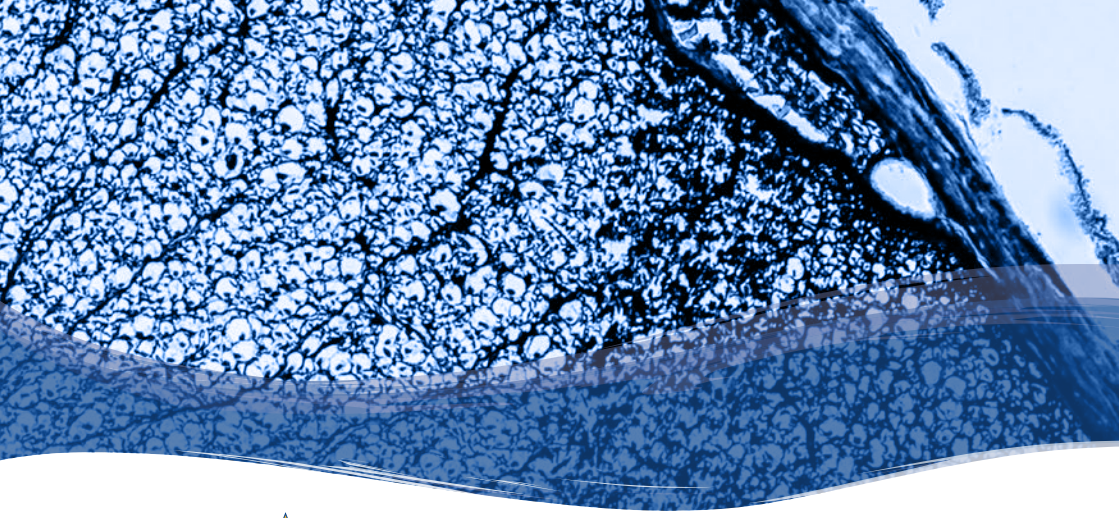
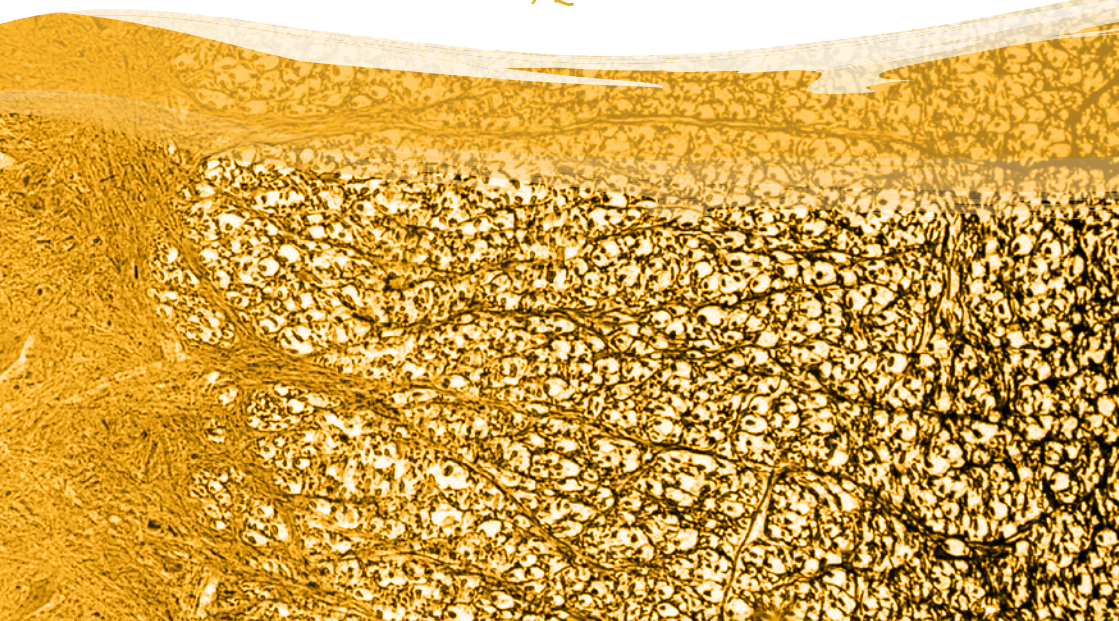


Australasian Neuromuscular Network 2023

24TH - 26TH MAY 2023

SURFAIR CONFERENCE CENTRE

MARCOOLA, QUEENSLAND



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CONTENTS

WELCOME

Welcome to the ANN Congress 2023!

On Thursday February 25th 2010, a group of 33 clinicians, pathologists, geneticists, researchers and patient advocates from around Australia and New Zealand met to discuss how to network more effectively for diagnosis, research, therapy and advocacy of patients with neuromuscular disorders. Out of this meeting, the Australasian Neuromuscular Network was established.

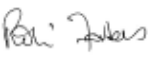
Since then, there have been annual workshops and meetings for members to be able share their research, keep up-to-date with current scientific progress and discuss future collaboration potentials in a formal way, within a conference. These meetings have rapidly grown in size and attendance. Unfortunately, the global pandemic prevented the ANN from being able to meet in person, and it has been three years since our last face to face meeting. With the lifting of lockdown restrictions and resumption of face-to-face meetings the organising committee are planning to resume the annual Congress with a two-day meeting on the Sunshine Coast in Queensland.

This year we are extremely privileged to welcome three international speakers to the ANN Congress. **Prof. Volker Straub** in a renowned expert in the field of neuromuscular disease, particularly in Limb Girdle Muscular Dystrophy, and is the current President of the World Muscle Society. We are very excited to hear his updates in Limb Girdle Muscular Dystrophy, his views of equity in DMD clinical trials and his team's recent description of a new muscle disease. **Prof. Basil Darras** has led the way in SMA research for over twenty years and we are looking forward to discovering how best to tweak the current SMA arsenal. **A/Prof. Katelyn McGrattan** is a speech pathologist whose research has led to publications in swallow dynamics in SMA. A/Prof. McGrattan will enlighten us in speech and swallowing problems in neuromuscular disease.

Along with our esteemed international guests, we are blessed with a plethora of expertise within Australia and New Zealand, and much of this expertise from bench to bedside will be highlighted in the two-day program of invited talks. There are two sessions of oral presentations selected from local researchers who submitted abstracts for consideration. We were delighted with the extremely high standard of abstracts submitted and it is so pleasing to see the volume and quality of research continuing around Australasia despite the recent pandemic challenges.

We feel that the program has something of interest to all ANN members and we hope you enjoy the congress as much as we will,




Ian Woodcock Anita Cairns Kate Carroll Robin Forbes Daniella Villano

The local organising committee

PLATINUM SPONSOR

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Volker Straub

Professor of Neuromuscular Genetics
Harold Macmillan Professor of Medicine and Professor for Neuromuscular Genetics
Director, John Walton Muscular Dystrophy Research Centre
Deputy Dean, Institute of Translational and Clinical Research, Newcastle University, Newcastle upon Tyne, UK

Professor Straub trained as a pediatric neurologist at the University of Düsseldorf and the University of Essen in Germany. He wrote his PhD thesis on Duchenne muscular dystrophy (DMD) and worked as a postdoctoral research fellow in Dr Kevin Campbell's laboratory at the Howard Hughes Medical Institute at the University of Iowa in Iowa City, USA. He joined the Institute of Genetic Medicine at Newcastle University, UK, in 2003.

Professor Straub has a long-standing interest in the pathogenesis of genetic muscle diseases, with research involving zebrafish and mouse models, the application of magnetic resonance imaging, next generation sequencing and other –omics technologies.

One of Professor Straub's main interests in muscle diseases is around translational research. He was the co-founder of the EU FP6 funded network of excellence for genetic neuromuscular diseases, TREAT-NMD (https://treat-nmd.org/), and he continuous to be involved in many large European projects funded by the EU. He is the Chief/Principal Investigator for several natural history and interventional trials in DMD, LGMD, Pompe disease, spinal muscular atrophy, and other NMDs. He is the current president of the World Muscle Society and an author on over 400 peer-reviewed publications.

Katlyn McGrattan

Dr. McGrattan is an Assistant Professor in the Department of Speech-Language-Hearing Science at the University of Minnesota with a clinical appointment at Masonic Children's Hospital. She completed doctoral training in Health & Rehabilitation Science at the Medical University of South Carolina, and post-doctoral training in Neonatal Gastroenterology at Nationwide Children's Hospital and Pediatric Otolaryngology at Medical University of South Carolina. Her research focuses on the use of refined physiologic assessment to identify impairments in pediatric upper aerodigestive physiology and apply targeted therapeutic interventions to maximize treatment effect.

Basil Darras

Basil T. Darras, MD, is the Joseph J. Volpe Professor of Neurology at Harvard Medical School. At Boston Children's Hospital, Dr. Darras is Chief of the Division of Clinical Neurology and Director of Boston Children's Neuromuscular Center, which includes one of the oldest and most active Muscular Dystrophy Association clinics in the country. Dr. Darras is a pediatric neurologist with advanced training and certification in human genetics and neuromuscular medicine. His primary research focus is in the field of pediatric neuromuscular disorders. His specific research interests and major publications have focused on the molecular genetics, diagnostics, and therapeutics of Duchenne/Becker muscular dystrophies and spinal muscular atrophy (SMA), and on defining the indications for new diagnostic methodologies in the evaluation of children with pediatric neuromuscular diseases. His clinical focus is the care of children with neuromuscular conditions originating from inherited or acquired conditions of the motor unit. He is Principal Investigator for the Boston Children's site of NIH's NeuroNEXT clinical research network; for the Pediatric Neuromuscular Clinical Research (PNCR) Network, originally funded by the SMA Foundation and CureSMA; and for trials testing novel treatments for SMA, including the clinical trials for Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec-xioi), approved by the FDA as the first two treatments for SMA, and for Evrysdi™ (risdiplam), approved as the third treatment. He receives frequent invitations to lecture at national and international meetings on topics related to his expertise in neuromuscular disorders and genetics. He has published over 250 original reports in peer-reviewed journals and over 80 chapters, reviews and editorials. He is Editor-in-Chief for the second edition of *Neuromuscular Disorders of Infancy, Childhood, and Adolescence: A Clinician's Approach*, published by Elsevier in 2015, and served as Editor of the section on Neuromuscular Disorders in the sixth edition of *Volpe's Neurology of the Newborn* (Elsevier, 2018).

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(onasemnogene abeparvovec)

One dose, continuous possibilities*

*Sustained motor function improvements for up to 6.2 years after dosing[1–3]

The first approved gene therapy for SMA in Australia[1,4]

PBS Information: Section 100 Public Hospital Authority Required for the presymptomatic treatment of SMA patients with 1 to 2 copies of the SMN2 gene or for treatment of patients with Type 1 SMA under 9 months of age. Refer to PBS Schedule for full authority information. This product is not listed for the presymptomatic treatment of SMA patients with 3 copies of the SMN2 gene.

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at **www.tga.gov.au/reporting-problems.**

WARNING: HEPATOTOXICITY

- Acute serious liver injury, acute liver failure and elevated aminotransferases can occur with ZOLGENSMA. Cases of acute liver failure with fatal outcomes have been reported.
- Patients with pre-existing hepatic impairment may be at higher risk.
- Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, prothrombin time, albumin, partial thromboplastin (PTT) and international normalised ratio (INR)). Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion and at other times as clinically indicated.

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References: 1. ZOLGENSMA Australian approved Product Information. **2.** Mendell JR, et al. N Engl J Med 2017; 377(18): 1713–1722. **3.** Mendell JR, et al. JAMA Neurol. 2021; 78(7): 834–841. **4.** Novartis AG. March 15, 2021 [media release]. Available at: www.novartis.com/news/media-releases/new-zolgensma-data-demonstrate-ageappropriate- development-when-used-early-real-world-benefit-older-children-and-durability-5-years-post-treatment.

NOVARTIS

	WEDNESDAY 24TH MAY 2023
14:00 - 18:00	**Registration opens**
14:00 - 16:00	**Future Planning Meeting** *(all welcome)*
16:00 - 17:00	**Gene Therapy Panel Discussion** – Setting up a site for gene therapy
18:00 - 19:30	**Welcome Canapes** *(Surfair Conference Centre)*

	THURSDAY 25TH MAY 2023
08:00 - 08:45	**AHNA breakfast meeting** *(Surfair Conference Centre)*
07:45 - 09:00	**Registration** *(Breakfast is provided for all delegates)*
09:00 - 11:00	**SESSION 1** - Chairs: Kate Carroll & Gina O'Grady
09:00	Welcome to ANN 2023 - *Ian Woodcock & Anita Cairns*
09:10	What's new for the limb girdle muscular dystrophies? - *Volker Straub*
10:00 	Rapid fire presentations *(supported by travel bursaries from Pfizer):* • Candidate biomarkers of disease onset and progression in individuals with ⩾3 copies of SMN2 - *Lakshimi Balaji* • Quantitative muscle ultrasound in adult spinal muscle atrophy - A preliminary report - *Luciana Pelosi* • Fishing for a cure for collagen VI congenital muscular dystrophy - *Avnika Ruparelia* • Hypogammaglobulinemia and infection risk in myotonic dystrophy type 1 - *Katrina Morris* • Duality of the FHL1 gene in myopathy and exercise performance - *Meagan McGrath* • Measuring function in childhood FSHD - Does the FSHD-COM Peds make the cut? - *Katy de Valle*
11:00 - 11:30	**Morning tea**
11:30 - 13:00	**SESSION 2** - Chairs: Matt Lynch & Daniella Villano
11:30	Speech and Swallow in Neuromuscular Disease - *Katlyn McGrattan*
11:50	Titin: an emerging "titan" of the skeletal and cardiac muscle disease world - *Emily Oates*
12:05	Australian Neuromuscular Disease Registry Update - *Robin Forbes*
12:20	Screening for Neuromuscular Disease - *Nigel Laing*
13:00 - 13:45	**Lunch**

	THURSDAY 25TH MAY 2023 (CONTINUED)
13:45 - 15:15	**SESSION 3: Theme - Consent / Ethics** - Facilitated session by Lynn Gillam RCH Bioethics
	Equality, diversity and inclusion in DMD - *Volker Straub*
	Ethical Case Study - *Anita Cairns*
	Equitable Access to "competitive" clinical trials in DMD: considerations for researchers - *Helen Young*
	Inferred Ought and the Committee of Five - *Robin Forbes & Ian Woodcock*
	How do we select patients for gene therapy studies / Managing patient expectations - *group discussion facilitated by Lynn Gillam*
15:15 - 15:45	**Afternoon tea**
15:45 - 17:00	**SESSION 4** - Chairs: Kristi Jones & Kristy Rose
15:45	Summary of Pre-clinical research - *Peter Houweling*
16:00	Steroids and Beyond - Update in clinical trials - DMD - *Michelle Lorentzos*
16:15	Update in clinical trials - FSHD - *Ian Woodcock*
16:30	Update in clinical trials - CMT - *Eppie Yiu*
16:45	Update in clinical trials - Adult Perspective – *Anthony Winkle*
17:00 - 18:00	**ANN Annual General Meeting** *(Surfair Conference Centre)*
19:00 - 23:00	**ANN 2023 Conference Dinner** *(Off Tap Tapas, Marcoola)*

	FRIDAY 26TH MAY 2023
08:00 - 08:45 NOVARTIS	**Breakfast Symposium** - Sponsored by Novartis *(Breakfast is provided for all delegates, but due to Medicines Australia rules, members from Parent Advocacy and Support Group are not able to attend this symposium)*
09:00 - 10:40	**SESSION 5** - Chairs: Nigel Laing & Paula Bray
09:00	Unravelling the pathogenesis of a new form of skeletal myopathy - *Volker Straub*
09:40 PTC THERAPEUTICS measured by moments	Rapid fire presentations (supported by travel bursaries from PTC): • Managing capacity and demand in a busy Neuromuscular Clinic - *Nicole Thomas* • Improving the transition journey for neuromuscular patients in Queensland - *Rebecca Leung* • Implementing clinical guidelines for neuromuscular disorders - *Rachel Kennedy* • Healthcare Experiences of people living with Myotonic Dystrophy Type 1 - *Karen O'Maley* • Bladder and Bowel dysfunction in children and infants with Neuromuscular Conditions - *Megan Reading* • Lung volume recruitment therapy in people with neuromuscular disease: a randomised controlled trial - *Nicole Sheers*
10:40 - 11:00	**Coffee break**
11:00 - 13:30	**SESSION 6** - Chairs: Penny Deavin & Miriam Rodriguez
11:00	Tweaking the current SMA arsenal - *Basil Darras*
11:20	Neurogenetic Research in New Zealand - *Richard Roxburgh*
11:35	ADAPT-CMD: the Australian functional Diagnostics platform for Advancing Personalised Treatment of Congenital Muscle Disorders - *Catriona McLean*
11:50	Update on Myasthenia - *Stefan Blum*
12:15	Transition Panel Discussion - *Anita Cairns, Ravindra Urkude, Cullen O'Gorman*
13:20	Closing Remarks - *Anita Cairns & Ian Woodcock*
13:30	**Conference Close**

THINK 3 FOR SMA

SPINAL MUSCULAR ATROPHY (SMA)

– a rare but devastating and often fatal disease[1]

SMA Type 1 is the most severe form of SMA with symptoms starting within the first 2 months[1]

Approximately

17

births per year in Australia are

SMA TYPE 1*[2–4]

Early diagnosis and intervention can improve outcomes for infants with SMA[5]

THINK 3 FOR SMA TEST FOR 3 SIGNS OF POSSIBLE SMA AT 3 MONTHS OF AGE

Head lag[6,7]

Hypotonia (floppy baby)[8–10]

Inability to reach[6,11]

DON'T DELAY IF YOU SUSPECT SMA

If you suspect SMA refer your patient to a paediatric neurologist for urgent assessment.

Scan the QR code for a list of paediatric neuromuscular centres.

References: 1. Mendell JR, et al. N Engl J Med. 2017; 377(18): 1713–1722. **2.** Australian Bureau of Statistics (ABS). Available at: www.abs.gov.au/statistics/people/population/births-australia/2020. Date accessed: April 2023. **3.** Ali HG, et al. Gene Ther. 2021 Nov; 28(10-11): 676–680. **4.** Spinal Muscular Atrophy: epidemiology and Genetics. Available at: https://hcp.smanewstoday.com/spinal-muscular-atrophy-epidemiology-and-genetics/. Date accessed: April 2023. **5.** Govoni A, et al. Mol Neurobiol. 2018; 55(8): 6307–6318. **6.** Wang CH, et al. J Child Neurol. 2007;22:1027–1049. **7.** Markowitz JA, et al. JOGNN. 2004; 33: 12–20. **8.** Leyenaar J, et al. Paediatr Child Health. 2015; 10(7): 2005. **9.** Hammersmith Infant Neurological Examination (v 07.07.17). **10.** Mercuri E, et al. Neuromusc Disord. 2018; 103–115. 10. De Sanctis R, et al. Neuromuscul Disord. 2016; 26(11): 754–759. **11.** De Sanctis R, et al. Neuromuscul Disord. 2016; 26(11): 754–759.

Candidate biomarkers of disease onset and progression in individuals with ≥3 copies of SMN2

Lakshmi Balaji [1,2], *Michelle Farrar* [1,2], *Hugo Sampaio* [2], *Arlene D'Silva* [1,2], *Karen Herbert* [3], *Didu Kariyawasam* [1,2]

[1] *Department of Neurology, Sydney Children's Hospital Network, Sydney, New South Wales, Australia*
[2] *Discipline of Paediatrics and Child Health, School of Clinical Medicine, UNSW Medicine and Health, UNSW Sydney, New South Wales, Australia*
[3] *Discipline of Physiotherapy, Sydney Children's Hospital, Randwick, Sydney, New South Wales, Australia*

Abbreviations: EMG: electromyography; CMAP: compound muscle action potential; LSMUP: largest single motor unit potential; MUNE: motor unit number estimation; NBS: newborn screening; SMA: Spinal Muscular Atrophy; SMN: survival motor neuron

Background: Treatment algorithms for spinal muscular atrophy (SMA) are based on SMN2 copy numbers, the most important modifier of phenotype. As clinical decisions vary globally for screen positive newborns with ≥3SMN2, there is an imperative to develop biomarkers with prognostic, predictive and pharmacodynamic utility.

Aim: To describe the role of clinical and electrophysiological parameters in defining disease onset and monitoring progression in SMA.

Methods: This is a case series of a presymptomatic proband diagnosed through NBS with 4SMN2 copies who does not have recourse to treatment and his older symptomatic sibling diagnosed and treated after symptom onset. This prospective longitudinal study employed clinical, functional and electrophysiological outcome measures to evaluate disease progression and therapeutic efficacy.

Results: The proband demonstrated age-appropriate developmental milestones and functional gains in the first year of life. Around 15 months, intermittent toe walking was noted with no other clinical signs/functional changes. CMAP (ulnar nerve/ADM) showed modest increase from 4.5 mV at 2 months to 6.9 mV at 15 months. Motor unit number decreased over time [MUNE (19 at 5 months, 22 at 15 months)] with accompanying rise in measures of collateral innervation [LSMUP (0.37 at 7 months to 0.68 at 15 months) and A50 (0.15 and 0.2 respectively)]. Disease onset defined by these findings called for therapy initiation. The symptomatic older sibling was treated with risdiplam. Over a 2-year period, he demonstrated greater number of motor units (78 pre-treatment to 111 post-treatment) correlating with clinical and functional improvements.

Conclusions: This data demonstrates the utility of electrophysiological measures in the process of dynamic flux of denervation and collateral reinnervation in SMA to provide the rationale for therapeutic intervention in presymptomatic infants with ⩾3SMN2 copies and illustrates the role of deep phenotyping using clinical, functional and electrophysiologic assessments in defining disease onset.

Quantitative muscle ultrasound in adult spinal muscle atrophy - A preliminary report

Luciana Pelosi [1], *Miriam Rodrigues* [1], *Richard Roxburgh* [1]

[1] *Centre of Brain Research Neurogenetics Research Clinic, University of Auckland, Auckland, New Zealand*

Introduction: Muscle ultrasound has been investigated in children with spinal muscular atrophy (SMA) and proposed as a potential biomarker. We studied the ultrasound properties in adults with SMA to see whether they may also have potential as a biomarker in older patients.

We report our preliminary findings in a small patient cohort.

Methods: Muscle thickness and quantitative echogenicity were compared between eight prospectively recruited adult patients with SMA and eight controls matched with the patients for age, sex, weight, height and ethnicity. Measurements were made in the right deltoid, biceps, triceps, forearm extensors, first dorsal interosseous, quadriceps, tibialis anterior and gastrocnemius. The muscle:subcutaneous tissue (M:S) thickness and echogenicity ratios were also calculated for each muscle. A mean value across all muscles was then calculated for each parameter in each subject and compared between the two groups. Significance was set at 0.01 after Bonferroni correction for multiple comparisons.

Results: In the SMA patients, muscle echogenicity was significantly higher than in controls (106 vs. 63 on the greyscale level), muscle thickness significantly smaller (1.2 cm vs. 1.9cm) and subcutaneous tissue thickness significantly larger (0.9cm vs. 0.3cm). The M:S echogenicity ratio was increased and the M:S thickness ratio significantly reduced in the patients. The worst ultrasound scores occurred in wheelchair-bound patients and the mildest scores in patients who walked independently.

Discussion: Ultrasound can detect and quantify severity of muscle atrophy and structure in adults SMA, suggesting a potential role as a biomarker of disease severity, to be validated by further studies on larger populations.

Fishing for a cure for collagen VI congenital muscular dystrophy

Avnika A. Ruparelia, Peter D. Currie

Collagen VI congenital muscular dystrophies (CMD), characterised by progressive muscle weakness and joint deformities, are exclusively caused by mutations in genes encoding collagen VI, an extracellular matrix protein that not only surrounds and supports muscle cells and connective tissue, but it is also regulates muscle stem cell function. Despite the generation of several mammalian models of collagen VI CMD, the mechanistic basis of the disease remains elusive, and there are currently no treatments for it. Using innovative techniques, and the unique advantages of the zebrafish model, we have explored the underlying disease mechanisms. Our results indicate that a depletion of collagen VI not only results in severe muscle fibre detachment, but also results in impaired muscle stem cell dynamics, which may contribute to disease pathogenesis. These findings indicate that therapies that aim to restore muscle function in collagen VI CMD need to target both aspects of the disease. I will present this data, discuss future directions, and highlight novel therapeutic strategies for the treatment of collagen VI CMD pathologies.

Hypogammaglobulinemia and infection risk in myotonic dystrophy type 1

Dr Shadi El-Wahsh MD [1,2,3], Dr Katrina Morris MBBS PhD [1,3], Dr Sandhya Limaye MBBS PhD [3,4], Professor Sean Riminton MBChB PhD [3,4], Professor Alastair Corbett MBChB MD [1,3], Dr James D Triplett MBBS [1,3,5]

[1] Department of Neurology, Concord Repatriation General Hospital, Sydney, NSW, Australia
[2] South Western Sydney Clinical School, University of New South Wales, Sydney, NSW, Australia
[3] Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[4] Department of Clinical Immunology, Concord Repatriation General Hospital, Sydney, NSW, Australia
[5] Department of Neurology, Royal Adelaide Hospital, Adelaide, SA

Background & Objectives: Hypogammaglobulinemia is a common yet under-recognised feature of myotonic dystrophy type 1 (DM1). The aim of our study was to assess the association between immunoglobulin levels and cytosine-thymine-guanine (CTG) repeat lengths in the *DPMK* gene, and to ascertain whether low immunoglobulin G (IgG) levels are associated with an increased risk of infection in DM1 patients.

Methods: We conducted a single-centre, retrospective cross-sectional study of 65 adult patients with DM1 to ascertain the frequency of IgG deficiency, the association with CTG repeat expansion size, and the infection risk profile.

Results: Forty one percent (41%) of DM1 patients had IgG deficiency despite normal lymphocyte counts, IgA, IgM, and albumin levels. There was a strong association between CTG repeat expansion size and the degree of IgG deficiency (F = 9.11, p-value 0.006). There was no association between IgG deficiency and frequency of infection in this group (p-value 0.512).

Discussion: Our study provides further evidence for the frequent occurrence of IgG deficiency in DM1 patients as well as the association with CTG repeat expansion size. Furthermore, reduced IgG levels were not associated with increased infection frequency in our patient group, indicating that a history of recurrent infections should be assessed prior to commencement of immunoglobulin replacement therapy in DM1 patients.

Duality of the *FHL1* gene in myopathy and exercise performance

Saveen Giri [1,2], Rachel Templin [3], Senthil Arumugam [2,4,5], Chrysovalantou E. Xirouchaki [1,2], Denis Korneev [3], Gediminas Gervinskas [3], Jihane Homman-Ludiye [6], Sonia Lourdes [1,2], Esther Garcia-Dominguez [7], David J. Bishop [8], Samuel Rodgers [1,2], Luke E. Formosa [1,2], Michael T. Ryan [1,2], Georg Ramm [2,3], Joachim Schessl [9], Carsten G. Bönnemann [9,10], Tony Tiganis [1,2], Christina A. Mitchell [1,2] & Meagan McGrath [1,2]* (* Authors contributed equally.)*

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[2] *Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia*
[3] *Monash Ramaciotti Centre for Cryo Electron Microscopy, Monash University, Clayton, VIC, Australia*
[4] *Depart. Anatomy and Developmental Biology, Monash University, Clayton, VIC, Australia.*
[5] *European Molecular Biological Laboratory Australia, Monash University, Clayton, VIC, Australia*
[6] *Monash Micro Imaging, Monash University, Clayton VIC, Australia*
[7] *Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia and CIBERFES Fundación Investigación Hospital Clinico Universitario/INCLIVA, Valencia, Spain*
[8] *Institute for Health and Sport (iHeS), Victoria University, Melbourne, VIC, Australia*
[9] *Division of Neurology, the Children's Hospital of Philadelphia, Pennsylvania Muscle Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA*
[10] *National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA*

FHL1 mutations cause a range of muscle disorders including Reducing Body Myopathy (RBM) and Emery-Dreifuss Muscular Dystrophy (EDMD) ("*FHL1* myopathies", OMIMs: 300163, 300695, 300696, 300717, 300718, 300280, 310300). Despite over a decade since their discovery, the disease mechanism and cause of their marked clinical heterogeneity remains enigmatic. These can be rapidly progressive infant/childhood onset disorders, fatal within 5 years due to cardiorespiratory failure (RBM). We provided the first insight, revealing mutant *FHL1* protein accumulates as aggregates linked to disease onset and progression. Others report milder disorders including EDMD, where mutations result in *FHL1* protein loss from muscle. In a new breakthrough, we generated unique *FHL1* mouse models that recapitulate this clinical spectrum,

for analysis of disease mechanism(s) and pre-clinical evaluation of treatments. We also uncovered a new role for *FHL1* in maintaining muscle mitochondrial function. *FHL1* loss reduces the mitochondrial network expanse and its energy-generating function thereby decreasing muscle strength, exercise tolerance and enhancing fatigue. Intriguingly *FHL1* is also an exercise-responsive muscle gene. Increasing wild type *FHL1* in muscle (by as little as 4-fold in transgenic mice), was sufficient to stimulate the effects of endurance exercise training including marked expansion of the mitochondrial network that enhances energy production and exercise performance. Advanced volumetric electron microscopy revealed marked changes to mitochondrial structure in muscle when wild type *FHL1* levels are elevated compared to when it is lost. Therefore, *FHL1* is a gene at the nexus of muscle disease and athleticism, with a new opportunity to develop mitochondria-targeted therapies for *FHL1* myopathies.

Measuring function in childhood FSHD - Does the FSHD-COM Peds make the cut?

de Valle, K [1,2,3], Dobson, F [3], Woodcock, I [1,2], Carroll, K [1,2], McGinley, J [3]

[1] Neurology Department, The Royal Children's Hospital, Melbourne
[2] Neurosciences Theme, Murdoch Children's Research Institute, Melbourne
[3] Physiotherapy Department, University of Melbourne, Melbourne

Despite being the third most common of the muscular dystrophies, childhood onset facioscapulohumeral dystrophy (FSHD) is rare. Low incidence, diagnostic challenges, variable severity, and slow progression have impacted progress in development and validation of functional outcome measures, especially for children. The novel FSHD-COM developed in adult FSHD, was adjusted and its reliability, validity and the longitudinal utility explored in a group of children and adolescents.

Measurement properties of the FSHD-COM Peds was evaluated in 18 participants (7-18yrs, mean age 13.3yrs, 10 males). Intra-rater test re-test reliability (n=15) was excellent $ICC_{1,2}$>0.99 (CI95% 0.98-0.99), standard error measurement low SEM 1.31 (CI95% 0.96-2.1) and minimal detectable change (MDC95) score calculated at 3.6 points. Convergent validity was supported by moderate to very good correlations with FSHD-specific severity scales, PUL 2.0, and self-reported measures of disease burden. The ability to discriminate between FSHD and age matched typically developing individuals (n=18) was excellent (p=0.0005). Longitudinal utility (n=16) indicates the FSHD-COM Peds can identify change in function related to typical development and disease progression overtime. Agreement between change in function measured with FSHD-COM Peds and participant-reported global rating of change was strong in 50% and moderate in 33% of participants.

The FSHD-COM Peds shows potential and would benefit from larger scale studies with increased numbers to explore responsiveness and inter-rater reliability when measuring function in childhood FSHD.

Managing capacity and demand in a busy Neuromuscular Clinic

Nicole Thomas [1], *Kate Munro* [2] & *Anita Cairns* [2]

[1] *Physiotherapy Department, Queensland Children's Hospital*
[2] *Neurosciences Department, Queensland Children's Hospital*

The QCH Neuromuscular service aims to provide high quality, specialist care to children with confirmed or suspected neuromuscular disorders to improve their health, function, and quality of life. Since its establishment in 2015, there has been a substantial increase in the number of patients seen through the clinic. This progressive increase in demand has resulted in patients waiting longer than recommended for clinical care, clinics being overbooked and high workloads, potentially impacting on patient care and staff wellbeing. As the demand for services is expected to increase over the coming years due to ongoing advances in diagnosis, treatment and life expectancy of children with NM disorders, it is critical that we streamline our current service to ensure it remains sustainable into the future.

The QCH Neuromuscular team is currently undertaking a clinical redesign project to explore issues leading to delays in accessing care and the potential impacts this is having on patients and staff. Staff have participated in workshops to identify issues and develop unique

solutions to address these issues. Data has been gathered and analysed to confirm and explore concerns raised by staff and patients. Key themes emerged including issues with referral criteria, discharge practices as well as variation, delay and duplication of clinic reports. Lean methodologies have been used to develop solutions to target the key issues identified through the diagnostic phase.

Improving the transition journey for neuromuscular patients in Queensland

Rebecca Leung, Kate Munro, & Anita Cairns

Neurosciences Department, Queensland Children's Hospital

Children with neuromuscular disease are now able to live into adulthood thanks to advancements in medical care and this has created the need for adult specialists for conditions originating in childhood. Currently, there aren't any published guidelines to help this population's transition from paediatric to adult services. The transition phase, representing the process of moving from adolescence to adulthood, can be severely affected by growing up with a neuromuscular disorder, with significant impact on the patient and family's quality of life. It takes time and planning to move from paediatric to adult services, and this is not something that happens all at once. Transition should be common practice, but many children with serious and continuing medical issues do not experience successful transition outcomes; this can be due to a lack of standardisation, poor planning, and inadequate communication. A successful transition process is one that includes early introduction and ongoing discussion that engages the adolescent to plan and prepare for the eventual transfer of care. We aim to evaluate our current neuromuscular transition model by developing an online survey that will be distributed to both clinicians, young people, and parents. We intend on developing a working group to use the information collated from the above surveys to refine our current service model and identify any unmet needs to ensure the right support for our neuromuscular patients.

Implementing clinical guidelines for neuromuscular disorders

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In 2022, two clinical practice guidelines were published, one for allied health and nursing assessment and management of Duchenne muscular dystrophy and the other, for the management of paediatric Charcot-Marie-Tooth disease. Despite the proliferation of practice guidelines for neuromuscular disorders in the last 10 years, very little is known about adherence to guidelines by health professionals delivering neuromuscular care across Australia and New Zealand. To develop strategies for guideline implementation, we must first understand what evidence to practice gaps exist as well as the enablers and barriers to uptake of guideline recommendations. This project will assess health professionals' awareness of and adherence to recently published guidelines via an online survey administered through REDCap. Health professionals (medical, nursing and allied health) who manage the clinical care and treatment of individuals with Duchenne muscular dystrophy and/or children with Charcot-Marie-Tooth disease across Australia and New Zealand will be invited to participate in this once only survey. The survey will be distributed to all neuromuscular clinics and centres and through community health networks and professional associations. The overall aim is to determine current practice and implementation of clinical guidelines for neuromuscular disorders in Australia and New Zealand. This project will provide preliminary evidence around awareness of guidelines, as well as enablers and barriers to compliance with guidelines. This information will be used to design tailored guideline implementation strategies and inform further research in clinical practice uptake of the guidelines.

Healthcare Experiences of people living with Myotonic Dystrophy Type 1

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Myotonic dystrophy type 1 (DM1) is a progressive multisystem disorder with highly variable symptoms affecting muscle movement, strength, dexterity, and mobility.

International neuromuscular clinical experts have developed consensus-based care recommendations based on clinical experience whilst in wait for research-based evidence (Ashizawa et al., 2018) . The quality of health care delivery for DM1 patients seems dependent on geographical location, resources, and the knowledge held by non-specialised health professionals of the special needs of this group. Clinicians often face challenges attempting to deliver care for DM1 patients due to neuropsychiatric symptoms. Health care delivery often occurs as crisis management rather than a preventative approach due to all the above factors. Objective: This research aims to explore the health care experiences of DM1 people from around Australia, who generously and openly told their stories. Methods: Using a qualitative phenomenological approach, 21 adult participants took part in in-depth, semi-structured interviews. Three different groups took part and included health care professionals, people with DM1, and caregiver family members. The interview content has provided multiple points of view around health care for people with DM1. Identification of themes is being guided by thematic analysis method (Braun & Clarke, 2006) . Results and Conclusion: Preliminary themes have been identified which include "fragmented care", "illness not laziness", "physiotherapy provides hope". Theme identification is yet to be finalised. It is intended that results from this research will add to DM1 clinical care by providing insight into current Australian DM1 care practices.

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Bladder and Bowel dysfunction in children and infants with Neuromuscular Conditions

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Queensland Children's Hospital established a Physiotherapy led Paediatric Continence Service in 2018. This provided a pathway for children with bladder and bowel dysfunction to access specialist physiotherapy assessment and management. It quickly became apparent that children with neuromuscular disorders were requiring physiotherapy input to manage bladder and bowel dysfunction and we began screening for this through our Neuromuscular Complex Care clinic. Children with neuromuscular conditions are known to have muscle weakness with functional limitations. However, little is understood has about the impact of weakness on a child's ability to achieve normal bowel and bladder function. Review of our NM patients has demonstrated that this is a significant issue for children and their families, with at least one third of children having dysfunction requiring medical and/or physiotherapy intervention. In addition, we identified that some diagnostic groups were over-represented and displayed consistent patterns of dysfunction. Physiotherapy assessment and management of bladder and bowel dysfunction is not currently included in the established Standards of Care documents for neuromuscular disorders. Proactive management can have a substantial impact on the child and family's quality of life, participation, health, and well-being. This presentation will share our experiences of identifying bladder and bowel dysfunction in our neuromuscular patients and the management strategies utilised to assist with improving continence.

Lung volume recruitment therapy in people with neuromuscular disease: a randomised controlled trial

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Introduction: Care guidelines recommend daily lung volume recruitment (LVR) to preserve respiratory system compliance (C_{rs}) and help slow lung function decline in neuromuscular disease (NMD), despite no Level I evidence.

Aim: To prospectively investigate the effects of regular LVR on respiratory function and quality of life (QoL) in people with NMD.

Methods: A RCT of LVR versus an active control (breathing exercises), performed twice-daily for three-months, was conducted.

Consecutively recruited participants (age >14 years) were stratified *a priori* by disease type (motor neurone disease [MND]), slowly-progressive NMDs [SlowNMD]). Respiratory function was assessed at baseline then monthly for 3-months (lung insufflation capacity [LIC], vital capacity, C_{rs}, static lung volumes, maximal inspiratory and expiratory pressures, peak cough flow). Disease-specific and generic QoL were collected at baseline and final assessments. Data were analysed using linear mixed models.

Results: Seventy-six participants (median[IQR] age 57[31-68] years, mean(SD) VC 40(18) %pn) were randomised (LVR=37, Control=39). There was a statistically significant difference in LIC between groups (linear model interaction effect X^2=14.9, p=0.002; observed mean difference = 0.19 [95% CI = 0.00, 0.39] L). No interaction or treatment effects were observed in secondary outcomes of lung volumes, respiratory system compliance or QoL. No adverse events were reported.

Conclusion: This is the first RCT to demonstrate that regular LVR increases the maximum attainable lung capacity (LIC) in adults with NMD. We found no direct evidence that regular LVR modifies respiratory mechanics or slows the rate of lung volume decline. The impact on clinical outcomes remains to be determined.

Keep CaLM and carry on with calf length management for young people with Duchenne muscular dystrophy

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Neuromuscular team, Neurology department, Royal Children's Hospital, Parkville, VIC
Australian Neuromuscular Disease Registry, Parkville, VIC

Background: Best practice guidelines recommend calf length management programs be prescribed to young ambulant people with Duchenne muscular dystrophy (DMD). Typically including calf stretches, night-time resting ankle-foot-orthoses (NAFO) and occasionally serial casting, these high burden programs are resource-intensive for both families and health services. Specifics around prescription are yet to described, particularly regarding methodology, goals, escalation and feasibility. This project proposes a clinical algorithm to support clinicians in the prescription of calf length management programs for young ambulant people with DMD (CaLM-DMD).

Methods: Five physiotherapists and an orthotist, experienced in the treatment of paediatric DMD at the Royal Children's Hospital (RCH) in Melbourne, underwent a process to describe what constitutes best practice in prescribing calf length management programs for young ambulant people with DMD. Assessment findings, along with social and physiological factors were discussed in the context of clinical experience, scientific evidence and care guidelines. Agreement was built into a decision-making algorithm intended for use within the clinical setting.

Results: Differences were identified between clinicians regarding methodology and language used in practice, but not program goals, indications and precautions. Utilising common language to describe assessment, goal-setting and in clinical collaboration was key to building an algorithm acceptable to each clinician.

Conclusion: The CaLM-DMD algorithm proposes a decision-making tool to support clinicians with prescription of calf-length management programs for young ambulant people with DMD. An ethics-approved protocol is in place to test its content and utility more broadly across Australia and New Zealand.

Real World Experience of Treatment for SMA – A single centre experience

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Children with spinal muscular atrophy have been able to access disease modifying therapies in Australia since 2018. This has resulted in improvements in life expectancy, especially in patients with spinal muscular atrophy type 1. We have collated data on the patients with SMA attending the Neuromuscular Clinic at the Queensland Children's Hospital.

There has been a 320% increase in the number of patients with SMA type 1 since 2018, with the number of patients increasing from 5 to 16. Three patients with SMA 1 and 2 copies of SMN 2 have died – 2 families made a joint decision with health care professionals to proceed down a palliative pathway and one child had an unexpected sudden death at home. All surviving patients with SMA type 1 have shown gains in motor function, with those with 3 copies of SMN2 or earlier diagnosis showing the most improvements.

The increase in the number of patients with SMA 2 and 3 has been more modest but has been influenced by patients moving internationally to access treatment. One patient with SMA type 2 on treatment died following transition to adult services, likely due to respiratory failure. Most patients have demonstrated stability in function. Patients who started treatment at a younger age have shown the most gains.

Our findings add to the real world experience of treatment of patients with SMA with disease modifying therapies.

Intravenous and Intrathecal Onasemnogene Abeparvovec Gene Therapy in Symptomatic and Presymptomatic Spinal Muscular Atrophy: Long-Term Follow-Up Study

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Objective: Examine the long-term safety and durability of intravenous or intrathecal onasemnogene abeparvovec in symptomatic and presymptomatic patients with spinal muscular atrophy (SMA) in the LT-002 study (NCT04042025).

Methods: Safety was assessed by medical history/record review, physical examination, laboratory evaluation, and pulmonary/cardiac assessments. Efficacy was assessed by developmental milestones and Hammersmith Functional Motor Scale Expanded (HFMSE).

Results: As of May 23, 2022, 81 patients (intravenous, n=63 [symptomatic, n=38; presymptomatic, n=25]; intrathecal, n=18) were enrolled. Mean (range) follow-up was 3.4 (1.0–4.3) and 3.6 (2.6–4.3) years for the intravenous and intrathecal cohorts, respectively. No deaths or treatment-emergent adverse events (TEAEs) causing discontinuation occurred. The most frequently reported TEAEs were gastroenteritis, nasopharyngitis, pneumonia, respiratory distress, and viral infection. All patients survived and maintained developmental milestones.

Mean (range) age was 3.7 (2.4–4.7) and 5.3 (3.4–7.5) years for the intravenous and intrathecal cohorts, respectively. One patient required permanent ventilation. Twenty-seven patients achieved new milestones (presymptomatic-intravenous, n=6; symptomatic-intravenous, n=16; intrathecal, n=5); more than half (n=16) did so without add-on therapy. HFMSE improvements were clinically significant (≥3 points; presymptomatic-intravenous, 81.25%; symptomatic-intravenous, 66.7%; intrathecal, 50%). No patients treated presymptomatically required ventilatory/nutritional support; few symptomatic patients required ventilatory (intravenous-symptomatic, 32%; intrathecal, 5.6%) or feeding (intravenous-symptomatic, 20%; intrathecal, 0%) support. Most fed orally (intravenous, 92.1%; intrathecal, 100%). The majority (57/81) never received add-on therapy; of those who did, half did not achieve new milestones.

Conclusions: Intravenous/intrathecal onasemnogene abeparvovec demonstrates consistent, substantial, and durable efficacy and no new safety signals in symptomatic and presymptomatic patients with SMA.

Eadweard Muybridge and the Nineteenth-century origins of Gait Lab

Kathryn B. Irving

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In 1878, pioneering photographer Eadweard Muybridge won a bet for millionaire Leland Stanford by proving that his prize stallion had four limbs off the ground when galloping, using a new technology that recorded the horse's movement frame by frame. A decade later, Muybridge collaborated with the University of Pennsylvania and neurologist Francis Dercum to produce "Animal Locomotion." Muybridge's masterpiece used chronophotography to record his human subjects, largely nude or scantily clad, involved in various physical activities, including walking, running, climbing and throwing.

In addition to Muybridge's "normal" subjects, he included examples of "abnormal" adults and children, with conditions such as hemiparesis, movement disorders, and limb deformity. Some of the adult subjects have recently been identified in casebooks from Penn, but the identity of the children remains unknown. The technology allowed neurologists and musculoskeletal experts to visualise the precise components of normal and abnormal gait, with a degree of detail difficult to recognise with the naked eye. As such, it was the precursor to modern "gait-lab" analysis.

This paper highlights some of Muybridge's "abnormal" subjects, and considers their images from various angles—as works of art, as products of emerging photographic technologies, and as key moments in the history of neurology. Importantly, the photographs also record glimpses of the subjects' personalities and adaptive strategies, that were perhaps unintended by Muybridge and Dercum. For the modern viewer, reconciling these different perspectives allows us to approach historical medical data in an ethically-sensitive manner.

A Diagnosis A Long time In The Making

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Patient RB was diagnosed with adult onset SMA aged 65 after being misdiagnosed as having inclusion body myositis based on initial clinical and pathological features over 20 years ago. She had been receiving monthly IVIg for over 15 years. When reviewed clinically she had predominantly proximal upper and lower limb weakness with sparing of bulbar and respiratory muscles. Genetic testing confirmed a homozygous deletion in SMN1 gene with four copies of the SMN2 gene, which was likely contributing to her late and relatively mild presentation of SMN. Her daughter was found to be a carrier on routine pre-reproductive testing in the USA. An Invitae Neuromuscular Gene Panel did not reveal any other gene defects. Her muscle biopsies showed marked and progressive dystrophic changes on two muscle biopsies (vastus lateralis, aged 51 and 54). The patient was classed as clinically having SMA 3 and commenced treatment with nusinursen.

This case highlights the challenges of adult SMA and suggests it may be more prevalent than traditionally considered due to misdiagnosis. It demonstrates the changes emerging due to the widespread availability of genetic testing including new treatment options. It remains unclear why serial muscle biopsies showed marked dystrophic changes. It is known that SMN gene expression is widespread in multiple tissues including skeletal muscle and in animal models defects can lead to intrinsic on muscle structure. It may be that the mitigating effects from the SMN2 led to a different balance of pathological effects on muscle along with the anterior horn cells.

Perspectives on starting disease modifying therapy in adults with 5q SMA – a single Australian centre's experience

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Neuromuscular Clinic, Royal North Shore Hospital

Objectives: Disease-modifying therapies have become available to adults with 5q SMA in Australia. We explore the considerations for adult patients when deciding on treatment, the practicalities of clinical assessments, and the progress up to the first 18 months for those on treatment.

Methods: We assessed patients' baseline characteristics, including clinical assessments with spirometry, 2/6MWT, mTUG, RULM, HFMSE, ATEND; and patient-reported outcome measures: EAT-10, SMAFRS, MYMOP. We surveyed the initial experience, side effects, perceived benefits or detriments in adults on treatment.

Results: 21 adults, aged 19-64, 12 requiring CPAP/ nocturnal ventilation, 6 being remote from the centre. 2 adults were on therapy prior to age 18, both switched from nusinersen to risdiplam. 17 adults (aged 25-64) commenced on therapy with nusinersen, 2 decided against, 2 pend further optimisation of standards of care. Disease severity varied widely with RULM score 0-39. Only 3 adults were able to complete the 2/6MWT. One could perform mTUG. The ATEND was practical in the most severely affected. The RULM and ATEND were possible with assistance of a carer via Telehealth. Those on therapy considered ongoing treatment as worthwhile, and some would consider changeover to risdiplam if available.

Conclusions: Australian adults with SMA have realistic expectation of treatment. The severity of disease did not affect decision on therapy with the majority attending an adult clinic deciding to proceed to therapy and saw it as worthwhile to continue despite inconveniences and minor improvement or stabilisation. Clinical assessments need to be tailored to patient's disease severity.

Taking care of Business – using business intelligence solutions to support clinicians to ensure best practice in the clinical setting

Kate Munro, Anita Cairns

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Standard of care guidelines are an important tool to guide care and management of patients with Neuromuscular disorders. However, coordination of care within the service is very complex and time consuming. Whilst often appearing seamless for consumers, it is a high-cost workload for clinical staff, and although consumers usually receive timely care, it is challenging to ensure routine monitoring investigations are not missed and standards of care are met.

In February 2022, our clinic had the opportunity to create a service overview dashboard with the Business Intelligence team. The objective was to integrate existing data from fragmented systems to a unique dashboard solution to support and coordinate clinical care and went live in August 2022.

The dashboard has provided seamless visibility to the overall service, and real time cohort data for active patients, and primary neuromuscular disorder, age, location, medications, appointments and investigations and treatments due. We have also built KPIs for specific patient cohorts. The next update will include patients by consultant, KPIs for transition and a pre clinic summary.

Limitations of the dashboard include quality of the data available in the ieMR and the other systems available in the data warehouse.

The dashboard demonstrates how investment in business intelligence solutions can add value to busy clinics and optimise care.

Cost Effectiveness of Newborn Screening (NBS) for Spinal Muscular Atrophy (SMA) in Australian Hospitals

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Background: Early diagnosis of SMA through NBS enables prompt intervention, treatment and reduces hospital resource utilisation.

Objective: Cost-effectiveness of NBS followed by therapeutic intervention for eligible neonates versus a management pathway without NBS was evaluated to determine if NBS offers value for money from an Australian state hospital perspective.

Methods: A cost-utility analysis was conducted to estimate the lifetime costs and health effects of NBS for SMA compared to a scenario with no NBS. A decision tree captured the costs and outcomes of NBS, and a cohort analysis modelled the long-term implications of NBS testing post-diagnosis. The decision tree probabilities were based on Australian epidemiology data, existing international literature, and Australian expert opinion. Markov model health states were characterised based

on developmental milestones, using published clinical trial data on currently available disease modifying therapies to inform transitions between health states. Natural history data was used to model long-term survival. State healthcare resource utilisation and costs details of included hospital admissions, outpatient visits, and treatment administration costs. Quality-of-life weights aligned with international standards for SMA. Sensitivity and scenario analyses were conducted to assess the robustness of the model and validity of the results.

Results: Introduction of NBS for SMA across Australia would identify approximately 29 neonates with SMA from 293,514 NBS tests each year. NBS ($1.5 million) resulted in lower cost to hospitals ($8.6 million versus $11.8 million with no NBS) over the lifetime of the identified cohort.

Conclusion: NBS for SMA is a cost-effective use of resources from the perspective of Australian state hospitals.

Safety and efficacy of ataluren in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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Study 041 (NCT03179631) is an international, phase 3, randomised, double-blind, placebo-controlled 72-week ataluren trial in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) followed by a 72-week open-label period. We describe efficacy and safety results from the placebo-controlled phase.

Boys with nmDMD aged ⩾5 years, on corticosteroids, and with a 6-minute walk distance (6MWD) ⩾150m were eligible. The primary objective was to determine ataluren's effect on ambulatory function, assessed by the 6-minute walk test. Boys were randomised 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomised boys who received ⩾1 dose of study treatment. Predefined subgroups included boys with ⩾300m 6MWD and ⩾5s stand from supine (primary) and those with 300-400m 6MWD.

Ataluren and placebo groups in the ITT population and key subgroups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and time to stand from supine. Significant differences in mean 6MWD change from baseline and rate of change favoured ataluren in the ITT population (14.4m; 0.20m/week; p=0.0248) and 300-400m 6MWD subgroup (24.2m; 0.34m/week; p=0.0310), representing a 21% and 30% slowing of the decline rate in 6MWD in these groups, respectively. There were significant treatment benefits in time to 10% worsening of 6MWD. The number of ITT patients who lost ambulation receiving placebo was almost double that of those receiving ataluren. Ataluren was well tolerated, had no probable drug-related serious adverse events (AEs), and AE frequency (85.3%) was similar to placebo (84.7%).

Study 041 confirms ataluren's favourable risk-benefit as shown in previous clinical and real- world evidence studies.

Bulbar Function in Children with Two or Three *SMN2* Copies Who Received Onasemnogene Abeparvovec Presymptomatically for Spinal Muscular Atrophy

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Objective: We conducted a *post-hoc* analysis of bulbar function from a phase 3 study (SPR1NT; NCT03505099) of children with presymptomatic spinal muscular atrophy (SMA) with two (n=14) or three copies (n=15) of the *survival motor neuron 2* gene (*SMN2*) who received onasemnogene abeparvovec.

Methods: Experts on deglutition, respiratory function, physical therapy, nutrition, and neurology, and Novartis Gene Therapies staff defined bulbar function as the ability to establish verbal communication and to swallow to orally meet nutritional needs and maintain airway protection. Four endpoints represented key components of bulbar function: (1) achieving item #6 or above on the Bayley Expressive Communication subtest, (2) receiving full oral nutrition, (3) absence of clinician-identified (clinical/fluoroscopic) physiologic swallowing impairment, and (4) absence of respiratory health–related adverse events (aspiration/aspiration pneumonia). Because communication skills were not assessed during SPR1NT, numbers/percentages of children who achieved each of the three available endpoints and all three endpoints (composite endpoint) were descriptively assessed (last follow-up: age 18 and 24 months for children with two and three *SMN2* copies, respectively).

Results: Twenty-nine children were included in the analyses of three outcomes pertaining to bulbar function. At study end, 100% (29/29) received full oral nutrition, 100% (29/29) had evidence of a normal swallow, and 100% (29/29) had no respiratory–related adverse events; 100% (29/29) met the composite endpoint.

Conclusions: Children with presymptomatic SMA treated with onasemnogene abeparvovec could swallow, meet nutritional needs orally, and maintain airway protection, indicating they achieved bulbar function and motor milestones consistent with typically developing children.

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