Treatment of muscular dystrophies: Present and future

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Disclaimer

- Professor and Honorary Consultant in Newcastle NHS Trust
- PI on several industry and academic funded drug studies
- Consultant to several companies with interests in the drug development field for muscular dystrophies
  - No personal financial relationships with any company
  - No specific endorsement of any products

Learning objectives

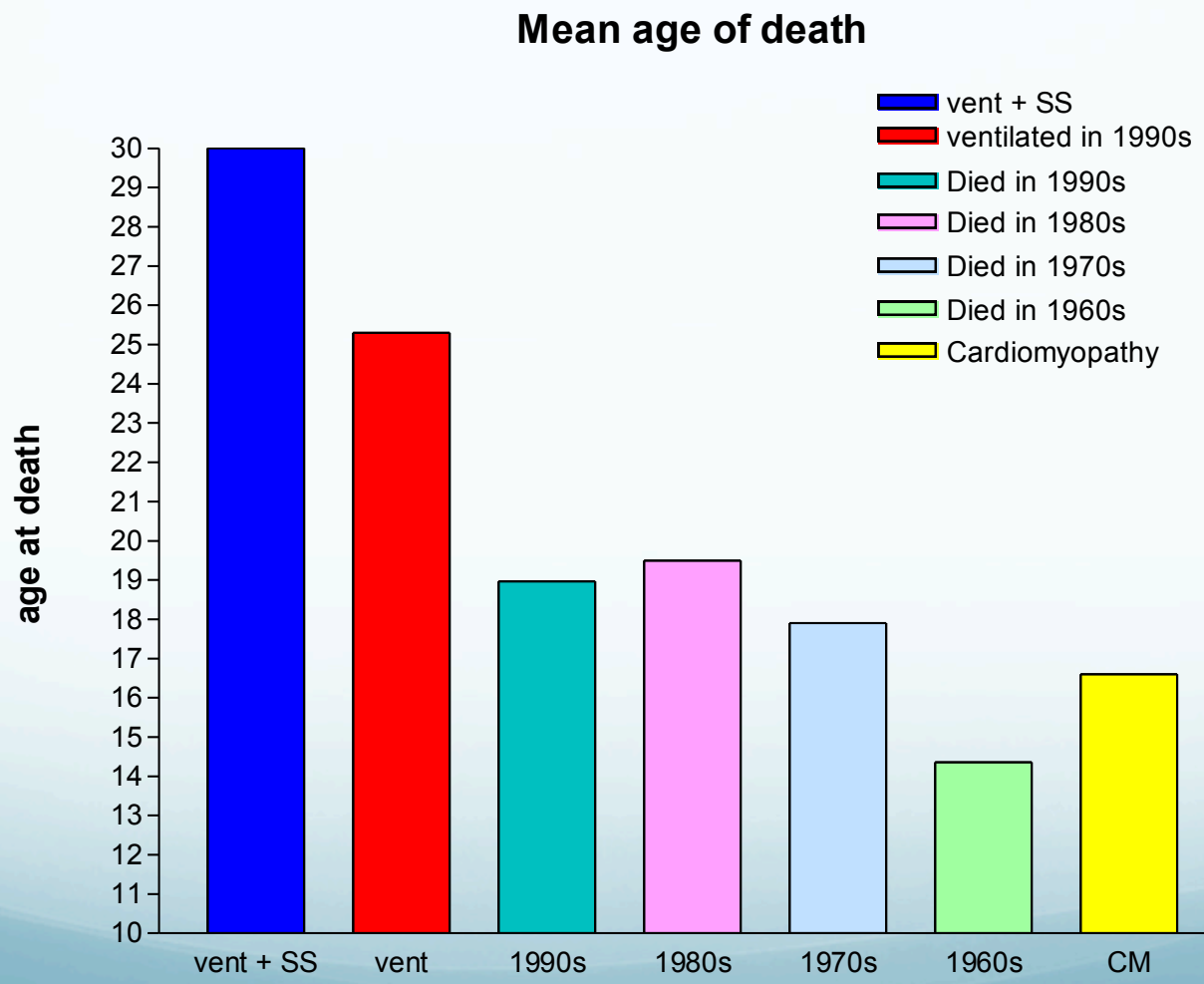
- Why is the current treatment of muscular dystrophy important?
- What are the pivotal points in disease progression to recognise and plan for?
- What is the toolkit and the team who are required?
- What is the perspective for innovative therapies changing our treatment paradigms?

- Disclaimer: not a lecture on all the interventions necessary for all muscular dystrophies, nor all therapies.....

Why is management of inherited NMD important?

- No cure- but no reason for nihilism either
- Life-long conditions, patients need to be empowered to understand their care needs
- Frequently simple principles underpin interventions which may extend life expectancy and enhance quality of life
- Overarching aim of medical management is to anticipate and manage problems to facilitate participation in normal life

How do we know this makes a difference?



What are the components of quality care?

- Knowledge
- A lifelong anticipatory approach
- Patient centred (nothing about me without me)
- A holistic attitude
- Multidisciplinary approach with different skill sets represented and available when needed

What does multidisciplinary care look like? (eg DMD)

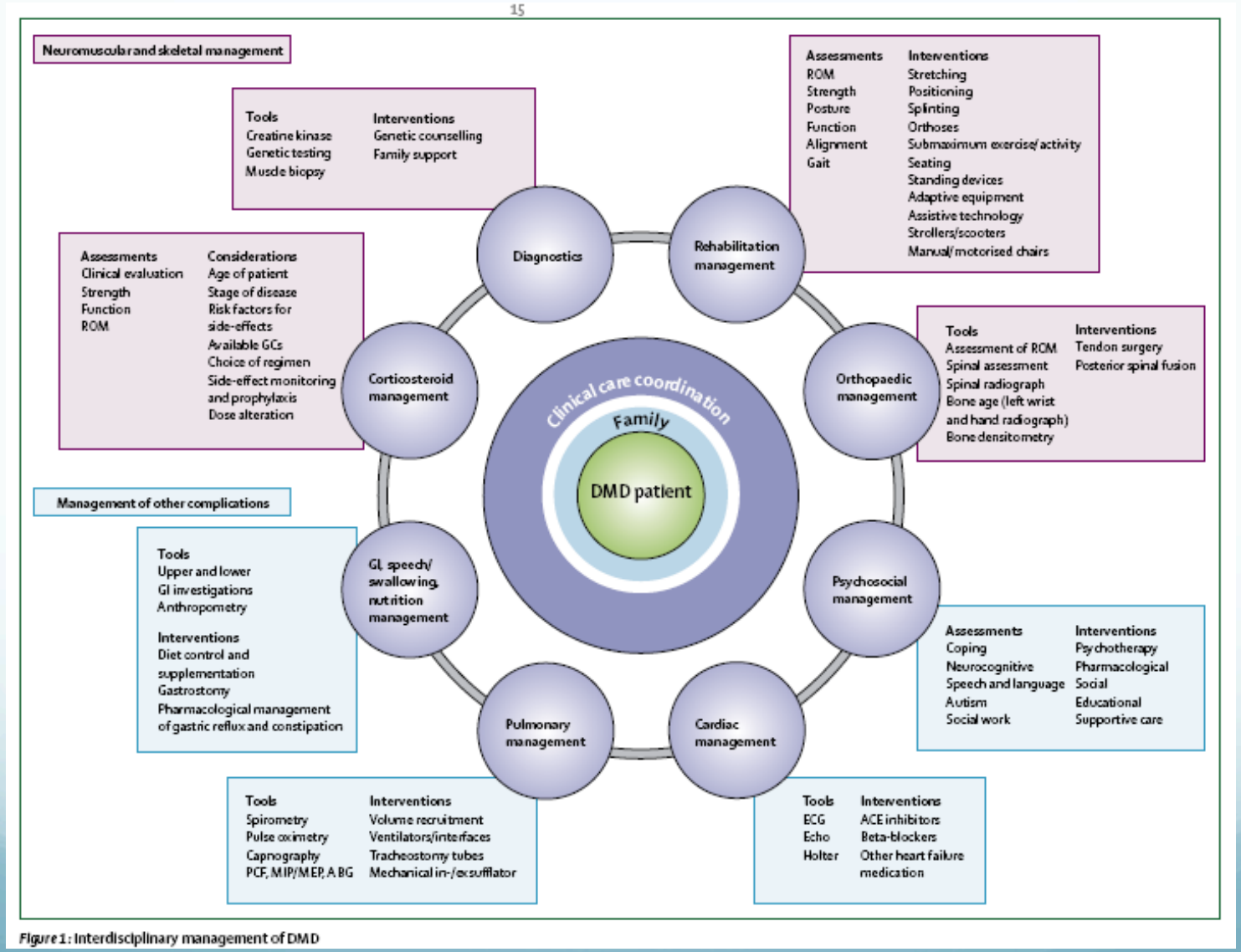
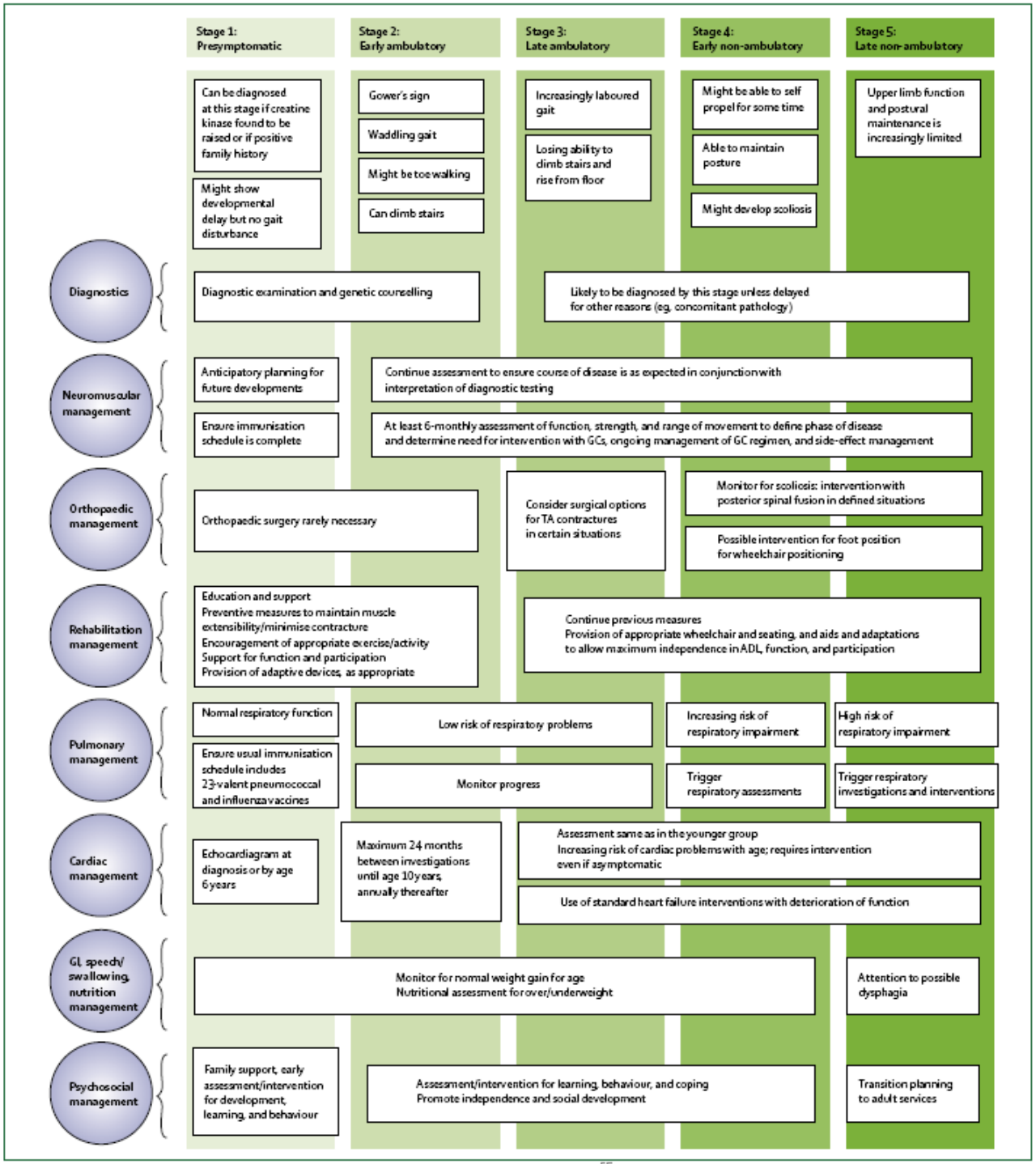


Figure 1: Interdisciplinary management of DMD



Inputs need to be aligned with disease progression (example from DMD)

Management starts before and at diagnosis

- Diagnostic tools
  - Clinical assessment
  - Creatine kinase levels
  - EMG
  - Muscle MRI
  - Muscle biopsy
  - DNA testing

*genetic counselling is not only an issue at diagnosis!! Remember carrier issues, affected individuals reaching reproductive age, new interpretations of genetics.....

- Interventions around diagnosis
  - Best practice will include time for diagnostic appointment, rapid opportunity for follow up
  - Genetic counselling*
  - Family support
  - Information
  - Prospective care planning: hope! “planning for the best”
  - Contact with patient organisations, registries

Diagnosis determines management

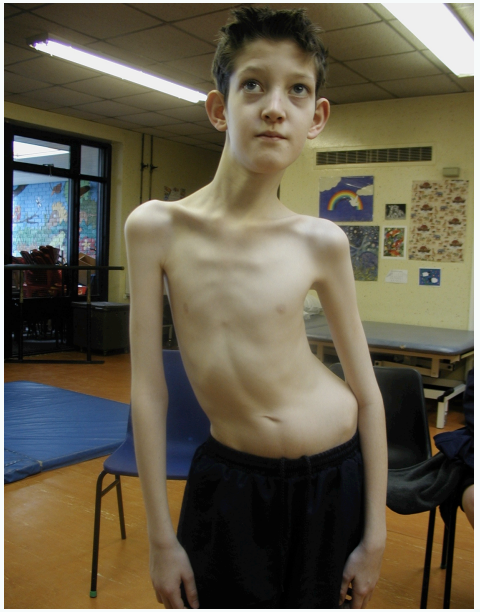
- 28% myotonic dystrophy
- 23% DMD/BMD
- 10% FSHD
- 5% SMA
- 6% LGMD
- <3% each Bethlem, congenital muscular dystrophy, congenital myopathies
- <2% myofibrillar myopathies, distal myopathies
- ~20% undiagnosed/ under investigation

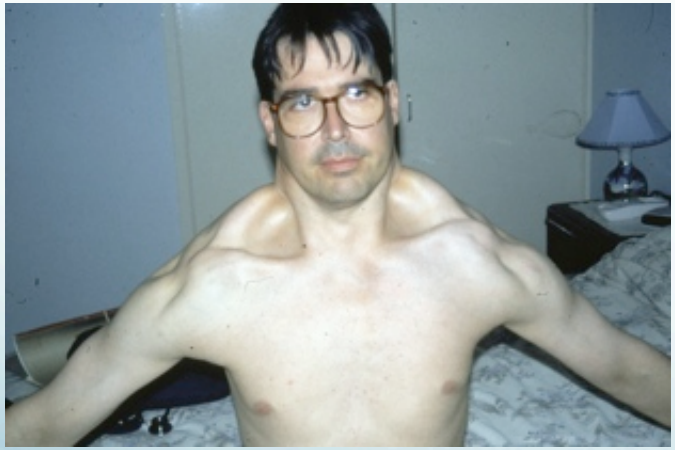
Local clinic population of ~1200 patients

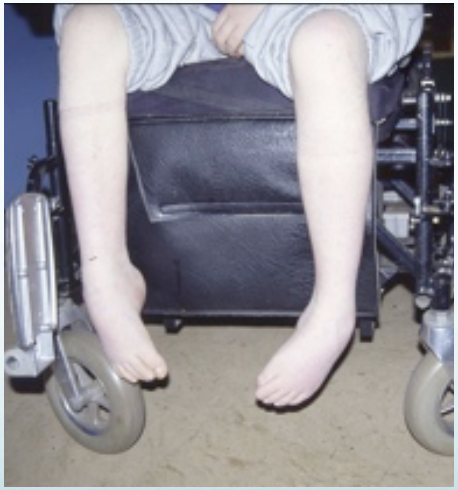
(Norwood et al 2009)

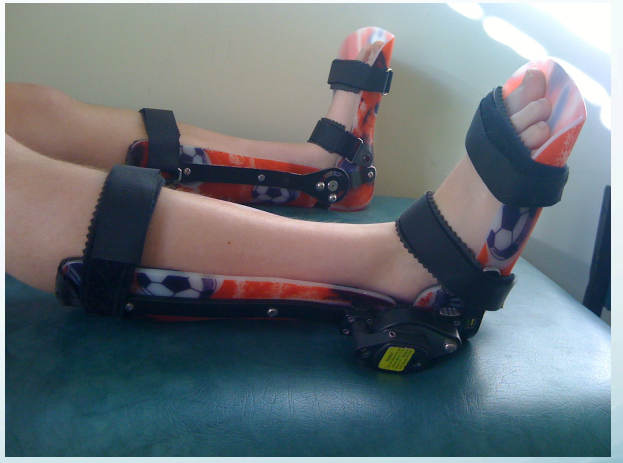
Neuromuscular management

- Aim
  - The optimal maintenance of muscle strength and function
  - Facilitate participation, access to education, employment, fun
  - Involves the NM specialist, physiotherapy, occupational therapy, rehabilitation medicine, orthotics, wheelchair services.....









Varied muscular dystrophies: varied NM management issues

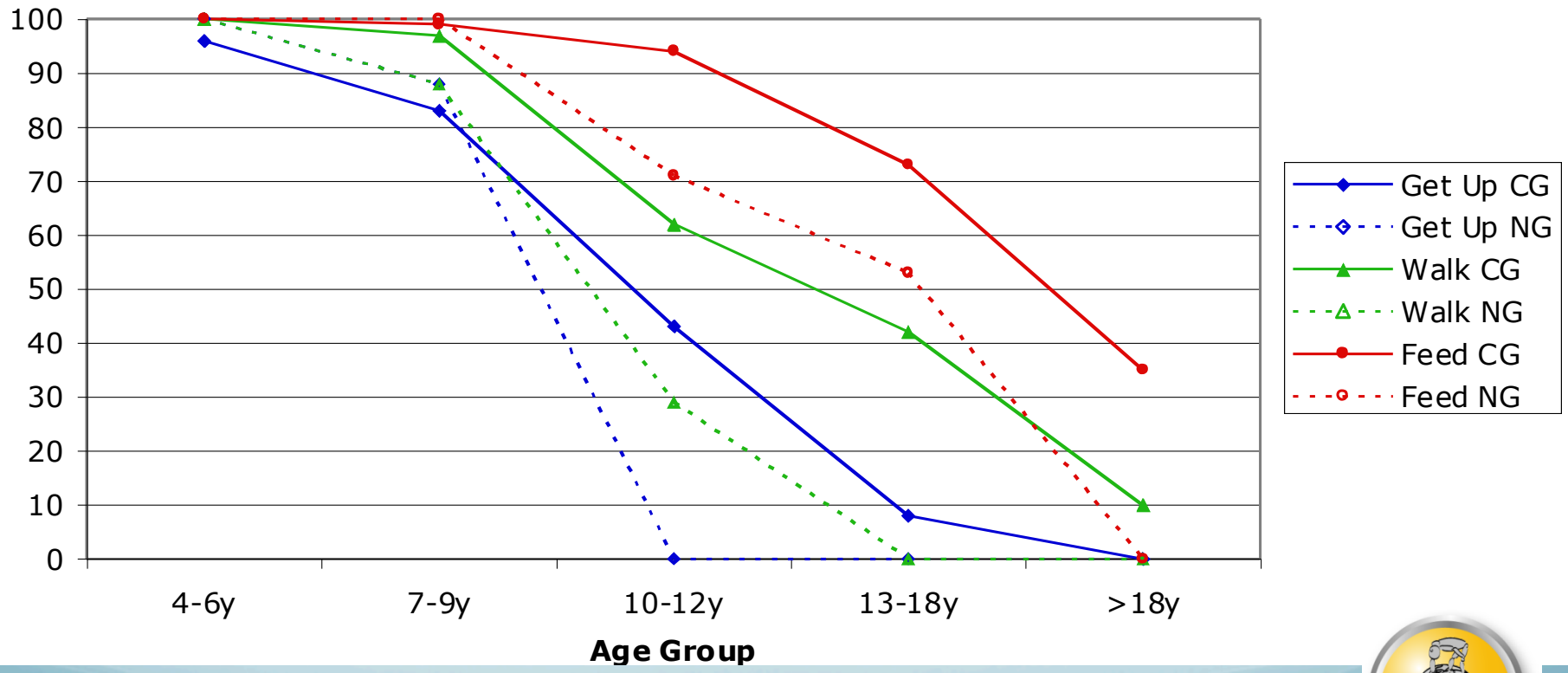
Neuromuscular management toolkit

- Assessments
  - Range of motion
  - Posture
  - Strength
  - Function
  - Alignment
  - Gait
- Interventions
  - Stretching
  - Splinting
  - Orthoses
  - Standing devices
  - Seating
  - Wheelchairs
  - Adaptive technology
  - Exercise
  - Pharmacological
- Targeted to specific disease and stage of disease and anticipation of progression

Impact of steroid use in DMD and its monitoring

- Prolongation of ambulation
  - Functional scales, timed testing
- Prevention of scoliosis
  - Serial assessment
- Improved respiratory function
  - Serial assessment
- Longer self feeding
  - Non ambulant assessment
- ? Cardioprotective
  - Cardiac follow up
- Short stature and weight gain
  - Measurement, referral for dietetic advice
- Delayed puberty
  - Endocrine assessment
- Osteoporosis and vertebral fracture
  - Bone health
- Cataract
  - Ophthalmological assessments
- Metabolic issues....

Relationship between measures and endpoints



C McDonald[1], RT Abresch[1], E Henricson, J Han[1], R Leshner[6] E Hoffman[6], D Escolar[6], A Cnaan[6], F Hu[6], A Zimmerman[6], T Duong[6], J Mayhew[14], J Florence[13], A Arrietta[6] and the CINRG Investigators[2-20]

In addition to neuromuscular issues: very specific risks of complications determine the importance of different issues in anticipatory care

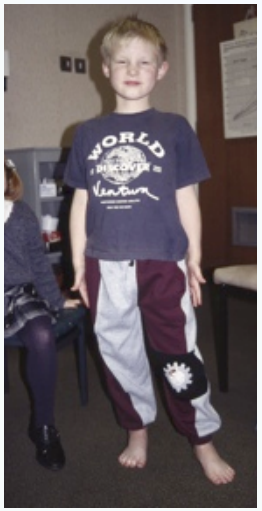
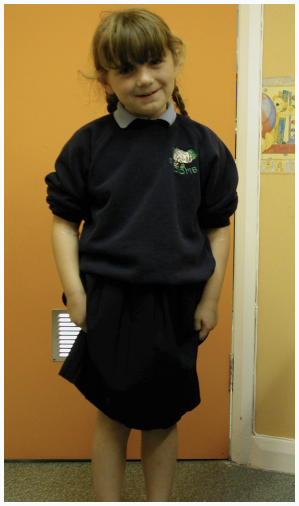
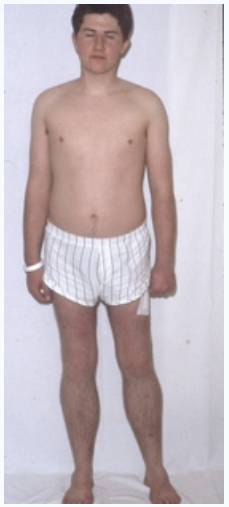
	DM1	DMD/ BMD	FSHD	SMA	LGMD	CMD	MFM	Unknown
Cardiac arrhythmias	X	(X)			(X)		X	?
Cardiomyopathy		X			(X)	(X)	X	?
Respiratory failure	X	X	(X)	X	(X)	X	X	?
GI problems	X	X		X		X	X	?
Endocrine issues	X	X						?
Anaesthetic implications	X	X	(X)	X	(X)	X	(X)	?
Scoliosis	(X)	X	(X)	X		X		?
Learning problems	(X)	(X)				(X)		?
Adjjustment	X	X	X	X	X	X	X	X
Other	X		X					?

Respiratory care in NMD

- Diagnosis gives you a guide to relative risks of
  - Poor cough, failure to clear secretions, chest infections
  - Diaphragmatic involvement
  - Decreasing respiratory muscle strength during or after loss of ambulation
  - Remember concomitant problems with swallowing can add risk of aspiration
  - Symptoms of respiratory failure can be insidious and need to be specifically sought

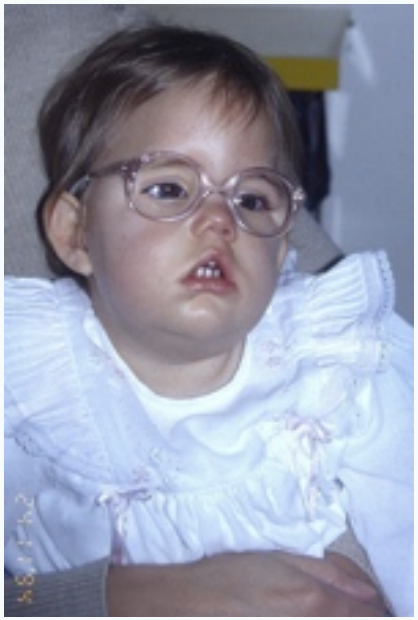
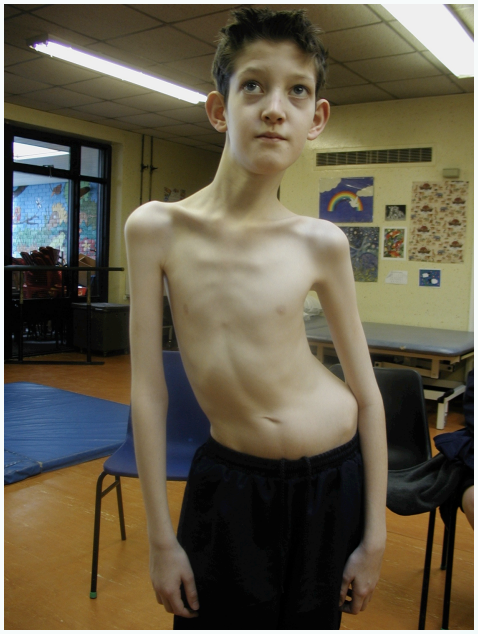
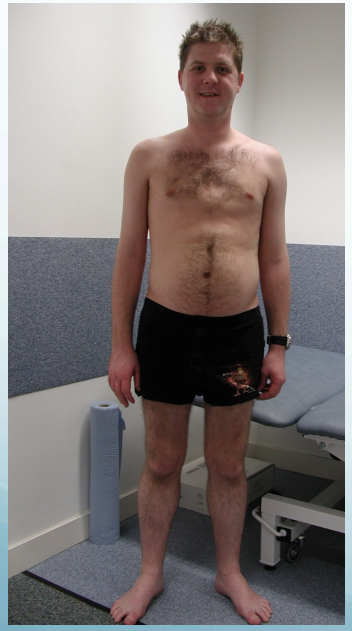
- Diagnosis is also key to determining age/ stage of disease at which problems may arise

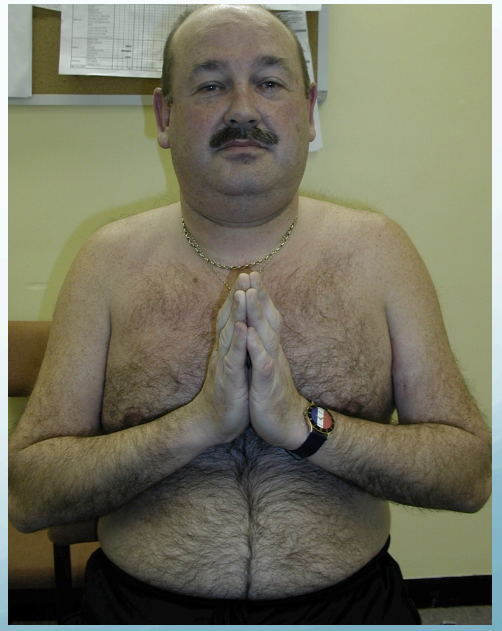
DGC related diseases: relatively stereotypical progression to respiratory failure


FVC monitoring, clinical assessment, peak cough flow, overnight oximetry capnography: clear predictors of nocturnal hypoxaemia and hypercapnia (see care considerations)

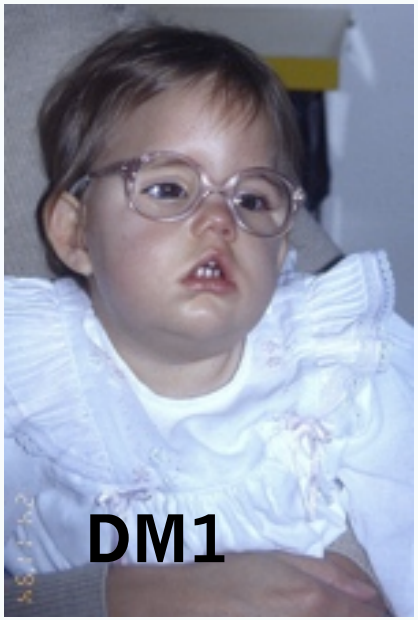


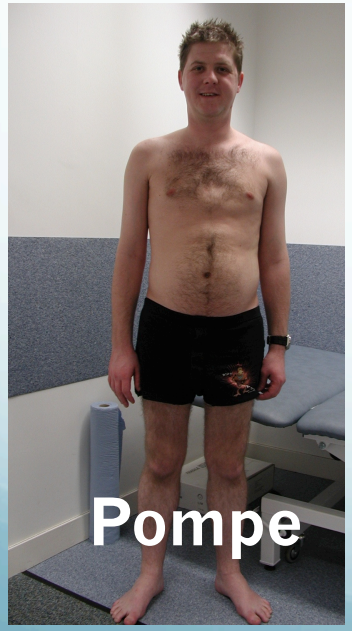




Ullrich


SMA

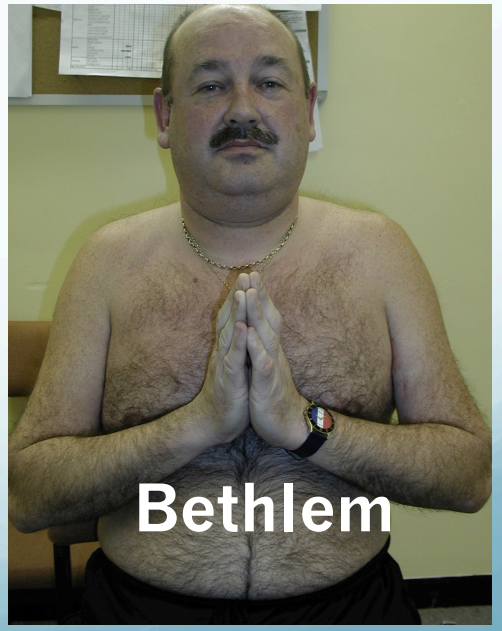

DM1


Multicore
and other
myopathies


Pompe


LGMD2I


ADEDMD


Bethlem

Respiratory care in NMD: toolkit

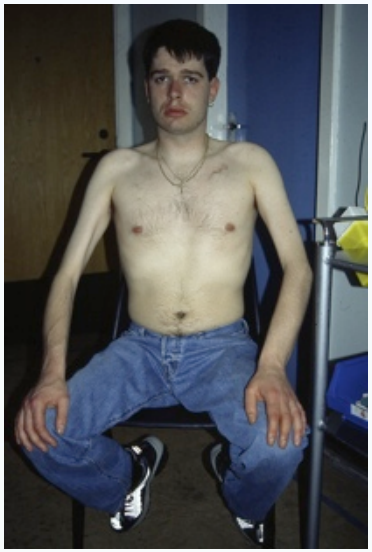
- Assessment
  - Forced vital capacity
  - Peak cough flow
  - Capnography
  - Overnight oximetry
- Staged interventions
  - Volume recruitment
  - Cough enhancement
  - Nocturnal ventilation
  - Daytime ventilation
  - Tracheostomy
- Prophylaxis
  - Immunisations
  - Prompt treatment of chest infections
  - Pre-operative care
- Personnel
  - Respiratory consultant
  - Access to assessments
  - Home ventilation care team for ongoing care and risk management

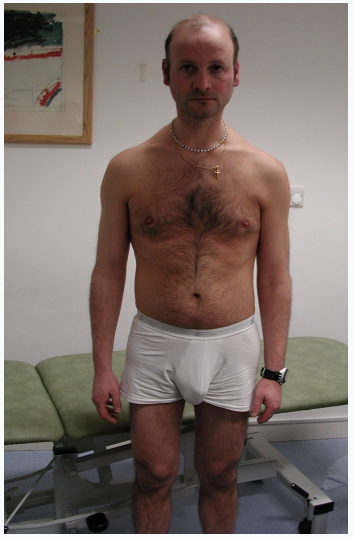
Aim: proactive prediction of respiratory problems and prevention of emergencies through timely intervention

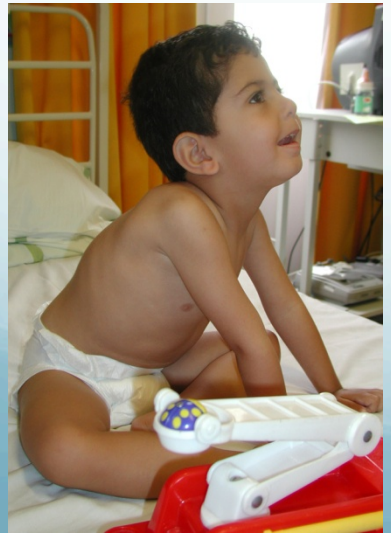
Cardiac care in inherited NMD

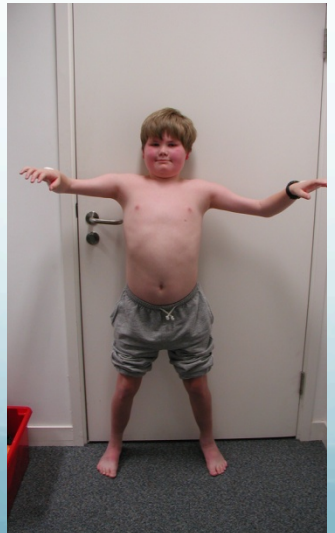
- Diagnosis gives you relative risk of
  - Arrhythmias, their likely effect and treatment
  - Cardiomyopathy
  - Timing of problems
  - NMD are rarely symptomatic: you must NOT wait for symptoms before acting on cardiac risk
- Important interplay with respiratory care: both need to be optimised

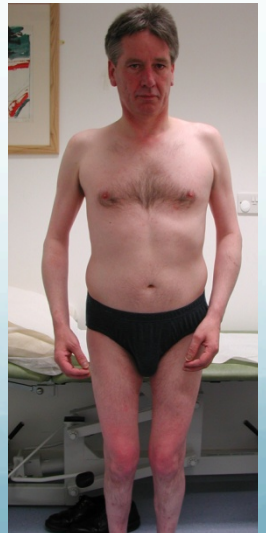
Prominent risk of arryhthmia

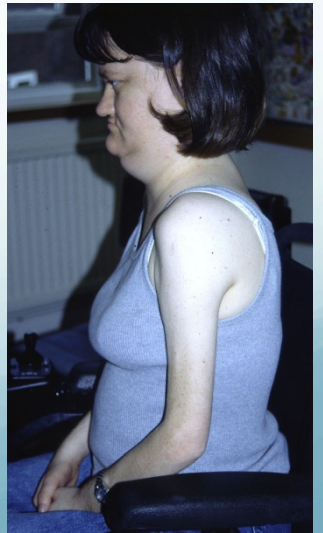




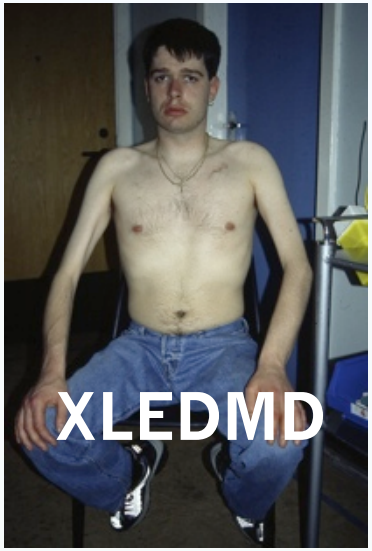


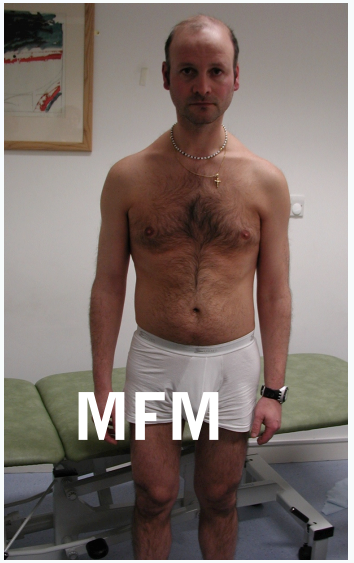


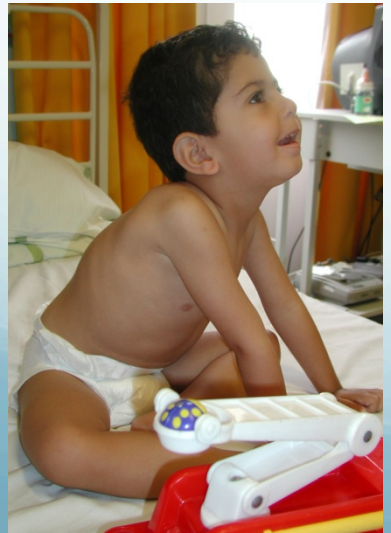


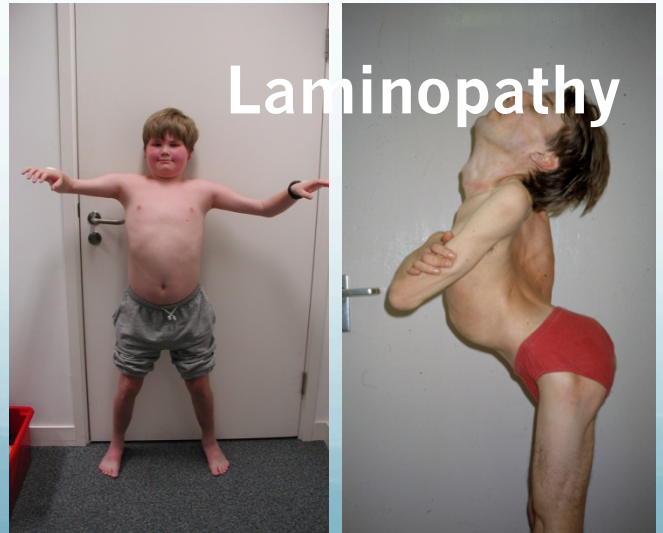


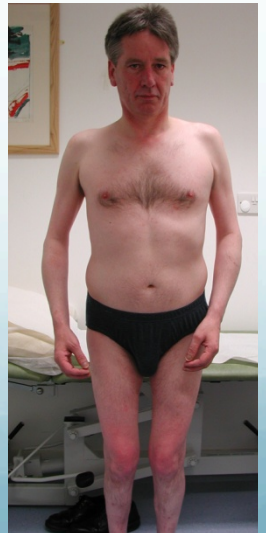
Prominent risk of arryhthmia

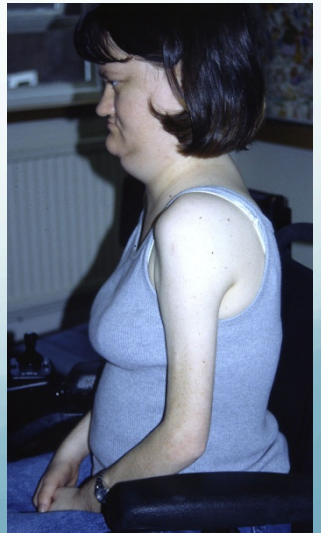




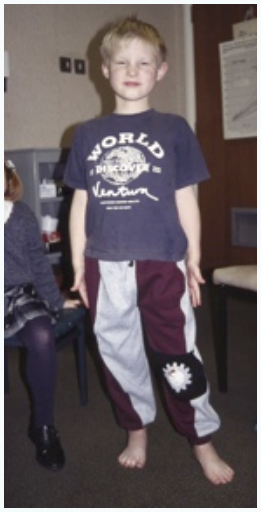
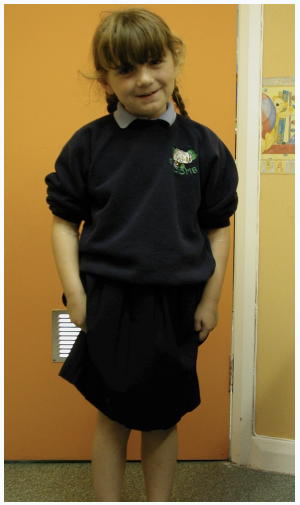
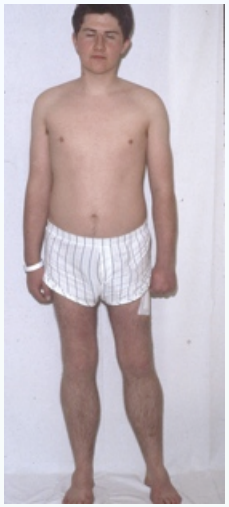


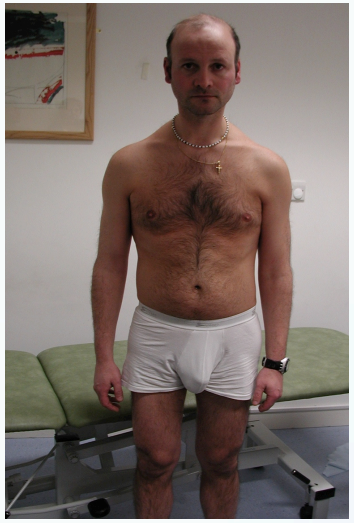
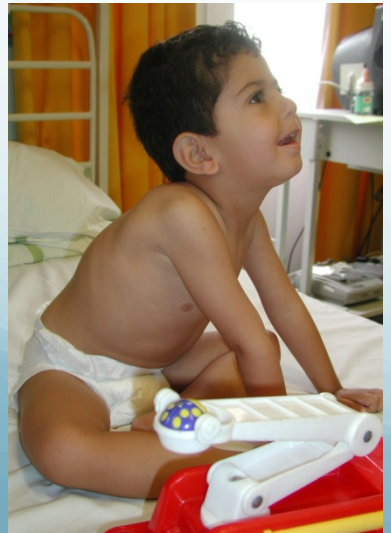
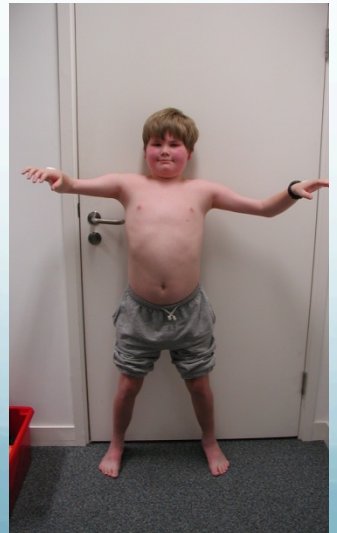


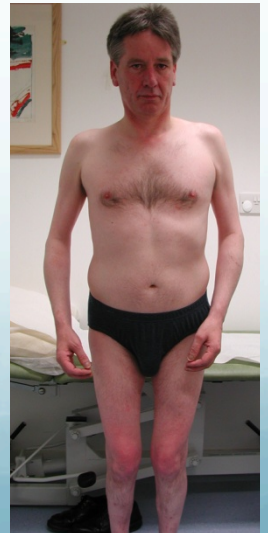
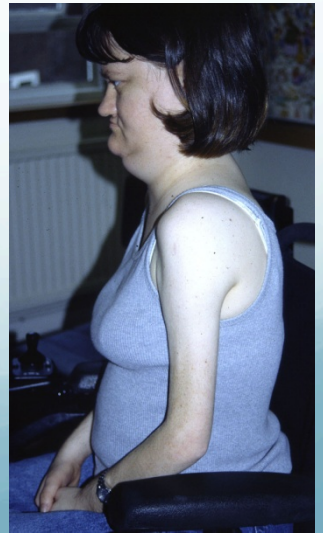




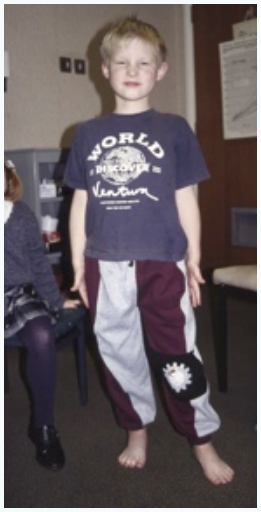
Prominent risk of cardiomyopathy

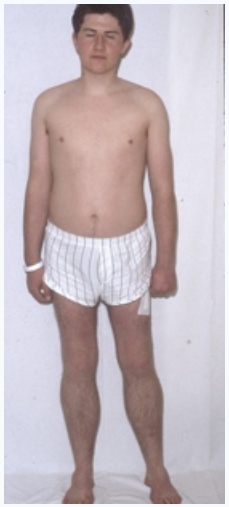




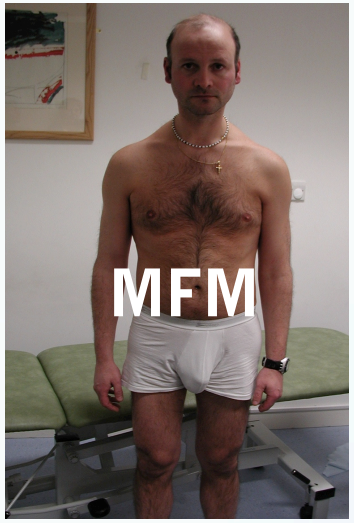





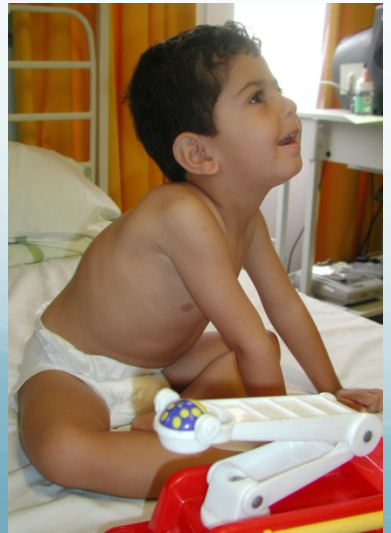



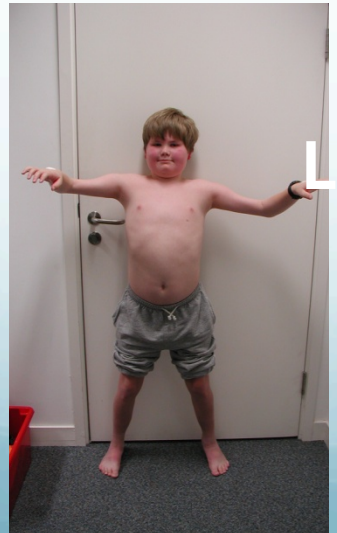
Prominent risk of cardiomyopathy

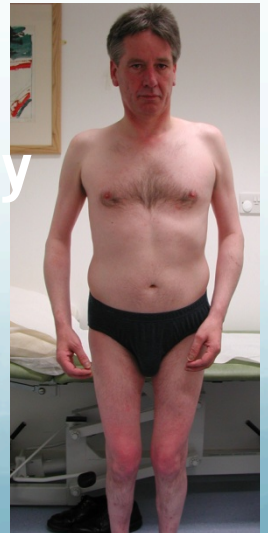


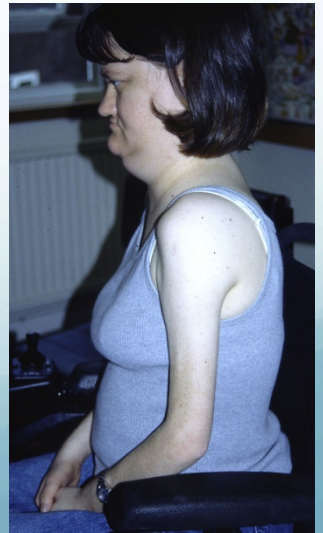












Cardiology toolkit

- Assessments
  - ECG
  - Echocardiogram
  - Holter monitoring
  - (Cardiac MRC)
  - (Tissue doppler)....
- Routine timing depends on level of risk
- Always
  - If symptomatic
  - Before planned surgery
  - Pregnancy

- Interventions
  - Pacing
  - Implantable defibrillator
  - ACE inhibition
  - Beta blockade
  - Other pharmacological interventions as per heart failure recommendations
  - Artificial heart
  - Cardiac transplantation

Aim: proactive prediction of cardiac problems and prevention of emergencies through timely intervention

Nutritional issues

- Probably under reported and managed
- Obesity risk (steroids, immobility)
  - Further limitation of mobility
- Risk of underweight
  - Long meal times
  - Choking episodes
  - Failure to thrive
  - Cachexia
  - Increased risk of chest infections and respiratory failure
- Other GI issues: IBD, constipation also probably under reported and managed
  - (myotonic dystrophy and pseudo ileus)
- Assessments
  - Weight
  - Swallowing evaluation
  - Time of meals
- Interventions
  - Exercise advice
  - Dietary and SALT advice
  - Supplementation
  - Nasogastric feeding
  - PEG

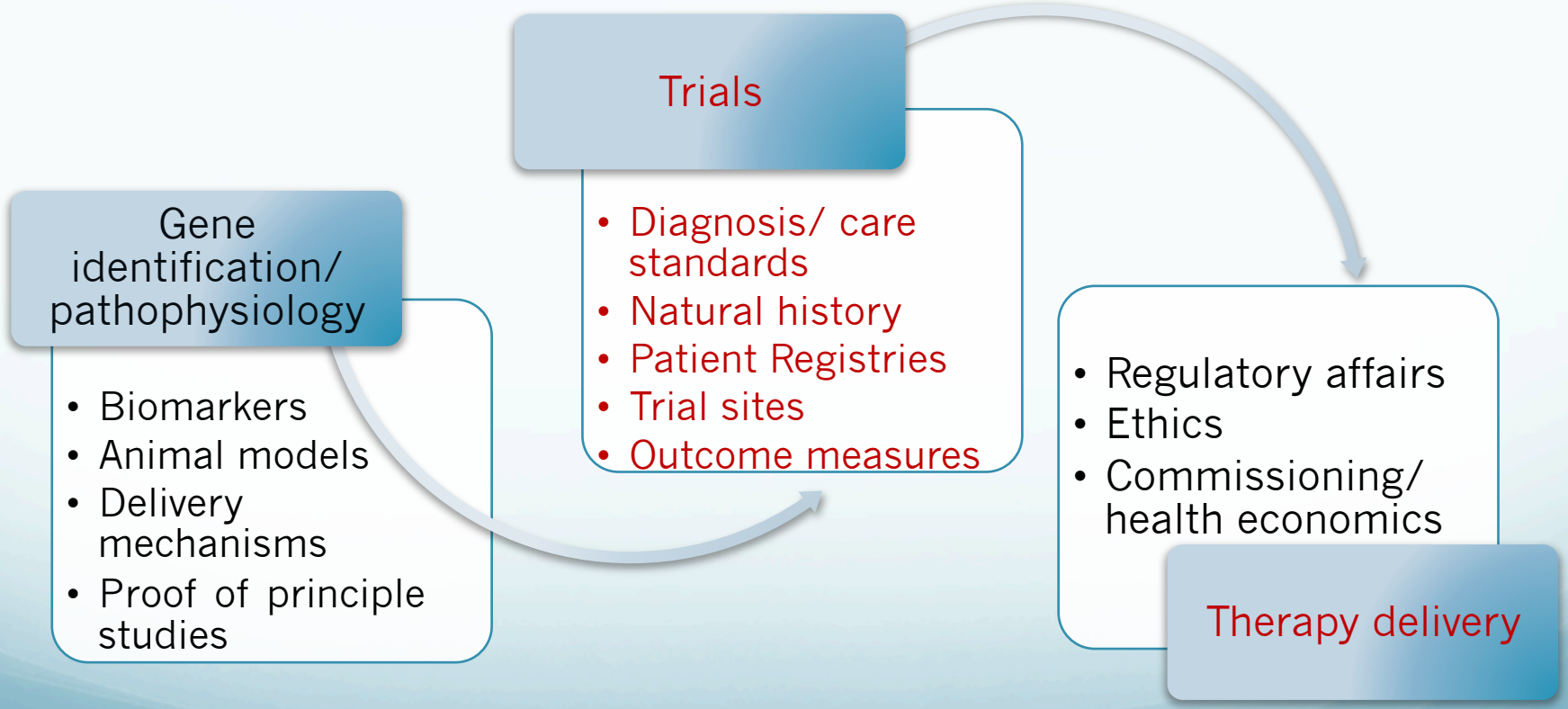
Other general issues

- Pain
  - Underrecognised but reported if you ask about it! Often stage specific
  - Prominent in many forms of MD especially on exercise in ambulant phase
  - FSHD may be a particular problem as muscles weaken
  - PROMM....
    - Reported in almost all conditions at least sporadically
  - Postural problems in later disease
- Look for the specific cause and see if there is a physio/ exercise solution
  - ?surgery (eg painful dislocation)
- Prevention
- Don't be shy of utilising painkillers/ pain specialists
- Emergency and perioperative care
- Psychosocial issues
  - Depression, anxiety, coping, impact on QOL
- Fatigue
  - Primary problem in DM1: many patients report benefit from modafanil
  - Fluctuating fatigue levels and weakness should prompt consideration of myasthenias
  - Beware of confounding/ confusing effect of respiratory impairment
  - Often a major cause of failure to continue in employment
- Creatine and other supplements
- Pregnancy and childcare

The advent of personalised medicine for muscular dystrophies

- Gene and RNA based therapy development for DMD and other muscular dystrophies (exon skipping, stop codon suppression)
- Gene therapy in development for several indications
- Modifying the pathology: many possible indications, many diseases, drug repurposing efforts
  - Impetus currently for more advanced and more available diagnoses, registry efforts, NH studies
  - Clinical management supported by trial readiness remains key
  - Future push for earlier diagnosis and treatment?

New therapy development: we are at a critical point of transition from research to possible clinical application via new regulatory and pricing challenges....



Newcastle University

MRC Centre for Neuromuscular Diseases

TREAT-NMD Neuromuscular Network

Thank you

THE John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE

Neuromuscular Research Group

Diagnostics group

Clinical group

Clinical trials team

Networking group ENMC and EU partners

Volker Straub and Hanns Lochmuller