SUMMARY OF THE 7TH INTERNATIONAL MEETING ON RARE DISORDERS OF THE RAS-MAPK PATHWAY;

June 15th-16th, 2018. Una Hotel Scandinavia, Milan.

The meeting combined a half-day session on Promotion of Development of the Noonan syndrome guidelines with a Scientific and Clinical meeting. The scientific meeting was attended by over 100 registrants, from a variety of backgrounds, both clinical and scientific. Colleagues were present from Japan, USA, Australia, Hong Kong, Canada, Sweden, Finland, Denmark and Switzerland, as well as most member states of the EU.

Since the last meeting in Barcelona, the European Union has funded 23 networks concerned with improving the health of people with rare disorders across Europe. One of these networks, ITHACA (Intellectual Disability, TeleHealth and Congenital Anomalies), is co-ordinated from Manchester and has Expert Patient Care as a work-stream. An update of the guidelines for Management of Noonan syndrome (NS) is part of this work package.

Professor Bronwyn Kerr presented an overview of the previous work on NS guidelines and the work undertaken so far by the ITHACA team. This latter is seeking the views of patients and families from the UK, Spain, and The Netherlands, using a translated Google poll. A parallel survey has asked for views on a table of Minimal Medical Surveillance. The overwhelming message from families is the difficulty of obtaining co-ordinated care, and in particular around transitions. The majority felt that a recommendation re the minimal required care would be useful, albeit with less medical jargon.

Dr Giuseppe Zampino did a review of Minimal Medical Care in Costello syndrome (CS) and Cardio-facio-cutaneous syndromes (CFC), including the differences in metabolism and manifestations established by his research group.

Other talks focused on specific aspects of Expert Patient Care in Rasopathies;

Professor Bruce Gelb discussed the importance of mutation testing for Rasopathies in infants with a cardiomyopathy and the importance of expert evaluation and counselling if a mutation is found.

Dr Alessandro de Luca reviewed the literature and his laboratory's experience in undertaking prenatal diagnosis of the Rasopathies. Just over 50% of foetuses with two or more ultrasound findings consistent with a Rasopathy will have an abnormal prenatal test, most commonly a change in PTPN11 (consistent with this being the commonest cause of NS).

Professor Martin Zenker chaired a session on the difficulty of deciding what the diagnostic criteria for different Rasopathies are, given the number of genes, and the variability of the effects of mutations between and within genes.

The first session of the scientific meeting had a theme of Cancer predisposition. The talks included discussions of the importance of considering an underlying genetic diagnosis in all children with cancer, the biology of the RAS pathway in leukaemia and the relevance to treatments, an overview of tumour risks in CS, and the biology of HRAS mutations in sperm.

The second session was titled “Cardiovascular system/ Hypertrophic Cardiomyopathy”. The outcome of the CARNET study, an overview of congenital heart disease in NS published in 2016, was presented. The study demonstrates that the congenital heart disease seen in NS is atypical in a significant number of patients, especially in those with no mutation found. Other talks described cellular and zebrafish studies that are increasing understanding of the biology of the pathway in the heart, and providing models that can be tested for potential treatments. These studies suggest that, because of the complexity of the inter-reactions of the pathway, treatment response may be mutation specific. Successful treatment of a patient with a severe prenatal onset hypertrophic cardiomyopathy with a MEK inhibitor was presented.

A post dinner clinical session illustrated the clinical findings associated with some of the newer Rasopathy genes, particularly LZTR1, which while mostly autosomal dominant, can be associated with an autosomal recessive form of NS.

In the fourth session on Nutrition, energy and bone, the research presented has looked at basal metabolic rate and glucose metabolism in patients with CS and CFC. Cellular studies have evaluated glucose metabolism. A mouse model of NS with Growth hormone insensitivity has been treated and evaluated with MEK inhibitors and statins; the outcome has led to a human clinical trial in France, reporting in two years, on the effect of statins on growth in NS. Mouse studies are also illuminating the premature aging seen in CS. A different mouse model is evaluating BMI, glucose metabolism, insulin responsiveness and markers of fat metabolism in NS.

The final session combined a number of important clinical issues. A clinical study of epilepsy in the Rasopathies is comparing seizure types and frequencies across different conditions and mutations, with the aim of improving diagnosis and therapy. Behavioural studies confirm the difficulties with aspects of learning, behaviour and emotion seen in other studies. A major difficulty for some patients is lymphoedema, the cause of which remains poorly understood. It appears to be a common feature of patients with SOS2 mutations.

A major feature of this meeting was presentations from families about the impact of living with cancer, lymphoedema, and heart disease and how research might be directed to benefit families.

This 7th European meeting on Rasopathies (the first having been in 2008) had an attendance much greater than any of the previous meetings. The presentations were of a uniformly high quality, and show the depth of basic science and clinical research into Rasopathies across Europe and beyond. The meetings are a unique collaboration between families, clinicians and scientists; the increases in understanding cellular biology and the clinical studies presented in the meeting are essential if we are to improve treatments.

Bronwyn Kerr and Emma Burkitt Wright, 2018