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280th ENMC International Workshop: The ERN EURO-NMD mitochondrial diseases working group; diagnostic criteria and outcome measures in primary mitochondrial myopathies. Hoofddorp, the Netherlands, 22-24 November 2024

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ABSTRACT

The 280th ENMC International Workshop, held in Hoofddorp, The Netherlands, November 22–24, 2024, focused on primary mitochondrial myopathies (PMM). The workshop aimed to update diagnostic criteria, outcome measures, and explore new digital health technologies (DHTs) in the context of clinical trial design and conduct for PMM. Key points discussed included: (i) PMM definition and phenotypes; PMM are genetically determined mitochondrial disorders with prominent skeletal muscle involvement with two major phenotypes: mitochondrial myopathy (MiMy) either with or without chronic progressive external ophthalmoplegia (PEO); (ii) diagnostic criteria, with emphasis on the importance of genetic testing and muscle biopsy for accurate diagnosis; (iii) outcome measures: consensus on clinical scales, functional tests, performance measures, and patient-reported outcome measures (PROMs) for both adults and children; (iv) digital health technologies, with exploration of wearable and non-wearable technologies for gait analysis, physical activity monitoring, and other assessments; (v) potential and limitations of biomarkers for PMM diagnosis and monitoring. The workshop concluded with a strong consensus on the updated definition of PMM, its phenotypes, and the recommended outcome measures for clinical studies. Further research is needed to validate digital health technologies and biomarkers for PMM.

1. Introduction and background

Primary mitochondrial myopathies (PMM) have been classified as genetic disorders of the oxidative phosphorylation (OXPHOS) system affecting predominantly, but not exclusively, skeletal muscle [1]. Secondary involvement of mitochondria is frequently observed in various neuromuscular diseases, but those are not considered as PMM.

PMM may present at any age, although typically the more severe conditions tend to present earlier in life. The most common clinical presentation of PMM is chronic progressive external ophthalmoplegia (PEO) [1]. PEO is often associated with other signs of skeletal muscle involvement, typically slowly progressive axial and proximal limb weakness affecting predominantly the hip and shoulder girdle muscles, often with muscle wasting. Muscle weakness may also cause difficulty in swallowing, hypophonia and respiratory failure. Distal muscle weakness may be present but is rarely seen early in the disease. Other manifestations of PMM are exercise intolerance with myalgia, muscular atrophy, fatigue, muscle cramps or recurrent rhabdomyolysis with myoglobinuria triggered by exercise. Any of these symptoms or signs may be present in isolation or in combination with multiple other symptoms depending on the gene causing the specific PMM and the severity of the disease. PMM symptoms can also present without PEO, which can make the correct diagnosis of Mitochondrial Myopathy (MiMy) challenging.

Hypotonia, generalized weakness, respiratory insufficiency, feeding difficulties and reduced/absent tendon reflexes are common in early onset forms of PMM, which is frequently complicated by multisystem

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disease and often fatal in early childhood.

Previously, in November 2016, many of the attendees of the current workshop met in Rome and published a consensus paper on "Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults" [1]. This study was the first one to provide a clear definition of PMM as a specific entity and also detailed suggested outcome measures to be used in both children and adults with PMM. Since then, several observational studies have been published on PMM [2,3] and >10 pharmaceutical companies have announced the development of new molecules targeting PMM. Several clinical trials based on the proposed outcome measures (OMs) have been performed [4–7], are still running or are ready to start (https://clinicaltrials.gov/ct2/results?cond=Mitochondrial±Myopathies&term=&cntry=&state=&city=&dist=).

Based on the recent experiences in the above-mentioned observational studies and data collection in national registries and clinical trials, the PMM consensus needs to be updated and expanded to include new OMs, new patient-reported outcome measures (PROMs), and new biomarkers, which all have demonstrated potential validity in both PMM natural history studies and interventional clinical trials. Moreover, at the time of the previous consensus, the utility of the new digital health technologies (DHTs) [8] was not fully known. Guidance regarding the use of DHTs in PMM is needed.

With this ENMC workshop, endorsed and co-founded by the ERN EURO—NMD and its mitochondrial working group (https://ern-euro-nmd.eu/group-of-people/mitochondrial-diseases/), we planned a joint European and United States of America (USA) collaboration to update the consensus recommendations to harmonize and improve the conduct of natural history studies and clinical trial readiness in PMM.

The 280th ENMC international workshop was held in Hoofddorp, The Netherlands, from November 22 to 24, 2024.

The aims of the workshop were:

- to review and update the definition of PMM, harmonizing criteria for diagnosing PMM and its phenotypes
- to explore OMs and real-life challenges expanding experiences from the previous consensus paper and drawing lessons from past and current clinical trials
- to reach a consensus on an optimal set of OMs, PROMs, functional outcome measures, disease biomarkers, and measures of disease burden for natural history studies and investigational trials
- to explore new DHTs that can be applied in the field.

2. Preparatory work and methodology

The Delphi method was used to develop this updated consensus. The Delphi method provides a systematic approach for collecting opinions from experts (the 'Delphi Panel') and has been widely applied to obtain consensus recommendations on well-defined topics, including several aspects of primary mitochondrial diseases [9–12] and in the previous consensus workshop in Rome in 2016 [1]. Although described as a 'panel', experts provide their opinions freely, individually and vote anonymously. Moreover, the recently published supporting tool published by the ERN was followed (available at https://www.erknet.org/fileadmin/files/user_upload/0._Intro_Toolkit_D-B.2_.pdf).

2.1. Phase I: pre-meeting phase

The mitochondrial working group of the ERN EURO—NMD, co-chaired by M. Mancuso and C. Kornblum, invited experts from recognized centers of excellence within the ERNs across Europe, along with specialists from USA. These participants were selected based on their established expertise in mitochondrial medicine, including the management of adult and pediatric patients. To ensure diversity, invitees were asked to suggest additional participants to achieve a balanced representation in terms of geography and gender. Invitations were sent via email, outlining the study objectives and the Delphi process. Dr. Stoyanova-Beninska from the European Medical Agency (EMA) was also invited and attended the workshop. Additionally, representatives from mitochondrial patient advocacy groups (MITOCON from Italy, UMDF from the USA, and the Lily Foundation from the UK) were invited, along with two early-career researchers (P. Lopriore and L. Semmler) who actively contributed.

The in-person consensus panel comprised 26 participants from seven European countries and USA, including one patient representative. During the initial virtual meeting, participants discussed revising the conclusions from the prior consensus workshop based on new developments in the field of PMM. They unanimously approved the literature search strategy and agreed to divide pre-meeting tasks among seven working groups (see Supplementary File S1).

Each working group conducted a review of the published literature from January 1, 2016, to April 1, 2024, by searching electronic databases including MEDLINE via PubMed, ClinicalTrials.gov, and the European Clinical Trials Register. For the discussion on the definition of PMM and clinical phenotypes, the following search string was used: "mitochondrial myopathy" (MeSH term) AND/OR diagnostic criteria AND/OR definition AND/OR diagnosis. For the remaining working groups' topics, peer-reviewed case reports, case series, case-control studies, prospective or retrospective cohort studies, non-randomized uncontrolled trials, and randomized controlled trials focusing on genetically confirmed PMM or "metabolic myopathies" were included. For DHTs, the search was also expanded to include natural history studies and interventional studies in any neuromuscular disease. Additionally, the search for OMs was broadened to include OMs used as primary endpoints in successful clinical trials (listed in ClinicalTrials.gov and the European Clinical Trials Register) for any muscle disease. Non-English articles were excluded. Articles were categorized by type (books and documents, clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews) and age category (children <16 years old and adults). Each working group provided the results as a PRISMA Flowchart and a list of included articles from which the survey queries were developed (Supplementary File S2), which were shared with all experts by the facilitator (M. Mancuso). During the live discussions, additional evidence not included in this list, was presented and discussed by the speaker for each topic of the working groups.

M. Mancuso developed two surveys (Supplementary Files S3 and S4) to assess consensus levels among the experts. The first survey (Supplementary file S3) aimed to assess the validity of the OMs, scales, and PROMs approved in the previous consensus within the context of PMM. The second survey (Supplementary file S4) focused on addressing the new questions developed by the seven working groups. Responses were collected anonymously through the SurveyMonkey platform, analyzed and discussed ahead of the in-person meeting. Participants used a 5-point Likert scale [13] to express their agreement with each statement (1: absolutely disagree; 2: disagree; 3: neutral; 4: agree; 5: absolutely agree). A strong consensus was defined as >70 % of responses scoring ≥4 or ≤2, with a mean score of ≥4 or ≤2. If only one condition was met, a consensus was formally reached. Statements failing to meet these criteria were considered to lack consensus.

3. Results

3.1. Live meeting general considerations

At the workshop, following a warm welcome and introductory remarks by Patricia van Dongen, Programme Manager of ENMC, and co-organizers M. Mancuso and C. Kornblum (also the co-chairs of the ERN EURO—NMD mitochondrial working group), the sessions commenced with M. Mancuso presenting the results of the two surveys, followed by an overview of the current state of European and USA registries, as well as the structure of national and international networks, delivered by C. Lamperti, T. Klopstock, R. McFarland, M. Bellusci, and M. Hirano.

During the first voting round, held prior to the workshop, the majority of experts supported a revision of the PMM definition from the previous consensus. The prior definition described PMM as "genetically defined disorders leading to defects of oxidative phosphorylation, predominantly but not exclusively affecting skeletal muscle." The experts also emphasized the need for a better classification of PMM based on phenotype (Supplementary Data S3).

The second half of the first day focused on an in-depth discussion of diagnostic criteria and clinical phenotypes of PMM (led by working group 7), covering both adults and children. This discussion was led by R. Horvath, V. Carelli, and F. Distelmaier, with support from ECR P. Lopriore, who presented the findings of the second survey. By the end of the day, new statements were formulated, some existing queries were revised, and an anonymous voting session was conducted.

The second day began with an overview by A. Karaa on the OMs used in previous clinical trials, followed by K. Waller from the Lily Foundation, who provided the perspective of patient organizations on outcome parameters. Most of the day was dedicated to discussing the results of working groups 1 and 2, which focused on clinical scales and PROMs. A variety of PROMs addressing diverse topics—such as pain, fatigue, exercise intolerance, activities of daily living, and caregiver burden—were proposed. These PROMs were informed by experiences from other neuromuscular diseases, including myasthenia gravis and metabolic myopathies. A similar approach was applied to the development of a set of clinical scales. This was followed by discussions and additional voting under the coordination of R. McFarland. Subsequent sessions included presentations on the findings of working groups 5 and 6 (functional tests and performance outcome measures, led by Y. Ng and T. Taivassalo), biomarkers (working group 4, presented by R. Artuch), and DHTs by working group 3 (A. Karaa). Finally, V. Stoyanova-Beninska shared the perspective of regulatory agencies on rare diseases.

At the end of the second day, new statements were drafted, some previous queries were revised, and an anonymous voting session was conducted.

On the final day, the results of all new voting sessions were reviewed and discussed, with a focus on outcomes for children (led by E. Bertini) and adults (C. Kornblum). A few additional queries were formulated, followed by a further voting round. The workshop concluded with all experts agreeing on the importance of ongoing monitoring and a commitment to revisiting this new consensus within the next 3–4 years if necessary. All statements and results developed live at the workshop are available as supplementary data S5.

3.2. Definition of PMM, clinical phenotypes and diagnostic approach (Table 1)

The experts agreed on the following new definition of PMM: “Primary mitochondrial myopathies (PMM) are genetically determined mitochondrial disorders with prominent skeletal muscle involvement. Other diseases with secondary involvement of mitochondria are not considered PMM”.

Regarding PMM phenotypes, the experts agreed to differentiate the umbrella term of PMM according to the presence or absence of chronic progressive external ophthalmoplegia (PEO). Two PMM major phenotypes are therefore proposed: [1] PEO spectrum, defined as mitochondrial myopathy (MiMy) with external eye muscle involvement, and [2] MiMy spectrum without PEO. Regarding the diagnostic process in the investigation of suspected PMM, the experts agreed that a diagnosis of PMM cannot be excluded if respiratory chain enzyme activities are normal in a skeletal muscle biopsy specimen (if available).

Table 1
Statements of the Delphi working group.

Definition and diagnostic approach	Consensus	
	Percentage of sum 4 + 5	Mean score
Primary mitochondrial myopathies (PMM) are genetically determined mitochondrial disorders with prominent skeletal muscle involvement. Other diseases with secondary involvement of mitochondria are not considered PMM.	100	4.82
PMM Phenotypes: 1. PEO spectrum 2. Mitochondrial Myopathy (MiMy) spectrum without PEO	91	4.32
Isolated ptosis (without ophthalmoparesis) should be classified within the PEO spectrum	100	4.85
PEO spectrum refers to a phenotype with predominant involvement of external eye muscles. Exercise intolerance, fatigue or mild proximal muscle weakness can be present.	100	4.82
PMM can present with exercise intolerance and fatigue or proximal muscle weakness without PEO	100	4.68
Exercise intolerance and fatigue without PEO and/or fixed muscle weakness justify the attribution to a MiMy phenotype.	86	4.32
If PMM is suspected, except for clear mtDNA related phenotype, whole exome or whole genome sequencing is preferable prior to direct mtDNA sequencing.	94	4.55
PMM can be suspected if myopathic clinical symptoms AND a skeletal muscle biopsy presenting with mitochondrial changes (like ragged red fibers and/or COX-negative fibers) above the expected age range AND/OR respiratory chain enzyme deficiency in skeletal muscle tissue AND mtDNA multiple deletions, depletion or both above the expected age range are present (in absence of mutations in nuclear mitochondrial genes).	77	4.4
A PMM diagnosis cannot be excluded if respiratory chain enzyme deficiency is not detectable in skeletal muscle biopsy specimens (if available).	100	4.91
If PMM is suspected, genetic testing of DNA from blood leukocytes is an appropriate first-line approach. However, if negative, or for the confirmation of the diagnosis, muscle biopsy may be needed in some cases.	83	3.92
For mtDNA single-large scale deletion detection in adults, muscle and urine sediment are better sources than blood leukocytes for DNA extraction (adults only).	96	4.46
More evidence should be generated to endorse the use of biomarkers to reflect disease severity and progression and to monitor therapy response in PMM. For this purpose, thymidine/deoxyuridine for MNGIE is the only established biomarker in PMM.	100	4.82
In clinical practice, FGF-21, GDF-15, amino acids, organic acids, acyl carnitine profiles, basal blood lactate and CK may provide supportive information to differentiate patients with possible PMM from other conditions. However, normal values of these biomarkers do not exclude the possibility of PMM.	100	4.64
There are no validated digital tools for PMM assessment to date, with no pivotal studies on this topic published. More studies need to be done to further develop and validate such digital tools in PMM.	100	4.63

Furthermore, given the continuous discovery of new genes associated with mitochondrial diseases and the fact that several genes have yet to be linked to a specific mitochondrial phenotype [14], the experts agreed that PMM can be suspected under the following conditions: the presence of myopathic clinical symptoms and (i) a skeletal muscle biopsy showing mitochondrial abnormalities (e.g. ragged red fibers and/or cytochrome-*c*-oxidase (COX)-negative fibers) beyond those expected for the patient's age and/or (ii) respiratory chain enzyme deficiency in skeletal muscle tissue and (iii) mitochondrial DNA multiple deletions, depletion or both exceeding the expected age range, even in the absence of mutations in nuclear mitochondrial genes.

In the absence of a clear mitochondrial DNA related syndrome and/or maternal inheritance, the first line testing for suspected PMM should be a whole exome or whole genome sequencing prior to direct mitochondrial DNA sequencing. If a mitochondrial DNA single-large scale deletion is suspected in adults, muscle and urine sediment are the preferred tissues to test compared to blood leukocytes.

3.3. *Consensus of measures suitable to assess PMM patients in clinical studies*

Table 2 shows all measures endorsed by the experts to assess PMM patients, both children and adults. Notably, several scales have been proposed as potentially useful in PMM; however, most have neither been utilized nor validated specifically for PMM and were recommended based on their applicability in other neuromuscular diseases. Experts advocated for prospective studies in PMM to better evaluate the relevance of these scales in meeting the specific needs of this condition. Regarding the biomarkers, in current clinical practice various methods are being used to differentiate mitochondrial diseases from other conditions. These include laboratory testing of blood and urine, cerebrospinal fluid analysis, muscle biopsy, and imaging techniques. Recent studies have investigated potential new biomarkers, focusing on two blood markers: Growth Differentiation Factor 15 (GDF-15) and Fibroblast Growth Factor 21 (FGF-21). These biomarkers were evaluated for their potential utility in the differential diagnosis of PMM, as a tool to assess disease severity and progression as well as clinical endpoints. However, none of the studied parameters demonstrated the high specificity and sensitivity required for reliable biomarkers. Consequently, we concluded that, other than thymidine/deoxyuridine for Mitochondrial neurogastrointestinal encephalopathy (MNGIE), more data are needed before recommending the widespread adoption of specific biomarkers. Additionally, we believe that a biomarker for distinguishing phenotypes of mitochondrial diseases is unnecessary, as this differentiation can already be achieved effectively through clinical investigations.

Finally, after a deep discussion on the possible role of DHTs, the experts agreed that, to date, there are no validated DHTs specifically for PMM assessment, nor have any pivotal studies on this topic been published. Further research is needed to develop and validate such tools for use in PMM. Drawing on insights from research literature and experience with other neuromuscular diseases, the group proposed a set of DHTs for future studies focused on PMM. The proposed tools (Table 2) include gait and movement analysis using wearable technologies (e.g., accelerometers for remote physical activity monitoring) and non-wearable technologies (e.g., gait mats), as well as customized foot sensor inserts and smartphone-based monitoring tools, particularly for children. Additionally, digital tools for evaluating sleep parameters, pharyngeal weakness, and breathing were recommended.

Table 2
Endorsed measures suitable to assess PMM patients in clinical studies (for both adults and children unless specified).

Clinician-reported outcome measures: Clinical scales
Newcastle Mitochondrial Disease Adult Scale, adult only
Short Form 36 Health Survey (SF-36) score
Newcastle Pediatric Mitochondrial Disease Scale (3 age range), children only
Hammersmith Functional Motor Scale Expanded*
Physician Global Assessment (PhGA)*
Modified Fatigue Impact Scale*
Clinical Global Impression (CGI)
Gait, Stair, Gower Manoeuvre and Chair (GSGC) composition score*
International Pediatric Mitochondrial Diseases Scale (IPMDS), children only
Pediatric Quality of Life Inventory (PedsQL), children only*
Functional tests
6-Minutes Walk Test
6-Minutes Walk Test fatigue index ([minute 2 distance –minute 6 distance]/minute 2 distance], positive value represents fatigue
12-Minutes Walk Test
Balance assessment in different conditions, such as tandem stance (TS) Eyes Open and Closed, adult only
Timed Up-and-Go test (x3), adult only
Spontaneous gait speed
Five times Sit-To-Stand test, adult only
North Star Ambulatory Assessment (NSAA), children only
Hammersmith Infant Neurological Examination (HINE), children only
Quick Motor Function test (QMFT), adult only
Performance outcome measures
30 Seconds Sit-To-Stand test
Maximal inspiratory pressure (MIP) when respiratory weakness is suspected
Spirometry with FVC when respiratory weakness is suspected
Cardiopulmonary exercise test (CPET): PEAK VO2 (maximal) and OUES/BSA (submaximal), in children above the age of 6-yrs and adults
Blood lactate and the heart rate during constant submaximal exercise (for individual > 6-yrs old who are not compliant with CPET)
Patient-reported outcome measures: measurements of patient function or feeling
NMDAS/NPMDS Section IV
Fatigue severity scale (FSS)
Multidimensional Fatigue Inventory (MFI)
NeuroQoL Fatigue Short-Form scores
Quality of Life: PROMIS
PedsQL (Pediatric quality of life inventory), children only
Patient Global Assessment (PGA)
Rotterdam Handicap Scale
MG Symptoms PRO scales
Caregiver burden scale 22 items (*unaffected caregiver only*)
5-level EQ-5D version (EQ-5D-5 L)
West Haven-Yale Multidimensional Pain Inventory (WHYMPI)
Brief Pain Inventory - Short Form (BPI-sf)
Ages and Stages Questionnaires (ASQ), in children ≤ 5-yrs
Five to Fifteen-R (FTF-R) questionnaire, in children ≤15 yrs
Digital tools
Stride velocity 95th centile (SV95C)
Wrist along ankle accelerometer to capture remote physical activity
Wrist accelerometer to capture remote physical activity
Instrumented 7 minutes timed up and go (iTUG)
Non-wearable 3D gait analysis using optoelectronic systems
Digital tools evaluating sleep
Digital tools evaluating breathing
Digital speech evaluation to assess pharyngeal weakness
Customized foot sensor inserts
Smartphone-based monitoring tools, children only
Biomarkers
Body Mass Index (exploratory)

* These scales should be better studied and validated in prospective cohort.

4. Conclusions

The working group achieved a strong consensus on both the updated definition of PMM and its phenotypes. Using the Delphi method, the group revised the recommended OMs to be implemented in PMM

clinical studies, proposing a set of clinical scales, functional tests, performance measures, and PROMs to be applied in both adults and children affected by PMM, as shown in Table 2. More data are needed for considering DHTs and biomarkers in clinical studies.

The working group also noted that substantial funding and efforts should be undertaken to start systematically validating these tools to identify the most relevant ones for PMM specifically and for primary mitochondrial diseases more broadly. The short list of finalized tools was specifically designed to list the most robust curated items that merit further validation by this expert group.

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CRediT authorship contribution statement

Michelangelo Mancuso: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. **Piervito Lopriore:** Data curation, Formal analysis, Investigation, Methodology. **Luisa Semmler:** Data curation, Formal analysis, Investigation, Methodology. **Cornelia Kornblum:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Validation, Writing – original draft.

Declaration of competing interest

Michelangelo Mancuso, Piervito Lopriore, Luisa Semmler and Cornelia Kornblum have nothing to disclose related to this publication

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2025.105340.

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