Tracking Disease Progression in Ambulatory and Nonambulatory Boys with Duchenne Muscular Dystrophy

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Disclosures

I’m a pediatric cardiologist…

…talking about skeletal muscle outcomes

Florida birds named by an ornithologist

Florida birds named by a cardiologist

Outline

- DMD background
- Why is a cardiologist looking at skeletal muscle outcome measures?
- Actigraphy in DMD
- Future directions

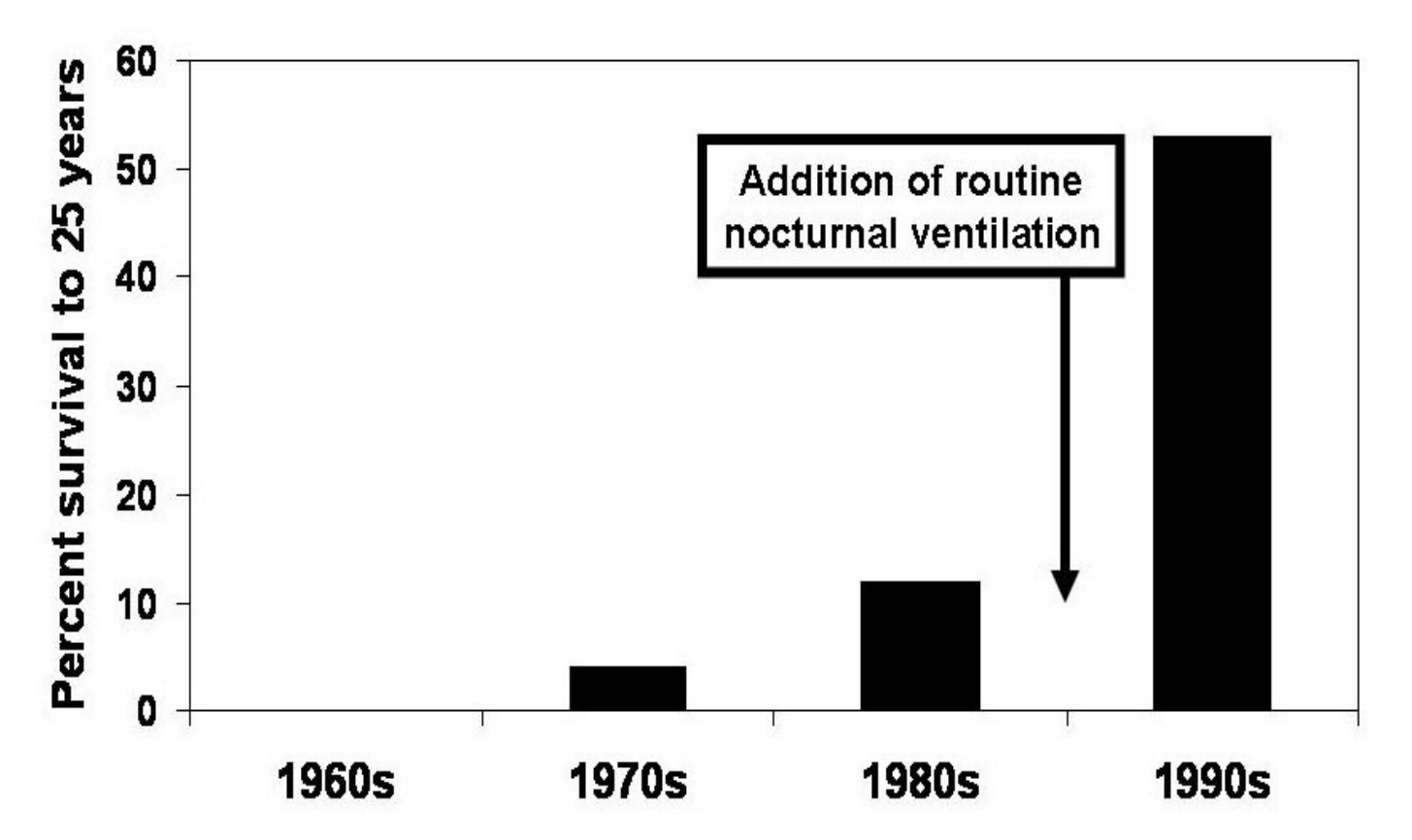
DMD Background

What is Duchenne Muscular Dystrophy?

Atlas of Clinical Neurology 2011

- X-linked recessive skeletal and cardiac myopathy
- 1 in 3500-5000 male births
- Diagnosis between 3-6 years of age
  - Due to skeletal weakness
- Loss of ambulation between 10-12 years of age
- Untreated:
  - Death from respiratory failure in 2nd-3rd decade of life

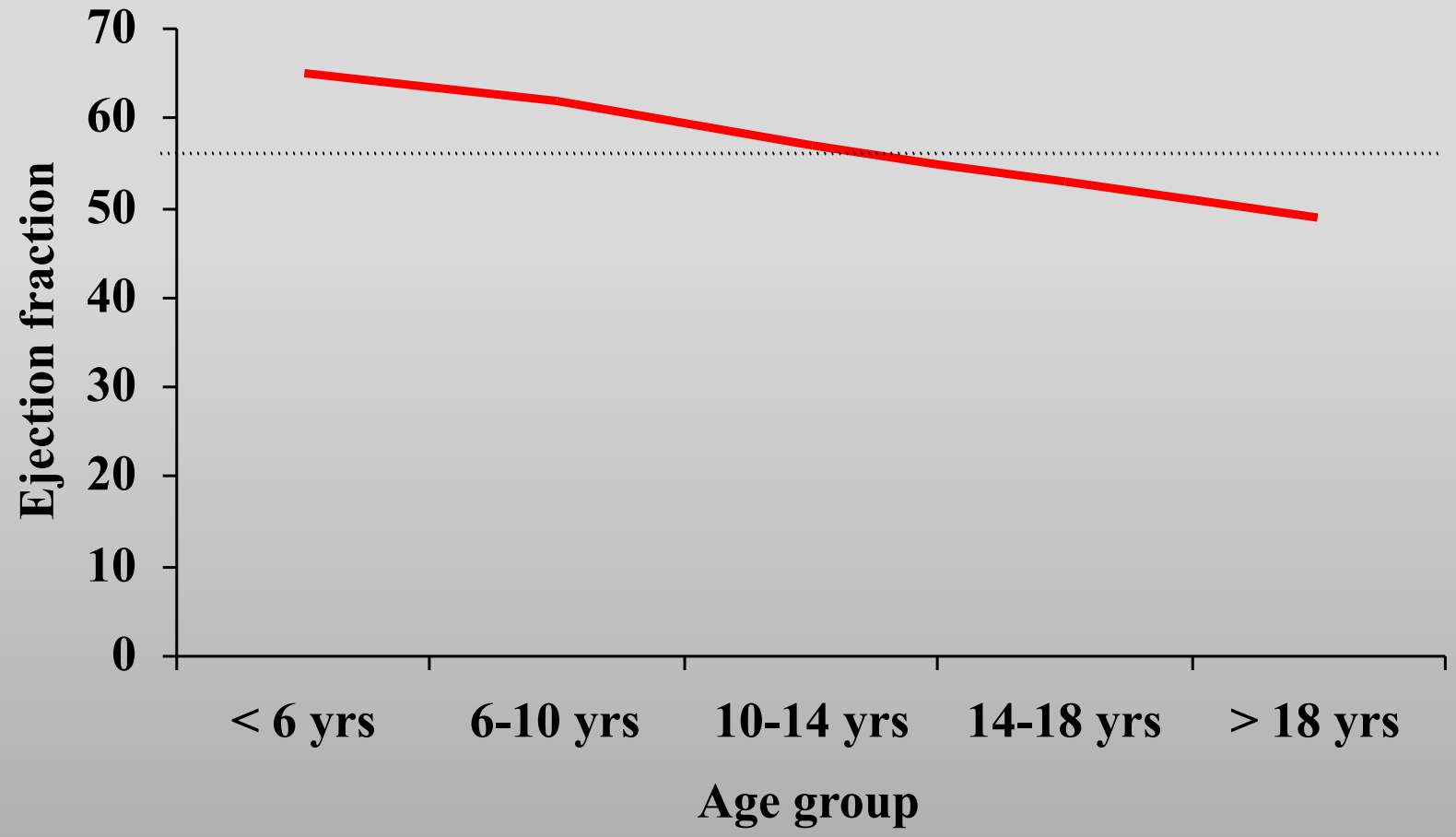
Survival Has Improved Significantly



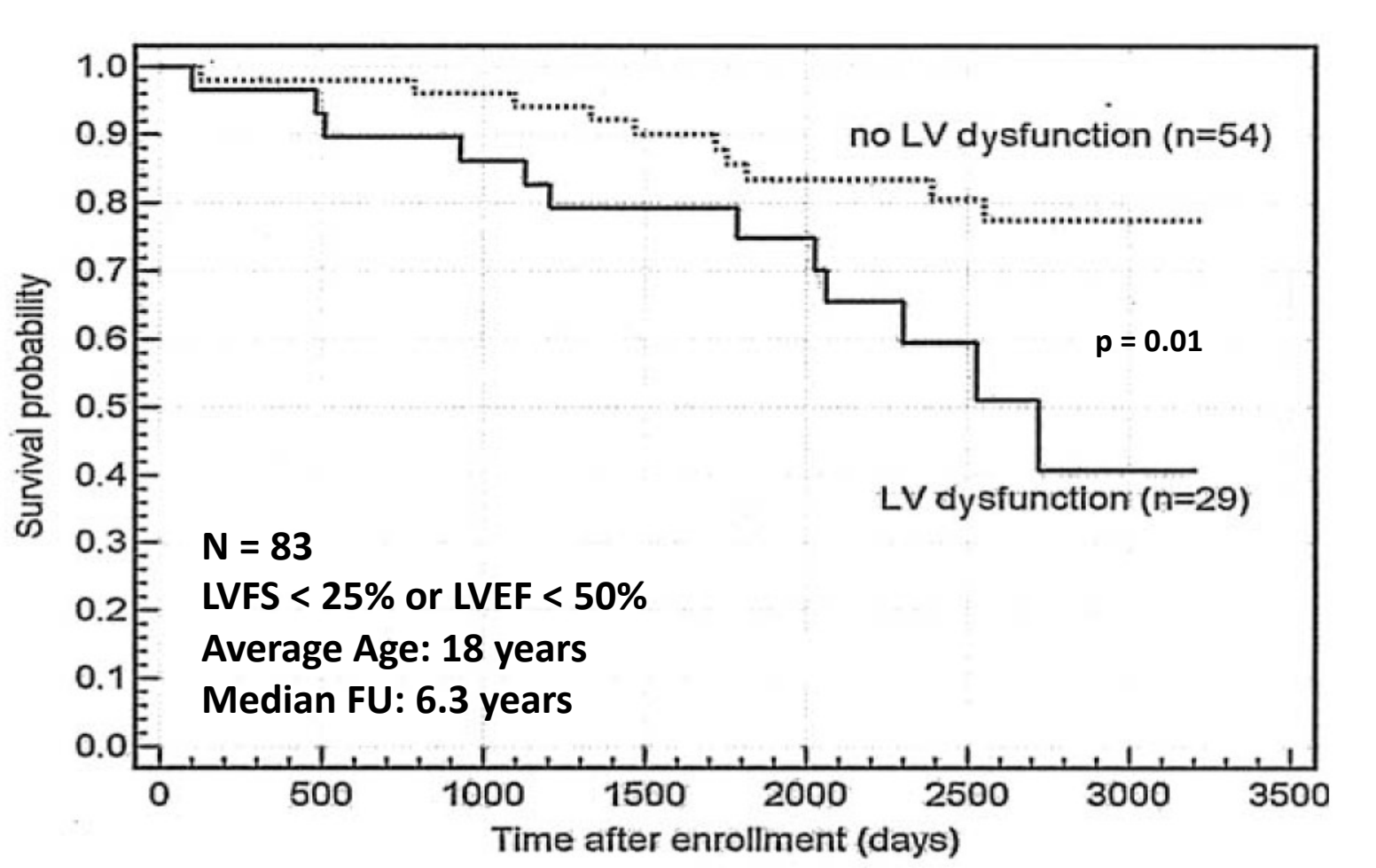
Eagle, *et al. Neuromuscular Disord,* 2002.

- 40-50% of DMD deaths in current era attributable to cardiovascular disease

Ventricular Function vs Age



Survival – LV dysfunction by echo



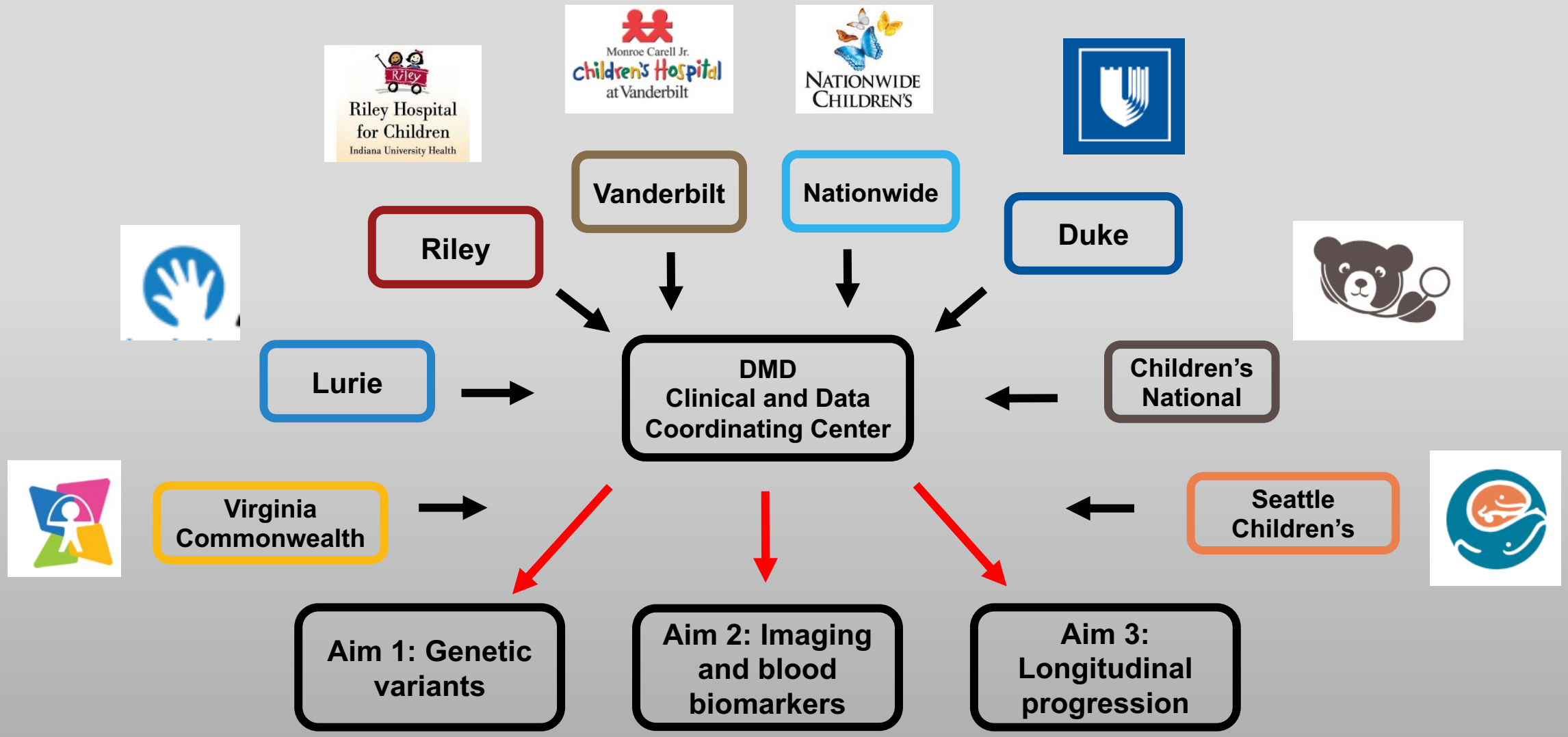
Corrado, *et al*. *Am J Cardiol* 2002.

Why is a cardiologist looking at skeletal muscle outcome measures?

DMD Cardiovascular Care Consortium (DMDCCC) Goals

- Identify serum and imaging biomarkers that can be used as surrogate endpoints in clinical trials
- Identify serum and imaging biomarkers or genetic variants that predict progression so that patients can be risk-stratified when entering clinical trials, thus reducing the total number of patients enrolled
- Leverage the DMDCCC to begin clinical trials of novel therapeutics

DMDCCC



FDA and NIH/NHLBI funded

The Problem

- Cardiac studies
  - *We also need to assess skeletal muscle progression*
  - *We need to enroll non-ambulatory patients*
- There are few validated outcome measures for skeletal muscle assessment in DMD

The Problem – Validated Outcome Measures

- Most commonly used outcome measures are for ambulatory patients
  - 30 feet walk test
  - 6 minute walk
  - North Star Ambulatory Assessment
  - SV95C (digital outcome measure approved by EMA)
- Metrics for non-ambulatory patients (none available when we started)
  - Quantitative muscle testing
    - Effort dependent
  - Performance of Upper Limb (PUL) – 11/2013
    - PUL 2.0
    - Effective but time-intensive
  - Casimir
    - Effective but expensive
  - Skeletal muscle MRI
    - Expensive
    - Time-consuming

Our Goals

- Skeletal muscle assessment
  - Work in both ambulatory and non-ambulatory DMD patients
  - Fast
  - Inexpensive
  - Accurate
  - Reproducible
  - Sensitive
    - Test that detects change over 1 or 2 years
  - Meets the definition of FDA clinical outcome assessment
    - Feel, ***Function***, Survive

Actigraphy in DMD

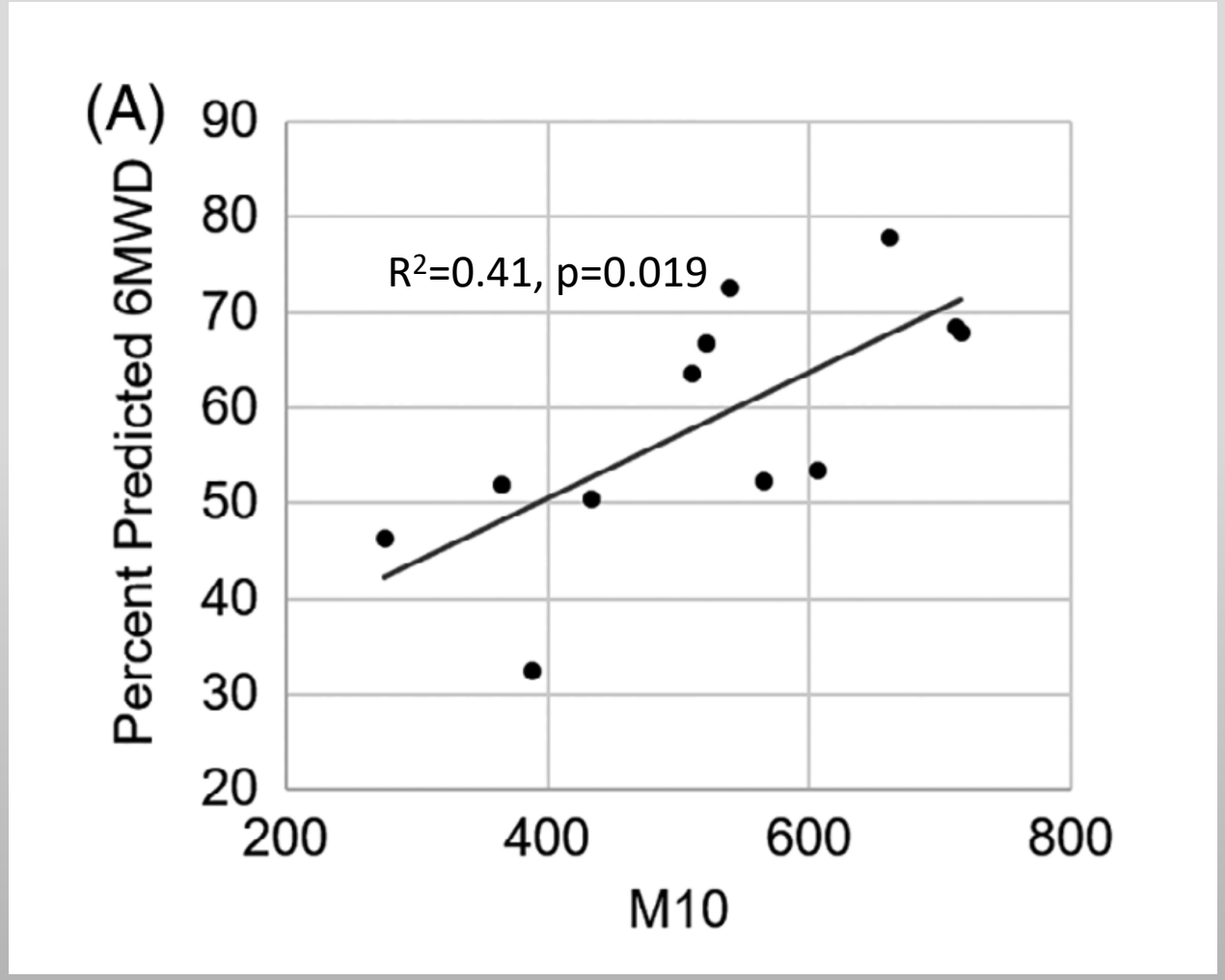
Actigraphy

Actigraph

- Easy to place
  - Can be placed in clinic
  - Can be shipped to the home
- Not effort dependent
- Multiple metrics
  - Total counts
  - Counts per minute
  - Steps
- Can it be used in non-ambulatory patients?

Actigraphy
Ambulatory Patients

- M10 = most active 10 hours
- Strong correlation between M10 and 6-minute walk in ambulatory patients



Siegel et al, *Muscle and Nerve*. 2019

Actigraphy
Ambulatory Patients

Correlation coefficients between wearable-derived gait variables recorded over 180 hours and the 6MWT and NSAA [13]

Gait variable	N	6MWT		NSAA	
		Spearman coefficient	Pearson coefficient	Spearman coefficient	Pearson coefficient
Stride length, median, m	45	0.552**	0.649**	0.554**	0.607**
Stride length 95th centile, m	45	0.679**	0.772**	0.779**	0.816**
Stride velocity, median, m/s	45	0.652**	0.758**	0.712**	0.724**
Stride velocity 95th centile, m/s	45	0.542**	0.616**	0.645**	0.689**
Distance walked/hour recorded	45	0.371*	0.436**	0.424**	0.435**

*$p < 0.05$. **$p < 0.01$. Abbreviations: 6MWT, 6-minute walk test; NSAA, North Star Ambulatory Assessment.

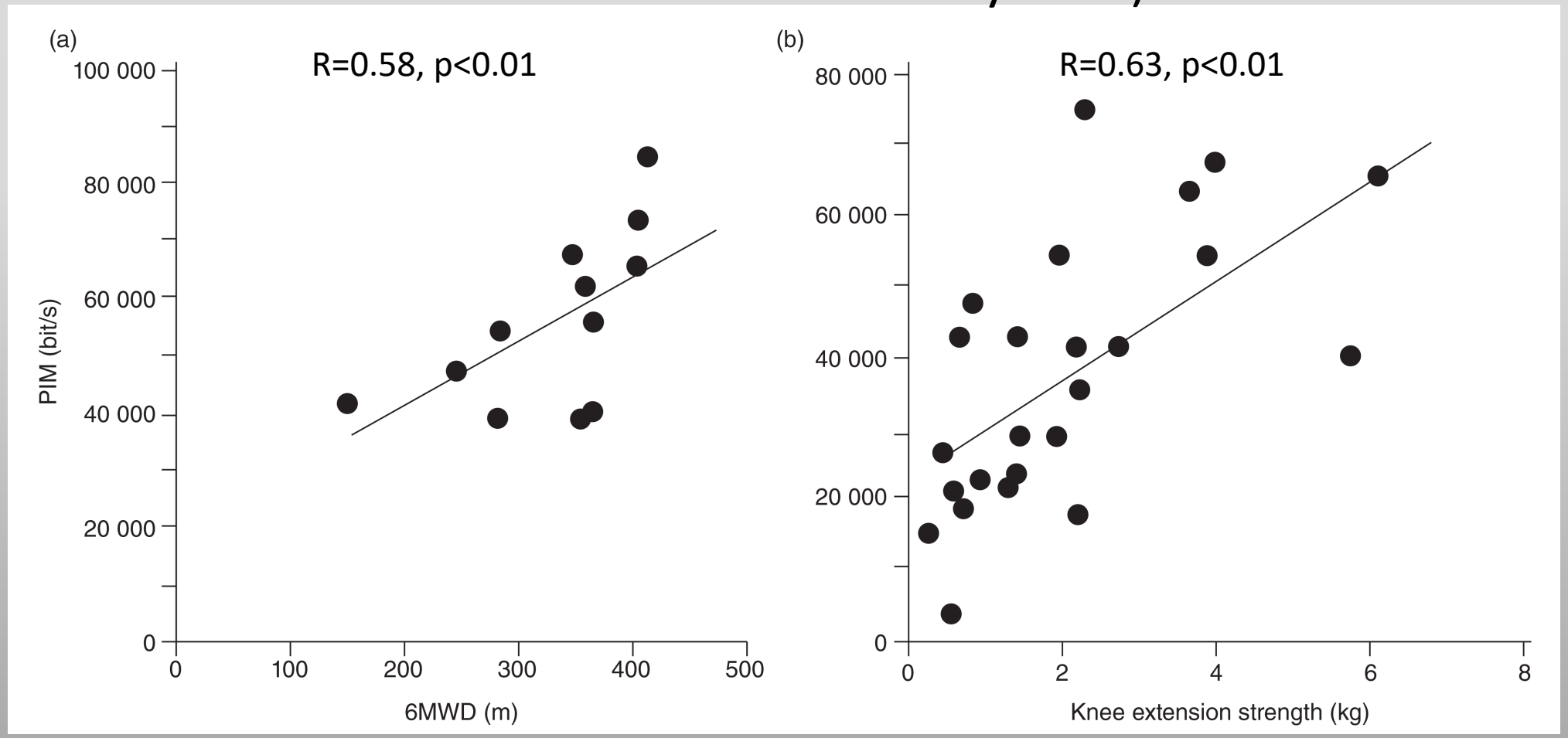
Servais et al, *Jounral of Neuromuscular Diseases*. 2022

- SV95C measures – speed of the fastest stride taken in a 180 hour monitoring period
- SV95C increases in patients after initiation of corticosteroids

Actigraphy

Ambulatory and Non-ambulatory

PIM – proportional integration mode (area under the curve - activity level)



Kimura et al, *Pediatrics International.* 2014.

Actigraphy Progression

Ambulatory (N=16) and Non-ambulatory (N=32)

Mary Killian, MD

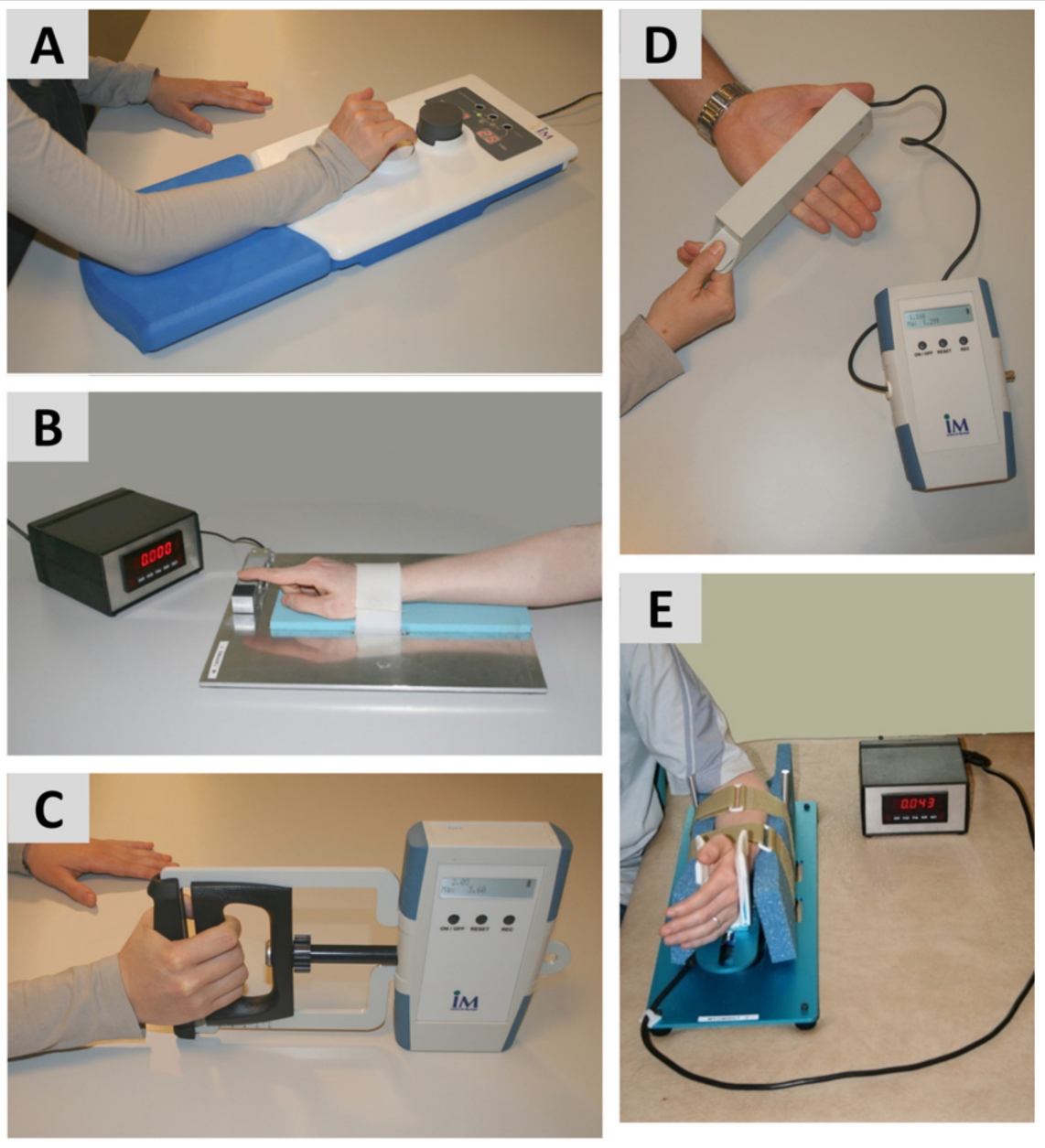
Measure	N	Baseline median (IQR)	Visit 2 median (IQR)	p-value
Total wrist VM (counts/min)	36	1240 (644, 2000)	1210 (598, 1680)	0.040
Awake wrist VM (counts/min)	33	2010 (1140, 2590)	1710 (1050, 2290)	0.020
Total ankle VM (counts/min)	27	77 (30, 471)	94 (46, 250)	0.080
Awake ankle VM (counts/min)	24	102 (52, 692)	130 (52, 356)	0.068

Killian et al, *Neuromuscular Disorders*. 2020.

QMT

- Reproducible
- Strong correlation between other metrics of strength/function
- Effort Dependent

Dynamometer



Servais et al, *Neuromuscular Disorders*. 2013.

Actigraphy and QMT

	Total wrist VM	Awake wrist VM	Total ankle VM	Awake ankle VM
Total arm QMT	Rho=0.69, p<0.001 (n=41)	Rho=0.50, p=0.002 (n=38)		
Indexed arm QMT	Rho=0.85, p<0.001 (n=41)	Rho=0.69, p<0.001 (n=38)		
Total leg QMT			Rho=0.53, p<0.001 (n=37)	Rho=0.44, p=0.009 (n=33)
Indexed leg QMT			Rho=0.69, p<0.001 (n=37)	Rho=0.66, p<0.001 (n=33)
Total QMT	Rho=0.62, p<0.001 (n=41)	Rho=0.41, p=0.001 (n=38)	Rho=0.56, p<0.001 (n=37)	Rho=0.46, p=0.007 (n=33)
Indexed total QMT	Rho=0.80, p<0.001 (n=41)	Rho=0.64, p<0.001 (n=38)	Rho=0.71, p<0.001 (n=37)	Rho=0.68, p<0.001 (n=33)

Killian et al, *Neuromuscular Disorders*. 2020.

Actigraphy Breakdown

Mac Buchowski, PhD

	DMD total	Healthy controls		DMD ambulatory	DMD non-ambulatory	
Participants	N=44	N=11		N=13	N=31	
Minutes awake (%)	mean ± SD		p-value*			p-value*
sedentary	85.0 ± 12.3	75.8 ± 8.3	0.007	70.7 ± 8.8	91.0 ± 7.7	<0.001
low-intensity	13.8 ± 10.9	19.2 ± 5.8	0.023	26.0 ± 8.0	8.7 ± 7.3	<0.001
moderate-to-vigorous	1.2 ± 1.6	5.0 ± 2.9	0.001	3.3 ± 1.4	0.3 ± 0.6	<0.001

* p-value<0.0083 considered significant after Bonferroni correction

Arteaga et al, *Neuromuscular Diseases*. 2020.

Actigraphy Breakdown

	DMD ambulatory	DMD non-ambulatory	
Participants	N=13	N=31	
Minutes awake in sedentary behaviors (%)	mean ± SD		p-value†
sedentary-1	31.5 ± 8.1	47.0 ± 18.2	<0.001
sedentary-2	25.5 ± 4.2	25.2 ± 6.7	0.865
sedentary-3	43.0 ± 9.1	27.9 ± 14.4	<0.001
Minutes awake in low-intensity activity (%)			p-value‡
low-intensity-1	36.0 ± 5.2	61.4 ± 15.6	<0.001
low-intensity-2	64.0 ± 5.2	38.6 ± 15.6	<0.001

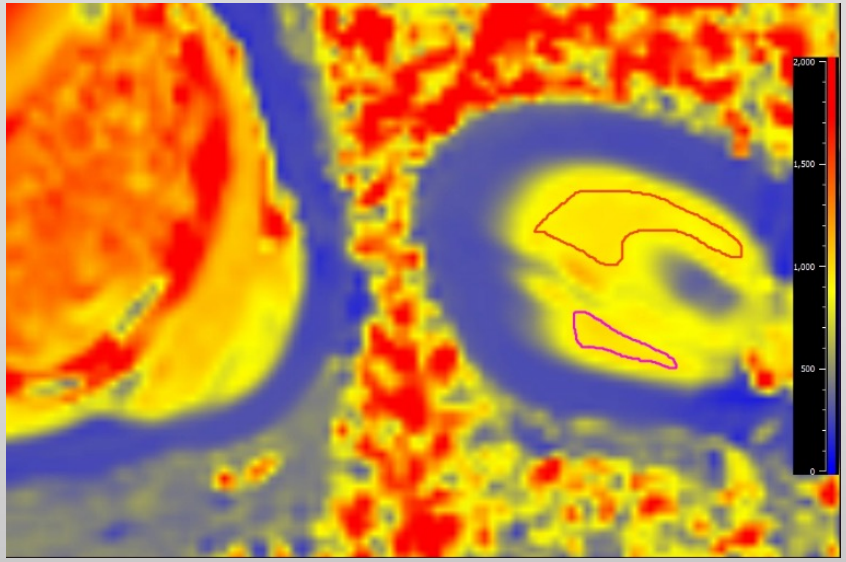
† p-value<0.017 considered significant after Bonferroni correction
‡ p-value<0.025 considered significant after Bonferroni correction

Arteaga et al, *Neuromuscular Diseases*. 2020.

Actigraphy Cut-Offs

Physical Activity Category	Cut-points (VM/min)
Sedentary	**0-3660**
Sedentary-1	*0-481*
Sedentary-2	*482-3660*
Low-intensity	**3661-9804**
Low-intensity-1	*3661-5154*
Low-intensity-2	*5155-9804*
Moderate-to-vigorous	**>9804**

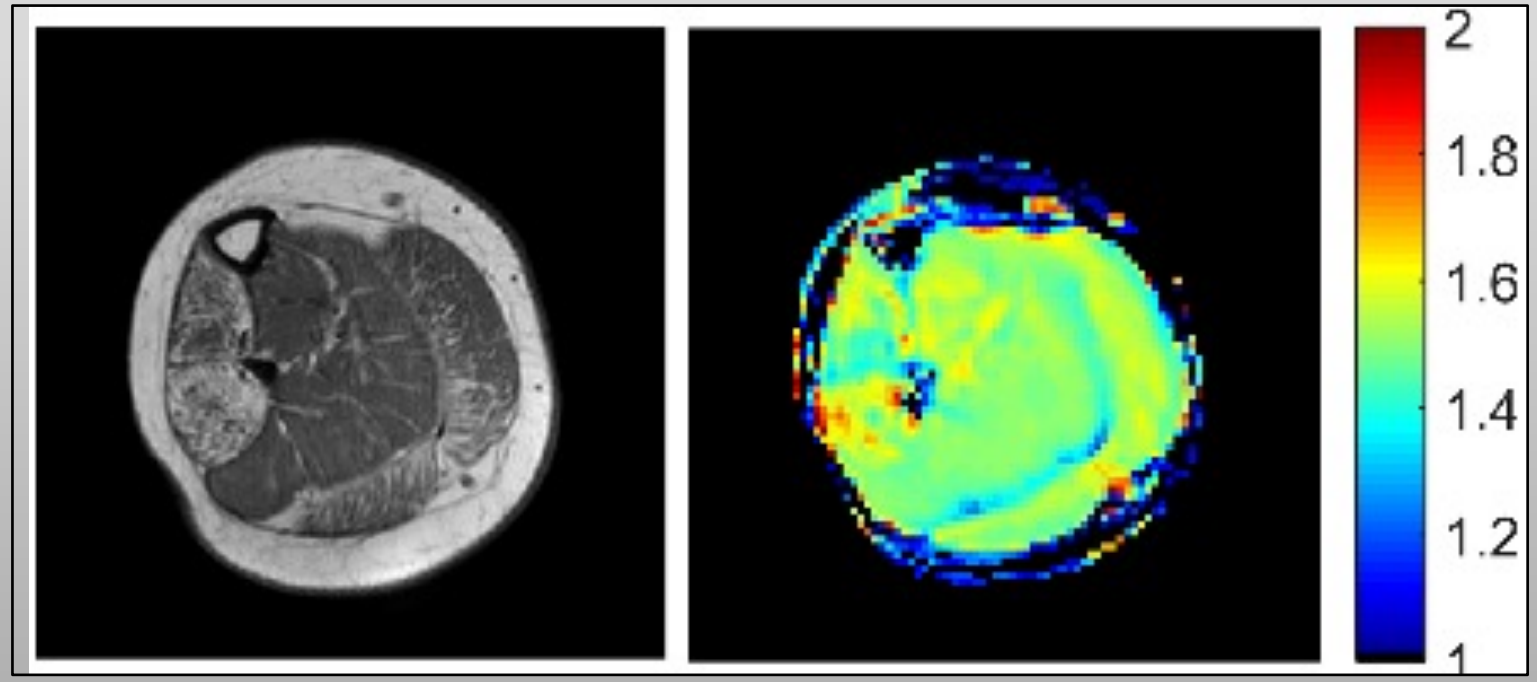
Cardiac MRI



- Fast
- Cheap (free)
- Average/poor image quality

Skeletal Muscle MRI

- Great image quality
- Now validated as an outcome measure
- Expensive
- Time-consuming



T1 Weighted

Water Map

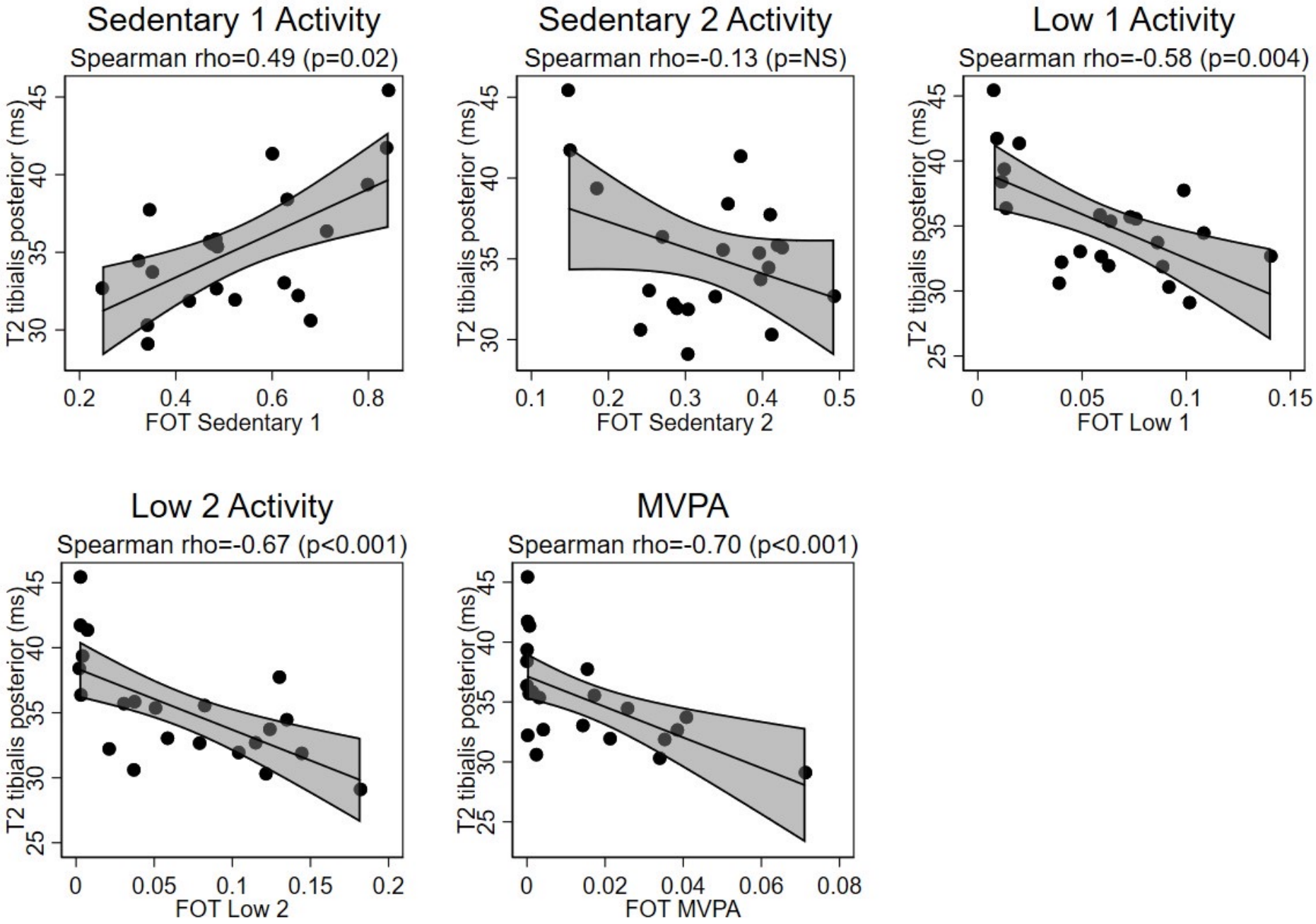
Actigraphy and MRI images from CMR

Jake Kaslow, MD

Correlation between actigraphy and cardiac MRI images of the arm

	Wrist VM/min	Wrist awake VM/min	Ankle VM/min	Ankle awake VM/min
Triceps (ms)	Rho=0.52 p=0.002 (n=33)	Rho=0.50 p=0.004 (n=31)	Rho=0.55 p=0.003 (n=28)	Rho=0.39 p=0.051 (n=26)
Biceps (ms)	Rho=0.52 p=0.002 (n=33)	Rho=0.51 p=0.003 (n=31)	Rho=0.54 p=0.003 (n=28)	Rho=0.39 p=0.051 (n=26)

Kaslow et al, *Neuromuscular Disorders*. 2022.


Sedentary 1 Activity
Spearman rho=0.49 (p=0.02)
T2 tibialis posterior (ms)
FOT Sedentary 1
Sedentary 2 Activity
Spearman rho=-0.13 (p=NS)
T2 tibialis posterior (ms)
FOT Sedentary 2
Low 1 Activity
Spearman rho=-0.58 (p=0.004)
T2 tibialis posterior (ms)
FOT Low 1
Low 2 Activity
Spearman rho=-0.67 (p<0.001)
T2 tibialis posterior (ms)
FOT Low 2
MVPA
Spearman rho=-0.70 (p<0.001)
T2 tibialis posterior (ms)
FOT MVPA

Actigraphy and Skeletal Muscle MRI

Evaluation of VMs per minute using multivariable linear regression b-coefficient (p) 95% confidence interval			
Tibialis Posterior T_2	-108 (0.002) (-171, -46)	-87 (0.016) (-157, -18)	-141 (0.001) (-216, -65)
Age (years)	-132 (0.002) (-207, -56)		
Ambulatory status		938 (0.003) (371, 1505)	
Glucocorticoid use			302 (0.36) (-378, 983)

Pulmonary Function Testing and Actigraphy

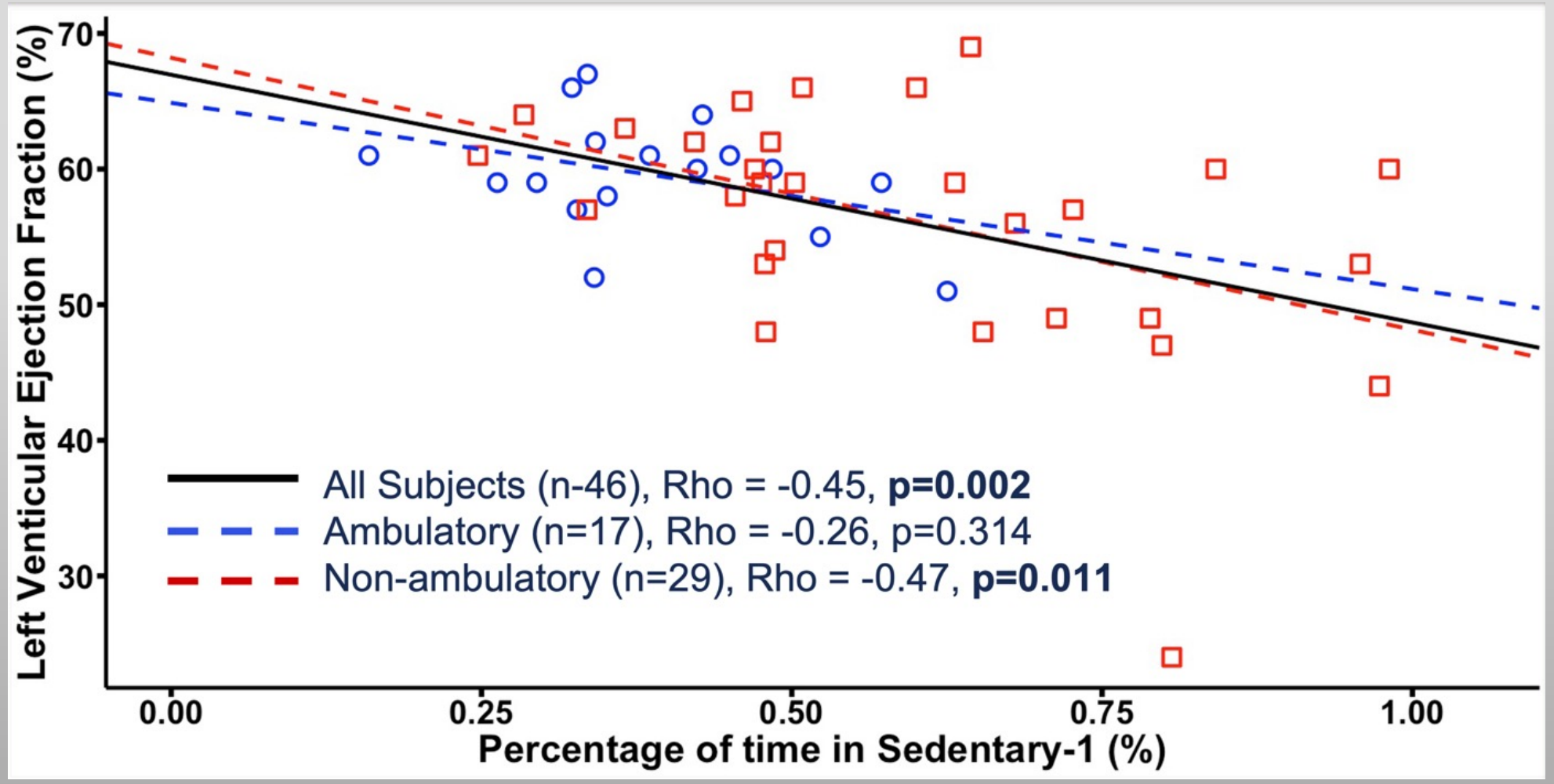
Jake Kaslow, MD

TABLE 2 Correlation between spirometry measures and accelerometry VMs

	n	*ρ*	*p*
FVC%p			
Wrist VM (counts)	31	0.6523	0.0001
Awake wrist VM	29	0.6148	0.0004
Wrist VM per minute	31	0.6527	0.0001
Awake wrist VM per minute	29	0.4810	0.0083
Ankle VM	26	0.6753	0.0002
Awake ankle VM	22	0.6586	0.0009
Ankle VM per minute	26	0.6117	0.0009
Awake ankle VM per minute	22	0.3434	0.1176

Kaslow et al, *Pediatric Pulmonology*. 2023.

Actigraphy – Skeletal/Cardiac



Future Directions

- Larger sample size
  - Wrist actigraphy in all patients in Natural History Study
  - Currently 172 patients enrolled
- Anchor measures to clinically meaningful endpoints
  - Loss of ambulation
  - Time since loss of ambulation
  - FVC% predicted
  - Absolute FVC <1L
- Correction of wheelchair motion
- Novel metrics

Limitations

- There is variability with actigraphy data
  - How many minutes the patients wore the monitor
  - Variability related to seasons/weather/intercurrent illness
  - *Longer monitoring may address some of these issues*
- Difficult to tease out cardiac and skeletal effects of actigraphy
  - If a treatment is increasing activity levels, this may not matter

Conclusions

- Actigraphy
  - Not dependent on patient effort and is easy for research team to place
    - Also potential to ship to home and perform remote monitoring
  - Sensitive enough to detect changes over 1 year
  - Multiple metrics available
  - Correlates with QMT and skeletal muscle MRI
  - Potential variability needs to be addressed
  - Needs further study in larger cohorts

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Cardiologist… getting better at skeletal muscle

Actigraphy Data - DMD

- >99% of time spent in sedentary or low-intensity activity
- Split time into 3 categories of sedentary and 2 of low intensity