophthalmoparesis, and, in cases with severe antenatal weakness, congenital contractures. In the older child and in adults, the clinical presentation can be more discriminatory. In addition to proximal limb weakness, diffuse muscle hypotrophy, and the features mentioned above, patients may also present with axial weakness, rigid spine, scoliosis and/or distal-predominant weakness. There are also some unique clinical features, such as muscle tremor and muscle hypercontractility.

Gina Ravenscroft (GR) reviewed the earliest onset cases of CMYO in her discussion of *in utero* presentations. These include fetal akinesia or hypokinesia, abnormal limb positioning, arthrogryposis, pterygia, fetal hydrops and/or polyhydramnios [12]. At birth there is often respiratory insufficiency, in part due to lung hypoplasia and restricted chest wall movement (in addition to respiratory muscle weakness). There are several clinical syndromic terms given to these presentations including Pena-Shokeir syndrome, arthrogryposis multiplex congenita (AMC), distal arthrogryposis, multiple pterygia syndrome (lethal and Escobar-variants), and lethal congenital contracture syndromes. Histopathology studies suggest ~50 % of AMC cases are myogenic, with most having dystrophic features; however, muscle biopsies may be uninformative, showing non-specific changes [13].

In the genomics era, variants in CMYO genes account for a substantial proportion of these *in utero* presentations, with autosomal recessive *TTN* disease-causing variants being the most frequent cause (~10 % of diagnoses, and frequently with amyoplasia) in cohort studies [14,15]. In particular, these cases include variants within regions of *TTN* that are poorly mapped by short read massively parallel sequencing-based testing, thus requiring a high degree of suspicion for their detection [14,16]. Other major contributors include recessive loss-of-function variants in *NEB* and *RYR1* [14,15]. *De novo* dominant *ACTA1* variants can also result in onset of muscle weakness *in utero* and fetal anomalies [17,18]. Autosomal recessive loss-of-function variants, including functional nulls, in genes also associated with periodic paralysis (*CACNA1S, SCN4A*) as well as a critical EC-coupling gene, *STAC3,* have also been identified as an important cause of fetal-onset myopathies [14,15,19,20]. Variants of uncertain significance in *CACNA1S, RYR1* and *SCN4A* remain a challenge; functional assays are needed to aid variant curation. Around 50 % of cases remain without a molecular diagnosis, suggesting there are likely more causative genes or non-inherited conditions (including autoimmune conditions such as fetal acetylcholine receptor antibody–related disorders (FARAD)) [21]. Given the contribution of genetic conditions, timely genetic diagnosis is imperative to aid family planning, which is the reason why a significant subset of autosomal recessive and X-linked CMYOS are targeted by reproductive carrier-screening programs.

At the other end of the age spectrum, Nicol Voermans (NV) shared her experience with CMYO in adulthood. A neonatal or infantile onset is easily identifiable in >80 % of individuals with CMYO. However, milder or less typical forms may not present to a clinician until adolescence or adulthood, and typically have a (near) normal life expectancy. Adult patients with CMYO will most likely retrospectively report delayed motor milestones and lower athletic capacity compared to their peers in childhood and adolescence. The milder forms will have attained many motor skills and might have apparently normal motor ability in daily life. As a result, adult patients often have a long diagnostic delay or have been misdiagnosed [22,23]. This might be due to mild symptoms, slow progression, non-specific findings on muscle biopsy, and/or lack of awareness of adult CMYO amongst clinicians, particularly in non-specialized settings. These patients have to be creative in living with their motor disabilities, may not have received guidance on management of their condition, and often need to be re-invited back into the adult neuromuscular clinic. Patient organizations can play an important role in raising awareness of these currently probably underdiagnosed presentations.

In parallel, improved standards of care and development of new therapies are expected to result in an increasing number of patients with early-onset, more severe presentations transitioning to the adult neuromuscular clinic. This poses new challenges for clinicians and researchers, including selecting specific sets of clinical outcome measures appropriate for the older and milder end of the spectrum.

Amongst adult CMYO patients, *RYR1* CMYO (mostly of pediatric onset) is the most common genetic subtype [24,25], with recessive titinopathies caused by biallelic *TTN* disease-causing variants emerging as the second most common group. Nemaline myopathy is the most frequently encountered individual histopathological subtype [22,26], whereas core myopathies (including both central and multi-minicore forms) are the most frequent as a group [22,27]. NV also highlighted three specific CMYO that typically present later in life: (1) *KBTBD13* nemaline myopathy, which is most common in the Netherlands due to a founder variant and which has a unique 'muscle slowness' phenotype [28] (2) Females with *MTM1* variants (often relatives of males with X-linked myotubular myopathy, XLMTM) who have progressive muscle weakness, often with asymmetric facial weakness [29] (3) Adults with *RYR1* variants associated with malignant hyperthermia susceptibility that also have neuromuscular symptoms, such as muscle cramps and myalgia, often appearing late in life (see below) [30].

Although the clinical course of CMYO is often referred to as "static" or "non progressive", the group discussed that there are some individuals, particularly later in adulthood, who do have slowly worsening weakness and function, possibly accelerated by the physiological aging process. This slow progression does distinguish CMYO from other similar disorders such as more rapidly and reliably progressive muscular

dystrophies and therefore would be important to include in the definition. It is also worth mentioning that there is a paucity of data regarding the disease manifestations and course in older individuals, which further hinders their correct diagnostic identification and the implementation of appropriate management approaches.

Cardiac and respiratory involvement is variable. In general, cardiomyopathy is rare except in association with certain genotypes such as *TTN, SPEG, MYH7*, and *ACTA1* [7,31–35]. Respiratory insufficiency is common and typically correlates with the degree of weakness, with some exceptions such as *SELENON* and *NEB* CMYO, where respiratory involvement is often severe and out of proportion to extremity weakness [36,37] Orthopedic complications are numerous, including spine deformities (rigid spine, scoliosis), contractures, joint (in particular hip) dislocations, fractures and low bone density. Bulbar dysfunction leading to impaired swallowing, slow eating, fatigue with chewing, dysarthria and a soft voice can occur and can highly impact quality of life.

2.2. Myopathology

Edoardo Malfatti (EM) provided a historical overview and discussed the changing role of muscle biopsy for CMYO. He emphasized the importance of distinguishing between a myopathic and dystrophic pattern in cases of early-onset muscle weakness. He also mentioned that, in the premolecular era, histochemistry, histoenzymatic reactions and electron microscopy (EM) studies helped to define the main CMYO histological groups: the nemaline (rod) myopathies, the core myopathies, the centronuclear myopathies, and the CMYOs with congenital fiber type disproportion (CFTD) [3].

Next-generation sequencing or massively parallel sequencing (MPS) (e.g., MPS-based panel, exome and genome sequencing) has led to the identification of a constantly expanding number of novel CMYO genes and has demonstrated that there is a wide histopathologic overlap between different genetic subtypes [4,38]. It is now clear that the same histotype (for example, cores) can be found in patients with different genetic etiologies [2]. Currently, muscle biopsy, a safe but invasive procedure, is not required as a first line CMYO diagnostic test, if the turnaround time of genetic testing is sufficiently short and the resulting molecular diagnosis unequivocal. However, the role of muscle biopsy remains fundamental in the characterization of new entities and to better understand the pathophysiology of these conditions [39]. Muscle biopsy is particularly useful in cases of inconclusive genetic findings. Strategies for validation of findings may include immunohistochemical and protein studies, transcriptomics (including bulk and single nuclei RNA-Seq), proteomics or developing cell culture and 3D muscle models. Clinical-genetic-myopathological correlations remain key to advancing our understanding of CMYOs.

EM also illustrated some clinical and practical challenges for interpretation of muscle histology. Appropriate muscle biopsy site selection is crucial. Muscle imaging, clinical examination, and electromyography (EMG) can be useful guides. The age of the patient drastically influences the sensitivity of findings, with biopsies at different ages potentially revealing different pathologic findings [36]. Thus, re-biopsy at a later stage can be considered in initially inconclusive cases. Neonatal biopsies are particularly challenging to interpret given the small myofiber size. Some cases of severe neonatal muscle disease can have overlapping histopathologic features with congenital muscular dystrophies (CMD). EM can be helpful in these scenarios [40]. Lastly, there exist rare histopathologic features such as tubular aggregates that can be seen in CMYOs, but also in other inherited or acquired muscle disorders [41].

2.3. Genetics

While muscle histology has historically defined CMYO subtypes, primary genetic testing is becoming the main diagnostic modality. The first disease gene discoveries were made in the early 1990′s with the reports of *RYR1* disease-causing variants in dominant central core disease (CCD) and *TPM3* in nemaline myopathy [42–44]. By the mid 2000′s close to two dozen CMYO genes had been identified, and the concept of genetic heterogeneity for many of these conditions was well established. Increasingly, some CMYOs are defined by their underlying genotypes (e.g., *TTN, SELENON*) rather than their histotypes. In particular, the rarer genotypes may not have established distinctive histologic features. Alan Beggs (AB) reviewed the current landscape of genotypes. At the time of this conference, the WMS/Neuromuscular Disorders Gene Table of Neuromuscular Disorders (www.musclegenetable.fr) listed 41 genes in association with 59 distinct congenital muscle diseases, and the ClinGen Congenital Myopathies Gene Curation Expert Panel has evaluated 52 disease-gene associations [45]. In the Beggs laboratory congenital myopathy cohort, which includes 1110 affected individuals in 918 families, 70 % have a confirmed genetic diagnosis, with the remaining 30 % having clinicopathologic evidence of a CMYO but without genetic etiology. Eighty-four percent of the “solved” cases had disease-causing variants in one of nine most common causative genes (*ACTA1, DNM2, MTM1, NEB, RYR1, SELENON, TPM2, TPM3* and *TTN*). Among the remaining 105 diagnosed families, pathogenic variants were found in 53 different genes, indicating that there is significant genetic heterogeneity with many rare and ultra-rare forms of CMYO.

AHB illustrated advanced diagnostic techniques being used for unsolved cases including RNA sequencing (bulk and single cell), new aberrant splice detection algorithms (Intron Jaccard Index), and long read sequencing. AHB discussed some examples of cases solved with these techniques including a patient with a CMYO and neck stiffness who was found to have a retained intron that adversely impacted *RYR1* splicing (found by RNAseq) and a patient with a large *de novo* deletion in *TTN* found by long read sequencing. AHB concluded by summarizing some of the challenges faced in the genomic era. First and foremost, CMYOs represent a clinically and genetically heterogenous population. Existing understanding of CMYOs is based on knowledge gathered with significant ascertainment bias such that individuals with more severe clinical presentations, or whose biopsies happened to exhibit particular histopathologic features, may be more likely to be recognized and studied. Furthermore, existing molecular diagnostic methods have poor sensitivity for uncovering some types of variants. Therefore, we need to probe further in our undiagnosed cases to understand splicing effects, regulatory variants and modifiers, and epigenetic alterations.

2.3.1. Gene specific considerations

There are some genes that for various reasons pose a particular challenge for clinicians, investigators, and patients and were highlighted during the meeting.

2.4. SELENON-related congenital myopathy

AF reviewed *SELENON*-related CMYO, which is marked by severe axial (neck and trunk) muscle weakness disproportionate to the degree of limb involvement. Most patients show early signs, delayed motor milestones being noticed within the first 2 years in 85 % of cases [36,46]. Typical early signs include poor head control noticeable from age 3 months and inability to lift the head from supine. However, nearly all patients achieve independent walking, most before 18 months, and retain ambulation into adulthood, although motor function often declines after age 35y. Interestingly, a subgroup experiences more severe progression, losing ambulation before the end of adolescence; these severe cases often have high BMI and increased abdominal fat in childhood [36,47]. Patients frequently present also with low muscle bulk, failure to thrive or fatigue. Localized amyotrophy, especially in the inner thighs (‘bracket thighs’), is a characteristic feature.

Spinal contractures may develop early, with 88 % of patients under the age of 10y showing a ‘Rigid Spine’ phenotype. This feature coined the phenotype “Rigid spine muscular dystrophy/myopathy”. Motor function generally remains stable until puberty, when axial weakness drives progressive scoliosis, often requiring spinal fusion, and restrictive

respiratory insufficiency which is disproportionate to limb weakness and includes diaphragmatic fatigue [48]. Nocturnal non-invasive ventilation is almost always required while patients remain ambulant.

Muscle biopsies typically reveal type 1 fiber predominance and multi-minicores, although mild fibrosis or eosinophilic inclusions may occur. Histopathological changes are more severe in axial muscles and correlate with age: younger patients may have non-specific abnormalities, while older patients tend to show "classic" multi-minicore lesions [36]. Diagnosis can be delayed until adulthood due to relatively preserved limb function which often masks early axial signs. Furthermore, exon 1 of *SELENON*, a hotspot for pathogenic variants, is GC-rich and poorly covered by standard MPS, necessitating targeted Sanger sequencing if clinical suspicion is high [36].

SELENON—CMYO accounts for 11.65 % of CMDs [49] and 16 % of CMYO [27] in the UK. AHB and AF noted that *SELENON*-CMYO, a purely recessive or biallelic disorder, may be a more common CMYO genotype, though it is likely underrecognized. Based on allele frequencies from gnomAD, an estimated 9000–17,000 individuals are affected worldwide (1.18–2.21 per million), consistent with prevalence extrapolated from genetically diagnosed cases in France (~1 per million) [36].

Finally, AF summarized the main features of ASC-1 related CMYO, a rare autosomal recessive CMYO due to *TRIP4* mutations with a wide phenotypical, histopathological and severity spectrum. It must be included in the differential diagnosis when SELENON-related myopathy is considered, due to the presence of muscle atrophy and weakness which is predominantly axial and proximal, scoliosis, rigid spine, potentially lethal respiratory failure in some patients and multi-minicores in most biopsies. However, other features of ASC1-related CMYO, including hypotonia, delayed or no ambulation, joint contractures and/or hyperlaxity and a skin phenotype, resemble COL6-related disorders. *TRIP4* is, unlike *SELENON* or *COL6*, one of the rare CMYO genes potentially associated with cardiomyopathy in adulthood.

2.5. TTN-related congenital myopathies (congenital recessive titinopathy)

Emily Oates (EO) discussed the unique case of *TTN*. Over the last decade it has become increasingly apparent that recessively inherited titinopathies caused by biallelic disease-causing *TTN* variants are one of the most common causes of congenital and childhood-onset genetic muscle disease [32]. Diagnostic confirmation of this group of disorders (considered by some to be one disorder with variable clinical manifestations and severity) can be challenging. Many affected individuals likely remain without a confirmed genetic diagnosis because standard diagnostic pipelines have 'missed' at least one of their two causative variants e.g., variants that do not impact the N2A (canonical skeletal muscle) isoform, as well as non-canonical splice-impacting, triplet repeat region and intronic variants. In addition, the enormous coding region of *TTN* includes many missense variants that do not have a clinical impact. Differentiating these from truly pathogenic missense variants remains extremely difficult.

An additional challenge is that the clinical features of recessive titinopathies, including age-at-onset, severity, complication profile, rate of progression and muscle histopathology findings, are highly variable. For example, a subset of affected individuals develops severe-to profound weakness prenatally and succumb prior to birth or during early infancy [32,50]. Others do not develop symptoms until childhood, adolescence, or even later and survive well into adulthood [32,50–53]. The mechanisms that underlie this striking clinical variability have not been fully elucidated.

These marked clinical differences have also hampered cohesive diagnostic labelling and classification. Sometimes the clinical picture is consistent with a classical CMYO, sometimes it is more consistent with a congenital or limb girdle muscular dystrophy (LGMD). This variability has, in part, resulted in more than 15 diagnostic labels used to describe this group of disorders in published literature. This, in turn, has contributed to confusion for patients and families and the wider clinical community. It has also resulted in fragmentation of the relevant literature.

It is anticipated that at least some of this clinical variability is due to differences in the impact of causative variants at *TTN* transcript and protein levels. Examples include differences in the level of nonsense-mediated decay triggered by causative variants, the presence of additional (often unrecognized) splicing impacts and/or differences in the isoform transcript-level PSI (percent spliced in) usage of exons that harbor causative variants. Endeavors to explore these possibilities using existing and emerging RNA- and protein-directed methodologies are currently underway and will hopefully provide improved diagnostic, mechanistic and clinical predictive clarity.

2.6. RYR1-related congenital myopathies and related diseases

Heinz Jungbluth (HY) discussed pathogenic variants in *RYR1* which encodes the skeletal muscle ryanodine receptor (RYR1) with a crucial role in sarcoplasmic reticulum (SR) calcium release and Excitation-Contraction Coupling (ECC). *RYR1* pathogenic variants are the most common genetic cause of CMYOs and have been associated with a very wide spectrum of clinical manifestations, ranging from early-onset CMYOs to the Malignant Hyperthermia Susceptibility (MHS) trait. Collectively they are termed *RYR1*-related myopathies (RYR1-RM) and encompass mainly dominantly inherited CCD and recessively inherited multiminicore disease [54], centronuclear myopathy [55], and CFTD [56]. Despite their histopathological variability, the recessively inherited forms share common clinical features, in particular extraocular muscle (EOM) involvement, which distinguish them from dominantly inherited RYR1-RM. At the extremes of the clinico-pathological range, RYR1-RM shows overlap with the AMC, CMD and LGMD spectrum.

The MHS trait, a pharmacogenetic predisposition to a potentially life-threatening anesthesia reaction in response to volatile anesthetics and muscle relaxants, has been associated with the distinct myopathy phenotype King-Denborough syndrome (KDS) [57], and, more commonly, intermittent induced phenotypes such as (exertional) rhabdomyolysis (ERM) [58] in individuals that are otherwise healthy or may have only subtle myopathic manifestation. ERM, MHS and other *RYR1*-related episodic phenotypes present a particular challenge, as they reflect an interaction between genetic predisposition and environmental factors and *RYR1* variants implicated may not necessarily meet full pathogenicity criteria [59].

Based on the considerations above we propose a classification of RYR1-RM based on i) the mode of inheritance (autosomal-dominant, AD / autosomal-recessive, AR / X-linked, XL); ii) certain histopathological findings, namely cores, central nuclei, CFTD and non-specific or multiple features (in cases where a muscle biopsy is available); and iii) the presence of certain clinical features (in particular the presence of EOM involvement and MHS, and/or features suggestive of KDS or AMC) and histopathological features. Despite some clinical overlap in individual cases, patients where MHS is the primary feature should be considered as a separate pharmacogenetic phenotype rather than a CMYO.

2.6.1. Consensus on definition of congenital myopathies

To establish a nomenclature and diagnostic recommendations for CMYOs, the group first set out to establish a definition of CMYO. Defining this term first established the scope and breadth of a nomenclature scheme and informed diagnostic recommendations.

It was agreed that 'congenital myopathy' remains the best umbrella term for the group of disorders discussed in the workshop. Consensus was achieved to define **"congenital myopathies" as a heterogeneous group of genetic muscle disorders that typically present perinatally or in infancy with hypotonia and muscle weakness. They are usually nonprogressive or slowly progressive with age. The main histopathological findings are distinctive structural abnormalities in skeletal muscle fibers without overt dystrophic features.**

It was noted that the term "congenital" implies an early onset

disorder. Although many patients survive into adulthood and they may not present to a clinician until adolescence or adult age, it is rare to truly have no early symptoms at all in infancy or childhood. Their "non-progressive" character does not exclude age-related decline in muscle mass and strength, particularly in middle or late-adulthood.

The group also agreed that the best acronym for "congenital myopathies" is CMYO. Often "CM" has been used, however Cassandra Arnold (CA) from OMIM explained that "CM" is already used in association with another medical condition and should thus be avoided for CMYO.

3. Part 2: Nomenclature and classification

3.1. Patient perspective on nomenclature and classification

Anne Lennox (AL), founder of the Myotubular Trust, highlighted the importance of taking into consideration the widespread recognition of the term *X-linked Myotubular myopathy (XLMTM)* and hoped to gain more clarity in naming the types of centronuclear CMYO that are caused by genetic variants other than XLMTM. The patient community highlighted a strong rejection of any form of a scoring system to describe disease severity included in the nomenclature.

Sarah Foye (SF), from Team Titin, highlighted challenges with titinopathies, including inconsistent naming, broad phenotypes spanning both myopathies and dystrophies, variable age of onset (congenital to adult), and involvement of skeletal, cardiac, or both systems.

Marc Guillet (MG), founder of A Foundation Building Strength, supported a change in nomenclature, citing potential benefits such as improved clinical communication, better engagement with industry, and more effective data organization for machine learning.

Michael Goldberg (MG), representing the RYR1 Foundation, pointed out that the current nomenclature for *RYR1*-related diseases (*RYR1*-RD) causes confusion and hinders clinical trial readiness. *RYR1*-RD has been associated with a wide range of histopathologic diagnoses. This creates confusion within the patient community and can spuriously segregate patients with the same genetic diagnosis of *RYR1*-RD (but with disparate histopathologic diagnoses) or, conversely, spuriously aggregate patients with same histopathologic diagnosis (but with disparate genetic diagnoses). In addition, *RYR1*-RD patients with the pharmacogenetic phenomenon of MHS may have normal biopsies. Within any given individual with *RYR1*-RD, there may be different histopathologies depending on the muscle group that was biopsied and/or the age at which a patient was biopsied, and individuals with identical genotypes may have different biopsy results [60]. Relying exclusively on the genetic diagnosis of "*RYR1*-RD" also has limitations. Significant heterogeneity within the *RYR1*-RD population is based on mode of inheritance, pathomechanism of disease and heterogeneity of clinical presentations with wide variance in degrees of functional limitations and disability. Therefore, a more holistic approach is needed that would include, not only histopathology and genetic testing results, but also pathomechanism of disease, multi-omics, mode of inheritance and type/severity of clinical features.

3.2. Nomenclature examples in other neuromuscular disorders

Volker Straub (VS) provided a summary of the lessons learned from the revision of the nomenclature for the LGMDs. When the LGMDs were first classified at an ENMC workshop in 1995 [61], the consensus was to name the autosomal dominant forms as LGMD 1 and the autosomal recessive forms as LGMD 2. The relevant sub-types were assigned consecutive letters of the alphabet based on the historic order in which their genetic loci or genes were identified. When LGMD 2Z was characterized in 2016 [62], the classification had to be revised. In a subsequent ENMC workshop [63], key opinion leaders, patient advocacy representatives, patients with LGMD, and representatives from OMIM, ICD11, and Orphanet first agreed on how to define LGMD, then proposed a new nomenclature, and finally applied it to previously classified LGMDs and newly identified diseases. The updated system renamed autosomal dominant forms as LGMD D and autosomal recessive forms as LGMD R, assigning sub-types consecutive numbers based on the historical gene discovery order.

Although the revised nomenclature for LGMD was first published in 2018 [63], the previous nomenclature is still frequently used and some patient advocacy groups are committed to the old nomenclature from 1995, as the names of their organizations may include the old LGMD names. Disease names can become identities and taking on a new identity can understandably be extremely challenging.

Carsten Bönnemann (CB) compared current classifications for three paradigmatic forms of CMD, related to pathogenic variants in *LAMA2, COL6A1–3* and genes involved in the glycosylation of alpha-dystroglycan [9,64]. A proposal for a three-axis disease classification was made, in which the first two axes determine the diagnosis: Axis 1 denotes the gene or protein and the genetic mechanism of action of relevance and axis 2 the clinical class or syndrome. A third optional axis would be a signifier of disease impact and age of onset.

LAMA2 related congenital muscular dystrophy is caused by recessive biallelic variants in the *LAMA2* gene encoding the alpha2 chain), this would therefore be Axis 1. The most commonly used historical term was merosin deficient congenital muscular dystrophy, which however refers to the alpha2 chain containing heterotrimer laminin 211. A milder presentation was referred to as partial merosin deficiency. Complete and partial deficiency, however, only poorly correlate with the motor outcomes and therefor is not entirely suitable for an axis 2 designation. A recent study suggested a designation of *LAMA2* RD1 for patients achieving sitting but not walking, and of *LAMA2* RD2 for those who achieved ambulation, which could be used as a second axis with implied axis 3 components [65].

For the *COL6A1*–3 genes, pathogenic variants can act either as recessive or as dominant, so the inclusion of the genetic mechanisms is essential. There are the three clinical classes of typical COL6 related dystrophy referred to as 1) Ullrich – may not achieve ambulation or achieve ambulation but not be able to get up from floor without assistance, 2) intermediate – can get up from floor with Gowers but not climb 4 steps without rail, and 3) Bethlem – able to also get up 4 steps without holding on [66]. Axis 3 determinants of functional impact therefore underscore the clinical classes of axis 2. For example, a possible axis 1 and 2 with implied axis 3 designation would be "*Dominant COL6A1 congenital muscular dystrophy type Ullrich*".

For the alpha dystroglycanopathies there are close to 30 genes involved, mostly via biallelic recessive variants, and associated with a wide clinical spectrum [67]. A number of classically defined syndromes are associated with this spectrum: Walker-Warburg Syndrome, Fukuyama CMD and Muscle Eye Brain Disease. OMIM recognizes three groups: With brain malformation, without brain malformation but with cognitive involvement, and LGMD. The OMIM groups do correspond to three important clinical classes and could be adopted in a 2-axis classification that denotes the involved gene and the clinical class, for example "*POMT1 CMD with brain malformation*".

3.3. Nomenclature databases

Sandra Donkervoort (SD), representative from the *Clinical Genome Resource (ClinGen)*, noted that advances in genomic sequencing and understanding of genetic contributions to disease often require re-evaluating disease classifications. ClinGen has developed frameworks to classify the strength of evidence underlying monogenic gene-disease relationships, variant pathogenicity, and clinical actionability. Defining the disease entity is essential but challenging, especially for genes linked to multiple conditions or broad phenotypes. Criteria have been created to guide decisions on "lumping and splitting" of entities, balancing factors like molecular mechanism, phenotypic variability, and inheritance. Scientific advances in genomic sequencing and understanding of genetic contributions to disease pathomechanisms often provoke a need

to reassess these classifications as disease nomenclatures must continue to evolve with the accumulation of more evidence.

Mickael De Carvalho (MD) spoke about the *Orphanet* database (https://www.orpha.net/) and Orphacode (https://www.orphadata.com/), a unique and stable identifier for each entity. Each Orphacode is associated with a preferred name, a classification level, and a detailed definition. This system ensures consistency and reliability in the identification and classification of rare diseases across various health information systems. In addition to the Orphacode, Orphanet can integrate a wide range of information related to each disease. This includes clinical signs using Human Phenotype Ontology (HPO, https://hpo.jax.org/) terms and genes associated with each disorder or subtype. Orphanet aligns its data with several other prominent medical and research terminologies, such as OMIM (https//www.omim.org/), ICD-10, ICD-11 (https://icd.who.int/), and GARD (https://rarediseases.info.nih.gov/). This ensures interoperability and consistency in rare disease data across hospitals, regions, and countries, aiding public health initiatives and research efforts. Its hierarchical classification includes groups of disorders, individual diseases, and subtypes. A single disease can belong to multiple parent categories, reflecting its multisystemic nature and relevance to different medical specialties. Currently, there are two groups in the Orphanet classification for CMYOs. These groups correspond to the historical nomenclature based on muscle histopathology. However, many conditions no longer fit these categories. A more comprehensive and updated classification is needed to reflect current knowledge and accurately represent all conditions.

3.3.1. *Consensus on nomenclature and classification*

The group concluded that, while the designation "congenital myopathy" is the common starting point, the mode of inheritance, gene, and muscle biopsy features, if known, should be part of an individual's more specific diagnosis. Based on this, they formulated a framework for a new nomenclature and companion classification incorporating these features.

The proposed nomenclature includes, for each diagnosis, the following components (Fig. 1 and Table 1): 1) Inheritance pattern (AD, AR, XLD, XLR, for autosomal dominant and recessive and X-linked dominant and recessive, respectively), if there are various modes of inheritance for the gene involved; 2) Gene; 3) Congenital myopathy; 4) Main histopathological features (Table 1). An illustrative example of this new nomenclature is as follows: "autosomal recessive *RYR1*-congenital myopathy with cores" (AR *RYR1*-CMYO with cores). The components incorporated in this nomenclature depend on what clinical, genetic, and histopathological knowledge is available for each affected individual. In cases where the gene is unknown and the biopsy is unavailable, the diagnosis of probable CMYO alone may be transiently used, although by definition the term congenital myopathy should be applied only to individuals who either have a confirmed genetic diagnosis (i.e., pathogenic variant(s) in a known CMYO gene) or consistent muscle histopathological features, including a non-specific but compatible pattern. The group requested that online databases (e.g., ClinGen, OMIM, Orphanet, ICD-11) coordinate their classification and nomenclature to establish a minimum core of consistent/compatible systems that the academic communities can work with and that reflect the recommendations from this meeting.

A classification system, distinct from but consistent with the nomenclature, was proposed to include key features as follows: 1) Congenital myopathy; 2) Gene; 3) Inheritance pattern; 4) Main histopathological (or other phenotypical) features (i.e., Congenital myopathy, *RYR1*-related, AR, with cores; Congenital myopathy, genetically unresolved, nemaline). The specifics of additional phenotypic and histologic classification will be formalized by a virtual working group. Additional clinical information regarding motor function, distribution of weakness, and comorbidities are important but would not be part of the diagnostic label.

Table 1
Examples of proposed nomenclature. AD: autosomal dominant; AR: autosomal recessive.

Old nomenclature	New nomenclature
Congenital myopathy 1A	AD *RYR1* CMYO with central cores
Congenital myopathy 1B	AR *RYR1* CMYO with multi-minicores
Congenital myopathy 3	AR *SELENON* CMYO with multi-minicores
Congenital myopathy 4A	AD *TPM3* CMYO with fiber-type disproportion
Congenital myopathy 7B	AR *MYH7* CMYO with myosin storage
Nemaline myopathy 2	AR *NEB* CMYO nemaline
Congenital myopathy 2A	AD *ACTA1* CMYO nemaline
Congenital myopathy 6 with ophthalmoplegia	AD or AR *MYH2* CMYO with cytoplasmic and intranuclear inclusions

4. Part 3: Diagnostic considerations

4.1. *Current recommendations for the diagnostic evaluation of congenital myopathies*

The second aim of the workshop was to update recommendations for the diagnostic evaluation of a suspected CMYO. In order to determine the current published diagnostic guidelines for CMYO, the PubMed, Scopus and Web of Science online databases were searched, using the following search terms "congenital myopathy" OR "congenital myopathies" OR "congenital dystrophy" OR "congenital dystrophies" AND "nomenclature" OR "definition" OR "classification" OR "terminology" AND "guidelines" OR "recommendation" OR "recommendations" OR "guideline". A total of 49 articles underwent review, with 4 articles suitable for inclusion [1,8,68,69].

Anna Sarkozy (AS) reviewed the previous standard of care document and provided an overview of current status of genetic diagnostics. The diagnosis of CMYO can be made when there are compatible clinical symptoms and either a confirmed genetic diagnosis that accounts for the clinical presentation or a compatible muscle biopsy. In cases where neither are available or have not been obtained yet, a probable or possible CMYO could be referenced, though such patients more accurately belong in a broader category of congenital muscle disease that allows for consideration of alternative diagnoses.

In 2014, a consensus statement summarized international diagnostic recommendations for CMYO [7] including 1) key features helping to differentiate CMYO from other causes of hypotonia and weakness, and 2) clinical, MRI and pathological features helping to discriminate between different genetic subtypes of CM, prioritize genetic testing, and identify pathogenic sequence variations.

Now and in the past, the diagnostic evaluation always begins with a comprehensive and often multidisciplinary clinical evaluation with careful attention to family history and ancestry. Differences in local

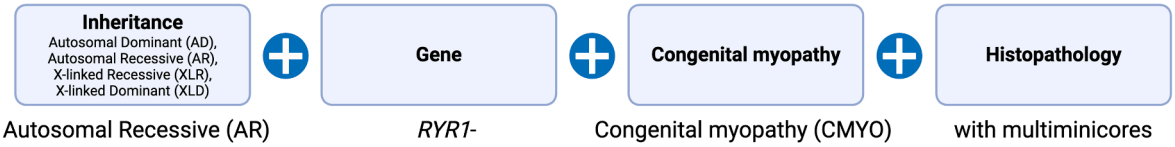

Fig. 1. Proposed CMYO nomenclature including, in sequencial order, the following components: pattern of inheritance, gene, CMYO and main histopathological features.

expertise and availability of resources (e.g., access to genetic testing) should be acknowledged. Traditionally, key investigations include electroneuromyography (ENMG) (including single fiber EMG and repetitive nerve stimulation as indicated for exclusion of myasthenic syndromes), muscle imaging (i.e., muscle ultrasound or MRI depending on the age and respiratory function of the patient and local availability), and muscle biopsy. Previous guidelines promote genetic testing, at that time done by sequential, single gene Sanger sequencing, to be completed after muscle biopsy [7]. However, presently, with wider availability of MPS, broad based gene testing (panels, WES, WGS) has increasingly become the first-tier test for patients with CMYO and congenital hypotonia [70], often preceding muscle biopsy, after age-appropriate exclusion of alternative diagnoses. When genetic testing is not informative or inconclusive, additional investigations should be performed initially using clinically available testing (i.e., biopsy, imaging) and may go on to include research-based technologies such long read exome sequencing, muscle RNA sequencing using patient's muscle or fibroblasts or other "omic" technologies being explored for diagnostic utility. Importantly, non-genetics mimics of CMYOs (i.e., acquired autoimmune conditions such as FARAD, severe late onset nemaline myopathy (SLONM), etc.) need to be excluded through appropriate testing [21].

As a group, we advocate for this 'genetics first' approach (when/where available) to CMYO diagnostics. While not directly documented for CMYOs specifically, abundant data from other rare diseases and from cohorts such as those with neonatal hypotonia have shown that early utilization of broad-based genetic testing is time and cost effective and directly impacts patient treatment and management [71,72]. In addition, a confirmed genetic diagnosis, when established, facilitates focused screening for subtype-specific comorbidities (e.g., cardiomyopathy in patients with *TTN*—CMYO), family planning, and clinical trials.

4.2. Ancillary testing

Ancillary tests such as serum creatine kinase (CK), ENMG, imaging, and muscle biopsy may be performed depending on the local availability to further characterize the clinical phenotype. They may also be conducted ahead of genetic testing for the purposes of excluding other possible disorders, or when genetic studies are inconclusive. Conversely, ancillary tests can help support pathogenicity of variants of unknown significance (VUS) and can help to characterize the clinical spectrum associated with CMYOs, especially in the setting of novel genes or recently discovered forms. Serum CK in CMYOs is usually normal or mildly elevated. Significantly raised CK levels (more than five times normal) should prompt consideration of a muscular dystrophy, though rarely can be seen with some CMYO genetic subtypes (e.g., CMD or exertional myalgia presentation of *RYR1* CMYO, *TTN* CMYO).

4.2.1. Electrodiagnostic studies

Electroneuromyography confirms the clinical suspicion of muscle involvement revealing an early and rich recruitment pattern with low-amplitude motor unit potentials (MUPs) [73,74] and allows for characterization of the pattern of muscle involvement. Together with nerve conduction studies (NCS), it can exclude neurogenic or peripheral nerve involvement. Other techniques such as 3 Hz-Repetitive Nerve Stimulation (RNS) or single fiber EMG can be useful to investigate for a significant decrement, typically found in Congenital Myasthenic Syndromes, whose symptoms and presentation often overlap with those of CMYOs [75,76]. Nonetheless, it's worth noting that some CMYO can also be associated with neuromuscular junction abnormalities [77,78] and (rarely) changes on nerve conduction studies (particularly in neonates). While ENMG is routinely used in the adult population and one of the first-line tests in neuromuscular diseases, it may be less well tolerated and difficult to interpret in the pediatric population, especially in newborns and infants.

4.2.2. Muscle imaging

Susana Quijano-Roy (SQR) presented the state of the art regarding the use of muscle imaging in the diagnosis of CMYOs. MRI is the preferred tool and detects different degrees of fibroadipose replacement of the affected muscles, either by T1-TSE weighted sequences, or by fat images on Dixon techniques.

Since CMYOs show often selective involvement in certain head muscles (pterygoids, tongue) or in neck, arm or trunk muscles, whole body scanning (WB-MRI) is preferred. WB-MRI patterns have been well characterized in different CMYOs (*SELENON, AD RYR, DNM2, MYH7* or *ACTA1* CMYOs) [79,80]. Other entities are not explored enough or present more heterogeneous profiles (e.g., *NEB* CMYO nemaline). In young children, to avoid sedation for MRI, ultrasound can be used as a first approach to search for a particular myopathic profile in the presence of a suggestive clinical phenotype, whenever MRI is not feasible or to help determine biopsy site [81]. Interestingly, muscle imaging can be more informative than muscle biopsy in certain clinical contexts.

The diagnostic yield of muscle MRI varies according to age and time of evolution of the disease, being more informative in patients with moderate weakness and less so in infants and young children. Identification of a given pattern depends on existing knowledge and local expertise and is particularly useful in certain clinical contexts (spinal rigidity, hyperlaxity). For example, imaging of patients with Rigid-Spine Syndrome has been particularly well studied, and algorithms have been developed for a number of them [82]. Pauci-symptomatic family members can also be identified, allowing to properly evaluate genetic transmission. In the last years, heatmap graphical representations and analysis using random forest analysis have been popularized. Heat mapping graphics display visual representations useful to identify at a glance the fingerprint of a myopathy (regional heatmap) or to provide information about muscles affected in different ways or at different times (hierarchical heatmaps). These may be useful to characterize the topography and evolution of muscle involvement, which are important for natural history studies or to define potential outcome measures for therapeutic trials.

To illustrate the usefulness of WB-MRI in interpreting VUS, SQR presented preliminary results from a study on early-onset hereditary myopathies (unpublished results). Three blinded experts assessed 30 WB-MRI scans of children with suspected early-onset myopathy and variants (classified into five ACMG categories: pathogenic, likely pathogenic, VUS, likely benign, or benign) in one of ten genes with well-defined imaging patterns. A sequential process studied coherence between MRI patterns and genetic results. WB-MRI showed total coherence with genetic results in over 80 % of cases, with more than half of the causative genes correctly identified by the experts in the absence of any phenotypic data. Coherence was 100 % in cases with pathogenic variants, and 75 % and 80 % for confirming likely pathogenic variants and VUS, respectively.

4.2.3. Muscle biopsy

Ichizo Nishino (IN) discussed the role of muscle biopsy in the current diagnostic strategy. Although genetic testing is now widely available and generally considered first-line, biopsies remain essential for new gene-disease characterization and for understanding disease pathophysiology. Biopsy samples can also provide critical source material for ancillary diagnostic studies such as mtDNA analysis and RNA-seq [83]. Moreover, in cases with inconclusive MPS results, muscle biopsy allows for immunohistochemical and protein studies, transcriptomics (single nuclei RNA-Seq), and the development of cell culture and 3D muscle models. Biopsy tissues can also be used for functional studies; for example, MHS can be evaluated using the calcium-induced calcium release (CICR) assay, which is considered more specific than the in vitro contraction test [84].

CMYOs are associated with wide genetic and histopathological heterogeneity. For instance, more than ten causative genes have been identified for nemaline myopathy, whereas a single gene, *RYR1*, is

implicated in at least ten different muscle diseases. Notably, AD pathogenic variants in the C-terminal region of *RYR1* are linked to typical central cores accompanied by type 1 fiber uniformity and decreased CICR, indicating for in most cases, they do not confer susceptibility to MHS, except for certain specific mutations such as the p.G4638D variant [85,86]. In contrast, AD variants in other regions are associated with atypical central cores with poor demarcation and/or multiple cores and increased CICR, indicating MHS. Thus, even cases pathologically diagnosed as CCD due to *RYR1* variants may represent physiologically different diseases.

Importantly, recent evidence indicates that central cores in the C-terminal *RYR1* disease often appear later in the disease course [87]. Consequently, in early-life biopsies, patients with C-terminal variants may display only type 1 fiber uniformity without any cores, which can lead to an initial diagnosis of congenital neuromuscular disease with uniform type 1 fiber. This *RYR1*-specific observation illustrates how biopsy timing can directly influence pathological classification.

4.3. Genetic testing

The current genetic strategy includes as first line testing either by WES/WGS or MPS-based multigene panels, depending on local availability (including the number of clinically relevant genes within locally available panels), age and clinical situation of the patient, age at onset, duration of symptoms and family history. Whereas WES/WGS is considered the first option in some pediatric settings (neonatal hypotonia, unusual presentations including extra-muscular involvement, critically-ill infants), neuromuscular multi-gene panel testing may be more appropriate and suitable for older children and adults.

Dr Mark Davis (MD) discussed the Australasian experience with MPS-panel genetic strategy. The first custom gene capture panel was designed in their laboratory in 2012 and formal reporting of cases began in 2013. As new gene discoveries have been published, the panel gene list is updated to keep it relevant, and constant updates to the methodology, as well as the ability to sequence to high depth (>300x average coverage), have allowed to incorporate initially comprehensive copy number variation (CNV) calling down to single exon resolution, and more recently repeat expansion detection, into the analysis pipeline. This has increased the diagnostic yield significantly, as 10 % of solved cases involve a CNV, including a number of childhood and adult cases of myopathy that were due to homozygous deletion of *SMN1*. Similarly, a number of cases referred for myopathy testing have been found to have *DMPK* repeat expansion at the myotonic dystrophy type one (DM1) locus. Custom designing a panel also allows the addition of non-coding regions of interest, allowing the detection of deep intronic variants. The use of a comprehensive muscle gene panel has resulted in a number of cases of 'diagnosis by genetic analysis', such as a case of an initially suspected FSHD2 due to a variant in the *RYR1* gene and a late-onset case initially suspected to be a LGMD resulting from a variant in the *ACTA1* gene, thus expanding the clinical spectrum associated with these genes.

In the age of ever-decreasing sequencing costs, custom gene capture panels are still beneficial in terms of coverage, throughput and cost. On another note, genome level approaches are associated with a significant risk of secondary findings, which come with their own set of challenges for families. Appropriate pre- and post-test counseling must be performed prior to and after all forms of genetic testing. Ultimately, the choice of genetic testing is highly dependent on clinically available testing options and expertise in each environment. Many clinical teams around the world don't have access to either WES or WGS or the appropriate counselling support to facilitate the comprehensive pre- and post-test counselling needed. Moreover, existing genomic databases are largely derived from patients of European ancestry, which limits the interpretation of variants in other populations and may obscure unique or region-specific genetic expressions that have yet to be identified.

It is also of utmost importance to consider and exclude conditions that could be missed by MPS, in particular those due to deletions/duplications or those associated with repeat expansions like spinal muscular atrophy (SMA) or DM1. The discussion also stressed the complexity of variant interpretation and the key role of specialist, clinical, multidisciplinary team assessments to aid variant validation. Particular attention is also needed for complex and extremely polymorphic genes, such as *TTN* and *NEB*, as well as for genomic regions less well covered by MPS, like exon 1 in the *SELENON* gene. Of note, clinical RNA-seq is starting to become available but is still not implementable as a routine test in many laboratories due to complexities around specimen collection and data analysis.

4.4. Genetic testing in the neonatal intensive care unit (NICU) setting

Pankaj Agrawal (PA) discussed genetic testing in neonatal intensive care units (NICUs). Genetic disorders collectively cause significant morbidity and mortality rates in the NICU and are responsible for up to 10–20 % of NICU admissions. Lamentably, many infants with a suspected genetic disorder undergo a long, complex, costly, and potentially invasive diagnostic odyssey. When locally available, rapid WES/WGS may be a first line of genetic testing in the NICU. Many studies have shown that rapid WES/WGS in NICU infants is associated with high diagnostic yield (20–60 %), faster genetic diagnosis, significant impact on clinical care, high utility perception among clinicians and parents, and cost-effectiveness [88,89].

Hypotonia in infants is defined as reduced resistance to a passive range of motion, often accompanied by weakness. It can be secondary to causes such as hypoxia, hypoglycemia, congenital heart disease, electrolyte imbalances, sepsis, and perinatal depression, which should be first ruled out. Unexplained hypotonia can be due to a primary neuromuscular disorder, as seen in CMYOs, or it can entail multisystem involvement. In unexplained hypotonia, rapid WES/WGS is beneficial as it not only shortens the diagnostic odyssey but additionally expedites medical management and facilitates decision making, such as respiratory and feeding support, utilization of personalized therapies, and family counseling. In a recent review, the use of rapid WES/WGS was proposed as a first line of diagnostic test while considering rapid chromosomal microarray and specific genetic testing for Prader-Willi syndrome, DM1 and SMA [70]. Based on the SMA experience with the availability of three novel therapies [90], many congenital conditions presenting in the NICU will potentially be amenable to personalized therapies where time to diagnosis will be critical in their effectiveness, emphasizing the need for a rapid WES/WGS approach.

4.5. Resource limited settings

Neuromuscular diseases affect more than 15 million people globally [91]. While in high-income settings DNA-based diagnosis enabled care pathways and gene-specific therapies are increasingly regarded as standard of care, their availability is limited in low- and middle-income countries. Moreover, 86 % of published genetic data are derived from individuals with European ancestries and this inequality hampers understanding of genetic diversity as well as accurate genetic diagnosis. Jo Wilmshurst (JW) summarized the challenges faced in the African region which, with its high disease burden and limited resources, represents an extreme challenge for access to genetic testing. The disease focus leans towards communicable and acquired neuromuscular diseases, resulting in a lack of data on genetic neuromuscular diseases and the misperception that they are less prevalent.

Achieving a diagnosis in resource-limited settings through genetic closure has multiple barriers. Failure to recognize that a patient has a genetic neuromuscular disease is common. Birth typically occurs at home and subsequent care is focused in primary healthcare or community clinics. Underlying weakness and motor delay are often missed, and management is focused on respiratory and nutritional complications which caregivers in these settings are more equipped to manage. Indeed, most patients are unable to access a tertiary setting. Point of entry

diagnostic screens are often limited, from basic bloods tests such as creatine kinase, through to performing and interpreting EMG as well as access to muscle biopsy and effective histopathology analysis and interpretations. This is compounded by lack of access to specialists as well as very few dedicated pediatric neuromuscular services [92,93]. For the few children seen in a specialist setting, access to genetic testing is another barrier. In-country genetic testing, when available, is typically limited to SMA and Duchenne muscular dystrophy. Some centers have set up testing for locally common variants [94]. Otherwise, samples are sent overseas. The cost is often prohibitive, and the analysis limited by the lack of inclusion of local variants and the impact of common polymorphisms that are not in fact disease causing [95,96]. A prime example of this is the clinicopathological phenotyping of children in the Western Cape of South Africa where the CMYO patients with central nuclei on their histology analysis are the predominant subtype of myopathy seen. Collaborative work enabled common *RYR1* variants to be identified, identifying probable founder mutations and this resulted in the testing for the common variants to be set up locally [55]. Collaborations have proved effective in pushing the boundaries to understand the genetic landscape but still have a long way to go for sustainable local access to genetic diagnosis for many patients with neuromuscular diseases [97, 98].

4.6. Consensus on diagnostic considerations

The group considered current strategies for the diagnosis of CMYOs. A central point of agreement was that a "genetics-first" approach is now the preferred strategy whenever available. The 3 options are NGS, through targeted panels, exome or genome sequencing, increasingly serves as the first-tier investigation for patients with congenital hypotonia or suspected CMYO. Such an approach is time- and cost-effective, shortens the diagnostic odyssey, and directly informs management. At the same time, exclusion of non-CMYO and also non-genetic mimics remains essential through appropriate testing. The group emphasized the importance of rapid WES/WGS in NICUs, where unexplained hypotonia is common and early diagnosis may guide acute management and access to novel therapies. In resource-limited settings, limited access to specialists and high costs remain barriers, making collaborative initiatives and targeted local testing useful interim solutions.

Regarding ancillary testing, serum CK is usually normal or mildly elevated in CMYOs; high values should prompt differential diagnosis with (congenital) muscular dystrophies. Electrodiagnostic studies and muscle MRI are particularly valuable. In very young children, technical limitations may make these studies difficult, so genetics is the first step; however, in older children and adults, these tests can be part of first-line investigations to help distinguish CMYOs from congenital myasthenic syndromes and/or neurogenic disorders, and to characterize the clinical phenotype. Ultrasound may serve as an imaging alternative in young children where MRI is not feasible. Muscle biopsy, though less frequently required initially, remains critical in unresolved cases, in the discovery of new gene-disease associations, and for functional validation.

Overall, the consensus supports a genetics-first diagnostic framework, complemented by ancillary investigations and context-sensitive strategies to ensure accurate diagnosis across age groups.

The revision of the standards of care guidelines will be undertaken by a dedicated expert working group.

5. Conclusions

A precise and accurately named diagnosis is part of each patient's identity and has implications for the development of therapies, clinical trials, and access to resources. The group concluded that while the designation as "congenital myopathy" (CMYO) is the common starting point, the mode of inheritance, gene, and muscle biopsy features, if known, should be part of an individual's more specific diagnosis. Based on this, the group formulated a framework for a new nomenclature and companion classification incorporating these features.

An updated diagnostic algorithm and supporting guidelines manuscript will be completed by an expert working group. In general lines, the diagnosis of CMYO can be made when there are compatible clinical symptoms, and either a confirmed genetic diagnosis that accounts for the clinical presentation or muscle biopsy supporting the diagnosis. Despite all the diagnostic efforts, a relevant number of patients with suspected CMYO remain genetically undiagnosed, even more so in low-income countries with limited access to testing. Improved evaluation of variants, identification of novel disease genes and application of novel genetic testing (including RNA sequencing, long-read WGS and/or proteomics) will help to increase diagnostic yields for CMYO.

The meeting concluded by emphasizing the need for education and increased awareness of CMYOs within the patient and medical community. Patient advocacy organizations and key leaders will help to disseminate this information world-wide. We must improve our engagement with low- and middle-income countries that are often underrepresented in these academic meetings. Future discussions around nomenclature, diagnostics, and treatment in CMYOs must include patient advocates and global representation.

6. List of participants

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Declaration of competing interest

The 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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