8-9 MARCH 2012

ANN Workshop REPORT

Australasian Neuromuscular Network

Executive Summary

The Australasian Neuromuscular Network (ANN) was formally launched in April 2011, and since that time it has grown to over 280 members from Australia and New Zealand with representation from clinical care, allied health, pathology, nursing, research and patient advocacy and parent groups.

The ANN is structured to address issues relating to clinical care, diagnosis, clinical trials and research. Each area has a Steering Committee comprising individuals with relevant expertise.

The vision of the ANN is to ensure excellence in diagnostic methods and clinical management, and equal access to clinical trials and new therapies, for all individuals in Australia and New Zealand affected by neuromuscular disorders.

In 2011 the ANN established a roadmap for improving health outcomes for patients (available here) - short (achievable within 1 year with limited funding) and longer term (1-5 years that are likely to require funding) goals were identified. The priority areas included: Clinical Care; Clinical Trials; Diagnostic Network and Research. Within the last 12 months, a number of short term goals have been achieved or are nearing completion.

Our Achievements

✳ Developed a generic set of procedures for the collection of muscle, nerve and skin that can be easily adapted within local health areas - Status: **Nearing completion**

✳ Provided access to Standards of Care - Status: **Current SOC and guidelines available on the ANN website**

✳ Developed guidelines for the establishment of multi-disciplinary clinics - Status: **Draft**

✳ Supported and contributed to the expansion of registries through the Neuromuscular Disorders Registry Advisory Committee led by Dr Hugh Dawkins - Status: **DMD and SMA are operational, Myotonic dystrophy is nearing completion and FSH will follow (all link to TREAT-NMD global registry and Myotonic will also link into the US registry)**

✳ Clinical trial readiness - develop and validate accurate and sensitive outcome measures - Status: **Underway**

✳ Run pilot studies of population screening for Duchenne muscular dystrophy - Status: **Underway**

✳ Maintain a list of what tests are available and where - Status: **Near completion**

✳ Opportunities for patients to participate in trials via CINRG and TREAT-NMD (including links through registries)

The ANN is a virtual network, and operates on minimal funding. The ANN Executive was committed to seeking infrastructure funding to underpin and progress the goals of the ANN and in 2012 members of the ANN were awarded $2.5M over 5 years by the National Health and Medical Research Council (NHMRC) to establish the Centre of Research Excellence in Neuromuscular Disorders (CRE-NMD).

The CRE-NMD is a 5-year research project with specific goals and will effectively form the 'research arm' of the ANN. As a number of the Chief Investigators on the CRE-NMD also have major roles within the ANN as Steering Chairs, this will strengthen the research aims of the ANN - a number of goals of the ANN that required funding to achieve were incorporated into the CRE-NMD proposal. The aims of the ANN and the CRE-NMD overlap and are complementary.

The CRE-NMD will progress a number of key ANN goals

- Development of next generation sequencing (NGS) protocols - this will underpin the aim to improve the molecular diagnostic success rate to 90%, accelerate gene discovery and establish a national diagnostic network
- Undertaking a feasibility and acceptability study of NGS-based preconception screening for recessive NMDs
- Establishment of a national integrated patient database as a valuable resource for studies of natural history and genotype-phenotype correlations, and will provide a platform for research collaborations (also underpins gene discovery, improved diagnosis and clinical trial readiness)
- Establishment of a clinical trials network
- Establishment of a muscle bank
- Translation of best evidence into best practice - develop new policies, undertake a study by study economic evaluation of health impact to influence health policy and funding, promote universal uptake of best standards of care, educate and engage the community
- Formalisation of a training program for early career researchers and PhD students

The aim of this workshop was for clinicians, scientists, nursing and allied health professionals, pathologists and patient support and parent groups to formulate a list of priorities and determine how these priorities will be implemented. Over the one-and-a-half day workshop there were a number of presentations and passionate and enthusiastic discussion that resulted in a clear path towards achieving significant health outcomes for patients through a coordinated and integrated neuromuscular network.

The workshop participants agreed on a number of important issues to address gaps in patient care.

plan.

DIAGNOSIS AND PREVENTION

1 year

Promote continuous and rapid translation of new tests into standardised best practice	Publish list of genetic and pathology tests available - where and who (ANN website and update quarterly)
Develop and utilise a telepathology network	Trial sending slides to Victoria to scan and store in central database Investigate cost to access and cost per slide to digitise
Investigate the applicability, including feasibility and acceptability, of NGS-based pre-conception screening for recessive NMDs	Undertake a normative pilot study between WA and NSW

1-5 years

Establish a national biospecimen bank	Adapt consent templates from brain bank Establish how the bank will be managed Identify funding opportunities for sustainability Develop standard protocols around specimen collection for muscle, nerve and skin, and primary myoblast culture
Establish a national neuromuscular diagnostic network	Participate in the implementation of the Federal Government National Diagnostic Network for Genetics
Identify potential ANN interaction with the Human Variome Project (HVP)	ANN representative to attend the HVP meeting
Investigate acceptability and feasibility of preconception carrier screening of severe recessive disorders	Investigate the use of NGS in such preconception carrier screening
Increase molecular diagnostic success rate to 90%	Develop NGS protocols Develop recommendations for exome sequencing (in consultation with HGSA)

CLINICAL CARE

1-5 years

Expand national registries	Roll out FSH with others to follow
Enhance communication	Education and engage patients, parents and the community
Develop and promote standards of care and guidelines	Develop and implement NMD standard of care Develop guidelines for the transition from paediatric to adult care By 2014 all patients will have their clinical information on a USB device
Expand the ANN community	Develop nursing standards of care via the Nursing and Allied Health Steering Group Engage adult clinicians, as well as professional groups including ANZAN Expand Myotonic dystrophy into adults

CLINICAL TRIALS

1 year

Enhance clinical trials readiness	Develop and validate accurate, sensitive patient relevant outcome measures Identify training opportunities Increase allied health involvement in clinical trials Provide training for clinical and allied health professionals - establish the Nursing and Allied Health Steering Group and network
Establish a national clinical trials networks	Identify a project that could be expanded to additional states Establish and formalise a training network

Within 5 years

Establish multi-disciplinary clinics - adult and paediatric - in each state

Establish new clinical trials centres

Expand existing trials programs

1-5 years

RESEARCH

Develop a national integrated secure patient database	Adopt the Biogenix database for cohort studies Design smart form for data collection Publish cohort studies on the website with a call for patients
Encourage collaborative genotype-phenotype and natural history studies	Centronuclear myopathy Congenital fibre type disproportion Congenital muscular dystrophy Duchenne muscular dystrophy Dystrophinopathies Facioscapulohumeral dystrophy Foetal akinesia Inclusion body myositis Limb girdle muscular dystrophy Myotonic dystrophy Necrotising myopathy Nemaline myopathy
Enhance research support	Able to support seed funding - possibility of funding bodies to utilise the NHMRC review process to support larger research grants

do, act.

TASK	RESPONSIBILITY
Diagnosis and Prevention	
Finalise and publish list of molecular tests: include indicative wait time to generate result list of routine NATA and non-NATA research tests	Mark Davis (and Coordination Centre)
Finalise and publish list of pathology tests: including approx. time to generate result	Paul Kennedy (and Coordination Centre)
Finalise and publish the specimen collection procedures manual: Add skin collection procedure Add primary myoblast procedure	Paul Kennedy (and Coordination Centre) Phillipa Lamont, Vicki Fabian Leigh Waddell, Steve Wilton, Sue Fletcher
Generic consent form	Catriona McLean (and Coordination Centre)
Develop recommendation for exome sequencing (in consultation with HGSA)	Diagnosis and Prevention Steering Group
Clinical Care	
Standard of Care document - feedback	Alastair Corbett (and Coordination Centre)
DMD portal - add link to ANN website	Coordination Centre
Datastick “patient passport”: standard template for information to be uploaded qualitative outcome measure	Klair Bailey, Phillipa Lamont and Coordination Centre Paula Bray
‘Gap’ analysis (CARE-NMD study)	Kristi Jones, Anita Cairns and Coordination Centre
Expand Myotonic dystrophy research opportunities for adults	Alastair Corbett, Tim Day, Merrilee Needham, Phillipa Lamont
Transition guidelines: working group	Merrilee Needham, Nigel Clarke, Phillipa Lamont, Jan de Franck, Anita Cairns, Sandra Holland
Clinical Trials	
Establish the Allied Health and Nursing Steering Group: Coordinate/advertise Michelle Eagle and RCH training Nursing Standards of Care	Coordination Centre Daniella Villano, Kristy Rose Allied Health and Nursing Steering Group
Identify potential trials that could involve other states	Monique Ryan, Joshua Burns
Upload clinic coordinator and evaluator information onto website	Coordination Centre
Formalise training exchange program involving adult and paediatric trainees	Coordination Centre
Research	
Upload and promote collaborative research opportunities	Coordination Centre
Adopt Biogenix database - negotiate support fee Develop smart forms within Biogenix for cohort studies Write Biogenix article for publication	Leigh Waddell and Coordination Centre Leigh Waddell and Coordination Centre Leigh Waddell

Introduction

Meeting the challenges of caring for children and adults affected by neuromuscular disorders in Australia and New Zealand

The Australasian Neuromuscular Network (ANN) is committed to establishing a cohesive, integrated neuromuscular network that enables people to work together across Australia and New Zealand for the well being of patients.

We will provide a forum to advance and disseminate information, be a single voice to advocate for patients and guide best practice in diagnosis, care and treatment.

Our membership is open to all and includes patient organisations, clinicians, researchers, academics, industry and individuals with an interest in neuromuscular disorders.

Vision

To ensure excellence in diagnostic methods and clinical management, and equal access to clinical trials and new therapies, for all individuals in Australia and New Zealand affected by neuromuscular disorders.

Mission

To be a coordinated and collaborative voice at a national level to advocate for improved funding for diagnostic services, registers and clinical trials infrastructure. We can achieve our vision by establishing a cohesive, integrated neuromuscular network which enables people to work together across Australia and New Zealand, for the well-being of patients.

Goal

- To improve health outcomes by providing:
- Guidance in best practice in diagnosis, care and treatment
- Ready access to Standards of Care
- A unified approach to ethical approvals and consent
- Improved communication
- Integrated training programs for clinicians and researchers
- Assistance to set up multidisciplinary services
- A single voice to advocate for our patients
- Notification of opportunities to participate in registries, research studies and clinical trials
- Improved coordination of research

Themes and Aims

The ANN supports the translation of best evidence into improved clinical outcomes for patients and their families. This requires a multi-disciplinary coordinated approach to integrating laboratory and clinical research, through to clinical trials and improvements in medical practice.

The ANN has established themes and aims to ensure that the best evidence is translated into best practice.

1. Patient Diagnostic Network
To coordinate a national collaborative diagnostic service and research network for neuromuscular disorders that is cost-effective, maximises availability and minimises duplication of services. This will include introduction of new diagnostic methods.
2. Patient Registries
To develop nationwide disease registers, based on accurate molecular diagnosis for patients with neuromuscular disorders, aligned with international registries such as the TREAT-NMD registries.
3. Clinical Trials and Clinical Network
To establish a clinical trials framework for neuromuscular disorders accessible to patients around Australia and New Zealand.
4. Research
Coordination of data collection and storage to facilitate large cohort studies initiated by individual investigators.

ANN Community

The ANN has a number of community partners and is a member of TREAT-NMD and the Cooperative International Neuromuscular Research Group (CINRG). The relationship with advocacy and patient groups is a very important part of the ANN.

MUSCULAR DYSTROPHY FOUNDATION • AUSTRALIA

MUSCULAR DYSTROPHY Association of New Zealand Inc. Te Rapu Mate Horokiwa o Aotearoa

DuchenneFoundation for boys with Duchenne Muscular Dystrophy

TREAT-NMD Neuromuscular Network

MUSCULAR DYSTROPHY RESEARCH FOUNDATION

MDD MUSCULAR DYSTROPHY

CINRG

Centre for Research Excellence in Neuromuscular Disorders (CRE-NMD)

CHIEF INVESTIGATORS	ASSOCIATE INVESTIGATORS
Prof Kathryn North*	Prof Steve Wilton
Prof Nigel Laing*	A/Prof Phillipa Lamont
A/Prof Andrew Kornberg*	Dr Kristi Jones*
A/Prof Joshua Burns*	Prof Nadia Rosenthal
A/Prof Monique Ryan*	Prof Peter Currie
Dr Nigel Clarke*	Prof Garth Nicholson
Prof Alastair Corbett*	Mr Phil Martin*
Prof Kathryn Refshauge	Dr Hugh Dawkins
Dr Michael Buckley*	
Prof Catriona McLean*	

* Chairs/members of ANN Steering Groups

Australian Government

National Health and Medical Research Council

A 5 year research program to translate best evidence from clinical and laboratory-based research into best clinical practice under two themes:
Diagnosis and Prevention and Treatment.
The CRE-NMD will be the national hub for consolidating and expanding our national research and training initiatives.

CURRENT STATUS AND EXISTING PROJECTS	NEW CRE-NMD PROJECTS AND INITIATIVES
Theme I: Diagnosis and Prevention	
Fragmented state-based laboratory diagnostic services provide pathology and genetic diagnosis for only the most common disorders in most states. Ad hoc referral to reference, research and overseas laboratories for diagnosis of the majority of disorders.	1.1 National diagnostic network. Linkage between research and diagnostic laboratories across states to promote the continuous and rapid translation of new tests and technologies into standardised diagnostic protocols. Establishment of standardised guidelines. (Laing, Clarke, Buckley, McLean)
Dispersed storage of clinical data in individual research groups for of cohort and natural history studies (all CIs and AIs)	1.2 Centralised database of de-identified clinical, pathological and genetic data to facilitate cohort studies and new gene discovery (all CIs and AIs)
Ongoing collaborative studies of: Congenital fibre type disproportion (Clarke) Hereditary motor and sensory neuropathy (neuronal type) (Burns, Ryan, Nicholson) Hereditary motor and sensory neuropathy (demyelinating types) (Burns, Ryan ,Nicholson) Natural history of DMD (with CINRG: North, Kornberg, Ryan)	1.2 Additional national collaborative studies to characterise clinical phenotype, natural history and genotype-phenotype correlation in: Centronuclear myopathy (North, Clarke, McLean) Congenital muscular dystrophy (North, Kornberg, Clarke) Facioscapulohumeral dystrophy (Kornberg, Corbett, Lamont) Foetal akinesia (Ravenscroft, Laing) Hereditary axonal neuropathies (Ryan, Burns, Nicholson) Myotonic dystrophy (Corbett, Lamont) Nemaline myopathy (North, Laing, Ryan, Clarke, Buckley)
National patient registry for Duchenne muscular dystrophy (DMD) and Charcot-Marie-Tooth Disease (North, Burns, Ryan)	1.2 New national patient registries for SMA, myotonic dystrophy, facioscapulohumeral dystrophy, congenital myopathies and muscular dystrophies. (North, Kronberg, Ryan, Corbett, Lamont)
Gene discovery using classical approaches (linkage analysis and positional cloning): 60% diagnosis success rate (CIA, CIB, CIF)	1.3 Accelerate gene discovery using next- generation sequencing technologies. Aim: 90% molecular diagnosis success rate (North, Laing, Clarke, Buckley)
Research into the acceptability of population screening for DMD (CIC) and pilot study of population-based screening for DMD (Laing).	1.4 Investigation of the applicability of population screening for multiple NMDs using next generation sequencing technology (Laing).

CURRENT STATUS AND EXISTING PROJECTS	NEW CRE-NMD PROJECTS AND INITIATIVES

Theme II: Treatment

Clinical Trial Readiness

1.5 Ongoing Research with anticipated Phase II/III clinical trials given CRE-NMD support

Trials of gene up-regulation and pharmacological therapies in animal models of inherited myopathy (Laing, NHMRC 2011 Project APP 1026963).

Trials of dynamin stabilisers for centronuclear myopathies (North, Clarke with Prof Phil Robinson)

Exon skipping for DMD and SMA (Wilton)

Stem cell therapy for inherited myopathies and dystrophies (Rosenthal,Currie)

Current status and existing projects	New CRE-NMD projects and initiatives
Development of reliable outcomes measures of muscle strength and motor function in children as young as two years (Burns)	1.6 Establish reliable instruments to measure balance, agility, joint range and deformity, respiratory function and quality of life for use from the earliest stage of disease (Burns, Refshauge).
Clinical trials capacity in Sydney and Melbourne (North, Kornberg, Burns, Ryan)	1.7 National clinical trials network (North, Kornberg, Burns, Ryan, Lamont, Jones)

Clinical Trials

1.7 National clinical trials network (North, Kornberg, Burns, Ryan, Lamont, Jones)	1.8 Leadership of new international clinical trials Phase II trials for novel exercise mimetic agents (AICAR, GW-501516) and novel steroid derivatives in DMD (North, Kornberg, Ryan) Phase II/III trial of resistance strength training for inherited neuropathy (Burns, Ryan, Refshauge) Phase II trial of oral curcumin in severe inherited neuropathy (Burns, Ryan) Phase II trials of exon skipping for range of DMD deletions (Wilton, Lamont, North, Kornberg)

PLAN FOR RESEARCH TRANSLATION INTO HEALTH OUTCOMES

Research	Translation	Outcomes for Health Policy and Clinical Practice
Diagnosis and prevention		
Genetic diagnosis and identification of new disease genes	Incorporate immediately into diagnostic screening	Accurate information on recurrence risk and prognosis, optimal surveillance and therapy. Prevention through prenatal diagnosis. Essential for inclusion in many clinical trials.
	Genotype-phenotype correlation	Increased frequency and sensitivity of new genetic diagnoses. Guides genetic testing in new patients.
	Patient databases	Facilitate screening of undiagnosed cases. Facilitate natural history studies, genotype-phenotype correlation, and establishment of registries.
Establishment of patient registries	National centralisation.	National centralisation.
National centralisation.	Collaborative diagnostic network	Increased cost efficiency and increased availability of genetic testing for rare inherited neuromuscular disorders.
Treatment		
Develop and validate outcome measures	Establish natural history	Informs disease surveillance, best practice in medical care, and frequency of investigations. Influences best-evidence clinical trial design and outcome measures.
Clinical trials of novel agents and therapies	Introduction of new treatments into routine clinical practice	Decreased patient morbidity, decreased hospital inpatient stays, increased patient survival, increased patient function and health-related quality of life. Prevention of morbidity through early diagnosis and commencement of therapy.
	Interface with international networks	Novel therapies immediately accessible for Australian patients.

ANN/CRE: Shared Goals

Improving diagnosis & treatment

Expand the number of multidisciplinary clinics – adult and children

Establish new clinical trial centres

Increase clinical trial availability to individuals in all state

Accelerating gene discovery: increase molecular diagnostic success rate

Implementation of next generation sequencing into diagnostics

National diagnostic network

Population screening

Muscle bank

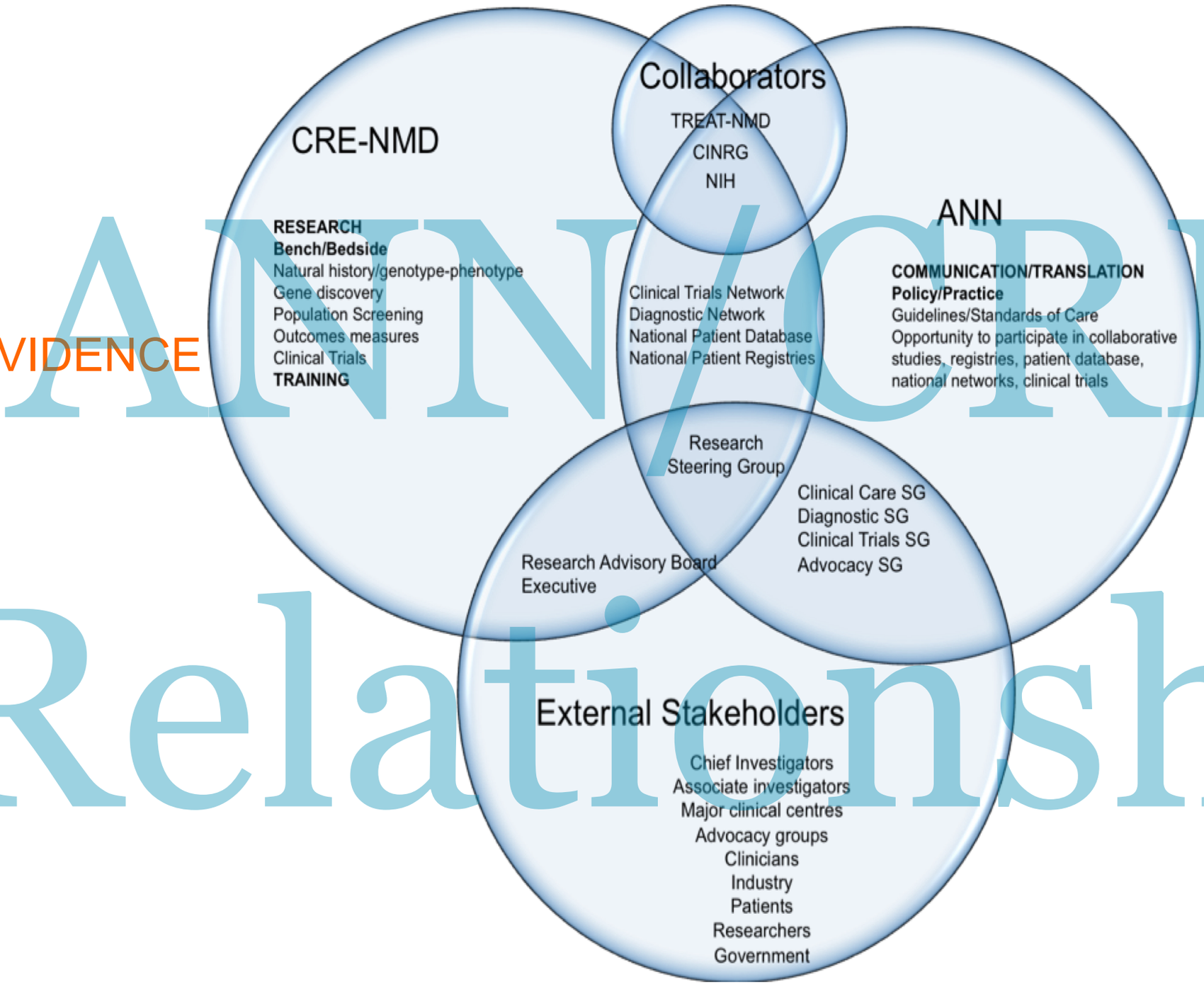
Centralised national patient database

Characterise disease phenotype, natural history and genotype-phenotype correlation

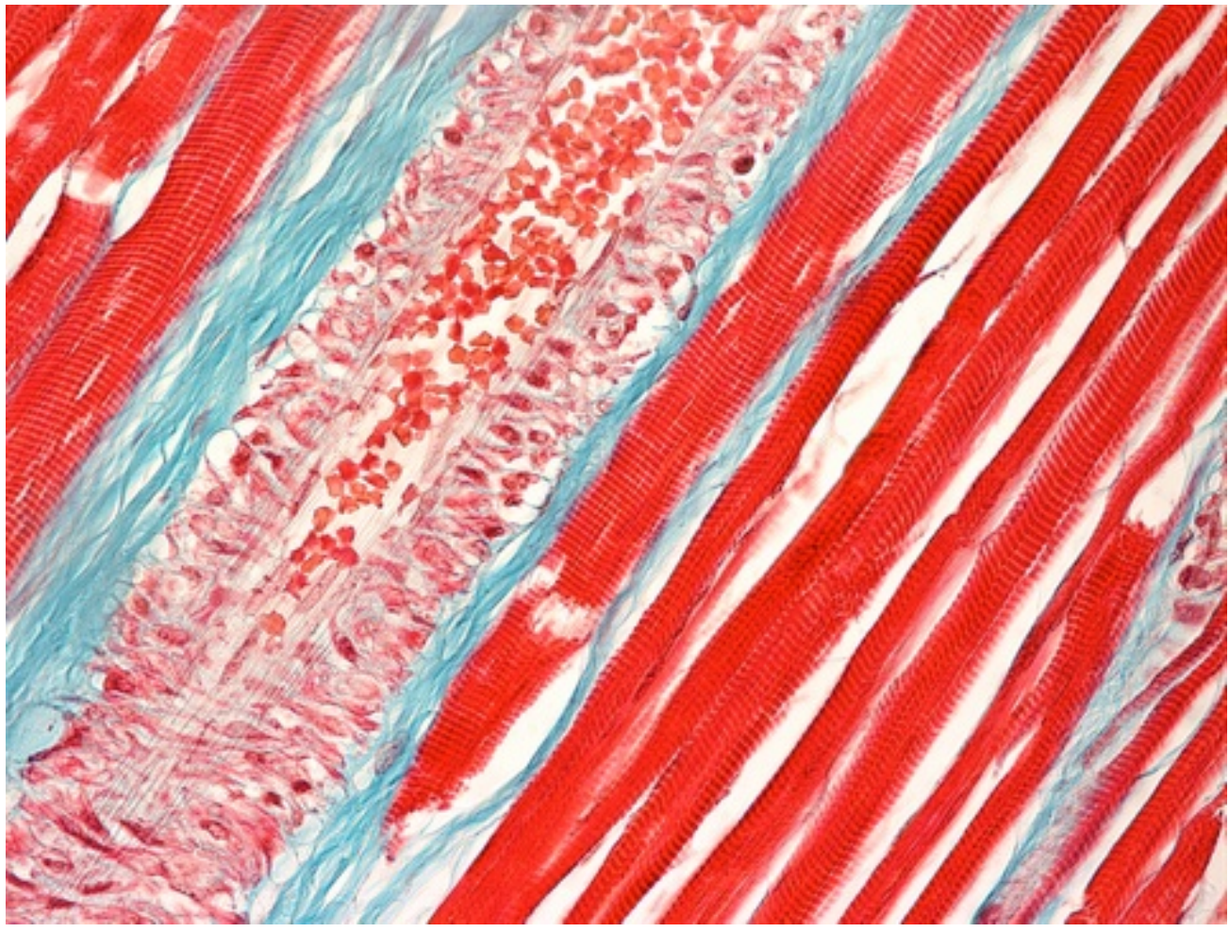
Promote universal uptake of best standards of care

Registries

Educate and engage



Diagnosis and Prevention



Diagnostic and Prevention Steering Committee:

Nigel Laing (Chair)
Paul Kennedy
Mark Davis
Nigel Clarke
Peter Taylor
Catriona McLean
Leigh Waddell
Michael Buckley
Tom Robertson

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

GOALS

- Develop guidelines for the translation of established diagnostic tests from research laboratories into accredited diagnostic laboratories
- Develop guidelines for the collection of clinical information and specimen collection
- Publish a list of what tests are available and where on the ANN website
- Establish a NGS user group
- Establish a muscle bank

Specimen Collection

Lead: Paul Kennedy

Tissue specimens are used to describe the biology of the patient and the biology of his or her disease and good quality specimens are paramount in arriving at a rapid and accurate diagnosis. As such specimens must be collected and processed following standards that safeguard quality.

Without standardised guidelines, inefficiencies arise in obtaining, handling, storage and processing of samples. In some cases this has a significant negative impact on the diagnostic process and patient welfare. To address this, the ANN has developed a generic set of guidelines for the collection of muscle, nerve and skin that can be easily adapted within local health areas.

ACTIONS

- Write a procedure for the collection of a skin biopsy [Vicki Fabian/Phillipa Lamont]
- Compare and develop a primary myoblast procedure [Kathryn North/Leigh Waddell/Steve Wilton/Sue Fletcher]
- Publish the specimen procedures manual on the ANN website [Leanne Mills]

Standard tests

Pathology

Lead: Paul Kennedy

STATE SERVICE	CONTACT		TESTS AVAILABLE
Victorian Neuromuscular Laboratory Service	Paul Kennedy	p.kennedy@alfred.org.au	Muscle - Enzyme-Histochemistry, paraffin processing/embedding & electronmicroscopy. Protein anaylsis (Western Blot) , immunohistochemistry and immunofluorescence. Nerve - paraffin and EM processing, sectioning, montage & teased fibre prearations.
South Eastern & Illawarra Area Health Service NSW	Ella Sugo	ella.sugo@sesiahs.health.nsw.gov.au	Muscle - Enzyme-Histochemistry, paraffin processing, embedding, immunohistochemistry and immunofluorescence.
Royal Perth Hospital Department of Pathology	Drs Rei Junckersdorff & Vicki Fabian		Muscle frozen sections - routine staining panel, immunohistochemistry, paraffin, electron microscopy and western blot.
Queensland Health	Tom Robertson		TBC
South Australia	TBC	TBC	TBC
New Zealand	TBC	TBC	TBC

Molecular

Lead: Mark Davis/Nigel Laing

Currently there is no coordination of testing between states, with core disorders tested for varying between each laboratory and separate tests undertaken in research laboratories, and no list of what tests are available and where.

Diagnostic testing has been developed within a number of Australasian research laboratories based on individual interests. While this has significantly improved the diagnosis for a number of individual conditions – usually free of charge - this decentralised and non-systematic approach to testing is not sustainable in the long-term, and is not best practice to ensure the optimal health outcomes for patients on a national scale. The diagnostic services provided by research laboratories are vulnerable to changing research priorities. An integrated network linking research and diagnostic laboratories would promote the continuous and rapid translation of new tests to standardised diagnostic protocols.

In addition, there is no process for the transfer of tests developed within research laboratories into NATA accredited routine testing laboratories.

Clinicians do not know what tests are available or where within Australia. The RACP is undertaking a study to assess how best to coordinate testing, however in the meantime the ANN has developed a list that will be made available on the ANN website and will be updated on a regular basis.

In addition, the Federal Government has established a working party to look into developing a national diagnostic network. Michael Buckley is on the working party and will ensure that the ANN is engaged in the process.

ACTIONS

- Develop a list of other tests performed in non-NATA accredited laboratories ie. research basis and estimated time taken to generate a result [Mark Davis]
- Publish lists on the ANN website [Leanne Mills]

Routine diagnostic genetic testing available in Australasia

Central core disease	RYR1 (gDNA & cDNA)	P
CMT	PMP22 duplication	A, B, P, S2
	PMP22 sequencing	P, S2
	MPZ	P, S2
	GJB1	P, S2
	MFN2	P, S2
	DNM2	S2
DMD/BMD	DMD duplication / deletion	A, B, P, S1
	gDNA sequencing	B, S1
	cDNA sequencing	P
DRPLA	ATN1	A, P
Distal arthrogryposis	MYH3	P
	TPM2	P
Distal myopathy (of Laing)	MYH7	P
Emery-Dreifuss MD	LMNA	P, S1
Friedreich ataxia	FXN	A, B, P, S2
FSH	D4Z4 repeat deletion	P, S2
HNPP	PMP22 deletion	A, B, P, S2
HSN1	SPTLC-1	S2
HyperK periodic paralysis	SCN4A	P
HypoK periodic paralysis	CACNL1A3 / SCN4A	P
hIBM	GNE	P
IBMPFD	VCP	P
Kennedy's disease	AR	A, B, P, S2
LGMD1A	TTID	P
LGMD1C	CAV3	P
LGMD2A	CAPN3	P
LGMD2E	SGCB	P
LGMD2I	FKRP	P
LGMD2L	ANO5	P

Routine diagnostic genetic testing available in Australasia

McArdle disease	PYGM	P
Mitochondrial disorders		
KSS/CPEO	Deletions	P
MELAS	MT-TL1	P
MERRF	MT-TK	P
NARP/MILS	MT-ATP6	P
Motor neurone disease	SOD1	P, S2
	FUS	P
	TARDBP	P, S2
Myofibrillar myopathy	TTID	P
	DES	P
	CRYAB	P
	LDB3	P
Myotonia congenita	CLCN1	P
Myotonic dystrophy (DM1)	DMPK	A, B, P, S2
Myotonic dystrophy (DM2 - PCR)	ZNF9	P
Myotubular myopathy	MTM1	A*, P
Nemaline myopathy	ACTA1	P
	TPM2	P
	TPM3	P
	KBTBD13	P
OPMD	PABPN1	A, B, P
Paramyotonia congenita	SCN4A	P
SCA1	ATX1	A, B, P, S2
SCA2	ATX2	A, B, P, S2
SCA3	ATX3	A, B, P, S2
SCA6	CACNA1A	A, B, P, S2
SCA7	ATX7	A, B, P, S2
SCA17	TBP	P
Spinal muscular atrophy	SMN1	A, B, P, S1

* Only available to South Australian patients

NATA accredited testing laboratories

Adelaide
Genetics and Molecular Pathology, SA Pathology (Women's and Children's Hospital)
Contact: Kathie Friend

Brisbane
Molecular Genetics Laboratory, Pathology Queensland
Contact: Val Hyland

Melbourne
Molecular Genetics Laboratory, Victorian Clinical Genetics Services
Contact: Desirée DuSart?

Perth
Neurogenetics Laboratory, Royal Perth Hospital
Contact: Mark Davis

Sydney 1
Prince of Wales Hospital, South Eastern Sydney and Illawarra Area Health Service.
Contact: Peter Taylor

Sydney 2
Molecular Medicine Laboratory, Concord Repatriation General Hospital
Contact: Danqing Zhu

Next Generation Sequencing

Lead: Nigel Laing

Next Generation Sequencing (NGS) is the 'next step' in molecular diagnosis. The goal of improving the molecular diagnostic success rate (aim is 90%) and accelerating gene discovery and establishing a national diagnostic network is underpinned by NGS.

Currently, WA and NSW are investigating different protocols (WA has been awarded seed funding by the WA government to support the establishment of NGS) and NSW and WA were also awarded a NHMRC grant that will incorporate NGS in a study of families for whom all known disease genes have been excluded.

WA has purchased four (4) NGS machines and are waiting on a fifth ion torrent machine. The WA team have focussed on developing a protocol around a superarray.

They have designed a capture array targeting over 300 genes, including all known Neuromuscular Disease genes and most Cardiac disease genes.

The list is based on the current Neuromuscular Disorders (online gene table) plus genes identified since that list was put together last year.

The NMD Superarray will allow the simultaneous sequencing of all the >300 genes. The system is designed to test 96 samples at once. It is a system best suited to rare diseases with a small number of patients and is the focus of a system that could be incorporated into diagnostic centres in the future.

The WA team aim to test the Superarray on a set of proband samples from Phillipa Lamont where they are likely to find something, where all the known genes have been excluded.

The current estimated cost for the WA laboratory to perform the tests are:

- $1000/sample - generates list of possible variants
- + Sanger sequencing to confirm if reporting
- $200 (single variant)
- $400 (single but not routine gene)
- $2000 (5 variants not routine)

The NGS studies being undertaken in WA and NSW will allow the CRE-NMD/ANN to investigate and establish standardised protocols as well as study design for the desired application.

Diagnosis using NGS is complex and includes a pre-analytical component of clinic- pathological diagnosis and an interpretative post-analytical component. It will therefore be important for clinicians to be knowledgeable in this area.

Human Variome Project

interface with the ANN/CRE-NMD

Richard Cotton (Scientific Director)

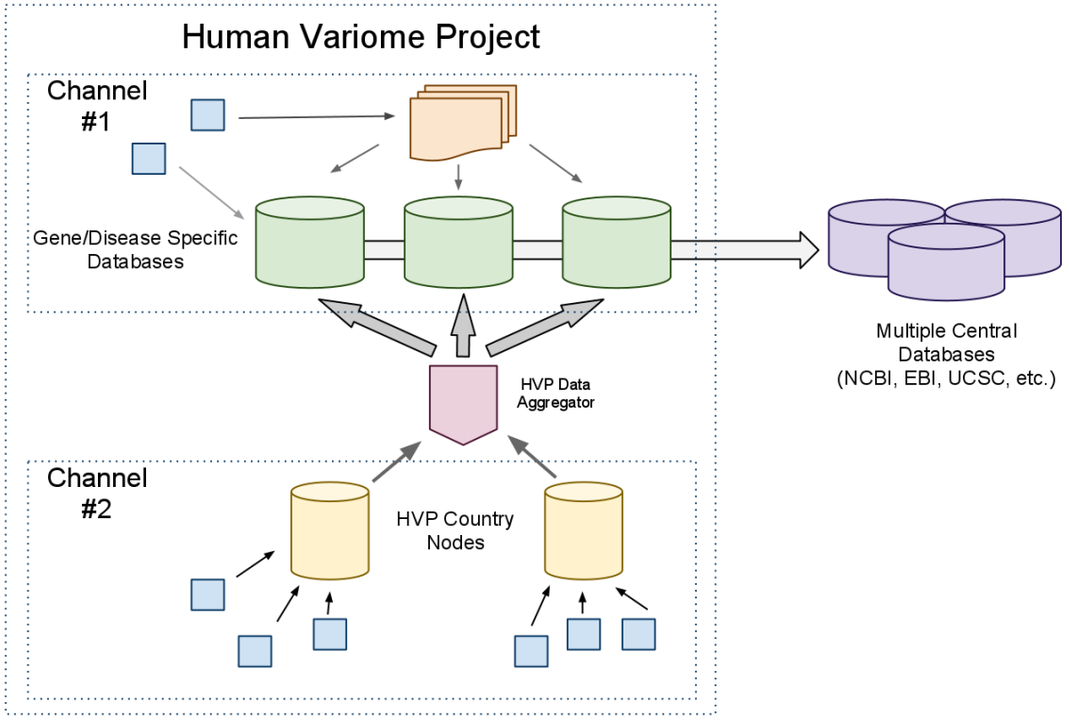
Core Purpose is to alleviate needless human suffering for many millions of the world's people by collecting, organising and sharing data on genetic variation

Aim
Every variant reported in the world available in a database

Need
To make collection process as effortless as possible

Solution
Collect data directly from the source

The Human Variome Project (HVP) facilitates the collection of all mutations in all genes in all countries. The project has financial support from WHO, the EC and China to establish databases to collect data in a standardised way around the world - there are currently 150 countries participating.



Each country is a separate 'node' and works locally with existing databases/specific activities within that country to collect data. There is an Australian node, involving Val Hyland and Desiree du Sart, key people within the neuromuscular community.

Reference:
Cotton et al. Genetics in Medicine (2009) 11:843–849

Benefits

Each lab now has access to a new resource: the HVP Country Node

Represents the cumulative experience of all the country's diagnostic laboratories

Provide faster and more accurate diagnosis of genetically based illnesses within the country's populations, reducing the cost and suffering of patients

Help clinicians make more accurate prognoses and develop better treatment plans

Improve the quality of genetic counselling for families

Improve national healthcare planning leading to reduced costs within national healthcare systemProvides a simple mechanism for sharing local data with international databases

Ensures compliance with ethical, legal and cultural requirements at the point of data collection

Human Variome Project structure gives each country an equal voice

ACTIONS

The limiting step is data entry, though there may be an opportunity for the ANN to undertake a pilot project as part of existing database projects.

Proposed minimum dataset:

- Gene Name—described in the form of both the HUGO Nomenclature Committee approved gene name and a sequence accession number and version number
- Variant Name—written as HGVS nomenclature
- Pathogenicity—classified as five levels of pathogenicity
- Test date—the date that the results where produced
- Patient ID—a deidentified code which is unique to a patient
- Patient Age—the age of patient when tested
- Patient Gender
- Submission date
- Disease associated with the mutation—if diagnosed
- Lab Operator ID—a code that identifies the operator who uploaded the data
- Laboratory Name/ID
- Country/Region Name/ID—if a regional repository is used
- Level of consent obtained
- Can the patient be recontacted for other studies?
- Can clinical and/or molecular data be used for statistical analyses (with options for local laboratory, country, and/or international)?

Telepathology

Lead: Catriona McLean

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

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

The University of Melbourne system operates via the internet, and users are issued a login and password to access. The ANN/CRE-NMD would support the cost of scanning patient slides ($10 per slide) - the slides would be sent to Melbourne where local equipment to digitise slides isn't available.

ACTIONS

- Adopt The University of Melbourne system
- Discuss difficult/interesting cases on an as needs basis via telepathology (coordinated through Catriona McLean)
- A number of interesting patient slides with clinical information would be made available on the ANN website as a training tool

Population Screening

Lead: Nigel Laing

The clinical diagnosis of Duchenne muscular dystrophy (DMD) is often delayed until the age of 4-6 years, by which time there may be multiple affected younger boys within the sibship or affected boys born to other women in the family who did not know that they were carriers. Many other NMDs are recessive, meaning that they affect children in families with no family history.

Population screening has been associated with decreased incidence of specific diseases within specific populations eg. Tay Sachs. Duchenne Muscular Dystrophy (DMD) screening occurs in a small number of countries, and has generated much controversy and debate.

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

There appears to be increasing support for DMD screening as Francesco Muntoni has applied to the ENMC for a workshop to be convened in the area.

Reference

Mendell et al. Annals of Neurology (2012) 71(3):304-313

Muscle Bank

Lead: Catriona McLean

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

The muscle bank will be based on the successful Australian Brain Bank Network. The Brain Bank has collected 996 tissues in Victoria, there are 119 continuing projects and 500 publications have resulted from the tissue made available through the bank.

An internet-based database would be developed to store the de-identified muscle information. This would be held nationally but the physical tissue would be stored locally within each laboratory. This has to be done prospectively. Tissue already collection cannot be used due to inadequate consent.

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

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

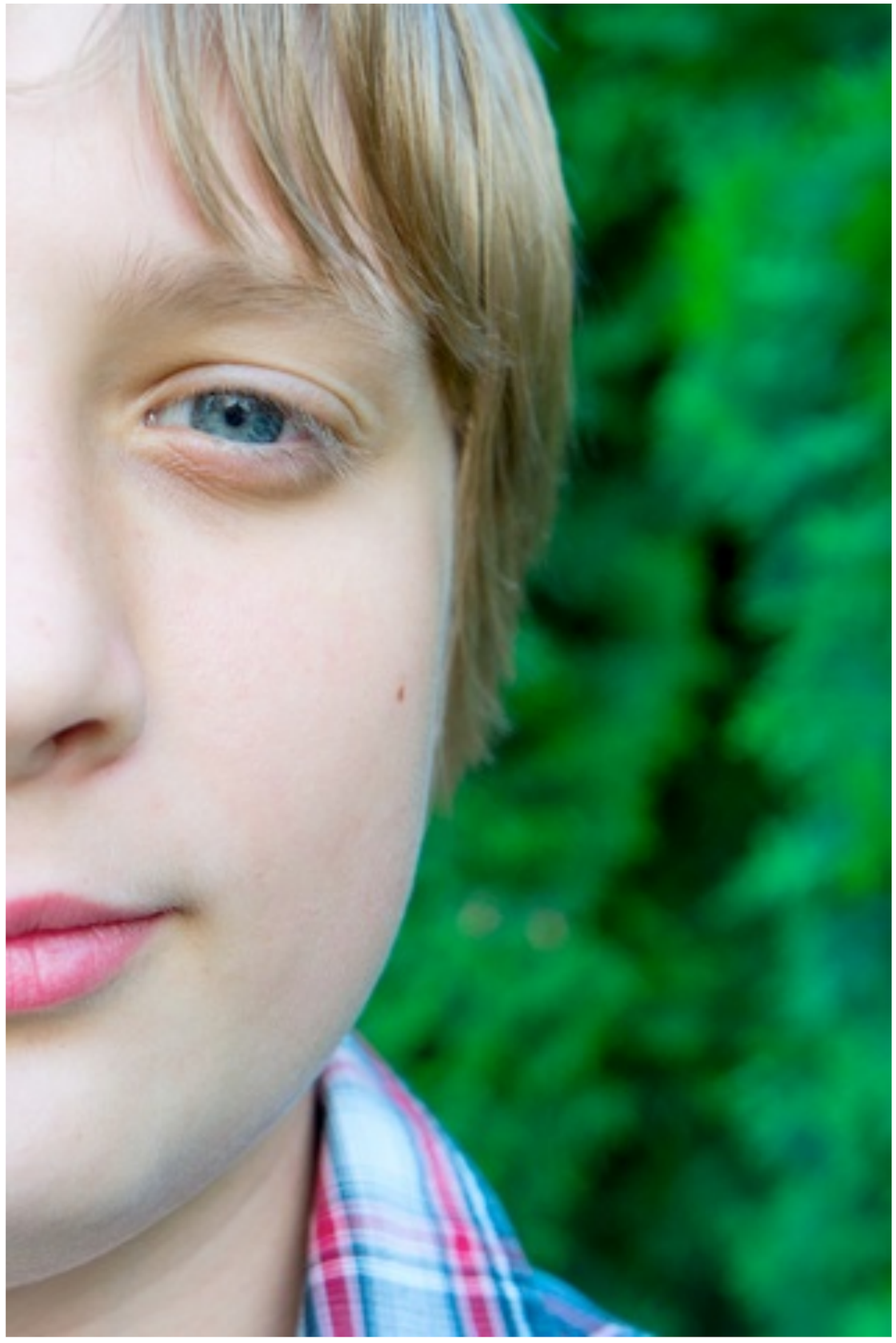
There is a cost involved in sending the sample, however researchers are provided with the fee structure and agree to pay for the cost to send the sample/s.

Infrastructure costs required to establish the bank include a part-time coordinator to oversee the central database and liaise with the local banks, as well as local staff to enter the data into the database and to be the point of contact to send sample/s.

ACTIONS

- Generic consent and information forms will be developed

Clinical Care



Clinical Care Steering Committee:

Alastair Corbett (Adult) and
Kristi Jones (Paediatrics) (Co-Chairs)
Monique Ryan
Anita Cairns
David Mowat
Rakesh Patel
Paula Bray
Michelle Farrar

Promote and achieve high quality and equitable care for patients

The focus of the Clinical Care Network will be to provide:

Ready access to Standards of Care and Data Collection Proformas for patient management and diagnosis;

A unified approach to ethical approvals and consent;

Improved communication to discuss patients;

Notification of opportunities to participate in registries, research studies and clinical trials;

Opportunity for Special Interest Groups to develop in areas not covered by the initial plans (which have a muscle focus) – e.g. diagnosis of neuropathies, adult neuromuscular disorders, allied health network;

Opportunities to provide integrated training programs for clinicians and researchers; and

Assistance to centres to set up multidisciplinary services.

While it may be difficult to provide every patient with immediate access to a multi-disciplinary clinic and specialist care, the ANN will disseminate standards of care via its website and regular newsletters, with links to the TREAT-NMD website as a source of international standards of care and other resources.

For neuromuscular disorders, guidelines need to provide an evidence based approach to:

✳Pulmonary assessment, monitoring and management

✳Cardiac monitoring assessment and management

✳Swallowing assessment and management

✳Nutritional assessment and management

✳Orthopaedic care

✳Rehabilitation management of cognitive and behavioural disorders

✳Other organ involvement

✳Perioperative care

✳Critical care

✳Palliation

✳Swallowing assessment and management

✳Nutritional assessment and management

✳Orthopaedic care

✳Rehabilitation including

- Exercise, stretching, physiotherapy, occupational therapy
- Orthotics and assistive devices
- Posture management
- Pain management

Standards of Care

draft

Target

Clinicians running or working in an NMD and in particular those planning an NMD service

Aim

- A template for NMD clinical services
- Guidelines that promote a high standard of care that should be achievable with optimal staffing, funding and administrative support
- Document to present to administrations and support groups to justify requests for appropriate resources and funding
- Inability to reach all criteria should not be a reason not to proceed with starting a service
- Clinics may fall short of the guidelines but should aspire to at least this standard of care.

Diagnosis

1. Clinical diagnosis based on thorough history, including family history, and clinical examination

2. Genetic diagnosis where possible with the tests requested based on clinical presentation and family history. Blood testing for CK, nerve conduction and EMG studies and MRI imaging may be helpful but are not diagnostic.

3. Where diagnosis by genetic testing is not possible or there are many possible alternative diagnoses muscle biopsy may be required to achieve a diagnosis. This should be processed for histochemistry and then if indicated for immunocytochemistry, immunoblotting and electron microscopy. It is important that sufficient muscle is obtained to allow for all likely investigations and that it is processed appropriately.

Genetic Counselling

1. For inherited disorders genetic counselling is essential to provide information regarding diagnosis, prognosis, risk to offspring and pregnancy. This may precede obtaining a definitive genetic diagnosis in symptomatic patients but will generally follow achieving a diagnosis. Most asymptomatic patients at risk of inheriting a disorder should receive genetic counselling prior to genetic testing. This information should be provided to patients and as appropriate to other family members and carers.

2. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) is possible when a definitive genetic diagnosis is reached. These procedures should be discussed with patients and spouses who may be considering having children and should be discussed by a geneticist fully aware of the limitations of these procedures for the specific disorder. These procedures are a strong motivation to achieve a genetic diagnosis for patients entering their reproductive years

Clinical Management

1. All patients who have significant functional limitations should receive a rehabilitation assessment. This should address management of functional limitations including gait balance and posture. This should include assessment for orthoses, mobility aides, wheel chairs and seating. Patients should be assessed regarding an appropriate exercise regimen including stretching, resistive and aerobic training and hydrotherapy. Appropriate review should be arranged depending on patient requirements. Physiotherapy, occupational therapy and speech pathology assessment and management should be available as indicated.

2. Patients and as appropriate families and carers should be provided with information and advice regarding the nature of their NMD and as far as possible likely clinical course, complications and future management. They must be made aware of potentially serious complications that may arise during the course of their NMD eg cardiac arrhythmias, respiratory failure and malignant hyperthermia.

3. Pain and fatigue are frequent symptoms for patients with muscular dystrophies and should be elicited and managed. The aetiologies of the pain are multiple and should be investigated appropriately. Chronic pain should be dealt with using standard approaches to the management of chronic pain including, physical therapy and pain medications. Fatigue is also a frequent complaint. It is multifactorial in origin and is experienced by patients with most NMDs. Energy conservation strategies can help some patients as can aerobic training. Mood disorders and phobias including agoraphobia are frequent and should be elicited and managed.

4. Clinically significant respiratory insufficiency occurs in many NMDs and requires clinical vigilance. Patients should be routinely screened for symptoms of hypoventilation. Measurement of supine and sitting forced vital capacity (FVC) is recommended for any patient with NMD who has any breathing symptoms, has a disorder associated with early respiratory impairment and for all patients prior to any surgical procedure requiring general anaesthesia or conscious sedation. Yearly FVC is recommended for all patients who are wheelchair bound, have pelvic girdle weakness and superimposed pulmonary disease, and have moderate to severe kyphoscoliosis or lumbar hyperlordosis or chest wall deformities such as pectus excavatum. Signs and symptoms of night-time hypoventilation or a drop of FVC to less than 50% of predicted is an indication of probable requirement for nocturnal non invasive ventilatory support and the need for formal sleep polysomnography.

5. Cardiac involvement occurs in many NMDs and may manifest as a disorder of cardiac conduction with a predilection to atrial, ventricular arrhythmias or heart block or as a cardiomyopathy with cardiac failure or a combination of both cardiac conduction defect and cardiomyopathy. Patients who have an NMD that is known to be associated with cardiac involvement should be reviewed by a cardiologist and have Echocardiogram, ECG and for many Holter monitor study. It is important to note that cardiac involvement may precede skeletal muscle involvement, for example the first presentation of a person with myotonic dystrophy can be with cardiac arrhythmia. Patients should be treated early with ACE inhibitors, ARBs and/or beta blockers to help prevent the development of cardiac complications. Patients with cardiac involvement should be monitored regularly and for most at least once a year. Patients with a myopathy but no genetic diagnosis should have a minimum of Echocardiogram and ECG to help exclude cardiac involvement. Patients should be instructed to report episodes of palpitation or syncope which may indicate life threatening arrhythmias immediately and should be investigated urgently.

6. Maintaining good nutritional status, defined as weight for age or body-mass index for age from the 10th to 85th percentiles on national percentile charts, is desirable. It is important to avoid mal- or under-nutrition as well as obesity. Vitamin D status should be checked as deficiency is common and results in bone disease. Thyroid dysfunction may also accelerate the progression of an underlying muscle disorder, and is easy to detect and treat.

7. Clinical swallowing examination is indicated if there is a history of coughing or choking with food or fluids or an unintentional weight loss of 10% or more. Clinical indicators of dysphagia make referral necessary, as do persistent coughing, choking, gagging, or wet vocal quality during eating or drinking. An episode of aspiration pneumonia, unexplained decline in pulmonary function, or fever of unknown origin might be signs of unsafe swallowing, necessitating assessment. Speech pathology assessment and consideration for a modified cine barium swallow are indicated. This may result in dietary modification or gastric tube placement.

8. Bone health is important for patients who are taking corticosteroids or have marked limitations of their mobility. They should be considered for Calcium and Vitamin D measurement and a DEXA scan to guide management.

9. Many NMDs are associated with involvement of other organ systems. It is important that the NMD physician is aware of possible complications and addresses these appropriately and continues to monitor the patient for complications eg myotonic dystrophy

10. Patients should be provided with advice and support regarding education and employment. They should be assisted to obtain appropriate community services and provided with advice and assistance in obtaining pensions and benefits.

11. The clinic should liaise with appropriate patient support organisations and be aware of the services they provide. Clinics should assist patients to contact them.

Pregnancy

1. Most women with NMD can have a safe and successful pregnancy. There is an increased risk of obstetric complications depending on the disorder. It is recommended that pregnant women be followed by high risk obstetricians and that delivery occurs in a centre that can provide comprehensive perinatal care. Additionally, it is recommended that pregnant women with NMD and reduced lung function have serial monitoring of their FVC during the course of their pregnancy.

2. There is a significant chance that women with Muscular dystrophies will have a significant permanent deterioration in their strength following a pregnancy – FSHD, LGMD.

Anaesthesia

1. A number of NMDs carry a significant risk of malignant hyperthermia like reactions with inhalational agents. Intravenous anaesthetics should be used and depolarising agents avoided where possible. . Volatile anaesthetics and depolarising muscle relaxants are contraindicated in patients with RYR1 gene mutations or when these are considered possible or probable unless an in-vitro contraction test has excluded a predisposition to malignant hyperthermia.

Transition

1. Transition is an essential function for both paediatric and adult NMD clinics and requires planning and appropriate organisation. Planning for transition should and education about the transition process for patients and families should begin several years before the transition occurs.

2. Transition should normally occur in the last year of schooling or the following year but may vary when appropriate.

3. Where possible clinicians from adult clinics and clinic coordinators/genetic counsellors should meet patients in the paediatric clinic prior to transition to enable a seamless transfer of clinical and social information and familiarisation with the patient prior to clinic transition

4. Communication is essential to ensuring that all relevant information and data accompanies the patient in a timely fashion.

5. The psychological impact on patients and families of moving from paediatric to adult services must be recognised and managed . As a general rule transition to the adult clinic means greater autonomy for the patients and acceptance of a more supportive role for families. It will often occur at the same time as other major life changes. Ongoing education and training , transition to employment, availability of community and respite services, sexuality and appropriate social activities all become significant issues to the late teenage patient.

6. Transition to adult care will generally involve sourcing more support and rehabilitation services locally rather than centrally, a process that can be facilitated by case management.

7. The transition process should be supported on a statewide basis by a coordinator and allied health services to assist with case management and facilitate the transition to local services.

8. Transition is a good time for the patient and family to access the patient support organisation for assistance and support outside the medical model and patient organisations should be encouraged to become involved and support this process.

Training and Research

1. Clinics should remain alert to opportunities to participate in research and clinical trials.

2. Use of registries and databases to document patient clinical course and to identify patients appropriate for clinical trials.

3. Clinics should take available opportunities to provide clinicians and trainees with exposure to patients with NMDs and their management.

Constitution of a Neuromuscular Disease Service

Continuity of expert care and ready accessibility to services required for NMD patients are the key requirements.

Core Staff

1. Neurologist/Paediatric Neurologist with training and experience in the management of NMDs
2. Geneticist with experience in NMDs
3. Genetic counsellor
4. NMD nurse
5. Rehabilitation specialist with experience in managing NMDs and /or physiotherapist and OT with experience in managing NMDs
6. Dedicated secretarial staff/clinic coordinator
7. Data manager

Additional services readily accessible to the clinic

1. Physiotherapy with experience in managing NMDs
2. Social worker
3. Orthotist
4. Respiratory/sleep physician with experience in managing NMDs
5. Seating service/OTs with NMD expertise
6. Speech pathologist with experience in managing NMDs
7. Cardiologist with experience in managing NMDs
8. Psychological counselling
9. Muscle biopsy service with close linkage to laboratories.
10. Palliative care service
11. Pain service

For adult services in NSW most of the rehabilitation services will be provided locally due to the funding model and ease of access. The clinic will provide a management plan but much of this will be instituted by local facilities and services.

Clinic Requirements

1. Adequate clinic space with good W/C access
2. Adequate disabled parking facilities
3. Disabled toileting
4. Members of the treating team should meet after each clinic to review management plans and make certain that appropriate management, investigations, referrals and clinical review are organised.

Frequency of review

1. Minimum review yearly.

2. Patients reviewed more frequently when there are active issues with diagnosis and/or management.

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Transition

Lead: Merrilee Needham

Transition from paediatric to adult services is an important area where patient services are often inadequate. The reasons for this are complex but the focus must be on best outcomes for the patient. Patients and adult clinicians often struggle to develop new relationships after patients have experienced a long period within the paediatric environment, and adult clinicians need to become familiar with neuromuscular disorders.

This is an increasingly critical gap in care as boys affected by DMD are living longer.

Royal North Shore Hospital has trialled a number of initiatives, including making the transition process start earlier, inviting adult clinicians to the children's hospital for the initial introduction, inviting specialists along to clinic and linking patients to services and maintain the link.

RNSH has no funding and there is limited capacity to expand beyond 2 transition clinics per year. However applications for funding via transition executive underway to fund state neuromuscular transition co-ordinator/allied staff to link patients with local adult services. RNSH is also planning a PhD project to take an evidence based approach to prospectively follow and compare overseas data with local patients to demonstrate impact on quality of life.

ACTIONS

- Develop a combined program involving paediatric and adult clinicians [Merrilee Needham, Nigel Clarke]

DMD portal

Boris Struk

The Muscular Dystrophy Australia (MDA) has developed a website to make available information regarding best practice/evidence in the care and treatment of neuromuscular disorders, starting with DMD and Becker muscular dystrophy.

The website is easily searchable and multiple words can be used to search.

The site is open to the lay community and clinicians.

The MDA will expand to include a forum for frequently asked questions as well as additional neuromuscular disorders.

www.mda-net.md

Mobile clinical management for patients

Phillipa Lamont and Peter Rowe

There are two (2) recent deaths involving patients affected by neuromuscular disorders whose fate may have been avoided if the treating physicians had been provided with disorder-specific clinical issues.

The Duchenne Foundation is undertaking a pilot study for boys affected by DMD. MDA and MDF are supportive of a roll-out to all neuromuscular disorders.

ACTIONS

✳Develop a standard template of information to be uploaded onto a USB datastick [Klair Bailey, Phillipa Lamont, Dani Villano and Sandra Holland]

Gaps in care

Queensland

Anita Cairns

There is no funding to support a multidisciplinary clinic at Mater or Royal Children's Hospital, though a successful pilot of a multidisciplinary paediatric neuromuscular clinic has been run.

Currently, patients have access to care through an outreach clinic at Montrose. Key funding is needed to support a clinic coordinator who could work between Montrose and Mater and Royal Children's Hospitals.

South Australia

Damian Clark

South Australia has a strong rehabilitation department and the majority of care for neuromuscular patients was being provided through this department, however this support has recently ceased due to funding constraints.

MDF is supporting a clinic one (1) month and Novita, a community organisation, is also providing support for physiotherapists and occupational therapists.

There is an opportunity to participate in a clinical trial but nurse support is required.

Western Australia

Phillipa Lamont

Western Australia is unfunded for adult services.

New Zealand

Miriam Rodrigues

Adult services are fractured, due to changes within adult medicine.

ACTIONS

- Include rehabilitation representation within the ANN and at subsequent meetings

Clinical Trials

Clinical Trials Steering Committee:

Monique Ryan and Andrew Kornberg (Co-Chairs)
Kathryn North
Anita Cairns
Joshua Burns
Phillipa Lamont

The ANN aims to consolidate a clinical trials network involving centres in Australia and New Zealand give all patients access to new clinical trials, ensuring immediate access to new therapies.

In order to ensure access to new therapies, the Australian and New Zealand sites must:

- ✳Know our patient numbers
- ✳Have patients well characterized
- ✳Adhere to uniform Standards of Care (assess impact)
- ✳Access to good tissue
- ✳Functional measures
- ✳Identify expertise and experience in conducting clinical trials

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

Currently, the main paediatric clinical trial centres are in NSW and Victoria, with adult trials undertaken in WA.

Expanding to additional sites will attract patients - *there is increased interest in participating in clinical trials than a clinic visit.*

Trial update

GSK Exon skipping	12 month trial complete Extension trial started
WA Exon skipping	22 men recruited >18 yo
Ataluren PTC124	PhIIb completed 2 years ago Extension study planned for 2012
Novel agents: VBP15	Steroid analog (less side effects than prednisone) - PhII in the future

Potential new trials

New CINRG trials
FSH natural history trials
Inherited neuropathy (opportunity for new centres)

STAFFING REQUIREMENTS TO ESTABLISH A CLINICAL TRIAL CENTRE

Clinical trials are complex and require much planning and established infrastructure. Essential requirements include: knowledge of the number of patients that can potentially be recruited, funding to support a clinical trial coordinator well ahead of patient recruitment to enable ethics and other approvals, access to and funding for genetic testing, physiotherapy and pharmacy support.

Essential Staff requirements to run a clinical trial

- A PI (physician) and two backup clinicians
- Medical staff always available for initial/ follow-up appointments and on-call for possible adverse events
- A clinical trials coordinator to oversee the following:
- Ethics submissions
- Data entry and management
- Reporting of labs and other results
- Organisation of patient visits and appointments
- Preparation for audits
- Send- away of specimens
- At least two trained evaluators

Additional Support

- Reliable flexible competent surgeon for taking muscle biopsies
- Helpful kind cardiologist
- Endocrinologist (BMD studies)
- Trial / research pharmacologist
- Blood collector- timely taking of samples
- Laboratory staff able to process specimens in a timely fashion +/- dispatch for analysis

Clinical Trial Coordinator

- Responsible for the management and logistics of a research project
- Approaches research from an organizational perspective
- Vital link between participant, investigative site (study team) and sponsor team
- Tasks have support and practice base
- Positioned as part of a research team
- Responsible for conducting clinical trials using good clinical practice (GCP)Protocol submission – preparation of an IRB (institutional review board) application and informed consent document

- Implementation of clinical trial from initiation through the stages of development
- Recruitment & coordination of the trial subjects – informed consent, screening and inclusion of the subjects adhering to safety and compliance issues
- Coordination and management of the clinical trial – communication with sponsor, study team, EC, participants; visit coordination/scheduling; sampling, time management, product accountability.
- Administration of appropriate tasks/procedures – specimen sampling, questionnaires
- Data collection & management – collection of source documents, using and developing CRFs, management adverse events (AE's), filing & archiving, documentation, managing monitoring visits, dealing with queries. Confidentiality of participants is protected
- Close out of the clinical trial – contributing to research article (if applicable), audit preparation, trial closure, communication with EC, study team & participants, assisting in final study report and completing financial obligations

Plays one of the most important roles in every research project

Ideal Candidate

- Generally hold Bachelor's, master's or doctorate level degree in chosen field – Bio, medical, nursing field
- Current clinic nurse, allied health ideally
- Some experience in research
- Some experience in neuromuscular disease
- Proactive attitude
- Open and clear communicator
- Recognizes potential obstacles and work to resolve them within set time limits
- Conscientious and precise delivery of work even when under pressure
- Flexible and open to change
- Ongoing training/competencies
- Unusual work hours at times
- Adhere to specific study windows
- Attend investigator meetings
- Participate in conference calls

Clinical Evaluator

Role

- ✳Individual with expertise in measures of strength, function, joint range and pulmonary function
- ✳Specialist assessment skills in NMD
- ✳In dedicated clinics (clinic evaluator)
- ✳At designated visits during a clinical trial (clinical trials evaluator)
- ✳Physiotherapist

Why do I need a NM clinic evaluator?

- ✳Longitudinal assessment of strength, function, joint range and pulmonary function
- ✳Can be used for natural history and outcome measure related research
- ✳Help to anticipate changes in disease status
- ✳Assist with decision making regarding therapy
- ✳To meet current standards of care

Why do I need a clinical trials evaluator?

- ✳Primary outcome measures in clinical trials of NMD usually function related
- ✳In most cases CEs will be taking primary outcome measures
- ✳These measures can make or break a trial
- ✳Very important those taking primary outcome measures have right skills, expertise and training

Ideal candidate

- ✳Physiotherapist
- ✳Current clinic Physiotherapist ideal
- ✳Some experience in neuromuscular disease
- ✳Neurology or rehabilitation background
- ✳Able to get the best out of the patient
- ✳Readily available, flexible
- ✳Back-up in the system
- ✳Eye for detail

Commitment

- ✳Attend training/retraining
- ✳Certification in certain outcomes (TREAT-NMD)
- ✳Attend investigator meetings
- ✳Participate in conference calls
- ✳Data queries
- ✳Equipment checks/inventory/ordering/calibration

ACTIONS

Training

- Incorporate clinical trials as part of training - formalise exchange program
  - Training opportunities inVIC and NSW (paediatric) and WA (adult)
- Increase availability of clinical trials outside VIC and NSW
- Coordinate Michelle Eagle physiotherapist training in clinical trials during WMS visit in October
- Advertise VIC physiotherapist education day - August 10th
- Lobby ANZAN etc for additional training opportunities

Allied Health network

- Identify sites requiring clinic
- Identify possible staff already working within these environments
- Identify training needs/appropriate state specific guidelines
- Provide specific training
- Provide ongoing education & support
- Establish network [Dani Villano/Kristy Rose]

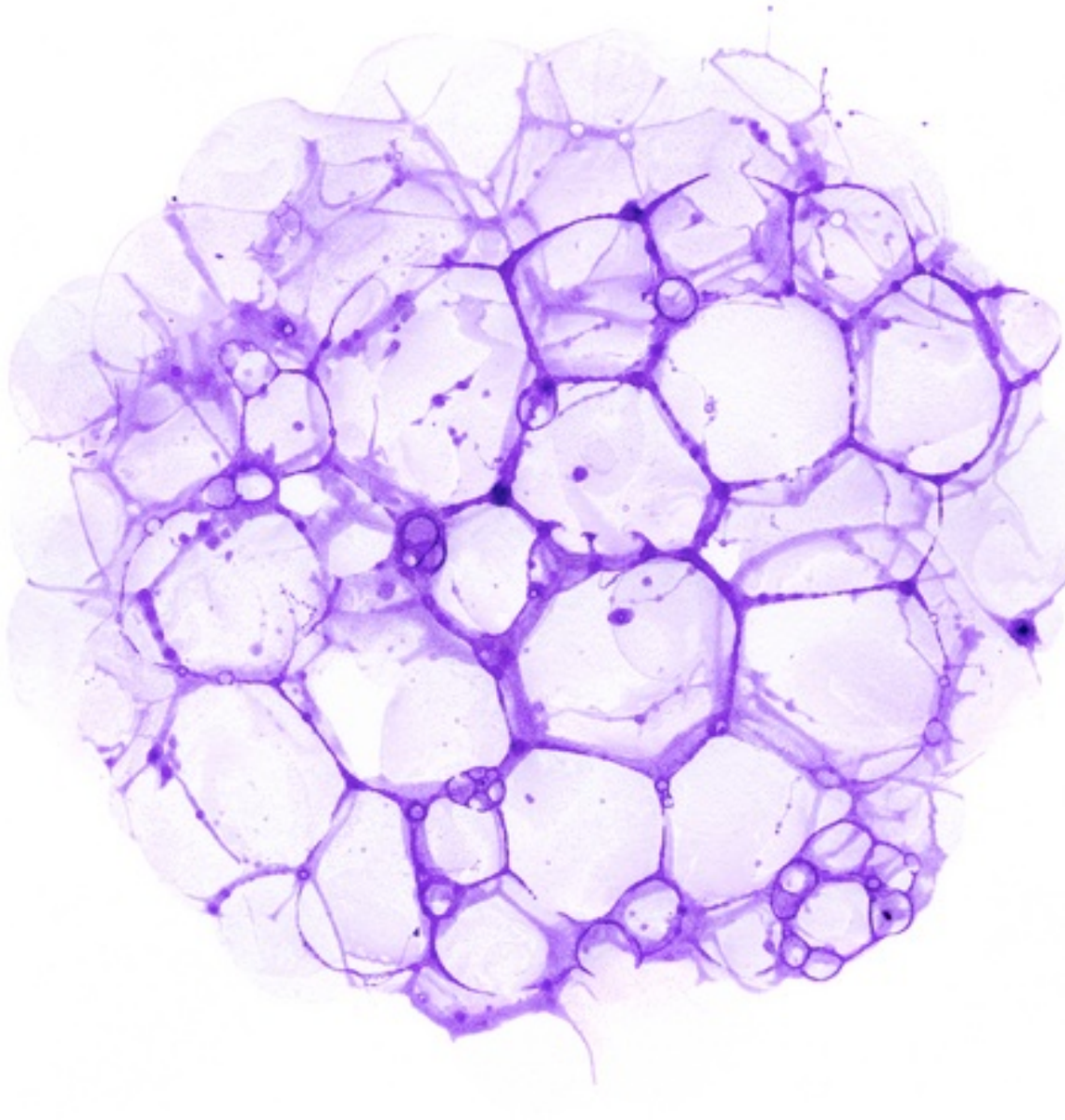
Allied Health network

- Incorporate data from study of outcome measures of a multidiscipliary clinic [Dani Villano]

Research

Research Steering Committee:

Kathryn North (Chair)
Nigel Laing
Nigel Clarke
Monique Ryan
Joshua Burns
Richard Roxburgh



A formal network will strengthen research excellence by overcoming fragmentation of research efforts, and will connect researchers, and clinicians with research questions, to support collaborations, and avoid duplication of effort, competing for the same funding dollar and identifying new areas of research.

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

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

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

Patient Database

The ANN/CRE-NMD aims to establish national integrated secure databases of patient data combining clinical, molecular and pathology data with longitudinal standardised assessments. This resource will be invaluable for clinical researchers in studies of natural history and genotype-phenotype correlation, and will provide a platform for research collaborations.

The development of a patient database goes hand in hand with gene discovery and improved diagnosis and clinical trial readiness. For example, when a new gene is described, a search of the database can be made for a clinical phenotype associated with the gene and then a search for those who don't have a diagnosis.

The INMR uses Biogenix, it stores patient information such as diagnostic tests performed and results, documents and where tissue, blood and DNA samples are stored in the laboratory. It is a database that has a sophisticated search tool. Data can be collated and data fields can easily be added or modified.

The database could easily be set up for individual ANN/CRE-NMD projects, with data collected in a standardised way. Smart forms can easily be developed for each disease/project and collection of informationCo and data entry could form part of the role of an early career researcher doing a study on a cohort for example.

ACTIONS

- Adopt Biogenix as the patient database - CRE-NMD will support the cost to expand the database to each site ($5,000 per site - the initial set-up cost of $35,000 has been covered by the INMR)
- Negotiate the ongoing support costs
- Develop smart forms

Cohort studies: research opportunities

Centronuclear myopathy

Coordinated by Dr Emily Oates (Clinical Geneticist, PhD studies)

Aims

1. Clinical study: Natural history/diagnostic clues

2. Histological clues to genetic cause and pathogenesis

3. New genetic causes

4. Pathogenesis – especially of DNM2-related CNM

Methods

- Diagnosing known causes: Ampliseq screen (DNM2, RYR1, BIN1, MTM1)
- Exome sequencing if no cause identified.
- Pathogenesis: Patient fibroblast/myoblast studies, protein studies (WB, IHC), planning AAV-mouse models
- Surveillance and management of hip dysplasia in CMT - would involve the CRE- NMD in the NIH consortium. Victoria, WA and NSW could collaborate on a CMT study to bring a national focus on the disease.

Contact: Nigel Clarke

Congenital fibre type disproportion

Aims

1. Clinical study: Natural history/diagnostic clues

2. Histological clues to genetic cause and pathogenesis

3. New genetic causes

4. Pathogenesis – especially of tropomyosin myopathies

Methods

- Diagnosing known causes: Ampliseq screen (TPM3, RYR1, TPM2, MYH7) + actin
- Exome sequencing if no cause identified.
- Pathogenesis: Identifying basis of muscle weakness, drug development

Contact: Nigel Clarke

Congenital muscular dystrophy

Aims

Focus is on gene discovery: current undiagnosed cohort of approx. 80 patients

Methods

1. Diagnose patients with known genetic causes

- Guided by clinical information
- IHC/WB for Duchenne, aDG, Col VI, merosin
- Currently can sequence SEPN1, LMNA, FKRP, (RYR1, DMN2)
- Collaboration with Shireen Lamande (Melbourne) for Col VI analysis
- Approach likely to incorporate Perth NMD-platform once available

2. New gene discovery using exome sequencing pipeline

Contact: Nigel Clarke

Duchenne muscular dystrophy

Hypothesis

That below-knee serial casting in boys with DMD who have well-preserved strength can reduce ankle contractures and improve gait parameters, without adversely affecting function**.**

Inclusion criteria

- A diagnosis of DMD confirmed by DNA testing or muscle biopsy
- Aged 4 years or greater
- Independently ambulant over a distance of at least 75 metres and able to complete a 6 minute walk test
- With a measurable calf contracture
- With full passive knee extension or a knee flexion contracture ≤ 5°
- With quadriceps lag < 5°
- With hip and knee flexor and extensor strength of at least grade 4+ on manual muscle testing
- Who are cognitively and emotionally able to cope with the treatment
- Whose family supports the treatment and undertakes to complete the protocol

Contact: Kate Carroll

Dystrophinopathies

Aim

There is a specific cohort of patients who have demonstrated genetic changes in their dystrophin gene with cognitive impairment but no muscle weakness.

Hypothesis

Does dystrophinopathy manifest with cognitive impairment?

Inclusion criteria

✳Genetic changes in the dystrophin gene with cognitive impairment by no muscle phenotype

Methods

✳Chromosomal microarray

Contact: Monique Ryan

Facioscapulohumeral muscular dystrophy

There is no animal or tissue culture model for FSHD, there is no obvious candidate treatments for clinical trials and likely specific treatment still well in the future.

There are a number of collaborative opportunities in this area:

✳clinical markers

✳longitudinal studies - registries

✳muscle MRI as a marker of disease activity

✳atypical cases

✳vascular leakage

✳biology of muscle biopsy

Contact: Alastair Corbett

Foetal akinesia/hypokinesia

This research is funded by a NHMRC grant and exome sequencing is supported by the Association Francaise Contre les Myopathies (AFM).

The cohort currently includes 68 families with 86 affected individuals from Australia, NZ, Turkey and the UK, as well as whole exome data from 6 cases from 4 families.

Patients affected by foetal akinesia/hypokinesia, arthrogryposis, pterygia or multiple contracture syndromes can participate in the studies.

Saliva kits for DNA collection can be provided if required.

Contact: Nigel Laing and Gina Ravenscroft

Inclusion body myositis

In collaboration with Mike Figure -.-, UK

Current situation

There is no cure for IBM, nor is there a standard course of treatment - IBM does not respond to immunosuppressive therapy.

Future potential therapy

Mike Hanna in the UK is screening the exome and has access to a large biobank in the UK.

Mike Hanna is also adopting a novel treatment trial approach to IBM - PhIII trial is a possibility later this year and may involve an Australian site.

Australia has an opportunity to nominate patients for the study and to contribute patient samples to this bank (stored locally in NSW).

Contact: Merrilee Needham

Limb girdle muscular dystrophy

Aims

Focus is on gene discovery: current undiagnosed cohort of approx. 100 patients

Methods

1. Diagnose patients with known genetic causes

✳Guided by clinical information, muscle MRI

✳IHC/WB for dystrophin, aDG, SGs, calpain, dysferlin, telethonin

✳Sequence FKRP, dysferlin, CAV3, TCAP, FHL1, ANO5

✳Approach likely to incorporate Perth NMD-platform once available

2. New gene discovery using exome sequencing pipeline

Information needed for the project

✳Clinical information + pathology report

✳For dystrophies; current screens require the frozen muscle biopsy

✳Consent - can supply CHW consent forms

Contact: Nigel Clarke

Myotonic dystrophy

Current situation

Animal models and tissue culture systems have been developed to assess the results of potential therapies.

Future potential therapy

There is the likelihood of human trials within 5 years.

There are a number of collaborative opportunities in this area:

✳Clinical markers of disease progression or biomarkers to be used for future therapeutic trials

✳Longitudinal studies - registries

✳Management of cardiac complications

✳Cognitive impairment

✳Management of fatigue and sleep disturbance

✳Susceptibility to infection

Contact: Alastair Corbett

Nemaline myopathy

Coordinated by Dr Sarah Sandaradura, Neurogenetics Fellow

1. Investigation of recent improvements in clinical care on the natural history of nemaline myopathy.

Clinical study:

- How advances in clinical care have impacted the natural history of NM.
- Reviewing bone health, respiratory care, experiences with tyrosine, muscle MRI, characterising natural history by genetic cause
- Identifying new genetic causes
- Screening NM patients without genetic diagnosis by ACTA1 sequencing, Ampliseq screen
- Exome sequencing if no cause identified.

2. Assess the therapeutic effect of Tyrosine: retrospectively looking at patients who have been on tyrosine through a questionnaire.

This study is open to patients to participate in a retrospective study (over past 15 years) of an international cohort.

Contact: Kathryn North

Necrotizing autoimmune myopathy (NAM)

In collaboration with Frank Mastaglia and Chris Blundell, WA

Necrotizing autoimmune myopathy (NAM) is a treatable disease - patients respond to immunosuppressive agents such as prednisone.

Statins have been associated with necrotising myopathies and is strengthened by the discovery that the serum of some patients contains an anti-HMGCR antibody.

Patients on statins with necrotising myopathy are needed for further studies in this area.

- ✳Longitudinal studies - registries
- ✳Management of cardiac complications
- ✳Cognitive impairment
- ✳Management of fatigue and sleep disturbance
- ✳Susceptibility to infection

Contact: Merrilee Needham

the future.

Sustainability is an important issue that needs to be incorporated into planning discussions - in fact a recent meeting convened by TREAT-NMD highlighted the importance of planning for the future - a critical meeting was held two (2) months before the five (5) year funding was coming to an end to secure ongoing funding. A number of the goals of the ANN and the CRE require a significant amount of funding to support in an ongoing basis to provide excellence in clinical care and treatment for all individuals affected by neuromuscular disorders and we need to be involving state and federal government, industry and support groups in our planning discussions. Core resources that underpin excellence in clinical care include multidisciplinary clinics, registries and patient databases to underpin clinical trial readiness, a muscle bank as an important source of research material and the support of early career researchers.

The ANN Workshop was attended by representatives from the Muscular Dystrophy Foundation, state Muscular Dystrophy associations, the Muscular Dystrophy Association of New Zealand and Muscular Dystrophy Australia. There is a very positive relationship within the muscular dystrophy community with strong links to clinical and research groups. Funding from the muscular dystrophy community has provided much needed support for patients including equipment, counselling and camps, salary support for clinic staff, sponsorship of meetings, pilot initiatives including postgraduate scholarships for social workers and psychologists (and may expand), field worker service, data entry into registries, and research.

In the future, this balance between patient support and improving health outcomes and quality of life will be better served through the ANN. Expanding clinical trials centres, providing training opportunities and support to establish multidisciplinary clinics, establishing patient databases and registries and working towards a national diagnostic network are only a few of the aims of the ANN that are an integral component of improving care and providing equitable access to a high standard of care.

Key areas of importance for ongoing support:

- Multidisciplinary clinics and Transition support – essential for provision of standards of care and for conduct of clinical research and clinical trials.

- Common clinical databases linked with registries up and running in each state – essential for national approach to research/ diagnosis and clinical trials. Ongoing support for national database and local research data coordinator. These individuals can also support data collection on patients and clinical trial coordination

✳ Sponsorship of meetings of ANN and CRE. Representation by ANN and CRE at State meetings to talk about national research initiatives.

✳National Muscle Biospecimen Bank – a core research need

✳Research Projects

State based:

✳Support for individuals - early career researchers and PhD students

✳Support for pilot projects/small grant scheme – ie support of a research idea for one year so that data can be collected to support application for more extensive funding

National

✳Larger research grants – scheme can be set up in association with NHMRC – so that grants can be submitted to NHMRC and assessed by expert reviewers – resulting in assessment and score. Grants that are not funded by NHMRC can then be considered for partial or full funding by MDAs/MDF and other organisations.

Appendix

In Attendance

Alastair Corbett	alastair.corbett@sydney.edu.au
Anita Cairns	Anita.Cairns@mater.org.au/ anita_cairns@health.qld.gov.au
Boris Struk	bms@mda.org.au
Catriona McLean	C.McLean@alfred.org.au
Damian Clark	DamianR.Clark@health.sa.gov.au
Daniella Villano	Daniella.Villano@rch.org.au
Desiree du Sart	dusart.desiree@mcri.edu.au
Dick Cotton	cotton@unimelb.edu.au
Eppie Yu	eppie.yiu@rch.org.au
Graeme Hammond-Cooke	Graeme.Hammond-Tooke@southerndhb.govt.nz
Hugo Sampaio	Hugo.Sampaio@sesiahs.health.nsw.gov.au
John Gummer	john.gummer@mdwa.org.au
Kate Carroll	kate.carroll@rch.org.au
Kathie Friend	Kathryn.friend@adelaide.edu.au
Katie Duvall	katy.devalle@rch.org.au
Kathryn North	kathryn.north@health.nsw.gov.au
Klair Bailey	klairbayley@hotmail.com
Kristi Jones	kristi.jones@health.nsw.gov.au
Kristy Rose	kristy.rose@health.nsw.gov.au
Leanne Mills	leanne.mills@health.nsw.gov.au
Leigh Waddell	leigh.waddell@health.nsw.gov.au
Lynda Rigby	Lynda.Rigby@genzyme.com
Mark Davis	Mark.Davis@health.wa.gov.au
Merrilee Needham	MNeedham@nsccahs.health.nsw.gov.au
Miriam Rodrigues	MRodrigues@adhb.govt.nz/Miriam@mda.org.nz
Monique Ryan	Monique.Ryan@rch.org.au
Nigel Clarke	nigel.clarke@health.nsw.gov.au
Nigel Laing	nigel.laing@uwa.edu.au
Paul Kennedy	P.Kennedy@alfred.org.au
Rachel Kennedy	rachel.kennedy@rch.org.au
Paula Bray	paula.bray@health.nsw.gov.au
Peter Rowe	Peter.Rowe@health.wa.gov.au
Phil Martin	pmartin@mdasa.org.au
Phillipa Lamont	phillipa.Lamont@health.wa.gov.au
Ric Sicurella	Ricardo.Sicurella@genzyme.com
Sandra Holland	Sandra.Holland@sesiahs.health.nsw.gov.au
Tim Day	Timothy.Day@mh.org.au
Tom Robertson	thomas_Robertson@health.qld.gov.au

Future Meetings

2012

8th October	Perth (in conjunction with WMS)

2013

February TBA	Sydney