


ORIGINAL ARTICLE OPEN ACCESS

# Diagnostic Criteria and Management of MELAS and Stroke-Like Episodes: Consensus-Based Statements

Michelangelo Mancuso<sup>1,2,3</sup> | Marcello Bellusci<sup>4</sup> | Valerio Carelli<sup>5,6</sup> | Irenaeus de Co<sup>7</sup> | Daria Diodato<sup>8</sup> | Felix Distelmaier<sup>9</sup>  | Omar Hikmat<sup>10,11</sup> | Michio Hirano<sup>12</sup> | Rita Horvath<sup>13</sup>  | Amel Karaa<sup>14</sup> | Thomas Klopstock<sup>15,16,17</sup> | Mary Kay Koenig<sup>18</sup> | Cornelia Kornblum<sup>19</sup> | Chiara La Morgia<sup>6,20</sup> | Piervito Lopriore<sup>1,21</sup> | Mika Henrik Martikainen<sup>22,23</sup> | Robert McFarland<sup>24,25</sup> | Olimpia Musumeci<sup>26</sup> | Robert D. S. Pitceathly<sup>27,28</sup> | Guido Primiano<sup>29,30</sup>  | Shamima Rahman<sup>31</sup>  | Fernando Scaglia<sup>32,33,34</sup>  | Andrew Schaefer<sup>35</sup> | Manuel Schiff<sup>36,37</sup>  | Luisa Semmler<sup>38</sup> | Costanza Lamperti<sup>39</sup> | Serenella Servadei<sup>29,30</sup>

**Correspondence:** Michelangelo Mancuso ([michelangelo.mancuso@unipi.it](mailto:michelangelo.mancuso@unipi.it))

**Received:** 10 January 2026 | **Revised:** 11 March 2026 | **Accepted:** 17 March 2026

**Keywords:** consensus | diagnostic criteria | management | MELAS | primary mitochondrial diseases | recommendations

## ABSTRACT

**Background and Purpose:** Mitochondrial Encephalomyopathy, Lactic acidosis and Stroke-like episodes (MELAS) is a rare multisystem mitochondrial disorder with clinical heterogeneity. Diagnostic criteria and management strategies for MELAS and mitochondrial stroke-like episodes (SLE) remain inconsistent. This work provides international consensus recommendations on the definition, diagnosis, and management of MELAS and SLE in pediatric and adult populations.

**Methods:** An international Delphi consensus process was conducted within the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD), in collaboration with the US Mitochondrial Medicine Society, the ERN for Hereditary Metabolic Disorders (MetabERN), and patient representatives. Following a systematic literature review, 54 statements addressing diagnostic definitions and management of MELAS were evaluated. Statements not reaching consensus were revised and re-evaluated during a face-to-face meeting.

**Results:** Consensus supported defining MELAS as a clinical syndrome characterized by one or more SLE in the context of mitochondrial dysfunction caused by a pathogenic mitochondrial DNA variant, particularly m.3243A>G in *MT-TL1*. The use of terms such as “MELAS-like” or “MELAS spectrum” was discouraged. The panel agreed that the efficacy of L-arginine, L-taurine, L-citrulline, coenzyme Q<sub>10</sub>, vitamins, and other supplements remains unproven and requires validation in clinical trials. Antiseizure medications should be initiated promptly when seizures are suspected during SLE, and intravenous corticosteroids may be beneficial acutely. Multidisciplinary management of neurological, neuropsychiatric, and systemic complications was endorsed.

**Conclusions:** This international consensus provides updated definitions and practical guidance for the diagnosis and management of MELAS and SLE, aiming to harmonize clinical practice and inform future evidence-based research.

## 1 | Introduction

Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) syndrome is a rare, maternally inherited disorder caused by variants in mitochondrial deoxyribonucleic

acid (mtDNA), most notably the m.3243A>G variant in *MT-TL1* encoding the mitochondrial tRNA for leucine<sup>UUR</sup>[1].

The pathophysiology of MELAS is complex, and driven by heteroplasmic pathogenic mtDNA variants, resulting in variable

The last two authors contributed equally as senior authors.  
For affiliations refer to page 7.

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degrees of tissue dysfunction, particularly in energy-demanding organs such as brain and skeletal muscle [1, 2]. Consequently, the clinical phenotype is highly heterogeneous. Early manifestations commonly include seizures, diabetes mellitus, recurrent headaches, exercise intolerance, and sensorineural hearing loss. Stroke-like episode (SLE), a hallmark feature of the disease, frequently leads to rapid neurological deterioration and represents a major cause of morbidity and mortality. SLE is usually characterized by headache, nausea and vomiting, encephalopathy, focal neurological deficits with or without seizure activity, and cortical and subcortical signal abnormalities on neuroimaging that typically do not conform to large vascular territories (stroke-like lesions, SLL). Although MELAS was initially described in individuals younger than 40 years, late-onset presentations are increasingly recognized [3, 4].

The original diagnostic criteria for MELAS included: (i) SLE before the age of 40 years, (ii) encephalopathy characterized by seizures or dementia, and (iii) evidence of mitochondrial myopathy, such as lactic acidosis or ragged-red fibers on skeletal muscle biopsy [2]. Since the initial definition of these diagnostic criteria, several alternative diagnostic frameworks have been proposed based on national cohort studies, narrative reviews, and expert opinions [5, 6]. Furthermore, as only a subset of individuals carrying the m.3243A>G mtDNA variant, the most common genetic cause of MELAS, develop SLE, the concept of a *MELAS spectrum* or *MELAS-like syndromes* has been suggested to identify clinical syndromes related to the m.3243A>G variant [7]. This broader framework highlights the multisystem nature of the disorder, with potential involvement of the brain, skeletal muscle, heart, gastrointestinal tract, kidneys, endocrine system, respiratory system, and visual and auditory pathways. However, considering that multiple novel therapeutic agents are currently under preclinical or clinical investigation for primary mitochondrial diseases (PMD) in general, and MELAS in particular, a clearer and shared definition of MELAS and its clinical manifestation is needed.

Given the marked clinical heterogeneity across organs and disease stages, and the absence of comprehensive, evidence-based guidelines, both the diagnosis and management of MELAS and SLE remain challenging. Apart from a consensus-based statement on the management of SLE published in 2019 [8] there is no unified approach to either acute or chronic treatment of MELAS. In clinical practice, several agents, including idebenone, cofactors, antioxidants, L-arginine, L-citrulline and L-tyrosine are commonly used in attempts to support mitochondrial respiratory chain function, reduce oxidative stress, induce vasodilatation by increasing nitric oxide production or provide a substrate to restore a crucial modification of the tRNA for leucine<sup>UUR</sup>; however, no consensus exists regarding their use in prophylactic or acute settings. Similarly, the role and optimal dosing of antiseizure medications in the management of SLE remain unclear.

To address these unmet needs, the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD), through its Mitochondrial Diseases Working Group (<https://ern-euro-nmd.eu/group-of-people/mitochondrial-diseases/>), initiated and funded a joint European–United States collaboration. The initiative has also been endorsed by the Mitochondrial Medicine

Society and the European Reference Network for Hereditary Metabolic Disorders (MetabERN). The aim of this workshop was to develop a consensus statement on the diagnosis and management of MELAS, in both pediatric and adult populations.

## 2 | Material and Methods

The Delphi method was used to develop consensus around diagnosis and management of MELAS. 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 PMD [8–12]. Although described as a ‘panel’, experts provide their opinions freely, individually and anonymously. In addition, the study was reported in accordance with the ACCORD (ACcurate CONsensus Reporting Document) checklist to ensure transparent and comprehensive reporting of the consensus process [13]. Furthermore, we followed the recent supporting tool published by the ERNs (available at [https://www.erknet.org/fileadmin/files/user\\_upload/0\\_Intro\\_Toolkit\\_\\_D-B.2\\_.pdf](https://www.erknet.org/fileadmin/files/user_upload/0_Intro_Toolkit__D-B.2_.pdf)) as well as the European Academy of Neurology guidance for developing and reporting clinical practice guidelines on rare neurological diseases [14].

### 2.1 | Phase I: Pre-Meeting Phase

The mitochondrial working group of the ERN EURO-NMD invited experts from recognized centers of excellence within the ERN across Europe, along with specialists from the USA as delegates of the Mitochondrial Medicine Society (<https://www.mitosoc.org/>). MetabERN delegates (<https://metab.ern-net.eu/>) were also invited. Participants were selected based on their known experience in the field of mitochondrial medicine with expertise in management of adults and/or children. To broaden the panel of experts, we also asked invitees to nominate other potential participants to achieve geographical and gender balance in the selection of panelists. Candidate panelists were invited by e-mail outlining the study aims and the Delphi Process. Patient representatives from two mitochondrial patient advocacy groups (MITOCON from Italy and International Mito Patients -IMP-) were also invited to participate, along with two early-career researchers (P. Lopriore and L. Semmler) who actively contributed.

The final consensus panel included 27 participants from seven European countries and the United States, along with the two patient representatives. During the first virtual meeting, the group focused on how to evaluate a patient with suspected MELAS and/or SLE within this heterogeneous spectrum of disorders—conditions that frequently present as part of complex, syndrome-specific phenotypes. The group also discussed strategies for managing both SLE and MELAS comorbidities, in both acute and chronic settings. The group unanimously approved the literature search strategy and agreed to divide pre-meeting tasks among five working groups (see File S1). We searched for articles published between database inception and May 15th, 2025, in MEDLINE via PubMed, [ClinicalTrials.gov](https://www.clinicaltrials.gov) and the European Clinical Trials Register. Only articles published in English were considered. Data from unpublished trial registries, abstracts, or conference proceedings were not included.

Detailed study inclusion/exclusion criteria and the full search strategy are provided in Supplemental File S1, which was distributed to all experts.

The facilitator (M.M.) working with the group coordinators created one survey (File S2) with 54 statements to gauge the level of consensus among experts; responses and votes were collected anonymously through the SurveyMonkey platform ([surveymonkey.com](https://www.surveymonkey.com)), analyzed prior to the face-to-face meeting in a second conference call.

Participants voted using a five-point Likert scale [15] to indicate their level of agreement on each statement (1, absolutely disagree; 2, disagree; 3, no judgment; 4, agree; 5, absolutely agree). A ‘strong consensus’ was defined if >70% of scores were  $\geq 4$  or <2 and the mean score was  $\geq 4$  or <2. If either of the conditions were met, the result was considered a ‘consensus’. If both parameters were not met, the statement was considered to lack consensus agreement.

## 2.2 | Phase II: Delphi Panel

The experts met in a face-to-face meeting in Pisa, Italy, from November 28th to the 30th, 2025. The two delegates from the patient advocacy groups took part in the meeting without voting but were actively involved in the planning of the Delphi workshop and in the discussions.

Statements from Phase I that did not reach consensus were brought forward for discussion. The working group experts reviewed each of these items, summarizing the first-round survey results, presenting corresponding data, and outlining the available evidence surrounding the statement. Following discussion, statements from the initial round were revised or removed as necessary, and participants then voted again on the updated versions. Additional new statements were also formulated and evaluated. All participants contributed to every phase of the Delphi process.

## 3 | Results

In the first Delphi round, several statements did not reach the predefined consensus threshold and were therefore selected for structured discussion in the subsequent phase (File S2). Notably, divergent opinions emerged regarding the clinical definitions and diagnostic framework for MELAS and SLE. Similarly, considerable disagreement was observed for multiple acute-phase therapeutic strategies. Beyond diagnostic definitions and acute neurological management, the first-round survey also explored strategies for psychiatric symptoms, headache treatment, and systemic complications associated with MELAS and SLE.

During the face-to-face meeting, the group agreed to reformulate several queries, the majority of which had not reached approval in the earlier survey round. The overall conclusion of the Delphi process—reflecting expert consensus (level IV evidence)—was that updated and more precise definitions for both MELAS and SLE are required. The statements that ultimately reached consensus are summarized in the text below, presented

in full in the accompanying Table 1, and all statements detailed with complete response data are presented in File S3.

### 3.1 | General Considerations

The consensus process highlighted the need for clearer and more uniformly applied diagnostic terminology within the field of mitochondrial medicine, particularly regarding MELAS and SLE. Experts emphasized that MELAS represents a distinct clinical syndrome defined primarily by the presence of SLE supported by evidence of mitochondrial dysfunction due to a causative variant in mtDNA. Imprecise terms such as *MELAS-like* or *MELAS-spectrum* were considered inappropriate, as they contribute to ambiguity and potentially hinder diagnostic accuracy, research comparability, and communication across clinical settings.

Moreover, the following definition of SLE was endorsed by the experts: a SLE is an acute/subacute, evolving brain syndrome that can manifest at any age with neurological and/or psychiatric symptoms typically occurring in association with cortical/subcortical MRI changes with or without EEG abnormalities.

MELAS is exclusively associated with pathogenic mtDNA variants, whereas SLE may occur in various clinical syndromes not restricted to MELAS that can be due to either mitochondrial or nuclear pathogenic DNA variants. The panel also highlighted that SLE may occur across the lifespan, including in late-onset cases, and that both brain imaging and EEG play an important role in the early evaluation of suspected SLE.

### 3.2 | Management of SLE

Management of SLE remains largely empirical, reflecting the limited evidence base supporting current therapeutic options. The consensus highlighted that the efficacy of intravenous L-arginine in the acute phase and of oral L-arginine, L-taurine or L-citrulline as long-term prophylaxis is unproven, underscoring the need for future well-designed randomized controlled trials and further safety data. Similarly, no evidence currently supports the use of coenzyme Q<sub>10</sub>, vitamins, or other dietary supplements for either acute management or prevention of SLE. Intravenous corticosteroids may be considered in the acute phase on a case-by-case basis, although evidence remains limited. Antiseizure medications should be initiated when seizure activity is clinically suspected, even in the absence of EEG confirmation, and clinicians are encouraged to follow the 2024 InterERNs Mitochondrial Working Group consensus [9] on managing seizures and status epilepticus associated with SLE in PMD. The use of propofol for the management of status epilepticus in MELAS patients should be avoided if possible or limited to short infusions when necessary. Finally, owing to the underlying pathophysiological mechanisms, systemic fibrinolysis and antiplatelet therapy are not indicated in the treatment of SLE, in accordance with prior consensus statements [8, 16].

Management of neuropsychiatric and systemic complications in MELAS requires a comprehensive and multidisciplinary

**TABLE 1** | Statements of the Delphi working group.

Statements	Consensus	
	Percentage of sum 4 + 5	Mean score
<b>MELAS and SLE definition</b>		
MELAS is a primary mitochondrial syndrome caused by a pathogenic mtDNA variant characterized by one or more SLE with associated epileptic and/or encephalopathic features, in the context of either genetic or biochemical or muscle histological evidence of oxidative phosphorylation dysfunction	96	4.36
A mitochondrial SLE is an acute/subacute, evolving brain syndrome that can manifest at any age with neurological and/or psychiatric symptoms typically occurring in association with cortical/subcortical MRI changes with or without EEG abnormalities	96.15	4.69
<b>MELAS and SLE general statements</b>		
MELAS syndrome is a well-defined clinical entity; therefore, terms such as 'MELAS-like' or 'MELAS spectrum' should be avoided	92	4.48
The acronym MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke like episodes) is still useful but should be limited to the clinical syndrome and not to the m.3243A>G variant in the <i>MT-TL1</i> gene	92	4.48
The term MELAS—an acronym for Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes—is a traditional diagnostic label. A full phenotype may not always be present; however, for the syndrome to be defined as MELAS, a SLE must occur	88	4.44
MELAS syndrome can be caused by various pathogenic variants in mitochondrial DNA and is not limited to the m.3243A>G variant in the <i>MT-TL1</i> gene	96	4.64
SLE can be caused by pathogenic variants in either mitochondrial or nuclear DNA and is not limited to the m.3243A>G variant in the <i>MT-TL1</i> gene	96.15	4.81
SLE represents the core clinical feature required for the definition of MELAS syndrome	96	4.52
A MELAS diagnosis without the occurrence of SLE, despite molecular confirmation of a pathogenic variant, is inappropriate	84	4.16
SLE can occur at any age, including late-onset cases (> 40 years old)	100	4.64
EEG is an important early investigation of acute SLE	100	4.72
<b>Management of SLE</b>		
<i>Intravenous L-arginine should be administered in the acute phase of SLE (STRONG NEGATIVE CONSENSUS)</i>	76.92 (sum 1 + 2)	1.96
The efficacy of intravenous L-arginine is unproven in the acute phase of SLE	100	4.69
Randomized controlled clinical trials are needed to assess the efficacy of intravenous L-arginine in the acute phase of SLE management	92.3	4.62
The use of intravenous L-arginine in the acute phase of SLE is considered safe on a case-by-case basis	73.08	3.65
The efficacy of oral L-arginine as long-term treatment to reduce SLE frequency is unproven	100	4.73
<i>Oral L-taurine should be used as a long-term medication to reduce SLE frequency in tRNA Leu<sup>UUR</sup> related MELAS (STRONG NEGATIVE CONSENSUS)</i>	88.47 (sum 1 + 2)	1.58
The efficacy of oral L-taurine as long-term treatment to reduce SLE frequency in tRNA Leu <sup>UUR</sup> related MELAS is unproven	96.15	4.62

(Continues)

TABLE 1 | (Continued)

Statements	Consensus	
	Percentage of sum 4 + 5	Mean score
More data are needed to investigate efficacy and safety of long-term oral L-aurine supplementation in <i>MT-TL1</i> gene related MELAS	92.3	4.42
There is currently no evidence demonstrating that oral L-citrulline is effective in the acute phase of SLE	96.15	4.85
A future clinical trial is required to evaluate the efficacy of oral L-citrulline as long-term treatment to reduce SLE frequency	88.46	4.23
Based on the available experience, the use of i.v. steroids (either methylprednisolone or dexamethasone) may have a beneficial effect in the acute phase of SLE	80.77	4.15
There is no evidence that any coenzyme Q <sub>10</sub> formulation or its analogues, vitamins or other dietary supplements have a beneficial effect in the acute management of SLE	100	4.65
There is no evidence that any coenzyme Q <sub>10</sub> formulation or its analogues, vitamins or other dietary supplements have a beneficial effect in long-term treatment to prevent SLE	92.3	4.58
ASMs should be used in SLE if there is a strong clinical suspicion of seizure activity, irrespective of EEG findings	88.46	4.42
The InterERNs Mitochondrial Working Group consensus published in 2024 regarding the management of status epilepticus in association with acute SLE in PMD patients should be followed	96	4.44
<b>Cognition and psychiatry</b>		
Anti-seizure medications are important in treating SLE or acute encephalopathic episodes, including its possible psychotic manifestations	92.3	4.38
Antipsychotic drugs can be used to manage acute psychotic symptoms associated with SLE	96.15	4.58
There is no rationale nor evidence that dietary supplements are useful to manage acute psychotic symptoms associated with SLE or acute encephalopathic episodes	96.15	4.81
Cognitive deficits are common in patients with MELAS. Multi-domain cognitive assessments are recommended	100	4.73
Cognitive rehabilitation should be considered to treat cognitive symptoms in MELAS	100	4.42
SSRI and SNRI should be used in patients with MELAS according to best psychiatric practices to treat depression and anxiety	96.15	4.42
Psychological support for both patients and caregivers should be provided if required	100	5
<b>Management of headache</b>		
In patients with MELAS syndrome, headache should be systematically assessed to enable timely intervention and optimize quality of life	100	4.52
In mitochondrial diseases, there are no specific contraindications to the use of standard pharmacological classes of medications for migraine prevention. VPA should not be used in <i>POLG</i> related disease	84	3.84
Pharmacological and non-pharmacological headache management in MELAS syndrome can be applied regardless of genotype and age	80.77	3.77
Persistent headache unresponsive to treatment should prompt neuroimaging to exclude a SLE	80	3.92

(Continues)

TABLE 1 | (Continued)

Statements	Consensus	
	Percentage of sum 4 + 5	Mean score
There are no specific contraindications to the use of standard pharmacological classes for acute headache treatment (NSAIDs, triptans, paracetamol, combination analgesics, opioids, ditans, and gepants in adults)	88	3.96
There is no known contraindication to the use of monoclonal antibodies for the prevention of migraine in patients with MELAS, but their use should be carefully monitored until more evidence is accumulated	96	4.40
<b>Management of comorbidities</b>		
Gastrointestinal dysmotility is frequently seen during SLE. Conservative management with hydration and nutrition started early and continued are typically sufficient to prevent surgical intervention	96.15	4.42
Prokinetics should be considered if other conservative measures such as laxatives fail to achieve full resolution of gastrointestinal symptoms, and to prevent intestinal pseudo-obstruction	96.15	4.38
Sometimes infections precede or complicate SLE. The index of suspicion should be high and appropriate measures should be tailored to the underlying infection	100	4.69
Cardiac manifestations including cardiomyopathy, cardiac arrhythmia, acute cardiac failure, and cardiogenic shock can occur in the setting of SLE and MELAS. Patients should be closely monitored for these complications	100	4.69
Acute kidney injury can be a concomitant event in SLE and must be treated promptly. Sodium and potassium balance and the use of diuretics are the first approach. Dialysis should be initiated if necessary	96.15	4.35
In MELAS rhabdomyolysis is an extremely rare life-threatening complication; it should be carefully managed with intravenous fluids and electrolyte correction to prevent further complications such as kidney damage.	92.3	4.35
SLE in MELAS may be accompanied by multi-organ failure. Cardiac, renal, and gastrointestinal function should be assessed on admission and during the course of any inpatient stay.	100	4.76
In the acute management of metabolic acidosis in MELAS, clinicians should consider that elevated lactic acid and anion gap may be baseline findings and not all cases require treatment. In case of severe lactic acidosis, we recommend appropriate hydrations with fluids, avoiding high dextrose concentration and using bicarbonate in case of severe base deficit	92.31	4.42

Note: Statements in italic text: negative consensus.

Abbreviations: ASMs, antiseizure medications; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke like episodes; NSAIDs, non-steroidal anti-inflammatory drug; PMD, primary mitochondrial disease; SLE, stroke-like episode; VPA, valproic acid.

approach. Acute encephalopathy or SLE may present clinically with seizures or psychiatric manifestations, for which anti-seizure medications and, when necessary, antipsychotics are appropriate, while dietary supplements offer no acute benefit. Cognitive impairment is common, warranting multidomain assessment and consideration of cognitive rehabilitation, alongside evidence-based psychiatric standard of care and – where needed – of psychological support for patients and caregivers. Headache should be routinely evaluated, and standard pharmacological and non-pharmacological migraine treatments can generally be used across ages and genotypes. Persistent or atypical headache should prompt neuroimaging to exclude a SLE. Clinicians should be vigilant for pre-existing MELAS comorbidities which can precipitate SLE or worsen during a SLE. These include gastrointestinal dysmotility,

infections, cardiac complications, acute kidney injury, and, very rarely, rhabdomyolysis. In particular, conservative management of gastrointestinal dysmotility with early hydration and nutrition started early and continued are typically sufficient to prevent surgical intervention. Prokinetics should be considered if other conservative measures fail to achieve full resolution of gastrointestinal symptoms, and to prevent intestinal pseudo-obstruction. Early supportive care, targeted therapies, and close monitoring of organ function are essential. Metabolic acidosis should be managed judiciously, recognizing that elevated lactate and anion gap may reflect baseline pathophysiology in MELAS, with treatment reserved for severe derangements requiring hydration, avoidance of high-dextrose intravenous fluids, and bicarbonate administration when indicated.

## 4 | Discussion

In this study, 25 experts (21 from Europe and 4 from the US) together with two early-career researchers and two patient representatives met to discuss the diagnostic criteria and management of acute and chronic manifestations of MELAS and SLE, to assist clinicians and patients in decision-making.

The consensus process underscored the need for clearer and more consistently applied diagnostic terminology in mitochondrial medicine, particularly in relation to MELAS and SLE. This supports the adoption of updated definitions for MELAS, its key clinical features, and SLE, with the goal of improving terminological consistency, minimizing diagnostic misclassification, and aligning clinical practice and research reporting with current understanding of mitochondrial pathophysiology.

The pathological mechanisms resulting in headache occurrence and SLE are complex and poorly understood. Proposed mechanisms include primary mitochondrial energy failure leading to impaired oxidative phosphorylation and neuronal metabolic stress, dysfunction of nitric oxide metabolism with altered cerebrovascular autoregulation, and a metabolic-vascular mismatch resulting in regional hyperperfusion rather than ischemia [7, 8]. Cortical spreading depolarization and epileptiform activity are also thought to contribute, potentially explaining the frequent association of SLE with seizures and the non-vascular distribution of stroke-like lesions on neuroimaging. The relative contribution of each component is unclear, and consequently therapeutic approaches have included a diverse range of treatments. One of the principal aims of this Delphi-based workshop was to establish consensus statements on the optimal clinical management of patients experiencing SLE, particularly in situations where the underlying pathological etiology is unclear.

The management of SLE in mitochondrial disorders should be fast and multidisciplinary, reflecting their complex pathophysiology and multisystem impact. Early recognition is essential, with prompt use of neuroimaging, EEG, and genetic testing to confirm the diagnosis and exclude mimics. Acute management should prioritize seizure control, stabilization of vital functions, and prevention of secondary brain injury and peripheral organ decompensation. Antiseizure medications should be initiated promptly when seizures are clinically suspected, irrespective of EEG confirmation, while therapies targeting vascular ischemia, including antiplatelet agents and thrombolysis, are not indicated. Intravenous corticosteroids may be considered in the acute phase on a case-by-case basis, although evidence remains limited to almost exclusively anecdotal reports [17]. Supportive care, including careful fluid and electrolyte management, treatment of metabolic derangements, and monitoring for systemic complications affecting cardiac, renal, and gastrointestinal function, is also important. Given the absence of proven disease-specific therapies, management of SLE should be individualized, regularly reassessed, and ideally coordinated within experienced multidisciplinary teams, with early involvement of mitochondrial disease experts.

It is important to emphasize that consensus-based guidance can support clinical decision-making, but treatment options for both children and adults must always be individualized according

to each patient's specific needs and risks. We acknowledge that these recommendations are not evidence-based; although consensus methods are commonly used when empirical data are limited, expert opinion remains low in the hierarchy of evidence. Our recommendations arise from a structured consensus process informed by the clinical experience of leading mitochondrial specialists across multiple European ERNs and the USA, together with a critical appraisal of the existing literature. Our goal was to provide transparent, well-reasoned opinions grounded in the best available studies and clinical expertise.

The consensus process also underscored several important gaps in knowledge that should guide future research priorities. There is an urgent need for well-designed randomized controlled trials to evaluate both acute and preventive treatments for SLE. Harmonized definitions and standardized outcome measures, as proposed in this document, are essential to enable robust interventional studies. In addition, longitudinal natural history studies, international patient registries, and the identification of reliable biomarkers for early diagnosis, patients' stratification, and disease monitoring are needed. Finally, further translational research aimed at clarifying the complex metabolic, vascular, and epileptogenic mechanisms underlying SLE may facilitate the development of targeted and mechanism-based therapies.

In conclusion, the consensus statements developed in this Delphi process seek to address an unmet need for providing recommendations on diagnosis and management of patients with MELAS and SLE.

### Author Contributions

All authors contributed to the acquisition of data, preparation, and critical revision of the manuscript. M.M., C.L., and S.S. contributed to the study conception and design, analysis and interpretation of data, and drafting the manuscript. All authors contributed to the different phases of the consensus process and, with the exception of F.D., participated in the workshop.

### Funding

This work was supported by the European Reference Network for Neuromuscular Diseases (ERN EURO\_NMD), EU4Health programme 2021-2027.

### Affiliations

<sup>1</sup>Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy | <sup>2</sup>CTMM – Interdepartmental Research Centre for Translational Medicine in Neuromuscular and Mitochondrial Diseases, University of Pisa, Pisa, Italy | <sup>3</sup>Azienda Ospedaliero Universitaria Pisana, Neurological Clinic, Pisa, Italy | <sup>4</sup>Reference Center for Inherited Metabolic Disorders MetabERN, Mitochondrial Disorders Research Group (imas12), '12 de Octubre' University Hospital, Madrid, Spain | <sup>5</sup>IRCCS Istituto Delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Bologna, Italy | <sup>6</sup>Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy | <sup>7</sup>Mental Health and Neuroscience Research Institute, Graduate School MHeNS, Department Translational Genomics, Maastricht University, Maastricht, the Netherlands | <sup>8</sup>Unit of Muscular and Neurodegenerative Diseases, Children Hospital Bambino Gesù, Rome, Italy | <sup>9</sup>University Children's Hospital, Düsseldorf, Germany | <sup>10</sup>Department of Paediatrics and

Adolescent Medicine, Haukeland University Hospital, Bergen, Norway | <sup>11</sup>Department of Clinical Science (K2), University of Bergen, Bergen, Norway | <sup>12</sup>H. Houston Merritt Neuromuscular Research Center, Department of Neurology, Columbia University Irving Medical Center, New York, USA | <sup>13</sup>Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK | <sup>14</sup>Division of Genetics, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts, USA | <sup>15</sup>Department of Neurology, Friedrich-Baur-Institute, LMU University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany | <sup>16</sup>German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany | <sup>17</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany | <sup>18</sup>Department of Pediatrics, Division of Child & Adolescent Neurology, University of Texas McGovern Medical School, Houston, Texas, USA | <sup>19</sup>Department of Neuromuscular Diseases, Center for Neurology, University Hospital Bonn, Bonn, Germany | <sup>20</sup>IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy | <sup>21</sup>Scuola Superiore Sant'anna, Ph.D School in Translational Medicine, Pisa, Italy | <sup>22</sup>Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland | <sup>23</sup>Neurocenter, Oulu University Hospital, Oulu, Finland | <sup>24</sup>Mitochondrial Research Group Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK | <sup>25</sup>NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK | <sup>26</sup>Department of Clinical and Experimental Medicine, Unit of Neurology and Neuromuscular Disorders, University of Messina, Messina, Italy | <sup>27</sup>Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, University College London Queen Square Institute of Neurology, London, UK | <sup>28</sup>NHS Highly Specialised Service for Rare Mitochondrial Disorders, the National Hospital for Neurology and Neurosurgery, London, UK | <sup>29</sup>Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy | <sup>30</sup>Dipartimento Di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy | <sup>31</sup>Mitochondrial Research Group, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK | <sup>32</sup>Department of Molecular and Human Genetics, Baylor College of Medicine/Texas Children's Hospital, Houston, Texas, USA | <sup>33</sup>Baylor Genetics, Houston, Texas, USA | <sup>34</sup>Joint BCM-CUHK Center of Medical Genetics, Prince of Wales Hospital, Hong Kong, SAR, China | <sup>35</sup>NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK | <sup>36</sup>Reference Center for Mitochondrial Disorders (CARAMMEL) and Reference Center for Inborn Errors of Metabolism, Department of Pediatrics, Necker-Enfants-Malades Hospital, Assistance Publique-Hôpitaux de Paris, University of Paris-Cité, Paris, France | <sup>37</sup>INSERM UMR5\_1163, Imagine Institute, Paris, France | <sup>38</sup>Department of Neurology, Klinikum Rechts der Isar, Technical University Munich, Munich, Germany | <sup>39</sup>Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy

## Acknowledgments

We are grateful for the support of Mrs. Manuela Lavorato, WP7 Project Manager of ERN EURO-NMD. M. Mancuso receives support from the European Union within the framework of the “EU4Health programme 2021-2027”. <http://ec.europa.eu/health/ern>, from EJPRD project GENOMIT 01GM1920A, the Italian Ministry of Health (RF-2021-12373111), and from the European Union—Next-GenerationEU—National Recovery and Resilience Plan (NRRP) – Mission 4 component 2, investment N. 1.1, Call PRIN 2022 D.D. 104 02-02-2022 – (2022B9WY4A) CUP N. D57G23000430008. He is a member of the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD) and the European Reference Network for Rare Neurological Diseases (ERN-RND). M. Bellusci receives support from the Instituto de Salud Carlos III (AC23\_2/00028), from EJPRD project GENOMIT, and patients' association AEPMI through research grants to the MitoSpain Network (CIBERER). D.D. is a member of the European Reference Network for Neuromuscular Diseases and of

the European Reference Network for Metabolic Disorders, and is supported by the European Union—Next-Generation EU PNRR grant “MNESYS: A multiscale integrated approach to the study of the nervous system in health and disease”—Spoke7. G. Primiano and S. Servidei are supported by the European Union—Next Generation EU—PNRR M6C2 (National Recovery and Resilience Plan)—Investment 2.1 Enhancement and strengthening of biomedical research in the National Health Service, grant no. PNRR-MR1-2022-12376346. I de Coo receives support from ‘Stichting NeMo’, patient foundation, through a research grant to the Translational Genomics dept., Maastricht. R.H. is supported by the Wellcome Discovery Award (226653/Z/22/Z), the Hereditary Neuropathy Foundation, the AFM-Telethon, the Action for AT, the Muscular Dystrophy UK, the Rosetrees Trust (PGL23/100048), the LifeArc Centre to Treat Mitochondrial Diseases (LAC-TreatMito), and the UKRI/Horizon Europe Guarantee MSCA Doctoral Network Programme (Project 101120256: MMM). This research was supported by the NIHR Cambridge Biomedical Research Centre (NIHR203312). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. R.D.S. Pitceathly is supported by The Lily Foundation, Muscular Dystrophy UK (MDUK), The Rosetrees Trust and Stonegate Foundation, a Medical Research Council (UK) Transition Support award (MR/X02363X/1), a Medical Research Council (UK) award (MC\_PC\_21046) to establish a National Mouse Genetics Network Mitochondria Cluster (MitoCluster), and the LifeArc Centre to Treat Mitochondrial Diseases (LAC-TreatMito, grant number G125217). The University College London Hospitals/University College London Queen Square Institute of Neurology sequencing facility receives a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The clinical and diagnostic ‘Rare Mitochondrial Disorders’ Service in London is funded by the UK NHS Highly Specialized Commissioners. F.S. received travel support from the United Mitochondrial Disease Foundation to participate in this meeting. He is supported by research grants from PTC Therapeutics, Tisento Therapeutics, UCB Pharma, Saol Therapeutics, FDA (5R01-FD005407), and the NIH (U54 NS078059 and U54 NS115198). He has received consulting payments from Tisento Therapeutics and UCB. He has received research support from the Mervar Foundation and he receives research support from the Courage for a Cure Foundation. C.L.M. is a member of the European Reference Network for Neuromuscular Diseases and is supported by research grants from PNRR-MR1-2022-12376617 and PNRR-MR1-2023-12377223 and from the European Union—Next-GenerationEU PNRR grant “MNESYS: A multiscale integrated approach to the study of the nervous system in health and disease”—Spoke6. V.C. is a member of the European Reference Network for Neuromuscular Diseases and is supported by research grants from PNRR-MR1-2023-12377223 and from the European Union—Next-GenerationEU PNRR grants “MNESYS: A multiscale integrated approach to the study of the nervous system in health and disease” and “National center for gene therapy and drugs based on RNA technology”. O.M. is a member of the European Reference Network for Neuromuscular Diseases and received support by research grants from the European Union—Next-Generation EU PNRR-MR1-2023-12377223 CUP H43C24000470006 and PRIN 2022—D.D. n.104 del 02-02-2022 (2022B9WY4A) CUP J53D23010870006. S.R. acknowledges grant funding from Great Ormond Street Hospital Children's Charity and the Lily Foundation. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. T.K. acknowledges funding from the German Ministry of Research, Technology and Space (BMFTR) until 2023 through the German Network for mitochondrial disorders (mitoNET; 01GM0862, 01GM1113A, 01GM1906A) and currently through the E-Rare project GENOMIT (01GM1920B, 01GM2404B). He is a member of the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD) and the European Reference Network for Rare Neurological Diseases (ERN-RND). M.K.K. thanks the United Mitochondrial Disease Foundation for travel support to participate in this meeting. M.H. received travel

support from the United Mitochondrial Disease Foundation to participate in this meeting. He has received grant support from the US Department of Defense (FPA W81XWH2010807), the J. Willard and Alice S. Marriott Foundation, the Muscular Dystrophy Association (577392), and the National Institutes of Health (NIH; U54 NS078059 and P01 HD32062). He has also received research support, honoraria, or both from Entrada Therapeutics, Modis Therapeutics (a wholly owned subsidiary of Zogenix/UCB), Precision BioSciences, Cycleron Therapeutics, Reneo Pharmaceutical, Sarepta Therapeutics, and Stealth BioTherapeutics. R.M. receives research funding support from The Lily Foundation, Great Ormond Street Hospital Charity, Wellcome (206001/Z/16/Z), The Noah Jordan Foundation, The Leigh Syndrome Consortium and the NIHR Newcastle Biomedical Research Centre (BRC) awarded to the Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University and Cumbria, Northumberland, Tyne and Wear Foundation Trust. He has consultancies via Newcastle University with Abliva AB, Pretzel Therapeutics and UCB. A.S. received travel support from the NIHR Newcastle Biomedical Research Centre (BRC) awarded to the Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University, and Cumbria, Northumberland, Tyne and Wear Foundation Trust. C.L. is funded by the European Union—Next Generation EU—NRRP M6C2—Investment 2.1 Enhancement and Strengthening of Biomedical Research in the NHS (PNRR395 MR1-2022-12376617), the Italian Ministry of Health (RF2021-12373111; RCC/Ricerca Corrente 2024), by the BMFTR (German Federal Ministry of Research, Technology and Space) through the EJP RD project GENOMIT (01GM1920A, 401 01GM2404A) and by the European Union and by the EU Horizon 2020 project: Recon4IMD (101080997). P.L. is supported by the EJPRD project GENOMIT 01GM1920A. M.H.M. is a member of the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD) and the European Reference Network for Rare Neurological Diseases (ERN-RND). He thanks the Finnish Neurological Society for travel support to participate in this meeting. A.K. thanks the United Mitochondrial Disease Foundation for travel support to participate in this meeting.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available in the [Supporting Information](#) of this article.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ene70588-sup-0001-Supinfo1.pdf. **Data S2:** ene70588-sup-0002-Supinfo2.pdf. **Data S3:** ene70588-sup-0003-Supinfo3.pdf.