ANN Congress 2024 – Abstracts

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Rachel Kennedy	The presence and outcomes of falls among children with physical disability: a scoping review	Children with physical disability, including neuromuscular weakness, often report falling. However, little is known of the extent and impact of falls in children. We aimed to determine what is known about falls in children with physical disability, including frequency, incidence and prevalence; causes and risk factors; fall-related injuries and impact of falls on physical activity participation. A scoping review was conducted according to Joanna Briggs Institute recommendations and reported per PRISMA-ScR checklist. The protocol was published on Open Science Framework. Full text papers in English were included that reported falls in ambulatory individuals with childhood-onset physical disability aged ≤ 18 years. Four databases were searched (Medline, Embase, CINAHL, PubMed) with search terms 'paediatric', 'physical disability' and 'falls'. Yields were imported to EndNote, duplicates removed and exported to Covidence. Three reviewers determined eligibility. Data from included studies were extracted into Excel for analysis. Twenty-nine studies included children with Duchenne muscular dystrophy (n=9), Charcot-Marie-Tooth disease (n=6), cerebral palsy (n=5), Developmental Coordination Disorder (n=3) Down Syndrome and other developmental (n=3) and neuromuscular disorders (n=3). Reported falls frequency ranged from 0-71 falls/week (muscular dystrophy) and prevalence 4.4% (FKRP-associated dystroglycanopathy) to 100% (Down Syndrome). Younger age, gait dysfunction, reduced balance, environment, and in males with DMD, older age and steroid-naivety were associated with falls. Falls-related injuries were reported in children with neuromuscular disorders (34-66% of falls) including fractures, cuts and bruises. Fear of falling, reduced confidence and function were reported post falling. Falls in children with physical disability are common, cause injury and impact function.
Kate Carroll	Putting one foot in front of the other – an update on the Ambulate NMD project	Achievement and maintenance of independent walking is a target of treatments for neuromuscular conditions (NMD) and the loss of ambulation is considered a significant disease milestone. The Ambulate NMD project is a physiotherapist-led prospective longitudinal study of gait and ambulatory function embedded in the Neuromuscular Clinic at the Royal Children's Hospital, Melbourne. Independently ambulant children and adolescents attending the clinic are eligible to enrol. Gait is assessed using an electronic walkway at self-selected walking speed and during a Six Minute Walk Test. Anthropometrics, functional outcome measures and information about past falls are recorded. To date, 311 children (69.5% male) have enrolled and assessed at least once, with a total of 827 assessments performed as of March 31st, 2024. The most common diagnoses are Charcot-Marie-Tooth (n=87), Duchenne muscular dystrophy (n=76), congenital myopathy (n=42) with smaller numbers of facio-scapulo-humeral dystrophy (n=22), Becker muscular dystrophy (n=17), spinal muscular atrophy (n=15) and other NMD. At baseline participants had a mean age of 9.8±3.6 years. Over community distances (500+ metres), typical mobility was reported with some limitations in walking for 58% whilst 14% used wheeled mobility. Sixty-three percent reported falling every month

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		with 13% falling every day; tripping and "legs giving way" were the most common causes of falls. Of children who fell, 66% reported injuries with 27% seeking medical care. Detailed longitudinal analyses of diagnostic subgroups relating spatiotemporal gait parameters to functional ambulation measures are planned and ongoing to allow us to better understand gait changes and optimise walking in children who have NMD.
Kate Carroll	Staying on their feet – a study of walking in Duchenne muscular dystrophy	Understanding walking and mobility in Duchenne muscular dystrophy (DMD) is essential given that loss of ambulation is a key marker of disease progression. Physiotherapists commonly employ low-tech clinical measures of walking to assess response to medication, and to predict and manage change in walking function. This study reports the findings of spatiotemporal gait analysis with clinical measures in a cohort of boys with DMD. Seventy-one boys with Duchenne muscular dystrophy (DMD) who enrolled in the AmbulateNMD study of gait and functional ambulation are included in this exploratory analysis. Data from baseline (n=71) and 12 month follow-up visits (n=37) includes spatiotemporal gait analysis and functional measures of walking and mobility. At baseline, participants had a mean age of 9.5±2.8 years and completed a 10m walk/run in 5.9±2.3sec. Thirty-one typically used a wheelchair over community distances (500m) and 53 reported falling each month (median falls 2(IQR 0, 4). Their self-selected walking speed of 99.2cm/sec was slower (76.9%) with greater step width (183.2%) when compared with typically developing age-matched peers. After 12 months, most gait measures remained stable except for step width (increased from 12.3±4.7 to 13.9±4.9). Small declines in mean North Star Ambulatory Assessment scores (26/34 to 24/34, n=29) and 6 minute walk distances (415m to 384m, n=26) was also noted over this period. Spatiotemporal gait analysis offers additional information which complements existing clinical measures of ambulatory function.
Zoe Davidson	A 50 year retrospective cohort study describing survival in Duchenne muscular dystrophy	Objective: To describe the effect of decade of birth on survival in individuals with DMD. Methods: This retrospective cohort study collated information on survival from medical records of males with DMD attending Royal Children's Hospital, Melbourne from 1973 – 2021 and linked this to survival information from two adult tertiary sites (Austin Health and St Vincent's Hospital, Melbourne). Data were stratified by decade of birth and survival analysis using Kaplan Meier plots was conducted to identify median survival (age at which 50% of patients were still alive). If over 50% of the stratum were still alive, survival function was determined. Results: The cohort included 356 patients with year of birth ranging from 1958 to 2014 and median (interquartile range, IQR) follow up from diagnosis of 10.5 (4.1, 15.7) years. Of the 356 patients, 156(44%) were deceased, 132(37%) were alive and survival status was unknown for 68(19%). The median (IQR) survival by decade of birth was: before 1970(n(stratum)=41): 18.2(15.2, 20.4)years; 1970-1979(n=68): 18.8(16.8, 23.2)years; 1980-1989(n=64):

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		20.6(15.9, 26.0)years; and 1990-1999(n=66): 24.0(20.3, 27.5)years. For boys born in 2000-2009, the chance of survival to over 10 years was 99% (95% confidence interval, CI: 91%, 99.8%) and to over 20 years was 79% (95% CI: 55%, 92%). For boys born in 2010-2019, the chance of survival to over 10 years was 97% (95% CI: 79%, 99.5%). Conclusion: Survival in individuals with DMD has increased over the last five decades. There is a need for better surveillance of neuromuscular disease in Australia, especially in adult populations. Funding: Independent Research Grant, Pfizer.
Fiona Martin	The psychological support needs of patients with Facioscapulohumeral Muscular Dystrophy (FSHD): Relationship between disease burden on perceived quality of life and mental health.	FSHD is a common inherited muscular dystrophy in Australia, affecting an estimated 1 in every 7500 individuals. Diagnosis is challenging and requires genetic testing, with no effective treatments currently available. The gradual onset of muscle weakness and loss, particularly in facial, shoulder, and upper arm muscles, can lead to lifelong disability and severe physical impairment. Despite the physical symptoms being well-documented, there is limited research on the psychological impact of FSHD. Patients often report feeling isolated because of their condition, as well as anxious or depressed as they adjust to their diagnosis. The study aims to investigate the prevalence and severity of psychological problems such as anxiety, depression, and stress among FSHD patients. Quality of life (QOL) research is important for improving symptom relief, care, and management of symptoms. Research into QOL for FSHD is scarce. The study will investigate QOL in patients with FSHD. Additionally, the study will explore locus of control – the belief one has control over the outcome of events in their life – and its relationship with disease burden, quality of life, and mental health in FSHD patients. The study aims to recruit 220 genetically confirmed FSHD patients who will complete standardized psychometric tests and questionnaires assessing disease burden, quality of life, locus of control, and symptoms of depression, anxiety, and stress. The data will be compared to a control group without neuromuscular diseases. Furthermore, the study will examine the potential benefits of accessing a patient-led registry for FSHD. Patient led registries are advocated for in rare diseases, offering participants a sense of agency over their data. The experimental component of the study will explore how participation in a patient-led registry influences perceived quality of life, locus of control, and mental health functioning among FSHD patients. Overall, the study aims to better understand the psychological challenges faced by FSHD patients and better support their mental health to improve outcomes
Chantal Coles	Creating an immune cell atlas of the peripheral blood for Facioscapulohumeral muscular dystrophy (FSHD)	The immune system is vital for effective skeletal muscle regeneration, with immune dysfunction known to impair regeneration and impact muscle wasting in chronic muscle disease. An immune infiltrate is present in muscle of FSHD patients, preceding the replacement of fat. However, very little is known about how the immune system influences

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		disease pathology in FSHD. This lack of understanding has limited our ability to provide the best quality of care and hampers the development of the next generation of treatments for patients with FSHD. To address this, we have recruited 23 patients with childhood onset FSHD through the neuromuscular clinic at Royal Children's Hospital (Melbourne, Australia), as part of FSHD longitudinal outcome study (iFSHD-LOS). Blood samples have been collected and screened using high-dimensional flow cytometry to identify 55 subtypes of immune cells. Our initial analyses identified alterations in immune cell subtypes in patients with FSHD. This study aims to create an immune cell atlas of patients with FSHD over the next 5 years using the iFSHD-LOS study. This will involve a yearly blood sample for immune cell phenotyping, transcriptomic and plasma cytokine analyses which will be coupled with key clinical outcome measures to determine severity.
Michaela Yuen	A new genetic cause for a lethal brain disorder and what it teaches us about the biology of neurodevelopment.	Finding a genetic diagnosis for individuals with inherited neuromuscular disorders can be life-changing for affected families, ensuring improved clinical care, access to available therapies and genetic counselling/family planning. Despite significant improvements in the diagnosis of rare genetic disorders, genetic variants in some parts of the genome remain difficult to interpret - requiring advanced investigations such as RNA sequencing and functional laboratory studies. Here we describe two siblings with neonatally-lethal fetal akinesia, global growth restriction and brain malformations – specifically pontocerebellar hypoplasia. Using whole genome and RNA sequencing we discovered a segregating, homozygous deep-intronic variant in a novel disease gene, CDK5RAP3 (NM_176096.3 c.409+243G>A). To confirm pathogenicity of the CDK5RAP3 variant and characterise CDK5RAP3-related disease in our probands, we performed mRNA and protein expression analysis. We established that the deep-intronic variant induces abnormal pre-mRNA splicing, resulting in the inclusion of a pseudoexon into the canonical CDK5RAP3 transcripts. The pseudoexon encodes a premature termination codon, causing nonsense-mediated decay of transcripts and markedly reduced levels of full-length CDK5RAP3 protein. A small amount of canonically spliced CDK5RAP3 could be detected (<2% of control levels). Analysis of patient tissue and cells confirmed cellular dysfunction in concordance with the critical role CDK5RAP3 protein plays in protein UFMylation. In conclusion, we have compelling evidence supporting biallelic variants in CDK5RAP3 as a novel cause of severe, neonatally-lethal fetal akinesia - and recommend screening of CDKRAP3 in undiagnosed individuals presenting with pontocerebellar hypoplasia. Our study highlights that CDK5RAP3 protein may have an under-recognised, vital role in human neurodevelopment.
Lauren Sanders	Treatment with nusinersen in adults with Spinal Muscular Atrophy: clinical results from	Background: Access to nusinersen for adults living with Spinal Muscular Atrophy has been available in Australia since 2021. There is increasing evidence regarding the benefits of nusinersen, however given the lack of clinical trial data for adults, ongoing review of real world data is essential to optimising use in clinical practise. We report the clinical trajectory for adults participating in the SMA CSF biobank at St Vincent's Hospital, Melbourne.

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	the SMA cerebrospinal fluid biobank.	Methods: The SMA CSF biobank was established in 2021. At each nusinersen treatment, 3mL of CSF is sent for routine microscopy and biochemistry. Biobank participants are invited to contribute the remaining 2 mL of CSF to the biobank to be frozen for future research. Clinical parameters (e.g. Revised Upper Limb Module, Hammersmith score) are extracted from the clinical record. Results: Since December 2021, 27 adults with SMA (15/27, 55% female) have consented to the biobank. Clinical phenotype is Type 2 (7/27, 30%) and Type 3 (20/27, 70%) with average age of first dose 42±14years (range 25-74). The majority of patients reported stabilisation or improvement in functional status with similar findings on objective outcome measure. With the availability of subsidised access to risdiplam, 7 (30%) patients have changed therapy, mostly due to lumbar puncture intolerance. Conclusion: Most adults treated with nusinersen in the sample have experienced a meaningful response, however almost a third of patients have switched to oral treatment. Ongoing collection of real world data plays an important role in understanding management in rare diseases.
Lauren Sanders	Proposal for an Asia-Pacific guideline for management of Spinal Muscular Atrophy in adults	Background: In the past few years, the treatment landscape for adults living with Spinal Muscular Atrophy has significantly changed. Guidelines for management of SMA in are typically paediatric focussed and do not currently cover contemporary approaches to topics such are therapeutics, respiratory monitoring, bone health, physical therapy or nutrition. Importantly, the lived experience voice is under-represented, if not absent, in existing guidelines. There is significant interest from clinicians from several countries across the Asia Pacific region to develop a co-designed guideline or consensus statement to optimise clinical outcomes in line with best practise approaches. Methods: A proposal to develop co-designed regional guideline for management of SMA in adults will be presented. This will describe possible approaches, considering the barriers and enablers for various options. Discussion: Conference attendees will be invited to provide feedback on the proposed methodology using interactive polling and during the Q&A.
Catherine Watts	Motor function characteristics of adults with spinal muscular atrophy (SMA) in Aotearoa New Zealand	Background: SMA refers to a group of autosomal recessive neuromuscular diseases characterised by progressive degeneration of alpha motor neurons in the spinal cord and brainstem. There are 44 adults with SMA throughout Aotearoa, with an additional 5 residing overseas where they have access to disease modifying therapies (DMTs) that is not accessible in Aotearoa. Importantly, many of these patients are not engaged with healthcare services. Results: Of the people with SMA residing in Aotearoa 15 have type2, 12 have type3A, 11 have type 3B, 4 have adult onset. 20 are ambulatory and 24 are full time wheelchair users.

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		We have developed ambulatory and non-ambulatory assessment protocols for these patients; including motor, respiratory, timed function and patient reported outcomes. Methods: Current data being presented is available from Pūnaha Io –New Zealand's NeuroGenetic Registry and Biobank. We have established a multi-disciplinary SMA clinic at the University of Auckland Centre for Brain Research Neurogenetics Clinic. Patients from throughout Aotearoa will be supported to travel to Auckland for the clinic where they will be reviewed by a neurologist and a physiotherapist who will complete a variety of functional measures relevant to their type of SMA. The combined information will be reported back to the patient and their GP with recommendations for management and referrals for local allied health and support services. Purpose: Data from the clinic will inform Pharmac of the need for reimbursement of DMTs in Aotearoa. Additionally, participants will be supported to access healthcare services to meet best practice standards of care.
Gabrielle Donlevy	Body Fat is associated with disability severity in children with Charcot-Marie-Tooth disease	Children with Charcot-Marie-Tooth disease (CMT) experience progressive, lifelong disability. Being severely underweight or overweight according to the Body Mass Index (BMI) has been shown to compound disability severity and rate of progression. Since BMI cannot differentiate between fat and fat-free-mass, we explored the relationship between body composition measured by bioelectrical impedance analysis (BIA) and disability measured by the CMT Pediatric Scale (CMTPedS). Body-fat percentage and Fat-Mass was captured in 107 children with CMT aged 11.6 years (range 4-18 years) using the Tanita MC-780MA BIA and disability with the CMTPedS at baseline, and 51 children at 1-year follow-up. BMI was classified into five categories according to the International Obesity Task Force. BMI classification at baseline was 2.8% severely underweight, 14.7% underweight, 58.7% healthy weight, 15.6% overweight and 8.3% obese. Mean body-fat percentage was 25.8% (SD, 9.4), mean Fat-Mass Index (FMI) was 5.35kg/m 2 (SD, 0.3), and mean CMTPedS was 16.4 points (SD, 9.4). Body-fat percentage was significantly correlated with the CMTPedS (r=0.514, p<0.001) and the FMI (r=0.948, p<0.001). FMI was significantly correlated with the CMTPedS (r=0.456, p<0.001). At follow-up, body-fat percentage increased to 27.2% (SD, 11.1), FMI increased to 5.90 kg/m 2 (SD, 4.6) while CMTPedS increased to 18.0 points (SD, 9.4). Rate of change in body-fat percentage and FMI was related to CMTPedS change. Higher body-fat percentage and Fat-Mass Index was associated with more severe disability severity and progression in children with CMT. Evaluating body composition might explain heterogeneity in

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		disease severity and therapeutic response, and identify dietary and lifestyle treatment targets.
Cara A. Timpani	Pre-clinical Evaluation of Long-term Dimethyl Fumarate Treatment in Dystrophic Mice: An Interim Report	Duchenne muscular dystrophy (DMD) is a fatal inherited myopathy with few therapeutic options. We have shown that dimethyl fumarate (DMF), an immunomodulatory drug used for Multiple Sclerosis, reduces disease biomarkers in mdx mice. For indices including inflammation, metabolism, and fibrosis, DMF was more effective than standard care prednisone (PRED) indicating it could be a useful pharmaceutical for DMD management. Toward translation, we have evaluated longitudinal DMF treatment in mdx mice using clinically-compatible function and biomarker measures. Male mdx mice were treated by gavage from 3 to 8w age with either vehicle, PRED, or half or full dose DMF (50 (DMF50) or 100 (DMF100) mg/kg, respectively) alone or in combination with PRED. Vehicle or DMF were given daily, while PRED was given once weekly. From 8w until the experimental endpoint at 15m, DMF50 and 100 were provided in food to mimic slow-release clinical formulation. PRED was delivered weekly by gavage. Grip strength (fore- and fourlimb), neuromotor co-ordination (Rotarod test) and plasma creatine kinase (CK), a clinical muscle damage biomarker, were assessed fortnightly from 3 to 8w and bi-monthly thereafter. DMF treatment at any dose, alone, or in combination with PRED, was effective at improving muscle function indices (p<0.01 for grip strength tests, p<0.05 for rotarod (except DMF100 p=0.0704) and lowering plasma CK levels (p<0.05). PRED lowered plasma CK levels (p<0.001) but had no significant effect on muscle function measures. Our interim data indicate that long-term DMF may be more effective at treating loss of muscle function than standard care PRED.
Adelaide Withers	Feasibility and accuracy of home polysomnography in children with neuromuscular disorders	Objectives: The clinical utility of home polysomnography is limited for children with neuromuscular disorders as CO2 is not measured so hypoventilation cannot be identified. This assessed feasibility home polysomnography that included measurement of transcutaneous CO2 and compared the accuracy to the current gold standard, laboratory polysomnography. Methods: Children had at least one paired laboratory polysomnogram and home polysomnogram performed with a Type 2 portable monitoring device and a transcutaneous CO2 monitor for comparison with Mann-Whitney U test for unpaired continuous variables and random intercept regression models for paired continuous variables to account for repeated pairs of observations for some participants. Results: 19 paired polysomnograms were performed for 13 participants, including 10 males, six with Duchenne Muscular Dystrophy. Median age was 9 years. Overall feasibility was 68%, 74% for the Type 2 portable monitoring device and 89% for the transcutaneous CO2 monitor. Statistically significant differences were higher total sleep time, lower awake time and less N1 sleep during home polysomnography. Home polysomnography had a sensitivity of 50% and specificity of 92% for diagnosis of nocturnal hypoventilation and sensitivity of 78% and specificity of 100% for obstructive sleep apnoea.

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		Conclusions: This is the first study to describe measurement of transcutaneous CO2 during home polysomnography in children with neuromuscular disorders. Differences in sleep architecture imply better sleep quality during home polysomnography. Sensitivity and specificity of home polysomnography for the diagnosis of sleep disordered breathing was too low for clinical use and the severity of obstructive sleep apnoea was often under-estimated by home polysomnography.
Adelaide Withers	Prevalence and cross-sectional associations of sleep disordered breathing in children with neuromuscular disorders	Objectives: We aimed to determine the prevalence and cross-sectional associations of sleep disordered breathing (SDB) in a cohort of children with neuromuscular disorders. Methods: Children from three sites over the age of five had a laboratory polysomnogram and clinical data collection. Cross sectional associations between SDB, age, diagnosis, ability to ambulate, race and BMI z-score were examined using Chi Squared for categorical variables and Mann Whitney U for continuous variables. Results: There were 66 children aged 6.0-16.7 years (median 11.5), 73% (48) were male and 27 with Duchenne Muscular Dystrophy, 18 with Spinal Muscular Atrophy, 8 with congenital muscular dystrophy and 12 with congenital myopathy. The most common self-reported ethnicity was Caucasian (67%), median BMI z-score was -0.24, 55% could ambulate, 51% had scoliosis. Of the 13 who used non-invasive ventilation, 10 used it during the polysomnogram. At least one type of SDB was present in 52% (n=34), OSA in 32% (n=21), CSA in 14% (n=9) and hypoventilation in 18% (n=12). Hypoventilation was more likely in children with congenital myopathy compared to other diagnoses and children with a lower BMI z-score. Obstructive sleep apnoea was more likely in children who could not ambulate and older children. Conclusions: The prevalence of SDB was high in this cohort and likely under-estimated due to use of non-invasive ventilation during polysomnography. The findings reflect the heterogeneity of the cohort and suggest that there are individual risk factors for each type of SDB, such as underlying diagnosis, BMI and age.
Adelaide Withers	Factors influencing participation in home, school and community settings by children and adolescents with neuromuscular disorders: a qualitative descriptive study	Objectives: To explore the enablers and barriers to participation that children and adolescents who live with a neuromuscular disorder experience and how these may vary in different settings. Methods: : Data was collected during semi-structured interviews with one or both parents of a child or adolescent living with a neuromuscular disorder, and the child or adolescent could contribute if desired. Interviews were transcribed and content analysis was performed using the family of Participation-Related Constructs (fPRC) to code and characterise the different components of participation. Results: Seventeen parents and eight children/adolescents from fourteen families participated. Meaningful participation was described by the personal categories of the fPRC that included sense of self, preferences and competence to perform activities. The barriers and enablers to participation that were identified mapped to social relationships, inclusion, adaptive equipment/activity modification, accessibility, social attitudes and policies.

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		Conclusions: The fPRC is a useful tool for understanding participation for children and adolescents with neuromuscular disorders, and personal motivators underpins how these individuals define their own meaningful participation. Social and physical supports within the immediate environment as well as accessibility and advocacy in the community support and enable participation in home, school and the wider community for children and adolescents living with a neuromuscular disorder.
Adelaide Withers	Respiratory health, sleep dysfunction and mental health in children and adolescents with a neuromuscular disorder: a descriptive qualitative study	Objectives: Individuals with neuromuscular disorders are at risk of respiratory failure, lower respiratory tract infections and sleep disordered breathing. There is a known association between mental and physical health. This qualitative descriptive studied aimed to explore the relationship between respiratory health, sleep disorders and the mental health of children and adolescents with neuromuscular disorders. Methods: Detailed, semi-structured interviews were conducted which included one or both parents of a child or adolescent living with a neuromuscular disorder. The child or adolescent could participate if desired. Interviews were transcribed and content analysis was performed to code data to themes and categories. Results: A total of 17 parents and 7 children (aged 5-17 years) from 14 families participated in interviews. Positive contributors to mental health that were identified included meaningful relationships, engagement in community activities, achieving independence and feeling well. When respiratory and/or sleep health was sub-optimal, there were additional challenges such as difficulties with behavioural regulation, changes to mood and thinking identified that had a negative impact upon mental health. Children and their families reported nurturing and self-management strategies to manage the impact of poor respiratory and/or sleep health upon their mental well-being as well as the benefits of medical treatment such as non-invasive ventilation. Conclusions: The findings of this study demonstrate that changes in mental health and wellbeing in children and adolescents with neuromuscular disorders can indicate a deterioration in respiratory and/or sleep health, and effectively treating respiratory and sleep problems can improve mental health and general wellbeing
Miriam Rodrigues	From Neuromuscular Registry to Pūnaha Io - the New Zealand NeuroGenetic Registry & Biobank	The NZ Neuromuscular Disease Registry was established in 2011. Registries for rare disorders are essential to overcome the challenge of bringing eligible patients and clinical trials together. Internationally networked the NZ NMD Registry aimed to lower the barriers to participation in clinical research. In 2022 Pūnaha Io - the New Zealand Neuro-Genetic Registry & Biobank was developed to facilitate all stages of translational research in rare neuro-genetic disorders. Pūnaha Io aims to be a repository of clinical data linked to biological samples, donated from patients with neuromuscular and neuro-genetic disorders, accessible to researchers globally. To achieve this Pūnaha Io partnered with an established biobanking facility, Te Ira Kāwai, and The Neurological Foundation Human Brain Bank. Sample collection, storage, and governance is according to procedures that incorporate Tikanga Māori and acknowledge Te Tiriti o Waitangi.

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		The Registry population comprises paediatric and adult patients with muscular dystrophies (n = 346), spinal muscular atrophies (n = 78), hereditary neuropathies (n = 188), congenital myopathies, myasthenias, myotonic syndromes (n = 238), metabolic myopathies, inflammatory myopathies; and also CNS diseases such as Huntington's disease (n = 220), inherited ataxias (n = 136), inherited movement disorders, and hereditary spastic paraparesis (n = 40). To date, samples from participants with Huntington's, Friedreich's, spinocerebellar ataxias as well as SMA and DM1 have been banked. Pūnaha Io has recruited participants for eight clinical trials and three observational studies with more studies on the horizon. New Zealanders with neurogenetic disorders are now being involved in translational research. We invite researchers to access banked samples or discuss future projects.
Emily Galea	National Muscle Disease Bio-databank (NMDB)	In 2021, a national network of clinicians, scientists and patient advocacy groups joined forces to improve outcomes of patients with congenital muscle diseases (including dystrophies and myopathies). Enabled by a grant from the Medical Research Future Fund (MRFF), the team have developed a national functional diagnostic program that aims to establish an individual treatment pipeline for children with congenital muscle diseases in Australia. As part of this project, The National Muscle Disease Biobank (NMDB) was established. The NMDB will consist of a collection of donated biological samples (including blood, skin and muscle tissue) and clinical data from patients diagnosed with a genetic muscle disease. National ethics approval has been obtained through the Royal Children's Hospital (RCH) Human Research Ethics Committee (HREC #90530) and site-specific approvals (SSA) are currently underway for children's hospitals in Queensland, New South Wales and South Australia. Once consented, patient clinical data (collected from medical records) and biological samples are stored in a secure database and biorepository freezers in PC2 accredited laboratories at the Murdoch Children's Research Institute biobank facility. The data and samples stored within the biobank can then be used for ethically approved research following approval of projects by the NMDB Scientific Advisory Board. The NMDB aims to develop a high-quality bio-databank with well-annotated clinical data and biological samples from patients with genetic muscle diseases. This national collaboration between clinicians, researchers, and patient advocacy groups will facilitate research aimed at improving our understand of disease aetiology and aid in the development of new personalised therapies for patients with genetic muscle diseases.
Miranda D. Grounds	Oxidised albumin levels in plasma and skeletal muscle, as a biomarker of muscle necrosis and inflammation, to measure treatment efficacy in DMD.	There is an urgent need for robust blood biomarkers to rapidly measure the capacity of therapies to protect muscle necrosis in clinical trials with DMD boys. Our recent data strongly support the use of plasma albumin thiol oxidation, for cysteine 34 (Cys34), as a validated simple biomarker to track active myonecrosis in DMD. Redox modifications to Cys34, have been investigated in the mdx mouse model and shown to be an accurate biomarker of disease progression and treatment efficacy associated with muscle necrosis (the central problem in DMD), closely associated with inflammation and increased oxidative stress. We have visualised high levels of various oxidised molecules localised

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		specifically in foci of necrotic mdx muscles, with associated high levels of neutrophils and macrophages that generate highly reactive oxygen species. In turn this high oxidation in the damaged dystrophic muscles (throughout the body) result in albumin in the interstitial fluid circulating throughout muscles, to result in high levels of oxidised Cys34 in plasma. A range of experiments that reduce or increase necrosis, track with appropriate levels of this blood biomarker. We have demonstrated this is highly responsive in human studies of exercise, and in archived plasma of DMD boys. Plus we developed a convenient 'blood collection device' for finger or ear blood drop collection, that can be stored at room temperature and mailed for rapid protein analysis. These data strongly support the use of plasma albumin thiol oxidation Cys34 as a biomarker for wide use to track active myonecrosis in DMD.
Frances Evesson	PYROXD1 myopathy update: from phenotypic expansion to therapy development	Recessive variants in the oxidoreductase enzyme PYROXD1 are associated with both a congenital myopathy and an adult onset limb girdle muscular dystrophy with muscle weakness, significant respiratory and feeding difficulties and nasal speech. However, with only ~30 patients with PYROXD1 myopathy currently known world-wide, it is likely many individuals are yet to be genetically diagnosed. Our group has recently identified a subset of individuals with atypical PYROXD1 myopathy who have connective tissue features including osteopenia and blue sclera in addition to their skeletal muscle involvement, thus expanding the known phenotype associated with PYROXD1 variants. We believe this may warrant consideration of PYROXD1 variants in broader patient cohorts. In the lab, our group is focussed on defining the pathobiology of PYROXD1 myopathy using cell and mouse models. We have created the first Pyroxd1 mouse model homozygous for the recurrent patient variant, p.N155S found on at least one allele in 80% of individuals with PYROXD1 myopathy. *Pyroxd1*$_{N155S}$ mice accurately phenocopy the human myopathy with skeletal muscle atrophy and significant bone and skeletal muscle pathology. *Pyroxd1*$_{N155S}$ mice are significantly smaller than wild-type controls and ex vivo contractile studies show *Pyroxd1*$_{N155S}$ mice are functionally weaker than wild type controls. Proteomics provides further evidence that the cell essential roles of PYROXD1 involve multiple important cellular pathways including mitochondrial function and protein synthesis. Our ongoing work is focussed on pursuing novel therapeutic options including the effect of PYROXD1 replacement and voluntary exercise on disease progression in *Pyroxd1*$_{N155S}$ mice.
Molly Reynolds	An Audit of Advanced Care Planning in an Australian Tertiary Hospital Adult Neuromuscular Outpatient Clinic	There is limited evidence to direct the process of advanced care planning in the adult neuromuscular clinic, for conditions other than amyotrophic lateral sclerosis. In the paediatric literature, there are efforts to find evidence based processes to ensure the physical and emotional wellbeing of patients. 1 As the treatment paradigm shifts for our adult cohort, there is a need for evidence to guide the best pathway to advanced care planning in neuromuscular disease. We report the results of a retrospective review of the current experience in an Australian tertiary hospital outpatient clinic. During study

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		period of four months, over 150 patients were seen with a diverse range of conditions including Myotonic Dystrophy, Duchenne Muscular Dystrophy, Facioscapulohumeral Muscular Dystrophy, Spinal Muscular Atrophy, Charcot-Marie Tooth and Spinocerebellar Ataxia. There was a scarcity of documented advanced care plans and the planning experiences for those patients with existing documentation varied. Amongst those with documented advanced care plans there was a lack of consistent indicators for initiating this process. As a result of this review, intervention and follow up study is planned following formation of an indicator tool to address the need for a uniform holistic approach to advanced care planning in the adult neuromuscular cohort.
Peter Houweling	Developing pre-clinical models of childhood onset FSHD	FSHD typically presents in the second or third decades of life. The presentation of symptoms in early childhood is less common and thought to correlate with a more rapid disease progression. Early-onset FSHD is typically classified as the presence of symptoms before 10 years of age and while less is known about the factors that impact disease progression and severity in children, improved diagnostics is resulting in an increase in recognized cases of childhood-onset FSHD. At the Murdoch Children's Research Institute (MCRI) we are in the third year of a childhood onset FSHD longitudinal outcome study (iFSHD-LOS) involving the collection of clinical natural history data (including functional and patient reported outcome measures and whole-body MRI) and the collection of biological samples (blood and saliva) for research. The biobanking of patient blood has enable us to generate patient specific induced pluripotent stem cell (iPSC) lines from children with FSHD to improve disease modelling and aid in the identification of novel therapeutics. The ultimate goal of this project is to understand the disease trajectory of FSHD in childhood and establish the laboratory-based tools needed for ongoing research into childhood onset FSHD. This program aims to link laboratory-based research with patient management to aid in the identification of new pathways to treat patients with FSHD.
Ian Woodcock	Lower body muscle MRI shows annual progression of fat fraction in Australian children with FSHD.	Paediatric FSHD is a rare genetic muscle disease caused by the aberrant expression of DUX4. MRI is a biomarker for disease severity previously found to correlate well with disease specific functional severity measures. Paediatric FSHD is an area of unmet need and focus for international collaborative efforts to establish better disease measures in the search for a disease modifying therapy. Participating children were recruited from neuromuscular clinics across Australia into the iFSHD-LOS, a single-site natural history study performed at the Royal Children's Hospital, Melbourne. In this study, lower body MRI data was retrospectively analysed by Springbok Analytics artificial intelligence platform to determine fat fraction at the individual muscle level in 70 lower limb muscles. Data was quantitatively expressed to examine patterns of disease progression over time and to correlate changes seen on MRI with disease severity as measured using established and emerging clinical measures. To date lower body muscle MRI taken twelve months apart have been analysed for 15 participants. Preliminary results show there is a mean increase in the average fat fraction across all lower limb muscles of 1.5% (range -1.4% to 5.7% increase) over twelve months,

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		with individual muscle results forthcoming. Further planned analysis addition of upper body muscle analysis, and detailed integration of paediatric normative growth models as covariates for assessing MRI biomarkers and functional results.
Katy de Valle	Early-onset FSHD natural history and pre-clinical research pipeline at Melbourne Children's Campus	FSHD is a genetically complex neuromuscular disorder that typically presents in the second or third decades of life. The manifestation of symptoms in early childhood is less common and thought to correlate with greater symptom severity and more rapid disease progression. Early-onset FSHD is rare and less is known about disease natural history or factors that may impact disease severity and progression. The Royal Children's Hospital (RCH) and Murdoch Children's Research Institute (MCRI) are in the third year of a childhood onset FSHD longitudinal outcome study (iFSHD-LOS) involving the collection of biological samples (blood and saliva), functional and patient reported outcome measures and whole-body MRI. This project involves three pillars of work 1) the clinical / MRI assessment and longitudinal analysis of children with early-onset FSHD, 2) biobanking of patient material (saliva, blood and induced pluripotent stem cell (iPSC) lines) for current and future research initiatives and 3) analysis of the role that other biological or environmental factors play in FSH disease mechanism and outcomes. The ultimate goal of this project is to understand the disease trajectory and the impact of development and childhood growth, validate existing outcome measures, and develop a framework for laboratory-based pre-clinical drug testing to facilitate wholistic patient management and research into childhood onset FSHD.
Ian Woodcock	Methylation analyses of Australian Children with FSHD	Paediatric FSHD is a rare genetic disease caused by the aberrant expression of DUX4 because of a hypomethylated D4Z4 area at the telomeric end of chromosome 4. Hypomethylation of the D4Z4 region is a surrogate marker of DUX4 expression, can be diagnostic of FSHD and may correlate with disease severity. Participants in the iFSHD-LOS natural history study run at the Royal Children's Hospital in Melbourne Australia had saliva samples sent to the Jones Lab at the University of Nevada, Reno. The relevant methylation status for each sample was determined using targeted bisulfite sequencing of the distal 4qA or 4qAL D4Z4 repeat unit and data was analyzed using the D4Z4caster program. In addition, the relevant methylation status of all internal D4Z4 repeat units was similarly assessed to determine the presence of epigenetic modifiers of the region. The percent methylation was low in the first quartile (Q1) of the distal 4qA repeat unit in all 21 participants with a range of 0-23.8%, in keeping with the established level of <26% being diagnostic of FSHD1. Of this early onset cohort, 11 (52%) had undetectable methylation at Q1. Hypomethylation in Q1 showed strong correlation with parent-reported age of symptom onset (r=0.61). The data from the Australian paediatric cohort shows that measurement of D4Z4 hypomethylation can be used to diagnose FSHD. Further studies with larger cohorts are required to establish if hypomethylation could be used to predict rapidity of disease progression.
Katy de Valle	Preparing for clinical trials in childhood-onset FSHD – the MOVE Peds protocol	Background: Early onset of symptoms in paediatric FSHD is part of a disease continuum which can occur across the lifespan of affected individuals. Clinical trial preparations demand the mapping of disease trajectory and availability of robust and responsive outcome measures and biomarkers to evaluate efficacy. Understanding the disease

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		trajectory of paediatric onset FSHD represents an area of unmet need and the focus of international collaboration to establish better outcome measures. A recently developed disease-specific measure, the FSHD-Composite Outcome Measure has been adapted for use in children with early studies suggesting good reliability and validity. The Reachable Workspace is currently the primary outcome measure in a phase three clinical trial in adults with FSHD and has recently been used in a small single site study at the Royal Children's Hospital, Melbourne. Magnetic Resonance Imaging is a biomarker for disease severity previously found to correlate well with disease specific functional measures. Aims and Methods: Following on from two small Dutch and Australian natural history studies, the authors aim to recruit eighty children with FSHD across eight sites in the USA and Australia to assess clinical trial utility of novel outcome measures in children to ready the paediatric population for clinical trials. Participant's functional capacity, disease severity and whole-body muscle MRI biomarkers will be evaluated at baseline, 6, 12 and 24 months. Conclusion: Following successful application to the NIH to fund this clinical trial preparedness study, we aim to start recruiting throughout Australia and across US sites before the end of 2024.
Aicee Dawn Calma	Cerebral Venous Sinus Thrombosis after Intrathecal administration of Nusinersen	We report a case of a 42 year old female presenting with 48 hours of persistent headache following intrathecal administration of nusinersen for Spinal Muscular Atrophy (SMA Type 3). There were no focal neurological signs or symptoms outside from baseline symmetrical proximal limb weakness attributed to SMA. Initial investigations revealed radiological evidence of an acute cerebral venous sinus thrombus (CVST). The patient was promptly started on anticoagulation. Partial recanalization was seen as soon as 48 hours after commencement of anticoagulation, with almost full resolution of the thrombus at follow up in 2 months. Awareness of CVST as a potential complication of intrathecal therapies and dural punctures allows for early identification, management, and prevention of serious neurological consequences.
Douglas Sproule	***FORTIFY: a Phase 3 study to evaluate safety, tolerability, and efficacy of BBP-418 in LGMD2I/R9***	***Introduction: Limb-Girdle Muscular Dystrophy type 2I (LGMD2I/R9) is caused by bi-allelic partial loss-of-function of the fukutin-related protein (FKRP) gene, resulting in ypoglycosylation of alpha-dystroglycan (αDG) and progressive muscle damage in skeletal muscle. Alongside the skeletal myopathy resulting in progressive extremity weakness, symptomatic respiratory weakness and left ventricular dysfunction may develop and can be major causes of morbidity and mortality in LGMD2I/R9.*** ***BBP-418 is an investigational oral substrate supplementation intended to saturate the partially functional FKRP enzyme, intending to drive increased glycosylation of αDG, and potentially stabilizing orimproving muscle integrity.*** ***Methods: FORTIFY (NCT05775848) is a Phase 3 multinational, multicenter, double-blind placebo-controlled study enrolling ~81 individuals with genetically confirmed LGMD2I/R9, aged 12 to 60 years in US, UK and Australia and 18 to 60 years in EU. Individuals will be randomized in a 2:1 ratio to receive oral BBP-418 or placebo, respectively.***

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		The primary endpoint will be change in NSAD from baseline in BBP-418-treated individuals relative to placebo at 36 months. Secondary endpoints evaluated will include FVC, PUL 2.0, and ambulatory measures (100mTT and 10mWT). Troponin I, electrocardiograms, and Echocardiograms will be obtained to assess progression of cardiomyopathy. The effect of BBP-418 treatment on glycosylated αDG, the hallmark of disease at the molecular level, will be investigated at 12 months with potential to use glycosylated αDG as a surrogate endpoint in LGMD2I/R9.
Leonit Kiriaev	Understanding dysferlin-deficient mice: Outcome measures for pre-clinical therapeutic strategies	Dysferlinopathies encompass limb girdle muscular dystrophies stemming from the loss of the dysferlin gene, which leads to progressive muscle weakness. Therapeutic options for dysferlinopathies remain limited, necessitating a deeper understanding of disease mechanisms to aid in the identification of potential novel interventions. In this study, 13-month-old dysferlin-deficient (dysf-/-) BLAJ mice and matched wild-type C57BL/6J healthy control mice (AEC approved A946), provided by the Jain foundation, were used to investigate disease pathology. Our experimental approach included functional analyses for grip strength and ex vivo muscle physiology of the extensor digitorum longus (EDL) and soleus muscles to determine the impact on dysferlin deficiency on muscle function. Outcome measures encompassed hindlimb muscle function, bodyweight, muscle mass, grip strength and immune cell profiling and infiltration in quadriceps (QUAD) muscles. 13-month-old female BLAJ mice exhibited decreased bodyweight (12%) and grip strength (14%), increased immune cell infiltration (F4/80 & CD8) in QUAD muscles, and decreased muscle mass in gastrocnemius (20.3%), quadriceps (27.4%), and psoas (31%), contrasted with increased soleus mass (18%). Interestingly, EDL muscle physiology showed no differences between genotypes and soleus muscles demonstrated enhanced fatigue resistance and recovery in BLAJ mice compared to controls. Histological analysis also revealed elevated perilipin deposition and increased fibrosis in QUAD muscles. In conclusion, our study provides comprehensive insights into dysferlin-deficient mice, elucidating critical aspects of disease pathophysiology and highlight the need for further analysis of muscle function measures to aid in identifying potential novel therapeutic targets.
Jane Seto	ACTN3 genotype influences androgen response in skeletal muscle	Androgens are vital for the maintenance of muscle mass and their anabolic effects are primarily exerted through the androgen receptor (AR). Accumulating evidence in humans and mice suggests that circulating androgens, AR and androgen response are influenced by ACTN3 (α-actinin-3), also known as “the gene for speed”. One in 5 people worldwide are α-actinin-3 deficient due to homozygous inheritance of a common null polymorphism (577X) in ACTN3. In this study, we show that α-actinin-3 deficiency decreases baseline AR in skeletal muscles of mice and humans, in both males and females, and that AR expression directly correlates with ACTN3 in a dosage dependent manner. We further demonstrate in Actn3 knockout mice that α-actinin-3 deficiency increases muscle wasting induced by androgen deprivation and reduces the muscle hypertrophic response to dihydrotestosterone and this is mediated by differential activation of pathways regulating amino acid metabolism, intracellular transport, MAPK signalling, autophagy, mitochondrial activity and calcineurin signalling. Geneset enrichment and protein analyses indicate that the absence of α-actinin-3 results in a failure to coactivate many of these pathways in response to changes in androgens and relies on leveraging mitochondrial remodelling and calcineurin signalling to restore muscle homeostasis. We further identified 7 genes that are androgen sensitive and α-actinin-3-dependent in expression, and whose functions correspond to these processes. Our results highlight the pivotal role of α-actinin-3 in various

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		processes associated with the regulation of protein turnover and muscle mass, and suggest that ACTN3 genotype is a genetic modifier of androgen action in skeletal muscle.
Sophie Manoy	BASELINE CONTINUOUS GLUCOSE MONITORING IN CHILDREN DIAGNOSED WITH SPINAL MUSCULAR ATROPHY IN INFANCY ON DISEASE-MODIFYING THERAPIES	Background: Children with disease-modified spinal muscular atrophy (SMA) on medical treatment are at risk of hypoglycaemia (BSL <2.6 mmol/L) due to several factors including low muscle mass and reduced hepatic glycogen stores. This is further exacerbated by malnutrition, low weight and progressive bulbar impairment as children with SMA have longer life expectancies and improved motor progress on treatment. Aim: The primary objective of this study is to determine if baseline hypoglycaemia is present in children with disease-modified SMA when well. The secondary objectives are to assess for the highest risk times, evaluate the impact of standard diet and review previous fasting tolerances for this cohort of children. Methods: We will perform a prospective study of 10 children with disease-modified SMA assessing for baseline hypoglycaemia using continuous glucose monitoring with a FreeStyle Libre 2 Glucose Monitoring Sensor and evaluate with a manual dietary record over a 7 day period. Results: Results will be available by the time of the meeting. Conclusion: Children with disease-modified SMA are at risk of hypoglycaemia and we aim to evaluate this using continuous glucose monitoring and manual dietary records over a 7 day period. Future research areas include assessment of this cohort of children when unwell to further evaluate high risk periods for hypoglycaemia.
Avnika Ruparelia	Dissecting the genetic basis of, mechanisms in, and therapies for muscle diseases using zebrafish	Zebrafish are an incredible model for neuromuscular disease research. Their prolific reproductive capabilities, conservation in muscle structure, optical clarity of embryos, along with ease with which genetic manipulation can be performed, has enabled successful modelling of human muscle disease in zebrafish. Using these unique advantages of the zebrafish model, we are interrogating the genetic basis of, disease mechanisms in, and therapies for muscle disorders. We will present two examples of how we have used zebrafish for muscle disease research. We will present data on how zebrafish can be utilised as a model to rapidly determine the pathogenicity of variants of uncertain significance in genes that are known to cause muscle disease. Further to that, we will present data on how utilising the zebrafish model for basic muscle biology research can shed light into identifying novel mechanisms and therapies for muscle diseases using Duchenne muscular dystrophy as an example.
Harmony Clayton	BIONANO OPTICAL GENOMIC MAPPING FOR FSHD1 MOLECULAR DIAGNOSIS	Background: Facioscapulohumeral muscular dystrophy (FSHD) is a common neuromuscular disease mainly affecting the face, shoulder girdle and upper arms. FSHD typically presents in adolescence and is predominantly caused by contraction of the Chr4 D4Z4 repeat array on a 4qA haplotype (FSHD1). Southern blot is the standard diagnostic test for FSHD1 and sizes the contraction, but the technical requirements and labour-intensive nature of this method mean that molecular diagnosis for FSHD is not readily available in Australia. Aim: We aimed to validate Bionano optical genomic mapping (OGM) for FSHD1 diagnostic testing in Australia. Methods: We obtained blood samples from 18 individuals from 11 families and extracted ultra-high molecular weight DNA using the Bionano DNA extraction kit. DNA was fluorescently labelled, counterstained to label the DNA backbone, loaded onto a nanochannel chip and imaged on the Bionano Saphyr instrument. Data were analysed using the automated Bionano EnFocus FSHD analysis pipeline. Results: The Bionano OGM FSHD1 test was found to be highly reproducible and robust, and showed 100% concordance with the results of Southern blot testing. The new test showed superior performance in terms of

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		precision of D4Z4 repeat size estimation, determination of haplotype, establishment of the chromosomal location of array, detection of somatic mosaicism, turnaround time, and simplicity. Conclusion: We have validated Bionano OGM for FSHD1 diagnostic testing. The reduced turnaround time and more informative molecular results will be of indisputable benefit to clinicians and their patients, leading to faster and more confident FSHD diagnoses nationwide.
Fatwa Adikusuma.	Efficient Single-AAV Delivery of CRISPR Therapy for Duchenne Muscular Dystrophy with Exon-50 Deletion	Duchenne muscular dystrophy (DMD) remains a devastating disease lacking effective treatment options. However, the advent of CRISPR technology offers a promising therapeutic avenue, particularly through DNA cleavage approaches aimed at restoring the reading frame of the disease-causing allele, a process known as "reframing." Here, we introduce REMAX (Reframing to the Max), an innovative strategy designed to enhance the efficiency of reframing in DMD treatment. REMAX employs dual-cut CRISPR cleavage, strategically positioning cuts to support efficient reframing via exon skipping and indel reframing mechanisms. We screened Cas variants and gRNAs targeting human DMD exon-51, utilizing immortalized myoblast cells from a DMD patient with exon 48-50 deletion. Transfection of CRISPR constructs revealed high genomic editing efficiency, up to 90%. Following the treatment, we observed abundant exon-51 skipping in transcripts and robust dystrophin restoration in patient-derived myoblast cells. To validate these findings in vivo, we developed a novel humanized DMD knockout transgenic mouse model harboring a full-length single-copy of the human DMD transgene with exon-50 deletion (hDMD-Ex50del). Leveraging SaCas9 due to its smaller size, allowing for the packaging of all components, including dual gRNAs, into a single AAV vector, we injected the CRISPR AAV into neonatal hDMD-Ex50del mice. Treated mice exhibited significant dystrophin restoration, with over 90% of muscle fibers positive for dystrophin, leading to improved muscle function as demonstrated by grip strength analysis. Our CRISPR candidates, coupled with single-AAV delivery, present a promising therapeutic approach for DMD patients with mutations involving exon-50 deletion.
Angus Lindsay	Stress exacerbates glucose intolerance in the mdx mouse model of Duchenne Muscular Dystrophy	Loss of brain-specific dystrophin has been implicated in the heightened predisposition of patients and vertebrate models of Duchenne muscular dystrophy (DMD) to stressful stimuli. Using 18F-fluorodeoxyglucose uptake by positron emission tomography (18FDG PET) to assess metabolic tissue activity, we measured decreased 18FDG uptake in most brain regions and marginally increased uptake in skeletal muscle of wildtype mice following stress. By contrast, 18FDG uptake did not change in brain and decreased in striated muscle in the mdx mouse model of DMD in response to stress, suggesting dysfunctional glucose-insulin signalling. Glucose intolerance in mdx mice was exacerbated by stress and driven not by an insensitivity to insulin, but by an inability to synthesize insulin. Exogenous administration of naked insulin mitigated immediate stress-induced physical inactivity (indirect measure of stress sensitivity), lowered 18FDG uptake in brain and normalised 18FDG uptake in striated muscle of mdx mice in response to stress. These data indicate that during stress, dystrophin-deficiency impairs the ability of brain and striated muscle to respond metabolically appropriately. It also suggests that the hypersensitive stress phenotype of mdx mice is associated with dysfunctional glucose-insulin signalling that can be mitigated with exogenous insulin.
Dr Archana Chacko	DIFFERENTIAL RESPIRATORY FUNCTION RESPONSE IN PAEDIATRIC SPINAL MUSCULAR ATROPHY TYPES 2	Aim: To establish whether the initial positive effect of nusinersen (NUS) on respiratory outcomes was maintained in children with Spinal Muscular Atrophy (SMA) type 2 and to further define the effect on children with type 3 treated over 3 years.

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	AND 3 TREATED WITH NUSINERSEN OVER 3 YEARS.	Methods: A prospective observational study of children with type 2 and 3 beginning NUS in Queensland, Australia between June 2018 – December 2020. Investigations conducted included age-appropriate lung function and polysomnography. Lung function data for two-years preceding NUS initiation was retrospectively collected. Change in lung function/polysomnography was assessed using mixed effects linear regression. Results: 24 of 38 children with type 2/3 (14 males; 0.4-17.3 years) were included (type 2 n=12; type 3 n=12). No child with type 2/3 had respiratory-related admissions pre-/post-NUS. For type 2, annual decline in FVC z-score pre-treatment was -0.76 (95% CI: -1.14, -0.39, p<0.001), post was -0.20 ([95% CI: -0.33, -0.06, p=0.01] difference p=0.008). For type 3 ongoing decline was seen: pre-NUS and post FVC z-scores -0.20 (95% CI:-1.00, 0.61, p=0.054) and -0.17 (95% CI:-0.88, 0.53, p=0.57) respectively (difference p=0.96). Mean change in total apnoea-hypopnoea indices (total AHI) in type 2 tended to reduce -1.75 (95% CI: -4.95-0.9, p=0.24); type 3 appeared to remain stable (-0.39 [95% CI: -1.1-0.33, p=0.28). A child with type 2 ceased NIVdue to normalisation of total AHI. Conclusion: Nusinersen stabilised lung function (FVC-z-scores) and tended to improve total AHI for up to 3 years in type 2, but the long-term effects in type 3 are less clear.
Dr Archana Chacko	Respiratory outcomes of nusinersen and risdiplam treatment in children with Spinal Muscular Atrophy	Spinal Muscular Atrophy (SMA) is a rare genetic disorder that causes lower motor neuron weakness, with some types associated with poor prognosis. All available disease modifying treatments (DMTs) in SMA have been shown to improve survival and peripheral motor function. However there is limited literature pertaining to the respiratory effects. A prospective study by Chacko et al. (2023) demonstrated that 12 months post-treatment, nusinersen (NUS) had slowed respiratory function decline as determined by spirometry and polysomnography parameters. There are no comparative studies of DMT, such research would be difficult given the rarity of SMA. The aim of this study was to present real-world experience of NUS/Risdiplam (RIS) treatment. This is a report of real-world polysomnography and spirometry findings of 12 children with SMA commenced on NUS, and later changed to RIS. Participants tended to have increases in apnoea-hypopnoea indices (AHI) and decline in Forced Vital Capacity z-score (FVC z-score). This report raises the possible decline in respiratory/sleep parameters following treatment changes. Postulated reasons for decline include: 1. Mechanism of action of RIS is still debated; 2. Timing of RIS commencement too late; 3. Treatment effectiveness may vary between DMTs in specific cohorts or overall. Further DMT comparative studies need to be undertaken to better understand efficacy of each treatment and which cohorts may receive the most benefit from available DMT.
Sarah Mollet	Balance and Coordination in Myotonic Dystrophy Type 1	Myotonic Dystrophy Type 1 (DM1) is an autosomal dominant multisystem disorder that causes progressive disability and shortened life expectancy. Falls are 10 times more common in DM1 than in aged matched healthy volunteers. This has been attributed to muscle weakness but more recently attention has turned to other aspects of balance including proprioception, vestibular dysfunction, and cerebellar ataxia. The aim of this study is to assess patients with DM1 for balance problems and to analyse how much impairment of the different components of balance; strength, vision, proprioception, vestibular function, and cerebellar coordination, contribute to this dysfunction. Twenty participants from 18 to 70 with confirmed DM1, who can walk 10m without a walking aid will be recruited. This is a local extension of the international END-DM1 natural history study and the analysis will include demographic, health, strength, functional tests, and patient reported outcome measures from that study.

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		Visual acuity, modified Inflammatory Sensory Sumscore (mISS) which includes an assessment of proprioception, and Scale for Assessment and Rating of Ataxia (SARA) will be assessed by a trained physiotherapist. In addition, postural sway under different conditions in standing (eyes open and closed; with and without proprioceptive deprivation) and walking (with and without head turning) will be assessed using the Gait and Balance App. An audiologist will assess tympanometry, 3D video Head Impulse Test (vHIT), Vestibular-Evoked Myogenic PotentialS (VEMPS), oculomotor (smooth pursuit and tracking traces) and caloric test. We hypothesise that
Vanessa Crossman	Using induced pluripotent stem cell derived skeletal muscle to model ACTA1 nemaline myopathy	Introduction Nemaline myopathy (NM) is a group of genetic skeletal muscle diseases which vary in both genetic cause and clinical presentation. Common clinical features include muscle weakness and hypotonia affecting the face, neck, and proximal muscles. Many severe early-onset cases of NM are caused by mutations in the skeletal α-actin gene, ACTA1, which accounts for ~26% of all NM cases. Currently there are no effective treatments available for NM. To better understand NM disease mechanisms, we generated an induced pluripotent stem cell (iPSC) line with matched gene corrected (isogenic) control from a 6-year-old with severe ACTA1 NM (p.Gly148Asp). Methods iPSCs were generated by the MCRI's iPSC Derivation and Gene Editing Facility. Both the patient line and isogenic control were differentiated to myogenic progenitors and fused to form myotubes in monolayer culture conditions. Patient and corrected myotubes also underwent electric pulse stimulation (EPS) to mimic muscle contractions. At five days post fusion, myotubes were collected to investigate disease specific changes. Results Bulk RNAseq revealed differences in gene ontology terms related to actin filament formation and muscle contraction. 24 hours after the EPS protocol, myotube hypertrophy was observed in the isogenic control line but not in the patient line. Together, these suggest a defect in muscle contractility like that seen in NM patients. Conclusion These data suggest that ACTA1 nemaline myopathy can be successfully modelled in vitro using skeletal muscle derived from iPSCs. This analysis lays the groundwork to investigate targeted therapies for patients with NM and other congenital myopathies.
Amanda Griffiths	Evaluation of a transition model of care for adolescents on home respiratory support: description of a cohort	Introduction/Aim: Transition of adolescents with chronic health conditions to adult care requires early, considered planning to support medical, psychosocial, educational and vocational needs. This project aimed to evaluate a transition program for adolescents on respiratory support established in 2014 between our paediatric and adult centres. Methods: Adolescents on respiratory support and their carers were invited to participate in a 20-minute survey at their final combined paediatric and adult transition clinic, which included questions about their experience of transition care. Demographic and clinical information was also collected from the EMR at that time. Results: Thirty adolescents on respiratory support transitioned to adult care between September 2021 and November 2023. Most participants (18, 60%) had a primary diagnosis of neuromuscular disease, whilst genetic syndromes, complex

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		upper airway obstruction and cerebral palsy made up the remainder. Sixteen patients had a co-morbid developmental or mental health disorder. Eighteen (60%) had been admitted 1 to 3 times in the 24 months prior to transfer, with 77.5% elective admissions. Ventilation modes were bilevel (16, 53.3%), CPAP (6, 20%), invasive ventilation (1) & no respiratory support (7). Twenty-one patients were on nocturnal support, 1 patient was 24-hour dependent and 1 patient used diurnal support. Survey results completed by 10 adolescents and 13 carers (60% of families) showed 90% satisfaction with the program. Conclusion: A tailored program which includes preparatory support and combined paediatric and adult healthcare systems is essential to transition patients with complex needs, such as those on respiratory support. Our program will undergo quality improvement after this evaluation is complete. Grant Support: Nil
Monica Marzouk	Prevalence of self and parent reported tiredness in children and adolescents with Charcot Marie Tooth disease	Introduction: Charcot-Marie-Tooth (CMT) disease is among the most common inherited neurological disorders. Previous investigations suggest that fatigue and diminished quality of life are more frequent among children with CMT compared to unaffected peers. However, the prevalence of fatigue in paediatric CMT has not been investigated. This study aims to determine the prevalence of tiredness, as a proxy of fatigue, in paediatric CMT. Methods The international Inherited Neuropathy Consortium has assessed children aged 3-18 years across 9 sites in 3 countries using the Pediatric Charcot-Marie-Tooth Quality of life (pCMT-QOL) instrument and parent proxy versions. Results of three questions: 'I feel tired even with little activity'; 'I cannot do things I want to because I am tired'; 'I tire out faster than others during physical activity' were analysed. Results Results from 647 participants (10± 4 years, 57% male) and/or their parents were included in this study. Over 50% of children aged 8-18 and their parents reported that they feel tired even with little activity. >35% of parents reported that their children (3-7 years and 8-18 years) cannot do the things they want to because they are tired. Over 75% of parents reported that their child (3-18 years) tires out faster than others during physical activity. Conclusion These findings demonstrate that tiredness is prevalent in children with CMT as young as 3 years. Future research investigating onset, progression and consequences of fatigue in children and adolescents with CMT is essential to further understand fatigue and evaluate the benefit of interventions that manage fatigue.
Joshua Clayton	Comprehensive collation and analysis of variants in the skeletal muscle α-actin (ACTA1) gene	The ACTA1 gene encodes skeletal muscle alpha-actin, which forms the core of the sarcomeric thin filament in adult skeletal muscle. ACTA1 is one of six very highly conserved actin proteins that have all been associated with human disease. The first 15 pathogenic variants in ACTA1 were reported in the year 1999, which expanded to 177 by 2009. Such variants cause a range of congenital myopathies, including nemaline myopathy (NEM) and congenital fibre type disproportion (CFTD). Several ACTA1 variants also cause cardiomyopathy. As part of a '2023 mutation update' we collated the 607 ACTA1 variants reported in LOVD, HGMD, and/or ClinVar, which includes 343 reported pathogenic/likely pathogenic (P/LP) variants. We reviewed these against ACMG guidelines and provided suggestions

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		as to how ACMG criteria should be used to classify ACTA1 variants. This included analysis of all P/LP missense changes in other human actins to assess which amino acid residues are most insensitive to change. From a clinical perspective, we reviewed the breadth of phenotypes associated with ACTA1 variants, which has now grown to twenty. The vast majority (74%) cause nemaline myopathy, but there are increasing numbers that cause cardiomyopathy and novel phenotypes such as distal myopathy. Overall, our findings and analyses provide a useful resource for interpretation of ACTA1 variant reports and diagnosis of neuromuscular disease patients.
Katie O'Brien	A systematic review describing nutrition outcomes of disease modifying therapies in spinal muscular atrophy.	Background The nutritional implications of spinal muscular atrophy (SMA) are profound. Disease modifying therapies (DMT) have improved clinical outcomes. This systematic review describes the impact of DMT on nutrition outcomes. Methods A systematic search strategy was applied across seven databases until May 2023. Eligible studies measured nutrition outcomes in individuals with SMA on DMT (nusinersen, risdiplam or onasemnogene abeparvovec [OA]) compared to untreated comparators. Nutrition outcomes included anthropometry, feeding route, swallowing dysfunction, dietary intake, dietetic intervention, nutritional biochemistry, metabolism, gastrointestinal issues and energy expenditure. Articles retrieved were screened in duplicate, data were extracted and appraised systematically. Results Sixty-three articles from 54 studies were included; 41% (n = 22) investigated nusinersen in paediatric participants with SMA type 1. Anthropometry (n = 18), feeding route (n = 39) and swallowing dysfunction (n = 18) were the most commonly reported outcomes. In combined paediatric and adult cohorts, BMI z-score remained stable post nusinersen therapy. The proportion of children with SMA requiring enteral nutrition was stable post nusinersen therapy. Ability to thrive at age 1.5 years was higher in children treated in early infancy with OA compared to historical controls. Significant heterogeneity existed across participant characteristics and outcome measures. Conclusion Nusinersen may prevent deterioration in some nutrition outcomes; OA in early infancy may be associated with improved nutrition outcomes. Timing of DMT initiation is an important consideration for future nutrition research. Studies investigating nutrition as a primary outcome of DMT, using consistent outcome measures are required to tailor nutritional management strategies for this cohort.
Rachel Kennedy	Implementation of Physical Activity and Exercise for Children and Young People Living with Neuromuscular Disease: A Churchill Fellowship	Background: Children and young people living with neuromuscular disease are less physically active than their peers. There is good evidence that physical activity and exercise can slow or ameliorate disease progression. In Australia, knowledge of the benefits of physical activity and exercise is limited and old (disproved) beliefs that exercise is harmful remain. The aim of this fellowship was to explore exercise and physical activity programs for neuromuscular disorders. Method: An international travel fellowship to visit centres of neuromuscular and exercise expertise. Information was gathered during semi-structured interviews, clinical and research observation. Results: Thirteen centres were visited across five countries (UK, Denmark, Netherlands, USA and Canada). Thirty-seven interviews were conducted, recorded, transcribed and content analysed. Seven clinics and eight research assessments were observed, five group presentations were made and a conference poster presented (World Muscle Society, 2023).

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		Key themes emerged: • Any movement is good and inactivity is detrimental • Fatigue and fatigability in the context of neuromuscular disorders • Measuring physical activity • Types of physical activity and exercise programs • Self-efficacy, self-management, empowering patients • Embedding research in clinical care and clinicians in research • Disseminating knowledge and expertise from specialist centres to community health professionals • The problem with guidelines, uptake and implementation of recommendations. Conclusion: Physical activity and exercise are an important adjuvant in the management of neuromuscular disease irrespective of age or ability. Individual preferences need to be considered and programs tailored, meaningful, functional and FUN! Twelve recommendations are set out in the full report, including a dissemination and implementation plan.
Kayla M.D. Cornett	ClinicalOutcomeMeasures.org: Implementing a web-based training and quality assurance program for standardising the evaluation of CMT trial endpoints	Introduction Reliable, sensitive and responsive clinical outcome assessments (COAs) exist for patients with Charcot-Marie-Tooth disease and related neuropathies (CMT) across the lifespan (CMTInfS, CMTPedS, CMT-FOM and RTDPedS). To standardise training and quality assurance for use of these COAs as clinical trial endpoints, the aim of this study was to develop and implement a comprehensive training and quality assurance program to ensure accurate multicentre data collection. Methods The ClinicalOutcomeMeasures.org training and quality assurance program was created following eight rounds of review by seven CMT experts. Then training resources were co-designed with key stakeholders including CMT experts, clinical evaluators, pharmaceutical representatives, and patients through a collaborative, multi-method approach involving surveys and focus groups/interviews. Professional videos and still images of each item in each COA were captured. An online portal hosting all training and quality assurance resources was activated and usage statistics monitored. Results To date, 970 users from >40 countries are registered on ClinicalOutcomeMeasures.org. A 3-phase training and quality assurance program was developed and implemented i.e., Phase 1:‘Self-directed e-learning’ through review of equipment and training resource manuals; Phase 2:‘Training’ via online basic and advanced level courses and quizzes and/or in-person training followed by reliability assessments; Phase 3:‘Monitoring’ involves refresher/annual training courses. Conclusion ClinicalOutcomeMeasures.org is a web-based automated scoring system and resource hub for deep phenotyping and monitoring response to therapy. This new training and quality assurance program promotes accurate and reliable data collection to overcome unnecessary delays in the translation of rational therapies for individuals with CMT across the lifespan.

Presenting Author	Title	Abstract
Rebecca Leung	Evaluation of the Queensland Paediatric Neuromuscular transition model	Patients with a diagnosis of neuromuscular disease must navigate a complex web of state and community services through the transition from child and family-centred to adult-oriented healthcare. This study examined barriers to successful transition from the patients and caregiver perspective as well as the clinician perspective. Adolescents with a primary diagnosis of a neuromuscular condition who were 16 years and over in Queensland were eligible to be included in the study. Surveys were collected over a 6-month period and descriptive statistics were used to summaries and characterise survey responses. A working group of clinicians created a transition checklist to help guide future neuromuscular transition. A total of 40 young people or their carers completed the patient survey with a response rate of 42% and 19 clinicians with a response rate of 54%. There was a high degree of anxiety reported about transition with almost 50% of patients and families surveyed reporting concerns about moving across to the adult hospital system. The main barriers to effective transition identified by clinicians were limited time (84%) and clinic space (58%) as well as a lack of an identified transition coordinator (79%). This study has informed a checklist to guide the transition of neuromuscular patients from paediatric to adult care. A new model has been developed to enable a slow, personalised transition that is led by a multidisciplinary team to ensure the continuity of high-level care from paediatric to adult healthcare services and the achievement of the highest possible quality of life for these patients.