Roundtable discussion topics

1. Critical issues in diagnosis and treatment of NDDs

Chairs: Zeynep Tümer, Hülya Kayserili, Marco Tartaglia

Genomic research has been transformed by rapid advancements in next-generation sequencing technologies (NGS-T), bioinformatics, and machine learning. In the session ‘genes & pathways’ an overview will be provided of the recent advancements in NGS technology, and beyond, by the different presenters in this session.

During this roundtable session, we will have time to dive in more detail into the topics that were briefly discussed on stage by Hülya Kayserili, Anais Begemann, Danielle Veenma, Solveig Heide and Dmitrijs Rots.

The following topics will be addressed at our roundtable:

- Disease Biology Characterization (gene identification, genetic diagnosis, biological function, effect of variants, relevant in vitro and in vivo models)
- Therapeutic potential (identification of druggable targets, safety assessment etc)
- Clinical trial readiness (Biomarkers, clinical trial end points, inclusion of expert clinicians etc)
- Patient population and engagement (epidemiology, patient registry, natural history etc)

2. Identifying chances for optimization of transdisciplinary (health)care networks

Chairs: Katarzyna Świeczkowska, Anja Bos-Roubos, Ellen Wingbermühle, Jos egger

An important starting point of this roundtable discussion is to *focus on the abilities* of people living with a rare genetic neurodevelopmental disorder! So, a broader scope than only the medical approach, expressed in physiological functioning, medical facts, energy and pain.

The format of this interactive session is the 'World café'. This format enables a creative process for stimulating a dialogue, sharing knowledge and identifying short- and long-term solutions for current challenges building transdisciplinary teams in which ALL experts learn and work together.

The first step is making an inventory of the different educational material that's already available to train (para)medics and experts by lived experiences in transdisciplinary care. This inventory will be compiled by taking the broader scope and looking at the person behind the patient!

In the second step we will express our ideas for solutions directions for improving (postgraduate) training of the different experts in planning and organizing the transdisciplinary care that supports the person in all aspects of their life.

In the last step we will share our ideas on what is needed to realise the solution directions that will optimize the teamwork in transdisciplinary (health)care networks, which might be differ between countries and regions?

3. Diagnosis and treatment of NDD with complex psychopathology

Chairs: Claudine Laurent-Levinson, Michael Owen

This Round Table is designed to complement the Invited Lecture by Professor Owen on: Psychiatric Genetics and the Neurodevelopmental Continuum. Professor Owen will review evidence suggesting that neurodevelopmental disorders lie on an etiological and symptomatic continuum with severe adult psychiatric conditions. This reflects a gradient of decreasing neurodevelopmental impact that is manifest as follows: intellectual disability, autism/ADHD, schizophrenia and bipolar disorder. Clinical outcomes reflect the contributions of rare high-penetrance mutations, multiple common alleles of small effect and environmental factors. This implications of these findings for research and practice will be described in the talk.

In the Round Table, two detailed case histories will be presented for discussion. They are representative of some of the complexities that are encountered in daily practice with the many NDD patients who have complex psychopathology:

a. Many of these patients have combinations of symptoms and functional difficulties that do not fit neatly into any DSM or ICD category of psychiatric syndrome, yet these features are major contributors to the difficulties that are confronted by the patient and family.

b. Consistent with Professor Owen's approach, the discussion will focus on the value of *dimensional* approaches to diagnosis and intervention, as illustrated in the case reports and in the experience of members of the audience.

4. What is aging – and why is it different in patients with rare genetic syndromes?

Chairs: Laura de Graaff, Stephanie Miot, Francesco Mattace Raso,

During the round table session, we will have time to dive in more detail into the topics that were briefly discussed on stage by Francesco Mattace Raso and Laura de Graaff: multimorbidity, polypharmacy, sarcopenia, hypertension and decline in mood and cognition. We will address the following questions, which we will discuss with the participants. Which problems arise when premature aging is not recognized? How can we quantify aging in order to prove that a patient is aging prematurely? How could we score premature aging, by using clinical markers (muscle strength, vascular stiffness etc.) as well as biomolecular markers (oxidative stress profile, DNA methylation, miRNAs, telomere shortening, etc)?

We will discuss clinical cases and, for each real-life patient, we will address both the clinical problems as well as the underlying fundamental (molecular, biochemical) pathways and mechanisms.

5. How to go beyond the genetic diagnosis for NDD

Chairs: Gaëtan Lesca, Maurizio Taglialatela, Cláudia Valente

During this round table session, we will explore the topics underlying the session “Mechanisms of diseases, model systems & translational pre-clinical work”, such as in-silico prediction tools for monogenic epilepsies (SCN and GRIN genes), functional testing in potassium channelopathies related to epilepsy (KCNQ2, KCNQ3, KCNQ5) and ex vivo models of epilepsy as tools to understand epileptogenesis mechanisms and screen potential therapeutic targets.

We will address and discuss with the participants the following questions:

- Can dedicated in-silico tool help to predict the functional consequences of genes causing neurodevelopmental disorders ?
- Do gain- and loss-of-function (GoF and LoF, respectively) effects in vitro predict phenotypes and personalized therapies?
- How can epilepsy models, whether ex vivo or in vivo, serve as effective screening pathways for identifying new therapeutic targets?

Rare, genetic epileptic encephalopathies caused by gene mutations (SCN, GRIN, KCNQ2, KCNQ3, KCNQ5 genes) and pathways (NLRP3) involved in the pathophysiology of epilepsy will be matter for discussion.

6. From gaps & challenges towards future avenues of interdisciplinary care

Chairs: Sylvia Huisman, Annette van der Putten

We warmly invite you as an expert audience of psychologists, medical doctors, other care professionals, scientists AND parents or relatives for this (2 hour) interactive roundtable! It is a great opportunity and privilege to exchange experiences and ideas with those involved with the care and support of persons with Profound Intellectual and Multiple Disabilities from different countries.

During this session we will 1. collate various gaps and challenges in the care and support of persons with PIMD and their relatives and 2. propose potential (evidence, practice and experienced based) solutions and future avenues to improve care and support, and (family)quality of life in the end.

In a 3-step interactive program we strongly focus on bringing together expertise and on interprofessional collaboration. Finally, we will jointly draw up a research and practice agenda in order to optimize the quality of life of these persons with PIMD and their families.

Step 1: Brief introduction of people with PIMD as a basis for a broad inventory of gaps and challenges on a personal, professional, organizational and national level regarding care and support of persons with PIMD. We will then structure and prioritize the findings for step 2.

Step 2: Brief introduction of 1. current knowledge of management of motor abilities, pain, sleep and mood based on systematic literature search and 2. the development of PIMD guidelines' recommendations. Together we will then inventory best practices, effective strategies, and potential solutions to tackle the gaps and challenges from step 1.

Step 3: Brief summary of findings of step 1 and 2. We will outline the remaining questions and draw up an (10 point) plan of action plan and research agenda, including how we will proceed (who does what when and how), in association with guideline development.

Meet our Roundtable Chairs

Anja Bos-Roubos, psychologist in training as a specialist in clinical neuropsychology & PhD candidate at the Expertise Centre for Neuropsychiatry, Vincent van Gogh Institute for Psychiatry

Jos Egger, PhD, is professor of Contextual neuropsychology at the Donders Institute of Radboud University Nijmegen and has his main interest in psychopathology. As scientific director of Vincent van Gogh Institute for Psychiatry he chairs its Centres of Excellence for Neuropsychiatry. His research primarily focuses on the neurocognitive aspects of psychiatric and genetic disorders and the assessment and treatment thereof. He currently chairs the Dutch national board of program directors in postmaster professional education of Clinical psychology and Clinical neuropsychology.

Laura de Graaff is associate professor Internal Medicine for Rare Genetic Syndromes (RGS) and founder of the Erasmus MC Center for adults with RGS in Rotterdam, the Netherlands. In 2015 she finished her medical training in Internal Medicine-Endocrinology and launched the Center for adults with RGS. Its multidisciplinary team takes care of over 1100 adults with over 90 (ultra-) rare genetic syndromes. Dr. de Graaff leads both clinical research and fundamental research lines investigating biomolecular pathways and cellular mechanisms involved in rare endocrine genetic syndromes.

Sylvia Huisman, is an Intellectual Disability Physician, demonstrated in her PhD research a translational and transdisciplinary approach is the basis for understanding and treatment of self-injurious behavior. Current research areas: 'Modelling NDD and mosaicism in CdLS using human brain organoids', 'Tailor made care for people with NDD and genetic syndromes with challenging behavior: interprofessional collaboration and parents as experts' and 'Tacit Knowledge: implicit expertise in the care for people with PIMD'. Sylvia runs expert clinics at Amsterdam UMC and Zodiak. She is active in ITHACA's guidelines for genetic syndromes and PIMD

Hülya Kayserili, MD. PhD., is a professor of medical genetics and chief of the Medical Genetics Department and Diagnostic Center for Genetic Diseases at Koc University School of Medicine (KUSoM), Istanbul, Turkey. Dr. Kayserili's area of expertise is clinical genetics focusing on neurogenetics and prenatal genetics, and she is an experienced clinician on rare single gene disorders and dysmorphology. Dr. Kayserili's group investigates the etiopathogenesis of rare, very rare craniofacial dysmorphic syndromes and limb malformations.

Claudine Laurent-Levinson is a child psychiatrist at Hôpital Pitié-Salpêtrière and a faculty member (MCU-PH) at Sorbonne University (Paris, France). She completed her PhD (Neurosciences), trained in clinical genetics and received post-doctoral training on proteomics (Vanderbilt University and NIMH). She was Associate Professor of Child Psychiatry at Stanford University (2013-2016). She leads a clinical research group (clinical and genetic characterization of early-onset psychoses), and is interested in specific learning disabilities. She belongs to the PGC schizophrenia group. She has published more than 100 peer-reviewed articles.

Gaetan Lesca, MD, PhD is a professor of Medical Genetics at the University Claude Bernard Lyon 1. He is leading the reference laboratory for genetic epilepsies at the University hospital of Lyon. In the research field he has contributed to the identification of novel disease-causing genes, phenotype-genotype correlation studies, and functional testing in neurodevelopmental disorders and especially monogenic epilepsies. He is co-chair of the working group of genetic research of the ERN-EpiCARE and co-chair of the task force on Genetic Testing of the International League Against Epilepsy (ILAE).

Stephanie Miot is a geriatrician and psychiatrist by training. She has a geriatric consultation for aging adults with neurodevelopmental disorders (NDD) in University Hospital of Montpellier. She is also developing a dedicated health care network for these adults in Occitanie, France. Neurobiologist trained at *the Liliane Bettencourt INSERM-School* (French MD-PhD program) and alumnae of the For Women in Science – L'Oréal Unesco program, she studies aging trajectories of NDD adults within the Centre de recherche en Epidémiologie et Santé des Populations (CESP, INSERM U1018) and is interested in identifying biomarkers of pathological aging in this population.

Francesco Mattace-Raso is Professor of Geriatrics at the Erasmus MC University Medical Center of Rotterdam, The Netherlands, He chairs the division of Geriatric Medicine and is Principal Investigator Vascular Aging Science Center Erasmus MC. From 2010-2021 he has been the of the Head Postgraduate School of Geriatrics at the Erasmus MC University Medical Center of Rotterdam. Main research interest is to investigate the causes and consequences of age- related cardiometabolic changes: a model of aging which allows to investigate the complex biological process of senescence and the possible consequences on individual vitality. In this field, Francesco Mattace Raso has an international leading role, author of milestone studies and coauthors of guidelines and expert papers.

Michael Owen is Professor of Psychological Medicine, at Cardiff University. From 1998-2019 was Head of the Department of Psychological Medicine and Clinical Neurosciences in Cardiff Medical School. He was Director of the MRC Centre for Neuropsychiatric Genetics and Genomics from 2009-2019, and of the Cardiff University Neuroscience and Mental Health Research Institute from 2010-2014. He practiced as a consultant psychiatrist until February 2016. His research focusses mainly on the genetics of psychiatric conditions and also their relationship to childhood neurodevelopmental disorders.

Annette van der Putten is professor at the University of Groningen (RuG), the Netherlands, in the field of the support of people with profound intellectual and multiple disabilities (PIMD) and their families. She is chair of the Academic Collaborative Center PIMD (www.aw-emb.nl); a workplace in which professionals from science and practice together generate and implement knowledge, assessment procedures and interventions to improve the (family)lives of people with PIMD. She is (co)author of several international publications and supervises researchers in small and large scale

Katarzyna Świeczkowska, vice-president of PSONI Gdańsk, is a parent of a person with PWS, educator, co-founder and a director of the Group of Non-Public Educational Institutions in Polish Association for Persons with Intellectual Disability in Gdańsk. Katarzyna Świeczkowska is a member of EPAG at the ERN ITACHA and the Patient Council at the Center for Rare Diseases in Gdańsk .Since 2020, she has been cooperating with EACD, IAACD, Canadian association CanChild and the Polish Academy of Childhood Disability. For several years, she has been a board member of the international organization CARAVAN 2000, European Movement for Diversity and Understanding and the Polish AAC and ETR Council.

Maurizio Taglialatela MD/PhD is Professor of Pharmacology, Coordinator of the PhD Program in Neuroscience and Head of the Clinical Pharmacology and Toxicology Division at the Department of Neuroscience at the University of Naples Federico II, Italy. Dr. Taglialatela is world renowned for his studies of a variety of ion channels, and their role in myriad diseases, with particular focus on the Kv7 (KCNQ, "M-type") K+ channels. His research focuses on developing novel therapeutic strategies for early-onset epilepses and comorbid neurodevelopmental disorders.

Zeynep Tümer is a medical doctor by training and after completing PhD studies on the X-linked copper metabolism disorder Menkes disease in 1996, ZT's research interest has been focused on understanding the underlying genetic mechanisms of rare NDDs. Currently, ZT is employed at the Copenhagen University Hospital, Rigshospital and affiliated to the University of Copenhagen as professor. Apart from research she is carrying out genetic diagnosis of patients with intellectual disabilities and imprinting disorders. She has 220 peer-reviewed publications and has supervised 25 PhD students, 12 PostDocs, and more than 80 Master/bachelor students.

Cláudia A. Valente's obtained her Chemical Engineering degree (1997) and PhD in Biotechnology (2003) from Instituto Superior Técnico, University of Lisbon (UL), Portugal. Subsequently, she pursued postdoctoral studies in Developmental Biology and Neurosciences at IMM. Presently, she is a senior researcher and invited professor at UL Medical Faculty. Her scholarly interests are centered on the intricacies of NLRP3 inflammasome, a pivotal pathway governing immune responses, with a keen interest in its potential as prospective therapeutic target for Epilepsy and Alzheimer's disease.

Ellen Wingbermühle, PhD, clinical neuropsychologist and clinical neuropsychology practice trainer at Vincent van Gogh mental health centre, The Netherlands