Annual Report 2013

Centre of Research Excellence in Neuromuscular Disorders (CRE-NMD) and Australasian Neuromuscular Network (ANN)

www.ann.org.au

Australian Government
National Health and Medical Research Council

Australasian Neuromuscular Network

Who we are

The CRE-NMD will enable us to implement an Australia-wide multidisciplinary approach to neuromuscular disorders, and consolidate a national network of excellence in these areas to link in with international networks.

The CRE-NMD will reduce the burden of neuromuscular disorders, and promote excellence and innovation in research and clinical practice so that the latest in diagnosis and therapy is available throughout Australia.

Executive Report

The establishment of the CRE-NMD brings together researchers who have worked together for more than 15 years, and who are at the forefront of gene discovery and translational research in neuromuscular disorders.

The CRE-NMD will translate ‘best evidence’ from our clinical and laboratory-based research, including gene discovery, disease mechanism and therapy development, into ‘best clinical practice’ under two themes of diagnosis and prevention and treatment. The CRE-NMD will consolidate our place at the forefront of neuromuscular research internationally.

It will foster future research leaders and international partnerships to ensure the sustainability of excellence in neuromuscular research, and ultimately vastly improve health outcomes and quality of life for thousands of patients and their carers.

Since the establishment of the CRE-NMD in January 2012, we have worked towards developing a sustainable model for collaborative research. Firstly, we have built the Australasian Neuromuscular Network (ANN), to disseminate and

communicate the research being conducted throughout Australia and New Zealand, as well as identifying where we collaborate internationally.

Secondly, the CRE-NMD supports a number of outstanding research fellows (clinicians, physiotherapists and researchers) and PhD students at key research sites in Australia (WA, VIC, NSW). The focus on supporting and providing high quality training for early career researchers will contribute to a sustainable future for research in neuromuscular disorders across Australia. A number of our early career researchers presented at our most recent annual meeting in Sydney in March 2013. This was a unique opportunity for all chief investigators, associate investigators and early career researchers to share knowledge and forge new collaborations.

Lastly, to work towards our ongoing sustainability and in recognition of the global reach of both the CRE-NMD and ANN, investigators and associate investigators from the CRE-NMD were invited to formally partner with European Union groups on an FP7 rare disease research program (Neuromics, RDConnect and RAREbestpractice). The research programs funded through the NHMRC, aim to address key themes of the CRE-NMD and the ANN, by improving diagnostics, developing clinical guidelines and standards of care and developing shared platforms for data analysis and repositories.

The CRE-NMD and ANN are leading this initiative for neuromuscular disorders and will pave the way for other rare diseases that impact Australians and in areas where we have national and international leadership and expertise.

CRE-NMD/ANN Executive

Prof Kathryn North

Prof Nigel Laing

A/Prof Monique Ryan

A/Prof Nigel Clarke

Prof Joshua Burns

Introduction

The CRE-NMD's research program will translate 'best evidence' from our clinical and laboratory-based research, including gene discovery, disease mechanism and therapy development, into 'best clinical practice' under two themes of diagnosis and prevention and treatment.

We have established a growing national collaborative diagnostic network involving multidisciplinary clinics and testing laboratories, to ensure that all patients have access to an accurate genetic diagnosis to inform prevention through prenatal diagnosis and to guide prognosis and surveillance.

We are investigating prevention strategies built on population screening methods and build a coordinated clinical trials program so that potential new treatments developed in Australia and overseas will be quickly accessible to all individuals regardless of where in Australia they live.

We are also developing a nationally integrated training program, using our comprehensive and complementary

expertise in laboratory and translational research to provide an unparalleled experience for future clinical and laboratory research leaders. The CRE-NMD will thus be the national hub for consolidating and expanding our national research and training initiatives.

The CRE-NMD and ANN aim to address deficiencies in timely diagnosis and treatment, fragmented research efforts, shortcomings in data collection and lack of effective care for all individuals regardless of where they live.

Within the themes of Diagnosis and Prevention, Clinical Care, Clinical Trials and Research, we will turn best evidence in best practice through a number of key initiatives.

Specifically, the CRE-NMD aims to achieve the following major outcomes:

• **Instigation of a national diagnostic network** to coordinate diagnosis to increase access, efficiency and diagnostic accuracy, decrease costs and develop research patient cohorts.

• **Accelerated gene discovery.** We have established large and unique patient cohorts and will use state-of-the-art next-generation sequencing technologies to find the causative genes for disorders where it was previously impossible to do so. We predict that within the next 10 years, almost all Australian NMD patients will have access to an accurate genetic diagnosis, which is essential for guiding management, for prediction of recurrence risk, for prevention through prenatal diagnosis, and, increasingly, for eligibility for clinical trials of new therapies.

• **National patient registries for each NMD.** Registries represent an important interface between researchers and patients and are the first port of call for enrolling patients in clinical trials. They also enable clinical research into natural history and genotype-phenotype correlation.

• **Establishment of the applicability of population screening programs** for NMDs, aimed at reducing the health, social and economic burden of NMDs in Australia.

• **Australian leadership in phase II/III clinical trials for NMDs within a national clinical trials framework.** We have already established centres with the expertise to participate in international clinical trials, as well as developing novel therapeutic agents as part of their laboratory-based studies of new drugs, gene up-regulation, exon skipping and stem cell therapy. We are also pioneering physical therapy and rehabilitation trials targeting day-to-day difficulties of patients with NMDs. The CRE-NMD will enable us to initiate and lead new clinical trials and to engage all states to ensure patients have equal access to state-of-the-art therapies.

• **The development of a nationally integrated research training program** will draw together early career researchers in

medicine, science and allied health from all states, promote interchange of staff and students, and encourage collaborative projects between sites.

The CRE-NMD will consolidate our place at the forefront of neuromuscular research internationally. We are currently leaders in gene discovery and diagnosis, and the CRE-NMD will elevate us to leaders, rather than participants, in the treatment of NMDs. The CRE-NMD will enable Australia to build a critical mass in all areas of basic and clinical research into disorders of muscle and nerve. It will foster future research leaders and international partnerships to ensure the sustainability of excellence in neuromuscular research, and ultimately vastly improve health outcomes and quality of life for thousands of patients and their carers.

Our Staff

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Education and training of healthcare professionals plays a crucial role in the improvement of patient diagnosis and care. Many trainees have limited access to specialty clinics, particularly adult neurologists in training who do not see neuromuscular cases unless they attend a specialist clinic. The CRE-NMD/ANN will identify and publicise training opportunities for medical trainees as well as nursing and allied health professionals, via the website and newsletter.

Our Team

CHIEF INVESTIGATORS

Prof Kathryn North

Prof Nigel Laing

A/Prof Andrew Kornberg

Prof Joshua Burns

A/Prof Monique Ryan

Dr Nigel Clarke

Prof Alastair Corbett

Prof Kathryn Refshauge

Dr Michael Buckley

Prof Catriona McLean

ASSOCIATE INVESTIGATORS

Prof Steve Wilton

A/Prof Phillipa Lamont

Dr Kristi Jones

Prof Nadia Rosenthal

Prof Peter Currie

Prof Garth Nicholson

Mr Phil Martin

Dr Hugh Dawkins

RESEARCHERS

Western Australia

A/Prof Kristen Nowak

A/Prof Gina Ravenscroft

Dr Mark Davis

Ms Elyshia McNamara

Mr Royston Ong

Kyle Yau	PhD
Emily Todd	PhD
Klair Bayley	Masters
Macarena Cabrera	CRE-NMD Fellow

Victoria (Murdoch Childrens Research Institute)

Prof Kathryn North

Dr Peter Houweling

Dr Fleur Garton

Merryn Pearce

Kelly Roeszler

Victoria (Royal Children's Hospital)

A/Prof Monique Ryan	
Daniella Villano	
Dr Kate Carroll	CRE-NMD Fellow
Katy de Valle	
Rachel Kennedy	
Zoe Davidson	
Dr Eppie Yiu	CRE-NMD PhD
Dr Katherine Howell	

Victoria (Alfred Hospital/Monash)

Prof Catriona McLean	
Dr Paul Kennedy	

New South Wales (INMR)

Dr Nigel Clarke	
Dr Emily Oates	
Dr Leigh Waddell	
Dr Kristy Rose	
Dr Sarah Sandaradura	CRE-NMD Fellow
Lyndal Douglas	
Marnee Mackay	CRE-NMD Phd
Jennifer Baldwin	CRE-NMD Phd
Clare Miller	

New South Wales (University of Sydney)

Prof Joshua Burns	
Prof Kathryn Refshauge	
Dr Paula Bray	
Melissa Mandarakas	

Research Support

Dr Paula Bray

Dr Leanne Mills

Elena Mamontov

Michelle Burns

Melissa Mandarakas

Our Early Career Researchers

Dr Zoë Davidson is an Accredited Practising Dietitian specialising in paediatric nutrition. Her research program focuses on advancing the evidence base of children with neuromuscular disorders.

Current research projects continuing in 2014:

Nutriceuticals in Duchenne muscular dystrophy

The aim of this study is to test the efficacy of an enhanced nutritional supplement in maintaining or improving functional ability in boys with DMD. The primary outcome is the six minute walk test. Secondary outcomes include community ambulation, body composition, and quality of life. Pilot data indicates that the nutritional supplement is associated with a 25m improvement in a six minute walk test compared to a standard nutritional supplement. This is a double blind, randomised controlled crossover trial of a multi component supplement intervention. Zoë is continuing to coordinate the nutriceuticals study with sites running at the Royal Children's Hospitals in Melbourne and Brisbane, and a new site at the Children's Hospital at Westmead opening in Sydney in 2013. There are currently 33 boys enrolled (8 active, 19 complete, 5 withdrawn). The target for recruitment is 54 participants. Through the ANN, there has been potential interest

for further sites at the Sydney Children's Hospital and in New Zealand in 2014.

Energy expenditure in Neuromuscular Disorders

Children with neuromuscular disorders can experience both states of under and over nutrition, which can have considerable implications on disease progression as well as respiratory issues and daily care. There are currently no specific dietetic guidelines for management of the neuromuscular disorders. Understanding energy expenditure in these conditions is fundamental to the provision of appropriate nutrition counselling to prevent or manage obesity and under nutrition. As such, this study consists of two related projects exploring energy expenditure in various neuromuscular disorders.

The first project aims to investigate how energy expenditure and body composition change over time in males with Duchenne muscular dystrophy. Secondary aims of this project are to explore relationships between changes in energy expenditure and body composition with functional outcomes; and to investigate if a step counter can be used as surrogate measure for energy expenditure in boys with Duchenne. Twenty ambulatory boys will be recruited and will attend four assessments over a three year period.

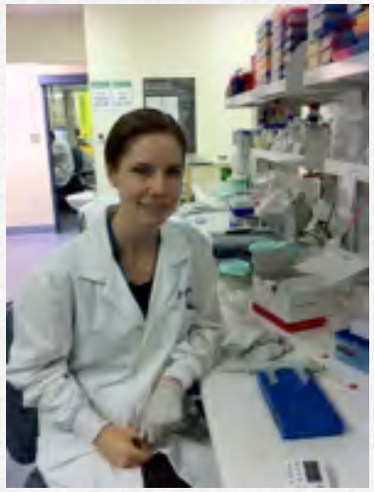
The second project aims to explore total and resting energy expenditure and body composition in children with spinal muscular atrophy and congenital muscular dystrophy at one point in time. This is an exploratory study that will measure energy expenditure in these population groups for the first time. Ten children (aged 5-17 years) with spinal muscular atrophy type 2 or 3 and 10 children (aged 5-17 years) with congenital muscular dystrophy will be recruited.

Zoe has been successful in obtaining funding ($60,000) to support these projects. The study is currently undergoing ethics review and will open for recruitment in the second half of 2014.

Exploring the link between dystrophin mutations and cardiac outcomes

This project aims to document the natural history of echocardiogram parameters in Duchenne muscular dystrophy and to explore if specific dystrophin mutations are predictors of cardiac outcomes. This is a retrospective clinical audit occurring in collaboration with cardiology at the Royal Children's Hospital. The audit has identified 330 males with Duchenne muscular dystrophy who have attended the hospital since 1970. Data collection included dystrophin mutation, echocardiogram outcomes, use of steroids and cardiac medications, age at loss of ambulation and death if known. Collection of echocardiogram outcomes is continuing, and early statistical exploration has also com-

menced. It is expected that data collection and statistical analysis will be completed in 2014.



Rachael Duff is a postdoctoral research fellow working under Bill Gole and has worked in the area of neuromuscular genetics for fifteen years. Rachael's PhD, which was an investigation of the genetic causes of several neurodegenerative disorders, was completed in 2008 at UWA under the supervision of Professors Nigel Laing, Steve Wilton and Frank Mastaglia. The work resulted, amongst other findings, in the successful identification of a mutation in FLNC responsible for a novel form of distal myopathy. Between 1999 and 2009, Rachael worked at the Neurodegenerative Disorders Centre located at the Australian Neuromuscular Research Institute's high throughput genetic screening facility.

In 2009, Rachael relocated to the United Kingdom to complete a post-doctoral position at the National Heart and Lung Institute (NHLI), Imperial College, London. Working with Professors Bill Cookson and Miriam Moffatt, projects involved investigating the role of microbial flora on the development and progression of respiratory conditions using molecular biology techniques and bioinformatics.

Since returning to Nigel Laing's Laboratory in October 2010, Rachael has been awarded a three year Bill Gole postdoctoral fellowship from the Motor Neurone Disease Research Institute of Australia. The fellowship project involves the use of next generation sequencing technologies and bioinformatics to identify disease causing genes in motor neurone disease. Rachael also has funding from the Australian Mitochondrial Disease Foundation to develop and validate Next Generation Techniques for the diagnosis of mitochondrial disease.

Gina Ravenscroft is a postdoctoral researcher, holder of an Australian National Health and Medical Research Council Early Career Fellowship, within Prof Nigel Laing's Molecular Neurogenetics Laboratory in Western Australia. Gina joined Prof Laing's group as a PhD student after obtaining her undergraduate degree and Honours qualifications majoring in Physiology at the University of Western Australia.

Her main research interests include identification of disease genes and mechanisms for neuromuscular foetal akinesias and strongman syndrome; and investigating routes to therapy for a group of severe congenital muscle diseases caused by mutations in the skeletal muscle alpha-actin gene.

The foetal akinesias are a clinically and genetically heterogenous group of disorders in which the unifying feature is lack of foetal movement1. Most cases are lethal during the prenatal or early postnatal period. Other characterisics of this disease entity include: joint contractures, pterygia, polyhydramnios, hydrops, respiratory hypoplasia, craniofacial abnormalities and reduced muscle mass. A number of foetal akinesia cases are due primarily to muscle defects and some also present with pathologies seem in the congenital myopathies and dystrophies. The overlap in structural lesions observed in foetal akinesia and the congenital myopathies as well as overlap in disease genes have lead some to hypothesise that some of the foetal akinesias and the congenital myopathies may represent a disease continuum rather than separate disease entities. Despite some success in recent years at identifying the genetic cause of cases of foetal akinesias, the vast majority of published cases do not have a genetic diagnosis. The overall success rate for published cohort studies of the foetal akinsias is only ~ 25%. With the emergence of next generation sequencing (NGS) it is now possible to meet the need for genetic diagnosis of the foetal akinesias. To date we have performed NGS of probands from 20 foetal akinesia families: this has resulted in the identification of two novel foetal akinesia-nemaline myopathy genes (three families), and a genetic diagnosis in a further six families where previously this was not possible2. The two new genes are responsible for a significant number of recessive foetal akinesia-nemaline myopathy cases worldwide.

Strongman syndrome, a newly recognised entity described by Dr Bernard Brais in the French-Canadian population in Quebec, in which patients present with excessive muscle strength and bulk, in the absence of training. Patients also exhibit numerous medical complications: muscle fatigue, cramping, poor sleep; and in some cases life-threatening compartment syndrome and rhabdomyolysis. In collaboration with Drs Brais and Phillipa Lamont, we are trying to unlock the genetic cause/s of strongman syndrome in Australian patients using NGS.

Dr Ravenscroft, is also involved in projects investigating potential therapeutics for skeletal muscle alpha-actin based congenital myopathies3, using mouse models4-6. The main focus currently, is using up-regulation of the foetal actin isoform, cardiac alpha-actin, to replace the missing or defective skeletal muscle alpha-actin gene in mouse models of recessive and dominant disease, respectively. This includes investigation of viral delivery of actin.

Leigh Waddell has a PhD in improving the diagnosis of muscular dystrophies. Leigh is employed as the Laboratory and Diagnostics Manager for the INMR, and is a postdoctoral scientist coordinating the gene discovery research with Dr Nigel Clarke.

As part of a research project into gene discovery, we have sent 249 samples from 125 families with neuromuscular disorders, collated from around Australia and New Zealand, to the Broad Institute for whole exome sequencing (protein coding regions of genome). The majority of these samples have previously been analysed through the INMR standard research-based diagnostic testing processes, which typically achieves ~50% diagnosis but excludes the common forms of muscular dystrophy such as Duchenne muscular dystrophy, Facioscapulohumeral muscular dystrophy and the myotonic dystrophies. The preliminary results on the first 88 samples (33 families) demonstrate a 73% diagnostic rate; 19 families with mutations in known genes and 5 in novel genes.

Dr Emily C. Oates is a Clinical Geneticist and is currently enrolled in a PhD.

Emily is a clinical geneticist with a long-standing interest in both clinical and basic science-based medical research – particularly genetics-focussed research. She worked on numerous research projects during her undergraduate Medical Science and Medical degrees. After completing clinical training in paediatrics, and advanced clinical training in clinical genetics, she recommenced her research career by enrolling in a full time PhD in 2010 at The Institute for Neuroscience and Muscle Research. Whilst undertaking her PhD, she has maintained her clinical skills by continuing to work as Neurogenetics fellow in the Children's Hospital at Westmead Neurogenetics Clinic. Her primary clinical and research interests are outlined below:

Clinical Genetics

As a clinical geneticist Emily has developed expertise in the careful evaluation of family and clinical history, examination findings, and the interpretation of relevant investigations to establish an accurate clinical diagnosis, an important first step

in establishing a formal genetic diagnosis, and in formulating an effective clinical management plan. She is currently developing expertise in the use of new technologies e.g. next generation sequencing, to establish genetic diagnoses in previously undiagnosed individuals. She also has a keen interest in the provision of accurate, well-considered genetic counselling, and in the education of clinical genetics trainees.

Clinical management of paediatric neuromuscular diseases and Neurofibromatosis Type 1 (NF1)

Emily has worked as a clinical geneticist in the CHW-based tertiary referral Neurogenetics clinic for over four years, and during this time have been actively involved in the management of a range of nerve and muscle disorders, and in the management of an autosomal dominant genetic disorder, NF1, in hundreds of children. In the final year of her training, she incorporated current best practice guidelines, and recommendations from local consultants into a guideline for management of Duchenne muscular dystrophy patients for use by the CHW Neurogenetics team - which remains in active use. She has also participated in the conduct of clinical trials for novel pharmacological and gene-based therapies for neurogenetic disorders, and has first and middle author publications arising from my NF1-related clinical work.

Centronuclear myopathy (CNM), and non-5q Spinal Muscular Atrophy (SMA)

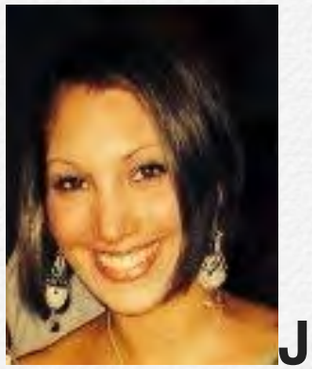
During the last three years, Emily has been undertaking a PhD, supervised by Dr Nigel Clarke, Professor Kathryn North, and Dr Biljana Ilkovski. Her research has focussed on the further-evaulation of the clinical, pathological and genetic basis of two paediatric neuromuscular disorders; CNM, and an atypical lower-limb predominant form of SMA (an anterior horn cell disease which is quite distinct from the better known recessive SMA caused by deletions and mutations of the SMN1 gene on chromosome 5q). She has several publications arising from this work, including first author publications in Brain, and The American Journal of Human Genetics. During the course of her PhD she has played a key role in the exciting discovery of a new Dominant SMA gene, BICD2, and is now leading an international research collaboration to further-characterise disorders caused my mutations within this gene. The ultimate goal of this research is improved genetic diagnosis rates for patients with these disorders, and the identification of novel targets for effective future therapies.

Childhood-onset disorders of nerve and muscle result in severe weakness, chronic disability and early death. Almost half the children with neuromuscular disorders do not have a specific diagnosis, which adversely affects their medical care, provision of accurate genetic counselling, and access to potential new

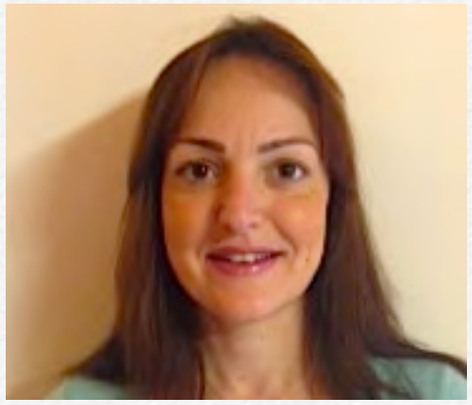
therapies. The overseas phase of this project will be with one the world's leading paediatric neuromuscular centres, where Emily will learn to apply state of the art next generation sequencing techniques, muscle MRI analysis and biomarker technologies to the task of neuromuscular diagnosis. Emily will at first be applying these skills to the detailed analysis of Australian Centronuclear Myopathy and Dominant Spinal Muscular Atrophy patient cohorts established during the course of her PhD, with the aim of improving genetic diagnosis rates for patients with these diagnoses. If time permits, she will also be undertaking studies to analyse the effects of mutations on cell function, to further-confirm pathogenicity, and to gain further insight into the underlying mechanism(s) of disease. Emily will then return to Australia to apply these same skills to the task of improving genetic analysis rates in Australasian paediatric neuromuscular patients, including patients seen by myself, and other clinical members of the Children's Hospital at Westmead Neurogenetics clinic, as well as patients from centres around Australia and New Zealand. With its potential to significantly improve genetic diagnosis rates in Australasian neuromuscular patients, this project is anticipated to have a significant impact on lives of this vulnerable patient group, and their families, within just a few short years. In addition to its clinical relevance, the project will form the foundation of a future research career which, it is hoped, will contribute to a body of high quality gene discovery-related research, and eventually lead to development of effective pharmacological and gene-based therapies.

Sarah Sandaradura is a clinical genetics trainee, who is currently completing a MPhil through the Institute of Neuroscience and Muscle Research at the Children's Hospital at Westmead, supervised by Professor Kathryn North and Dr Nigel Clarke. She completed her medical training in New Zealand, before moving to Australia to train in Clinical Genetics. Sarah's research focuses on nemaline myopathy and includes a natural history study on nemaline myopathy, though which she hopes to gain evidence for genotype-phenotype correlation, and a survey of parents of children on tyrosine, looking at the benefits and side effects of this medication. This project has also involved clinical characterisation of a new disease gene for nemaline myopathy, identified through use of exome sequencing.

Kayla Cornett is a Research Assistant working with Professor Joshua Burns at the Institute for Neuroscience and Muscle Research. Kayla recently completed her MSc in neuromuscular physiology at the University of British Columbia in Canada. During this degree she received a scholarship to conduct research abroad allowing her to join the INMR to perform a study evaluating muscle strength in Neurofibromatosis Type 1. This really flourished her interest in paediatric neuromuscular conditions. After completing her MSc, Kayla stayed on at the INMR as a clinical evaluator and trials coordinator working on a variety of studies in many different neuromuscular conditions. Kayla plans to start her PhD in July 2014 evaluating upper limb strength and function in Charcot-Marie-Tooth Disease.



Joy Goubran is an accredited Occupational Therapist at the Royal Children's Hospital Melbourne, practicing in the area of neurosciences, including the Neuromuscular Clinic at the Royal Children's Hospital Melbourne. Joy is currently undertaking a Master of Science (Biomedical & Health Sciences) through The University of Melbourne, under the supervision of A/Prof Monique Ryan. As part of her two-year Masters degree, Joy is conducting a cross-sectional study investigating the natural history of upper limb function in ambulant and early non-ambulant boys with Duchenne Muscular Dystrophy (DMD). 29 boys with DMD have been assessed on a range of outcome measures examining upper limb function and performance in activities of daily living. Amongst the outcome measures being conducted, is The Performance of the Upper Limb (PUL) assessment, recently devised and validated by an international Clinical Outcomes Group for the DMD population (Mayhew et al., 2103). As little is known about the upper limb trajectory in DMD, this research project aims to describe upper limb function and independence in relation to disease stage, as determined by the North Star Ambulatory Assessment scale. Joy will complete her Masters degree at the end of 2014, but will continue her research project throughout 2015 to re-assess participants' upper limb function following a one-year period.



Dr Roula Ghaoui is an Adult Neurologist and is currently enrolled in a PhD through the University of Sydney and the Institute for Neuroscience and Muscle Research at the Children's Hospital at Westmead, supervised by Associate Professor Nigel Clarke and Professor Carolyn Sue. Roula worked on numerous research projects during her undergraduate Biomedical Science and Medical degrees. She completed her Bachelor of Biomedical Science in 2001 with majors in Pharmacology and Genetics. She was awarded a First Class Honours in Pharmacology in 2002 which also resulted in two publications and an award received at the Australasian Society of Clinical Pharmacology and Toxicology in New Zealand. She then completed a Bachelor of Medicine and Surgery in 2005 at Flinders University of South Australia and completed training as an adult basic physician trainee. She commenced her Adult Neurology training in South Australia and then moved to Sydney to complete training as an adult neurologist in 2011. In the last year of neurology training she worked as a neuromuscular and neurophysiology fellow at the Royal North Shore hospital and developed an interest in neuromuscular disorders.

Whilst undertaking her PhD, she has maintained her clinical skills by continuing to work as Neurologist at Royal North Shore Hospital and also does private Neurophysiology clinics. Her primary clinical and research interests are in diagnoses and treatment of muscle disorders. She has a recent publication in the Internal Medicine Journal on Muscle disorders: latest investigations.

Her PhD focuses on diagnosing the Limb-girdle dystrophies (LGMDs). She is currently developing expertise in the use of new technologies such as whole exome sequencing, to establish the genetic diagnoses in previously undiagnosed limb-girdle muscular dystrophies. LGMDs are a heterogeneous group of genetic disorders that result in muscle weakness most prominent in muscles around the shoulder and pelvic girdles. The Gene Discovery Laboratory within the INMR has an established collaboration with A/Prof Daniel MacArthur, Broad Institute, Boston to perform whole exome sequencing on large patient cohorts. To date, whole exome data on 50 LGMD families has been received and analysed. So far preliminary results have allowed us to establish a diagnosis and identify pathogenic mutations in 47% of Limb-girdle dystrophy patients. The ultimate goal of this research is improved genetic diagnosis rates for patients with these disorders. This project aims to ultimately achieve higher rates of diagnoses to optimise healthcare and genetic counselling for people living with limb-girdle muscular dystrophy in Australia. This study also has a

high chance of identifying new limb girdle dystrophy (LMGD) genes that are common in the Australian LMGD population.

Hooi Ling Teoh is a 2nd year paediatric neurology trainee at Sydney Children's Hospital. She is currently enrolled in the UNSW Masters of Clinical Research programme, supervised by Dr Michelle Farrar and Professor Matthew Kiernan. She completed her medical training at University College London, United Kingdom, before moving to Australia to train in general paediatrics and now in paediatric neurology. Hooi Ling's research focuses on the application of next generation sequencing (NGS) to inherited neuromuscular disease.

Exome sequencing allows us to selectively sequence the coding regions of the genome that are translated into protein. The aim of the project is to determine how this new technology can be incorporated into existing algorithms of investigating patients with neuromuscular disorders. It's sensitivity, specificity and cost effectiveness will be analysed. In addition, the genetic diagnoses achieved may provide further insights into disease mechanisms, enabling further clinical and pathophysiological studies in children with neuromuscular disease. Her main role in the project is to collect data on undiagnosed patients and their families attending the Sydney Children's Hospital neuromuscular clinic and provide an accurate phenotypic description of their condition.

Dr Macarena Cabrera is a Neurologist with a medical practice focused on neuromuscular disorders. After finishing her residency in Neurology in Seville, Spain, in 2007 she was awarded a 3 year governmentally-founded position (Rio Hortega) for a training program in neuromuscular diseases, during which both clinical work and research were juggled.

To complete her training in Neuromuscular disorders, she did a 15 months Research Fellowship at Mayo Clinic, Rochester, Minnesota, USA, under Andrew G Engel's supervision. During this period, Macarena worked on genetics of congenital myasthenic syndromes (CMS), which culminated with the description of a new CMS gene recently published: LRP4. Since then, she has had a growing interest in the genetic causes of neuromuscular diseases.

After coming back from the Unites States in 2010, she continued to work as a Neurologist in Seville getting involved in

several research projects including some national and international ones.

Since 2013 she enrolled in a PhD under Nigel Laing's supervision at Harry Perkins Institute for Medical Research in Perth, WA. Her PhD project is focused on the application of next generation sequencing methods to different neuromuscular disease categories for diagnosis and gene discovery.

Tegan Pinese is an occupational therapist, and is currently completing a PhD through the University of Queensland, supervised by Dr Merrill Turpin and Dr Jodie Copley. Tegan completed a Bachelor of Occupational Therapy (Honours) at the University of Queensland and is currently working at MontroseAccess, where she has been employed for the past 5 years. Tegan's research focuses on the experience of young people with Duchenne Muscular Dystrophy (DMD) as they make the transition from adolescence to adulthood. The research project adopts a qualitative methodology and includes interviews with young people with DMD, parents and caregivers of young people with DMD and health professionals. Given that young people with DMD are living longer into adulthood, it is essential that they are provided with opportunities to engage in meaningful occupations within adulthood and maintain quality of life. This research aims to identify ways that health professionals can best facilitate the engagement of young people with DMD and their families in planning and preparing for the transition to adulthood, as well as identifying what factors contribute to a successful transition to adulthood for these young people.

Manoj Menezes is a paediatric neurologist with a clinical and research interest in childhood neuromuscular disease and inherited neuropathies. He is currently employed as a paediatric neurologist at The Children's Hospital at Westmead (CHW) where he runs the peripheral neuropathy service (which includes the Peripheral Neuropathy Diagnostic and Peripheral Neuropathy Management Clinics). Manoj continues his research at the Institute for Neuroscience and Muscle Research (INMR) and is currently pursuing a PhD in metabolic and mitochondrial neuropathies at the University of Sydney.

Manoj trained in Neurology at the Sydney Children's Hospital and The Children's Hospital at Westmead, under the guidance of Prof. Kathryn North and Prof. Robert Ouvrier. He then spent his post-fellowship training at the National Hospital for Neurology and Neurosurgery, Queen Square and Great

Ormond Street Hospital, London, on a Churchill Fellowship, training in peripheral neuropathy and neuromuscular medicine. He returned to Australia in 2012 to take up his current position at CHW.

Brown-Vialetto-Van Laere syndrome (BVVL) is a rapidly progressive neurodegenerative syndrome which results in unsteadiness (due to sensory nerve damage), hearing loss, skeletal muscle weakness, loss of the ability to walk and respiratory muscle weakness. Recently, mutations in the transporters responsible for riboflavin transport across the gut and into the brain have been identified in a significant number of children with BVVL. Treatment with high-dose riboflavin has been shown to be beneficial in children with riboflavin transporter mutations. Manoj's research focuses on the benefits of riboflavin therapy, and methods to measure the baseline difficulties and improvement with riboflavin (in collaboration with Prof. Joshua Burns). He is also looking at nerve excitability studies as a means to understand the cause for nerve dysfunction, and its use as a biomarker to follow affected children (in collaboration with Dr Michelle Farrar).

Charcot-Marie-Tooth disease (CMT) affects 1 in 2500 individuals, and is the commonest inherited neuromuscular disorder, responsible for a third of neuromuscular clinic presentations. CMT can vary from mild to severe, and results in significant disability in childhood. Manoj's interests include the methods to achieve a genetic diagnosis in children with genetically unclassified CMT, and clinical trials for rehabilitative and disease-modifying therapy in CMT. He is involved in the FAST (Foot and ankle strength training for children with CMT) trial that is looking at benefits of exercise on muscle strength in children with CMT.

Our Goals

3

Transforming the management of neuromuscular disorders from ‘compassionate assistance’ to targeted therapy and prevention

Diagnosis and Prevention

A diagnostic network will link research and diagnostic laboratories across states to promote the continuous and rapid translation of new tests into standardised best practice diagnostic protocols. Its aims is to coordinate a national collaborative diagnostic service and research network for neuromuscular disorders that is cost-effective, maximises availability and minimises duplication of laboratory services.

Currently there is no coordination of testing between states. Core disorders that are tested for and the separate tests undertaken vary between laboratories and no list exists of what tests are available and their locations

Diagnostic testing has been developed within a number of Australasian research laboratories based on individual interests. While this has significantly improved the diagnosis for a number of individual conditions – usually free of charge - this decentralised and non-systematic approach to testing is not sustainable in the long-term, and is not best practice to ensure the optimal health outcomes for patients on a national scale. The diagnostic services provided by research laboratories are vulnerable to changing research priorities. An integrated network linking research and diagnostic laboratories would promote the continuous and rapid translation of new tests to standardised diagnostic protocols. In addition, there is no process for the transfer of tests developed within research laboratories into NATA accredited routine testing laboratories. Clinicians do not know what tests are available or where within Australia. The RACP is undertaking a study to assess how best to coordinate testing, however in the meantime the CRE-NMD/ ANN has developed a list that will be made available on the ANN website and will be updated on a regular basis.

A list of genetic tests available in NATA accredited laboratories is available on the ANN website http://www.ann.org.au/neuromuscular-gene-tests/

Improving diagnosis: Accelerating gene discovery

Next Generation Sequencing (NGS) is the next step in molecular diagnosis. The goal of improving the molecular diagnostic success rate (aim is 90%) and accelerating gene discovery and establishing a national diagnostic network is underpinned by NGS. It is a powerful tool, best described by Prof Nigel Laing from his own personal experience:

Between 1993 and 2011, 15 new genes were discovered

Since March 2012, more than 5 new genes have been discovered.

While the rate at which whole exomes can been screened is increasing rapidly (within 1-2 years, new machines will be able to screen up to 50 exomes in 4 hours), and the cost per sample is also rapidly decreasing to approx. $1000, the enormity and complexity of the data generated requires interpretation by experts.

WA and NSW, along with collaborators such as the Broad Institute, continue their focus on gene discovery. NGS technologies have helped researchers identify more than 100 new neurogenetic disease genes within the last 18 months. Identification of new disease genes is crucially dependent on accurate clinical and pathological information and greatly facilitated by linkage analysis data from other family members wherever possible, including homozygosity mapping in consanguineous families.

We are focussed on performing both targeted panel sequencing and diagnostic exome sequencing in parallel to offer the best results for patients. Our strength is our seamless connection between our research laboratories, pathology centres and our health professionals – our research findings can be readily made available as new disease genes are identified, and our research technologies are being investigated as useful diagnostic tools for a larger cohort of patients than existing methods. Our current experience is resulting in approx. 65% of patients being diagnosed using standard clinical and laboratory work-up for undiagnosed patients. The new technologies are providing answers for an additional 30%. Our aim is to increase the number of diagnosed patients to 90% within a standardised equitable diagnostic framework.

Gene discovery not only provides information about new pathogenic genes for diagnosis, but also provides new insights into undiagnosed disorders and muscle biology and pathobiology. The CRE-NMD/ANN is one of the leaders in this area internationally.

Gene testing in Australia – a snapshot

Queensland

- Paediatric neurologists can order testing and there have been no limits placed on this
- Testing is done through QLD pathology
- Most tests are $1,000-2,000 and performed as requested (it is more expensive to order a muscle biopsy)

New South Wales

- Funding for tests differs across hospitals pathology, patient or neurology department
- Adult services neurologist: patient pays for testing, sometimes the neurology department will pay.
- Concord: If a patient is seen within the hospital then testing is billed to NSW Pathology, patients pay for samples outside of the hospital setting
- Westmead: the testing is paid for by the Western Sydney Genetics Program (WSGP), which has a budget for testing. Clinicians must apply to the 'gatekeeper' clinical geneticists within WSGP for approval of testing. All appropriate testing is funded if the cost is reasonable and sufficient reason for testing, including carrier testing, is given.

Victoria

- Like NSW, funding for tests differs across Hospitals pathology, patient or neurology department.
- Overseas testing is not funded and it is most often difficult to organise for funding of tests outside of the state (national).
- Sometimes costs are funded by individual departments, area health services, or the patient.
- Victorian Clinical Genetics Service (VCGS): carrier testing/ cascade testing – cost passed onto families
- Duchenne muscular dystrophy: have to order biopsy if mutation not found by multiplex ligation-dependent probe amplification (MLPA), as support for further genetic testing not provided
- St. Vincent's Melbourne Neuromuscular Diagnostics Laboratory: Mitochondrial DNA tests funded by Department of Human Services

Northern Territory

- Covered by VCGS (until end of 2013 was covered by SA)
- NT has budget for genetic testing

Australian Capital Territory

- Patient is billed; if the patient cannot afford the test then day clinic takes patients for bloods since then cost of testing covered by health system
- Clinical genetics very slow (>1 yr)

Tasmania

- Supported with a budget and testing performed by VCGS

South Australia

- Children's Hospital clinical geneticists sign off on test orders, (act as gate keepers)
- Adult neurologists can order a test directly if case discussed with a geneticist.
- All cascade testing covered
- Funded by genetic service,
- Testing funded up to ~$2,000 limit
- Managed by SA pathology.

Western Australia

- Covered by Diagnostic Genomics budget within PathWest for genetic testing
- All the consortium of laboratories within Diagnostic Genomics have to operate within the budget.
- The budget has not grown rapidly.
- Some patients billed if seen in private rooms.

Gene testing in New Zealand – a snapshot

A national genetic service was established in 2012. Genetic Health Service New Zealand (GHSNZ) provides genetic testing throughout NZ and is funded by the public health system, the National Health Board.

Access to genetic testing is better than in Australia; however there are some limitations with neurologists unable to consult in different areas, as there are cost implications, and there could be an improvement in how geneticists and neurologists interact.

Within the paediatric population, genetic testing is also available through Starship Hospital in Auckland.

The "send it to Adelaide" national plan

One shining example of a successful national diagnostic plan for genetic disorders in Australia is the 'send it to Adelaide' plan for lysosomal etc disorders. The centre of excellence that is the National Referral Laboratory for Lysosomal, Peroxisomal and Related Disorders, Women's and Children's Hospital, Adelaide, provides a service for samples sent from all over the country for

analysis for these rare conditions. In some jurisdictions around the country different health services or particular departments pay for this, in other jurisdictions it falls to the patient to pay. Not withstanding the vagaries of paying for the service around the country, this Centre of Excellence approach has worked well over many years.

Summary

In Australia, the jurisdiction-based approach to funding genetic tests has led to inconsistent practices and inconsistent accessibility to testing between states and territories. The perception of ANN members that it is a “dog’s breakfast”, was more than confirmed by the meeting. The situation in NZ is significantly better with a national coordinated approach.

In the Australian context, there are accredited laboratories that are able to test for many known disease genes and the number of genes that they can test has increased rapidly through the implementation of next generation sequencing diagnostics. There is also an informal arrangement through a national system of centres of excellence, where testing is sent to experts in the respective disease areas. However, in Australia, in some areas it falls to the patient to pay, in others, to different health services or particular departments. This inequality impacts on patients, where funding boundaries place limitations on accessibility to an accurate diagnosis and appropriate treatment.

For the sake of the patients and families affected by neuromuscular disorders, a small working party from the ANN should initiate discussion with State and Federal health services about the implementation of a national plan for diagnosis of neuromuscular diseases.

The ideal system would build on the services already provided by the States with superadded Federally funded resources. For example, some standard tests could be funded Federally, such as exome-based diagnosis, though this would require rigorous gate-keeping. Generated data should be interpreted through a system of centres of excellence around the country.

Muscle Bank

A muscle bank will provide a valuable resource for researchers, to understand the mechanisms of disease, improve diagnosis and identify novel genes and potential new therapies.

The muscle bank will be based on the successful Australian Brain Bank Network. The Brain Bank has collected 996 tissues in Victoria, there are 119 continuing projects and 500 publications have resulted from the tissue made available through the bank. An internet-based database would be developed to store the de-identified muscle information. This would be held nationally but the physical tissue would be stored locally within each laboratory. This has to be done prospectively. Tissue already collection cannot be used due to

inadequate consent. Requests for tissue would be made via the website and a scientific advisory committee would oversee the application process. All samples made available through the bank must be consented for diagnosis and research purposes. Each site will need to ensure that they are handling and storing material in a standardised way and that consent is in place - the ANN will develop generic consent and information forms that can be broadly circulated.

Researchers can search the central database and formally apply for tissue to be sent to them. Each application is assessed by an Advisory Board - ethics approval must be in place by the institution so the Advisory Board's role is to review the research protocol and if the requested tissue is available.

Population Screening using NGS

The clinical diagnosis of Duchenne muscular dystrophy (DMD) is often delayed until the age of 4-6 years, by which time there may be multiple affected younger boys within the sibship or affected boys born to other women in the family who did not know that they were carriers. Many other NMDs are recessive, meaning that they affect children in families with no family history. Population screening has been associated with decreased incidence of specific diseases within specific populations eg. Tay Sachs. DMD screening occurs in a small number of countries, and has generated much controversy and debate.

The US is currently undertaking a pilot study supported by the CDC (Annals of Neurology) and, in Australia, Nigel Laing and Klair Bailey have funding for a feasibility study of DMD screening that is being run in collaboration with NSW Newborn Screening.

Telepathology

Telepathology uses the internet to transfer high quality pathology images between distant locations for the purpose of diagnosis, education and research. The virtual slide system uses an automated digital slide scanner to create a digital image file of an entire glass slide. The file is then stored and can be viewed over the internet.

The ANN/CRE-NMD would utilize telepathology in diagnosis to discuss difficult or interesting cases, and it would also play a role in the national diagnostic network. Images would also be uploaded onto the website along with clinical information as a teaching tool. The implementation of telepathology will improve diagnostic capacity within Australasia.

Treatment

Australia is considered, along with the US, UK and Europe, as a viable first line site in which to conduct clinical trials. Our strengths are that we have experience and world-class expertise in neuromuscular disorders, in diagnosis, clinical care and research. In addition, we are a relatively small neuromuscular community with a positive history of close collaboration.

It will take a significant increase in funding to establish clinical trials in each state. In the meantime, the ANN will support local evaluator training to support less intensive trials that can be undertaken through local clinics.

Progress has been made in the development of disease specific outcome measures. NSW and VIC are leading studies to develop outcome measures for clinical trials. The CRE-NMD is supporting PhD scholarships for allied health students to undertake studies to determine normative data against which disease specific outcome measures can be identified.

The next five (5) years will be challenging, however there has been progress towards identifying clinical trial projects that can perform at sites without established clinical trial infrastructure. The Neutriceuticals trial will be undertaken across VIC, QLD and NSW, and the VIC serial casting in DMD project has been expanded into Sydney Children’s Hospital.

There has also been progress towards providing training for allied health professionals and their involvement in clinical trials. There are fellowships provided through VIC and NSW, however there needs to also be a more formal exchange of trainees and encouragement and support for new trainees to specialize in neuromuscular disorders.

Our minimum standards guidelines for establishing a multi-disciplinary clinic will provide much needed evidence to leverage funding. This funding will not only allow the establishment of clinics, but it will support the recruitment of dedicated nurse clinic coordinators and the training of associated specialists in the area of neuromuscular disorders.

Enhanced clinical trial readiness

The CRE-NMD provided support for Michelle Eagle from the UK to lead a clinical trials workshop for physiotherapists as part of the Duchenne Foundation's Riding the Wave Conference and RCH organized a training day for 55 physiotherapists in August. NSW is also providing training for local allied health professionals as part of the serial casting project.

Establishment of a national clinical trials network

There is increasing involvement of allied health professionals in clinical trials. NSW, VIC and WA are all leading studies with allied health involvement.

NSW: physiotherapy and podiatry

Congenital myopathy - tyrosine questionnaire

Curcumin –1 year follow-up pilot study

Nemaline myopathy – vibration study

Sleep parameters in DMD

Vic: physiotherapy, dietetics, OT, sleep therapists

Sleep parameters in DMD

Genetics: extended family support program

Physiotherapists' study of complementary medicine

Physiotherapists' study of serial casting in DMD

Physiotherapists' development of standardised assessment methods in NM clinic

Sleep parameters in DMD, SMA

OT study of upper extremity function in DMD

Psychological profiling in DMD, BMD and carriers

Review of transition services

WA: neonatal screening

Clinical Trials Update - National and International

VICTORIA

Some highlights of clinical trials that the Royal Children's Hospital is currently participating in:

- DMD114349 – An open label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne muscular dystrophy.
- Open-label PTC GD-019 study-anticipation of enrolment of 4-6 children in this study.
- The RCH research physiotherapists are also undertaking a survey of use of traditional and complementary therapies in patients seen in our NM clinic.
- Ongoing involvement in the CINRG UC Davis natural history study.
- Ongoing study on serial casting in selected patient of ambulant boys with DMD.
- Ongoing study of Nutriceuticals in DMD (collaboration with Zoe Davidson and Helen Truby from Monash University, Department Nutrition and Dietetics).
- Study of bone mineral density and zoledronic acid in boys with DMD (collaboration with A/Prof Margaret Zacharin, paediatric endocrinologist), RCH.

NEW SOUTH WALES

Some highlights of clinical trials that the Children's Hospital at Westmead is currently participating in:

- Congenital myopathy - progressing well with the tyrosine questionnaire
- Curcumin – Sarah Sandadura is involved in a 1 year follow-up pilot study
- LaminA and Centronuclear myopathy – single family trials of novel therapies (pre-treatment)
- Nemaline myopathy – vibration study
- DMD114349 – An open label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne muscular dystrophy.
- Open-label PTC GD-019 study-anticipation of enrolment of 4-6 children in this study.
- Ongoing study of Nutriceuticals in DMD (collaboration with Zoe Davidson and Helen Truby from Monash University, Department Nutrition and Dietetics).

Reliable Measures

Prof Joshua Burns is leading the 1000 Norms project which has two CRE-NMD supported PhD students taking normative data to establish an online repository of normative data for use internationally.

National clinical trials network

Allied health and Nursing steering groups have been established through the ANN to progress the goal of supporting the objective of clinical trial readiness at more centre's in Australia. Currently, NSW and VIC participate in international trials.

Physio training day- Organisation of one day training workshop at Royal Children's Hospital Melbourne on 10 August 2012 for community physiotherapists, to equip them to provide physiotherapy management at a consistently high standard in line with the current international standards of care. Organised by Kate Carroll, Chiara Tewierik, Rachel Kennedy, Katy de Valle - 50 physios attended

Dr Michelle Eagle CRE training- The CRE-NMD supported travel for an international expert to complete training in QLD to provide evaluator training for physiotherapists. This training is a requirement for all clinical trials, as trained evaluators are required to take the primary outcome measures.

Serial casting- a collaborative study of serial casting in boys with DMD is currently underway across VIC and NSW (PI: Dr Kate Caroll, The Royal Children's Hospital, Melbourne).

To ensure our patients are clinical trial ready for trials undertaken anywhere in the world, the CRE-NMD has supported and contributed to the expansion of registries through the Neuromuscular Disorders Registry Advisory Committee led by Dr Hugh Dawkins.

Registries

The Duchenne muscular dystrophy, Spinal muscular atrophy and Myotonic dystrophy registries are operational in Australia and New Zealand, with FSHD and Congenital muscular dystrophy to follow.

New Zealand has benefited enormously from inclusion in the ANN and with support from Dr Hugh Dawkins – the MDANZ has a database of 60-70 conditions covered by a single ethics application, and to date 175 patients have uploaded their information into the DMD registry.

Develop guidelines in neuromuscular disorders in an Australian context

Establishment of multi-disciplinary clinics

A draft guideline for the establishment of a multi-disciplinary clinic was circulated for discussion and comment. This guideline will provide a minimum standard of care and will also

provide a useful and powerful tool to leverage funding from local and state governments. Once finalized the document will be broadly circulated, including ensuring that state health departments receive a copy and will be available on the ANN website.

The guidelines are being developed to be of most relevance for clinicians who do not have specific expertise in neuromuscular disorders but are looking for guidance. The guidelines will also provide a template for neuromuscular clinical services.

Gap analysis

The CARE-NMD survey will be implemented throughout Australia and New Zealand. The survey was developed by Janbernd Kirschner to evaluate current practices and has been run in 7 countries with a 64% response rate.

The survey will be a powerful tool to gather evidence for a business case requesting support for establishing new and expanding existing clinics.

The results of the survey will also provide important information for patients who can use it to affect change.

Top 10 guidelines for Australia

A survey of ANN members was undertaken to ascertain where standards of care and guidelines are needed. Nine (9) people responded to the survey ahead of the workshop.

All respondents identified the following disorders as needing specific standards of care to be developed: Becker, CMT, Congenital MD, Congenital myopathy, DMD, Emery-Dreifuss, FSHD, Friedreich's Ataxia, Limb girdle, SMA and Peripheral neuropathy

The top 3 areas requiring the development of clinical care guidelines were:

- Rehabilitation Management including: exercise, stretching, physiotherapy, occupational therapy; orthotics and assistive devices; postural management; pain management
- Pulmonary assessment, monitoring and management
- Cardiac monitoring assessment and management

A working party will be established to modify existing standards of care for an Australian application and prioritise areas for the development of clinical care guidelines.

A snapshot of clinical care around Australia and NZ

In South Australia, a clinic is held once a month, with support from the MDASA and the Rehabilitation department.

In Queensland, a clinic is held once a month, and also includes attendance by a respiratory specialist and cardiologist. Home outreach has been undertaken through Montrose. The clinic is in need of a nurse coordinator – a nurse has been assigned to the clinic but is not dedicated to the neuromuscular clinic.

In Victoria, there are ongoing issues with transition. Royal Children's Hospital has met with transition services to improve the process.

In New South Wales, there is no coordinated planning across adult care for caring for patients affected by neuromuscular disorders. There is a dedicated adult clinic at Royal North Shore Hospital and their clinicians participate in a transition clinic held at The Children's Hospital at Westmead There has been a significant level of support provided by MDNSW, with caseworkers being provided to assist patients through the transition process. A social worker and genetic counselor work with the patients from high school and meet every year or two. Merrilee Needham has funding for a research project around transition – a useful project to benchmark services.

Transition continues to be an issue for most states, with the exception of Western Australia. In WA, transition guidelines have been developed. Phillipa Lamont attends clinics in adult hospitals and is supported by a coordinator and respiratory and cardiology physicians. WA provides an ideal model for other states to aspire to.

In New Zealand, there is resistance among adult neurologists (there is a perception that all of the interesting cases are neuromuscular), however transition clinics occur in Auckland with attendance from respiratory physicians but not in Wellington.

Research

The CRE-NMD/ANN will promote and facilitate the sharing of information and expertise between basic and clinical researchers, clinicians and clinician researchers, to accelerate improved outcomes for patients.

A collaborative network would allow large cohorts of patients to be included in gene discovery, screening and linkage studies, as part of a research work-up to underpin diagnostics, registries and clinical trials.

It is through research effort, for example, that the introduction of next generation sequencing and the analysis of large data sets (informing diagnosis and inclusion in registries) will be developed for translation into diagnostic laboratories.

We are in the process of developing a national integrated secure database that will store patient data combining clinical, molecular and pathology data with longitudinal standardised assessments. This resource will be invaluable for clinical researchers in studies of natural history and genotype/phenotype correlation, and will provide a platform for research collaborations.

The development of a patient database goes hand in hand with gene discovery and improved diagnosis and clinical trial readiness. For example, when a new gene is described, a search of the database can be made for a clinical phenotype associated

with the gene and then a search for those who don't have a diagnosis.

National patient database

Basic epidemiological data and information on the natural history of many rare diseases is very limited. However, this knowledge is essential to assess the impact of preventive or treatment activities and the implementation of best practice guidelines. Rare disease patient databases underpin improving clinical care and we aim to identify existing databases and prioritise and expand the collection of data for other rare diseases.

Australia is slowly developing patient registries, however they contain very limited information to largely determine if patients are eligible to enrol in a trial (eg. ambulant/non-ambulant; genetic diagnosis; walk time over a certain distance).

A critical step in the design of a clinical trial protocol is a more detailed database of patient information that is collected from researchers, clinicians and pathologists – a comprehensive set of data that describes the progression of the disease over time. This provides researchers and pharmaceutical companies with sufficient information to ensure that the outcome measures (how to determine the success of the trial) and the treatment are well designed for maximum benefit to the patient.

The proposed database for housing patient data and availability of muscle for research use will be a national centralised repository that will share inter-operability with existing registries established through the OPHG. The database will be incorporated into platforms that are to be developed as part of the RDConnect, RAREBestpractice and Neuromics programs.

The database will not duplicate the information stored in registries (post-diagnosis), but will add and link additional detailed levels of data on sub-sets of patients for gene discovery and investigator led genotype/phenotype and natural history studies (pre-diagnosis).

A working party will be established to develop an implementation plan and will address issues such as ethics, information to be stored in the database, access, retrieving data from existing databases to populate the national database and data entry (resourcing is being sought from patient groups, with an additional option of utilizing students as part of cohort studies).

Research studies

Over 15 research studies are underway in Australia, with details available on the ANN website.

- Centronuclear myopathy
- Congenital fibre type disproportion

- Congenital muscular dystrophy
- DMD: Serial casting in ambulant boys
- DMD: Survey of attitudes to population screening
- Dystrophinopathies
- Facioscapulohumeral dystrophy
- Foetal akinesia/hypokinesia
- Inclusion body myositis
- Limb girdle muscular dystrophy
- Myotonic dystrophy
- Nemaline myopathy
- Non-myotonic dystrophy
- Spinal muscular atrophy
- Syndrome of cerebellar ataxia with prominent motor and sensory neuropathy and chronic cough

Awards/ Presentations/

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Awards/Presentations/Appointments

Kathryn North

Appointments

Director, Murdoch Childrens Research Institute

David Danks Professor of Child Health Research, Department of Paediatrics, University of MelbourneHonorary

Visiting Medical Officer, Children's Neuroscience Centre, Royal Children's Hospital

Honorary Emeritus Consultant, The Children's Hospital at Westmead

Honorary Professor, Sydney Medical School, The University of Sydney

Presentations

David Danks Oration, University of Melbourne, May 2013

Hopkins Symposium, Melbourne March 2013

Walter and Eliza Hall Institute of Medical Research seminar series, Melbourne March 2013

8th David Danks Oration, University of Melbourne , May 2013

Baker Institute Research Seminar Series, May 2013

Australian and New Zealand Association of Neurologists ASM, Sydney May 2013

23rd Annual Pediatric Neurology Update, Bethesda USA June 2013

Plenary speaker, International Congress of Paediatrics, Melbourne August 2013

Keynote speaker, Alfred Hospital Research Week, October 2013

Invited Speaker, Stanford University School of Medicine Nemaline Myopathy Satellite Meeting, October 2013

Joshua Burns

Awards

Peripheral Nerve Society Fellowship to present at the meeting in Saint-Malo, France, 29th June - 3rd July.

Appointments

Director, Sydney Arthritis and Musculoskeletal Research Network, The University of Sydney, 2014

Chair, Allied Health and Nursing Steering Group, Australasian Neuromuscular Network, 2012 - current

Associate Professor, Faculty of Health Sciences, The University of Sydney, 2010-2013

Invitations and Presentations

Occasional address at the Faculty of Health Sciences graduation ceremony, The University of Sydney, March 2013

Developments in the management of Charcot-Marie-Tooth disease. In: Tasmanian Charcot-Marie-Tooth Disease Awareness Day, 1st June 2013, Hobart, Australia.

Developments in the management of CMT. In: National Charcot-Marie-Tooth Disease Awareness Day. Concord Hospital, 13th October 2013, Sydney, Australia.

Developments in the management of CMT. In: Victoria Charcot-Marie-Tooth Disease Awareness Day, Austin Repatriation Hospital, 24th November 2013, Melbourne, Australia.

Nigel Laing

Appointments

Winthrop Research Professor

NH&MRC Principal Research Fellow

Member of Senate of the University of Western Australia

Invitations and Presentations

EU FP7 NEUROMICS kick off meeting – Barcelona: “NEUROMICS Australia - application of next generation sequencing to neuro-genetic disorders in Australia.” Full overseas participant. 25th-27th January 2013.

Murdoch Children’s Research Institute, Melbourne, Seminar: “Next generation DNA sequencing: how far can it take us?” 18th March 2013.

Australian Regenerative Medicine Institute, Melbourne, Seminar: “Novel disease genes from single patients is the power of next generation sequencing, but how useable are treatments going to be?” 19th March 2013.

RACP Annual Scientific Meeting – Talk Title “" The genomic revolution and translational medicine, where are we now and where will we be in 5 and 10 years?" 28th March 2013.

Wassenberg Lecture – San Diego State University - "Next generation DNA sequencing: gene discovery, improved diagnostics and disease prevention." 26th September 2013.

University of California San Diego: "Seeing muscle biology through the window of genetic disease." 30th September 2013.

Killam Lecture, Montreal Neurological Institute, McGill University: “Seeing muscle biology through the window of genetic disease.” 8th October 2013.

Montreal Neurological Institute Grand Rounds: “Next generation DNA sequencing: gene discovery, improved diagnostics and population health.” 9th October 2013.

Children's Hospital Boston: "NGS disease gene discovery and diagnostics: an Australian perspective." 11th October 2013.

Newcastle-upon-Tyne, UK: TREAT-NMD Alliance Conference 2013: Plenary speaker: "Next generation sequencing and NEUROMICS." 30th-31st October 2013.

Monique Ryan

Appointments

Neurologist, Royal Children's Hospital

Honorary, Murdoch Childrens Research Institute

Invitations and Presentations

RCH Clinical Trials in Children: International networks in paediatric neuromuscular disorders

Murdoch Childrens Research Institute, Melbourne Australia: clinical trials in paediatric neuromuscular conditions.

Nigel Clarke

Appointments

Associate Professor, Discipline of Paediatrics and Child Health, Sydney Medical School, University of Sydney

Head, Institute of Neuroscience and Muscle Research, Children's Hospital at Westmead

Invitations and Presentations

European Muscle Conference, Amsterdam, Netherlands. Platform presentation: Recent Developments in the Congenital Myopathies. Sept 23 2013.

Australian and New Zealand Child Neurology Society 2013 Annual Scientific Meeting. Genomic aspects of neuromuscular junction disorders. Sydney, May 4 2013.

Australian and New Zealand Association of Neurologists Annual Scientific Meeting, Sydney. Genetic concepts. Sydney, May 6 2013.

Annual Scientific Meeting, Sydney. Approach to diagnosis of LGMD. May 7 2013.

Invited speaker: Muscular Dystrophy NSW Member Education Day, 16 Nov 2013.

Catriona McLean

Appointments

Professorial Fellow, Howard Florey Brain Centre

Honorary Consultant Neuropathologist , Royal Children's Hospital and Monash Health

Invitations and Presentations

Oral presentation – AMEE, Prague, 2013

Neuro-opthalmology meeting of Australasia, Noosa, QLD, 2013

National CJD conference, Melbourne, 2013

Achievements

1. A published list of diagnostic tests available for neuromuscular genes in Australia on the ANN website
2. Whole exome sequencing and Next Generation Sequencing has been trialled and is progressing well
3. The rate of diagnosis has increased from 50% to 60%
4. A specimen procedures manual has been developed to standardise the collection and processing of samples
5. A national patient database is in development
6. Over 8 novel disease genes have been discovered
7. A pilot study examining the feasibility of population screening for Duchenne Muscular Dystrophy (DMD) is underway
8. Supported and contributed to the expansion of registries through the Neuromuscular Disorders Registry Advisory Committee led by Dr Hugh Dawkins *Status*: DMD, myotonic dystrophy and SMA are operational in both Australia and NZ with FSHD and congenital muscular dystrophy to follow (all link to TREAT-NMD global registry and myotonic will also link into the US registry)
9. Training opportunities have been provided for physiotherapists
10. Developed guidelines for the establishment of multi-disciplinary clinics *Status*: Draft document for feedback
11. Whole exome sequencing has been trialled in WA and NSW
12. Submission of three (3) successful NHMRC-EU applications: Neuromics (CIA Laing), RDConnect (CIA Dawkins), RAREBestpractice (CIA North) – to provide additional funding for key CRE-NMD/ANN aims including gene discovery, development

of guidelines and inter-operability of existing registries and databases and guidelines for the development of future databases. The initial focus will be on neuromuscular disorders and will expand to rare diseases.

Funding

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NHMRC Project Grants

1048814 Dysferlinopathy: A genetic disease sheds light on membrane repair for muscle and cardiac injury, $755,954. Sandra Cooper, Kathryn North, Jonathan Egan.

NHMRC-EU

1055131 Improving health outcomes for chronic rare diseases and reducing inequality of care. $614,128. Kathryn North and Hugh Dawkins.

NHMRC Fellowships

Career Development Fellowship (RD Wright Biomedical): 1048816 Dysferlin coordinates membrane repair for skeletal and cardiac injury. $439,920. Sandra Cooper.

Early Career Fellowship (CJ Martin - Overseas Biomedical Fellowship): 1053827 Improving the genetic diagnosis of neuromuscular disorders. $338,836. Monkol Lek.

Foundations/Councils/Organisations

Commonwealth Department of Health and Ageing, Population Health Division, Chronic Disease Prevention and Service Improvement Fund: Reducing the health burden of CMT in Australia. $220,000. Joshua Burns.

Charcot-Marie-Tooth Disease Association of Australia: Pilot study of progressive resistance training for sedentary adults with CMT. $10,093. Fiatarone Singh M, Burns J, Fornusek C, Hackett D.

Publications

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Amburgey, K., A. Bailey, J. H. Hwang, M. A. Tarnopolsky, C. G. Bonnemann, L. Medne, K. D. Mathews, J. Collins, J. R. Daube, G. P. Wellman, B. Callaghan, N. F. Clarke and J. J. Dowling (2013). "Genotype-phenotype correlations in recessive RYR1-related myopathies." Orphanet J Rare Dis 8: 117.

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