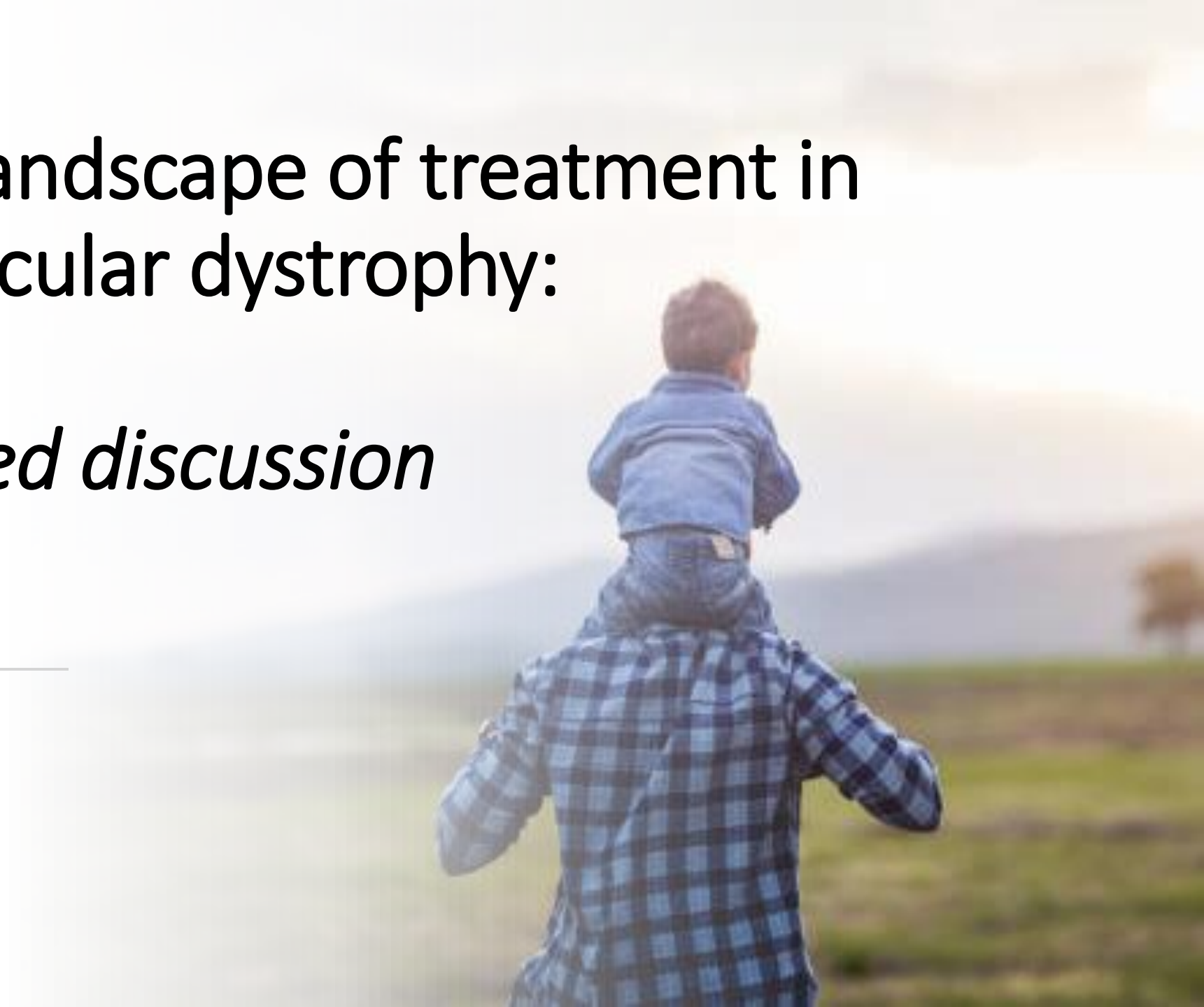
The changing landscape of treatment in Duchenne muscular dystrophy:

a scenario-based discussion



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Sydney Children's Hospitals Network

9th October 2021

The Sydney children's Hospitals Network

care, advocacy, research, education

The aim of this session

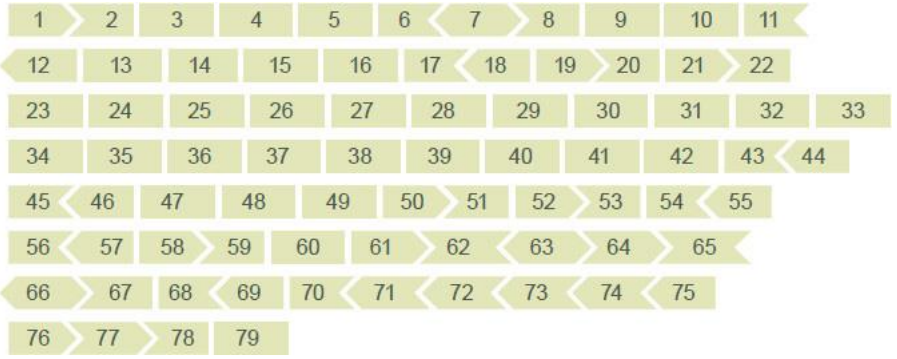
To present practical patient-based questions that will aid discussion of the new and emerging therapies in DMD

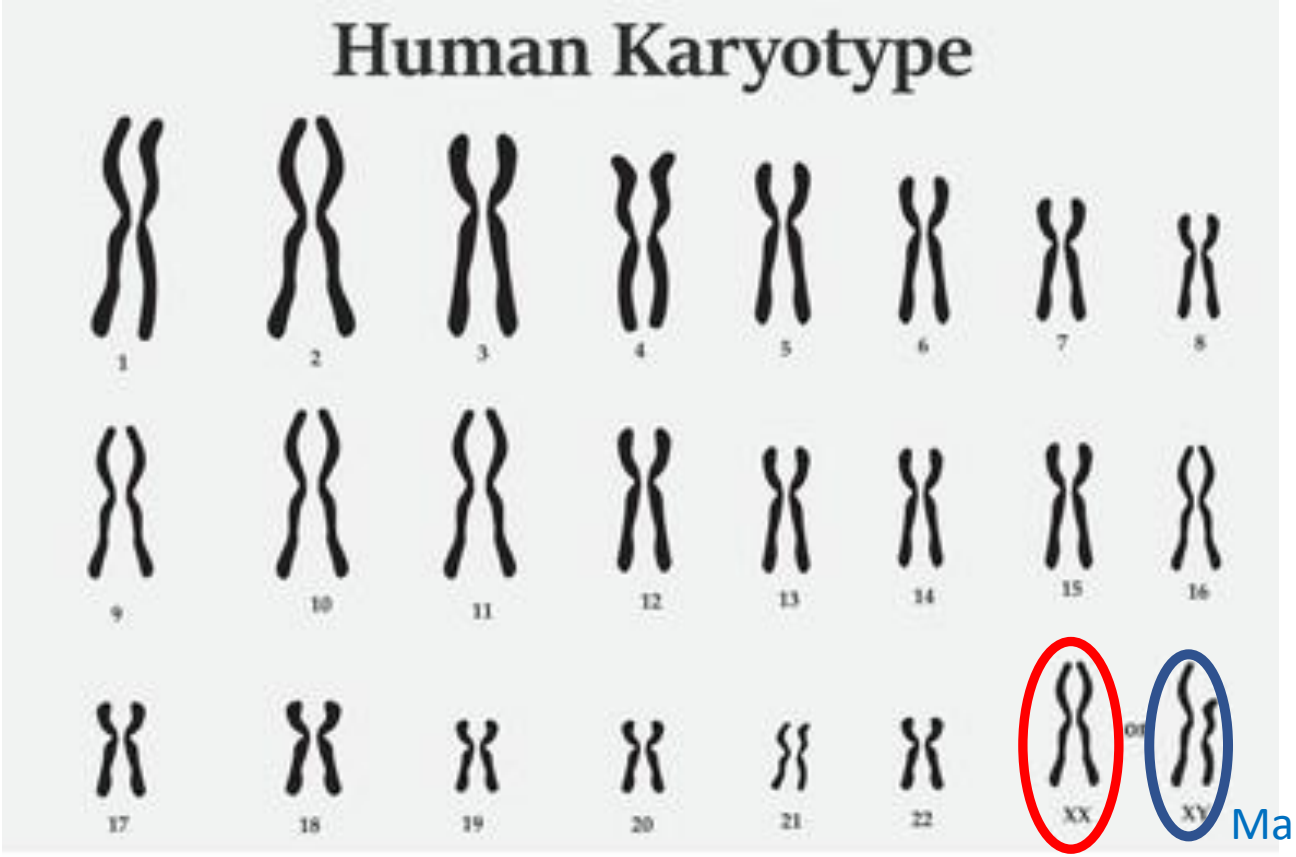
Fundamental concepts

The Genetics of DMD

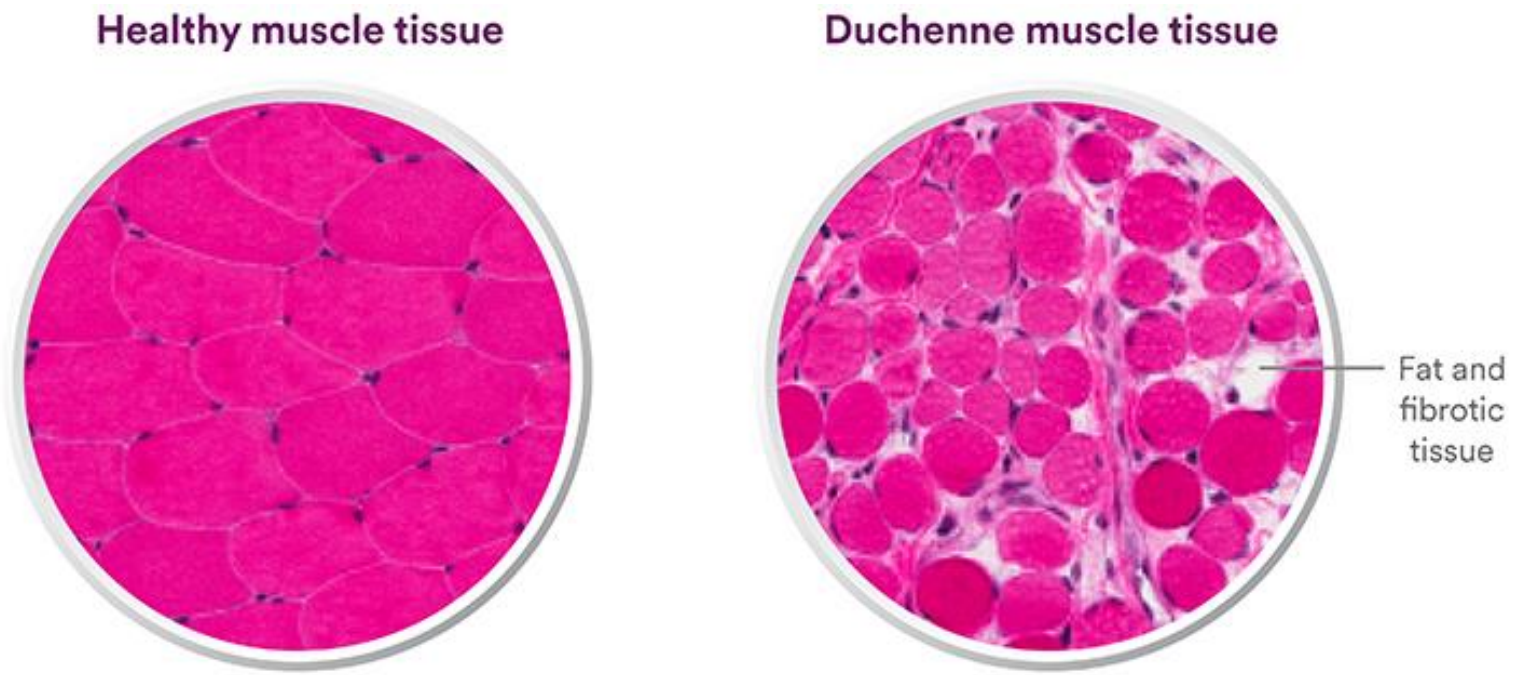
There is a mutation on the dystrophin gene, which is located on the x chromosome

The dystrophin gene is made up of 79 exons





There is an inability to make dystrophin,
leading to progressive muscle weakness and fibrosis



What are the current treatments?

- Education and counselling (ending the diagnostic odyssey)
- Targeted physiotherapy and occupational health interventions
- Targeted learning and behavior interventions
- Supportive care including cardiac, respiratory, musculoskeletal
- Surveillance for complications
- Evidenced based steroid regimen
- Access to peer and community support

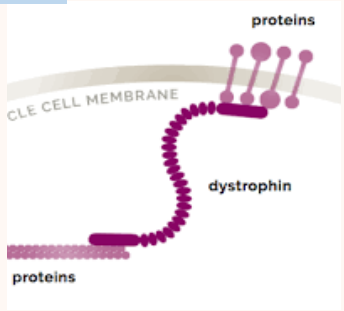
How can drugs impact the DMD process?

Ataluren

Exon skipping

Mutation in the DMD gene or ‘recipe’

Cells read the mistake in the gene



Inability to make dystrophin

Muscle injury and scarring

Gene replacement therapy

Steroids

Anti-fibrotic agents

Patient vignettes

Patient 1

My 5yo son has DMD. He has been taking daily prednisolone for 1 year.

He recently started kindergarten and I have noticed a worsening of his behavior.

Could this be the prednisolone? Should we stop it? Are there any alternatives?

What other treatment options might be possible for him?

Current medications

- High dosed steroids have been effective in delaying loss of ambulation, and preserving upper limb strength and cardiac function
  - Daily steroids
  - Weekend only steroids (US trial demonstrated tolerability and benefit in babies as young as 4 months)
  - Alternate day steroids

- Other supportive treatments (ACE-inhibitors, vitamin D, bisphosphonates)

Synthetic steroids

- Vamorolone is a synthetic steroid design to have the therapeutic effects of steroids without the side effects
- Early evidence (small trials) has demonstrated safety and efficacy
- Larger trials are ongoing

  VISION DMD (Phase 2b trial)

  https://clinicaltrials.gov/ct2/show/NCT03439670

  A Phase IIb Randomized, Double-blind, Parallel Group, Placebo-and Active-controlled Study With Double-Blind Extension to Assess the Efficacy and Safety of Vamorolone in Ambulant Boys With Duchenne Muscular Dystrophy (DMD)

Anti fibrotic agents

- Two antimyostatin proteins (Pfizer and Roche) had trials that were terminated early due to lack of efficacy
- Fibrogen drug, *pamrevlumab,* is currently being investigated in a trial
- *Pamrevlumab* inhibits the activity of connective tissue growth factor (CTGF) which is an important step in the fibrosis pathway
  - 2 Phase 3 trials LELANTOS (NCT04371666) (non-ambulatory) and LELANTOS-2 (NCT04632940) (ambulatory)

Patient 2

My 10yo son has DMD and the cardiologist has suggested starting an ACE-inhibitor as a medicine for his heart.

All his heart tests have been normal. He is already on steroids for his DMD, and I am concerned about adding another medication if it is not necessary.

Should I give him the ACE-inhibitor?

He has a nonsense mutation. What can you tell me about Ataluren?

Ace-Inhibitors in DMD

- Cardiomyopathy is very common in DMD (~ 90% of patients)
- Preventative use of ace-inhibitors (ie lisinopril, perindopril) has been shown to slow progression of cardiomyopathy leading to
    - increased life expectancy
    - decreasing hospital admissions related to cardiac causes

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)

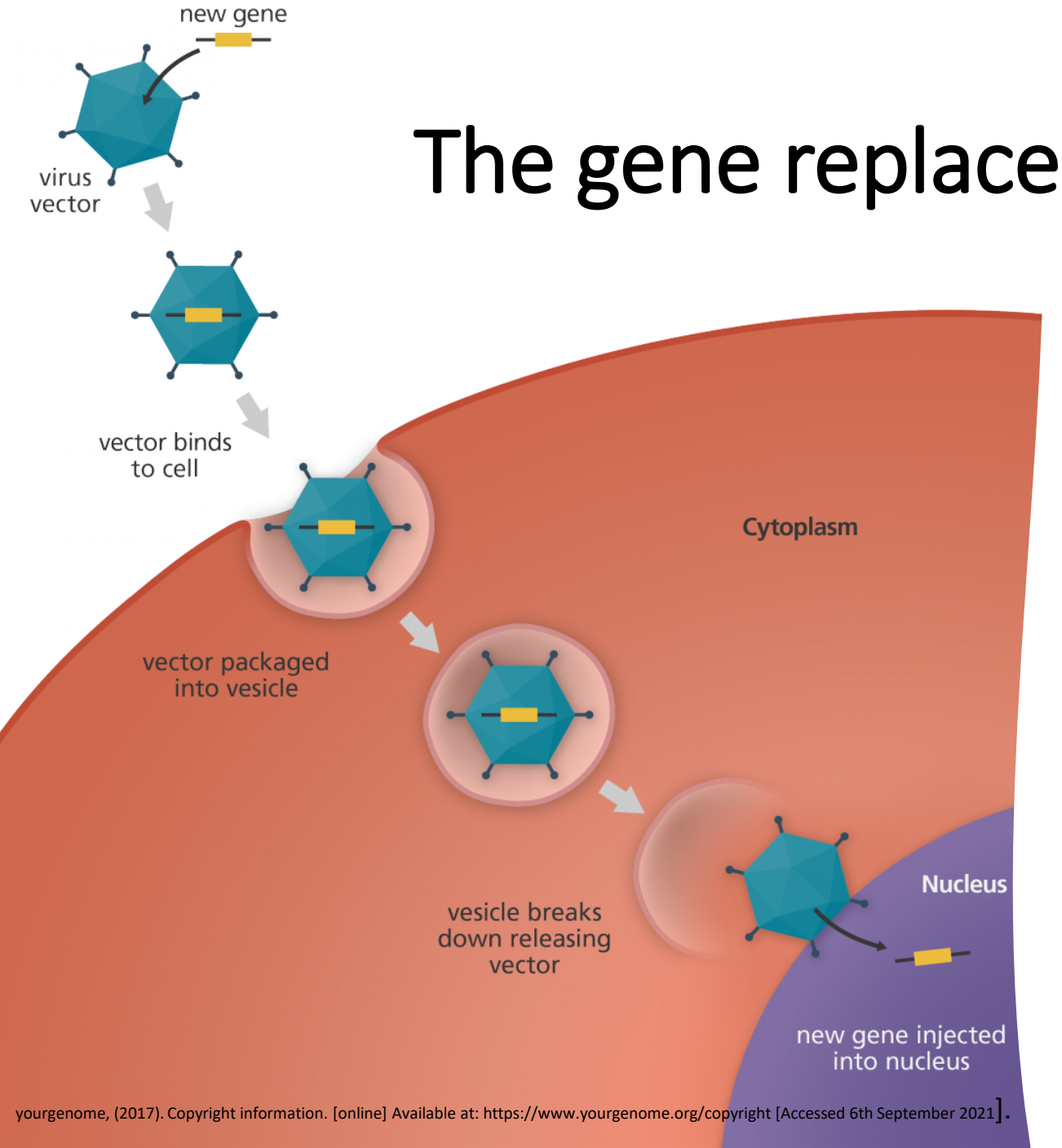
- Only indicated for nonsense mutations (10-15% of patients)
- It aims to work in these patients by enabling the protein-making equipment in cells to move past the defect, allowing the cells to produce a functional dystrophin protein.
- Early data suggests that ataluren delays loss of ambulation
- Main side effects are gastrointestinal
- Ataluren is not approved by the TGA or the FDA, however the European Medicines Agency has granted *conditional authorisation*

Patient 3

My 13yo son is now non-ambulant. Is there any benefit to his continuing his steroids?

Are there any new therapies or clinical trials that he might be eligible for?

The gene replacement therapy process



DMD gene replacement therapies rely on an adenovirus vector

If the patient has adenovirus antibodies, they will not be a candidate for this gene therapy

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

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

Gene replacement therapy trials

- Significant increases in mini or micro dystrophin
- There were variable results in functional improvements, however the numbers were too small to draw conclusions
- Serious adverse events reported in some patients (all resolved)
- There are risks to gene therapy (liver damage, immune responses, kidney damage)
- We think patients can only receive gene therapy once and it can’t be ‘ungiven’

Patient 4

My 7yo boy with DMD has deletion of exons 45-50, meaning he might be eligible for an exon 51 skipping medication.

Would he be better enrolling in an exon skipping trial or should we wait for a gene therapy trial?

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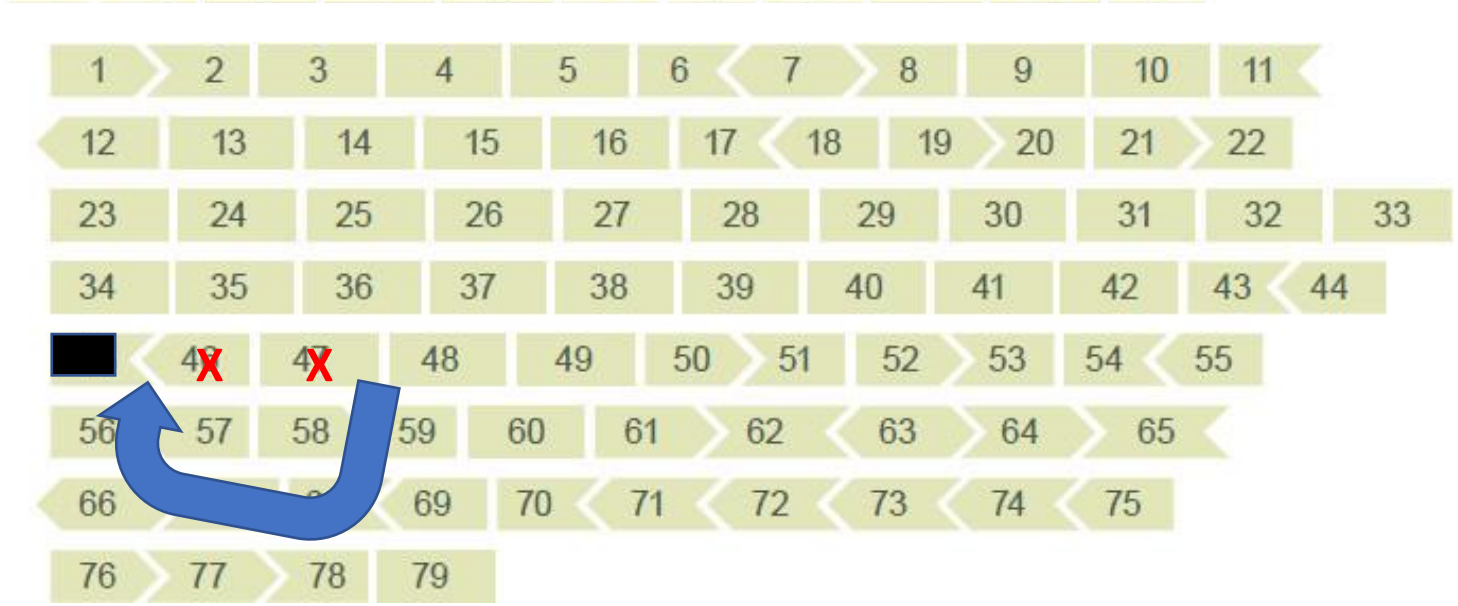
National Society of Genetic Counselors

How does exon skipping work?



Exon deletion tool

If you know your/your child's genetic change (mutation) is an exon deletion, this educational tool can help you understand if you/your child may be a candidate for an exon skipping therapy. If you are unsure of your/your child's mutation, or if you are confused by your/your child's genetic test results you've received, please contact one of our genetic counselors to learn more.

Call 888-520-8675 or email coordinator@duchenneregistry.org

Instructions: Enter the first and last number correlating to your child's deletion in the fields below. If a single deletion, enter the same number in both fields.
Example: 12-12, 12-14, 12-75.

EXON 46 to EXON 47 SUBMIT

Based on the information you entered, there is an FDA-approved treatment option available that skips **exon 45**. Talk with your local doctor or genetic counselor to learn more. You may also contact one of our genetic counselors by calling 888-520-8675 or emailing us at coordinator@duchenneregistry.org.

There may also be other care options and/or clinical trials available for you/your child. To learn more general information about research, visit PPMD's Drug Development Pipeline. For information on specific clinical trials, please visit PPMD's Explore Clinical Trials or visit ClinicalTrials.gov.

.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
- The intended outcome is transforming DMD to a Becker phenotype
- All these drugs have conditional FDA approval on the basis of increased dystrophin expression
- They currently require weekly infusions
- Renal toxicity has been raised as possible concern and renal function is closely monitored

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

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 transition from trials to therapy

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)

Advanced therapeutics present risks and challenges, however,

- There is considerable attention and industry focus on DMD treatments
- Medicine and policy- makers are embracing this new paradigm of precision medicine and advanced therapeutics
- We are witnessing the benefits of gene therapy in other diseases

Good resources for more information

- https://www.parentprojectmd.org/
- https://treat-nmd.org/
- https://clinicaltrials.gov/
- https://www.duchenneaustralia.org/
- https://saveoursons.org.au/

Email SCHN-CHW-Neurogenetics@health.nsw.gov.au

Or speak with your treating physician

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- Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C; 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.
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- https://www.parentprojectmd.org/wp-content/exondeletiontool/