RESEARCH & CLINICAL TRIALS

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

Bridget McGowan, MD
Lurie Children's Hospital

Overview

- Introduction to clinical trials
- Considerations for participating in clinical trials
- Resources for finding clinical trials
- Current drug development landscape

Purpose of a Clinical Trial

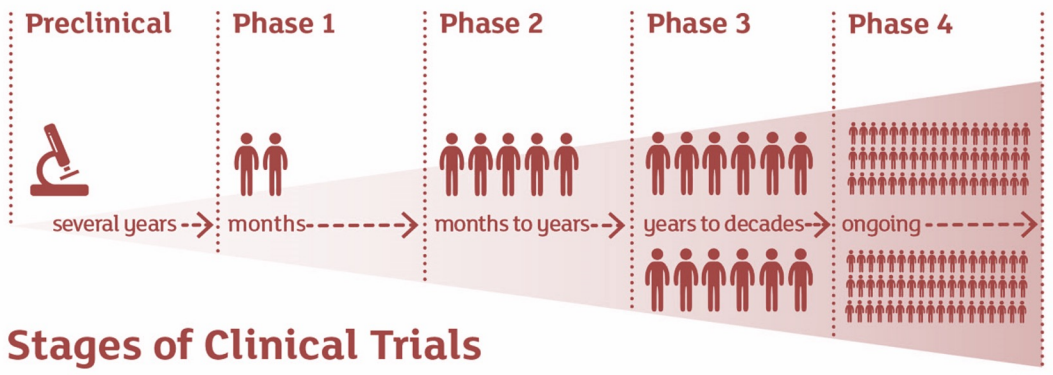
- Studies to understand the effect of a drug or device in a human population

- In Duchenne and Becker this has typically involved evaluating the safety and efficacy of new or repurposed drugs, referred to as ‘investigational products’

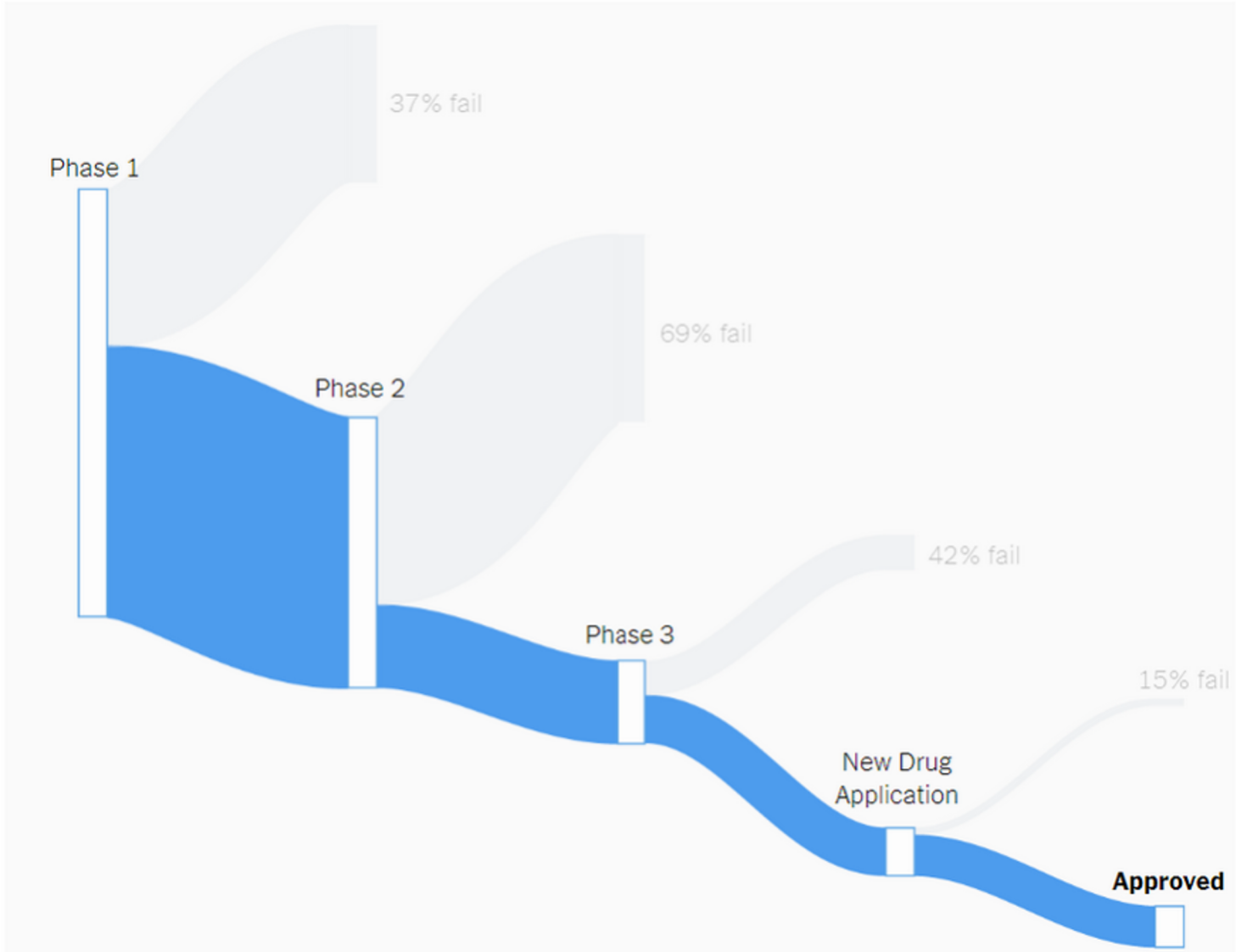
- Clinical trials are **research,** not treatment – the data collected during trials is what is necessary to shift an ‘investigational product’ to an ‘approved product’ by the FDA.
  - There may be benefits from an investigational product, but there is no guarantee, the trial is how we find out if an investigational product is effective.

Phases of Clinical Trials

- **Preclinical** – Lab and animal studies that help us understand potential of an investigational product
- **Phase 1** – First in humans, assessing safety – Small numbers, sometimes done in healthy adults before the pediatric trial
- **Phase 2** – Typically dose finding studies, safety still primary endpoint, will collect functional data
- **Phase 3** – Pivotal trial to show efficacy in large number of patients – Likely to include placebo
- **Phase 4** – Post-marketing or post-approval studies. Continued assessment of drug safety and efficacy



Probability of success at each phase of research



Frequently Used Clinical Trial Terminology

Inclusion/Exclusion Criteria

Set of requirements to be eligible for a trial.

Can include things like:

- Age
- Ambulation Status
- Steroid Use
- Genetic Variant

Placebo

- Inactive product given to patients to compare to investigational product
- Important for evaluating if the investigational product is truly providing benefit

Primary Outcome Measure

The test (functional/biomarker) to assess the effect of the investigational product

Adverse Event

- An unfavorable change in a patient's health. May or may not be related to the investigational product
- Serious Adverse Events are a type of Adverse Event that is considered life-threatening

Understanding Your Participation

Informed Consent

- The Consent Form – is the document you will sign to agree to participate in a trial, it contains information on the trial: risks, benefits, timeline of the study.
  - You can receive a copy before signing to review with your family and physician.
  - During the consent process you will learn about the trial and it is your opportunity to ask questions of the research team.
- These can be long documents with a lot of information so come prepared:
  - Come with a list of questions you want answered, bring a notebook to write down additional questions while discussing, no question is too small!
  - Ask whatever questions you need to feel comfortable – from ‘what were the side-effects seen in the animal models?’, to ‘will you cover the cost of gas?’
- Assent – Your child may also be asked to sign a consent document (usually once 7+ years of age), investigators should be developing assent forms and explanations that help your child understand the trial.

Risks of Participating

- The investigational product may not work or be better than routine standard of care
- You may receive placebo rather than the investigational product
  - For most studies you will eventually receive the investigational product; the access and timeline should be available in the informed consent
- Investigational products may have unwanted or harmful side-effects
- May impact your ability to participate in other clinical trials
  - Exclusion criteria often restricts the use of multiple investigational products
  - May have to wait a certain amount of time before joining another trial – referred to as a ‘washout’ to ensure the product you had been taking isn’t impacting the results of the new trial

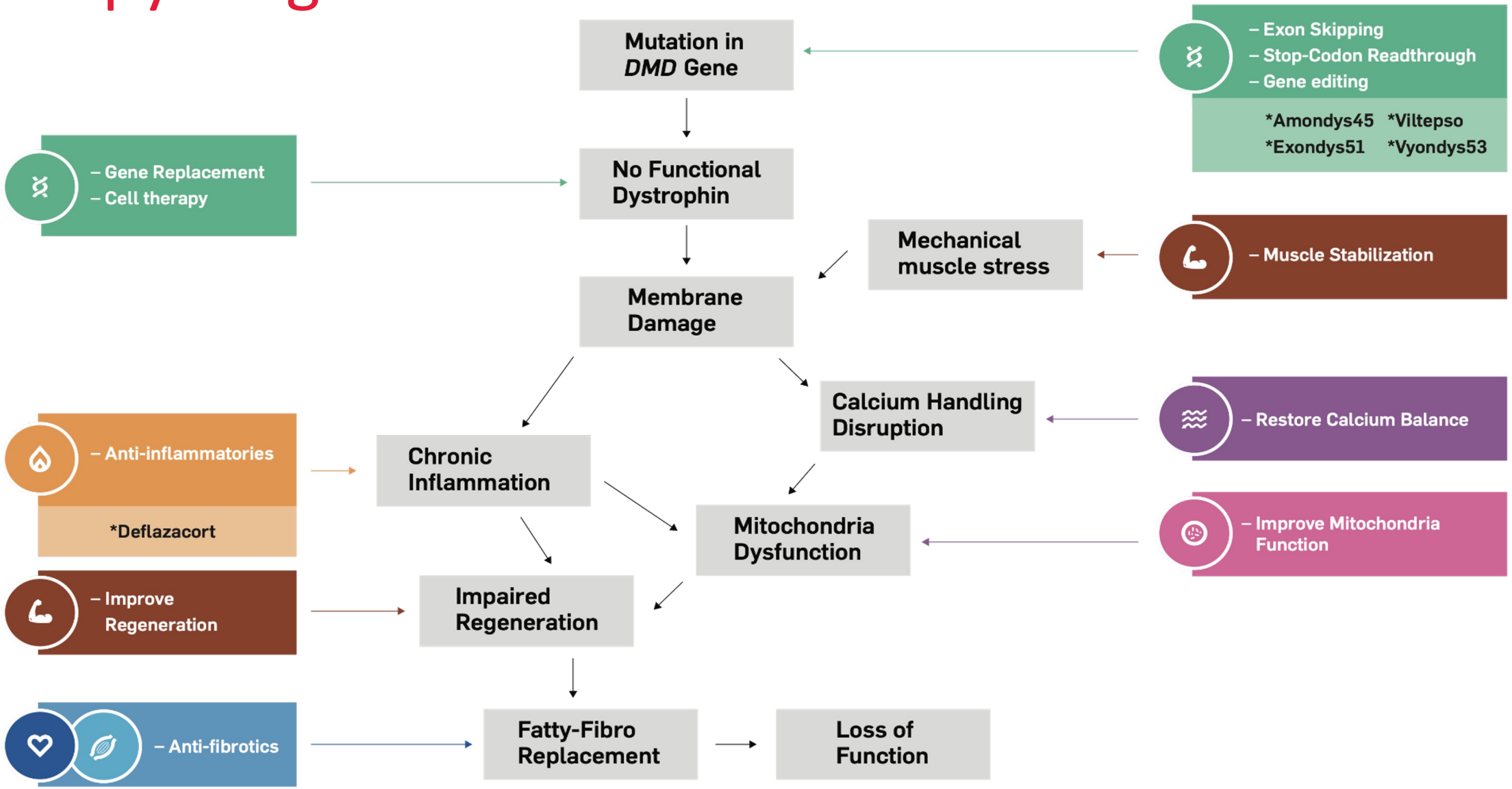
Burdens of Participating

- Costs associated with the study
  - Gas, hotels, parking, food
  - Child care for children not in the study
  - Some costs may be reimbursed by the study Sponsor; ask about reimbursement during your informed consent process.
- Schedule of visits
  - May lose time at work or have to use vacation/personal leave
  - Missing school or other activities with their peers
  - Visits could be multiple days, weekly visits, monthly; schedule should be outlined in consent document.
  - A particular trial may not have a site that is local to your area

Benefits of Participating

- Access to the investigational product
  - Products could provide benefit and this is an opportunity to have access prior to approval
  - Many studies offer Open Label Extensions – providing you an opportunity to continue having access to the product after the initial trial is completed
- Providing benefit to the community
  - Investigational products can't be approved without appropriate testing and that requires willing participants
  - The more individuals willing to participate, the faster a trial can gather data to see if the products are providing benefit or not
- Access to medical experts and standard of care
  - Visits may occur outside of the typical 6 month visit allowing for more interaction with care providers
  - May visit with other expert care providers outside of your traditional care team

Therapy Targets

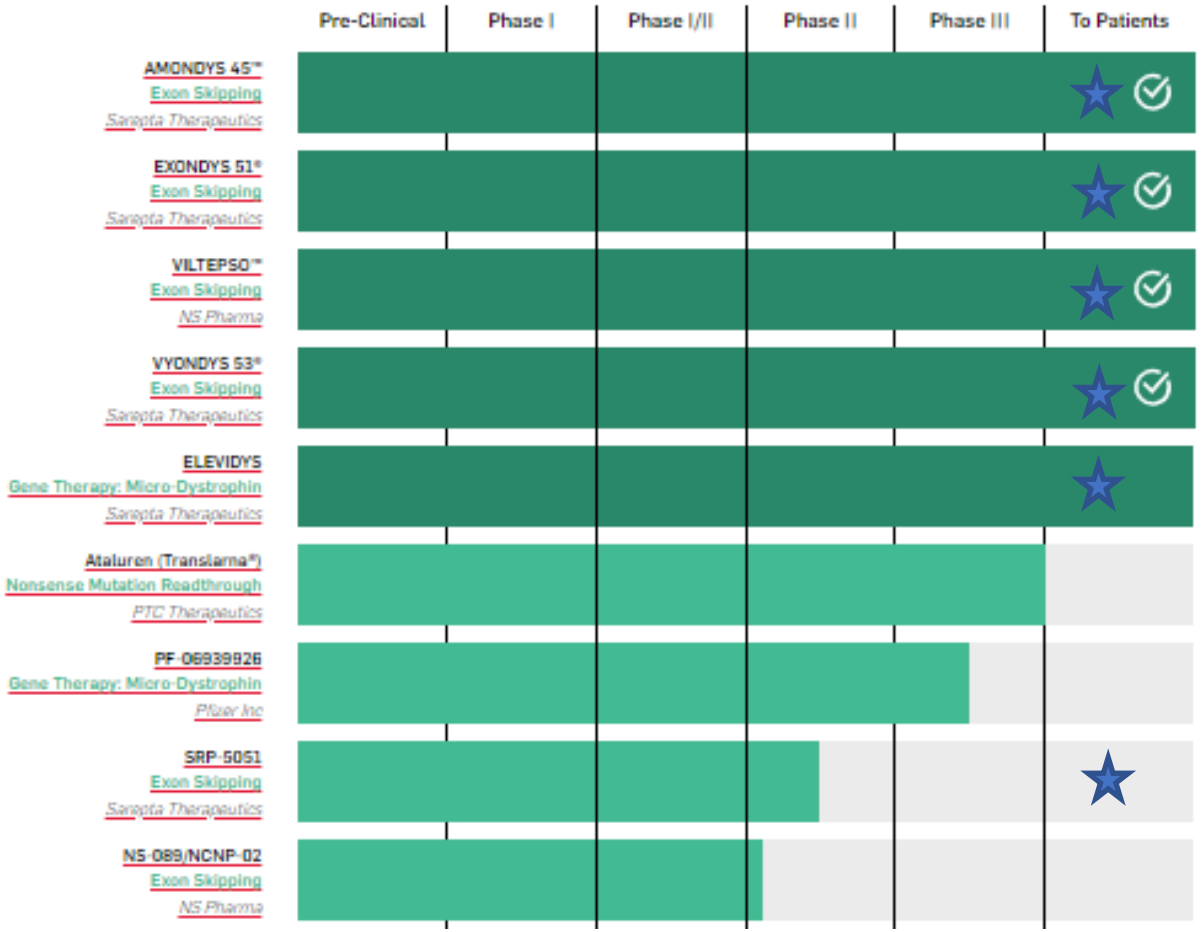


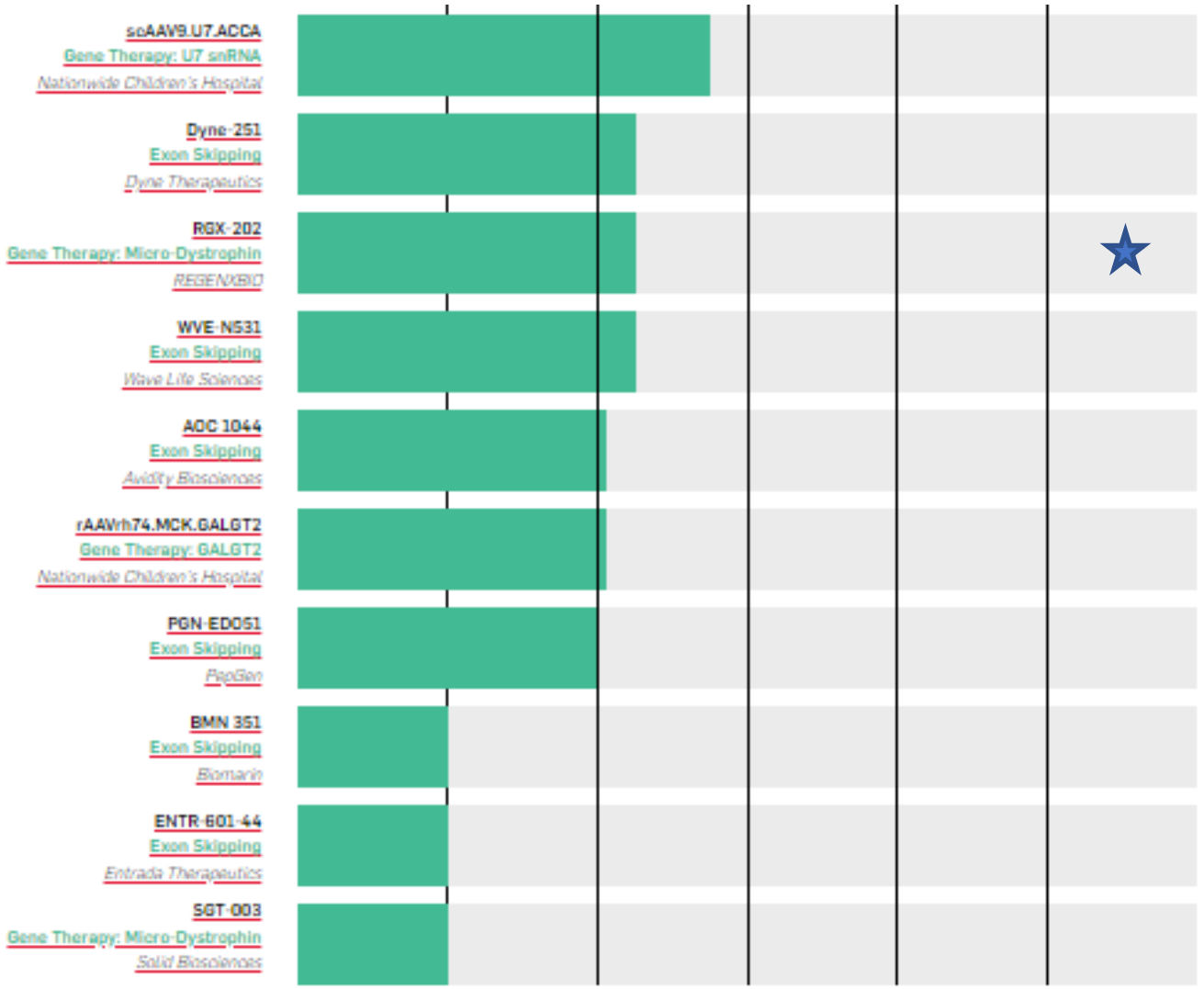
Adapted From - Verhaart, I.E.C., Aartsma-Rus, A. Therapeutic developments for Duchenne muscular dystrophy. Nat Rev Neurol 15, 373–386 (2019). https://doi.org/10.1038/s41582-019-0203-3

*FDA Approved Therapies

Restoring or Replacing Dystrophin | LEARN MORE »

Dystrophin restoration or replacement aims to treat the underlying cause of Duchenne which is the lack of dystrophin, the protein that provides stability to the muscles. Exon skipping and nonsense mutation readthroughs are both ways that dystrophin *restoration* is being explored. Strategies to *replace* the missing dystrophin protein include gene therapy, which uses a modified smaller version of the dystrophin gene, called micro-dystrophin, to produce a modified micro-dystrophin protein.



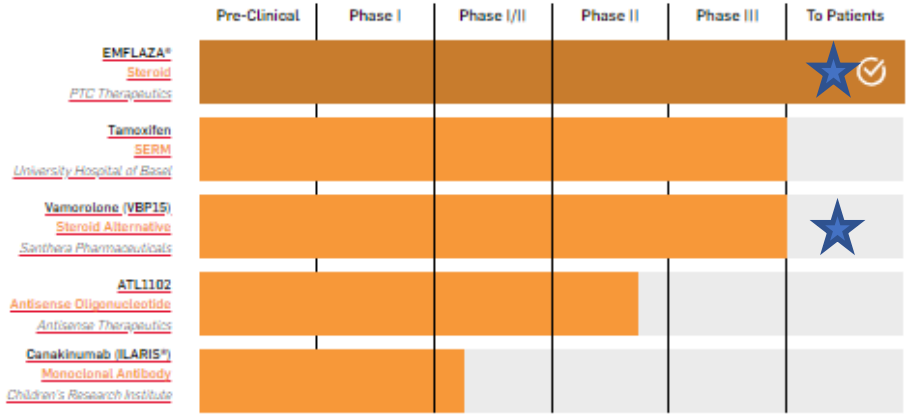


Combating Fibrosis | LEARN MORE »

Fibrosis, defined as the thickening and scarring of connective tissue, is a downstream symptom of the lack of dystrophin. Fibrosis occurs in Duchenne when chronic inflammation inhibits muscle repair. Reducing fibrosis may help decrease the breakdown of mature muscle cells and increase muscle strength.

Reducing Inflammation | LEARN MORE »

Inflammation is a critical characteristic of Duchenne disease progression. Due to muscle degeneration and the resulting immune cells brought in to help regenerate the muscle, a whole host of inflammatory substances are released. The muscles of individuals with Duchenne are constantly in a state of inflammation. Corticosteroids are currently the standard of care to treat inflammation but have a number of side effects associated with long-term use. There are a number of experimental therapies in development that are aimed at reducing inflammation.

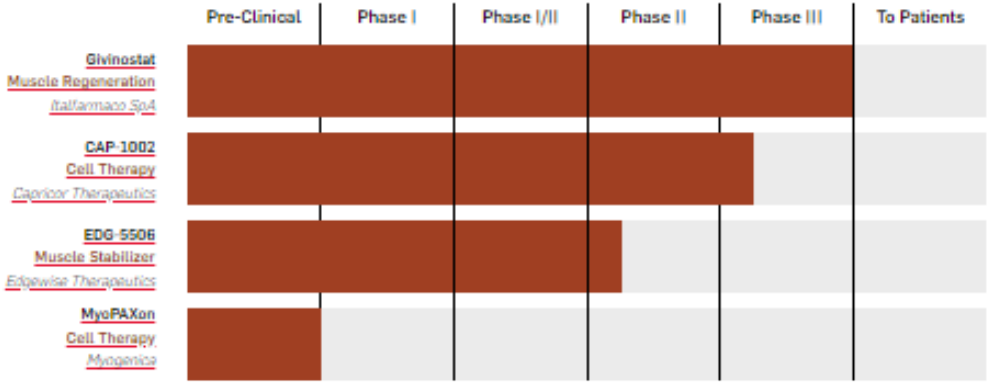


Regulating Calcium Balance | LEARN MORE »

In Duchenne, because of the instability of the muscle membrane due to the lack of dystrophin, leaks in the muscle cell membrane can develop. These leaks can let too much calcium flow in and out of the muscle cell, disrupting cellular functions which further exacerbate cellular repair. Companies are developing compounds that aim to help regulate the calcium flow.

Improving Muscle Growth & Protection | LEARN MORE »

Several therapeutic options intend to encourage muscle growth and discourage muscle breakdown. There are many strategies that can be explored in this domain, including approaches to enhance repair capabilities of the muscle, protect the muscle from breakdown, reduce inflammation and fibrosis, or induce muscle development.



Restoring the Cells Energy | LEARN MORE »

Mitochondria are specialized structures within cells that supply chemical energy to power the activities of the cells, such as repairing muscle cells. Individuals with Duchenne lack efficient mitochondria in their cells. It is thought that by increasing or enhancing the mitochondria in muscle cells, the cellular functions of the muscle could be improved.

Improving Heart Function | LEARN MORE »

Cardiac function is a concern in Duchenne, as the heart is a muscle and is affected by the lack of dystrophin. There are a number of therapies in development that may impact both the skeletal muscle and cardiac muscle. However, some strategies are aimed primarily at the heart. Use of known cardiac interventions – Angiotensin-converting-enzyme (ACE) inhibitors, Angiotensin receptor blockers (ARBs), Eplerenone, or Betablockers – are part of care management of the heart based on physician recommendation.

Thank you