Clinical trials and the ANDMR

Monique Ryan and Robin Forbes

MDNSW 2021

Disclosures

- Site PI: ISIS/Ionis Pharmaceuticals, Roche, Biogen Idec, AveXis, GSK, PTC Therapeutics, Roche, Sarepta, BioMarin, EryDel, Genzyme, WAVE, Catabasis, Reveragen, Antisense Therapeutics
- Advisory Boards: Biogen, PTC Therapeutics, BioMarin, CSL
- Global Scientific Advisory Board: Biogen Idec
- Data Safety Monitoring Board: Eli Lilly

Neuromuscular disorders: a change in focus

- NMDs have historically been seen as neurodegenerative conditions with no effective treatments
  - Acquired NMDS have sometimes had specific therapies
  - Genetic NMDs have generally been managed with symptomatic therapy
- Neuromuscular disorders are now at the forefront of therapy development
  - Seven new treatments for genetic NMDS approved internationally in the last 24m
- This has resulted in a transformation in the focus of neuromuscular care
- **We have moved from support to intervention**
- **This carries its own challenges**
  - **Rapid diagnosis, best practice management, capacity building, collaboration**

Common NMDs

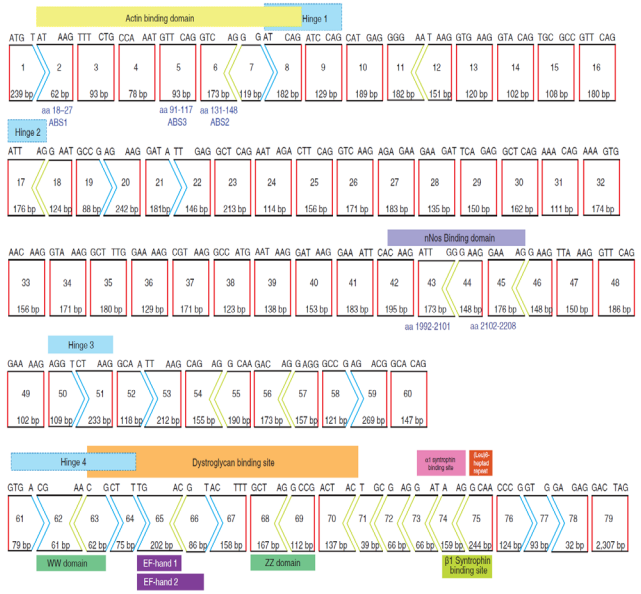
- CMT: 1 in 2500 individuals
- Myotonic dystrophy: 1 in 7000 individuals
- FSHD: 1 in ~8000 individuals
- SMA: 1 in 10 000 individuals
- Duchenne muscular dystrophy: 1 in 5000 boys
- Congenital myopathies: ~1 in 20 000
- Motor neurone disease: 1 in 50 000 individuals
- Congenital muscular dystrophies ~1 in 100 000

Duchenne muscular dystrophy

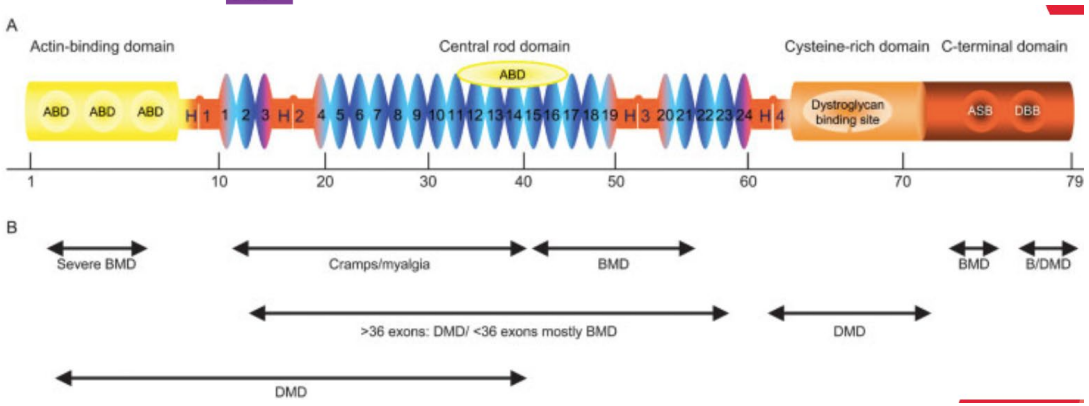
- X-linked recessive disorder affecting in 1 in 5000 boys
- Presents at 3-5 years with weakness and falls
- Gradual loss of muscle function
  - Wheelchair use ~12 y, assisted ventilation ~20 y
- Life expectancy previously ~30 years
  - Deaths 80% respiratory, 20% cardiac

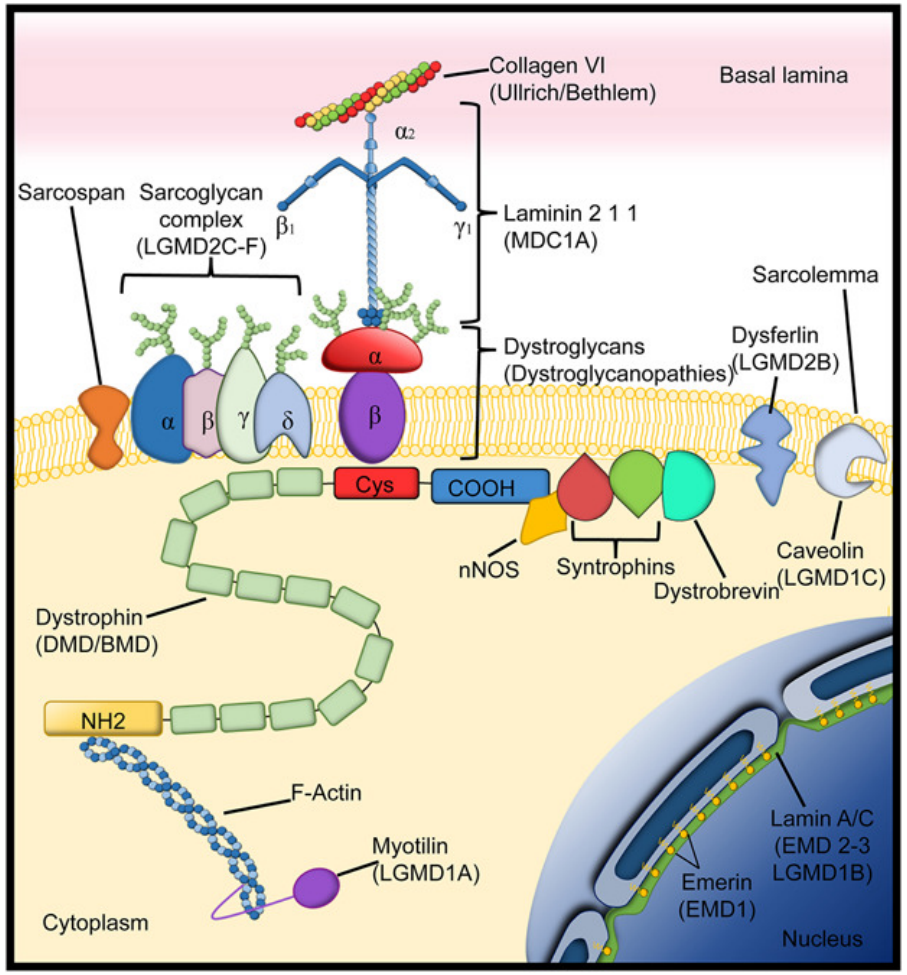
DMD is caused by mutations in dystrophin

Amino terminal



Carboxyl terminus





Therapeutic advances in DMD

- **Standard of care includes:**
  - **Steroid therapy**
  - (Non)invasive ventilation and assisted cough
  - Greater emphasis on GI/nutritional health
  - Better monitoring and treatment of bone health
  - Nutritional management
  - Treatment of cardiomyopathy

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management

*David J Birnkrant, Katharine Bushby, Carla M Bann, Susan D Apkon, Angela Blackwell, David Brumbaugh, Laura E Case, Paula R Clemens, Stasia Hadjiyannakis, Shree Pandya, Natalie Street, Jean Tomezsko, Kathryn R Wagner, Leanne M Ward, David R Weber, for the DMD Care Considerations Working Group**

Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management

*David J Birnkrant, Katharine Bushby, Carla M Bann, Benjamin A Alman, Susan D Apkon, Angela Blackwell, Laura E Case, Linda Cripe, Stasia Hadjiyannakis, Aaron K Olson, Daniel W Sheehan, Julie Bolen, David R Weber, Leanne M Ward, for the DMD Care Considerations Working Group**

Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan

*David J Birnkrant, Katharine Bushby, Carla M Bann, Susan D Apkon, Angela Blackwell, Mary K Colvin, Linda Cripe, Adrienne R Herron, Annie Kennedy, Kathi Kinnett, James Naprawa, Garey Noritz, James Poysky, Natalie Street, Christina J Trout, David R Weber, Leanne M Ward, for the DMD Care Considerations Working Group**

Birnkrant et al. *Lancet* 2018

Optimal steroid regimens: still not defined

EARLY CORTICOSTEROID TREATMENT IN 4 DUCHENNE MUSCULAR DYSTROPHY PATIENTS: 14-YEAR FOLLOW-UP

LUCIANO MERLINI, MD,[1] MONIA GENNARI, MD,[2] ELISABETTA MALASPINA, MD,[2] ILARIA CECCONI, MD,[2] ANNARITA ARMAROLI, MD,[3] SAVERIO GNUDI, MD,[4] BERIL TALIM, MD,[5] ALESSANDRA FERLINI, MD,[3] ALESSANDRO CICOGNANI, MD,[2] and EMILIO FRANZONI, MD[2]

Muscle Nerve **45:** 796–802, 2012

Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study

Neurology® 2015;85:1048-1055

Developing standardized corticosteroid treatment for Duchenne muscular dystrophy☆

Michela Guglieri[a,*], Kate Bushby[a], Michael P. McDermott[b], Kimberly A. Hart[b], Rabi Tawil[b], William B. Martens[b], Barbara E. Herr[b], Elaine McColl[c], Jennifer Wilkinson[c], Janbernd Kirschner[d], Wendy M. King[b], Michele Eagle[a], Mary W. Brown[b], Tracey Willis[e], Deborah Hirtz[f], Perry B. Shieh[g], Volker Straub[a], Anne-Marie Childs[h], Emma Ciafaloni[b], Russell J. Butterfield[i], Iain Horrocks[j], Stefan Spinty[k], Kevin M. Flanigan[l], Nancy L. Kuntz[m], Giovanni Baranello[n], Helen Roper[o], Leslie Morrison[p], Jean K. Mah[q], Adnan Y. Manzur[r], Craig M. McDonald[s], Ulrike Schara[t], Maja von der Hagen[u], Richard J. Barohn[v], Craig Campbell[w], Basil T. Darras[x], Richard S. Finkel[y], Giuseppe Vita[z], Imelda Hughes[aa], Tiziana Mongini[ab], Elena Pegoraro[ac], Matthew Wicklund[ad], Ekkehard Wilichowski[ae], W. Bryan Burnette[af], James F. Howard[ag], Hugh J. McMillan[ah], Mathula Thangarajh[ai], Robert C. Griggs[b]

Contemporary Clinical Trials 58 (2017) 34–39

TWICE-WEEKLY GLUCOCORTICOSTEROIDS IN INFANTS AND YOUNG BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

ANNE M. CONNOLLY, MD,[1,2] CRAIG M. ZAIDMAN, MD,[1,2] PAUL T. GOLUMBEK, MD, PhD,[1,2] MARY M. CRADOCK, PhD,[2] KEVIN M. FLANIGAN, MD,[3] NANCY L. KUNTZ, MD,[4] RICHARD S. FINKEL, MD,[5] CRAIG M. MCDONALD, MD,[6] SUSAN T. IANNACCONE, MD,[7] PALLAVI ANAND, MBBS,[1] CATHERINE A. SIENER, PT, MHS,[1] JULAINE M. FLORENCE, PT, DPT,[1] LINDA P. LOWES, PT, PhD,[3] LINDSAY N. ALFANO, PT, DPT, PCS,[3] LINDA B. JOHNSON, PT,[6] ALINA NICORICI, BS,[6] LESLIE L. NELSON, PT, PhD,[7] JERRY R. MENDELL, MD,[3] and FOR THE MDA DMD CLINICAL RESEARCH NETWORK

Muscle Nerve **59**:650–657, 2019

Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy

OPEN

Neurology® 2016;87:2123-2131

DEFLAZACORT VERSUS PREDNISONE/PREDNISOLONE FOR MAINTAINING MOTOR FUNCTION AND DELAYING LOSS OF AMBULATION: A POST HOC ANALYSIS FROM THE ACT DMD TRIAL

PERRY B. SHIEH, MD, PHD,[1] JOSEPH McINTOSH, MD,[2] FENGBIN JIN, PHD,[2] MARCIO SOUZA, PHARMD, MBA,[2] GARY ELFRING, PHD,[2] SIVA NARAYANAN, MS, MPH,[2] PANAYIOTA TRIFILLIS, PHD,[2] STUART W. PELTZ, PHD,[2] CRAIG M. McDONALD, MD,[3] and BASIL T. DARRAS, MD,[4] AND THE ACT DMD STUDY GROUP

Muscle Nerve **58**:639–645, 2018

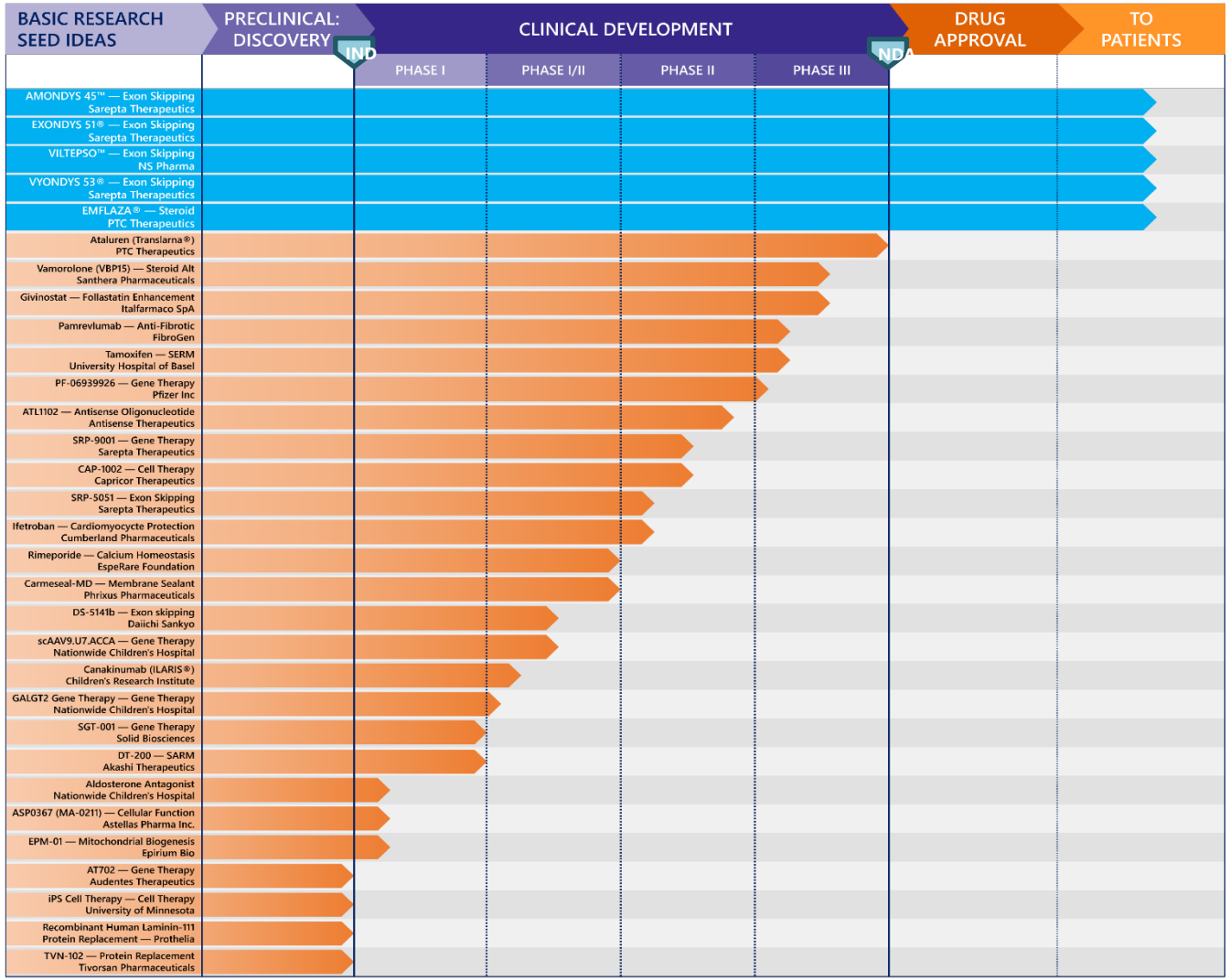
Gene and genetic therapies for NMDs

1. Treatments aimed at the primary genetic cause

- Exon skipping
- Stop codon readthrough
- Gene therapy
- Genome editing
- Stem cell therapy

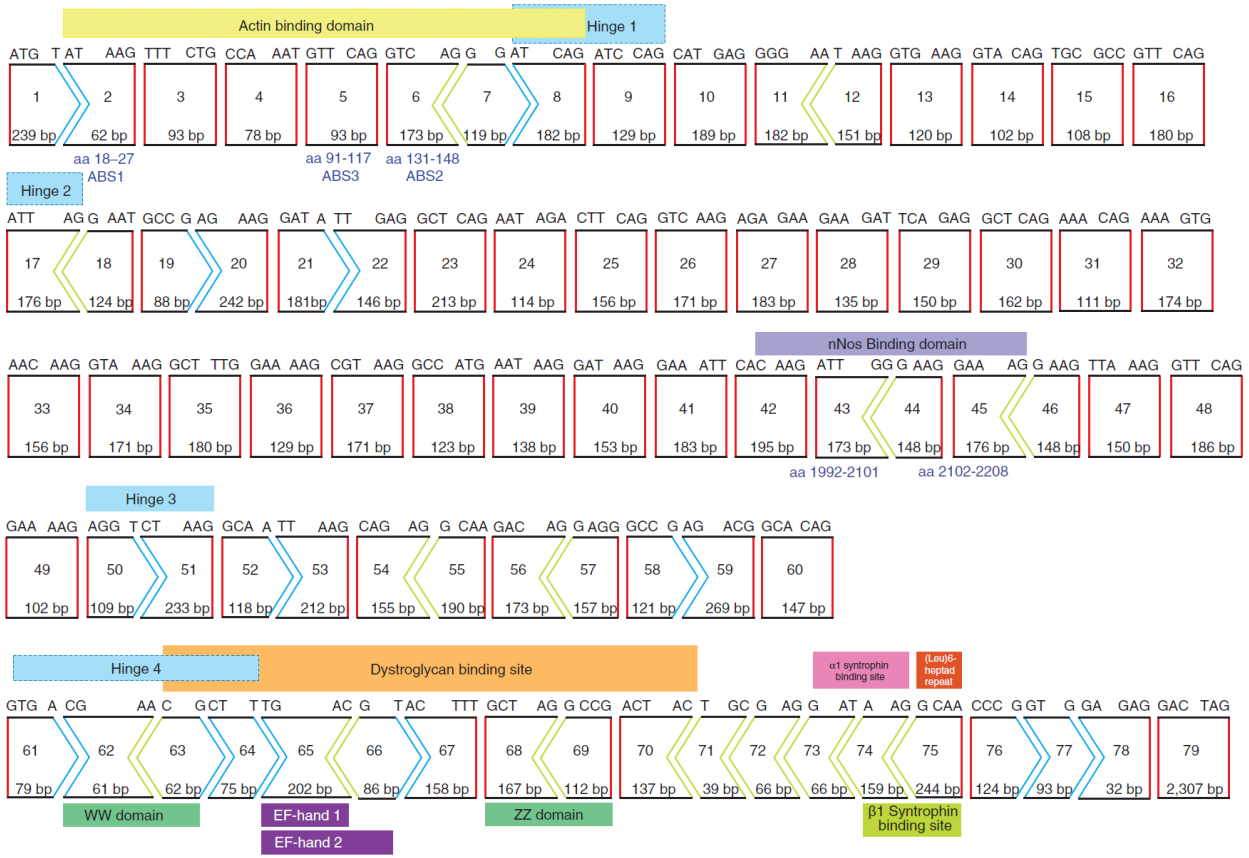
2. Treatments aimed at the secondary disease pathology

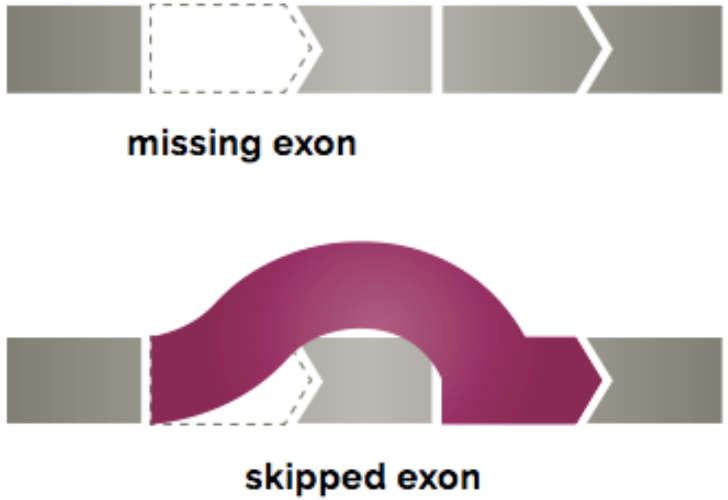
DMD therapies in development



Exon ‘skipping’ in DMD

The ‘reading frame’ hypothesis



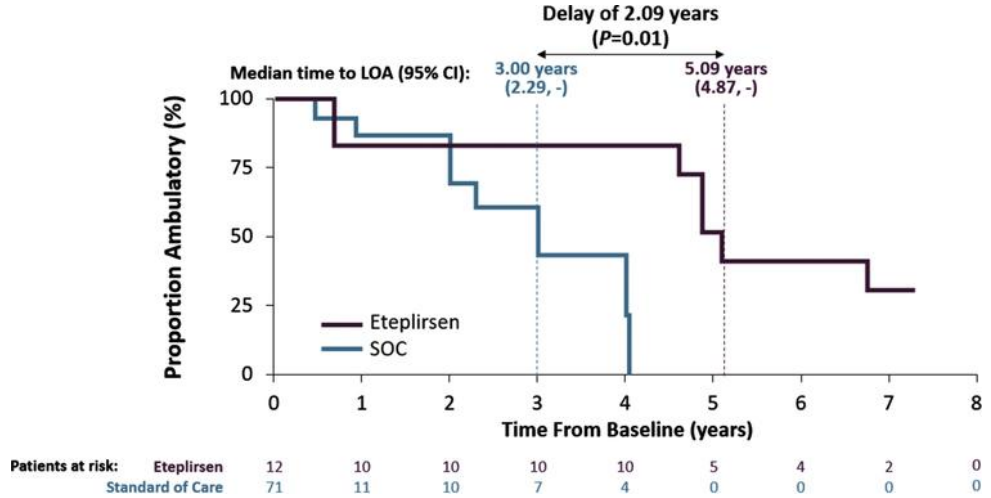


Target Exon	Deleted Exon	Patient % out of DMD [1]
51	29-50, 50, 45-50, 48-50, 49-50, 52, 52-63	13
53	***43-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52***	***8***
45	18-44. 44. 46-47, 46-48, 46-49, 46-51, 46-53	8
44	35-43, 45, 45-54	6
43	44, 44-47, 44-48	4
46	45, 47-54	4
50	51, 51-53, 51-55	4
52	51, 53, 53-55	4

Aartsma-Rus et al. *Hum Mutation* 2009

Eteplirsen

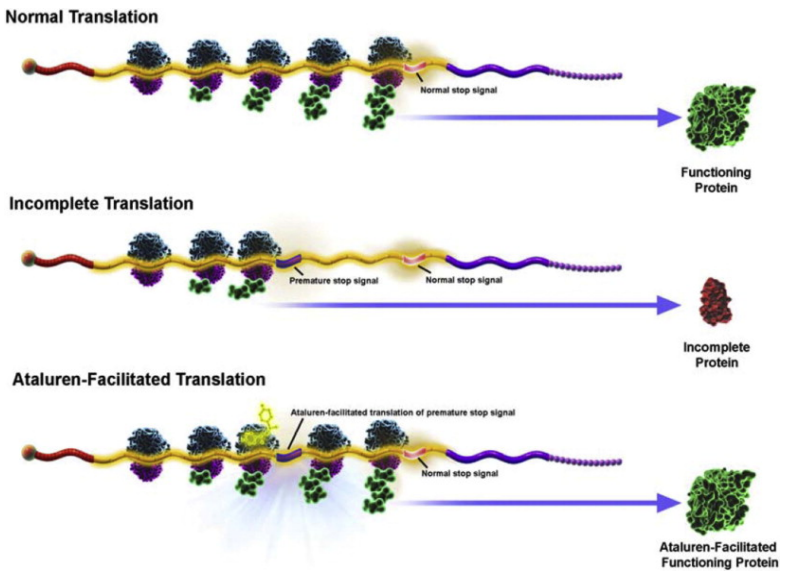
- Morpholino AO given weekly IV for exon 51 deletion
- Initial study: subjects compared to a historical cohort.
- Approved by FDA, not by EMA, not approved in Australia
- Confirmatory phase 3 study overdue
- Recent data suggests may slow loss of ambulation in DMD by ~2 years to ~15.2 y



Journal of Neuromuscular Diseases xx (2021) x–xx

Ataluren

- Oral agent which binds ribosomal subunits, impairs recognition of premature stop codons
- Multiple phase II-III trials: safe and well tolerated



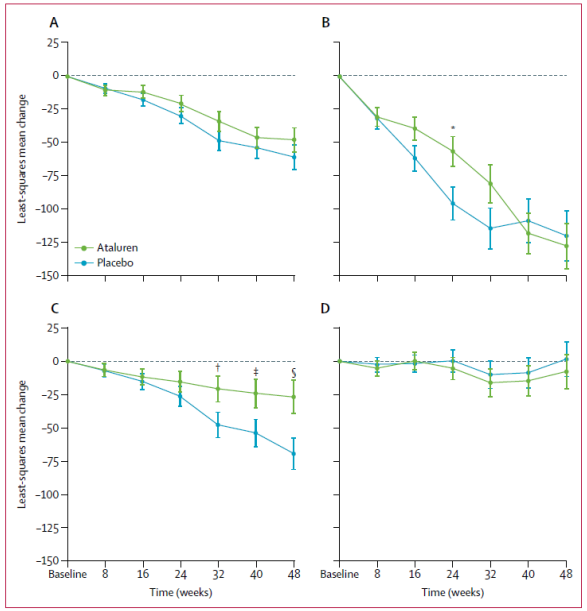
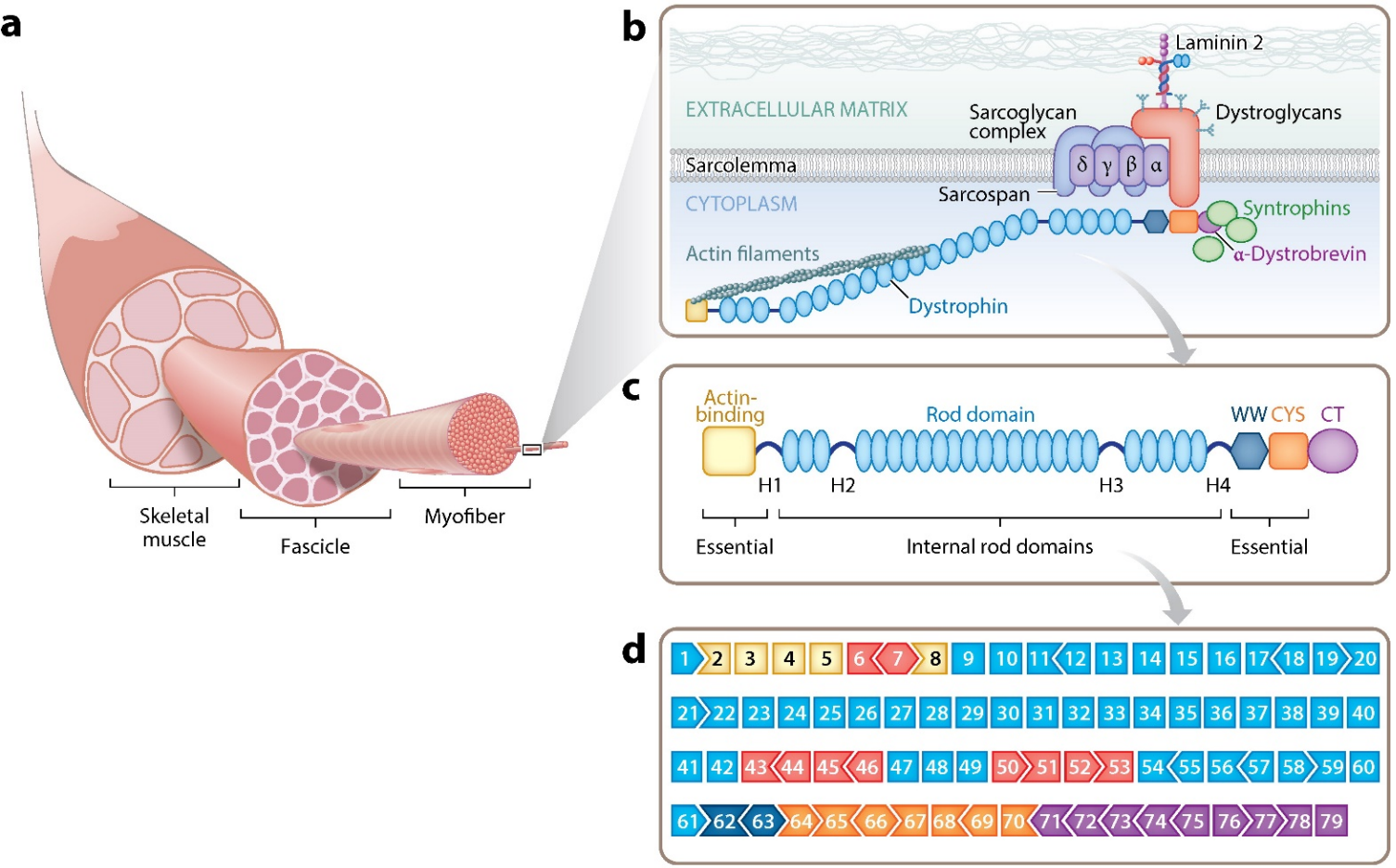


Figure 2: Least-squares mean change in 6-minute walk distance from baseline to week 48
(A) For patients in the ataluren (n=114) and placebo (n=114) groups of the intention-to-treat population. (B) For patients in the ataluren (n=24) and placebo (n=21) subgroup of patients with a baseline 6-minute walk distance of less than 300 m. (C) For patients in the ataluren (n=47) and placebo (n=52) subgroup of patients with a baseline 6-minute walk distance of 300 m or more to less than 400 m. (D) For patients in the ataluren (n=43) and placebo (n=41) subgroup of patients with a baseline 6-minute walk distance of 400 m or more. Error bars show SEs. ANCOVA model based on change from baseline as the dependent variable; independent variables included stratification for age (<9 years *vs* ≥9 years), duration of previous corticosteroid use (6 months to <12 months *vs* ≥12 months), and baseline 6-minute walk distance (<350 m *vs* ≥350 m), treatment, and baseline 6-minute walk distance as a covariate. p values were obtained via ANCOVA applying multiple imputation. *p=0·012. †p=0·032. ‡p=0·030. §p=0·007.

- ACT-DMD: McDonald et al. *Lancet* 2017)
  - 6MWD in favour of ITT
  - Difference greatest in 6MWD 300-400m window
- Ongoing phase 3 study
- FDA: rejected
- EMA: Conditional approval
- Registry: Long-term treated: median age of LOA **16.5y**



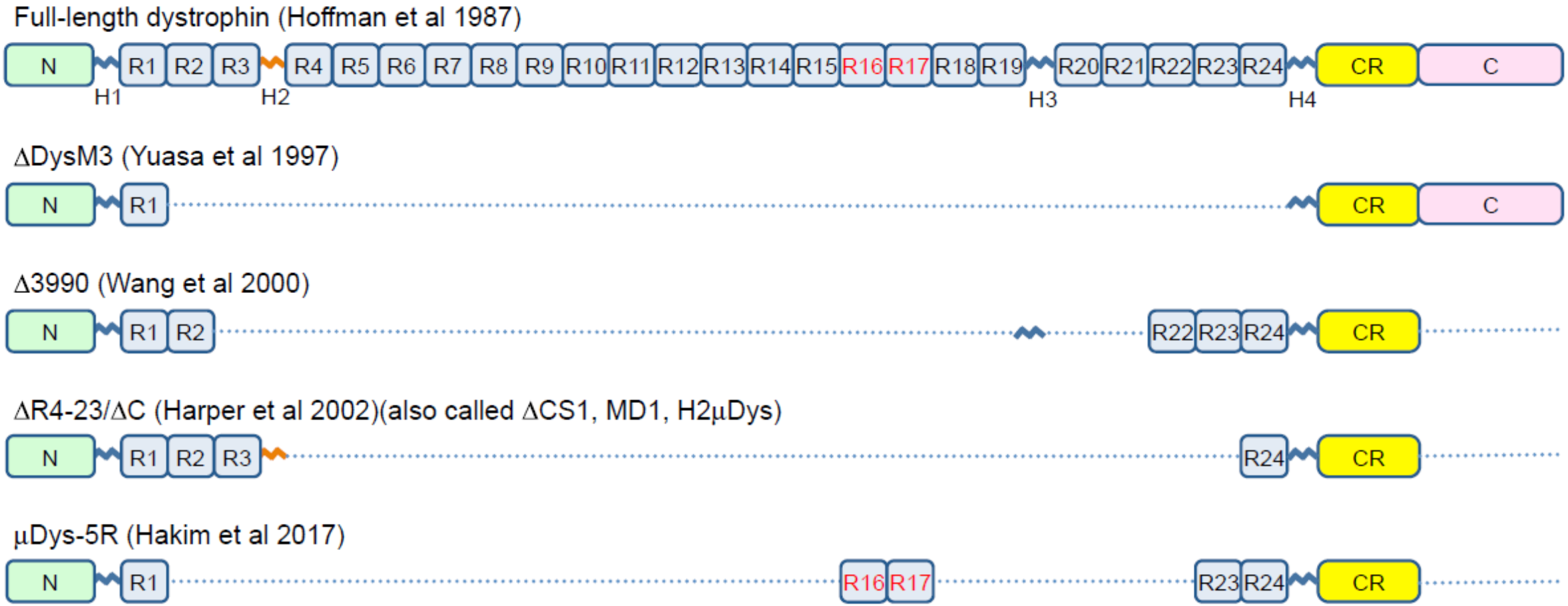
Min Y-L, et al. 2019.
Annu. Rev. Med. 70:239–55

Table 1. Dystrophin Large In-Frame Deletion and Clinical Phenotype

Genotype	% Lost	Level of Expression	Clinical Phenotype	Reference
Full-length	0%	+++	normal	16
Δ17–48	46%	+++	BMD	19
Δ13–47	47%	++ ∼+++	BMD	23
Δ10–44	48%	++	DMD	143
Δ10–44	48%	N/A	BMD	28
Δ10–44	48%	N/A	BMD	28
Δ13–48	49%	N/A	BMD	27
Δ13–48	49%	++ ∼+++	BMD	24
Δ13–48	49%	++	BMD	26
Δ4–41	50%	+	DMD	24
Δ4–41	50%	++	DMD	145
Δ4–41	50%	–	DMD	26
Δ3–41	51%	++	DMD	26
Δ3–41	51%	++	IMD	144
Δ3–41	51%	+	DMD	143
Δ3–42	52%	+	IMD	24
Δ11–48	52%	N/A	DMD	142
Δ5–44	54%	N/A	DMD	28
Δ10–53	60%	N/A	DMD	25
Δ10–53	60%	+++	DMD	141
Δ14–60	61%	N/A	DMD	140
Δ2–50 (Δ2–44)[a]	63%	++	DMD	139

Abbreviations: BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; IMD, intermediate muscular dystrophy (clinical phenotype between BMD and DMD); N/A, information not available.
[a]The patient has a Δ2–44 deletion in DNA but a Δ2–50 deletion in mRNA due to alternative splicing.

Duan *Mol Ther* 2018, Min et al. *Ann Rev Med* 2019



Duan *Mol Ther* 2018, Min et al. *Ann Rev Med* 2019

Dystrophin restoration in DMD: challenges

- Loss of muscle tissue and function starts very early in DMD: ? irreversible
- Functionality of microdystrophins in humans
  - ~40% smaller than smallest dystrophin reported in BMD
- Longevity of transgene expression: limited by muscle turnover
- Immune effects
  - ~50% of patients have anti-AAV antibodies; patients can be treated only once
- Any increase in dystrophin expression is likely to have *some* effect
  - Restoration of dystrophin unlikely to restore lost muscle tissue
  - ? Minimal level required for effective therapy of DMD at different ages

Spinal muscular atrophy

- SMA affects 1 in 10 000 people worldwide
- SMA causes hypotonia, progressive weakness and loss of motor function
- SMA is the 2nd most frequent recessive disease
- SMA was formerly the most common genetic cause of death in infancy
- 60-70% of all SMA patients have the most severe form, type 1 SMA
- Until very recently there have been no specific therapies for SMA

SMA therapy overview

	ZOLGENSMA® (onasemnogene abeparvovec-xioi)	SPINRAZA® (nusinersen)	EVRYSDI® (risdiplam
	NOVARTIS avexis	IONIS PHARMACEUTICALS Biogen	
Strategy	DNA	RNA	RNA
Mechanism	Replaces *SMN* gene	Increases SMN protein by modifying *SMN2* splicing	Increases SMN protein by modifying *SMN2* splicing
Drug type	Gene therapy	ASO	Small molecule
Delivery method	IV	Intrathecal	Oral
Body distribution	Systemic	CNS	Systemic
Dosing	Single dose	4 loading doses over 63d then 4monthly IT	Daily
Half-life	N/A	135-177 days in CSF 63-87 days in plasma	40-69h in blood

Onasemnogene SMN protein expression levels cannot be detected in blood (do not transduce in hematopoietic cells).
ASO, antisense oligonucleotide; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Zolgensma® (onasemnogene abeparvovec-xioi). Prescribing information. https://www.avexis.com/content/pdf/prescribing_information.pdf. 2. Spinraza® (nusinersen). Prescribing information. https://www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf. 3. Evrysdi™ (risdiplam). Prescribing information. https://www.gene.com/download/pdf/evrysdi_prescribing.pdf. 4. Charnas L, et al. *Neuromusc Disord.* 2017;27:S207–S208. 5. https://clinicaltrials.gov/ct2/show/NCT02644668. 6. https://clinicaltrials.gov/ct2/show/NCT03921528. All websites accessed August 2020.

Challenges in SMA therapeutics

- Optimising timing, dosage, delivery route, distribution and uptake
- ? Importance of targeting other cell populations
- Long-term effect, long-term toxicity
- Biomarkers of disease progression and response to therapy
- Ways to quantitate SMN expression in target tissues
- **Studies of ‘combinatorial’ therapy**
- **Cost of therapy**

Gene therapy: adverse events

- Liver dysfunction
    - Potential for long-term oncogenesis
- Thrombocytopenia and bone marrow suppression
- Cardiac toxicity
- Renal: atypical HUS
- SMA: DRG inflammation remains a preclinical finding, significance unclear
- Ocular gene therapies: local inflammatory reactions

Uncertainty

Advances in treatment of the congenital myopathies

Table 2 Therapeutic Approaches to the Congenital Myopathies

Therapeutic Approach		Condition/Gene	Compound(s)	Reference(s)
Genetic	Viral-based gene transfer	XLMTM, others	AAV8 vector-based *MTM1* transfer	62,64
	Gene editing	Various	Various	65
	Suppression of premature stop codons	Various	Various	68
	Exon skipping	CCD, other AD CMs	Various	67
	Protein downregulation (DNM2)	CNM (*MTM1, BIN1*)	Various	71
	Targeting of class II and III PI3 kinases	CNM (*MTM1*)	Various	72
	Protein upregulation (ACTAC)	NM (*ACTA1*)	Various	74
ERT	Myotubularin replacement	XLMTM	Myotubularin	75
Pharmacologic	Modification of RyR1 receptor calcium release	*RYR1*-RM (AD)	Dantrolene, Rycals, AICAR	76-81; 84,87
	Targeting thin/thick filament interactions	NM, others	CK-2017357, CK-1827452	90,91
	Reduction of oxidative stress	*RYR1* + *SEPN1*-RM	*N*-acetylcysteine (NAC)	92
	Enhancement of neuromuscular transmission	CNMs, others	Pyridostigmine, Salbutamol*	95-99
	Stimulation of muscle growth pathways	Various	ActRIIB inhibitors, others	102
	Prevention of protein aggregates	*MYH7*-RM, others	4-phenylbutyrate (4-PBA)	105,107

AD, autosomal-dominant; CCD, Central Core Disease; CNM, Centronuclear Myopathy; NM, Nemaline Myopathy.

Among the therapeutic strategies summarized, enzyme replacement therapy (ERT) and viral-based gene transfer in X-linked myotubular myopathy (XLMTM), as well as antioxidant therapy in *RYR1*-and *SEPN1*-related myopathies have already reached (or are approaching) the clinical trial stage.

*Salbutamol probably exerts its effects through additional mechanisms other than enhancement of neuromuscular transmission (see main text).

Jungbluth and Muntoni *Semin Ped Neurol* 2019

Pompe disease

- Metabolic myopathy caused by (AR) GAA mutations
- Effect of ERT proven for infantile-onset PD: motor and cardiac function
  - Adults: motor and respiratory parameters improved
- Effect dependent on mannose-6-phosphate content of rhGAA and abundance of CI-MPR in target tissue
- Approaches to improved outcome:
  - ERT with increased M6P or increased affinity for CI-MPR
  - Chaperone or gene therapies

Corti et al. *Hum Gen Ther Clin Dev* 2018; Pena et al. *Neuromusc Disord* 2019; Parenti et al. *Fut Med Chem* 2014

New therapies for Charcot-Marie-Tooth disease

PMP22	GJB1	MPZ	MFN2	Other
PXT3003 (3) [66–69] *ClinicalTrials.gov* NCT03023540	CAMKII inhibitors (p) [81–83,116]	Curcumin (p) [89,90,92]	Coenzyme Q10 [99]	Follistatin-based therapy (2) [115] *ClinicalTrials.gov* NCT03124459
Vitamin C (P, 1–3) [6,58,61–63,117–120]	Cx32 gene therapy (p) [85,86]	Sephin 1 (p) [94]	Mitofusion agonists (p) [100]	Stem cell research (p) [104,105]
Progesterone Antagonists (p) [59,121]				Gene therapy (p) [85,86,107,108,122,123]
siRNA (p) [60]				HDAC6 Inhibition (p) [101–103]
Antisense Oligonucleotides(p) [74]				NT-3 (p) [106–108]
Lipid supplementation (p) [75]				Nrg-1Type III (p) [109,110]
Schwann cell differentiation (p) [50,77]				TACE modulation (p) [111,112]
Curcumin (p) [89,90,92]				CSF1R inhibition (p) [114]
				Intermittent Fasting (p) [46]

(p) = Preclinical; (0) = Phase 0 clinical trial; (1) = Phase 1; (2) = Phase 2; (3) = Phase 3.

Morena et al. *Int J Mol Sci* 2019

Charcot-Marie-Tooth disease: challenges

- > 100 genes, >1000 different mutations
- All forms of Mendelian inheritance possible, plus some cases *de novo*
- Different CMT phenotypes caused by mutations in the same gene
- Mutations in different genes may result in the same phenotype
- Often unclear why mutations cause length-dependent degeneration of peripheral nerves
- Gene replacement may be more useful for recessive neuropathies
- Dominant neuropathies may require ‘knock down’ interventions

Challenges with new treatments for NMDs
Optimal clinical care

- Mandated for clinical trials but often not well-defined
- Variation in standards of care internationally
- Variation between paediatric and adult centres
- Standards of care are not always achievable by all centres
- Standards of care impacted by new therapies and altered expectations
- Need for best practice diagnostics

Ethical considerations

- Long-term prognosis in NMDs
  - Conversion of rapidly fatal disorder to one with long-term severe morbidity
- Defining a meaningful clinical response in adults
- Difficulty choosing between different trials
- Difficulty choosing between different agents
- Ethics of placebo-controlled studies
- Subject selection for trials
- Inequity of access to trials and therapies

HEALTH NEWS AUGUST 14, 2018 / 9:07 AM / 2 MONTHS AGO

Biogen's pricey muscle drug Spinraza too costly for Britain

2 MIN READ

LONDON (Reuters) - Biogen's muscle disease treatment Spinraza has been deemed too expensive for use on Britain's state-run health service, even after a price discount offered by the U.S. drugmaker.

Pharma

Novartis struggling to win payer coverage for $2.1M gene therapy Zolgensma: analysts

by Arlene Weintraub | Jul 3, 2019 8:16am

Treatment of neuromuscular disorders has changed radically

- Many new therapies are being studied
- This offers exciting opportunities for all clinicians engaged in this field
- Things will continue to change quickly

… as will our patients

Thank you

Members of the RCH neuromuscular team

Our financial supporters: SOS Duchenne Foundation, MDA and MDNSW