

**Minutes LSD subnetwork meeting.** 3 November 2018,  
Inntel hotel, Rotterdam, The Netherlands



**European  
Reference  
Network**

for rare or low prevalence  
complex diseases

 **Network**  
Hereditary Metabolic  
Disorders (MetabERN)

**Participants:**

Maurizio Scarpa, Kurt Ullrich, Mireia del Toro Riera,  
Mirjam Langeveld, Julia Hennerman, Flavia Tubili, Maria Alice Donati,  
Hanka Dekker, Maja di Rocco, Lukasz Pawlinski, Maria José Guimaraes,  
Stella Mazurova, Giancarlo Parenti, Tarekegn Hiwot, Nuno Marques  
Colin Brown, Hanka Dekker, Nadia Minopoli, Dominique Germain, Nathalie Weinhold,  
Julia Neugebauer, Ans van der Ploeg, Hidde Huidekoper, George Ruijter,  
Pim Pijnappel, Esmee Oussoren

**1. Update on LSD subnetwork activities: what has been achieved?**

**WP1 (H. Huidekoper):** mapping our network: 45 HCPs from 13 countries want to participate in the LSD SNW, not all HCPs are responding to surveys. Several inventories were made during the first 1.5 yrs of MetabERN:

- *WP participation (39 out of 45 HCPs responded):* HCP listed in what WP's they want to participate and leadership was appointed for each WP in the LSD SNW. At the moment WP3 (evaluation) and WP8 (continuity of care) leaders are missing. **Please let us know if you are interested in taking leadership in either of these WPs.**
- *Disease preferences (39 out of 45 HCPs responded):* HCPs were asked to list their disease preferences on which they want to work. The top 5 of diseases to work on is: Fabry, Gaucher, MPS II, Niemann-Pick type C, Pompe.
- *Patient inventory (36 out of 45 HCPs responded):* in order to map the patient base in the LSD SNW a patient inventory was sent out listing all LSDs. The MetabERN coordinating office sent out survey to map all IEM patients within MetabERN at a later time point. Based on the response until now 5848 patients with LSDs are represented within the LSD SNW.

*Next steps:* it was proposed to start forming disease specific working groups within the LSD SNW in order to connect HCPs and expertise with respect to different LSDs. These working groups can work on different deliverables from the WPs (e.g. guide lines, care pathways, awareness, training & teaching programs, patient registries & natural history studies etc).

**WP2 (M. del Toro Riera):** organizational structure: editorial board, news team, liaison with patient associations, SOPs team (development of SOPs for accreditation, regulation of interaction and collaboration with companies). Activities during first 1.5 yrs of MetabERN:

- Development of the MetabERN website and social media channels.
- Patient representative meeting in jan 2018
- Development of a MetabERN brochure

*Next steps:*

- Development of a sound dissemination plan
- Identification of patient associations per country
- Showcase MetabERN activities (input wanted: please let us know any activities that you are doing including meetings, workshops, courses etc. Use the MetabERN logo.
- Policy of affiliation of MetabERN: authors cannot yet list themselves as being affiliated to MetabERN as this is not yet a legal entity. Authors have the option to mention that their HCP is a member of MetabERN in the Acknowledgements.

Question: is it possible to set-up targeted newsletters for specific conditions / groups of professionals as this may limit the flow of emails and assure that information reaches the target population? => to be discussed

**WP3 (S. Mazurova):** Main objectives and progress:

- *Monitoring / evaluation of ERN activities:* general tools for the evaluation of ERNs are being developed and will become available in the beginning of 2019
- *Conflict of interest / disclosure policy:* is being drafted in general for all ERNs with input from the different stakeholders. It is yet unclear when this will be finalized.
- *Impact of MetabERN activities on patient care / patient needs / expectations of stake holders:* A survey was sent out in September to make an inventory on patient needs. Until now the response is poor. **All HCPs are asked to please complete this survey.**

**WP4 (G. Parenti):**

- The process and format for guideline development within ERNs was explained
- Working groups have been formed for the development of guidelines for Pompe's disease, Niemann Pick type C and Fabry. A concept guideline for Pompe's disease is drafted (lead G. Parenti), for NPC this is under development (lead T. Hiwot) and for Fabry this process will be started (lead D. Germain).
- Suggested diseases for guideline development after completion of the above: LAL deficiency, MPS VII and alfa-mannosidosis

*Questions/discussion:*

- Patient involvement in guideline development: patient organizations should be involved in the development of guidelines. It is suggested not to involve them in the conceptual stage, but in the evaluation stage as part of the readers group for feedback.
- Guideline development is now driven by LSDs for which treatment is available or will become available. Standardized follow-up and management for LSDs for which no treatment is available should also be a main objective of WP4 as this enable us to better assess the natural history of these conditions, improve supportive care and possibly identify new targets for treatment.
- Guidelines should define a standard for the minimal follow-up protocol at all HCPs treating LSDs and in addition state the standardized protocol for follow-up/treatment as centers of expertise / excellence centers for specific LSDs.

**WP5 (G. Parenti on behalf of G. Ciana):**

- The use of CPMS is an important deliverable for each ERN and should be stimulated!
- Suggested use of CPMS per HCP: three cases to be submitted or participated in per year.
- Cases to be discussed and evaluated in CPMS can only be submitted by HCPs. HCPs may suggest experts for the participation in CPMS themselves or can ask the MetabERN coordinating office for advise on which experts to include.

**Help is being asked for the coordination of this WP, please let us know if you would like to help.**

**WP6 (D. Germain):**

- A general survey on research interests and capabilities of each HCP has been done by the MetabERN coordinating office.
- An additional survey to map specific research interests and current lines of research at each HCP for LSDs will be send out.

*Questions/discussion:*

- It was suggested to list LSD expertise and research interests/projects on the MetabERN website for each HCP.
- Treats: 1. lack of financial support for (collaborative) research projects. 2. Competing interests between HCPs and MetabERN.

**WP7 (M. del Toro Riera on behalf of N. Belmatoug):**

- A survey has been done to map all teaching activities and programs at each HCP. Results are listed on the MetabERN website. HCPs are asked to make known all their teaching activities related to IEMs and of possible interests for patients and caregivers.
- A training program in collaboration with the SSIEM academy is under development for the transition of care for patients with IEMs from pediatric to adult practice.

**Speakers who are experienced with the subject are asked to participate in this course and contact Nadia Belmatoug.**

*Questions/discussion:*

- It is suggested to create a forum for active discussion on casus pro diagnosi. Each SNW of MetabERN could then upload at least one case per year (NB overlap with Metab-list?).

**2. Interaction with other professional networks and patient organizations for LSDs**

**WP8 / ERNDIM (G. Ruijter, chair ERNDIM):**

- An important deliverable of WP8 is mapping the diagnostic capabilities for LSDs (and IEMs in general) within MetabERN and per HCP. This will be done in collaboration with ERNDIM.
- The quality assurance program of ERNDIM for diagnostic tests for IEMs at the different laboratories was explained. This is not an accreditation program, but a voluntary program to monitor diagnostic performance at laboratories and assist with improving performance if necessary.
- **HCPs are encouraged to ask their laboratories if they participate in the ERNDIM QA program and if not, to stimulate them to do so.**
- **Diagnostic samples are needed for the ERNDIM QA schemes. Please contact ERNDIM at [www.erndim.org](http://www.erndim.org) for further information on how to contribute samples.**

**ESGLD (P. Pijnappel, treasurer ESGLD):**

- Consists of 90 research groups from 22 European countries focused on fundamental and translational research in LSDs.
- A 2-yearly workshop is organized to present current work and promote collaboration between research groups. Next meeting will be held in sept/okt 2019 (to be announced)
- More information on [www.esgld.org](http://www.esgld.org)

**Brains for Brain Foundation (M. Scarpa):**

- Creating a network of clinicians and (basic) scientists to promote expanding insight in the pathophysiology of and the development of innovative treatments for neurodegenerative diseases.
- PhD program for rare diseases in Europe in collaboration with the Marie-Curie program.
- More information on [www.brains4brain.eu](http://www.brains4brain.eu)

### **Interaction with patient organizations (N. Marques, patient board liaison LSD SNW):**

- Patient organizations would like each HCP to really specify what they are doing with respect to IEMs in order to create transparency for patients on what expertise is present at what HCP (e.g. expertise in LSDs (patient numbers), patient information on LSDs, guidelines/care pathways for LSDs, composition of the multi-disciplinary team, waiting lists, reports on patient outcomes, participation in clinical trials and other research interests).
- Independent (from industry) registries to collect clinical outcome data on both natural history and treatment efficacy when available are necessary and should be a primary objective for MetabERN. It is expected that U-IMD can play a major role for this objective.
- Development of clinical apps / tools for patient management can promote patient empowerment.
- The role of patient organizations in MetabERN needs to improve. There are many patient organizations for IEMs (44 registered with MetabERN), but collaboration between PO's needs to be optimized in order to set common objectives for MetabERN.

### **3. Proposals for collaborative projects to work on within the LSD subnetwork**

#### **A. Creation of disease specific genetic databases to list mutation pathogenicity (D. Germain):**

- With the advancement of NGS techniques more and more genetic variants are being picked up. It is essential to develop reliable databases that collect and curate these variants per disease in order to list their (possible) pathogenicity and prevent patients being put on (expensive) treatments without clearly having established that the genetic variant is indeed causative for the phenotype.
- Dominique Germain plans to do this for Fabry disease in collaboration with other expertise centers. Mirjam Wamelink mentions a similar initiative at the Amsterdam University Medical Center. At the Erasmus MC in Rotterdam such a database has been developed for Pompe disease.

#### *Action plan:*

- Select LSDs for which to create such a genetic database. Form working groups for specific diseases. **HCPs are asked to make suggestions for both. To be further discussed at the MetabERN meeting in Frankfurt in April**

#### **B. Defining uniform start & stop criteria for the use of orphan drugs in LSDs (M. di Rocco):**

- Large differences exist between EU countries in the access to orphan drugs for the treatment of LSDs. Different criteria are used for starting and stopping these treatments. Defining uniform criteria for the use of orphan drugs in European countries will improve equality and (hopefully) access to treatment.
- Criteria should be developed using a Delphi based procedure and should be published in order to promote equality between countries.

#### *Action plan:*

- Select LSDs for which to develop uniform start/stop criteria for the use of orphan drugs. Create expert panels for the Delphi procedures. **HCPs are asked to make suggestions for both. To be further discussed at the MetabERN meeting in Frankfurt in April**

**C. Patient experiences as a basis for mapping centres of expertise in LSDs (H. Dekker):**

- The Dutch patient organization for patients with IEMs (VKS) has set-up a project to map expertise for IEMs from the patient perspective. Centers are assessed by a delegation of patients based on predefined criteria and the expertise at the center is mapped according to a model. A publication in OJRD describing the procedure is pending. More information at [www.expertisemapped.org](http://www.expertisemapped.org)
- Hanka suggests to do the same for LSD centers of expertise but funds are required (travel expenses etc.). The idea for this project is supported by the LSD SNW and MetabERN, funds will need to be required as currently no funds are available within MetabERN

*Action plan:*

- PO's (lead by Hanka) will discuss the plan of action further with the MetabERN coordination. Sources of funds need to be acquired.

**D. Identification of new biomarkers for Pompe's disease (G. Parenti):**

- The group of Giancarlo Parenti has established a potential new biomarker for Pompe's disease based on microRNAs. A summary of the work is presented. Publication: Tarallo et al, Genetics in Medicine 2018.
- In order to develop this work further additional samples of Pompe patients are required. Collaboration for this within the LSD SNW is asked.
- For this project, and possible other future collaborative projects, the development of a virtual biobank listing the availability of patient samples is suggested.

*Action plan:*

- HCPs can contact Giancarlo Parenti ([parenti@tigem.it](mailto:parenti@tigem.it)) if they want to collaborate on the project.

**E. Natural history of Mucopolidosis II/III (E. Oussoren):**

- A natural history study was conducted for ML III based on the collaboration of three HCPs, results have recently been published in JIMD (Oussoren et al JIMD 2018).
- To learn more about the clinical spectrum and natural history of ML II/III more data are needed. A collaborative project to set-up a patient registry for ML II/III is suggested.

*Action plan:*

- HCPs can contact Esmee Oussoren ([e.oussoren@erasmusmc.nl](mailto:e.oussoren@erasmusmc.nl)) if they want to collaborate on the project.

**F. Pilot study for newborn screening on LSDs (F. Tubuli):**

- Data on a pilot study for NBS based on enzyme analysis in DBS for MPS I, Fabry disease and Pompe disease in the Florentine area were presented. Positive patients were confirmed by molecular analysis. Based on the results MPS I, Pompe and Fabry will now be included in NBS in the Tuscany region.
- There was discussion on the current status of NBS enzymatic assays to screen for LSDs and the use of confirmatory molecular analysis as variants of unknown clinical significance may be picked up as well as patients with late onset of disease that should not be treated from birth onward.

**G. Odiparcil in MPS VI (J. Hennerman):**

- Odiparcil is small molecule based therapy promoting the synthesis of soluble GAGs, thus promoting GAG clearance.
- A clinical trial will be started in adult MPS VI patients.

- HCPs can contact Julia Hennerman ([Julia.Hennermann@unimedizin-mainz.de](mailto:Julia.Hennermann@unimedizin-mainz.de)) for further information on the trial and possible patient inclusion.

**Next LSD SNW meeting will be at MetabERN meeting in Frankfurt (April 4-6 2019). We hope to see you there!**