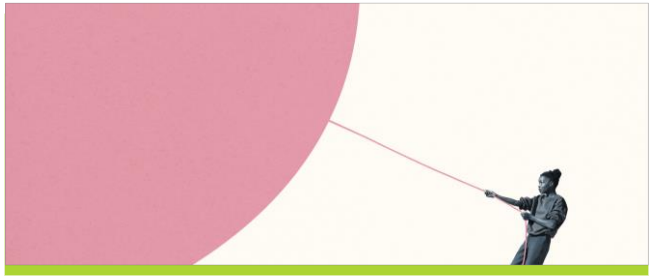
# New and Emerging Treatments in Neuromuscular Disorders

MDNSW Information Day, 5th August 2023



Dr Michelle Lorentzos
Paediatric Neurologist and Clinical Trials Medical Lead

kr kids research

The Sydney children's Hospitals Network
care, advocacy, research, education

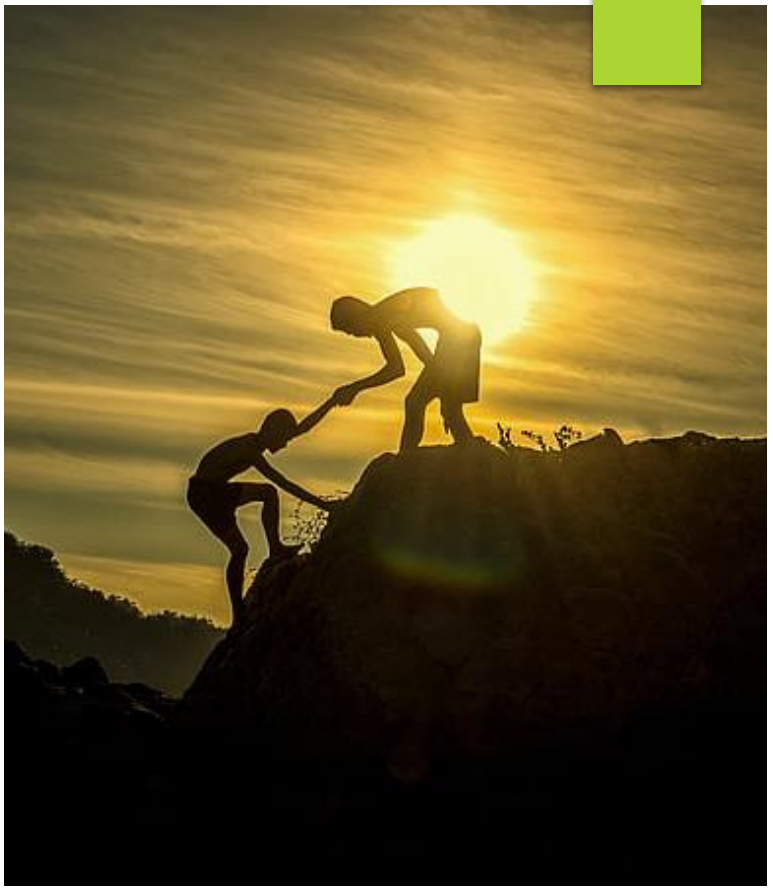
# Disclosures

- I am an investigator on several clinical trials funded by Pfizer, Sarepta, PTC and Dyne therapeutics but I do not receive personal revenue through these studies.

- I have contributed to advisory board for Novartis and received an honorarium for this.

# Overview

| Describe | Discuss | Discuss |
| --- | --- | --- |
| Describe the Australian treatment pipeline and process | Discuss AAV gene therapy | Briefly discuss other treatments in DMD, SMA, myotonic dystrophy type 1, LGMD |

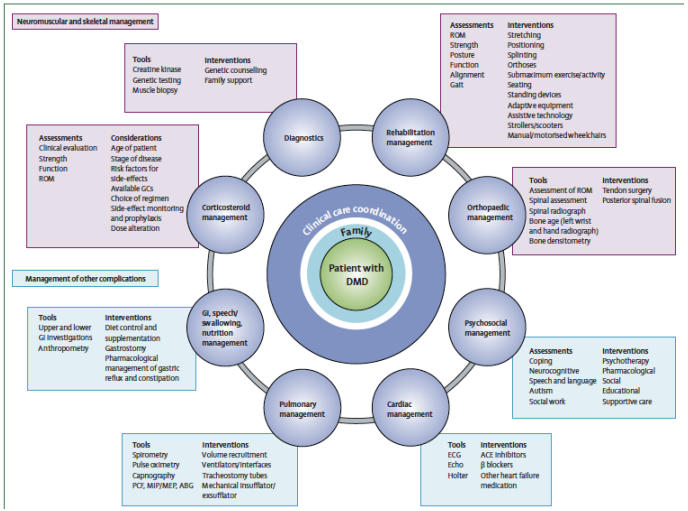


# Scope

- It is estimated that 40,000 Australians have one or more neuromuscular conditions.
- Muscle and nerve disorders affect at least one in 1,000 children in Australia.
- Most neuromuscular diseases are genetic in origin

Murdoch Children's Research Institute https://www.mcri.edu.au/impact/a-z-child-adolescent-health/m-n/neuromuscular-disorders

# The value of multidisciplinary care




Bushby K, et al. ; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010 Jan;9(1):77-93. doi: 10.1016/S1474-4422(09)70271-6. Epub 2009 Nov 27. PMID: 19945913.

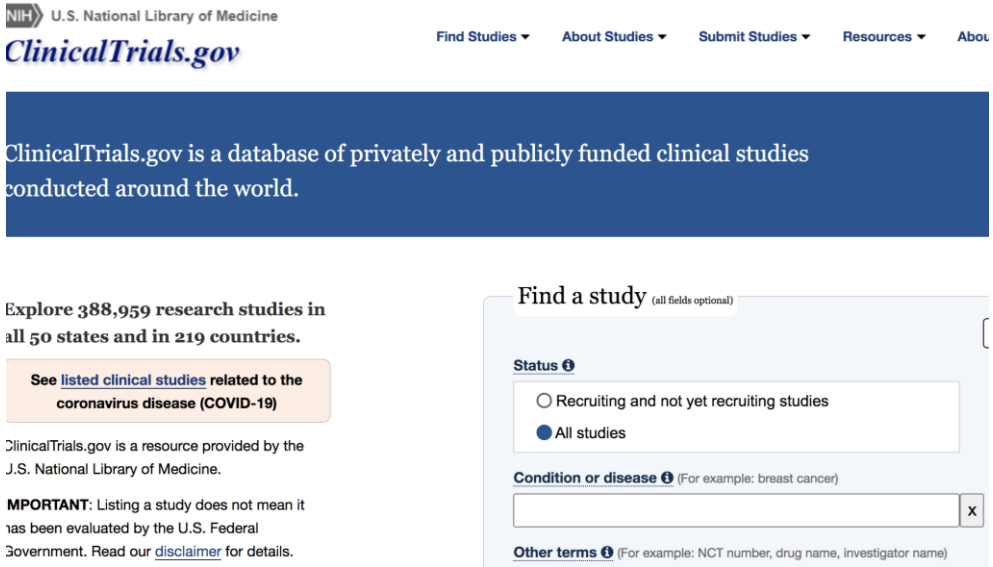
# How do you treat a genetic disease?

Change the gene

Change the way a gene is expressed

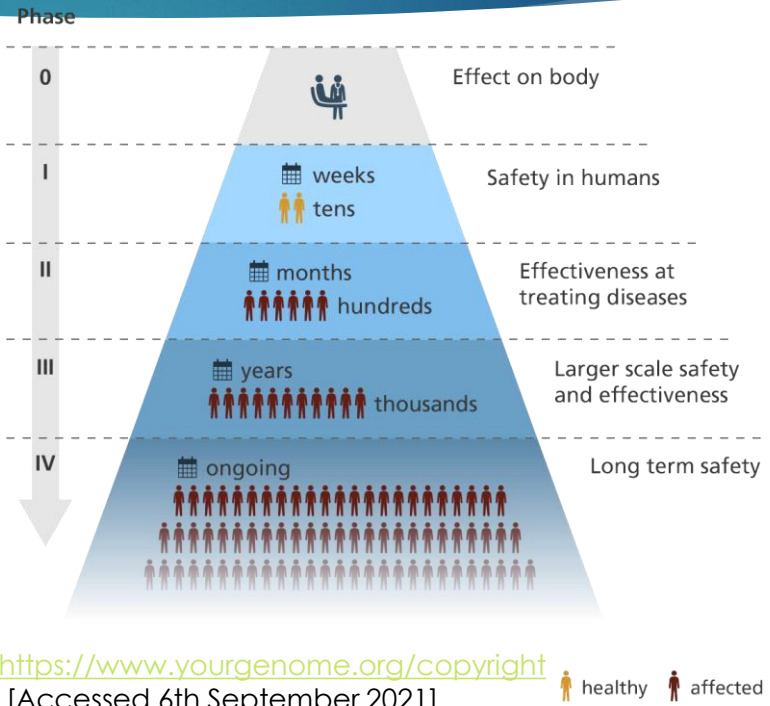
Manage the symptoms the gene causes

# Most drugs are investigated in clinical trials




- These are usually industry initiated and conducted at major hospitals
- Most trials use randomization and a placebo arm
- Clinical trials have strict eligibility criteria
- Clinical trials are voluntary and have strict ethical requirements
- There may be an opportunity to receive the drug through compassionate access at the end of the trial
- Some trials are stopped early due to concerns about safety and lack of efficacy

# Clinical trial pipeline

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[Accessed 6th September 2021]

# A clinical trial is not a standard clinical therapy

- Potential benefits are uncertain
- Risks are uncertain
- Dosing regimens are uncertain
- Patient cohort is clearly defined by the trial protocol
- Prescribing and procedures are clearly defined by the trial protocol
- There is an obligation to protect the scientific aims of the trial

# For drugs to become available

- They need to demonstrate safety and efficacy
- They need to be at least as good as the current treatments
- They need to be approved (TGA in Australia, FDA in America)
  - There are conditional approval programs

More expensive drugs generally need to be subsidized or funded (PBS or compassionate access) as

# Let's talk about AAV gene replacement therapy

# What is AAV?

**Adeno associated virus (AAV)** is a small virus that occurs in humans without causing illness in health individuals

First discovered as a contaminant of adenovirus preparations

There are at least 12 natural serotypes

It can be utilised as a vehicle that can be used to deliver a variety of different therapeutic treatments to disease-relevant cells including brain, muscle, liver

# AAV benefits and complexities

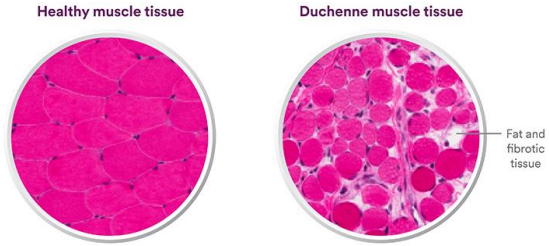
## Benefits of AAV

- It has not been shown to cause disease in humans
- Relatively, they don't cause a huge immune response
- They don't spread easily

## Issues associated with AAV

- People may already have antibodies (estimated to be between 30 and 80%)
- It has a limited cargo capacity (~5kb
- The antibodies hang around

# Duchenne Muscular Dystrophy




- An X-linked disorder (on the x chromosome)
- The most common muscular dystrophy (incidence of 1 in 5000 boys)
- An inability to make dystrophin leads to progressive muscle weakness
- Presenting symptoms include falls, gross motor delay, difficulty rising from the ground of incidental CK/transaminase levels

# The genetics of DMD

There is a deletion in the dystrophin gene, which is located on the x chromosome

1 2 3 4 5 6 7 8 9 10 11
12 13 14 15 16 17 18 19 20 21 22
23 24 25 26 27 28 29 30 31 32 33
34 35 36 37 38 39 40 41 42 43 44
45 46 47 48 49 50 51 52 53 54 55
56 57 58 59 60 61 62 63 64 65
66 67 68 69 70 71 72 73 74 75
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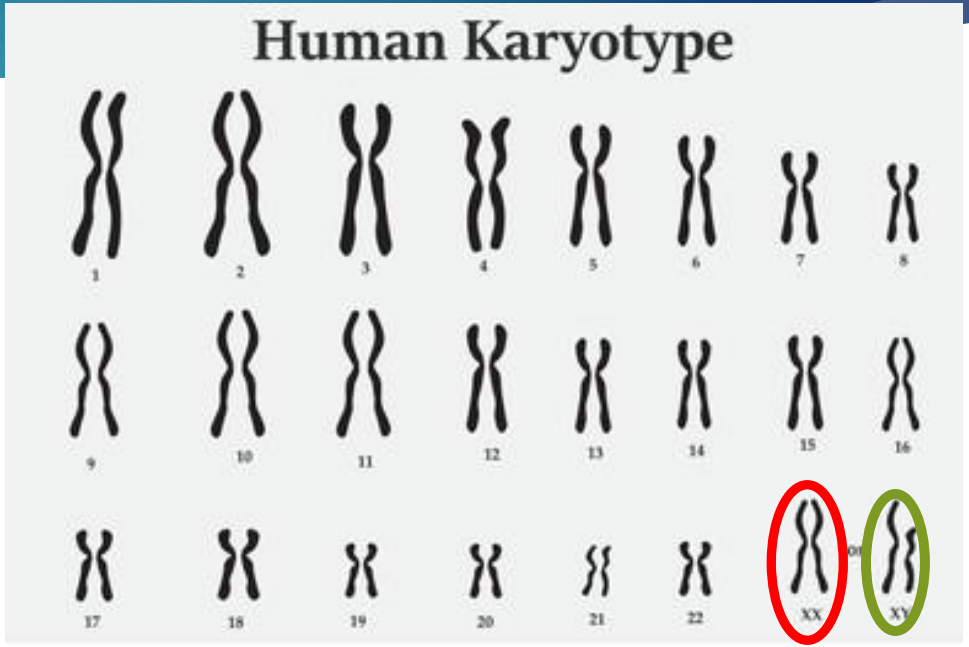
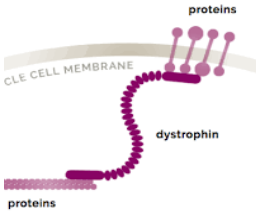


# Let's look at gene therapy

Mutation in the DMD gene or 'recipe'

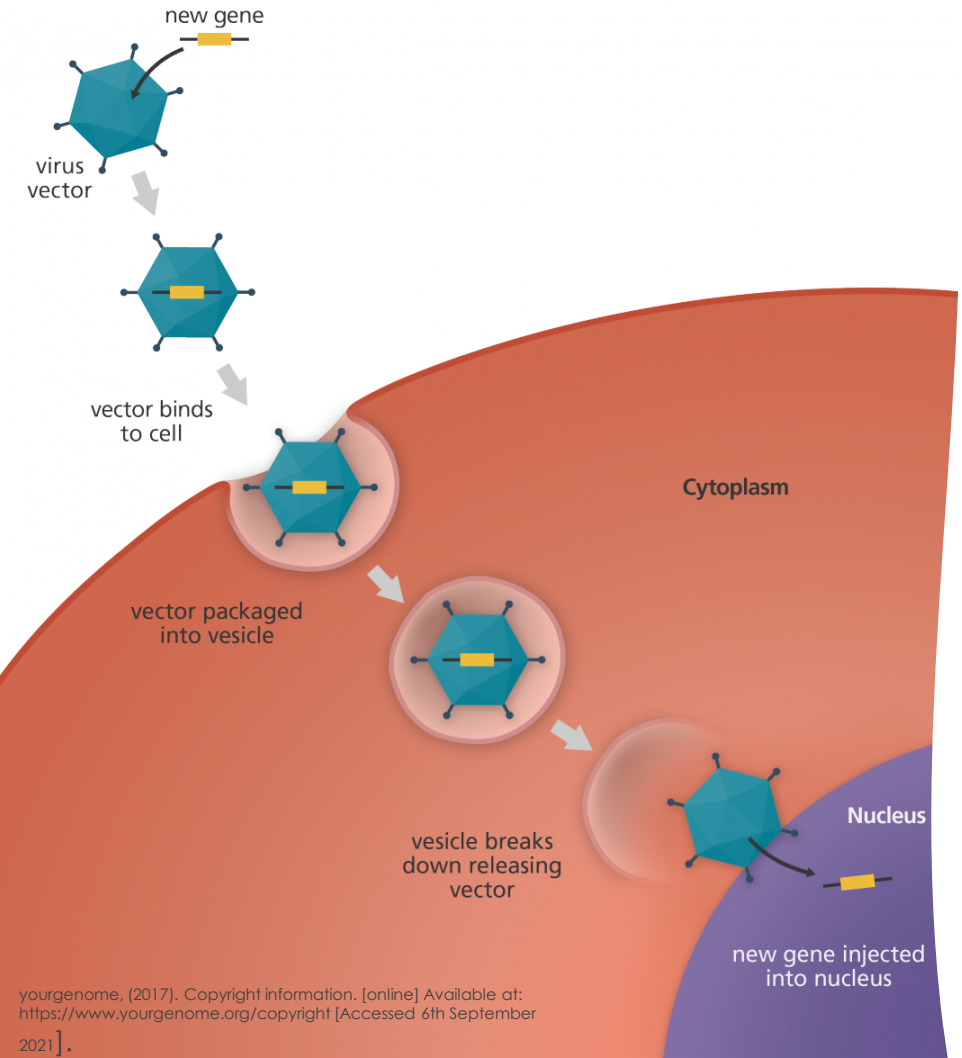
Cells read the mistake in the gene




Inability to make dystrophin

Muscle injury

**Gene replacement therapy**




yourgenome, (2017). Copyright information. [online] Available at: https://www.yourgenome.org/copyright [Accessed 6th September 2021].

DMD gene replacement therapies rely on an adeno-associated virus vector

The aim is to insert a smaller version of the dystrophin gene

# Muscle complicates matters

- There have been more than 250 clinical trials in AAV therapies

What makes muscle special?

- By the time of diagnosis, there is already muscle injury and fibrosis
- Muscles are multinucleated and constantly degenerating and regenerating
- AAV genomes are less than 5 kb in length
  - The dystrophin gene is 2300 kb in length

# Antibodies

- AAV Ab exclude you from an AAV gene therapy trial
- Once you have been dosed, you can't be dosed again (for now…)

# 2 hundred trillion is a big number

# AAV Gene therapy has considerable risks

- Deaths have been reported
- Patients may experience inflammation of the heart, or injury to liver, kidneys or muscle
- Usually, side effects can be detected early and managed. This may require additional procedures or treatments
- Many children experience milder side effects such as vomiting, nausea or loss of appetite
- It is essential to take steroids for weeks to months following gene replacement therapy
- It is an option that should be considered very seriously.

# Gene therapy in DMD are still under investigation

- But IF it works it may be a game changer (early phase studies suggest mini-dystrophin in muscle increases to ~40%) and improvement in function, particularly in younger boys
- Phase 3 trials are ongoing
- The FDA has recently granted conditional approval for Sarepta gene therapy for DMD in 4-5 yo boys

# Other treatments in DMD

# Other treatments in DMD

- ACE-inhibitors for cardiac protection
- Vamorolone (synthetic steroids)

# How can drugs impact the DMD process?

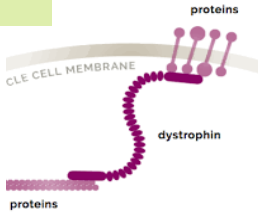
Mutation in the DMD gene or ‘recipe’

**Gene replacement therapy**

**Ataluren**

**Exon skipping**

Cells read the mistake in the gene




Inability to make dystrophin

Muscle injury and scarring

**Steroids**

**Anti-fibrotic agents**

# Types of genetic variants

| | |
|---|---|
| **The gray cat ran down the hall.** | **Original** |
| The gray cat ran down the ball. | **Missense** |
| The gray green cat ran down the hall. | **Insertion** |
| The gray ____ ran down the hall. | **Deletion** |
| The gray cat cat ran down the hall. | **Duplication** |
| The gray. | **Nonsense** |

National Society of Genetic Counselors

# Ataluren (translarna)

- Only indicated for nonsense mutations (10-15% of patients)
- It aims to work in these patients by enabling the protein-making equipment in cells to move past the defect, allowing the cells to produce a functional dystrophin protein.
- Early data suggests that ataluren delays loss of ambulation
- Main side effects are gastrointestinal
- The company are about to seek approval from  the FDA, however the European Medicines Agency has granted *conditional authorisation*

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**Ataluren**

**Exon skipping**

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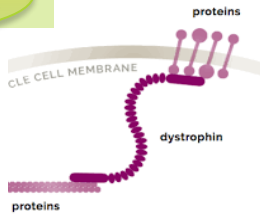


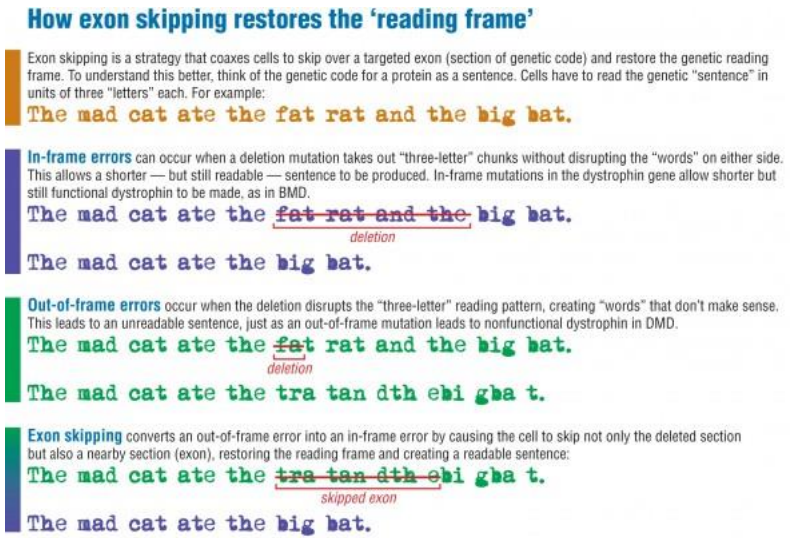

Inability to make dystrophin

Muscle injury and scarring

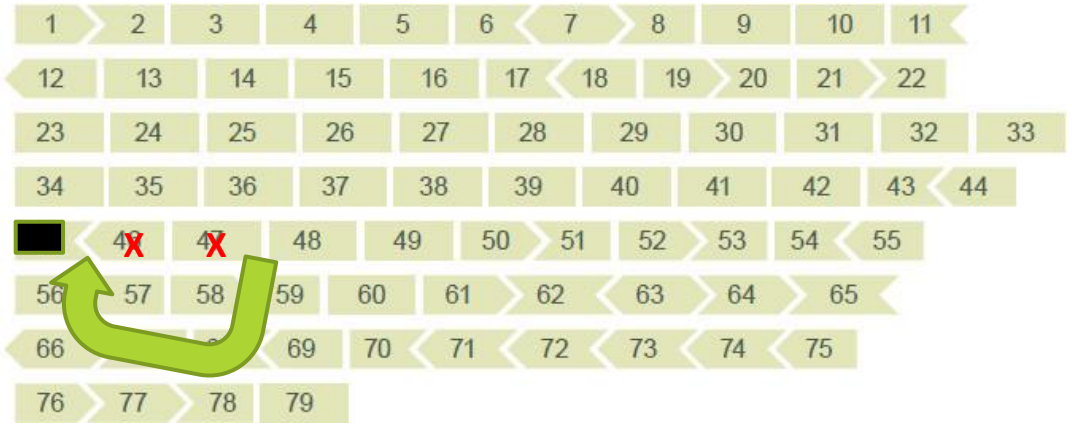
**Steroids**

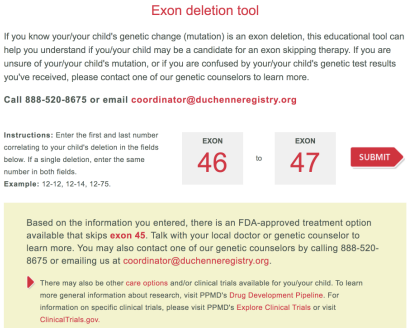
**Anti-fibrotic agents**

# How exon skipping works



# How does exon skipping work?




.parentprojectmd.org/wp-content/exondeletiontool/

# Emerging exon skipping agents

- Exon 45 skipping agent – Casimersen
- Exon 51 skipping agent – Eteplirsen (exondys 51)
- Exon 53 agent - Vitolarsen and Golodirsen

- About 30% of patients may have mutations amenable to these treatments
- All these drugs have conditional FDA approval on the basis of increased dystrophin expression (not TGA)
- They require weekly infusions
- Renal toxicity has been a concern (more-so in animal models)

Second generation exon skipping agents are in development, with adjustments to increase affinity for muscle cells, allowing for lower doses and decreased dosing schedules

# Other neuromuscular conditions

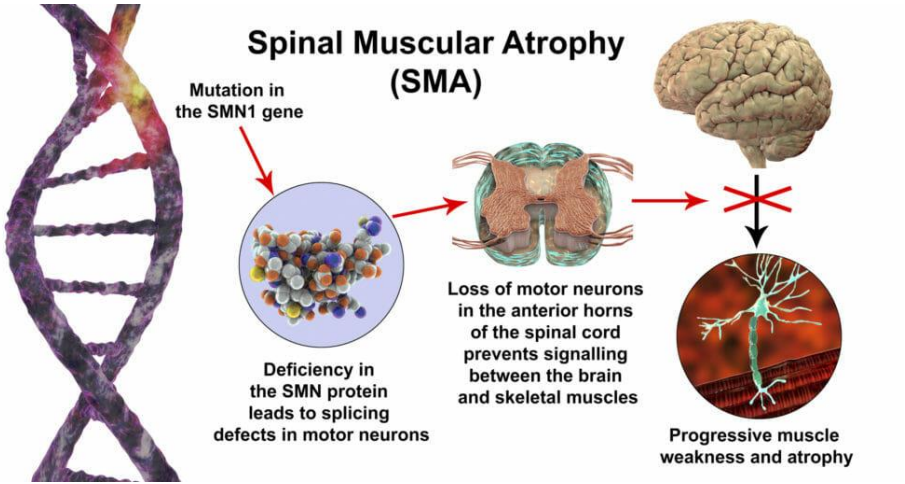
# Myotonic dystrophy

- A form of muscular dystrophy that results in muscle weakness and myotonia (inability to relax a muscle). It is also associated with cardiac arrhythmia

# Myotonic dystrophy

- There are currently clinical trials underway for
  - Tideglusib GSK3β inhibitor initially developed to treat Alzheimer's disease
    - Phase 3 clinical trial has recruited
    - Shown to improve muscle strength and reduce myotonia in mouse models
    - Well tolerated
  - Metformin (anti-diabetic treatment)
  - Mexiletine (anti-arrhythmic)
  - Several pre-clinical studies and at least phase 1 trial in AAV therapy of myotonic dystrophy type 1

# Spinal muscular atrophy




- Most common genetic cause of infant mortality
- Incidence of SMA in 1 in 11,000 live births (carrier 1 in 54)
- Causes muscle weakness and atrophy

Saoko, M Rare Disese Advisor, https://www.rarediseaseadvisor.com/hcp-resource/spinal-muscular-atrophy-pathophysiology/

# Nusinersen and risdiplam are approved and PBS funded

- An antisense oligonucleotide that makes more complete SMN protein.
- Nusinersen This is in an intrathecal injection. Maintenance doses are given every 4 months
- Risdiplam is an oral daily medication
- It has shown to be highly effective in preventing loss of motor neurons and preserving function

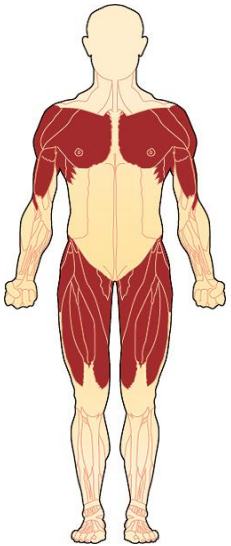
# Zolgensma – AAV gene therapy in SMA

- Follow up data of 15 years showed that

  100 percent) in a presymptomatic intravenous cohort of LT-002 maintained or achieved all assessed motor milestones, including independent walking

# Limb girdle muscular dystrophy

- A group of genetic diseases that cause progressive muscle weakness
- Muscles affected include shoulders, upper upper arms, pelvis and thighs
- Several companies are trialing AAV gene therapy in various subtypes of LGMD
  - 2E/R4
  - 2B/R2



# What else is in the pipeline?

# Gene editing

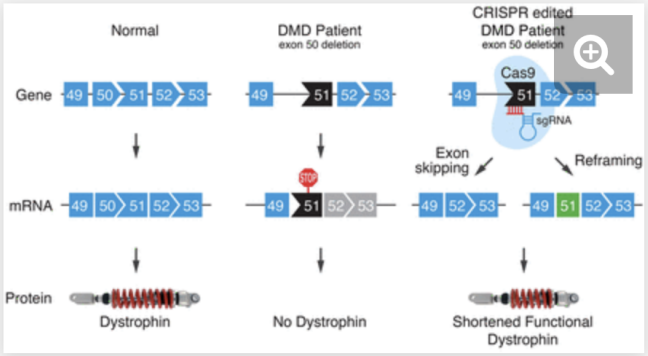



**Fig. 2.**

Download figure | Open in new tab | Download powerpoint

Single-cut gene editing of an exon 50 DMD deletion. Normal DMD gene and mRNA from exon 49 to 53 is shown (*Left*). An exon 50 DMD mutation is shown (*Middle*). Splicing of exon 49 to exon 51 places the dystrophin protein out of frame due to a stop codon. Single-cut gene editing (*Right*) with an sgRNA directed against a sequence within exon 51 can restore dystrophin expression by exon skipping or reframing, depending on the type of INDEL introduced. Dystrophin protein is schematized as a shock absorber.

- The potential to modify the gene and allow it to produce dystrophin
- Proof of concept studies (lab, animal models) have suggested potential
- These technology is currently being applied in oncology and infectious diseases

Olson EN, PNAS June 1, 2021 118 (22) e2004840117; first published April 30, 2021; https://doi.org/10.1073/pnas.2004840117

# Value of good data and an accurate diagnosis

- Check in with your doctor if you haven't seen them in a while
- Register with the Australian Neuromuscular Disease Registry

# What matters to patients?

# Finally…

# Deciding about treatments and trials is stressful

- Talk to your doctor
- Seek a second opinion if you would find that helpful
- Surround yourself with constructive and supportive people
- Try to separate the hope from the hype
- Be prepared for uncertainty (as much as you can)
- Consider seeking professional support for your own wellbeing
- Be kind to yourself

# Acknowledgements


- Patients and families
- A/Prof Kristi Jones, Dr Manoj Menezes, Dr Richard Webster, Ms Lisa Tang
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- The Neurology and Neuromuscular teams at SCHN
- SCHN Clinical Trials Centre
- Kids Research
- The Neurology Ward Nursing Staff
- Collaborating departments (Cardiology, Medical Imaging) and sub-specialists)

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# Thank you