European Reference Network

for rare or low prevalence complex diseases

Network
Neuromuscular Diseases (ERN EURO-NMD)

Mitochondrial diseases

- Chairs: Rita Horvath (Newcastle, UK) and Cornelia Kornblum (Bonn, Germany)
- Most centres in the ERN-NMD are adult mitochondrial disease centres, however there are a few paediatric NMD centres (Nijmegen, Barcelona, etc).
- Many paediatric mitochondrial centres are involved in the metabolic ERN (ERN-METAB)
- We discussed with the members of ERN-METAB (Enrico Bertini, Eva Morava and Shamima Rahman) to organise linked activities in mitochondrial diseases between ERN-NMD and ERN-METAB after the main structure of each ERN is established

Planned working groups in mitochondrial diseases

Chair: Rita Horvath (Newcastle, UK), Co-Chair: Cornelia Kornblum (Bonn, Germany)

Clinical diagnosis, treatments, guidelines, clinical trials – adult mitochondrial disease

Veronique Paquis (Nice, France)
Constanza Lamperti (Milan, Italy)
Marian Janssen (Nijmegen, Netherlands)
Serenella Servidei (Rome, Italy)
Michelangelo Mancuso (Pisa, Italy)
Thomas Klopstock (Munich, Germany)
Grainne Gorman (Newcastle, UK)

Clinical diagnosis, treatment, guidelines, clinical trials – paediatric mitochondrial disease

Bobby McFarland (Newcastle, UK)
Rafael Artuch (Barcelona, Spain)
Daria Diodato (Rome, Italy)
Jan Smeitink (Nijmegen, Netherlands)
Ulrike Schara (Essen, Germany)

Diagnostics

Rob Taylor (Newcastle, UK)
Richard Rodenburg (Nijmegen, Netherlands)
Bert Smeets (Maastricht, Netherlands)

affiliated:

Holger Prokisch (Munich, Germany)
Patrick Chinnery (Cambridge, UK),
Valerio Carelly (Bologna, Italy)

List of named participants in mitochondrial diseases

	Italy	Belgium	Germany	France	Spain	UK
People	31	11	9	7	7	6
Institutes	11	3	5	3	2	1

	Hungary	Poland	Netherlands	Bulgaria	Slovenia
People	11	3	2	1	1
Institutes	2	1	2	1	1

Patient Organisations

IMP **AMM** **AEPM**

Mitochondrial disease: guidelines, diagnostic criteria and outcome measures

- **Common data elements for clinical research in mitochondrial disease: a National Institute for Neurological Disorders and Stroke project.** Karaa A, Rahman S, Lombès A, Yu-Wai-Man P, Sheikh MK, Alai-Hansen S, Cohen BH, Dimmock D, Emrick L, Falk MJ, McCormack S, Mirsky D, Moore T, Parikh S, Shoffner J, Taivassalo T, Tarnopolsky M, Tein I, Odenkirchen JC, Goldstein A; Mito Working Group Member Participants. *J Inherit Metab Dis*. 2017 May; 40(3):403-414.

- **Wellcome Centre for Mitochondrial Research Newcastle:: Clinical Guidelines: http://www.newcastle-mitochondria.com/clinical-professional-home-page/clinical-publications/clinical-guidelines/**

- **MMS Mitochondrial Care Guidelines Project, 2016-2017** Parikh S, Goldstein A, Karaa A, Koenig MK, Anselm I, Brunel-Guitton C, Christodoulou J, Cohen BH, Dimmock D, Enns GM, Falk MJ, Feigenbaum A, Frye RE, Ganesh J, Griesemer D, Haas R, Horvath R, Korson M, Kruer MC, Mancuso M, McCormack S, Reimschisel T, Salvarinova R, Saneto RP, Scaglia F, Shoffner J, Stacpoole P, Sue CM, Tarnopolsky M Karnebeek CV, Wolfe LA, Cunningham ZZ, Rahman S, Chinnery PF. Patient Care Standards for Primary Mitochondrial Disease: A Consensus Statement from the Mitochondrial Medicine Society. *Genetics in Medicine* 2017, 27 July Epub ahead

- **Revisiting mitochondrial diagnostic criteria in the new era of genomics** Witters P, Saada A, Honzik T, Tesarova, M, Kleinle S, Horvath R, Goldstein A, Morava E.. *Genetics in Medicine* 2017, in press.

Mitochondrial disease: guidelines, diagnostic criteria and outcome measures

- **International Workshop:: Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations. Rome, Italy, 16-18 November 2016.** Mancuso M, McFarland R, Klopstock T, Hirano M; consortium on Trial Readiness in Mitochondrial Myopathies. *Neuromuscul Disord*. 2017 Sep 8. pii: S0960-8966(17)30581-3
- **Mitochondriale Erkrankungen, Leitlinien für Diagnostik und Therapie in der Neurologie.** Hrsg. "Kommission Leitlinien der Deutschen Gesellschaft für Neurologie", H.C. Diener. 5., aktualisierte und erweiterte Auflage 2012, Georg Thieme Verlag KG – *update in processing* (2017)
- **A Guideline for the Diagnosis of Pediatric Mitochondrial Disease: The Value of Muscle and Skin Biopsies in the Genetics Era.** Wortmann SB, Mayr JA, Nuoffer JM, Prokisch H, Sperl W. *Neuropediatrics*. 2017 Aug;48(4):309-314
- Wolfram syndrome guidelines: **http://www.orpha.net/national/data/IE-EN/www/uploads/Wolfram2014.pdf**
- Guidelines from Barcelona: **http://ae3com.eu/protocolos/protocolo13.pdf**

Next steps

- Include some institutions who did not claim mitochondrial activity, but have clear national or international leading role in mitochondrial disease (Nijmegen etc.)
- Agree in the rules of being a specialised mitochondrial centre for existing and new centres

Discuss in the expert group:

- how to implicate existing guidelines or create new guidelines
- how will actual patient referrals be managed

Developing novel treatments in mitochondrial disease

Gene identification/ pathophysiology

- Biomarkers
- Model systems
- Delivery mechanisms
- Proof of principle studies

Trials

- Diagnosis/ care standards
- Natural history
- Patient Registries
- Trial sites
- Outcome measures

Therapy delivery

- Regulatory affairs
- Ethics
- Commissioning/ health economics

International Workshop on trial readiness in primary mitochondrial myopathies

Ideas for hunting down the right path to a cure

Rome, Hotel Mediterraneo
November 16-18, 2016