

# Challenges in Duchenne Muscular Dystrophy Clinical Trial Design

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**Parent** JOIN THE FIGHT.  
END DUCHENNE.  
**Project**  
**Muscular**  
**Dystrophy**

# Disclosures

## Consulting work on Duchenne muscular dystrophy clinical trials for:

- Santhera Pharmaceuticals\*\*, Catabasis Pharmaceuticals, Inc\*\*, PTC Therapeutics\*\*, Sarepta Therapeutics\*\*, Prosensa, Pfizer, Eli Lilly\*\*, Halo Therapeutics, Bristol Myers Squibb, Novartis, Italfarmaco\*\*, Astellas / Mitobridge, Cardero Therapeutics, Gilead, Capricor\*\*

\*\*Dr. McDonald has received research funding for the conduct of clinical trials.



# Clinical Experience with Eteplirsen (Dr. McDonald): Three Youngest Patients Treated for > 3 Years

**How do we demonstrate safety and efficacy of a therapeutic in DMD?**



7.5 yrs (Study 203)



8.5 yrs (Study 203)



10 yrs (Study 301)

# Challenges in DMD Study Design

- Selection of responsive, reliable, meaningful **endpoints varies with age and disease stage**
- **Variability** (due to multiple issues)
- **Maturation**
- **Required sample sizes for trials challenging** in setting of a rare disease, competitive landscape and precision medicine approaches

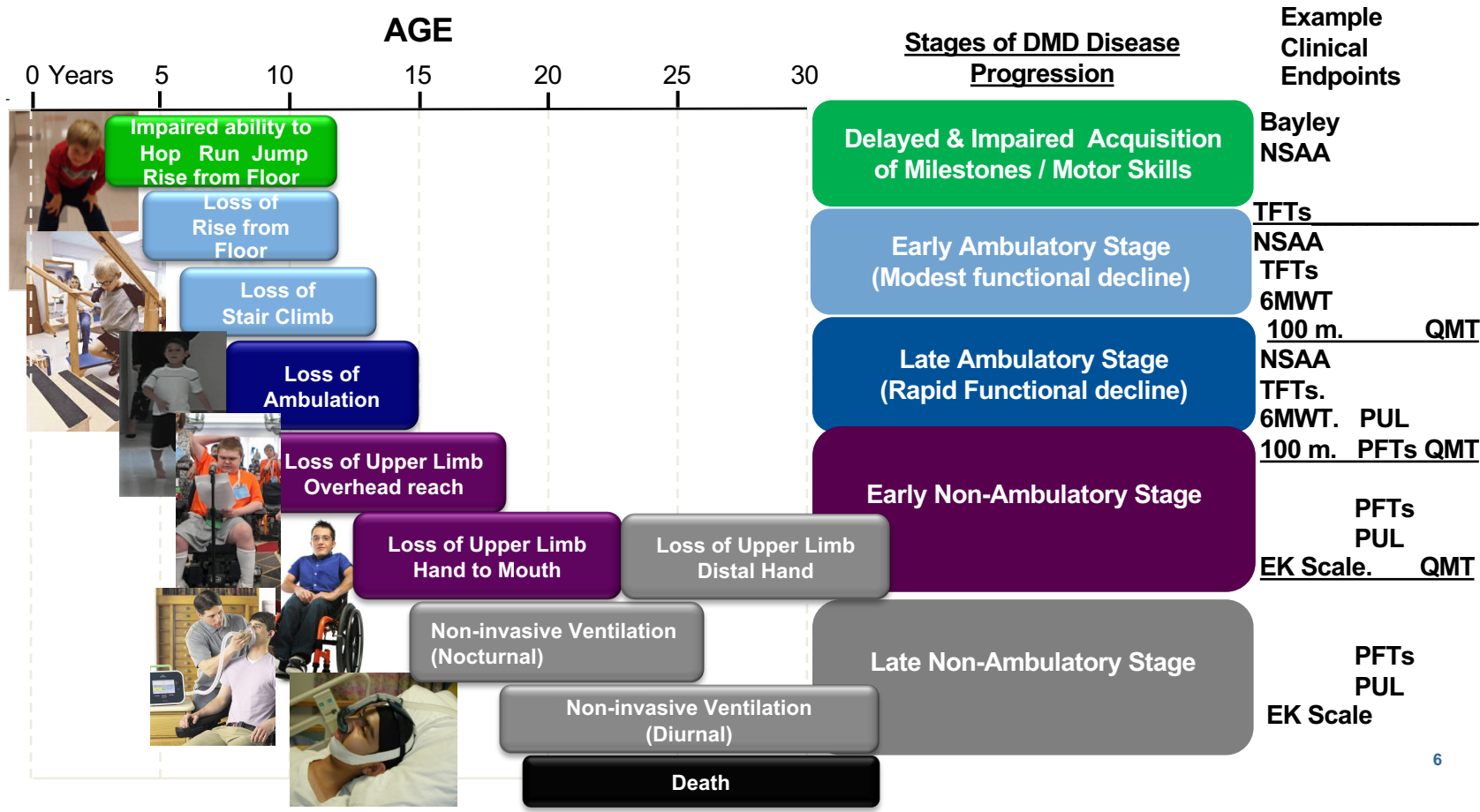


# Challenges in DMD Study Design

- Need for **enrichment** of inclusion criteria or a primary analysis subgroup often based on factors making the selected subgroups more responsive to shorter duration treatment
- **Desire for Extrapolation** beyond the trial population is balanced by desire for inclusivity and need for broader safety database.
- Regulatory desire for **placebo arms** stands in contrast to community desire to minimize placebo exposure



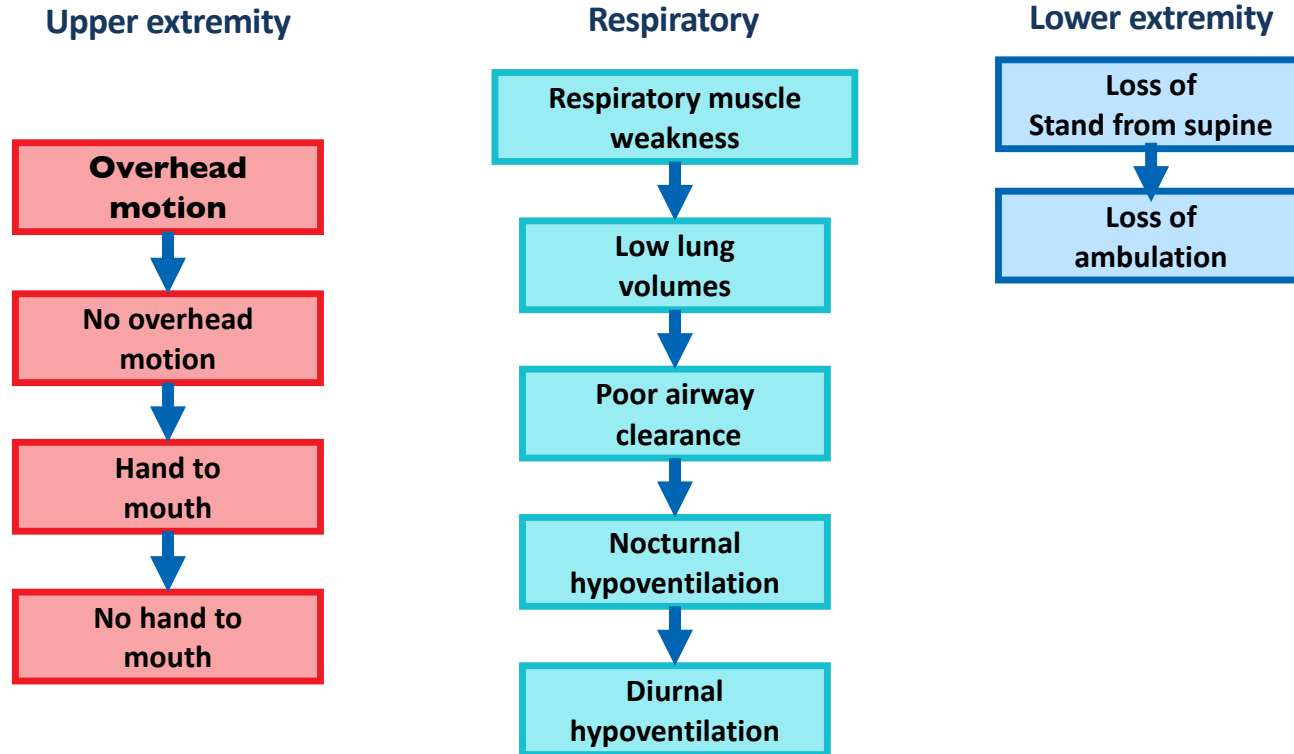
# Stages of DMD Disease Progression are captured with the use of multiple clinical endpoints



9 Year Old Boy: Baseline Assessment  
Rise From Floor 7 Sec; 6MWD 414 Meters



# Progressive loss of skeletal muscle fibers and muscle weakness in DMD leads to a sequential loss of function



1. Mayer OH, et al. US Neurology 2017;13:35–41; 2. Finder JD, et al. Am J Respir Crit Care Med;Article in Press 2017; 3. Finder JD, et al. Am J Respir Crit Care Med 2004;170:456-65; 4. Johnson JD and Theurer WM. Am Fam Physician 2014;89:359-66; 5. Humbertclaude V, et al. Eur J Paediatr Neurol 2012;16:149-60; 6. Mayer OH, et al. J Neuromuscul Dis 2017;4:189-98; 7. Bushby K, et al. Lancet Neurol 2010;9:177-89; 8. McDonald CM, et al. Neuromuscular Disorders 2016;26:473-80; 9. Brooke MH, et al. Neurology 1989;39:475-481.

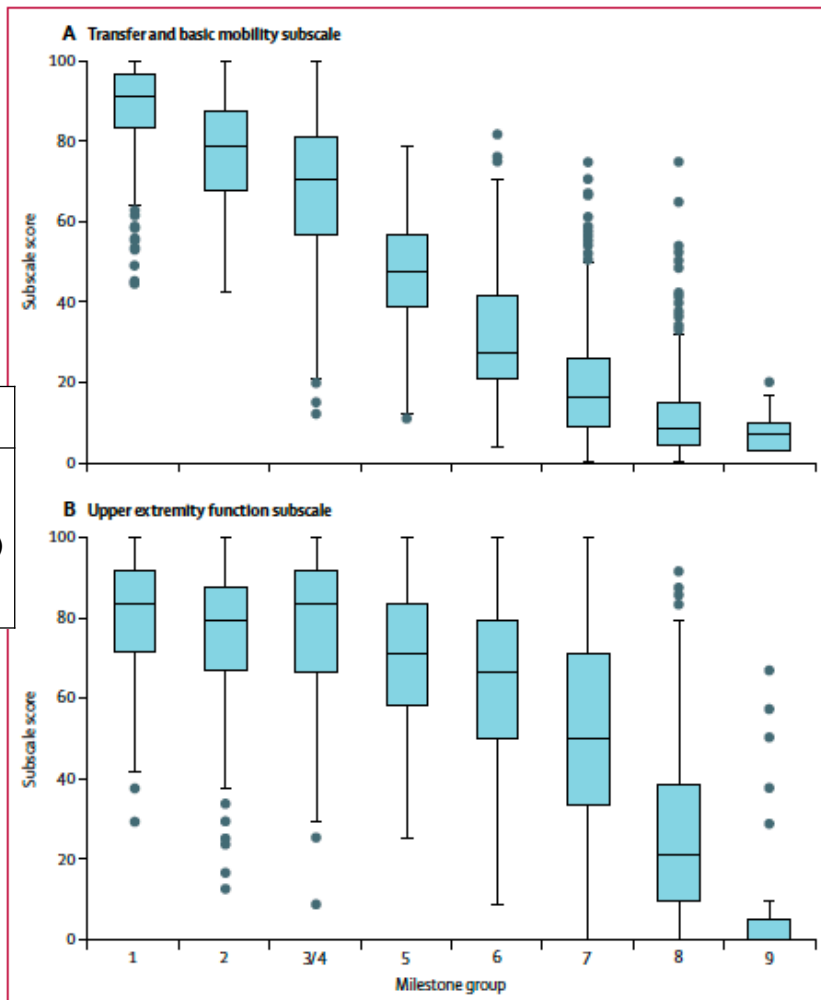


# Milestones of Disease Progression and Health-related QoL (PODCI)

1	2	3/4	5	6	7	8	9
Stand from supine < 5 sec	Stand from supine 5-10 sec	Stand from supine > 10 sec or Lost Rise from Floor	Lost 4-Stair Climb Still Amb	Non-Amb Full Overhead reach	Lost Full Overhead Reach (Retains hand to mouth)	Lost Hand to Mouth (Retains Hand Function)	Lost Lost Hand Function (Brooke 6)

**Clinical endpoints used in DMD capture how a patient “functions and feels.”**

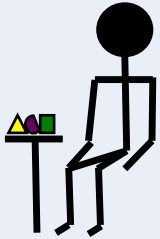
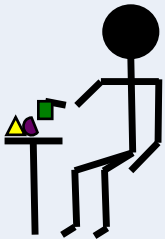


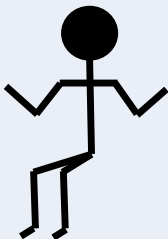


McDonald et al. Lancet, 2018



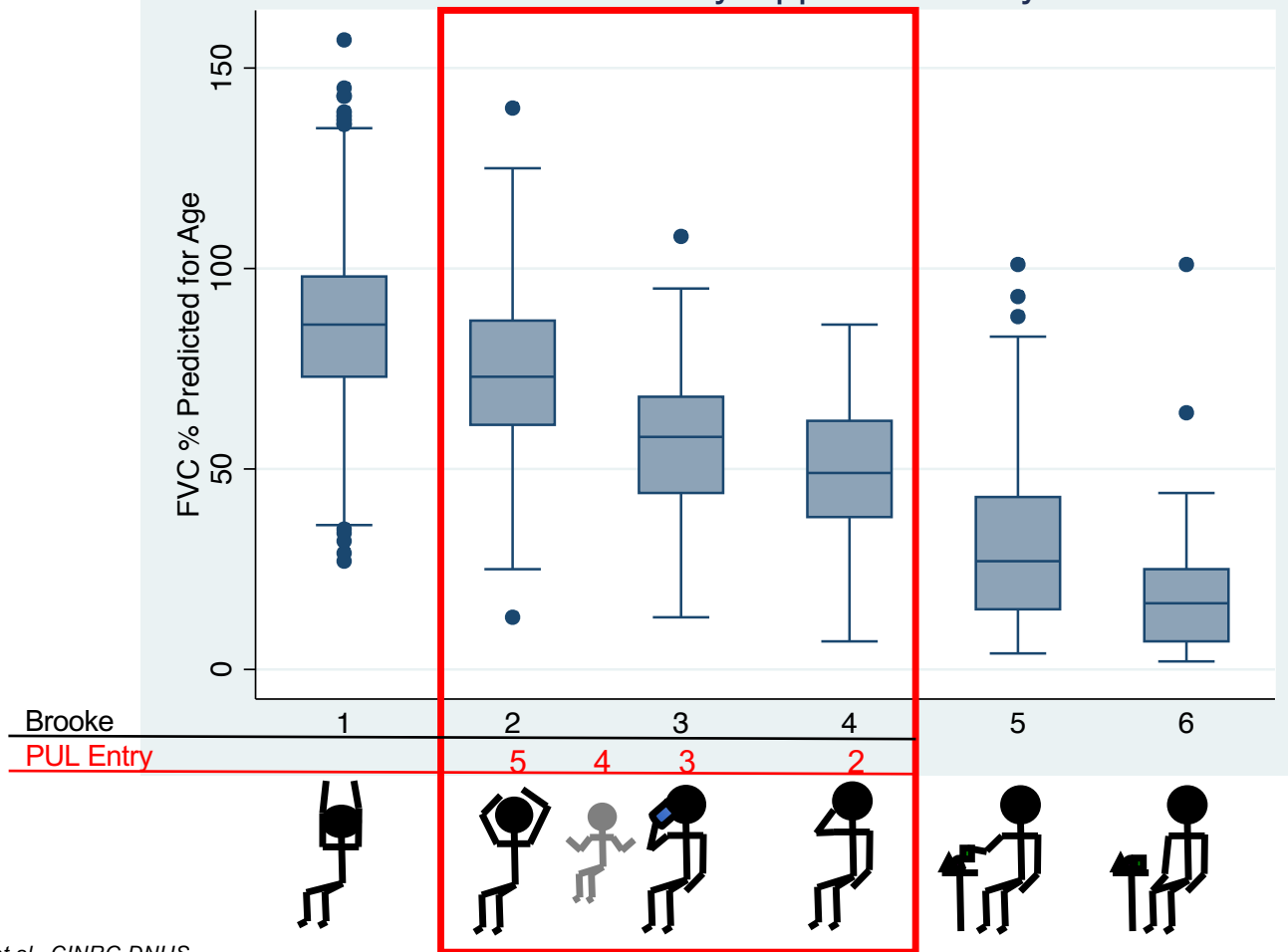
# Performance of the Upper Limb (Entry Items)

Floor

Ceiling

		Target Population				
0	1	2	3	4	5	6
						
No useful function of hands.	Can use hands to hold pen or pick up a coin or drive a powered Chair	Can raise 1 or 2 hands to mouth but cannot raise a cup with a 200g weight in it to mouth	Can raise standardized plastic cup with 200g weight in it to mouth using both hands if necessary	Can raise both arms to shoulder height simultaneously w/ or w/o compensation	Can raise both arms simultaneously above head only by flexing the elbow	Can raise both arms simultaneously above head only by flexing the elbow

## FVC % Predicted by Upper Extremity Grade



# Sources of Variability:

- Gene Mutation
- Genetic Modifiers (Sponsors do not want narrow label)
- Baseline level of function impacts expected course of disease
- Adherence to care standards; (e.g. differing steroid regimens)
- Effort / motivation
- Complexity of testing (ease of standardization important)
- Maturity / developmental status / behavioral phenotype
- Fatigue / time of day of testing
- Responders / non-responders to a therapeutic agent evident
- Duration of treatment can effect clinical response (e.g. dystrophin)



# Maturation

- Young DMD patients gain motor skills early on but at a reduced rate and acquired level versus typically developing children
  - Greater improvements than expected needed to establish efficacy of a drug in the young
  - Longer duration clinical trials often necessary with younger patients
- There are levels of skill acquisition that are highly unusual and persistent stable levels of function past specific ages are highly unusual
- Lung volumes increase with growth
- Need to normalize data for age / growth



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**NSAA Hop (Steroid Treated)**

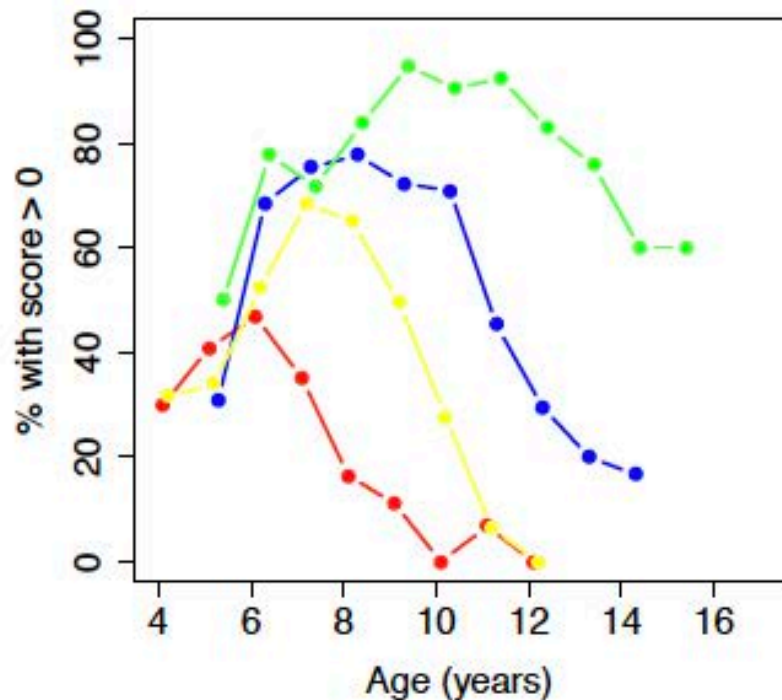


**NSAA Jump (Steroid Treated)**

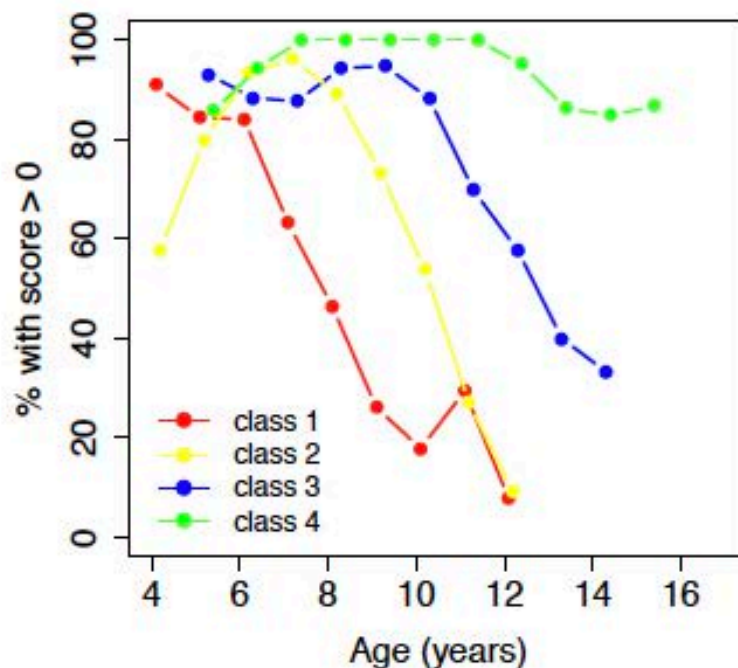


# Maturation, stability, and decline on hop and jump

D. Hop (left leg)



C. Jump



- Maturation phase is similar across cluster classes
- Proportion of patients who can hop and jump is highest in patients with milder trajectories
- Decline phase is separated by cluster class

Rise from Floor



Run



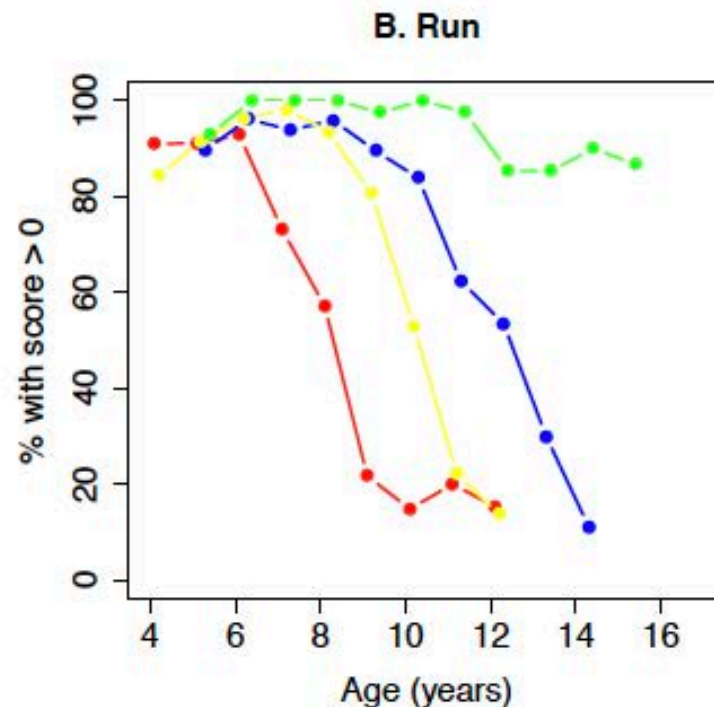
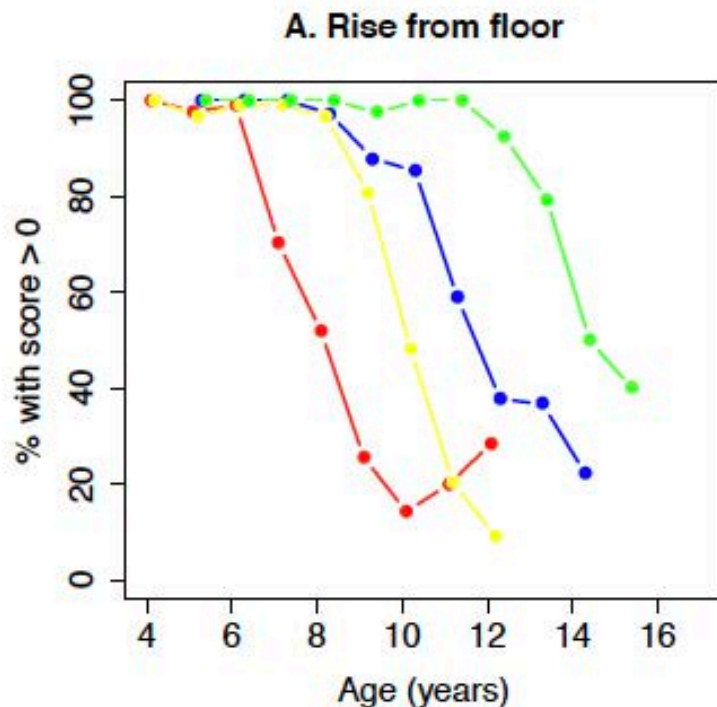


# Performance on rise from floor and run NSAA items by latent trajectory class

- class 1
- class 2
- class 3
- class 4

Proportion of patients with  
NSAA item score > 0

A



# Complete Loss of Function on NSAA, 1 to 0 Change, Different from 2 to 1 Change

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Stand from Supine  
NSAA: 1

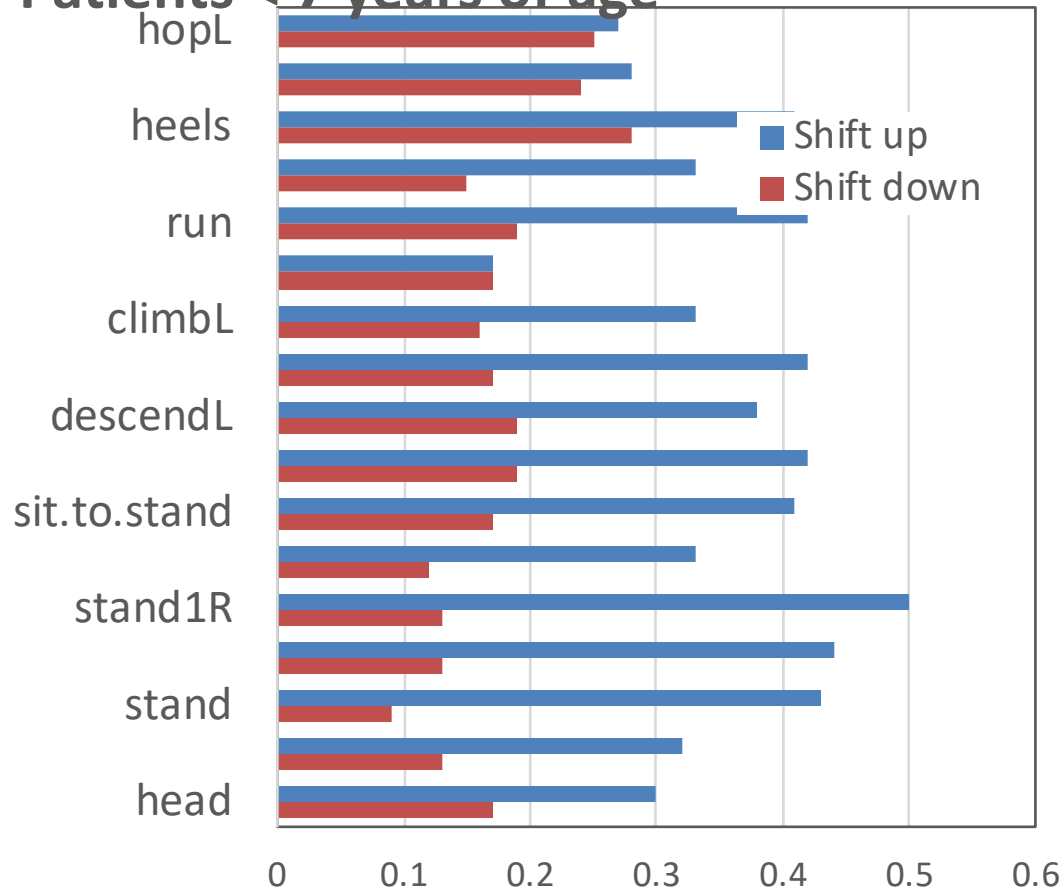


Stand from  
Supine  
NSAA: 0



# Probability of NSAA items to shift up or down over 1 year

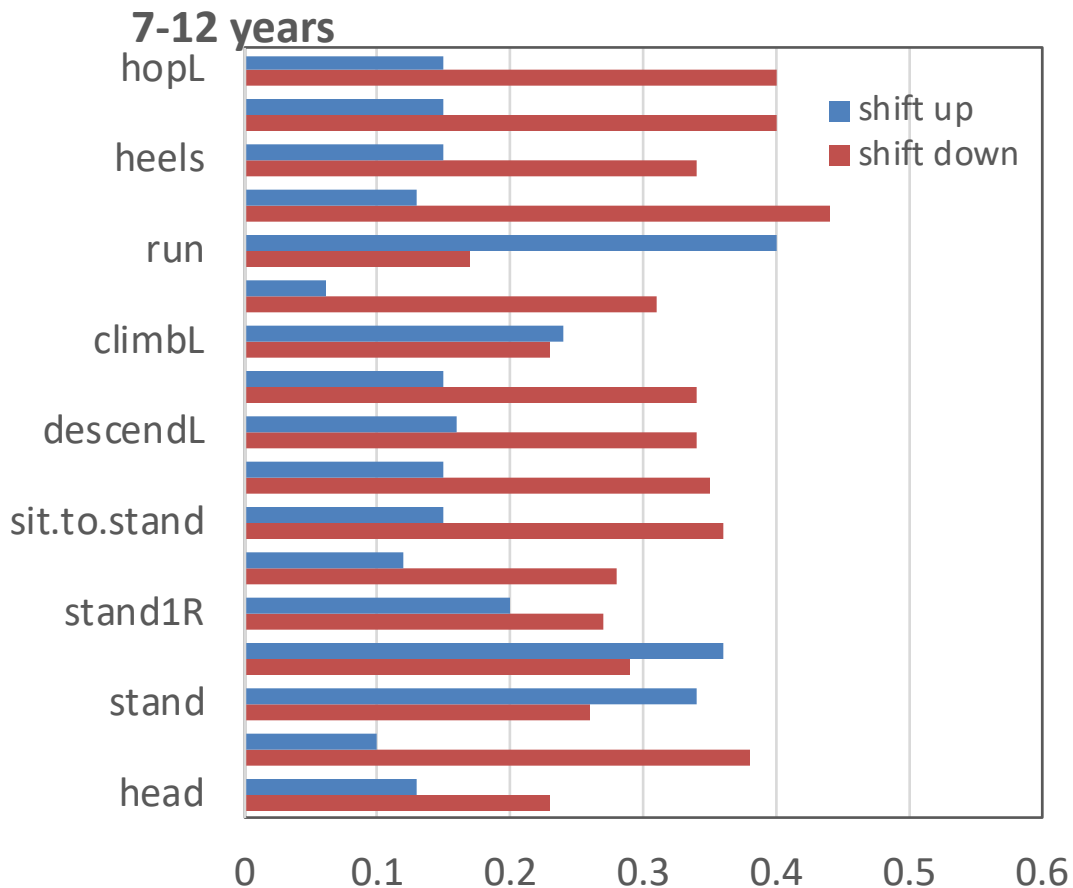
## Patients < 7 years of age



*On most NSAA items, young patients are more likely to gain function than to lose it*

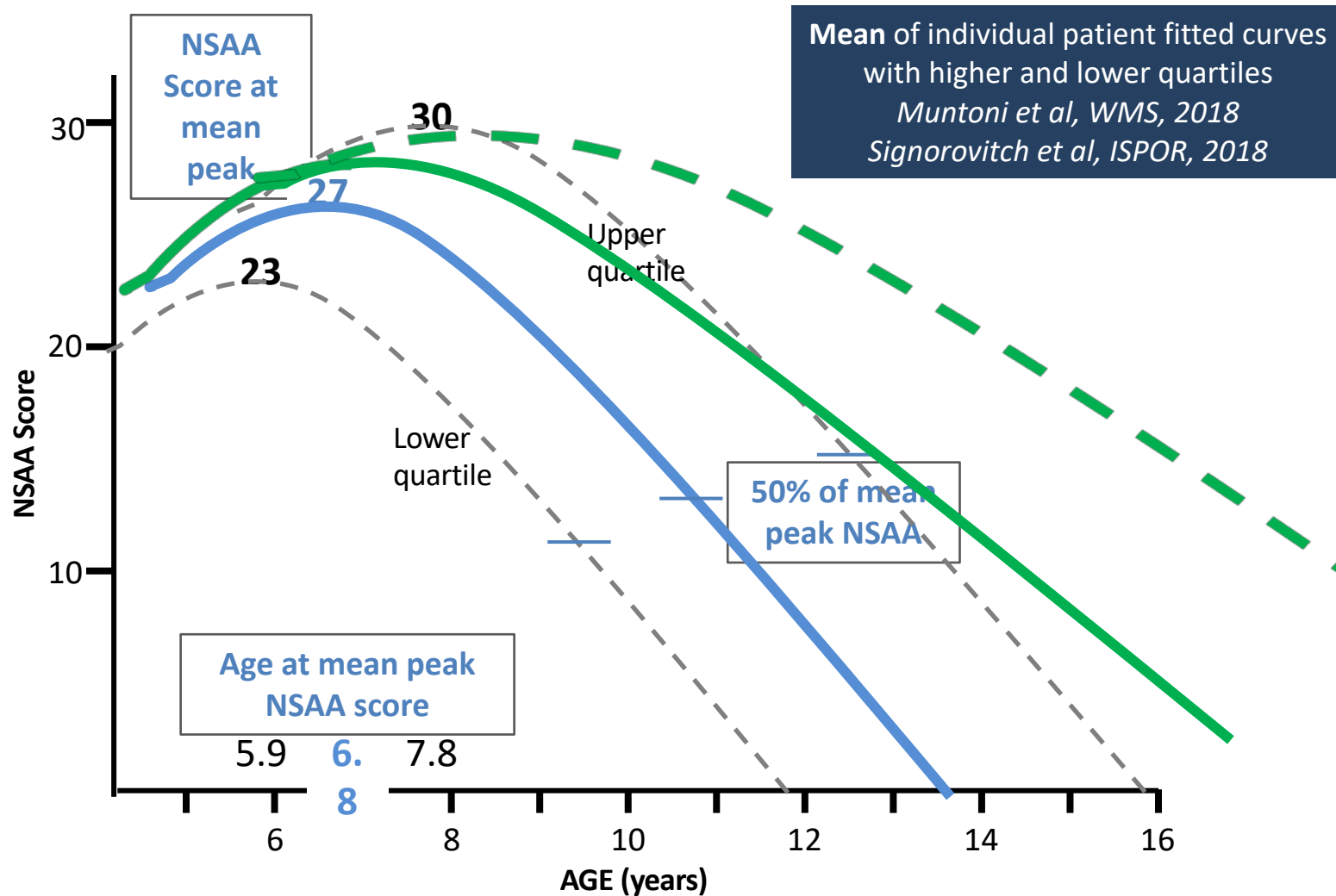
*The probability of patients to decline in their ability to hop and to jump is the same as the probability of improvement*

# Probability of NSAA items to shift up or down over 1 year



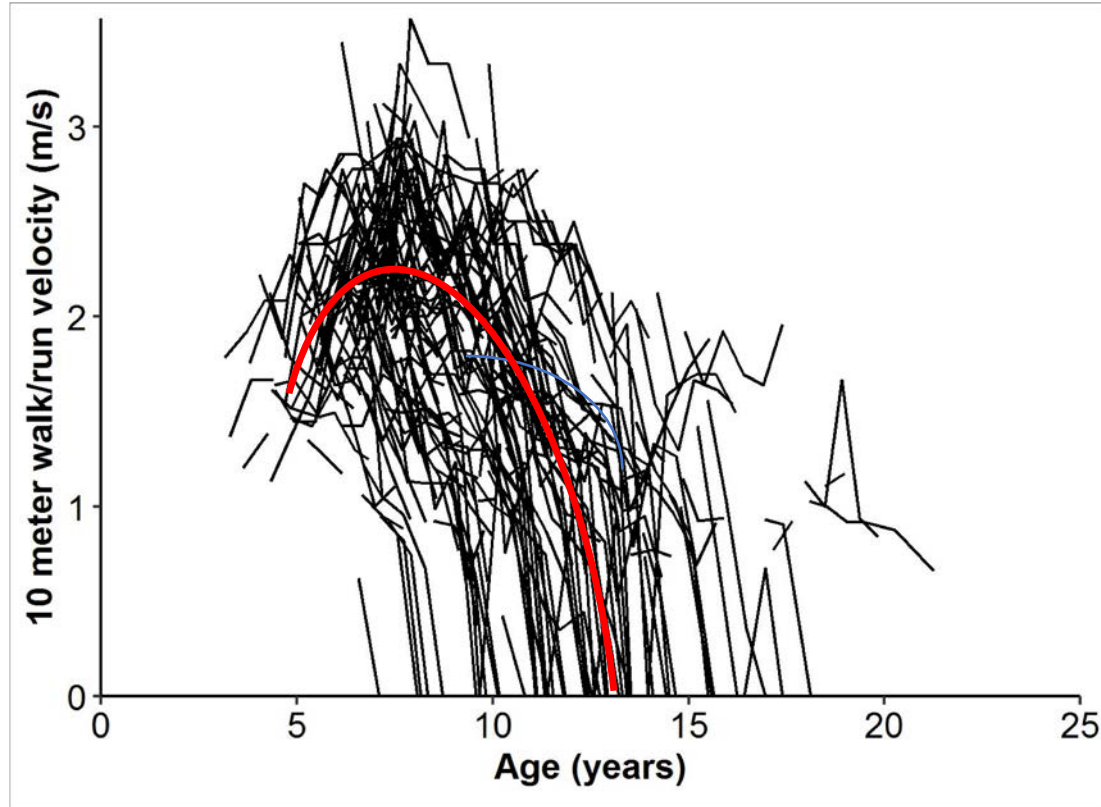
*In older patients, shifting down is more likely than shifting up*

*However, some patients continue to gain function after the age of 7, especially on run, walk and stand*



# 10 meter walk /run (velocity – meters / sec)

Prosensa / Biomarin Natural History data (cTap)



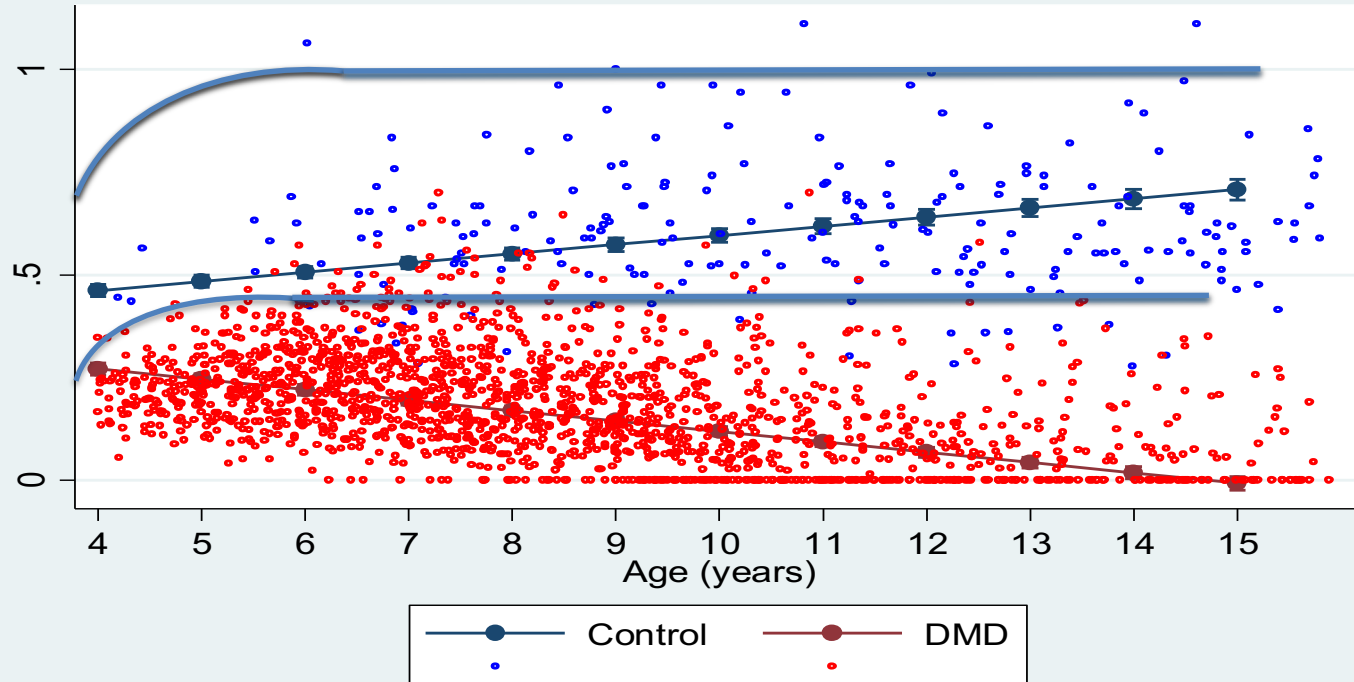
# Stand from Supine

## 5<sup>th</sup> %tile to 95<sup>th</sup> %tile (CINRG)

### TTSTAND velocity over time in DMD and control participants

Lines represent linear model accounting for repeated measures

Dots represent collected or imputed data values

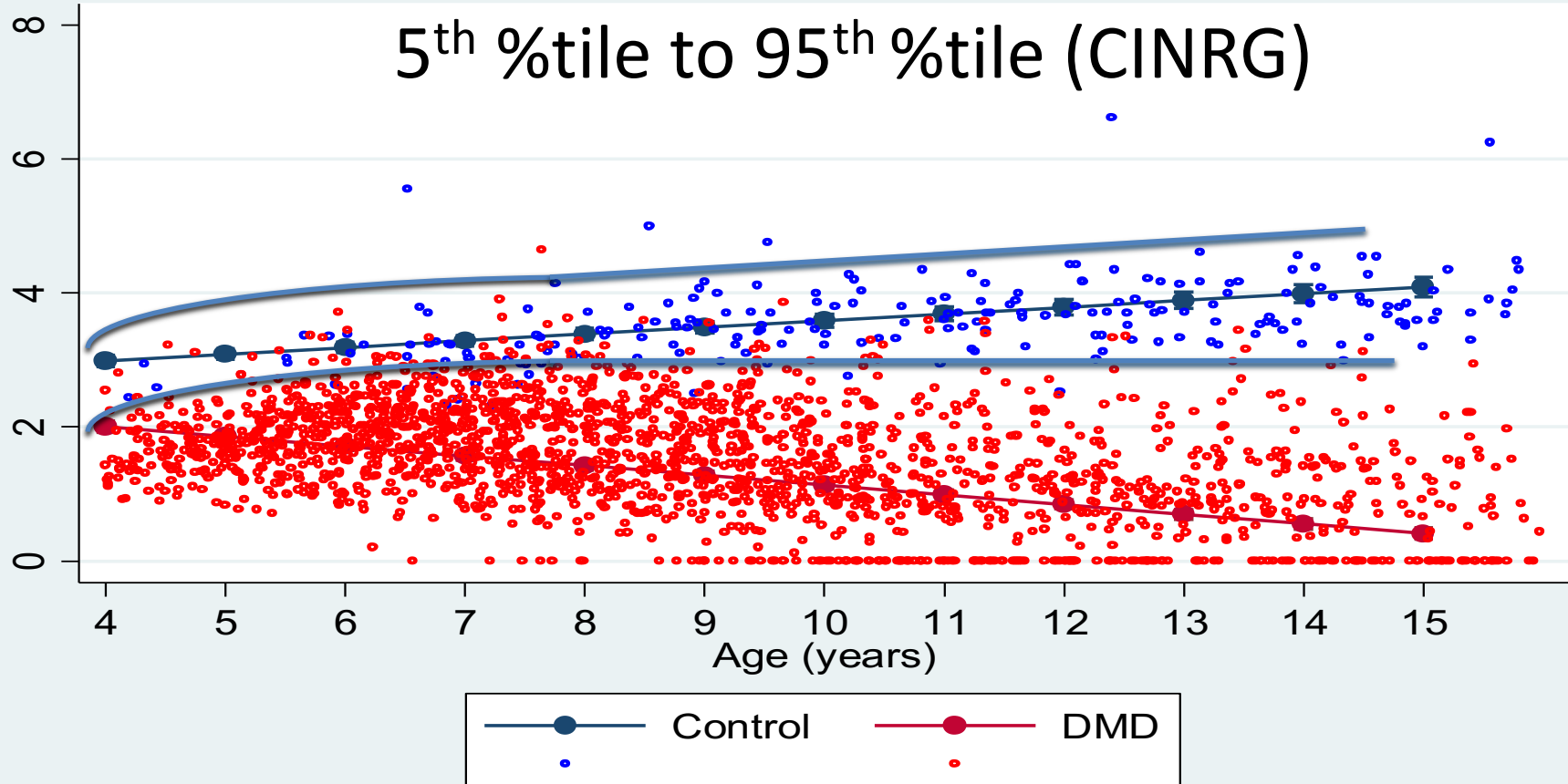


# TTRW velocity over time in DMD and control participants

Lines represent linear model accounting for repeated measurements

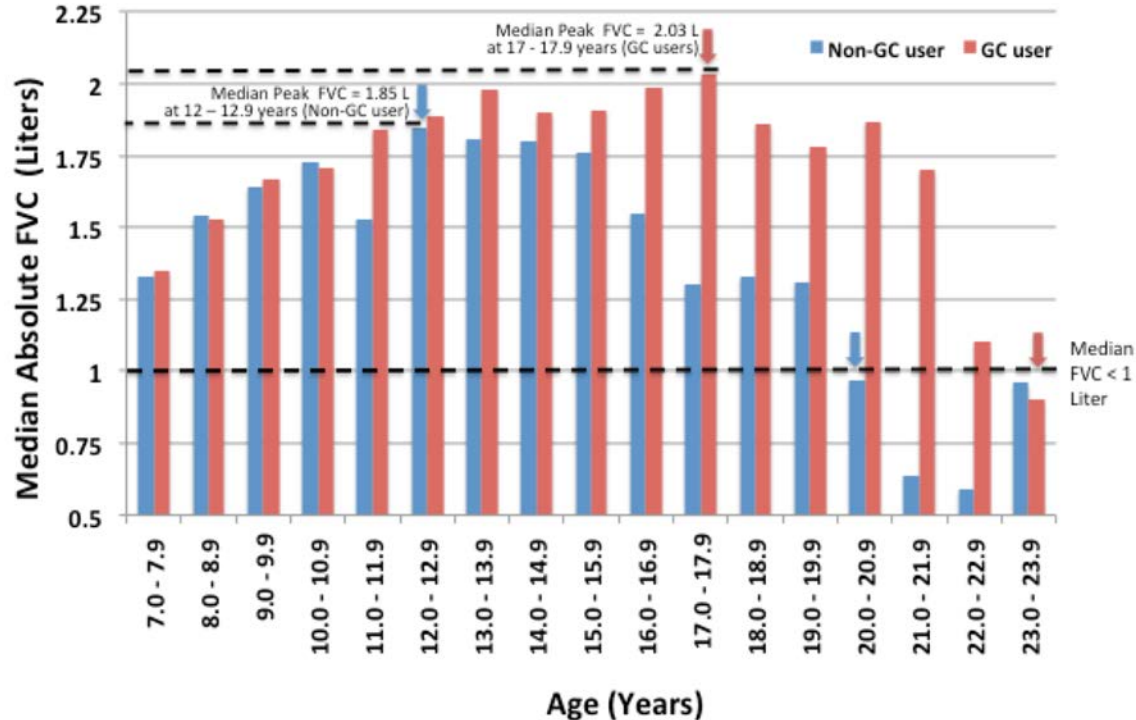
Dots represent collected or imputed data values

5<sup>th</sup> %tile to 95<sup>th</sup> %tile (CINRG)

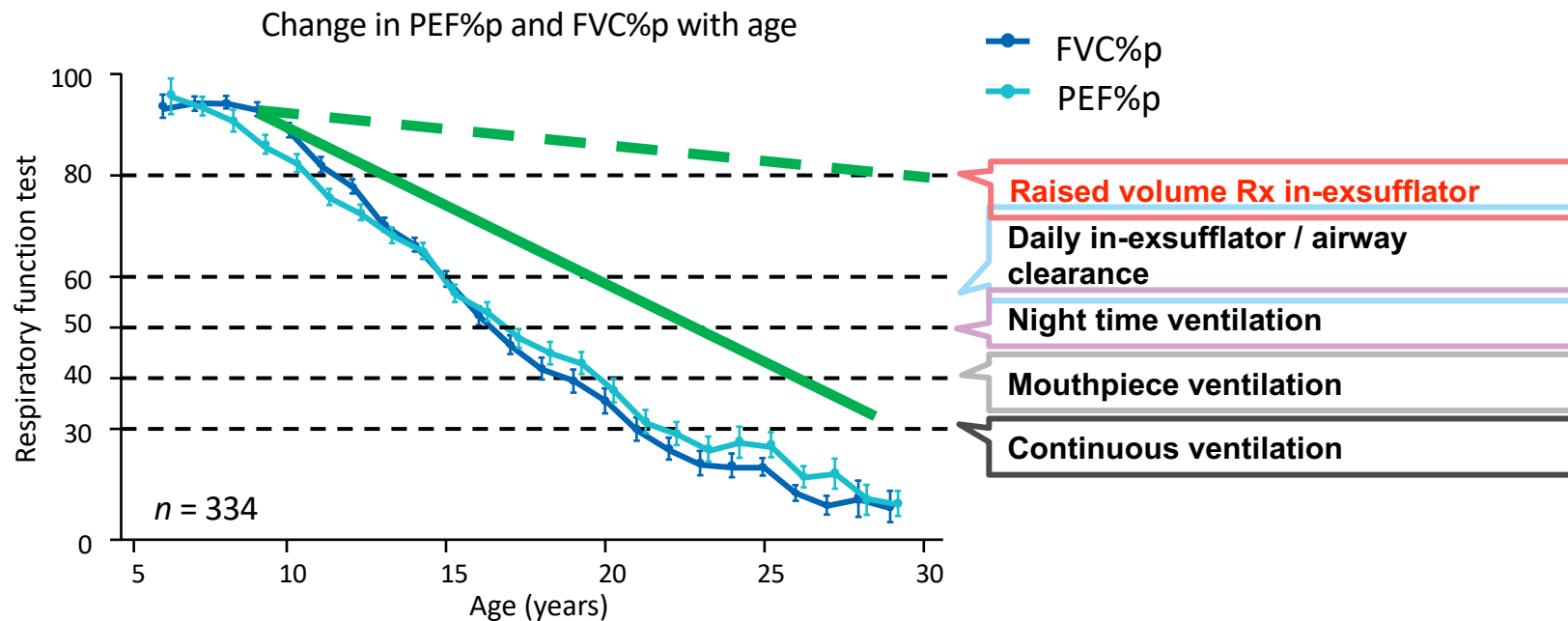




Median Absolute FVC (Liters) by Age and GC use.  
Peak in median FVC is shown and  
the point at which the median absolute FVC value drops below 1 liter.

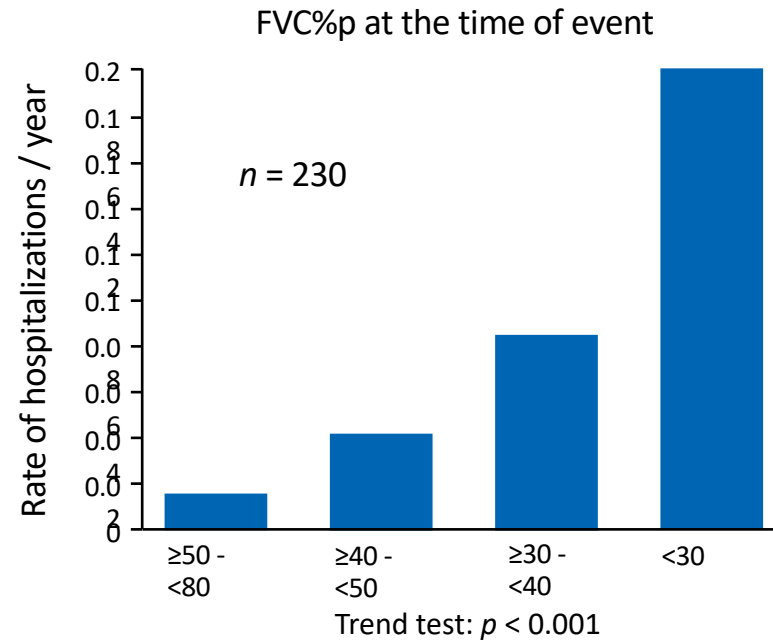
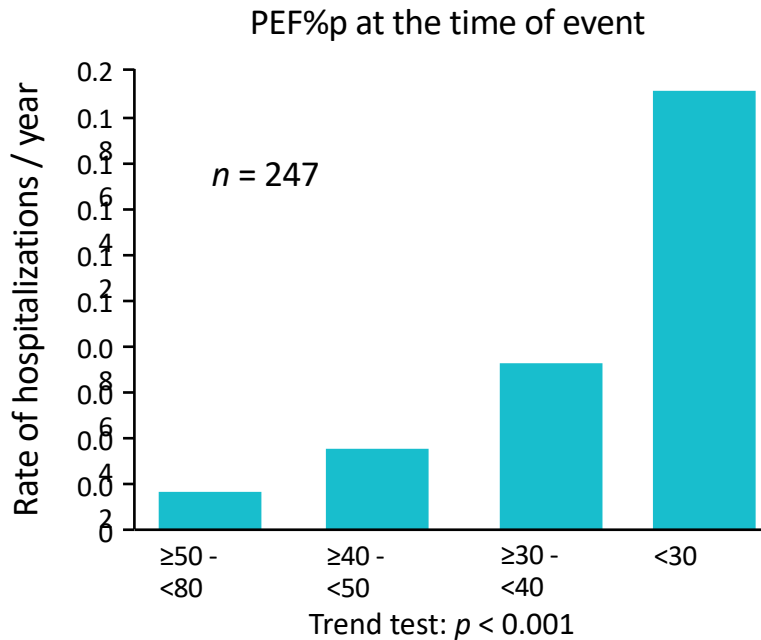


# Clinical thresholds of respiratory function can guide patient management



**For every 10% reduction in FVC, odds of hypoventilation increase by 20%**

# Decline in respiratory function correlates to risk of hospitalization due to respiratory events



# Required sample sizes can be challenging for trials

- Stage of disease, choice of primary endpoint, expected disease progression and anticipated effect of treatment (improvement vs. slowing rate of decline) all impact sample size for trial
- Symptomatic treatment versus disease-modifying approach (both likely on top of standard of care)
- Landscape increasingly competitive
- World-wide reach of trials creates challenges with standard of care



# Need for Enrichment (for those patients predicted to be responsive over a specific time frame)

- Should be enriched for the primary analysis subgroup; not for inclusion / exclusion criteria
- Frustrating for families/patients when inclusion criteria are not met
- Companies becoming more flexible and inclusive
- Should not negatively impact broad labels for drugs (FDA and EMA not the same in this regard)



# Regulatory Approaches to Extrapolation of Trial Results

- Steroids preserve ambulatory, upper limb and pulmonary function (proof of concept regarding “extrapolation” of treatment effects)
- FDA more flexible regarding extrapolation than EMA



# Community desire to minimize placebo exposure is being considered by FDA and EMA

- Smaller placebo arms enriched (validated) by natural history data will make prospective natural history data collection critical
- Platform trial designs may allow the sharing of placebo data and 2:1 or 3:1 randomization
- Lead-in natural history data collection could bolster the evidence for drug effectiveness



# Accelerated approval for AAV-microdystrophin gene replacement treatments

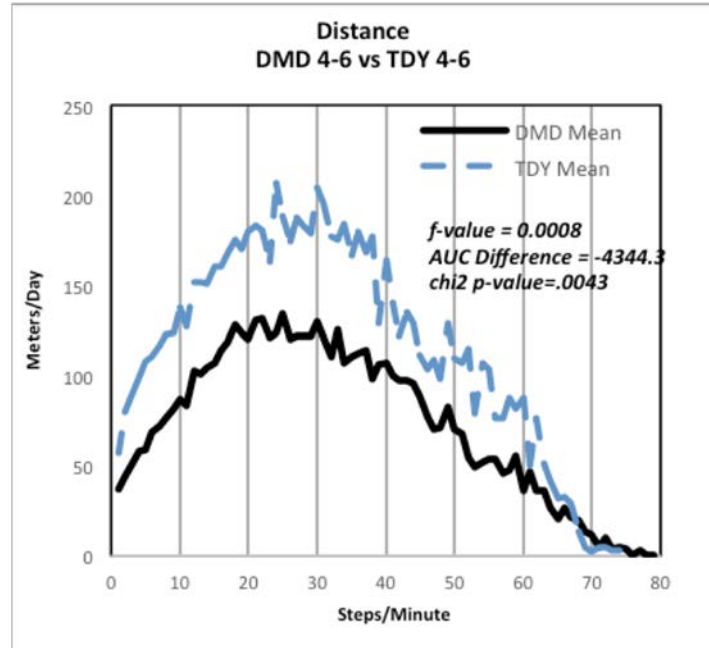
- Confirmatory trials using manufactured / future commercial product were necessary for AAV gene therapy in SMA
- Clinical data will be required to establish that increased levels of microdystrophin expression are reasonably likely to predict benefit
- Natural history data will be critical to contextualize trial results
- Durability of clinically meaningful clinical results will be important for continued marketing authorization and third party payor reimbursement



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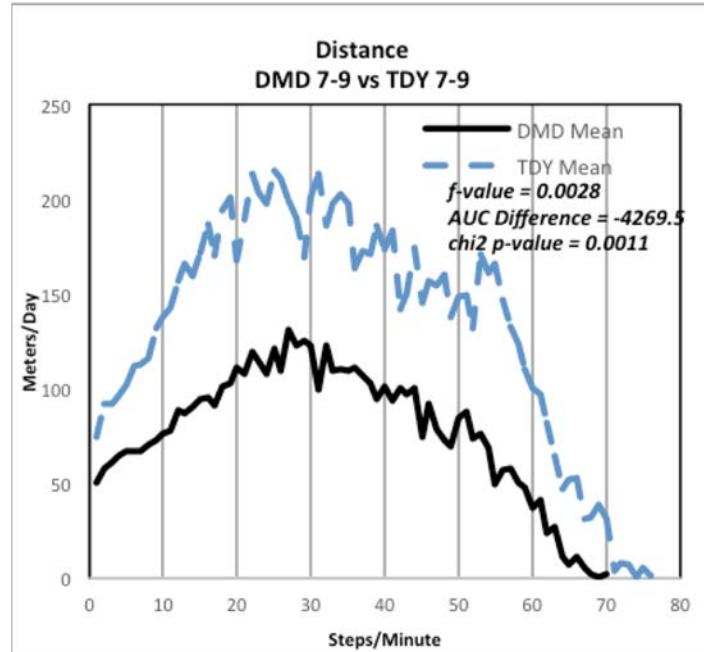


# Distance in the Community by Activity Monitoring (Ages 4-6)



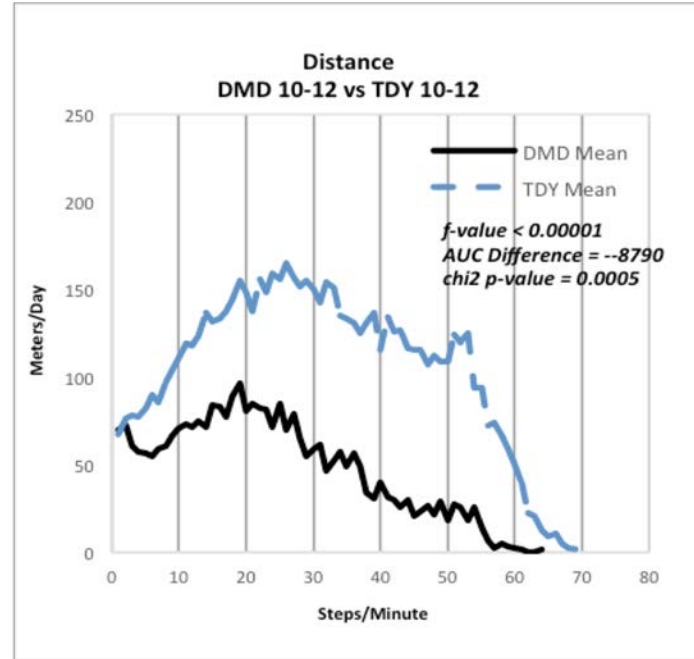
Distance (m/day) at range of step-rates (1-79 steps/min) for ambulatory DMD boys 4-6 years ( $n=7$ , sample size=87 days) versus TDY 4-6 years ( $n=7$ , sample size = 41days) over 24 hours (1440 mins).

# Distance in the Community by Activity Monitoring (Ages 7-9)



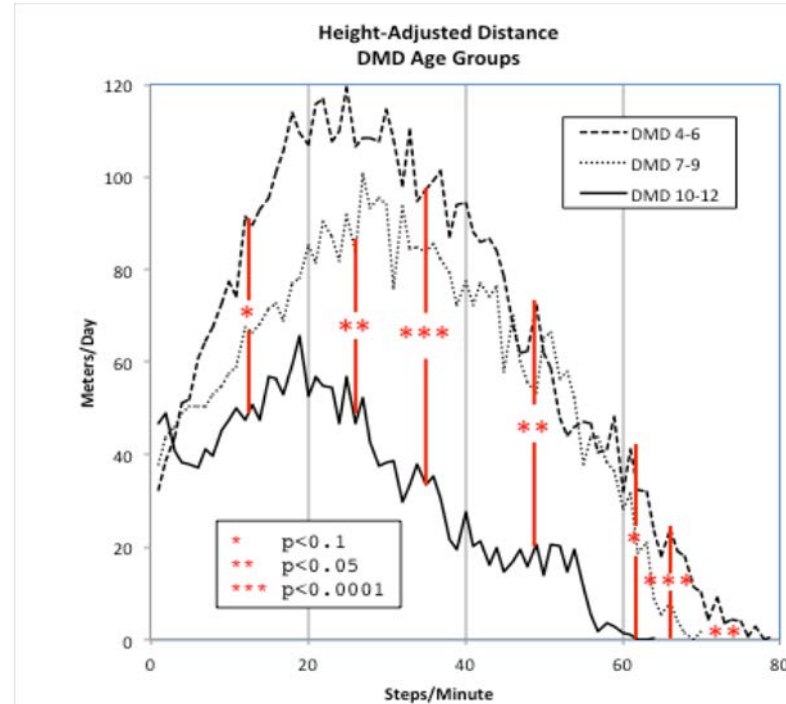
Distance (m/day) at range of step-rates (1-79 steps/min) for ambulatory DMD boys 4-6 years ( $n=7$ , sample size=87 days) versus TDY 4-6 years ( $n=7$ , sample size = 41days) over 24 hours (1440 mins).

# Distance in the Community by Activity Monitoring (Ages 10-12)



Distance (m/day) at range of step-rates (1-79 steps/min) for ambulatory DMD boys 4-6 years ( $n=7$ , sample size=87 days) versus TDY 4-6 years ( $n=7$ , sample size = 41days) over 24 hours (1440 mins).

# Height-adjusted distance over 24 hours shows disease progression in DMD



- Height-adjusted distance ambulated becomes significantly reduced in DMD with disease progression from age 4-6 to 7-9 to 10-12 using both Chi-square and Hotelling's T2 test.
- The pattern of loss of function in DMD shows that differences between 4-6 and 7-9 year old groups are more readily apparent at high step rates (>60 SPM).
- Measureable differences between 7-9 and 10-12 year age groups are best seen at household (20-40 SPM) step rates.
- Differences between 4-6 and 10-12 year age groups are seen at all step rates.

# Things to Consider

- Trial design driven by therapeutic mechanism, stage of disease and anticipated benefit (improvement, stabilization or slowing of rate of decline)
- Maturational issues growth / addressed by normative data for age / height
- Need for placebo-controlled design can be mitigated by:
  - Natural history enrichment of Placebo groups
  - Off treatment lead-in (patient serves as own control)
  - Platform designs
- Variability of gene mutation, genetic modifiers, and progression rate
- Consistent standard of care provided
- Impact of floor, ceiling on progression rate



# Future Directions: Opportunities to improve

- Wearables
  - Real world community data
  - Objective
  - Part of precision health trend
  - Reduces burden of travel for clinical efficacy assessments
- Innovative composite endpoints
- Platform trials
- Biomarkers in addition to dystrophin will expand eligibility for trials, and reduce timeframe for efficacy read-out



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The background of the slide features the letters 'PMP' in a large, bold, dark red font. The letters are positioned such that they span across the top and bottom of the frame, with the top 'P' and 'M' partially cut off. The 'P' on the right is also partially cut off. The text 'Thank you!' is centered over the middle of the 'M' and the first 'P' of the bottom row.

**Thank you!**



**Questions?**