Neuromuscular aspects of Duchenne Muscular Dystrophy

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

Jena Krueger
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Conflict of interest

I am currently or was previously a principal investigator for funded pharmaceutical trials with Avexis/Novartis*, Scholar Rock Inc, Fibrogen and Genentech

* Published work at least partially produced utilizing medical writers supported by pharmaceutical company

This presentation may include non-FDA approved use of medication and treatment in pediatric neuromuscular disorders

Objectives

- Define Duchenne Muscular Dystrophy
- Discuss the multidisciplinary care model

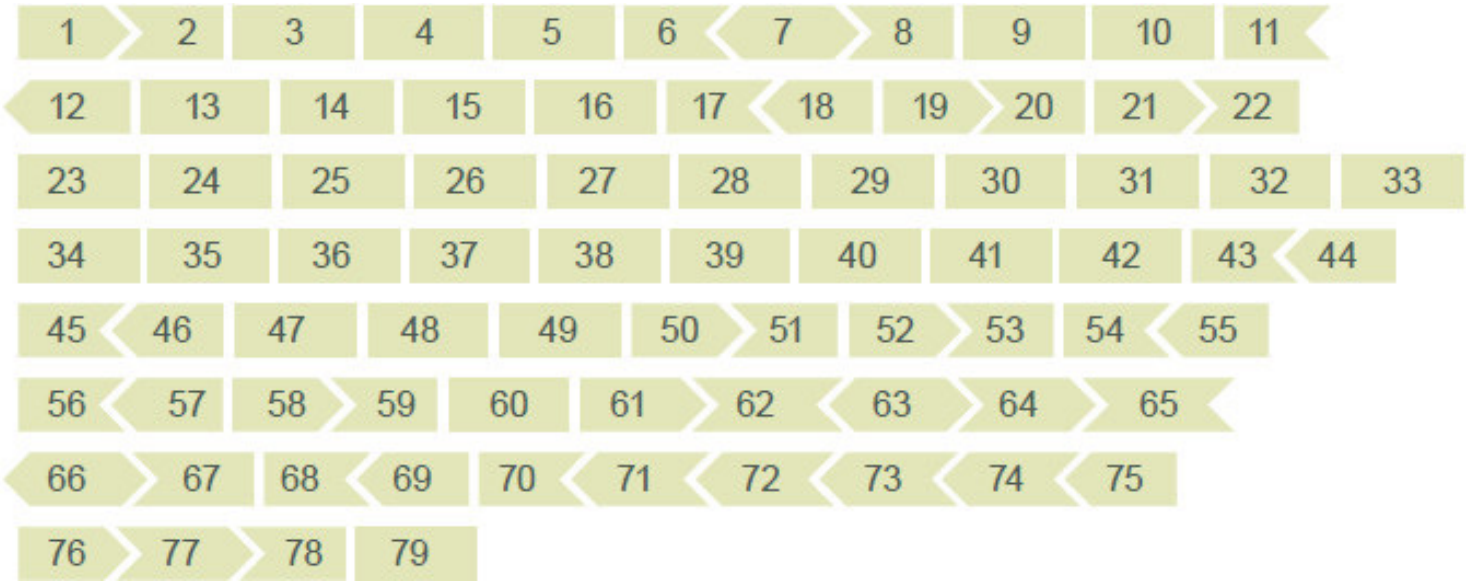
History[1]

- Described by Meryon, 1852 and Little in 1853
- 1861 Duchenne established diagnostic criteria
- Becker Muscular Dystrophy described in 1955
- DMD gene mapped on Xp21

Duchenne Muscular Dystrophy

- Absent or deficient dystrophin
- Dystrophin = protein responsible for strength, stability, function of muscle fibers[2]

DMD gene[3]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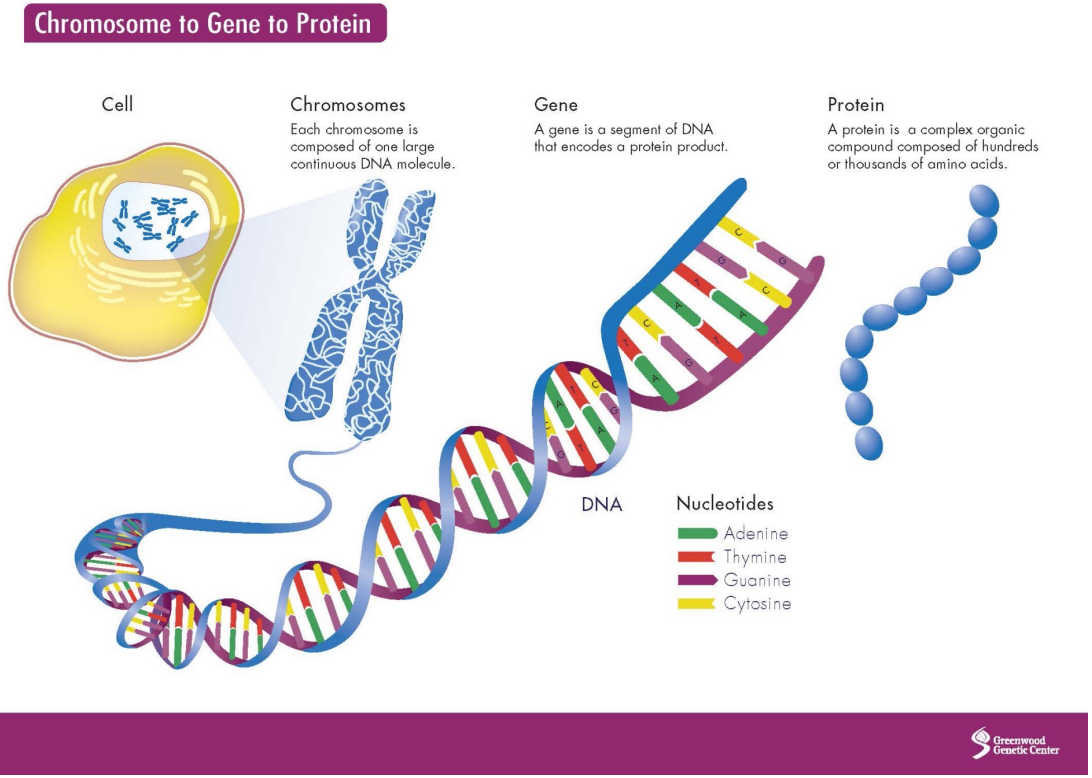
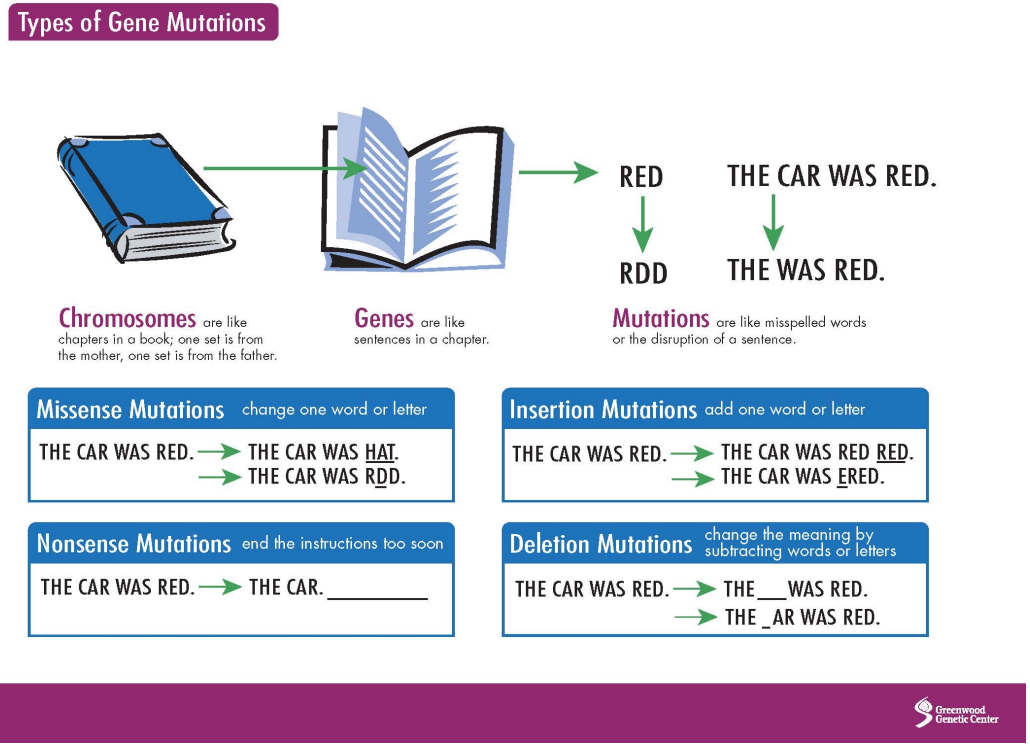
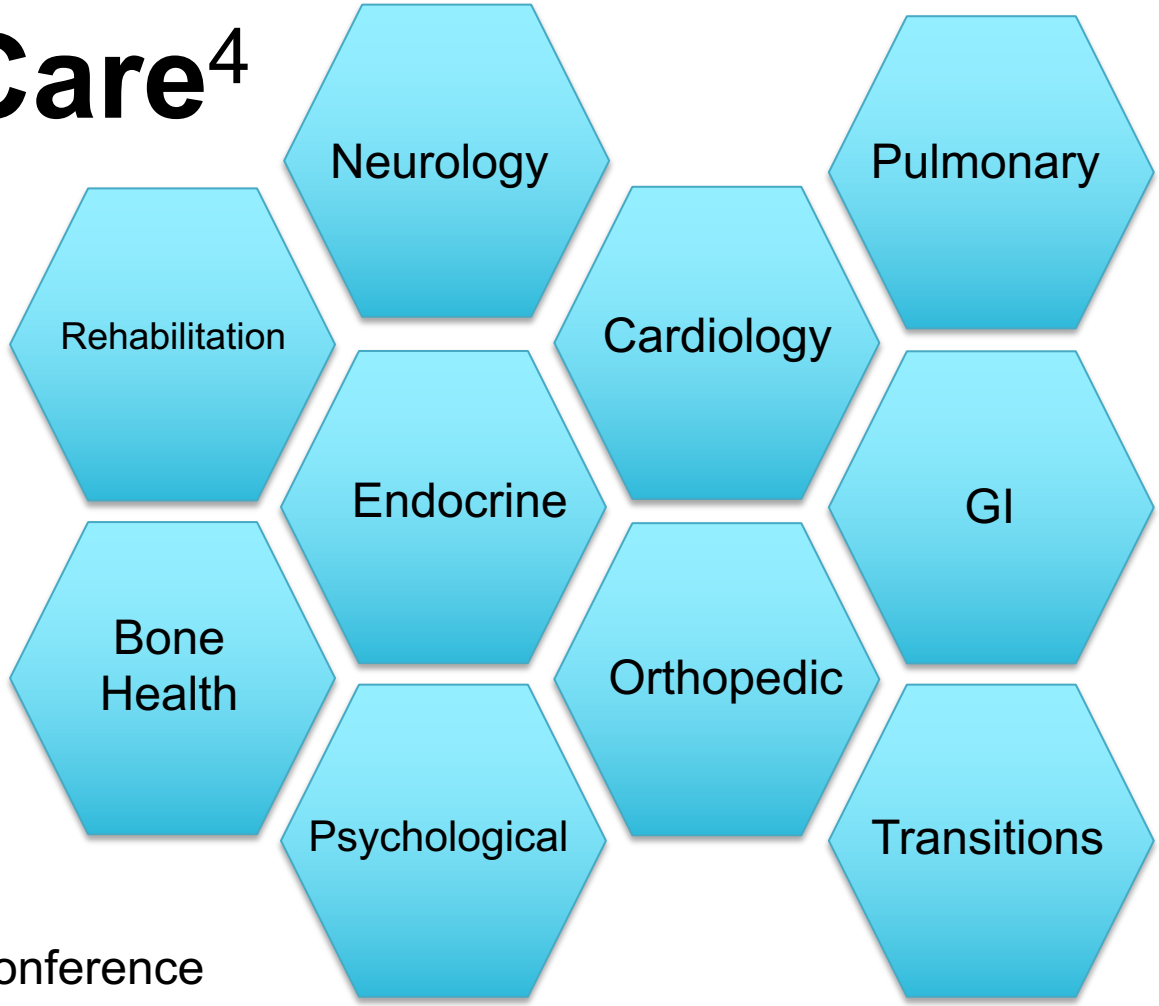
Genetics


Chromosome to Gene to Protein
Cell
Chromosomes
Each chromosome is composed of one large continuous DNA molecule.
Gene
A gene is a segment of DNA that encodes a protein product.
Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.
DNA
Nucleotides
Adenine
Thymine
Guanine
Cytosine
Greenwood Genetic Center

Genetics


Types of Gene Mutations
RED
RDD
THE CAR WAS RED.
THE WAS RED.
Chromosomes are like chapters in a book; one set is from the mother, one set is from the father.
Genes are like sentences in a chapter.
Mutations are like misspelled words or the disruption of a sentence.
Missense Mutations change one word or letter
THE CAR WAS RED. → THE CAR WAS HAT.
→ THE CAR WAS RDD.
Insertion Mutations add one word or letter
THE CAR WAS RED. → THE CAR WAS RED RED.
→ THE CAR WAS ERED.
Nonsense Mutations end the instructions too soon
THE CAR WAS RED. → THE CAR. _____
Deletion Mutations change the meaning by subtracting words or letters
THE CAR WAS RED. → THE ___ WAS RED.
→ THE _AR WAS RED.
Greenwood Genetic Center

DMD Care[4]


Neurology
Pulmonary
Rehabilitation
Cardiology
Endocrine
GI
Bone Health
Orthopedic
Psychological
Transitions

Multidisciplinary Clinic Visit

- Height/Weight
- Neurology
- Pulmonary
- Physical Therapy
- Social Work
- Genetics
- Treatment
- Cardiology
  EKG, ECHO/cMRI
- Endocrine
  DEXA / X-Ray
- Orthopedics
- Rehabilitation
- Durable Medical Company
- Orthotics
- Speech therapy
- Occupational Therapy
- Neuropsych
- Palliative Care

Google images

Neurology's Role[2]

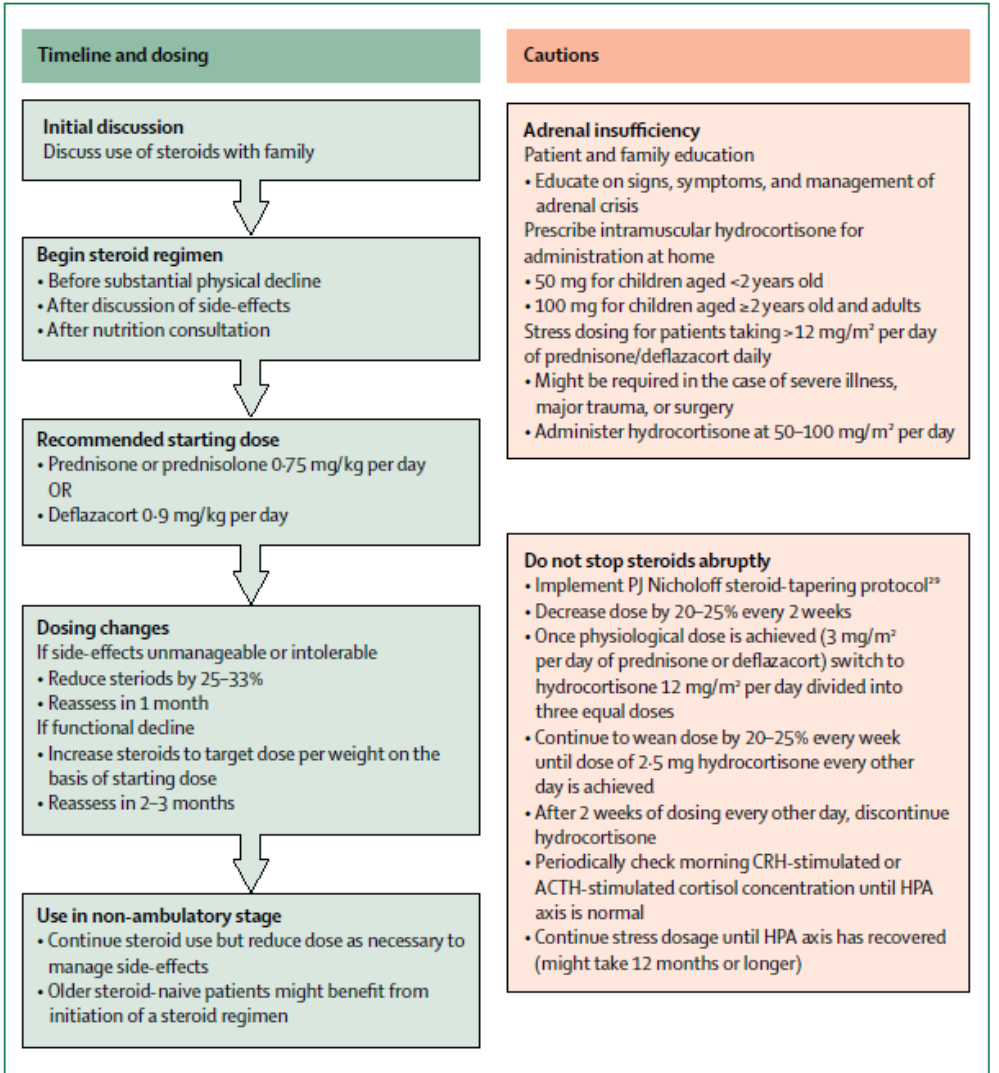
- Evaluate each patient individually
- Establish baseline and trajectory with validated assessment tools
- Management
  - Medications, research options
  - Respiratory and cardiac technology
  - Surgical options: scoliosis, contractures
- Coordinate multidisciplinary team

Treatment[2]

- Steroids
- Approved therapies
  - Exon skipping
- Treating symptoms
  (constipation, sleep, ect)
- Research options
- PT and Stretching
- Orthotics

Steroids

- Prednisone
- Deflazacort (Emflaza)



Timeline and dosing

Initial discussion
Discuss use of steroids with family

Begin steroid regimen
- Before substantial physical decline
- After discussion of side-effects
- After nutrition consultation

Recommended starting dose
- Prednisone or prednisolone 0·75 mg/kg per day
  OR
- Deflazacort 0·9 mg/kg per day

Dosing changes
If side-effects unmanageable or intolerable
- Reduce steriods by 25–33%
- Reassess in 1 month

If functional decline
- Increase steroids to target dose per weight on the basis of starting dose
- Reassess in 2–3 months

Use in non-ambulatory stage
- Continue steroid use but reduce dose as necessary to manage side-effects
- Older steroid-naive patients might benefit from initiation of a steroid regimen

Cautions

Adrenal insufficiency
Patient and family education
- Educate on signs, symptoms, and management of adrenal crisis

Prescribe intramuscular hydrocortisone for administration at home
- 50 mg for children aged <2 years old
- 100 mg for children aged ≥2 years old and adults

Stress dosing for patients taking >12 mg/m² per day of prednisone/deflazacort daily
- Might be required in the case of severe illness, major trauma, or surgery
- Administer hydrocortisone at 50–100 mg/m² per day

Do not stop steroids abruptly
- Implement PJ Nicholoff steroid-tapering protocol[29]
- Decrease dose by 20–25% every 2 weeks
- Once physiological dose is achieved (3 mg/m² per day of prednisone or deflazacort) switch to hydrocortisone 12 mg/m² per day divided into three equal doses
- Continue to wean dose by 20–25% every week until dose of 2·5 mg hydrocortisone every other day is achieved
- After 2 weeks of dosing every other day, discontinue hydrocortisone
- Periodically check morning CRH-stimulated or ACTH-stimulated cortisol concentration until HPA axis is normal
- Continue stress dosage until HPA axis has recovered (might take 12 months or longer)

Steroids

- Able to walk longer
- Arms stay stronger longer
- Helps to keep breathing muscles strong
- Avoid scoliosis surgery
- Delays cardiomyopathy (heart dysfunction)
- Improves survival

- BUT … steroids have side effects too

Prednisone	Deflazacort
Preferred by US insurance	More like to cause cataracts
More behavioral side effects	Decreased height
More like to cause diabetes	More osteopenia
More weight gain	

Both improve strength (compared to placebo)
*deflazacort may be more effective at delaying loss of muscle strength, motor function
Daily and weekend only regimens were both effective

Preparing for your appointment

- Bring snacks
- Bring activities for your child
- PPMD Care Checklists

  www.parentprojectmd.org

  → Care

  → Duchenne Care Guidelines


CARE CONSIDERATIONS CHECKLIST
LATE AMBULATORY STAGE

Parent Project Muscular Dystrophy

This checklist is intended for use by parents and caregivers of individuals with Duchenne muscular dystrophy to help you manage your child's care. Not all people with Duchenne will need to see a specialist in each medical area below. Talk with your child's neuromuscular specialist about any concerns and referrals.

At this stage, your child will likely have more trouble walking, getting up from the floor, and climbing stairs.

Neuromuscular Care

Your neuromuscular specialist (NMS) is the lead doctor for your care, who specializes in muscle care. The NMS will help you and your family understand Duchenne and the right care for you. You should see the NMS about every 6 months.

- The NMS, along with the rehabilitation team, measures your function, strength, range of motion, posture, and positioning of arms and legs. They should use the same measures and tests during each visit in order to track your progress. This occurs every 6 months or as needed.
- Make sure you are up-to-date on all immunizations. This website has information on immunizations for individuals with Duchenne: **ParentProjectMD.org/Vaccinations.**
- Consider starting corticosteroids (steroids) before you start to lose muscle function or have difficulty walking; these are recommended lifelong.
- Tell your NMS about side effects your child experiences while on steroids.
- Never stop taking steroids abruptly.
- The NMS will send a summary of each visit to you, your primary care provider (PCP), and communicate with other providers as needed.

Cardiac Care

A cardiologist is a doctor who specializes in the heart who you will see every year.

- Your heart health should be evaluated every year using an electrocardiogram (ECG) and an echocardiogram or cardiac MRI (magnetic resonance image). These show your heart rate, rhythm, structure, and function.
- The cardiologist may require you to wear a Holter monitor for 24 hours. This is a device that shows your heart rate and rhythm over 24 hours.
- Start taking heart medications when cardiac tests show a decline in heart function or scarring of the heart muscle, or by age 10 even if all tests are normal. Cardiac medications should be continued lifelong.

Notes

CARE CONSIDERATIONS CHECKLIST
EARLY AMBULATORY STAGE/CHILDHOOD

This checklist is intended for use by parents and caregivers of indiv
Duchenne muscular dystrophy to help you manage your child's care
with Duchenne will need to see a specialist in each medical area be
your child's neuromuscular specialist about any concerns and refer
At this stage, children are usually showing signs of Duchenne, like a
type of walk, walking on their toes, or needing to support themselv
hands when they get up from the floor (called a Gower's manouver
Duchenne may also have speech and other development delays.

Neuromuscular Care

Your child's neuromuscular specialist (NMS) is the lead doctor for your child's
specializes in muscle care. The NMS will help you and your family understand
right care for your child. You should see the NMS about every 6 months.

- The NMS, along with the rehabilitation team, measures your child's functi
range of motion, posture, and positioning of arms and legs using the same
tests at each visit. This evaluation occurs every 6 months or as needed.
- Make sure your child is up-to-date on all immunizations. This website has
immunizations for individuals with Duchenne: **ParentProjectMD.org/Vacc**
- Discuss the benefits and side effects of corticosteroids (steroids), such a
deflazacort (also known as Emflaza) and other appropriate therapies wit
as possible. Consider starting steroids before your child starts to lose mu
has difficulty walking, also known as the plateau phase.
- Never stop taking steroids abruptly.
- The NMS will send a summary of each visit to you, your child's primary ca
and communicate with other providers as needed.

Cardiac Care

A cardiologist is a doctor who specializes in the heart who you will see every y

- Your child's heart health should be evaluated every year using an electroc
and an echocardiogram or cardiac MRI (magnetic resonance image). These show your
child's heart rate, rhythm, structure, and function.
- Start taking heart medications when cardiac tests show a decline in heart function or
scarring (fibrosis) of the heart muscle, or by age 10 even if all tests are normal.

Respiratory Care

A pulmonologist is a doctor who specializes in the lungs who you will see every year.

- Your child should have regular pulmonary function testing (PFT) starting at the time of diagnosis or by age 6. This will get your child used to doing the test, and will allow your pulmonologist to track the strength of muscles responsible for breathing over time.
- Ensure your child receives the injectable flu vaccine every year and pneumococcal vaccine as recommended.
- Your child's pulmonologist may suggest a cough assist if your child's cough is weakening.
- Your child's pulmonologist may suggest a sleep study if there are signs and symptoms of shallow breathing, called hypoventilation, while sleeping.

#PPMDConference

Monitoring

- Height, Weight, BP
- QOL
- New symptoms or concerns
- Labs
- Pulmonary function testing
- EKG / ECHO

Monitoring

- PT assessment every 6 months
  - Range of motion, strength
  - North Star Ambulatory Assessment, timed function tests (6MWT)
  - BayleyIII and Griffiths mental development in infants
  - Brooke upper extremity, Egan Klassifikation in non-ambulatory

After your appointment

- Daily Stretching !! 4-6 times per week
- AFO
  - Night while ambulatory, day if non-ambulatory
- Submaximal, aerobic exercise (swimming, cycling)
  - Avoid high-resistance, over exertion

References

1. BT Darras, CC Menache-Starobinski, V Hinton, L Kunkel. “Dystrophinopathies” ch 30, p551-592. BT Darras, H Royden Jones Jr., MM Ryan and DC De De Vivo (Eds): Neuromuscular disorders of Infancy, Childhood and Adolescence, 2nd ed.
2. DJ Birnkrant, K Bushby, CM Bann, et al “Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine and gastrointestinal and nutritional management” Lancet Neurology 2018
3. www.parentprojectmd.org
4. DJ Birnkrant, K Bushby, CM Bann, et al “Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, orthopedic management” Lancet Neurology 2018
5. DJ Birnkrant, K Bushby, CM Bann, et al “Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care and transitions of care across the lifespan” Lancet Neurology 2018
6. WD Biggar, A Skalsky, CM McDonald “Comparing Deflazacort and Prednisone in Duchenne Muscular Dystrophy”. Journal of Neuromuscular Diseases 9 (2022) 463-476

Thank you!